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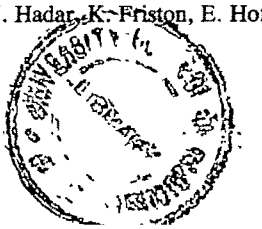

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SIMULTANAGNOSIA

TO SEE BUT NOT TWO SEE

by H. BRANCH COSLETT *and* ELEANOR SAFFRAN

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SUMMARY

Simultanagnosia is a disorder of visual perception characterized by the inability to interpret complex visual arrays despite preserved recognition of single objects. We report a series of investigations on a simultanagnosic patient which attempt to establish the nature of this visual processing disturbance. The patient performed normally on a feature detection task but was impaired on a test of attention-requiring visual search in which she was asked to distinguish between stimuli containing different numbers of targets. She was not impaired on a visual-spatial orienting task. She identified single briefly presented words and objects as rapidly and reliably as controls suggesting that access to stored structural descriptions was not impaired. With brief, simultaneous presentation of 2 words or drawings, she identified both stimuli significantly more frequently when the stimuli were semantically related than when they were unrelated. On the basis of these and other data, we suggest that the patient's simultanagnosia is attributable to an impairment in the process by which activated structural descriptions are linked to information coding the location of the object.

INTRODUCTION

Models of cognitive processes that provide an explanatory framework for normative data should also be able to account for phenomena that arise from impairments in these processes. In this paper we describe a perceptual disturbance that presents a challenge for current theories of visual processing. The disorder, known as simultanagnosia, is characterized by the inability to interpret complex visual arrays despite preserved recognition of single objects. This investigation of a patient with simultanagnosia is, we believe, the first attempt to characterize this disorder within the framework of an information-processing model.

The syndrome was described in detail as early as 1909, in Balint's report of a patient who readily identified single objects, both large and small, but claimed to see only one object when confronted with a complex display. Balint's patient also exhibited a 'psychic paralysis' of gaze, an impairment of voluntary eye movements in which oculomotor reflexes are preserved, and 'optic ataxia', a disorder of visually-guided movements which is not attributable to weakness, incoordination or visual loss (Perenin and Vighetto, 1988). This constellation of symptoms, subsequently designated 'Balint's syndrome', has been described by a number of investigators (Holmes 1918; Holmes and Horrax, 1919; Hécaen and Ajuriaguerra, 1954; Luria, 1959; Luria *et al.*, 1963; Tyler, 1968). The syndrome is relatively rare, perhaps because bilateral lesions (to parieto-occipital cortex) are generally required to produce it. It is interesting, in this regard, that the

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symptom complex has been reported in patients with degenerative disorders (e.g., Benson *et al.*, 1988) in which the pathological changes are diffuse and hence likely to be bilateral.

An ostensibly similar perceptual impairment has also been reported with unilateral parieto-occipital lesions. Thus Wolpert (1924) described a patient who exhibited an impairment in the interpretation of complex visual arrays as well as letter-by-letter reading subsequent to a left parieto-occipital infarct; abnormalities of gaze, however, were not present in this patient. Similar cases have been described by Head (1920), Pötzl (1928), Kinsbourne and Warrington (1962, 1963), and Levine and Calvanio (1978). We will provide data below that differentiates this unilateral disturbance from the simultanagnosic disorder found in our patient.

A number of explanations have been proposed for the impaired interpretation of complex visual arrays. Some investigators have argued that simultanagnosia as well as other 'higher' visual processing disorders are attributable to elementary visual processing impairments in combination with other nonvisual cognitive deficits (Faust, 1947; Bender and Feldman, 1972). Bay (1953), for example, proposed that the disorder was due to 'shaft vision', perhaps in combination with general intellectual loss and aphasia. This position was undermined by demonstrations that simultanagnosia is not always associated with intellectual impairment or aphasia and, furthermore, that performance is not affected by object size as one might predict if patients suffered from 'shaft vision'. Additionally, Ettlinger (1957) convincingly demonstrated that the low level visual deficits which figured in Bay's account of simultanagnosia and other perceptual impairments are also observed in patients who do not manifest these 'higher' disorders of visual perception.

Other investigators have regarded simultanagnosia as a type of visual agnosia or 'higher' level processing impairment but have disagreed about the nature of the deficit which underlies it. Unfortunately, these accounts have not been fully elaborated. Thus, for example, Wolpert (1924) and others (e.g., Pötzl, 1928) attributed the disorder to a failure of visual integration at the highest level, while Luria and colleagues (1959, 1963) argued that the disorder was due to the suppression of competing visual elements by an abnormal 'visual analyser'. Other investigators have proposed that this disorder is attributable to a disturbance of visual attention (Balint, 1909; Hécaen and Ajuriaguerra, 1954; Bauer and Rubens, 1985); the nature of the postulated attentional deficit has not, however, been specified.

We report a series of investigations of a patient with simultanagnosia which attempt to establish the nature of the visual processing problem. These experiments were motivated by a working model of visual processing, to be outlined below, which assumes that selective attention plays a critical role at multiple levels of visual processing. On the basis of these investigations we conclude that the impairment is attributable to an impairment in the process by which activated structural descriptions are linked to information coding the object location.

CASE DESCRIPTION

The patient was a 67-yr-old right-handed retired shopkeeper with a high school education who noted a transient episode of mild word-finding problems and reading difficulties in the spring of 1982. She did not seek medical attention and was subsequently in good health until April of 1984, when she noted the sudden onset of weakness of the left side. Neurological examination at that time revealed a mild hemiparesis

and neglect of the left body and environment. The clinical diagnosis was ischaemic infarction of the right parietal lobe.

When first examined by the authors 4 mos after the right hemisphere infarction, the patient's major complaint was that her environment appeared fragmented; although she saw individual items clearly, they appeared to be isolated and she could not discern any meaningful relationship among them. She stated, for example, that she could find her way in her home (in which she had lived for 25 yrs) with her eyes closed but she became confused with her eyes open. On one occasion, for example, she attempted to find her way to her bedroom by using a large lamp as a landmark; while walking towards the lamp, she fell over her dining room table. Although she enjoyed listening to the radio, television programmes bewildered her because she could only 'see' one person or object at a time and, therefore, could not determine who was speaking or being spoken to; she reported watching a movie in which, after hearing a heated argument, she noted to her surprise and consternation that the character she had been watching was suddenly sent reeling across the room, apparently as a consequence of a punch thrown by a character she had never seen. Although she was able to read single words effortlessly, she stopped reading because the 'competing words' confused her. She was unable to write as she claimed to be able to see only a single letter; thus when creating a letter she saw only the tip of the pencil and the letter under construction and 'lost' the previously constructed letters.

Neurological examination at that time showed her to be alert and oriented. Cranial nerve examination revealed normal visual fields to confrontation and normal ocular movements; muscle strength, reflexes, sensation and coordination were also normal.

Examination of higher nervous system functions showed no general intellectual impairment. The patient performed well on tests of abstract reasoning. She demonstrated no impairment in the production or recognition of gesture. No hemisensory neglect or extinction of auditory, tactile or visual stimuli was noted; she exhibited mild hemispatial neglect on a line bisection task, erring to the right an average of 8.2 ($\pm$24.1) mm when bisecting 16 lines presented in the midline. She exhibited a profound dressing impairment; she was unable to put on a single item of clothing without assistance. She also exhibited mild optic ataxia with the left hand; she could, however, reach quickly and accurately with her right hand in right and left hemispaces.

Formal language assessment including the Boston Diagnostic Aphasia Examination (BDAE; Goodglass and Kaplan, 1972) and Boston Naming Test (Kaplan *et al.*, 1982) demonstrated no significant abnormality Reading of single words was essentially normal; she correctly read aloud 79 of a corpus of 80 words which included functors and nouns of high and low imageability.

A CT scan performed immediately after the onset of symptoms revealed only a small left temporo-occipital infarct. MRI scan performed 2 yrs after the onset of symptoms revealed a small discrete left temporo-occipital infarct as well as an infarct on the right involving the posterior portions of the right middle and superior temporal gyri and extending into the supramarginal and angular gyri as well as small portions of the lateral occipital lobe (*see* figs 1–3).

The data reported here were collected over a 2 yr interval, during which there was a modest improvement in her condition; the patient continues, however, to exhibit obvious and, in many instances, disabling symptoms.

INVESTIGATIONS

Preliminary visual investigations

Neuro-ophthalmological examination showed corrected visual acuity of 20/40 in both eyes. Ocular movements were normal; the patient voluntarily gazed to the right and left without difficulty. Opticokinetic nystagmus was present bilaterally but slightly asymmetric with the eyes deviating a greater distance to the right prior to the initiation of saccades. Visual fields as assessed by static perimetry with a Goldmann no. 3 test object using a Humphrey Field Analyzer were normal.

When asked to describe a picture she identified individual elements in a laborious serial manner before offering an interpretation. Relationships between pictured elements were often not appreciated; when viewing the cookie theft picture from the BDAE for example, she identified the boy, girl and chair but did not know who was standing on the chair or who was reaching for the cookie. Performance was not influenced

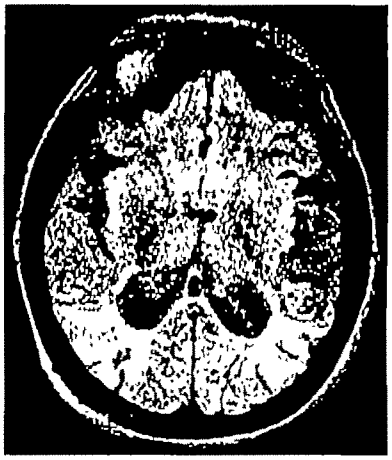

FIG. 1. MRI scan demonstrating areas of infarction in the right and left lateral temporo-occipital regions.

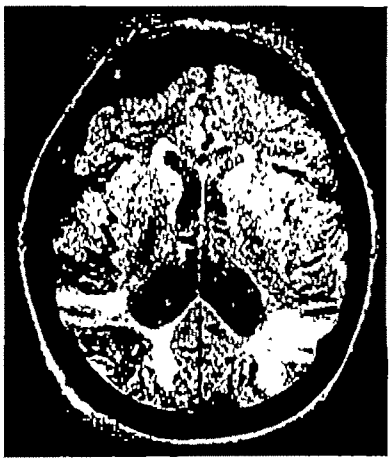

FIG. 2. MRI scan demonstrating areas of infarction involving the right and, to a lesser extent, the left temporo-occipital regions.

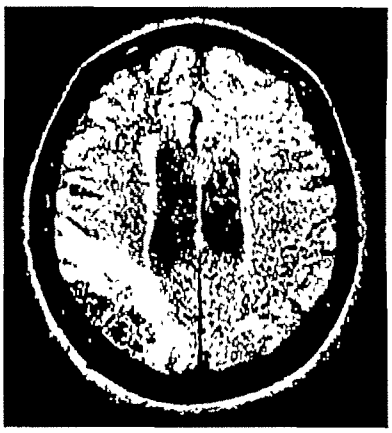

FIG 3. MRI scan demonstrating an area of infarction involving the right posterior inferior parietal region

by the size or nature of the visual stimuli; she performed equally poorly with pictures, colour drawings and line drawings.

The patient performed well on a variety of visual tests which required that only one stimulus be processed at a time. She performed perfectly, for example, on a 20 trial object-nonobject task in which she was required to indicate which of 2 unrelated line drawings was a real, familiar object; stimuli for the task were drawn from those developed by Snodgrass and Vanderwart (1980) and Kroll and Potter (1984).

Although slow, she also performed normally in terms of accuracy on tasks that involved comparing pictures of single objects. In one such task she was asked to match a picture of an object to pictures of the same object taken from a different perspective Stimuli for this test included 3 pictures of each of 33 different objects, for each object, pictures were taken from 'standard' (that is, prototypical), 'familiar' (less typical but readily recognized) and 'odd' (unusual) views. The patient's task was to match each of the 99 pictures to the 'standard' view of the same object. She correctly matched 98 of 99 pictures.

A test modelled after the functional similarity test of Warrington and Taylor (1978) was also administered; in this test, she was shown 3 pictures and asked to point to the 2 objects which were similar in function or 'served the same purpose' Two of the objects were related in terms of function but were dissimilar in appearance whereas the foil was visually similar to 1 of the 2 functionally related objects. Examples of the objects pictured in a trial include a zipper, button and coin. Again, although she was quite slow in completing the task, she responded correctly on 29 of 32 trials, a performance which is normal.

She performed poorly, in contrast, on tasks requiring that she judge or compare 2 composite or multi-item arrays. Thus she performed at chance on the dot localization task (Warrington and Rabin, 1970) in which the subject is presented with 2 squares, 1 with a dot placed in and 1 with a dot placed near the centre, and asked to indicate in which square the dot is centred. She also performed at chance on a variant of this task in which only a single square containing a dot was presented and she was asked to indicate if the dot was in the centre of the square. Similarly, she performed at chance (5/16) on the visual form discrimination task (Benton *et al.*, 1978) in which the subject is asked to match a target array containing several geometric stimuli to 1 of 4 arrays. Finally, she was impaired on visual search tasks such as the Trail Making Test (Reitan, 1958) in which the subject is asked to draw lines connecting a series of numbered circles; her performance on Part A, on which she required 290 s, was well beyond the normal range.

To document and quantify the patient's impairment in the processing of simultaneously presented visual stimuli, a tachistoscope was used to control stimulus presentation. Twenty stimulus cards containing a single press-on black and white drawing of a common object (e.g., car, airplane, flower) were prepared; the drawings varied from approximately 1 to 4 cm in height and width. Line drawings were presented in the centre of the card. The patient identified 100% of single objects with an exposure time of 40 ms. (No poststimulus mask was used on this or other tachistoscopic presentations unless stated otherwise.) Two age-matched controls required 30 and 45 ms to achieve perfect performance. Twenty stimulus cards containing 2 press-on black and white drawings were also prepared; the drawings were separated by approximately 3 cm and were vertically (10 cards) or horizontally (10 cards) aligned. In different sessions, the 20 stimuli were presented with exposure times as indicated in fig. 4. Although the patient accurately identified at least 1 stimulus on the trials, she required 2 s to reliably identify both objects. With briefer exposure she typically reported seeing only a single object; on 1 trial a second object was reported but misidentified. Objects were reported from all sites (that is, right and left, top and bottom) with equal frequency. Similar results were obtained using geometric shapes rather than objects. Age-matched controls reliably identified both objects with 100 ms stimulus presentation.

The patient was also asked to identify tachistoscopically presented words and nonword letter strings. With 75 ms stimulus exposure, she correctly identified 29 of 30 four-letter words; in contrast, she identified only 4 of 30 four-letter strings which were visually similar to real words (e.g., 'MOND') and 0 of 30 letter-strings with unusual or illegal letter sequences (e.g., 'GRNT'). Errors with 'word-like' nonwords included 12 real word substitutions as well as 8 trials on which she reported seeing only 1 letter and 4 trials on which she reported 2 letters; on 4 trials she reported seeing 'nothing'. Errors with orthographically illegal nonwords included 8 real word responses, 12 trials on which she reported a single letter and 4 trials on which she reported 2 letters; she reported seeing 'nothing' on 5 trials. Quite similar results were obtained with three-letter stimuli

Finally, the patient's ability to generate visual images was assessed. She was asked to describe the floor plan and contents of her home. Although she often offered adequate descriptions of specific items (e.g., 'a long low sofa with a gold brocade and clear plastic cover'), she was unable to indicate the locations

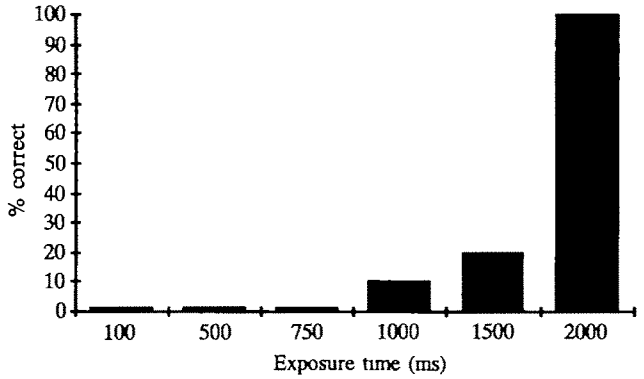

FIG 4 Percentage of trials on which both simultaneously presented objects were identified

of household items relative to landmarks such as doors or walls; when asked to imagine that she was standing in the living room and looking into the dining room, she stated that she simply could not 'picture' it. She was unable to describe the route she had used for many years to walk from her home to the nearby market.

Experimental investigations

These investigations of the simultanagnosic deficit were motivated by a working model of visual processing which postulates 3 distinct levels of representation of visual information. Support for a multistage account along these lines comes from a number of different sources which space limitations allow only brief mention of here. Among the considerations which entered into the account are the following: (1) the literature on selective attention which argues for a distinction between parallel and serial processing stages in visual perception (e.g., Treisman and Gormican, 1988); (2) studies using partial report techniques which attempt to distinguish between processing stages on the basis of temporal parameters (e.g., Irwin and Yeomans, 1986; Di Lollo and Dixon, 1988); (3) studies that focus on spatial aspects of visual processing, in particular the deployment of attentional capacity with respect to the visual array (e.g., Posner *et al.*, 1984); (4) anatomical and physiological studies of the primate visual system which suggest parallel streams of analysis of visual information (*see* Maunsell and Newsome, 1987, DeYoe and Van Essen, 1988); and (5) theoretical analyses of vision which have come out of work in artificial intelligence (e.g., Marr, 1982; Ullmann, 1984). The model postulates the following stages and processes.

1. *Visual feature maps.* There is now a good deal of evidence that basic attributes of the visual array, such as colour and line orientation, are registered effortlessly and in parallel in separate retinotopically organized maps (Treisman and Gormican, 1988). Detailed physiological and anatomical investigations in animals have demonstrated that as many as 20 discrete cortical areas receive visual information, several of which appear to operate in parallel as analysers of specific visual 'features' such as colour, line orientation, spatial frequency and movement (Maunsell and Newsome, 1987; DeYoe and Van Essen, 1988). Behavioural evidence that the analysis of visual features proceeds in parallel over large arrays comes from experiments which have demonstrated that a stimulus which differs by a single parameter from other items in an array (e.g., an 'X' in an array of 'O's) 'pops out' of the field of distractors in as little as 10 ms regardless of the number of items or dimensions in the array (Treisman and Gelade, 1980; Sagi and Julesz, 1985). This parallel or 'preattentive' form of processing is thought to proceed automatically and to provide a set of maps specific to each visual feature which identify the spatial location(s) of the feature; preattentive processing would generate, for example, maps of the location of angles, colours, vertical lines and so on (Sagi and Julesz, 1985).

2 *Visual analog representation (VAR).* Although the visual feature maps collectively provide sufficient data to assemble a veridical image of the visual environment, 'seeing' requires two types of integrative processes: the integration of information across feature maps, which results in the conjoining of features as a function of location; and integration across arrays as a function of similarity to yield surfaces. The

integration of visual feature information is a capacity-limited process that requires 'selective attention'. Thus, under conditions where attentional capacity is limited (e.g., by an auxiliary task), the observer is at risk of perceiving 'illusory conjunctions' of visual features (e.g., angle and colour) actually present at different loci in the array (Treisman and Schmidt, 1982). Selective attention deployed over a limited area of the visual field is, in other words, the 'glue' that binds the separately analysed visual features together.

Feature integration results in the achievement of the VAR, a retinocentric map in which coherent regions of the array are represented as surfaces and attributes such as depth and orientation are encoded. The VAR decays over a 150–300 ms interval and is susceptible to visual masking (Irwin and Yeomans, 1986). The VAR, which is recomputed for each fixation, provides the input to object and word recognition systems ('structural descriptions' and 'visual word forms', respectively)

When confronted with a novel visual display, the visual system must first determine the site to which the spotlight of selective visual attention should initially be deployed. A number of investigators have described visual processing mechanisms which may help guide the initial deployment of selective attention. Prinzmetal and colleagues (Banks and Prinzmetal, 1976; Prinzmetal, 1981), for example, have demonstrated that visual feature integration is influenced by the grouping principles developed by Gestalt psychologists. There is also evidence to suggest that the deployment of selective attention is slowed by the presence of other elements in the array. Thus data from Kahneman *et al.* (1983) and Treisman *et al.* (1983) demonstrate that the presence of a nonverbal distractor significantly alters the time required to read a single word. The cost associated with the distractor suggests that most or all visual stimuli are, at least briefly, analysed.

Attentional capacity must be deployed serially across the array to achieve an integrated representation (e.g., Triesman and Gormican, 1988); this entails shifting the attentional 'spotlight' from one locus to another, in itself a complicated process (Posner *et al.*, 1984).

3. *Visual buffer.* A more stable representation of the visual environment is built up at the level of the visual buffer, which stores information about object location. The buffer is a viewer-centred map of locations which binds visual information (the current display at the VAR) to stored structural descriptions. Information in the visual buffer, which persists over seconds (Kroll *et al.*, 1970; Phillips, 1974; Irwin and Yeomans, 1986), accumulates over several fixations and is not susceptible to visual masking. We hypothesize that conscious perception of the visual environment normally involves articulation of the VAR with the corresponding region of the visual buffer; while it is the representation of surfaces in the VAR that is explicitly 'visible', it is the information bound to it in the buffer that enables interpretation of the visual input, localizes it with respect to the observer, and serves as the basis for action.

The process by which structural descriptions are linked to specific sites at the visual buffer has been investigated in an elegant series of experiments by Styles and Allport (1986). These investigators asked young normal subjects to name a letter in a specified position within an array of letters presented tachistoscopically with pattern masking. They found that although letters could often be identified with relatively brief presentation (e g., 50 ms), the correct integration of target identity with location required at least 100 ms. Furthermore, they found that performance continued to improve with increasing stimulus exposure from 100 to 200 ms, suggesting that the process of linking structural descriptions to sites marked at the visual buffer does not occur in parallel but depends on a resource-limited procedure.

The experiments described below were performed to assess the integrity of the putative visual processing mechanisms described above.

Preattentive and attention-requiring processes in vision

One possible explanation for the patient's visual processing impairment is that a low-level processing deficit prevents effective monitoring of the full visual field (Faust, 1947; Bay, 1953). Although the observations that the patient's visual fields are full and that object recognition is independent of object size suggest that the disorder is not attributable to a local failure to register visual feature information, these tasks do not assess the capacity for processing of visual information in parallel across the visual field. It is conceivable, for example, that a patient could perform normally on visual field tests, which involve detection of a single luminance point anywhere in the visual field, yet fail in tasks (like scene recognition) in which it is necessary to monitor information displayed at multiple sites in the field. The following experiment was performed to examine the integrity of both parallel 'preattentive' and serial 'attention-requiring' visual processes over complex visual arrays.

For this purpose we used a modified version of a paradigm reported by Sagi and Julesz (1985). The test of preattentive processing involved the detection of one or more lines differing in orientation from

the diagonal lines in the array, as targets differ from the background lines by virtue of a single visual feature—that is, orientation—this task can be performed without the integration of visual feature information and is therefore a test of 'preattentive' function. The attention-requiring task involved report of the number of lines (1, 2 or 3) which differed from the diagonal lines in the array. It should be noted that our attention-requiring task differs from that used by Sagi and Julesz (1985); these investigators reported that their young, practised (thousands of trials) subjects were able to determine the number of targets (1, 2 or 3) by means of a parallel, preattentive process, though discrimination of orientation of the targets required serial processing. Using older subjects with less practice, we found that both tasks were influenced by the number of targets, controls were significantly slower on trials requiring a discrimination between 2 versus 3 targets as compared with trials requiring a discrimination between 1 versus 2 targets. We therefore regarded the number discrimination task as a test of serial, attention-requiring procedures. The explanation for the discrepancy between the Sagi and Julesz data and our findings is not clear: one possibility is that extended practice permitted Sagi and Julesz's subjects to 'automatize' the counting or subitizing task (*cf* Schneider and Shiffrin, 1977).

Experiment 1A: Preattentive task

Methods. Stimuli included 144 5×7 inch white cards on which 37 lines 8 mm long were drawn in bold black ink; the lines were evenly spaced in a hexagonal region of the cards extending approximately 4° in all directions from the fixation point. On 72 cards all the lines were identical in orientation (45°); on 24 cards 1 line differed from the others by 45° (either 0° or 90°), on 24 cards 2 lines differed by 45°, and on 24 cards 3 lines differed by 45° in orientation. On trials with multiple targets, targets sometimes differed in orientation (0° or 90°).

Stimuli were presented in random sequence using a tachistoscope. For training purposes, an exposure duration of 500 ms was used, the exposure duration was progressively reduced until the patient's performance fell to 75% correct on a set of 20 cards. The entire set of 144 stimuli was presented at the shortest exposure duration at which the patient scored 75% in the training session. A central fixation point was presented for 1000 ms before the stimulus. The patient was instructed to indicate verbally whether all the lines were of the same orientation.

Results. The patient scored 80% correct with an exposure duration of 30 ms in the training session. Further reduction in the stimulus duration led to a performance below the desired 75% accuracy level. With 30 ms exposure duration the patient responded correctly on 89% of the trials on which the lines were oriented in the same and 77% of the trials with lines of differing orientation for an overall score of 83% (120/144). With stimuli containing 1, 2 and 3 lines of differing orientation, she was correct on 71%, 67% and 96% of trials, respectively. She was more accurate on trials on which the line(s) of differing orientation were on the right (88%) as compared with the left (69%). The difference in performance in the right versus left visual field did not reach significance ($\chi^2 = 2.9$, $P > 0.05$).

Four age-matched controls were also tested. Two controls achieved comparable overall levels of performance with slightly shorter intervals (20, 25 ms); 1 subject required 30 ms exposure and another 40 ms to achieve comparable levels of performance. Controls also exhibited a small effect of number of lines of differing orientation, averaging 70%, 77% and 86% correct for stimuli with 1, 2 and 3 lines of differing orientation, respectively. They responded quite accurately (less than 2% errors) on No-Target trials and showed no effect of visual field of presentation.

Experiment 1B. Attention requiring task

Methods. Stimuli included the 72 cards described above containing 1, 2 or 3 lines which differed in orientation from the other lines in the array. The experiment was performed in two sessions. In the first, the 24 cards with 1 and 24 cards with 2 lines of differing orientation were presented in random order with a tachistoscope. In the second session the cards with 2 and 3 lines of differing orientation were presented in a random sequence. In session 1, the patient was told that each card would contain 1 or 2 lines which differed from the other lines and was asked to indicate whether the card contained 1 or 2 such lines and, if possible, to indicate the orientation (vertical or horizontal) of the targets. The second session was similar except that the patient was asked to indicate whether the card contained 2 or 3 lines of differing orientation. Stimuli were initially presented for 4 s. As described previously, exposure time was reduced to produce an error rate of 25%

Results. The patient performed at chance level with stimuli presented for 4 s. She not only failed to discriminate the orientation of the lines but she failed to distinguish between cards reliably with 1 versus 2 and 2 versus 3 lines. The stimuli were subsequently presented free-field for an unlimited time; she was unable to discriminate between cards containing 1 versus 2 targets or 2 versus 3 targets.

Two of the normal controls performed Experiment 1B. One subject required exposure times of 430 and 570 ms to reach the desired level of performance when discriminating between 1 versus 2 and 2 versus 3 lines of differing orientation; the second subject required exposure times of 465 and 610 ms.

Discussion. Thus the patient performed well on the preattentive task; the exposure time required to reach the predetermined performance level of 75% was within the normal range. The only suggestions of differences from controls were a tendency to produce more false positives and a nonsignificant accuracy advantage for the right visual field. These data argue that the patient's symptoms do not reflect a failure to register visual feature information presented simultaneously at different sites in the visual field. Additionally, the fact that she performed well with a relatively large 37-item array suggests that the impairment is not attributable to a reduction in the capacity to process feature information.

In contrast, the patient failed completely on the attention-requiring task. One possible explanation for this failure is that the mechanism which serves to integrate information from different visual feature maps is impaired. This seems unlikely, however, in light of her excellent performance on tasks requiring visual recognition of single objects, a task which is critically dependent on the ability to integrate information from the full range of feature maps. Similar results were obtained on tests of preattentive and attention-requiring processing using a paradigm developed by Treisman and Souther (1985, Experiment 1); the patient exhibited no effect of display size on the pre-attentive task but was significantly impaired relative to controls on the attention-requiring task

There are other possible explanations for the patient's inability to perform the attention-requiring task. The deficit may reflect an impairment in the mechanism which shifts selective attention. As the attention-requiring task requires serial search of all items in the array, a disruption in this mechanism might impair performance by preventing an efficient and systematic shift of selective attention from one item to the next.

The following 2 experiments were undertaken to explore this possibility.

Shift of selective attention

One possible explanation for the patient's poor performance on the attention-requiring tasks in the first 2 experiments is that she is unable to shift selective attention accurately and rapidly from one portion of the visual array to another. Such a deficit would lead to disorganized and ineffective serial search of the stimuli resulting in a failure to process all of the targets in the array On a behavioural level such a deficit might be manifested as poor 'scanning' of the visual array with a tendency to identify only a portion of the objects in view. Impaired scanning of a visual array with a tendency to report the same object more than once was, in fact, observed in our patient and has been frequently reported in patients with simultanagnosia (Hécaen and de Ajuriageurra, 1954; Luria, 1959).

To examine the patient's ability to shift visual attention from one site to another in the visual field we used a paradigm developed by Posner *et al.* (1984). In this task, the patient was asked to respond as quickly as possible to a target (a diamond) presented in 1 of 2 locations. Before each trial, a cue was provided which directed the patient's attention to the eventual site of the target (valid condition) or to another location (invalid or neutral conditions). With this paradigm normal subjects are typically (but not invariably) quicker to respond to a target presented in the location to which their attention has been summoned by the preceding cue; alternatively expressed, reaction times are longer when subjects' attention is cued to one location but the target is presented at a different location. The slowed reaction time to the invalidly cued trials is attributed to the fact that on these trials subjects must disengage and shift selective attention from the cued site to the site at which the target is presented (Posner *et al.*, 1984).

If the mechanism controlling the shift of selective attention from one site to another is impaired, one might expect to observe a greater than normal cost on invalid trials. Thus, for example, if the subject were impaired in 'disengaging' attention for the incorrectly cued site, as has been reported in patients with parietal lobe lesions (Posner *et al.*, 1984), one might expect that reaction times on invalidly cued trials would be substantially longer than reaction times on validly cued trials; the difference between RTs on invalid and valid trials has been termed the 'validity effect'. Similarly, if the patient was impaired in the movement of selective attention (Coslett *et al.*, 1988), one might also expect a greater than normal cost on invalid trials.

It should be explicitly stated here that, on the model described previously, this paradigm assesses simple shifts of selective attention from one site defined solely by the presence of visual feature information to another similarly defined site; in contrast to the 'filtering' tasks such as those described by Kahneman and Treisman (1984), in which subjects are required to report targets defined by location and object name, this task assesses shifts of selective attention occurring prior to or at the level of the VAR

Methods. The patient sat facing a monitor controlled by an Apple IIe on which 3 outline boxes were depicted; 1 box was in the midline and the other 2 were centred at 4° of visual angle to the right and left of the fixation point The patient was asked to depress a telegraph key when a diamond-shaped target appeared inside the right or left box The patient was instructed to attempt to maintain her gaze in the midline throughout the trial.

Each trial was initiated by the experimenter after determining by direct observation of the patient's eyes that she was gazing at the central box. The trial began with the appearance of a cue which consisted of the brightening of 1 of the 3 outline boxes The cue remained visible for 300 ms; the target appeared in 1 of the 2 laterally placed boxes at varying intervals of 50, 150, 500 and 1000 ms after the onset of the cue. Reaction times (RTs) were measured in ms.

The experiment was performed in 3 sessions of 200 trials each; on 72% of trials the cue and target were presented at the same site (valid condition); valid trials were equally divided between the right and left sides and the 4 different interstimulus intervals (ISIs). On 20% of trials the cue appeared at 1 of the laterally placed boxes but the target appeared inside the opposite box (invalid condition); on the invalid trials the target appeared with equal frequency on the right and left and with each of the 4 ISIs. Finally, on 8% of trials, the cue appeared at the central box and the target at the right or left (neutral condition). There were 40 practice trials before each session.

Results. Mean RTs for the valid and invalid trials on the right and left for each of the four ISIs are presented in Table 1. (Data from the neutral trials were omitted to facilitate presentation.) The patient's data were analysed using an ANOVA in which the variables included ISI (50, 150, 500, 1000 ms), trial type (value, invalid, neutral) and visual field of target presentation (right, left). A significant effect of trial type was noted ($F = 7.07$, $df = 2$, $P < 0.001$). Subsequent analysis of this effect with Tukey's

TABLE 1 MEAN REACTION TIMES IN ms AS A FUNCTION OF TRIAL TYPE, SIDE OF TARGET AND ISI (VALIDITY EFFECT IN PARENTHESES)

	Patient	*Control*	*RH+neglect*	*RH−neglect*
ISI 50				
Left valid	652±131	586±162	758±192	440±130
Left invalid	805±277 (153)	741±462 (155)	1100±192 (342)	470±172 (30)
Right valid	661±140	542±168	663±244	467±139
Right invalid	936±415 (275)	648±82 (106)	790±126 (127)	482±109 (15)
ISI 150				
Left valid	691±218	538±121	699±177	414±125
Left invalid	800±193 (109)	670±184 (132)	1128±276 (429)	548±294 (115)
Right valid	605±190	550±140	594±138	391±104
Right invalid	809±207 (196)	628±64 (78)	728±221 (134)	446±148 (55)
ISI 500				
Left valid	516±101	529±113	532±128	338±105
Left invalid	618±52 (102)	618±115 (89)	924±290 (392)	495±150 (157)
Right valid	548±164	573±162	569±175	322±56
Right invalid	587±97 (39)	528±104 (−45)	646±194 (77)	472±98 (150)
ISI 1000				
Left valid	566±128	526±71	610±206	384±84
Left invalid	506±156 (−60)	507±81 (−19)	734±222 (124)	418±58 (34)
Right valid	586±261	507±107	538±112	411±143
Right invalid	574±81 (−8)	554±140 (47)	638±151 (100)	432±158 (21)

test revealed that RTs on invalid trials (708.2 ms) were significantly longer than RTs on valid (600.2 ms) or neutral (609.9 ms) trials ($P < 0.01$). A significant effect of ISI was also noted ($F = 12.9$, $df = 3$, $P < 0.0001$). Post hoc analysis with Tukey's test revealed that RTs for trials with ISIs of 50 (734.9 ms) and 150 ms (703.9 ms) were significantly longer than RTs for trials with ISIs of 500 (562.0 ms) or 1000 ms (556.9 ms) ($P < 0.01$). There was no effect of visual field of presentation ($F = 1.33$, $df = 1$, $P < 0.249$). No significant interactions were noted.

Nineteen normal controls have also been tested on this paradigm, 4 with the same stimulus eccentricity (4° of visual angle) employed in the present experiment. Although the variability in performance exhibited by controls renders the interpretation of the performance of a single patient difficult, it should be noted that the *pattern* of performance exhibited by the patient was essentially similar to that of normal controls who as a group exhibited validity effects with targets in both right and left visual fields. Table 1 also provides data for a normal control (age 69 yrs) and for 2 patients with RH lesions, 1 who manifested neglect of left hemispace and 1 who showed no clinical evidence of neglect. As seen in Table 1, the performance of this normal control was qualitatively very similar to that of the patient; like our patient, the age and sex-matched control was quicker to respond to valid as compared with invalid cues and this effect was particularly pronounced with short ISIs.

Discussion. While this simultanagnosic patient showed larger validity effects than the normal control under some conditions, she did not demonstrate the consistently large validity effect for targets in the contralateral field that is typical of neglect patients (Table 1: *see also* Posner *et al.*, 1984); moreover, she showed substantially smaller effects of invalid cues than many of the brain-damaged subjects of Posner *et al.* (1984) who, like our patient, did not manifest significant neglect. Given her unexceptional performance on this task, relative to that of other brain-damaged patients who do not demonstrate comparable perceptual abnormalities, it is difficult to attribute her impaired processing of complex arrays to a deficit in the mechanism which shifts the spotlight of selective attention from one site in the visual field to another.

These data also indicate that the patient is capable of effectively monitoring unattended areas of the visual field. It can be inferred from the fact that the subject exhibited a validity effect that she shifted attention to the cued location; if this focusing of attention effectively excluded unattended areas of the visual field, one would expect the patient to fail to respond on invalidly cued trials in which the target is presented at an unattended location. She never failed to respond, however, suggesting that even when attention was focused at one location, she was sensitive to input in other areas of the visual field.

Cost of filtering

If a complex visual array is to be processed efficiently, there should be minimal delay in directing selective attention to the regions of greatest salience. Although the control mechanisms guiding this initial deployment are not well understood, one possibility is that some or all of the sites are briefly analysed in a serial, attention-requiring process. Those sites which are of greatest relevance by virtue of task-specific demands or ecological salience may be marked for subsequent scrutiny.

Several investigators have reported data consistent with this hypothesis (Erikson and Schultz, 1978; Kahneman *et al.*, 1983; Triesman *et al.*, 1983). Kahneman *et al.*, (1983), for example, presented arrays containing either 1 or 2 words and asked subjects to read 1 word aloud. Oral reading latencies were significantly longer when 2 words were presented. The same effect was observed when subjects were presented a word in conjunction with a dot patch. In a subsequent experiment, the authors demonstrated that the 'filtering cost' was proportional to the number of items in the display. Finally, they found that precueing the location of the target eliminated the filtering cost

The following experiment was performed to assess the mechanisms which subserve initial attentional processing of items in the visual array.

Methods. Stimuli included 4×6 inch black cards containing either 1 or 2 rows of 3 white 'X's or 'O's (Chartpak Helvetica Medium, 24 pt). The rows were centred 1 cm above and below the centre of the card. Half of the cards contained 2 and half contained 1 row of 3 letters. The cards with 2 rows included 4 different types of cards in equal numbers: 2 rows of Xs, 2 rows of Os, a row of Xs at the top and Os on the bottom and a row of Os on the top and Xs on the bottom. There were also an equal number of 4 types of cards with a single row of letters in the following configurations: a row of Xs above the centre, a row of Xs below, a row of Os above and a row of Os below The rows of letters were 2 cm long.

Stimuli were presented tachistoscopically, with a central fixation point present for 1 s before stimulus presentation. The patient was told to depress a telegraph key as quickly as possible if the display contained

a row of Xs and not to respond if no Xs were present. Stimuli were presented until the subject responded or until 4 s had elapsed. Stimulus presentation was controlled and reaction times recorded by an Apple IIe. A total of 48 trials per condition were performed over 2 sessions in random order.

Results. Mean reaction times and SDs for the 5 conditions requiring a response are presented in Table 2; there were no incorrect responses to stimuli containing only Os. The patient was significantly slower with two as compared with a single row of Xs ($t = 2.70$, $P < 0.05$ for columns 1 vs 4 and $t = 3.20$, $P < 0.05$ for conditions 1 vs 5 in Table 2). The most striking effect, however, is that she was markedly slower with stimuli containing both Xs and Os than in any other condition. Finally, there was no effect of site (top, bottom) of presentation.

TABLE 2 MEAN REACTION TIMES IN ms FOR EXPERIMENT ON COST OF FILTERING

	Condition				
Subject	*XXX* *XXX*	*XXX* *OOO*	*OOO* *XXX*	*XXX* –	– *XXX*
Patient	713 ± 172	1186 ± 321	1212 ± 392	636 ± 105	615 ± 130
C1	490 ± 46	510 ± 55	501 ± 38	406 ± 34	421 ± 39
C2	469 ± 76	481 ± 69	463 ± 88	414 ± 40	428 ± 53
C3	399 ± 62	408 ± 58	403 ± 56	390 ± 36	405 ± 39
C4	392 ± 82	390 ± 75	418 ± 94	404 ± 49	401 ± 45

– = absence of stimulus

Four normal controls were also tested. Comparing the 3 conditions in which 2 rows of stimuli are present to the 2 conditions in which only a single row of Xs was present reveals that 2 of the controls are significantly slower with the former stimuli (for C1, $t = 11.53$, $P < 0$ 05; for C2, $t = 4.55$, $P < 0.05$); for 2 controls the reaction times did not differ significantly. Reaction times to stimuli containing rows of Xs and Os and stimuli containing 2 rows of Xs did not differ for any control.

Discussion. Like normal subjects, the patient demonstrated a cost of filtering an extraneous stimulus, whether it be a second row of Xs or a far more costly line of Os. This finding supports the previously articulated contention that the patient's deficit is not attributable to a 'subtle' visual field impairment; an object which is not processed would not be expected to slow reaction times.

What is clearly abnormal, however, is the size of the increase in reaction time to stimuli containing both Xs and Os. The task might in principle have been performed 'preattentively' on the basis of the different visual features contained in the 2 types of stimuli. In fact, the suggestive reports and reaction times of some of the controls indicate that they may have performed the task in this manner. However, the long response latencies suggest that the patient adopted a serial, attention-requiring examination of the 2 rows of stimuli; if so, her slow response times are not unexpected, given the previously documented deficit on the attention-requiring task in Experiment I. There is one complication for this account, however. If the slowing were due solely to performance of the task in serial fashion, one would expect to see a bimodal distribution of reaction times—short RTs when she attended to the Xs first, and long RTs when they were second. There was no evidence of such an effect in the data, which showed a single peak at the mean (*see* Fig. 5). This suggests that the problem may not lie in shifting attention from one locus to another but rather in some other aspect of attentional processing of multi-item arrays. Indeed, as we pointed out in our discussion of her performance on the attentional shift paradigm, attentional shift mechanisms do not appear to be grossly impaired in this patient We will take up this matter again in the General Discussion below.

Speed of visual processing

An alternative explanation for our patient's visual processing impairment (suggested to us by Dr Tim Shallice) is that she suffered from a general slowing of the rate at which visual information was analysed. It might be proposed, for example, that the patient was impaired in the identification of simultaneously presented objects because the process by which single objects or words were identified was pathologically

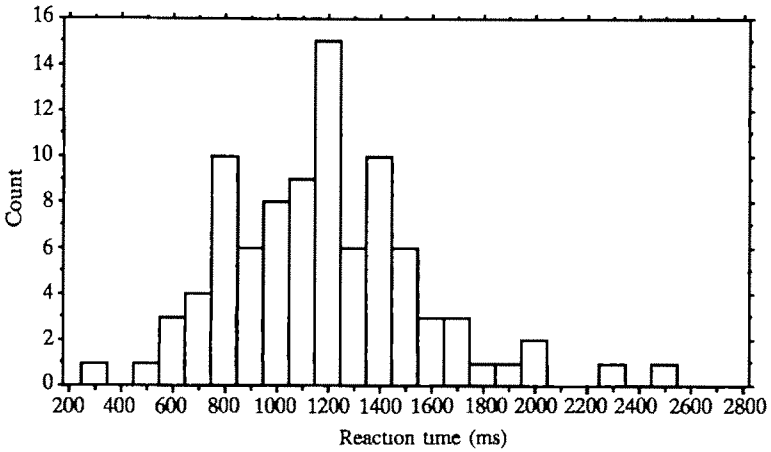

FIG. 5 Histogram of response frequency as a function of reaction time for responses to stimuli containing rows of Xs and Os in experiment on cost of filtering

slowed, leaving insufficient time to process other objects in the array. Kinsbourne and Warrington (1962) and Levine and Calvanio (1978) have, in fact, demonstrated an impairment in the speed of visual processing in patients with disorders of recognition of simultaneously presented objects.

Although we have shown that our patient is able to identify single objects as accurately as controls with brief (unmasked) stimulus presentation, it could be argued that this task is not a particularly sensitive index of high level recognition procedures The following experiment employs the Rapid Serial Visual Presentation paradigm (Forster, 1971) as a more stringent test of the slowing hypothesis. In this study, the patient was required to make semantic judgements about rapidly presented words.

Methods. The experiment was performed in 3 blocks, each consisting of 24 trials on which 4 words were rapidly presented. For all 3 blocks, half of the 24 trials contained the name of a representative member of a designated semantic category and the other half contained 4 words which bore no semantic relationship to members of the semantic category in question. On trials that included a member of the designated semantic category, the 3 foils were matched to the target item in length and frequency (Kučera and Francis, 1967). The lists containing 4 words with no semantic relationship to the designated category were matched in length and frequency to the target words. The sequence of trials was randomized within each block The target word appeared equally often in the 4 serial positions. For the first block the target words were drawn from the semantic category of clothing; targets for the second and third blocks were drawn from the semantic domains of animals and fruits. For all 3 blocks, semantic category members were judged by normals to be representative of the semantic category from which they had been drawn; all targets had 'goodness of example' ratings of less than 2.73 (Rosch, 1975)

A central fixation point was visible between trials. When trials were initiated the fixation point was replaced by the first word of the series. Each word was presented for 50 ms and was immediately replaced by the succeeding word. The first 3 words were masked by the succeeding word but no mask followed the fourth word The subject was told that half of the trials would contain a member of the specified semantic category; she was asked to indicate if a target word was present and, if possible, to name the word

Results and Discussion. The patient performed flawlessly; she explicitly identified every target word in all 3 blocks and produced no false-positive errors. Interestingly, she reported the task to be 'effortless'. With the same stimulus exposure 2 elderly controls failed to identify targets on 2 and 4 trials, respectively.

These data provide no support for the hypothesis that the patient's visual processing impairment is attributable to a slowing of the rate at which visual information is processed.

The fact that single visual targets can be identified at normal rates argues against a deficit involving recognition procedures per se, that is, in matching a visual stimulus to a stored visual word form, in the case of a word, or to a structural description, in the case of an object. It is also evident, from the patient's

performance on the preattentive task in Experiment 1, that she processes multiple items normally at the feature level. The purpose of the next set of experiments was to examine the fate of multiple items at higher levels of processing.

Semantic factors and recognition

Our patient's simultanagnosia was most dramatically demonstrated by her inability to identify two objects at exposures more than 20 times those required to identify a single stimulus of the same type In a variety of studies with normal subjects, object and word recognition has been shown to be facilitated by semantic priming, that is, presentation of a semantically related item prior to or along with the target (e.g., Meyer *et al.*, 1975). In this set of studies, we sought to determine whether the patient's ability to identify a second word or object in a 2-item display could be influenced by the relationship between the two items. Demonstration of a priming effect would indicate that multiple items were being processed to a high level.

Experiment 1: Oral reading of word pairs

The level of processing of multiple stimuli was investigated by examining the patient's ability to read aloud briefly-presented pairs of unrelated and related words. The latter took two forms· words which were semantically associated and words which could be combined to generate a compound word. The latter included word pairs such as NEWS and PAPER or BASE and BALL with could be combined to form a single compound word (e.g., NEWSPAPER, BASEBALL).

A priming effect would be indicated by better performance on related words as compared with unrelated word pairs. Thus the patient might be able to identify both words in the potential compound and semantically related pairs but not in the unrelated pair condition.

Methods. Stimuli included 90 pairs of words. Thirty word pairs were potential compound words; 30 stimuli consisted of word pairs of high association value (Jenkins, 1970; Postman, 1970) such as HOT and COLD or TOWN and CITY; finally, 30 stimuli consisted of word pairs with no obvious semantic, phonologic or visual relationship, these pairs were constructed by combining words from the potential compound and associated pairs (e.g., PAPER and HOT). All 3 groups of stimuli were approximately matched for letter length and word frequency.

Stimuli were presented in capital letters with two spaces separating words on a green screen monitor controlled by an Apple IIe. Stimuli were preceded by a central fixation point and remained on the screen for 300 ms. The patient was told that 2 words would be presented on each trial and was asked to identify both words.

Results and Discussion. The patient correctly identified both words on 25 of 30 (87%) trials with potential compounds, 21 of 30 trials (70%) with semantically associated words and 10 of 30 (33%) trials with unrelated words. On 31 trials she correctly identified only 1 word and, in fact, claimed to have seen only 1 word. On 3 trials she reported only a single word which was visually similar to one of the stimuli (e.g., BIRD—BIRTH). On those trials on which only a single word was reported, the patient reported an almost equal number of words from the left (16) and right (15). Performance with potential compound and associated words was significantly better than with unrelated words (χ^2 = 15.4 and 8.1, respectively, df = 1, $P < 0.005$); performance with potential compounds and associated words did not differ.

With a stimulus exposure of 300 ms 2 elderly normal controls identified both words on all but 3 and 2 trials, respectively. When exposure times were reduced to generate an error rate approximating that of the patient, performance on the 3 types of trials did not differ. With exposure times of 150 and 175 ms, controls identified both word pairs on 67% and 63% trials with potential compounds, 60% and 57% of trials with associated words and 60% and 67% of trials with unrelated words.

These data are not readily accommodated by accounts of simultanagnosia which attribute the impairment to 'tunnel vision' or other low-level visual impairments. They indicate, rather, that both items in the display must be processed to a fairly high level.

Experiment 2

An additional experiment was performed to determine whether the identification of simultaneously presented words pairs was influenced by the variable of semantic category

Methods. Stimuli for this experiment included 56 pairs of words generated by combining 14 names drawn from the semantic categories of clothing and fruit. Words varied in length from 3 to 6 letters but the 14

names from the 2 semantic domains were matched for length and degree to which they were judged by normals to be 'typical' or representative of the semantic category from which they were drawn (Rosch, 1975). Half of the pairs were composed of words drawn from the same semantic category ('Within Category' pairs, e.g , 'shirt pants', 'apple orange') and half included 1 word from each category ('Across Category'; e.g., 'corn vest'). Each word appeared twice in Within Category and twice in Across Category pairs. As words were paired with a different word on all 4 presentations, no pair of words was repeated. Each word was presented twice in both the left and right positions The sequence of presentation was randomized

Word pairs were presented with an Apple IIe for 225 ms; each trial was preceded by a central fixation point. The words were aligned horizontally so that the terminal letter of the left word and first letter of the second word were each one space from the fixation point. The patient was told before the experiment that 2 words would be present on each trial and that all words would be names of articles of clothing or vegetables. She was instructed to name all words which she could identify.

Results and Discussion. On Within Category trials the patient correctly identified both words on 12 of 14 trials with vegetable names and 11 of 14 trials with clothing names for a total of 23 of 28 (82%) correct. On Across Category trials she identified both words on only 14 of 28 (50%) of trials. She performed significantly better on Within as compared with Across Category trials ($\chi^2 = 5.10$, $P < 0.05$). The patient correctly identified at least 1 word on every trial. Errors included 15 trials on which only a single word was correctly reported and 2 trials on which 1 of the 2 reported words was incorrect but visually similar to the stimulus.

Two elderly normal controls exhibited no influence of the semantic relationship between words With an exposure time of 75 ms 1 control identified both words on 82% of Within and 86% of Across Category trials; with 100 ms exposure time the second control identified both words on 78% of Within and 74% of Across Category trials

These data support and extend the findings of the previous experiment; semantically related words, whether linked by association or on the basis of class membership, are identified more reliably than unrelated words.

Experiment 3

This experiment was performed to determine whether semantic factors influence the perception of nonverbal as well as verbal stimuli. The experiment was quite similar to that outlined above except that line drawings were used instead of words.

Methods. Stimuli included 56 6×4 inch white cards on which 2 line drawings copied from the Snodgrass and Vanderwart (1980) corpus were pasted. Drawings included depictions of 14 tools and 14 animals. As described in the previous experiment, half of the stimuli contained pictures from the same (Within Category) and half from different (Across Category) semantic categories. Each picture appeared twice with different exemplars of the same and twice with different exemplars of a different semantic category. The 56 stimuli were presented in random sequence. The drawings were vertically aligned in the midline so that the top of the lower drawing and the bottom of the upper drawing were approximately 1 cm from the middle of the card.

A central fixation point was presented for 1000 ms before stimulus presentation. Stimuli were presented tachistoscopically for 800 ms; with briefer exposures the patient reported seeing only 1 object regardless of the category of the pictures. She was told that 2 drawings would be present on each trial and that all drawings would be of animals or tools. She was instructed to name all drawings she could identify. The stimuli were individually presented free-field prior to testing to verify that the patient could identify all the drawings.

Results. The patient correctly identified both drawings of animals on 11 of 14 (79%) and both drawings of tools on 10 of 14 (71%) of trials. She correctly identified both drawings on Across Category trials on only 11 of 28 (39%) of trials. She was thus significantly more likely to report seeing both drawings when the depicted items were members of the same semantic category ($\chi^2 = 7.29$, $P < 0.01$). She correctly identified at least 1 drawing on every trial. All errors were failures to report one of the stimuli.

Discussion. In all 3 experiments, then, the patient's ability to identify simultaneously presented words and pictures is significantly improved if the stimuli are semantically related. These data reinforce the conclusion drawn from the patient's normal performance on the preattentive task in Experiment 1: the limitation does not arise at early levels of visual processing; both stimuli are available to high level recognition processes. Below we will consider possible explanations of this deficit.

GENERAL DISCUSSION

We have reported data from experiments motivated by the working model of visual processing described earlier which lead us to reject several a priori plausible accounts of our patient's disorder of simultaneous form recognition.

First, in light of normal visual fields and, more importantly, the apparently normal registration of visual feature information, we have argued that our patient's symptoms are not attributable to visual field impairments (Bay, 1953) or to a reduction in the capacity to process visual feature information. Secondly, we have argued that the problem is unlikely to arise from impairment in the mechanism controlling the movement of selective attention from one site in the visual field to another. The patient's performance in the attention shift study was comparable with that of other brain-damaged patients who do not manifest gross perceptual impairments. Furthermore, her performance on the cost of filtering paradigm did not show the bimodal pattern that would be expected if the problem lay in shifting from one item to another. Thirdly, we have demonstrated that, unlike several previously reported patients with simultanagnosia (Kinsbourne and Warrington, 1962; Levine and Calvanio, 1978), our patient's deficits cannot be attributed to a slowing of the rate at which visually-presented information is processed. Finally, we have shown that recognition of a second word or object in a two-item display is facilitated if the 2 stimuli are semantically related; on the basis of these data, we have argued that information from both stimulus locations must be available to higher level recognition processes.

What, then, is the nature of the patient's limitation in multiple item perception?

Unfortunately, current theoretical approaches to visual cognition focus on detection (e.g., Treisman and Gormican, 1988) or recognition (e.g., Marr, 1982) of single targets or objects and do not deal with the perception of multiple item arrays. From the work of Treisman and others, however, it is reasonable to assume that, beyond a certain level, processing of multiple objects in an array cannot be conducted in parallel; perception of each object is an attention-requiring process and, consequently, identification of objects in an array must be carried out serially.

It follows that there must be some mechanism for storing the products of the identification process as the 'spotlight' of visual attention moves from one location to another. A visual short-term memory or buffer is also required to maintain the information yielded by successive fixations (e.g., Neisser, 1967). Studies that have focused on temporal aspects of visual processing provide support for a buffer lasting for seconds after stimulus presentation (e.g., Kroll *et al.*, 1970; Phillips, 1974; Di Lollo and Dixon, 1988); characteristics of the buffer as defined by these studies include insensitivity to poststimulus pattern-masking and some imprecision with respect to stimulus location (Di Lollo and Dixon, 1988). These properties suggest that information is stored in a somewhat abstract form at this level. The relationship of the buffer system to other aspects of the perceptual apparatus has not been elaborated in any detail, however. Above, we proposed a model which incorporates a buffer into the perceptual process. The model is presented in schematic form in fig. 6.

One important aspect of this model is its distributed architecture: information of different types is represented in separate subsystems. Thus, for example, basic visual features such as colour, line orientation and the like are encoded in different modules; as noted earlier, there is a good deal of evidence to support this assumption. We also

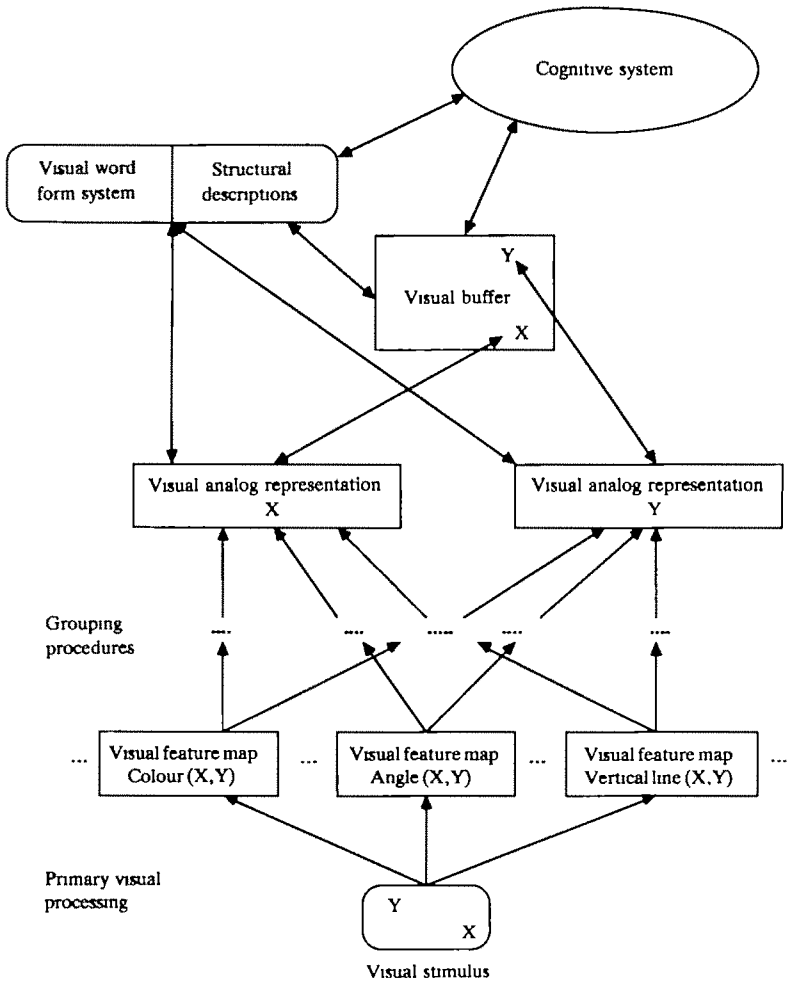

FIG 6. Schematic diagram of the proposed model of visual processing

assume that location and object identity information are separately encoded; the spatial map contains a blob that marks a location, and the blob, in turn, is linked to a structural description that specifies the identity of the object at that location. The separation between object recognition processes and location information is consistent with evidence from primate lesion studies (e.g., Ungerleider and Mishkin, 1982; DeYoe and Van Essen, 1988), as well as with human neuropsychological data (e.g., Newcombe and Russell, 1969; Botez, 1975); thus object identification is disrupted by lesions of the inferotemporal area (the 'what' of vision) while parietal lesions result in impaired ability to locate objects in space (the 'where').

We assume that what is perceived at any instant is the product of joint activity in several subsystems that is bound together or, to use another term, kept 'in registration' (Jackendoff, 1987): the transient VAR (which changes with each fixation) is in registration

with loci in the buffer, which are in turn bound to activated word forms or structural descriptions. The capacity to bind, or link, representations across several different subsystems is therefore crucial to our model. We make the further assumption, which is consistent with the findings of Styles and Allport (1986), that binding capacity is limited, and that this capacity-limited linking function is one facet of the capacity psychologists refer to under the rubric of 'attention'.

How might the patient's deficit be accounted for on this model? As we argued earlier, the evidence obtained in Experiments 1 and 2 indicates that parallel processing of visual features is normal in our patient. Though we have not directly assessed the integrity of the VAR, the ease of recognition of single objects and words implies that integrative processes at this level are essentially normal. We assume that the buffer, qua viewer-centred spatial map, is not itself impaired; if it were, we would expect to see gross failures of orientation in visual space, which were not evidence in our patient (*cf* Holmes, 1918). Thus having targeted an object, she could reach for it without difficulty with her right hand and she could navigate adequately in space (except, as noted earlier, for the problem of unattended obstacles in her path).

We propose that the patient's deficit is attributable to a limitation in the attention-requiring process by which sites marked in the buffer are linked to structural description or word form information. On the account described above, 'seeing' involves the articulation of stored information with information linked to specific sites in the visual buffer. An inability to establish or maintain the linkages—that is, a failure to keep more than one structural description in registration with the appropriate site in the buffer—would result in an inability to see more than 1 object at a time. Thus, for example, the patient's extreme difficulty with nonword strings could be accounted for by the binding capacity required to link each letter to a different stored representation; for single words, where there is need for only a single link between the buffer and an entry in the word form system, her performance is essentially normal.

Given the present level of specification of the model, the precise nature of the patient's impairment is not clear. There are, however, a number of admittedly quite speculative possibilities which may be identified. One might propose that the patient is impaired at *establishing* the necessary linkages; thus, for example, the process of integrating object identify and spatial location information, which appears to require 100 ms in young normals (Styles and Allport, 1986), may be pathologically slowed. It should be noted that such a hypothesis is not inconsistent with the demonstration that she identifies single objects as rapidly as normal subjects; object identification involves access to structural descriptions but does not require the linkage of structural descriptions to specific sites at the visual buffer. If this were the only deficit, however, it might be expected that the patient would be slow to establish the identity and location of objects in her environment, but once having done so would maintain the linkages and, presumably, function relatively well in her environment. Such an account seems unlikely in that it does not account for the fact that, even after having identified a series of objects in her environment, the patient 'sees' only one object at a time.

An alternative proposal is that the patient's deficit was attributable to an inability to *maintain* more than one linkage between structural descriptions and sites at the buffer. On this hypothesis, it might be expected that the patient would perceive her environment as a disjointed series of rapidly presented single objects; although her perception of the environment was indeed fragmented, her comments and performance suggested that, in a naturalistic setting, she was slow to identify and catalogue the individual items in her environment. Thus, for example, having identified the light switch on the wall, she walked into the dining room table because, while gazing at the light switch, she never saw the table.

We believe it likely, therefore, that the patient's simultanagnosia is attributable to two impairments. The first is a capacity limitation in the process by which linkages between structural descriptions and sites at the visual buffer are *maintained.* The second is a slowing of the shifting from one linkage to another; this proposal is not inconsistent with the fact that the patient performed at least relatively well on the task

assessing the shift of selective visual attention (*see slight of selective attentions* above). On the model described previously, the shifts of spatial attention assessed by this task may be performed at or prior to the VAR; thus this task does not assess the process by which linkages between structural descriptions and sites at the visual buffer are shifted.

This account of the patient's deficits also provides an explanation for the semantic priming effects. When 2 stimuli are related, activation from semantic/conceptual systems results in feedback to the structural description (or word form entry), which in turn feeds back to reinforce the weak binding site at the buffer. Consider, for example, the stimulus 'deer elk'; in this situation, the identification of the word 'deer' would serve to activate related information in the semantic/conceptual system, including, presumably, the node for 'elk'. Feedback from the semantic/conceptual system to the word form system would serve to activate both entries; on the assumption that increasing the activation of entries in the structural description or word form systems reduces the burden on the capacity limited procedure by which structural descriptions are kept in registration with sites at the visual buffer, the semantic priming effects reflect a facilitation of the process which binds entries in the word form/structural description systems and sites in the visual buffer.

What remains to be accounted for is the result of the cost of filtering study, in which the presence of the distractor (a line of Os) markedly increased reaction time to the target (a line of Xs). As noted earlier, the results did not appear to reflect a slowed serial inspection process. An alternative explanation of the abnormally slow response time in the X/O condition invokes the notion of limited binding capacity proposed above: 2 buffer locations must be linked to 2 different stored representations, which strains the limited binding resource. In contrast, in the X/X condition, both sites are bound to the same representation, a situation which is analogous to the semantic relatedness condition in that the multiply-activated X entry reinforces the weak binding to the 2 buffer locations.

These data may account for perhaps the most puzzling aspect of the performance of patients with simultanagnosia: when confronted with a complex visual array these patients often report 'seeing' only a single item, yet when confronted with a large depiction of a single 'object' that is coextensive with the multi-item array, such as a drawing of an elephant, subjects generally report seeing the entire object rather than components of the object (e.g., an ear, trunk, etc.) despite the fact that many of the components may be, in themselves, 'objects'. Based on these data, we speculate that patients with simultanagnosia frequently identify the elephant rather than the trunk because stored structural information about the visual form of an elephant facilitates the perception of the component parts of a single object. As complex scenes are presumably not represented by single stored entries, these scenes are processed by serial object identification but the limitation of the visual buffer renders this procedure inefficient or, in some cases, unusable. There are, of course, a variety of other factors such as continuity and texture which may also contribute to better performance with single versus multi-item arrays.

It should be noted that these proposals implicating the visual buffer and attentional factors in the genesis of simultanagnosia are in general accord with anatomical and electrophysiological data regarding the role of the parietal lobes in vision. Thus, for example, data from single-cell recordings (e.g., Mountcastle *et al.*, 1975, 1981; Robinson *et al.*, 1978; Goldberg and Bruce, 1985) implicate the inferior and posterior parietal

cortex in monitoring and directing attention within the visual environment. Electrophysiological data are also consistent with the hypothesis that the posterior parietal cortex is critical for the representation of viewer-centred spatial information; Andersen *et al.* (1985), for example, have argued on the basis of work with monkeys that neurons in 7a exhibit properties that suggest a mechanism for generating an egocentric rather than retinotopic representation of space. Lastly, it should be noted that recent data (*see* DeYoe and Van Essen, 1988) demonstrate interconnections between structures in the 'what' and 'where' streams of visual processing (e.g., V4 and MT); these connection may permit the integration of information from these processing streams and provide the physiological basis for the 'linkages' described above.

A final point of interest concerns possible subtypes of simultanagnosia. Although the term was introduced in the description of a patient with a posterior left hemisphere lesion, it is currently used to designate an impairment in simultaneous form perception regardless of the site of the associated lesion(s) (e.g., Bauer and Rubens, 1985). The visual processing disorder exhibited by patients with unilateral and bilateral lesions may, however, be distinguishable. Patients with simultanagnosia secondary to unilateral, dominant hemisphere lesions in whom speed of processing has been assessed have consistently exhibited a slowed rate of information processing even on tasks (e.g., RSVP paradigm) in which structural descriptions need not be linked to sites at the visual buffer (Kinsbourne and Warrington, 1962; Levine and Calvanio, 1978). Our patient, whose dominant hemisphere infarct was relatively small, exhibited no such impairment. Thus we speculate that the disorder in simultaneous form perception associated with unilateral dominant hemisphere lesions may, at least in part, be attributable to a slowing of information processing, while the disorder associated with bilateral lesions may be secondary to an impairment in the integration of object identity and spatial location information.

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THE NATURE OF THE NAMING DEFICIT IN ALZHEIMER'S AND HUNTINGTON'S DISEASE

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SUMMARY

A comparison of naming performance, on the Boston Naming Test, of 52 patients with dementia of Alzheimer's type (DAT), 16 patients with Huntington's disease (HD) and 52 normal control subjects was performed using a comprehensive classification of error types. Spontaneous and cued naming scores were significantly impaired both in the DAT and HD groups, but performance in the DAT patients was significantly worse than that of the HD patients Normal controls made predominantly semantic-category and circumlocutory errors. The HD group differed from normal only in the proportion of visually based errors, which was greater in the patient group. By contrast, the DAT patients made a significantly greater proportion of semantic-superordinate and semantic-associative errors. The same pattern of naming errors was found when a group of DAT and HD patients matched for overall naming ability was compared. A subgroup of 22 DAT patients was followed longitudinally over 3 y. Their deterioration in overall naming performance was accompanied by a consistent change in the profile of naming errors: the proportion of semantic-associative errors increased significantly as did the proportion of visual errors.

These results are considered in the light of current cognitive models of naming. They suggest that in HD, naming deficits initially involve disruption of perceptual analysis, whereas in DAT such impairments in the early stages reflect a breakdown in semantic processes. However, as DAT progresses, perceptual problems also begin to contribute to the patients' naming difficulties. Postlexical (phonemic) processes remain relatively intact throughout in both diseases.

INTRODUCTION

This study examines the nature of the naming deficit in patients with dementia of Alzheimer's type (DAT) and with Huntington's disease (HD). Although it is now well established that DAT is associated with a progressive anomia, the cause of the naming deficit remains unclear (for review, *see* Hart, 1988). Whilst a number of studies have suggested a primary perceptual deficit as the major cause of the naming disorder (Barker and Lawson, 1968; Rochford, 1971; Kirshner *et al.*, 1984), other more recent investigators have favoured a central semantic defect (Bayles and Tomoeda, 1983; Martin and Fedio, 1983; Huff *et al.*, 1986; Bowles *et al.*, 1987; Smith *et al.*, 1989). The latter finding is in keeping with other evidence of a breakdown in semantic memory (Tulving, 1983) in patients with DAT, such as impaired generation of specific exemplars (e.g., dog, cat, lion) comprising superordinate categories (e.g., animals) on verbal fluency tasks (Martin and Fedio, 1983; Ober *et al.*, 1986; Butters *et al.*, 1987), defective ranking of object attributes (Grober *et al.*, 1985), and impaired semantic priming (Salmon *et al.*, 1988).

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The evidence supporting a semantically based naming deficit in DAT derives, to a large extent, from the analysis of the types of errors produced on confrontation naming tasks. In these tasks, DAT patients tend to produce the name of the broad superordinate class (e.g., animal, fruit, etc.) or another item from the same semantic category (Bayles and Tomoeda, 1983; Huff *et al.*, 1986; Smith *et al.*, 1989). This evidence can, however, be criticized on the following grounds.

First, a number of the earlier studies did not use precise diagnostic criteria for DAT and merely classified their patients as demented (Barker and Lawson, 1968). Furthermore, only the study of Bayles and Tomoeda (1983) compared DAT patients with those with other causes of dementia in order to establish whether the types of naming deficit differed qualitatively in DAT from those in other demented patients.

Secondly, only two studies (Bayles and Tomoeda, 1983; Smith *et al.*, 1989) have provided a detailed analysis of the naming errors. Other investigators have used very broad, and largely undefined, categories such as 'language related, no response or perceptual' (Martin and Fedio, 1983), or 'semantically related, semantically unrelated or near synonyms' (Bowles *et al.*, 1987). Furthermore, the error classification systems previously applied have failed to distinguish between visual, semantic-category and ambiguous semantic category/visual errors. This is an important point because many members of certain categories (e.g., fruit, animals, etc.) are visually very similar. For instance, the examples of a semantic error given by Smith *et al.* (lemon for orange) and by Bayles and Tomoeda (peach for pear) could just as easily be classified as perceptual errors, whereas members of other categories are usually visually dissimilar (e.g., vehicles, musical instruments). The a priori assumption that all errors sharing category membership are semantically based is clearly a source of considerable potential bias. Bayles and Tomoeda addressed this question by making their error categories mutually nonexclusive, but this makes the results difficult to interpret. Also, their otherwise comprehensive error classification did not include circumlocutory responses which other workers have found to occur frequently in both normal elderly and DAT patients (Bowles *et al.*, 1987; Nicholas *et al.*, 1985).

Thirdly, the number of normal control subjects used in most previous studies (combined often with the simplicity of the naming task administered) have provided few classifiable errors. For instance, the 18 controls of Smith *et al.* (1989) produced only 63 errors, and in the study of Bayles and Tomoeda (1983) the small number of errors (4) produced by their 33 normal elderly controls precluded any comparison of error type between the patient groups and controls. The relevance of this is highlighted by the finding of Nicholas *et al.* (1985) that healthy older adults also produced predominantly semantically related errors of the type frequently described in DAT. Hence it is far from certain that the types of errors given by DAT patients differ qualitatively from those given by normal elderly subjects.

Finally, there have to date been no longitudinal studies of the error types in DAT to determine if the pattern of responses evolves as the disease progresses. The demonstration that the distribution of error types progressively diverges from normal would considerably strengthen the argument in favour of a central semantic deficit in DAT.

In contrast to DAT, the nature of the naming deficit in HD has received little attention. In fact, a number of studies have failed to demonstrate a significant naming impairment

in HD patients (for review, *see* Brown and Marsden, 1988), probably as a result of the simplicity of the naming tasks employed. Our recent study did find that groups of DAT and HD patients, who were matched for overall level of dementia, were impaired on the Boston Naming Test, but the DAT group subsequently deteriorated more rapidly than the HD group (Hodges *et al.*, 1990). Bayles and Tomoeda (1983) also found HD patients to be impaired on a naming test and that semantically related errors occurred most frequently, although visual errors were much more common than in DAT patients.

The aims of the present study were to compare the pattern of errors produced by patients with DAT, HD and normal controls using a comprehensive classification system (which takes into account the criticisms raised above), and to analyse the longitudinal change in the pattern of error types of the DAT patients over a period of at least 3 yrs. It was predicted that the DAT patients would show evidence of progressive semantic breakdown and that the HD patients would show more evidence of perceptual impairment than patients with DAT.

METHODS

Subjects

Three groups consisting of a total of 120 subjects participated in the study: 52 patients with DAT (34 males, 18 females), 52 neurologically intact normal control subjects (30 males, 22 females) and 16 HD patients (8 males, 8 females) Written informed consent was obtained from all subjects or the care-givers where appropriate. All subjects were evaluated on two occasions. (1) on entry to the study and (2) 12 mos later. A subgroup of 22 DAT patients underwent testing over 3 consecutive years

The HD patients in the study had been previously diagnosed by a senior staff neurologist on the basis of a positive family history of the disease, the presence of involuntary choreiform movements and the presence of dementia Their functional capacity was assessed with Shoulson and Fahn's scale (1979), which rates functional disability from 1 (minimal) to 5 (total) Three of the HD patients were rated at Stage 1, 7 at Stage 2, 5 at Stage 3 and 1 at Stage 4.

The diagnosis of probable DAT was made by 2 senior staff neurologists according to the criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) (McKhann *et al* , 1984) which consist of inclusion and exclusion criteria. All patients achieved a score of 4 or less on the Hachinski scale (Hachinski *et al.*, 1975), thus reducing the possibility of multi-infarct dementia.

Normal control subjects were either spouses of patients or volunteers obtained through newspaper advertisements. Subjects with a history of alcoholism, drug abuse, learning disability, serious neurological or psychiatric illness were excluded.

The DAT patients were chosen from a data base of approximately 100 patients undergoing prospective evaluation at the University of California San Diego Alzheimer's Disease Research Center (ADRC). All patients who had undergone evaluation over 2 yrs were chosen. No other selection criteria were applied. The normal controls were selected to match the DAT patient group for age.

Demographic data on the three groups are shown in Table 1 A one-way ANOVA of the mean age showed a highly significant group difference ($F(2,117) = 43.75$, $P < 0.001$), and post hoc analysis, using Duncan's procedure, confirmed as expected that the HD group were significantly younger than both the DAT and control groups ($P < 0.05$). There was no significant difference in the mean age of the DAT and normal control groups. A comparison of the mean education levels of the three groups also revealed a significant difference ($F(2,117) = 4.48$, $P < 0.05$) Post hoc analysis showed a significant difference between the DAT and normal controls ($P < 0.05$); however, the difference in real terms was only 1.4 yrs and is unlikely to have influenced the results. A one-way ANOVA of the Mini Mental State Examination (MMSE; Folstein *et al* , 1975) scores of the three groups revealed a highly significant difference ($F(2,117) = 141.1$, $P < 0.0001$), post hoc analysis showed a significant difference between the controls and both patient groups, as well as between the DAT and HD groups ($P < 0.05$).

Neuropsychological tests

All subjects were administered the Boston Naming Test (Goodglass and Kaplan, 1983) divided over two test sessions approximately 12 mos apart. Thus one-half of the full 60 outline drawings comprising the BNT were presented at each test session. All 30 items were administered to all subjects on each test session. On the first occasion, either the even or the odd numbered items from the test were administered. Subsequently, the other half were administered. In the subgroup of 22 DAT patients tested over 3 consecutive years, the items given in the first year were again administered on the third occasion. There was no evidence of bias in the selection of items for the shortened version of the test since the normal control subjects obtained virtually identical mean scores on the two versions.

The test was administered according to the following standard protocol: if a subject was unable to name an object, a predetermined stimulus or semantic cue ('an ocean animal' for octopus; 'used for air travel' for helicopter, etc.) was given, and if the subject was still unable to name the item, a phonemic cue consisting of the initial sound of the target word, was provided. Two scores were obtained· the total number of items named spontaneously and the total number named after stimulus cueing. All errors produced by the subjects were recorded

Error classification

The subjects' responses were initially categorized using the system described by Bayles and Tomoeda (1983). However, due to the reasons discussed above, this classification was found to be inadequate and an expanded system of coding categories was developed drawing on the work of Kohn and Goodglass (1985). The first response to the target (i.e., before stimulus or phonemic cueing) was classified, and in the case of multiple errors only the first was used. The categories used in the error analysis are as follows.

1. *Nonresponse*: includes 'don't know' and nonresponses.
2. *Visual errors*: responses visually similar to the target *and* from a different semantic category ('spear', 'snake', 'fountain pen' for asparagus; 'tie' for stethoscope; 'head of hair' for octopus). Also included were whole-part responses where subjects named either a part of the target item ('blocks' for pyramids) or something incidentally present in the picture ('door' for knocker, 'boy' for stilts).
3. *Ambiguous visual/semantic category errors*: responses from the same semantic category as the target *and* visually similar such that the error could be either perceptually or semantically based ('hippopotamus' for rhinoceros; 'otter' for beaver; 'stork' for pelican; 'dice' for dominoes; 'headphones' for stethoscope; 'mountain' for volcano; 'peanut' for acorn).
4. *Semantic: within-category errors*. responses from the same semantic category as the target but clearly *not* visually similar ('atlas' for globe; 'lettuce' for asparagus; 'violin' for accordion; 'thermometer' for protractor; 'easel' for palette).
5. *Semantic: superordinate errors*: responses denoting the general class or category to which objects belong ('vegetable' for asparagus; 'animal' for rhinoceros; 'musical instrument' for accordion).
6. *Semantic: associative errors*: responses showing an obvious semantic association with the target item including statements of action or function ('painting' or 'artist' for easel; 'blow' or 'music' for harmonica), physical attributes ('ice' for igloo; 'green' for asparagus), contextual associates ('ocean' for octopus; 'desert' for camel; 'Egypt' for pyramid; 'doctor' for stethoscope), and specific subordinate or proper noun examples of the target ('Vesuvius' for volcano).
7. *Semantic: circumlocutory errors*: multiword responses showing accurate identification of the target by physical attribute, function or action ('doctors use them for listening to your heart' for stethoscope; 'African animal with a horn' for rhinoceros; 'used at school for drawing circles' for compass; 'Eskimo's snow house' for igloo). If the distinction between error types 6 and 7 was unclear, we applied the following criterion: does the response describe a specific item? If it did, the error was categorized as a circumlocutory response. Also included in this category were acceptable slang terms, synonyms and creative neologisms ('squeezebox' for accordion; 'dromedary' for camel; 'toadstool' for mushroom; 'autostairway' for escalator).
8. *Phonemic errors*: mispronunciations or distortions of the target name sharing at least one syllable ('iglow' for igloo; 'propractor' for protractor).
9. *Perseverations*: reutterances of a response (correct or incorrect) which had previously been used to name 1 of the previous 5 pictures.
10. *Unrelated errors*: in which no clear connection between the target and response could be deduced ('a mess' or 'one of those things' for snail).

The classification of error responses was performed independently by 2 of the authors (J.H., D.S.).

Agreement between these 2 coders for a sample of 500 independently scored items was 85%. Discrepancies were discussed and agreement reached regarding the appropriate classification of the errors.

RESULTS

For the purposes of the initial comparison of the DAT, HD and normal control groups, the BNT scores and the total number of errors made on the two test sessions were combined in order to increase the corpus of classifiable error types. The groups' spontaneous and total (i.e., with stimulus cueing) BNT scores, out of a possible total of 60 correct, are shown in Table 1. One-way ANOVAs revealed a highly significant

TABLE 1 AGE, EDUCATION, MMSE, BNT SCORES (MEAN±SD) AND NUMBER OF ERRORS FOR THE DAT AND HD PATIENTS AND FOR NORMAL CONTROL SUBJECTS

	DAT (*n* = 52)	*HD* (*n* = 16)	*Controls* (*n* = 52)
Age	71 7±6 3	52.5±11.6	68.7±8.4
Education (yrs)	12 4±3 6	14 1±2.4	13.8±1 9
MMSE score	19 5±4.0	25 2±2.2	28.8±1 2
BNT scores (max. = 60)			
Spontaneous	35.3±6.8	47 0±4 3	54 7±1.9
Total	37 3±6 7	50 3±3.8	55 9±1.8
BNT errors			
Mean no. of errors	24.7	13 1	5 3
Nonresponses as % of total errors	38 7	31 9	24.1
All others as % of total errors	61 3	68.1	75 9

group effect for spontaneous ($F(2,117) = 36.7$, $P < 0.0001$) and total scores ($F(2,117) = 34.39$, $P < 0.0001$). Post hoc comparisons, using Duncan's procedure, confirmed significant differences between the controls and both patient groups, as well as between the DAT and HD groups ($P < 0.05$) for spontaneous and total scores. The mean number of errors and nonresponses made by each group are also shown in Table 1. It can be seen that the proportion of nonresponses did not differ significantly between the DAT (38.7%) and HD groups (31.9%), but the proportion in both patient groups was significantly greater ($P < 0.05$) than in the normal controls (24.1%).

The distribution of error types, analysed as the proportion of total errors, in the three groups is shown in fig. 1. The proportion of each error type was calculated for every subject by dividing the number of times an error of a particular type occurred by the total number of errors (excluding nonresponses) made by that subject. It can be seen that the pattern of errors produced by the normal controls and by the HD group was extremely similar with semantic within-category errors predominating in both groups, followed in frequency of occurrence by ambiguous visual-semantic and circumlocutory errors. Purely visual and phonemic errors were rare, accounting for approximately 15% of the error types in total. The pattern of error types produced by the DAT group was very different to that seen in the controls and HD patients. Superordinate errors predominated and semantic-associative errors (which occur rarely in normals and HD) were as common as semantic within-category responses. Since the number of

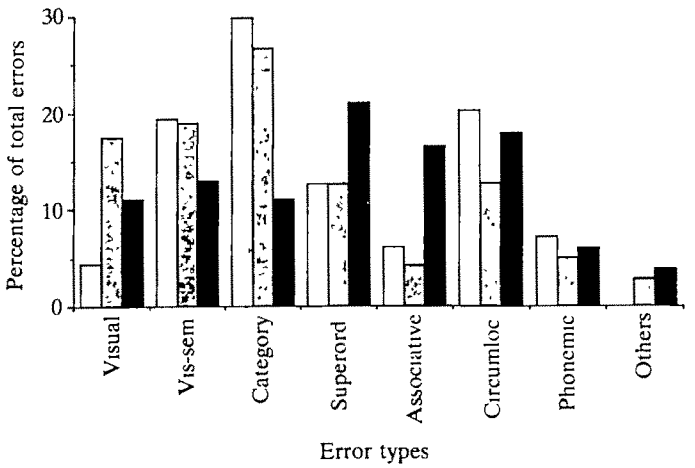

FIG. 1 Distribution of the naming error types in the DAT and HD patients, and the normal controls. Vis = visual, Vis-sem = ambiguous visual-semantic, category = semantic-category, superord = semantic-superordinate, associative = semantic-associative, circumloc. = semantic-circumlocutory, others = miscellaneous (*see* Methods for definitions of error types) Normal controls (open bars), HD (closed bars), DAT (hatched bars)

perseverations and unrelated responses were very small these were collapsed to form a miscellaneous error group.

One-way ANOVAs of the proportions of each error type in the three groups revealed significant group differences for visual ($F(2,117) = 3.07$, $P < 0.05$), semantic within-category ($F(2,117) = 8.49$, $P < 0.001$), superordinate ($F(2,117) = 10.72$, $P < 0.001$), semantic-associative ($F(2,117) = 8.34$, $P < 0.001$) and miscellaneous error types ($F(2,117) = 5.30$, $P < 0.05$). Post hoc analyses, using Duncan's procedure, revealed the following significant differences, at at least the $P < 0.05$ level, between the groups: (1) DAT vs controls: semantic-associative, superordinate and miscellaneous errors occurred more commonly in DAT patients, while within-category semantic errors were more common in the controls; (2) HD vs controls: visual errors were made significantly more often by the HD group; (3) DAT vs HD groups: within-category semantic errors were more common in the HD group, and semantic-associative errors were more common in the DAT group.

Since the overall naming performance of the DAT patient group was significantly worse than that of the HD group we considered the possibility that the observed differences in the profile of naming errors might merely reflect this greater degree of anomia. We therefore selected a group of DAT and HD patients matched on the basis of their spontaneous naming scores on the BNT. To equate the groups further, only the errors produced on the first test session (*see* Methods) were used in the analysis. However, because the available corpus of errors was thus relatively small, 5 additional HD patients, not included in the original group because of limited longitudinal data, were added to make a total group of 21. Each HD patient was then individually matched to a DAT patient achieving the same score on the BNT. As shown in Table 2, mean BNT scores for the two groups were identical. As with the larger sample, the HD patients were significantly younger ($t = 3.5$, $df\ 20$, $P < 0.005$), but there was no significant difference

TABLE 2 AGE, EDUCATION, MMSE AND BNT SCORES (MEAN±SD) FOR THE DAT AND HD PATIENT GROUPS MATCHED FOR OVERALL NAMING ABILITY

	DAT (*n* = 21)	*HD* (*n* = 21)
Age	72 8±6 2	50 3±13.3
Education (yrs)	13 6±2 9	14 1±2.3
MMSE score	19 6±4 2	24 6±4 4
BNT scores (max. = 30)		
Spontaneous	23.5±4.8	23 5±4 6
Total	24 3±4.6	24.8±4 7

in educational level between the two groups. Comparison of the proportions of each error type in the two groups, using matched t tests, showed significant differences for two error types (*see* fig. 2); visual errors were made significantly more often by the HD patient group ($t = 2.72$, df 20, $P < 0.05$), whereas semantic-superordinate errors were more commonly produced by the DAT patients ($t = 2.18$, df 20, $P < 0.02$).

The mean BNT naming scores of the subgroup of 22 DAT patients followed longitudinally declined at a steady rate over the course of the 3 yrs in parallel with their worsening MMSE scores (*see* Table 3). The proportion of nonresponses rose from 33.8% in year 1 to 43.5% in year 3, although this increase was not significant. As shown in fig. 3 the distribution of error types changed over time. Most striking was the increase in the semantic-associative and visual errors coupled with the progressive decline in other types, particularly circumlocutory responses. One-way ANOVAs of the proportion of each of the error types in years 1, 2 and 3 revealed significant effects only for visual ($F(2,63) = 3.90$, $P < 0.05$) and semantic-associative errors ($F(2,63) = 3.63$, $P < 0.05$). We considered the possibility that the increase in visual errors was due to a small group

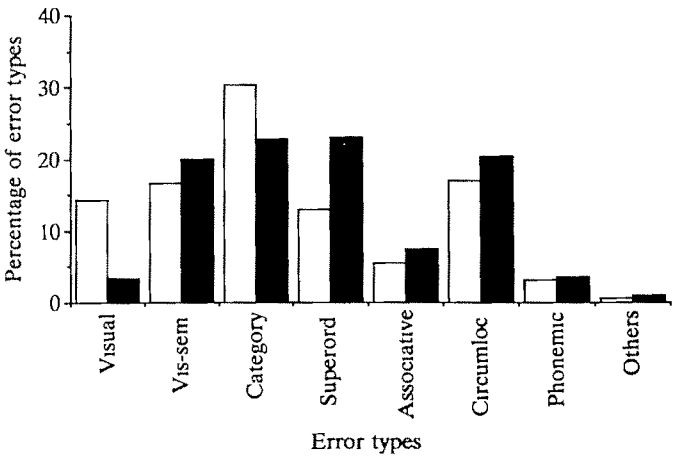

FIG 2 Distribution of the naming error types in the group of 21 DAT and HD patients matched for overall naming ability on the Boston Naming Test. Abbreviations as in fig 1 HD (open columns), DAT (hatched columns).

TABLE 3 MMSE, BNT SCORES (MEAN±SD) AND NUMBER OF ERRORS FOR THE SUBGROUP OF 22 DAT PATIENTS FOLLOWED OVER 3 YRS

	Year 1 *(n = 22)*	*Year 2* *(n = 22)*	*Year 3* *(n = 22)*
MMSE score	20 9±4.4	17.4±4.5	13.3±6 6
BNT scores (max = 30)			
Spontaneous	21.1±5 7	17.9±6.4	15 3±8 1
Total	22 1±5 5	19 2±6.7	16.2±8 5
BNT errors			
Mean no of errors	8.9	12.1	14.7
Nonresponses as % of total errors	33.8	31 4	43.5
All others as % of total errors	66 2	68.6	56 5

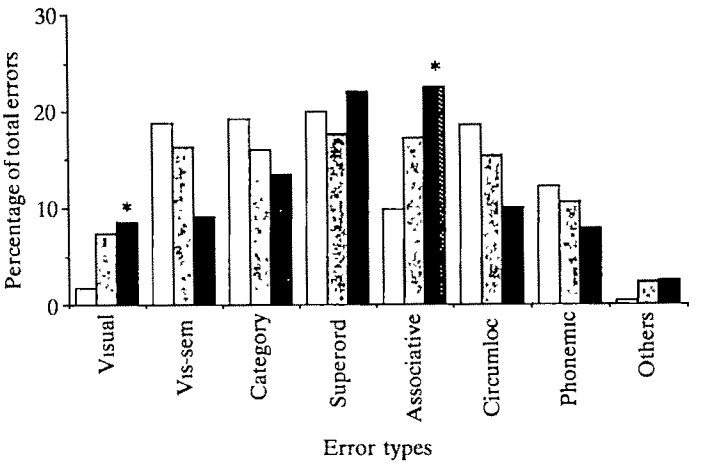

FIG 3 Distribution of the naming error types in the group of DAT patients (n = 22) followed over 3 consecutive years. Abbreviations as in fig. 1. Year 1 (open columns); year 2 (closed columns); year 3 (hatched columns) * Significant difference at $P < 0\ 05$.

of DAT patients making progressively more errors of this type rather than an increased number of DAT patients making visually-based errors. However, this was not the case. In year 1, only 1 patient (4.5%) made more than a single visual error, in year 2 7 patients (31.8%) made more than 1 such error and in year 3 the number had increased to 9 (40.9%). Thus it would appear that the increase in visual errors reflects a general change in the profile of errors made by a substantial proportion of the group.

DISCUSSION

The results of the present study confirm that the pattern of naming errors made by DAT patients differs qualitatively from that of normal control subjects, and from that of patients with HD. The anomia of DAT reflects progressive semantic knowledge disruption. In HD, by contrast, the deficit is primarily perceptual. The results of the longitudinal study support this dichotomy but suggest that, in addition to the semantic

deficit, there is a secondary less marked visuoperceptual defect in DAT as the disease progresses.

To address the cognitive implications of the naming errors in these two disorders it is necessary to consider the categories of error in the context of current models of naming. Although there are a number of different such theoretical models, all agree that normal naming proceeds in a series of basic stages (Gainotti *et al.*, 1981; Ratcliff and Newcombe, 1982; Kohn and Goodglass, 1985; Riddoch *et al.*, 1988; Coslett and Saffran, 1989). The first stage is perceptual in which analysis of the structural features of the target picture or object occurs. There follows a semantic stage in which the visual percept is matched with broad superordinate category knowledge (e.g., animal, musical instrument, etc.) before more specific subordinate and specific identifying semantic knowledge is accessed. Next is the lexical stage in which the correct target word that corresponds to the semantic concept is retrieved. Finally, there is a phonemic or word production stage.

Naming errors of different types result from breakdown at these stages (Kohn and Goodglass, 1985). Perceptual errors indicate a defect at the visual analysis stage. Superordinate naming errors imply that only broad category membership knowledge is accessed. Semantic-associative errors suggest that although some appropriate semantic category knowledge is available, this is inadequate to generate a correct descriptive response or category exemplar. Semantic within-category errors are more difficult to interpret; when this label is reserved for responses which are clearly distinct from the target visually (as in the present study) then it can be assumed that the defect is at a late stage of the semantic process. If circumlocutory responses occur then it can be assumed that appropriate activation of the semantic knowledge network has occurred but that the correct target word cannot be accessed (i.e., defect at lexical level). Phonemic paraphrasias imply impaired articulatory processing of phonological information.

In the present study, the incorrect responses of the normal controls are either within-category semantic or circumlocutory errors. The defect presumably occurs at the lexical or word-finding stage, while perceptual and central semantic processing remain intact. This finding is in keeping with that of Nicholas *et al.* (1985) who also analysed the naming errors made by healthy elderly subjects.

By contrast, in DAT the pattern of errors indicates breakdown at an earlier stage of the naming process with disruption of semantic knowledge. Semantic-associate and superordinate errors are significantly more common than in controls. As the disease progresses semantic-associate errors become significantly more prevalent and circumlocutory responses reduce in frequency, suggesting a decrease in the specificity of available semantic information. The issue as to whether there is actual loss of central representational knowledge or whether access is impaired is currently under investigation in a complementary research project. There is also evidence, from the present longitudinal study, that with worsening dementia the first stage (of perceptual analysis) is also disrupted since the prevalence of visually based errors increases significantly. The latter is not due to an obvious subgroup effect since the number of individual patients who made visual errors increases substantially over time.

Thus the present results support both proponents of a semantically based naming deficit in DAT (Bayles and Tomoeda, 1983; Martin and Fedio, 1983; Huff *et al.*, 1986; Smith *et al.*, 1989) and the proponents of a perceptually based deficit (Barker and Lawson,

1968; Rochford, 1971; Kirshner *et al.*, 1984). Indications are that the former deficit predominates from an early stage whilst, in general, the latter defect occurs at a more advanced stage in the natural history of the disease. Since the presentation of DAT can be extremely variable it remains likely that in some cases perceptual problems will dominate from an early stage. Indeed, patients presenting with visual agnosia (for faces) and with visuoperceptual syndromes have been reported (e.g., Nissen *et al.*, 1985).

Although a number of investigators have reported a predominance of semantic errors in DAT (Bayles and Tomoeda, 1983; Martin and Fedio, 1983; Smith *et al.*, 1989) there have been considerable differences in the pattern of error subtypes within this broad rubric. Bayles and Tomoeda (1983) found that semantic category errors occurred most frequently, and that superordinate and associative errors were relatively less common. Smith *et al.* (1989), using a more extensive classification system, found semantically related (noncategory) errors to be the predominant error type. One reason for this difference may have been the classification criteria applied, and the fact that neither group separated clear-cut category (i.e., visually distinct) errors from ambiguous visual-semantic category errors. A further explanation for the differences relates to the degree of dementia of the patients studied. The patients of Smith *et al.* were all hospitalized with at least moderately severe disease, whereas the patients studied by Bayles and Tomoeda (1983), and those in the present investigation, had mild to moderate disease. The types of errors produced also depend to some extent on the target items used in the naming test. The studies under discussion all used different test material. The BNT contains a high proportion of items which are not easily classifiable into standard superordinate categories (e.g., globe, muzzle, unicorn, scroll, wreath, stilts, etc.) and this may account for the relative lack of superordinate responses.

Turning to the HD patients, the finding of significant, albeit mild, impairment in naming confirms that anomia occurs in HD but to a less marked degree than in DAT (Hodges *et al.*, 1990). The profile of naming errors made by the HD group differed from controls and DAT patients in the proportion of visually based errors which was greater in HD, implying a defect at the first stage of the naming process (i.e., perceptual analysis). The proportion of ambiguous visual-semantic category errors was also greater than in controls or DAT patients, and although the difference did not reach significance, it suggests that a number of these errors may also have been perceptually based. The well-established visuoperceptual and visuospatial deficits of HD patients (Butters *et al.*, 1978; Josiassen *et al.*, 1982; Brouwers *et al.*, 1984) are clearly in keeping with the present findings. The relatively intact semantic processing in these patients is also consistent with previous reports of normal semantic priming in HD (Salmon *et al.*, 1988).

The dissimilarity in the pattern of naming errors produced by the DAT and HD patient groups cannot be explained on the basis of differing degrees of anomia, since significant differences were found between the groups of patients carefully matched for naming performance on the BNT, the DAT patients making significantly more semantic-superordinate errors and the HD group producing a greater proportion of visual errors. The results of this analysis clearly demonstrate that, even at a relatively early stage of dementia, breakdown occurs at different stages of the naming process in the two diseases. The failure to find a significant difference in the proportion of visually based errors between the larger group of DAT and HD patients, not matched for overall naming ability, can be explained by the inclusion of more severely impaired patients within

the DAT group, a proportion of whom had almost certainly developed secondary perceptual deficits, as evidenced in the longitudinal study. Similarly, the progressive change in the pattern of the semantic errors over time in the DAT group (i.e., an increase in the semantic-associative errors) accounts for apparent discrepancy between the results of the matched and the larger unmatched comparisons. In the former, superordinate errors were significantly more common in the DAT group than in the HD group. However, in the larger DAT group, which contained more severely impaired cases, semantic-associative errors were significantly more common.

In conclusion, the observed differences in the profile of naming errors between patients with DAT and HD add to the growing evidence that aetiologically distinct forms of dementing diseases produce qualitatively distinct patterns of cognitive deficit. In DAT, which predominantly affects association cortices, the naming defect results from the general breakdown in the hierarchical organization of semantic knowledge, whereas in HD, which is associated with primarily subcortical neuropathological changes, the anomia results from perceptual deficits.

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EARLY ONSET CEREBELLAR ATAXIA WITH RETAINED TENDON REFLEXES

CLINICAL, ELECTROPHYSIOLOGICAL AND MRI OBSERVATIONS IN COMPARISON WITH FRIEDREICH'S ATAXIA

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SUMMARY

Fourteen patients with the clinical diagnosis of early onset cerebellar ataxia with retained tendon reflexes (EOCA) were examined and compared with 11 patients with Friedreich's ataxia (FA). The mean age of onset in EOCA was 15.9±6.0 yrs (FA: 14.0±5.7 yrs). Annual progression rate and the percentage of patients who were wheelchair-bound was lower in EOCA as compared with FA, although the difference did not reach statistical significance. The latency until becoming wheelchair-bound, however, was significantly longer in EOCA than in FA. The segregation ratio in EOCA was significantly lower than 0.25. Clinically, EOCA and FA patients presented with a progressive cerebellar syndrome. Associated symptoms, such as muscle wasting, sensory disturbances, foot deformity, scoliosis and electrocardiographic abnormalities were encountered less frequently in EOCA than in FA patients. The electrophysiological findings in EOCA were variable and pointed to axonal degeneration in peripheral nerves and central pathways. Posturographic measurements revealed a higher incidence of anteroposterior sway direction in EOCA as compared with FA, suggesting a cerebellar type of ataxia in EOCA. Eleven out of the 14 EOCA patients had cerebellar atrophy in MRI. The characteristic MRI finding in FA was upper cervical cord shrinkage and only minor atrophy of the cerebellum. The demonstration of cerebellar atrophy in the majority of EOCA patients supports the view that EOCA is distinct from FA. It is uncertain, however, whether EOCA is a homogenous disease entity or a group of phenotypically similar syndromes

INTRODUCTION

In 1981, Harding drew attention to a distinctive clinical syndrome characterized by progressive cerebellar ataxia of unknown aetiology with an onset before the age of 25 yrs. The disorder was distinguished from Friedreich's ataxia (FA) by the preservation of the tendon reflexes. This led Harding (1981*a*) to label this disorder as early onset cerebellar ataxia with retained tendon reflexes (EOCA). Apart from preserved tendon reflexes the patients of Harding's series had less severe upper limb ataxia and less reduction of joint position sense in comparison with patients suffering from FA. In addition, accompanying symptoms such as optic atrophy, scoliosis, cardiomyopathy or diabetes mellitus were rare or completely absent. Genetic data suggested an autosomal recessive mode of inheritance. Most importantly, prognosis was better in EOCA patients than in those with FA. Since Harding's (1981*a*) original description 3 studies appeared reporting clinical data of EOCA patients (Claus, 1989; Özeren *et al.*, 1989;

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Filla *et al.*, 1990). The clinical and genetic characteristics of these patients were similar to those of Harding's patients.

Knowledge about the morphological and neuropathological basis of the disorder is extremely limited. The patients described by Huppert (1877), Fraser (1880), Nonne (1891) and Case 7 of the series of Jellinger and Tarnowska-Dziduszko (1971) may fulfil the clinical criteria of EOCA. However, some of them had clinical characteristics, such as optic atrophy (Fraser, 1880; Nonne, 1891) or mental impairment (Huppert, 1877; Fickler, 1911) which are unusual in EOCA. At necropsy, all patients had cerebellar atrophy; 2 of them had additional degeneration of the brainstem nuclei and middle cerebellar peduncle suggesting the presence of olivopontocerebellar atrophy (OPCA) (Fickler, 1911; Jellinger and Tarnowska-Dziduszko, 1971).

Systematic and detailed neuroradiological investigations, which could give information about macroscopic brain morphology in vivo, have not been undertaken. Harding (1981*a*), Vanasse *et al.* (1988), Özeren *et al.* (1989) and Filla *et al.* (1990) mentioned the occasional presence of cerebellar atrophy on computed tomographic (CT) scans in some of their patients. In FA, cerebellar atrophy of minor degree is found only in advanced cases (Claus and Aschoff, 1980; Diener *et al.*, 1986). The characteristic magnetic resonance imaging (MRI) finding in FA patients is shrinkage of the upper cervical cord (Wessel *et al.*, 1989).

Recently, attempts have been made to characterize EOCA electrophysiologically. In 6 out of Harding's (1981*a*) original 20 patients results of nerve conduction studies were available. Motor nerve conduction velocity was normal in all, whereas sensory nerve action potentials were reduced in 2 patients. The usual findings in FA are normal motor nerve conduction velocity and small or absent sensory nerve action potentials (Hughes *et al.*, 1968; McLeod, 1971). Vanasse *et al.* (1988) studied somatosensory evoked potentials (SEPs) after median nerve stimulation in 6 EOCA patients and found evidence for pathological central conduction in all. In FA, cortical responses after median nerve stimulation are absent or delayed. P40 responses after tibial nerve stimulation are usually missing, whereas positive waves with latencies of 60–80 ms may be recorded in some patients (Jones *et al.*, 1980; Pedersen and Trojaborg, 1981; Beltinger *et al.*, 1987). Brainstem auditory evoked potentials (BAEPs) were pathological only in 1 out of 5 patients with EOCA. In contrast, Filla *et al.* (1990) obtained pathological BAEPs in 6 out of 8 EOCA patients. In FA, most investigators found BAEP abnormalities (Satya-Murti *et al.*, 1980; Jabbari *et al.*, 1983; Nuwer *et al.*, 1983; Pelosi *et al.*, 1984; Vanasse *et al.*, 1988). Abnormalities consisted of absence or delay of waves III and V, whereas wave I was usually preserved, suggesting pathological conduction along the central auditory pathways. The extent of BAEP abnormalities is correlated with clinical disability in FA (Pelosi *et al.*, 1984).

Taking all available data together, it must be admitted that—a decade after its description by Harding (1981*a*)—EOCA is still a poorly defined entity. In particular, our present ignorance about the underlying neuropathology makes it difficult to decide if EOCA is more than a group of phenomenologically similar syndromes. The present study was undertaken to provide detailed clinical, genetic, neurophysiological and MRI-morphological data about EOCA in comparison with FA. To this end, 14 patients fulfilling the clinical criteria of EOCA, and 11 patients with FA were examined clinically and underwent nerve conduction studies, evoked potential testing and posturography. In

addition, MRI was performed in all to gain information about the in vivo morphology of the brain and upper cervical spinal cord.

PATIENTS AND METHODS

The clinical records of all patients with cerebellar or spinocerebellar ataxia referred to our department between 1982 and 1990 were reviewed. Of these, 14 fulfilled the diagnostic criteria of EOCA (Harding, 1981*a*) i.e., (1) progressive ataxia with an onset before the age of 25 yrs; (2) normal or increased tendon reflexes; 27 fulfilled the diagnostic criteria of FA (Geoffrey *et al.*, 1976, Harding, 1981*b*): (1) progressive ataxia with an onset before the age of 25 yrs; (2) tendon areflexia in the lower extremities; (3) dysarthria within 5 yrs of the onset of ataxia.

Patients with evidence of autosomal dominant inheritance, pigmentary retinal degeneration, cataract, myoclonus or hypogonadism were not included in this study. Neurographic studies were performed in all to exclude patients with hereditary motor and sensory polyneuropathy. The cerebrospinal fluid was examined in all to identify patients with multiple sclerosis and other inflammatory diseases of the CNS. All patients with focal abnormalities or white matter changes on MRI were excluded from the study Levels of phytanic acid and lactate dehydrogenase were determined in all patients. Activity of β-hexosaminidase A was measured in 7 EOCA patients. In 1 patient with low motor nerve conduction velocity additional assays for β-hexosaminidase B, β-galactosidase, arylsulfatase A and very long chain fatty acids were performed.

All patients with EOCA and 11 patients with FA were personally interviewed and clinically examined by one of us (T.K.) using a standardized examination procedure. Severity of cerebellar symptoms was rated on a scale ranging from zero (absent) to 5 (most severe) (Klockgether *et al.*, 1990). The annual progression rate was calculated by dividing the rated severity of gait ataxia by the disease duration in years. All of them underwent MRI, nerve conduction studies and SEP investigations. BAEPs were recorded in all patients with EOCA and 7 patients suffering from FA. Static posturography was performed in all patients who were able to stand. Electrocardiographs were available for all patients.

MRI was performed using a superconducting system operating at 1.5 tesla field strength (Magnetom, Siemens AG, Erlangen, Germany) with a head coil of 30 cm diameter. Data were acquired and displayed on a 256×256 matrix. A standard examination program was used which included sagittal and axial T_1-weighted images without gap (spin echo, TR = 0.6 s, TE = 15 ms, slice thickness = 4 mm, 2 averages). The first axial slice was at the body of C2, the last was situated apical to the lateral ventricles. In addition, one set of T_2-weighted axial slices (spin echo, TR = 2.1 s, TE = 45–90 ms, slice thickness = 4 mm) was taken. Severity of atrophic changes of the cerebellar hemispheres, the upper vermal region, the lower vermal region, the brainstem at the level of medulla oblongata, the pons, the upper cervical cord and enlargement of the fourth ventricle were rated twice by 2 independent experienced examiners (D.P., W.G.) who were not aware of the clinical findings using a score ranging from zero (normal) to 3 (severe). For reasons of comparison the MRIs of 13 age-matched healthy control subjects were rated together with those of patients.

Motor nerve conduction velocity of the tibial nerve was measured using standard neurographic procedures. Sensory nerve conduction velocity was measured following antidromic stimulation of the sural nerve. The values for the velocity and amplitude of the sensory nerve action potentials were compared with normative data from our laboratory (Stöhr and Bluthardt, 1987).

Cortical SEPs were recorded from Cz′ (2 cm dorsal to Cz) against Fz following tibial nerve stimulation by bipolar surface electrodes placed at the ankles. SEPs after median nerve stimulation were recorded from C3′ (2 cm dorsal to C3) The median nerve was stimulated at the wrist. Rectangular pulses of 0.1 ms were delivered at 5 Hz and at a stimulus strength set 4 mA above the motor threshold; 1024 sweeps were averaged with bandpass filters at 10 Hz and 1 kHz Latency of P40 (tibial nerve) or N20 (median nerve) was measured and compared with normative data from our laboratory (Stöhr *et al.*, 1989). The amplitude of P40 was measured from the baseline and considered to be pathological if it was less than 50% of the contralateral side.

BAEPs were recorded simultaneously from both mastoids against a Cz reference electrode following

rarefication click stimulation with pulses of 0.1 ms delivered monaurally at 70 dB SL and 11.9 Hz. In some instances stimulation with alternating polarity was performed additionally; 2048 sweeps were averaged with bandpass filters at 100 Hz and 3 kHz. Latencies of waves I, III and V and interpeak latencies I–III, I–V and III–V were measured and compared with normative data from our laboratory (Stöhr *et al.*, 1989). The amplitude ratio V/I was calculated and considered to be pathological if the value was smaller than 1.

For static posturography, subjects stood on a force measuring platform, which permitted computation of the displacement of the centre of foot pressure from forces acting on 4 strain gauges at the corners of the platform. The following parameters of postural sway were calculated and compared with normative data from our laboratory (Diener *et al.*, 1984): sway path, sway area, amplitude of body sway in the anteroposterior direction, amplitude of body sway in the lateral direction. The Romberg quotient indicating the amount of visual stabilization was calculated by dividing sway path or sway area with eyes closed by sway path or sway area with eyes open. The quotient amplitude of body sway in the anteroposterior direction/amplitude in lateral direction was calculated to estimate the predominant sway direction. Graphical plots of the sway path and sway direction histograms were obtained and depicted for each patient.

For those patients with FA who were not seen personally (n = 16), age at disease onset, disease duration and latency until they became wheelchair-bound were determined from the clinical records. In addition, information was obtained about the presence or absence of scoliosis, foot deformity, diabetes mellitus or electrocardiographic abnormalities. It was also established whether or not they had affected siblings or if their parents were consanguinous.

RESULTS

Patients and genetic aspects

Three out of 14 patients with EOCA were female and 11 male, whereas 16 out of 27 patients with FA were female and 11 male ($P \leq 0.05$, χ^2 test). The mean age at examination was 34.2 ± 11.7 yrs in EOCA as compared with 28.1 ± 7.4 yrs in FA ($P \leq 0.05$, Student's t test). There were no statistically significant differences between both groups with respect to age of onset (EOCA: 15.9 ± 6.0 yrs, FA: 13.0 ± 4.6 yrs) and disease duration (EOCA: 18.4 ± 13.6 yrs, FA: 15.1 ± 8.3 yrs). The percentage of patients who were wheelchair-bound (EOCA: 21%, FA: 48%) and annual progression rate (EOCA: 0.21, range: 0.06–0.67, FA: 0.33, range: 0.15–0.75) were lower in EOCA, but the differences did not reach statistical significance. The latency until becoming wheelchair-bound, however, was significantly longer in EOCA as compared with FA (EOCA: 21.0 ± 10.6 yrs, FA: 7.8 ± 3.3 yrs, $P \leq 0.01$, Student's t test). The respective values for the 11 FA patients examined personally were: age: 28.3 ± 6.3 yrs; age of onset: 14.0 ± 5.7 yrs; disease duration: 14.3 ± 8.5 yrs; percentage of patients who were wheelchair-bound: 36%; latency until becoming wheelchair-bound: 6.3 ± 0.4 yrs. These values did not differ significantly from those of the whole FA population.

The 14 EOCA patients came from 14 different families. Two EOCA patients gave a history of a similar disorder in 2 siblings; both were unavailable for study. There was no evidence of consanguinity between parents. Segregation analysis was performed on these families using Weinberg's proband method with correction for family size (Crow, 1963). The segregation ratio was 0.11 and its 95% confidence limits 0.01–0.21. This value was significantly different from 0.25 ($P \leq 0.05$).

The 27 FA patients came from 19 families. In 12 families only 1 sibling was affected, in 5 families 2 siblings were affected and in 2 families 3 siblings were affected. As in EOCA, there was no evidence of consanguinity between parents. The segregation ratio was 0.35 and its 95% confidence limits 0.17–0.53.

Clinical findings

The incidence and severity of various clinical features of EOCA in comparison with FA is shown in Table 1. The prominent clinical finding in all EOCA patients was ataxia of gait and stance. Ataxia of the limbs was present in all patients and was more pronounced in the lower limbs. Intention tremor of moderate degree was found in 8 of the 14 patients. Dysarthria was a common finding, but speech was intelligible in all but 2 patients. With the exception of 1, all presented with oculomotor abnormalities. Impaired smooth pursuit, reduced optokinetic nystagmus, nystagmus on lateral gaze and incomplete suppression of vestibulo-ocular reflex by fixation of a stationary target were the most frequent findings, whereas fixation instability with square-wave jerks and vertical gaze palsy were observed in 2 patients, respectively. Saccadic hypermetria occurred in 1 patient. Weakness of the lower limbs was present in 5 out of the 14 patients and distal muscle wasting in 3. One patient presented with atrophy of the tongue. Extensor plantar responses were

TABLE 1 CLINICAL FEATURES OF EARLY ONSET CEREBELLAR ATAXIA WITH RETAINED TENDON REFLEXES (EOCA) IN COMPARISON WITH FRIEDREICH'S ATAXIA (FA)

	EOCA (n = 14)			*FA (n = 11)*			
	Severity		*Incidence*	*Severity*		*Incidence*	
	(Median)	*(Range)*	*(%)*	*(Median)*	*(Range)*	*(%)*	*P*
Wheelchair-bound			21			48	n.s.
Ataxia of gait	3	2–4	100	3	2–5	100	n s
Ataxia of stance	3	1–4	100	3	2–5	100	n.s.
Upper limb ataxia	2	0–3	86	3	1–4	100	n.s
Dysdiadochokinesia	2	0–3	71	2	0–5	91	n s.
Intention tremor	1	0–4	57	1	0–5	82	n s.
Lower limb ataxia	3	1–5	100	3	2–5	100	n s.
Dysarthria	2	0–4	93	2	1–4	100	n s
Impaired pursuit			93			64	n.s
Reduced OKN			64			45	n.s
Impaired suppression of VOR			79			82	n s
Fixation instability			14			55	0 05
Gaze nystagmus			57			36	n.s.
Saccadic hypermetria			7			9	n s
Vertical gaze paresis			14			0	n s
Weakness			35			73	n s
Muscle wasting			21			64	0 05
Spasticity			21			18	n s
Extensor plantar responses			29			55	n.s
Impaired vibration sense			64			100	0.05
Impaired joint position sense			43			91	0 05
Impaired sensation of light touch			7			45	0 05
Scoliosis			7			85	0 001
Foot deformity			36			70	0 05
ECG abnormalities			7			67	0 001
Diabetes mellitus			0			15	n s

n.s. = not significant. Statistical comparison by Mann-Whitney U test or χ^2 test

found in 4 patients and manifest spasticity of the lower limbs was present in 3. Sensory deficits of the lower limbs were encountered in 9 out of the 14 patients and mainly affected vibration sense and joint position sense. Five patients had foot deformity, whereas scoliosis was rare. Electrocardiographic abnormalities with negative T waves in precordial recordings were present in 1 patient. Hypertrophic obstructive cardiomyopathy was confirmed echocardiographically in this patient. This patient had exaggerated knee and ankle jerks. None of the EOCA patients had diabetes mellitus.

The frequency and severity of ataxia and dysarthria were similar in FA patients as compared with EOCA patients. As indicated in Table 1, the statistically significant differences between EOCA and FA were: higher incidence of fixation instability, sensory deficits affecting vibration sense, position sense and sensation of light touch, distal wasting, scoliosis, foot deformity and electrocardiographic abnormalities in FA. By definition, the two disorders are distinguished by the presence or absence of tendon reflexes of the lower limbs.

MRI findings

MRI was performed in all patients and in 13 age-matched healthy control subjects. There was a high correlation between the atrophy rating scores of 2 independent examiners ($r = 0.89$, $P \leq 0.001$, Spearman's rank correlation test). The rating scores were identical in 76 of 175 instances (7 rating scores per patient); they differed by 0.5 in 61, by 1.0 in 33, by 1.5 in 5 and by 2.0 in 1 instance.

In all patients signal intensities of the brainstem and cerebellum were found to be normal on T_1 and T_2-weighted images. Median rating scores in control subjects ($n = 13$) were zero for all structures analysed. Estimation of atrophic changes of infratentorial structures and upper cervical cord yielded an almost mirror image in patients

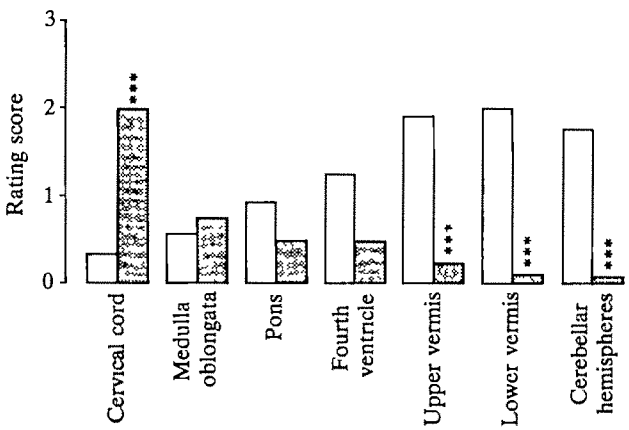

FIG. 1 Severity of the atrophy of the upper cervical cord, brainstem (medulla oblongata, pons), fourth ventricle and cerebellum (upper vermis, lower vermis, hemispheres) in patients with early onset cerebellar ataxia with retained tendon reflexes (EOCA) (open bars) and Friedreich's ataxia (FA) (shaded bars) as estimated from magnetic resonance imaging. The degree of atrophy of each structure was rated independently by 2 experienced examiners who were unaware of the clinical findings, using a rating scale ranging from zero (normal) to three (severe) Median values are given. Significances *** $\alpha \leq 0\ 02$ vs EOCA, Mann-Whitney U test

with EOCA and patients with FA (fig. 1). On average, EOCA had marked atrophy of the cerebellum affecting upper vermis, lower vermis and hemispheres to almost the same degree. The fourth ventricle was usually enlarged. There was no evidence of spinal cord atrophy in EOCA patients. A representative example of an EOCA patient is given in fig. 2A (Case 4). All FA patients had atrophy of the upper cervical cord (score $\geq$ 1) whereas cerebellar structures were usually unaffected. Cerebellar atrophy of moderate degree was observed only in 1 bedridden FA patient with a disease duration of 29 yrs. Fig. 2B shows a typical MRI of an FA patient (Case 4). In both patient groups, moderate shrinkage of the pons and medulla oblongata was observed. Whereas the pattern of atrophic changes was rather uniform in FA patients, it was more variable in EOCA patients. Three patients had evidence of spinal cord atrophy (score $\geq$ 1) and absence of cerebellar atrophy, thus resembling FA (fig. 2C, Case 10). In 2 EOCA patients the prominent finding was shrinkage of the pons in conjunction with cerebellar atrophy suggesting the presence of OPCA.

Neurographic findings

The neurographic data are summarized in Table 2. In both EOCA and FA, motor nerve conduction velocity of the tibial nerve was in the lower normal range or slightly reduced with the exception of 1 male EOCA patient in whom conduction velocity was reduced to 35 $m \cdot s^{-1}$. Sensory nerve action potentials from the sural nerve were normal in 6 out of the 14 EOCA patients, reduced in 4 and absent in 4. In contrast, sensory nerve action potentials were abnormally reduced (n = 6) or absent (n = 5) in all FA patients ($P \leq 0.05$, χ^2 test). There was also a statistically significant difference between the mean amplitude values of sensory nerve action potentials (EOCA: $7.4 \pm 7.4\ \mu V$, FA: $0.6 \pm 0.7\ \mu V$, $P \leq 0.01$, Student's t test). Sensory nerve conduction velocity was normal or moderately reduced in those patients of both groups in whom action potentials were evoked.

Evoked potentials

Cortical P40 responses after tibial nerve stimulation were recorded with normal amplitude and latency in 3 of the 14 EOCA patients; they were delayed in 2 patients (fig. 3, Case 13) and absent in the remaining 9 (fig. 3, Case 6). In 4 of these 9 patients, positive responses of longer latency were recorded, whereas in 5 no potentials were evoked at all. A P40 response of normal latency was recorded only on one side of 1 female FA patient, whereas it was absent in all other instances (fig. 3, Case 8). Positive waves of longer latency were preserved in 3 FA patients.

SEPs after median nerve stimulation were recorded in 10 EOCA patients and 7 FA patients. Cortical N20 responses of normal amplitude and latency were obtained in 4 of these 10 EOCA patients; 3 of them had absent cortical potentials after tibial nerve stimulation. There was moderate delay of N20 responses in 2 patients on both sides and in 1 patient on the left side. In the remaining EOCA patients, short-latency potentials were absent. In FA, N20 potentials were normal in 1 patient, delayed in 2 and absent in 4.

BAEPs were pathological in 10 out of the 14 patients of the EOCA group and normal in the remaining 4. The pathological BAEP findings were both loss of waves and increase of interpeak latencies. In 2 patients no reproducible potentials could be obtained on either side, whereas in another patient waves were completely missing on one side.

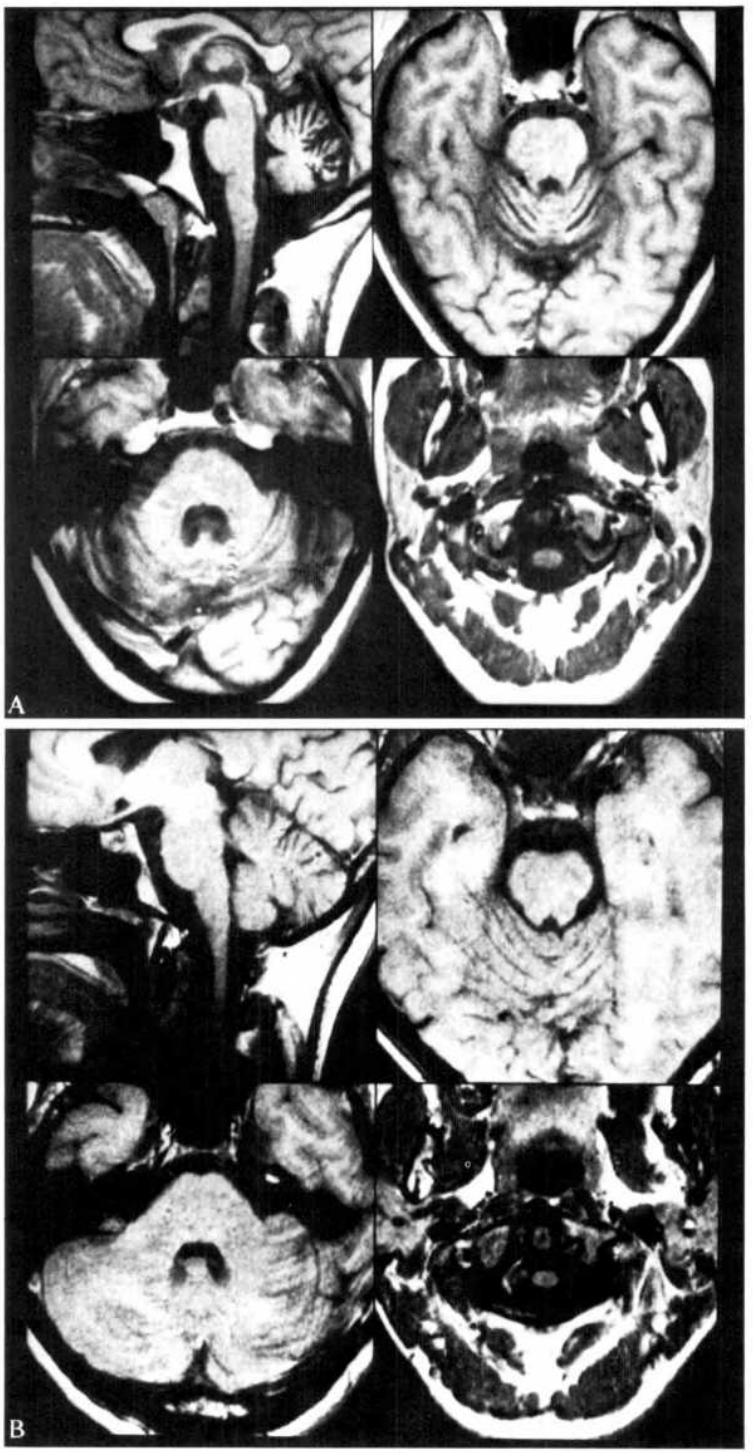

FIG. 2A and B.

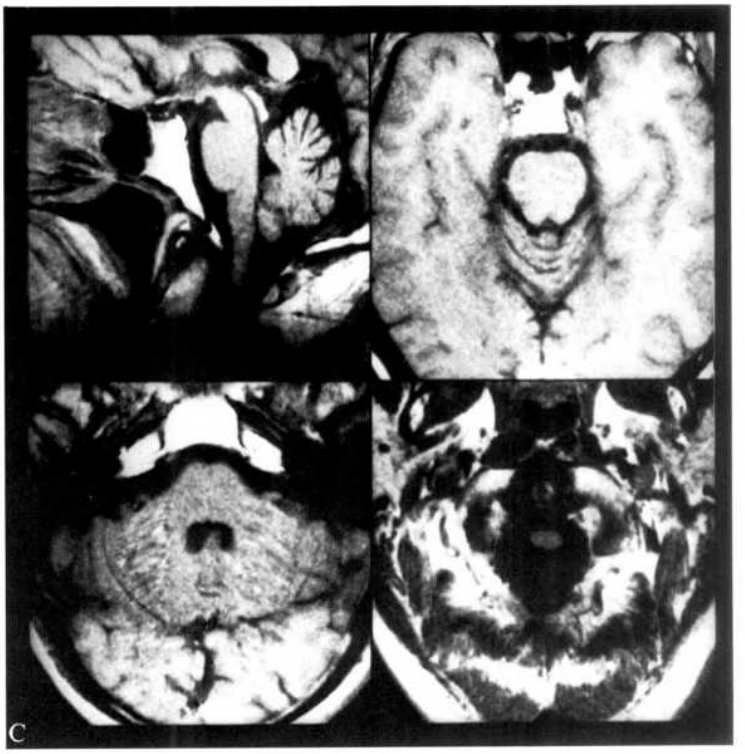

FIG. 2. A, magnetic resonance imaging (MRI) of a 25-yr-old female patient with early onset cerebellar ataxia with retained tendon reflexes and a disease duration of 5 yrs (EOCA, *Case 4*). Midsagittal and axial T_1-weighted spin echo images (1.5 T, TR = 0.6 s, TE = 15 ms) demonstrate atrophy of the cerebellum affecting upper and lower vermis and hemispheres. The cervical cord is not atrophic. B, MRI of a 35-yr-old female patient with Friedreich's ataxia and a disease duration of 16 yrs (FA, *Case 4*). The cervical cord is markedly shrunken, whereas the cerebellum and brainstem appear intact. C, MRI of a 43-yr-old male patient with EOCA and a disease duration of 33 yrs (*Case 10*). Cerebellar structures appear normal, but the cervical cord is moderately atrophic.

TABLE 2. NEUROGRAPHIC DATA IN EARLY ONSET CEREBELLAR ATAXIA WITH RETAINED TENDON REFLEXES (EOCA) IN COMPARISON WITH FRIEDREICH'S ATAXIA (FA)

	Normals		*EOCA*				*FA*			
	Mean	*SD*	*n*	*Mean*	*SD*	*% abn.*	*n*	*Mean*	*SD*	*% abn.*
Tibial MNCV ($m \cdot s^{-1}$)	49.0	3.0	14	40.3	4.8	79	11	40.5	5.0	55
Sural SNCV ($m \cdot s^{-1}$)	50.7	5.0	10	46.5	6.9	30	6	43.5	6.0	33
Sural SNAP (μV)	> 10		14	7.4	7.4	57	11	0.6**	0.7	100*

% abn. = percentage incidence of abnormal nerve conduction velocity ($\geq$ 2.0 SD as compared with normals) or reduced amplitude of the sensory nerve action potential ($\leq$ 10 μV); MNCV = motor nerve conduction velocity; SNCV = antidromic sensory nerve conduction velocity; SNAP = amplitude of the antidromic sensory nerve action potential. Significances: ** $P \leq 0.01$ vs EOCA, Student's t test; * $P \leq 0.05$ vs EOCA, χ^2 test.

Both patients with bilateral loss of waves were wheelchair-bound. In 3 patients unilateral loss of waves III and IV/V occurred, whereas wave I was preserved on that side. In 2 patients BAEPs were considered pathological because of amplitude reduction or desynchronization of IV/V. A pathological increase of interpeak latencies was observed

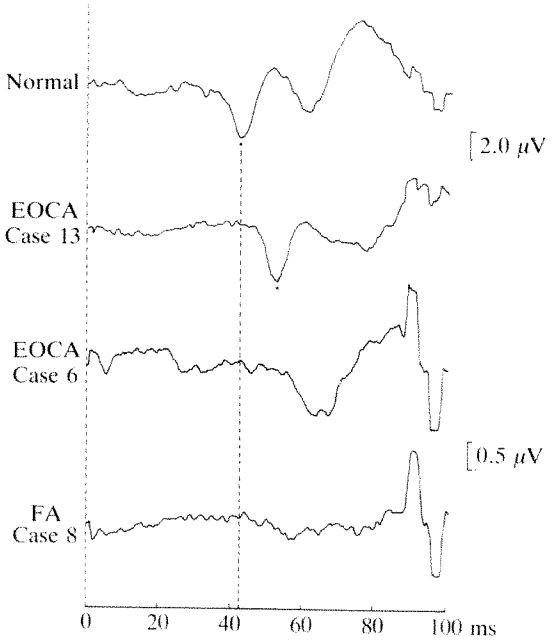

FIG. 3. Somatosensory evoked potentials following tibial nerve stimulation in a normal control subject, 2 patients with early onset cerebellar ataxia with retained tendon reflexes (EOCA, *Cases 6 and 13*), and 1 patient with Friedreich's ataxia (FA, *Case 8*). Note different calibrations.

TABLE 3. POSTUROGRAPHIC DATA IN EARLY ONSET CEREBELLAR ATAXIA WITH RETAINED TENDON REFLEXES (EOCA) (n = 11) IN COMPARISON WITH FRIEDREICH'S ATAXIA (FA) (n = 6)

	Normals		*EOCA*			*FA*		
	Mean	*SD*	*Mean*	*SD*	*% abn.*	*Mean*	*SD*	*% abn.*
Sway path, EO (mm/s)	7.9	2.8	40.8	27.3	91	41.4	20.1	100
Sway path, EC (mm/s)	12.7	5.8	81.3	36.2	91	127.0	43.2	100
Sway area, EO (mm^2/s)	9.0	9.8	214.9	251.6	100	190.1	170.9	100
Sway area, EC (mm^2/s)	18.2	14.7	493.0	343.1	91	1254.8**	369.9	100
Romberg quotient								
Sway path	1.6	0.5	2.9	1.7	73	3.4	1.0	83
Sway area	2.3	1.2	6.0	5.1	64	9.7	4.2	83
Quotient AP/LAT, EO	1.3	0.6	2.9	2.4	46	1.2	0.7	0*

% abn. = percentage incidence of abnormal values ($\geq$ 2.0 SD as compared with normals); EO = eyes open; EC = eyes closed; Quotient AP/LAT = quotient of sway amplitude in anteroposterior direction and sway in lateral direction. Significances: $^{**}P \leq 0.01$ vs EOCA, Student's t test; $^{*}P \leq 0.05$ vs EOCA, χ^2 test.

in 6 patients; 4 of them had also loss of waves. In 5 patients interpeak latency I–V was pathological, in 4 interpeak latency I–III and in 2 interpeak latency III–V.

BAEP investigations were performed in 7 FA patients. BAEPs were pathological in 3. In 1 of them only wave I was preserved, in another the IV/V complex was missing on one side and delayed on the other, and in the third the IV/V complex was desynchronized bilaterally and reduced in amplitude. The 2 patients with loss of waves

were wheelchair-bound, whereas the patient with reduced amplitudes and those with normal BAEPs were ambulant.

Posturography

Posturography was performed in 11 EOCA patients and 6 FA patients; all the others were unable to stand. Measures of sway path and sway area were pathological in the majority of EOCA patients and in all FA patients (Table 3). The significant differences between both groups were a greater sway area under nonvisual conditions in FA patients ($P \leq 0.01$, Student's t test) and a higher incidence of anteroposterior sway direction in EOCA ($P \leq 0.05$, χ^2 test). A pathological Romberg quotient indicating an abnormal degree of visual dependance was found in the majority of patients of both groups (EOCA: 73%, FA: 83%).

DISCUSSION

Loss of tendon reflexes in FA was first reported by Nicholas Friedreich himself in one of his later papers (Friedreich, 1876). Tendon areflexia in the lower extremities is now considered an essential criterion for the diagnosis of FA (Geoffroy *et al.*, 1976; Harding, 1981*b*). On the other hand, several cases have been published under the label of FA in whom the tendon reflexes were present or exaggerated (Burgess, 1892; Hodge, 1897; Bell and Carmichael, 1939) and the status of the tendon reflexes in FA was controversial in earlier reviews of the literature (Ladame, 1890; Wilson, 1954; Tyrer, 1975). Patients with progressive ataxia of early onset and preservation of tendon reflexes are now considered to represent a distinct clinical entity labelled early onset ataxia with retained tendon reflexes (EOCA) (Harding, 1981*a*). The present study is the first to provide a systematic clinical, genetic, neurophysiological and MRI characterization of EOCA patients in direct comparison with FA.

Clinically, EOCA patients presented with progressive ataxia, cerebellar oculomotor disturbances and dysarthria. Associated symptoms, such as muscle wasting, sensory disturbances, foot deformity, scoliosis and electrocardiographic abnormalities were encountered less frequently in EOCA than in FA. Fixation instability is a highly characteristic oculomotor finding in FA (Furman *et al.*, 1983) and is rarely present in EOCA. Overall, the clinical presentation of our EOCA patients was similar to those of the series of Harding (1981*a*), Claus (1989), Özeren *et al.* (1989) and Filla *et al.* (1990). It is noteworthy, however, that 1 of our patients had electrocardiographically and echocardiographically proven cardiomyopathy, whereas cardiomyopathy has been absent in all EOCA patients published so far.

Prognosis appears to be better in EOCA than in FA (Harding, 1981*a*; Claus, 1989). In the present series the proportion of EOCA patients who were wheelchair-bound was half of that of FA patients, although the average disease duration was 4 yrs longer. Furthermore, the latency until becoming wheelchair-bound was greater in FA. In addition, the calculated annual progression rate was lower in EOCA than in FA, although the difference did not reach statistical significance.

Harding (1981*a*) suggested that EOCA is a hereditary disorder with an autosomal recessive mode of inheritance. Segregation analysis in the present study and those of Harding (1981*a*) and Filla *et al.* (1990) yielded segregation ratios which were lower

than the expected value of 0.25 for autosomal recessive inheritance. The difference was statistically significant in the present study but not in those of Harding (1981*a*) and Filla *et al.* (1990). Combination of all available family data, however, would yield a significant difference between the calculated value and the expected value of 0.25. This consideration suggests that there may be genetic heterogeneity among EOCA patients. Although inheritance may be autosomal recessive in some of them, others may be phenocopies or new dominant mutations. The high proportion of male patients in our series suggests the possibility that inheritance in some is X-chromosomally linked. Spira *et al.* (1979) described a family with an X-linked disorder having some resemblance to the present EOCA cases. An X-linked inheritance, however, is unlikely to account for all cases of our study, since 3 of them were female and 1 male patient had an affected sister, unless the disease can be expressed in carrier females.

Extending the results of earlier studies (Harding, 1981*a*; Vanasse *et al.*, 1988), our electrophysiological investigations of somatosensory pathways revealed abnormalities in the majority of EOCA patients. These abnormalities consisted of attenuation of sensory nerve action potentials, reduced nerve conduction velocity and absence or moderate delay of cortical potentials after median and tibial nerve stimulation. These findings point to axonal degeneration both in peripheral nerves and central somatosensory pathways. The finding that some patients had normal SEPs after median nerve stimulation but absent SEPs after tibial nerve stimulation suggests particular involvement of the somatosensory pathways in the lumbar and thoracic spinal cord. Pathological BAEPs were found in 10 out of 13 patients. The abnormalities comprised loss of wave I, loss of waves III and V and delay of waves III and V. These findings suggest pathology of the auditory nerve and the central auditory pathways. As in FA, there is a tendency for the extent of BAEP abnormality to be greater in advanced cases.

Electrophysiology contributes little to distinguish between FA and EOCA. There are two highly characteristic electrophysiological abnormalities which occur in almost all FA patients: attenuation or absence of sural sensory nerve action potentials and loss of cortical P40 responses after tibial nerve stimulation. The same abnormalities, however, were found in about two-thirds of the EOCA patients. In particular, no characteristic abnormality was identified in EOCA patients which FA patients do not share. The variability of the electrophysiological findings in EOCA was remarkably high.

The main finding of the posturographic measurements is a higher incidence of abnormal anteroposterior sway direction in EOCA than in FA patients. Whereas a pathological degree of anteroposterior sway was encountered in about half of the EOCA patients, it was not found in any FA patient. Anteroposterior sway is thought to be a characteristic sign of cerebellar anterior lobe pathology, whereas lateral sway predominates in spinal ataxia, such as FA (Dichgans, 1984). The posturographic results therefore suggest that involvement of the cerebellum, in particular the anterior lobe, is more likely in EOCA than in FA.

The posturographic findings fit well with the results of the MRI studies: in contrast to FA patients, EOCA patients usually have diffuse cerebellar atrophy which can be demonstrated by MRI. Two had additional brainstem atrophy and enlargement of the fourth ventricle suggesting the presence of OPCA. The upper cervical cord is usually intact, whereas it is shrunken in most cases of FA. There were only 3 out of 13 EOCA patients with spinal cord atrophy and intact cerebellum. As pointed out in the Introduction,

there is an almost complete lack of knowledge as to the neuropathological basis of EOCA so that it is difficult to correlate the present MRI findings with neuropathological abnormalities. The MRI morphology in the majority of EOCA patients was comparable with the necropsy findings in Huppert's (1877) patient. OPCA has been found at necropsy in the patients of Fickler (1911) and Jellinger and Tarnowska-Dziduszko (1971). The present MRI investigations, however, show that OPCA is unusual in EOCA.

The contrasting MRI findings in EOCA and FA with demonstration of cerebellar atrophy in the majority of EOCA patients make it unlikely that EOCA is no more than an abortive form of FA. This possibility, however, cannot be excluded for those 3 patients who had an FA-like pattern of cerebellar and spinal atrophy. Interestingly, these patients also resembled FA in other respects: all of them had absent P40 responses after tibial nerve stimulation, 2 had reduced sensory nerve action potentials and 1 had cardiomyopathy. None of them had anteroposterior sway direction in posturography, which is the typical finding in EOCA, and never found in FA. These findings leave the possibility that these patients have an atypical form of FA with retained reflexes. Recently, Filla *et al.* (1990) reported 2 siblings, 1 of whom fulfilled the criteria of FA, whereas the other had spasticity and hyperreflexia. Similar examples were cited by Wilson (1954). A definite answer to the problem of atypical cases will hopefully be given by future molecular genetic research (Chamberlain *et al.*, 1988).

The genetic and morphological heterogeneity suggested by the present data, in conjunction with the variability observed in electrophysiological investigations, raises the general question whether EOCA is a homogenous disease entity. Our data seem to suggest that it is not. On the other hand, it is known from families with autosomal dominant cerebellar ataxia that clinical and neuropathological variability within one family may be surprisingly high (Carter and Sukavajana, 1956; Kraus-Ruppert, 1964). Further investigations, including molecular genetic studies, will be required to provide a definite answer to the outstanding questions regarding EOCA.

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MECHANISMS OF VISUAL SPATIAL NEGLECT

ABSENCE OF DIRECTIONAL HYPOKINESIA IN SPATIAL EXPLORATION

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SUMMARY

This study examines whether visuospatial neglect derives from failure in directing hand movements to the left (directional hypokinesia), or from loss of mental representation of the left side of space. Forty right brain-lesioned patients, 28 of whom revealed mild, moderate, or severe neglect in clock drawing and cancellation tasks, were asked to search for concealed targets on a stimulus display board, by either (1) moving a covering panel with a small window until the target appeared, or (2) moving the stimulus display board beneath a stationary covering panel until the target became visible through the window. In the second procedure, the direction of physical space exploration and hand movement is reversed, so that in order to bring a target from the *right* side of the stimulus into view (under the window) the entire display board had to be moved to the *left*. This pair of procedures was supplemented by an analogous pair of visual tasks in which the entire display board was visible during the search. As expected, response times were generally longer for targets located on the left side of the display board; however, the direction of required hand movement (left vs right) did not have a significant effect on response times, irrespective of the degree of clinically assessed neglect.

INTRODUCTION

Of the various types of 'spatial' disorders described by clinical neurologists, few are as dramatic as the syndrome of visual spatial neglect, which often accompanies lesions in the parietal region of the right hemisphere (De Renzi, 1982; Heilman *et al.*, 1985). In these cases, there is an absence of normal attention and response to events in the visual field contralateral to the lesion. In tasks such as drawing and reading, which require a systematic exploration or scanning of space, neglect patients will draw only one side of an object and will read only parts of a word. The most severe cases may also fail to groom or shave on one side of their face, or 'forget' to clothe or dry one side of the body after bathing. Compounding the mystery, neglect patients typically deny the existence of any such deficits, and are quite facile in dismissing evidence to the contrary. When pressed hard, they blithely confabulate an 'explanation' that is patently inadequate or absurd by normal standards (Bisiach and Berti, 1987). In other respects, however, they may show no signs of confusion or mental deterioration, nor, for that matter, do they necessarily reveal a primary sensory loss or motor weakness.

Viewed as a neuropsychological puzzle, neglect suffers from a redundancy of possible theoretical explanations, any one of which could account for its gross behavioural

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manifestations. These explanations can be differentiated by two issues, the first being the level of processing at which the critical deficit is postulated to occur (e.g., sensory, motor, attentional, representational) and the second being whether the deficit is understood as a failure of the afflicted (right) hemisphere, or the exaggerated influence of the intact (left) hemisphere.

A comprehensive list of the theories would start with the sensory-perceptual hypothesis, which has conceptualized neglect as involving attenuation of sensory input to the right hemisphere from the contralateral side of the body and space (Denny-Brown and Banker, 1954; Battersby *et al.*, 1956). Numerous experimental findings, however, have demonstrated the distinct status of neglect, that is, (1) sensory disorders do not as a rule appear in association with neglect phenomena (Volpe *et al.*, 1979); (2) neglect has been shown to extend to the left side of tactile, auditory and olfactory space (De Renzi *et al.*, 1970; Bisiach *et al.*, 1984; Bellas *et al.*, 1988).

Two currently prominent nonsensory accounts attribute neglect, respectively, to attentional (Kinsbourne, 1970, 1987; Heilman *et al.*, 1972, 1987) and representational (Bisiach and Luzzatti, 1978; Bisiach and Berti, 1987) deficits. Heilman *et al.* (1987) hypothesized that neglect results from a failure of attention or intention (i.e., readiness to respond) produced by the under-aroused right hemisphere. That is, the authors suggest that the intact right hemisphere contains the neural apparatus for attending to both sides of space, although the dominant tendency is for attending to the contralateral left hemispace. Accordingly, damage to the right hemisphere should cause not only contralateral neglect but also some neglect of the ipsilateral hemispace. This hypothesis places a strong emphasis on deficits in motor program activation (hypokinesia), which make movement in or towards the contralateral hemispace difficult or altogether impossible (Watson *et al.*, 1978). The authors further postulated that the loss of intention to perform a given act, produced by the under-aroused right hemisphere, is not limited to the contralateral extremity but is an akinesia for any act which may be performed in or toward the neglected (contralesional) hemispatial field.

Another influential attentional theory, but with different neurological premises, is Kinsbourne's (1987) attribution of neglect to a powerful rightward orienting tendency of the intact left hemisphere which, after the lesion, is no longer held in check by an intact right hemisphere. As a consequence, the rightmost stimuli will capture the subject's attention independently of the hemispatial field in which it is presented. According to Kinsbourne, orienting behaviour is understood to cover both gross movement, as well as the direction of attention about the visual and representational space.

A different explanation, advanced by Bisiach and Luzzatti (1978), is that neglect patients have simply lost the ability to conceptualize one side of space—their internal representation has been reduced by half. In a convincing illustration of neglect as a disorder of central representation, Bisiach and Luzzatti (1978) asked 2 patients to describe the Piazza del Duomo in Milan, according to two perspectives: imagining in one case that they face the Duomo, on the other that they have turned their back to it. In both perspectives, the patients demonstrated more or less complete neglect of left-sided details, where the left side was defined relative to their imagined orientation.

The purpose of this paper is to report the results of an experiment that narrows the range of theoretical options for explaining the neglect syndrome. In a number of variations on a single paradigm, subjects were asked to search for target locations on a stimulus

display board by moving the board beneath a stationary covering panel, which was opaque except for a small central window. In such a procedure, the direction of physical space exploration and hand movement are reversed, so that in order to bring a detail from the right side of the stimulus into view, the subject has to move the entire display board to the left. This procedure was then supplemented by control procedures in which the direction of hand movement and exploration coincided, as well as by conditions in which the entire display board was visible during the search.

In this arrangement (1) impaired exploration of the left side of visible stimuli, irrespective of hand movement direction, would indicate a visual neglect; (2) impaired exploration of the left side of concealed stimuli, irrespective of hand movement direction, would indicate a representational neglect; (3) impaired leftward hand movement, independent of the side of stimulation, would indicate a motor (intentional) neglect, and thus confirm the presence of directional hypokinesia.

These possibilities are by no means mutually exclusive—a single subject could, in principle, be afflicted by sensory, representational and motor neglect. In each case, the degree of impairment is measured by an elevation of response times for left side targets, or leftward hand movements. It is also possible that patients with severe neglect will be completely unable to locate left targets or make leftward hand movements.

MATERIAL AND METHODS

Subjects

The experiment was conducted on 40 patients with vascular lesions located in the right hemisphere (all recruited from the Sveti Sava Hospital for Cerebrovascular Diseases in Belgrade, Yugoslavia) and a control group of 14 subjects (also tested in Belgrade) free from history or present evidence of any disease involving the nervous system above the cervical cord. All subjects were right handed. The mean age was 63 y in the patient group and 64 y in the control group.

Evidence for right hemisphere lesions was determined by clinical and (when possible) by imaging methods (CT scans and angiography). The 40 patients were divided into 4 groups according to the presence or absence of contralateral neglect, which was assessed by two cancellation tests and two clock drawing tasks. The first test, adapted from Bisiach *et al.* (1979) consisted of crossing 17 circles, 4 in each quadrant, symmetrically arranged around a central one which formed the starting point of the task. The second cancellation task, which consisted of crossing 17 randomly arranged lines, 8 on each side of a central one, is similar to the Albert (1973) line-crossing test. The 2 clock drawing tasks involved (1) copying hours from a model clock, and (2) filling in the numbers on a circle blank except for the 12 o'clock numeral. Of the 3 tests, the clock drawing task proved to be much more discriminative since all but 12 patients were fully successful on the cancellation tasks.

Scoring

RH N−: no neglect (n = 12). (1) All circles and lines cancelled, and (2) no distortion or omission on the clock drawings.

RH N1: mild neglect (n = 14). (1) All circles and lines cancelled, and (2) mild counterclockwise distortion in the drawings, most easily seen in the noticeable displacement of the 9 o'clock−3 o'clock axis away from the horizontal.

RH N2: moderate neglect (n = 7). (1) From 0 to 7 lines or circles omitted, and (2) all numbers on both drawings concentrated in the first three clock quadrants (12−9 o'clock).

RH N3: severe neglect (n = 7). (1) From 3 to 13 lines or circles were omitted, and (2) all numbers concentrated on the right side of the clocks.

Samples of the clock drawing task for RH N1, RH N2, and RH N3 are presented in fig. 1. Table 1 lists all patients, and provides a numerical index of clock compression, calculated as follows. Each drawing

TABLE 1. SUMMARY OF CLINICAL DATA AND PERFORMANCE FOR RIGHT HEMISPHERE

Case	Sex	Age (y)	Locus of lesion	Neurological deficits	Clock distortion (%)	Cancellation omissions		Target bias	Hand bias
						Circles	Lines		
RH N3									
1	M	63	FP	hpl, hps	52	12	14	3 58***	0.88
2	F	72	FTP	hpa	67	2	4	2.02**	1.02
3	F	75	na	hpa, hps	58	3	1	2.40**	1 02
4	F	65	FTPO	hpl, hps	55	7	4	2.02**	1 07
5	F	70	TP	hpl	57	7	10	2.00**	0.88
6	F	54	FTP	hpa, hps	69	3	5	8.85***	0.65*
7	F	68	TPO	hpl, hps	50	13	14	6.49***	1 09
RH N2									
8	M	65	P	hpa	29	0	0	2.02***	0 98
9	M	78	FTP	hpa	19	0	2	1.87**	0.97
10	M	74	na	hpa	26	0	0	1 33*	1 03
11	F	60	P BG	hpl, hps	38	3	5	2 42**	0 73
12	M	61	FP	hpl, hps	23	3	2	2 26***	0 84*
13	M	46	TP	hpl, hps	4	7	1	3 72***	1.06
14	F	69	P	hpl	33	1	2	2 11***	0.89
RH N1									
15	F	59	TP	hpa	13	0	0	1.15*	0 99
16	M	77	na	hpa	13	0	0	1.15	0.98
17	M	63	P	hpa, hps	9	0	0	1.15	1 03
18	M	47	FTPO	hpl, hps	14	0	0	1.69*	1.00
19	F	58	OP	hpa, hps	10	0	0	1.46**	0.88
20	M	57	TP	hpa	8	0	0	1 22***	0.95
21	F	68	FP	hpa	12	0	0	1 20***	0.97
22	M	62	P	hpa	9	0	0	1.34**	0 95
23	M	69	na	hpa, hps	10	0	0	1.18*	1.07
24	F	62	FTP	hpa	9	0	0	1.44*	1 00
25	M	77	na	hpa	11	0	0	1.22**	1.06
26	F	58	TPO	hpa, hps	10	0	0	1 07	1.02
27	M	56	P	hpa	14	0	0	1.27**	0 98
28	M	70	TP	hpa	13	0	0	1.11	0 95
RH N−									
29	M	33	FT	hpa	1	0	0	1.01	1.04
30	M	42	TP	hpa	5	0	0	1.05	1.03
31	M	51	P BG	hpa, hps	7	0	0	1 17**	0 97
32	F	53	P	hpa	5	0	0	1 16*	0 96
33	M	59	FT	hpa	1	0	0	1.32**	0 96
34	M	70	na	hpa, hps	2	0	0	1.13**	1 05
35	M	57	P	hpa	0	0	0	1.09	0.99
36	M	64	na	hpa	3	0	0	1 09	1.01
37	M	36	TP	hpa	5	0	0	1 22*	0 96
38	M	68	na	hpa	2	0	0	1 13	1 04
39	M	67	na	hpa	6	0	0	1.04	0.99
40	M	60	OP BG	hpa, hps	1	0	0	1.04	0 98

F = frontal, T = temporal, P = parietal, O = occipital, BG = basal ganglia; hpa = hemiparesis; hpl = hemiplegia, hps = hemianopia, assessed by confrontation testing, na = not available As described in the text, Clock distortion is an estimate of the percentage blank space on clock drawings, Target and Hand bias refer to the mean ratio of response times to targets in the left and right hemispace, and to the mean ratio of response times when the required hand movement was directed toward the left and right hemispace (values significantly different from 1 are marked by: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$).

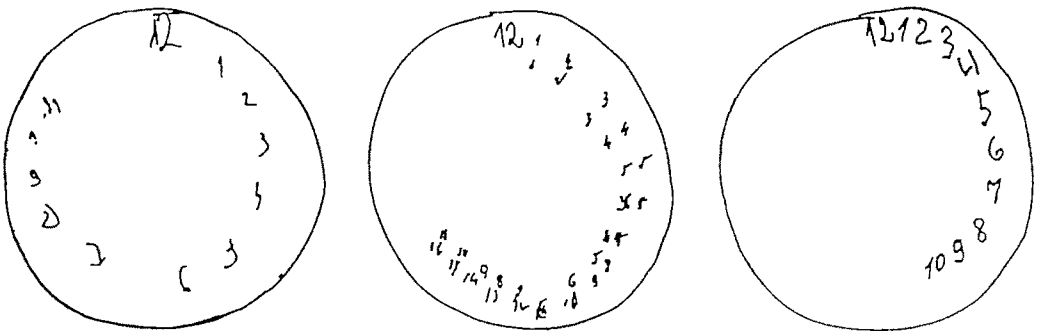

Fig 1. Samples of drawings produced by patients classified as Mild (*left*), Moderate (*middle*) and Severe Neglect (*right*) The corresponding Clock distortion percentages are 10%, 29% and 57%, respectively.

was first encoded as a series of angle readings, one for each number drawn, and measured clockwise from the vertical 12 o'clock position. These angles were then regressed against the *true* angle locations (i.e., 30°, 60°, . . ., 330°, for 1, 2, . . ., 11 o'clock), with the regression line constrained to pass through zero. The deviation of the regression slope below +1 is then a numerical estimate of clock compression; for example, a slope of 0.5 would indicate 50% compression, with the numbers filling out the right half of the clock face.

Apparatus

The experiment made use of 4 types of apparatus (*see* fig. 2).

Apparatus 1 consisted of a pen and a framed stationary panel (48×33 cm) which served as the display board

Apparatus 2 consisted of a stationary panel adapted from Apparatus 1 by suspending a pen over its centre. The pen was held in position with a curved plexiglass arch, which was itself rigidly attached to the back of the panel. A separate moveable panel (26×18 cm) with a handle (28.5 cm) served as the stimulus display board.

Apparatus 3 consisted of a larger framed stationary panel (72×48 cm) which served as the display board, and a smaller covering panel (50×33 cm) which had a central window (2×2 cm). The smaller panel could be freely moved over the surface of the display board by means of a handle (28 5 cm). The range of movement is restricted by the frame of the large panel whose dimensions ensure that the stimulus remains completely hidden (except for the window) as the covering panel is moved about.

Apparatus 4 was adapted from Apparatus 2 by removing the suspended pen from the stationary panel and then covering it with a new panel of the same size. This top panel had a central window (2×2 cm). The moveable display board (as in Apparatus 2) was then sandwiched between the two panels (and again moved by means of the handle, which now protruded from the 'sandwich').

Stimuli

The stimuli fell into 4 basic types

(1) *Dot.* A dot stimulus was, essentially, a spider-like dot on a white background.

(2) *Web.* A 'spider web' type design, in which an array of straight lines originated from a single point. This stimulus had the property that the location of the centre of the web could be inferred from an observation of any single detail of it, by noting the direction in which the radial lines of the web fan out.

(3) *Clock.* A clock with no hands.

(4) *Fish.* (a) 'swordfish', which was an outline with a blank interior; (b) 'goldfish', which had a textured (scaly) surface. The scales provided directional cues, like the radial lines in the Web stimulus.

Each type of stimulus had a distinguishing target detail which the subject was asked to find, or identify. For Dot and Web stimuli, the target was the spider; for the Clock stimuli, it was the location of a particular hour; for Fish stimuli it was the eye of the fish. The target for each stimulus type fell in 1 of 6 possible

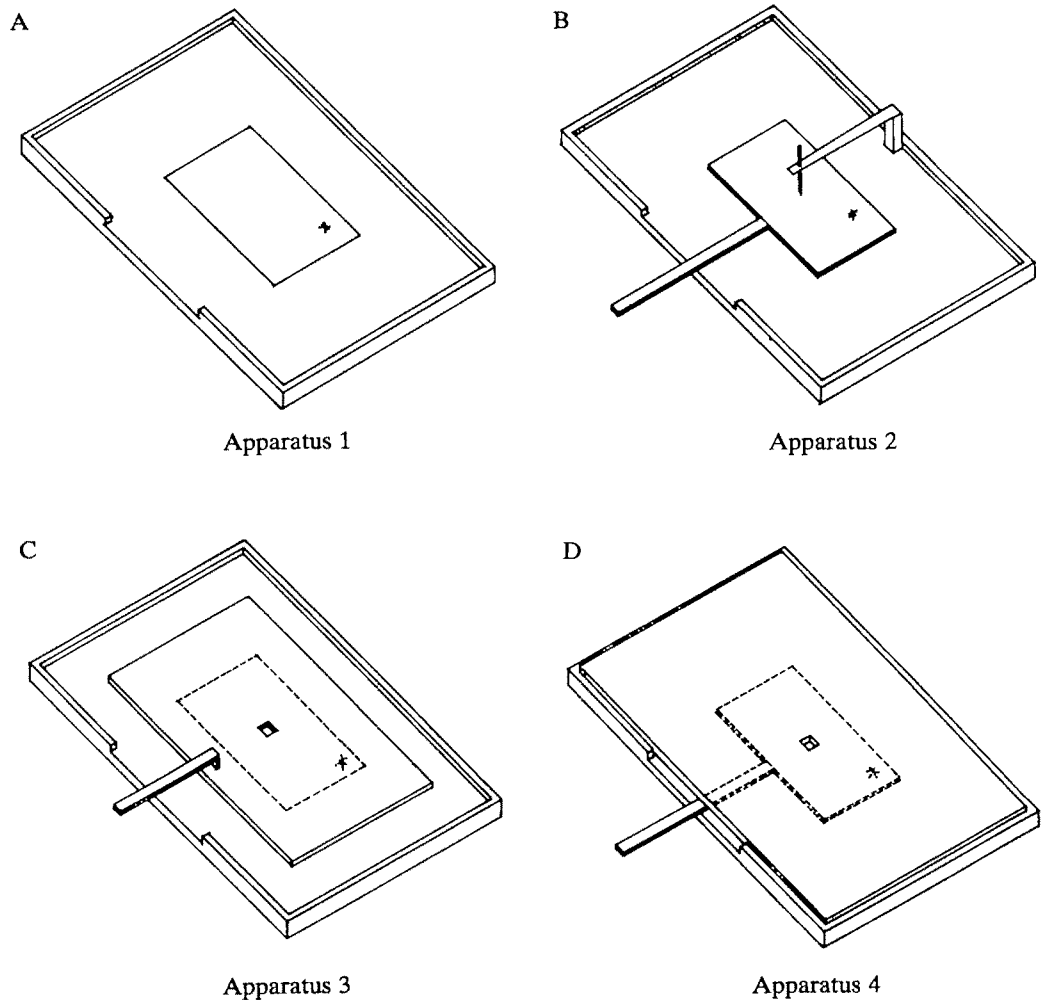

FIG. 2. The 4 types of apparatus used in the experiment. The corresponding conditions are identified as (1) Standard-visual (A), (2) Reversed-visual (B), (3) Standard-representational (C), (4) Reversed-representational (D).

locations, which corresponded to the 1, 3, 5, 7, 9 and 11 h locations on a clock face. Samples of stimuli with the target falling at the 1 o'clock location are presented in fig. 3.

Design

The experiment was divided into 4 blocks according to the type of stimulus used. Within each block the following conditions were presented in a fixed order for all subjects: (1) Standard-visual (Apparatus 1); (2) Reversed-visual (Apparatus 2); (3) Standard-representational (Apparatus 3); (4) Reversed-representational (Apparatus 4). This order ensured that subjects were familiar with each stimulus type before commencing the representational task.

Visual exploration refers to conditions in which the entire stimulus is continuously visible to the subject, while representational exploration refers to conditions in which a small fragment of the stimulus is shown through a window.

In order to control for the direction of hand movement, both visual and representational tasks were further

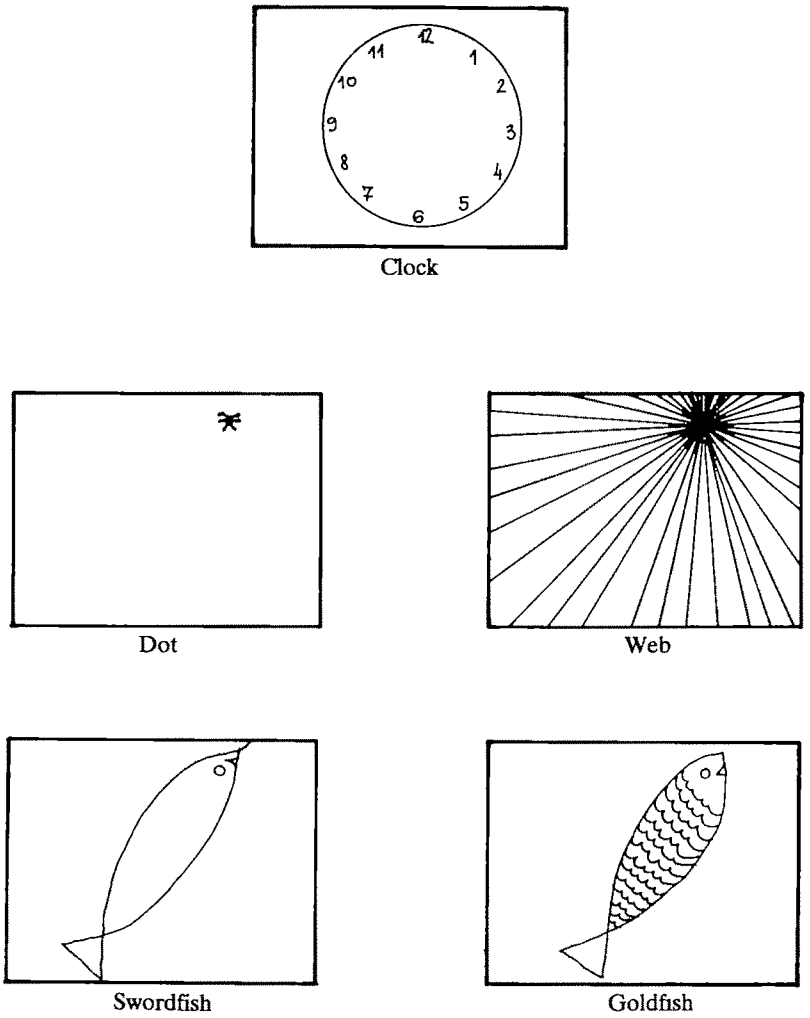

FIG 3 Samples of the 5 stimulus types with the target fully at the 1 o'clock position (with the clock, the subject would have been told that the target was 1 o'clock for that trial)

divided into 2 conditions: a standard condition, in which the direction of visual or representational exploration coincides with the direction of hand movement, and a reversed condition, in which visual or representational exploration in one direction requires hand movement in the opposite direction.

The subjects were presented with 2 versions of the representational task. In the first (preview) version, the stimulus was shown for 5 s, and then covered. As indicated in Table 2, only Dot and Swordfish stimuli were previewed. In the second version, subjects were shown samples of stimuli before the first exploration test, but were not given information about target location on any given trial.

Table 2 summarizes the number of presentations for all stimulus conditions. Since each basic pattern generates 6 distinct stimuli, and each pattern is presented twice, in the standard and reversed conditions, the total of 12 basic pattern presentations yields $12 \times 6 \times 2$, or 144 distinct stimulus presentations.

The stimulus condition combinations were constructed in order to vary the type of visual cue that they provided (1) The entire stimulus was continuously present: all visual exploration tasks (2) The stimulus

TABLE 2 SUMMARY OF DIFFERENT STIMULUS PRESENTATIONS

	Visual	*Representational*		
	. no. of repetitions	*Preview?*	*Directional cue?*	*No. of repetitions*
Dot	1	Yes	No	2
Web	1	No	Yes	2
Clock	1	No	No	2
Swordfish	1	Yes	No	1
Goldfish	1	No	Yes	1

The representational presentations are classified according to whether the subject is allowed to see the stimulus before the task (preview), and whether the stimulus provided a directional cue about target location.

was previewed and was presumably available from short-term visual memory: representational conditions with Dot and Swordfish stimuli. (3) The stimulus was not previewed but is available from long-term memory: representational conditions with the Clock stimulus. (4) The stimulus was not previewed but visual ('directing') cues were continuously available through the window: representational conditions with Web and Goldfish stimuli.

Procedure

The entire apparatus was placed on a table directly in front of the subject. In the Standard-visual condition the stimulus was placed on the centre of the board. The subject was told to position the pen in the centre of the stimulus display and on hearing a verbal signal, to touch the target as fast as possible. In this and all subsequent conditions, response time was measured by one experimenter while a second experimenter recorded the direction of initial movement. For each stimulus a time limit of 60 s was established; if the subject could not locate the stimulus within that interval, the trial was stopped and scored as 60 s.

In the Reversed-visual condition the stimulus was positioned on a display board directly in front of the subject and aligned so that the stationary pen touched the centre point. The subject was told that on hearing a verbal signal he should move the display board so that the target touches the stationary pen

In the Standard-representational condition with preview (*see* Table 2), the subjects were shown the stimulus and asked whether they saw the target. Subjects who failed to recognize the target at first were encouraged to search for it, with no time constraints. For some subjects with severe neglect this took as long as 2 min even though they were guided by the experimenter After the target was found, the stimulus was covered with a covering panel whose central window was positioned at the centre of the stimulus. As in the previous 2 conditions, the subjects were verbally instructed to move the top panel so that the target appears in the window. In the condition without preview (*see* Table 2), the subject was merely told to find the target (1) by following the visual cues, or (2) by imagining a particular hour location for the Clock stimulus.

In the Reversed-representational condition the procedure was the same as in the Standard-representational condition except that the subjects searched for the target by moving the display board beneath the stationary window. Because the subjects had to fixate at the same spatial locus (the window), attention and visual scanning were controlled in this condition.

The control subjects performed all the tasks in one session which lasted approximately 1 h. Most RH N− and RH N1 patients were tested in 2 sessions, although some completed all the tasks in 1 session. The number of sessions for each patient with moderate and severe neglect was dictated by their general condition, energy level, and other forms of therapy to which they were committed. Patients were screened before each session.

The first testing session took place as soon as the patient's condition permitted, in the first 3 days of hospitalization for most subjects, but if a patient was initially unable to cooperate it was delayed for 1 or even 2 wks.

Data analysis

ANOVA description

A preliminary examination of the data showed that the SDs of response times increased in rough proportion to the mean response time, across the various group-condition combinations. Consequently, individual response times were given a logarithmic transformation prior to analysis. The first 4 columns in Tables 3, 4, 5, 6 and 7 (*see* Appendix) report the mean response times by condition and target hemispace, for the control group and 4 patient groups. (Each reported mean is the antilog of the mean log response time, i.e., the geometric mean. An advantage of the geometric mean in this context is that it sharply attenuates the impact of the 60 s response times encoded when subjects failed to locate the target altogether.)

The remaining 3 columns in Tables 3–7 report the parameter estimates and significance levels of the repeated measure ANOVA, conducted separately for each subject group and each stimulus type, in the visual and representational conditions. The response times to the 6 target locations in the standard and reversed conditions served as the repeated measures, thus giving 12 measures altogether. The two main effects tested (within subjects), were the location of the target within the left or right stimulus hemispace, and the direction of required hand movement towards the left or right (physical) hemispace. Given this choice of main effects, the interaction effect measured the difference between standard and reversed condition response times. Asterisks label the effects that are significant (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$).

Since the analysis was performed with transformed response times, the parameter estimates of the effects appear as proportional rather than additive quantities. To obtain estimates of target location and hand movement coefficients for individual subjects, a separate ANOVA was performed on all response times provided by a single subject. The repeated measures were the same as in the group ANOVA; however, the response times drawn from the different conditions were treated as if they were produced by different subjects. The estimates for the target location and hand movement coefficients, as well as the significance levels, are given in the last two columns in Table 1.

RESULTS

Estimates of direction of hand movement effects

As indicated, the sixth column in Tables 3–7 (*see* Appendix) gives the ratios of response times when the required hand movement is to the left and to the right. Numbers greater than 1.00 indicate proportionately slower response times in the leftward direction (i.e., directional hypokinesia). A significant bias in favour of the right did not appear for any of the groups in any of the conditions. Indeed, in 4 instances, there was a significant hand movement bias in favour of the left (the Mild group, for Dot, Clock-Visual stimuli, and Moderate group, for Goldfish stimuli). It should be borne in mind, however, that 45 significant tests will produce 2–3 significant results (at the 0.05 level) through pure chance. The same conclusion is supported by individual subjects' estimates for the hand movement coefficient, shown in Table 1. There is no case with significantly longer response times in the leftward hand movement direction; 2 patients, however (Cases 6 and 12), show significantly longer response times in the rightward direction.

Estimates of target location effects

The fifth column in Tables 3–7 reports the target location effect, which is the mean ratio of response times to stimuli located in the left (7, 9 and 11 o'clock) and the right (1, 3 and 5 o'clock) hemispace. The prevailing pattern for each stimulus type is a progressive increase in left-right bias for the groups with greater neglect, as well as a greater degree of rightward bias in representational than in the visual tasks (the most

severe neglect group excepted). The results by each subject group can be summarized as follows.

Right hemisphere without neglect group (Table 4). In the visual condition the deficit ranges from 6% (n.s.) in the Web tasks to 9% ($P < 0.001$) in the Dot tasks. In the representational conditions, the deficit is generally larger (17−24%) except for Web (6%, n.s.) and Fish (9%, n.s.) stimuli. The difference between the visual and representational deficits is not significant, however.

Mild neglect group (Table 5). This group manifested the same pattern as the RH N− group but with a higher degree of bias, which ranged between 15% and 18% in the visual tasks and 27% to 50% in representational tasks. Again, the difference in bias between the visual and representational tasks is not significant, except for the Dot stimuli, where the difference between 1.50 and 1.18 is significant at the 0.05 level.

Moderate neglect group (Table 6). Except for the clock stimuli, this group shows an exaggerated form of the pattern found with the RH N− and RH N1 subjects. The left-right bias is significantly greater in the representational tasks: 2.62 vs 1.21 ($P < 0.01$) for Dot stimuli; 1.84 vs 1.41 ($P < 0.05$) for Web stimuli; 1.90 vs 1.41 ($P < 0.05$) for Swordfish stimuli; and 2.33 vs 1.41 ($P < 0.05$) for the Goldfish stimuli. The single exception occurs with Clock stimuli, when the degree of bias is approximately equal for representational and visual tasks: 2.18 vs 2.38. A possible explanation for this discrepancy will be introduced in the Discussion section.

Severe neglect group (Table 7). With this group, the bias pattern reverses (for Dot, Web and Clock stimuli), in that it is now the visual tasks that exhibit a greater target location effect (the difference is not significant, however, for any stimulus type). The same reversal was already present in the RH N2 group in the Clock stimuli. The reduced degree of bias in the representational tasks is due to their relatively poor performance with right as well as left-sided targets.

Estimates of condition effects

The rightmost column in Tables 3−7 presents the mean ratio of response times in reversed and standard conditions. Although the reversed condition is more difficult, the degree of difficulty does not have a simple relationship to neglect. The impact of the reversed condition is generally greatest for the RH N2 group, followed by the RH N1 and Control groups. The group with most severe neglect, RH N3, did not show a significant condition effect except with visual Clock stimuli.

DISCUSSION

Hand movement bias

Two previous studies, by Bisiach *et al.* (1985) and Butter *et al.* (1988), have investigated both sensory and motor aspects of neglect on the same subjects. In order to disentangle the input and output aspects of unilateral neglect, Bisiach *et al.* (1985) asked 16 right brain-damaged patients with neglect to press a key with their right hand in response to left and right stimuli, in crossed and uncrossed conditions. The apparatus consisted of a vertical panel which had 8 LEDs, 4 in each hemifield, aligned in 2 rows. When activated, the LEDs in the upper row emitted a green light, those in the lower a red light. In the left and right lower corners of the panel, just below the lateral LEDs, were

4 square response keys aligned in 2 rows: 1 green (above) and 1 red (below) on either side. The subjects started each trial by pressing a trigger button which lay in the centre of the linear edge of the panel. The button triggered a 200 ms flash from a LED. Two response keys of different colour on either side were lit simultaneously with the flashing of a diode. The subjects were instructed to press the lit key corresponding to the colour flashed by the diode irrespective of the side.

The analysis of mean correct response and mean omission and commission errors showed a decrement in left response, irrespective of the side of stimulation, which may be interpreted as evidence for hypokinesia. It is perhaps significant that the procedure used by Bisiach *et al.* requires a discrete response to a key in the contralesional space, while the reversed visual condition in the present study requires a contralesional hand movement that brings an ipsilesional target into the centre of the display. If intention to act presupposes representation (Kinsbourne, 1987), then the first procedure makes it necessary for the subject to imagine, that is, represent the response key location in the left side of space.

Butter *et al.* used a similar paradigm: they performed crossed and uncrossed response tests in order to distinguish between sensory and motor neglect. In the uncrossed response test the subject was instructed to move his eyes from a central point to the examiner's left or right index finger when one of the fingers moved. In the crossed response test, the subject was instructed to move his eyes to the side opposite to it and toward the index finger that was not moving. Directional motor neglect was defined as the failure to move the eyes away from the stimulus and into contralateral hemispace when the stimulus was presented ipsilateral to the lesion in the crossed-response test. The authors found that their patient's directional motor neglect was somewhat more severe than his contralateral sensory inattention. It is possible, however, that this is due to a specific difficulty in disengaging attention from ipsilateral stimuli (Riddoch and Humphreys, 1983; Posner *et al.*, 1984, 1987).

Related findings on line bisection

Most recently a number of studies have tried to isolate a purely motor contribution to the rightward displacement error in line bisection tasks (Bisiach *et al.*, 1990; Coslett *et al.*, 1990; Reuter-Lorenz and Posner, 1990). In a direct attack on this problem, Bisiach *et al.* constructed a bisection apparatus that permitted simple mechanical dissociation of direction of hand movement and visual attention. Their apparatus consisted of a string shaped into a continuous loop around 2 pulleys, spread 75 cm apart, and aligned in parallel to a 60 cm bisection line. A triangular pointer affixed to the far side of the string loop served as the marker for the bisection task. The subjects could bisect the line in one of two ways—either by grasping the pointer and aligning it to the subjective line midpoint, in which case the direction of hand and pointer motion coincide (the *congruent* condition), or by grasping and sliding the near side of the string loop, in which case the direction of hand and pointer movement are exactly reversed (the *noncongruent* condition).

In the absence of any directional hypokinesia, the two conditions should produce equivalent errors; conversely, if the bisection errors are produced *exclusively* by directional hypokinesia, then the errors in the noncongruent condition should be of the same absolute magnitude but in the opposite (i.e., leftward) direction. Notably, all but

2 of the subjects made smaller errors in the noncongruent condition, and for 6 of these subjects the difference was significant at the individual level.

Using a video camera, Coslett *et al.* (1990) had subjects monitor their own bisection performance on a screen, with the line stimulus concealed from direct sight. The hemispatial location of the stimulus and the monitor were then independently varied, in a 2×2 design. Two out of 4 subjects revealed a pattern of significant rightward error when bisecting in the left (physical) hemispace, and essentially no error when bisecting in the right hemispace, in line with the directional hypokinesia hypothesis.

Reuter-Lorenz and Posner (1990) constructed a 'passive' bisection task, in which the experimenter moved the pen along the bisection line and the patient announced when the pen crossed the midpoint. The magnitude of the bisection error was strongly influenced by the direction of motion: when the pen moved from right to left, the rightward error was comparable with that found in the standard manual bisection procedure; when the pen moved from left to right, however, the bisection error was essentially eliminated. The bearing of these results on directional hypokinesia is unclear; they do contribute, however, to the impression that bisection accuracy is a somewhat volatile behavioural measure, sensitive to the direction of visual scanning, as well as to cues placed at either line endpoint (Riddoch and Humphreys, 1983).

The first 2 of these 3 studies found greater evidence of hypokinesia in patients with lesions extending into the frontal lobe, which would be consistent with the conjectures of Watson *et al.* (1978) and Mesulam (1981) about the different varieties of neglect specific to anterior and posterior lesions. While we cannot completely rule out the possibility that a difference in patient populations underlies the discrepant findings of the present study, it is not a likely explanation, given the large pool of patients used, and given the fact that patients with frontal lesions do not as a group have greater hand bias coefficients (*see* Table 1).

In thinking about the divergent conclusions of the present study, it should be kept in mind that line bisection and the spatial exploration task impose two quite dissimilar behavioural definitions on the concept of directional hypokinesia. In the bisection task, hypokinesia affects the misjudgement of linear extension along the horizontal axis, exaggerating or attenuating the rightward bias depending on whether the required movement is to the left or to the right. In the present task, hypokinesia would be revealed by a hesitation in moving the arm leftward, or, in severe cases, by a complete failure to execute a leftward movement. It is possible, in principle, that the bisection task does not well discriminate a difficulty in *initiating* hand movement toward the left, with a subjective *overestimation* of leftward limb extension, which alone could produce the hypokinetic error patterns if the subjects are using limb extension as a cue.

Such an overestimation may be related to the misreaching behaviour observed in optic ataxia patients following posterior parietal lesions (Garcin *et al.*, 1967; Levine *et al.*, 1978). Indeed, a functional connection between spatial neglect and optic ataxia has already been advanced by Jeannerod and his associates (Ventre *et al.*, 1984; Jeannerod, 1988). Like the orienting deficits in spatial neglect, the impaired reaching behaviour in optic ataxia is characterized by a constant directional error towards the lesioned side. The authors postulate that both of these biases may result from a displacement of the egocentric coordinates (where the egocentric coordinates are conceived as an internal representation of body midline which serves as a reference for movements).

Finally, it is worth noting that the absence of directional hypokinesia in the present study does not necessarily rule out the possibility of an impairment of motor processes at the level of covert (attentional disengagement) and overt (visual scanning) stages, as proposed for the premotor theory of spatial attention by Rizzolatti *et al.* (1987, 1988). According to this theory, a stimulus endowed with attentional properties triggers neurons that elicit a motor plan, which, in turn, activates the representation of space where the plan will be transformed into action. To accommodate the present findings, however, the theory would need to give an explicit account of premotor neuron activity in situations where action and the spatial consequences of action are mechanically reversed.

Target location effects

Considering jointly the target location biases for the 4 RH groups (Tables 4–7), it is evident that the bias increases in proportion to the severity of neglect, as measured by the Clock drawing tasks. Along this continuum, however, there is a clear break between the performance of the Moderate (RH N2) and Severe neglect (RH N3) groups. Only patients with severe neglect have a strong target location effect in the simpler visual tasks (Dot and Web). This is not surprising, given that only the severe group contained patients who manifested strong contralateral neglect on the 2 cancellation tests.

In accord with their relatively good performance on the cancellation tests, patients with moderate neglect have relatively little difficulty in finding visual 'spider' targets in either hemispace, with or without the benefit of a web. Nevertheless, these patients reveal 3 specific left hemispace deficits in the present study (the same deficits are also found, to a lesser degree, in the mild neglect group).

(1) *Short-term visual memory deficit.* In representational conditions with preview (Dot and Swordfish), patients are asked to search for a concealed target that they themselves had identified visually a few seconds earlier. This operation releases a strong hemispatial asymmetry (*see* Table 6). The contrast between visual and representational conditions with Dot stimuli is especially striking: in the visual search condition, RH N2 subjects generally needed between 0.8 and 1.5 s to find targets in either hemispace; hiding the target with the covering panel is clearly disruptive for targets in the left hemispace, with response times climbing to between 4.5 and 8.2 s, but produces only a modest increase for targets in the right hemispace.

(2) *Directional cue deficit.* A similar pattern is evident with Web and Goldfish stimuli. The slight bias in the visual conditions is amplified by forcing the subject to rely on directional cues, in the representational conditions.

(3) *Clock search deficit.* Visual identification of the Clock targets also releases a hemispatial asymmetry. Locating left targets on the clock face, for example, takes 4.79 s on average, while only 1.26 s are needed to locate a simple dot in that hemispace. This resembles a level of task difficulty effect, suggested by Pillon (1981), Caplan (1985), and most recently by Rapcsak *et al.* (1989) who found that the presence of distractors in a cancellation task increases the relative proportion of omissions on the left side.

In summary, for patients with moderate neglect, the hemispatial target location bias is specially elicited by tasks that require the subject to represent a target as falling to the left of a central fixation point. All representational tasks meet this criterion, as does the one visual task—clock search—in which the patient must essentially superimpose a representation onto the visual display.

The absence of a large target location effect in the remaining visual tasks creates an apparent puzzle for attentional explanations of neglect, at least if the attentional bias is understood as a magnetic attraction, exerted by incoming sensory stimulation from the right side (Kinsbourne, 1987; Posner *et al.*, 1987). By placing the covering board over the spider web display, for example, the subject is shielded from ipsilateral stimulation, but is still left with clear directional (and centrally positioned) information about where the target lies. The absence of ipsilateral distractions during the search should reduce the asymmetry between performance to the left and right side, yet it is precisely this representational version of the task that produces a strong elevation of response times to targets in the left hemispace.

Turning now to the Severe neglect group, we find the same constellation of deficits for targets in the left hemispace (indeed, this group has the largest target location effect in every task; Tables 4–7). Significantly, however, the RH N3 group is also distinguished by its relatively poor performance with right hemispace targets in representational tasks. The extension of the deficit to the right hemispace is most pronounced in representational conditions without preview, where the subjects cannot rely on a previously visualized target location, but instead have to infer the location from a stimulus detail (Web and Goldfish) or from knowledge of the global stimulus structure (Clock).

While at first glance this bilateral deficiency might be attributed to the increased demands of the tasks (Heilman *et al.*, 1987), a detailed examination of clock search patterns in the representational condition (Mijović, 1990) showed that neglect patients' conjectures about target location are broadly consistent with the distortions exhibited by their freehand clock drawings. Judging by the direction of the initial search movement, most or all of the numbers are located in the right hemispace and shifted counter-clockwise relative to the correct position. This was true for both standard and reversed conditions, that is, irrespective of the direction of hand movement.

The fact that RH N3 patients are not helped much by the directional cues in the spider web design suggests a more general—and bilateral—disorder in their representational schema. They do not readily grasp the direction of convergence of two line fragments, even when the lines converge to a point in the right hemispace. Likewise, they are not sure of the exact location of *right* side clock targets, taking on average 10.83 s to find them in the representational conditions. Whatever the exact nature of the underlying disorder, then it is sufficiently severe to disrupt the representation of parallel, orthogonal, and convergent lines.

Conclusions

The present study failed to detect directional hypokinesia in a spatial exploration task, irrespective of the severity of clinically assessed neglect, and lesion site. It appears, therefore, that neglect patients are perfectly able to execute movements to the left, provided they wish to do so. What they are evidently reluctant to do, or resist altogether in this procedure, is to slide the hand to the right, and so bring the left portion of the display board into view under the window. In the absence of any compelling alternative explanation, it seems most natural to attribute the rightward search pattern to a genuine belief that the target lies in the right hemispace.

Such an interpretation of the results is not incompatible with the hypothesis of Bisiach *et al.* (1978, 1979) that the left portion of the representational map is missing, which

may in turn cause parts of information directed to the left side of the map to be displaced to the right half. Indeed, Bisiach *et al.* (1981) have also noted that patients often transferred details from the left to the right side of the Cathedral ('displacements from left to right were almost three times as frequent as displacements in the opposite direction' (p. 550)). Commenting upon these mislocations, the authors suggest that 'such errors may in part be interpreted as indicating a concurrent, though unrelated, disorder of topographical memory' (p. 550). However, they also advance the possibility that 'in some instances, the mere transposition of details from the relevant to the opposite side might have had a different causation, more strictly related to contralateral neglect' (p. 550).

Similar displacements of details have also been reported in a number of drawings other than a clock, such as a bicycle (Riddoch and Humphreys, 1983), daisy (Jeannerod, 1985), drawing of the floor plan of a patient's house (Ratcliff, 1982), localizations of cities and states on a geographical map (Benton *et al.*, 1974), as well as in copies of crosses (Gainotti, 1968). Indeed, the tendency to mislocate a contralesional stimulus as ipsilateral (allaesthesia) is not uncommon in neglect (*see* Brain, 1941; Bender *et al.*, 1949). More recently, allaesthetic mislocations were also observed in olfactory (Bellas *et al.*, 1988), auditory (Bisiach *et al.*, 1984), and manual pointing tasks (Joanette and Brouchon, 1984).

Subjects in the present study gave ample evidence of a tendency to search for left hemispace targets in the right half of the concealed display board (Mijović, 1990). Should this be viewed as an instance of *visuo-representational allaesthesia*, in which the act of imagining a stimulus detail automatically displaces it towards the right representational hemispace? Such a formulation might account for two otherwise unexplained aspects of the present data, namely the greater severity of left neglect in representational rather than visual tasks, and the fact that subject groups with more severe left neglect reveal a bilateral weakness in representational performance.

Note, first, that allaesthesic dislocations can occur only if the representation of the right hemispace is 'receptive' to the intruding detail. Any operation that reduces interference from concurrent visual stimulation (such as covering the stimulus with a blank panel) should make rightward displacements more frequent because the subject is free to superimpose the imagined details on a neutral background. When the entire stimulus is present (in visual tasks), however, there is no room for the new detail, unless the perceptual system can override the incoming visual stimulation and squeeze the detail in.

Even in representational tasks, however, the absorption of left-sided details presupposes a damaged or 'pliant' representation of the right hemispace. A structurally intact representation of the right half of the clock face, for instance, should not be able to accommodate the numbers displaced from the left side, because all available positions are already occupied. If, however, the representation of the right half has lost its structural integrity—if it is no longer organized in analogue of Euclidian space—then the door is left open for the distortions and displacements that are frequently found in the drawings of neglect patients (Benton *et al.*, 1974; Ratcliff, 1982; Riddoch and Humphreys, 1983; Jeannerod, 1985), as well as for a denial of illness, because any imagined item is efficiently placed somewhere in the ipsilateral hemispace. In this view, the degree of damage to ipsilateral representational structures places a ceiling on the severity of neglect symptomatology: in the limiting case when the representation of the right side of space is perfect, there should be no left neglect, only left hemianopia.

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APPENDIX

Mean response times and ANOVA parameter estimates, for the 5 subject groups. Target location bias is the ratio of response times to targets in the left and right hemispace, hand movement bias is the ratio of response times when the required hand movement was directed toward the left and right hemispace, condition effect is the ratio of response times in the standard and reversed conditions (values significantly different from one are marked by * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$)

TABLE 3 CONTROL GROUP

Condition	*Standard*		*Reversed*		*Target location bias*	*Hand movement bias*	*Condition effect*
Target location	*Left*	*Right*	*Left*	*Right*			
Dot visual	0.65	0 64	0.94	0.96	1 00	1.02	1.47***
Dot representational	1.17	1.15	1 40	1.38	1 01	1.00	1 20**
Web visual	0.68	0 67	0.94	0 96	0 99	1.02	1.41***
Web representational	1 44	1.41	1.47	1.47	1 01	1 01	1.03
Clock visual	1.22	1.22	1 57	1.60	0.99	1.01	1 30***
Clock representational	2.45	2.36	3 16	3.04	1.04	1 00	1.29*
Fish visual	0 67	0.67	0.98	0.89	1 05	0 96	1 40***
Swordfish	1.20	1 18	1.75	1 75	1 01	1.01	1 47***
Goldfish	3 33	3 52	4.18	3.58	1 05	0 90	1 3

TABLE 4. RH PATIENTS WITHOUT NEGLECT

Condition	*Standard*		*Reversed*		*Target location bias*	*Hand movement bias*	*Condition effect*
Target location	*Left*	*Right*	*Left*	*Right*			
Dot visual	0 70	0.65	0 88	0.80	1 09***	0 99	1.24***
Dot representational	1 27	1.15	1.53	1.20	1.19*	0 93	1 12
Web visual	0 66	0.60	0.81	0.79	1 06	1 03	1.27***
Web representational	1.31	1 32	1.38	1.23	1 06	0 94	0.99
Clock visual	1.21	1.03	1.29	1.28	1 09**	1.08	1 15*
Clock representational	2.46	2.02	2.67	2 38	1.17**	1.04	1.13
Fish visual	0 68	0.60	0.77	0 75	1.08*	1 05	1.19**
Swordfish	1 05	0.92	1.18	1 14	1.09	1 05	1.18**
Goldfish	3 26	2.66	3.26	2 60	1 24*	0 99	0 99

TABLE 5 MILD NEGLECT GROUP

Condition	*Standard*		*Reversed*		*Target location bias*	*Hand movement bias*	*Condition effect*
Target location	*Left*	*Right*	*Left*	*Right*			
Dot visual	0.85	0.77	1.53	1.22	1.18**	0 94*	1 69***
Dot representational	2.30	1.92	5 04	2 69	1 5**	0.80*	1 75***
Web visual	3.32	3.05	6 22	5 04	1 16***	0.94	1.76***
Web representational	3.33	2.57	3 27	2 63	1 27***	1.02	1.00
Clock visual	1.65	1 53	2.43	1 95	1 16**	0.93*	1.37***
Clock representational	4 58	3 37	5.49	4 54	1 28***	1.06	1.27***
Fish visual	0 96	0 84	1.50	1 30	1 15***	1.00	1.56***
Swordfish	2 58	1.86	2 90	2 35	1 31**	1 06	1.19*
Goldfish	7 88	6.17	6 85	5 26	1.29**	0.99	0.86

TABLE 6 MODERATE NEGLECT GROUP

Condition	*Standard*		*Reversed*		*Target location bias*	*Hand movement bias*	*Condition effect*
Target location	*Left*	*Right*	*Left*	*Right*			
Dot visual	1.04	0.86	1 52	1 25	1.21*	1 00	1 46**
Dot representational	4 54	1 90	8 12	2 82	2 62**	0 91	1.63*
Web visual	1 10	0 78	1.82	1 29	1 41*	1 00	1 66**
Web representational	4 40	2.23	6.20	3 61	1.84**	1.07	1.51*
Clock visual	4.46	1.99	5 17	2.04	2 38***	0.94	1 09
Clock representational	7 68	3.92	14.51	5 99	2.18**	0.90	1.70***
Fish visual	1 01	0.91	2 08	1.17	1 41*	0 79	1.63**
Swordfish	2.53	1 64	6.37	2 71	1 90***	0.81	2 04**
Goldfish	12.42	6 27	22 36	8.16	2 33**	0 85**	0.53**

TABLE 7 SEVERE NEGLECT GROUP

Condition	*Standard*		*Reversed*		*Target location bias*	*Hand movement bias*	*Condition effect*
Target location	*Left*	*Right*	*Left*	*Right*			
Dot visual	7 38	1 01	8.45	1.78	5 90**	1.24	1 42
Dot representational	9.15	3.59	15 33	4 14	3.07**	0 83	1 39
Web visual	4.48	1.05	6.10	1 49	4.17*	1 02	1.39
Web representational	22.41	8.08	19.79	6 30	2 95**	0.94	0.83
Clock visual	7 79	1 93	8 68	3.20	3.31**	1 22	1 36*
Clock representational	24.62	12 02	33.58	9.72	2 66***	0 77	1 05
Fish visual	2.42	1.03	3 39	1 42	2.37	0 99	1.39
Swordfish	7.17	3.33	8.07	2 90	2 45*	0 88	0.99
Goldfish	28 92	8.48	33 10	6.68	4 11**	0 83	0 95

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CEREBRAL POTENTIALS EVOKED BY PAINFUL LASER STIMULI IN PATIENTS WITH SYRINGOMYELIA

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SUMMARY

Brief cutaneous heat stimuli generated by a CO_2 laser were used to elicit late somatosensory evoked cerebral potentials (SEPc) in 10 patients with syringomyelia. For comparison, early and late cerebral potentials in response to electrical nerve stimuli (SEPn) were recorded in the same session. In 8 patients with localized impairment of pain and temperature sensitivity we found complete absence of SEPc after stimulation of the affected area; in another patient with similar sensory deficits, the SEPc was grossly attenuated and delayed. In 1 patient with intact pain sensitivity but absent temperature sensitivity, a well defined SEPc could be recorded. Both early cortical SEPn and late SEPn in response to conventional nerve stimuli were normal in all patients and thus did not differentiate control and affected areas. These data indicate that alteration of SEPc correlates with altered pain sensitivity in patients with a circumscribed spinal lesion. SEPc may thus be used as a neurophysiological test in the assessment of hypalgesic dermatomes.

INTRODUCTION

The most common symptom in syringomyelia is the selective loss of pain and temperature sensitivity with intact tactile sensitivity (e.g., Schliep, 1978). If a patient exhibits these symptoms, the differential diagnosis has become straightforward with the current magnetic resonance imaging techniques, which allow a precise determination of the presence and the extent of a spinal cavity (Kokmen *et al.*, 1985; Tashiro *et al.*, 1987). These methods, however, do not assess the functional significance of the syrinx or its prognosis. For this purpose, objective methods are needed that can corroborate the subjective clinical symptoms of syringomyelia.

Standard nerve conduction or somatosensory evoked potential studies do not permit the investigation of pain and temperature pathways (e.g., Desmedt, 1988). As a consequence, no unique pattern of clinical neurophysiological findings has emerged in spite of multiple studies in patients with syringomyelia (Nakanishi *et al.*, 1974; Mastaglia *et al.*, 1978; Small *et al.*, 1978; Green and McLeod, 1979; Stöhr *et al.*, 1982; Stockard and Iragui, 1984; Anderson *et al.*, 1986). On the other hand, late components of somatosensory evoked potentials are widely used as neurophysiological correlates of pain sensitivity, especially in pharmacological studies on analgesic efficacy (for review, *see* Bromm, 1989). In one of these experimental pain models, brief radiant heat stimuli

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are generated by a CO_2 laser stimulator (Mor and Carmon, 1975; Biehl *et al.*, 1984; Pertovaara *et al.*, 1988; Kakigi *et al.*, 1989; Gibson *et al.*, 1991). These radiant heat pulses of a few milliseconds duration specifically activate superficial Aδ and C nociceptors (Bromm and Treede, 1984).

The somatosensory evoked cerebral potentials after cutaneous heat stimuli (SEPc) consist of late components with about 200–400 ms peak latencies (Carmon *et al.*, 1978) and ultralate components with about 1200 ms peak latency (Bromm *et al.*, 1983). Both late and ultralate SEPc have maximum amplitudes at the vertex (Treede *et al.*, 1988*a*; Treede and Bromm, 1988). With preferential nerve blocks it was shown that the late SEPc are mediated by Aδ fibres and the ultralate SEPc by C fibres (Bromm *et al.*, 1983; Bromm and Treede, 1987). Cerebral potentials evoked by painful radiant heat stimuli thus provide a noninvasive tool to study Aδ and C fibre mediated pain sensitivity in humans.

Late SEPc have recently been found to be significantly altered in patients with dissociated sensory loss (Zangemeister *et al.*, 1987; Bromm *et al.*, 1991). The aim of the present paper was to use these techniques to document a neurophysiological correlate of the impairment of pain and temperature sensitivity in spinal lesions due to syringomyelia. Detailed sensory testing was performed for the same dermatomes as the laser-evoked SEPc; for comparison late evoked potentials in response to electrical nerve stimuli (SEPn) and standard early SEPn were also recorded.

METHODS

The study was performed on 10 patients with radiologically confirmed syringomyelia (8 men, 2 women, mean age 47 y). Patients gave written informed consent. They were comfortably seated in a noise reduced chamber (room temperature 24° C). All testing was completed within one session of about 4 h duration.

Table 1 summarizes the data from the medical records of these patients. In all patients, pain or temperature sensitivity or both were impaired. In 8 patients at least one upper limb was affected, and in 6 patients at least one lower. All patients had motor signs (reduced reflexes, atrophy and loss of strength at upper limbs and/or enhanced reflexes at lower limbs). Five patients had signs of autonomic dysfunction (swelling, altered sweating and skin atrophy). In 6 cases, spontaneous pain of burning character was reported in the affected areas. The extent of the lesions was quantified by magnetic resonance imaging. All lesions involved

TABLE 1 CLINICAL DATA FROM THE MEDICAL RECORDS OF 10 PATIENTS WITH SYRINGOMYELIA

						Location of sensory symptoms				
						Pain/temperature				
Case	*Age (y)*	*Sex*	*Time from onset (y)*	*Possible pathogenetic factors*	*Extent of syrinx*	*Affected levels*	*Affected side*	*Tactile/ proprioception*	*Signs of autonomic dysfunction*	*Ongoing pain*
1	47	M	20	Trauma	C1–C3	V1–T9	L	Not affected	Yes	Yes
2	52	M	9	Chiari I	Obex–conus	All	L>R	Same as pain	Yes	Yes
3	58	F	1	Unknown	C3–T1	C2–T5	R>L	Not affected	No	Yes
4	50	F	24	Cerebellar cyst	C2–T5	V2–T4	L=R	Not affected	No	No
5	18	M	8	Tumour	C3–C4	Below C3	L>R	Not affected	No	No
6	45	M	3	Chiari I	C6–T6	C5–T4	L	Same as pain	Yes	Yes
7	43	M	13	Trauma	C2–T12	All	R>L	Both lower limbs	Yes	No
8	40	M	14	Trauma, spina bifida	C1–T4	Below T3	L	Not affected	No	Yes
9	65	M	23	Dysraphic state	Obex–T1	All	R>L	Same as pain	Yes	Yes
10	49	M	20	Spina bifida	C1–conus	All	R>L	L body side	No	No

the cervical region. The following conditions that have been linked to the pathogenesis of syringomyelia were found: dysraphic conditions (n = 5), trauma (n = 3), intramedullary tumour (n = 1).

Sensory testing

At the beginning of the session, semiquantitative sensory testing was performed distally on all four limbs. Since no absolute normative values have been established for the clinical application of laser-evoked potentials, the study was designed to let each patient be his/her own control. For this purpose, we selected two test sites in each patient: the skin area that displayed the most pronounced sensory symptoms (affected site), and one site, which was either completely unaffected or least affected by the sensory change (control site).

Results of the sensory testing were condensed into 3 summary scores (*see* Bromm *et al.*, 1991). (1) M score: sum of points for vibration, joint position, touch and pressure; (2) T score: sum of points for warm and cold tests; (3) P score: sum of points for single pin prick, sharp/blunt discrimination and hair-pulling. Vibration sense was tested with a 128 Hz tuning fork. Joint position sense was tested with passive finger and toe movements. Touch and pressure sense were tested with cotton wool and calibrated von Frey hairs (10−160 mN), respectively. Temperature sensitivity was investigated by brief contact with water-filled test-tubes that delivered skin/probe interface temperatures of 37° C for warm and 22° C for cold testing. Pain sensitivity was tested with pin pricks, strong pulling of a single hair and with a discrimination task between the sharp and blunt end of a safety pin. Each individual test was scored on a 3-point scale: normal (2 points), disturbed (1 point), or absent (0 points). The 3 summary scores were normalized to percentages of the maximum possible value, with 100% indicating normal sensitivity and 0% indicating complete sensory loss for that modality.

Evoked potential recordings

For late components of the somatosensory evoked potential in response to cutaneous heat stimuli (SEPc) and to electrical nerve stimuli (SEPn), the EEG was recorded with Ag/AgCl electrodes from 5 leads (Fz, C3, Cz, C4, Pz, linked earlobes reference, bandpass 0.1−70 Hz) with eyes closed. For artefact control, the vertical component of the EOG was recorded from supraorbital and infraorbital electrodes with the same bandpass. The skin under the electrodes was scratched with an abrasive paste; this virtually eliminated skin potential artefacts. The interelectrode impedances were less than 5 kΩ (12 Hz).

Cutaneous heat stimuli were generated by a CO_2 laser stimulator (10.6 μm wavelength, 5−60 W output power, 5 mm beam diameter, 20 ms duration; for details, *see* Biehl *et al.*, 1984). They were applied to the dorsal hairy skin of either the foot or the hand. Stimulus intensities were 15 and 20 W, which is above pain threshold in healthy volunteers (10 ± 4 W, mean ± SD). These heat pulses are harmless; in some patients, several of the stimuli caused punctate erythemata (slight superficial burns), which vanished within 3−5 days without any residue (*see* Biehl *et al.*, 1984). Between successive stimuli, the laser beam was slightly moved using 2 orthogonal mirrors in order to minimize effects of nociceptor fatigue or sensitization (*see* Campbell and Meyer, 1983).

Electrical nerve stimuli (0.2 ms duration, constant current) were applied with saline-soaked pads to the median nerve at the wrist or to the tibial nerve at the ankle. Stimulus intensity was adjusted to be the sum of the individual sensory and motor thresholds.

Two stimulus blocks were given to each test site in the following sequence: control-affected-affected-control. This sequence was chosen in order to balance for possible habituation effects (*see* Bromm *et al.*, 1991). Each stimulus block lasted 20 min and included 20 laser stimuli of 20 W, 20 laser stimuli of 15 W, and 20 electrical nerve stimuli in randomized order and with randomized intervals (10−30 s). Between stimulus blocks there was a 5−10 min break. For each stimulus, a peristimulus EEG segment with 1 s before and 3.5 s after stimulus onset was digitized (200 Hz sampling rate) and stored on disc. EEG segments were averaged off-line according to stimulus modality, intensity and site.

At the end of each experiment, early cortical SEP components were obtained with electrical nerve stimulation. They were recorded from electrode positions over the respective somatosensory projection area (e.g., 2 cm posterior of C3 for right median nerve stimuli) versus a frontal reference (Fz). These recordings were averaged on-line (bandpass 10−1000 Hz, sampling rate 3000 Hz, 256 artefact-free trials, interstimulus interval 0.5 s).

RESULTS

Sensory testing confirmed that sensory loss in syringomyelia may affect multiple dermatomes on both sides of the body. Table 2 shows the normalized test results for the most affected area (affected site for SEP testing) and for the least affected area (control). In 5 patients the sensory loss was sufficiently localized to one side of the body so that the two test sites could be chosen within the same dermatomal level. In the other 5 patients, sensory loss was equal on both body sides, and we therefore compared upper and lower limbs. In 1 patient (Case 8), the limbs were not affected by sensory impairment. The T10 dermatome on the anterior abdominal wall was therefore stimulated with the CO_2 laser. In this case the median nerves were used for electrical stimulation.

TABLE 2. SENSORY TESTING RESULTS

Case	*Control test site*	*M score (%)*	*T score (%)*	*P score (%)*	*Pain threshold (W)*	*Affected test site*	*M score (%)*	*T score (%)*	*P score (%)*	*Pain threshold (W)*
1	RH	100	100	100	11 0	LH	87	0	17	Not tested
2	LF	50	100	83	9 0	LH	62	0	50	21 0
3	RF	100	100	100	19 5	RH	87	75	67	26 5
4	LF	75	100	100	7 0	LH	100	0	17	24 0
5	LH	100	100	100	7 0	LF	100	0	100	12 0
6	RH	100	100	100	16 0	LH	50	0	17	31 0
7	LH	100	50	50	11 0	RH	100	50	33	31 0
8	RT	100	100	100	20 0	LT	100	50	0	>31 0
9	LF	50	100	100	20 0	RH	25	0	0	>31 0
10	LH	37	50	17	15 0	RH	75	0	17	>31 0
Median		100	100	100	13 0		87	0	17	31 0

Scores for sensory testing (0% = complete loss, 100% = undisturbed) M score mechanosensitivity, T score temperature sensitivity, P score pain sensitivity RH/LH = right/left hand, RF/LF = right/left foot, RT/LT = right/left T10 dermatome, W = Watts

Due to the extent of the syrinx, in 5 patients even the control area showed some sensory abnormalities. For example, 3 patients had some impairment of pain and temperature sense at the control site. At the affected site, however, there was nearly complete loss of these modalities in 7 cases and partial loss in the other 3. Thus in all patients the sensory symptoms were much less pronounced at the 'control' than at the 'affected' sites. Nevertheless, only 2 patients were completely analgesic in the affected area (P score = 0%). These patients did not perceive the test stimuli for SEPc recording at all. Seven other patients perceived some of the test stimuli, but never as painful. This is consistent with the observation that pin pricks in the affected areas were occasionally perceived as sharp, indicating severe hypalgesia rather than analgesia. In 1 patient (Case 5) pain and temperature sense were dissociated: this patient had a nearly complete unilateral loss for temperature but preserved pain sensitivity. He perceived all laser test stimuli in the affected area as painful. Five patients had impairment of dorsal column function (M score less than 80%). No patient had a completely anaesthetic area.

Fig. 1 shows examples of late somatosensory evoked potentials in response to cutaneous heat stimuli (SEPc) recorded from the vertex in 2 patients. Both patients had a loss of pain and temperature sensitivity including the left arm. The SEPc after painful stimulation of the dorsum of the right hand (fig. 1, left) were highly reproducible and

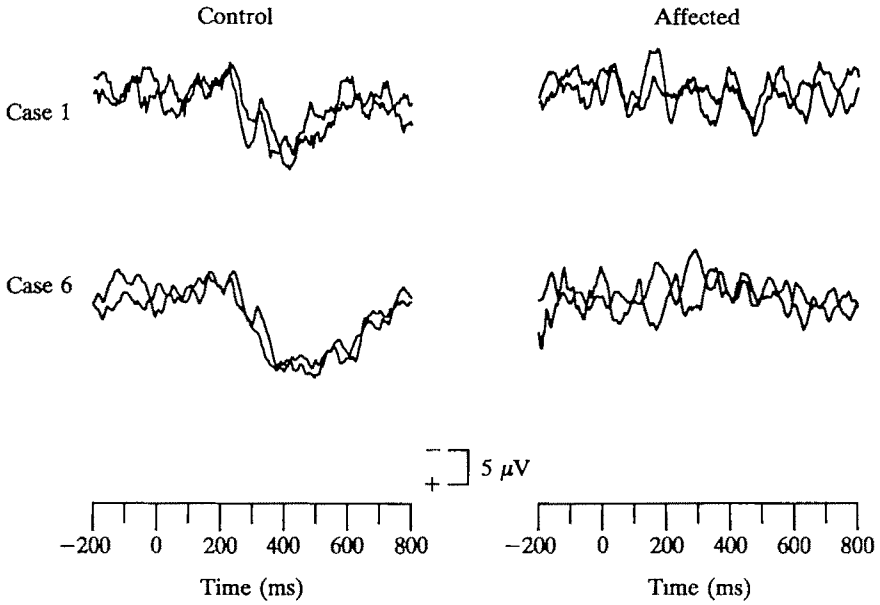

FIG 1. Late somatosensory evoked potentials in response to cutaneous heat stimulation (SEPc) of the affected left hand and the unaffected right hand in 2 patients with syringomyelia Each trace represents an average across 20 repetitions of the 20 W stimulus. Vertex versus linked earlobes, negativity upwards. *Top row: Case 1*, a man aged 47 y with a cervical syrinx. Pain and temperature sensitivity were lost over the left upper body quadrant including the left face. *Bottom row: Case 6*, a man aged 45 y with a cervicothoracic syrinx and Chiari I malformation. He had complete analgesia over the left upper body quadrant without affection of the face In both cases, the SEPc were normal after stimulation of the control site and absent after stimulation of the affected site.

of normal configuration in both stimulus blocks (*see* Carmon *et al.*, 1978; Treede *et al.*, 1988*a*; Kakigi *et al.*, 1989; Gibson *et al.*, 1991). They consisted of a vertex negativity (225 and 235 ms latency) followed by a large positivity (425 and 450 ms) with peak-to-peak amplitudes of 13.6 and 14.0 μV. In contrast, after stimulation of the affected left hand with the same stimulus intensities, no SEPc could be evoked. Thus it was possible to identify on which body side pain and temperature sensitivity was affected from recordings of evoked potentials in response to cutaneous heat stimuli.

The evoked potentials in response to conventional electrical nerve stimulation (SEPn) in the same 2 patients are shown in fig. 2. All latencies of early SEPn after stimulation of the median nerves on both sides (fig. 2A) were within the normal range. Also the latencies and amplitudes of late SEPn components (fig. 2B) were similar for the control and the affected side. Thus neither early nor late SEPn could identify the affected body side.

Table 3 summarizes the results of the neurophysiological tests in all patients. For late SEPc and late SEPn, data are given only for the vertex lead, where these components were of maximal amplitude. Differences between control and affected areas in the other EEG leads were similar. Late SEPc after laser stimulation on the affected site were completely absent in 8 patients. Ultralate SEPc did not appear in any patient, neither at the control nor at the affected sites. In 6 of the 8 patients, the loss of late SEPc was

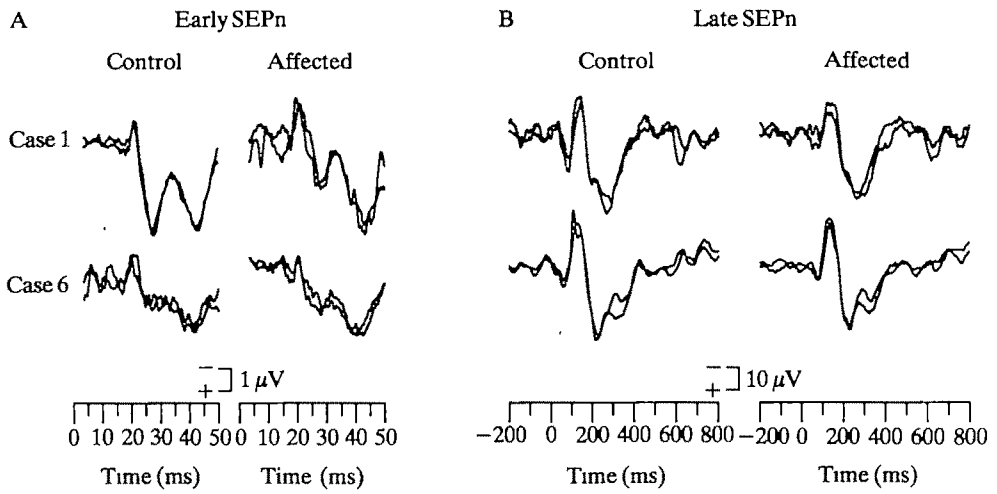

FIG 2. Somatosensory evoked potentials in response to electrical stimulation of the median nerve (SEPn) of the affected left hand and the unaffected right hand in 2 patients with syringomyelia. Same patients as in fig 1 (*top and bottom*). A, early SEPn components Each trace represents an average across 256 stimulus repetitions. Hand projection area (2 cm posterior to C3 or C4) versus Fz, negativity upwards. B, late SEPn components. Each trace represents an average across 20 stimulus repetitions. Vertex versus linked earlobes, negativity upwards. In both cases, all SEPn were normal after stimulation of both test sites.

TABLE 3. NEUROPHYSIOLOGICAL DATA

	Late SEPc Peak-to-peak amplitudes (μV)		*Late SEPn Peak-to-peak amplitudes (μV)*		*Early SEPn Latencies (ms)*			
					Control		*Affected*	
Case	*Control*	*Affected*	*Control*	*Affected*	*Med.n*	*Tib.n*	*Med.n*	*Tib.n*
1	14	–	47	39	21	n d	20	n d
2	12	–	12	26	n d.	49*	21	n.d.
3	12	–	26	30	n.d.	43	21	n.d
4	56	10*	69	37	n d.	–	19	n d
5	30	36	58	60	22	n.d	n.d.	46
6	14	–	51	47	20	n.d	20	n d.
7	–	–	37	52	21	n d	22	n d
8	34	–	35	28	22	n.d.	22	n d
9	5	–	15	13	n.d	45	22	n d
10	16	–	33	62	–	n.d	22	n d

– = absent response, * = delayed response; n d. = not determined, Med.n = median nerve, Tib.n = tibial nerve.

strictly unilateral, as in the 2 cases shown in fig. 1. In 2 other patients, we also observed some changes at the control site. In 1 of these (Case 9), SEPc were absent for the affected site and poorly identifiable for the control site. Sensory testing did not show any loss of pain and temperature sensitivity at the control site, but late SEPn were also of low amplitude. In the other patient (Case 7), the SEPc was absent for both stimulus sites. This was not due to poor recording conditions, since in the same stimulus blocks electrical stimulation of the median nerve evoked late SEPn of 40−50 μV amplitude. Sensory testing showed some impairment of pain and temperature sense at the control site.

Late SEPn were unremarkable for both control and affected sites in all 10 patients. The mean peak-to-peak amplitudes between the vertex negativity at about 140 ms and the positivity at about 260 ms were not significantly different between the affected site (41 ± 16 μV, mean $\pm$ SD) and the control site (39 ± 19 μV). Early SEPn abnormalities were observed only after stimulation of the 'control' areas: the latency of the cortical primary complex was delayed in Case 2. In 2 other patients there were no identifiable responses. In these 3 control areas mechanosensitivity was impaired (*see* Table 2). Notably, late SEPn were also unremarkable for these areas.

In 2 patients, cutaneous heat stimuli at the affected site elicited identifiable late SEPc. The results from 1 of these patients (Case 4) are given in fig. 3. This patient had a dissociated sensory loss from the trigeminal region down to T4 dermatome on both sides. The SEPc from the control site on the left foot was normal. Although this and the following figure give the impression that the initial negative deflection of the SEPc was more marked from the foot than from the hand, this is not a general finding, as shown in a systematic study of 24 healthy subjects (Treede *et al.*, 1988*a*). The SEPc from the affected area was reduced in amplitude by 82% compared with the control area. In addition, the latencies of both the vertex negativity (345 ms) and the vertex positivity (560 ms) were outside the 3 SD range for healthy young adults.

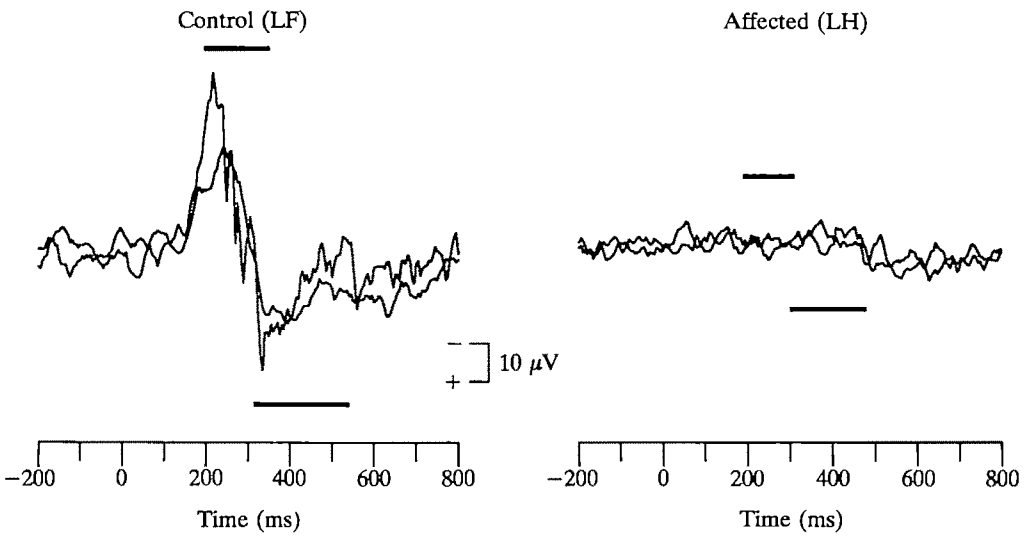

FIG. 3. Late somatosensory evoked potentials in response to cutaneous heat stimulation (SEPc) of the affected left hand (LH) and the unaffected left foot (LF) in a woman aged 50 y with a thoracocervical syringomyelia (*Case 4*) Each trace represents an average across 20 stimulus repetitions. Vertex versus linked earlobes, negativity upwards. Pain and temperature sensitivity was lost bilaterally from the trigeminal region down to T4 dermatome. The SEPc for the affected site was greatly attenuated, and its latency was outside the 3 SD range in normal subjects (horizontal bars).

The results from the other patient (Case 5) are shown in fig. 4. In this case, a well defined SEPc could be recorded from the affected and the control site. The latencies from both sites were within the normal range, but the latency difference of SEPc between hand and foot stimuli was exceptionally large. On the other hand, pain sensitivity was

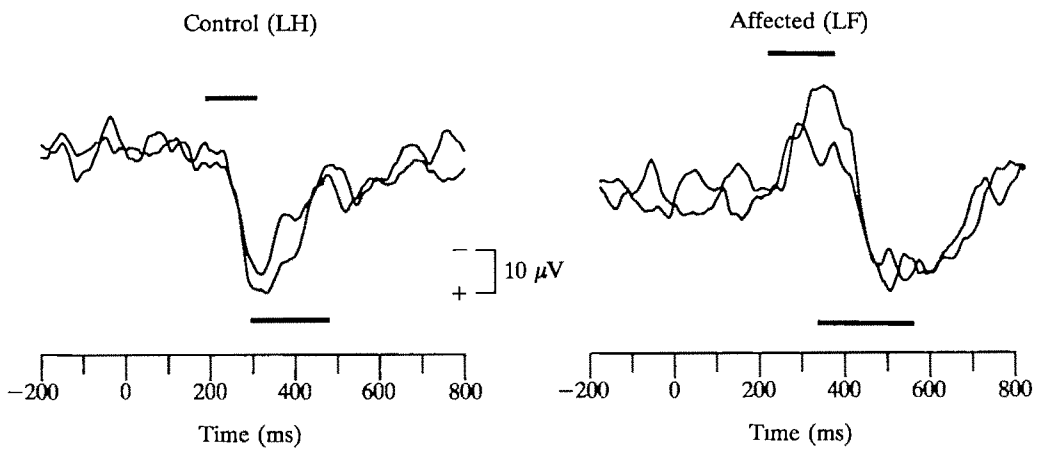

FIG. 4. Late somatosensory evoked potentials in response to cutaneous heat stimulation (SEPc) of the affected left foot (LF) and the unaffected left hand (LH) in a man aged 18 y with cervical syringomyelia due to a central tumour at the C3–C4 level (*Case 5*). Each trace represents an average across 20 stimulus repetitions. Vertex versus linked earlobes, negativity upwards. The horizontal bars indicate the range of latency variability (±3 SD) of the respective SEPc components in normal subjects. Temperature sensitivity was lost at both feet while pain sensitivity was not disturbed In this case SEPc were normal in all investigated areas.

completely normal at both the affected and the control sites; only the ability to discriminate nonnoxious temperatures was lost. Case 5 thus seems to be an exception on several counts, having more marked impairment in the lower limbs, normal amplitude SEPc, and diminished temperature but intact pain sensitivity.

DISCUSSION

In the present study, somatosensory evoked potentials after cutaneous heat stimuli (SEPc) were used to test a group of patients with impaired pain or temperature sensitivity due to syringomyelia. All 9 patients in whom both modalities were affected had either a greatly attenuated and delayed SEPc or no evoked response at all. The one patient with loss of temperature sensitivity but intact pain sensitivity had SEPc of large amplitude. These findings indicate that (1) SEPc are closely related to pain sensation, as has previously been demonstrated experimentally, and (2) SEPc are useful in the clinical assessment of patients with hypalgesia due to a morphologically defined spinal lesion.

Disturbances of pain and temperature sensitivity occur in over 80% of patients with syringomyelia at the first neurological investigation (McIlroy and Richardson, 1965; Hertel *et al.*, 1973; Schliep, 1978). Consistent with this, all 10 patients in this study had impaired temperature sensitivity, and 9 of them had reduced or absent pain sensitivity. The secondary symptoms in this series included mostly motor and autonomic disturbances, as in other studies (Aminoff and Wilcox, 1972; Schliep, 1978; Nogués *et al.*, 1982; Veilleux and Stevens, 1987). With the lesion site being mostly in the cervical cord (McIlroy and Richardson, 1965; Larroche, 1984), lower limbs are often spared by the symptoms, as in 4 of our patients. The location of the lesion in syringomyelia usually

begins at the central canal and extends into the commissures and the grey substance (Larroche, 1984). In contrast, the long ascending and descending tracts are often spared initially (Netsky, 1953). In accordance with these patho-anatomical findings, pathways for pain and temperature sensitivity may be interrupted either postsynaptically in the dorsal horn or at the anterior commissure.

Standard clinical neurophysiological studies using evoked potentials after electrical nerve stimulation (SEPn) in patients with syringomyelia have often yielded normal early cortical components (e.g., Anderson *et al.*, 1986; Urasaki *et al.*, 1988). This was also true in 7 patients in this study. In the other 3 cases, mechanosensitivity was impaired. Thus also in syringomyelia, altered early SEPn correlate with loss of mechanosensitivity (*cf* Stöhr *et al.*, 1982; Veilleux and Stevens, 1987). Investigations of the spinal components of the SEPn have sometimes revealed delayed or absent N13/P13 responses (Emerson and Pedley, 1986; Kaplan *et al.*, 1988; Urasaki *et al.*, 1988). These potentials are not part of the chain of signal transmission in the dorsal column system, but are believed to be dorsal horn postsynaptic potentials (Mastaglia *et al.*, 1978; Desmedt, 1988). They may sometimes be useful to delineate the extent of the lesion in the dorsal horn. Not even the most sophisticated techniques for spinal SEPn, however, get around the long established fact that neither early nor late SEPn components contain information about pain and temperature pathways (Halliday and Wakefield, 1963; Giblin, 1964). Other methods are necessary to test these pathways, which are more often affected in syringomyelia.

We used a CO_2 laser to excite superficial nociceptors and to elicit long-latency SEPc. The complete absence of an evoked response in 80% of the syringomyelia cases in this study clearly represents a pathological result. Similarly, in a recent study in 18 patients with unilateral dissociated sensory loss of various aetiologies, significant amplitude reductions and latency increases of late SEPc were found (Bromm *et al.*, 1991). Since the CO_2 laser generates a heat stimulus, these SEPc changes may be related to changes in pain sensitivity or in temperature sensitivity. Microneurography showed that CO_2 laser stimuli are capable of exciting warm receptors (Bromm *et al.*, 1984). However, the quality of sensation after CO_2 laser stimulation of a small skin area (below 30 mm^2) was rarely reported as warm but as a slight stinging pain (e.g., Carmon *et al.*, 1978; Bromm *et al.*, 1984; Pertovaara *et al.*, 1988; Kakigi *et al.*, 1989). Thus the contribution of specific thermoreceptors to sensation appears to be negligible. This may be due to their low innervation density and/or deep intracutaneous location in contrast to nociceptors. Notably, the one case in our sample with an exclusive loss of temperature sensitivity had no clear-cut evidence of an abnormal SEPc. This may indicate that the cerebral potentials evoked by a CO_2 laser correlate with pain and not with temperature sensitivity.

In contrast, other thermal methods to elicit evoked potentials have a much larger contribution of specific thermoreceptors. Argon laser stimuli, for example, penetrate much deeper into the skin than CO_2 laser stimuli (Cummins and Nauenberg, 1983). Those stimuli evoke sensations of warmth with weak intensities and the corresponding evoked potential is supposed to contain components of warm and of pain sensations (Arendt-Nielsen and Bjerring, 1988). With thermodes that stimulate large skin areas, nonnoxious temperatures have been shown to elicit evoked potentials (Fruhstorfer *et al.*, 1976; Chatt and Kenshalo, 1977). The absence of these evoked potentials in a case of

syringomyelia with reduced pin prick and temperature sensation (Jamal *et al.*, 1989) is probably related to the thermosensitivity abnormality.

In spite of several recent reports of clinical applications of laser evoked SEPc (Coger *et al.*, 1980; Treede *et al.*, 1988*b*; Casey *et al.*, 1989; Zangemeister *et al.*, 1989; Kakigi *et al.*, 1990; Bromm *et al.*, 1991), this technique is not yet an established clinical method. Unless the late SEPc is completely absent, it is thus difficult to decide whether the response is abnormal. SEPc latency may be a problematic criterion because of the marked latency variability of late evoked potentials. On the other hand, the latency of the VEP, which is the most commonly studied late evoked potential, has proved to be diagnostically useful. SEPc amplitude ratios between affected and unaffected regions may be a useful measure, since in normal subjects late SEP amplitudes correlate with the intensity of sensation (e.g., Carmon *et al.*, 1978). In this study, only one patient had an SEPc from the affected side that was present but possibly abnormal. In this case, both the latency and the amplitude ratio of the SEPc were outside the range of variability in healthy young adults (according to data from Treede *et al.*, 1988*a*). The sensory deficit in this case was as severe as in the group with absent SEPc (*see* Table 2).

SEPc are a specific test of Aδ fibre mediated first pain pathways: with microneurographic recordings (Bromm *et al.*, 1984), latency comparisons (Kenton *et al.*, 1980) and selective A fibre blocks (Bromm and Treede, 1987) it had previously been established that the peripheral neural substrate of late SEPc components is the excitation of thin myelinated nociceptive afferents. The evoked potential correlate of the excitation of unmyelinated C fibres, ultralate SEPc components, has been more elusive. Ultralate SEPc were only discovered when first pain and Aδ fibre related late SEPc were absent under a preferential A fibre block (Bromm *et al.*, 1983; Harkins *et al.*, 1983). Selective attention to second pain can sometimes lead to ultralate SEPc, but these are not reliable (Treede and Bromm, 1988), and were therefore not detected from the control sites in the patients of this study. Nevertheless, indirect conclusions can also be drawn for C fibre mediated second pain pathways, because C fibre related ultralate SEPc should have been recorded from the affected areas if only first pain pathways were affected in syringomyelia. Such a constellation has for example been found in neurosyphilis (Treede *et al.*, 1988*b*). Thus the complete absence of all SEPc components in patients with syringomyelia probably indicates that both first and second pain pathways were affected.

The differentiation of Aδ and C fibre functions may also be important for the understanding of the association of hypalgesia with spontaneous pain. Several recent studies have demonstrated that so-called 'central pain' is often associated with interruption of pain pathways (e.g., Berić *et al.*, 1988; Casey *et al.*, 1989; Holmgren *et al.*, 1990). Interestingly, more than half of our patients with hypalgesic skin areas complained of ongoing pain in the same areas. In summary, the clinical application of somatosensory evoked potentials due to cutaneous heat stimuli will not only provide objective neurophysiological evidence of dissociated loss of pain sensitivity, but will also open new ways to investigate mechanisms of chronic pain.

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A HISTORY OF BORON NEUTRON CAPTURE THERAPY OF BRAIN TUMOURS

POSTULATION OF A BRAIN RADIATION DOSE TOLERANCE LIMIT

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SUMMARY

Boron neutron capture therapy (BNCT) is a form of radiation therapy mediated by the short-range (less than 10 μm) energetic alpha (^{4}He) and lithium-7 (^{7}Li) ionizing particles that result from the prompt disintegration by slow neutrons of the stable (nonradioactive) nucleus boron-10 (^{10}B). Recent advances in radiobiological and toxicological evaluation of tumour-affinitive boron-containing drugs and in optimization of the energies of neutrons in the incident beam have spurred interest in BNCT. This article presents a history of BNCT that emphasizes studies in the USA. A new dosimetric analysis of the 1959–1961 clinical trials of BNCT at Brookhaven National Laboratory is also presented. This analysis yields an acute radiation dose tolerance limit estimate of ~10 Gy-Eq to the capillary endothelium of human basal ganglia from BNCT. (Gy-Eq: Gray-equivalent, or relative biological effectiveness of a radiation component multiplied by the physical dose of the component (Gy), summed over the component kinds of radiation.)

INTRODUCTION

The existence of the neutron, an electrically neutral atomic particle with a mass equal to that of the nucleus of hydrogen, the proton, was first postulated in Great Britain (Rutherford, 1920). Experimental verification of the concept originated from discovery of radiation with strange properties 10 years later in Germany (Bothe and Becker, 1930*a*, *b*). When alpha particles (energetic helium-4 nuclei) bombarded certain light elements (most effectively, beryllium), electrically neutral radiation with unprecedented penetrability in lead was detected by a Geiger counter. This so-called 'beryllium radiation', at first considered to be ultra high energy gamma radiation, was found to eject protons with energies of up to 4.5 million electron volts from hydrogen-containing materials (Curie and Joliot, 1932). James Chadwick, Rutherford's student and colleague, finally explained the puzzling kinetics of the ejected protons when he suggested that the beryllium radiation was a stream of neutrons (Chadwick, 1932, 1937). He held that the protons resulted from elastic collision of neutrons with hydrogen nuclei. Such collisions are comparable with those of billiard balls. A collision of a fast neutron with a hydrogen nucleus imparts some (on the average, half) of the kinetic energy of the neutron to the nucleus, which recoils as a proton. Enrico Fermi and his associates in Rome discovered that neutrons slowed by passage through paraffin or water are more likely to be absorbed by atomic nuclei than are fast neutrons. The capacities of boron

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and lithium nuclei to absorb slow neutrons were greater than those of any other elemental nuclei examined (Fermi *et al.*, 1934; Amaldi *et al.*, 1935; Fermi, 1939; Stranathan, 1942).

The first observation of charged particles from slow-neutron irradiation of boron was made at Cambridge University on December 10, 1934 (Goldhaber, 1986). Charged particles, including protons, alpha particles and tritons (energetic tritium nuclei), are produced during bombardment of specific stable isotopes of boron, lithium and nitrogen with slow neutrons (Chadwick and Goldhaber, 1935; Taylor and Goldhaber, 1935; Burcham and Goldhaber, 1936).

$$^{10}B + {}^{1}n \rightarrow {}^{7}Li + {}^{4}He$$
$$^{6}Li + {}^{1}n \rightarrow {}^{4}He + {}^{3}H$$
$$^{14}N + {}^{1}n \rightarrow {}^{14}C + {}^{1}H$$

Nuclear reactions such as these were discovered in elegant experiments. Fast neutrons were produced at the rate of about 1×10^6/s when ~100 mg of radium, an alpha and gamma emitter, was mixed with beryllium powder. The mixture was surrounded by lead plates that transmitted most of the fast neutrons so generated and attenuated gamma rays. The neutrons were slowed by multiple elastic collisions with the light nuclei (most effectively, with the hydrogen nuclei) in a layer of paraffin. The slow-neutron target was either a powder applied thinly to part of the inner wall of an ion detection chamber or a gas that filled the chamber. The electrodes of the chamber were connected to an amplifier and an oscilloscope to detect pulses of ionization from reactions between slow neutrons and their targets. The energies of charged particles emanating from a solid target could be estimated by shielding the target with various layers of aluminium and noting the suppression of pulse intensities.

When the neutron capture nuclear reactions became known in the USA, it was proposed that they be applied to radiation therapy by the selective uptake of a suitable isotope into a patient's tumour, followed by slow-neutron irradiation of the tumour-bearing tissue (Locher, 1936). Of the readily available nuclei that can react with slow neutrons to produce short-range ionizing particles and that can be incorporated into a variety of tumour-affinitive drugs, the stable isotope boron-10 (^{10}B) is the most likely to react with a neutron in a slow-neutron irradiation field (Farr and Robertson, 1971).

The first radiobiological studies using the neutron-^{10}B reaction were performed at the University of Illinois in 1938 (B. V. Hall, M. Goldhaber and P. G. Kruger, cited in Kruger, 1940). Within the next few years, several articles described reduced viability of mouse tumour transplants after their exposure to boric acid and irradiation by slow neutrons in vitro (Kruger, 1940) and regression of mouse sarcomas infiltrated with a paste of boric acid powder in sesame oil after their irradiation by slow neutrons in vivo (Zahl *et al.*, 1940). It was realized that there would be clinical advantages to irradiation with neutrons of intermediate energies that could be slowed down further ('thermalized') in the brain, where the slower neutrons would be more likely to react with ^{10}B (Zahl, 1941). Although the use of uranium-235 for slow-neutron capture therapy was foreseen (Zahl and Cooper, 1941), a radiobiological study of the ^{235}U-fission reaction was not reported until the late 1940s (Tobias *et al.*, 1948). It was also suggested that a vital dye, appropriately labelled by ^{10}B or ^{235}U, might be useful in BNCT (Zahl and Cooper, 1941).

After World War II, studies in radiobiology and medical physics were begun at institutes in the USA such as Brookhaven National Laboratory (BNL), which were established by the United States Atomic Energy Commission (AEC) primarily for nonmilitary nuclear physics research. In 1947, William Herbert Sweet, a neurosurgeon at the Massachusetts General Hospital (MGH) and professor at the Harvard Medical School, began collaborations with physicists at BNL and elsewhere to search for techniques to improve diagnosis and therapy of brain tumours. By 1949, these collaborations led to ^{32}P-labelled phosphate being used at the MGH as a radioactive tracer to localize brain tumours during neurosurgical operations. Working with the physicist Gordon Brownell, Sweet was among the first clinical investigators to image brain tumours with positron-emitting isotopes. However, no radiolabelled substance was known that would concentrate adequately in a brain tumour after its injection into a patient so as to deliver therapeutic doses of radiation to the tumour while sufficiently sparing normal brain and radiation-sensitive haematopoietic and gastrointestinal tissues. Sweet's search for a proton beam to be used for human brain tumour therapy eventually led to the establishment of a proton radiation therapy unit at the Harvard University cyclotron, but most malignant cerebral gliomas were considered to be too large and their margins too irregularly demarcated for proton therapy. The first clinical trial of fast-neutron therapy (radiation therapy mediated by fast recoiling protons in neutron-irradiated tumours), which had been carried out between 1938 and 1943 in California, was deemed to have failed 10 years after it began (Stone, 1948). Thirteen patients with brain tumours were among those treated with fast neutrons, without much success. By the late 1940s circumstances in the USA were thus appropriate for a renewal of interest in neutron capture therapy. Although the potential importance of BNCT was recognized by the British radiobiologist Douglas Lea in the 1940s (Lea, 1956), to my knowledge there were no British studies on BNCT published until the late 1970s (Constantine *et al.*, 1986, 1989; Mill *et al.*, 1986; Morgan *et al.*, 1986).

After 36 months under construction, the Brookhaven Graphite Research Reactor (BGRR) was commissioned in August, 1950. Lee Edward Farr, a paediatric research physician who was appointed chairman of the newly formed BNL Medical Department on September 1, 1949, became interested in new applications of the BGRR to slow-neutron radiation therapy (L. E. Farr, personal communication). Work on BNCT began at the BNL Medical Department in the summer of 1950 (Brookhaven National Laboratory, 1951). Independently, a proposal by Sweet for BNCT of brain tumours at the BGRR and for later development of a major intermediate ('epithermal') energy component in a neutron beam for BNCT was submitted to the AEC in 1950 (Sweet, 1986*a*, *b*) and published, in part, over 1 year later (Sweet, 1951; personal communication). Under the aegis of Donald Van Slyke, an eminent biochemist who was then BNL's Assistant Director for Biology and Medicine, A. Baird Hastings, a distinguished Harvard biochemist and BNL trustee, and Shields Warren, a noted pathologist who was the Director of the Division of Biology and Medicine in the AEC, plans by Sweet, Farr and others for BNCT of malignant gliomas at the BGRR were coordinated and quickly brought to fruition (Brookhaven National Laboratory, 1951). An irradiation facility with a 5 cm × 10 cm rectangular neutron port in its steel/lead/boron-shielded floor was built at the top of the BGRR, surrounded by concrete. The neutron port was at the apex of a 3½ foot high conical air space in the reactor shielding beneath

the floor of the facility, with bismuth plates used as extra gamma shielding at the base of the cone. Preliminary experiments were performed at the MGH in which nontoxic doses of borax (~70 mg/kg) were injected intravenously into volunteers with brain tumours (Javid *et al.*, 1952; Sweet and Javid, 1952). Beginning early in 1951, some patients with glioblastoma multiforme were referred from the MGH to Brookhaven for BNCT at the irradiation facility of the BGRR.

About 15 vital dyes were screened in tumour-bearing mice at BNL for possible use, after their boronation, in BNCT (Brookhaven National Laboratory, 1951; Sinex *et al.*, 1953). Winton Steinfield, who joined the BNL group in February, 1952, announced his success in the boronation of the vital dye Bismarck Brown after about 1 year's work. Unfortunately, Steinfield died accidentally in 1953 and his notebooks on the technique could not be deciphered (L. E. Farr, 1990, unpublished). Steinfield also performed a preliminary in vivo study relating to uranium neutron capture therapy (Steinfield, 1952). Coincidentally, the untimely death of another scientist, Leslie McKlintock, prevented a method for preparation of uranium-binding tumour-affinitive antibodies developed at a US Army laboratory (McClintock and Friedman, 1945) from being repeated (Knock, 1959). Such antibodies were thought to be potentially useful for uranium neutron capture therapy.

About 20% of boron in the earth's crust is ^{10}B. The production of ^{10}B-enriched boron did not begin in the USA until 1943 when the first method for ^{10}B-enrichment of boron, equilibrium counter-current distillation of a boron trifluoride dialkyl etherate, was developed at Columbia University in New York under the leadership of Harold Urey. A distillation column 1 inch in diameter and 5 yards high could produce 500 mg of 95% ^{10}B-enriched boron per day. Methods of large scale production of ^{10}B are now well known as, for example, in a factory commissioned in 1954 that was capable of producing over 1 lb of 95% ^{10}B-enriched boron per day (Miller *et al.*, 1958).

The first patient in Brookhaven's initial 24-month, 10-patient BNCT study (Farr *et al.*, 1954*a*, *b*, *c*; Godwin *et al.*, 1955; Robertson *et al.*, 1962; Farr and Robertson, 1971) was irradiated at the BGRR on February 15, 1951, just 6 months after the BGRR was commissioned. All the patients had undergone a neurosurgical operation for malignant cerebral glioma and showed clinical evidence of tumour recurrence. Eight of the patients had received conventional radiation therapy for their brain tumours. These advanced malignant cerebral gliomas were irradiated by thermal neutrons (and by the inevitable concomitant gamma, proton and fast-neutron radiations), after an aqeuous solution of 96% ^{10}B-enriched borax was administered intravenously over a period of several minutes. The patient was positioned horizontally with the tumour zone apposed to the neutron port. Since there was then no irradiation shutter, the reactor pile was shut down during the preirradiation infusion and alignment procedure, which took about 10 min. Critical reactivity of the pile was then reestablished and the reactor power was raised to 40 MW for irradiations of 17–40 min duration.

There were no serious side-effects of BNCT in the first 10 patients, although the large doses of borax infused before irradiation, ~200 mg/kg, were slightly toxic (Farr *et al.*, cited in Sweet and Javid, 1951; Conn *et al.*, 1955; Locksley and Farr, 1955). A 20-ton armour steel irradiation shutter was installed below the BGRR treatment port to allow a more rapid rise to full reactor power after the injection of borate without shutting

down the reactor (Brookhaven National Laboratory, 1953). The neutron port was enlarged to 10 cm×10 cm.

A second series, comprising 9 malignant glioma patients, was treated with a less toxic borate preparation, sodium pentaborate with D-glucose in the molar ratio 2:1 (Easterday and Farr, 1961; Easterday and Hamel, 1963), but at a higher ^{10}B dose than in the first series: 32−50 mg ^{10}B per kg body weight (median, 42 mg/kg) instead of 16−43 mg ^{10}B/kg (median, 26 mg/kg). Incident thermal neutron fluences were $2.34-3.84\times10^{12}$ per cm^2 (median, 3.38×10^{12} per cm^2), higher than the previous fluences, which were $0.44-1.93\times10^{12}$ per cm^2 (median, 0.93×10^{12} per cm^2). A troublesome side-effect of BNCT in the second series was intractable radiation dermatitis of the scalp (Archambeau, 1970), sometimes with ulceration, despite later efforts to prevent it by application of tight head bandages during borate infusion. The median survival time after BNCT for the second series was 147 (range 93−337) days, which was longer than that for the first series (median 97, range 43−185 days) (Farr *et al.*, 1958).

In the third series of patients treated by BNCT at the BGRR, in order to reduce the radiation dose to the scalp, the neurosurgeon H. J. Bagnall delivered the pentaborate (26−60 mg ^{10}B/kg, median 50 mg/kg) through a long warmed tube into the internal carotid artery of the tumour-bearing hemisphere while the patient was positioned at the irradiation port. Neutron fluences were reduced to $0.39-1.5\times10^{12}$ per cm^2 (median, 0.72×10^{12} per cm^2). Survivals after BNCT in the 9 patients of the third group (median, 96 days, range 29−158 days) were similar to those of the 10 patients in the first group and to those of patients in the north-east USA with similar cerebral tumours treated only by conventional postoperative therapies during the 1950s (Slatkin *et al.*, 1986*a*). None of the 9 developed severe radiation dermatitis, a fortunate outcome that sustained prospects for further clinical trials of BNCT at Brookhaven (Farr *et al.*, 1958; Farr, 1960).

Sweet was involved in the first two series of patients treated by BNCT at Brookhaven. Thereafter, he turned his attention to development of a brain tumour BNCT facility at the Massachussetts Institute of Technology (MIT) (Brownell and Sweet, 1958). To identify a ^{10}B-carrier that yielded more favourable tumour:brain boron concentration ratios than were obtainable with borates, the MGH chemist Albert Soloway investigated a series of monosubstituted derivatives of phenylboronic acid. Of 8 derivatives studied, the m-carbamido, the m-carboxy and the p-carboxy derivatives yielded tumour:brain ratios in the 2.5−9.0 range between 15 min and 3 h after their prompt intraperitoneal injection in mice bearing subcutaneous transplanted gliomas (Soloway, 1958). None of the other 5 derivatives yielded a tumour:brain ratio greater than 1.6. The p-carboxy derivative of phenylboronic acid was selected as a ^{10}B-carrier for 16 of the 18 brain tumour patients treated with BNCT by Sweet and his colleagues at the MIT reactor during 1959−1961. The outcome of the MIT trial of BNCT was unsatisfactory (Asbury *et al.*, 1972), with an average post-BNCT survival time of 6 months (Hatanaka, 1986).

While clinical trials of BNCT were in progress at the BGRR, a study in mice of the in vivo relative biological effectiveness (RBE) of heavy particles from the $^{10}B(n,\alpha)^7Li$ reaction was carried out at BNL (Bond *et al.*, 1956). Studies on BNCT of a mouse tumour were carried out by Farr and his laboratory assistant Tadeusz Konikowski during the 1950s and early 1960s at BNL. A methylcholanthrene-induced glioma was

transplanted intramuscularly into the mouse thigh. BNCT could cure the transplanted tumour almost predictably with no visible residual effects on the mouse (Table 1) (Farr and Konikowski, 1967, 1976). The thigh tumour could also be eradicated by x-ray therapy, but this was only achieved with severe damage to the irradiated limb (Farr and Konikowski, 1964). These results were the first extensive experimental demonstration of the BNCT concept in vivo.

TABLE 1 BNL-10-584-89 SUMMARY OF TUMOUR REGRESSION DATA FROM FARR AND KONIKOWSKI (1967, 1976) ON 1587 MICE WITH A NONMETASTATIC GLIOMA TRANSPLANTED TO THE THIGH AND TREATED BY BNCT USING 96 ATOM % ^{10}B-ENRICHED SODIUM PENTABORATE WITH D-GLUCOSE (MOLAR RATIO 2 1) VIA PROMPT INTRAVENOUS INJECTION

	Injection-irradiation time interval (min)			
	7–23	*25–48*	*50–72*	*74–92*
	Average boron concentrations (μg/g)			
Sarcoma	25	28	28	28
Blood	34	26	21	18
Tumour diameter (mm)	*Fraction (%) with permanent regression*			
8–9	115/137 (84)	165/185 (89)	79/125 (63)	40/95 (42)
10–11	48/82 (59)	98/128 (77)	63/128 (49)	15/90 (17)
12–13	25/68 (37)	46/130 (35)	28/82 (34)	1/52 (2)
14–15	1/51 (2)	9/86 (10)	6/86 (7)	0/62 (0)

Surface fluence $1.41-1.67\times10^{12}$ n/cm^2· BMRR; 5 MW, 23 s.

It was suggested that untoward complications of BNCT for human gliomas might be avoided if adequate numbers of neutrons could be delivered to the tumour during the few minutes when the tumour:brain ^{10}B concentration ratio was considered most favourable. To achieve this, thermal neutrons would have to be generated at a much greater rate than was possible at any acccessible port of the BGRR. Accordingly, plans were made to build a compact, high-flux, broad-beam thermal neutron facility for BNCT at the BNL Medical Department (Robertson *et al.*, 1955). The 5-MW H_2O-moderated Brookhaven Medical Research Reactor (BMRR) became operational in 1959 (Godel, 1960). It was a great disappointment that BNCT of 17 cerebral tumours (all but 1, malignant gliomas) carried out at the BMRR during 1959–1961 was not nearly as useful as had been anticipated; the median post-BNCT survival was only 3 months (Table 2). Failure to show substantial extensions of lifespan resulted in suspensions of both the BNL and the MIT clinical trials of BNCT. There has been no patient treated by BNCT in the United States since 1961.

TABLE 2. BNL-12-23-89 CLINICAL PARAMETERS AND INCIDENT THERMAL NEUTRON DOSES FOR 17 PATIENTS WITH MALIGNANT CEREBRAL TUMOURS TREATED BY BNCT AT THE BMRR DURING THE 1959–1961 STUDY THE PATIENTS' SERIAL NUMBERS, ASSIGNED IN ORDER OF INCREASING NEUTRON DOSES, ARE NOT NECESSARILY IN CHRONOLOGICAL ORDER OF IRRADIATION

Serial no	*Age at first operation (yrs)*	*Survival after first operation (days)*	*Survival after BNCT (days)*	*Previous radiotherapy*	*No. of major craniotomies*	*Incident thermal neutron fluence × treatment area ($\times 10^{14}$ neutrons)*
1	58	148	87	No	1	0 6
2	38	192	123	No	1	1.6
3	44	181	31	Yes	2	1.7
4	61	488	165	Yes	2	1.8
5	35	1128	98	Yes	2	1.8
6	44	68	19	No	1	4.6
7	65	~220	~170	No	2	5.6
8	57	144	87	No	1	5.9
9	43	313	153	No	1	6.8
10	56	1121	143	Yes	2	6.9
11	66	123	26	No	1	7.5
12	30	1750	57	Yes	2	16.0
13	51	425	151	Yes	1	20 0
14	35	636	12	Yes	3	25.5
15	32	50	4	No	1	26 2
16	66	36	6	No	1	26 7
17	50	312	3	Yes	1	29 7
Median	50 yrs	220 days	87 days	–	–	$5\,7 \times 10^{14}$ neutrons

In the early clinical trials of BNCT, no technique was available that was fast enough to allow estimation of the patient's blood-^{10}B concentration in planning the duration of irradiation. In retrospect, this problem is seen to be important because radiation damage to the cerebral vasculature turned out to be a complication of the early BNCT trials and because there was considerable variation from one patient to another in the concentration of ^{10}B observed in the blood at a given time after administration of a standard dose of ^{10}B-carrier. Recently, a gamma spectrometry facility has been constructed at BNL to measure ^{10}B quickly and accurately in less than a gram of blood or tissue (Fairchild *et al.*, 1986). In this so-called 'prompt-gamma' method, the sample is irradiated with slow neutrons. Gamma photons in the narrow energy range (~478 keV) produced instantly by ^{10}B-neutron capture reactions are counted. The amount of ^{10}B in the sample is proportional to the net count. The ^{10}B analysis of one blood or tissue sample at the prompt-gamma facility of the BMRR takes only several minutes.

Another important aspect of the initial clinical trials of BNCT was the unavailability of boron-containing compounds that would enter glioma tissues freely and not cross the blood-brain barrier. Such boron compounds were first synthesized in the 1960s from polyhedral boranes (Miller *et al.*, 1963; Knoth *et al.*, 1964). The applicability of these compounds to BNCT was studied initially at the MGH (Soloway *et al.*, 1967). This led to the selection of sodium mercaptoundecahydrododecaborate ($Na_2B_{12}H_{11}SH$) for a trial of BNCT of brain tumours in Japan. The first BNCT irradiation of a human brain tumour in Japan took place in August 1968 (Hatanaka *et al.*, 1986*a*; Hatanaka and Urano, 1986).

It is instructive to estimate radiation doses to the normal cerebral capillary endothelium in patients who underwent BNCT at the BMRR 30 years ago, and to review those doses in relation to post-BNCT survival. The capillary endothelium of a tissue receives doses from BNCT that reflect ^{10}B concentrations in blood and tissue parenchyma weighted in the ratio of about 1:2, respectively (Kitao, 1975; Rydin *et al.*, 1976; Slatkin *et al.*, 1988). Decreases of normal brain capillary endothelial cell radiation dose (*see* Appendix) with increasing penetration of neutrons are indicated in Table 3. As shown in the Appendix

TABLE 3 BNL-10-375-89 IRRADIATION PARAMETERS AND ESTIMATES OF CAPILLARY ENDOTHELIAL DOSE FOR 17 PATIENTS WITH CEREBRAL TUMOURS TREATED BY BNCT AT THE BMRR DURING 1959–1961

Serial no	*Reactor exposure (MW-min)*	*Maximum surface thermal neutron fluence ($\times 10^{12}$n/cm^2)*	*Maximum surface thermal neutron flux/MW ($\times 10^{10}$n/cm^2-s)*	*Treatment area (cm^2)*	*Endothelial radiation doses at depth D cm (Gy-Eq)*				
					(D = 0)	*(D = 2)*	*(D = 4)*	*(D = 6)*	*(D = 8)*
1	0 83	0.6	1 28	100	5 0	2.2	1 0	0 5	0 3
2	3 50	1.6	0 76	100	13 3	6 0	2 9	1 5	0 9
3	3 33	1 7	0 87	100	14 3	6 4	3 1	1 6	0 9
4	2 33	1 8	1 31	100	14 4	6.3	2 9	1 4	0 8
5	2 50	1 8	1.22	100	14.5	6.4	3 0	1 4	0.8
6	8.33	7 4	1 48	62	57 1	22.4	9 4	4.4	2 4
7	9 67	7.1	1.22	79	55 8	23 4	10 4	5 0	2 8
8	8 33	9 5	1 89	62	71 6	27 6	11 3	5 0	2 6
9	9 67	8 6	1 47	79	66 1	27.5	12 0	5 6	3 0
10	10 42	8 8	1.40	79	68 1	28 4	12 4	5 9	3 2
11	11 08	12 1	1.82	62	91 8	35.5	14 6	6 5	3 4
12	8 33	9 5	1.90	168	74 0	35.3	16.9	8 1	4 3
13	10 92	11 9	1.82	168	92 8	44.3	21 2	10.3	5 4
14	12.50	15 2	2.02	168	117 8	56 0	26 6	12.8	6 7
15	12.50	15 6	2 08	168	120 7	57 3	27 3	13 1	6 8
16	12.50	15.9	2 12	168	122 9	58 4	27.7	13 3	6 9
17	13 42	20.6	2 56	144	125 5	71 8	33 0	15.4	7 8

and in Tables 4 and 5, BNCT also involves radiations other than those from the neutron-^{10}B reaction that, in principle, cannot be limited to the tumour even if ^{10}B were limited exclusively to the tumour. These non-^{10}B-related radiations increase in relative importance with increasing depth in the brain.

In retrospect, Case 13 (Tables 1–5) is of particular interest because BNCT apparently arrested the growth of his malignant cerebral tumour. An ~ 4 cm diameter carcinoma was removed from his anterior parietal region at a left temporoparietal craniotomy. Seven weeks later, a 6-week course of cobalt-60 gamma radiation therapy (51 Gy to the whole brain) was begun. Recurrence of neurological signs, including right hemiparesis, led the patient to undergo BNCT at the BMRR 6 months after the termination of cobalt-60 therapy. The patient developed right hemiplegia, acute increased intracranial pressure and a slight drop in systemic blood pressure (150/90–110/60 mmHg) about 10 h after BNCT. Following emergency treatment with intravenous urea, the patient slowly recovered and became ambulatory within 10 days. Before he left BNL 53 days

TABLE 4 BNL-11-275-89 ESTIMATES OF DOSES TO CAPILLARY ENDOTHELIAL CELLS IN NORMAL BRAIN TISSUES FOR CASE 13 AT DEPTH D cm (Gy-Eq)

	D				
Source of radiation	*0*	*2*	*4*	*6*	*8*
43 μg ^{10}B/g (RBE = 2 0)	79.2	34.0	14.6	6.3	2 7
Fast neutrons (RBE = 2.0)	3.9	2.6	1 7	1.1	0 7
22 mg ^{14}N/g (RBE = 2.0)	3.7	1.6	0.7	0.3	0.1
Intrinsic gamma (RBE = 1.0)	4 1	4.4	2.7	1.4	0.7
Extrinsic gamma (RBE = 1.0)	2 0	1 7	1 5	1.3	1.1
Total endothelial dose	92.8	44 3	21 2	10.3	5.4
(% ^{10}B)	(85)	(77)	(69)	(61)	(50)
(% gamma)	(7)	(14)	(20)	(26)	(35)

The contributions to total doses from neutron-induced proton radiation (mainly from ^{14}N), from neutron-induced intrinsic gamma radiation (mainly from hydrogen), and from extrinsic radiations (mainly reactor-generated fast neutrons and gamma radiations) are listed. Numerical values of doses are given to the nearest 0.1 Gy-Eq.

TABLE 5 BNL-10-583-89 COMPONENTS OF THE MIXED-FIELD RADIATION DOSES TO CAPILLARY ENDOTHELIAL CELLS IN NORMAL BRAIN TISSUES AT VARIOUS DEPTHS IN CM (D) ASSOCIATED WITH BNCT OF 17 CEREBRAL TUMOURS TREATED BY BNCT AT THE BMRR DURING 1959–1961

	Proportion of total Gy-Eq dose (% ± SD)	
Source of radiation (D cm)	*^{10}B (RBE = 2.0)*	*Gamma (RBE = 1.0)*
0	85.0±2.0	5.6±1 0
2	76.2±2.9	12 2±1 5
4	65.7±4.6	19.8±1.8
6	54.3±6 9	28 3±3.0
8	40 3±8 9	40.7±5.0

later, not only had the paresis largely disappeared but remarkable improvements in speech, ability to read, and vision were observed in comparison with the serious deficits in these functions (right hemiparesis, complete expressive aphasia, complete right homonymous hemianopia) that developed before BNCT. The patient did not deteriorate neurologically thereafter, but he died at BNL, severely jaundiced, 5 months after BNCT with widespread extracranial metastases, probably from a primary anaplastic carcinoma originating in the head of the pancreas (autopsy no. A-151-61; BNL). At necropsy, there was no evidence of viable brain tumour tissue or of brain oedema.

Patients treated at the BMRR, many of whom had radiation therapy previously, were provided with meticulous care by the neurosurgeon Y. L. Yamamoto. Temporary skin flaps were reflected and shielded by sheets of ^{6}Li before irradiation. Although this precaution avoided nonhealing ulceration of the skin, it did not prevent radiation dermatitis altogether. Moreover, it was not always possible to prevent postoperative infections within the irradiation field. These responded favourably to drainage and antibiotic therapy. Postirradiation rises of intracranial pressure were treated by continuous drainage of CSF from the brain and by intravenous urea. Nevertheless, 4 of the 17 patients died within 2 weeks after irradiation (Table 2) with cerebral oedema and intractable shock, the explanation for which was not immediately apparent.

It was stated by the Amerian radiation oncologist Philip Rubin (1989, unpublished) that large-field photon irradiation of the human brain with a single dose of 16 gray or 20 gray carries with it a 5% or 95% risk, respectively, of clinically unacceptable injury to the brain. Doses equivalent to these were apparently reached or exceeded in one hemisphere of the cerebrum during BNCT in Cases 6−13 to a depth of about 2 cm and in Cases 12 and 13 to a depth of about 4 cm (Tables 2 and 3) with no dire consequences within 2 weeks after BNCT. Progressive deeper coma, cardiovascular collapse (shock) and death ensued within 2 weeks after BNCT only in Cases 14−17, who also received the highest neutron doses in the series (Table 2). Dosimetric calculations for these patients, when contrasted with similar calculations for Cases 1−13, suggest that the acute (single fraction) BNCT tolerance dose for endothelial cells in basal ganglia at depths of ~6 cm is unlikely to be much greater than 10 Gy-Eq. Perhaps neuronal centres in the basal ganglia that were involved in cardiovascular homeostasis were secondarily compromised by doses to the endothelium of more than 10 Gy-Eq from BNCT and BNCT-associated reactor radiations in Cases 14−17. It is postulated that Case 13, who responded well to BNCT after a difficult postirradiation syndrome of acute cerebral oedema and mild hypotension, received nearly the maximum acutely tolerable dose of radiation to the capillary endothelium of his left cerebral hemisphere, especially in his left basal ganglia.

An ongoing clinical trial of BNCT for malignant gliomas and other brain tumours has been led by the neurosurgeon Hiroshi Hatanaka in Japan since 1968. The age distribution of patients treated for malignant glioma in Japan, the median age of incidence of whom was approximately 40 y (Sano, 1981), seems to be quite different from the age distribution of patients with supratentorial malignant gliomas treated in Boston, where the median age at first operation was 59 y between 1952 and 1981 (Slatkin *et al.*, 1986*a*). Thus differences in age might contribute to differences in the survivals of groups of patients with malignant glioma treated similarly in Japan and in the West since age is an important prognostic of postoperative survival among glioma patients. Moreover, it is conceivable that some preparations of $Na_2B_{12}H_{11}SH$ (monomer) may have developed variable amounts of the spontaneous oxidation products $Na_4B_{24}H_{22}S_2$ (dimer) and $Na_4B_{24}H_{22}S_2O$ (dimer monoxide) by the time they were infused into patients (Hatanaka *et al.*, 1986*b*; Sweet *et al.*, 1986; Soloway, 1988). Consequently, inferences from the results of the Japanese trial of BNCT to date may not be unreservedly applicable elsewhere.

There have been reports of excellent clinical results in some malignant glioma patients treated with BNCT in Japan. For example, a man with glioblastoma multiforme so treated

in 1972 at age 50 y was alive and neurologically stable in the spring of 1990 with no radiographic evidence of a brain neoplasm (Hatanaka, 1990, unpublished). Nine days after ~20 g of tumour was removed from a large glioblastoma in the posterior-inferior region of the left frontal lobe, 40 mg ^{10}B/kg body weight of monomer was infused into the left carotid artery over 2 h. A 7 h irradiation that delivered a thermal neutron fluence of $5.3-9.6\times10^{12}$/cm^2 to the residual tumour began 14 h after the end of the infusion. Half an hour before irradiation, a 3.5 cm diameter sterile ping-pong ball was inserted into the bed of the residual tumour, in a sample of which the ^{10}B concentration was 15.3 μg/g. Half an hour after the beginning of irradiation, the blood-^{10}B concentration was 27.5 μg/g (Hatanaka *et al.*, 1986*a*). Post-BNCT instillation of 25 mg of methotrexate into the patient's tumour cavity over a 5-day period (Hatanaka *et al.*, 1986*a*), conceivably may have contributed to the long-term control of this tumour. Despite Hatanaka's successes with some patients, American and European oncologists are reluctant to endorse the Japanese BNCT technique in preference to alternative methods of postoperative brain tumour therapy. However, the astonishing energy and bold initiatives of the Japanese BNCT team are followed in the West with great interest because that team demonstrated for the first time that BNCT and BNCT-associated reactor radiations can be useful for some patients with brain tumours.

The microscopic distribution of boron in the brains of 2 $Na_2B_{12}H_{11}SH$-infused patients with malignant glioma has been studied in joint BNL-MGH investigations (Finkel *et al.*, 1989; Slatkin *et al.*, 1989*a*, *b*). One of these patients, who had a right temporal malignant glioma, demonstrated a continuum of concentrations of ^{10}B in tumour and in peritumour brain tissue by neutron-induced ^{10}B radiography (fig. 1, right) of an air-dried, unfixed, unstained cryomicrotome section of a surgical specimen from the right temporal lobe (fig. 1, left). The specimen was snap-frozen in isopentane cooled

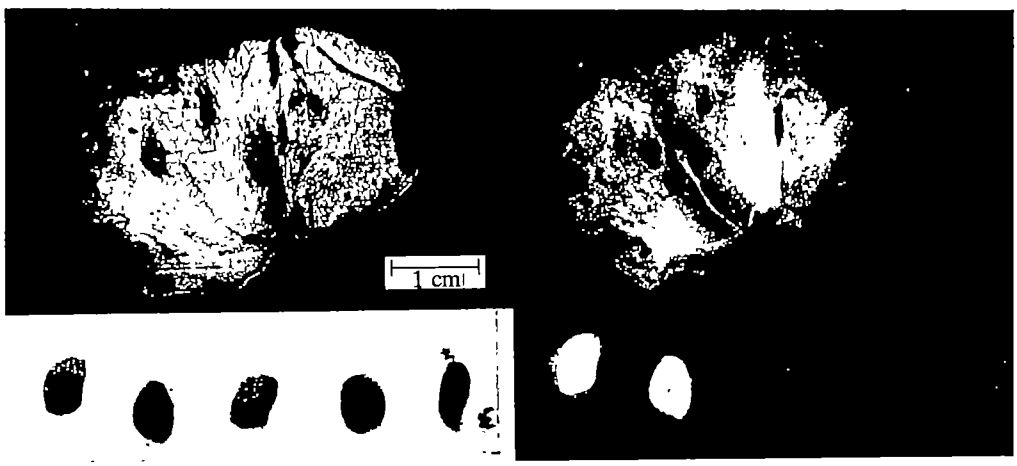
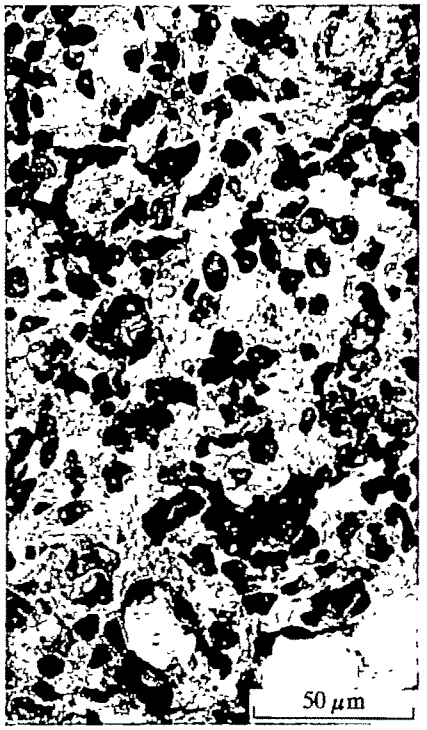


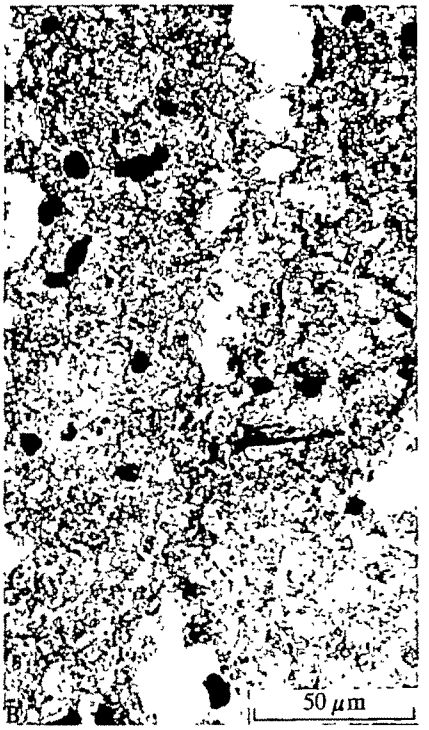
FIG. 1. BNL-1-140-88 Reflected-light (left upper frame) and alpha-track (right upper frame) images (Slatkin *et al.*, 1989*a*, *b*) of unfixed, unstained, 50 μm thick cryostat microtome sections from a right temporal lobe specimen removed during operation on a patient with a malignant glioma. The small left and right lower frames are the corresponding reflected light and alpha track images of cross-sections of frozen brain homogenates to which have been added 30, 9, 3, 0.3 and 0 μg ^{10}B/g, respectively, as non-^{10}B-enriched sodium tetraphenylborate.

with liquid nitrogen within 1 min after its excision by the MGH neurosurgeon Charles Poletti to preserve the microarchitecture of fluid-filled spaces in tumour and peritumour tissues in microscopic sections and to minimize loss of ^{10}B from the specimen. Fig. 2 shows intermediate-power views by light microscopy of haematoxylin and eosin-stained, 8 μm cryomicrotome sections from several areas of the temporal lobe specimen shown in fig. 1. Fig. 2A is from a 2–3 μg ^{10}B/g zone, heavily infiltrated by glioma cells, that is contiguous with the intermediate alpha track density zone near the left margin of the specimen (fig. 1, right). Fig. 2B is from a 1–2 μg ^{10}B/g, apparently tumour-free, slightly oedematous, low alpha track density zone just to the right of centre of the specimen. Fig. 2C, shown at the same magnification as figs. 2A and B, is from a highly oedematous, high alpha track density zone further to the right of centre of the specimen. Only two isolated tumour cells are noted in this field, but alpha track densities in the alpha radiograph of that zone correspond to 4–6 μg ^{10}B/g of tissue, the highest seen in the specimen. It is surmised that the relatively high extravascular ^{10}B concentration was due mainly to diffusion of protein-bound sulphydryl borane from the blood plasma through leaky capillary endothelium (Slatkin *et al.*, 1989*b*). The patient had received an intravenous infusion of 95% ^{10}B-enriched $Na_2B_{12}H_{11}SH$ to a total dose of 15 μg ^{10}B/g of body weight over a 20 h period. The specimen was removed about 26 h after the end of infusion during a neurosurgical debulking. The total dose of $Na_2B_{12}H_{11}SH$ infused into this patient was 2- to 5-fold less than the doses administered to BNCT patients in Japan (Hatanaka *et al.*, 1986*a*). The uniform distribution of boron tracks in the peritumour oedema zone suggests that BNCT has the potential to deliver therapeutic doses of radiation to oedematous brain tissues that harbour tumour cells beyond the macroscopic limits of malignant gliomas.

It was shown that $Na_4B_{24}H_{22}S_2$, one of the spontaneous oxidation products of $Na_2B_{12}H_{11}SH$, has more favourable properties as a carrier of boron to a transplantable mouse melanoma than does the parent monomer (Slatkin *et al.*, 1986*b*). Other favourable aspects of the dimer were recognized earlier (Hatanaka and Sano, 1973) and concurrently (Slatkin *et al.*, 1986*c*; Sweet *et al.*, 1986). There is striking improvement in boron uptake and in tumour boron retention in rat gliosarcomas after delivery of boron as dimer as compared with delivery of boron as monomer (Joel *et al.*, 1989). Indeed, recent studies have shown a prolonged amelioration of neurological symptoms and a greatly increased median duration of survival in rats with otherwise rapidly lethal transplanted intracranial gliosarcomas treated with BNCT using ^{10}B-enriched dimer as the boron transport agent (Joel *et al.*, 1990). The estimated radiation dose to these tumours was 25.6 Gy-Eq, whereas the estimated dose to capillary endothelial cells of the normal cerebral parenchyma of these rats was 15.2 Gy-Eq, which is somewhat higher than the postulated tolerance dose limit ($\sim$10 Gy-Eq) to such cells in the human basal ganglia. The estimated dose to the normal rat brain parenchyma was only 6.9 Gy-Eq, which corresponds to a tumour-to-brain radiation dose ratio of nearly 4:1 (Joel *et al.*, 1990). As in the 1972 BNCT of one of Hatanaka's long-term surviving patients (cited above), ^{10}B concentrations in the rats' blood were higher than in the gliosarcomas during irradiation.

The spatial distributions of slow neutrons in BNCT patients at MIT during 1959–1961 were different from those at BNL. At MIT, Sweet used an air-filled balloon to facilitate the transport of thermal neutrons to the deep margins of the tumour bed. This idea was adopted by Hatanaka for certain cases, including his outstanding case of 1972. Although





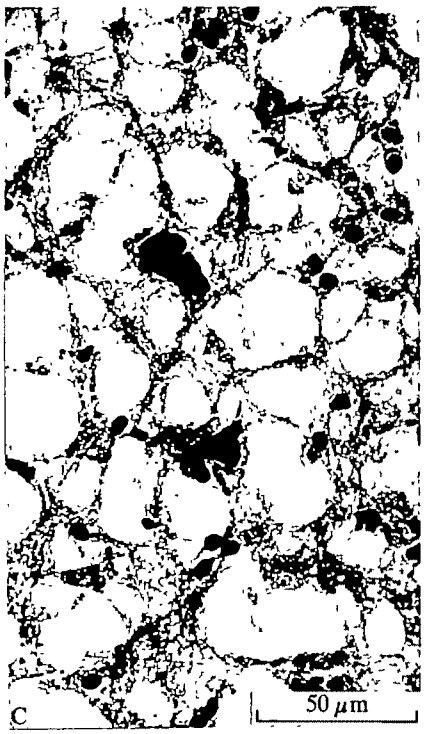


FIG. 2. A, BNL-6-342-88. Photomicrograph of human glioma tumour tissue in a temporal lobe specimen containing 2–3 μg ^{10}B/g (*see text* and fig. 1) B, BNL-6-343-88. Photomicrograph of slightly oedematous brain tissue in a temporal lobe specimen containing 1–2 μg ^{10}B/g (*see text* and fig. 1). C, BNL-6-341-88. Photomicrograph of highly oedematous brain tissue in a temporal lobe specimen containing 4–6 μg ^{10}B/g (*see text* and fig 1).

the MIT BNCT trial failed, it is not clear that the usefulness of a gas-filled space in the tumour cavity during BNCT can be discounted. Not only might it aid penetration of slow neutrons into the brain, but it could also be used to mitigate postirradiation brain swelling and to apply postirradiation hyperthermia to the residual tumour. Conceivably, a semipermeable balloon could provide a steep concentration gradient of oxygen in tissue at the margin of the tumour cavity to enhance the radiotherapeutic efficacy of the concomitant gamma radiation. The catheter leading to the balloon might also serve as a conduit for delivery of chemotherapeutic agents directly to the residual tumour bed.

Current research on BNCT focuses on the pharmacological and radiobiological evaluation of new boron-transport agents (Barth *et al.*, 1990). Besides that, a major accomplishment has been the design, construction and physical evaluation of an intermediate energy or 'epithermal' neutron beam at the BMRR suitable for clinical BNCT (Fairchild, 1965; Fairchild *et al.*, 1990). An epithermal beam produced by a different neutron-moderation technique (G. Constantine, unpublished) is near completion at a nuclear reactor in The Netherlands under the sponsorship of the Commission of the European Communities (Gabel, 1990). Epithermal beams for clinical BNCT can be constructed at several nuclear reactors that are not far from centres of population in the USA (Fairchild *et al.*, 1990; Brugger and Herleth, 1990), probably at modest cost. Whether the monomer $Na_2B_{12}H_{11}SH$, its dimer $Na_{24}B_{24}H_{22}S_2$, a boronated porphyrin (Kahl *et al.*, 1990), a boronated amino acid (Coderre *et al.*, 1990), or some other boron carrier will be tested clinically for BNCT of malignant gliomas in the USA has not been determined. It is likely that the distributions of trace amounts of several boron carriers will be studied in volunteers before trials of BNCT of human gliomas will resume in the USA, and that the new trials will use epithermal neutron beams. The use of ^{10}B-microlocalization techniques such as neutron-induced alpha track registration in etchable plastic films (Becker and Johnson, 1970; Amano and Sweet, 1973; Abe, 1982; Fairchild *et al.*, 1986; Gabel *et al.*, 1987; Finkel *et al.*, 1989), as in fig. 1, should facilitate such distribution studies.

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APPENDIX

Dosimetry for normal human brain capillary endothelial cells

The normal brain capillary endothelium received radiation doses during BNCT of brain tumours at the BMRR, 1959–1961, that were estimated indirectly as follows. Fig. 3 shows the average time course of ^{10}B concentrations in whole blood and in brain after prompt i.v. injection into mice of 100 μg ^{10}B/g body weight as 96 atom% ^{10}B-enriched sodium pentaborate with D-glucose in the molar ratio 2:1. The crosses and large dots represent measurements of boron

concentrations in tissues by a modified quinalizarin method (Konikowski and Farr, 1965). The time curves for ^{10}B concentrations in blood, B(t), and brain C(t), are related by a first-order differential equation:

$$dC(t)/dt = 0.012[B(t)-C(t)] \quad [1]$$

where concentrations are expressed in $\mu g/g$ tissue or blood, and time (t) is expressed in min The same equation describes, with less precision, the mouse blood-brain boron concentration relationship when the i v. dose was reduced to 35 μg $^{10}B/g$ body weight, the dose which was given in the 17-patient series at the BMRR. Blood and brain boron concentrations (measured by the prompt-gamma technique) after a single i.p injection into mice of boric acid at a dose of 125 μg boron/g body weight (Slatkin *et al* , 1988) can be correlated by the same kind of equation with a slightly greater rate constant.

$$dC(t)/dt = 0.015[B(t)-C(t)] \quad [2]$$

These equations are analogous to the expression of Fick's first law of diffusion, whereby the rate of diffusion of a substance across a boundary between two compartments is proportional to the concentration gradient between the compartments Since tissue constituents and their microscopic dimensions in human and mouse brains are similar, Equation [1], which contains no term that is an explicit measure of a macroscopic brain dimension or of a macroscopic brain boron concentration, can be used to estimate the average concentration of boron in nonoedematous zones of the human cerebrum after i v. injection of pentaborate. The net rate of entry of pentaborate into oedematous zones of the radiation-damaged human brain most probably exceeds the rate of entry into the nonoedematous brain, so that concentrations so derived for brain tumour patients from Equation [1] are low estimates. Upper estimates are reasonably equated with blood concentrations. The upper curve of fig. 4 follows ^{10}B concentrations in 4 of the series of 17 patients with cerebral tumours (Tables 1–5) treated at the BMRR who had the lowest measured blood concentrations after a standard 5-min i.v. infusion of 35.1 ± 0.9 (SD) μg $^{10}B/g$ body weight (range· 32.4–36.9 μg $^{10}B/g$) as sodium pentaborate decahydrate.D-glucose in the molar ratio 2:1 (Hospital of the Medical Research Center, BNL, unpublished medical records, 1959–1961). This standard infusion ended about 30 min before the start of irradiation at the BMRR. Blood concentrations measured in other patients of the same series were about one-fifth to one-third greater than those of the 4 patients indicated in fig. 4. The doses, timing and other conditions of administration of pentaborate, as well as the infusion-irradiation time intervals (~30–35 min), were almost identical in the 17 patients. Thus for the purpose of these comparative dosimetric calculations, the blood and normal brain concentrations of ^{10}B during irradiations are estimated to be 60 ± 10 $\mu g/g$ and 35 ± 5 $\mu g/g$, respectively.

Radiation doses from the ^{10}B-neutron capture therapy reaction to capillary endothelial cells in the brain are derived

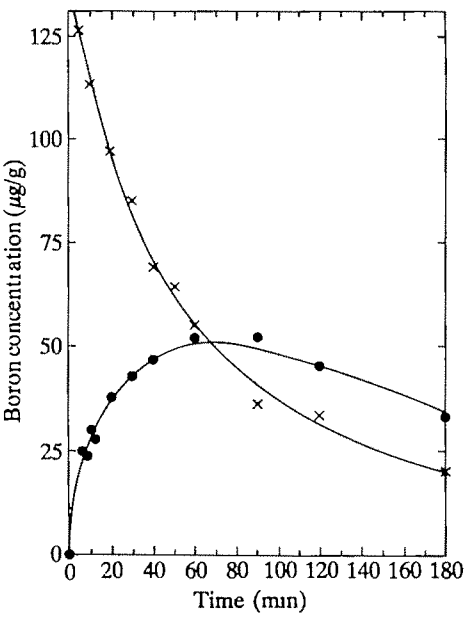

FIG. 3. BNL-9-109-89 Concentrations of ^{10}B in mouse blood (crosses) and brain (circles) after prompt i v. injection of 100 μg $^{10}B/g$ body weight as 96 atom % ^{10}B-enriched sodium pentaborate with D-glucose, molar ratio 2:1 (T. Konikowski and D N. Slatkin, unpublished data).

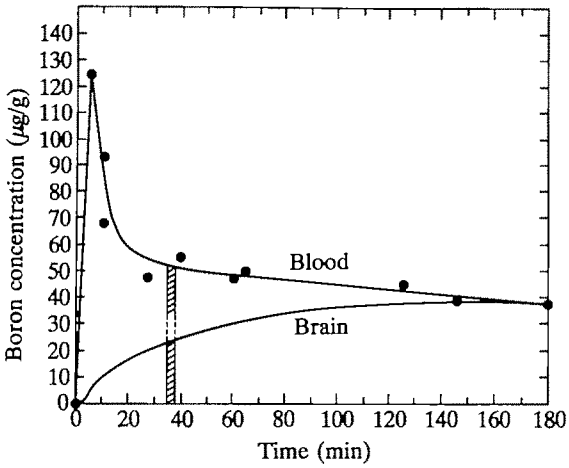

FIG 4. BNL-9-111-89. Concentrations of ^{10}B in patients after a 5 min i.v infusion of 35 μg ^{10}B/g body weight as 96 atom % ^{10}B-enriched sodium pentaborate with D-glucose, molar ratio 2.1. measured in the blood (circles) and calculated in the brain (lower curve) for the 1959–1961 BMRR BNCT study. Estimated minimum concentrations during the irradiations correspond to the intersections of the vertical bar with the two curves (T. Konikowski, unpublished data, D N Slatkin, Appendix)

in part from ^{10}B in blood and from ^{10}B in brain parenchyma in the relative proportion of approximately 1:2 (*see text*) That is, the effective ^{10}B concentration for irradiation of normal brain capillary endothelial cells in the 1959–1961 BMRR study was about 1/3 (60)+2/3 (35), or 43.3 μg ^{10}B/g Similarly, since the parenchymal brain ^{14}N concentration is about 19 mg/g and the blood ^{14}N concentration is about 28 mg/g, the effective ^{14}N concentration for brain endothelial irradiation from the neutron-^{14}N reaction was approximately 1/3 (28)+2/3 (19), or 22 mg ^{14}N/g. Assuming that the effective thermal neutron capture cross-sections for the neutron-^{10}B and neutron-^{14}N reactions are 3.40×10^{-21} cm^2 and 1.64×10^{-24} cm^2, respectively (Slatkin *et al.*, 1988), the doses to endothelial cells from these reactions are 6.651×10^{-12} Φ Gy-Eq from ^{10}B and 0.311×10^{-12} Φ Gy-Eq from ^{14}N, where Φ is the thermal neutron fluence in neutrons per cm^2. These formulae are based on an assumed RBE of 2.0, which is appropriate for acute effects in normal mammalian brain capillary endothelium of the short-range ionizing particles produced by the neutron-^{10}B and neutron-^{14}N reactions (Slatkin *et al.*, 1988). It is calculated from published data (Matsumoto *et al* , 1986) that the half-attenuation depth, $D_{1/2}$ cm, for thermal neutrons in the human head is approximately 0 32 ln A, where A is the surface area exposed to the thermal neutron beam, in cm^2.

It is surmised (Fairchild *et al* , 1966) that during 1959–1961, fast neutrons (RBE = 2) from the BMRR delivered radiation doses to skull surfaces of 0.0030 Gy-Eq/s per MW reactor power. It is also surmised (Fairchild *et al* , 1966) that the extrinsic gamma dose rate (RBE = 1) at skull surfaces was 0.0030 Gy/s per MW reactor power, and that the intrinsic gamma dose at skull surfaces was 0 0204 Gy/10^{13} neutron/cm^2 maximum surface fluence/cm^2 of surface exposed to the thermal neutron field The relative attenuation as a function of depth of penetration in the head of each component type of radiation is given by the following chart, which was inferred from published studies of thermal neutron beams (Stickley and Farr, 1960; Fairchild *et al* , 1966; Robertson *et al* , 1967, Matsumoto *et al.*, 1986):

Depth D (cm)	*Extrinsic gamma*	*Intrinsic gamma*	*Fast neutrons*
0	1.00	1 00	1.00
2	0 87	1.07	0.67
4	0 77	0.66	0.43
6	0.67	0.33	0.27
8	0.60	0.18	0.17

The endothelial radiation dose estimates of Tables 3, 4 and 5 are based on these attenuation parameters. The justification for adding radiation doses and radiation dose-equivalents arithmetically from several different kinds of irradiation is, in part, inferred from other experiments (Zirkle, 1950). The sum of such doses is considered to be a conservative predictive measure of the effect of different, concurrent ionizing radiations on a living target, because superadditivity of the effects of biologically-defined doses of different kinds of ionizing radiation delivered concurrently has never been observed

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IMPAIRED PHONOLOGICAL READING IN PRIMARY DEGENERATIVE DEMENTIA

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SUMMARY

This case study reports the profile of preserved and impaired capacities in a left-handed patient suffering from primary degenerative dementia of unknown aetiology. She was remarkable because her relatively preserved object naming and semantic categorization abilities contrasted with severe deficits in speech fluency, oral reading, inability to execute spoken and written commands, and severely impaired auditory-verbal short-term memory. Her reading disorder could be characterized as a disturbance of assembled phonology. She had great difficulty reading pronounceable nonwords, but she could correctly read irregular words. She showed effects of word imageability or concreteness (more than word frequency). She also showed effects of part-of-speech, where nouns and adjectives were read more easily than inflected verbs. She had difficulty reading function words. The syntactic category effects could be proven (by hierarchical log-linear analysis) not to be an artefact of imageability differences between verbs, adjectives and nouns. In reading aloud she made visual and morphological errors, but no semantic errors. This interesting pattern of preserved semantic information and disrupted phonological processing is unusual in dementia and contrasts with the severe dysnomia of patients with surface dyslexia who are able to read by the indirect, assembly-of-phonology route and show better reading of nonwords than irregular words. Her reading by a direct visual-semantic route appeared to be associated with relatively intact object naming, concrete word reading, and irregular word reading. This selective impairment of phonological reading in the context of partly preserved semantic abilities was interpreted as confirmation of the dissociability of language functions in primary degenerative dementia.

INTRODUCTION

Neuropsychological investigations of patients with brain damage caused by relatively focal, mostly cerebrovascular lesions, have demonstrated that specific patterns of dysfunction and preserved abilities can occur. Even neurological diseases that cause an apparently global dementia syndrome do not always result in undifferentiated loss of cognitive abilities, as careful scrutiny of the patients reveals. Thus patients with primary degenerative diseases of the central nervous system are described whose deterioration of visual perception, tactile object recognition or language preceded impairment of episodic memory (Crystal *et al.*, 1982; Kirshner *et al.*, 1984; Benson *et al.*, 1988; Poeck and Luzzatti, 1988).

Even in advanced stages of dementia there are patients who, apart from being severely amnesic, are clearly differentially impaired in other neuropsychological domains. Some

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patients may have predominantly lexical semantic impairment with intact visuospatial and constructional skill, while other patients may show the opposite profile of abilities (Marin *et al.*, 1983; Martin *et al.*, 1986; Martin, 1987; Becker *et al.*, 1988).

The analysis of language disorders consequent on brain damage reveals that different components of language processing (phonological, morphological, syntactic and lexical-semantic) can be differentially impaired (Saffran, 1982). In senile dementia of the Alzheimer type a characteristic pattern of language impairment has been described with marked semantic deterioration and relative preservation of phonological and syntactic operations (Diesfeldt, 1986, 1989; Bayles and Kaszniak, 1987; Kertesz and Kertesz, 1988; Rapcsak *et al.*, 1989). Thus oral reading can be normal in dementia, but reading comprehension may be severely disturbed (Cummings *et al.*, 1986). Although it is often stated that the mechanical aspects of reading are largely spared in early and moderate dementia, it may well be that this is too much of a generalization. In the particular domain of reading, different dementing patients may show different disorders of the individual functional components of the reading process.

Neuropsychological approaches to the study of reading have revealed a number of different patterns of acquired dyslexia, that is, reading impairment resulting from brain damage in a previously competent reader (Marshall and Newcombe, 1973; Patterson, 1981). Different dyslexia syndromes have been described where the performance in reading aloud individual words appears to be dependent on certain stimulus dimensions and experimental manipulations (e.g., exposure duration and quality of visual display). Relevant stimulus characteristics are syntactic category, meaningfulness, imageability and concreteness, word length and regularity of spelling. Four syndromes of acquired dyslexia have been investigated thoroughly: deep dyslexia, phonological dyslexia, letter-by-letter reading and surface dyslexia. Deep dyslexia is a disorder of oral word-reading in which the patient cannot read nonwords, reads concrete words better than abstract words, reads function words worse than content words, has disproportionate difficulty reading words with grammatical inflections and shows a tendency to make semantic errors in reading. The main deficit in phonological dyslexia is a severe inability to read nonwords in the context of relatively preserved real word-reading. In letter-by-letter reading the patients appear to be unable to read a word as a whole unit and can only tell what the word is by naming the letters one by one. In surface dyslexia words with regular spelling are read much more accurately than words with irregular word spelling. Nonwords can often be read as accurately as regular real words. These four syndromes have been extensively documented in many textbooks and articles so that they are only briefly described here (Patterson, 1981; Howard and Hatfield, 1987; Marshall, 1987; Ellis and Young, 1988; Friedman, 1988).

Although each of these syndromes can occur with various aetiologies, it is not well known if the fractionation of reading shows the same diversity in degenerative neurological disease as with other aetiologies such as stroke or head injury. This is an interesting question, since evidence that each of these dyslexia syndromes can occur as a result of brain dysfunction regardless of aetiology could be accepted as support for the general suitability of a psycholinguistic approach of reading disorders. There is no a priori reason to suppose that the fractionation of impairments and preserved abilities, which are often found after a restricted cerebrovascular lesion, could not occur in degenerative neurological diseases.

It can be derived from the very few published case studies of reading disorders caused by degenerative neurological disease that surface dyslexia appears to be the most common dyslexia syndrome in the context of primary degenerative dementia. Warrington (1975) and Shallice and Warrington (1980) described 3 patients with diffuse cerebral lesions (cerebral atrophy of unknown cause or secondary to atherosclerosis) whose expressive speech was fluent, but who had significant difficulty naming objects. On reading tests it was observed that relatively high frequency words, departing from the standard phonetic rules of English, presented most difficulty. Yet the mechanical aspects of reading were remarkably well preserved in these patients who could correctly read words that were meaningless to them. Warrington argued that in these patients, who showed significant failure in recognizing or identifying common objects, the semantic system was so much impaired that information from the visual word-form could not be linked with the concept-meaning units which are thought to be necessary for reading comprehension and for reading aloud exception words not conforming to regular spelling patterns. Shallice *et al.* (1983) studied a patient who was diagnosed as suffering from a progressive dementing illness of unknown aetiology, with fluent spontaneous speech but particularly poor performance on tests of picture naming and comprehension. Her ability to read by any lexical or semantic route was gravely impaired, so that regular words were read far more easily than exception words, while nonsense words could be read as well as regular words. A case study by Mehler (1988) of a patient with dementia associated with progressive left perisylvian involution, again demonstrated the association between severe semantic impairment and serious difficulties in reading aloud irregular words. Another relevant case study described a patient with presenile dementia presenting with prominent language pathology against a background of generalized and progressive memory loss (Schwartz *et al.*, 1979, 1980). Neurological examination revealed no evidence of focal pathology, being consistent with bilateral diffuse involvement of the cerebral hemispheres. Language impairment involved severe picture naming deficits, fluent speech and relatively preserved syntactic operations. The patient retained the ability to read words aloud with successful pronunciation of pseudowords. So far she had a similar clinical picture to the other patients with language impairment in the context of a dementing illness, but the exception was that she was still able to read irregular words. Her ability to read exception words, which means that she had to recognize the stimuli as words which have characteristic pronunciations, showed that her reading was not purely dependent on nonlexical recoding, but that she was using lexical knowledge in reading. Only later in the course of her illness was her reading influenced by spelling patterns so that she read regular words more accurately than exception words; she ultimately developed surface dyslexia. This case study showed that word-specific print-to-sound associations in reading aloud can be preserved for a considerable time even in the context of severe semantic and lexical loss.

Surface dyslexia is a syndrome of nonlexical or phonological reading. The converse impairment is phonological dyslexia in which whole-word lexical reading is preserved while the nonlexical or phonological reading route does not function properly. The following reports (with appropriate control subjects) a single case study of a patient who suffered from a degenerative neurological disease and developed a reading disorder that did not show the typical features of surface dyslexia but was rather characteristic of disturbed phonological reading with preservation of a lexical-semantic reading process.

CASE REPORT

R.K.C., a housewife aged 56 yrs and a native Dutch speaker with 10 yrs of formal education, was admitted to our department for psychogeriatric day care because of a 5 yr history of slowly progressive mental deterioration and apathy. The history of her neurological illness began in 1980 with significant mood and character changes (sadness, irritability and self-deprecation). There were also cognitive impairments in that she made errors in shopping and showed serious memory lapses. Neurological examination was negative and a provisional diagnosis of presenile dementia was made. Routine haematology and biochemistry were normal, as were thyroid function tests, chest x-ray, EEG and brain scan. Serum folate and vitamin B12 levels were reduced. She was treated with vitamin B12 replacement, amitriptyline and perphenazine, but her intellectual abilities slowly deteriorated. Formerly an avid reader of detective novels, by 1984 she was no longer able to read. She also lost the ability to write and to do needlework, and needed assistance with cooking, simple household tasks and dressing. She began to experience serious difficulty in finding her way about in familiar surroundings and had to be supervised day and night. A repeat CT scan with intravenous contrast revealed diffuse widening of the cerebral sulci and enlargement of the ventricular system indicating mild generalized cerebral atrophy. No focal abnormalities were seen in the brain (*see* fig. 1). A second repeat scan in 1987 showed an increase in the degree of cerebral atrophy.

No other members of the patient's family had suffered psychiatric illness or progressive dementia. Her parents had died past the age of 75 yrs without symptoms of dementia. It was known from the history that the patient was left handed but had been taught to write with her right hand. At least 3 family members (sister, aunt and niece) were known to be left handed. There was no history of childhood dyslexia.

The clinical features of multi-infarct dementia such as abrupt onset, fluctuating course, a history of hypertension or of strokes, were absent. The clinical history, and the results of physical, psychiatric and neurological examination strongly suggested the diagnosis of Alzheimer's disease (McKhann *et al.*, 1984).

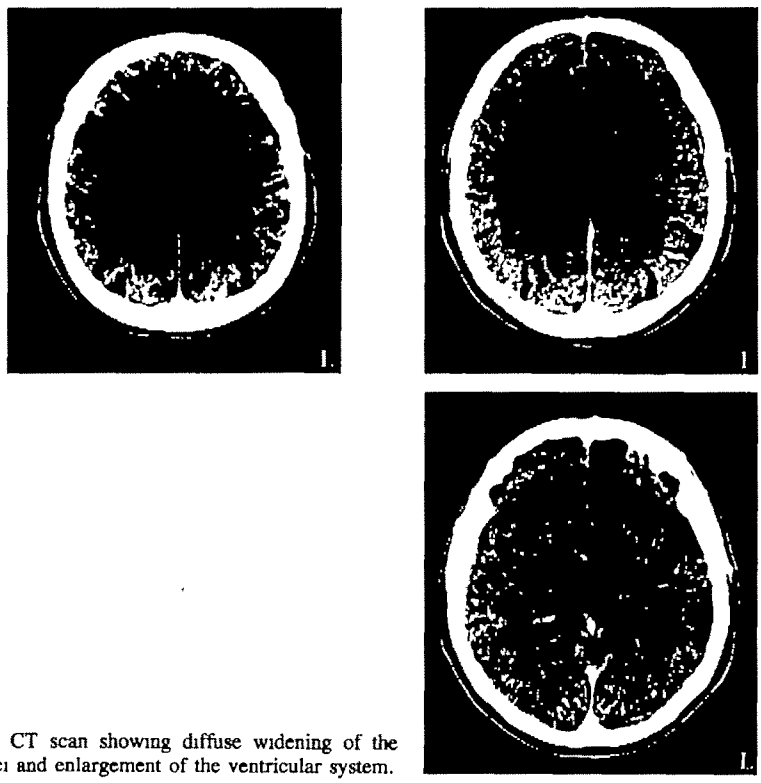

FIG 1. A CT scan showing diffuse widening of the cerebral sulci and enlargement of the ventricular system.

In 1986 she was admitted to a psychogeriatric day care department on a schedule of 3 days per week. In 1987 she became incontinent of urine at night and needed increasing help with activities of daily life, such as eating, dressing and toilet. Because of this she was admitted to a psychogeriatric nursing home. At the time of writing, her state had deteriorated to very severe dementia with occasional major generalized seizures.

Psychological test findings

The results of the neuropsychological investigations were collected during the period of 8 mos that the patient visited the day care department. On admission there were no motor and sensory deficits, or visual or hearing problems. Her general lack of initiative and voluntary action was remarkable, but she was fully alert and not excessively distractible. She scored far below the normal score on the Cognitive Screening Test, a standardized checklist for orientation to place and time (Deelman *et al.*, 1984). On 3 trials of free recall of 5 object names (the objects presented as pictures) she could name all objects but never recalled more than 1 object name. On a forced-choice delayed recognition test she failed to recognize any of the 5 objects. This contrasted with her occasional ability to remember recent events which was attested to by her accurate answers on questions about a new house change, visits of her children and a recent sick leave of her husband. After a few visits to the day care centre she recognized several members of the staff, her speech therapist and the psychologist, and occasionally mentioned the first name of some of them. She had normal vision. There were no symptoms of unilateral neglect. She correctly named all colours in an 11-item test of colour naming. She could read the single-digit numbers from the Ishihara plates, and separated the pseudofigure, given in Gregory (1970, p. 14), of a dalmation (a white dog with dark spots) from a background of a pseudorandom black and white dot pattern, indicating that her visual processing capacities and perceptual analysis (apperception) were intact.

Calculation ability was severely disturbed. She made 2 errors (on '5' and '6') on reading a random sequence of the written numbers 1 – 10 aloud and could not read any multidigit numbers (number alexia). She showed no appreciation of number values if asked to state which of 2 spoken or written numbers was greater. She could count aloud from 1 to 20, but not from 20 to 1. She was unable to perform (by oral response) simple tests of the fundamental arithmetical operations of addition, subtraction, multiplication and division, limited to single-digit numbers, neither on visual, nor on auditory presentation On a standardized clock-reading test she correctly read 1 of the clock faces (set at 10.10) but failed on 4 other clock faces (11.00, 7.50, 3.05 and 9.50).

She was apraxic as was disclosed by her severe difficulties with sequencing the acts necessary to reach a given goal (ideational apraxia). She performed normally on tests of buccofacial gestures (e.g., stick out tongue, blow out cheeks), but she made clear parapraxic errors when required to execute limb movements (e.g., combing her hair, drinking) on verbal command or by imitation (ideomotor apraxia). She could easily grasp small objects (small coins) between index finger and thumb of either the left or the right hand. Severe constructional apraxia was disclosed by her complete failure to copy simple drawings.

Her conversational speech was characterized by an abnormally decreased output (less than 30 words/min) associated with her general lack of initiative. Her responses to questions put to her sometimes had an echolalic quality. Many of her sentences lacked a normal grammatical sentence structure. Though she mostly spoke in a soft voice, speech was not characterized by increased effort, dysarthria or dysprosody. Striking examples of agrammatism were revealed on the Sentence Production subtest of the Dutch Aphasia Test Battery (DATB) (Deelman *et al.*, 1981) where the words she produced to describe action pictures were mostly nouns, but not action verbs. When prompted to produce a list of words from a given category she could not retrieve a single exemplar of each of the three categories 'animals', 'articles of clothing' and 'fruits'.

She had severe difficulties in comprehension of spoken sentences which were revealed by the Sentence Comprehension subtest of the DATB, which requires that spoken sentences (ranging from 2 to 9 words) are matched to 1 of 2 action pictures. Also her performance on the Word Comprehension subtest of the DATB (matching a spoken or written word to 1 of 4 pictures, consisting of the target and 3 distractors: semantic, phonemic and unrelated) fell far below the performance of a normal age-matched control group, both in visual and auditory presentation conditions. Her results on these multiple-choice comprehension tasks were difficult to interpret, since mere confrontation with the necessity of making a choice appeared to perplex her. Her far more adequate associative oral responses to the 15 items of a Depression Inventory, however, indicated good comprehension of personally meaningful and emotionally nonneutral concepts such as 'friends', 'sad' and 'appetite'.

Her ability to repeat was tested with the Dutch version of the Aachen Aphasia Test. She made no errors on a test of repetition of natural speech vowels, consonants and monosyllabic words, spoken by the examiner in a normal voice. She could not, however, reliably repeat words of more than 3 syllables, making phoneme substitution errors, such as saying 'metamormose' (a nonword in Dutch) for 'metamorfose'. She refused to repeat sentences that were longer than 4 words, commenting that this was too difficult. Her total score of 103/150 meant that her problems of repetition were of a moderate degree of severity (on a scale ranging from severe, moderate, mild to no impairment). On the Digit Span subtest of the WAIS she could only repeat sequences of 2 digits forwards and none backwards.

Her difficulties with repetition of digits, polysyllabic words and sentences revealed serious problems of immediate verbal memory This contrasted with her occasional ability to remember recent events (*see above*). Her difficulties with repetition might be due to difficulties with phonological processing To examine this possibility she was presented with a word-rhyming task in which she had to decide whether 2 visually presented words rhymed or not. Her performance was at chance level in this task, both for visually similar and dissimilar words (63% and 58%, respectively).

A 12-item sentence completion task was used to test her ability of rhyme production. In this test she was presented with pairs of short written sentences of five monosyllabic words that were read to her by the investigator. She was asked to complete the second sentence of each pair with a word that rhymed with the last word of the preceding sentence. Though an age and education-matched normal control group succeeded on at least 91% of the test items, she was unable to provide any rhyming words

She was requested to read aloud a very simple short paragraph from the Reading Comprehension subtest of the Cahn and Diesfeldt Test Battery for the Psychological Examination of the Elderly (CDTB) (Diesfeldt, 1987). Although she experienced severe difficulties in reading sentences, she could read some isolated words (such as 'tuinman' (gardener) and 'dochtertje' (little daughter)). The paragraph contains a girl's name that has a low frequency of occurrence in Dutch ('Roosmarijn') which she very laboriously read as 'mare . . rees . . ree'. Though she could read isolated words, she appeared to be unable to read a connected text of more than 2 words. To determine her ability to read longer sequences, she was presented with a task that systematically varied word length and number of words (nouns) on a card. Word length varied between 3 and 8 letters, the number of separate words varied between 2 and 5. If presented with 2 words, she correctly read 50% of the stimulus cards. Her performance dropped to 33%, 0% and 0%, respectively, if cards were presented with 3, 4 or 5 words, irrespective of word length.

She failed completely to recognize 3-letter words spelled aloud by the examiner, though she was able to repeat the letter-string letter by letter. Writing was severely disturbed. She was unable to sign her name, could not copy single written words and refused further writing tests.

In striking contrast with her impaired conversational abilities—very poor category fluency, and poor auditory comprehension and repetition—was her good performance on several picture naming tasks She correctly and quickly named all 10 pictures (with difficult items such as 'mushroom' and 'pincers') and all 6 line drawings of the Object Naming subtest of the CDTB. She also named 17 of the 18 pictures of the Graded Object Naming subtest of the DATB, which performance was well within the range of an age-matched healthy control group. Her single error was a semantic paraphasia ('to brush your teeth') on 'tooth-brush'. Her results on these object naming tests could be compared with those of a recent sample of 45 consecutive dementia patients in our clinic who had received extensive aphasia testing. No other patient was found with a profile similar to that of R.K.C., that is, nonfluent spontaneous speech, poor auditory comprehension, poor repetition, oral reading impairment, but relatively good naming. This remarkable profile of selective difficulties and spared performance prompted us to study her language abilities more thoroughly in order to obtain a better insight into her cognitive capacities.

Experimental investigations

For tests with no available norms, control data were collected from 12 normal volunteers, all women, matched for age and education level. Their average age was 57.9 yrs (SD = 4.9, range 51−67 yrs). Years of education ranged between 6 and 11 (mean 9.3, SD = 1.5). As the patient was left handed, we tried to recruit left-handed subjects for our control group. This resulted in 3 out of 12 control subjects being left handed.

All stimuli were presented without time pressure and then remained in view until the patient made her response. Pictures were derived from various sources (Otto Maier Verlag, 1969; Winslow Press, 1980). The testing verbal material was in Dutch, and is available from the author on request. Name frequencies,

age of acquisition data and imagery values were derived from Uit den Boogaart (1975), Kohnstamm *et al.* (1981) and Van Loon-Vervoorn (1985), respectively.

Picture and letter naming. In order to explore her presumably preserved ability to name pictures (*see* the first 4 rows of Table 1), several word categories were tested more extensively, such as household objects, actions, animals and fruits (*see* Table 1).

TABLE 1 NAMING TASKS, NAME FREQUENCIES (MEDIAN AND RANGE/MILLION), PERCENTAGES OF PICTURES CORRECTLY NAMED BY R K C AND THE CONTROL GROUP (RANGE), AND R K C 's ERRORS IN NAMING (NO. OF ERRORS IN PARENTHESES)

*Naming task (no. of items)**	*Name frequency median (range)*	*% Correct (control group range)*	*Errors***
Coloured pictures CDTB (10)	15 (0–618)	100 (90–100)	
Line drawings CDTB (6)	21 (7–171)	100 (67–100)	
Colours (11)	72 (8–233)	100 (100)	
Coloured pictures DATB (18)	13 (0–118)	94 (94–100)	Semantic (1)
Household objects (27)	18 (0–341)	85 (100)	Semantic (1); unrelated (2), omission (1)
Fruits (12)	6 (0–19)	83 (83–100)	Omissions (2)
Actions (27)	18 (0–480)	70 (100)	Semantic (3); omissions (5)
Mammals (21)	3 (0–97)	62 (67–95)	Semantic (4); omissions (4)
Birds (9)	3 (0–6)	11 (75–100)	Semantic (4); omissions (4)

* CDTB = Cahn-Diesfeldt Test Battery; DATB = Dutch Aphasia Test Battery ** Semantic errors are meaningfully related to the correct picture name (e.g., 'tiger' for lion), unrelated errors are not meaningfully related to the pictorial representation (e.g., 'umbrella' for telephone), omissions are nonresponses

Object names and action names (verbs) may be differentially affected in subtypes of aphasic speech deficits (Miceli *et al* , 1984; McCarthy and Warrington, 1985; Gainotti, 1990). R.K.C. appeared to have particular difficulty with the retrieval of main verbs in her spontaneous speech, whereas her ability to retrieve object names (nouns) appeared to be preserved. Therefore test material was selected that would allow for a systematic comparison of action-naming and object-naming. Twenty-seven photographs of easily picturable actions (A) and household objects (B) were presented for naming in an ABBA design. R.K.C. named 85% of objects and 70% of actions, a slight but nonsignificant difference in favour of her object naming ability ($\chi^2 = 0.96$). Thus in confrontation naming, her retrieval of nouns versus verbs did not appear to be differentially impaired. Her performance on both naming tasks was clearly below the level of the normal control group who named all pictures without error.

Her performance in naming examples of other categories was within or close to the range of the normal control group (fruits, mammals, but not birds). The probability of a naming error on the pictures of mammals was significantly related to the frequency of the animal name: animals with less frequent names elicited relatively more errors (Fisher's test, $P = 0.02$, two-tailed). A relationship between naming errors and word frequency could not be demonstrated for the other word categories.

The 26 letters of the alphabet (lower case, random order) were presented to the patient for naming on 2 days, 1 wk apart. She took 4 min to name 26 letters and gave the correct alphabetic name of 69% of the single letters on the first and 58% on the second occasion. The control subjects' performance varied between 92 and 100%. Her 19 errors were 12 omissions, 2 perceptual misidentifications (e.g , 'one' for 'l') and 2 phonological errors (e.g., 'd' for 'j'). Three errors were whole-noun responses, starting with the given letter, instead of letter-names. These whole word responses demonstrated that her ability to recognize or identify a given individual letter was intact but that her deficit in sounding and naming letters was at a phonological level. R.K.C.'s difficulty in naming letters of the alphabet is remarkable since letters are the most frequently preserved category for naming in aphasia (Goodglass and Budin, 1988). Isolated letters may be regarded as nonlexical orthographic stimuli. We shall see below that her difficulties with single letter naming might be associated with her difficulties in reading nonsense words.

Reading words of high and low imageability (concreteness effect). Two sets of 84 and 64 nouns each were constructed which crossed high and low word frequencies and high and low imageability. Table 2 shows the main characteristics of the words used in this test.

The patient was presented with the 2 different lists on separate occasions, 3 wks apart. Each word was printed (Courier 10) on a separate index card. The presentation order randomized high and low-imageability words, and words from several frequency classes. Table 2 shows that R.K.C., in naming low-imagery words, was correct on 76% and 72% of each list, respectively. Her 21 errors consisted of 8 omissions, 10 visual paralexias and 3 partial responses. Visual paralexias were recorded if at least 50% of the letters in the response were also in the stimulus. Partial responses were recorded if less than 50% of the letter string was read aloud. Ten out of 13 (77%) of her wrong pronunciations were neologistic responses. Subjects in the control group did not make any reading errors.

TABLE 2. RATED IMAGERY VALUES (MEDIAN AND RANGE), FREQUENCY OF OCCURRENCE (PER MILLION) IN DUTCH (MEDIAN AND RANGE), AND PERCENTAGES OF WORDS CORRECTLY READ IN EACH OF TWO LISTS OF NOUNS

	List 1 (n = 84, 21 words per i-f combination)					*List 2 (n = 64, 16 words per i-f combination)*				
	Imagery		*Frequency*			*Imagery*		*Frequency*		
	M	*Range*	*M*	*Range*	*% correct*	*M*	*Range*	*M*	*Range*	*% correct*
1 hi-hf	6.50	6 00–6 93	97	61–436	100	6 47	6 03–6 90	39	17–178	100
2 hi-lf	6 50	6.03–6 83	3	0–11	100	6 47	6.07–6 80	4	0–15	88
3. li-hf	3 47	1 90–3 97	111	68–576	86	3 55	2.07–3 83	35	15–228	75
4 li-lf	2 86	1 90–3 90	7	0–11	67	3 25	2 40–3 97	1	0–14	69
1+2 hi	6 50	6 00–6.93	36	0–436	100	6 47	6 03–6 90	16	0–178	94
3+4 li	3.13	1 90–3 97	40	0–576	76	3.42	2.07–3 97	15	0–228	72
1+3 hf	4 99	1 90–6 93	110	61–576	93	4 93	2 07–6 90	35	15–228	88
2+4 lf	4.97	1.90–6.83	5	0–11	83	5.02	2 40–6 80	3	0–15	78

i-f = imagery-frequency, hi = high imageability, li = low imageability, hf = high frequency, lf = low frequency. M = median

The significance of the imageability effect was tested by log-linear analysis (Feinberg, 1983), taking the potentially confounding effects of age-of-acquisition, word length, frequency and imageability on reading performance into account. The partial χ^2 value for the association between reading performance and imageability (controlling for the effects of other variables or interactions) was 11.41 ($df = 1$, $P < 0.01$) and 4.93 ($df = 1$, $P = 0.03$) for Lists 1 and 2, respectively. These findings confirmed the hypothesis that her oral reading of concrete words was clearly better than her reading of abstract words.

Oral reading of irregular words, nonword reading and nonword repetition. Irregular word reading was tested by presenting R.K.C. with 25 words, the pronunciation of which deviated from the normal Dutch grapheme-to-phoneme conversion rules. The nonwords used in this test were orthographically legal and pronounceable letter strings which bore no obvious relationship to any known word in Dutch (Hudson and Bergman, 1985). These nonwords, as well as 25 normal words, matched for length and letter frequency, were printed on separate index cards and presented in a randomized order. Her reading performance is given in Table 3.

R.K.C. was clearly able to pronounce exception words, as her oral reading was 96% correct. Her correct reading of irregularly spelled words can be regarded as proof of her ability to access lexical whole-word phonology. Her good ability to pronounce written exception words contrasted with her poor performance on nonword reading (*see* Table 3), which task requires phonologically based grapheme-to-phoneme conversions.

She read 92% of the words correctly, but her performance on nonsense words was only 32%. The difference between word and nonword reading was highly significant (χ^2: 16.64, $P < 0.01$, two-tailed). Her performance was significantly worse for nonwords larger than one syllable (2/17) than for monosyllabic

TABLE 3 PERCENTAGE OF WORDS CORRECTLY READ BY R K C (AND NORMAL CONTROLS) FOR LISTS OF IRREGULAR AND REGULAR WORDS, AND ORTHOGRAPHICALLY LEGAL NONWORDS*

Word type	*% correct*	*Errors*
Irregular	96 (96–100)	Phonological (1)
Regular	92 (96–100)	Omission (1), visual (1)
Nonwords	32 (92–100)	Omissions (6), visual: real words (7); visual neologism (1); partial response (3)

* There were 25 words in each list.

nonwords (6/8) (Fisher's test, $P < 0.01$, two-tailed). Some nonwords were read as if they were real Dutch words. From these errors it could be derived that she tried to read these words by means of lexical analogies.

The availability of a lexical entry also appeared to influence her performance on a repetition task that used the same 25 words and 25 nonwords as the oral reading task. Her repetition performance on words was significantly better than on nonwords (100% and 68% correct, respectively; $\chi^2 = 7.29$, df = 1, $P < 0.01$, two-tailed). Word length, measured in number of syllables, did not significantly affect nonword repetition. The 12 normal subjects scored between 92% and 100% correct on repetition of words and nonwords.

Syntactic category effects. Formal testing of the ability to read aloud single printed items of various syntactic categories was done by presenting R K.C. with 228 words from several syntactic categories, such as nouns, verbs, adjectives and function words (determiners, articles, pronouns, prepositions, conjunctions and some adverbs). These words were derived from 2 fragments of coherent text chosen from 2 short novels.

Since R.K.C. was unable to read running text, each single word was presented on separate index cards. During presentation the natural word order of the text was maintained. This was to avoid the artificiality of tasks that present series of unrelated content or function words for reading. Her performance is shown in Table 4.

TABLE 4 PERCENTAGE OF WORDS CORRECTLY READ AND ERROR TYPES IN EACH OF FOUR SYNTACTIC CATEGORIES

Syntactic category	*n*	*% correct*	*Error types**				
			Morphological	*Visual*	*Phonological*	*Partial*	*Omissions*
Nouns	49	87 8	0 (0)	4 (67)	0 (0)	0 (0)	2 (33)
Adjectives	17	82 4	0 (0)	3 (100)	0 (0)	0 (0)	0 (0)
Verbs	41	63.4	6 (40)	4 (27)	1 (7)	0 (0)	4 (27)
Function words	121	87.6	0 (0)	1 (7)	8 (53)	2 (13)	4 (27)
Total	228	82 9	6 (15)	12 (31)	9 (23)	2 (5)	10 (26)

* Absolute numbers and percentages per syntactic category in parentheses

The 12 control subjects made no errors except very few (2%) on nouns. R.K.C. performed best on nouns, a little worse on adjectives and worst on verbs. Most errors on verbs were morphological errors (the base lexical item was read correctly and the bound morpheme dropped, added or substituted) (Table 4). Nine out of the 29 wrong pronunciations (31%) were neologistic responses. R.K.C. apparently had no selective difficulty reading function words, though her performance was clearly below the level for the normal controls. Also, she displayed a notable difficulty with a specific category of very short, 2-letter function words (an article, 3 pronouns and an infinitive-marking particle) which had in common the fact that they consisted of a consonant and the vowel 'e'. On 8 out of 19 occasions (an error rate of 42%) R.K.C. produced a wrong pronunciation (phonological error) for these very common, short words, which serve an almost purely syntactic role in Dutch and carry no semantic content if presented in isolation.

Syntactic class is typically confounded with imageability in that the mean imagery values of verbs are lower than those of adjectives or nouns (Davelaar and Besner, 1988). Therefore, a log-linear analysis with syntactic category (nouns, verbs and adjectives), imagery ratings, and other potentially confounding independent variables, such as frequency, age-of-acquisition and word length was carried out. The imagery ratings were collected in a study with 31 students by Diesfeldt (1990). The partial χ^2 value for the association between reading performance and syntactic category, controlling for all other effects and interactions, was 12.14 ($df = 2, P < 0.01$). Thus when nouns, adjectives and verbs were equated statistically for imageability (by hierarchical log-linear analysis) the syntactic class effect was still significant.

Semantic categorization and confrontation naming. Semantic categorization of printed words was tested by presenting R.K.C. with 82 concrete nouns. These nouns were divided over 3 sets. In the first set she was required to sort 40 nouns into 'animal' and 'not animal' categories by responding 'yes' or 'no' if a word represented an animal or not. The other 2 sets of 20 and 22 nouns, respectively, required the distinction of 'vegetables' and 'articles of clothing' from words that did not belong to these categories. Within each set the distribution of exemplars and nonexemplars was randomized. Each item was printed (Courier 10) on separate cards and read aloud by the subject. The 8 words she could not or could only partially identify, were read to her by the examiner.

R.K.C.'s classification performance was 87% correct, which was well above 50% chance level (99% confidence level: 74–95%), though less than the performance of our normal control group, which was almost faultless (> 98%). Her 11 classification errors were 5 errors for category-exemplars (false-negative errors) and 6 for nonexemplars (false-positive errors).

By her reliable ability to discriminate between exemplars and nonexemplars of names of animals, vegetables and articles of clothing, R.K.C. showed relatively preserved knowledge of general categorical information Though it should be noticed that categorization does not require the attaining of the same degree of specification of a word's meaning as does naming (categorization can be preserved in patients who cannot attain a sufficiently precise semantic representation so as to allow naming), the results of this test are fully compatible with preserved semantic abilities as shown on several picture naming tests (Warrington and Shallice, 1979; Shallice *et al.*, 1983). To be sure that her picture naming ability had not deteriorated over the period of this investigation, R.K.C. was retested with the graded object naming test of the DATB. She did not make a single error on this test so that it seemed improbable that a significant deterioration of her lexical knowledge had occurred since the start of this study.

DISCUSSION

A profile of preserved and impaired capacities

This study of reading abilities in a patient suffering from primary degenerative dementia was prompted by the initial observation that she had severe deficits in speech fluency, reading aloud, comprehension of spoken and written language, and auditory short-term memory (repetition). She was unable to judge whether printed words rhymed, and unable to copy or write to dictation. These disabilities contrasted with her relatively preserved object naming and semantic categorization abilities. Further investigation added the following elements to this profile. Letter naming was impaired, though there was a relative preservation of the global identification of words, in that concrete, high-imagery words were more likely to be read correctly than abstract low-imagery words. She also could correctly read irregular words, but not nonsense words. There was a significant part-of-speech effect in that she read nouns better than adjectives, and adjectives better than verbs. In reading aloud she made phonological, visual and derivational errors, but neither semantic errors, nor function word substitutions. The pattern of impaired and preserved reading abilities can best be classified as a phonological dyslexia (Coltheart, 1980; Shallice and Warrington, 1980). The constellation of neurolinguistic and associated cognitive deficits is compatible with cortical degeneration with a predilection for the anterior perisylvian language zones (Benson, 1979; Goodglass *et al.*, 1986).

As the focus of this article is more on the cognitive than on the neural part of the brain-cognition equation, an attempt will be made to specify the nature of the cognitive mechanisms that were involved in this complex psycholinguistic syndrome of relatively intact lexical-semantic processes and disturbed phonological processing.

A functional model to interpret disturbances of oral reading

Extensive descriptions of recent functional models for the recognition, comprehension and naming of written words in reading have been given by Funnell (1983), Coltheart (1987), Ellis and Young (1988) and Friedman (1988). A particular model is based on the version of the logogen model proposed by Morton and Patterson (1980). This functional model proposes three routes for oral reading. First, a lexical-semantic route from print-to-speech via the visual input lexicon, the semantic system, where meaning is derived from print, and the phonological output lexicon, where phonemic representations are accessed to be transformed via phonological output into articulated speech (route A in fig. 2).

Studies of aphasic patients have provided evidence for the existence of a second route which is called the lexical nonsemantic or direct route (B) (Lytton and Brust, 1989). This route allows for familiar written words to be identified and pronounced as wholes without (or in parallel to) activating their meanings in the semantic system. The third postulated route (C) for word reading is a nonlexical or sublexical one. This

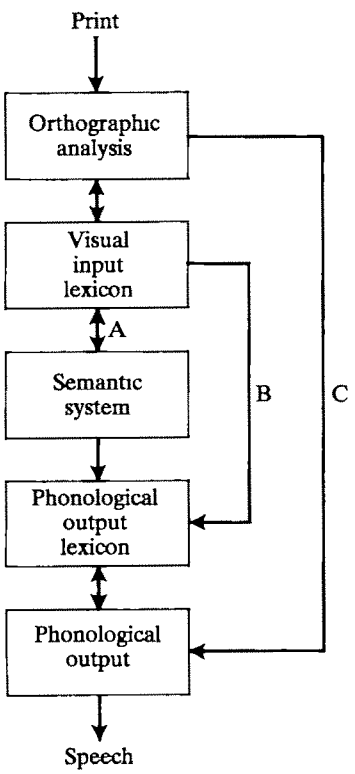

FIG. 2. Schematic diagram of processes involved in oral reading. A, semantic route to phonology, B, lexical phonological route, independent of semantic processing, C, nonlexical grapheme-to-phoneme conversion route.

route allows for the pronunciation of new or unfamiliar words thanks to an orthographic-to-phonological conversion process that bypasses the lexicosemantic system (Coltheart, 1982; Funnell, 1983). We shall see below how this model can help us to interpret R.K.C.'s reading disorders.

Application of the functional model

This patient's reading performance, in particular her great difficulties in reading nonwords, strongly suggests that the nonlexical route for reading was not available. Impairments of nonlexical grapheme-to-phoneme conversion processes can be localized at the input side of orthographic analysis, the output side of phonological assembly or in the transmission process from orthographic analysis to articulated speech.

Relevant to the question of impaired orthographic analysis are R.K.C.'s difficulties in reading connected discourse and word length effects influencing her performance in reading nonwords. These phenomena might be explained by deficiencies of orthographic analysis. Also a selective inability to read nonwords in itself does not exclude an impairment of orthographic analysis. Compensation for deficiencies in orthographic analysis by feedback from the visual input lexicon would clearly favour words more than nonwords, since the latter do not have representations in the visual input lexicon (*see also* Reuter-Lorenz and Brunn, 1990).

However, malfunctions of processes at the level of phonological output appear to be a more likely explanation for R.K.C.'s paraphasias and her particular reading difficulties.

First, gross impairments of orthographic analysis would not only disrupt nonword but also word reading, and would not explain why high-imagery words were read better than low-imagery words. Secondly, orthographic analysis is not implied in repetition of auditorily presented words, which was also impaired. Though word length effects are suggestive for input disturbances, word length had no effect on the naming of regular and irregular meaningful words, which means that R.K.C.'s visual analysis system had the capacity for recognition of visually complex letter strings. This stood in sharp contrast with her severe impairments in the correct pronunciation of less complex visual stimuli such as individual printed letters.

It thus appears that R.K.C. was less able to transform orthographic stimuli into the correct phonological output, particularly if the reading material was not amenable to lexical or semantic mediation. The fact that oral word reading varied with the concreteness of the word and its grammatical class indicates that reading depended on the use of a lexical-semantic route.

It is proposed that R.K.C. relied on a procedure of addressed phonology, that is, a direct lexical phonological route (B) for the pronunciation of familiar printed words, independent of semantic processing. Besides, her reading performance was presumably, at least in part, mediated by semantic processing strategies (route A), and in particular by the visual-semantic system.

The semantic system may be partitioned according to the nature of the information in a visual semantic system containing codes for picture names and imageable, concrete words, and a verbal semantic system containing conceptual knowledge of a less sensory, more abstract type (Hillis *et al.*, 1990). The visual-semantic system would be implied in object recognition and would via the verbal-semantic system mediate access to object names in the phonological output lexicon. The visual-semantic system would by the

sensory nature of the cognitive codes, also mediate the access to names of imageable, concrete words (Funnell, 1987; Riddoch and Humphreys, 1987; Coslett and Saffran, 1989). A verbal semantic system would contain word meanings that are independent of sensory properties and would be necessary to allow the correct pronunciation of abstract, low-imagery words. According to this model, R.K.C.'s access to phonological codes could be mediated by a supportive, visual-semantic system that could understand concrete sensory information and partly compensate for the selectively handicapped verbal-semantic system being deficient in understanding information of a more abstract-verbal nature.

Interestingly, the patient's relatively intact object naming and preserved irregular word reading contrasts with the severe dysnomia of patients with surface dyslexia, who show better reading of nonwords than exception words. By this account, there appears to be a double dissociation between naming impairment and certain types of reading disability in that intact nonword reading and impaired irregular word reading (surface dyslexia) is associated with severe dysnomia, whereas the reverse pattern (relatively intact object naming and exception word reading with disturbed nonword reading) is true for phonological dyslexia (Shallice and Warrington, 1975, 1980; Patterson and Marcel, 1977; Patterson, 1982; Caramazza *et al.*, 1985; Denes *et al.*, 1987). Thus reading by the direct visual route (A or B in fig. 2) is associated with intact object naming, whereas reading by the indirect assembly-of-phonology route (C in fig. 2) appears associated with naming disturbance. A comparable kind of double dissociation has recently been described by Murphy *et al.* (1988) in children with developmental dyslexia.

It is generally held that language deterioration in Alzheimer type dementia predominantly affects lexical-semantic abilities, whereas phonological and syntactic operations are largely spared. R.K.C., however, gave evidence that the reverse is possible, in that phonological function may become compromised first, while lexical-semantic processes remained relatively intact.

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VISUAL RECOGNITION MEMORY

NEUROPHYSIOLOGICAL EVIDENCE FOR THE ROLE OF TEMPORAL WHITE MATTER IN MAN

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SUMMARY

A novel event-related potential (ERP) elicited by a visuospatial recognition memory task was recorded in 20 patients with temporal lobe epilepsy using depth electrodes sited in the temporal lobes. The ERPs comprised two components, an N400 and a P600, and were similar in morphology to the previously reported ERP to verbal recognition memory tasks. The two ERP components in both verbal and visuospatial tasks were dependent on stimulus type and our data suggest that they do not simply represent delayed P300 ERP responses. In 17/20 patients robust, reliable bilaterally present ERPs were elicited by both verbal and visuospatial memory tasks. N400 amplitude was larger in response to novel stimuli, whereas P600 amplitude was larger to repeated stimuli. P600 amplitude was larger in the right temporal lobe to both visuospatial and verbal stimulus material. N400 and P600 latencies did not vary with task, stimulus type or side of recording. In 3/20 patients, no ERPs were elicited by either memory task. In all 3 cases, unilateral temporal white matter abnormalities were demonstrated by magnetic resonance imaging. Behavioural measures, expressed in the form of standardized accuracy scores, did not differ from those of a normal control group, and hence are unlikely to account for the abnormalities in ERPs. These results are discussed with reference to the primate visual recognition memory pathway and suggest that ERPs to recognition memory tasks are generated by an interaction between the two homologous inferotemporal recognition memory pathways.

INTRODUCTION

Endogenous event-related potentials (ERPs) are thought to reflect neuropsychological correlates of cognitive processes. The most studied has been the P300 ERP (Sutton *et al.*, 1965, 1967), which is a target detection response. It has been postulated to reflect stimulus expectancy (Duncan-Johnson and Donchin, 1977), and orienting reflex (Roth *et al.*, 1976), stimulus evaluation time (Kutas *et al.*, 1977; Duncan-Johnson, 1981; McCarthy and Donchin, 1981; Magliero *et al.*, 1984), or the updating of representations in working memory (Karis *et al.*, 1984; Fabiani *et al.*, 1986).

P300-like ERPs have been recorded from depth electrodes from a variety of cortical and subcortical structures, both in humans and animals (Halgren *et al.*, 1980; Wood *et al.*, 1984; Yingling and Hosobuchi, 1984; Katayama *et al.*, 1985; O'Connor and Starr, 1985; Wood and McCarthy, 1985). These studies indicate that there are multiple

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putative generators of P300-like activity, including the hippocampus, thalamus and frontal lobes. Although it is tempting to suggest that scalp P300 activity is composed of a summation of the P300-like activity from such sources as neocortex, hippocampus and thalamus, the relationship of depth P300 to scalp P300 ERPs is yet to be determined. In man, the scalp P300 is apparently unaffected by unilateral temporal lobectomy (Wood *et al.*, 1982; Stapleton *et al.*, 1987; Johnson, 1988).

The use of more sophisticated target detection type paradigms requiring subjects to remember and also detect various errors in semantic and/or pictorial stimuli has produced a large body of literature on ERPs elicited by cognitive processes. Kutas and Hillyard (1980*a*, *b*, *c*) were the first to show a negative centroparietal ERP peak, occurring at around 400 ms poststimulus, which was sensitive to visually-presented semantic incongruities in sentences. Subsequent studies also showed the existence of an N400-like peak to auditory semantic incongruity tasks (McCallum *et al.*, 1984; Herning *et al.*, 1987). A number of N400-like components have also been elicited in response to incongruous words in lists (Polich, 1985), nonrhyming word pairs and nonword pairs (Rugg, 1984), as well as reading and naming tasks (Neville *et al.*, 1982; Stuss *et al.*, 1983). It has been concluded that the N400 reflects inappropriateness of semantic context (Kutas and Hillyard, 1980*a*, 1983; McCallum *et al.*, 1984; Polich, 1985) or phonological mismatch (Rugg, 1984). It is interesting to note that incongruities in melodies, scale notes and geometric figures do not elicit N400 (Besson and Macar, 1986); however, mental rotation of line drawings (Stuss *et al.*, 1983) and semantic facial matching tasks do produce an N400-like ERP (Barrett and Rugg, 1989).

Verbal recognition memory tasks were found to elicit a negative/positive ERP complex, which occurred nominally at 400 ms and 600 ms poststimulus (N400 and P600), using depth electrodes sited in the medial temporal structures (Smith *et al.*, 1986). In this study both novel and repeated stimuli were presented. The N400 was preferentially larger in response to novel stimuli, whereas repeated stimuli elicited larger P600s. Smith *et al.* (1986) also demonstrated large amplitude gradients and local polarity reversals in their recordings, implying a local generator for these potentials. Subsequent investigations of ERPs elicited during verbal recognition memory tasks using scalp electrodes have demonstrated ERPs of similar morphology and latency, in which the N400 component is enhanced to novel stimuli and the P600 is preferentially larger in response to repeated stimuli (Smith and Halgren, 1988; Nagy and Rugg, 1989; Rugg and Nagy, 1989). Even more interesting is the observation that the N400 component, as recorded at the scalp, is severely attenuated following unilateral anterior temporal lobectomy (Smith and Halgren, 1988), suggesting that the temporal lobe may have an important role in processing this kind of visual information. Pictorial recognition memory ERPs (Friedman, 1990) also elicited a N400/P600 complex; however, the P600 component did not vary as a function of stimulus type. In this study all the stimulus items were highly verbalizable, concrete items, hence it could be argued that these ERPs may not truly represent pure visuospatial recognition memory processes.

We have previously studied the auditory oddball limbic P300, as recorded from medial temporal depth electrodes of patients being investigated for surgical relief of complex partial seizures (Puce *et al.*, 1989*a*, *b*). Unilaterally absent limbic P300 responses were predictive of the side of the temporal lobe seizure focus and the finding of hippocampal sclerosis (Puce *et al.*, 1989*b*). We have now designed experiments to explore the

processing of recognition memory information using depth electrodes. Here, we show that *nonverbal (visuospatial)* recognition memory tasks, using abstract nonverbalizable stimuli, elicit ERPs of similar morphology to their verbal analogues and that abnormalities in recognition memory ERPs may occur independently of abnormalities in P300 in patients with temporal lobe epilepsy. Analysis of P300 and recognition memory ERPs recorded from depth electrodes allowed us to examine the putative relationship between these two potentials. The results were also correlated with neuroimaging and interpreted using Mishkin's model of recognition memory in primates (Mishkin, 1982).

METHODS

Subjects

Twenty patients admitted to the Comprehensive Epilepsy Program at the Austin Hospital for the investigation of intractable complex partial seizures were studied. The presurgical evaluation consisted of neurological, neuroradiological (CT and MRI scan) and neuropsychological assessment, as well as the recording of video and depth EEG correlates of at least 3 spontaneously occurring seizures.

The clinical details of the 20 patients are listed in Table 1. Mean age was 32.4 ± 8.6 (range 16–50) yrs and there were 12 female patients. All patients were dominantly right handed, as measured by the Edinburgh Handedness Inventory (Oldfield, 1971), with the exception of Case 6 who was left handed. All patients were tested while they were on full or reduced levels of anticonvulsant polytherapy.

Depth recording electrodes

Depth electrodes were implanted into the temporal lobes bilaterally, using an orthogonal approach, with the tip of the electrode being targeted at the anterior hippocampus (Puce *et al.*, 1989*a*, *b*). The distance between adjacent recording contacts on the depth electrodes was 10 mm. Correct electrode position was verified on CT scan or by skull x-ray and subsequently from the pathological specimen. Other depth recording electrodes were sited according to the individual clinical indications for each patient.

TABLE 1 CLINICAL PATIENT DATA (n=20) AND DISSOCIATION BETWEEN ERP ABNORMALITIES

Case	*Age(yrs)/sex*	*Side of focus*	*Handedness***	*P300*	*N400/P600*
1 (M C.)	50/F	R	R100	Unilaterally absent	Present bilaterally
2 (S.I.)	42/M	R	R90	Bilaterally present	Present bilaterally
3 (M W.)	38/F	R	R100	Bilaterally absent	Present bilaterally
4 (J B.)	26/F	R	R90	Unilaterally absent	Present bilaterally
5 (D S.)	27/M	R	R80	Unilaterally absent	Present bilaterally
6 (J.D)	39/M	R	R100	Present	Absent
7 (T P)	28/F	R	L-50	Bilaterally present	Absent bilaterally
8 (D W.)	36/F	L	R100	Unilaterally absent	Present bilaterally
9 (V.G.)	16/F	L	R68	Unilaterally absent	Present bilaterally
10 (C A)	21/F	L	R47	Unilaterally absent*	Present bilaterally
11 (G.L)	39/M	L	R90	Unilaterally absent	Present bilaterally
12 (N.H)	33/M	L	R75	Unilaterally absent	Present bilaterally
13 (B K)	39/M	L	R80	Unilaterally absent	Present bilaterally
14 (A M)	32/F	L	R80	Bilaterally present	Present bilaterally
15 (J.G.)	44/F	L	R100	Unilaterally absent	Present bilaterally
16 (W.P)	23/M	L	R75	Unilaterally absent	Present bilaterally
17 (L.C.)	28/F	?	R68	Bilaterally present	Present bilaterally
18 (W.McG.)	34/M	?	R80	Bilaterally present	Present bilaterally
19 (T.D)	28/F	?	R68	Bilaterally present	Present bilaterally
20 (L B)	23/F	?	R90	Unilaterally absent	Absent bilaterally

* Absent contralateral to seizure focus. F = female, M = male, L = left, R = right, ? = query. ** Edinburgh Inventory (Oldfield, 1971).

Seizure localization

In 16/20 patients a localized, unilateral temporal lobe seizure focus was determined for their complex partial seizures. Nine of the 16 patients had a left temporal lobe seizure focus, while in 7 a right temporal lobe ictal onset was demonstrated. Fifteen of the 16 patients underwent unilateral anterior temporal lobectomy. One patient chose not to proceed with surgery.

In 4/20 patients a clear ictal onset could not be determined, despite the use of bilateral medial temporal and orbitofrontal depth electrodes.

Cognitive ERP experiments

Ethics

The protocol was approved by the Austin Hospital's Ethical Review Committee and each patient gave informed consent for the study.

Recognition memory tasks

All stimuli were presented on an Apple IIe microcomputer. The microcomputer also controlled task timing, categorized the responses and calculated an accuracy score (Green and Swets, 1966).

Both recognition memory tasks consisted of the sequential presentation of a list of items. The presentation of each item was repeated once at a random point during the trial. The subject was required to categorize each stimulus item as either a novel or repeated item and indicated his/her choice by pressing 1 of 2 push-buttons. Following a push-button response, an auditory feedback tone signalled to the patient that the response (correct or incorrect) had been registered. If no tone was sounded the response had not been registered by the computer and hence the subject repeated the button press.

Verbal task. Sixteen word lists of 60 items were selected using words with an imagery rating of less than 5, according to normative data (Paivio *et al.*, 1968) Each stimulus item was presented for a period of 6 s and the interstimulus interval (ISI) was 9 s. The minimum interval for repetition was 6 items (45 s), with a mean repetition interval of 18 (range 6–45) items. The inter-item repetition intervals were not significantly different from a normal distribution, using the Kolmogorov-Smirnov test for goodness of fit for either version of the verbal task (version 1: $d = 0.14$, $P = 0.20$; version 2: $d = 0.17$, $P = 0.08$).

Visuospatial (nonverbal) task. Sixteen lists of nonverbal material consisting of 30 items each were constructed. Nonverbal material consisted of abstract 'shapes' (e.g., fig. 1) which were presented in 1 to 3 colours (green, violet and white). Shapes were designed to be resistant to verbal description, with all designs being tested for possible verbal interpretation by 2 independent assessors. Items designated as 'verbalizable' were replaced by new items. Each stimulus item was presented for 9 s with an ISI of 15 s. The minimum interval for repetition of stimulus items was 3 items (45 s), with a mean repetition interval of 8 (range 3–15) items. The inter-item repetition intervals were normally distributed for both versions of the visuospatial task (Kolmogorov-Smirnov goodness of fit test, version 1: $d = 0.19$, $P = 0.24$; version 2: $d = 0.21$, $P = 0.14$).

The level of difficulty between the 2 tasks was equalized by using a longer stimulus presentation time in the visuospatial version of the recognition memory task. The relatively lengthy stimulus presentation time in both tasks was adopted, so that patients could perform this task in the postictal state. The behavioural measures in the interictal and postictal states to these tasks have been described elsewhere (Andrewes *et al.*, 1990). As the minimum time for repetition of stimuli was 45 s for each task, the task was effectively seen to be activating long-term memory processes (Peterson and Peterson, 1959).

Control tasks. In order to determine if the ERPs were specific to memory processing, 3 control tasks using similar stimulus material were administered.

1. 'PASSIVE' control task, where novel stimulus material (verbal and visuospatial versions) was viewed without responding.

2. A set of 'ACTIVE' control or P300-type paradigms. (1) The auditory oddball, where 2 sinusoidal tones were presented at an average rate of 0.3/s, with rare tones being presented with a probability of 0.20. This paradigm has already been described in detail elsewhere (Puce *et al* , 1989*a*, *b*). (2) Identical (nonrepeated) stimulus material to memory tasks, where differentiation was required between. (a) words of animal names from all other words; (b) words containing the letter combination 'oo' from all other words; (c) tricoloured shapes from those presented in 1 or 2 colours.

FIG 1 Example of a visuospatial stimulus, consisting of an abstract form presented in 3 colours (white, green and purple) The 3 different levels of shading in this black and white reproduction delineate each area of colour

The subject pressed 1 of 2 push-buttons, depending on which of the 2 stimulus types were presented, to every presented stimulus

ERP recordings

ERPs were recorded on an Medelec 4 channel Sensor system. This was remotely triggered by the Apple IIe microcomputer, which also controlled the presentation of the memory and visual control tasks. The auditory oddball paradigm was generated on the Apple IIe, which in turn controlled a Medelec ST10 stimulator.

Memory tasks. ERPs were recorded from the 3 deepest contacts of 4 on each medial temporal electrode, with respect to linked earlobes and a ground electrode on the forehead. Silver/silver chloride electrodes were used for all extracranial placements and electrode impedence was 2−6 kΩ. The EEG signal was filtered using a bandpass of 0 1−30 Hz (−3 dB down). A 2 s recording epoch was used and included a 500 ms prestimulus baseline (250 point slices, sampling ratio of 62.5 Hz)

At 2 s before the presentation of each stimulus item, a fixation character (*) was presented in the centre of the video monitor. ERP recording commenced during the last 500 ms of the presentation of the fixation character, as shown schematically in fig. 2 ERP recording duration was a subset of the total stimulus presentation time.

A test session consisted of subjects performing both memory tasks. ERPs were recorded over 8 test sessions. In a given session ERPs were recorded in response either to novel and repeated stimuli, or from right or left medial temporal electrodes, ensuring that 2 trials of ERPs were recorded for each condition. This method was adopted, as only 4 channels of ERP data could be recorded in any given session. For each test session (and patient), the order of task presentation and sampling of electrodes and stimulus types were counterbalanced across test sessions.

Test session were conducted only if no seizures had occurred in the preceding 24 h period, and were always on separate days. Video and depth EEG were recorded throughout each test session. If a patient had a seizure during the session, testing was abandoned.

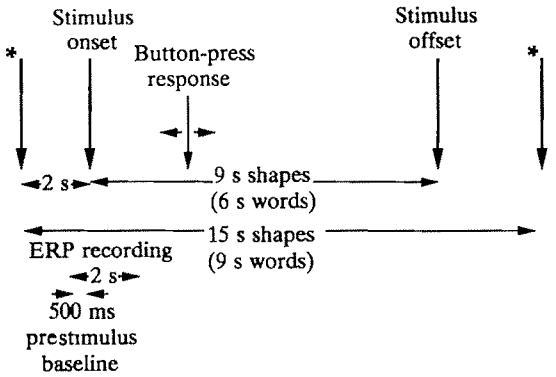

FIG. 2. Timing diagram for presentation of stimuli and ERP recording. The fixation stimulus (*) which is presented for 2 s begins the stimulus cycle. The stimulus remains on for a period of 6 s for words and 9 s for shapes. During this time the subject indicates his/her response by button-press. The fixation stimulus is represented to initiate the next cycle for 9 s for words and 15 s for shapes. ERP recording begins 500 ms before stimulus onset and a 2 s recording epoch is used for both types of memory task.

Control tasks. ERPs were recorded using a 4 channel montage from the 2 deepest contacts of each temporal depth electrode (right and left) on 2 occasions. The recording epoch of 2 s also included a 500 ms prestimulus baseline.

Data analysis

Amplitude and latency of all peaks occurring in the ERP waveform was determined. ERP waveforms were inspected visually for maxima in amplitude occurring in the latency range 300–500 ms for N400, and 500–1200 ms for P600. ERP peak latency was determined by visually selecting the poststimulus time at which a peak occurred. ERP peak amplitude was measured with respect to prestimulus baseline. Prestimulus baseline level was determined by summing amplitude measurements at 50 ms intervals over the 500 ms prestimulus period and taking their average. If no peak(s) were observed in the latency regions of interest ERPs were deemed as being 'absent'.

Memory task ERP data were analysed statistically using a three-way (2×2×2) multiple analysis of variance (MANOVA) using repeated measures (within-subjects comparison) in a nested design. ERP data from the deepest electrode contact from the right and left temporal depth electrodes were included in this analysis. A MANOVA was performed on the latency and amplitude data of each ERP component, with the 3 factors being TASK (visuospatial vs verbal), SIDE (left v right) and STIMULUS TYPE (repeated vs novel items). Only ERP data from patients with clearly lateralizable temporal lobe seizure foci were included in the MANOVA. Note that no interaction terms are generated in this type of MANOVA (repeated measures, within-subjects design).

Control task ERP peak latencies and amplitudes were calculated and the control task ERP morphology was compared with that of the memory task ERPs.

Behavioural measures

Methods used to elicit behavioural measures for this study have been described in detail elsewhere (Andrewes *et al.*, 1990). Briefly, performance measures for both memory tasks were expressed as accuracy scores, utilizing a probability expression which included the probability of correctly recognized items and the probability of false-positive items. Scores ranged from −1 to +1. An average accuracy score was calculated from all test sessions, excluding the first trial. These averaged accuracy scores were then standardized into z scores, using a multiple regression model for memory performance data for both tasks, generated using a group of normal subjects. Factors such as sex and age of subjects were taken into account using the model. Reaction times were not measured in this study.

RESULTS

Behavioural measures

Behavioural measures for both memory tasks, in the form of (raw) accuracy scores and standardized z scores for each patient are listed in Table 2. Patient z scores which were significantly different from normal ($P < 0.01$, one-tailed) are marked in Table 2 with an asterisk. It is important to note that the standardized z scores of Cases 6, 7 and 20, to be discussed subsequently, did not differ from those of the population of normal subjects in either of the two memory tasks.

TABLE 2 BEHAVIOURAL MEASURES IN THE FORM OF ACCURACY SCORES (AVERAGE OF ALL TRIALS) AND CORRESPONDING STANDARDIZED Z SCORES FOR EACH MEMORY TASK FOR EACH OF THE 20 PATIENTS TESTED

		Verbal		*Visuospatial*	
Case	*TLE*	*Accuracy*	*Z score*	*Accuracy*	*Z score*
1	R	0 78	+0.95	0.61	+1.02
2	R	0.68	−1.11	0.72	+0.21
3	R	0 90	−0.01	0.54	−1.38
4	R	0.45	−5.30	0 31	−3.19
5	R	0 80	−0.50	0 66	−0.97
6*	R	0 90	+0 98	0.60	−0.93
7*	R	0 81	−1 25	0.81	+0 01
8	L	0 87	−0 50	0.56	−1.47
9	L	0 91	+1 51	0.83	+1 18
10	L	0 83	−0 23	0.85	+0 80
11	L	0 62	−2 16	0 36	−2 47
12	L	0 72	−1 53	0 81	+0 05
13	L	0 60	−2 46	0 34	−2.59
14	L	0 73	−2 30	0 44	−2.45
15	L	0 46	−4 19	0 64	+0.03
16	L	0 77	−0.44	0 51	−1.78
17	?	0.97	+0 53	0 86	+0.25
18	?	0 71	−1 52	0 70	+0.80
19	?	0 80	−1 35	0.84	+0 17
20*	?	0 90	+0.17	0 86	+0 47

TLE = temporal lobe epilepsy, L = left, R = right, ? = unknown * Patients in whom no ERP activity was elicited in response to either memory task

ERP recordings

Memory task ERP characteristics

Robust reliable ERPs were elicted bilaterally in response to both types of memory task in 17 patients. ERP morphology was similar across task type (fig. 3A) and 2 ERP components were identified. The first component was a negative wave peaking at around 400−600 ms poststimulus (N400). The second component peaked at 600−1000 ms poststimulus and was positive in polarity (P600). The polarities of both ERP components remained unaltered across the recording contacts of each depth electrode (fig. 3B).

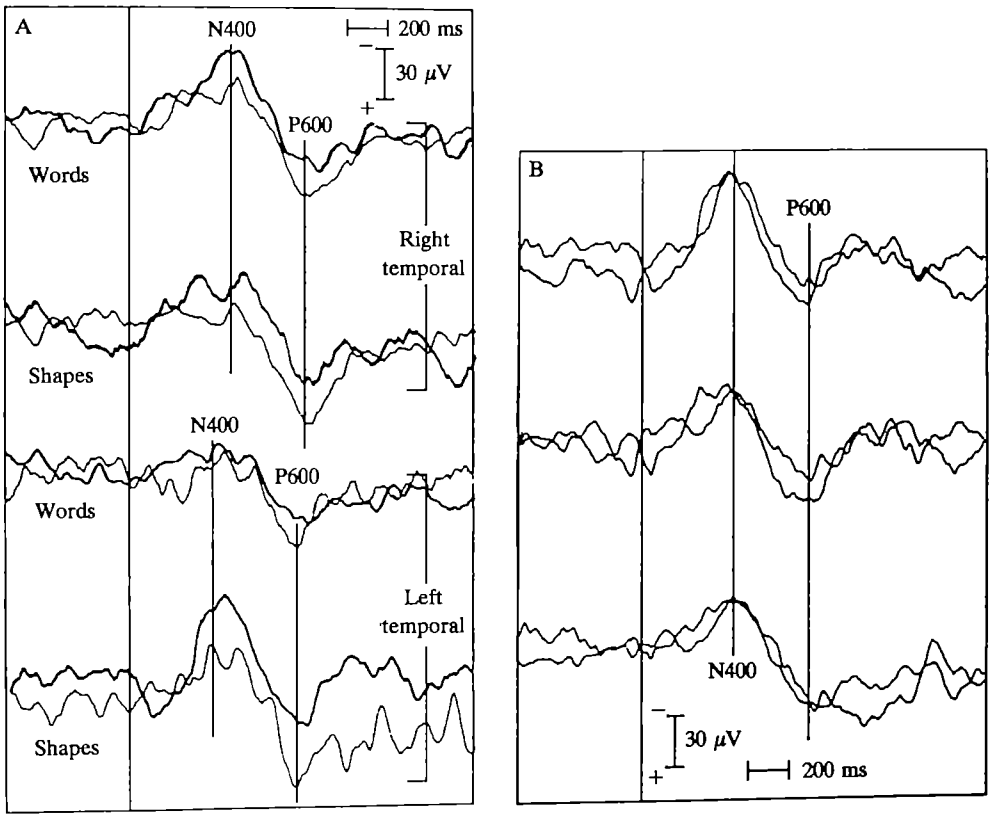

FIG. 3. A, ERP morphology as a function of type of memory task. Top two sets of traces show ERPs recorded from the most medial contact of the right temporal depth electrode for each type of memory task, whereas the bottom two sets of waveforms have been taken from the left temporal depth electrode Two components are elicited, an N400 and a P600. In each set of traces, the solid line represents the ERPs elicited to the novel stimuli, whereas the repeated stimulus waveforms are illustrated by the light solid line. Each waveform is the average of two sets of trials. (Typically, approximately 70–80% of each stimulus type were averaged) Positivity is down and time of stimulus delivery is indicated by the solid vertical line B, ERP morphology across successive electrode contacts of the (right) temporal depth electrode remained similar. No polarity reversals were noted. ERP waveforms from 2 sets of trials are superimposed

In 3/20 patients studied *no* ERPs were elicited either to the verbal or the visuospatial memory task. Accuracy (performance) scores in these 3 individuals were comparable with the rest of the patients studied and to a population of normal subjects (Andrewes *et al.*, 1990). Memory task ERPs were absent *bilaterally* (fig. 4) in 2 patients (Cases 7, 20). In 1 patient (Case 6), who was explored unilaterally with depth electrodes, the memory task ERPs were also absent.

MANOVA analyses were performed on ERP data of 14 patients, in whom bilaterally present ERPs and clearly lateralized seizure foci were demonstrated. Raw ERP data are listed in Appendices 1 and 2.

MANOVA results on N400 latency (Table 3) failed to reveal any significant main effects for task (visuospatial vs verbal), side (left vs right) or stimulus type (repeat or novel). Testing on N400 amplitude data (Table 4) showed, however, that stimulus type

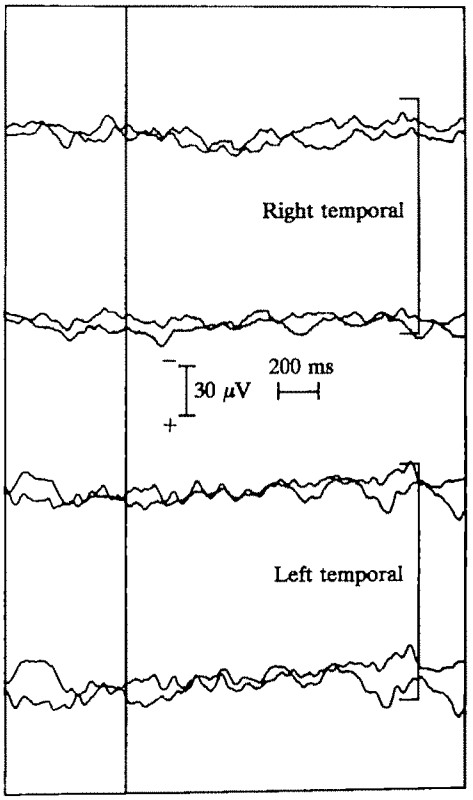

FIG. 4. Bilaterally absent memory task ERPs in a patient (*Case 7*) with a unilateral (left) posterior temporal lesion. Responses shown have been recorded in response to verbal stimuli from 2 sets of trials.

was an important variable ($F_{4,52} = 7.61$, $P < 0.0005$). The group means for N400 amplitude for each stimulus type indicated that N400 amplitude was larger in response to novel stimuli and smaller to repeated stimuli (fig. 5A). The other main effects of task and side were not significant.

Similarly, the P600 latency MANOVA analysis (Table 5) showed no significant main effects for task, side or stimulus. P600 amplitude (Table 6) varied with stimulus type ($F_{4,52} = 10.99$, $P < 0.00005$) and side of recording ($F_{2,26} = 3.38$, $P = 0.05$). Group

TABLE 3. MANOVA ANALYSIS OF N400 LATENCY AS A FUNCTION OF TASK, SIDE OF RECORDING AND STIMULUS TYPE

Source of variation	*Sum of squares*	*df*	*Variance estimate*	*F, P*
Task	622.4	1	622.4	0.13, $P > 0$ 1
Error	61529.4	13	4733.1	
Side	155.6	2	82 8	0 02, $P > 0.1$
Error	$1.2 \times 10^{+5}$	26	4514.9	
Stimulus	7940.7	4	1985.2	0 91, $P > 0.1$
Error	$1\ 1 \times 10^{+5}$	52	2188.2	

df = degrees of freedom.

TABLE 4 MANOVA ANALYSIS OF N400 AMPLITUDE AS A FUNCTION OF TASK, SIDE OF RECORDING AND STIMULUS TYPE

Source of variation	*Sum of squares*	*df*	*Variance estimate*	*F, P*
Task	448.8	1	448.8	2 81, $P > 0.1$
Error	2074 6	13	159.6	
Side	333.0	2	166 5	0.65, $P > 0.1$
Error	6613.2	26	254.4	
Stimulus	3662.8	4	915 7	7 61, $P < 0$ 0005
Error	6253 0	52	120.3	

df = degrees of freedom.

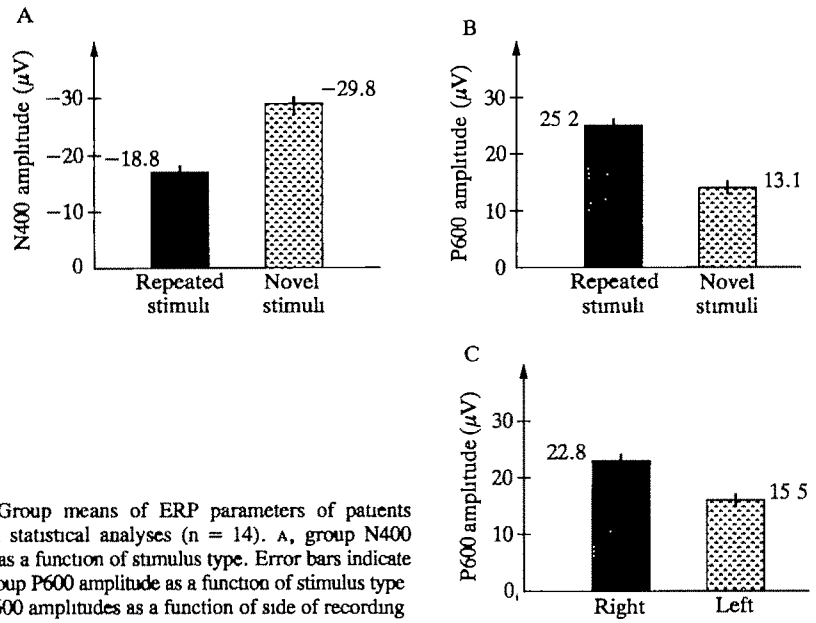

FIG. 5. Group means of ERP parameters of patients included in statistical analyses (n = 14). A, group N400 amplitudes as a function of stimulus type. Error bars indicate 1 SD. B, group P600 amplitude as a function of stimulus type C, group P600 amplitudes as a function of side of recording

means for P600 amplitude data indicated that repeated stimuli elicited larger P600s (fig. 5B) and these were larger on the right side (fig. 5C). No effects of task were noted.

Control task ERPs

The specificity of the memory ERPs was established by the control tasks. No response was elicited to the passive control task (fig. 6A) in any of the 20 patients.

The active control task of the classical auditory oddball paradigm showed that in 11/20 cases the limbic P300 was unilaterally absent ipsilateral to the seizure focus (fig. 6B, Table 1). In 6/20 cases robust P300s were elicited bilaterally. In the final 3 cases P300 was bilaterally absent (Case 3), absent contralateral to seizure focus (Case 10) and present ipsilateral to seizure focus in a unilateral recording (Case 6). Details of these cases have been published previously (Puce *et al.*, 1989*b*). The polarity, latency and amplitude

TABLE 5 MANOVA ANALYSIS OF P600 LATENCY AS A FUNCTION OF TASK, SIDE OF RECORDING AND STIMULUS TYPE

Source of variation	*Sum of squares*	*df*	*Variance estimate*	*F, P*
Task	24073.8	1	24073 8	1 46, $P > 0$ 1
Error	$1\ 2\times10^{+5}$	13	16509.5	
Side	13073.5	2	6536.8	0.76, $P > 0$ 1
Error	$2\ 2\times10^{+5}$	26	8566.4	
Stimulus	2376 0	4	594.2	0 13, $P > 0.1$
Error	$2.4\times10^{+5}$	52	4520.0	

df = degrees of freedom

TABLE 6. MANOVA ANALYSIS OF P600 AMPLITUDE AS A FUNCTION OF TASK, SIDE OF RECORDING AND STIMULUS TYPE

Source of variation	*Sum of squares*	*df*	*Variance estimate*	*F, P*
Task	73 8	1	73.8	0.82, $P > 0$ 1
Error	1163.9	13	89 5	
Side	1568.3	2	784 1	3 38, $P > 0$ 05
Error	6038 1	26	232.2	
Stimulus	4930.7	4	1232 7	10 99, $P < 0.0005$
Error	5827 6	52	112.1	

df = degrees of freedom

of the limbic P300 for each patient has been included in Appendix 3. In general, P300 polarity was either positive across all depth electrode sites or was negative in the most medial recording contact of the depth electrode and became positive in polarity in all subsequent lateral recording contacts.

The visual discrimination tasks, using similar stimulus material to the memory task, failed to generate an N400 or P600. Instead, the ERP elicited to these tasks consisted of a single component which was either positive in polarity or reversed its polarity across depth contacts. This P300-like ERP component was absent unilaterally in the 11/20 cases in whom no limbic P300 was elicited ipsilateral to the seizure focus (fig. 6c). This component was also bilaterally present in the 5 cases in whom bilaterally present auditory oddball P300 were recorded and in the 1 case with a unilateral recording. In 1 patient (Case 20), a technically inadequate study was obtained, due mainly to the presence of high amplitude delta activity (Puce *et al.*, 1989*b*) which precluded the recording of reliable ERPs. The recording session was not repeated due to withdrawal of depth electrodes. Similarly, in a further patient (Case 14), removal of depth electrodes precluded further study.

Dissociation between P300 and N400/P600 abnormalities

There was a dissociation between the P300 and N400/P600 ERP abnormalities (Table 1). In the 17/20 cases where the N400/P600 ERPs were elicited bilaterally, the

P300s were absent unilaterally in 11 cases, present bilaterally in 5 cases and absent bilaterally in 1 case.

In none of the 3 cases with absent memory task ERPs were the P300s bilaterally absent. In 1 patient (Case 7) P300s were present bilaterally and in the second (Case 6) P300 was present ipsilateral to the seizure focus (unilateral recording). In the third case (20) the P300 was absent ipsilateral to the seizure focus. While the P300s elicited to the auditory oddball task and those of the simple visual discrimination tasks showed an identical distribution with regard to ERP abnormality, the N400/P600s of the memory tasks produced a different pattern of abnormality.

Clinical and anatomical correlation of ERP abnormalities

Unilaterally absent P300s, found in 12/20 cases, correlated with the side of the epileptogenic temporal lobe, with the exception of Case 10, as previously described (Puce *et al.*, 1989*b*). Unlike the situation for P300s, N400/P600s were either present bilaterally or absent bilaterally, and thus were not of value in localizing the epileptogenic focus.

The 3 patients with bilaterally absent N400/P600s all had ipsilateral temporal white matter lesions shown on MRI scans (fig. 7). These lesions were ipsilateral to the seizure focus. Case 6 had a large (8 cm long) posterior temporal neocortical and white matter

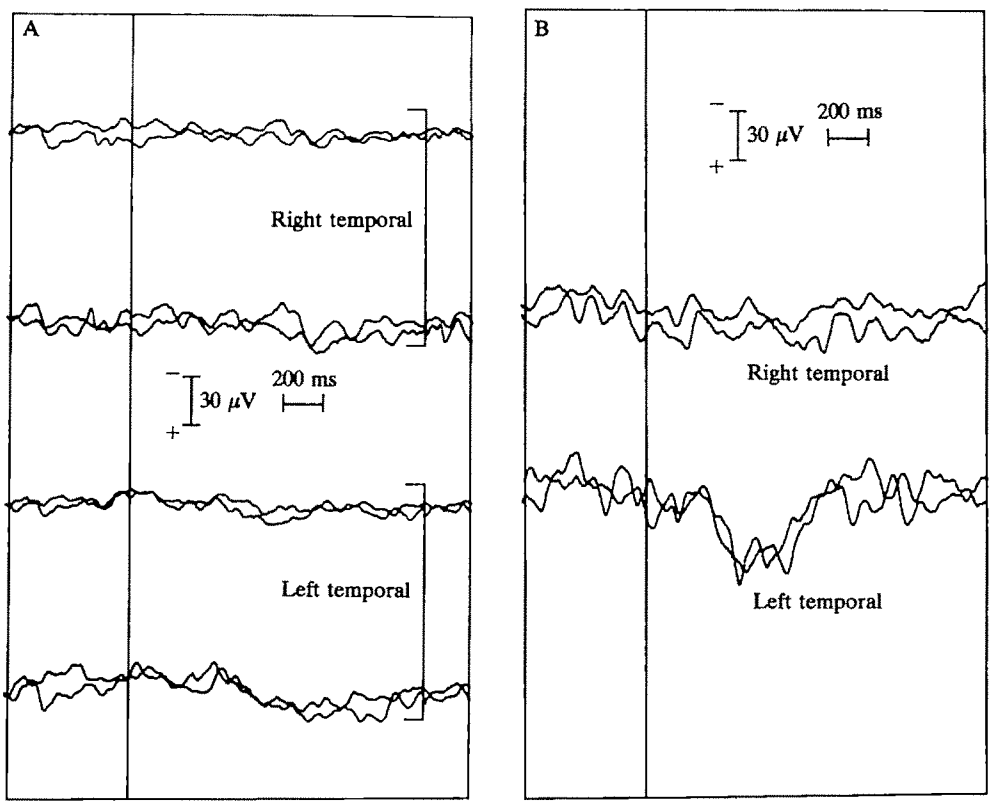

FIG 6A and B.

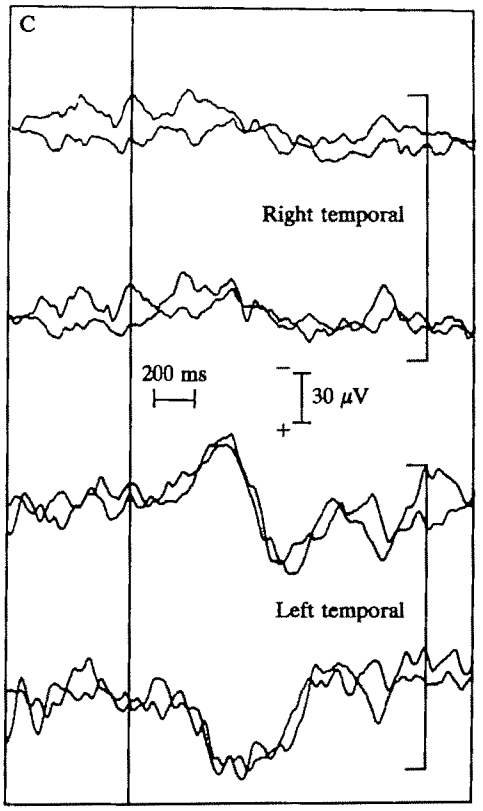

FIG. 6 Control task ERPs from the same patient as in fig. 3. A, passive task ERP waveforms show no discernible ERP activity in 2 sets of trials recorded from the 2 most medial recording contacts of each depth electrode. B, auditory oddball task recordings show a P300 which is present in the left temporal lobe, but absent in the right (epileptogenic) temporal lobe Results from two sets of trials have been recorded from the most medial recording contact of each electrode C, visual discrimination task ERPs show a similar distribution to auditory oddball P300s as indicated by the absence of ERP activity in the epileptogenic (right) temporal lobe. (Two sets of trials taken from the 2 deepest recording contacts on each electrode.)

lesion due to a head injury (fig. 7A). Case 7 had a similarly sited lesion (4 cm long) due to a probable perinatal posterior cerebral artery occlusion. Case 20 had a small anterior temporal white matter lesion (1 cm diameter) whose cause and nature remains unknown.

None of the 17 patients with bilaterally present N400/P600s had white matter lesions on MRI. Sixteen of these had normal MRI scans, apart from subtle hippocampal abnormalities due to proven or suspected hippocampal sclerosis in 9 cases. The only major MRI abnormality in this group was a 1 cm diameter lesion in the left posterior temporal region, confined to the neocortex, with sparing of the white matter (Case 16). This lesion was not visualized on CT and its nature is unknown.

DISCUSSION

ERP morphology: effects of task demand and stimulus type

We have demonstrated that ERPs of reproducible morphology may be recorded from depth electrodes sited in the temporal lobes to *visuospatial* recognition memory tasks. The morphology of the visuospatial memory task ERPs was comparable to those previously described to *verbal* recognition memory tasks (Smith *et al.*, 1986), also confirmed in this study. The ERPs elicited to both types of memory task consisted of

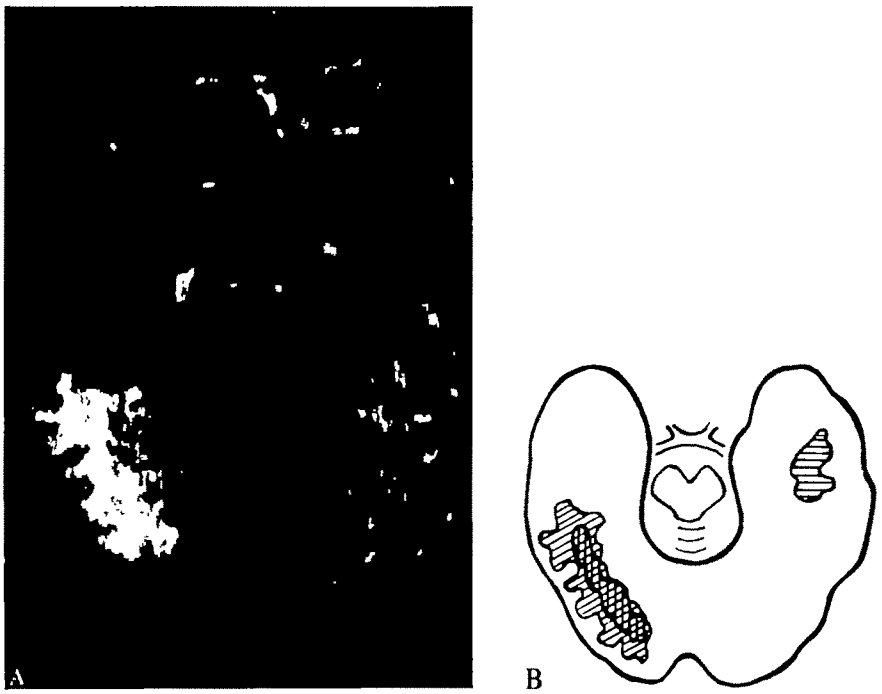

FIG. 7 A, axial MRI scan showing an extension lesion in the neocortex and white matter of the right posterior temporal region (*Case 6*). B, tracings of lesions seen on MRI scans showing the axial section of brain parallel to the base of the temporal lobe. Three temporal lobe white matter lesions (2 right and posterior, 1 left and anterior) in the patients with absent recognition memory ERPs are represented by altered orientations of striped lines.

a negative/positive ERP complex, an N400 and a P600. N400s tended to be larger to novel stimuli and P600s to be larger for repeated stimuli in both recognition tasks—verbal and visuospatial—verifying the effect of stimulus type seen previously with verbal stimulus material (Smith *et al.*, 1986). In this study no effects were seen in ERP morphology between sides and task type and there were no differences in the N400/P600 component latencies or N400 amplitude across sides of recording.

The relationship between the depth and surface correlates of recognition memory task ERPs remains to be clarified. Scalp recordings of N400/P600 ERPs in response to recognition memory tasks (Smith and Halgren, 1988; Nagy and Rugg, 1989; Rugg and Nagy, 1989; Friedman, 1990) have shown waveforms with peaks of similar morphology and comparable latency range to depth-recorded potentials, which appear to be generated simultaneously in several neocortical and subcortical structures. Recognition memory task ERPs, recorded from the surface, are found to be attenuated following anterior temporal lobectomy (Smith and Halgren, 1988), unlike auditory oddball P300s, which remain unaffected. Smith *et al.* (1986) postulated that the depth P600, observed preferentially in response to repeated items, was a delayed P300, as it is elicited in a target detection type task. The increased latency was attributed to increased stimulus evaluation time in these relatively difficulty memory tasks compared with auditory oddball tasks, as it is now well established that scalp P300 latency increases with task difficulty

(Poon *et al.*, 1976; Magliero *et al.*, 1984; Pfefferbaum *et al.*, 1986; Polich, 1987). Our results suggest that the P300 and P600 are two different entities. This is best demonstrated by the dissociation of ERP abnormalities, in that P600s (and N400s) were abolished in patients with posterior temporal lesions, while P300 remained unaffected. Conversely, robust P600s were elicited in cases where the P300 was absent ipsilateral to the temporal lobe seizure focus. The P600 (and N400) appear to be specifically generated by recognition memory tasks, as seen by the difference in ERP morphology to tasks with similar stimulus material. In the 'passive' task, effectively no ERPs were elicited by stimulus material which required no response and was presented *without* repetition. Similarly, the visual discrimination task produced P300-like ERPs which were abolished ipsilateral to seizure focus, in line with the auditory oddball responses. ERP data in scalp recordings also allude to the difference in the two ERP peaks: N400/P600 and P300 show different behaviour following anterior temporal lobectomy.

The precise generators of the recognition memory ERPs are not yet known. We did not observe any local polarity reversals or large amplitude gradients in our orthogonal depth electrodes targeted at the anterior hippocampus, confirming the data of Smith *et al.* (1986). In more posteriorly placed electrodes, however, local polarity reversals were noted to occur within the mid and posterior hippocampus and hippocampal gyrus in depth electrodes sited along an anteroposterior medial temporal axis, being consistent with a local generator in the medial temporal regions.

Two hypotheses have been suggested for the apparent stimulus specificity of the N400 and P600. First, each ERP peak may subserve different aspects of information processing, that is, the N400 is related to processing of novel stimuli and the P600 to the recognition of 'familiar' stimuli (Smith *et al.*, 1986). The N400 may therefore reflect associative activation, whereas the P600 could subserve cognitive closure (Halgren and Smith, 1987). Hence novel stimuli will produce augmented N400s, which will decline in amplitude as the stimulus becomes familiar, in parallel with the increase in P600 amplitude, which reflects cognitive familiarity. It is, at this stage, unclear whether N400/P600 consists of a single component or is composed of multiple components. Presumably, if the multiple component theory is more likely, a dissociation between the N400 and P600 would have to be demonstrated, for example, in cases with different pathological mechanisms. Conversely, if the N400/P600 ERP complex was a single entity, then lesions would affect both parts of the complex. The case for a single entity is made using the idea that the N400/P600 ERP complex is superimposed on a variable baseline (Rugg and Nagy, 1989). The baseline shifts in polarity as a function of stimulus type. If the baseline shift becomes more positive, then larger N400s and smaller P600s will be seen. Conversely, if the baseline shift is negative, then larger P600s and smaller N400s will be recorded, as in the repeated stimulus presentations, thereby explaining the apparent separate behaviour of each peak as a function of stimulus type. The preliminary results seen in this study would support this idea, in that *both* N400 and P600 were affected in the presence of a lesion.

Memory task ERP absence and the primate recognition memory pathway

In patients with temporal lobe epilepsy, the commonest P300 ERP abnormality is a unilaterally absent response that correlates with the epileptogenic side and the frequent finding of sclerosis in the anterior hippocampus (Puce *et al.*, 1989*b*). In this sample

of patients, the same trend applied, with 12/20 patients showing unilaterally absent auditory oddball P300s. In contrast, using the same group of 12 patients, we found that recognition memory ERPs were either present bilaterally or absent bilaterally in these cases. Whilst the left hemisphere is thought to be predominantly involved with verbal information, and right with nonverbal, at least from a neuropsychological perspective, the verbal and visuospatial memory ERPs were morphologically identical across sides. The lack of lateralization may be due to at least two factors: (1) lack of specificity of the memory tasks; (2) a physiological nonlateralization across tasks.

It is unlikely that the memory tasks were not specific, as behavioural data reported elsewhere (Andrewes *et al.*, 1990) showed selective memory deficits in a subset of these patients tested in the immediate postictal period and also postoperatively. Behavioural data demonstrated decreased verbal memory performance in cases of left sided seizure/temporal lobectomy, with the converse selective (visuospatial) memory deficit being demonstrated with right sided seizures/surgery. It appears therefore that N400 amplitude, at least, remains unaffected as a function of recording side and task. P600 amplitude elicited to both memory tasks was larger in the right temporal lobe, but the significance of this finding is unclear. Of the 14 patients included in the analysis, 9 had a left temporal lobe seizure focus. The differences in P600 amplitude across sides could be due either to genuine left-right ERP asymmetry or differences between epileptogenic and nonepileptogenic temporal lobes. Study of a larger group of patients is needed to resolve this question.

The bilateral absence of memory task ERPs may be interpreted in the light of theoretical and experimental studies of primate recognition memory. Mishkin (1982) proposed a pathway for visual recognition memory which involved the passage of visual information from the occipital cortex to the inferior temporal cortex (area TE). The inferior temporal cortex then sends its connections to the amygdala and hippocampus, via temporal white matter, which in turn then passes on the information via the dorsomedial nuclei and anterior nuclei of the thalamus to midline thalamic structures. Mishkin noted that *bilateral* lesions to area TE and beyond this point in the recognition memory pathway markedly impaired *performance* in primate recognition memory. Subsequent studies of primate memory have examined and confirmed the effects of lesions at various points in Mishkin's memory pathway (Mahut *et al.*, 1982; Aggleton and Mishkin, 1983; Zola-Morgan and Squire, 1984; Salmon *et al.*, 1987). Recent studies of single unit activity have confirmed the role played by the inferotemporal cortex in primate recognition memory processes (Rolls *et al.*, 1982; Brown *et al.*, 1987; Miyashita and Chang, 1988; Phillips *et al.*, 1988). Reciprocal connections between inferotemporal cortex and hippocampus (field CA1) have also been demonstrated (Iwai and Yukie, 1988; Yukie and Iwai, 1988).

In the 3 patients with absent N400/P600s it is possible that the unilateral lesion in the temporal white matter interrupted the passage of visual information on its way to the ipsilateral inferior temporal cortex (area TE) and subsequent recognition memory pathway structures. The memory performance of these patients, however, was *not* significantly impaired, suggesting some compensation by the intact hemisphere. The identical ERPs seen on both type of recognition memory task may reflect an *interaction* between two intact recognition memory pathways. If this assumption is true, then a lesion in one of these pathways may preclude an interaction between the hemispheres, and hence the ERPs will be absent bilaterally, as seen in this study. Thus while the

material-specific neuropsychological response may be structurally more dependent on one hemisphere rather than the other, both hemispheres may actually be activated during the memory process with regard to neuropsychological function. Certainly, Smith and Halgren (1988) have postulated a bilateral generator for the recognition memory ERPs, as recorded at the scalp. Further studies using simultaneously recorded scalp and depth recordings are needed in order to investigate the relationship between the scalp and depth correlates of memory recognition ERPs and the issue of bilateral versus unilateral generators. Other functional assessment techniques, such as the magnetoencephalogram, could prove useful in resolving these issues.

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APPENDICES

APPENDIX 1 P600 LATENCIES IN ms POSTSTIMULUS FOR BOTH RECOGNITION MEMORY TASKS IN 14 SUBJECTS INCLUDED IN MANOVA ANALYSES

	N400 latency (ms)								*P600 latency (ms)*							
	Words				*Shapes*				*Words*				*Shapes*			
	Right		*Left*		*Right*		*Left*		*Right*		*Left*		*Right*		*Left*	
Case	*Rep*	*Nov*	*Rep*	*Nov*	*Rep*	*Nov*	*Rep*	*Nov*	*Rep*	*Nov*	*Rep*	*Nov*	*Rep*	*Nov*	*Rep*	*Nov*
1	536	520	584	552	496	464	472	536	1090	1070	1200	1180	856	808	984	856
2	416	480	456	464	408	448	520	424	776	744	736	808	744	688	728	728
3	440	464	432	400	560	512	424	528	760	792	672	736	896	848	584	816
4	392	480	448	464	360	424	480	488	720	760	824	736	640	776	728	728
5	464	440	400	376	480	496	392	376	856	824	896	704	928	912	808	792
8	448	336	560	544	408	360	480	528	728	848	1050	960	736	752	824	864
9	448	440	368	480	408	432	408	464	744	824	704	816	712	720	760	760
10	488	592	408	544	552	616	600	456	1040	936	840	936	1080	1060	1000	944
11	512	512	400	448	424	424	440	360	776	688	760	808	616	808	880	648
12	464	536	464	480	312	424	416	472	864	888	952	872	688	768	768	864
13	384	512	384	392	488	512	464	416	592	704	736	808	736	720	640	816
14	472	472	520	400	448	464	504	512	928	928	880	816	712	888	928	912
15	376	360	384	408	544	448	496	360	816	728	792	856	784	736	752	768
16	364	372	376	488	432	456	400	392	696	728	664	704	760	648	936	816

ERP data for both tasks (words and shapes), sides (right and left) and stimulus type (repeated (Rep) and novel (Nov)) are included in the table

APPENDIX 2 P600 AMPLITUDES IN mV FOR BOTH RECOGNITION MEMORY TASKS IN 14 SUBJECTS INCLUDED IN MANOVA ANALYSES

	N400 amplitude (μV)								P600 amplitude (μV)							
	Words				Shapes				Words				Shapes			
	Right		Left		Right		Left		Right		Left		Right		Left	
Case	Rep	Nov	Rep	Nov	Rep	Nov	Rep	Nov	Rep	Nov	Rep	Nov	Rep	Nov	Rep	Nov
1	−52 6	−41 3	−33 3	−46 8	−49 7	−57 8	−34 0	−30 3	+38.4	−6 0	+11 7	+10 8	+15 7	+16 6	+5 2	+0 9
2	−6 8	−21 7	−37 6	−42 7	−5 8	−15 0	−46 4	−66 8	+37.1	+16 7	+34 4	+5 3	+35 4	+31 8	+38 2	+0 4
3	−13 6	−30 1	−3 7	−45 7	−19 4	−54 8	−16 7	−9 6	+22.0	+29 5	+17 1	+16 7	+51 4	+28 6	+17 7	+15 2
4	−19 8	−25 7	+0 2	−20 7	−33 8	−35 1	−28 0	−18 3	+3 D	−5 3	+12 6	+6 5	+8 1	−17 1	+2 0	−5 9
5	−14 3	−16 2	−15 3	−15 9	−24 2	−48 0	−15 8	−25 3	+7 2	+0 2	+13 1	+13 5	+69 4	+6 0	+28 2	+1 0
8	−22 0	−18 5	−18 6	−47 0	−20 6	−34 3	+4 0	−36 8	+31 0	+18 3	+6 6	+30 6	+35 3	+6 0	+28 4	+23 2
9	−10 9	−43 3	−32 6	−23 2	−28 5	−45 9	−10 1	−54 5	+8 4	+8 9	+34 0	+18 2	+35 1	+17 7	+20 0	+5 5
10	−9 8	−12 6	−41 5	−30 2	−11 3	−28 4	−14 1	−18 1	+3 0	+5 4	+24 5	+7 8	+6 7	+0 8	+41 1	+21 5
11	−13 5	−10 0	−17 8	−25 6	+11 3	−4 1	−12 7	−4 1	+92 5	+35 6	+30 2	+25 4	+64 7	+43 3	+34 7	+17 7
12	−8 8	−20 6	−8 6	−1 4	−23 8	−13 9	−8 9	−12 7	+17 6	+25 4	+14 2	+17 4	+30 6	+3 9	+19 1	+5 7
13	+1 6	−10 6	−6 4	−17 0	−6 6	−22 7	−21 8	−43 0	+7 2	+1 4	+4 8	−1 0	+21 8	−1 5	+5 2	+13 4
14	−17 8	−26 6	−17 8	−23 4	−32 0	−46 3	−32 8	−44 7	+39 4	+28 8	+8 2	+11 8	+26 0	+22 1	+25 4	+20 8
15	−36 0	−37 8	−34 8	−41 4	−14 0	−78 4	−24 6	−26 4	+52 2	+42 6	+33 0	+22 0	+58 8	+37 8	+32 4	+3 0
16	−2 9	−20 1	−13 8	−25 0	−11 4	−9 7	−14 0	−43 4	+19 1	+13 0	+1 8	+1 8	+20 4	+7 7	+8 2	+5 2

ERP data for both tasks (words and shapes), sides (right and left) and stimulus type (repeated (Rep) and novel (Nov)) are included in the table

APPENDIX 3 LIMBIC P300 POLARITIES, AMPLITUDES AND LATENCIES FOR THE CONTROL TASKS (AUDITORY ODDBALL AND VISUAL DISCRIMINATION TASK 'oo' WORDS) FOR THE 19 CASES IN WHOM P300s WERE ELICITED (CASE 3 HAD BILATERALLY ABSENT P300s)

	Auditory oddball task						Visual discrimination task					
	Right			Left			Right			Left		
Case TLE	Pol	Lat (ms)	Amp (μV)	Pol	Lat (ms)	Amp (μV)	Pol	Lat (ms)	Amp (μV)	Pol	Lat (ms)	Amp (μV)
1 R		Absent			424	40 6		Absent			480	38 2
4 R		Absent			352	34 8		Absent			592	28 0
5 R		Absent			312	40 0		Absent			568	33 6
6 R		336	43 7		Not recorded			496	19 9		Not recorded	
2 R	−1	304	57 0		322	64 9	−1	552	31 6		576	28 2
7 R		272	35 7		304	32 7		544	25 2		408	27 6
8 L	−1	376	61 7		Absent			784	52 6		Absent	
9 L		280	42 3		Absent			392	24 6		Absent	
11 L	−1	248	62 8		Absent		−1	456	42 3		Absent	
12 L		264	8 2		Absent			552	19 2		Absent	
13 L		448	41 9		Absent			520	11 2		Absent	
15 L		320	71 2		Absent			424	40 8		Absent	
16 L		464	67 2		Absent			840	29 6		Absent	
10 L		Absent			296	31 3	Technically inadequate			Technically inadequate		
14 L		288	10 1	−2	272	15 1	Not recorded			Not recorded		
17 ?	−1	264	48 0	−1	272	27 2	−2	392	26 4		344	10 7
18 ?	−1	304	38 0		304	40 6	−1	746	22 6		768	32 0
19 ?	−1	312	39 0		256	21 0	−1	464	15 4		472	10 8
20 ?		312	43 7		Absent			456	15 9		Absent	

TLE = temporal lobe epilepsy, R = right, L = left, ? = unknown, Pol = polarity, Lat = latency in ms, Amp = amplitude in μV Polarity can be assumed to be positive in all recording contacts if no entry appears in this column An entry of −1 denotes that P300 was negative in the most medial recording contact and was positive in the rest, whereas −2 indicates that the polarity of P300 was negative in the 2 most medial recording contacts and was positive in the rest In Case 6 only a unilateral recording was performed (*see text*) Visual discrimination task ERPs were not recorded in Case 14 because of removal of depth electrodes Visual discrimination task ERPs in Case 20 were deemed to be technically inadequate (*see text*)

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MOTOR FUNCTION OF THE MONKEY GLOBUS PALLIDUS

1. NEURONAL DISCHARGE AND PARAMETERS OF MOVEMENT

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SUMMARY

In order to examine the role of the basal ganglia (BG) in the regulation of basic movement parameters, we recorded extracellularly from pallidal neurons in conscious monkeys during the performance of a sequential wrist movement task which was composed of a series of holds and ballistic jumps. The movement sequence was predictable and had to be performed within specified time restraints. We recorded the activity of 297 neurons whose discharges were related to the movement task. We included only neurons whose discharges were related to movements at or about the wrist joint by prior examination outside the behavioural paradigm Each neuron discharged preferentially to one direction of movement at or about the wrist joint. No consistent correlation was found between neuronal discharge and initial joint position, static load application, amplitude of movement or velocity of movement. The mean onset of neuronal discharge was 2 ms after the onset of EMG activity.

The findings implied little contribution from the pallidal neurons in the execution of the current movement or to the movement's parameters. The implications are that the basal ganglia are likely to be concerned with other aspects of movement control.

INTRODUCTION

Since Wilson's early observations (Wilson, 1912, 1925), a vast amount of knowledge has accumulated regarding the role of the basal ganglia (BG) in the production of movements. Despite this, the details as to how it influences movement remains unknown. The best clues come from human studies of hypokinetic subjects with Parkinson's disease (PD) which have noted that hypokinesia correlates with slowness in making complex movements (Benecke *et al.*, 1986, 1987). Complex movements are slowed because it takes much longer than normal to switch from one segment of the movement to the next. In addition, the simple movements, which make up the complex movement, becomes slower the further along the sequence each one occurs. The implications from such studies are that the BG are required to switch from one segment of movement to the next in a movement sequence. This hypothesis implies that the BG are more concerned with movement of a higher level where the emphasis is on planning, expectation and intention to achieve a goal rather than the regulation of movement parameters, such as velocity and force required for the execution of movement. We refer to this as the cognitive aspect of movement.

An alternative proposal, again based on studies of patients with PD, suggests that

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the BG may be involved in the regulation of movement parameters (Hallett and Khoshbin, 1980). The findings from these studies have suggested that in hypokinesia, simple movements are slow and of smaller amplitude than required because of inadequate activity in the agonist muscle, but that the pattern of activation and the timing of activity in the respective muscles is normal. Hallett and Khoshbin (1980) hypothesized that the BG are concerned with the grading of movement amplitudes by appropriate energizing of muscles. However, the slowness of simple movements, as explained in such a hypothesis, does not correlate with the severity of the hypokinesia (Marsden, 1987).

Single cell studies from BG nuclei in awake primates have so far not elucidated the underlying neuronal mechanisms which might explain the observed clinical phenomena. Recordings from the GP have revealed that individual neurons discharge in association with a particular direction of movement of a specific joint (Iansek and Porter, 1980). A whole range of movement directions at different joints are represented within the neuronal population. Many attempts have been made to clarify the basis for this association between neuronal discharge and direction of joint movement but its purpose remains unclear (DeLong, 1971; Iansek and Porter, 1980; Georgopoulos *et al.*, 1983; Mitchell *et al.*, 1987). Several studies have examined the relationship between movement parameters and discharge in the GP (Georgopoulos *et al.*, 1983; Mitchell *et al.*, 1987). Patterns of neuronal discharge have been compared with various movement types such as ramps and sinusoids (Mink and Thach, 1987). Microstimulation has been used by other investigators in an attempt to delineate the role in movement performance (Horak and Anderson, 1984). Few of these studies have examined whether the BG may play a part in the execution of sequences of movements, in motor planning or other cognitive aspects involved in the execution of complex movements (Marsden, 1987). Almost all studies have examined simple movements and have concentrated on relationships between neural discharge and basic parameters of movement such as force, direction and velocity and the neural response to peripheral stimuli. A relationship between cellular activity and some of these parameters has been claimed (Georgopoulos *et al.*, 1983; Mitchell *et al.*, 1987). However, the clinical observations predict that the BG are concerned with cognitive aspects of movement and the relationships that have been found for a number of movement parameters may well be coincidental. A major problem with many of these studies is that neurons are selected simply on whether they have a statistical correlation with the particular test paradigm. When an animal is observed to move outside the restraints of a particular paradigm it is often possible to establish whether neuronal discharge is best related to the joint under study rather than to a neighbouring joint. The purpose of most paradigms is to provide controlled and detailed analysis of movement about a specific joint. They are usually not designed or able to establish whether or not the joint in question is the joint best related to neuronal discharge. If a paradigm uses movements about the elbow then it should only use neurons whose discharges are related to elbow movements and not to finger, wrist or shoulder movements. The use of inappropriate neurons may give misleading information about the movement parameter that was assessed in the paradigm. Taking these points into consideration we have reexamined the role of GP neurons in the production of movement. First, we reexamined the relationship between neuronal discharge and basic parameters of movement by selecting for analysis only those neurons whose discharges were best related to movements of the joint tested by our paradigm. Secondly, we examined the relationship between

neuronal discharge and cognitive aspects of movement. The results of the first study are described in this paper and the results of the second study are described in the accompanying paper (Brotchie *et al.*, 1991). Although a loose relationship was found between neuronal discharge and some parameters of movement, this seems to be an epiphenomenon. Instead, the discharge appears to be more intimately correlated with cognitive aspects of movement as predicted by clinical data (Brotchie *et al.*, 1991).

METHODS

Behavioural paradigms

Two monkeys (M. fascicularis and M. mulatta) were trained for 4–6 mos in a number of behavioural paradigms Both animals were placid as they were handled regularly from the age of 6 mos. During the training procedure, they learned to accept a head restraint which consisted of an occipital support and a nose strap to prevent significant head movement. The animals were trained to perform several tasks, each of which involved a rapid ballistic movement of the wrist joint. The monkeys sat in a primate chair and inserted one hand into a wedge-shaped manipulandum which was designed to fit the open hand firmly (*see* fig. 1). In order to move the manipulandum the monkeys had either to flex or extend their wrist joint. Wrist joint position was represented by a cursor on an oscilloscope screen placed in front of the animal. The monkey was required to move the cursor and track a 5° wide target on the screen to obtain a liquid reward. A trial began when the cursor was aligned in the target window with the wrist in the 'initial hold position'. This usually required the wrist to be in approximately 10° of flexion which will be referred to as the neutral position. The animals held the position for a randomly varied period of 1–2 s called the 'initial hold period' after which the target moved abruptly to a new position (in either flexion or extension). The monkey was allowed 500 ms to make a ballistic movement to realign the cursor in the new target position and was then required to maintain this 'final hold position' for a 'final hold period' (usually 600 ms), in order to receive a juice reward (*see* fig. 1). The reward was delivered by a solenoid valve, opening with an audible click, 2 ms after correctly completing the trial. Each monkey was trained in a number of different tasks which were based on the general outline given above. The tasks relevant to the current study are outlined below.

A task requiring a 21° ballistic movement of the wrist joint was used while searching for neurons. The direction of this movement was alternated every four trials. When a neuron was found that discharged in relation to the task, the cellular activity was recorded while the monkey performed the following series of paradigms.

Paradigm 1

This paradigm consisted of ballistic movements of 21° performed in blocks of eight, in first extensor, and then the flexor direction. When recording neuronal activity, this paradigm was performed first to determine whether the neuronal discharge modulated more in association with movements of a particular direction. It was necessary to determine this first as the following paradigm was performed in only one direction.

Paradigm 2

This was used to determine the relationships between neuronal discharge and movement amplitude.

Paradigm 2.1 This paradigm required wrist movements of four different amplitudes. Three tasks commenced from the neutral wrist position and each consisted of a series of trials requiring a movement of either 21, 14 or 7° amplitude. The fourth task commenced in the fully extended or fully flexed position and required movements of 42° amplitude

Paradigm 2.2. The consistency of a relationship of cellular discharge to amplitude was assessed using this paradigm. It consisted of 5 tasks, 3 requiring movements of 7° and 2 of 14°, starting from different initial joint positions. For convenience of analysis, 9 different tasks were described in Paradigm 2. However, only 7 of these were different and were performed in the order shown in fig. 2. Each task was performed as a series of six trials. After the first trial of each new task the monkey could anticipate the direction and amplitude of subsequent trials. To obtain the neuronal discharge pattern with the best relationship to movement, all movements of the tasks were performed in the direction determined during Paradigm 1.

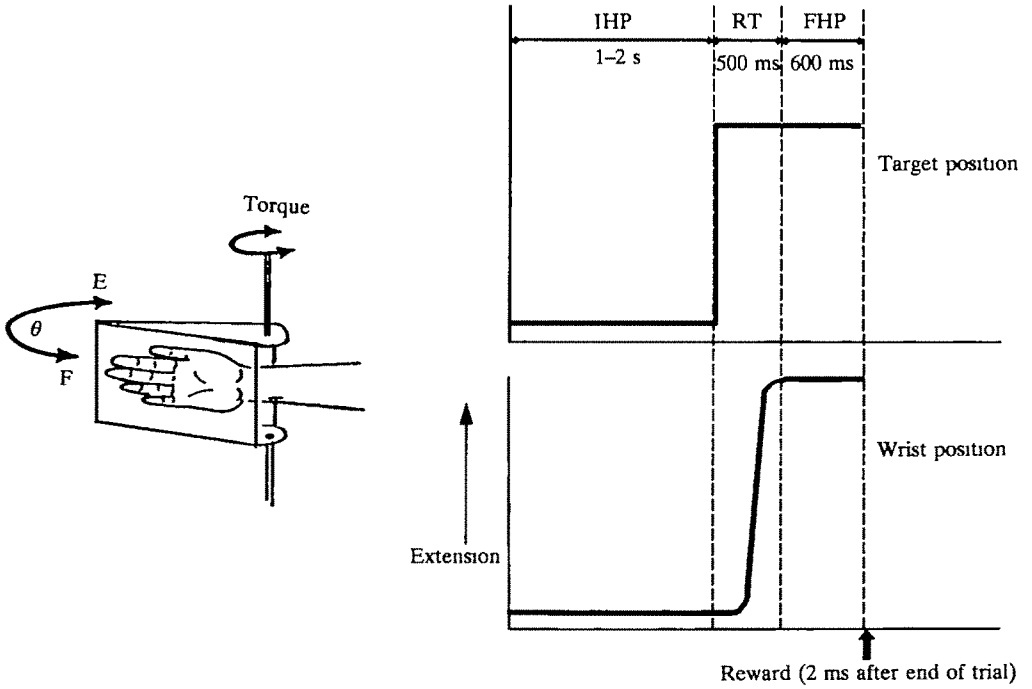

FIG. 1. Schematic diagram of the target position and wrist position during the three different phases of the behavioural paradigm These phases are separated by vertical dotted lines IHP = initial hold period; RT = allowed response time; FHP = final hold period The movement task is described in Methods. The diagram on the left demonstrates the monkey's wrist in the manipulandum which allows movement only in the flexor or extensor directions Load can be applied in either of these directions

Paradigm 3

This is a paradigm in which the monkeys first performed extension and then flexion movements of the wrist, with both assisting and opposing loads. Extensor movements, for example, were made with an opposing extensor load, and then with an assisting flexor load.

When all the tasks were completed, a clinical examination was performed to assess the relation of neuronal discharge to movements made by the monkey outside the behavioural paradigms and to search for sensory fields. The manipulandum was removed from the primate chair to allow the monkey to make unrestrained and spontaneous movements of the limbs. During these movements, we determined the joint to which neuronal discharge was best related This was established by enticing the monkey with food, to perform movements about a particular joint. Neuronal activity was passed through a loudspeaker and the examiner made a subjective judgement as to which joint the neuronal discharge was best related. In a similar way passive movements of joints, stroking of the hairs of the skin and tendon and muscle taps were given to determine neuronal responses to sensory inputs.

Since the repertoire of tasks required of the monkey during the recording of each neuron's discharge was quite large, the spike amplitude occasionally deteriorated before all the tasks could be completed. Also, a number of neurons deteriorated before a complete clinical examination, as described above, could be performed.

Surgical procedures

Once the monkeys had reached a success level of over 80% in each of the learned motor tasks, and had accepted clinical examination, they were prepared for the recording studies. A stainless steel recording chamber was attached over this site using dental acrylic (Espe-pro temp) which bound to stainless steel

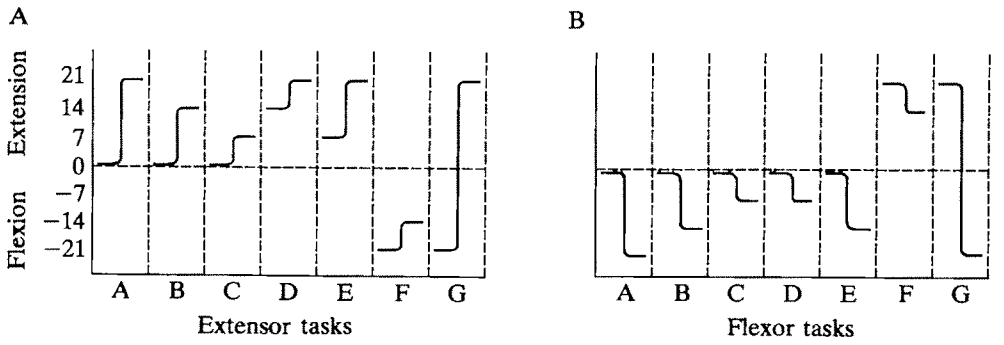

FIG. 2. Schematic diagram of the change in wrist position required for each of the tasks in paradigm 2. The vertical axis represents degrees of extension so the upward changes in joint position on the traces represent extensor movements. This paradigm consisted of 7 tasks, A–G, performed in the order depicted in the diagram. It required three 7° movements C, D and F, two 14° movements, B and E, a 21° movement, task A and a 42° movement, task G. The three 7° movements C, D and F were termed neutral, acute and obtuse, respectively

screws in the skull. The position and angle of the chamber was chosen to give full access to the globus pallidus while passing through as few other relevant structures as possible. In each animal the chamber was tilted 30° back from the vertical and positioned so that a line through its centre would pass through the middle of GP (A12, L8, H8). The chamber was held stereotaxically over the chosen site using an electrode holder, and fixed into position with acrylic.

Recording procedures

Daily recordings were made using glass-coated tungsten electrodes (Merrill and Ainsworth, 1972) fixed to a custom-made mechanical and hydraulic microdrive which was attached to the chamber at the start of each recording session. Recordings of discharges from pallidal neurons were made from the full extent of the GP. Physiological identification of the cerebral cortex, thalamus, putamen, caudate nucleus and substantia innominata assisted in the localization of the GP. Identification of the two segments of the GP, globus pallidus internus (GPi) and globus pallidus externus (GPe), was made at the time of recording by observing the background discharge patterns of the cells as described by DeLong (DeLong, 1971).

Data collection

The behavioral tasks, data recordings and data storage were all performed using an Olivetti M24 computer. The neuronal discharge spikes were amplified, converted into digital pulses using a Schmidt trigger, and stored. Analog signals from the potentiometer on the manipulandum were sampled at 100 Hz. This data stream was stored for later analysis while on-line rasters of the neuronal discharge spikes were produced, centred on the monkey's commencement of movement for immediate evaluation.

Data analysis

Custom-made computer programs were available for data display by comparing neuronal discharge, as represented by periresponse time histograms and rasters, with the position trace. The same programs allowed the measurement of the latencies of neuronal discharge relative to movement and integrated the neuronal activity over a specified period of time for each trial in a task. One-way analysis of variance followed by the Duncan procedure was used to assess relationships between neuronal discharge and a number of movement parameters statistically. A commercially available statistics program (SPSS) was used for this assessment.

EMG recordings

Surface EMG recordings were made from the flexors and extensors of the wrist and fingers. These muscles were considered the primary agonists in the learned tasks. Recordings were also made from biceps, triceps, deltoid, trapezius and pectoral muscles. All EMG recordings were made at separate times from the single

cell recording sessions. The EMG activity was amplified, full wave rectified, sampled at 100 Hz and stored on computer for analyses at a later stage.

Histological identification of neuron location

Electrolytic lesions were made at known coordinates at the borders of the electrode tracks from which recordings had been made from GP neurons. These neurons in turn had been identified on physiological grounds. The lesions were made by passing 25 μA of DC current for 20 s through a microelectrode. The animals were killed by intraperitoneal injection of phenobarbitone. They were perfused through the heart with 4% paraformaldehyde in 0.1 M sodium phosphate buffer in 0.9% saline at pH 7.4. The fixed brain was sectioned at thickness of 40 μm and stained with thionin. Microscopic examination of the sections allowed localization of the marked lesions, the electrode tracks and the neurons.

RESULTS

A total of 363 penetrations were made into the GP in three hemispheres of 2 monkeys. Recordings were made from each hemisphere for a period of 4−8 mos; 297 neurons modulated their discharges in relation to the task. We were able to characterize by clinical examination 145 neurons (49%); of these neurons, 92 (63%) modulated their discharges to movements at or about the wrist joint. The other 53 neurons modulated their discharges to movements at more proximal joints or displayed complex behaviour during the clinical examination and were removed from the sample group, leaving 244 cells. The discharge patterns of neurons which were characterized as discharging to movement at or about the wrist were similar in the behavioural paradigm to that of neurons whose activity was not tested in the clinical examination. On this basis, we concluded that this sample group of 244 neurons contained a predominance of neurons with activity related to wrist movement, 173 of which were in GPe and 71 from GPi. It was these 244 neurons which were then used to assess the relationship of neuronal discharge to various parameters of movement. These and the remaining neurons are examined further in the accompanying paper where the relationship of neuronal activity to cognitive aspects of the movement task will be presented (Brotchie *et al.*, 1991).

Definition of terms

We refer to neuronal activity which occurred at the time of the ballistic movement as 'movement-related activity', to distinguish it from other modulations of discharge which occurred during the hold periods. The change in discharge rate that occurred with movement was either an increase or a decrease in activity. This change in firing rate will be referred to as 'the neuronal response'. In some pallidal neurons the magnitude of the response often depended on the type of wrist movement being performed. We have described neurons of this type as having a preference for the movements that were associated with the greatest neuronal response.

Neuronal discharge relationship to direction of movement

In 188 of the 244 neurons (77%) there was an increase in discharge rate, and in 20 (8%) a decrease in discharge rate in association with movements in both flexion and extension. These neurons were called bidirectional. In the group of 208 neurons with a bidirectional discharge response to movement, 94 showed a preference for movement in one direction and 36 neurons (15%) displayed reciprocal activity, with an increase

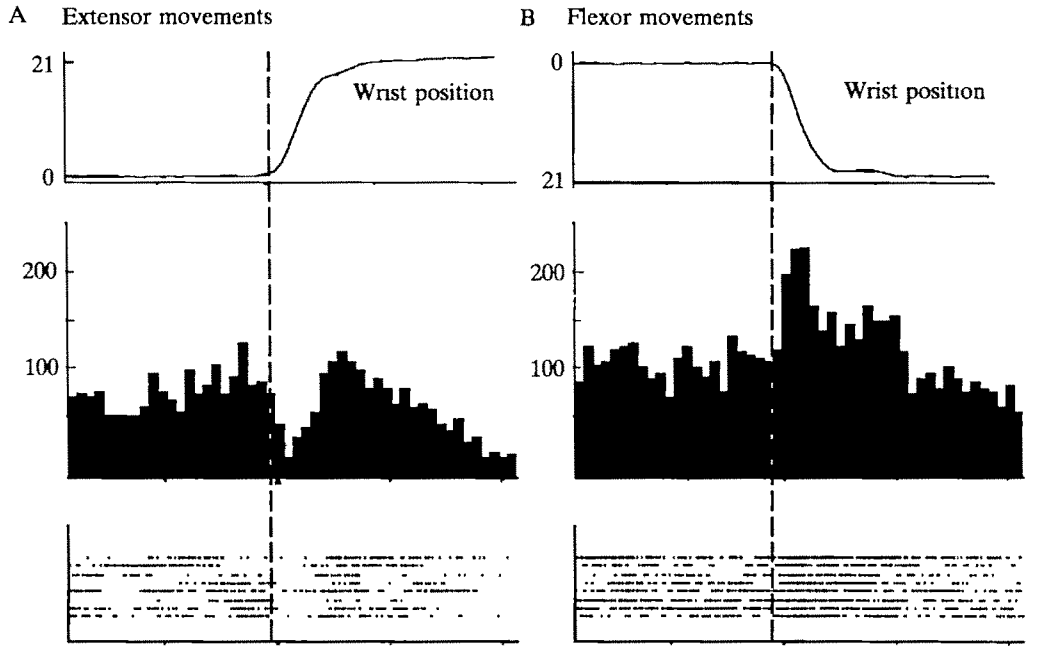

FIG. 3 Example of neuronal discharge which displayed reciprocal activity for the different directions of movement Each row of the raster indicates the neuronal discharge during the performance of one trial with each dot representing unitary discharge. The *top* trace represents the wrist position average over all the trials. The trials are aligned on movement onset which is indicated by the vertical dotted line. The trials in the raster are displayed in the order in which they occurred, with the first trial at the bottom. The vertical scale on the histogram is in impulses/s, the vertical scale on the position trace is in deg of extension, each division on the horizontal scale indicates 500 ms

in discharge rate during movements in one direction and a decrease in discharge rate in the opposite direction (fig. 3).

Neuronal discharge relationship to static load application

Paradigm 3 was designed to dissociate the direction of a movement from the muscles normally making that movement, by providing opposing and assisting loads. The load on the manipulandum was constant throughout the entire six trials of a task. The effect of the load on the activity of the pallidal neurons was assessed both during the initial hold period and the ballistic movement. We shall follow the convention of Mitchell *et al.* (1987) and refer to load applied during the hold period as a static load to distinguish it from the immediate effects of load application which is referred to as a dynamic load. The force was constant during both the initial hold period and the movement. Six ballistic movements were made in each direction against both flexor and extensor loads. Discharges from 62 neurons in the sample group were recorded during the performance of this task. The discharge in the initial hold period varied in only one neuron when the effects of flexor and extensor load were compared. This indicates that, as a generalization, there is no relationship between pallidal neuronal discharge and the application of static loads.

Maintained load did affect the degree to which a number of neurons modulated their

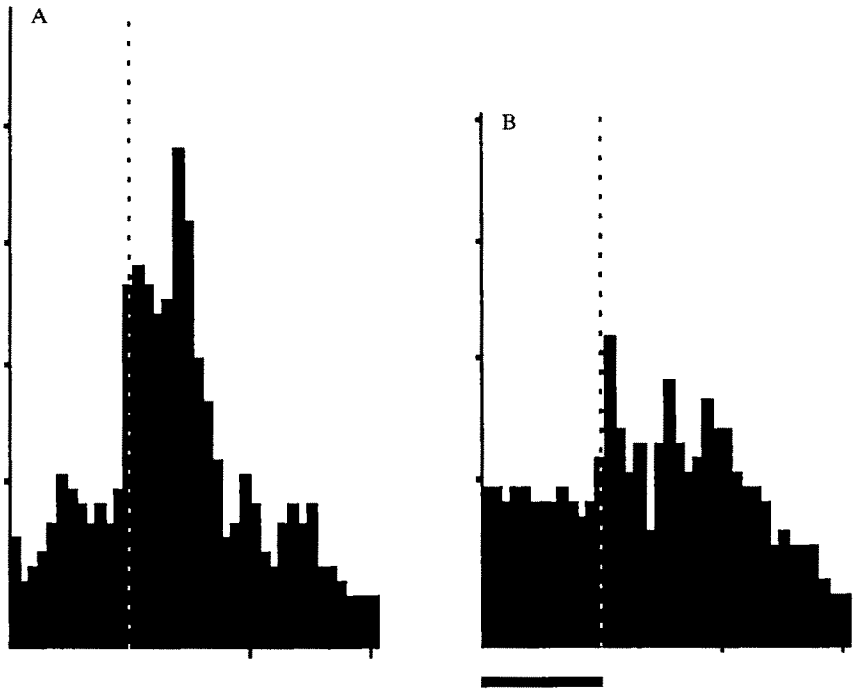

FIG 4 Example of a pallidal neuron whose discharge showed a preferential response for flexor movements in the unloading direction (A). Very little discharge occurred in this neuron for flexor movements against a static load (B). The trials are aligned on movement onset which is indicated by the vertical dotted line Each division on the horizontal scale indicates 500 ms. Each vertical division represents 50 impulses/s.

discharge during the movement. Fig. 4 shows the response of a pallidal neuron to flexor movements with assisting and opposing loads. We have referred to neurons with this behaviour as having a preference for unloading movements. Overall, 14 of the 62 neurons (23%) had a preference for unloading movements, 14 neurons (23%) had a greater response to movements with an opposing load, and 33 neurons (53%) showed no clear preference for loading or unloading movements. However, the animal's skill at performing these movements changed over the experiment. The relationship between dynamic load and skill is examined further in the accompanying paper (Brotchie *et al.*, 1991). Only one neuron displayed a pattern of activity similar to that of muscle.

Neuronal discharge relationship to joint position

The relationship of neuronal discharge to joint position was examined in 92 of the 244 neurons. This was done by comparing discharge rates during the initial hold periods of the 7° movement tasks of paradigm 2.2 (*see* fig. 2). The discharge pattern of 28 of these neurons was inconsistent during the initial hold period over several trials of each of these tasks, indicating that for these neurons, the discharge rate was not related to the stationary joint position. For the remaining 64 neurons, the average firing rate

during the initial hold period was calculated for each trial and the values were grouped according to joint position and compared using one-way analysis of variance (ANOVA). Only one neuron showed a statistically significant ($P < 0.05$) change in discharge frequency with different joint positions. For all other neurons the position of the wrist joint had no effect on the firing rate.

Neuronal discharge and relationship to amplitude of movement

The relationship between neuronal discharge and movement amplitude was assessed in a similar manner. Neuronal responses to movement were usually phasic with a well-defined beginning and end (*see* fig. 5). Neuronal activity was integrated during this period for each trial of paradigm 2 in order to compare the magnitude of the neuronal response with the amplitude of movement. Response of some neurons continued well beyond the end of the movement. In these cases the activity was integrated from the beginning of the response until the end of the movement. This was necessary in order to allow the procedure to be computerized. A manual computation which integrated the total discharges from beginning to end of the phasic burst was also performed as a comparison. No difference was found between the two techniques and thus the computerized data only are presented. The integrated values from each trial were grouped according to the amplitude of movement performed and these groups of values were compared using an ANOVA followed by the Duncan test at the 0.05 level of significance. A relationship to amplitude was said to exist only if: (1) there was a constant response to movement of the same amplitude irrespective of the initial hold position (paradigm 2.2). (Joint position has already been shown to have no effect.) (2) A statistically significant difference existed between the magnitude of the neuronal response for the movements of different amplitude.

Neuronal discharge was examined in 92 neurons during the performance of paradigm 2: 38 neurons did not satisfy the first part of this criteria. Fig. 5 illustrates the inconsistencies commonly found between neuronal discharge frequency and amplitude. In 27 of the remaining 54 neurons, the same magnitude of response occurred for movements of all amplitudes; that is, there was no difference in response between movements of 7 or 42 degrees, and therefore the second part of this criterion was not satisfied. The remaining 27 neurons (29%) displayed a relationship between the amplitude of the neuronal response and the amplitude of movement. Different possible relationships were assessed but few were found. The relationship was linear in 12 neurons (*see* fig. 6) and nonlinear in 15 neurons. For these 15 neurons a greater response was produced for the middle-sized movement of 21 or 14° than for the larger or smaller movements (*see* fig. 7); therefore, only 12 neurons out of the 92 studied (13%) produced responses in which magnitude was linearly related to the amplitude of the movement being performed.

Neuronal discharge relationship to the velocity of movement

The time taken to perform the various wrist movements was constant regardless of the amplitude of the movement, so that the peak velocities were proportional to the amplitude. Velocity could not therefore be assessed separately from amplitude of movement. However, the lack of a clear relationship between neuronal activity and movement amplitude implied that no relationship existed between neuronal discharge

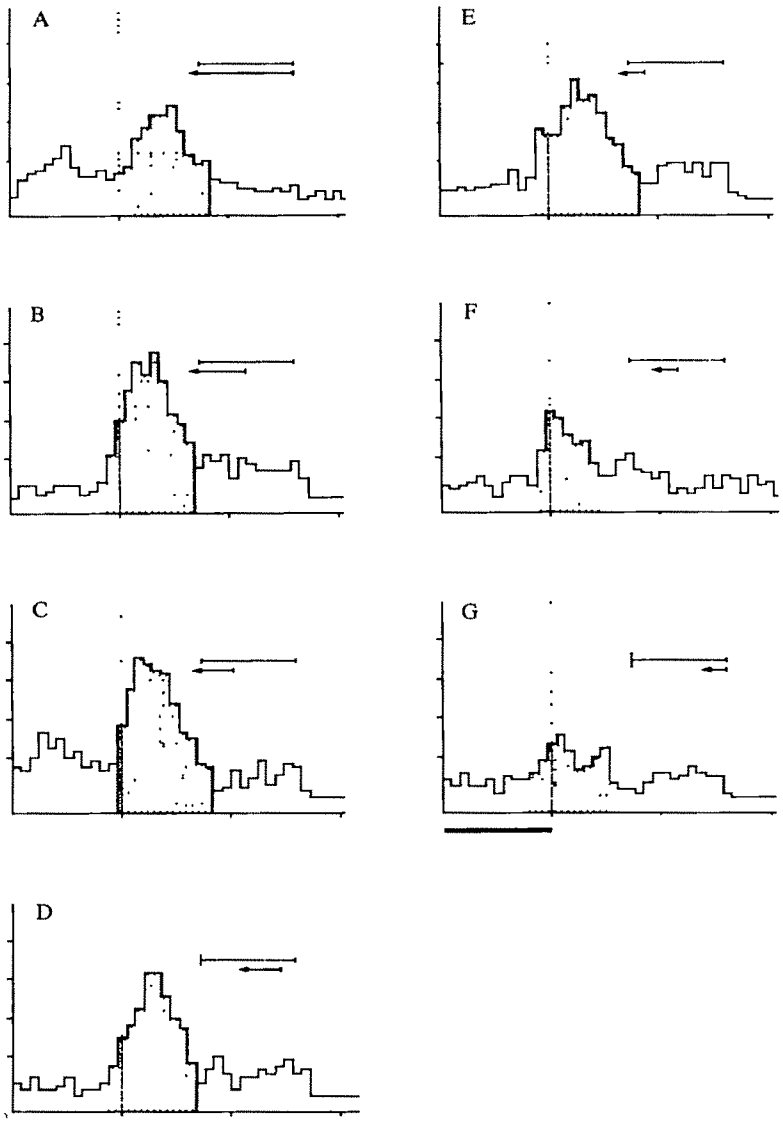

FIG. 5. Histograms of neuronal responses from a pallidal neuron to movements of different amplitudes and different initial joint positions. The size of the movement is represented in the lower of the two horizontal lines in the upper right-hand corner of each histogram. The upper horizontal line represents the maximum excursion possible: 42°. The small vertical line on the lower horizontal line represents the intial hold position and the point of the arrow represents the final hold position The direction of the arrow represents the direction of the ballistic movement; in this case, flexion. A, B, C, D, E, F and G represent 42, 21, 14, 14, 7° acute, 7° neutral and 7° obtuse jumps, respectively. The trials are aligned on movement onset which is indicated by the vertical dotted line. Each division on the horizontal scale indicates 500 ms. Each division on the vertical scale represents 50 impulses/s.

and velocity of movement. Two further observations support this conclusion. On a number of occasions the animal would tend to oscillate on reaching the final hold position, resulting in several brief movements of varying velocities. The resultant neuronal discharge also

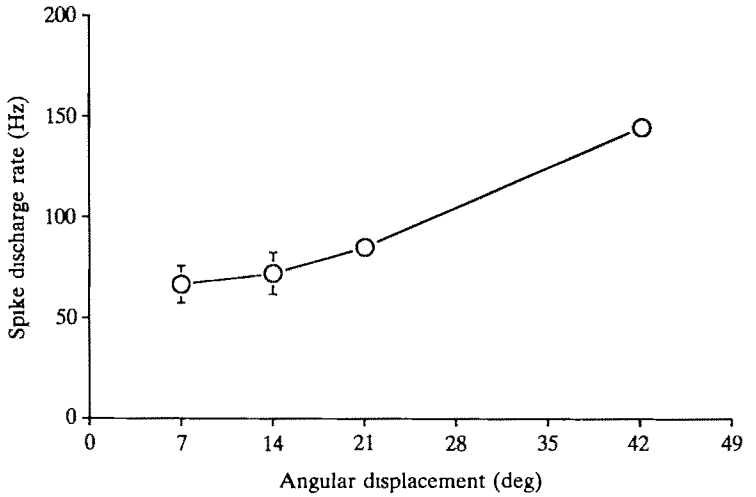

FIG 6 An example of a linear relationship between the magnitude of neuronal response to movement and the amplitude of movement. The vertical scale is in impulses/s. The horizontal indicates amplitude of movement in degrees

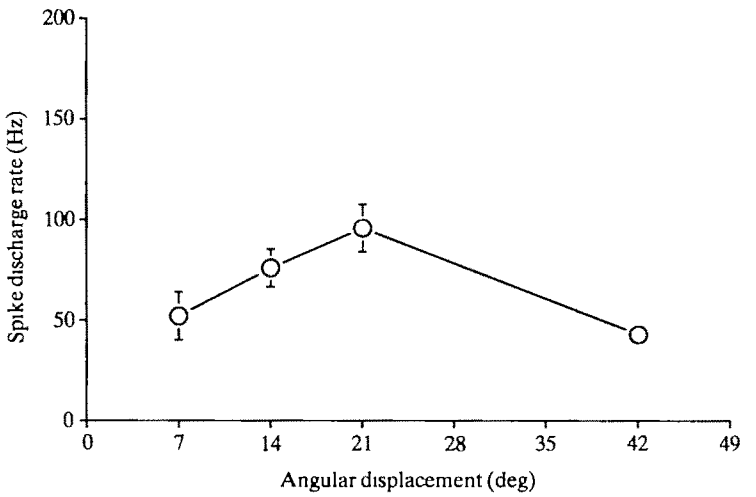

FIG. 7. An example of a nonlinear relationship between the magnitude of neuronal response to movement and the amplitude of movement This neuron discharged preferentially for the 21° amplitude The vertical scale is in impulses/s The horizontal scale indicates amplitude of movement in degrees.

showed appropriately timed bursts but without correlation between the amplitude of the velocity and the magnitude of the movement. In addition, during the initial hold period, cellular bursts would sometimes occur in the setting of zero velocity when the animal was stationary (fig. 8).

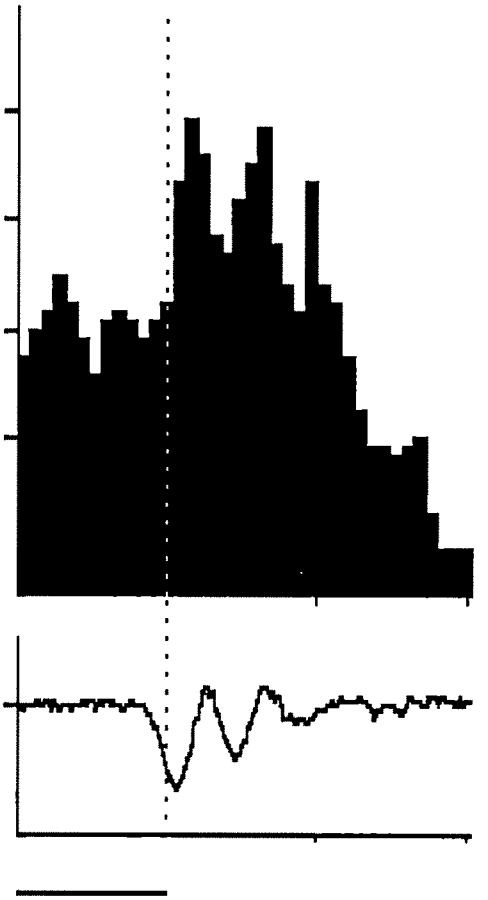

FIG. 8. Histogram of pallidal neuron with discharge relationship to flexor movements of the wrist compared with the velocity trace for 6 repetitions of the same movement task. The histogram construction and the velocity trace were aligned with the onset of movement, represented by the vertical dotted line. The horizontal scale is 500 ms per division and the vertical scale is 50 impulses/s for each division. Multiple peaks in the discharge correspond to multiple peak velocities

Timing relationships between neuronal discharge patterns, EMG and movement

The movement-related activity of most pallidal neurons began at a similar time to that of EMG activity, which in turn occurred approximately 40 ms before the movement. The majority of neurons (81%) in the GP commenced their response within a 60 ms time span on either side of the onset of the EMG activity (*see* fig. 9). In 46% of pallidal neurons the movement-related response led the onset of the EMG activity but led the movement by more than 60 ms in only 14% of cells. The mean onset of response of pallidal cells was 2 ms after the onset of EMG activity. The peak of the response, however, was found in almost all cases to precede the end of the ballistic movement, which for this measurement was taken as the time when the position trace first reached the final hold position.

Clinical examination

As well as recording neuronal discharge during the performance of the various paradigms, the animal was also examined clinically for evidence of neuronal responses

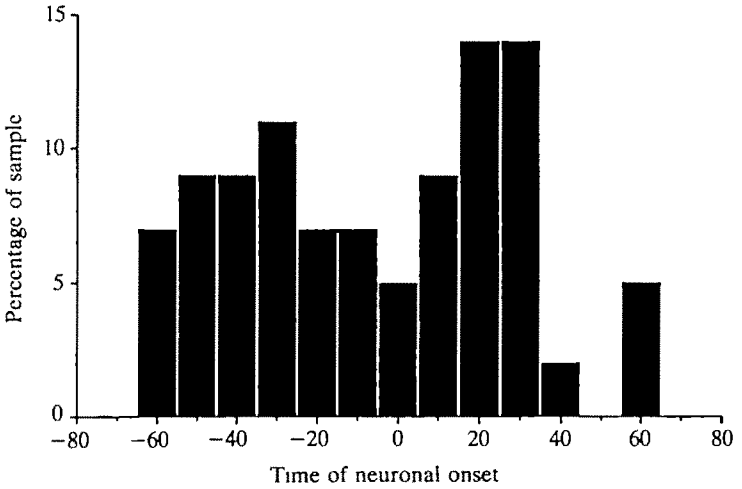

FIG. 9. Histogram showing the distribution of onset times of responses to movement of pallidal neurons relative to the onset of EMG activity.

to passively generated sensory fields. No neuron could be driven by cutaneous or deep stimulation or by passive manipulation of the limbs and joints.

DISCUSSION

The most consistent relationship demonstrated by pallidal neuronal discharge in this study was with the direction of movement, but no relationship was found for amplitude, velocity, static force application or joint angle.

The relationship between neuronal discharge and direction of movement has been commented on by others (Iansek and Porter, 1980; Georgopoulos *et al.*, 1983). No satisfactory explanation for its function in the production of movement has been elaborated. We note, as have others, that the discharge of pallidal neurons in relation to movement occurs late. Therefore it is unlikely that this activity can influence the simple ballistic movement that is currently underway. The accompanying paper (Brotchie *et al.*, 1991) addresses this question in detail and provides evidence that this activity may signal the transition from one segment of a sequence of movement to the next and that the directional preference of the burst is related to the intended direction of the next movement.

We have commented previously that pallidal discharge is best related to activity about one particular joint (Iansek and Porter, 1980). This observation was confirmed in this study. Others have not commented on this finding, perhaps because the animals have not been examined to establish a relation between neural discharge and other movements outside the one tested by the paradigm. The significance of this observation awaits further study. It has been noted that the same task, for example signing one's name, can be performed either by the shoulder to write on the blackboard or the wrist to write on paper. The signature is clearly the same in both instances, but different muscles are

used. Presumably the sequencing and set is similar for both tasks but different muscles must be selected. Perhaps the significance of a relationship to both a muscle and a direction indicates a linking, at this level, of the set to the muscle. Our findings described in this report are at variance with other studies which found some relationship between pallidal neuronal discharge and parameters of movement. Georgopoulos *et al.* (1983) examined the relationship between pallidal discharge and amplitude of movement. In that study the experimenters failed to exclude neurons whose discharges were not specifically related to elbow movements (the joint examined by their paradigm). We have shown, however, that when the discharge of pallidal neuron is related to movement, it is a precise relationship between discharge and movement direction of one particular joint. Therefore, if a paradigm studies movements about the elbow, it should examine only neurons whose discharge are related to movements at the elbow not neurons whose discharges are related to finger, wrist or shoulder movements. The use of such neurons could give misleading information about the movement parameter that was assessed in the paradigm. For example, fixation of more proximal joints may well be performed at a more subconscious level than intricate movements at distal joints, which most paradigms assess. If neuronal discharge were related to the level of automaticity then neurons with activity related to proximal movements would have a better relationship to movement than neurons related to distal movements. Fluctuations in the level of movement automaticity required to perform movements of different amplitude may lead to different levels of discharge which could be misinterpreted as having a relationship to amplitude. If only the neuron whose discharges were related to the appropriate distal joint was used then a relationship may not have been observed.

The study by Georgopoulos *et al.* (1983) included neurons related generally to arm movements as distinct from the leg or the face. We, on the other hand, specifically excluded neurons whose discharge was not related to the joint under study. This may well be a factor explaining the differences between the two studies.

Georgopoulos *et al.* (1983) found that the discharge rate of the pallidal neuron was linearly related to amplitude. The findings of that study were based on a total of 39 cells, 18 of which behaved as they described, but the discharges of an unknown number may have been associated with joints other than the elbow. They compared 3 different amplitudes and did not test the consistency of response to each amplitude. Over one-third of our neurons were excluded because they failed to show a consistent response on reteating of the same amplitude. It may be, therefore, that if similar criteria were used in both studies the incidence of neurons signalling amplitude may have been similar. Inspection of fig. 5 indicates that the rigorous criteria that we have employed are important if incorrect associations are to be avoided. It can be seen that a spurious relationship could have emerged if the discharge rate for 21, 14, and 7° of movement were used in isolation. Repetitions of similar sized jumps and with the inclusion of the 42° jump changes the relationship altogether.

In our study we found neurons which discharged preferentially for each size of movement. Neurons with preferential responses for the middle size movements would not be apparent with the technique of linear regression used in the Georgopoulos *et al.* (1983) study. The relationship they found was variable with both positive and negative relationships of various strengths on linear regression. In addition, the resting discharge rate predicted by extrapolating from the calculated line of best fit did not correlate with

the observed discharge rate at rest, raising doubts that a linear relationship was the correct one.

In summary, by using more stringent testing of the relationship between amplitude and discharage rate, we found a possible relationship in only a small number of neurons. However, we have already noted that pallidal discharge occurs too late to influence the amplitude of the current movement. Even if neuronal discharge did code for the amplitude of the movement, its presence in such few neurons would suggest that it is either an epiphenomenon or not central to the function of the GP. In the following paper we provide evidence for an alternative interpretation (Brotchie *et al.*, 1991). If it is accepted that the relationship between neuronal discharge and amplitude of movement is uncertain, then the relationship to velocity is also unlikely to exist because the two are dependent variables. In addition, we have other examples of situations where bursts of neuronal activity have taken place but where no movement and certainly no velocity was apparent. The opposite has also been observed where small movements of different velocities have been performed and, coincidentally, there has been bursting of neuronal discharge in association with such movements but no correlation was found between the amplitude of the velocity peaks and the size of the bursts of discharge of the pallidal neuron.

Mitchell *et al.* (1987) examined the relation between pallidal discharge and the sudden application of load. Unfortunately, this study is not directly comparable with ours. They used a paradigm which used randomly applied step loads and concentrated on short-latency responses that followed the application of the load. In addition, they included any neurons in the study that had short-latency responses to a sudden load or to passive movement of the limb without necessarily requiring the neuronal discharge to be related to the active movement under study. The range of movement examined was small being only 7°. They found 10–12% of neurons with a load effect, 30% of neurons with a directional effect and 2% with a muscle pattern. They also found short-latency responses to application of load in 65% of neurons. They refer to effects of load on discharge during hold periods and found a slow incremental or decremental change in discharge leading up to the movement. Our study also examined responses of pallidal neurons to constant loads applied during the hold periods. No relationship has emerged. The responses of pallidal neurons to our static load paradigm were completely different to those observed in agonist muscles or corticomotor neurons which do respond prominently to static load. The number of neurons described by Mitchell *et al.* (1987) with responses to the sudden application of load is small, suggesting that the relation to load is peripheral to the GP's main role in movement regulation or that there is another explanation for the apparent relationship. The significance of their main finding of short-latency sensory responses to application of load is unknown. We also observed similar responses to torque pulses presented during the initial hold period but we have not systematically examined the nature of the responses. In the study of Mitchell *et al.*, as in ours, the perturbations were presented randomly. Such a state of unpreparedness may allow responses to occur which would not take place in a predictable paradigm. There is no doubt that sensory input can influence pallidal neurons in particular circumstances, for example following dopamine depletion in the striatum (Iansek, 1980; Filion *et al.*, 1988). Anticipation or movement set may be a situation when peripheral responses are not permitted to influence pallidal neurons.

The paradigm for ballistic movements used by Mink and Thach (1987) was similar to the task used in this study. They did not look, however, at the effects of load or differing amplitude. They found discharge to be better related to ballistic movements than to ramp, sinusoidal, remembered or self-paced movements. This finding, however, may be coincidental to the fact that ballistic movements are performed at a more subconscious level than any of the other movements (Brotchie *et al.*, 1991). After assessing pallidal activity over a variety of tasks, we have not observed a consistent relationship between pallidal activity and most physical parameters of movement. Given this finding, together with the comparatively late onset of activity in pallidal neurons in association with movement, it is unlikely that the BG have any influence on directing the muscular activity for the performance of a movement. Hallett and Khoshbin's (1980) view of BG function, as a selector and energizer of muscles, is therefore not consistent with our findings. This suggests that pallidal activity influence other aspects of the motor task. Since the output of the GP is directed to the supplementary motor area and probably the premotor cortex, a role in the cognitive aspects of movement control appears more likely as has been suggested by Marsden (1987). It is our findings in this regard which we outline in the subsequent paper (Brotchie *et al.*, 1991).

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MOTOR FUNCTION OF THE MONKEY GLOBUS PALLIDUS

2. COGNITIVE ASPECTS OF MOVEMENT AND PHASIC NEURONAL ACTIVITY

by PETER BROTCHIE, ROBERT IANSEK *and* MALCOLM K. HORNE

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SUMMARY

In order to study the role of the basal ganglia (BG) in cognitive aspects of movement, we recorded extracellularly from pallidal neurons in conscious monkeys while they performed a sequential wrist movement task consisting of a series of holds and ballistic jumps. The movement sequence had to be performed within specified time restraints and was predictable. We recorded the activity of 297 neurons whose discharges were related to the movement task. The movement-related response was found to be influenced by the contextual setting and by the degree of difficulty of the task in a subgroup of 82 neurons with a clear response to the first ballistic movement. Predictable and easy movements were usually represented by more prominent movement-related responses in 46% of these neurons; 35% of neurons from a different subset of 105 neurons also demonstrated a second phasic response just before the end of the final hold period of the task. This response was also found to be influenced by the predictability of the final hold period, both in its time duration and also by the direction of the following ballistic movement in double jump tasks. These findings were in keeping with a cognitive role for the BG in movement performance. In particular we suggest that the phasic neuronal activity was an internal cue generated by the BG for predictable movements of a subconscious nature which signals the end of a component of movement in a movement sequence. This cue is appropriately timed to terminate sustained neuronal activity in the SMA and to allow the next movement in the sequence to be executed.

INTRODUCTION

Clinical studies suggest that the basal ganglia (BG) are concerned with the elaboration of complex movement sequences, as this is the most severely affected disturbance in hypokinesia of Parkinson's disease (PD) (Marsden, 1987). How such a function might be expressed at a neuronal level has never been elucidated. Some indications come from studies of the neuronal properties of the cortical target areas of the pallidal outflow, the supplementary motor (SMA) and premotor (PMA) areas.

Cerebral blood flow studies in normal human subjects performing a variety of movements (Roland *et al.*, 1980) suggest that the SMA is concerned with the programming of sequences of movements and that the PMA is concerned with the selection of movement plans based on external cues. Clinical studies (Dick *et al.*, 1986) of patients with lesions of the SMA confirm this hypothesis. Many SMA neurons display sustained activity related to the preparation for making a single movement response

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in a delayed reaction time task (Tanji *et al.*, 1980). This area of cortex, therefore, appears to have a role in the preparation for motor responses. Unfortunately, single cell recordings from the SMA have not been made during the performance of sequential movements so that the behaviour of these neurons in such a situation is unclear.

Recordings from individual neurons in the neostriatum (Kimura *et al.*, 1984; Hikosaka *et al.*, 1989) have shown that a small number of neurons which, like those in SMA, also appear to discharge in relation to the preparation for a simple movement. Similar findings have not been observed in the globus pallidus (GP) and neuronal behaviour during sequential movements has not been examined either in the BG or the striatum. Furthermore, in the SMA, PMA and neostriatum, only sustained neuronal activity has been found to be associated with the preparatory stage of movement. In the previous paper (Brotchie *et al.*, 1991), we described phasic neuronal activity which occurred during movement. This was observed in many cells of the GP. The activity did not, however, appear to encode for movement parameters such as force, amplitude or velocity. In this paper we present observations of movement-related pallidal neuronal discharge of a phasic nature, which is influenced by the animal's preparation for movement and which appears to have a role in the performance of sequential movement tasks. Its role appears to be an internal cue which may signal the end of one movement in order that the next movement in the sequence may commence. We refer to such a function as cognitive to differentiate it from an executive function concerned with regulating parameters of movement.

METHODS

The methods used for experimentation, recording and data analysis are described in the previous paper (Brotchie *et al.*, 1991). We have recorded from the GP of monkeys during the performance of single and sequential movement tasks. All the tasks required the monkey to place its hand in a wedge-shaped manipulandum, which controlled a cursor on an oscilloscope screen, and to move the cursor into a target window within specified time restraints. The 3 paradigms described in the previous paper can be summarized as follows. Paradigm 1. Extensor and flexor movements of the wrist. Paradigm 2. Seven tasks containing movements of different amplitudes in either the extensor of flexor direction. Paradigm 3. Extensor and flexor movements with assisting and opposing loads.

The following 5 additional behavioural paradigms were used in this study.

Paradigm 4. This paradigm was essentially the same as Paradigm 1 except that it was only performed in one direction. The task began when the monkey aligned the cursor with the target in the initial hold position. After an initial hold period of 1–2 s, the target window moved abruptly to a final hold position, requiring the monkey to make a ballistic movement of the wrist in order to realign the cursor in the target window within 500 ms. The monkey was required to remain in this position for a final hold period of 600 ms to receive a juice reward. The target then returned to the initial position awaiting the animal to begin the next trial.

Paradigm 5. This task was similar to Paradigm 4 except that the final hold period was increased to 1600 ms. Therefore the monkey was required to hold the final position for 1 s longer to receive the reward (*see* fig. 1). No cue was given to indicate a switch from Paradigm 4 to Paradigm 5, as the movements were similar but only the final hold time was different. The monkey thus required at least one trial of the new task to realize that a change had occurred

Paradigm 6 This task contained two visually triggered ballistic movements which were performed sequentially. A trial began with an initial hold period of 1500 ms followed by a ballistic movement into the target window at a 'middle hold position'. A 'middle hold period' of 1 s was followed by a ballistic movement in the same direction, to a final hold position which was held for the final hold period of 1500 ms. Each ballistic movement was performed in 500 ms or less (*see* fig. 2A).

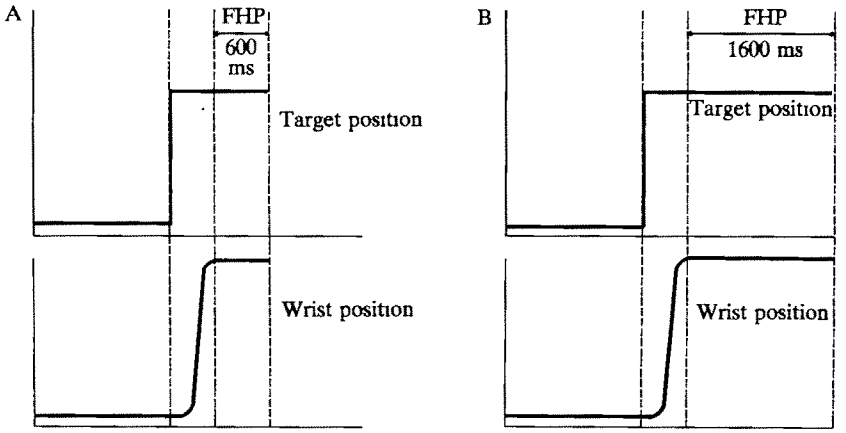

FIG 1 Target position and wrist position during Paradigms 4 (A) and 5 (B) The paradigms are described in Methods Vertical dotted lines delineate the 3 phases of each task. The only difference between the two tasks is in the length of the final hold period (FHP), being 600 ms in Paradigm 4 and 1600 ms in Paradigm 5

Paradigm 7. This task was also a sequential movement task, similar to Paradigm 6, except that the second target jump was in the reverse direction to the first, so that the final hold position was the same as the initial hold position (*see* fig. 2B).

All of the tasks described above were performed in blocks of 6 correctly performed trials. After the first trial of a new task the monkey could anticipate the nature of the following trials; the tasks were predictable.

Paradigm 8. This task consisted of 4 trials of both Paradigms 6 and 7 mixed in a pseudorandom order,

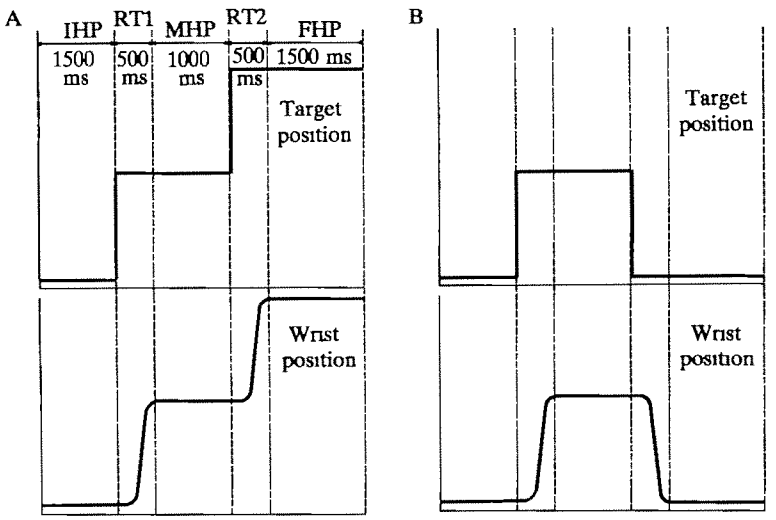

FIG 2 Schematic diagram of the target position and wrist position during the 5 different phases of the double movement Paradigms 6 (A) and 7 (B) The phases are separated by vertical dotted lines. IHP = initial hold period, RT1 = allowed response time for first wrist movement, MHP = middle hold period; RT2 = allowed response time for second wrist movement, FHP = final hold period The movement task is described in Methods

so that the monkey could not predict the direction of the second target movement. All neurons whose records were used in this report were anatomically localized to the GP by techniques described in the previous paper (Brotchie *et al.*, 1991).

RESULTS

A total of 297 pallidal cells whose discharges were correlated with movement were recorded during this study; 53 of these neurons were characterized during clinical examination as being related to movements about other joints of the upper extremity than the wrist joint. However, as the general pattern of behaviour for these cells was similar to the rest of the group, they were all included in the present analysis. All pallidal neurons described here displayed activity which occurred during the ballistic movements. We have called this activity 'movement-related activity' to distinguish it from activity which correlated with other aspects of the tasks. The relationship between movement-related activity and the physical parameters of movement was analysed in the previous paper (Brotchie *et al.*, 1991). In this report we assess the effects of cognitive aspects of the task on movement-related activity.

Set-dependent movement-related phasic activity

In approximately half the pallidal neurons, movement-related responses were influenced by the contextual setting of the task. If the animal was able to anticipate a particular movement, set in the context of several repetitions of the same task, then the movement-related response in these neurons appeared more prominent. This variant of the movement-related response, which we have called the set-dependent movement-related response, occurred in 38 (46%) neurons out of a sample of 82 pallidal neurons. The first task of the 21° jump was the only amplitude in which the animal could not anticipate the movement direction. The 21° jump was the first movement performed in the paradigm and as such the direction and amplitude was not specified beforehand. All other movements were predictable in direction. This task was thus appropriate for assessing the prevalence of the set-dependent movement-related response. Only recordings of neurons in which the first trial was correct were included in the sample group, as the direction of movement for trials after an incorrect first trial was predictable.

Fig. 3A shows an example of the discharge pattern of a neuron during the first task of Paradigm 2 (21° movement task). Before commencing the initial trial the animal was unaware of the direction of movement required in this task, and despite the correct performance of this movement the neuron showed little change in activity during the first trial (bottom trace). For the subsequent trials of that paradigm, however, when the direction could be predicted, this cell showed a clear increase in discharge rate during the movement. The difference in movement-associated activity in the first trial, compared with subsequent trials, cannot be attributed to any physical differences in the movement, as each trial was performed identically. The movement-related response of this neuron was, therefore, dependent on the setting of the task, occurring only when the animal was able to predict the direction of the next movement. Set-dependent movement-related responses also occurred in neurons which decreased their discharge rate in relation to movement. Fig. 3B displays the activity of a neuron which maintained a high rate of discharge during the movement of the first trial, yet in subsequent trials its discharge rate decreased with the movements.

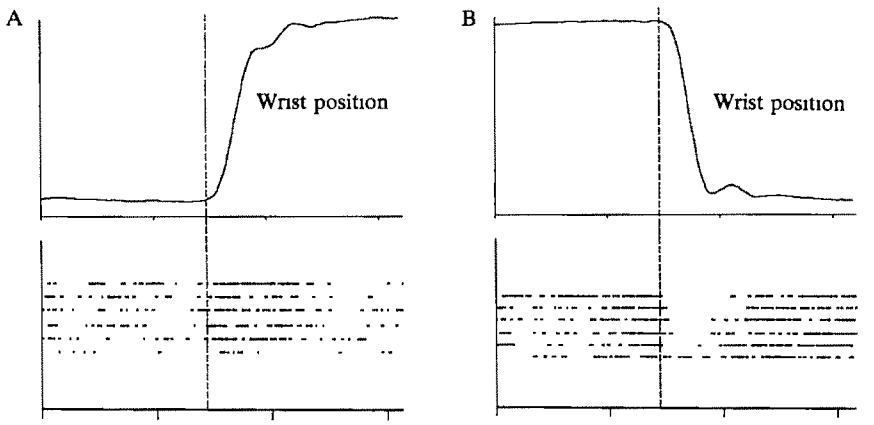

FIG. 3 Rasters of 2 neurons whose discharges demonstrated set-dependent movement-related activity during the performance of the first task in Paradigm 2 Raster A relates to a neuron with an excitatory response and raster B to a neuron with an inhibitory response The trials are aligned on movement onset which is indicated by the vertical dotted line. Trials are in order, with the first trial at the bottom. The raster indicates a minimal response with the movement during the first trial. In subsequent trials a phasic increase in discharge (A) or decrease in discharge (B) is seen with the movement. Each division on the horizontal scale indicates 500 ms.

Movement-related responses and difficulty of movement

At the start of the experiment with the second monkey, Paradigm 3, consisting of loaded and unloaded movements, was used whenever a recording was made from a neuron. In the latter half of the study on that particular monkey, the more complex paradigms were routinely used and Paradigm 3 was performed less frequently. An interesting consequence of this was a change in the error rate for performing loaded movements between the two halves of the study. When Paradigm 3 was used in the first half of the study, the monkey produced more incorrect trials during the performances of unloaded movements than loaded movements. But, in the latter half of the study, the loaded movements were performed less reliably than their unloaded counterparts.

Coincident with this decline in the monkey's performance of loaded movements was a decrease in the percentage of cells which showed a preference for loaded movements. This change in the proportion of cells responding preferentially to loaded movements occurred over several months. Of the first 35 neurons which were recorded from the second monkey during Paradigm 3, a higher proportion displayed greater responses with loaded movements than unloaded movements. During the recording of this group of neurons, the error rate for loaded movements was less than that for unloaded movements (*see* Table 1).

Of 35 neurons recorded in the latter half of the study the proportion of neurons which responded with greater magnitude for unloaded movements was greater than that for loaded movements. This decrease in the proportion of cells which responded better to loaded movements was mirrored by an increase in the error rate when performing loaded movements (*see* Table 1). Therefore it is possible that the proportion of cells preferentially related either to loaded or unloaded movements was not a consequence of a closer relationship of the pallidal neurons either to the agonist or antagonist muscles, but was a consequence of how reliably each movement was performed by the animal.

TABLE 1 MOVEMENT-RELATED RESPONSES AND DIFFICULTY OF MOVEMENT DURING LOAD APPLICATION

	Percentage of cells with preference for type of movement		*Percentage error rate for type of movement*	
Type of movement	*Early*	*Late*	*Early*	*Late*
Loaded	28	11	26	35
Unloaded	6	46	36	26

This conclusion is supported by observations of pallidal neuronal activity during the performance of movements from different initial joint positions. As mentioned in our companion paper (Brotchie *et al.*, 1991), 38 neurons had different magnitudes of response for the three movements of the same amplitude in Paradigm 2.2. These three movements were termed acute, neutral and obtuse, depending on the initial joint position. Although the firing rate of these neurons did not alter with joint position, they produced a significantly greater response for one or two of the three movements than for the other movement. We have referred to cells of this type as having a preferential response for either obtuse, neutral or acute movements. Fig. 4 is an example of a discharge pattern of a cell which responded preferentially to the acute movement. A greater number of pallidal neurons was found to discharge preferentially to movements from the acute position than from either the obtuse or neutral positions, despite all three types of movement being of the same amplitude.

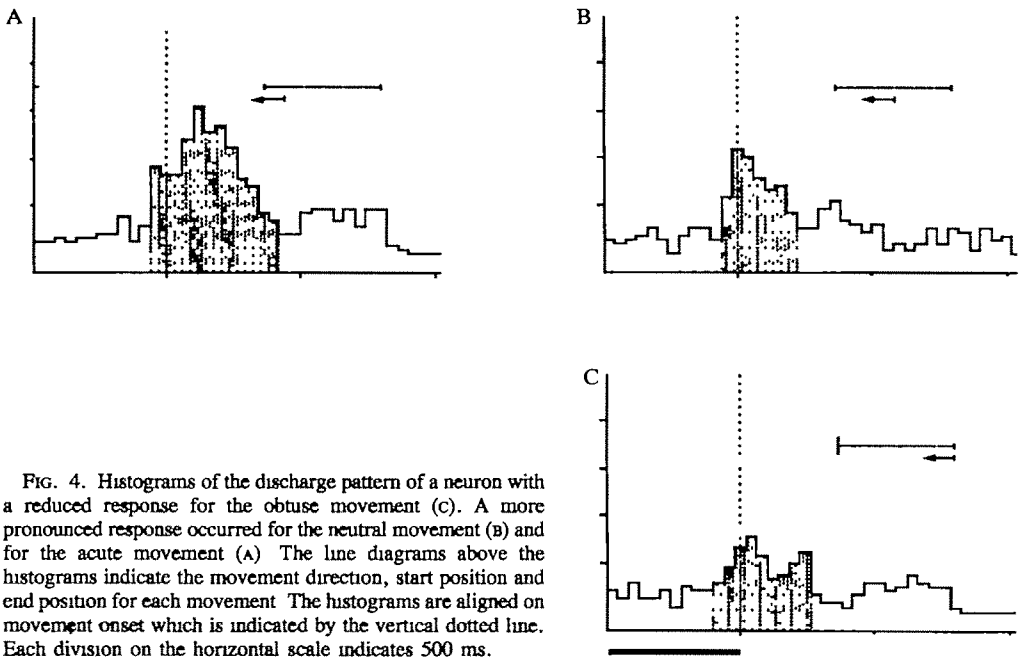

FIG. 4. Histograms of the discharge pattern of a neuron with a reduced response for the obtuse movement (C). A more pronounced response occurred for the neutral movement (B) and for the acute movement (A) The line diagrams above the histograms indicate the movement direction, start position and end position for each movement The histograms are aligned on movement onset which is indicated by the vertical dotted line. Each division on the horizontal scale indicates 500 ms.

Analysis of the error rate for each of these types of movement showed that the obtuse movements were erroneously produced more often than for the other two types of movement (*see* Table 2). This finding suggests that a correlation may exist between the proportion of pallidal neurons with a preferential response for a movement and the reliability of performing that movement.

Double bursting cells

Apart from the phasic increase in neuronal activity associated with the wrist movement, a number of pallidal neurons displayed a burst of activity immediately before the end of the final hold period. We have referred to neurons of this type as 'double bursting' cells (*see* fig. 5). Of the 297 neurons which were recorded from GP, 105 (35%) displayed

TABLE 2. MOVEMENT-RELATED RESPONSES AND DIFFICULTY OF MOVEMENT FOR DIFFERENT INITIAL LOAD POSITIONS

Type of movement	*Error rate for type of movement*	*Percentage of cells with poorly defined histogram*
7° neutral	9.0	36.1
7° acute	5 8	34 2
7° obtuse	31 0	71.4

Selected from 50 neurons with well-defined beginning and end to the burst associated with the ballistic movement.

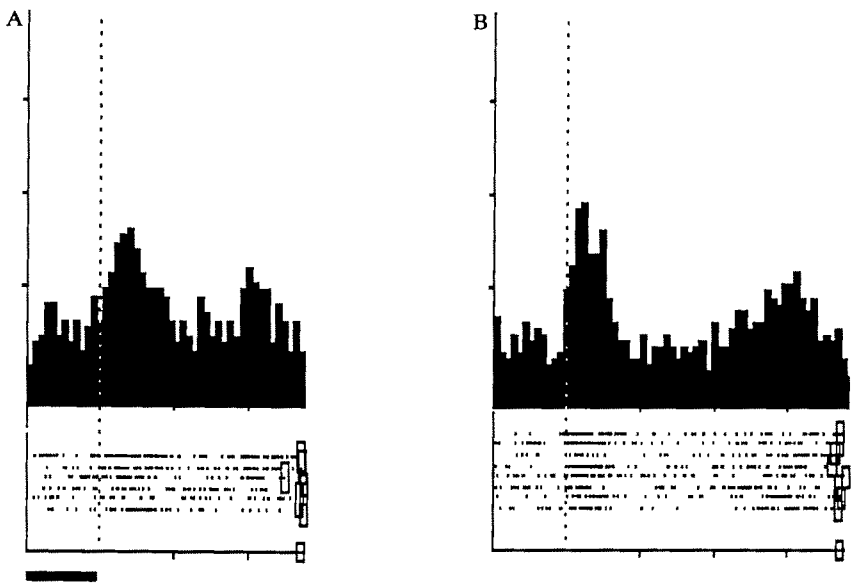

FIG 5. Double bursting pattern of discharge for the same neuron for two different hold times of Paradigms 4A (600 ms) and 5B (1600 ms) The trials are aligned on movement. Vertical dotted lines indicate the onset of wrist movement across all trials. Each division on the horizontal scale indicates 500 ms. Although the movements in each task are identical, the second burst of discharge occurs later during the task with the longer final hold period (Paradigm 5). Each division on the horizontal scale indicates 500 ms Each vertical division represents 50 impulses/s.

the double bursting behaviour pattern described above. The second burst of discharge occurred when the wrist was immobile at the final hold position and appeared near the end of a trial, 300–400 ms after movement. No EMG recordings from any of the muscles involved in the task produced a similar pattern of activity.

Recordings were made from 45 double bursting cells during the performance of both Paradigms 4 and 5. The discharge pattern of 36 of these cells altered after changing from Paradigm 4 (short final hold of 600 ms) to Paradigm 5 (long final hold of 1600 ms). Instead of the second burst of activity occurring 300–400 ms after the movement, it shifted out to precede the end of the longer final hold period, some 1400 ms after movement. With a number of repetitions of trials of Paradigm 5, the burst of activity which had occurred immediately preceding the end of the short final hold period usually diminished in size as the later peak emerged. Therefore on switching from Paradigms 4 and 5, the pattern of activity of the neuron changed despite the fact that exactly the same movement was produced in both tasks (*see* fig. 5). This change in the activity pattern of the neuron usually developed following the first few trials of the new task (*see* fig. 6). The switch between tasks occurred without any cues to the monkey, so that the animal required at least one trial before it knew a change in tasks had occurred.

Background discharge of double bursting neurons

For a number of double bursting neurons, the activity during the final hold period, between the first and second bursts, was less than that during the initial hold period of the task. Fig. 7 depicts a typical pattern of activity for such a cell. The second burst

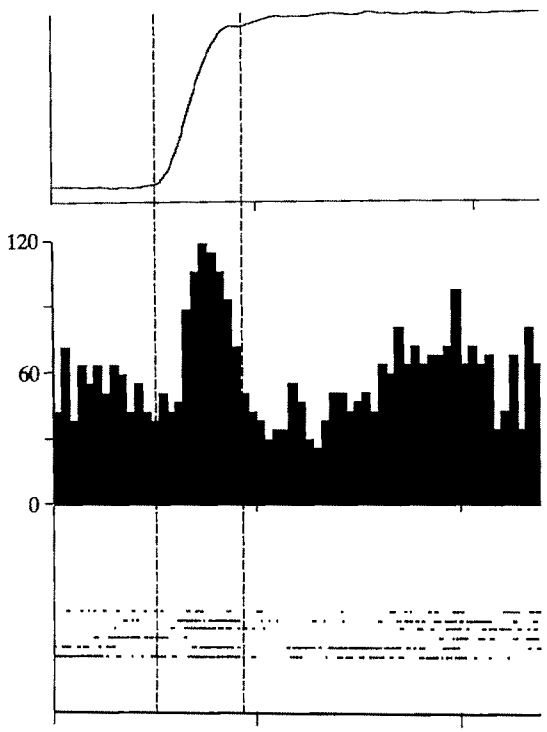

FIG 6. Histogram and raster of a neuron with a double bursting pattern of discharge during the task with a long final hold period (Paradigm 5) after changing from the task with a short final hold period (Paradigm 4) The discharge pattern during the final hold period for the first 2 trials (at the bottom of the raster) is different from that for the subsequent trials as the distinction between the first and second phasic neuronal burst is unclear. The trials are aligned on target movement. The *top trace* indicates joint position. Vertical dotted lines indicate the onset and end of movement across all trials. Each division on the horizontal scale indicates 1 s

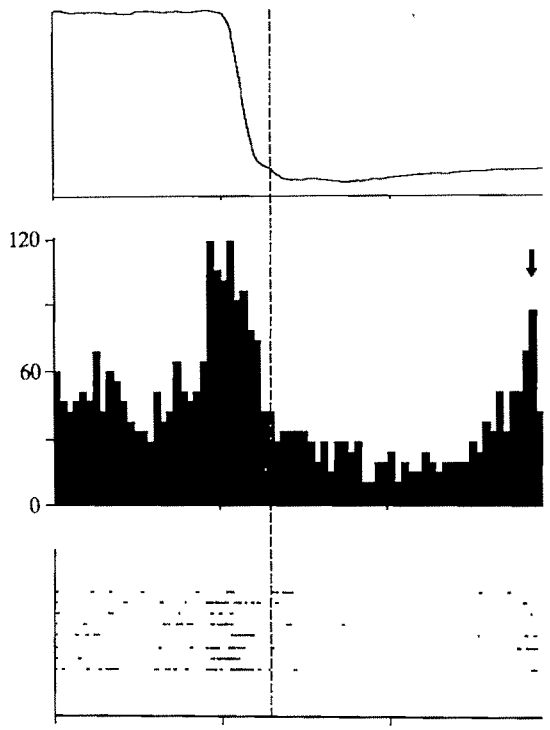

FIG. 7. Histogram and raster of the discharges of a neuron which demonstrated delayed phasic activity, indicated by the arrow, at the end of the final hold period of Paradigm 5. In this neuron there was a decrease in the level of activity during the final hold period, in between the movement-related response and the delayed activity, compared with that during the initial hold period. The trials are aligned on acquisition of target in the final hold position which is indicated by a dotted vertical line. The *top trace* indicates joint position. Each division on the horizontal scale indicates 1 s.

of activity in this neuron only reached the level of activity seen in the initial hold period. For many other neurons, however, the activity between bursts in the final hold period was the same as the activity in the initial hold period, and the peaks of the two bursts of discharge were above this level of activity. We have grouped all the double bursting neurons together, irrespective of whether or not their discharge rate between the peaks decreased below the level of activity in the initial hold period.

Predictive aspects of the double bursting behaviour

The second burst of activity generally began 200–300 ms before the end of the final hold period, and peaked immediately before the end of this period. This burst of discharge, which we will refer to as the 'delayed burst', may have predicted the end either of the trial or the forthcoming events. The forthcoming events at the end of each trial included the juice reward and the movement response of the wrist back to the initial position to commence the next trial.

It was not possible, with the single movement tasks used in Paradigms 4 and 5, to determine whether the second burst of activity was predicting the reward, the return movement for the next trial or the end of the current trial. We therefore trained the monkeys to perform a double movement task (Paradigm 6) which consisted of two successive wrist movements, with only the second followed by a reward. Recordings were made from 79 neurons during the performance of this double movement task, and 34 displayed delayed behaviour during the middle or final hold periods. Twenty-five

of these neurons displayed the double bursting behaviour after the first movement in the task, indicating that the delayed burst of discharge in these neurons was not related to the reward and must have been predicting either the next motor response or the completion of one segment of the task (*see* fig. 8A).

The delayed burst of discharge of the cell shown in fig. 8A occurred at the end of the middle hold period, well after the first movement and immediately preceding the second target movement. In most cells, this burst of activity was separate from the following burst of activity associated with the second wrist movement. However, in one-third of neurons these two bursts of activity were confluent (*see* fig. 9).

In 6 of the 25 neurons, delayed activity occurred only at the end of the final hold period, after the second movement, with no delayed activity occurring in the middle hold period (*see* fig. 10). The delayed burst of activity in these neurons was either related to the delivery of the juice reward or to the end of the entire double movement trial.

Delayed burst of activity and the direction of movement

The delayed burst of activity which occurred in pallidal neurons prior to the second movement predicted either the occurrence of the target movement or the end of the middle hold period. If the latter was the case, this type of activity should have occurred irrespective of the direction of the second target movement. On the other hand, if delayed activity was related to the preparation for the next motor response, it should differ depending on the expected direction of the second motor response; 8 neurons with delayed activity prior to the second movement in Paradigm 6 were also tested in Paradigm 7. In 5 of these neurons, the delayed activity prior to the second target movement was greater when the second movement was in a particular direction. The directional

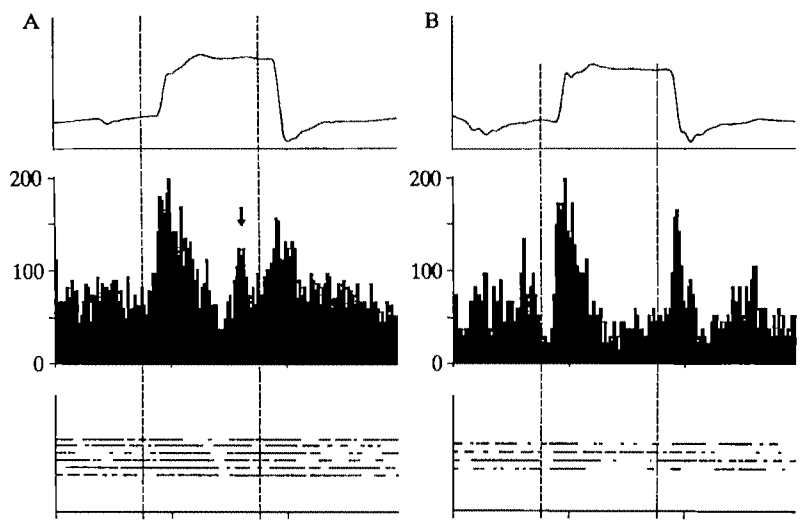

FIG 8. Predictive activity of neuronal discharge before the second target movement during Paradigm 7 (A) (arrow). No predictive activity is seen in the discharge pattern of the same neuron during the performance of the randomized task of Paradigm 8 (B). The trials are aligned on target movement which is indicated by dotted vertical lines The *top trace* indicates joint position. Each division on the horizontal scale indicates 1 s

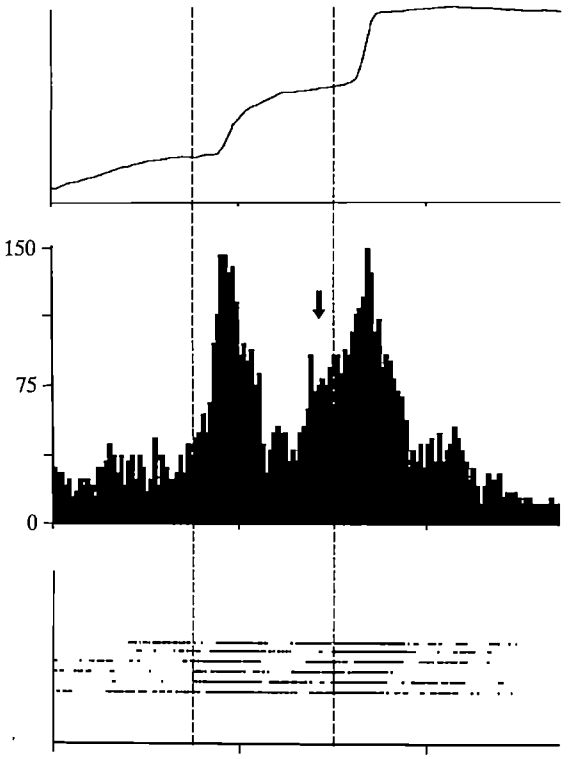

FIG. 9. Discharge pattern of a neuron with predictive activity (arrow) which coalesced with the movement-related activity of the second wrist movement. The trials are aligned on target movement which is indicated by dotted vertical lines The *top trace* indicates joint position Each division on the horizontal scale indicates 1 s.

preference of the delayed activity in these neurons was further tested using the random direction task of Paradigm 8. In each case the cell showed less delayed activity when the direction of the next movement could not be predicted by the animal (*see* fig. 8B).

Topography

Pallidal neurons related to wrist movements were found in both anterior and posterior portions of each segment of GP. Although the movement-related phasic activity in both portions of GP did not appear to differ, neurons with double bursting discharge patterns were more frequent in the anterior portion of GP than in the posterior portion (*see* Table 3).

TABLE 3 PROPORTION OF CELLS WITH DELAYED BURSTS IN DIFFERENT PARTS OF GP

Region of GP	*Delayed bursts*	*Task-related cells*	*Proportion of cells* (%)
Anterior GPe	66	164	40
Posterior GPe	12	37	32
Anterior GPi	15	45	33
Posterior GPi	12	51	24
Total cells	105	297	35

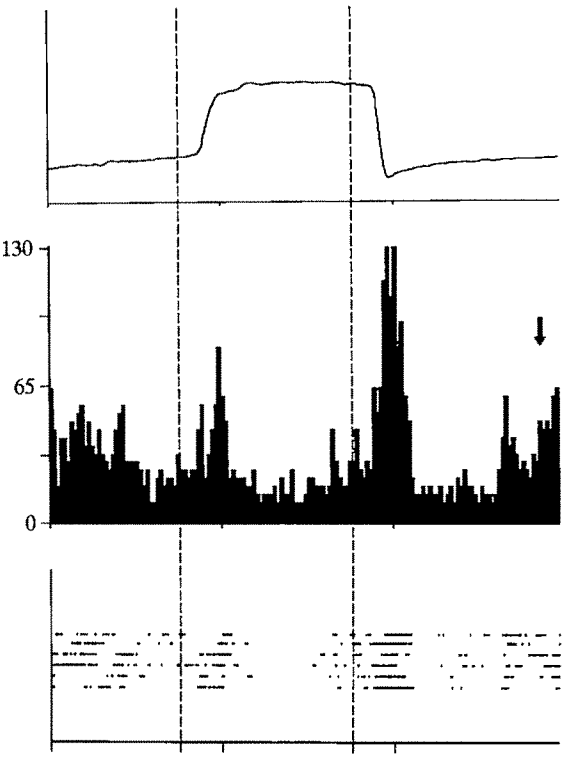

FIG 10 An example of a neuron whose discharges demonstrated predictive activity which only occurred at the end of the double movement task (Paradigm 7). The trials are aligned on target movement which is indicated by dotted vertical lines The *top trace* indicates joint position. Each division on the horizontal scale indicates 1 s.

DISCUSSION

This report demonstrates for the first time that the presence of phasic movement-related activity in the GP of the awake monkey may be dependent upon the context of the movement task. In particular, it might be dependent upon the predictability of the next movement. If the animal was unaware of the direction of the next movement the activity was often diminished or absent. This report therefore shows that cognitive aspects of the task are important in determining the magnitude of the movement-related response in pallidal cells, and may explain why we observed little relationship between pallidal activity and the physical aspects of movement (Brotchie *et al.*, 1991).

Another factor which may influence the relationship of neuronal discharge to movement is the automaticity of the movement. By automaticity we mean the degree of conscious effort required to perform the movement. The animals used in this study were trained to perform the same movements for several years before the recording and the movements became subconscious and ingrained. A number of variations which we introduced to the basic movement paradigm were taught to the animal only a few months before recording and did not become as ingrained or subconscious as the basic movement sequence. In particular, the animal had obvious difficulty with the performance of the obtuse movement and the unloaded movement. Because they were learned later and

because more errors were made, we believe that they would have required more conscious effort to complete the movement correctly. These movements were associated with a less well-defined phasic discharge than similar sized movements which were easier to perform and were presumably more automatic. This finding is consistent with the clinical information of movement behaviour in patients with hypokinesia secondary to PD. The way in which PD affects the execution of subconscious movements is demonstrated in several studies which have examined the performance of simultaneous motor tasks (Schwab *et al.*, 1954; Talland and Schwab, 1964). These studies demonstrated that it is not possible to perform two movements simultaneously in hypokinesia and that it is always the more subconscious movement that fails and that the more conscious movement is completed. These studies indicate that the role of the BG is important for the performance of subconscious movements and our results reveal a possible neuronal basis for this function.

The results of the study by Mink and Thach (1987) can also be interpreted in light of this idea. They found that GP neurons appeared to discharge in a better defined manner for ballistic movements than for a variety of other movement types. They interpreted this finding as suggesting a role for the BG in regulation only of ballistic movements. An alternative explanation, based on our findings, is that the ballistic movement is the most automatic movement requiring the least conscious effort to be performed correctly and therefore neuronal discharge would have better definition compared with other more difficult movements which would require more conscious effort to perform them correctly.

Delayed bursts of activity were observed in a large portion of pallidal neurons, especially in the anterior regions of the GP. The pattern of activity observed in neurons which display this behaviour is unlike the EMG recordings from any of the muscles used in performing these tasks (Brotchie *et al.*, 1991). The onset of delayed activity was usually 200−300 ms prior to the end of the trial (or the second target movement in a double movement task) and the peak of the activity usually occurred immediately before this event. In many cells it predicted both the timing and direction of the second target movement. The timing and nature of delayed activity therefore suggests that it predicts the occurrence of impending events upon which an animal must make a particular motor response. It is evident, however, that delayed activity was not responsible for the initiation of impending movements as the activity was occasionally observed in situations where no movement followed, such as in the initial trials after switching from a short final hold to a long final hold task. The motor centres which receive this response must therefore appear to be capable of ignoring it when it is inappropriate. Delayed activity has been shown to occur before movement responses of the wrist joint and before the end of the task. Delayed activity was absent for the initial one or two trials of a task with a new final hold period and during the performance of the randomized double movement task. In both these situations the animal was able to perform the task correctly, yet it appeared to produce more errors, implying that the occurrence of delayed activity may be associated with an increased reliability in the performance of the task. Intuitively it seems that the randomized task and the initial trials of a new task would be performed at a more conscious level than a predictable task. The occurrence of delayed activity may therefore be associated with the task being performed at a more subconscious level.

Another phenomenon which suggests that delayed activity occurred during the subconscious performance of tasks was that any disturbance, such as noises outside the

recording room, or the opening of the recording room door, resulted in the disappearance of the activity for the next two or three trials. After such a disturbance the animal was likely to be more anxious and may have performed the tasks at a more conscious level. The loss of delayed activity after the opening of the recording room door is interesting in view of the recent observation of caudate neurons which responded to such environmental stimuli (Hikosaka *et al.*, 1989), suggesting that the occurrence of delayed activity in the GP may be influenced by activity in the caudate nucleus. Activity which is similar to the delayed activity of pallidal neurons has also been observed recently in neurons of the caudate nucleus (Hikosaka *et al.*, 1989). These neurons increased their firing rate at the end of a trial in which the monkey made a saccade to a fixation point. The activity in some of these neurons only occurred when a hand movement was required at the end of the trial to cause the delivery of a reward. These neurons were therefore said to increase their activity in expectation of making a hand movement.

The burst of activity associated with the ballistic jump may also signal the end of the ballistic movement. Despite our lack of direct evidence for this idea we do have some circumstantial evidence in support of this concept. First, the predictive behaviour of the discharge of this burst was similar to that of the delayed burst of neuronal discharge, suggesting a similar role in movement performance. Secondly, the peak activity of the burst always occurred just before the end of the ballistic movement so that it could signal the end of the current movement. Thirdly, the onset of pallidal discharge during the ballistic movement occurred too late to influence the ongoing movement so that its function is unlikely to be concerned with the execution of that movement.

Modern anatomical studies demonstrate that the pallidal output is directed by the thalamus primarily to the SMA (Schell and Strick, 1984) and possibly also to premotor cortex (Jones, 1987). Since the SMA provides a major input to the GP via the striatum, an anatomical loop exists between this area of cortex and the BG (Künzle, 1978). The metabolic activity of this area of cortex increases during the performance of a complex sequential movement task of the four fingers and thumb, yet not during the performance of a simple repetitive movement of one finger and the thumb (Roland *et al.*, 1980). The SMA therefore appears to play an important role in the performance of complex sequential movements. Interestingly, the BG also increase their metabolic activity during the performance of the same sequential movement task (Roland *et al.*, 1982).

Tanji and Kurata (1985) have observed sustained activity in cells of the SMA in response to instructions specifying the direction of forthcoming movements. This activity appears to correspond to the preparation for active motor responses to specific trigger signals and indicates how this aspect of a motor program is represented in the SMA (Tanji and Kurata, 1985). Unfortunately, no studies have been recorded from SMA neurons during sequential movement tasks to observe the behaviour of these neurons during the switching of motor programs. However, an indication of neuronal behaviour during a sequence of motor programs comes from recordings of neurons in the posterior parietal cortex during the performance of a double saccade task (Gnadt and Anderson, 1988). Neurons displayed a sustained response related to the animal's intention to perform an eye movement, which ceased once the saccade was made. In the double saccade task, some neurons displayed a sustained response which commenced with the first saccade and lasted until the second saccade. Therefore the neuronal activity related to the intent to make the second saccade began only after the first saccade. If this activity is regarded

as a neuronal representation of a motor program, then it supports Marsden's (1982) view that to execute a motor plan, each motor program is delivered in sequence, with the execution of each program being the signal to deliver the next.

If the BG were responsible for assisting in the switch between motor programs, as suggested by the clinical evidence, it would have to provide the pattern of neuronal discharge which could terminate the sustained activity in the SMA related to one motor program and initiate the sustained activity for the next motor program. We suggest that the phasic neuronal activity we have described is appropriately timed to perform this function. The burst of phasic activity would terminate the sustained activity in SMA, so that the impending program would be executed and the preparatory phase for the successive program would commence. The motor system must be able to use both internal and external cues for this purpose, as sequential movements occurred normally in our task at times when pallidal phasic discharge was inappropriate.

Finally, our findings and hypothesis needs to be considered in light of the known functional disturbance that occurs in hypokinesia of Parkinson's disease. Similarities between the clinical manifestations of patients with SMA lesions and those with PD indicate a close functional dependence between the SMA and the BG (Dick *et al.*, 1986; Marsden, 1987). Both SMA lesions and diseases of the BG are associated with an impairment in the performance of sequential movements (Benecke *et al.*, 1986, 1987; Dick *et al.*, 1986; Watson *et al.*, 1986). The performance of a sequential movement task consisting of a hand movement followed by elbow flexion was assessed in both patients with PD and controls (Benecke *et al.*, 1987). The time taken to complete the sequential movements correlated more closely to the degree of clinical bradykinesia than did the slowness of single movements. Two factors contributed to the patient's slowness in performing the complex movements. The first factor was an increase in the movement time in each of the individual movements when they were performed in succession and the second factor was a marked increase in the time it took patients to initiate the second movement following completion of the first movement. This study prompted the conclusion that the BG are concerned with the execution of sequential movements, as well as the suggestion by Marsden that the BG are more concerned with directing what happens to the next movement in a sequence than with the initial movement (Marsden, 1987).

The concept of the motor plan has proved useful in discussing the deficits in performing sequential movements exhibited by patients with PD (Marsden, 1982). A motor plan represents an action requiring the sequential operation of simple motor acts (or motor programs). Complex motor actions such as a golf swing, a tennis serve, or the rapid sequence of finger movements required in playing a difficult piano piece can be thought of in this way. Visual or proprioceptive stimuli can signal the arrival at each point in a sequence, thereby providing the necessary cues for switching motor programs. When such stimuli are not present, however, internal cues generated by the motor system are probably required for the task of switching. An internal cue, in this context, represents information that is produced by the motor system that is not a sensory response to an external stimuli. The hypothesis that internal cues are produced in the motor system is supported by the observation that in patients with PD the impairments in performing sequential movements can be partially overcome by the presence of external stimuli (Marsden, 1985). This implies that normally functioning BG provide internal cues which

can substitute for the external cues in the environment. Even when external cues are present, however, PD patients are unable to use predictive information to improve their performance in the same way that normal people can (Marsden, 1984). This suggests that internal cues from the BG not only assist in the switching of motor programs when there is a lack of external cues, but also provide predictive information to improve performance when external cues are present.

Our theory is that phasic activity in pallidal cells may be the internal cue used by the motor system to switch between motor programs in SMA. The strength and definition of the phasic activity is influenced by several factors: the predictability, the direction and the automaticity of movements. This theory may explain some of the clinical phenomena observed in parkinsonian hypokinesia. The difficulty that patients have with sequential movement tasks, for example, may be explained by a lack of internal cues (phasic pallidal activity) needed for sequencing motor programs (Marsden, 1984). The improvement in performance noticed in patients when external cues are present emphasizes the need for cues in sequencing movements. The difficulty patients have in the use of predictive information may be due to the poor definition or absence of internal cues. The definition of the phasic activity appears to be directly influenced by predictability and automaticity of the movement. The movement can still occur with external cues but it is less reliable in performance.

The gradual deterioration of movement amplitude and velocity seen commonly in the performance of repetitive movements, handwriting being a good example, may be explained by the observation that BG involvement in the provision of the internal cue does not occur, at a neuronal level, until several repetitions of the same task have occurred. This suggests that the initial repetitions of the movements may be performed at a more normal level, using perhaps internal cues generated in other parts of the motor system, as these movements do not appear to be dependent on the internal cue from the BG, but as more and more repetitions occur then the dependence upon the internal cue from the BG becomes more important and its absence would result in a gradual deterioration in each successive movement. It is interesting in this regard that the compensatory mechanism for underestimated movements is via the performance of small ballistic movements (Hallett and Koshbin, 1980). The study of Roland *et al.* (1982) suggests that such movements are generated in the motor cortex and not the SMA or PMA. However, it is not obvious from our results how simple movements are underestimated in amplitude and velocity in PD. Marsden suggests that simple movements are defective because they must be based upon what has gone on before (Marsden, 1984). If previous motor programs have not been terminated properly then a new motor program may not run correctly, even if it is initiated by external cues. This problem may become exaggerated during the repetitions of simple movements, accounting for their progressive deterioration.

In summary, our findings indicate that the BG are concerned with cognitive aspects of movement and in particular that the phasic neuronal discharge is an internal cue which signals the switch between movements in a movement sequence. It has been suggested that this is achieved by terminating sustained activity in SMA for the impending movement and turning on the preparatory phase of sustained activity for the next movement. The definition of the neuronal discharge appears to be influenced by the predictability of the task and the level of conscious effort needed to perform the task.

ACKNOWLEDGEMENTS

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QUADRANTIC VISUAL FIELD DEFECTS

A HALLMARK OF LESIONS IN EXTRASTRIATE (V2/V3) CORTEX

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SUMMARY

We report 2 patients with homonymous quadrantic visual field defects. The first patient experienced scintillations in the left lower quadrant, leading to the discovery of an astrocytoma in the cuneus of the right occipital lobe. Postoperatively she had a left lower quadrantanopia that precisely respected the horizontal meridian. The second patient presented with a left lower quadrantanopia, sparing the central 10° of vision that also respected the horizontal meridian. An astrocytoma was resected from the right upper peristriate cortex.

We must explain how a lesion in extrastriate cortex produced a homonymous field defect with a sharp horizontal edge in these 2 patients. Areas V2 and V3 are each divided along the horizontal meridian into separate halves flanking striate cortex. Consequently, the upper and lower quadrants in extrastriate cortex are physically isolated on opposite sides of striate cortex. We propose that a lesion involving V2/V3 may be sufficient to create a visual field defect. Although the lesion may have irregular margins, if it crosses the representation of the horizontal meridian in extrastriate cortex, it will produce a quadrantic visual field defect with a sharp horizontal border because of the split layout of the upper and lower quadrants in V2/V3.

INTRODUCTION

The representation of vision in the cerebral cortex was explored early in this century by the clinical examination of soldiers wounded in battle. Striate cortex (primary visual cortex, V1) was mapped by correlating visual field defects with the trajectory of missiles penetrating the cranium. Soldiers with quadrantic field loss were examined with special interest because their lesions were considered particularly suitable for studying the retinotopic organization of striate cortex. In 1916 Holmes and Lister reported 7 cases of quadrantanopia resulting from apparent injury to striate cortex. Each case shared a remarkable perimetric feature: the border of the quadrantic field defect along the horizontal meridian was steep and rectilinear.

Six of the cases reported by Holmes and Lister (1916) involved lower quadrantic field loss, attributed to injury of the upper lip of the calcarine fissure. Only a single example of superior quadrantic scotoma was described. Holmes and Lister ascribed the scarcity of superior quadrantic defects to the fatal tendency of missiles striking the lower calcarine bank to lacerate the dural sinuses. They proposed that the upper and lower visual quadrants are localized to the lower and upper calcarine banks respectively, separated by the representation of the horizontal meridian along the base of the calcarine fissure. Their conclusions were consistent with the map of striate cortex published by Inouye (1909).

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The anatomical localization of lesions resulting in quadrantic field defects suggested by Holmes and Lister (1916) was later questioned by Monbrun (1919) and Rönne (1919), who expressed doubt that a lesion of one calcarine bank would leave the fellow calcarine bank untouched. They noted that a cortical quadrantanopia would require a missile to divide striate cortex exactly along the cortical representation of the horizontal meridian (fig. 1). It seemed improbable that a projectile could follow the meandering projection line of the horizontal meridian along the base of the calcarine fissure with sufficient accuracy to create a perfect quadrantic field defect.

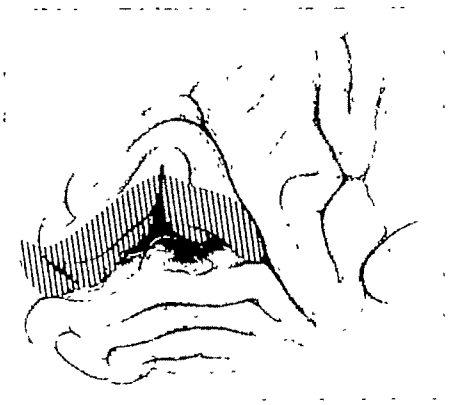

FIG 1. Medial view of the occipital lobe showing the opened calcarine fissure. To produce a quadrantanopia by injury to V1, a lesion (striped area) must follow precisely the representation of the horizontal meridian

In a subsequent publication, Holmes (1918*a*) offered a more plausible theory for cases of quadrantic field loss with a sharp horizontal edge. He reported 2 patients with quadrantanopia caused by a missile injury to the optic radiations. Holmes postulated that fibres in the optic radiations corresponding to the upper and lower halves of the retina are physically separated from each other by an 'anatomical interval', permitting selective injury to upper or lower quadrant fibres. This idea explained how an irregular, crude lesion caused by a projectile could produce a stereotypic field defect with a discrete horizontal border. Monbrun (1919) proposed that the lateral ventricle provided an anatomical interval, by splitting fibre bundles representing the upper and lower retinal quadrants around the posterior horn. Rönne (1919) suggested that an anatomical interval arose by interposition of macular fibres between fibres representing the upper and lower quadrants.

From this early debate concerning the anatomical localization of quadrantic field defects, agreement emerged that a lesion of the upper or lower bank of the calcarine fissure would produce only an approximate quadrantanopia, with an irregular horizontal border. Strict quadrantic field defects were assigned to lesions within the optic radiations.

Recently we have examined 2 patients with dense, congruous, quadrantic field defects that precisely bordered the horizontal meridian. In both cases magnetic resonance studies imaged a lesion involving extrastriate cortex. These findings prompted us to reconsider the issue of the anatomical localization of homonymous quadrantic scotomas.

CASE REPORTS

Case 1

A woman aged 39 yrs reported episodic visual phenomena that began when she was a schoolgirl She had a sensation of flashing multicoloured lights in her left lower quadrant of vision. The display lasted only a few minutes and occurred several times each week. At age 13 yrs she suffered a generalized motor seizure and was given anticonvulsant medications. During the following 25 yrs her seizures were well controlled and her visual scintillations occurred infrequently However, in the year before her hospital admission her visual symptoms became more troublesome. She would experience frequent spells consisting of brilliant light discharges, 'like coloured flashbulbs firing', in her lower left visual quadrant. After several minutes this display would be replaced by a dense lower left quadrantic scotoma that lasted 15 min.

Her visual acuity was 20/20 in each eye without correction. The visual fields were intact to confrontation testing. An MRI showed a focal signal abnormality within the cuneus of the right occipital lobe (fig. 2). The lesion was located in extrastriate cortex. At craniotomy the posterior cuneal gyrus appeared markedly expanded and discoloured A frozen section of a biopsy revealed an astrocytoma which was removed en bloc by resection of the abnormal cortical gyrus. An MRI scan obtained 2 days after operation showed a discrete tissue defect with minimal surrounding oedema (fig 3). The upper calcarine lip was spared.

Interrupted serial paraffin sections of a 3×2×3 cm surgical specimen were cut at 15 μm and stained for Nissl substance (fig. 4). The cerebral cortex and underlying white matter were infiltrated by cells from a mildly anaplastic (grade 1) astrocytoma. Near the resection margin the cortical cytoarchitecture was well preserved and Brodmann's area 18/19 could be recognized. Striate cortex was not present in any of the sections.

Immediately after the operation she had a dense left inferior quadrantic hemianopia determined by confrontation testing at the bedside. The field defect was tested using a Goldmann perimeter on the sixth postoperative day (fig. 5). The patient could detect gross hand motion within the quadrantic defect.

Case 2

A man aged 40 yrs recounted that 2 yrs before hospital admission he began to experience flashing lights in his lower left quadrant of vision. These episodes gradually became more frequent and prolonged. About 1 yr before admission he developed headaches and stumbled over objects to his left. On examination, visual

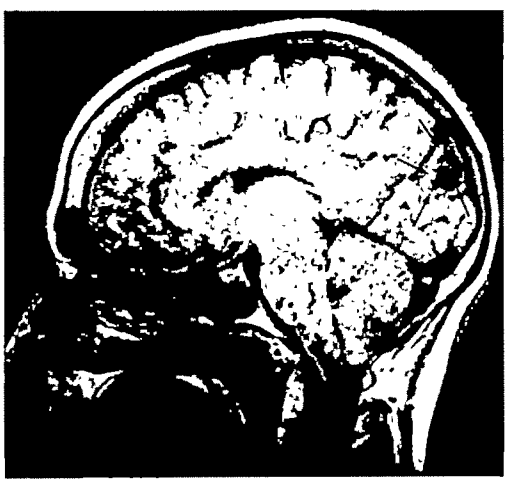

FIG 2. Sagittal magnetic resonance image of the right occipital lobe in *Case 1* (TR = 600 ms, TE = 20 ms) A lesion is visible in extrastriate visual cortex (arrows)

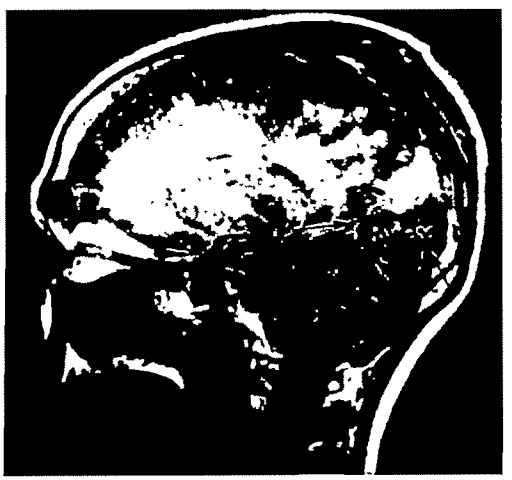

FIG. 3. Magnetic resonance scan performed in *Case 1* 2 days after operation. The resected cortical gyrus is replaced by fluid with bright signal characteristics. The calcarine fissure (between arrows) appears undisturbed.

acuity was 20/20 in each eye without correction. A left lower quadrantanopia with macular sparing was present on confrontation testing. An MRI revealed a 5×5 cm lesion within the right parieto-occipital lobe (fig. 6). The lesion appeared to border the upper calcarine lip, without involving the calcarine fissure. The posterior 3 cm of the right occipital lobe were intact.

At craniotomy a necrotic, highly anaplastic astrocytoma was resected. After the operation the patient reported no change in his visual field defect. One week after surgery a left inferior homonymous quadrantanopia sparing the central 10° of vision was confirmed using a Goldmann perimeter (fig. 7). The patient could not detect hand motion within the visual field defect.

DISCUSSION

The quadrantic nature of the visual field defect in our cases may be due to a lesion in one of 3 anatomical locations: primary visual cortex, optic radiations, or extrastriate cortex. In practice, lesions of the occipital lobes are likely to involve all three structures in varying combination and degree. For example, lesions of the cerebral cortex will usually encompass the underlying white matter. Many lesions of primary visual cortex also will involve extrastriate cortex. In our cases, both cortex and optic radiations were probably affected by tumour and subsequent surgery. Our challenge is to explain at what site in the visual pathway the lesion produced a strict quadrantic field defect.

A quadrantanopia could result if a lesion transected the primary visual cortex along the representation of the horizontal meridian at the base of the calcarine fissure. We have previously alluded to the faint likelihood of a projectile causing such an injury (fig. 1). It is equally improbable that a neoplasm would expand uniformly up to the representation of the horizontal meridian, but not beyond it. Moreover, in both our patients MRI (figs 2, 6) showed that the tumour bordered striate cortex, but did not extend into the calcarine fissure. For these reasons, we consider it unlikely that involvement of striate cortex by the tumour caused the quadrantanopias.

Holmes (1918*a*), Monbrun (1919), and Rönne (1919) localized quadrantanopia to lesions of the optic radiations. Damage to Meyer's loop in the temporal lobe often results in a superior homonymous field defect. A lesion of the parietal lobe may produce an inferior quadrantic field defect. However, the field defects in patients with lesions of the optic radiations have sloping borders that fail to respect precisely the horizontal meridian and often are incongruous (Van Buren and Baldwin, 1958).

The organization of fibres in the optic radiations has been studied in the cat. The optic radiations form a continuous sheet of fibres, without a gap separating fibres projecting to upper and lower field representations in striate cortex (Nelson and LeVay, 1985). No evidence has emerged to support the theory that an anatomical interval exists between the fibres of the optic radiations representing upper and lower visual quadrants. In the final few millimeters of their trajectory, radiation fibres undergo a mediolateral crossing that degrades the retinotopic order in the white matter underlying the visual cortex (Connolly and Van Essen, 1984; Nelson and LeVay, 1985). Tumour cells invading the subcortical white matter, or a tissue margin created by a surgeon, would be unlikely to divide the posterior optic radiations exactly along the representation of the horizontal meridian. For these reasons, we believe that involvement of the optic radiations is not adequate to explain the perimetric findings in our patients.

The most likely alternative is that damage to extrastriate cortex caused the quadrantic field defects in our patients. Little is known about the organization of extrastriate visual

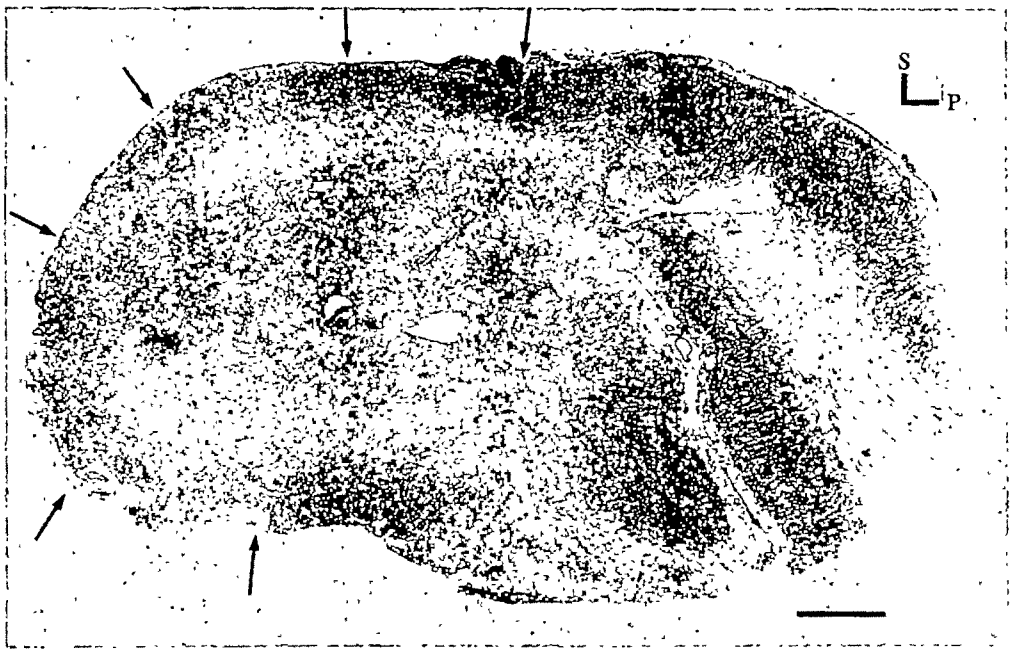

FIG 4 Parasagittal Nissl-stained section from the tumour specimen obtained in *Case 1*. Area 18/19 is recognizable in portions of the section, elsewhere neurons are replaced by malignant astrocytes (arrows). Bar = 2 mm, S = superior, P = posterior

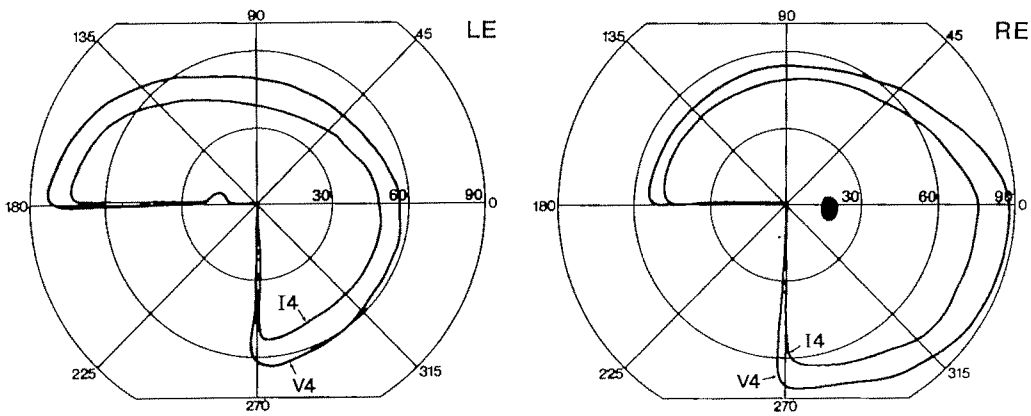

FIG. 5 Left lower quadrantanopia in *Case 1* plotted after operation using a Goldmann perimeter. The field defect respected the horizontal and vertical meridia with equal precision I4 isoptre refers to threshold determined using a 1000 apostilb test spot measuring 0 25 mm^2, V4 isoptre refers to a 1000 apostilb test spot measuring 64 mm^2 The background luminance of the hemispheric bowl is 31 5 apostilb and it is positioned 33 cm from the eye.

areas in the human brain. Therefore, to construct our proposal we must draw upon data from experimental work in monkeys. Our argument hinges upon the topographic arrangement of the first 3 cortical visual areas: V1, V2 and V3.

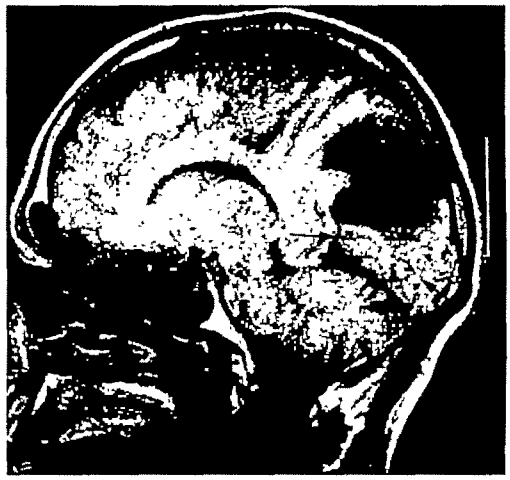

FIG 6. Sagittal magnetic resonance image of the right occipital lobe in *Case 2* (TR = 600 ms, TE = 20 ms) A large tumour is present in parieto-occipital cortex. The calcarine sulcus (between arrows) and occipital pole are preserved. Scale = 5 cm.

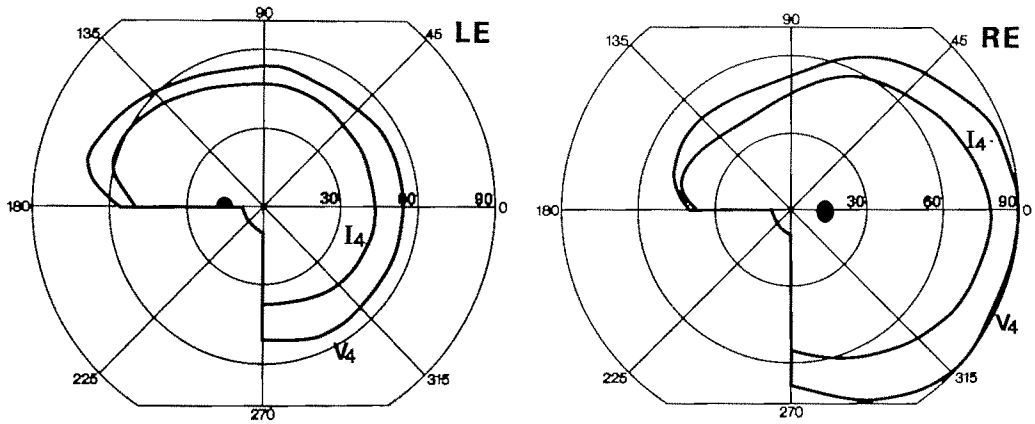

FIG. 7. Left lower quadrantanopia precisely bordering the horizontal meridian plotted in *Case 2* a week after operation. Note sparing of the central 10°.

Organization of human visual cortex

In primates the principal output of the lateral geniculate body is supplied to striate cortex. Brodmann (1909) designated striate cortex as 'area 17' in his cytoarchitectonic map. Area 17 is obvious in tissue sections because of the distinctive stria of Gennari. Surrounding striate cortex, Brodmann recognized two visual association zones: 'area 18' and 'area 19'. In humans, areas 18 and 19 measure together approximately 7800 mm^2, more than twice the surface area of area 17 (Filimonoff, 1933). In tissue sections stained for Nissl substance the cytoarchitecture of areas 18 and 19 appears remarkably uniform. In fact, anatomists cannot reliably distinguish between areas 18 and 19 in cortical sections. For this reason, some investigations have suggested that areas 18 and 19 constitute a single cytoarchitectonic field (Lashley and Clark, 1946).

Although histological sections through areas 18 and 19 prepared using classical neuroanatomical stains provide little hint of multiple functional subdivisions or cortical territories, this impression is deceptive. Recent studies in monkeys using electrophysiology combined with pathway tracing methods have revealed that areas 18 and 19 together contain at least 5 distinct cortical areas devoted to visual processing: V2, V3, V3A, V4 and V5 (Zeki, 1978*a*; Van Essen and Maunsell, 1983). These visual areas have been mapped and described in considerable detail. Other visual areas within Brodmann's areas 18 and 19 remain to be characterized. In macaque monkey approximately the posterior half of the cerebral cortex, containing as many as 20 separate areas, is engaged in processing visual information (Burkhalter *et al.*, 1986). In this context, 'area 18' and 'area 19' are not meaningful anatomical labels, except as general terms synonymous with 'extrastriate visual cortex'.

Striate cortex (V1)

In the human brain most of primary visual cortex is folded within the calcarine fissure (fig. 8). Consequently, it is necessary to represent V1 as an artificially flattened sheet of cortical tissue to plot the coordinates of the visual field upon the brain surface (fig. 9). The topographic representation of the contralateral visual hemifield established in humans (Inouye, 1909; Holmes 1918*a*) has been confirmed by detailed physiological studies in monkeys (Daniel and Whitteridge, 1961; Van Essen *et al.*, 1984). Striate cortex is a roughly oval piece of tissue, bordered by the representation of the vertical meridian and bisected by the representation of the horizontal meridian. More central portions of the retina have a relatively magnified representation (Holmes, 1918*a*, 1945; Talbot and Marshall, 1941; Daniel and Whitteridge, 1961; Van Essen *et al.*, 1984). Holmes (1945) underestimated the cortical magnification of central vision in humans. Daniel and Whitteridge (1961) have shown that in monkeys the central 10° of vision occupy slightly more than half the surface area of striate cortex. A similar proportion of striate cortex is devoted to central visions in humans, as shown by recent evidence correlating occipital lobe lesions imaged by magnetic resonance with visual field defects in patients (Horton and Hoyt, 1991). Accordingly, the isoeccentricity lines in fig. 9 reflect a revision of the original Holmes map (Horton and Hoyt, 1991).

Visual area 2 (V2)

No information is available about the topography of V2 in human visual cortex. Data from animal experiments (Cragg, 1969; Zeki, 1969; Allman and Kaas, 1971; Van Essen and Zeki, 1978; Gattass *et al.*, 1981; Weller and Kaas, 1983) indicate that V2 surrounds V1 completely, except anteriorly where the monocular crescent is represented (fig. 9). The representation of the vertical meridian is shared along the common border between V1 and V2. In the macaque monkey, the representation of the horizontal meridian in V2 is continuous with its representation in V1, but within a few degrees of the centre of gaze it splits to wrap around the outside of V2 (Van Essen and Zeki, 1978). As a consequence, nearby points above and below the horizontal meridian are represented in ventral V2 and dorsal V2 at widely separate locations in the occipital lobe. In V2 the representation of the central portion of the visual field is relatively magnified, as in V1. The isoeccentricity contours appear to pass from V1 to V2 without interruption (Allman and Kaas, 1974; Gattass *et al.*, 1981). In some monkeys, V2 breaks into separate

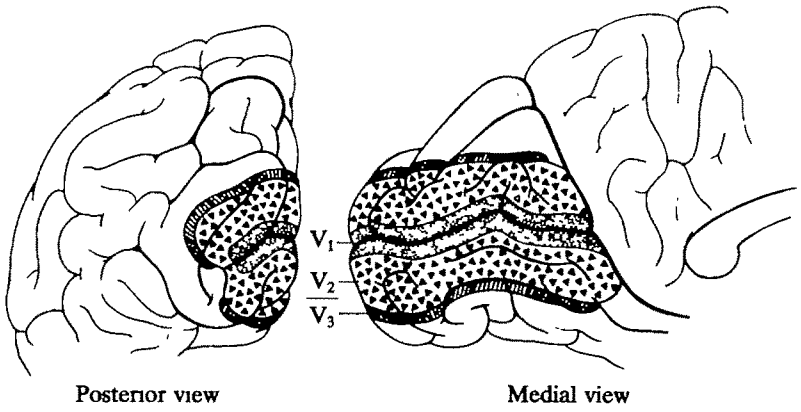

FIG. 8. Schematic diagram showing arrangement of V1, V2, and V3 along the medial and posterior occipital surface. Most of V1 is buried within the calcarine fissure. Considerable variation occurs among individuals in relative position and size of different cortical visual areas.

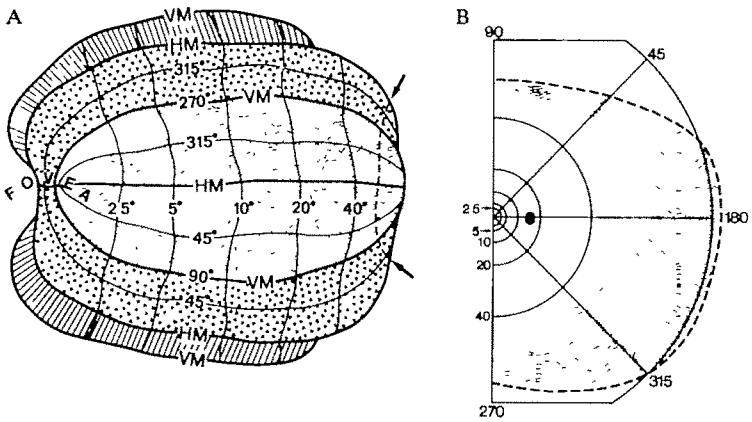

FIG. 9. A, artificially flattened map showing retinotopic organization of V1 (stippled area), V2 (small triangles), and V3 (hatched) in the left occipital lobe. B, right visual field coordinates corresponding to map in A. The monocular temporal crescent (stippled area) is represented within a small area at the rostral end of striate cortex (border between binocular and monocular field runs between arrows in A). V2 and V3 are split along the representation of the horizontal meridian into separate dorsal and ventral halves. More than half of visual cortex is devoted to processing the central 10° of vision.

dorsal and ventral portions at the representation of the fovea (Van Essen *et al.*, 1986). In other animals V2 simply becomes narrower in the foveal area, as shown in fig. 9.

Visual area 3 (V3)

The representation of the horizontal meridian in V3 is shared along the common border with V2 (Cragg, 1969; Zeki, 1969). The vertical meridian is mapped along the outer border of V3 (fig. 9). Thus V3, like V2, is split along the horizontal meridian into dorsal and ventral halves representing the lower and upper quadrants of the contralateral hemifield respectively. Mapping experiments suggest that V3 is probably discontinuous

near the representation of the fovea (Van Essen and Zeki, 1978; Zeki, 1978*b*; Gattass *et al.*, 1988). This gap is thought to be occupied by V4. Some authors have reported significant differences between the dorsal and ventral halves of V3, in terms of V1 inputs, myelin staining, and response properties of neurons (Burkhalter *et al.*, 1986; Newsome *et al.*, 1986; Van Essen *et al.*, 1986). They advocate using the term 'ventral posterior area' (VP) for the ventral portion of V3, to emphasize these differences. For our purposes, it is sufficient to note that V3 is physically separated into two halves, each containing a representation of a contralateral quadrant of vision.

Explanation of quadrantic field defects

Visual field defects due to lesions of the occipital lobe are usually attributed to damage to striate cortex. The layout of V2 and V3—wrapped about the perimeter of striate cortex—suggests that lesions of V1 will frequently include V2 and V3 (fig. 8). Indeed, V2 must also be damaged if a visual field defect reaches the vertical meridian. The topography of V2 is essentially a mirror image of the topography of V1, reflected across the shared representation of the vertical meridian (fig. 9). In an analogous fashion, the topography of V3 is mirrored across the representation of the horizontal meridian shared with V2. This arrangement results in a continuous representation of the visual field when moving along any isoeccentricity contour line from V1 into V2 and V3. Consequently, a lesion straddling the border between V1 and V2, or V2 and V3, will damage cortical tissue sharing common retinotopic coordinates. The resulting visual field defect will be a combination of scotomas produced by damage in each cortical area. Because the scotomas overlap, the relative degree of injury to V1, V2, or V3 will usually be impossible to determine by perimetric criteria alone. However, lesions that involve V2/V3 may produce a characteristic field defect, namely, a field defect which accurately follows the horizontal meridian.

The inferior quadrantanopia in our first patient can be explained by a dorsal lesion extending from the V2/V3 border to the V1/V2 border (fig. 10A). The exact size and shape of the lesion is not important: any lesion that crosses the representation of the horizontal meridian shared by V2 and V3 will produce a visual field defect that respects the horizontal meridian. The lesion may encroach upon V1, as long as it does not reach beyond the representation of the horizontal meridian in V1. A quadrantic visual field defect will result because of the split representation of the upper and lower visual quadrants in V2 and V3. Our proposal does not require that the lesion precisely follows the projection line of the horizontal meridian in cortex.

At the occipital pole, V2 may be discontinuous (Van Essen *et al.*, 1986). A gap between the dorsal and ventral halves of V2/V3 offers an obvious explanation for quadrantic field defects that reach fixation in some patients (Case 1). However, V2 usually remains continuous as it wraps around V1. Without physical separation between dorsal V2 and ventral V2 in the representation of the macula, the visual field defect in Case 1 becomes more difficult to explain. However, the extremely high cortical magnification factor at the occipital tip means that lesions in this area will result in field defects approaching very close to fixation. Lesions in V2/V3 further from the occipital tip will produce quadrantic field defects with varying degrees of macular sparing. An example is provided by the field defect in Case 2, which spared the central 10° of the lower quadrant (fig. 7). According to the retinotopic map of V1, V2, and V3 (fig. 9), the tumour must have

spared a considerable portion of the visual cortex (fig. 10B). This could be seen on the MRI, which showed preservation of the posterior occipital lobe (fig. 6).

Lesions damaging visual cortex will also affect association fibres travelling in the subcortical white matter between various cortical areas. V1 projects to retinotopically corresponding regions in V2 and V3 (Tigges *et al.*, 1973; Zeki, 1978*a*; Van Essen and Maunsell, 1983; Burkhalter and Bernardo, 1989). Reciprocal connections unite V2/V3 with V1. The lower calcarine bank contains association fibres passing between common retinal coordinates located exclusively in the upper quadrant of the contralateral hemifield (fig. 11). The upper calcarine bank contains fibres projecting only between points in the lower quadrant of the contralateral hemifield. A lesion situated in the lower calcarine bank will injure connections in the white matter passing medially, for example, from the horizontal meridian in V1 to the horizontal meridian in ventral V2. Thus the split configuration of V2/V3, flanking V1 along the calcarine fissure, creates the potential for lesions of either calcarine bank to selectively damage fibres between V1 and V2/V3, affecting one quadrant while sparing the other.

Previous studies of quadrantanopia

The first case of quadrantanopia was reported by Hun in 1887. Numerous examples of quadrantanopia have been published in the century that has elapsed since his report.

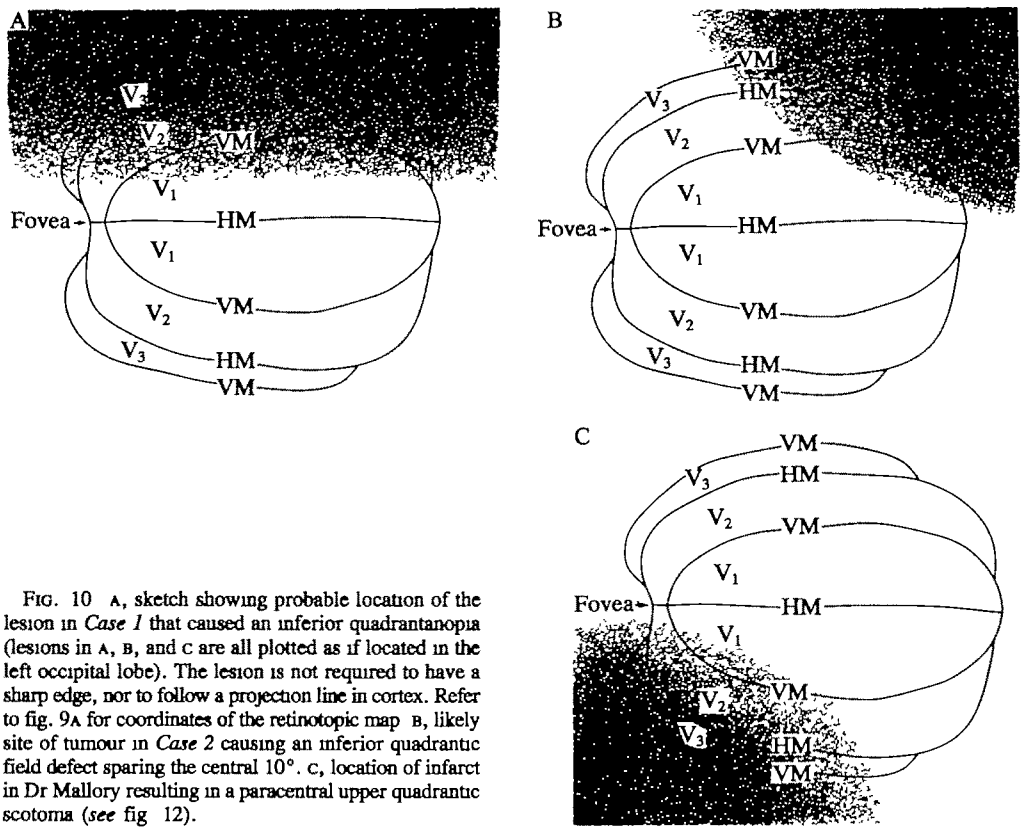

FIG. 10 A, sketch showing probable location of the lesion in *Case 1* that caused an inferior quadrantanopia (lesions in A, B, and C are all plotted as if located in the left occipital lobe). The lesion is not required to have a sharp edge, nor to follow a projection line in cortex. Refer to fig. 9A for coordinates of the retinotopic map B, likely site of tumour in *Case 2* causing an inferior quadrantic field defect sparing the central 10°. C, location of infarct in Dr Mallory resulting in a paracentral upper quadrantic scotoma (*see* fig 12).

Various theories have been offered to explain why the field defects in these cases respect the horizontal meridian. For the reasons outlined above, we believe that anatomical localization of precise quadrantic field defects to the optic radiations or primary visual cortex is unsatisfactory. We propose that homonymous quadrantic field defects are due to lesions involving V2/V3. Our review of the literature has yielded more than 50 cases of quadrantic field defects compatible with this explanation (Table). In some instances, quadrantic field loss was present in both hemifields. The most recent cases were reported with CT scans showing lesions in extrastriate cortex.

Cerebral achromatopsia often occurs in patients with superior altitudinal field loss (Meadows, 1974). Damasio *et al.* (1980) have documented achromatopsia and upper quadrantic scotoma in a patient with a lesion damaging the lingual and fusiform gyri, but sparing calcarine cortex. The concurrence of quadrantanopia and achromatopsia in some patients provides indirect evidence favouring our theory that lesions involving extrastriate cortex may produce quadrantic field defects.

Few cases of quadrantanopia of probable cortical origin have been correlated with neuropathological findings. Polyak (1957) described 3 cases in detail. He reported the case of Dr Mallory, the renowned Boston pathologist, who suffered a paracentral quadrantic scotoma (fig. 12A). At autopsy an old infarct occupied the lower calcarine bank, infringing slightly on the border of V1 (fig. 12B). There was no involvement of striate cortex at the base of the calcarine fissure, where the horizontal meridian is

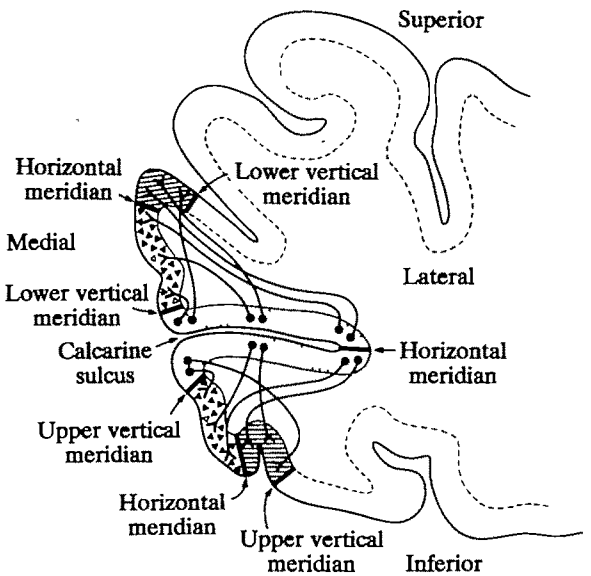

FIG 11. Schematic coronal section through right occipital lobe showing connections from V1 (stippled area) to V2/V3 (small triangles and hatched, respectively). Projections pass between common retinotopic coordinates. In V1 the horizontal meridian is represented along the base of the calcarine sulcus. Fibres coursing in the white matter of the upper and lower calcarine banks serve the lower and upper visual quadrants, respectively. For simplicity, feedback pathways from V2/V3 to V1, and the projection between V2 and V3 are omitted. The ventral V1 to V3 pathway is doubtful (Van Essen *et al.*, 1986)

TABLE REPORTS OF QUADRANTIC FIELD DEFECTS OF PROBABLE EXTRASTRIATE ORIGIN

Authors	*No. of cases*	*Comment*
Hun (1887)	1	Single case
Beevor and Collier (1904)	1	Single case
Holmes and Lister (1916)	6	Cases 1, 2, 3, 4, 16, 20
Riddoch (1917)	1	Case 4
Holmes (1918*a*)	2	Cases 5, 9
Holmes (1918*b*)	1	Case 6
Monbrun (1919)	3	Cases 1, 2, 3
Rönne (1919)	6	Cases 1, 3, 4, 5, 6, 7
Felix (1926)	1	Single case
Rea (1938)	1	Fig. 117
Money and Nelson (1943)	1	Case 4
Symonds (1945)	3	Cases 6, 7, 12
Traquair (1946)	1	Fig 231
Spalding (1952)	3	Cases 1, 2, 7
Wortham *et al* (1952)	1	Single case
Polyak (1957)	3	Cases Mallory, Holt, Munson
Harrington (1961)	1	Case 7
Cogan (1966)	1	Page 291
Meadows (1974)	1	Case A32660
Kaul *et al.* (1974)	2	Table 3, cases 3, 4
Cibis *et al.* (1975)	1	Case 5
Heller-Bettinger *et al.* (1976)	1	Single case
Damasio *et al* (1980)	1	Case 1
Spector *et al* (1981)	2	Cases 2, 6
Harrington (1981)	6	Figs 15–5, 15–16, 15–17, 15–43, 15–49, 15–51
Newman *et al* (1984)	2	Cases 1, 2
Bogousslavsky *et al.* (1987)	1	Single case
Gomez *et al.* (1990)	1	Single case
Lakhanpal and Selhorst (1990)	2	Cases 1, 2

represented in V1. The quadrantic visual field defect appeared to be caused by a vascular occlusion affecting ventral V2/V3 (fig. 10c) as predicted by our model.

Our proposal assumes that damage to V2/V3 is sufficient to cause a visual field defect. In the macaque monkey, V2 and V3 together approximately equal the surface area of V1. They are situated early in the hierarchy of cortical visual processing. V1 sends a major projection to only 3 cortical areas: V2, V3, and V5 (middle temporal area, MT) (Zeki, 1978*a*; Van Essen and Maunsell, 1983; Ungerleider and Desimone, 1986). Both the magnocellular and parvocellular systems pass from V1 through V2, before diverging to different cortical targets (Livingstone and Hubel, 1988; Zeki and Shipp, 1988). A lesion of dorsal or ventral V2/V3 will effectively cut off the flow of information emanating from one quadrant of V1 to the rest of association visual cortex. Because V1 and V2/V3 are arranged in a serial fashion, a lesion in V2/V3 is functionally equivalent to a lesion in V1, ignoring for a moment the projection from V1 to V5. V5 is a small cortical area believed to play a special role in motion processing (Allman and Kaas, 1971; Dubner and Zeki, 1971). Its location in the human visual cortex is still uncertain. We do not know whether the V1 to V5 pathway was intact in our patients. The ability of our first patient to detect hand movements in her blind quadrant implies preservation of some pathways from V1 to extrastriate cortex. Perhaps the pathway from V1 to V5 is sufficient to sustain some motion perception when V2 and V3 are damaged.

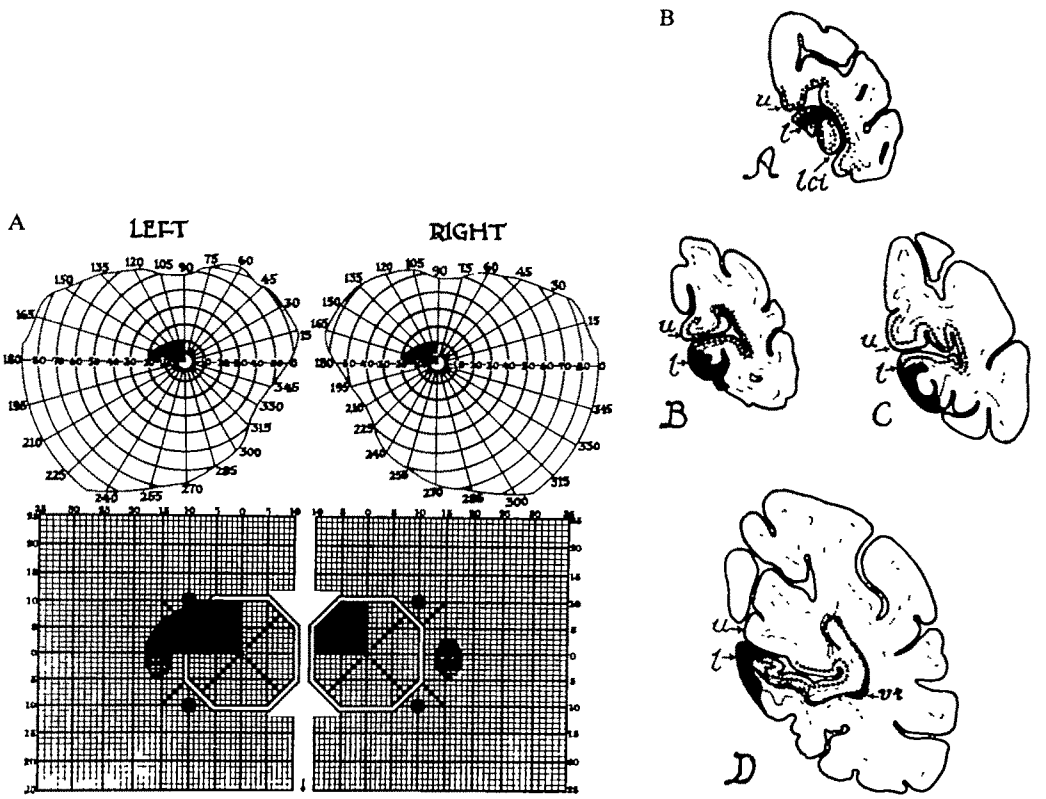

FIG 12. A, visual field for Dr Mallory showing left upper quadrantic defect extending to an eccentricity of 20°. The stereocampimetric chart (*below*) shows that the scotoma precisely respects the horizontal meridian. B, four coronal sections through Mallory's right occipital lobe Striate cortex is indicated by the intracortical black dots The infarct responsible for the field defect in (A) damages extrastriate cortex and white matter of the lower calcarine bank; striate cortex is largely spared. The relationship of the lesion to V1, V2, and V3 is postulated in fig. 10c. vr = visual radiation, u = upper calcarine lip, l = lower calcarine lip, lci = lower calcarine prong. (Polyak, 1957, figs 424 and 426, by permission, University of Chicago Press)

Few investigators have studied whether lesions of V2/V3 produce a scotoma in the visual field. Denny-Brown and Chambers (1976) attempted to ablate selectively areas 18 and 19 in the Rhesus monkey. A complex four-stage operation was required to remove areas 18 and 19 and leave area 17 intact. Results of these experiments are difficult to interpret because portions of extrastriate cortex were inadvertently spared. Moreover, the animals were tested simply by filming their visually-guided behaviour. It would be worthwhile to test in monkeys using modern techniques the effects of selective lesions in V2/V3 upon visual perception. Specific defects in motion perception in behaving monkeys have been reported after discrete chemical lesions in V5 (Newsome and Paré, 1988). We predict that chemical lesions in V2/V3 would produce a scotoma in the retinotopically appropriate region of the visual field.

The MR scans obtained in our patients show involvement of extrastriate cortex. However, the stria of Gennari cannot be resolved in MR images and hence the V1-V2

boundary is uncertain. In man, considerable variation occurs in cortical gyral pattern, and in the location and extent of primary visual cortex (Stensaas *et al.*, 1974). These factors make it hazardous to assign lesions to any given cortical area on the basis of MR images alone. In our first case, the cortical biopsy localized the tumour to extrastriate cortex. However, in the second case the cortex was so extensively replaced with malignant cells that reliable identification of cytoarchitectonic boundaries was impossible. Anatomical study of more cases is necessary to verify our contention that lesions of extrastriate cortex (V2/V3) can result in quadrantic field defects. If our notion is validated, these puzzling field defects may finally be explained.

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THE APHASIC ISOLATE

A CLINICAL-CT SCAN STUDY OF A PARTICULARLY SEVERE SUBGROUP OF GLOBAL APHASICS

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SUMMARY

This paper outlines the clinical and CT scan features of a subtype of global aphasia, characterized by an extreme loss of communicative abilities, verbal as well as nonverbal Three to four weeks after a left hemisphere stroke, 17 patients were completely unable to communicate with people addressing them. Though there were differences in their willingness to interact with the environment, they were characterized by complete loss of speech output and by inaccessibility to any kind of message, whether given verbally or through gestures. Patients who survived were reassessed 6 and 12 mos later and half of them were still found in a state of complete communicative isolation. The remainder had somewhat improved, but remained globally aphasic. The attempt to find a CT scan basis for this picture was disappointing. Only 35% of patients had a lesional pattern in agreement with the traditional view that ascribes global aphasia to the involvement of Broca's and Wernicke's areas. The location of lesion in the other cases spanned from anterior cortical damage, to posterior cortical damage, to deep nuclei damage and none of the lesions that have been proposed to account for subcortical global aphasia was consistently observed.

INTRODUCTION

In the early days after a left hemisphere stroke it is not uncommon to see patients who appear totally isolated from linguistic communication, being bereft of any form of speech output and unable to understand even the simplest verbal commands. Clinical wisdom suggests, however, that at this early stage of disease no prediction can be confidently made on the eventual outcome of the language impairment, which can evolve towards global or Wernicke's aphasia as well as towards milder aphasic forms (Pashek and Holland, 1988). Moreover, patients who can be reliably classified as global aphasics, once oedema and diaschisis have subsided, tend to regain a rudimentary capacity to interact with other people and in particular show an improvement over time in oral comprehension, which becomes sufficient to grasp the meaning of simple messages in real life (Edelman, 1984).

Boller and Green (1972) examined residual comprehension in 15 patients with severe global aphasia, and found that they were able to distinguish whether the question was addressed in correct English, in phonetic jargon or in a foreign language, could discriminate information questions from yes-no questions and reacted to 42% of items with responses that were generally appropriate or even correct. Tape-recorded commands were more poorly understood than those given by the examiner sitting in front of the patient (Green and Boller, 1974), a finding in keeping with the clinical observation that

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patients are greatly aided by contextual cues and that their performance markedly deteriorates in a formal testing situation relative to informal conversation (Stachowiak *et al.*, 1977).

On the expressive side, the ability to communicate wishes and thoughts verbally is reduced to a minimum in global aphasics, whose speech is thwarted by anarthric blocks, severe anomia, perseveration and, in some cases, recurring utterances. Although it has been suggested (Critchley, 1970; Hécaen and Albert, 1978) that they can use the intonation of their stereotypes to express their reaction to elementary questions, a careful analysis of the variation presented by the melodic contour of recurring utterances failed to substantiate the hypothesis (de Bleser and Poeck, 1985). Consequently, the main avenue which remains open for communication to these patients are gestures and pantomimes (Stachowiak *et al.*, 1977). With the passage of time a certain limited degree of improvement tends to occur but only a few patients reach a level of linguistic and extralinguistic communication sufficient to cope with their needs.

In our clinical practice we were impressed by a subtype of global aphasics who appeared to be completely bereft of the possibility of entering into any form of communication with other people and remained in a state of isolation long after the first weeks of disease. While most global aphasics try to understand urgent requests made to them and to express their own basic needs with whatever meaningful linguistic and gestural output is available, these patients appear to be uninterested in any form of human interchange as if completely incommunicado. To the best of our knowledge this extreme and pervasive disruption of all communicative abilities has received no mention in the literature. The present study sought to elucidate the features of this subtype of global aphasia, to evaluate its evolution and to investigate its pathological correlates, as evidenced from CT scan findings.

MATERIAL AND METHODS

Patients

Seventeen patients (10 males, 7 females), hospitalized in the neurological department of the Modena University Hospital for a stroke, participated in the study. Criteria for inclusion were: (1) absence of communicative speech both spontaneously and in response to elementary questions raised by the examiner and relatives, and a complete inability to understand verbal commands at bedside examination, even when accompanied by gestures; (2) that a period of at least 3 wks should have elapsed from the onset of disease and that consciousness was clear as far as could be judged from the patients' behaviour; they paid attention to the environment and reacted to sensory stimulation; (3) no sign of mental deterioration, of psychotic disorder or of severe hearing impairment noticed by relatives before the stroke. Of the total admissions to the neurological service over a year, 17 patients fulfilled the selection criteria. Table 1 gives their demographic, clinical and CT scan data. Ages ranged from 56 to 83 yrs (mean 69.3 yrs). Most patients had an elementary level of education. All were right-handed.

CT scan showed that damage affected the left hemisphere in all 17 patients, but was accompanied by a right hemisphere lesion in 4 of them. A more detailed analysis of the extension and locus of lesion is deferred to the Results section. Follow-up examinations were scheduled 6 mos poststroke and at 1 yr after the first examination.

Tests

In the initial testing session, formal assessment of patients' language abilities was carried out with a naming, a pointing and a repetition test. The first 2 tasks consisted of 6 common objects (glass, pen, keys, watch, thermometer and spectacles) that the patient had first to name and then to point to on verbal command.

Repetition was tested with the following items: (1) ba-ba, (2) da-da; (3) ga-ga; (4) mamma (mammy); (5) cane (dog), (6) scarpa (shoe); (7) frumento (wheat); (8) oggi fa caldo (today is hot); (9) il medico cura i malati (doctor treats patients). In the follow-up examinations testing was enlarged to include 4 new tests having the aim to assess comprehension at its most elementary level. Two tests were verbal.

Figure pointing test. The patient was presented with 10 pairs of figures (an animal and an object) in succession and requested to point to the figure named by the examiner. The pairs were given a second time in a different order, the target now being the figure that had been the distractor in the first presentation. Maximum score: 20

Verbal commands. The following commands were given (1) Look at the window. (2) Close your eyes. (3) Touch your hair. (4) Raise your left hand. (5) Pound the table. (6) Pick up the pencil Maximum score: 6.

Two tests did not involve verbal communication and the comprehension of the required performance rested entirely on decoding the context and gestures leading the patient to test material.

Cube and box test. This required the patient to reproduce the actions carried out by the examiner In the training stage, a cube and a box were placed on the table in front of the patient and the examiner, who was seated at his side, took up the cube and put it into the box. The cube was then removed, put back on the table and the patient was invited by gesturing to repeat the performance. If he did not understand the task, a second demonstration was given and, if he again failed, the examiner guided his hand through the performance. Testing began with 3 boxes displayed in line on the table and 3 cubes in front of them. The examiner carried out the following three performances· (1) 1 cube was put into each box; (2) all cubes were put into the central box; (3) 2 cubes were put into the left box and 1 into the right box. After each demonstration, the cubes were removed and the patients were invited with gestures to repeat the action. If they failed, a second demonstration was given. Two points were assigned for a correct execution on the first trial, 1 if only the second trial was passed. Maximum score: 6

Matching to sample test. Training began with the presentation of 2 white cards, 15 cm × 10 cm, one with a red square and the other with a red circle drawn in the centre. The examiner had 2 identical cards and put them on the corresponding samples. The cards were removed and given to the patient for him to repeat the matching. A second and a third trial were given if the previous ones were failed. The test consisted of two parts. In the first part, 6 cards, each with a different red geometric figure drawn in the centre, were laid down in 2 rows on the table. The patient was handed 6 identical cards, one at a time, and requested by gestures to match them to the samples. Gestures consisted of pointing to the handed card and then to the 2 rows of cards. The task was repeated a second time, with cards given to the patient in a different order. The second part of the task was identical to the first, except that the cards handed to the patient had yellow and not red figures as the samples. This part was also repeated. The total score of the test ranged from 0 to 24.

Assessment of apraxia. Limb and oral apraxia were assessed with two tests requiring the patients to imitate gestures made by the examiner with their left upper limb and with the oral musculature, respectively. The limb movement imitation test consists of 24 items, has a maximum score of 72 and has been described in detail by De Renzi *et al.* (1980). The oral movement imitation test consists of 10 items and was constructed in analogy to the limb test; the maximum score is 30.

RESULTS

All patients were examined from 3 to 7 wks poststroke, except Case 4 who had first been in hospital in another city and came to our department 4 mos after the onset of disease.

First examination

The general attitude of patients was characterized by the absence of any attempt to circumvent their speech block by resorting to pragmatic extraverbal skills, both when addressed by the examiner and in response to their own needs. For instance, they never took the initiative to point to a glass when they were thirsty, or to call the attention of their relatives when they had urinated or defaecated. They were vigilant and attentive

to people around them and looked at them if questioned, but failed to understand verbal requests as well as the examiner's attempts to transmit information by deictic gestures or pantomimes (e.g., in the course of the sensory and visual field examination).

Formal testing confirmed the patients' communicative isolation (*see* Table 1). On the 6 object pointing test, all of them scored 0/6 except Case 10 who scored 1/6. No speech production was obtained on the naming test and 15 patients failed to repeat any word.

In spite of this common behavioural pattern, there were differences in the patients' willingness to interact with the environment. Six patients (Cases 1, 4, 7, 12, 15, 16) were basically inert and did not respond to any verbal or nonverbal request to engage themselves in a performance, though not manifesting negativism during passive movements or when requested to maintain an attitude. Eleven patients (Cases 2, 3, 5, 6, 8, 9, 10, 11, 13, 14, 17), on the contrary, were more interested and willing to cooperate, for example, in the course of the neurological examination, although in some of them (marked +/− in Table 1) this positive attitude vanished and gave way to reactions of disheartenment and even refusal when they were given the tests. Only 3 patients of the latter group tried to imitate, albeit imperfectly, the gestures of the examiner in the apraxia tests. The remainder remained motionless. This picture is clearly different from that observed in usual forms of global aphasia, where the patient is not completely inaccessible to commands, takes advantage of explanatory gestures accompanying them, and tries to communicate his needs in whatever manner he can.

Second examination

Of the 17 patients originally examined, only 11 were available at follow-up carried out 6 mos later. Five had died in the interval and 1 did not return for examination.

TABLE I FIRST EXAMINATION

Case no.	*Sex*	*Comprehension*	*Naming*	*Repetition*	*Apraxia*		*Degree of cooperation*
					IMA	*OA*	
1	F	0	0	0	0	0	−
2	M	0	0	4	34	0	+/−
3	M	0	0	0	5	0	+/−
4	M	0	0	0	0	0	−
5	M	0	0	1	23	3	+/−
6	F	0	0	0	0	0	+
7	F	0	0	0	0	3	−
8	F	0	0	4	27	6	+
9	F	0	0	0	0	0	+
10	M	1	0	0	14	8	+
11	M	0	0	0	0	0	+
12	M	0	0	0	0	0	−
13	F	0	0	0	3	0	+
14	M	0	0	0	0	0	+/−
15	F	0	0	0	0	0	−
16	M	0	0	0	0	0	−
17	M	0	0	2	0	0	+

IMA = ideomotor apraxia; OA = oral apraxia; − = uncooperative patients in any situation; +/− = patients who did not cooperate in the testing situation; + = cooperative patients.

Table 2 summarizes the performance of the patients who underwent the second examination.

The upper part of the table reports patients who were still basically unable to communicate. They performed at chance level when requested to identify which of two figures corresponded to that named by the examiner. Elementary commands, involving

TABLE 2 SECOND EXAMINATION

	Verbal comprehension			*Nonverbal comprehension*				*Apraxia*	
Case no	*Objects Max 6*	*Figures Max 20*	*Commands Max 6*	*Boxes Max 6*	*Match to sample Max 24*	*Naming Max 6*	*Repetition Max 10*	*IMA Max 72*	*OA Max 30*
1	5	11	2	1	0	0	0	0	6
4	2	11	0	1	18	0	0	1	3
7	0	12	0	0	24	0	0	4	5
12	0	9	0	0	0	0	0	4	0
15	0	2	0	0	0	0	0	0	0
2	3	20	3	3	24	3	8	50	8
5	4	17	4	3	24	0	2	49	16
6	3	18	4	2	24	0	4	29	4
8	2	17	6	3	22	1	8	49	10
14	3	14	5	3	23	0	0	52	3
17	2	17	4	2	21	4	5	28	14

IMA = ideomotor apraxia, OA = oral apraxia

comprehension of a single information unit, were failed, with the exception of Case 1 who performed 2 out of 6 correctly and could point to 5 out of 6 objects; he too, however, performed at chance level on the figure pointing test and on the 2 nonverbal tests. There was just 1 patient (Case 7) who could match to sample flawlessly, but he too failed to imitate the cube and box performance. Naming and repetition were always absent. These patients remained almost totally unable to engage themselves in the imitation of limb movements. The impression of persistent isolation was confirmed by relatives who reported that the patients (with the exception of Case 4) failed to use extraverbal communication to manifest their urgencies and did not reply to questions concerning concrete problems and requiring yes-no answers.

The remaining 6 patients (lower half of the table) had partially regained the ability to understand elementary commands and to model their behaviour after the examiner on the 2 nonverbal tests. Although all of them still performed in the apraxic range on the limb movement imitation test, they did attempt to imitate the examiner and errors were executive and not from lack of comprehension of the task. Naming remained absent or poor, and speech had the characteristics found in nonfluent global aphasia. Improvement was also noted at home, where, though not speaking, they had regained a certain autonomy in eating, cooperated in dressing and in washing themselves and tried to indicate by gestures their needs.

It is worth underscoring the fact that all patients who had shown some signs of cooperation when first seen and could attend the follow-up examination improved, while those who had been found totally uncooperative remained in an isolated state.

Third examination

Ten patients attended the second follow-up 1 yr after initial testing, 1 patient having died in the interval. Of the 5 patients severely impaired on the first follow-up (upper part of Table 3), only 1 (Case 7) had substantially improved, though he too performed very poorly when required to match a spoken name to 1 of 2 figures. Here and there some improvement was also shown by other patients, but on the whole their comprehension level remained very inefficient, and their speech was practically absent. However, relatives reported a lack of communicative efforts in any circumstance and by any means in only 2 patients (Cases 1, 15). In the remainder, a degree of extraverbal communication had recovered in very concrete situations. The picture shown by the patients found to be improved on the first follow-up evaluation had not changed appreciably (lower part of Table 3).

TABLE 3. THIRD EXAMINATION

	Verbal comprehension			*Nonverbal comprehension*				*Apraxia*	
Case no	*Objects Max. 6*	*Figures Max. 20*	*Commands Max. 6*	*Boxes Max. 6*	*Match to sample Max. 24*	*Naming Max. 6*	*Repetition Max. 10*	*IMA Max. 72*	*OA Max. 30*
1	4	13	4	1	0	0	2	0	0
4	3	12	0	2	18	0	0	3	3
7	6	12	4	3	24	2	0	18	3
12	0	5	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0
2	6	20	5	3	24	0	8	58	12
5	6	20	4	3	24	0	5	53	17
6	3	16	5	3	22	1	5	19	3
14	0	19	3	3	24	0	0	54	8
17	6	16	6	3	24	3	5	30	9

IMA = ideomotor apraxia; OA = oral apraxia

Anatomoclinical correlations

CT scans, carried out 15–30 days poststroke, were available for all patients. The nature of disease was an infarct in 15 cases and a haematoma in 2 cases.

1. In 6 cases (3, 5, 10, 12, 15, 16) there was an infarct affecting the whole territory (cortical and deep) of the left middle cerebral artery (MCA). In 1 of them (Case 12) the territory of the posterior cerebral artery was also partially involved. All the classical language areas were destroyed and thus in these cases the picture of global aphasia was in good agreement with the extent of lesion. In the remaining patients the lesion was more restricted, as shown in figs 1 and 2 which map it at the level(s) where it was largest.

2. One patient (Case 1) had a haematoma extending from the frontoparietal cortex to the putamen, but leaving the temporal lobe undamaged (fig. 1A).

3. In 5 patients damage was confined to the territory of the superficial branches of the left MCA and did not encroach upon the deep nuclei or the internal capsule (fig. 1A). The infarct was in the territory of the anterior branches of MCA in 2 cases (8, 9) and in that of the posterior branches in 3 cases (4, 13, 14).

4. In 2 cases (2, 17) the lesion was at the level of the corona radiata (fig. 1B).

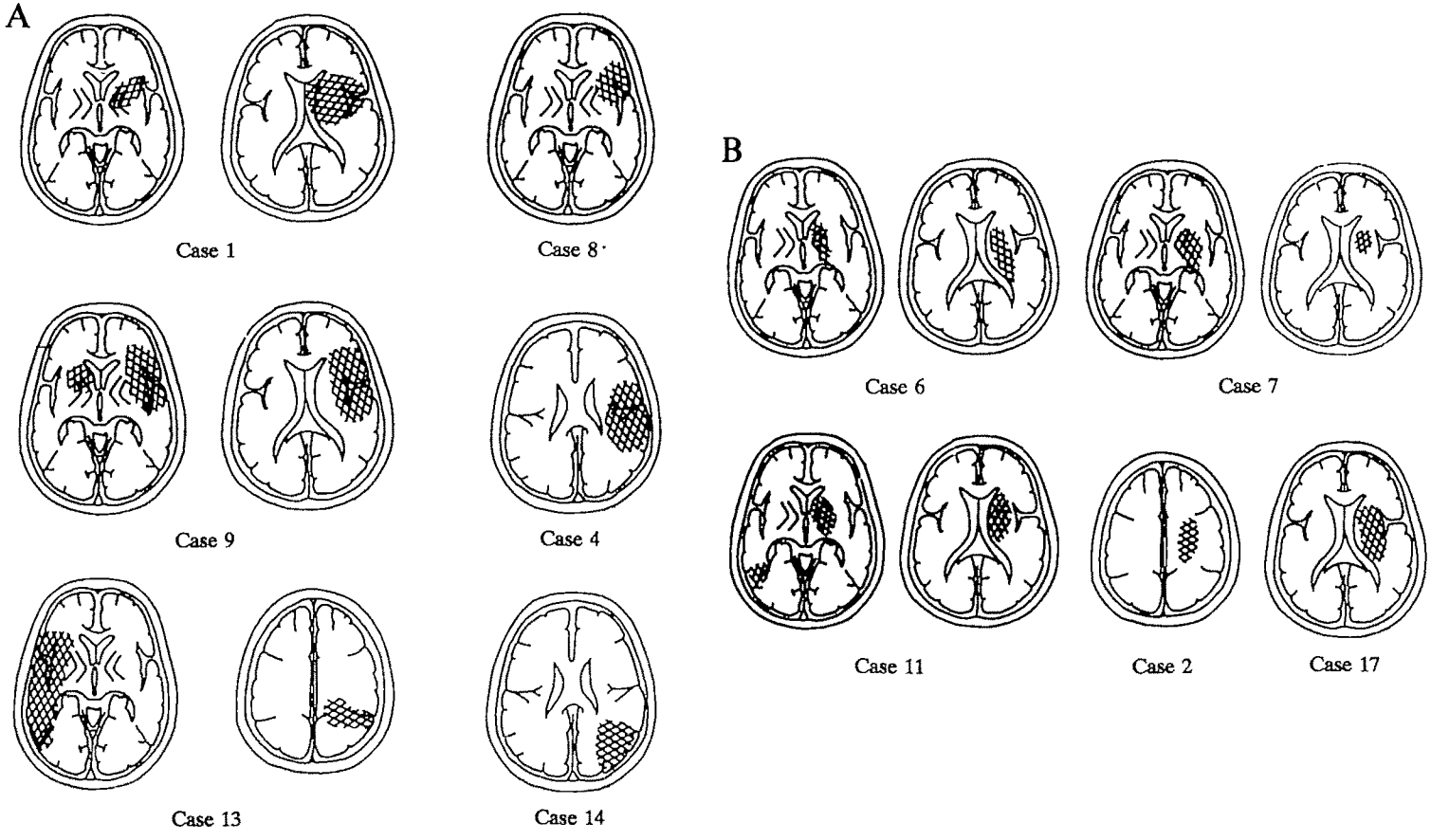

FIG 1. CT scan maps of patients with cortical damage (A) and subcortical damage (B). Numbers identify patients (*see* text) The left hemisphere is to the right.

5. Lesions confined to the deep nuclei were found in 3 cases, 2 infarcts and 1 haematoma (fig. 1B). Case 11 had a haematoma destroying the head of the caudate, the putamen and both limbs of the internal capsule and part of the thalamus. In Case 6, the infarct involved the putamen, the head of the caudate and the anterior limb of the internal capsule and in Case 7, the lentiform nucleus and both limbs of the internal capsule.

6. White matter lesions. In a series of papers on subcortical aphasia (Naeser *et al.*, 1982, 1989; Alexander *et al.*, 1987) have championed the view that small but strategically placed lesions may have devastating consequences if they interrupt crucial connections. In relation to global aphasia, this means that we must look for white matter lesions likely to cause disruption both in speech input and output. Alexander *et al.* (1987) have ascribed severe comprehension deficits in subcortical aphasics to a lesion of the temporal isthmus, which would interrupt the pathway from the ipsilateral medial geniculate body, combined with a lesion of the posterior periventricular white matter (PVWM), which would hinder the transmission of information from the contralateral auditory cortex. On the other hand, absence of speech or the mere production of stereotypes has been related (Naeser *et al.*, 1989) to the concurrent involvement of the subcallosal fasciculus, linking the supplementary motor cortex and the cingulum with the head of the caudate, and that part of the pyramidal tract where fibres from the cortical mouth area run downwards. Interruption of these two pathways would occur at the level of the lateral margin of the frontal horn and in the middle one-third of the PVWM, respectively.

We focused on the 11 patients who lacked the classical anatomical correlates of global aphasia, namely the 5 patients with lesions in the territory of the anterior or posterior branches of MCA, the patient with a haematoma sparing Wernicke's area, the 2 patients with corona radiata damage, and the 3 patients with a lesion of the deep nuclei. Neither the patients with an anterior cortical infarct nor the one with a haematoma showed extension of the lesion into the temporal isthmus or to the posterior PVWM, and no patient with a posterior cortical lesion had damage to the subcallosal fasciculus or to the middle one-third of the PVWM. In both patients with damage to the corona radiata the subcallosal fasciculus and the middle PVWM were involved, but neither had a lesion of the temporal isthmus or of the posterior white matter extension. In the 3 patients with deep lesions, the middle one-third of the PVWM was consistently damaged, the subcallosal fasciculus was possibly damaged in 1 case, and the temporal isthmus and the posterior PVWM extension were consistently spared.

7. Right hemisphere damage. In 4 cases there was also CT scan evidence of right hemisphere damage which in 3 cases (9, 10, 13) preceded the left side disease and in 1 case (Case 11) followed it. The right hemisphere areas encroached upon by the lesion were as follows: the occipital lobe (Case 10), the frontotemporoparietal region (Case 13), the anterior limb of the internal capsule and the head of the caudate (Case 9), and the inferior and middle temporal gyri (Case 11).

For 2 of these patients there are hints that the right hemisphere damage may have contributed to the severity of the aphasic picture. Case 13 had a relatively small lesion confined to the left supramarginal and angular gyri which would not have been expected to cause a persistent global aphasia. Six years earlier, she had been admitted to our department for a right-sided ischaemic attack, with complete recovery in a few days and subsequent wellbeing up to the date of the second stroke. Unexpectedly, a CT scan showed a large mature infarct involving the inferior frontal, superior temporal and

supramarginal gyri on the right. It must be questioned whether damage to the areas in the right hemisphere corresponding to those subserving language in the left hemisphere undermined the recovery potential of this patient. Even more suggestive is Case 11. This 56-yr-old man was admitted after the sudden onset of a right hemiplegia, hemianopia and aphasia shown by CT scan to be associated with a large haematoma in the lentiform nucleus extending to the posterior limb of the internal capsule and lateral thalamus. With the passage of time some language recovery occurred, and 2 mos later he was described as alert, partially understanding simple commands, scoring 4/6 on the 6 item pointing test, sometimes making gestures to express his wish to leave the hospital and able to imitate gestures made by the examiner, although still apraxic. Automatic language (days of the week, counting forwards) was present, but no naming or spontaneous speech was possible. A few hours after having a second CT scan which showed a reduction of the lesion, the patient was found with eyes and head deviated to the right and having lost any ability to communicate. A further CT scan demonstrated a small haematoma located in the posterior portion of the right inferior and middle temporal gyri. In the following month he was observed to be alert, to follow the examiner attentively and occasionally even to wave in response to the examiner's greetings, but to be completely unable to communicate, to understand elementary commands or to express his needs. He remained in this condition of extreme isolation for a month, then developed a urinary tract infection and died 15 days later. This clinical picture is compatible with the assumption that a marked deterioration of communicative abilities coincided with the occurrence of a right temporal lesion.

There have been hints in the literature (Pieniadz *et al.*, 1983) that the prognosis of global aphasia may be related to hemisphere asymmetries in the occipital region, measured with CT scan. Patients with a better recovery showed atypical asymmetries, namely a larger right than left occipital region both in terms of width and length, a finding suggestive of an increased capacity of the right hemisphere to participate in language functions and therefore to contribute to the recovery process. Following the procedure described by Faglioni and Scarpa (1989), we measured the width and length of the occipital bones in the 11 patients in whom there was no sign of mass effect. Four of them had typical asymmetries (left > right) and 3 atypical asymmetries (right > left) for both measures; the remainder had typical asymmetry on one measure and atypical on the other. Thus in this group of global aphasics with an overall poor prognosis there was no consistent pattern of asymmetry.

DISCUSSION

We have outlined in this paper the clinical profile and course of an extreme form of global aphasia which has hitherto received scanty consideration, possibly because the severity of impairment discourages any attempt at treatment, diverting attention from these patients. What characterizes them is not so much their loss of speech, which at least at an early stage of disease can also be found among other global aphasics, but their complete inability to understand any form of verbal as well as nonverbal information and the absence of any intention to communicate, even under the urgency of basic needs. This condition of extreme isolation seems to reflect not only the severing of all input and output channels but also the unavailability of extralinguistic skills capable of bypassing

the verbal block. This is well exemplified by the patients' performance on the cube and box test, a task requiring elementary abilities and whose nonverbal instructions are made self-explanatory by the context and by gestures leading the patients' attention to the objects and the way they must be manipulated. Yet 6–7 mos after the stroke, there were still 5 patients who failed the task almost completely, 3 of them not even passing the training session. The same was true for 4 of these patients for the matching to sample test. The finding that the 6 patients who showed comprehension improvement at the second examination passed these tasks fairly well, demonstrates that they are not beyond the capacity of the usual global aphasics.

It is possible that the loss of communicative abilities exhibited by these patients was further aggravated by noncognitive factors, such as inertia, depression or negativism, which may have conspired to hinder any effort to circumvent the linguistic failure. While clear manifestations of depressive mood or active negativism were not obvious, inertia was a conspicuous feature of the behaviour of some patients at the time of the first examination, and disheartenment sometimes occurred during the testing. To what extent these noncognitive factors contributed to the communicative block or, alternatively, represented its consequence, is open to question. Some patients became uncooperative only when confronted with tests. At follow-up they showed the same mild improvement exhibited by cooperative patients. Conversely, totally uncooperative patients remained isolated at follow-up, in spite of having regained a certain willingness to interact with the examiner. Thus at least at these later stages the communicative nature of the isolation would appear to be genuine.

The diagnosis of aphasic isolation made in the first month poststroke was associated with a high death rate (42%) and a poor functional prognosis: 5 out of the 10 patients that were available for follow-up at 1 yr were still deprived of any form of communication, while the others had evolved towards the picture of severe global aphasia. These findings are in keeping with longitudinal studies on global aphasics (Kertesz and McCabe, 1977; Pashek and Holland, 1988; Sarno and Levita, 1979, 1981) which have found that at 1 yr from the cerebrovascular event almost no patient had improved enough to merit a different classification.

The classical interpretation of global aphasia (Dejerine, 1914) assumes that it is due to damage to a large perisylvian region covering the posterior frontal gyri (Broca's area) as well as the posterior temporoparietal gyri (Wernicke's area). Although early clinical-CT scan correlation studies (Kertesz *et al.*, 1979; Damasio, 1981; Naeser, 1983) were in agreement with this proposition, Mazzocchi and Vignolo (1979) pointed out that it held in little more than 50% of cases and approximately the same percentage was reported by Poeck *et al.* (1984), Vignolo *et al.* (1986) and Scarpa *et al.* (1987). The 'exceptions' concerned cases whose lesion would have been considered by the classical theory predictive of Broca's, Wernicke's or transcortical sensory aphasia, or were confined to the deep nuclei. Present findings concur in showing that the involvement of the entire language region is not the rule in chronic global aphasia. It was found in 35% of our patients, and was replaced in the remainder by a wide spectrum of lesions ranging from involvement of the territory of the anterior or the posterior cortical branches of the MCA to damage restricted to deep hemisphere structures.

As these results show, attempts to correlate the lesion site with worse or better recovery at follow-up were unsuccessful. For instance, Case 7, who had a lesion confined to

the lentiform nucleus and both limbs of the internal capsule, remained isolated, while Case 5 who, in addition to these structures, had damage involving the fronto-temporoparietal white matter and cortex, improved.

It has been suggested (Vignolo *et al.*, 1986) that unusual localization of lesion in global aphasics may be related to sex, in that patients with damage confined to the anterior regions and without involvement of Wernicke's area would be female, while those with damage to the temporoparietal-occipital regions and sparing Broca's area would be male. In the present series this relation held for patients with anterior damage (both were female) but not for those with posterior damage (2 were male and 1 female).

Following Naeser and coworkers, the search for a common location of damage in global aphasics was extended to the white matter, focusing on the sites where lesions have been predicted to interrupt the pathways transmitting information from Wernicke's area and to the motor language centres. Our findings were negative. A severe and long-lasting comprehension deficit in the absence of superior temporal-inferior parietal damage was not accounted for by involvement of the temporal isthmus and/or the posterior PVWM extension, and only 2 or possibly 3 patients out of 10 with a total block of speech output and sparing of Broca's and supplementary motor areas had concurrent damage to the subcallosal fasciculus and the middle PVWM. For 2 patients (Cases 11, 13) there were hints that the co-occurrence of a right hemisphere lesion contributed to the severity of aphasia. The role played by the nondominant hemisphere in mediating language recovery in right-handed aphasics had been repeatedly pointed out since Gowers (1887), and there have recently been well-documented reports (Mazzocchi and Vignolo, 1979; Basso *et al.*, 1989) of patients whose language improvement after a left-sided brain lesion was suddenly reversed by a right-sided stroke. It seems, however, unlikely that right hemisphere participation in the restitution of verbal function represents a potential shared by the right-handed population in general since in the present study the majority of global aphasics improved very little or not at all, in spite of having a lesion confined to the left hemisphere.

In conclusion, the reason why certain patients show a particularly severe picture of global aphasia does not find an answer in a consistent anatomical pattern, at least as far as can be inferred from the evidence afforded by CT scanning. Although it is possible that studies carried out with MRI, SPECT and PET will bring out patterns of brain impairment specific for this picture, an alternative hypothesis remains that the differences are due to individual variability in the localization of cortical sites essential for language, as suggested by electrical stimulation mapping studies (Ojemann, 1979; Ojemann *et al.*, 1989).

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CONTROL OF THE TRANSITION FROM SENSORY DETECTION TO SENSORY AWARENESS IN MAN BY THE DURATION OF A THALAMIC STIMULUS

THE CEREBRAL 'TIME-ON' FACTOR

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SUMMARY

A 'time-on' theory to explain the cerebral distinction between conscious and unconscious mental functions proposes that a substantial minimum duration ('time-on') of appropriate neuronal activations up to about 0.5 s is required to elicit conscious sensory experience, but that durations distinctly below that minimum can mediate sensory detection without awareness. A direct experimental test of this proposal is reported here.

Stimuli (72 pulses/s) above and below such minimum train durations (0–750 ms) were delivered to the ventrobasal thalamus via electrodes chronically implanted for the therapeutic control of intractable pain Detection was measured by the subject's forced choice as to stimulus delivery in one of two intervals, regardless of any presence or absence of sensory awareness. Subjects also indicated their awareness level of any stimulus-induced sensation in each and every trial The results show (1) that detection (correct > 50%) occurred even with stimulus durations too brief to elicit awareness, and (2) that to move from mere detection to even an uncertain and often questionable sensory awareness required a significantly larger additional duration of pulses. Thus simply increasing duration ('time-on') of the same repetitive inputs to cerebral cortex can convert an unconscious cognitive mental function (detection without awareness) to a conscious one (detection with awareness).

INTRODUCTION

The existence of mental functions or operations that go on unconsciously, without reportable subjective awareness, is widely accepted. This is not the place to review the considerable clinical and experimental evidence that could be cited to support this view (*see*, e.g., Shevrin and Dickman, 1980; Marcel, 1983; Holender, 1986; Weiskrantz, 1986). The question of main interest here is what cerebral neuronal processes may control the transition between an unconscious and a conscious (subjectively experienced) mental function; that is, can a causal difference between (1) neuronal activity that supports/mediates an unconscious mental function and (2) neuronal activity that becomes sufficient to support/mediate a mental function carried out with conscious subjective awareness be identified?

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A 'time-on' theory has been proposed to provide one neural mechanism to distinguish between unconscious vs conscious mental functions (Libet, 1965, 1985, 1989). This entails two propositions. (1) A substantial minimum duration (or 'time-on') of appropriate neuronal activations is required to elicit a reportable conscious subjective experience. This duration can be up to 500 ms and more, when stimulation of a cerebral sensory system is at a liminal intensity for any sensory awareness. (2) Durations of activations which are less than the minimum required for awareness could mediate an unconscious mental function, one involving cognitive and conative responses to a sensory signal with no conscious sensory experience. The term 'unconscious' is used in a broad operational sense to mean a mental event which is not reportable as an introspective experience by the subjects (*see* Libet, 1987). This would include so-called preconscious and subconscious events. Considerable direct and indirect evidence for proposition (1) has already been developed (e.g., Libet *et al.*, 1979; Libet, 1981, 1982). Proposition (2), however, had thus far not been subjected to direct experimental testing of the kind that could potentially confirm or falsify it. Some indirect evidence was available from the timing of cerebral activity before a voluntary act (Libet, 1985, 1989).

The present study was designed to provide a direct test of the specific hypothesis that durations of repetitive inputs to sensory cortex too brief to elicit any sensory awareness can nevertheless be detected without awareness. Our previous study had shown that a stimulus of liminal intensity in the ventrobasal thalamus (or medial lemniscus) requires a minimum train duration of about 500 ms, independent of the pulse frequency, just as does S-I cortex (Libet *et al.*, 1964, 1979; Libet, 1973, 1982). In the present study train durations in a wide range above and below the minimum were delivered in different trials. Subjects were asked to give two kinds of responses after each stimulus delivery, one to test for psychological (mental) *detection* of the signal and another to report any *introspective experience or awareness* of a sensation. Detection was measured by a forced-choice response, as to which one of two time intervals may have been the one in which a stimulus was delivered, regardless of whether anything was felt by the subject. Thus propositions (1) and (2) of time-on theory were tested simultaneously in these direct comparisons of detection and awareness.

The design is based on our operational definition of conscious subjective awareness, that is, the introspective report of the subject that he/she has felt or experienced the simple sensation in question here. The case for the validity and reliability of such reports, when made under appropriate conditions, has been made elsewhere (e.g., Libet, 1987) and will be discussed further below. As will be shown below, an ambiguity of interpretation only arises when the subject reports that he is uncertain about whether or what he felt or experienced; how that category of subjective responses affects the overall conclusions will be considered in detail.

METHODS

Subjects

Subjects were drawn from a pool of patients in whom stimulating electrodes had been chronically implanted for the therapeutic relief of some forms of intractable pain (Hosobuchi, 1986; Levy *et al.*, 1987). The patients were ambulatory and for most study sessions they came from their homes. Each gave his/her fully informed consent in accordance with the Declaration of Helsinki, as prescribed by the Committee on Protection of Human Subjects of the University of California, San Francisco; the Committee also approved

the entire experimental study in accordance with its own rigorous guidelines and those required by the National Institutes of Health. This included reimbursement of incidental expenses and $25 for each half-day study session. It was agreed that no risk was added by the study; the intensity and duration of the experimental stimuli were all far lower than the therapeutic stimuli routinely self-administered via the same electrodes and electronic devices. Further, if there was any indication of fatigue or loss of interest, or of any preference by the subject not to continue, the study session was to be terminated, without any prejudice implied to the patient; this happened in only a few instances out of the total of approximately 50 half-day (2 h) study sessions for all subjects.

There were 6 males and 3 females who underwent the full study, ages ranged from 44 to 59 yrs. An additional male subject was studied extensively in 5 sessions in an initial pilot experiment to test and refine the procedure, including gaining experience with the nature of a subject's responses about the presence or absence of sensory awareness of the stimuli. The chronic pain in these patients was apparently brought on by injury (blow to back, fall) in 5, including 1 with paraplegia due to a spinal cord transection at T6 plus some spinal cord injury at C5 (Case B.D) In 1 (K.K.) the diagnosis was postherpetic neuralgia; in another (L.R.) it was lumbar arachnoiditis; and in another (H.C) the pain syndrome was apparently chiefly a result of partial damage to ascending somatosensory tracts in the midbrain during a previous surgical procedure. In the ninth subject (S.D.) the diagnosis was 'thalamic pain syndrome', with some residual loss in pressure and proprioceptive sensibility on the right side Thus in all of these 9 subjects, the pain syndrome was associated with damage to somatosensory pathways at some level.

Six subjects were taking daily medications for pain (in addition to using the thalamic stimulator). In 4 of these (K.D., J.S., J.P and L.R.) this was acetaminophen (500 mg) plus codeine (30 or 60 mg) one to three times a day In the fifth (M P.) it was Percocet (1 tablet three times a day). A sixth (K.K.) was taking low doses of methadone (10 mg/day) and thorazine (50 mg/day). Of the 3 not taking pain medications, 1 (S.D.) regularly took phenytoin, 300 mg/day and 2 others (H C. and B.D.) took L-DOPA. Although it is possible that some medications could have affected sensory perception, every subject appeared alert, attentive, responsive and articulate in the study sessions. In any case, it was not our objective to establish absolute levels of required stimulation, which might be sensitive to medications. The chief objective was to determine the *relative* train durations of stimuli required for detection without vs with sensory awareness, under given conditions of stimulus intensity and subjects' abilities in a given experimental session.

Many of the potential subjects experienced paraesthesiae (tingling, etc.) in the affected referral areas even at rest, that is, in the intervals between applying stimulation for relief of pain Any substantial amount of such resting paraesthesiae makes it difficult if not impossible for the subject to report consistently the usually similar additional paraesthesiae experienced with a threshold stimulus Consequently, we accepted for full study only those patients with few or no resting paraesthesiae, in whom near threshold sensations were discerned with consistency and without unmanageable difficulty.

Stimulation

The electrodes were bipolar platinum, with contact exposures of 1 mm and separation of 2 mm (Model 3380, Medtronics Inc., Minneapolis). The assembly had been implanted stereotaxically in the ventrobasal thalamus (n. VPL or VPM, depending on location of pain) with leads to a receiver coil which was implanted below the clavicles and internalized subcutaneously for permanent use. Location of the electrodes could not be verified by direct anatomical observation, but the physiological effects of stimulation were in accordance with the stereotaxic localizations. In any case, precise knowledge of electrode locations is not critical to the objectives of this study. A portable stimulator box (Models 3523, or 7520 or 3424, Medtronic, Inc.) supplied the electrical pulses, transmitted by another coil placed on the skin over the receiver coil. The initial pilot sessions showed that the battery supply in the box could not maintain a voltage sufficiently stable to enable us to achieve a relatively consistent threshold intensity during even 30−60 min of testing. Thus it was essential to replace the batteries with a constant voltage source at 9.0 V (Hewlett-Packard Power Supply, Model 6216A) during all experimental sessions. A stimulator box identical to that used therapeutically by patients was modified so that an external control could trigger the output of the box pulse by pulse, permitting us to control the frequency and number of pulses delivered by the box to its transmitter coil in each trial. Pulse shape and duration, 200 μs, remained a function of the box. Intensity (peak voltage) of pulses also remained regulatable only by the control knob on the box itself; since this proved to be too coarse to enable a sufficiently clear differentiation between a near-threshold (liminal) intensity and one giving a very strong sensation, we inserted an attentuator control in the circuit to the

transmitter coil. The intensity could then be graded more finely to liminal levels after setting the coarser control on the stimulator box.

A pulse frequency of 72 pps was adopted for all experiments, to provide a sufficient range of pulse numbers for the different stimulus trials (*see below*). The pulse number (train duration) was controlled by a gating signal delivered to a Grass S-44 stimulator, set to deliver the requisite frequency and number of trigger pulses to the stimulation box. An isolation unit disconnected the patients' stimulator box from ground and uncoupled it from direct connection to the Grass stimulator. Each gating signal was delivered from a IBM-PC/AT with Data Translation, DT2821-F-8DI, D/A converter. The duration of the gating signal (calibrated in pulse numbers for the Grass stimulator's output) was controlled and varied as desired by a program control written in ASYST.

Detection of the stimulus by the subject

Detection was measured by a simple forced-choice response. Each stimulus was delivered during 1 of 2 lighted intervals, L_1 and L_2, independently randomized with equal probability in successive trials L_1 and L_2 were indicated by two separate horizontally placed buttons; within each button a weak light went on for 1 s, first in L_1 (on the left) and after a 1 s interval, in L_2 (on the right). After L_2 light had turned on and off, the subjects had to choose that light (L_1 or L_2) during which the stimulus was delivered and to press the corresponding button for that choice. They were asked to make a choice even if they did not feel or experience any sensation either during the L_1 or the L_2 light-on time periods. In the absence of an associated sensory experience they were asked simply to give a best guess, letting this come spontaneously and quickly without trying to analyse their choice by deliberating about it. The use of 2 intervals in each trial, in which no stimulus is expected in 1 of the 2, allows the subject to compare *any* subjective sensory experience in 1 of the intervals with another putative blank interval. Also, the variation in the stimulus can be matched against an associated blank interval rather than against a past single-interval trial.

Feedback to the subject on the correctness of the choice was given only in those fewer series of trials so labelled. In these, a different small green light turned on briefly if the choice was correct or a similar red light if incorrect; this occurred immediately after the subject had acted to press button 1, 2 or 3 for awareness level which he did following his forced choice of L_1 or L_2.

With randomized actual deliveries of stimulus in L_1 or L_2, the subject will have a 50% chance of being correct even if he chooses L_1 or L_2 without any relationship to the stimulus. Detection would then be discernible only if correct responses are achieved in significantly more than 50% of the trials. The full statistical methods for handling and analysis of the observations are given below

Awareness of the stimulus by the subject

The subject was asked to report his awareness or unawareness of a sensory experience (due to the stimulus), whether during L_1 or L_2. This was indicated in each trial by pressing 1 of 3 buttons *after* having made his forced-choice detection response, as described above. The subject had to press button 1 if a sensation was felt in roughly the same bodily area as that experienced during the preliminary testing trials before each regular series of trials; he was to press button 1 even if the sensation was very weak and/or brief. If he simply felt nothing he was to press button 3. However, if he was uncertain about a sensory experience, or if he felt there was something more than nothing during one interval, he was to press button 2. It is important to note that the instruction to report button 2 extended beyond being uncertain about a sensation with the usual quality and location, it included any feeling of something being different about 1 of the 2 lighted intervals. The latter part of the instruction provided a possibility for responses that did not necessarily signify any sensory awareness, and these became evident in the descriptions by the subjects of what button 2 reponses actually meant to them.

For stimuli consisting of 1−19 pulses (i.e., train durations of approximately 0.26 s or less with 72 pps) it was initially expected that subjects would never feel any sensation, as stimulus intensities were set near the liminal level required by a 1−2 s train in the preliminary trials. (A 1 s train is normally distinctly longer than the minimum required with liminal I (defined later), but some subjects seemed to require > 1 s at the start of testing.) Therefore, for those series of trials in which all stimulus pulse numbers were in the range of 1−19, the subject was asked to give a confidence rating, even if he felt no sensation· button 1 was to be pressed if he was 'confident' about his forced-choice answer; button 2 if he had only a 'low confidence' in the forced-choice answer; button 3 if he had 'no confidence at all'. However, on questioning each subject after many such series of trials, it turned out that the basis for the confidence rating was

indistinguishable from that used in reporting the corresponding awareness level buttons 1, 2 or 3. Consequently, 1, 2 or 3 were all treated in the analysis as if respectively equivalent, whether the question to the subject was one of awareness or confidence level. The appropriateness of this is further discussed below.

It was emphasized to the subject that there was no 'correct' answer expected from him about his awareness report, and that we wanted and accepted his report of whether and what he felt, if anything.

General procedure

The subject sat in a comfortable chair at a table with the panel of responding buttons in an acoustically shielded room. The experimental observer sat alongside. The computer, Grass stimulator and other accessories, with the operator, were located in an adjacent anteroom.

Liminal I and utilization train durations (TDs). With 72 pps stimulation running continuously, the subject was initially asked to set the coarse intensity (I) control on the (modified) stimulus box to the level at which he just began to feel a weak sensation (usually a tingling) in the usual body part associated with therapeutic stimuli. The stimulation was then turned off and a series of trials was carried out to determine liminal I; with each stimulus set at 72 pps and a 1 or 2 s TD the observer used the attenuator fine control to achieve the intensity level at which the subject reported the weakest (threshold) sensory awareness. He reported his sensory response by pressing button 1, 2 or 3 (*see above*), as well as verbally when questioned. Holding to this fixed liminal I, the minimum TD (or pulse number) of the stimulus that could still elicit a conscious sensory experience was determined; this value had been named the 'utilization TD' (Libet *et al.*, 1964; Libet, 1973)

As in earlier studies, both liminal I and utilization TD were established by the common method of limits, in a sequence of stepwise changes up or down, with at least 2 consecutive trials in agreement on the threshold and subthreshold values. In the present study, establishing statistically rigorous values for liminal I and utilization TD was not essential; these values were needed only as indicators as to what level of I was to be adopted for the experimental trials in which *TDs* were varied in a statistically rigorous fashion Consequently, the method of stepwise limits tested minimally practicable step changes in I and TD here, to save time and the subject's energy. However, liminal I or the just supraliminal I to be used in the actual experimental trials were redetermined at the beginning and, if any uncertainty arose, at the end of each study session; this was necessary partly because stability of the actually delivered intensity depends on a constancy in the position of the transmitter coil on the patient's chest.

Utilization TDs were found to average approximately 0.4−0.5 s, close to the values previously reported (e.g , Libet, 1973). On this basis, the experimental design was arranged to have two types of series, each series containing blocks or cycles of 20 trials each, allowing the cycles to be repeated to the degree tolerated well by the subject. (1) *'Awareness' series* in which pulse (p) numbers would be randomly varied from 19 to 55 p in different trials, in intervals of 2 pulses (i.e , 19, 21, 23, etc.) This would provide 19 different TDs with 1 trial of the 20 total being a blank (0 p). Such a range of TDs was expected to elicit many responses with awareness (i.e., from button 1) and at least some with no awareness at all (button 3), if the intensity was suitably set at near liminal I (i.e., minimum required TD of about 30 p, but always > 19 p). (2) *'Detection without awareness' series*, in which pulse numbers were randomly varied 1−19 p with intervals of 1 pulse, plus 1 blank (0 p) to make 20 total trials. Such a range was expected to elicit no definite awarenesses (button 1) and, as indicated above, subjects were asked instead to make a confidence rating on their forced-choice response. (The actual results did not bear out this expected sharp division between awareness and non-awareness series, as seen below.)

Study sessions. The goal was to study each subject in 4 half-day sessions (about 2 h each) on 2 successive days. This schedule was adhered to in most but not all cases; interruptions occurred in some schedules when the patient felt indisposed to continue (because of pain or other discomforts) with a second session either on the same day or on the next day. The patient in such cases returned at a later date to complete the 4 sessions.

Each series of 'awareness' or 'detection' trials consisted of blocks of 20 trials which were repeated, after brief resting intervals of a minute or so, for up to 5 times, giving a desired total of 100 trials. Within each block or cycle of 20 trials, the pulse numbers were varied by the computer in a 'without repeating' random sampling This was done to achieve comparability of trial numbers at all of the tested pulse numbers. However, the randomization sequence was changed by the computer program for each successive cycle of 20, preventing any possible development of expectation of pulse number. Also varied at random was the appearance of the stimulus during L_1 or L_2 for each trial. Each individual trial began with a 0.5 s

warning auditory bleep, followed after 1.0 s by the sequence of L_1 flashing on for 1 s, an interval of 1 s, and L_2 on for 1 s. The stimulus began 0.25 s after onset of the 1 s light. When the subject had pressed L_1 or L_2 as his forced choice for the presence of stimulus, and then also had pressed button 1, 2 or 3 for his subjective response, the computer allowed an additional 15 s before starting the next trial with a warning bleep. When he reported, before pressing any buttons, that he had 'missed' any signal by inadequate attentiveness, etc., the program permitted the operator to repeat the same stimulus test, so that the randomized series of 20 was retained.

A brief series of training trials was administered on a preceding day or at the start of the first session. Each study session of about 2 h was started with determination of near liminal I and rough utilization TD values (*see above*) to establish a fixed intensity for the session. In sessions 1 and 2, 'awareness' and 'detection' series were alternated, with appropriate breaks between series, but the selection of which series came first was randomized among subjects. In sessions 3 and 4, usually on the next day, 'detection with feedback' alternated with 'awareness' series. In those sessions in which the subject (e g., H.C.) gave relatively few button 1 responses in the 'awareness' series, i.e., reported feeling few stimuli, liminal I was redetermined at the end of that session; this was done to establish that liminal I had *not* risen during the session to a level at which little or no excitation of sensory axons was occurring with the I used in the trials. In such cases, it was consistently found that TDs in the range of 0.5−1.0 s were still effective at the end of the session.

Verbal descriptions of introspective experiences. These were elicited from the subject in several ways. (1) The quality and referred anatomical location of stimulus-produced sensation was described in the initial testing for liminal I/utilization TD values, and at times thereafter. Most often a localized tingling or twinge-like sensation was reported, although other qualities appeared in some cases especially with brief TDs (< 0.5 s). For example, with short TDs J.S. reported 'feathery' or 'breeze wind-like' sensations; similarly, M.P. reported a 'light feathery brush' with both her low confidence and uncertain (both button 2) ratings in some detection and awareness series, respectively. (Both J.S. and M.P. reported tinglings with button 1 replies.) K.K.'s chief report was one of a 'warmth', 'warm air or warm water moving over surface', but she also reported a slight tingle with brief TDs or at the end of a sensation of warmth elicited by a longer TD (> 0.5 s). (2) Verbal descriptions of their sensory experiences during the trials were requested from the subjects at the end of some cycles in both 'awareness' and 'detection' series This included queries as to what they felt in connection with giving button 1, 2 or 3 response ratings of awareness or confidence, respectively. They were also asked, at these times, why they chose L_1 or L_2 in those trials when they reported feeling nothing or 'no confidence'. (3) Additionally, one or two cycles of 20 trials were devoted to obtaining verbal descriptions after each individual trial, so that the subject's memory at the end of a whole cycle would not be an issue. This was usually done in the fourth study session during a 'detection' series.

Statistical treatment

The results are presented in three different formats: (1) a tabulation of the raw data, that is, percentage correct choices (of L_1 vs L_2) for different pulse numbers (TDs) of stimulus, but given separately for each of the reported awareness/confidence ratings (buttons 1, 2 or 3); (2) a nonparametric analysis involving a few simple assumptions about the mechanism generating the data, (3) a parametric analysis which assumes a logistic regression model. The basis for formats (2) and (3) is given here; a fuller description of the statistical model for (2) is given in the Appendix.

Nonparametric analysis. This assumes (1) that different trials within any series are independent (i.e., that the probability of the subject's responses, as to choice of L_1 vs L_2 and awareness level report in a given trial is independent to that in other trials); (2) that when *no* pulses are administered there is a 50/50 probability of the subject being right or wrong, regardless of their awareness/confidence; (3) that the administered pulses can only increase the probability of a correct response, (4) that the two parameters being estimated, θ and α, are constants over the course of a single study session.

Assumptions (1) and (2) were basically validated by the experimental design, including the randomization of pulse numbers and of the settings as to whether L_1 or L_2 was right or wrong. (The feedback series are a slight exception to assumption (1), since a positive dependence was introduced by design; actual results, however, showed only a slight difference from nonfeedback series.) Assumption (2) is in fact validated by the results, in which very close to 50/50 correct was found for the aggregate of blank (0 p) trials. Assumption (3) is a reasonable postulate, and is borne out in the results. Assumption (4) is difficult to assess, but conditions within a session were fairly homogeneous and all sessions were terminated if the subject seemed to show any fatigue, even when he did not spontaneously report this.

Theta (θ) is defined as equal to the *mean number* of pulses required to make an *otherwise incorrect* response to be correct. Note again that even with 0 pulses, the subject was expected to make 50% correct choices; θ focuses, then, on making any of the otherwise (50%) incorrect responses into a correct choice. The qualitative meaning of this approach may be seen in a first approximation type of look at raw data values. There were a total of 1290 trials in which stimuli consisted of 1–10 pulses. In these, 758 produced correct choices (as to whether stimulus was delivered in L_1 or L_2), with 645 correct expected on sheer chance alone. Thus 758–645 = 113 (i.e., 17.5%) of 645 otherwise expectedly incorrect responses were instead correct, when administering stimuli with a range of 1–10 p. From moment to moment a different number of pulses, Y, may be required to ensure a correct response. For 113 of the 645 trials Y was 10 or less. Usually, more pulses were needed, and Y would be larger. θ is defined as the expected value of the number of pulses required to make any such otherwise incorrect response a correct one. Details of the procedure to estimate θ are deferred to the Appendix.

Alpha (α) is defined as equal to the average number of pulses required to move a subject, from the threshold of being correct *but just guessing*, to being correct but also with at least minimal or uncertain *awareness* of a stimulus induced sensation. That is, α = the mean additional pulses required, over and above those for detection, for the subject to achieve some possible awareness/confidence experience noted by him as rating 2 instead of 3 (which is no awareness at all). As noted above, a key assumption in estimating α by the statistical technique employed (*see* Appendix) is that α is a constant and thus independent of Y. However, this assumption did not play a role in our conclusions since recomputation of the estimated values of α under a worst case scenario (of an invalid assumption of constancy) produced only minimally different values.

Awareness or confidence rating 2 was used in defining α, rather than level 1. Rating 2 indicated only an uncertain and often debatable actual awareness (*see below*), not a definite feeling or sensation as in rating 1. Consequently, any convincing evidence that α was greater than zero would strongly support the hypothesis that it takes significantly more pulses (greater TD) to achieve *any* awareness of the stimulus than it does for detection.

Parametric analysis. In addition to assumptions (1)–(3) in the nonparametric analysis (*above*), the parametric one also assumed that the log of the odds of being correct depends in a linear fashion on both the number of pulses (in a stimulus) and also on the awareness/confidence level or rating by the subject. Here

$$\ln[\text{probability of correct response/probability of incorrect response}]$$

$$= A(\text{no. of pulses}) + B_i$$

where A is the increase in $\log_e$ odds per pulse, B is a value which depends on the awareness/confidence rating i in the trial (i.e., i = 1, 2 or 3).

As the study sessions were differently arranged to carry out the 'awareness' and 'detection' series (*see above*), logistical models that included a term which depended on this difference were also investigated. However, the magnitude of the estimated effect of this difference was almost always very small, and for 27 of the 33 cases its inclusion in the model gave no improvement in terms of goodness-of-fit.

The parametric analysis is the type more commonly encountered in problems such as the present one. However, the nonparametric analysis involves fewer assumptions and should be regarded as the most convincing approach. Fortunately, conclusions derived from all these statistical formats were in basic agreement, relative to the hypothesis being tested.

RESULTS

Actual detection and awareness responses

In each trial, the subject chose L_1 or L_2 (as the lighted period in which a stimulus was delivered), and his choice plus the correct answer were recorded by the computer. The subject's indication of his level of awareness of a sensation elicited by the stimulus in that same trial was also recorded.

Table 1 presents a compilation of all the correct responses and total trials, sorted

for ranges of stimulus pulse numbers. (Recall that 72 pulses = 1 s stimulus train duration.) These results are also segregated into 1 of the 3 levels of awareness reported by the subjects in those same trials. As described in Methods, level 3 meant no awareness of any sensation at all, level 2 meant uncertain (or low confidence) about any sensation although possibly something there, level 1 meant something was felt (in the appropriate body area) even if very weak or brief (with 'high confidence', when a confidence rating

TABLE 1 PROPORTIONS OF CORRECT CHOICES VS PULSE NO (TD) AND AWARENESS LEVEL*

Subject	*Awareness level*	*0 pulses*	*1–10 p*	*11–19 p*	*19–37 p*	*39–55 p*	*Total 1–55 p*
J.S							
	3	15/29 (0.52)	102/173 (0.59)	63/92 (0.68)	21/34 (0.62)	17/20 (0.85)	203/319 (0.64)
	2	1/2	20/23 (0 87)	59/61 (0 97)	43/48 (0.90)	34/34 (1.0)	156/166 (0.94)
	1	0/1	4/4	27/27 (1.0)	38/38 (1.0)	54/54 (1 0)	123/123 (1 0)
S D.							
	3	11/18 (0.61)	69/122 (0 57)	69/98 (0.70)	11/25 (0.44)	1/2	150/247 (0 61)
	2	1/1	5/8	19/19 (1.0)	19/19 (1.0)	26/26 (1.0)	69/72 (0.96)
	1	0/0	0/0	0/0	16/16 (1.0)	26/26 (1 0)	42/42 (1 0)
H C							
	3	13/24 (0.54)	81/148 (0.55)	102/126 (0.84)	69/82 (0.84)	61/66 (0.92)	313/422 (0.74)
	2	0/0	2/2	6/7	3/3	5/5	16/17 (0 94)
	1	0/0	0/0	2/2	5/5	10/10 (1.0)	17/17 (1 0)
K.D							
	3	8/17 (0 47)	43/89 (0.48)	39/65 (0.55)	17/23 (0.74)	3/7	99/184 (0 54)
	2	2/5	46/76 (0.61)	63/78 (0 81)	10/15 (0.67)	14/14 (1.0)	133/183 (0 73)
	1	0/0	3/5	10/10 (1 0)	11/12 (0.92)	23/24 (0.96)	47/51 (0 92)
M.P.							
	3	9/14 (0.64)	49/77 (0.64)	19/33 (0.58)	10/15 (0 67)	2/3	80/128 (0 63)
	2	1/4	23/35 (0.66)	49/57 (0.86)	15/19 (0.79)	12/13 (0.92)	99/124 (0.80)
	1	0/0	5/8	17/18 (0.94)	26/26 (1.0)	38/38 (1.0)	86/90 (0 96)
L.R.							
	3	13/22 (0.59)	90/145 (0 62)	90/113 (0.80)	33/50 (0.66)	32/38 (0.84)	245/346 (0.71)
	2	2/3	4/5	18/18 (1 0)	16/18 (0 89)	14/14 (1 0)	52/55 (0 95)
	1	1/1	0/0	4/4	41/42 (0.98)	47/47 (1 0)	92/93 (0.99)
K K.							
	3	8/18 (0 44)	48/96 (0 50)	50/71 (0.70)	9/16 (0.56)	6/8	113/191 (0.59)
	2	1/2	26/39 (0.67)	24/33 (0.73)	22/25 (0 88)	19/20 (0.95)	91/117 (0.78)
	1	0/1	9/15 (0.60)	28/31 (0 90)	17/19 (0 89)	25/26 (0 96)	79/91 (0 87)
J P.							
	3	4/7	48/70 (0 69)	55/61 (0 90)	2/4	0/0	105/135 (0.78)
	2	1/5	15/20 (0 75)	20/20 (1.0)	23/26 (0 88)	20/20 (1 0)	78/86 (0 91)
	1	0/0	0/0	0/0	0/0	7/7	7/7
B.D.							
	3	9/20 (0 45)	66/130 (0 51)	96/114 (0 84)	8/21 (0.38)	0/0	170/265 (0.64)
	2	0/1	0/0	3/3	30/31 (0.97)	21/21 (1 0)	54/55 (0.98)
	1	0/0	0/0	0/0	28/28 (1.0)	51/51 (1.0)	79/79 (1 0)

* Ratios: correct choices/no of trials.

was requested). Table 2 summarizes the totals for these values for all subjects. The following points may be derived from these tables.

1. When the 0 pulse trials are taken together, we have 100 correct answers in 195 trials, or 51% correct. This is close to the 50% correct expected on pure chance from our randomized delivery of a stimulus (or none) during L_1 vs L_2.

2. Although no awareness would be expected and therefore a level 3 response for all 0 p trials, a surprising 12% of the blank trials reported awareness level 2, though only 1.5% for awareness level 1 (*see* also fig. 5). The significance of these reports in relation to the interpretation of awareness level 2 will be discussed below.

3. The percentage of correct responses when subjects reported level 3, that is *no awareness* of any somatic sensation (during L_1 or L_2) or *no confidence* at all about their choice of L_1 or L_2, is of special interest. For all stimuli in the 1 to 10 pulse range, there were 57% correct responses out of 1050 such trials (Table 2), that is, with stimuli of up to 10 p, the estimated probability of eliciting a correct response from among the 50% of expected incorrect responses equals 14%, SE ± 3%. This value is seen to increase with increasing pulse numbers. For the total of all trials (2237) in which subjects reported no awareness at all (level 3) we observed 66% correct answers. In this group, there was an estimated probability of 32 ± 2% for eliciting a correct response with stimuli up to 55 p in duration, from among the otherwise expected 50% of incorrect responses in a randomized situation, even though subjects reported feeling nothing. On the other hand, with reports of some kind of awareness, even when uncertain or unclear as to its nature (i.e., level 2), there was a 71% estimated probability of eliciting a correct response (from among the otherwise expected incorrect ones) with SE ± 1%. For some definite awareness of a sensation (level 1) the otherwise incorrect responses overall are almost all made correct (i.e., 93% ± 1%). (If the 0−10 p range is omitted from this total, the values become 96.4% ± 1.1%.)

TABLE 2 TOTALS OF RESPONSES FOR ALL SUBJECTS IN TABLE 1

	No. of pulses											
	0 p		*1−10 p*		*11−19 p*		*19−37 p*		*39−55 p*		*1−55 p*	
Awareness level	*No. of trials*	*% cor*	*No*	*% cor*	*No*	*% cor*	*No.*	*% cor*	*No*	*% cor.*	*No.*	*% cor.*
Level 3	169	53	1050	57	773	75	270	67	144	85	2237	66
Level 2	23	39	208	68	296	88	204	89	167	99	875	85
Level 1	3		32	66	92	96	186	98	283	99	593	97
Totals	195	51	1290	59	1161	80	660	84	594	96		

Feedback of correct answers to subject

The correctness of the subject's choice of L_1 vs L_2 was indicated to him after he made his response, in some sessions in which stimulus pulse numbers were in the range of 1−19 p. In this range there were mostly reports of level 3 of awareness, i.e., no awareness of a sensation to serve as a clue to correctness. There is a slightly higher percentage of correct responses in the second 10 trials of each cycle of 20 (Table 3). This is true rather consistently for most subjects individually, as well for the totals for all subjects. This suggests that they may have been learning to improve slightly their ability to detect the stimuli in this range.

TABLE 3 FEEDBACK SESSIONS ONLY*

Subject	*Period*	*1–10 p*	*11–19 p*	*Total*
S.D	First 10 trials	14/23 (0.61)	16/26 (0.62)	30/49 (0 61)
	Second 10 trials	14/27 (0.52)	15/19 (0.79)	29/46 (0.63)
H.C.	First 10 trials	26/54 (0 48)	34/42 (0 81)	60/96 (0.625)
	Second 10 trials	27/46 (0.59)	40/48 (0.83)	67/94 (0.71)
K.D.	First 10 trials	50/93 (0 54)	51/72 (0.71)	101/165 (0.61)
	Second 10 trials	42/77 (0 55)	58/81 (0.72)	100/158 (0.63)
M P.	First 10 trials	19/24 (0 79)	23/24 (0.96)	42/48 (0.875)
	Second 10 trials	20/26 (0.77)	20/21 (0.95)	40/47 (0.85)
J.P	First 10 trials	8/13 (0.62)	13/14 (0.93)	21/27 (0.78)
	Second 10 trials	13/17 (0 76)	13/13 (1 0)	26/30 (0.87)
B.D.	First 10 trials	13/24 (0.54)	23/24 (0.96)	36/48 (0.75)
	Second 10 trials	13/26 (0 50)	21/21 (1 0)	34/47 (0.72)
Total	First 10 trials	130/231 (0 56)	160/202 (0.79)	290/433 (0 67)
	Second 10 trials	129/219 (0.59)	167/203 (0.82)	296/422 (0.70)

* Ratios: correct responses/no of trials.

The quantitative effect of the feedback procedure, however, was too small to affect the overall values for detection requirements. The percentage of correct responses with feedback, even for the second 10 trials of each 20, was not appreciably different from the comparable values (in the same pulse number range) for all trials, most of which were without feedback (*see* Table 2). Secondly, when estimated separately for these feedback sessions, the nonparametric value of θ (the mean TD required for detection, *see below*) shows a reduction of only about 1.2 p (± 0.6) from the overall mean value of about 19.7 p for all sessions. (We should note, however, that the 1 blank test (0 p) in each cycle of 20 trials was treated in the feedback report as if there were a correct answer. We realized belatedly that we should have informed the subject properly after each blank test that this trial had no correct answer, but we did not want to change the procedure in midstudy. Such misinformation on the blank trial could have been a confusing element that reduced the ability of subjects to improve during feedback cycles of trials.)

Parametric logistical regression analysis of data

The $\log_e$ of the odds of being correct, i.e., the $\log_e$ of the (probability of correct responses/probability of being incorrect), did in fact increase with the number of pulses in a stimulus. The estimated *increase per pulse*, for this $\log_e$ value, is given in Table 4 for each study session with each subject. To summarize this analysis, a histogram of these values for all trials in all subjects is given in fig. 1. It shows a skewed distribution although most values are near the median of about 0.05. For some of the sessions the increase per pulse in the log odds was not consistent enough to be statistically significant.

With respect to awareness/confidence levels reported by the subjects, the following points appear. (1) With level 3 (i.e., felt nothing) the odds of being correct are substantial

TABLE 4 LOGISTIC REGRESSION (PARAMETRIC) ANALYSIS

			ln (probability correct/probability incorrect)			
Subject	*Date*	*a.m./p m*	*Increase per pulse*	*Increase. With rise from awareness level 3 to 2*		*Increase With rise from awareness level 2 to 1*
J S	03/11/87	p.m.	0.131	0.882	τ	1.718
	05/11/87	p m	0.035	1 463		−0.146
	26/04/88	a m.	0.042	2 056		1.656
	26/04/88	p.m.	0.048	1.236	τ	2 034
S D.	01/12/87	p m	0.027*	1.854		1.735
	03/12/87	a.m.	0 032*	1.972		1.683
	03/12/87	p m	−0.001*	9.623		−3 202
H.C	07/12/87	p.m.	0.056	1.260	τ	1 836
	08/12/87	a m.	0.079	5 326	τ	−2.425
	08/12/87	p.m.	0.054	5.363	τ	−1.752
K D.	20/01/88	a m	0.034	1 013		−0.305
	20/01/88	p.m.	0 048	0.602		0.452
M P	15/02/88	p.m	0.048	0.906		−0 261
	16/02/88	a.m.	0 183	−0.439	τ	0.260
	16/02/88	p.m	0.037	−0.366	τ	3.155
L.R.	05/04/88	p.m.	0.004*	1.236		0.158
	06/04/88	a.m	0.048	4.365	τ	(no level 1 response)
	06/04/88	p.m.	0 043	0 751		2.139
K.K.	07/06/88	a.m	0.040	−0.031	τ	0 233
	07/06/88	p.m.	0.043	0 198	τ	0.258
	08/06/88	a.m.	0.018*	1.222	τ	−0 371
	28/06/88	p m	0.053*	2 438		1.500
	08/07/88	a.m.	0 252	6.613	τ	−3.085
J.P.	14/07/88	p.m	0.091	−1 198	τ	2.749
	15/07/88	a.m.	0.106*	−0 132	τ	(no level 1 response)
	15/07/88	p m	0.175	0.656	τ	1 0117
B D.	21/07/88	p m	0 046*	9.051		−3.085
	21/07/88	p m.	0.082	7.723	τ	−2.759
	22/07/88	a.m.	0.123	7 048		−2.652
	22/07/88	p m.	0 106	−0.239	τ	2 304

* Indicates that including the number of pulses in the model did not significantly improve the fit of the model to the data τ Indicates that including the awareness level in the model did not significantly improve the fit of the model to the data

and consistent. For example, the model indicates that typically about 14 pulses would be required to give 2:1 odds for a correct answer, with reports of awareness level 3. This indicates the existence of detection without any awareness of the stimulus. (2) However, there are large increases in the odds of being correct when the reported awareness level is 2 instead of 3. Actual estimated increases are given in Table 4; these values control for the pulse number, thus excluding the factor of higher pulse numbers (which produce a greater incidence of level 2 reports). Note, however, that the odds

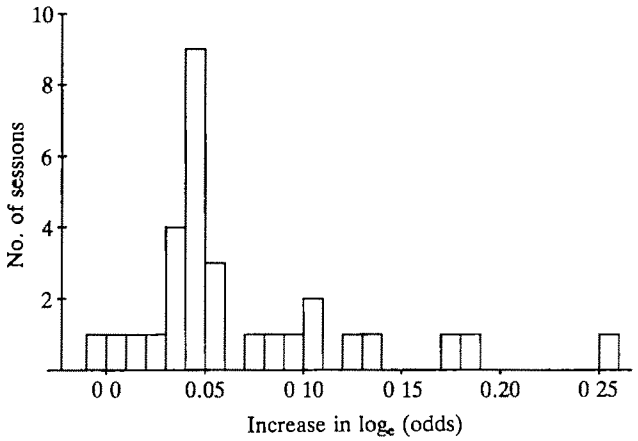

FIG 1. Histogram summarizing all values for the estimated increase per pulse in the natural logarithm (i.e., $\log_e$) of the odds of being correct, i.e., ln (probability of correct responses/probability of being incorrect), as derived from logistical regression. Each value is an estimate for each session of trials (*see* Table 4) Although the range is large, most values cluster about the mean of 0 069 (median = 0.048), with an average-within-subjects SD of 0.041.

of being correct went down in some cases, as in all 3 sessions with subject J.P. and in 2 of 3 sessions with subject M.P. Similar calculations comparing trials with reports of awareness level 1 vs those with level 2, but at the same pulse numbers, show a less consistent change in odds of being correct, even for the same subject in different sessions. At least 1 subject, B.D., generally performed much better with reports of awareness level 2 than at 1. A histogram in fig. 2 summarizes the changes when going from awareness level 3 to level 1, for all subjects. Note that 29 of these 30 whole session values are positive, indicating a consistently greater chance of being correct with

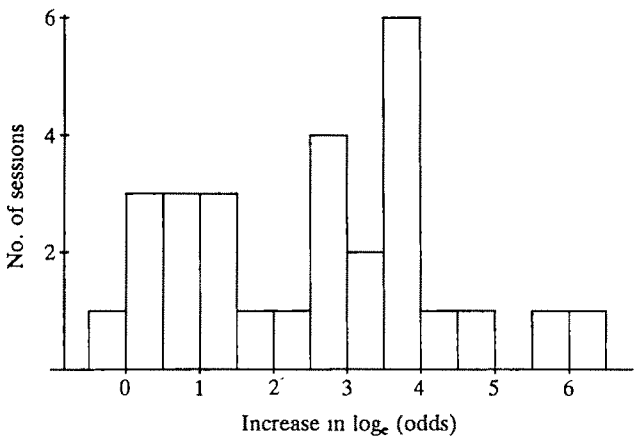

FIG. 2. Histogram summarizing effects of going from awareness level 3 (pure guess) to level 1 (felt it) on the ln of the odds of being correct (*cf* Table 4). The changes are estimated while holding the number of pulses fixed for both awareness levels.

awareness level 1 than with level 3. These quantitative, parametric estimations are all in accord with the differences seen in the raw data (Tables 1, 2), when the percentage of correct responses is compared for the 3 levels of awareness for each range of stimulus pulse numbers.

Variation among subjects was relatively small for the increase in the odds of being correct with each additional pulse. But there was significant person to person variation in how much the odds increase as subjects went from awareness level 3 to level 1.

Nonparametric analysis of data

As described in Methods and the Appendix, the parameter θ = the mean number of pulses required to make an otherwise incorrect response to be correct; while parameter α = the mean number of *additional* pulses which are required to move from mere detection to elicit even the uncertain questionable awareness level 2 (instead of to some definite awareness, level 1).

The estimated values for θ are given for each subject, in each separate session, in Table 5. A histogram summarizing the distribution of θ for all sessions in all subjects is given in fig. 3. The mean value for all θ estimates was 19.71 pulses. Individual subjects showed some variation in θ for different sessions, with an average-within-subjects SD 7.03 (Table 5).

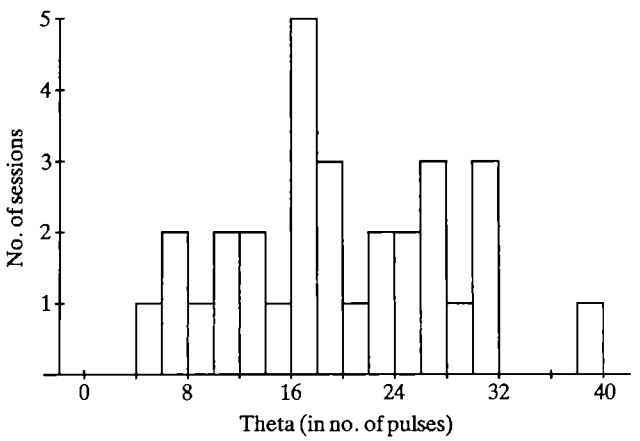

FIG 3. Histogram summarizing results for $\hat{\theta}$, from nonparametric analysis (*cf* Table 5). θ = mean number of pulses required to make an otherwise incorrect response to be correct (*see* Methods and Appendix). The mean value of all the θs here is 19.71 (median 18.42), with an average-within-subjects SD of 7.03.

Estimated values for α are given in Table 6, with a histogram of all values in fig. 4A. This gives a mean value for α of 27.80, average-within-subjects SD = 8.50. Of additional interest is the z value for each α; z value is how many SEs above zero it takes to equal the estimated value of α. The mean z = 11.98, average-within-subjects SD 2.83 (histogram of z values in fig. 4B).

The following points emerge from these tables of $\hat{\theta}$, $\hat{\alpha}$ and z. (1) Values of $\hat{\alpha}$ are much greater than zero. This means it takes substantially more stimulus pulses to elicit

TABLE 5 NONPARAMETRIC ESTIMATES OF θ FOR INDIVIDUAL SESSIONS*

Subject	*Date*	*a.m./p m.*	$\hat{\theta}$	*Estimated SE* ($\hat{\theta}$)	*Upper limit for SE* ($\hat{\theta}$)
J.S.	03/11/87	p.m.	5.328	1.138	2.444
	05/11/87	p.m.	18.100	2 356	3.560
	26/04/88	a.m	17.700	2.615	4 611
	26/04/88	p.m.	26 557	3.326	5.474
S.D	01/12/87	p.m.	22.128	3.291	5 654
	03/12/87	a.m.	25 385	2 248	4 468
	03/12/87	p.m.	17.700	3.030	4.531
H.C	07/12/87	p m.	18.742	2.953	4 464
	08/12/87	a.m.	17.967	2.889	4 891
	08/12/87	p.m.	24.608	3.349	5 157
K.D.	20/01/88	a.m.	29.142	3 522	5 157
	20/01/88	p m	27.238	3.064	5 803
M P.	15/02/88	p m.	23 728	3.617	5 654
	16/02/88	a m.	7 700	1.734	3 459
	16/02/88	p.m.	30 500	3.758	5.267
L R	05/04/88	p.m.	14.366	2.439	4.679
	06/04/88	a.m.	30.800	3.580	5.026
	06/04/88	p.m.	13.566	2.476	4.111
K.K.	07/06/88	a.m.	38.300	3 867	6.044
	07/06/88	p.m.	31.166	2 196	7 914
	08/06/88	a.m.	21.333	1.976	7 914
	28/06/88	p m.	6.500	1.457	2.151
	08/07/88	a.m.	10.000	1.172	3.002
J.P.	14/07/88	p.m.	19.250	1 940	5.535
	15/07/88	a.m	9.917	1 511	6.217
	15/07/88	p.m.	11.166	1 468	4.318
B.D.	21/07/88	p.m	26.366	2 841	4.066
	21/07/88	p.m	13.500	1 947	3.725
	22/07/88	a m	16 208	2.322	3.454
	22/07/88	p m.	16 433	2.244	3.540

* Combining the series for 1−19 p with those for 19−55 p, when done within 20 min of each other θ = mean number of pulses to make correct an otherwise incorrect response.

even a minimal and questionable level of awareness (level 2) than it does to produce correct detection of the stimulus without any awareness of a difference (level 3). (2) The generally large z values confirm the significance of the conclusion in point (1). If our hypothesis were false, $\hat{\alpha}$ (the extra pulse requirement for any awareness) would be zero. If $\hat{\alpha}$ were actually zero we would rarely see z values greater than 3. However, most z values here are much greater even than 3.

Additionally, subject-to-subject variation in values of $\hat{\theta}$ was on the whole relatively small. The P value is 0.81 in a significance test of the null hypothesis that all subjects are equal. However, inter-subject variation in values of $\hat{\alpha}$ was significant, with a P value of 0.02 (*see* Discussion section for some analysis of this inter-subject variation).

TABLE 6 NONPARAMETRIC ESTIMATES OF α FOR INDIVIDUAL SESSIONS*

Subject	*Date*	*a.m./p.m.*	$\hat{\alpha}$	*Upper limit for SE* ($\hat{\alpha}$)	*z value*
J.S.	03/11/87	p.m.	5 871	1.211	4.85
	05/11/87	p.m.	32.224	1.754	18.37
	26/04/88	a m.	30.676	2.271	13.51
	26/04/88	p m	42.095	2.696	15.61
S D.	01/12/87	p m.	45.13	2 7828	16.22
	03/12/87	a.m	32.6732	2 179	14.99
	03/12/87	p.m.	31.585	2.2146	14 262
H C.	07/12/87	p.m	40 649	2.196	18 51
	08/12/87	a.m.	47.267	2.412	19.60
	08/12/87	p m	51.267	2 547	20.13
K.D	20/01/88	a m.	21.725	2.549	8.52
	20/01/88	p.m.	23.976	2 863	8 37
M P.	15/02/88	p.m.	26 095	2.788	9 36
	16/02/88	a.m.	1 292	1.723	0.75
	16/02/88	p.m.	15.267	2.619	5.83
L.R.	05/04/88	p m	44.999	2 313	19.45
	06/04/88	a m.	49 267	2 481	19.86
	06/04/88	p m	26.199	2.028	12.92
K K.	07/06/88	a.m	25.033	2.980	8.40
	07/06/88	p m	14.125	3 952	3 57
	08/06/88	a m	43.408	3.897	11.14
	28/06/88	p m.	6.000	1 491	4 02
	08/07/88	a.m.	16.001	1 491	10.73
J P.	14/07/88	p.m.	19 000	2.756	6 89
	15/07/88	a.m.	18 816	3.090	6.09
	15/07/88	p.m.	24 000	2.055	11 68
B.D.	21/07/88	p.m	28.000	1 978	14 16
	21/07/88	p.m.	19.267	1 832	10.52
	22/07/88	a.m.	29.267	1 679	17.43
	22/07/88	p.m.	22.897	1.698	13.48

* Combining the series for 1−19 p with those for 19−55 p when done within 20 min of each other α = average number of pulses to move from correct but guessing to correct with at least minimal uncertain awareness (level 2).

The possibility of variation between results for morning vs afternoon sessions for each subject was also checked, as there could be a fatigue factor or other difference involved. No consistence or significant difference was found for a.m. vs p.m. results.

Awareness levels relative to pulse numbers

With stimulus pulses at near liminal intensity (I), minimum train durations required to elicit a sensory experience were determined for the present subjects at the start of a study session (employing the same method of limits as for determining liminal I, but varying the TD in this case). The resulting 'utilization-TD' (U-TD) values were in the same range as reported previously, average U-TD about 0.5 s (Libet, 1973). (Some

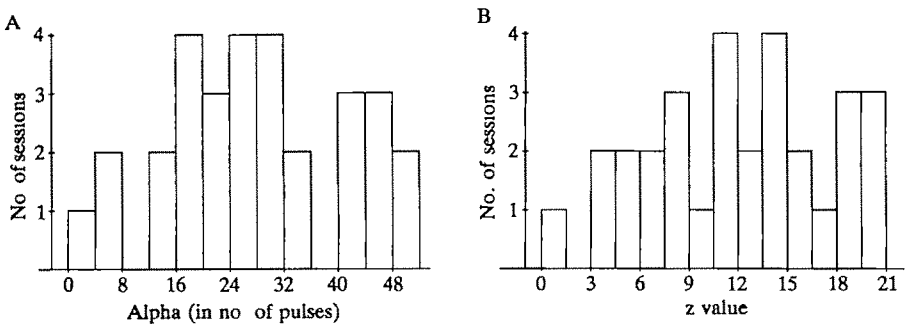

FIG. 4. Histogram summarizing results for $\hat{\alpha}$ and z from the nonparametric analysis (*cf* Table 6) A, α = the average number of (additional) pulses required to move a subject from being correct but just guessing to being at least minimally (even if uncertainly) aware of a stimulus-induced sensation (as well as being correct) (*see* Methods and Appendix) The mean value of all the alphas here is 27.80 (median 26.15), with an average-within-subject SD of 8.50 B, z = number of standard errors, above zero, that it takes to equal the estimated value of α The mean value of all the z values here is 11.98 (median 12.30) with an average-within-subject SD of 2 83

greater variability of values measured at different times in a given subject here is attributed to the greater difficulty in setting the liminal I value accurately and consistently, under the conditions in this study.) Present subjects were on the average 10−20 yrs younger than subjects in the previous studies, who were mostly patients with motor dyskinesias (although some had intractable pain); yet both groups exhibited a similar average U-TD. For use in the experimental forced-choice series of trials the intensity (I) was often raised somewhat above the apparent liminal I in order to minimize the chance of falling below the threshold for exciting any axons by some possible variations in the effective I actually transmitted to the subdermal receiver coil. However, the maximal accepted level of I was that at which the minimum TD, required for any sensory awareness, was not less than 0.3 s (22 p).

Reports of awareness during the experimental series did not precisely match the relationship to pulse number (TD) established in the initial tests. In the initial test not even an uncertain awareness was reported with TDs less than 0.3−0.5 s (i.e., 22−36 p, according to the I set in each case), but there were such reports with stimuli of < 22 p in the experimental series. Fig. 5 shows a plot of incidence of all awareness report levels 1, 2 and 3 relative to stimulus pulse number. There were significant differences between subjects with respect to the overall summed data plotted here. It may be seen that reports of level 1 (definite if slight sensory awareness) were mostly insubstantial until TDs achieved > 20 p (> 0.28 s TD) and then the incidence continued to rise to about 50% of responses at about 34 p or more (TD > 0.47 s). These TD requirements for awareness level 1 are not far off from those determined initially by the stepwise method of limits, but with two differences. (1) A small but significant number of level 1 reports appeared even with pulse numbers < 20 p, whereas this almost never occurred in the initial stepwise determinations of minimum TD. (2) The average proportion of level 1 responses rose only to a maximum of < 50 to 60% even with pulse numbers of 55 p (0.77 s TD). In the minimum TD determinations, level 1 or level 3 was reported in at least 2 consecutive trials in order for the TD value to be regarded as positive, or negative, respectively.

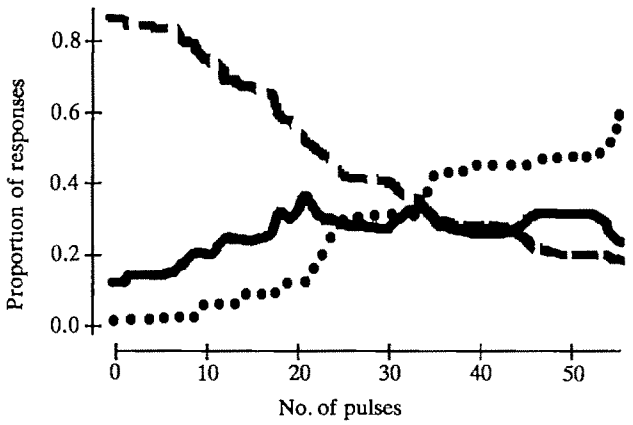

FIG. 5. Incidence of reports of each awareness level relative to number of stimulus pulses (train duration) Proportions of all trials (at each pulse number) which have reports of a given awareness level are plotted against the pulse number At the standard 72 pps stimulus employed throughout, the 0–55 p range the abscissa represents the 0–760 ms range of train durations (TDs) Dotted line = reports of awareness level 1 (felt sensation, even if very weak); solid line = level 2 (uncertain about any sensation), broken line = level 3 (felt nothing) (*see text*). (These are isotonized line plots, values are computed under the assumption that the expected proportion of level 3 responses decreases with pulse number and the expected proportions of level 1 responses increase with pulse number. This made the curves easier to distinguish visually but it did not appreciably alter the form of the plots of the direct data points here)

Reports of level 3 (no awareness at all of a sensation or any difference between L_1 and L_2 intervals) start high but are not 100% of responses even for 0 p and for 1–10 p. On the other hand, a surprising average of > 20% of reports were still level 3 at the maximal TD of 55 p.

Reports of level 2 (uncertain sensory awareness, or maybe something different between L_1 and L_2 intervals) exhibited surprisingly substantial incidences in the range of low pulse numbers (< 20 p). Indeed, even with 0 p trials (when there was no objective difference between the L_1 and L_2 interval), 12% of the trials (23/197) reported level 2! This levelled off at about 30% in the whole range of about 20–50 p. The interpretation of the incidence and meaning of level 2 reports will be dealt with in the Discussion.

Verbal description of awareness levels

All descriptions made by each subject for each awareness level were reviewed and summarized. Descriptions given after each individual trial, during 1 or 2 cycles of 20 trials so tested, were uniformly similar to those given by each subject in other situations, that is, at the end of some other cycles of 20 trials and during preliminary testings for liminal I and U-TD. Descriptions for levels 1, 2 or 3 which were given when awareness level was requested (i.e., felt slightly, uncertain, or not felt, respectively) were similar to those given by each subject when a confidence rating (for choosing L_1 vs L_2) was requested (i.e., confident, low confidence, no confidence or guessing, respectively). The introspective descriptions associated with each level were the same with both kinds of instructed requests.

Awareness level 1 was virtually always associated with the description by subjects that they felt a slight and brief though definite sensation, of the same quality and in

the same body location as the sensation produced by a somewhat stronger and longer-lasting (1−2 s) stimulus in the preliminary testings.

For response level 3, subjects consistently said they felt no sensation during either of the light intervals, L_1 or L_2.

The in-between response, level 2, was associated with more complicated and not uniformly consistent descriptions even by the same subject. However, the introspective descriptions of response 2 could be grouped into one of several types. (a) 'Maybe there was a slight sensation'—similar to the one felt more definitely in a level 1 response and located in the same or a nearby site. This is the 'uncertain' type of awareness that we expected for a level 2 report. Actually, the next description (b) turned out to be the most common type. In (b) the subject reported 'something different, more than nothing', not definable as a real sensation but nevertheless localizable to the general vicinity of (though often less distinctly than) the definite sensation reported for level 1. One subject (K.K.) added that it had an expectancy nature, as if something is about to touch you but does not touch. In type (c) subjects reported something different about one light interval, but this was not localized to the usual body site or (in most cases) to any site, and it was not regarded as a sensation. One subject (K.D.) added that to report this diffuse nebulous feeling was something like finding a black cat in a dark room. Another (B.D.) reported that it was just an intuitive impression of something different, and another (J.S.) reported that one light simply seemed a little different from the other light.

All three types of descriptions were given for level 2 by 2 subjects (S.D., J.S.) in different series of trials. One (H.C.) gave only type a, 1 (L.R.) only type b; 2 subjects (M.P., K.K.) gave a or b; (B.D.) gave b or c; 1 (K.D.) gave only c. Subject B.D. stated, spontaneously in his last session, that retrospectively most or all of his level 2 awarenesses were 'really intuitive, just an impression of something different'.

Reasons given for choosing L_1 or L_2. The subjects were also asked to tell the observer (B.L.) why they chose L_1 or L_2 as the interval in which a stimulus was delivered, in those trials when they reported an awareness level 3 (i.e., 'feeling nothing' or 'guessing'). H.C. consistently reported he 'had no reason for his choice, he was guessing'; yet his proportions of correct choices (associated with awareness level 3) were as good or better than for most other subjects who did give some reasons (*see* Table 1). Most other subjects gave this report for many but not all such trials. Several reported having some sort of hunch that one of the lights was a 'better choice' or was associated with some undefinable difference (M.P., S.D., J.P., K.D., B.D.). Some revealing psychological projections onto the lights themselves were described: B.D. and J.S. at times said *both* L_1 and L_2 seemed to be associated with some kind of bodily experience (both sides of the body in case of J.S.), but that it was something more during one light than the other. L.R. stated that 'the light itself tells him more about which one to choose' than any feeling of something in a body part! B.D. additionally volunteered that he went into a kind of trance of concentration, during each cycle of 20 trials, and that he felt he made worse choices when the 'trance' was interrupted; he based the latter conclusion on experiences during 'feedback' series in which he was informed of his correctness after each choice. On the other hand, several subjects (J.S., L.R., B.D.) reported that they often felt frustrated or surprised in a feedback series when they guessed something was different about one light and found their choice was incorrect.

DISCUSSION

Detection with no awareness

Stimulation of ascending somatosensory fibres at the thalamus can clearly be meaningfully detected even when the subject has no reportable introspective awareness of the signal. The evidence is especially striking for those trials in which subjects reported awareness level 3 (i.e., nothing felt, just guessing). They chose the correct light interval in 66% of all such trials (Table 2). This means the probability of correct detection (in the 50% of trials expected to be incorrect by chance alone) was 32% (SE ± 2%). The parametric analysis also showed that the odds of being correct were substantially greater than 1 when they reported level 3. In the nonparametric analysis, incorrect chance choices became correct ones at a mean of 19.7 pulses (TD = 0.27 s). To move from mere detection to elicit even the uncertain and questionable awareness level 2 required an additional mean of 27.8 pulses (α).

Interpretation of reports of awareness level 2. The subjects were instructed to report level 2 when they were uncertain about feeling a sensation, or if they felt there was something more than nothing. The latter instruction left open the possibility of reporting level 2 when they did not experience any sensory awareness at all, even one of an uncertain nature.

As reported in Results, the subjects descriptions of their associated introspective experiences could be grouped into three types. For two of these (types b and c) there can be serious doubt that an actual sensory awareness of even an uncertain nature occurred. Instead, the reports of 'something different, more than nothing, but not definable', etc., could represent feelings related to intuitive guesses, hunches, or rationalizations about the answer, based on unconscious cerebral effects of the stimulus input. (1) Some of the descriptions by subjects were expressed in just such terms. (2) Level 2 was reported inappropriately (especially by 3 subjects) in a significant proportion (12%) of blank trials (0 p) as compared with 1.5% for level 1 reports (Tables 1, 2). (3) In the series with feedback of correctness, several subjects volunteered that they were surprised and somewhat annoyed to find that they were often incorrect when they had reported a level 2 awareness; this reaction almost never occurred with level 1 reports, as those were associated with almost 100% correct answers (except for the small number of level 1 reports with stimuli below 11 p). (4) Further, more reports of level 2 were made in the trials with lower pulse numbers (< 20 p) than occurred in the preliminary trials for setting of the TD values just able to elicit a threshold sensation. The preliminary trials used only a single lighted period to indicate delivery of a stimulus and did not require a forced choice answer of L_1 or L_2; there was therefore no motive to look for a hunch or rationalization to justify the answer.

A substantial though unknown proportion of reports of awareness level 2 may thus represent expressions of intuitive hunches not based on any actual sensory awareness. This proposal is not inconsistent with our criterion of awareness, which accepts the subject's introspective report; the instruction permitted the subject to report level 2 if he/she felt there was something different, more than nothing, during one of the lighted intervals, even in the absence of any sensory awareness of any kind. The proposal is also in accordance with the reasons given by subjects for choosing L_1 vs L_2 (*see* Results). The putative need to rationalize the choice of L_1 or L_2, by reporting

awareness level 2 with this kind of diffuse, undefinable feeling, appeared to vary between the subjects. For trials with brief TDs (1−10 p), subject K.D. (an engineer) reported the highest proportion of level 2, 45% of the trials; for M.P., K.K. and J.P., level 2 reports constituted respectively 29%, 26% and 22% in this range of TDs, with much smaller proportions for other subjects (Table 1). (Interestingly, the inter-subject variation in values of α (*see* Table 6) seems to be related inversely to the proportion of level 2 reports by respective subjects. Those with the lowest proportion of level 2 reports (H.C., L.R.) had the highest αs, while the converse relation existed for K.D., M.P., K.K. and J.P. (B.D. appears to be an exception, with a low level 2 incidence but relatively low α values). This suggests that subjects who more readily reported awareness level 2 required a smaller addition of TD, over that for mere detection, to produce the level 2 report. Even so, their z values are still high enough to indicate their lower αs are highly significant.)

The degree of detection was related to the reported introspective level of awareness, regardless of the mean of these reports (Table 4, fig. 2). Even in the low range of 1−10 p the probability of a correct answer was substantially greater with reports of level 2 than with level 3 (Table 2). For example, of the 2451 trials in which only 1−19 p were delivered (TDs up to 0.26 s) there were 504 trials in which level 2 was reported, of which 80% were correct in the choice of L_1 vs L_2. (Probability of correct detection of otherwise incorrect chance reponses was 60% ±3.5%, in those trials.) This is also seen in the parametric analysis giving the ($\log_e$ of the) odds of being correct; the latter shows, in most subjects, a large increase (at the same p number) when awareness levels rises from 3 to 2. This indicates that whatever the basis for reporting level 2, that is, even if many did not represent an actual awareness of a sensation, it did signify an improved detection process compared with that in 'pure guess' reports.

Relation to reports, by others, of detection without awareness. The history of such phenomena, often referred to as 'subliminal perception', has been reviewed elsewhere (e.g., Shevrin and Dickman, 1980; Holender, 1986; Weiskrantz, 1986). In normal human subjects, the spread between stimulus intensity for threshold sensory awareness and that for any possible detection without awareness is relatively small, when stimuli are delivered to peripheral sensory receptors or nerve fibres (e.g., Libet *et al.*, 1967; Libet, 1982). It has been found that a human subject can probably *detect* the absolutely minimum possible peripheral sensory input to the CNS, i.e., a single nerve impulse in a single sensory nerve fibre from the skin (Johansson and Vallbo, 1979). That study employed forced-choice methods including one similar to that used in our study. Johansson and Vallbo did not raise or study the question of sensory awareness per se. In any case, the duration of cerebral, not peripheral, repetitive activations is at issue in the 'time-on' theory. Indeed, detection of microstimulation of striate cortex by macaques was achieved with minimum intensities only when 20−100 pulses at 50 Hz were applied; threshold intensity for detection increased 6−12 fold when only a single pulse was used (Bartlett and Doty, 1980). *If* a single peripheral nerve impulse were to be found to elicit awareness and not merely simple detection, we would predict that the later components of evoked potential would appear; late responses up to 0.5 s or more seem necessary to elicit sensory experience (*see* Libet *et al.*, 1967, 1975), and they would provide durations of cortical activity much longer than the primary cortical response to a single peripheral stimulus.

Much of the recent evidence to test for unconscious detection has employed indirect techniques, such as 'semantic activation without conscious identification' (e.g., Holender, 1986), or masking procedures to block awareness of signals (e.g., Marcel, 1983); interpretations of these experiments have been the target of much argument (*see* Holender, 1986) although the issue has in part been confused by differing definitions of 'subliminal' and 'awareness' (e.g., Dixon, 1986). Holender's proposal, that 'responding discriminately to a stimulus' could be a sufficient definition of conscious identification, is contradicted by our experimental results. It would seem also contradicted by the reported ability to respond to a skin stimulus with a reaction time that is independent of the subject's awareness of that stimulus (Taylor and McCloskey, 1990).

Direct evidence for detection of peripheral sensory inputs without awareness also has been found under other circumstances, as in the demonstration of 'blindsight' in which destruction of primary sensory cortex essentially eliminates the subject's conscious visual experience (Weiskrantz *et al.*, 1974; Weiskrantz, 1986; Stoerig and Cowey, 1989). The significant feature of the present contribution is to demonstrate a role for duration of repetitive input, at cerebral levels, in distinguishing detection-without-awareness from with-awareness. Such a role could not be directly demonstrated with a peripheral stimulus, with which durations of *cerebral* activations can only be minimally and uncertainly controlled. By contrast, stimuli in ventrobasal thalamus provided a potentially large range of durations in which production of awareness was mostly restricted to the longer durations of stimulus.

Greater stimulus durations required for awareness

The main hypothesis tested here had two components, one of which was discussed above. We can conclude that the evidence also strongly supports the other component, that the transition from detection-without-awareness to detection-with-awareness requires a significant increase in train duration of repetitive ascending volleys initiated in ventrobasal thalamus.

It should be emphasized that intensity (peak current) remained constant in any given series of trials; only the TD (number of pulses) was varied. There is no doubt that the electrically most excitable neural elements responding to each stimulus pulse were axons, either those arriving from the medial lemniscus and/or those ascending from the thalamic neurons to cerebral cortex (or to other forebrain structures). These axons are said to be predominantly in the small myelinated fibre range (H. J. Ralston III, personal communication). Myelinated axons are relatively insensitive to repetitive excitation with the brief TDs and the pulse frequency (72/s) employed (*see* Ochs, 1965, pp. 45–49). Increases in subliminal excitability persist for < 1 ms, so that one would not expect progressive recruitment of more firing axons during each train of stimulus pulses here. That is, each stimulus pulse (at a given intensity in that series of trials) would elicit delivery of essentially the same number of nerve impulses to the forebrain structures; only the number of such identical volleys—the duration of their repetition—would vary between stimuli with different TDs. Dropping out of some firing axons during each stimulus train is a possibility, if sufficient postfiring subnormality develops; but such an eventuality would not significantly affect our conclusions. It should also be noted that the absence of either sensory awareness or detection cannot be attributed to an inability of a stimulus to excite any axons; all stimuli, regardless of TD, must be exciting at

least some ascending axons, since awareness of a sensory experience is elicited by a sufficiently long TD in all series.

Evidence that a longer TD is required to elicit awareness, than for simple detection, is seen qualitatively even from the raw data (Tables 1, 2). However, the nonparametric analysis provided rigorous and definitive evidence for the difference in TD requirements of simple detection as opposed to awareness. A relatively large mean number (α) of *additional* pulses (27.8 p, or 0.39 s TD) was required to move from mere detection to elicit *any* even questionable awareness (level 2). Furthermore, the values for α were highly significant in almost all sessions for all subjects, as seen from the values of z (Table 6; *see also* fig. 4B). It should be emphasized that α was calculated for uncertain questionable awareness level 2 (*see* discussion above). The greater TD requirement for any awareness is therefore unambiguous; it does not depend upon achieving the more definite report level 1 and is independent of any argument that all reports of level 2 may be a form of actual awareness.

Signal detection theory and 'criterion' for response. It might be argued on signal detection theory that the distinction between detection without and with awareness is based on a difference in the 'criterion' adopted by the subject when making each type of response. But signal detection theory was developed specifically in relation to *detection* (Green and Swets, 1966); awareness was not directly studied or involved, and any extension of the theory to awareness would require ad hoc assumptions about the neural mediation of awareness.

The implication in the signal detection argument would be that subjects are really aware of the signal in some fashion at all degrees of detection but that *reportability* of awareness requires a higher criterion. Since subjects report no awareness of such a condition, the proponents would have to assume that they simply will not or cannot report this awareness; such an assumption is nonfalsifiable and without merit when it contradicts observation. When the subject reports that he feels nothing it would be a distortion of the primary evidence to insist, on the basis of a theory, that he really felt something (Libet, 1973, 1985, 1987, 1989). The subject's introspective report is the only valid primary evidence for his conscious subject experience (e.g., Libet, 1987). A possible secondary argument, that to *verbalize* an introspective report requires more stimulus input than the nonverbal response employed for detection, cannot be made for our study. Subjects indicated in every trial both their forced-choice selection (L_1 vs L_2) and their awareness level by nonverbal acts in pressing different sets of buttons. Actually, the verbal descriptions of awareness level given by subjects, after making their nonverbal responses, matched the latters' intended meanings. It may also be noted that they reported experiencing differing durations of the conscious sensation elicited by the different stimulus durations; namely, a 750 ms train felt longer than a 500 ms train, etc. This reported awareness of variable brevities of sensation would argue against the possibility that reports of no awareness with brief stimulus durations represented dismissal of actual but brief sensations.

It might be suggested that a 'criterion' for awareness was demonstrated operationally by our experimental finding that awareness does require substantially longer stimulus durations (in the thalamus) than does simple detection. But in doing so any implication that such a greater requirement is set consciously by the subject must be avoided (*see above*). Also, we are *not* proposing that there is an absolute minimum duration of

repetitive cerebral activation required to elicit awareness; this duration can be altered by increasing intensity of input and, at least conceivably, by the subject's motivation and attention. Any such alterations in required duration, however, would presumably also be achieved by unconscious processes, i.e., without the subject's awareness of a new 'criterion' for duration of cerebral activities. Consequently, the use of the 'criterion' concept would provide, at best, only a semantically different way of describing our findings. Simple detection can remain unconscious, and the greater duration of repetitive ascending activations required to elicit some awareness of the signal would reflect a meaningful physiological difference, not the continuous, qualitatively identical process for both detection and awareness proposed by some signal detection theorists.

Meaning of 'time-on' theory. The 'time-on' theory was based on several independent lines of evidence and makes predictions for a number of different though fundamental relationships between subjective timing of events and actual behaviour (e.g., Libet, 1989). One such prediction, which served as the specific hypothesis tested in the present study, is that a discontinuity will be found between duration of cerebral input producing detection-with-no awareness and duration for detection-with-awareness. A substantial discontinuity of great statistical significance (*see* the values of α and z in the nonparametric analysis) was indeed demonstrated. The specific hypothesis tested in this study was potentially refutable, had no difference been found between durations required for simple detection vs sensory awareness. The 'time-on' or duration of cortical activation can thus be a controlling factor in determining whether a mental function such as detection proceeds unconsciously or with conscious awareness.

The conclusion is not intended to mean that cerebral 'time-on' is the exclusive determinant of the transition between conscious and unconscious functions. Additional or alternative factors could include specificities of cerebral areas, or of dynamic activity patterns, as previously discussed (Libet, 1989). Attentional, motivational or psychodynamic processes could influence the transition by acting through the 'time-on' feature. Increase in intensity of an input to the cortex can reduce the 'time-on' required for awareness (Libet *et al.*, 1964; Libet, 1973, 1982). The present study was deliberately carried out with near-liminal intensities in input in order to maximize the potential role of the duration of repetitive inputs ('time-on'), in differentiating conscious and unconscious functions. The goal in the present study was to compare the *relative* TD requirements of simple detection and sensory awareness, in the same subject during the same trials, under a given set of psychological conditions. Had we performed the experiments with progressively supraliminal intensities we would expect, within limits, to have progressively briefer ranges of stimulus durations within which to distinguish detections-with from detections-without awareness.

There is, however, evidence against the possible suggestion that any integrative mechanism sensitive simply to intensity and duration produces awareness, instead of some more specific role in this for 'time-on' per se. (1) If stimuli to ventrobasal thalamus or S-I cortex (postcentral gyrus) are just *below* the liminal intensity (for eliciting sensory experience with long stimulus durations of > 1 s), then no conscious sensation can be elicited even with durations up to 5 s or longer (Libet *et al.*, 1964; Libet, 1973). Such 'subliminal' intensities are not below threshold for eliciting neuronal responses; substantial electrophysiological responses of large populations of neurons are recordable with each such 'subliminal' stimulus pulse. Were simple integration of intensity and

duration the controlling mechanism, a sufficiently long train duration of stimulus pulses would be expected to become effective for awareness. (2) At a liminal intensity which becomes effective with an average 0.5 s of train duration, the neuronal responses recordable electrically at the cortex exhibit no progressive alteration during the train and no unique event at the end of this effective train (Libet, 1973, 1982). Obviously, not all the possible neuronal activities were recordable, but this evidence at least offers no support for a progressive integrative factor. (3) The minimum train duration that can elicit awareness, when intensity is raised as high as possible, has not firmly been established although it would appear to be in the order of 100 ms. However, it was empirically quite definite that a single stimulus pulse localized to the medial lemniscus could not elicit any conscious sensation no matter how strong (Libet *et al.*, 1967); this was true even when the intensity of the single pulse was 20–40 times the strength of the liminal I sufficient with a 0.5 s train of pulses. Although intensity of stimulus may not necessarily correlate linearly with the number of axons excited here, the effectiveness of 10 pulses (at 20/s) at liminal I contrasted with the ineffectiveness of a single pulse at 40 times this liminal I argues against the proposal of a simple integrative mechanism.

Regardless of the potential contribution from intensity of input or of activation to the production of a conscious experience, the present findings demonstrate that 'time-on' of cortical activation can be one controlling factor in this production and in distinguishing an unconscious detection function from detection with conscious awareness. It would seem likely that many cerebral processes mediating mental function proceed at lower and relatively minimal levels of intensity, judging from normal patterns of recordable electrophysiological and metabolic activities relative to levels that are possible in states of hyperactivity such as seizures. If this is so, the quantitative role of the 'time-on' factor would be substantial.

Finally, 'time-on' theory implies (among other things) that conscious sensory awareness can lag behind the real world by as much as 0.5 s (depending on intensity of input). This counter-intuitive implication has been specifically addressed in an experimental fashion (Libet *et al.*, 1979). That earlier work produced evidence for a subjective referral of sensory experiences, from their delayed neural time of production backwards to the time of the initial fast projection signal, so that there would be no appreciable delay in the *subjective* timing of sensory events.

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APPENDIX*

Nonparametric analysis

In order to eliminate the possibility that the validity of our conclusions would depend on the uncertain assumptions of a statistical model, a nonparametric technique was developed which relies only on assumptions built into the nature

of the experiment. For example, when no pulses are administered, a subject has a 50/50 chance of being correct due to the randomization in setting L_1 or L_2 as correct. Secondly, we may assume that the administered pulses can only increase the chance of a correct response.

Focusing on the possibility of an incorrect choice, define the quantity Y as the number of pulses required to move an otherwise incorrect response just past the threshold into correct. From moment to moment, a different number of pulses, Y, may be required to insure a correct response and we call the expected value of this random variable θ.

In order to estimate the parameter θ, notation is needed for the observable random variables:

$$I_y = \begin{cases} 1 \text{ if subject gives a correct response when given y pulses} \\ 0 \text{ otherwise} \end{cases}$$

Taking the expected value of this indicator variable, and using the two assumptions above, gives:

$$\begin{aligned} E[I_y] &= P[\text{subject gives a correct response when given y pulses}] \\ &= P[\text{would be correct with 0 pulses}] + \\ &\quad + P[\text{no. of pulses administered} \geq Y] \cdot P[\text{would be incorrect with 0 pulses}] \\ &= 0.5 + P[Y \leq y](0.5). \end{aligned}$$

Hence $P[Y \leq y] = 2E[I_y] - 1$.

Since Y is a nonnegative valued random variable

$$\theta = B - \int_0^B P[Y \leq y]dy$$

where B is a number for which $P[Y > B] = 0$ (that is, when we administer B pulses we must be *certain* that the subject will give a correct response). In our work we assumed that a correct response is automatic when at least B = 57 pulses are administered. Substituting the result above gives

$$\theta = 2\{57 - \int_0^{57} E[I_y]dy\}. \tag{1}$$

A natural estimate of $E[I_y]$ is given by the proportion of times a subject is correct when given y pulses. This estimate has variance

$$\sigma_y^2 = E[I_y]\{1 - E[I_y]\}/n_y$$

where n_y is the number of trials with y pulses.

Finally, to compute the estimate of θ we just substitute the estimates of $E[I_y]$ into formula (1) above, using linear interpolation between the observed y values (that is, use the trapezoidal rule to approximate the integral).

We can also gauge the variability of $\hat{\theta}$ (the estimator of θ) In particular, we use the fact that the estimator is just a linear combination of the $E[I_y]$ estimates and that these estimates are independent random quantities Mathematically, we put our estimator in the form

$$\hat{\theta} = 114 - \Sigma w_y E[\hat{I}_y]$$

which gives us

$$\text{Var}[\hat{\theta}] = \Sigma w_y^2 \sigma_y^2 \tag{2}$$

(w_y depends on n_y and on the incremental number of pulses between administered values) The estimated standard errors which are reported in Table 5 come from substituting the estimates of $E[I_y]$ into the formula for σ_y^2 in (2) and taking the square root Also, since $E[I_y]$ is a number between 0 and 1 we know that σ_y^2 cannot be larger than $1/(4\ n_y)$. Substituting this limit into formula (2) and taking the square root, gives the reported values for the upper limit of the SEs

The validity of this theory depends only on the assumption that the different trials were administered independently (this is reasonable since, for example, the number of pulses delivered was randomized).

Statistical theory tells us that the sampling distribution of $\hat{\theta}$ will approximately follow the normal distribution This gives validity to inferential statements that can be made. For example, a conservative 95% confidence interval for $\hat{\theta}$ is given by $\hat{\theta} \pm 2$[upper limit for $SE(\hat{\theta})$].

Additional theory behind the estimates of α

The random variable Y describes the minimum number of pulses it would take to generate detection. The parameter α is then defined as the number of *additional* pulses it would take for the subject to achieve possible awareness (i.e.,

just past the threshold into awareness level 2) The key assumption that was needed for the estimation technique described below is that α is constant over the course of a single session and therefore independent of Y.

Since we assume the certainty of a correct response when more than 57 pulses are administered·

$$\alpha = \int_{\alpha}^{57+\alpha} E[I_y]dy - \int_{\alpha}^{57} E[I_y]dy = \int_{0}^{57} E[I_{y+\alpha}]dy - \int_{\alpha}^{57} E[I_y]dy. \quad (3)$$

An interesting consequence of our key assumption is that the chance that a subject gives a correct response when administered $y+\alpha$ pulses is the same as the chance of being correct or just-guessing-and-incorrect when administered only y pulses.

Now we may proceed in a similar fashion as with the estimation of θ. In particular, we can estimate $E[I_{y+\alpha}]$ by the proportion of times a subject is correct or just guessing when given y pulses. The integrals in expression (3) are then estimated by substituting the estimates of the expectations and interpolating between observed values (as before each integral is approximated by a weighted sum using the trapezoidal rule). Finally, α is estimated using an iterative procedure to find the value satisfying (3). The variability in this estimator of α and its approximate normal sampling distribution can be seen by expressing the final answer as a linear combination of independent proportions. The upper limit for the SE of α given in Table 6 again relies on the fact that

$$E[I_{y+\alpha}](1-E[I_{y+\alpha}]) \leq 0.25 \text{ since } E[I_{y+\alpha}] \text{ is between 0 and 1}$$

* Contributed by Dennis K. Pearl

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AN ANALYSIS OF LYMPHOCYTE ^{3}H-N-METHYL-SCOPOLAMINE BINDING IN NEUROLOGICAL PATIENTS

EVIDENCE OF ALTERED BINDING IN ALZHEIMER'S DISEASE

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SUMMARY

Muscarinic cholinergic receptors were analysed in lymphocyte membranes from 35 patients with early (n = 20) and late onset (n = 15) Alzheimer's disease (AD), 86 patients with other neurological disorders and 60 normal controls by the specific binding of ^{3}H-N-methyl-scopolamine (^{3}H-NMS). The number of binding sites of ^{3}H-NMS (Bmax) was significantly decreased both in early and late onset AD groups as compared with age-matched controls, by 54% and 40%, respectively, whereas the apparent binding affinity (Kd) was the same in all disease and control groups. In addition, the average Bmax in early AD was significantly lower than in late AD. The density of the binding of ^{3}H-NMS was also significantly lower in a subgroup of old subjects with Down's syndrome (DS), whereas no changes were found in younger individuals with DS or in patients with Parkinson's disease, whether they were demented or not, multi-infarct dementia, myasthenia gravis or epilepsy. In the AD group, the difference in binding sites was unrelated either to the severity of dementia or disease duration. Treatment of the patients with cholinergic agents did not alter the binding values in any of the examined group. We conclude that the alteration of lymphocyte muscarinic receptors is highly associated with AD, but whether this reflects the central cholinergic deficit in these patients is uncertain.

INTRODUCTION

Diagnostic identification of individuals with Alzheimer's disease (AD) according to biological markers has been a constant goal, but has met with limited success. A possible marker is the binding of the muscarinic cholinergic antagonist ^{3}H-quinuclidinyl-benzylate (^{3}H-QNB) to muscarinic receptors located on lymphocytes. Independent investigations have shown that there is a reduction in the number of lymphocyte ^{3}H-QNB binding sites in individuals with AD, suggesting their importance as peripheral markers of the central cholinergic deficit (Adem *et al.*, 1986; Rabey *et al.*, 1986). Alterations of cholinergic neurotransmission are well established in AD and changes in the central muscarinic receptors have also been reported (Bowen *et al.*, 1976; Davies and Maloney, 1976; Perry *et al.*, 1977; Reisine *et al.*, 1978; Mash *et al.*, 1985; Rinne *et al.*, 1985, 1989; Shimohama *et al.*, 1986; Reinikainen *et al.*, 1987; Araujo *et al.*, 1988; Lange *et al.*, 1989). Conversely, the specificity of ^{3}H-QNB binding sites

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in lymphocytes has been questioned by several pharmacological studies, indicating that the tracer may not label muscarinic receptors exclusively (Maloteaux *et al.*, 1982; Bidart *et al.*, 1983; Wazer and Rotrosen, 1984; Eva *et al.*, 1989). Thus the postulated decrease of muscarinic recognition sites in lymphocytes of AD patients still remains to be demonstrated. In previous investigations, we and others demonstrated that stereospecific and saturable muscarinic binding sites on lymphocytes can be measured by using the hydrophilic muscarinic ligand ^{3}H-N-methyl-scopolamine (^{3}H-NMS) that has less capability than ^{3}H-QNB to enter into the cells and bind nonspecifically to intracellular components (Bering *et al.*, 1987; Eva *et al.*, 1989). In the present study we used ^{3}H-NMS to monitor lymphocyte muscarinic receptors in a relatively large population of neurological patients and healthy controls. Data were analysed to answer the following main questions: (1) does lymphocyte ^{3}H-NMS binding differentiate individuals with AD from the general healthy population and from other neurological patients, particularly from those with other demented disorders, and (2) does this binding model allow us to extrapolate to possible pathology-induced abnormalities in the central cholinergic activity. In relation to these questions, the potential effect of certain cholinergic treatments on the ^{3}H-NMS binding sites was also examined.

MATERIAL AND METHODS

Subjects

Demographic details of the subjects are shown in Table 1. Two study groups were instituted. The first included 35 patients with probable AD. With respect to the age at disease onset, the diagnosis of probable dementia of Alzheimer's type (DAT) was made in younger subjects (onset of illness before or at 65 yrs) and that of senile DAT (SDAT) was made for the older individuals (onset after age 65 yrs). The second group consisted of 86 patients with other neurological diseases including multi-infarct dementia (MID), Parkinson's disease (PD) with or without dementia, Down's syndrome (DS), myasthenia gravis and epilepsy. A population of 60 healthy subjects, subdivided into various groups matched for age and sex to those of the patients, served as a control. Informed consent was obtained from all participants or from the patients' family or legal guardians when appropriate. With the exception of individuals with DS who were institutionalized at a private centre, the patients were all patients attending our Department of Neurology. The controls were normal volunteers recruited from the hospital staff or spouses of the patients. The diagnoses were made according to currently accepted consensus criteria and in the demented cases fulfilled the criteria of DSM III R (American Psychiatric Association, 1987) and that of the NINCDS-ADRDA (McKhann *et al.*, 1984). In Down's subjects, the diagnoses were based on the characteristic phenotype and evidence of mental retardation. Confirmation by chromosomal analysis was available in 23 subjects. Before inclusion in the study, all subjects were examined by at least one research neurologist and had a complete history and physical examination, including a detailed neurological and psychiatric evaluation, and routine blood test analyses that were normal in all cases. CT scans of the head were performed in all the demented, parkinsonian and epileptic patients but not in subjects with DS or myasthenia, and in the controls. Symptoms of depression and dementia were evaluated in controls and demented patients by the Hamilton Depression Scale (HDS) and Mini-Mental State Examination (MMSE) in the version with a maximum score of 30 (Hamilton, 1960; Folstein *et al.*, 1975). Accordingly, all cases were rated free from depressive disturbances (HDS <9). On the basis of the MMSE, dementia was graded as moderate in all subgroups. Patients with DS had been tested psychometrically several years earlier and, according to clinical test records, the mental deficit was of moderate or severe degree. Based on the information in all available clinical records and interviews from the clinical staff, none had shown a progressive decline in intellectual functions up to a 2 yr period prior to the examination. At the time of the study, none of the patients with AD, MID, DS and epilepsy was receiving psychoactive drugs for at least 3 mos, 11 PD subjects were receiving dopaminergic therapies (levodopa with inhibitors of dopa-decarboxylase, alone or in association with bromocriptine) and 8 PD patients were treated with anticholinergic drugs (triphexyphenidil or biperiden).

TABLE I CHARACTERISTICS OF THE PATIENTS

Subjects	*Sex (F/M)*	*Age (yrs)*	*Duration (yrs)*	*MMSE*
Alzheimer's disease				
Onset ≤65 yrs	12/8	62±1.0	3.6±0.5	16±1.0
Onset >65 yrs	8/7	71±0.9	4.0±0.6	13±1 7
Parkinson's disease				
Demented	6/4	68±1.8	7.2±0.9	13±1 5
Undemented	8/7	66±2.0	7.1±0.8	28±0.9
Multi-infarct dementia	6/7	68±1.4	3 8±0.4	14±1.5
Down's syndrome	9/18	29±2.2	–	–
Myasthenia gravis	6/7	45±6.6	2.7±0.5	–
Epilepsy	3/5	30±2.4	8.2±0.5	–
Controls				
<50 yrs	12/13	32±1.9	–	–
>50 yrs	16/19	66±1.2	–	29±0 2

Values are mean ± SEM.

Eight myasthenic patients were receiving cholinesterase inhibitors (neostigmine or pyridostigmine). For all drugs the average daily dosages were those currently used for therapeutic purposes.

Lymphocyte preparations and ^{3}H-NMS binding assay

Blood samples (40−60 ml) by antecubital venepuncture were collected into heparinized (10 IU/ml blood) glass tubes between 9 and 10 a.m. and then processed for lymphocytes purification not later than 2 h after drawing (Böyum, 1968). The preparation of lymphocyte subcellular fractions (crude membranes, P1 and P2 fractions) and binding assays were performed as previously described (Eva *et al.*, 1989) using ^{3}H-NMS (Amersham Int., S.A. 82 Ci/mmol) as a ligand and atropine (100 mM) to assess the extent of the nonspecific binding. Binding assays for the patients and the age-matched controls were performed in a randomized order. For each person studied, the binding of ^{3}H-NMS to intact lymphocytes or to lymphocyte membranes was determined in triplicate using at least 6 radioligand concentrations (1−40 nM). The maximal binding capacity (Bmax) and apparent affinity constant (Kd) were calculated by Scatchard analysis. Proteins were measured by the method of Lowry *et al.* (1951).

Statistical analysis

Student's t test was used to evaluate the difference of muscarinic receptor binding between patients and control groups. Correlation coefficients were determined by multiple linear regression analysis.

RESULTS

Lymphocyte ^{3}H-NMS binding in Alzheimer's disease

Saturation isotherms and Scatchard analysis of ^{3}H-NMS binding to crude lymphocyte membranes from normal controls and AD patients indicate that ^{3}H-NMS binds in a specific and saturable manner to a single population of muscarinic recognition sites in both diagnostic groups (fig. 1). Nonspecific binding increased linearly and was identical in controls and AD patients.

AD produces a significant decrease of the density of lymphocyte ^{3}H-NMS binding

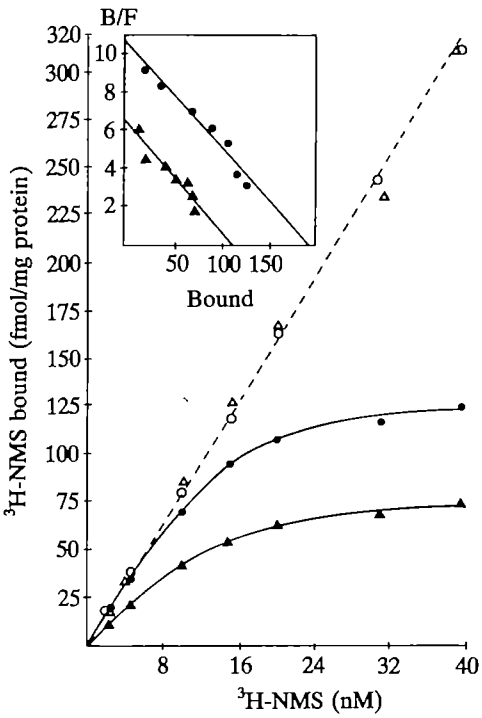

FIG. 1. Representative saturation isotherms and relative Scatchard plots (*inset*: B = bound ligand; F = free ligand) of ^{3}H-NMS specific binding to lymphocyte membranes from AD patients (closed triangles) and age-matched controls (closed circles) (n = 9 for each group). Data are mean values from 3 different experiments, SEMs were less than 10% of the mean Scatchard analysis shows that the affinity of the binding (slope) did not change, whereas the maximal number of binding sites (intersect at the x axis) was noticeably reduced in lymphocyte membranes from AD patients. The nonspecific binding (broken line), control (open circles), AD (open triangles) was not different in the two diagnostic groups.

sites without changing the apparent affinity. The maximal number of recognition sites (Bmax) of ^{3}H-NMS in lymphocyte crude membrane preparations from AD patients was decreased by approximately 50% whereas the average Kd value did not differ significantly from that of the age-matched controls (controls: Bmax = 200±6.8 fmol/mg protein; Kd = 19±0.6, n = 35; AD: Bmax = 100±6.7, Kd = 19±0.5, n = 35; $P < 0.001$).

Table 2 shows the binding of ^{3}H-NMS to intact cells, crude membrane preparations, and P1 and P2 membrane fractions prepared from the same individuals of a restricted group of controls and AD patients. Similar kinetic characteristics of ^{3}H-NMS binding were measured in intact lymphocytes, crude lymphocyte membranes and P2 membrane fractions from AD and control groups, and comparable reductions of muscarinic recognition sites were found in each of these preparations in AD patients. Conversely, in both the diagnostic groups, ^{3}H-NMS failed to bind to P1 subcellular fraction, that contains nuclear material and other intracellular components.

In examining the AD group, the patients were subdivided on the basis of age at onset (before or at and after 65 yrs) into DAT and SDAT. Fig. 2 shows the scattergram of individual and mean Bmax values in the demented subgroups and controls. The number of muscarinic binding sites was significantly decreased in the lymphocytes of both the DAT and SDAT subgroups when compared with the corresponding controls. Moreover, direct comparison shows that the DAT patients had a significantly lower mean Bmax value than those with SDAT. No significant correlation was observed with either disease duration (r = 0.12) or the clinical severity of the dementia as measured by the MMSE score (r = 0.07).

TABLE 2 ^{3}H-N-METHYL-SCOPOLAMINE SPECIFIC BINDING TO INTACT LYMPHOCYTES AND LYMPHOCYTE SUBCELLULAR FRACTIONS FROM CONTROLS AND PATIENTS WITH ALZHEIMER'S DISEASE

	^{3}H-NMS specific binding			
	Controls		*Alzheimer's disease*	
	Bmax (fmol/mg)	*Kd (nM)*	*Bmax (fmol/mg)*	*Kd (nM)*
Intact cells	180±7 5	19±0.8	69±9.3*	19±1.0
Crude membranes	210±7.5	20±0.8	95±11*	20±0 5
P2 membrane fraction	190±10	18±1 1	100±13	19±0 6
P1 membrane fraction	ND		ND	

Values are the mean±SEM from 10 subjects assayed for each group. (Age. controls = 66±1.5 yrs, demented = 67±1.7 yrs). Lymphocytes were homogenized in 0.32 M sucrose and fractionated by differential centrifugation Crude membranes (20 000 g, 20 min), membranes sedimenting in the P1 (100 g, crude nuclear pellet), and those sedimenting in the P2 (12 500 g, 20 min) pellets. In controls the respective values of the nonspecific binding, expressed as a percentage of the total binding at 15 nM ^{3}H-NMS were. 55% in crude membranes, 52% in P2 membrane fraction and 65% in intact cells In AD the correspondent values were 70%, 68% and 75% Kd = dissociation constant ND = not detectable * $P < 0.01$ versus the respective controls (Student's t test).

Alteration of ^{3}H-NMS binding to T lymphocytes from patients with AD

Among the various populations of peripheral mononuclear cells, muscarinic recognition sites are mainly localized on the T lymphocyte subset (Eva *et al.*, 1989). Table 3 shows that the ^{3}H-NMS specific binding at two different concentrations of the ligand (8 and 18 nM) was significantly lower in membranes prepared from T cells from a restricted group of individuals with AD as compared with controls.

Alteration of lymphocyte ^{3}H-NMS binding in other neurological patients

Binding parameters (mean Bmax and Kd) for all the disease subgroups and corresponding age-matched controls are compared in Table 4. The dissociation constant values were the same in all controls and diseases groups. Moreover, no significant differences were found between the ^{3}H-NMS Bmax values of the patients with MID or PD, whether they were demented or not, or in the myasthenia and epilepsy patients and their respective controls. Conversely, a significant reduction in Bmax was demonstrated in the individuals with DS as compared with their age-matched controls.

Data were analysed by dividing the DS patients into two age groups, taking 35 yrs as a division point. Comparison of mean Bmax values between these DS subgroups and their age-matched controls revealed a significant decrease in the number of binding sites in the older DS individuals (controls: age = 40±1.1 yrs, Bmax = 130±10 fmol/mg protein, n = 11; DS: age = 38±0.8 yrs, Bmax = 68±7.5 fmol/mg protein, n = 11; $P < 0.001$), whereas no significant difference in the younger DS individuals was observed (controls: age = 24±2.3 yrs, Bmax = 110±9.7 fmol/mg protein, n = 16; DS: age = 23±2.8 yrs, Bmax = 100±13, n = 16).

Effect of cholinergic medications on lymphocyte ^{3}H-NMS binding

Eight patients with PD were receiving antimuscarinic drugs (triphexyphenidyl or biperiden) and 8 myasthenic patients were treated with indirect cholinergic agonists

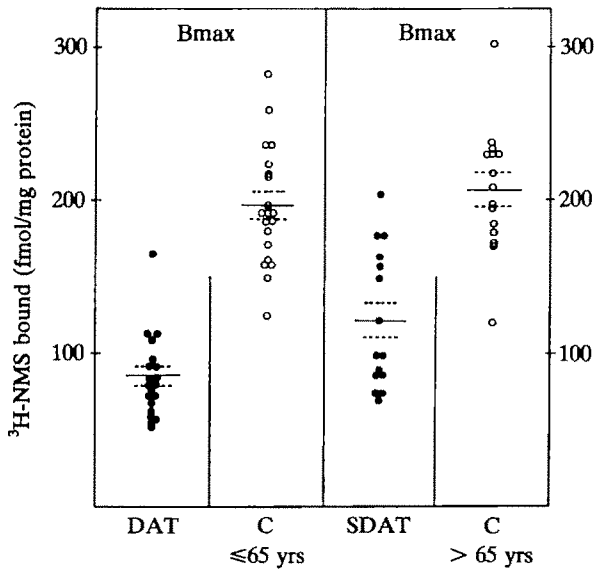

FIG. 2. Scattergram of Bmax values of ^{3}H-NMS binding to lymphocyte membranes for patients with Alzheimer's disease and age-matched controls. DAT indicates dementia of Alzheimer's type (onset ≤65 yrs; age = 62 ± 1.0 yrs), SDAT senile dementia of Alzheimer's type (onset >65 yrs; age = 71 ± 0.9 yrs). C = controls (age: younger = 61 ± 0.9 yrs; older = 71 ± 1 6 yrs). The large bar represents the mean; the small bars represent the SEM.

TABLE 3 SPECIFIC BINDING OF ^{3}H-N-METHYL-SCOPOLAMINE TO T LYMPHOCYTE MEMBRANES OF CONTROLS AND PATIENTS WITH ALZHEIMER'S DISEASE

Subjects	*^{3}H-NMS specific binding (fmol/mg protein)*	*^{3}H-NMS (nM)*
Controls	47 ± 5.1	8
Controls	210 ± 1.2	18
Alzheimer's disease	33 ± 3.8*	8
Alzheimer's disease	112 ± 9.7**	18

Values represent mean ± SEM from 8 subjects assayed for each group Statistical comparison between groups was performed by a two-tailed Student's t test. * $P < 0.05$, ** $P < 0.01$.

(neostigmine or pyridostigmine). None of these treatments was found to change the characteristics of lymphocyte ^{3}H-NMS binding sites with respect to the corresponding populations of patients who were unmedicated (Table 5).

Effect of age and sex on lymphocyte ^{3}H-NMS binding

No sex effect was observed for ^{3}H-NMS binding parameters (Bmax and Kd) in any of the studied populations (data not shown). A significant positive correlation between age and Bmax values was found in the entire population of healthy controls ranging in age from 5 to 85 yrs ($r = 0.76$, $P < 0.01$). However, with the exception of the

TABLE 4 SPECIFIC BINDING OF ^{3}H-N-METHYL-SCOPOLAMINE TO LYMPHOCYTE MEMBRANES OF CONTROLS AND PATIENTS WITH NEUROLOGICAL DISEASES

			^{3}H-NMS specific binding	
Subjects	*No.*	*Age (yrs)*	*Bmax (fmol/mg protein)*	*Kd (nM)*
Parkinson's disease				
Demented	10	68±1 8	210±9 6	20±1 0
Undemented	15	66±2 0	200±8.6	19±0.6
Multi-infarct dementia	13	68±1 4	200±5.1	18±0.8
Controls >50 yrs	33	65±1.2	200±6 8[a]	19±0.5
Down's syndrome	27	29±2.2	88±8.6[b]	19±0.5
Epilepsy	8	30±2.4	150±19	21±1.2
Controls <50 yrs	25	32±1.9	120±7.4	19±0.5
Myasthenia	13	45±6.6	170±20	19±0.8
Total controls	60	52±2 4	170±7.3	19±0.4

Values are mean±SEM Statistical comparison between groups was by a two-tailed Student's t test. Nonspecific binding, expressed as a percentage of the total binding at 15 nM ^{3}H-NMS was. 55% in PD patients; 59% in MID patients and 56% in their age-matched controls, 71% in Down's syndrome, 64% in epilepsy and 66% in their age-matched controls, 61% in myasthenia and 63% in total controls. [a] $P < 0.001$ compared with controls <50 yrs; [b] $P < 0.01$ compared with age-matched controls (<50 yrs)

TABLE 5 EFFECT OF CHOLINERGIC TREATMENTS ON LYMPHOCYTE ^{3}H-N-METHYL-SCOPOLAMINE BINDING

		^{3}H-NMS specific binding	
Subjects	*No.*	*Bmax (fmol/mg protein)*	*Kd (nM)*
Parkinson's disease			
Drug free	6	190±9 7	19±0.9
Dopaminergic treated	11	210±10	20±0 9
Anticholinergic treated	8	210±11	18±1 0
Myasthenia			
Drug free	5	150±26	20±0 9
Anticholinesterase treated	8	180±35	19±1.1

Values are mean±SEM

myasthenics ($r = 0.58$, $P < 0.05$), the correlation between individual Bmax values and age was not significant in any of the disease groups examined.

DISCUSSION

Our study clearly demonstrates that there are significant alterations of lymphocyte muscarinic receptors associated with AD. We found a 50% reduction of lymphocyte ^{3}H-NMS binding sites in the group with AD as compared with age-matched healthy controls. Our data also reveal that some differences in binding profile may exist between presenile and senile forms of the disease. The density in muscarinic binding was significantly lower in the subgroup of patients suffering from presenile disease onset

than in the one with senile disease onset. The significant difference in the average receptor density between DAT and SDAT groups reflects the substantial overlap in the range of individual Bmax values between SDAT cases and normal controls. In fact, in the group with early onset only 1 out of 20 patients showed normal binding density (mean +2 SD), whereas about half of the patients with late onset exhibited Bmax values overlapping with those of the corresponding controls. Thus the possibility that the difference in binding profile distinguishes subtypes of AD on the basis of age onset should be considered. On the other hand, our results indicate that the heterogeneity in binding does not reflect dementia severity, because no significant correlation was found between the receptor number and the degree of mental impairment, as assessed by MMSE.

The reduction of lymphocyte ^{3}H-NMS binding sites was highly associated with AD. The receptor density was not decreased in lymphocytes from patients with MID, PD, whether demented or not, myasthenia or epilepsy. We observed a significantly lower number of muscarinic binding sites only in lymphocytes from a subgroup of subjects with DS, who were older than 35 yrs. The neuropathological pattern of AD is present in nearly all cases of DS by the age of 40 yrs, although it is more difficult to document a clinical dementia in these patients (Burger and Vogel, 1973; Wisniewski *et al.*, 1979; Ropper and Williams, 1980; Mann *et al.*, 1984; Williams and Mattysse, 1986; Lai and Williams, 1989). These data suggest that age may represent an important factor to detect alteration of lymphocyte muscarinic recognition sites in these patients. On the contrary, no apparent relation exists with the dementia symptoms since none of our DS subjects showed clinical signs of a decline in mental deficit.

The abnormality in lymphocyte muscarinic receptors associated with AD does not appear to be due to nonspecific variables or methodological factors. The binding of ^{3}H-NMS to muscarinic receptors was specific and saturable both in demented and control individuals and no changes in the absolute amount of nonspecific binding could be measured between the two diagnostic groups. Moreover, our results indicate that the decrease of ^{3}H-NMS binding capacity in AD patients reflects a reduction in the number of muscarinic recognition sites located on lymphocyte membranes because no difference in the total number of ^{3}H-NMS specific binding sites was observed between intact lymphocytes and crude or P2 membrane preparations. Moreover, we were not able to detect any ^{3}H-NMS binding to the lymphocyte nuclear fraction P1. Other possible confounding variables were either controlled for or excluded as an explanation of our findings. Fasting blood samples were used, collected at the same day time and the binding assays performed not longer than 1 wk after the membrane freezing. None of the patients had been treated with psychotropic drugs or was suffering from infectious disease. Investigator bias, however, was not eliminated since the laboratory staff did not remain blind to most of the clinical data. We previously reported that the density of lymphocyte ^{3}H-NMS binding sites in normal persons increases with age (Eva *et al.*, 1989). The results reported in this paper, obtained in a larger and more uniformly age-distributed population of healthy controls, confirm this indication since the binding capacity showed a significant positive correlation with age. However, the differences in muscarinic binding sites between patients and controls could not be ascribed to age because pairs of samples from each control, matched for this variable, were included in each assay run.

Finally, it is unlikely that this difference in binding reflects changes in the relative proportion of the various populations of peripheral lymphocytes that might occur in association with AD (Miller *et al.*, 1981; Leffell *et al.*, 1985; Skias *et al.*, 1985; Torack, 1986). In fact, we found that the decrease of lymphocyte muscarinic binding in the AD patients reflects a parallel modification in T cells that are the lymphocyte subset where muscarinic recognition sites are mainly expressed (Eva *et al.*, 1989).

The results presented in this paper indicate that ^{3}H-NMS binding to muscarinic receptors located on human lymphocytes decreases in AD. The general agreement of our data with those obtained by Rabey *et al.* (1986) and Adem *et al.* (1986), both of which determined muscarinic receptors by using ^{3}H-QNB, suggests that the reduction of muscarinic recognition sites on lymphocytes of AD patients is a well reproducible phenomenon that can survive major changes in binding methodology and/or subject population. Our results also suggest that differences in lymphocyte muscarinic receptors might be related to a clinical heterogeneity of AD patients. However, since the overlap between AD and control groups indicates no absolute change due to the disease, further studies are required to establish whether the detection of such abnormality may have some utility in the diagnosis of Alzheimer's dementia.

The mechanisms responsible for the decrease of lymphocyte muscarinic receptors associated with AD are still unknown. The lack of binding abnormalities in the patients with PD or in those subjects who were receiving some cholinergic therapies, may argue against the possibility that this decrease reflects an adaptive response of the receptors to the central cholinergic deficit. Abnormalities in cholinergic neurotransmission have been demonstrated in individuals with PD, particularly in those with associated dementia (Ruberg *et al.*, 1982; Dubois *et al.*, 1983; Whitehouse *et al.*, 1983; Rinne *et al.*, 1989). On the other hand, it is well established that muscarinic receptors in brain and also in periphery are regulated by pharmacological treatments with cholinergic agents (Schiller, 1979; Costa *et al.*, 1981; McKinney and Coyle, 1982; Olianas *et al.*, 1984). Any conclusion concerning these data, however, should be considered with caution since the number of patients was small and the treatments too diverse. The decrease of muscarinic receptors found in lymphocytes might alternatively result from unknown factors that would influence lymphocyte membranes. This hypothesis would correlate well with the findings that modifications of lymphocyte membranes may occur during ageing and AD and that muscarinic agents can affect the lymphocyte membrane microviscosity (Rivnay *et al.*, 1980; Masturzo *et al.*, 1985; Zubenko *et al.*, 1987). Studies of ^{3}H-NMS binding in parallel with measures of membrane fluidity on cultured T lymphocytes from AD patients could be helpful to verify this suggestion.

A final point of discussion concerns the relation between lymphocyte and brain muscarinic receptors in the course of AD. At the present time, the status of central muscarinic receptor sites in AD is very controversial (Whitehouse and Au, 1986). Several investigators suggested that the various subtypes of brain muscarinic receptors are differentially affected in AD and that only the M2 receptors are selectively decreased (Mash *et al.*, 1985; Rinne *et al.*, 1989). Although the subtypes of muscarinic receptors expressed in lymphocytes have not yet been characterized, Bering *et al.* (1987) proposed that there might be a predominance of M2 receptors. This possibility would then fit well with the abnormality of lymphocyte muscarinic receptors in AD. Hence, the precise identification of muscarinic receptor subtypes in lymphocytes by using more selective

radioligands or, even better, by measuring messenger RNA encoding muscarinic receptors, might have important implications in understanding their regulation in disease.

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PREFERENTIAL GENERATION OF RECURRENT RESPONSES BY GROUPS OF MOTOR NEURONS IN MAN

CONVENTIONAL AND SINGLE UNIT F WAVE STUDIES

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SUMMARY

Conventionally recorded surface F waves over the abductor digiti minimi muscle sampled a wide range of conduction velocities (CVs) Single motor unit (MU) F responses to threshold stimulation of the ulnar nerve were recorded with bipolar needle electrodes (BNE); the mean latencies of their fastest associated surface single unit M and F potentials were similar to those of the compound muscle action potential and fastest F wave, indicating that the fastest F wave indexes adequately the fastest motor fibre of the ulnar nerve. The mean surface unit F amplitude of MUs recorded by a BNE was similar to that of voluntary MUs recorded with a spike-triggered averaging technique; an estimated mean of 2–3 MUs per F wave was found by two methods.

The frequency distribution of estimated F wave CVs was shifted towards faster values than expected from available studies of the distribution of CVs in single peripheral nerves; it was also higher than predicted from the expected relation between this distribution and the number of MUs per F wave, if an equal chance of activation and recording is assumed for each MU. There was a significant positive correlation between the frequency of F responses and their CV in 81 single MUs recorded by a BNE and tested with 200 threshold stimuli. These findings are consistent with preferential generation of recurrent responses by larger MUs, it may relate to a lesser chance of antidromic discharge in the smaller motor neurons and to a greater chance of collision of orthodromic (reflex) and antidromic impulses in their axons

The higher than expected percentage of all F waves that were repeater shapes or waves, and the presence of several distinct peaks in the distribution of intervals between repeaters of the same shape, suggest special, and heterogeneous, functional and anatomical arrangements in the groups of motor neurons generating them. Repeaters had greater amplitude and area, but similar latency and duration, than F wave shapes that did not repeat, suggesting that the former have a larger number of component MUs.

INTRODUCTION

F waves in man (Magladery and McDougal, 1950) represent recurrent discharges of antidromically activated motorneurons (Dawson and Merton, 1956; McLeod and Wray, 1966; Mayer and Feldman, 1967; Trontelj, 1973). A reflex may also be involved in their production (Gassel and Wiesendanger, 1965; Trontelj, 1973; Fox and Hitchcock, 1987). Clinically the F wave latency is used in assessing motor nerve conduction (Lachman *et al.*, 1980; Kimura, 1983). More recently, other F wave parameters such as amplitude expressed as percentage of the compound muscle action potential,

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chronodispersion, frequency of occurrence and percentage of repeater responses, have been used to study disorders of both the central and peripheral nervous systems (Eisen and Odusote, 1979; Panayiotopoulos, 1979; Abruzzese *et al.*, 1985; Petajan, 1985; Peioglou-Harmoussi *et al.*, 1986, 1987; Macleod, 1987; Fisher, 1988; Tang *et al.*, 1988). The interpretation of changes in F wave parameters in pathological conditions would be helped by knowledge on the relevance of the mechanisms of F wave generation to the parameters measured in humans.

It is uncertain whether F waves in man are generated randomly by all motor neurons within a pool or preferentially by certain groups (Kimura *et al.*, 1984; Fisher, 1985). It has been debated whether the shortest surface recorded F wave latency indexes maximal motor nerve conduction velocity (MCV) (Young and Shahani, 1978) and how closely the spectrum of F wave latencies reflects the CV of all the motor fibres within a peripheral nerve (Burke *et al.*, 1989). One difficulty is the lack of published evidence to document the optimum number of F waves required for many of the measured parameters. For example, for minimum latency evoking from 3–5 to 50–100 F waves has been recommended (Panayiotopoulos, 1979; Yates and Brown, 1979; Marra, 1987). For chronodispersion 20 or 100 F waves have been suggested (Panayiotopoulos *et al.*, 1977; Tang *et al.*, 1988). Little information is available on repeaters (Peioglou-Harmoussi *et al.*, 1985*b*; Macleod, 1986).

In this work the statistical properties of the surface-recorded F wave parameters with different sample sizes are established and the putative populations of motor neurons generating F waves are explored using such parameters. The behaviour of repeaters is also studied; the suggestion that they may index a distinct subgroup within the motor neuron pool will be discussed. The question of preferential generation of recurrent responses by certain motor neuron groups, as suggested by the distribution of estimated CVs of surface-recorded F waves is addressed with single unit surface and BNE recordings of F responses to establish whether: (1) the minimum F wave latency is in fact mediated by the fastest conducting motor fibre, (2) F responses are more often produced by the faster units *within* the population of motor units (MUs) sampled by threshold stimulation of a peripheral nerve. Since, as will be shown, the distribution of F wave CVs also depends on the average number of MUs per F wave, this is also estimated by physiological means. The findings will be discussed in the context of available knowledge on antidromic activation of motor neurons.

MATERIAL AND METHODS

Healthy subjects

Sixty-four were studied. Group I consisted of 16 males and 17 females (mean age 51 yrs, range 20–81 yrs), group II of 8 males and 7 females (mean age 38 yrs, range 21–45 yrs). Eight subjects were studied in group III and 8 in group IV (Tables 6, 7) Two (R.J.G., H.M.S.) were included in both groups III and IV. The height of the subjects was noted; they sat in an armchair and were advised to relax. Informed consent was obtained. The study was approved by the local ethical committee.

Recordings

A Neuromatic 2000M EMG machine (Dantec) was used. The skin temperature of the limb tested was maintained at 32°C with radiant heat. The surface compound muscle action potential (CMAP) and F waves were recorded initially in each subject with bipolar surface electrodes (13L20) positioned at the belly of the abductor digiti minimi muscle (ADM) and at the first metacarpophalangeal joint of the fifth digit.

Stimulation at 1 Hz was 25% supramaximal, with a pulse duration of 200 μs, delivered percutaneously through bipolar surface electrodes (Dantec 13L22) fixed over the ulnar nerve at the wrist (groups I, II, IV) or at the elbow (group III); 100 stimuli were given to the first 11 patients in group I, all the other subjects receiving 60 stimuli (fig. 1). A sweep speed of 5–10 ms/division, and filter settings of 20 Hz–2 kHz were selected. A gain of 0.2 mV or 0.5 mV/division was used for groups I and IV, 50 μV/division for group II, and 0.1 mV/division for group III. MCV from elbow to wrist in the same ulnar nerve used for F wave recordings was measured in each subject from groups I and II.

Following this study, with the surface electrodes in the same position, further recordings were performed in each subject of groups III and IV as follows.

Group III. Single unit F responses to threshold stimulation were recorded in 2 channels. The acquisition system was triggered by the stimulus applied. One channel was connected to a bipolar needle electrode

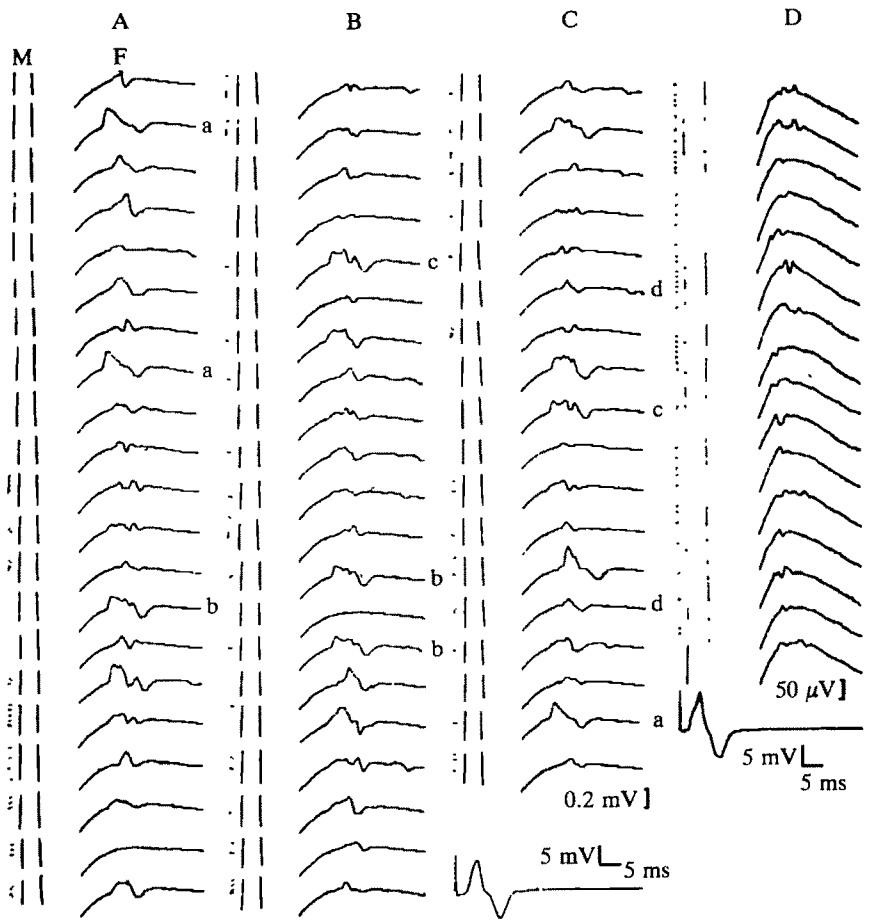

FIG. 1 A–C, F waves (F) recorded over the abductor digiti minimi following 60 consecutive stimuli at 1 Hz at the wrist in a healthy male subject aged 46 yrs (group I). Four repeater F wave shapes are shown (a, b, c, d). A total of 10 repeater F waves are seen. In this example: measurable F waves = 58, F wave frequency = 96.6%, total F wave shapes = 52, percentage repeater F wave shapes = 7.7%; percentage repeater F waves = 17.2%. D, all the F waves with an amplitude <40 μV, evoked by 60 stimuli in a male subject aged 31 yrs in group II, are shown. Larger F waves are not shown. The compound muscle action potentials are shown at the bottom. M = M wave

(Dantec 13K80) (BNE), which was inserted into the muscle beneath the surface electrode on the belly of the ADM. Filter settings of 2 Hz−10 kHz, gain of 0.1−0 2 mV/division and sweep speed of 5 ms/division were used. Threshold stimulation of the ulnar nerve at the elbow was delivered with a pulse duration of 100 μs; a mean intensity of 8.7 mA (SD 5.2) was required. Threshold stimulation was defined as the current intensity closest to that required to obtain and confirm an orthodromic unit recorded by BNE as an 'all-or-none' potential. Slight changes in the position of the stimulating electrode were occasionally made to facilitate the search for a unit at a given BNE position. In each subject 12−38 different orthodromic single MU potentials were recorded with the BNE at different random positions, during 3−5 muscle penetrations. Each orthodromic MU found was tested with 200 stimuli at 1 Hz and their F responses were identified. A late potential was considered to be a single unit F response if it was always preceded by an *identical* orthodromic single MU potential and if its latency was constant (fig. 2) (Thorne, 1965; Schiller and Stålberg, 1978).

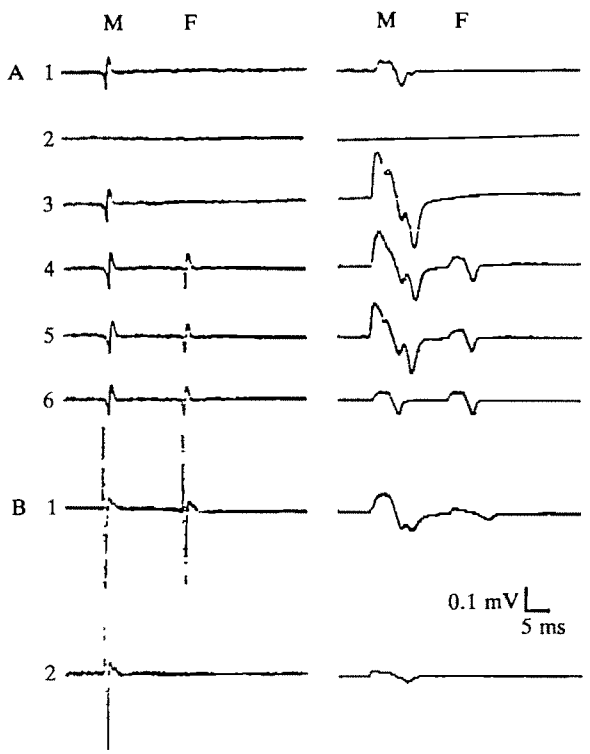

FIG. 2 Examples of surface recorded single motor units with identical orthodromic (M-SUs) and F responses (F-SUs). M = orthodromic response, F = F response Stimulation of the ulnar nerve at the elbow; recordings from the abductor digiti minimi with a bipolar needle (BNE, *left*) and surface electrodes (SE, *right*). A, single motor unit with (4,5,6), and without (1,3), its F wave in subject 3 (Table 6) Both BNE and SE recorded responses appeared in an 'all-or-none' manner (1,2) The size and shape of the SE recorded M response varied (1,3, 4,5,6); it was identical to its F response in record 6. The stimulus intensity was constant at 8 mA for this unit B, single motor unit in subject 2 (Table 6) with (1), and without (2) its F response In this example SE recorded M and F responses were identical but did not occur at the same time

The associated surface responses were studied in the second channel. Filter settings of 20 Hz−2 kHz, gain of 0.05−0 1 mV/division and sweep speed of 5 ms/division were used. In this channel the *orthodromic responses* (cM-SUs) reflected the surface potential of the MU recorded with a BNE in the first channel

plus that of other MUs stimulated at the same time (figs 2, 3); the *late responses* could reflect just the surface F potential of the unit recorded with a BNE (F-SU) or also that of the late potentials of one or more of other stimulated units

Group IV. Surface recorded potentials of single voluntarily activated MUs (V-SUs) were obtained with a spike-triggered averaging method (Brown *et al.*, 1988). One channel was used to record single MU potentials with a concentric needle electrode (CNE) (Dantec 13L50). Filter settings of 2 Hz−10 kHz, gain of 0.02−0.1 mV/division and sweep speed of 5 ms/division were used. The CNE was inserted at random depths in the belly of ADM, beneath the surface electrode. Single MU spikes, randomly found during slight to moderate isometric contraction, were used to average the time-locked V-SUs in the second channel; its settings were as those for group III. Averaging was continued (up to 200 discharges) until the V-SU of the triggering MU could be clearly identified from the background activity of other MUs, and no further change in the shape, or size, of the averaged surface potential was seen. To make sure that potentials of different MUs were being recorded with the CNE, those whose time-locked surface potentials (V-SUs) had a similar configuration to previous surface recorded ones were rejected. In this way 18−20 V-SUs were recorded for each subject (fig. 4).

Measurements and analysis

Groups I and II

All the F waves recorded were measured using a graphics tablet. The peak-to-peak amplitude and area of each F wave were measured (fig. 1). Latency to onset was measured from the stimulus artefact to the

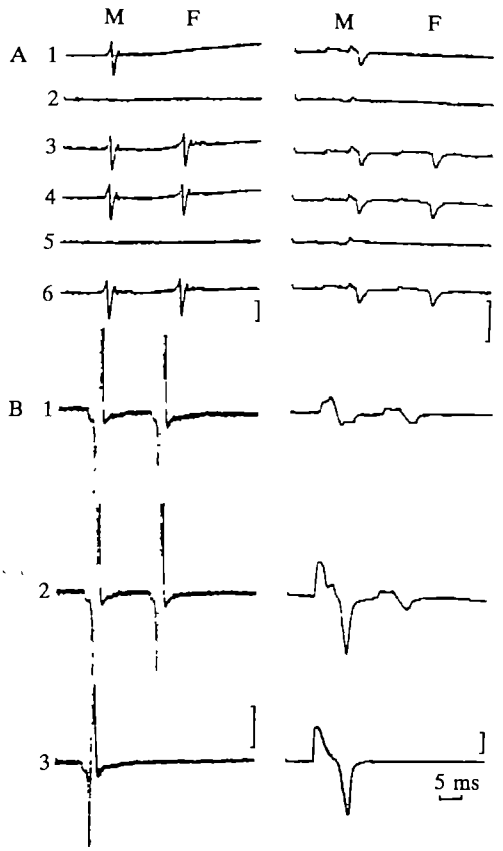

FIG 3. Examples of surface recorded single motor unit F responses (F-SUs) with orthodromic potentials of different shape (cM-SUs). The layout, stimulation and recordings are similar to fig. 2. Vertical bar = 0.1 mV. A, single motor unit in subject 6 (Table 6) with (3,4,6), and without (1,2,5), its BNE and SE recorded F responses. The BNE recorded unit M was 'all-or-none' (1,2). The SE recorded M response in 1,3,4,6 includes 2 units, 1 of which had a lower threshold (2,5) and another constantly associated with the BNE recorded M and F responses (1,3,4,6) B, single motor unit in subject 1 (Table 6). Note that the SE recorded F response is only seen when there is a BNE recorded F response (1,2) In these examples, the SE recorded M and F responses were not identical but the late potentials were also considered single unit F responses (F-SU).

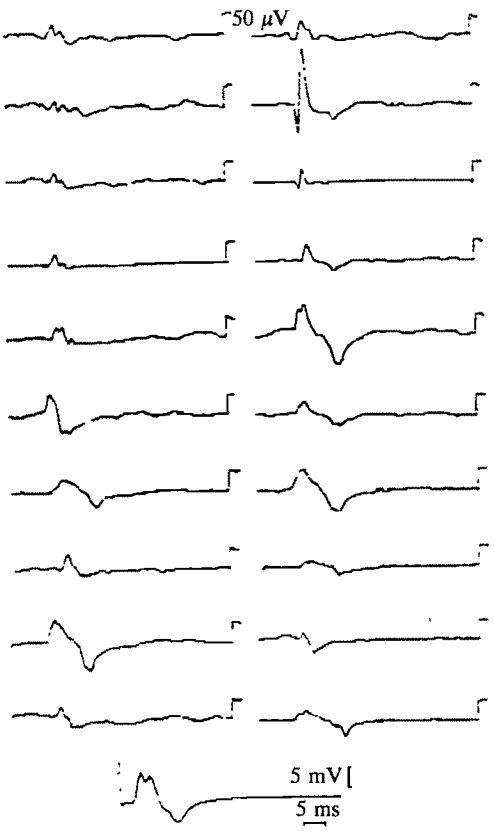

FIG 4. Voluntarily activated, surface recorded, single motor units obtained with a spike-triggered averaging technique (group IV). 20 consecutive motor unit potentials (V-SUs) recorded with surface electrodes over the abductor digiti minimi of subject 5 (Table 7) Each potential is the surface recorded average of 50–200 triggering discharges of a motor unit recorded by a concentric needle electrode activated during isometric voluntary contraction The compound muscle action potential following stimulation of the ulnar nerve at the wrist, with the surface electrodes in the same position, is shown at the bottom

first deflection of the late response, and duration from the onset of the first deflection to the final return to the baseline. The amplitude and area of the CMAP of ADM were measured in a similar way.

F wave frequency was defined as the percentage of stimuli evoking an F wave. In group I, because of the gain used, only those deflections with an amplitude of 40 μV or more were accepted as an F wave. In group II, the frequency of all the visible potentials in the F wave latency range, and the amplitude and frequency of F waves below 40 μV, were measured (fig. 1).

Each F wave was copied on a transparency and superimposed on previous waves. F waves with similar shape and latency were considered to be repeater responses (fig. 1). The mean difference in latency between repeaters considered to have the same shape was 0.17 ms $\pm$ SE 0.05. The frequency of repeater shapes is defined by the number of repeater shapes/total number of F wave shapes, and the frequency of repeater waves by the number of all repeater F waves/total number of F waves (fig. 1). In addition, the number of occurrences of each repeater shape was counted.

F wave latency ratio and estimated F wave conduction velocity. To find out the spectrum of CVs of the motor fibres mediating F waves, the F wave CVs corresponding to each F wave latency were calculated in the following way, in each subject of group I. To correct for the central delay (turn around time) 1 ms was subtracted from the latency of every F wave (Kimura, 1983). Each F wave latency in each subject was then divided by the shortest F wave latency in that subject (F wave latency ratio). No correction was made for the distal motor latency since the latter was only known for the fastest motor fibres If the difference in central delay in different motor neurons is negligible, and differences in the length of the fine terminal fibres and conduction in nonnervous tissue do not lead to major changes in latency measurements, the F wave latency ratio should closely reflect the inverse ratio of the CVs of the corresponding motor fibres.

Assuming that the elbow-wrist ulnar MCV is similar to the elbow-wrist CV of the fibres mediating the F wave with the shortest latency, the spectrum of F wave CVs could be estimated in each subject (F wave CV = ulnar MCV/F wave latency ratio), though the absolute values of these CVs would be lower than those of the proximal segments (Kimura, 1974). It will be shown later that if there is a difference between ulnar MCV and CV of the F wave with the shortest latency, it is so small that it can for this purpose be ignored. Each F wave CV was also expressed as its difference from the maximum F wave CV in each subject.

Amplitude and area. When the F wave amplitude and area of different subjects were pooled they were expressed as a percentage of the respective CAMP amplitude and area. In this way the effect of varying skin and soft tissue thickness, and of slight differences in electrode placement, could be minimized. In order to find the approximate proportion of motor neurons within the pool that generate F waves with each stimulus, the mean F wave amplitude and area (counting each absent F wave as zero) were also expressed as a percentage of the CMAP in each subject (Kimura *et al.*, 1984).

Group III

Single unit F frequency. The percentage of single orthodromic MUs recorded with a BNE with at least one F response, and the number of single unit F responses evoked by 200 stimuli, were established for each unit in each subject. The average number of single unit F responses per stimulation was estimated in each subject by dividing their total number in all the orthodromic MUs tested (including those without such a response) by the number of stimuli.

Single unit F conduction velocity. The peak-to-peak interval between the MUs recorded orthodromically with a BNE and their single unit F response (M-F interval) was measured (*see* 'z' in fig. 5). The CV of the motor fibres mediating single MU F responses was calculated by dividing the distance between the spinous process of C7 to the stimulating electrode at the elbow by (M-F interval — 1)/2 (Kimura, 1983).

Surface recorded single unit F potentials. The peak-to-peak amplitude of each of these potentials was measured. It was also expressed as a percentage of the CMAP amplitude for each subject and the data were then pooled.

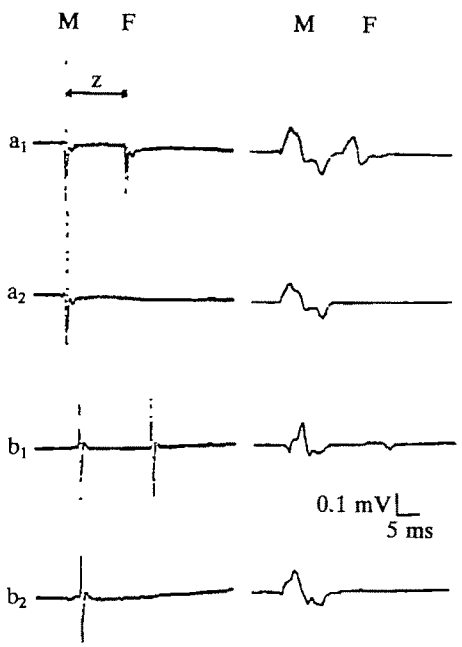

FIG. 5 Fastest and slowest single motor units with an F response in subject 1 (Table 6) The layout, stimulation and recordings are similar to fig. 2 z = M-F peak interval used for calculation of conduction velocity (*see* Methods) The fastest (a) and the slowest (b) of all 22 single motor units which produced an F response with 200 threshold stimuli, with (a_1, b_1), and without (a_2, b_2), their F response are shown. Their F-SU recorded by surface electrodes were identified as in fig. 2B. Unit a has an F CV about 10 $m \cdot s^{-1}$ faster than unit b (*see* Table 6). This corresponds to a latency difference of 5.6 ms between their F-SUs.

Surface recorded orthodromic potentials. For units recorded with a BNE with a single unit F response, the peak-to-peak amplitude of the associated surface recorded orthodromic potentials was also measured. There was considerable variation in the size of surface recorded potentials with constant threshold stimuli (figs 2, 3, 4); the average amplitude of these potentials for each BNE recorded unit with a BNE recorded single unit F response (n = 81) was calculated. This was expressed as a percentage of the CMAP in each subject. The average proportion of the motor neuron pool stimulated when a single unit F response was produced during threshold stimulation was estimated in this way.

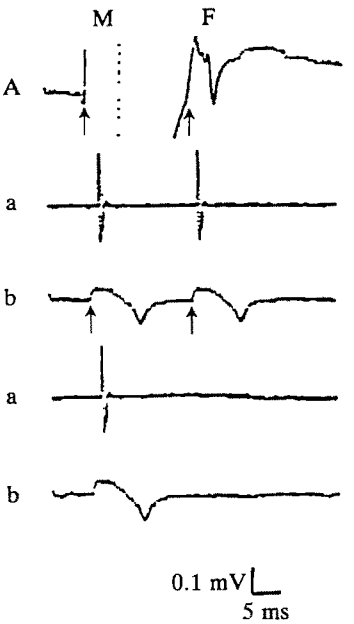

FIG 6 Comparison of the latency of the fastest single motor unit F response obtained with threshold stimulation with the minimum conventional F wave latency evoked by 60 supramaximal stimuli. M and F as in fig. 2. Stimulation of the ulnar nerve at the elbow, recordings from the abductor digiti minimi of subject 8 (Table 6) A = compound muscle action potential and minimum F wave latency evoked by 60 supramaximal stimuli The fastest single motor unit M evoked by 200 threshold stimuli, with and without its F response, as recorded by a BNE (a) and by SE (b), is shown. Note that the latency of the SE recorded single motor unit M is similar to that of the CMAP, and that the latency of the SE recorded F response of that unit is within 0.2 ms of the minimum F wave latency recorded by the conventional method in A (arrows)

Group IV

The peak-to-peak amplitudes of each V-SU, each F wave and of the CMAP in each subject were measured The number of MUs contributing to the CMAP was estimated in each subject by dividing the amplitude of the CMAP by the mean amplitude of the V-SUs (Brown *et al.*, 1988).

Average number of motor units per conventionally recorded F wave. Two estimations were made. (1) Division of the mean amplitude of the F wave (taking each absent potential as zero) by the mean amplitude of the V-SUs in each subject of group IV. In the pooled data the mean amplitude of the F wave as a percentage of the CMAP was divided by the mean amplitude of the V-SUs, again expressed as a percentage of the amplitude of the CMAP. (2) Using pooled data, the mean F wave amplitude as a percentage of CMAP amplitude for the subjects in group IV was divided by the same measure for the 34 F-SUs recorded in group III subjects. The Discussion considers the limitations of these estimations.

Statistics. Comparisons of the pooled data for different parameters in successive groups of F waves and of repeater and nonrepeater responses were made with a Kruskall-Wallis analysis of variance (ANOVA). Comparisons of the parameters of the pooled F waves in different, randomly selected, sample sizes with the total sample of 100 stimuli obtained in each of 11 subjects, were made with the Mann-Whitney U test. This test was used for comparison of samples. For correlations, the Spearman rank coefficient was used.

RESULTS

Group I

The time series and the effect of sample size on the F wave parameters. This was studied in the first 11 subjects of group I as follows. (1) First, amplitude, area, latency and duration of successive F waves, evoked by 100 consecutive stimuli were each considered a time series. An autocorrelation function of lag 1 showed no significant variation over time for any of them (i.e., no last period time dependency) either in each individual or in the group means. Secondly, these parameters and F wave frequency were analysed separately for the F waves evoked by 5 successive groups of 20 stimuli; there were no significant differences for any of them in any subject, or in all 11 when all the F waves were pooled (ANOVA) (not illustrated). (2) The parameters of the F waves evoked by randomly selected 60, 40, 20 and 10 (and 5 for latency) stimuli were then analysed separately and the results were compared with the F waves evoked by 100 stimuli. In 10/11 subjects the minimum F wave latency with 60 stimuli was within 0.5 ms of that obtained with 100 (Table 1). The minimum latency increased and maximal amplitude and chronodispersion decreased as the sample size decreased. These changes were small when comparing the F waves evoked by 100 and by 60 stimuli (Table 2). The F waves evoked by 60 stimuli in group I subjects were therefore used for a more detailed analysis of their latency distribution, frequency of F waves and F wave repeaters.

TABLE 1 MINIMUM F WAVE LATENCY OVER THE ABDUCTOR DIGITI MINIMI MUSCLE WITH DIFFERENT SAMPLE SIZES GROUP I

	Random samples				
ms	*60*	*40*	*20*	*10*	*5*
<0 5	10	8	7	5	1
<1 0	11	9	9	7	1
<1.5		11	11	10	7
<2 0				11	9
<2 5					10
<3.0					11

Number of subjects (total = 11) showing the stated differences (in ms) between their minimum F wave latency, obtained with 5–60 randomly taken stimuli, and that obtained with 100 stimuli.

F wave latency and estimated conduction velocities. In order to establish the range and the frequency distribution of the CVs of the motor fibres mediating F waves, we analysed 33 individual subjects and 1692 pooled F waves.

Individual subjects. Range. The group mean chronodispersion was 5.5 ms (range 3.7–10.8). Table 3 shows approximately similar ranges of F wave CVs in our 33 subjects and in peripheral nerves studied by others with F wave and other methods.

Distribution. The raw F wave latencies were skewed towards shorter latencies in 23/33 subjects and were normally distributed (6/33) or skewed towards longer latencies (4/33) in the others. The distribution of relative pooled individual F wave CVs is shown in fig. 7 (top right): 98% of the F wave CVs were within 10 $m \cdot s^{-1}$ of the respective

TABLE 2 VARIATION IN F WAVE PARAMETERS WITH RANDOMLY SELECTED SAMPLE SIZES*

	Random samples taken from 100 stimuli					
	100	*60*	*40*	*20*	*10*	*CoV*
Latency (ms)						
Median	29.6±2 6	29.6±2 6	29 7±2 7	29.5±2 5	29.8±2.4	0 8±0 6
Minimum	27.4±2.4	27.5±2.5	27.9±2 6	28.0±2 5	28.7±2.4	1.6±1.0
CHD	6 6±1 8	6.2±1.2	5 4±1 2	4.1±1 3	3 5±1.2	24 7±13 0
Amplitude (μV)						
Median	0.18±0 6	0.18±0.1	0.18±0 1	0 17±0 1	0.17±0.1	11.0±7.3
Maximum	0.6±0.24	0 56±0.24	0.54±0 26	0 42±0.16	0.38±0.15	21 7±10
F frequency (%)	83 0±14 3	83.6±14 7	83 8±13.3	83.6±17.3	86 3±15 6	4 4±2.6
Repeater shapes (%)	11.2±4.9	9.8±5.7	8.7±4.5	5.7±6.0	1.2±3.8	74 2±36 0

* Recordings over the abductor digiti minimi of 11 subjects of group I who received 100 stimuli at 1 Hz For each parameter, the group mean±SD are given. CoV = coefficient of variation for each parameter when different sample sizes were used CHD = chronodispersion.

TABLE 3 SPECTRUM OF ESTIMATED CONDUCTION VELOCITIES OF MOTOR FIBRES IN SINGLE PERIPHERAL NERVES. COMPARISON OF F WAVE WITH OTHER METHODS

				Individuals (group mean±SD)			*Pooled data*	
Method	*Muscle*	*n*	*Age (yrs)*	*Min*	*Max*	*Range*	*Min*	*Max*
F wave								
Present study	ADM	33	20–81	46 9±3 9	57 2±4 7	10 3±2 6	35 4	65 0
Burke *et al* (1989)	APB	10	21–43	50 4	59 2	8 8	45 4	64 6
Schiller *et al* (1979)	ADM	–	–	–	–	–	37 0	76.0
Collision								
Hopf (1962)[1]	ADM	20	20–45	–	–	5 3±0 9	49 0	65 0
Skorpil (1965)[2]	ADM	33	–	43.4±2 9	60 1±2 9	17 8	–	–
Leifer *et al* (1977)[3]	ADM	16	21–53	46 6±1 7	59 1±2.8	12 5±2 06	–	–
Shahani *et al.* (1980)	ADM	10	–	44 5±3 5	61 4±5.6	17 9±3 5	–	–
Dorfman (1984)[4]	APB	10	22–56	36 6±5 5	49 7±3 0	11 8±2.7	31 0	61 0
Ingram *et al.* (1987)[5]	ADM	6	22–44	50 6±3 6	59 3±3 8	8 7±2 4	46 1	62.2
	APB	20	19–59	52 7±3 1	59 1±3 0	6 4±1 4	42 8	63 6
Deconvolution of 2 CMAPs								
Dorfman (1984)	APB	10	22–56	37 8±3 7	49 6±3 8	13 2±4.0	35 0	61 0
Reconstruction of CMAP								
Lee *et al* (1975)[6]	APB	4	27–37	–	–	–	42 6	60 0
Single units								
Juul-Jensen and Mayer (1966)	ADM	17	20–50	–	–	–	46 0	83 0
Borg *et al* (1978)	EDB	13	–	–	–	–	33 0	54 0

All CVs in m s^{-1} EDB = extensor digitorum brevis, ADM = abductor digiti minimi, APB = abductor pollicis brevis CMAP = compound muscle action potential – = data not available [1] Minimum and maximum CVs are defined using 10% and 90% response criteria [2] As quoted by Lee *et al* (1975). [3] Minimum and maximum CVs are defined using 1% and 99% response criteria [4] Maximum CV defined as values of CV above which 5% of the cumulative CVs fall, minimum CV defined as values of CV above which 95% of the CVs fall. [5] Based on 5% (maximum CV) and 95% (minimum CV) of the test response [6] Maximum CV was recorded, minimum CV was calculated from the best fit for the CMAP reconstructed with a mean single unit potential obtained by a spike-triggered averaging technique

individual maximum F wave CV. A comparison of the proportion of faster CVs estimated from surface recorded F waves with that obtained from peripheral nerve studies shows that the percentage of CVs within 10 or 20% of the maximum CV obtained by other methods falls below 2 SD of the group mean obtained in our 33 subjects (Table 4); fig. 7 (top left) shows the distribution of the percentages used to calculate this group mean.

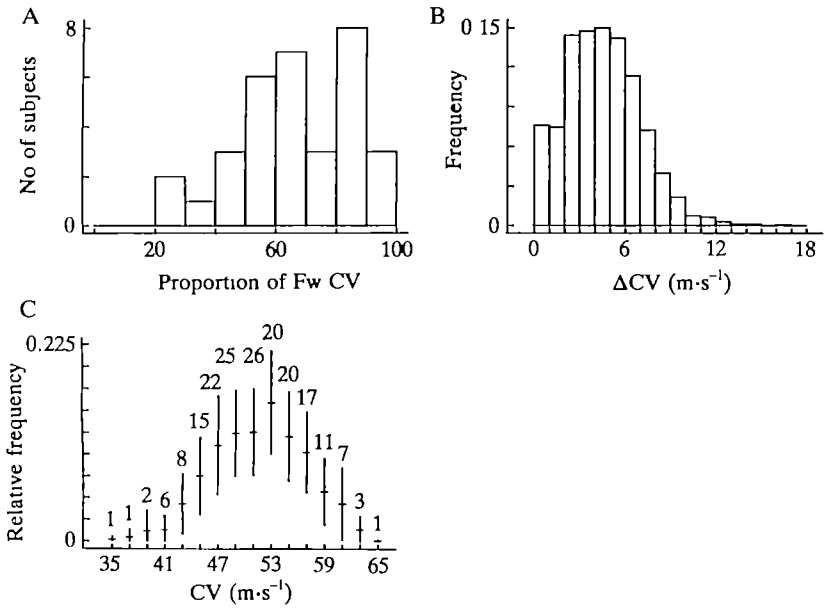

FIG 7 Distribution of F waves (Fw) estimated conduction velocities (CVs). Group I. A, distribution of the proportion of estimated F wave CVs (n = 1692) with values within 10% of that of their maximum CV in 33 subjects For example, in each of 8 patients 80–89% of their F wave CVs, evoked by 60 stimuli, are within 10% of their respective maximum F wave CV B, distribution of the difference in F wave CVs from the maximum F wave CV (standardized as 0 in each subject, *see* Methods) in 33 subjects. For example, each of the 98% F waves out of the total of 1692 had CVs within 10 $m \cdot s^{-1}$ of their subject's maximum F wave CV. C, relative frequency distribution of estimated F wave CVs (n = 1692) within the subject population range of F wave CVs (33 subjects). The group means and 95% confidence intervals are given. The number of subjects who had F waves with CVs within each 2 $m \cdot s^{-1}$ bin is also shown.

Pooled data. The range of F wave CVs is given in Table 3.

Distribution. Fig. 7C shows the relative distribution of all estimated F wave CVs, within the range of CVs found in the population of 33 subjects. A higher mean proportion of CVs within 10–20% of this population maximum was still found for F waves when compared with other methods (Table 4).

F wave amplitude

The distribution of F wave amplitude and area was skewed towards smaller values in each subject and in the pooled data. The median amplitude and area of the F waves correlated with the CMAP amplitude and area, respectively (n = 33, $r_1 = 0.62$, $r_2 = 0.55$, $P < 0.01$).

The F wave group mean amplitude and area as a percentage of the CMAP values in individual subjects were 1.47 (range 0.6–2.5)% and 1.1 (0.4–2.2)%, respectively. Both correlated with age (n = 33, $r_1 = 0.55$, $r_2 = 0.51$, $P < 0.05$).

There was a weak but significant negative correlation between the pooled estimated CVs (n = 1692) and the amplitude as a percentage of CMAP amplitude and the duration of individual F waves ($r_1 = 0.28$, $r_2 = 0.33$, $P < 0.001$).

TABLE 4 PERCENTAGE OF MOTOR FIBRE CONDUCTION VELOCITIES (CV) THAT ARE WITHIN 10% AND 20% OF THE MAXIMUM CV IN SINGLE PERIPHERAL NERVES BY DIFFERENT METHODS

Method	*Author*	*n*	*Muscle*	*10%*	*20%*
Individuals					
F wave	Present study	33	ADM	65.7±19 4	98.3±5 3
				92 6±10 3*	99.8±0 85*
Single units	Borg *et al.*, 1978 (fig. 3)	1	EDB	25 9	74.0
		1		31 0	75 9
		1		34 9	76 7
Collision	Dorfman, 1984 (fig. 5)	1	APB	17 7*	60 8*
Pooled					
F wave	Present study	33	ADM	13.3±20 3	59 8±37 1
				25.3±23 2*	68 8±35 4*
Collision	Dorfman *et al.*, 1982 (fig 5c)	8	APB	1.8±2.8*	29 7±25 0*
Deconvolution	Ibid.			3 5±6.2*	30.2±13 1*

For individual subjects in our study, the group mean ± SD is given For abbreviations, *see* Table 3 * The maximum CV has been taken as the value of CV above which 5% of the cumulative distribution of CV falls To facilitate comparison with the data of Dorfman *et al* (1982) and Dorfman (1984), ours were also analysed in a similar way and the percentages taken from the maximum CV were 9.83% and 19.6% *See also* fig 2.

F wave frequency

The group I median F wave frequency was 88% (range 42 − 100). It was above 70% in 30 subjects. The occurrence of measurable F waves evoked by 60 stimuli was random. There was a weak correlation between F wave frequency and age ($n = 33$, $r = 0.47$, $P = 0.01$), but no relation between F wave frequency and amplitude expressed as a percentage of CMAP amplitude (median or maximum).

Repeaters

The mean percentage of repeater waves was 19.5% and that of repeater shapes was 9.9% (Table 5). Fig. 1 shows 4 repeater shapes in 1 subject.

TABLE 5 COMPARISON OF REPEATER AND NONREPEATER F WAVES RECORDED OVER THE ABDUCTOR DIGITI MINIMI MUSCLE OF 30 HEALTHY SUBJECTS (GROUP I)

	Nonrepeater	*Repeater*	*P**
% F waves[1]	80 5±8 1	19.5±8.1	
% F wave shapes[2]	90 1±4.4	9 9±4 4	
% occurring twice		78.6±25.3	
3 times		18 7±25 1	
4 times		2 2±5 7	
≥ 5 times		0 4±2.2	
Latency (ms)[2]	29.6±2.1	29.5±2.6	n s
F wave CV ($m \cdot s^{-1}$)[2]	52.3±4.7	51 8±3 5	n.s
Amplitude (mV)[2]	0.22±0.2	0 38±0 4	<0 001
Area ($mV \cdot ms^{-1}$)[2]	0.6±0 6	0.9±1 0	<0 001
Duration (ms)[2]	10.8±3 4	10 6±3 4	n.s.

Mean ± SD are given for each parameter. n s = not significant. [1] Computed from a total of 1556 F waves. [2] Computed from a total of 1398 F wave shapes * ANOVA

The occurrence of repeater waves was random throughout the 60 consecutive stimuli and their frequency of occurrence was independent of their latency. There was no relation between the percentage of repeater waves and age.

Repeater shapes were compared with nonrepeaters to find out if they indexed particular groups of motor units. The repeater shapes had larger amplitude and area and a larger amplitude as a percentage of CMAP amplitude, but latency, F wave CV and duration were similar in the two groups (Table 5, fig. 8).

The intervals between repeaters of any shape had a unimodal distribution (median 3 s, range 1–27 s). The distribution of the intervals between the repeaters of the same shape showed at least 4 peaks; the majority occurred at intervals of less than 10 s (fig. 8). This distribution was similar when only the first interval of repeater shapes occurring more than twice was considered. There was no significant difference in amplitude as a percentage of CMAP amplitude between the repeaters of these 4 groups.

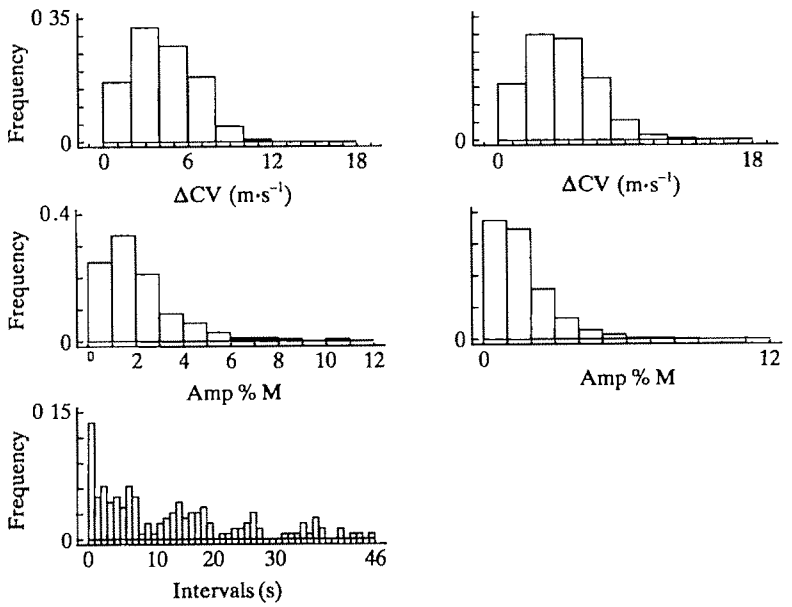

FIG 8 Group I. The top 4 histograms show the relative frequency distribution of the amplitude, expressed as a percentage of the CMAP amplitude, and estimated CV of repeater (*left*, n = 136) and nonrepeater (*right*, n = 1262) F wave shapes Each F wave CV is expressed in each subject as its difference from the fastest F wave in that subject. The lowest histogram shows the relative frequency distribution of intervals (n = 160) between F wave repeaters of the same shape in 30 subjects

Group II

F waves were evoked with all 60 stimuli in all subjects of group II using a higher gain (fig. 1). The group median 16% of F waves (range 0–32) with amplitudes below 40 μV was similar to the percentage of absent responses when a lower gain was used. The minimum F wave amplitude was 8–40 μV in 12 subjects and more than 40 μV in 3.

Group III

Single unit, surface recorded, orthodromic (M-SUs) and F (F-SUs) potentials. Orthodromic (M) surface recorded responses that were identical to their F responses, and appeared in an 'all-or-none' manner similar to their constantly associated BNE potentials (n = 8, 6 subjects), could safely be considered surface recorded single MU orthodromic potentials (M-SUs); their F responses were therefore also considered single MU F surface potentials (F-SUs). Three late surface potentials identical to 'all-or-none' M-SUs occurring separately, i.e., not simultaneously with the same stimulus, were identified in 2 subjects; they were also accepted as F-SUs (fig. 2).

When the morphology of the surface orthodromic response was different from that of the associated single unit F response, the late surface potentials that strictly and repeatedly occurred only when the BNE recorded single unit F response occurred were also considered to be F-SUs (fig. 3). This assumption seemed reasonable since the mean surface amplitude of these units (72 μV; n = 23, 7 subjects) was not significantly different from that of the 11 units mentioned above (104 μV); the mean CV of their F responses (58.5 and 57.1 $m \cdot s^{-1}$), and stimulus intensity (8.9 and 9.1 mA), were similar in the two groups.

In each of 6 subjects an F-SU identical to the M-SU with the latency closest to that of the CMAP could be identified. The mean latency of these M-SUs was indeed nearly identical to the mean latency of the CMAP (Table 6). The minimum latencies of the F wave evoked by 60 stimuli in the same subjects were all within 0.8 ms of the latency

TABLE 6 SINGLE MOTOR UNIT AND CONVENTIONAL F WAVE STUDIES IN THE ABDUCTOR DIGITI MINIMI IN GROUP III

		BNE units				*SE units*				*Conventional*	
		M	*F*			*F-SU*			*M-SU*	*CMAP*	*Fw*
Subject	*Age/sex*	*n*	*n*	*CV min.*	*CV max.*	*n*	*Amp.*	*Lat.*	*Lat*	*Lat.*	*Min. lat*
1	38/M	38	22	53.2	63.6	4	125	22.8	7 4	6 8	22.8
2	54/M	32	19	55.2	60 8	7	47	24.8	7 6	7 6	25 0
3	23/F	12	7	50 6	54.8	5	109	22.4	6 8	6 8	22 6
4	24/M	24	12	52 7	60 9	9	102	22.4	8.4	8 4	23 2
5	26/M	17	7	54.3	66.7	1	25	NI	NI		
6	25/M	24	7	58.1	72 9	3	70	NI	NI		
7	46/M	20	4	54.5	59 2	3	77	23 4	8 2	8.0	24.2
8	25/M	12	3	55.8	56 8	2	39	25 6	7 0	6.8	25 8
Total		179	81			34		6	6	6	6
Mean	33	22	10	54 3	62.0		*83	23 5	7.5	7 4	23 9
SD	11	9	7	2 2	5 8		64	1.3	0 6	0 7	1.3

Age in years BNE = bipolar needle electrode. SE = surface electrode. M = orthodromic motor units; n (column 3) = number recorded F = single unit F responses; n (column 4) indicates the number of motor units tested with at least one F response. CV min. and max. = conduction velocity of the slowest and the fastest BNE recorded unit F response M-SU = surface recorded orthodromic single motor unit potentials; the latency (Lat) of the fastest is given in each subject. F-SU = surface recorded single motor unit F responses; the number identified (n), their mean amplitude in μV (Amp) and the latency of the F-SU associated with the fastest M-SU are given for each subject. Conventional = the latency to the onset of the compound muscle action potential (CMAP) and the minimum latency of the F waves evoked by 60 supramaximal stimuli at 1 Hz, and recorded with SE, are given. * Mean and SD of the pooled data NI = no single unit F responses could be identified with SE in these subjects Latencies in ms.

of the surface single unit F response (F-SU) associated with the fastest M-SU. In 4 of them the fastest F waves were within 0.2 ms of the respective F-SU (Table 6, fig. 6).

The mean amplitude and amplitude as a percentage of CMAP amplitude of the F-SUs in the pooled data (n = 34) were 83.6 μV (range 25−260) (Table 6) and 0.75% (0.18−3.6), respectively, and are close to those obtained for single voluntary MU potentials in group 4 (*see below* and Table 7).

No relation was found between the amplitude, amplitude as a percentage of CMAP amplitude, or latency, of the 34 F-SUs, and their CV (as calculated from the respective BNE recordings).

TABLE 7 ESTIMATION OF THE NUMBER OF MOTOR UNITS PER F WAVE IN THE ABDUCTOR DIGITI MINIMI OF GROUP IV SUBJECTS

Subject	*Age/sex*	*CMAP*	*S-VU amp.*	*F wave amp.*	*Tot. MU*	*M/Fw*
1	38/M	15 6	123 1±16	272 6±26	126.6	2.2
7	46/M	11.3	63 9±7	236.3±16	176 9	3 7
9	55/F	18 8	207 4±27	269 1±35	90.6	1 3
10	33/M	14.0	77.5±10	207.1±21	180 7	2.7
11	29/M	12 5	76 6±11	110 6±12	163 1	1 5
12	22/F	14.6	48.7±11	383.2±39	299 7	7.9
13	23/M	12.0	131 8±27	188.2±12	91.1	1 4
14	53/F	13 8	120.1±19	191.0±20	114 8	1.6
Mean	37 3	14.1	106.1	232 3	155 4	2 8
SD	12 8	2 4	50.9	80 1	68.4	2.2

Age (yrs). CMAP = compound muscle action potential amplitude (mV) S-VU amp = mean ± SE amplitude (μV) of 18−20 surface recorded voluntarily activated single motor unit potentials F wave amp = mean ± SE amplitude (μv) of 54−60 F waves evoked by 60 supramaximal stimuli at the wrist Tot MU = estimated total number of motor units contributing to the CMAP MU/Fw = estimated average number of motor units contributing to each F wave.

Spectrum of single unit F conduction velocities and relationship with single unit F frequency. The range of single unit F CVs of the 81 BNE recorded units in the 8 subjects is given in Table 6. Fig. 5 shows the MUs with the fastest and the slowest single unit F CV in 1 subject.

The distribution of single F CVs, in individual subjects and in the pooled data, was skewed towards faster CVs. When each single unit F CV in each subject was expressed as its difference from the respective maximum single unit F CV and the data were pooled, 72% and 93% of the CVs were within 5 and 10 $m \cdot s^{-1}$ of the individual's maximum CV, respectively (fig. 9). There was a significant positive correlation between the single unit F CVs of single MUs and the number of single unit F responses that they produced with 200 stimuli (fig. 9).

Stimulus intensity and single unit F conduction velocity. There was a trend for MUs with slower single unit F CV, and for those which did not produce a single unit F response, to require higher stimulus intensities.

The mean variable surface recorded M response during threshold stimulation expressed as a percentage of CMAP amplitude in MUs with a BNE recorded single unit F response, indexing the proportion of the pool stimulated during threshold stimulation of single

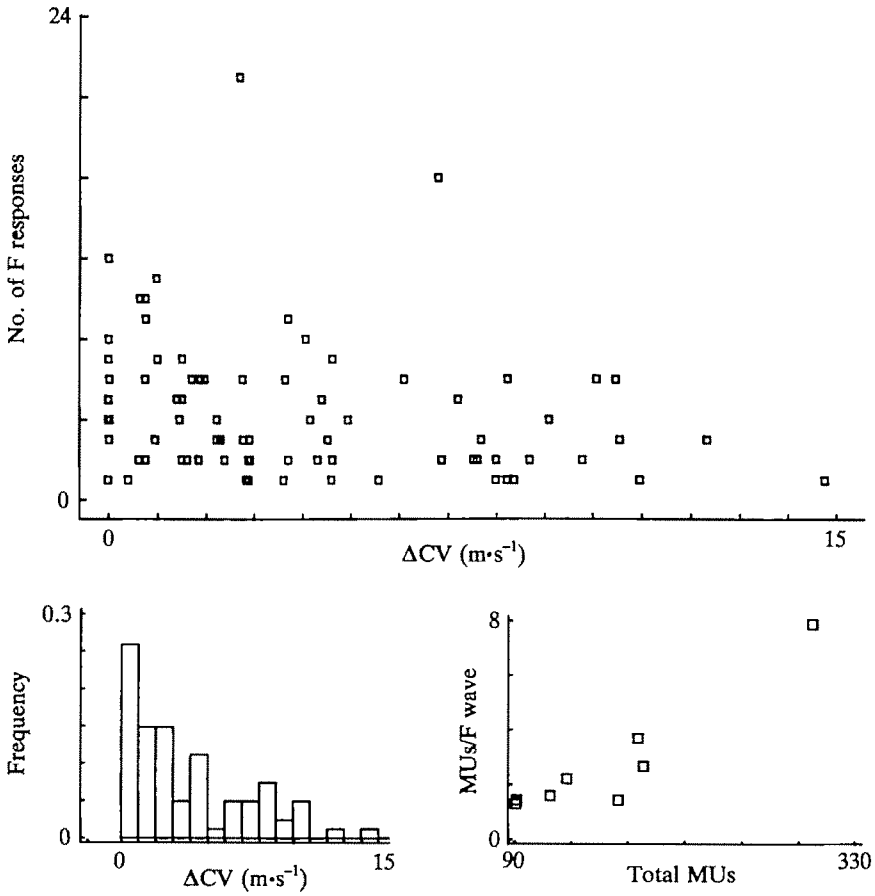

FIG. 9. *Top*, plot of single unit F CV against the number of responses seen in 81 out of 179 BNE recorded motor units tested in 8 subjects of group III, that produced at least one F response during 200 threshold stimuli at 1 Hz ($r = 0.35$, $P = 0.002$) X axis CV of single F units expressed, for each, as its difference from the respective maximum F CV in each subject. Y axis: number of F responses produced by each of the units. *Bottom left*, frequency distribution of conduction velocities in 81 BNE recorded F single units The CVs are expressed as in the top plot. *Bottom right*, relation between the estimated total number of motor units contributing to the compound muscle action potential of abductor digiti minimi (total MUs) and the estimated average number of motor units contributing to each conventionally recorded surface F wave (MUs/F wave) in the 8 subjects of group IV ($r = 0.9$, $P < 0.05$). *See also* Table 7

MUs, was 3.5% (range 0.3−9). This value was lower in MUs with faster CVs ($n = 81$, $r = -0.25$, $P < 0.05$).

Single unit F frequency. A group mean of 42% (range 20−59) of the BNE recorded MUs in the 8 subjects produced a group mean of 4.5 (1−21) F per 200 stimuli. The group mean percentage of single unit F responses per stimulation in all tested orthodromic MUs in individual subjects (including the MUs which did not produce a single unit F response) was 0.95 (range 0.15−1.5)%. In the pooled data, of the 81 BNE recorded MUs that gave single unit F responses, 69% produced 1−5, 26% 5−10 and 5% more

than 10 responses. BNE recorded single unit F responses occurred randomly and sometimes in pairs or groups.

Conventionally recorded F waves. Table 6 shows the minimum latency in each subject.

Group IV

Table 7 shows the amplitude of the CMAP, the mean amplitude of the V-SUs, the mean F wave amplitude, the estimated number of MUs contributing to the CMAP and of MUs per F wave in each of the 8 subjects.

Surface recorded voluntary single motor unit potentials (V-SUs) (fig. 4) were always detected when there was a suitable triggering spike. The mean amplitude as a percentage of CMAP amplitude of V-SUs in the pooled data (n = 158) was 0.73 (SD 0.57, range 0.02−4.4)%.

Conventionally recorded F waves. Their frequency ranged from 93.3 to 100%. In the pooled data (n = 480) the mean amplitude and the amplitude as a percentage of CMAP amplitude for surface recorded F waves were 233.8 (SD 206.7, range 0−1530) μV and 1.7 (SD 1.4, range 0−8.1)%, respectively.

Average number of motor units per F wave

The group mean number of MUs per F wave, estimated by dividing the mean surface amplitude of the F wave by the mean amplitude of the V-SUs in group IV subjects, was 2.8 (Table 7). Using the pooled data, a value of 2.3 was obtained when the mean F wave amplitude as a percentage of CMAP amplitude in group IV was divided both by the mean V-SU amplitude as a percentage of CMAP amplitude and by the same measure of the F-SU recorded in group III. There was a positive correlation between the estimated number of MUs contributing to the CMAP and the average number of MUs per F wave in group IV subjects (fig. 9).

DISCUSSION

Repeated antidromic activation of motor neurons at 1 Hz does not by itself lead to significant changes in F wave parameters. The mean or median values of latency, duration, amplitude and area showed no significant difference in randomly selected samples of as small as 10 stimuli compared with 100. For minimum latency and F wave frequency the results with 10−20 stimuli were fairly close to those with 100. For the assessment of chronodispersion, maximum amplitude and percentage of repeaters, F waves should be obtained from at least 60 stimuli. Single unit F responses were observed in 45% of the BNE recorded single MUs tested, with a maximum of 21 per 200 stimuli, as reported in other studies with single fibre or surface electrodes and threshold stimulation (Schiller and Stålberg, 1978; Yates and Brown, 1979).

F wave amplitude

The amplitude of surface recorded F waves may be influenced by (1) factors affecting the amplitude of the potentials of individual MUs, such as their complement of muscle fibres and the cross-sectional area and size of the active membrane potential of their individual muscle fibres; (2) the number of MUs contributing to each F wave and their

temporal dispersion; (3) recording variables such as the type, location and distance of the surface electrode from the sources, and the skin and soft tissue thickness (McComas *et al.*, 1971). The relatively larger amplitude (and duration) of the faster F waves could be related to larger component MUs and/or to a larger number of MUs in each faster F wave. The lack of a relation between amplitude and latency of surface recorded single unit studies of M (McComas *et al.*, 1971) and of F responses (Feasby and Brown, 1974; Yates and Brown, 1979) suggests that the second alternative may contribute more to the larger amplitude of the faster F waves.

The group mean amplitude as a percentage of CMAP amplitude at 1.47% is close to that found by others (Eisen and Odusote, 1979; Kimura *et al.*, 1984). This calculation assumes that CMAPs and F waves are formed by algebraic summation of the component MUs, which may not be entirely true for ADM (Sica *et al.*, 1974). The group mean area as a percentage of CMAP area at 1.1% should be nearer to the real figure, since it takes into account the temporal dispersion, although other factors, such as the relative distance of each component MU from the motor endplate, cannot be controlled.

F wave frequency

The range found was similar to, or greater than, other studies (Morimoto, 1980; Peioglou-Harmoussi *et al.*, 1985*b*; Mcleod, 1986).

Since F wave frequency is defined as the percentage of responses above a certain amplitude, factors that change the amplitude of F waves may affect the measurement (*see above*). Ideally F wave frequency should be measured using a gain that allows the detection of single MU potentials. The finding of 100% F wave frequency in all subjects of group II when a higher gain was used, suggests that the apparent absence of responses for a proportion of the stimuli used in group I relates to the recording technique.

F wave frequency also depends on the total number of functioning motor neurons and on central, segmental or suprasegmental, factors changing their excitability. The weak correlation between F wave frequency and age found in group I indicates a larger number of F waves above 40 μV with increasing age. The larger mean amplitudes and areas as percentages of the CMAP values seen with increasing age is consistent either with collateral reinnervation, leading to larger MUs in each F wave, or with a higher excitability of the motor neuron pool, with more MUs, or more synchronous MUs in each F wave (Peioglou-Harmoussi *et al.*, 1985*a*). The reported diminution in the total number of motor neurons with age (Sica *et al.*, 1974) could result in a reduction in F wave frequency. The net effect may depend on the relative contribution of each of these factors.

Average number of motor units per F wave

Up to 3 MUs have been identified in a late response with BNE recordings (Thorne, 1965). An estimated average of 2–3 MUs contributed to each conventionally recorded F wave in our study. In spite of the criticisms discussed below, the two methods we used gave similar results. The first, division of the mean F wave amplitude by the mean amplitude of voluntary single MUs recruited at low levels of force, can be criticized as follows. (1) F wave amplitude will be affected by the temporal dispersion of the component single MU potentials whose amplitudes do not necessarily summate algebraically; this may lead to underestimation of the number of MUs per F wave;

(2) the contribution of hypothenar muscles other than ADM to the F wave is not known; this would result in an overestimation of the number of MUs per F wave in that muscle; (3) during isometric contraction, at low levels of force, smaller MUs are sampled more often than larger ones (Milner-Brown *et al.*, 1973; Hannerz, 1974), while larger MUs may be preferentially recorded in F waves (*see below*); the net effect would be an overestimation of the number of MUs per F wave. The second method, division of the amplitude of F waves as a percentage of CMAP amplitude mean in group IV by the mean amplitude, again as a percentage of CMAP amplitude, for the 34 surface recorded single unit F responses in group III, can also be criticized. The points made about F waves also apply. The sample of surface single unit F responses is small and may be biased towards the larger and faster MUs recorded during threshold stimulation; this would result in an underestimation of the number of MUs per F wave. It could also be argued that the potentials considered as F-SUs could include single unit F potentials from other MUs which have the same threshold, and repeatedly produce single unit F responses at the same time as the late MU recorded with the BNE. The following considerations argue against this possibility. (1) The mean amplitude of the 34 F-SUs was not significantly different from the amplitude of surface recorded units by an independent method (group IV, Results). (2) If the proportion of the pool stimulated with threshold stimulation is indexed by the surface M responses recorded with these 34 F-SUs (mean 0.29 mV, SD 0.2), and the whole pool is indexed by the CMAP, an average of 2.5% (SD 2.3) of the MUs of the pool was stimulated antidromically, each time an F-SU was associated with a BNE potential. If the MUs generating a single unit F discharge independently from each other, the chance of the same 2 MUs consistently contributing to the F-SU seems remote. (3) The possibility that the late surface response represents the associated discharge of 2 or more MUs by a mechanism similar to that of repeaters also seems unlikely; the mean amplitude of the 34 F-SUs was not significantly higher than that of the surface voluntary single MUs (V-SUs) in group IV (Tables 6, 7). The total number of MUs contributing to the CMAP reported here is lower than that found with graded stimulation and surface recordings over the hypothenar region (Sica *et al.*, 1974). With both techniques the relative contribution of MUs of hypothenar muscles other than ADM to the CMAP recorded is not known. The spike-triggered surface unit potentials may be claimed to be a sample of single MUs of ADM, and not of other hypothenar muscles, but the previous point about algebraic summation of component MUs still applies. Physiological and anatomical estimations of the number of MUs in ADM are not in agreement either (Sica *et al.*, 1974; Santo Neto *et al.*, 1985; this paper).

Estimated F wave and single unit F conduction velocities

The latency difference between proximal and distal stimulation was similar for the M and F responses, indicating that the antidromic CV of the F wave is the same as the orthodromic CV of the M potential in a given nerve segment (Kimura, 1974). The MCV was reported to be similar to the CV of the F wave with the shortest latency (Barwick and Fawcett, 1988). Single unit studies addressing this point are not available. Our results support the assumption (Burke *et al.*, 1989) that the MU indexed by the latency to the onset of the CMAP, or by peripheral nerve MCV, is often the same as, or has a similar CV to, the fastest F wave evoked by 60 supramaximal stimuli. They

validate our use of MCV to study the distribution of F wave CV. The mean latency of the fastest surface recorded orthodromic single units was similar to that of the CMAP. The mean latency of the associated surface recorded single unit F response was only 0.4 ms shorter than that of the fastest F wave in the same 6 subjects.

The exclusion of the distal segment of the ulnar nerve in the calculation of the single unit F CVs may account for the higher maximum F CV found by us as compared with the maximum CV calculated by conventional methods (Thomas *et al.*, 1959; Kimura, 1974). A proximal-distal decrease in the average axon diameter of the fastest conducting motor fibres, due to branching and tapering may be implicated (Trojaborg, 1964).

A relation between maximum tetanic tension, axon diameter of MUs, and the CV of their axons was found in animals (Hursh, 1939; McPhedran *et al.*, 1965; Wuerker *et al.*, 1965). The lack of a relation between the CV and the surface amplitude of single MU F responses agrees with studies in human thenar and hypothenar muscles (Feasby and Brown, 1974; Yates and Brown, 1979) and may depend on factors that affect the amplitude of surface recorded units, such as the location of the MU in relation to the recording electrode, and others discussed above. In contrast, the single unit F CVs, calculated by using the M-F interval, are not affected by the distance between the BNE and the sources of the single MU potentials recorded. Similarly, the lack of a relation between threshold stimulus current and single unit F CV may relate to variations in the location of the stimulating electrode, and in the skin and soft tissue thickness, in different subjects. However, the significant negative correlation between the proportion of MUs in the pool activated by threshold stimulation (indexed by the variable surface recorded M response as a percentage of the CMAP) of a BNE recorded single F unit, and the CV of the latter, suggests indirectly that the faster MUs had a lower stimulation threshold.

The estimated range of CVs based on the range of F wave latencies in individual subjects was fairly close to the range of CVs for motor fibres in a single ulnar nerve calculated by some authors (Thomas *et al.*, 1959; Leifer *et al.*, 1977) and less (Skorpil *et al.*, 1965 cited by Lee *et al.*, 1975; Shahani *et al.*, 1980), and greater than that reported by others (Hopf, 1962; Ingram *et al.*, 1987). The spectrum of CVs in the pooled F wave data was comparable with that reported for the ulnar nerve by others (Table 3). Despite the limitations of the different techniques used (Dorfman, 1984; Ingram *et al.*, 1987), these comparisons, and the findings in other nerves (Table 3), indicate that motor fibres with a wide range of CVs contribute to the F waves evoked by 60 stimuli. With a collision technique it was shown that F waves are also produced by slower conducting motor fibres when the faster ones are blocked (Kimura *et al.*, 1984).

If (1) the CVs of individual motor fibres in a single peripheral nerve are normally distributed, (2) the latencies of recurrent responses mediated by any axon are equally measurable and (3) all the motor neurons have an equal chance of generating F waves, then a similarly normal distribution of F latencies and CVs would be expected. Equally, the relative percentage of F CVs within, say, 10–20% of their maximum CV, should be similar to that of the CVs of the motor fibres of a peripheral nerve. The higher frequency of faster F CVs in individual subjects, and the higher mean percentage of F CVs near the maximum CV in the pooled data, could be explained by one or more of the following.

1. *Larger number of axons with faster conduction velocities.* There is no firm evidence to support this. In one study the majority of the motor fibres to ADM in single subjects had CVs within 15–20% of the maximum, with a lower limit of 40% below the maximum CV (Thomas *et al.*, 1959). With recordings over ADM (Hopf, 1962; Leifer *et al.*, 1977; Domingue *et al.*, 1980), extensor digitorum brevis (Borg *et al.*, 1978) and abductor pollicis brevis (Dorfman *et al.*, 1982; Dorfman, 1984; Ingram *et al.*, 1987), the CVs followed a nearly normal distribution both in individual subjects and in the pooled data. Pooled data from unit studies in cat gastrocnemius and soleus muscles showed a slight shift towards faster CVs and larger axon diameters (Eccles and Sherrington, 1930; McPhedran *et al.*, 1965; Burke *et al.*, 1973). The size of anterior horn cells at C6, in human individuals (Tsukagoshi *et al.*, 1979) and in the ulnar nerve nuclei of the cat (Fritz *et al.*, 1982), was normally distributed. There is a direct relationship between motor neuron size and both axon diameter and CV (Hursh, 1939; Cullheim, 1978). The distribution of putative alpha motor neuron size and of motor axon diameter in man has been relatively normal (Dyck *et al.*, 1979), though the exact end-point towards smaller axon diameters can only be determined approximately.

2. *Greater chance of detection of faster F waves.* This discussion has treated F waves as consisting of one MU since the latency is measured to the onset of the signal. This assumption has been made before (Burke *et al.*, 1989). However, on average, 2–3 MUs contributed to each F wave. Thus the latency of the 2 slower component MUs is not considered. This might explain the higher frequency of F waves with shorter latencies. This possibility may not fully account for our findings, as discussed below.

From the data of Dorfman *et al.* (1982) it can be calculated that the fastest conducting fibres, defined as those with CVs within 10% of the maximal MCV, may constitute about 20% of the total number of motor fibres of a peripheral nerve. Fig. 10 shows the theoretical relation between the number of component MUs in a surface recorded F wave and the expected probability of at least one of them belonging to the 10 to 50% fastest MUs. This relationship is independent of how the proportion of MUs (and which MUs) within the pool is (are) defined as 'fastest'. If every F wave was a single MU, and each motor fibre had an equal chance of mediating an F wave, the probability of each F wave not belonging to the fastest 20% MUs would be 0.8. If each F wave contains the potentials of n MUs that probability would be $(0.8)^n$. Thus the probability of at least one of the n component MUs of each F wave to belong to the fastest 20% of the pool will be $1-(0.8)^n$.

The individual data in our 33 subjects showed that a group mean of 65% of the F wave CVs were within 10% of the fastest CV, whilst the expected figure, for 3 MUs in each F wave, would be 49%. The calculation is only approximate since the number of component MUs in different F waves may vary and the 'absent' F wave responses have not been considered. Further, our pooled F wave data showed that the mean proportion of faster CVs was 2–3 times higher than that calculated from Dorfman's (1984) data, obtained using a collision or deconvolution technique.

It is also apparent from fig. 10 that chronodispersion within one nerve not only depends on the range of CVs of the motor fibres mediating the F wave but also on the number of component MUs of the surface recorded F wave. Thus in conditions which lead to higher excitability of motor neurons (e.g., spasticity), with a higher number of MUs

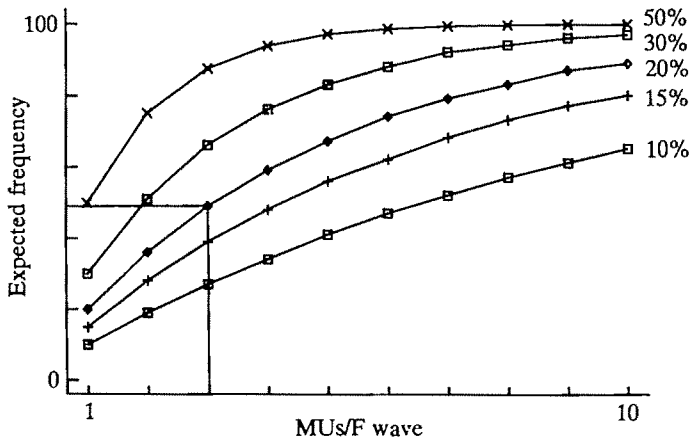

FIG. 10 Relation between the number of motor units in each F wave and the expected frequency of surface recorded F waves, containing at least one of the units belonging to various percentages of the fastest conducting ones within a pool. An equal chance of activation and recording is assumed for each motor unit. For example, if each F wave represents the activity of 3 motor units, the probability of at least one of them to belong to the fastest 20% units within the pool will be 49%.

per F wave, a smaller chronodispersion would be expected and has been reported (Komori *et al.*, 1981).

3. *Preferential generation of F waves by larger motor neurons.* The above discussion only suggests more frequent generation of F waves by faster MUs, and points to the difficulties in drawing firm conclusions based on the surface F wave recordings.

The distribution of CVs in single MUs of extensor digitorum brevis (Borg *et al.*, 1978), and in collision studies in the ulnar nerve (Hopf, 1962; Leifer *et al.*, 1977; Ingram *et al.*, 1987), has been normal. The shift in the distribution of BNE recorded single unit F CVs towards faster values could be related either to a sampling bias, with selective stimulation of larger MUs by threshold stimulation, and/or more frequent occurrence of single unit F responses produced by faster MUs. The smaller range of F CVs compared with other studies of single MU CVs, in subjects of similar age (Leifer *et al.*, 1977; Ingram *et al.*, 1987), is consistent with such bias.

The significant positive correlation between the CV of single MUs and the frequency with which they produce F responses, *within* the population of MUs sampled by threshold stimuli, has not hitherto been reported in man. It is consistent with the distribution of surface recorded F wave CVs and supports the interpretation that such distribution may also reflect more frequent generation of F waves by faster MUs. The lack of a relation between the surface amplitude of MU potentials, obtained with threshold stimulation, and the frequency of their single unit F discharge (Yates and Brown, 1979) is consistent with the lack of a relation between single MU F surface amplitude and CV.

What are the mechanisms underlying the more frequent occurrence of F waves (and single unit F responses) produced by faster MUs in conventional (and single MU) muscle recordings in man?

Evidence from animal studies. Recurrent discharges are produced if motor neurons (1) are antidromically activated and (2) there is enough delay of transmission across their axon-soma junction to permit repolarization of the nonmyelinated segment of the axon, where the recurrent discharges are produced and then propagate centrifugally (Brock *et al.*, 1953; Eccles, 1955). The resting excitability state of motor neurons depends on the balance of suprasegmental and segmental excitatory and inhibitory influences. With antidromic peripheral nerve stimulation, each motor neuron receives a variety of segmental excitatory (EPSP)and inhibitory postsynaptic (IPSP) potentials, including those mediated by sensory afferents (Eccles *et al.*, 1957; Fetz *et al.*, 1979), Renshaw cells (Renshaw, 1941; Willis, 1971) and direct connections from neighbouring motor neurons (Gogan *et al.*, 1977). Because of the wide range of CVs in both alpha motor neurons (Borg *et al.*, 1978) and afferent fibres (Burke *et al.*, 1983), the state of excitability of each motor neuron changes continuously during the arrival of antidromic impulses. The generation of recurrent responses by a motor neuron will depend on a critical range of membrane depolarization, at the time of arrival of the antidromic impulse at its axon-soma junction (Eccles, 1955). Recurrent responses can be prevented by excessive hyperpolarization leading to axon-soma blockage, excessive depolarization resulting in shortening of the axon-soma delay, and by collision of the antidromic impulse with an orthodromic discharge (Lloyd, 1943; Eccles, 1955).

Since recurrent responses, recorded in the muscle as F waves, occur in only about 1% of the motor neuron pool stimulated (Kimura *et al.*, 1984), the majority may be prevented by the above-mentioned mechanisms. The more frequent occurrence of faster F waves and single unit F responses, may relate to one or more of the following.

1. *Greater chance of axon-soma block in smaller motor neurons.* Renshaw cells can be activated by antidromic impulses via motor axon collaterals and generate IPSPs, leading to hyperpolarization, with axon-soma block, of neighbouring motor neurons in the same segment of the spinal cord (Eccles *et al.*, 1954, 1961). This recurrent inhibition is mainly exerted on smaller motor neurons (Eccles *et al.*, 1954, 1961; Granit *et al.*, 1957; Ryall *et al.*, 1972) but they are also efficient in producing it (Kato and Fukushima, 1974; Hultborn *et al.*, 1979). However, the inhibitibility of a motor neuron is directly related to its size (Henneman *et al.*, 1965*b*). In addition, some motor neurons in the cat exert a short latency excitatory influence upon close neighbouring neurons, either by an electrotonic interaction or through excitatory axon collaterals (Gogan *et al.*, 1977). There is evidence of direct connections between motor neurons by axon collaterals (Cullheim *et al.*, 1977).

The net effect of antidromic volleys on neighbouring motor neurons in the cat, depending on the motor nerve studied, was a 10–90% inhibition of motor neuron discharges, as measured by the efferent volley in a branch of a motor nerve, when preceded by an antidromic volley in another branch of the nerve to the same muscle (Renshaw, 1941). Using the range of CVs of alpha motor neurons in man (Borg *et al.*, 1978), and assuming a distance of 85 cm from the stimulus site to the cord, the time of arrival at the spinal cord of the impulses travelling in the fastest and the slowest motor axons should differ by about 14 ms. This time difference is well within the duration of the recurrent inhibition (Renshaw, 1941). There is indirect evidence that a similar pattern of recurrent inhibition is present in man (Veale and Rees, 1973; Pierrot-Deseilligny *et al.*, 1983). It would be expected that antidromic impulses in larger axons, arriving

at the cord earlier, will inhibit smaller motor neurons whose impulses arrive after the Renshaw cell inhibition generated by the larger neurons is established, and while it is still affecting these smaller neurons. This would lead to a greater chance of axon-soma block and a smaller chance of F production by the smaller neurons.

The importance of recurrent inhibition in preventing F production is suggested by the 2–3% of motor neurons that produced recurrent responses when the dorsal roots, and the spinal cord above the tested level, were sectioned in the cat (Renshaw, 1941).

2. *Greater chance of collision in smaller motor neurons.* When a peripheral nerve is stimulated supramaximally, afferent fibres are also activated. H waves in the small muscles of the hand were shown in a single fibre study (Trontelj, 1973). Ia afferent fibres will induce EPSPs by direct synaptic connections to motor neurons in the pool and Ia and Ib afferents will induce, shortly after, IPSPs via disynaptic and trisynaptic pathways (autogenetic inhibition; Fetz *et al.*, 1979). A number of inhibitory and excitatory influences, mediated by slower afferent fibres, will be exerted later. If the net result of this activity produces enough depolarization of a motor neuron, early enough, it may discharge. The orthodromic impulse may then collide with the antidromic impulse travelling in its axon, producing mutual cancellation (Lloyd, 1943). According to the size, principle, small motor neurons are more likely to be excited synaptically (Henneman *et al.*, 1965*a*). The order of synaptic activation of motor neurons would not change by the addition of an inhibitory input by recurrent collaterals or autogenetic inhibition (Henneman, 1965*b*). Furthermore, the influx of EPSPs, mediated by the faster afferent fibres and occurring before the arrival of the antidromic impulse at the axon-soma junction, would be greater in smaller neurons with slower conducting motor axons, giving them a greater chance of producing a reflex response. Thus the chance of collision of antidromic and orthodromic impulses would be greater in axons of small neurons.

3. *Greater chance of shortening of axon-soma delay in smaller motor neurons.* Since recurrent collaterals were not found in about 20–30% of motor neurons in animals (Scheibel and Scheibel, 1966), prevention of F production by this mechanism may be important. Subliminal excitation of motor neurons facilitates antidromic invasion in the cat (Lloyd, 1943; Barakan *et al.*, 1949; Brooks *et al.*, 1950; Brock *et al.*, 1953) but the production of recurrent discharges may still be inhibited in these neurons because of shortening of their axon-soma delay (Renshaw, 1941; Brock *et al.*, 1953). Recurrent discharges recorded in the peripheral nerve can almost disappear when preceded by an orthodromic impulse in the dorsal column in the cat (Renshaw, 1941). There is some evidence that shortening of axon-soma delay is more likely to occur in smaller motor neurons (Barakan *et al.*, 1949), decreasing further their chance of recurrent response. However, summation of the above-mentioned EPSPs and IPSPs from neighbouring motor and from afferent fibres may still modify the excitability of a number of small neurons, so as to facilitate the production of recurrent discharges.

The approximate 1% of single unit F responses per threshold stimulus recorded by us is consistent with the 1% of the motor neuron pool producing recurrent responses with each supramaximal stimulus, by amplitude criteria with F wave recordings (Kimura *et al.*, 1984). When 'slow' and 'fast' fibres mediating F waves were tested with a collision technique, both still represented 1% of the motor neuron pool stimulated (Kimura *et al.*, 1984). This suggests that the three mechanisms which prevent the occurrence of F

responses, and which affect all motor neurons in varying degrees, result in a constant proportion of the motor neuron pool being recorded as recurrent responses. However, within any fraction of the pool stimulated, preferential occurrence of F responses in the faster motor neurons would still occur. This interpretation agrees with the following observations: the fastest F wave is often recorded with as little as 10 or 20 supramaximal stimuli; frequency distribution of F wave CVs; correlation between F frequency and CV of single units; similar mean latency of F waves with supramaximal and submaximal stimulation (Kimura *et al.*, 1984); little variation in the mean F wave latency when the slower fibres were progressively blocked (Kimura *et al.*, 1984; Fisher, 1985).

Possibility of a reflex component in the responses observed

The EPSPs produced by afferent fibres during antidromic stimulation may result in enough change of the membrane potential of an individual motor neuron to activate it, leading to a reflex discharge. This is only recordable distally in the muscle if the orthodromic impulses in afferent fibres arrive at the neuron after the antidromic motor impulses, that is, if they are mediated by the slower afferent fibres. Collision will occur if the reflex discharge shortly precedes the arrival of the antidromic motor impulses. Reflex discharges are diminished but not abolished by a preceding antidromic response (Lloyd, 1943; Brooks *et al.*, 1950) because the soma of neurons which have been antidromically invaded becomes refractory to afferent stimulation and, on the other hand, others whose antidromic impulses have been blocked become more excitable synaptically and can be activated reflexly. Afferent stimulation may produce orthodromic responses as soon as 0.1−0.7 ms after the antidromic discharge reaches the axon-soma junction (Lloyd, 1943; Brooks *et al.*, 1950). However, the chance of occurrence of these reflex potentials may be low because the size of the EPSPs mediated by the slower conducting afferent fibres is much smaller in the cat (Mendell and Henneman, 1971; Scott and Mendell, 1976).

It is likely that the antidromic discharges and the reflex components of the late responses are mediated by different fibres with different CVs (Burke *et al.*, 1989). If such reflex responses are produced in man during supramaximal antidromic stimulation, their latency, recorded in the muscle, would be within the range of F wave latencies of the slower conducting fibres. These potentials might be seen in isolation or not, amongst those in that range, or as a late component of the faster surface recorded F wave seen in man. The 57% decrease in F response amplitude following acute deafferentation in the cat, attributed to abolished reflex discharges (Fox and Hitchcock, 1987), is consistent with those possibilities. This reflex component would be expected to increase if the excitability of the motor neurons generating it increases. This has been shown to be the case with upper motor neuron lesions (Gassel and Weisendanger, 1965; Thorne, 1965). Moreover, during posttetanic stimulation in normal human subjects, F waves were substituted by typical H waves in the small muscles of hand (Hagbarth, 1962).

F wave repeaters

The percentage of repeater shapes in our subjects was similar or slightly higher than that found by others (Peioglou-Harmousi *et al.*, 1985*b*; Mcleod, 1986). A wide range of the motor neurons in the pool are represented in the F waves obtained with 60 stimuli

(Table 3). Each F wave had on average 3 MUs (Table 7). Assuming that each of the motor neurons has an equal chance of being part of the 1% of the pool that generate F waves with each antidromic stimulus, the probability of a few neurons backfiring together repeatedly, by chance, would be clearly far less than the 10% repeater shapes and 19.5% repeater waves actually found.

The mechanisms leading to F wave repeaters are not clear. A specific group of motor neurons that are prone to recurrent discharges has been suggested (Kimura *et al.*, 1984). The similar latency of repeaters and nonrepeaters argues against the former being mediated by peripheral axon reflexes (Fullerton and Gilliatt, 1965). Their greater amplitude and area compared with nonrepeaters, but similar latency and CV, argues against preferential recurrent discharges of single larger motor neurons and suggests that a greater number of neurons contribute to each F wave repeater. We conclude that the associated discharges of motor neurons generating F wave repeaters are unlikely to be related to neuron size or to the CV of their axons.

Could the frequent associated discharges of the motor neurons generating F wave repeaters be related to proximity between motor neurons? This would require special cytoarchitectonic and functional arrangements in certain groups of neurons. Animal studies have shown a direct connection between some motor neurons through axon collaterals (Cullheim *et al.*, 1977). In the cat, pairs or small groups of motor neurons lying in very close apposition in the ventral horns have been shown (Rexed, 1954). Following antidromic activation of a peripheral nerve, a small percentage of motor neurons have a direct excitatory influence on their fairly close neighbouring neurons (Gogan *et al.*, 1977). Whether these arrangements also exist in man is not known, but such groups of neurons may be prone to discharge together following antidromic stimulation.

The four distinct peaks in the distribution of intervals between repeaters of the same shape suggests different functional arrangements within the groups of neurons generating repeaters.

In the above analysis, the F wave repeaters were treated as generated by a subpopulation of neurons and, from the definition of repeaters, they constitute a homogeneous group sampling the discharges of those neurons. The group of nonrepeaters may be heterogeneous since, with the surface technique used, it cannot be established whether some of their F waves may contain discharges of the neurons generating repeaters plus those of other neurons. The net result would be an underestimation of the frequency of discharge of neurons generating repeaters.

The mechanisms of generation of repeaters in disease states need not be the same. Assuming that random and equal activation of any 3 MUs of the pool available to each antidromic stimulus is equally detected as an F wave, the chance of the same 3 motor neurons discharges being evoked by repeated antidromic stimuli should increase as the number of neurons decreases. However, with such a decrease, the chance of detection of repeaters resulting from the discharge of single neurons may be higher, particularly if compensatory mechanisms associated with neuron loss have occurred. Further, the chance of detection of neurons repeatedly discharging together will depend on whether, and how, pathology affects the cytoarchitectonic arrangements of motor neurons and their function.

CONCLUSIONS

The complex changes in the excitability of other motor neurons, brought on each time antidromic stimuli to a mixed peripheral nerve arrive at the cord, and to a particular motor neuron, may partly determine the distribution of CVs of F waves and of single unit F responses, as well as the F frequency of single units of varying CV. We suggest that the apparent more frequent generation of F responses by faster MUs is likely to be related to a lesser chance of antidromic discharge of smaller motor neurons and to a greater chance of collision of reflex discharges and antidromic impulses in their axons. This suggestion is consistent with the small number of single unit F responses recorded in many fast MUs and with the absence of large numbers of them in the relatively slower MUs shown in fig. 9. It also agrees with the fact that a constant mean 1% of the motor neuron pool stimulated, as estimated by distal recordings in the muscle, discharges recurrently, irrespective of the stimulation intensity applied to a mixed peripheral nerve or of the mean latency of the responses obtained. Repeater F waves may represent a further subgroup of neurons that are preferentially generated following antidromic stimulation; these neurons may have special, and heterogeneous, functional and anatomical arrangements.

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DISTRIBUTION OF CORTICAL NEURAL NETWORKS INVOLVED IN WORD COMPREHENSION AND WORD RETRIEVAL

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SUMMARY

Six normal volunteers were studied with positron emission tomography to identify the cortical neural networks that participate in the processing of single words. Activity-related changes in regional cerebral blood flow were measured consecutively on 6 occasions in each subject, 2 while the subject was at rest and 4 while single word language tasks were being performed. The data from each subject were standardized for brain shape and size, reconstructed parallel to the intercommissural line, normalized for global flow differences, and then averaged for each activation condition across the 6 subjects. Significant areas of change in rCBF ($P < 0.05$, with appropriate Bonferroni corrections) between task and rest conditions were displayed with reference to the coordinates of a standard neuroanatomical atlas. We have demonstrated that categorical judgements on heard pairs of real words activate neural networks along both superior temporal gyri, but with an anatomical distribution no different from that seen when the subjects listened to nonwords: the tasks would appear to be very different in cognitive demands but not in terms of the distribution of activation. However, during a verb generation task that involved thinking of verbs appropriate to heard nouns presented at a slow rate, the only temporal region activated was the left posterior superior temporal association cortex (Wernicke's area). Further analysis showed that whereas activation in other superior temporal regions, both left and right, correlated with rates of word presentation during the 4 tasks, there was no such correlation in Wernicke's area; evidence that this site is responsible for more than early acoustic processing. During verb generation there was also activation of left premotor and prefrontal cortex (including Broca's area and the supplementary motor area). The supplementary motor area is thought to be involved in the motor planning of speech. The subjects did not vocalize during the task, and therefore it would appear that the act of retrieving words from semantic memory activates networks concerned with the production of speech sounds. We conclude that single word comprehension and retrieval activate very different distributed regions of cerebral cortex, with Wernicke's area the only region engaged by both processes and with participation during silent word generation of networks involved in vocalization.

INTRODUCTION

It is a tenet of cognitive neuropsychology that the human mind is organized on a modular basis (Fodor, 1983). To understand the functional components of normal language processing, cognitive neuropsychologists have intensively studied individual patients with abnormalities of language function: specifically, they search for dissociation of

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symptoms, expressed as discrete deficits of speech or comprehension in single patients with critically-sited lesions (Shallice, 1979, 1988). The loss of one component of a psychological process after brain injury while another component remains intact (as revealed by studies of the patient's performance on appropriately designed behavioural tasks) implies that the two are functionally distinct. This inference becomes more reliable if another patient can be found who shows an equally selective deficit, but in this case with an inability to perform the second component of the psychological process; the contrast between the performance of the 2 patients provides a double dissociation (Teuber, 1955; Shallice, 1979).

The accumulation in the literature of detailed case studies of patients with a wide range of specific language abnormalities has resulted in increasingly complex models of language processing (Caplan, 1987; Shallice, 1988), based on the assumption that the performance of an aphasic patient reflects the whole sequence of normal language processing minus the damaged component(s) (Saffran, 1982). Although the models are functional, if there is neurological specificity then each step in a model based on symptom dissociation in patients with focal lesions must have a specific anatomical representation in the brain. However, there are major problems when interpreting the clinical performance of aphasic patients with reference to the site of their lesion, as revealed by structural neuroimaging; the lesions are often large or multiple, and there are usually associated deficits in functionally independent cortical processors because they or their connections happen to lie in near proximity, which will result in correlation of one lesion site with a number of independent cognitive processes. Even more problematic is that a cognitive process may have a widely distributed, interconnected anatomical representation (Goldman-Rakic, 1988), and a lesion which effectively interrupts a whole process may occupy only a small part of the distributed network that subserves that process.

The use of positron emission tomography (PET) to measure activity-related changes in regional cerebral blood flow (rCBF) is a technique that avoids the problems of inferring the relationship between structure and function from patient studies. This technique has its origins in the pioneering work with two-dimensional blood flow measurements (Lassen *et al.*, 1978), but with the advantage of much greater precision in terms of detection and localization of significant changes in rCBF. Coupled with this increasing technical sophistication have come refinements to the tasks that the subjects are asked to perform during activation measurements, to try and relate specific brain regions to particular components of the process under investigation. While this has proved relatively straightforward for the investigation of sensory and motor cortex (Fox *et al.* 1987; Lueck *et al.*, 1989; Colebatch *et al.*, 1990), the study of the localization of cognitive processes presents a much greater challenge (Petersen *et al.*, 1988). We have investigated a group of normal subjects with a cognitive activation study that encompassed some of the basic elements of language processing. More specifically, we used 4 tasks that we predicted would differentially activate regions corresponding to hypothetical constructs of single word processing responsible for auditory, phonological and semantic analyses (Ellis and Young, 1988). We predicted that comparison of the activated images against those obtained during a rest condition would reveal the different distribution of neural networks involved in each task, an approach analogous to the search for symptom dissociation in neuropsychological case studies.

METHODS

Subjects and activation tasks

Six right-handed healthy males, aged 29–48 yrs, underwent one study each. All had English as their first language A scanning session lasted 1.5 h and consisted of 6 measurements of rCBF. The 6 conditions during the blood flow measurements are summarized in Table 1. The single word language tasks were delivered binaurally through earphones from prepared tapes. Each language tape was started 30 s before scanning commenced and was played continuously throughout the scanning period. The room lights were dimmed, the subjects' eyes were shut and the low background noise of the scanning room's fans was present throughout. The scanner was virtually silent during operation. During conditions 3 and 4 the subjects signalled their cooperation by opposing the thumb and index finger of the left hand when pairs were correctly categorized, and an observer monitored their performance (greater than 95% accuracy in all cases). In condition 5 they used the same signal when they had thought of the first verb to match the presented noun. In this condition the subjects were specifically instructed to think of a list of verbs in response to a heard noun (e.g., 'car' .....'drive, polish, crash'), not to form sentences (e g., 'apple' .....'I peel and slice an apple before I eat it'). On retrospective questioning all subjects reckoned their performance at 2–4 verbs per presented noun. To remove the decision to signal and its action as behavioural variables between conditions, the subjects were also asked to signal randomly every few seconds during conditions 1, 2 and 6. To test if there was a positive correlation between the rates of presentation of words and percentage increases in blood flow in activated regions, the frequency of word presentation was varied. The first 3 subjects heard nonwords at 40 per min (wpm), and noun-noun and verb-noun comparisons at 26–30 wpm (13–15 pairs): the rates for the other 3 subjects were nonwords at 60 wpm, and noun-noun and verb-noun comparisons at 50–54 wpm (25–27 pairs). Verb generation was a self-paced task and during this condition all 6 subjects had nouns presented at the slow rate of 15 wpm.

TABLE 1 ACTIVATION CONDITIONS

1 REST The subject was instructed to 'empty his mind'
2 NONWORDS The subject listened to nonwords with typical English phonological structure, e.g , 'ked', 'pretch'.
3. NOUN-NOUN COMPARISONS. Pairs of concrete nouns were presented. The first of each pair was a superordinate, the second a basic level noun. Only half the pairs, randomly distributed, were correctly categorized, e g , 'fruit . apple', but 'furniture ... shirt'
4 VERB-NOUN COMPARISONS Similar to condition 3, but action and object were paired, e.g , 'eat (an) orange', but 'knit (the) glasses'.
5. VERB GENERATION The subject was asked to think of, without vocalization, as many verbs appropriate to a presented concrete noun as he could in the time available between presentations, e.g., 'flower' (grow, cut, smell).
6 REST As condition 1.

The experimental conditions were formulated around the model of single word processing published by Ellis and Young (1988). At the level of *auditory analysis* the cortical analysers encode the phonological structure of a word. This triggers a comparison with a long-term memory store of the forms of known words in the *auditory input lexicon*. Further processing occurs in the *semantic system* to derive the meaning of the word There is evidence that the mental representations of the meanings of nouns are organized categorically (e.g., colour, body part, etc.), hierarchically (basic, superordinate, subordinate) and in terms of concreteness or abstractness (Caplan, 1987). In view of these complexities, and to keep a degree of uniformity across tasks, the nouns used in conditions 3, 4 and 5 were all concrete. In condition 3, the first presented noun was a superordinate from a wide range of categories and the second a basic level noun. The use of verbs in conditions 4 and 5 introduced further differences. At a semantic level, some aspects of verb processing appear to be different from that of nouns, and there is evidence that verbs comprise a functional subcomponent in the mental lexicon that is at least partially distinct from that for nouns (Miceli *et al.*, 1984; Williams and Canter, 1987). Inevitably, the association of a verb and noun will introduce

syntactical meaning, but this variable was minimized by structuring conditions 4 and 5 such that the verbs, whether presented or recollected, were all active and the nouns all direct objects

Words for objects and those for actions are fundamental components of spoken language, and the purpose of the study was to identify those regions of the cortex concerned with their representation in the brain. Condition 2 was expected to identify the stages of auditory analysis that precede single word comprehension Condition 3 was designed to activate searches through the memory store for the meanings of nouns, and condition 4 to identify any separate anatomical region responsible for the semantics of verbs. Condition 5 was similar to 4 in that it involved a matching of verbs to nouns, but it was the only task that required the active retrieval of words from the mental lexicon. This study was not concerned with the pathways involved in vocalization and the subjects were silent during all conditions

Written, informed consent was given by each subject. The study was approved by the Hammersmith Hospital ethics committee. Permission to administer the radioisotope was approved by ARSAC (UK).

Scanning and data analysis

The subjects were scanned on an ECAT 931-08/12 (CTI Inc., Knoxville, USA) positron emission tomographic scanner (Spinks *et al.*, 1988). Correction for attenuation was made by performing a transmission scan with an exposed $^{68}Ge/^{68}Ga$ external ring source at the beginning of each patient study. Images were reconstructed by filtered back projection (Hanning filter, cut-off 0.5) to give an image resolution of $8.5\times8.5\times7.0$ mm at full width, half maximum. rCBF measurements throughout the whole brain (15 transaxial planes) were made using inhaled oxygen-15-labelled carbon dioxide as tracer (Lammertsma *et al.*, 1989, 1990): estimations were completed in 3.5 min at 15 min intervals.

Data analysis was performed in PROMATLAB (Mathworks Inc.) on a SUN 3/60 workstation with ANALYZE (BRU, Mayo Foundation, Rochester, MI) image analysis and display software. The data from each subject were first standardized for brain size and shape and reconstructed parallel to the intercommissural line (Friston *et al.*, 1989). To increase the ratio of signal to noise and to account for the normal variability of the anatomy of the cerebral gyri and sulci between individuals, the reconstructed images were smoothed using a low pass filter of length 9 pixels in the transaxial plane As the study was designed to examine regional changes in blood flow across activation conditions, the data were first normalized for global flow differences by analysis of covariance, with measured global flow as the confounding covariate (Friston *et al.*, 1990), and then averaged for each condition across the 6 subjects. The result was 26 interpolated transaxial planes of quantitative rCBF images, from base to vertex, for each activation condition, in a standard cartesian coordinate reference space (Talairach and Tournoux, 1988), permitting the correlation of functional change to anatomy. These planes were displayed with a pixel size of $2\times2\times4$ mm. Due to the smoothing of the original scans, rCBF in each pixel was the mean of 81 pixels centred on the pixel chosen (corresponding to a brain region approximately 18 mm^2 in the transaxial plane).

Subsequent statistical analysis of the data to detect significant areas of change between task and rest was performed by a planned comparison of means with a Bonferroni correction at a P level of 0.05, accounting for the effective number of independent pixel measurements by analysis of the autocorrelation function of the images (Friston *et al.*, 1991).

RESULTS

The regions which showed significant increase in rCBF in response to the individual single-word tasks, compared with rest, are summarized in fig. 1. The peak values of rCBF across tasks in these regions are summarized in Table 2. An increase in rCBF does not distinguish between excitatory and inhibitory neurotransmitter function as either will require the consumption of energy and result in a secondary increase in rCBF; a significant decrease in rCBF will only occur one or more synapses away from an inhibitory synapse. However, whatever the regional balance between excitation and inhibition, listening to nonwords (condition 2) activated neural networks along both superior temporal gyri (primary and association auditory cortex). The tasks of semantic categorical judgements on noun-noun and verb-noun pairs (conditions 3 and 4) resulted

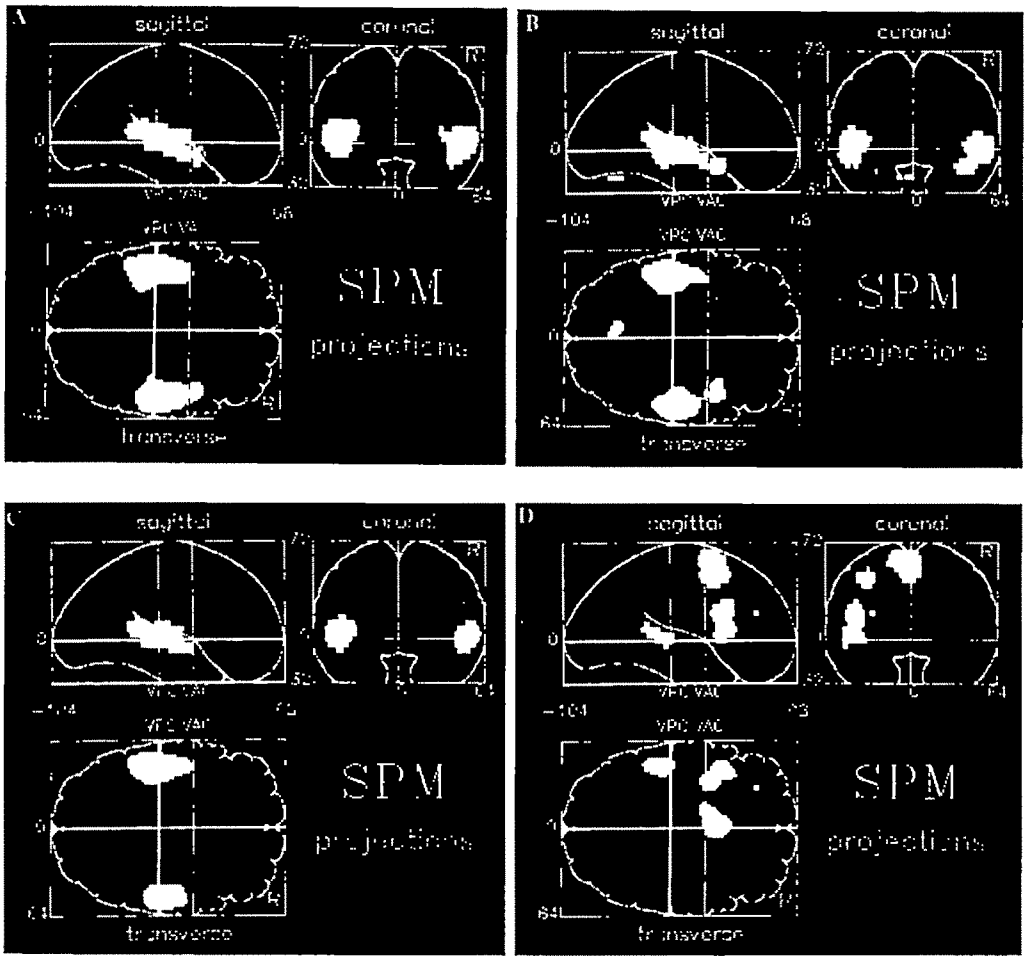

FIG 1 Comparisons of means (6 subjects) on each of the 4 language tasks against rest. A, listening to nonwords, B, categorical judgements on heard noun-noun pairs, C, categorical judgements on heard verb-noun pairs; D, silent retrieval of verbs from memory in response to heard nouns The results have been summarized as statistical parametric maps (SPM) in 3 whole brain projections: sagittal, coronal and transaxial. The intercommissural line is set at zero on the sagittal and coronal projections, and the vertical projections through the anterior commissure (VAC) and posterior commissure (VPC) are depicted on the sagittal and transverse projections. Distances in mm above and below the intercommissural line, anterior and posterior to the VAC line, and from the midline are shown Picture elements (pixels) where there has been a significant increase in rCBF (task vs rest) are displayed lighter than background Significance was set at $P < 0\ 05$ with a Bonferroni correction for the 4 comparisons. The regions significantly activated by each task are discussed in the text

in distributions of activation in the superior temporal gyri that appeared very similar to that for nonwords. This was confirmed by direct comparisons of the two category judgement tasks against listening to nonwords. A further comparison between the two category judgement tasks showed no significant difference between their distributions of activation; no separate anatomical regions for the comprehension and comparison of noun-noun and verb-noun pairs were identified.

TABLE 2. MEAN rCBF VALUES ACROSS CONDITIONS FOR ACTIVATED BRAIN REGIONS

	Conditions					
	1	*6*	*2*	*3*	*4*	*5*
Brain region	*Rest*		*Language tasks*			
L Heschl's gyrus (−50, −24, 12 mm)	36.5	36.8	40 3*	38.9*	38 3*	37 3
R Heschl's gyrus (50, −22, 12 mm)	39.5	39.7	43.5*	43.2*	43.5*	39.7
L posterior STG (−46, −38, 8 mm)	36 5	36 9	41 3*	40 8*	41 5*	40 2*
R posterior STG (48, −38, 8 mm)	37.8	36.8	40.5*	40.4*	39 7*	38.3
L middle STG (−50, −10, −4 mm)	39.6	39 6	45 1*	42.8*	43.2*	41.1
R middle STG (50, −10, −4 mm)	33.9	34.3	38.9*	38.1*	38 3*	35.9
L Broca's area (−40, 14, 16 mm)	35 7	36 4	36 8	37.6	38.0	39.3*
L posterior MFG (−36, 14, 40 mm)	37.1	36 2	35.5	36.5	36 7	38 3*
Midline SMA (0, 6, 60)	37 7	39 1	38 5	40 2	40.2	42.0*

Mean rCBF values (ml·100 ml^{-1}·min^{-1}) for brain regions significantly activated by the language conditions The pixel with the lowest *P* value was selected from each significantly activated region, and then mean rCBF for this pixel across activation conditions was taken from the blood flow data standardized for brain size and shape and normalized for global flow differences. Therefore, each mean rCBF value was taken from smoothed data, and represents a brain region approximately 18 mm^2 in the transaxial plane (*see* text). The x, y, z coordinates identifying each region in the stereotactic atlas of Talairach and Tournoux (1988) are given in parentheses. The rCBF values significantly increased in the comparison of activation condition against rest are identified (*). L = left; R = right; STG = superior temporal gyrus, MFG = middle frontal gyrus; SMA = supplementary area.

From the analysis so far, it is apparent that conditions 2−4 did not reveal a locus for semantic processing separate from those responsible for acoustic and phonological processing. The verb generation task (condition 5) was designed to reduce the ratio of the frequency of word presentation to the rate of semantic processing. The strategy was successful in that there was no detectable activation in the right hemisphere, and none in primary auditory cortex (Heschl's gyrus) and the more anterior part of the superior temporal gyrus on the left; a rate of word presentation of one every 4−5 s was below a level necessary to produce a signal in these regions. This is not to imply that they were not involved when the rate of presentation of words was slow, but we capitalized on the relative insensitivity of the technique to remove the components of the signal concerned with the early stages of processing of heard words. Comparing the percentage increases in rCBF in superior temporal regions with rates of word presentation for all activation conditions against rest showed significant correlations except in left posterior superior temporal gyrus (Wernicke's area) (Table 3). The poor correlation in Wernicke's area was due in part to a significant increase in rCBF in this region during the verb generation task (a mean of 9.5% in the 6 subjects, compared with 2.7% in the homologous region on the right), but was also due to relatively large increases in rCBF during the noun-noun and verb-noun comparisons in the 3 subjects who experienced the lower rate of presentation of paired words.

TABLE 3. CORRELATION OF PERCENTAGE INCREASES OF rCBF AND FREQUENCIES OF WORD PRESENTATION RATES CORRELATION COEFFICIENTS AND THEIR SIGNIFICANCE IN THREE REGIONS IN BOTH SUPERIOR TEMPORAL GYRI

Region	*Left*	*Right*
Heschl's gyrus	0.71 ($P < 0.001$)	0.72 ($P < 0.001$)
Posterior STG	0.36 ($P < 0.08$)	0.75 ($P < 0.001$)
Middle STG	0.58 ($P = 0.003$)	0.53 ($P = 0.007$)

The 3 regions in the left hemisphere and their homologous counterparts in the right were identified on the stereotactic atlas, and the coordination transferred to the smoothed, reoriented blood flow data. The percentage increases in normalized rCBF for each subject, comparing conditions 2, 3, 4 and 5 against the mean of conditions 1 and 6, were calculated Percentage increases in rCBF were plotted against the frequencies of word presentation during conditions 2–5 for each subject, simple linear regressions plotted, and the correlation coefficients and their significance calculated The significance (P) values have been tabulated without a Bonferroni correction for the 6 regional comparisons, but even with a correction there were significant correlations in both primary auditory cortices (Heschl's gyri) and right posterior superior temporal gyrus (STG), with weaker but still significant correlations more anteriorly in each STG: weaker at least partly for methodological reasons, from sampling heavily smoothed pixels towards the edge of an activated region. There was poor correlation in left posterior STG (*see* text).

Anterior activation that reached statistical significance only occurred during the verb generation task. Peak of increased rCBF were observed in the posterior part of the left inferior frontal gyrus (pars opercularis, Broca's area), the posterior part of the left middle frontal gyrus, and the supplementary motor area—as the left and right supplementary motor areas lie close to each other in the midline, it was not possible to determine whether activation in this region was bilateral or lateralized to the left.

DISCUSSION

The involvement of both superior temporal gyri when listening to words, real or otherwise, was expected. Psychophysical methods (dichotic listening tasks) have demonstrated a right ear advantage for consonant-vowel combinations, which has been interpreted as evidence that the left hemisphere acoustic analysers are better able than those on the right to identify the rapid changes in frequencies (formant transitions) that permit the discrimination of individual words (Shankweiler and Studdert-Kennedy, 1967; Kay, 1982). There is no ear advantage for vowel sounds, which are the most constant sounds in the English language, and there is evidence that the right hemisphere is involved in nonlinguistic aspects of language processing, such as comprehension of the affective intonation of speech (Heilman *et al.*, 1975). If it is assumed that listening to nonwords only activates the neural networks that are represented in the Ellis and Young model as the auditory analysis system and input lexicon (fig. 2), then these two networks considered together appear to be distributed throughout the auditory association cortices of both hemispheres. Pertinent to this conclusion is the localization of pathology in patients with pure word deafness, a syndrome associated with an inability to comprehend spoken language or repeat heard words, while reading, writing and spontaneous speech remain

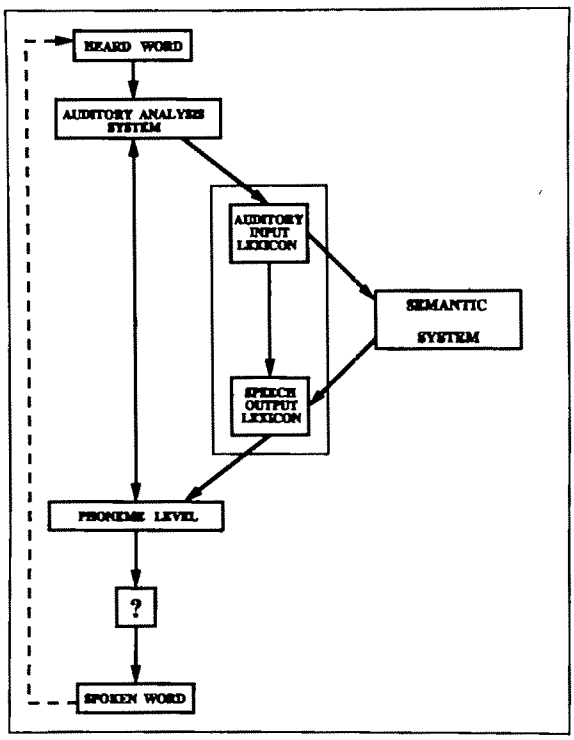

FIG. 2. A simple model of single word processing, adapted from Ellis and Young (1988). A heard word is analysed acoustically (acoustic analysis system) and its encoded form will activate an entry in the auditory input lexicon if it is a familiar word Its entry in the semantic system is then activated to make the meaning of the word apparent. Word retrieval for speech commences as an activation of the appropriate entry in the speech output lexicon, the word-form store for familiar spoken words. There is debate about whether the auditory input and speech output lexicons are separate entities or a single processor, indicated by the enclosing box. Subsequent processing ultimately results in a motor output to the muscles of articulation and respiration to produce the serial sequence of phonemes that form the sound code for the word. There are thought to be three routes available for repeating a heard word: nonlexical (auditory analysis system to phoneme level), the only route available for repeating a nonword; nonsemantic—lexical (auditory input lexicon to speech output lexicon, assuming that these are separate processors); and semantic—lexical (via the semantic system) Silent verb retrieval may activate 'inner speech' (reversal of the nonlexical route). The study of Petersen *et al.* (1988) suggests that monitoring of one's own speech after articulation (dashed line) does not normally occur, because reading aloud words did not result in activation of auditory cortex (*see* text)

intact. The problem in many of these patients seems to be a defect in an early stage of speech comprehension, at the level of the acoustic analysis system in the Ellis and Young model, and it is often observed only when there have been bilateral temporal lobe lesions involving the superior temporal gyri (Bauer and Rubens, 1985; Auerbach *et al.*, 1982).

The tasks of categorical judgements on noun-noun and verb-noun pairs must have involved the semantic system, and yet there was no additional region of activation compared with the nonwords task. One possibility is that the semantic processing required for noun or verb comprehension, with subsequent categorical judgement, is in neural networks that are distributed in parallel to some or all of the pathways involved in acoustic and phonological analyses. This would presuppose that any further increase in rCBF

as a result of semantic processing, over and above the increase consequent upon the earlier stages of word processing, was too small to be detected. However, there remains uncertainty about the involvement of the semantic system during the nonword task. As far as the subjects were concerned it was not engaged (the nonwords were perceived largely as 'nonsense', although 2 subjects reported that an occasional nonword reminded them of a real English word or a foreign word with which they were familiar). If strictly serial processing by the brain is assumed, where each stage in a functional sequence completes its analysis before sending information on to the next stage, then it would be reasonable to assert that nonwords do not engage the semantic system. An alternative model of neural function, incorporating notions of cascaded processing and interactive activation (McClelland and Rumelhart, 1981; Rumelhart and McClelland, 1982) suggests otherwise. Put simply, the argument would go as follows. The first phoneme of any word-like string (whether legitimate or not) activates entries in the input lexicon for all possible familiar real words that begin with this phoneme. These activations are then passed on automatically, and without conscious awareness, to appropriate entries in the semantic system. Then, as the whole sequence of phonemes is presented over time, inhibition within and between levels progressively extinguishes all the 'incorrect' entries. As excitation and inhibition cannot be distinguished by a regional blood flow measurement, a cascaded processing model predicts that nonwords will activate largely the same brain regions as real words in a PET study.

Significant activation was restricted to posterior structures in the categorical judgement tasks, which implies either that word comprehension is the product of posteriorly-sited cortical processors or any anterior networks involved were so weakly activated that the signal was not detected above noise. This is in contrast to the word retrieval task (verb generation), when both Wernicke's area and anterior regions were clearly activated. When the behaviour of Wernicke's area across all the tasks is considered, there was a double dissociation of activation in comparison with other superior temporal regions in terms of response to the rates of presentation of words (bias to input) and response to the verb generation task (bias to output) (Table 4). These results suggest a central role, possibly at the semantic level, for Wernicke's area in word comprehension and retrieval.

This finding appears to be in conflict with that of Petersen *et al.* (1988), who located

TABLE 4 ANALYSIS OF FUNCTION BIAS WITHIN LEFT AND RIGHT SUPERIOR TEMPORAL GYRI

Region	*Bias to input*	*Bias to output*
L and R Heschl's gyri	Significant	Not significant
L and R middle STG	Significant	Not significant
R posterior STG	Significant	Not significant
Wernicke's area	Not significant	Significant

All regions in the superior temporal gyri (STG), with the exception of Wernicke's area, showed significant correlations between the rates of presentation of words and the percentage increases in rCBF when comparing language conditions against rest—bias to input. During silent retrieval of verbs in response to a low rate of presentation of nouns there was only significant activation in Wernicke's area—bias to output Therefore, there is a double dissociation in the functional bias of the STG regions: anterior areas are sensitive to changes in input, Wernicke's area is sensitive to retrieval of verbs from semantic memory.

semantic processing in left dorsolateral prefrontal cortex, with roles of posterior structures confined to the earlier stages of lexical processing. However, inspection of the tasks in the earlier study suggests that this division into posterior-sensory processing/anterior-semantic processing was based on the assumption that some of the tasks elicited very limited processing responses by the brain. Thus familiar words presented to the ears and eyes of the subjects were assumed to excite regions corresponding only to primary sensory processing and the word-form system (for the heard word, analogous in the model we are employing to activation of the auditory analysis system and auditory input lexicon). The next level in the hierarchy of tasks was speaking aloud the heard or read words, which was assumed to engage, in addition to those processors activated by the previous tasks, the regions responsible for encoding and producing the correct sequential output to the articulatory and respiratory muscles.

Our interpretation of the tasks used by Petersen *et al.* (1988) is somewhat different. In particular, it seems likely that presentation of familiar words, even in a task not explicitly demanding comprehension, will automatically activate the semantic system. We base this interpretation not only on the results of the present PET study, which may suggest early partial semantic activation even by nonwords, but also on behavioural studies of semantic facilitation. For example, the reaction time to name a familiar object is significantly quicker after prior presentation of a semantically related word, even though the subject makes no response to (and thus is not obliged to comprehend) the prime word (Bajo, 1988). The most plausible interpretation of this result is that simply perceiving familiar words activates a semantic system containing representations common to both words and pictures. We therefore assume that the tasks of listening to or looking at familiar words, either silently or with the instruction to repeat or read aloud the presented word, will automatically involve some degree of semantic processing. As the study of Petersen *et al.* (1988) only showed posterior activation with presentation and repetition of heard and read words (other than the anterior regions involved in articulation during the repetition tasks), their study can be interpreted, like ours, as supporting involvement of a posterior region during word comprehension.

A similar argument applies to left posterior superior temporal activation during verb generation. We observed it when the control state was rest. Petersen *et al.* (1988) did not observe it, but when the control state was repeating heard or read words, which we have argued would activate semantic processing; any semantic processor common to both task and control states would then 'disappear' in the comparison.

Verb generation in our study also activated left dorsolateral prefrontal cortex, a similar result to that of Petersen *et al.* (1988) except that we found no involvement of the inferior surface of the left dorsal frontal lobe (Brodmann's area 47). In addition, there was strong activation of the supplementary motor area (SMA). As the SMA has been observed to become activated during speech (Larsen *et al.*, 1978; Petersen *et al.*, 1988), its participation was unexpected in our study where the subjects did not vocalize. Lesions of the left SMA result in an initial loss of speech although comprehension is largely spared (Masdeu *et al.*, 1978). During recovery the patient may go through a stage when verbal responses are whispered, although the poorly articulated words contain no major phonemic errors; the role of the left SMA has more to do with vocalization than linguistics (Caplan, 1987). This would suggest that the activated SMA cannot be considered part of the semantic system, and silent verb generation appears to involve structures concerned

with speech production. The Ellis and Young model of language organization proposes a connection between the word-form system for speech (the speech output lexicon) and the acoustic analysis system (fig. 2), which allows the internal generation of the second image of a word ('inner speech'). An explanation of SMA activation during silent verb generation would be that the act of retrieving words from memory results automatically in 'inner speech', and the SMA contains neural pathways concerned with this process.

The posterior end of the left middle frontal gyrus was engaged during verb generation. The syndrome of transcortical motor aphasia, characterized by nonfluent spontaneous speech but well-preserved repetition, is known to be associated with cortical and subcortical lesions in the left prefrontal region away from the sylvian sulcus (Freedman *et al.*, 1984), and we can speculate that the medial frontal gyrus is involved in the task of fluency when a number of associated words have to be generated in response to each cue. This region was not seen in the study of Petersen *et al.* (1988), but this may reflect a difference in the verb generation tasks; our study required a search for more than one verb for each presented noun, which will have been more difficult (and therefore required greater attention) and will have engaged a mechanism to monitor the output to check for perseveration. There is a literature on right lateral eye movements occurring during verbal tasks (for a review, *see* Code, 1987), and the posterior medial frontal gyrus is activated during voluntary saccades (Fox *et al.*, 1985). Although lateralized eye movements away from the dominant cerebral hemisphere is an unlikely explanation for the left middle frontal gyrus activation seen in our study, it may be necessary to monitor eye movements during future studies to exclude this possibility.

Therefore in terms of distribution of activation, silent single word retrieval is a complex interplay between left posterior superior temporal gyrus, two discrete regions in left dorsolateral prefrontal cortex and the SMA. In contrast, word comprehension activates only temporal lobe structures. Are we then in a position to assert that Wernicke's area, the only activated region common to single word comprehension and retrieval and the only temporal region without a bias to input, is the site of semantic processing? If so, then we are in disagreement with Petersen *et al.* (1988, 1989), who place semantic processing in left inferior dorsolateral prefrontal cortex (Brodmann's area 47). The conclusion must be that there remains an element of uncertainty, and this is for several reasons.

First, we may be in error in our choice of the hypothetical cognitive model that we have used to understand our results. It has been argued (Allport and Funnell, 1981; Allport, 1984) that the functions attributed to the auditory input lexicon and the speech output lexicon are performed by a single processor (fig. 2). As we suspect, because of the unexpected activation of SMA, that networks involved with vocalization were activated during the verb generation task, our results are also consistent with the hypothesis that left posterior superior temporal gyrus is acting as the auditory input lexicon during the category judgement tasks and as the speech output lexicon during the verb generation task. There are a number of arguments against the hypothesis of a single speech input and output lexicon, both from the behaviour of patients with a specific language disorder (deep aphasia) and from psychological studies on normal subjects (Shallice, 1988), and we consider it unlikely that left posterior superior temporal gyrus was activated because it functioned as a common input/output lexicon. However, the interpretation of PET activation results is critically dependent on the reliability of the cognitive model used.

A second area of uncertainty over the role of Wernicke's area in our study concerns the possibility that we have not adequately considered all the processes that separate the different activation tasks, a criticism we have already made in relation to the study of Petersen *et al.* (1988): attention will have differed across the tasks (the first author, who was one of the subjects, recalls that time during the category judgement and verb generation tasks seemed to pass much quicker than when simply listening to nonwords); and although auditory-verbal short-term memory (Warrington and Shallice, 1969) will have been engaged by all the tasks, its involvement is likely to have been greater during the category judgement tasks (the first of a pair of words had to be retained in memory until the second was presented) and verb generation (with retention of the stimulus noun during the period of recall of appropriate verbs) than during listening to nonwords—although all the subjects were able to recall some of the nonwords they had heard immediately after the cessation of the task, particularly those played at the end (the recency effect; Baddeley, 1990). How much the differences in 'effort' of the attentional and auditory-verbal short-term systems across the tasks will have affected our results (and, for that matter, those of Petersen *et al.*, 1988) is uncertain.

There is one piece of evidence in the work of Petersen *et al.* (1988, 1989) that seems incompatible with the hypothesis that single word comprehension involves the left posterior superior temporal gyrus: neither seeing familiar words (compared with simple visual fixation) nor reading words aloud (compared with simply seeing them) activated temporal regions in their study. As there is no evidence that the semantic processing of heard and read words is dissociable, and as we argued that reading and repeating familiar words will activate the semantic system in normal subjects, then if a temporal region is a site of semantic processing it should have been visualized. However, there are complexities in these results that have not yet been addressed; for instance, while reading aloud the subjects will have heard their own voices (at a rate of 60 wpm) and yet this was not detected as activation within the temporal lobes. If the correct interpretation of this result is that there is suppression of auditory analysis in response to one's own voice then such suppression may interfere with the visualization of activation, as measured by an increase in rCBF, in a semantic network distributed in the auditory association cortex.

A further study by the same group (Petersen *et al.*, 1989), looking at rhyme decisions on pairs of printed words, showed activation in left temporoparietal cortex. The interpretation was that this region is a centre for phonological coding of written words. This seems very plausible, but other processes were incorporated in the task state compared with the control (which was simply visual fixation on a cross hair). The words were real and familiar and therefore they will have engaged the semantic system. As the process of transcoding from print to sound can presumably operate only on a single word at one time, the rhyming comparison will have required short-term phonological memory; and clearly the task but not the control will have engaged attention. We are currently using single word reading tasks to attempt to separate phonological and semantic processing of read words in the superior temporal gyri, controlling for temporary memory and attention as far as is possible.

Ultimately, it may well prove that networks involved in auditory-verbal attention and short-term memory are so intimately intermingled with those concerned with semantic processing that it is unrealistic to expect to find unique anatomical coordinates for each

system, although their functional separation is not in doubt. Caution is also required when using a term such as the semantic system, a high order cognitive function that may not be so clearly modular as 'lower' processors (Fodor, 1983). The meaning of a word is heavily dependent on the circumstances when it is heard—for example, the word bed can, at different times, be associated with rest, warmth, temporary loss of freedom (to the erring child), sickness and sex. In the context of this study, bed was simply a word that was correctly paired with the word furniture.

Despite these many reservations, which will apply in greater or lesser degree to all future PET studies of language, our study indicates that word comprehension is a function localized to the superior temporal lobes, with the locus for the deeper processes in the left posterior superior temporal gyrus. The process of silent word retrieval requires the additional involvement of left dorsolateral prefrontal cortex and SMA; the selection of a few words from the many stored in memory depends on communication between left posterior and anterior regions. This is not a controversial conclusion, but we feel its main importance is in laying the groundwork for future studies, on patients with acquired language disorders, to investigate cortical reorganization, if any, after focal left cerebral hemisphere injury that is followed by at least partial recovery of language function.

There is a final, general caveat about PET activation studies, and that is the presentation of data in terms of significantly activated regions. The main effects of the activation tasks in this study are displayed in fig. 1. However, insignificant trends are lost in such a presentation, and such trends may ultimately increase our knowledge of cognitive processing when we are in a position to analyse the data in a more hypothesis-led way, at which time the level of significance can be justifiably reduced. In our study, there was a small increase of rCBF in both Broca's area and SMA during the two category judgement tasks (Table 2). These increases did not reach significance at a level of $P = 0.05$, and therefore cannot be interpreted in the context of this study, but the inclusion of this rCBF data for regions that we have demonstrated to be components of a distributed network that are engaged strongly by at least one task, may prove to be of importance as further similar studies appear in the literature.

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WARM AND COLD SPECIFIC SOMATOSENSORY SYSTEMS

PSYCHOPHYSICAL THRESHOLDS, REACTION TIMES AND PERIPHERAL CONDUCTION VELOCITIES

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SUMMARY

Perception thresholds for warm and cold sensation were measured by two methods, the method of levels and the method of limits, at various rates of temperature change. The following findings were obtained. (1) The threshold value is critically dependent upon the method through which it is obtained, being higher for the method that includes reaction time in the measurement. (2) When using a method that includes participation of reaction time, threshold increases with increasing rate of temperature change. (3) The artefactual threshold elevation recorded through the method of limits corresponds precisely to the reaction time. (4) Conduction velocities for the primary afferents mediating the sensations of warm and cold, calculated on the basis of reaction time and conduction distance are in keeping with the mediation of warm sensation by unmyelinated primary afferents and of cold sensation by small myelinated afferents. (5) Measurement of threshold by the method of levels and direct measurement of reaction time enables calculation of conduction velocity for the specific sensory submodality tested from a single stimulation site.

INTRODUCTION

Assessment of small calibre afferent fibre function as a part of the clinical evaluation of patients with peripheral neuropathy, particularly when painful, is attracting increasing attention (Lindblom and Verrillo, 1979; Kenshalo, 1986; American Diabetes Association, 1988; Fowler *et al.*, 1988; Yarnitsky and Ochoa, 1990*a*, *b*). Since measurement of thermal specific and thermal pain perception thresholds is a useful tool in assessing small calibre afferent fibre function, the need to identify key determinants of those thresholds is critical. It is known that factors such as rate of change of stimulus temperature, reaction time, and method of measurement of psychophysical thresholds significantly influence the measure of the threshold value (Fruhstorfer *et al.*, 1976; Croze and Duclaux, 1978; Pertovaara and Kojo, 1985; Yarnitsky and Ochoa, 1990*a*).

In the present study, thresholds for warm sensation (WS) and cold sensation (CS) were determined using two methods, the method of levels, a variant of the forced-choice paradigm (*see* Yarnitsky and Ochoa, 1990*a*) and the method of limits (Fruhstorfer *et al.*, 1976). In addition, reaction times (RTs) were directly measured, as well as indirectly calculated through the measured thresholds. Results clearly identify RT as the reason for artefactual elevation of psychophysical threshold when using the method of limits,

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and document the dependence of this artefact upon the rate of change of stimulus temperature. RTs were used for calculation of conduction velocity of primary afferents subserving cold and warm sensation. The calculated conduction velocity values are consonant with accepted association of WS to unmyelinated primary afferents and of CS to small myelinated afferents.

It was realized during the study that it is possible to measure conduction velocity of primary afferents concerned with CS and WS without the need to apply stimuli at two different sites to calculate conduction time by subtraction (Fruhstorfer, 1976; Fowler *et al.*, 1988). This is based on perusal of RT measured at threshold stimulus intensity.

METHODS

Psychophysical perception thresholds for sensations of warm and cold were measured using the Quantitative Thermotest (QTT, Somedic AB, Stockholm) (Fruhstorfer *et al.*, 1976). A Peltier type thermode measuring 2.5×5 cm was applied to the thenar eminence of normal human volunteers. Temperature of the thermode could either rise or fall, at various rates, depending on the direction and intensity of the current flow through the Peltier device. Two methods of threshold determination were used.

1. *The method of levels*

A temperature ramp was given to the skin and the subject was asked to describe, after the temperature returned to adaptation, whether or not a thermal sensation was perceived. When measuring WS threshold, the initial temperature step was from 32 to 33° C. If warmth was perceived, the following temperature step was 0.2° C lower. Further decrements of 0.2° C were implemented if necessary until warm sensation was not perceived. If, on the other hand, the subject did not perceive a thermal sensation after the first 1° C step, successive increments of 0.2° C were implemented, until warmth was perceived. For CS thresholds, the initial step was from 32 to 31° C, with increments or decrements of 0.2° C for successive stimuli depending on subject's response. Temperature midway between the highest negative response and the lowest positive response, which were always 0.2° C apart, was taken as the threshold. This threshold will be referred to as *detection threshold.*

2. *Method of limits*

The examiner triggered a ramp of either increasing or decreasing temperature, asking the subject to reverse the stimulus by pressing a switch, at the first thermal sensation perceived. Threshold was determined as the average reading of 4 successive stimuli. The threshold obtained by this method will be referred to as *signalled threshold.*

Having determined detection thresholds for warm sensation and cold sensation by the method of levels, the RT for these sensations was directly measured by delivering a thermal stimulus just beyond the identified threshold while asking the subject to press the switch at the moment a thermal sensation was felt. Both temperature step and subject's response were registered on a chart recorder (Gould ES1000, Elk Grove Village, Illinois), and RT was directly extracted from the record by measuring the time between the moment the stimulus reached detection threshold level and moment of signalled threshold was recorded (measurement accuracy 0.1 s).

Indirect measurement of RT was obtained by calculating the difference between thermal thresholds obtained by the two methods. Dividing this temperature difference by the rate of temperature change yields the time between the instant at which sufficient stimulus was delivered peripherally, ultimately to induce a sensation, and the time the subject reported the sensation (*see* Yarnitsky and Ochoa, 1990*a*). This time interval is, presumably, the reaction time; 200 ms for central processing and efferent conduction were then subtracted from the calculated RT, and conduction velocity was obtained by dividing distance between stimulus site and spinal process of C7, by the resultant RT.

The whole procedure was repeated at three rates of temperature change, both for high temperature and low temperature stimulation, at random order. Rates were 1.6, 4.2 and 6.7° C/s for high temperature stimuli and 2.4, 4.5 and 6.6° C/s for the low temperature stimuli.

RESULTS

Subjects

Fifteen healthy volunteers were tested, 5 males and 10 females, mean age was 29.3 (range 15–41) yrs. The QTT probe was attached to the right thenar eminence in 6 and to the left in 9 subjects. Mean distance between stimulus site and spinous process of C7 vertebra was 0.716 m.

Thresholds

Mean thresholds obtained by the method of levels, measured from adapting temperature of 32° C, were 32.47 ± 0.07° C for WS and 31.80 ± 0.05° C for CS (mean ± SEM). There was no detectable effect of rate of temperature change upon thresholds obtained through this method (Table 1). Thresholds obtained by the method of limits were always higher than those obtained by the method of levels. Differences between thresholds

TABLE 1 THRESHOLDS FOR WARM SENSATION AND COLD SENSATION OBTAINED BY TWO METHODS AT DIFFERENT RATES OF TEMPERATURE CHANGE (FROM ADAPTING TEMPERATURE OF 32° C)

Warm sensation			
Rate (° C/s)	1.5	4.2	6.7
Thresholds (° C)			
Method of levels	0.47	0.50	0.45
Method of limits	1.42	3 30	5.27
Difference between methods	0 95	2.80	4.82
Cold sensation			
Rate (° C/s)	2 4	4.5	6.6
Thresholds (° C)			
Method of levels	0.23	0.21	0.17
Method of limits	1.49	2 32	3.23
Difference between methods	1.26	2.11	3 06

obtained through the two methods were greater for WS than CS. In addition, differences increased with higher rates of rise of temperature stimuli (Table 1). Graphic representation of the influence of rate of temperature change on difference between thresholds obtained by the two methods for the two sensory submodalities displays a larger dependence for WS than CS (t test, $P < 0.001$) (fig. 1).

Reaction time

For both sensory submodalities, RTs were independent of rates of temperature change both for direct and indirect measurements. This was calculated by three-way ANOVA with repeated measures. The mean RT for WS was 0.73 s by direct measurement, and 0.67 s for indirect (Table 2). For CS, RTs were 0.50 s and 0.49 s, respectively. Thus within each modality, there was no difference between RTs obtained by either method. Comparing RTs for the two submodalities did reveal an anticipated difference, with RTs significantly shorter for CS than for WS ($P < 0.001$).

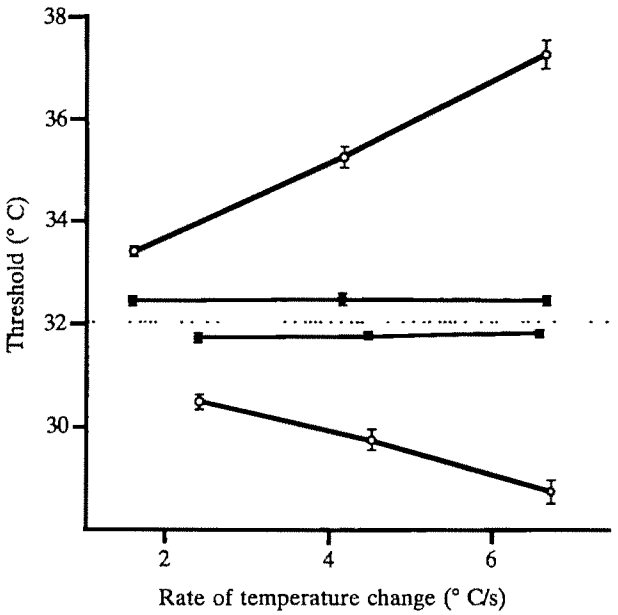

FIG. 1. Thresholds for warm and cold sensations measured from adapting temperature of 32° C (dotted line). Thresholds obtained by the method of levels (filled circles) are lower than those obtained by the method of limits (open circles), and are not affected by the rate of temperature used in the measurement, as are the thresholds obtained by the method of limits Note the steeper slope for warm thresholds as opposed to cold thresholds, suggesting slower conduction velocity in primary afferents mediating warm sensation.

TABLE 2 REACTION TIMES AND CONDUCTION VELOCITIES FOR WARM AND COLD SENSATIONS OBTAINED BY DIRECT AND INDIRECT MEASUREMENTS

	RT (s) for three rates of temperature change (° C/s)			*Mean RT (s)*	*Mean conduction velocity ($m \cdot s^{-1}$)*
Warm sensation					
	1 5	*4 2*	*6.7*		
Direct	0.70	0.77	0.72	0.73	1 5
Indirect	0.61	0.67	0.72	0 67	1 6
Cold sensation					
	2.4	*4 5*	*6.6*		
Direct	0.52	0 48	0 50	0 50	2.7
Indirect	0.53	0 47	0 47	0 49	2.6

Conduction velocity

For each individual the peripheral conduction distance was divided by the corresponding RT after subtracting 200 ms allowed for central and efferent times. For WS, conduction velocity based on directly measured RT was 1.5 ± 0.14 m·s^{-1} (mean ± SEM), and 1.6 ± 0.11 m·s^{-1} when based on calculated RT. For CS, velocities were 2.7 ± 0.28 m·s^{-1} based on directly measured RT and 2.6 ± 0.17 m·s^{-1} based on calculated RT.

DISCUSSION

Thermal specific thresholds

Measurement of threshold can depend either on reaction time or be independent of it. When a stimulus of predetermined intensity is given, and the subject is asked to judge the presence or absence of sensation post factum, RT is excluded from the threshold measurement. This paradigm was popularized by Dyck *et al.* (1984) and is used, in different ways in the Glasgow (Jamal *et al.*, 1985) and Middlesex (Fowler *et al.*, 1987) devices. The protocol used in this study under the name 'method of levels' represents an elaboration of such paradigms developed for a study on heat pain thresholds (Yarnitsky and Ochoa, 1990*a*). As shown in Table 1 and fig. 1, thresholds obtained by the method of levels are not affected by rate of temperature change. This is in agreement with studies by Hensel (1952) and Kenshalo *et al.* (1968), both showing that when rates of temperature change are increased, thresholds for WS and CS remain unaltered except at very low rates of stimulus change.

The method of limits, as routinely used for threshold determination through the QTT, does include RT in the measurement, leading to artefactual elevation of thresholds, as forecasted by Fruhstorfer *et al.* (1976), and as factually demonstrated for the sensation of heat-induced pain by Yarnitsky and Ochoa (1990*a*). In this method, temperature continues to change *after* a stimulus, intense enough to induce sensation, is delivered at the periphery. Temperature change is reversed by the subject only after the neural message induced by that stimulus at the periphery reaches the brain, is processed, and the efferent message is delivered to the signalling hand. Thresholds obtained by this method are therefore bound to be of higher value than those obtained by the method of levels. Indeed, as seen in Table 1, thresholds obtained by this method were always higher than those obtained by the method of levels. Further, this artefactual threshold elevation is clearly a function of the rate of rise of stimulus temperature, since a larger temperature step is covered by a steeper temperature ramp along a fixed time interval. Indeed, higher rates of temperature change induced larger artefactual threshold elevations. In addition, as anticipated, this artefactual threshold elevation was greater for slowly conducted messages, since the longer time interval allows coverage of a larger temperature step. Thus artefacts for WS were significantly larger than for CS (Table 1, fig. 1).

RT measurement for calculation of conduction velocity

Although RT interferes with psychophysical threshold measurements, it can be used for calculation of peripheral conduction velocity. The time sequence culminating in the psychophysical measurement of signalled threshold involves four components. The first is stimulus rise time, during which stimulus intensity approaches psychophysical detection threshold level. For stimuli that originate at a given baseline temperature and change at a specific rate, the detection threshold temperature will obviously govern the rise time; it will be longer for higher threshold values. Next is the peripheral afferent conduction time, a function of conduction velocity in the pertinent channels, and of conduction distance. The last two components are central processing and efferent conduction times. Central processing for sensory stimuli is estimated at 150–190 ms (Price *et al.*, 1977; Campbell and LaMotte, 1983) and efferent time consumes less than 20 ms (conduction of $> 50\ m \cdot s^{-1}$ along less than 1 m from brain to the signalling hand).

It was customary to calculate peripheral conduction velocity for cold sensation and warm sensation on the basis of RT in response to *suprathreshold* stimuli (Wright, 1951; Lele and Sinclair, 1955). An improved method involves measurement of RTs for stimuli applied at a proximal and a distal site, separated by a known distance, and subtraction of RTs, as reported by Fruhstorfer (1976) and Fowler *et al.* (1988). This method relies on the assumption that rise times at the two sites are equal, which is probably fair, except for minor variation in thermal thresholds between different body sites (Kenshalo *et al.*, 1967; Stevens *et al.*, 1974; Pertovaara and Kojo, 1985). Measurement of RT to stimuli applied to a single site allows further improvement of the method. This is possible when afferent conduction time is isolated from the preceding rise time and from the subsequent processing and efferent times. The end-point of the rise time, which equals onset of the afferent conduction time, occurs when stimulus intensity reaches detection threshold. Therefore, if a stimulus of this very intensity is given, afferent conduction immediately follows the stimulus end-point thus allowing for exact measurement of onset of afferent conduction. The demonstration by Jamal *et al.* (1985) that detection thresholds are remarkably consistent adds reliability to this procedure. In order to isolate afferent conduction time, its end-point is determined by subtracting central processing time and efferent conduction time. For a specific sensory modality in a uniform measurement set-up, such central processing time can be taken as a fixed value. As shown in Table 2, conduction velocities calculated in this way were 1.5 and 2.7 $m \cdot s^{-1}$ for warm and cold sensation respectively. Similar results were obtained by Fowler *et al.* (1988) by subtraction of RTs for two remote sites.

This method may be applicable to other sensory submodalities such as thermal or mechanical pain, particularly in disease, where the identity of the primary afferent responsible for transmission of abnormal sensation is debated, such as in hyperalgesia in reflex sympathetic dystrophy and other neuropathic pain disorders. There is another potential application to focal somatosensory dysfunction when the distribution of pathology does not allow measurement from two remote sites.

Indirect RT calculation

It is important to ascertain whether RT constitutes the whole difference between the two methods of threshold measurement described above. This can be tested by calculating the difference emerging from comparing times used for the same task from the same body part when applying the two methods. Dividing the temperature difference between the two thresholds by the rate of temperature change yields a time value. This value is remarkably similar to the directly measured RT. It proves to be the principal difference between the two methods and therefore the source of the artefactual threshold reading.

In conclusion, the present study defines RT for warm sensation and cold sensation from the human hand, the distinctive role of RTs in threshold determination and the dependence of thresholds measured through RT on rate of stimulus temperature change. In order to minimize the RT-induced artefact, it is recommended that for clinical purposes, the method of limits which includes RT is used at low rates of temperature change. The study contributes a further step in understanding relationships between thermal stimuli and subgroups of responsive primary afferents; the neural message induced by warm stimuli is associated with unmyelinated primary afferents, while the message induced

by cold stimuli is associated with small myelinated afferents. The present array of measurements can be derived from a single body site and easily processed to yield peripheral conduction velocity.

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Brain (1991), **114**, 1827–1853

THE PATHOPHYSIOLOGY OF CHRONIC RELAPSING EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS IN THE LEWIS RAT

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SUMMARY

Electrophysiological studies were performed in Lewis rats with chronic relapsing experimental allergic encephalomyelitis (EAE) induced by inoculation with guinea-pig spinal cord and adjuvants and treatment with low dose cyclosporin A. During clinical episodes there was conduction failure in the central nervous system (CNS), namely the spinal cord dorsal columns, and in the afferent fibres in the peripheral nervous system (PNS). The following observations indicated that the conduction failure was mainly due to demyelination-induced conduction block: (1) rate-dependent conduction block in the CNS and PNS; (2) temporal dispersion due to slowing of PNS conduction; (3) restoration of PNS conduction by cooling; (4) restoration of CNS conduction by ouabain; (5) previously demonstrated histological evidence of primary demyelination in the dorsal columns, dorsal root ganglia and dorsal roots; and (6) the temporal association of restoration of conduction with remyelination. However, it is likely that CNS and PNS axonal degeneration, which occurs in this disease, also contributed to the conduction failure. In clinical remissions there was restoration of conduction in the CNS and PNS which can be explained by ensheathment/remyelination by oligodendrocytes and Schwann cells, respectively. In most rats during clinical episodes the cerebral somatosensory evoked potential was reduced in amplitude and prolonged in latency, which can be accounted for by demyelination and axonal degeneration in the CNS and PNS components of the afferent pathway. In 2 rats with episodes of EAE, however, this potential was markedly increased in amplitude, which might have been due to demyelination-induced conduction block of descending pathways that normally inhibit synaptic transmission in the afferent pathway. In well-established remission there was residual conduction failure in the CNS and PNS which can be mainly accounted for by axonal degeneration.

INTRODUCTION

Experimental allergic encephalomyelitis (EAE) is an autoimmune demyelinating disease and is widely studied as a possible animal model of the human central nervous system (CNS) demyelinating diseases, particularly multiple sclerosis (Raine, 1984). EAE may have an acute or chronic relapsing course. Acute EAE is monophasic like the human disease, acute disseminated encephalomyelitis. Chronic relapsing EAE has a chronic relapsing course and produces large plaques of CNS demyelination as in multiple sclerosis. The pathophysiology of acute EAE has been studied in detail in the rabbit (Pender and Sears, 1982, 1984, 1985) and in the Lewis rat (Pender, 1986*a*, *b*, 1988*a*, *b*, 1989; Pender and Sears, 1986; Heininger *et al.*, 1989). These studies have revealed demyelination and nerve conduction abnormalities in the dorsal root ganglia of rabbits (Pender and Sears, 1982, 1984, 1985) and rats with acute EAE induced by inoculation with whole

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spinal cord (Pender and Sears, 1986) and in the CNS portions of the spinal cord ventral root exit zones in these rats (Pender, 1986*a*, 1988*a*). In rats with acute EAE induced by inoculation with myelin basic protein, demyelination and nerve conduction abnormalities were demonstrated in the dorsal roots, ventral roots and ventral root exit zones (Pender, 1986*b*, 1988*b*). In rats with acute EAE adoptively transferred with myelin basic protein-specific T lymphocytes, Heininger *et al.* (1989) demonstrated conduction abnormalities in the spinal cord and spinal roots which they attributed to demyelination. During recovery from acute EAE in the rat there is restoration of conduction in the CNS and peripheral nervous system (PNS) associated with ensheathment/remyelination by oligodendrocytes and Schwann cells, respectively (Pender, 1989).

Visual and auditory evoked potentials have been assessed in guinea-pigs with chronic relapsing EAE (Lidsky *et al.*, 1980; Wiśniewski *et al.*, 1982) but there have been no other studies of the pathophysiology of chronic relapsing EAE. We have therefore undertaken electrophysiological studies on the surgically exposed nervous system to assess function in the CNS and PNS during episodes and remissions of chronic relapsing EAE in the Lewis rat. These studies were performed on the background of a detailed neuropathological assessment which revealed inflammation and demyelination in the CNS, particularly the spinal cord, and in the PNS, specifically the ventral and dorsal roots and dorsal root ganglia, during the first and second episodes, and CNS and PNS remyelination during the first and second remissions (Pender *et al.*, 1990). Brief preliminary reports of these electrophysiological studies have been published in abstract form (Stanley and Pender, 1989; Pender and Stanley, 1989).

MATERIAL AND METHODS

Animals

Female Lewis rats (JC strain) bred by the Central Animal Breeding House of the University of Queensland were used. They were kept 5 to a cage and with an unrestricted cage supply of rat and mouse cubes and water.

Induction of chronic relapsing EAE

Each batch of inoculum was prepared by homogenizing a mixture of 1 g guinea-pig spinal cord, 1 ml 0.9% saline, 1 ml complete Freund's adjuvant (Difco) and 10 mg Mycobacterium tuberculosis H37RA (Difco). Under ketamine/xylazine anaesthesia, rats aged 7–10 wks were injected intradermally with 0.05 ml inoculum into the medial footpad of the right hindfoot. Commencing on the day of inoculation the rats were given subcutaneous injections of cyclosporin A (CyA) (Sandoz) (4 mg/kg) on alternate days until 22 days postinoculation (DPI), as described by Polman *et al.* (1988). In terminal experiments, electrophysiological studies were performed on rats at different stages of the disease. At the end of the electrophysiological study one of the rats was perfused with fixative for histological studies as previously described (Pender *et al.*, 1990).

Clinical assessment

The rats were examined daily from 7 DPI. Tail, hindlimb and forelimb weakness were each graded on a scale of 0 (no weakness) to 4 (complete paralysis) as previously described (Pender, 1986*b*), and these 3 scores were added together to give a total clinical score (maximal deficit = 12).

Controls

Electrophysiological studies were performed on normal control rats 9–13 wks old and on 3 rats treated with CyA as above but not inoculated.

Electrophysiological studies

Anaesthesia was induced by the intraperitoneal (i.p.) injection of ketamine (74 mg/kg), xylazine (9 mg/kg) and atropine (36 μg/kg) and maintained with further i.p. injections of half these doses. An adequate depth of anaesthesia was maintained without depressing the corneal reflex. The rats breathed spontaneously through a tracheal cannula. 8 ml of Hartmann's solution (compound sodium lactate BP, Travenol) were given i.p. at the beginning of each experiment, and 1 ml of Haemaccel (polygeline, Behring Ltd) was given i.p. after the laminectomy and craniectomy had been performed.

Dorsal root entry zone (DREZ) recordings. A T12–L6 laminectomy was performed, the animal was mounted on an animal frame, and a metal box, through which water at 37° C was circulated, was placed under the animal. A pool was made with the skin flaps and the dura opened. The left hindlimb was extended and supported in a horizontal position. The left sciatic nerve and gastrocnemius muscle were exposed in the posterior thigh and a skin pool formed. The sciatic nerve in the midthigh was dissected free with care to avoid damage to its blood supply. The exposed nervous tissues were rinsed in Hartmann's solution, and paraffin oil was added to cover the tissues. A controlled radiant heat lamp maintained the laminectomy and sciatic pools at 37° C. Under these conditions the rectal temperature was 37° C–38° C. The left sciatic nerve was lifted away from the volume conductor and stimulated in continuity with a pair of platinum electrodes 3 mm apart. Stimuli were 0.1 ms square-wave voltage pulses delivered at 1 Hz.

Volume conductor recordings were made over the left L4 DREZ with a 0.5 mm diameter silver ball electrode as the active electrode. The reference electrode was a platinum wire placed on the right paravertebral region at the same level as the active electrode. The recording electrodes were shielded leads connected to FET source-followers and thence to a preamplifier (bandwidth limited to 5.3–10 000 Hz) and then for display on an oscilloscope. For all recordings, negativity at the active electrode gave an upward deflection on the oscilloscope. Oscilloscope traces were photographed for measurements. Conduction velocities were calculated after allowing for a utilization time of 0.1 ms (Blair and Erlanger, 1936). To assess the transmission of high frequency trains of impulses the sciatic nerve was stimulated supramaximally at 10 Hz for 60 s or at 100 Hz for 10 s. The effect of repetitive stimulation was determined by calculating the ratio of the amplitude of the response evoked by the last stimulus of the 10 Hz or 100 Hz train to the amplitude of the response evoked by stimulation at 1 Hz. At the end of the experiment the dissection was extended to expose the entire length of the conduction pathway from the sciatic nerve to the L4 DREZ. Conduction distance was measured as the length of a thread placed along the conduction pathway. The L4 and L5 spinal nerves always gave larger contributions to the sciatic nerve, and the L3 and L6 spinal nerves gave small contributions.

Dorsal column recordings. Conduction through the dorsal columns was studied by stimulating the exposed left dorsal column 1 mm from the midline with two 0.25 mm diameter platinum wire electrodes (with J-shaped tips, the convexities being placed on the cord) 3 mm apart, with the cathode at the level of the L3 DREZ. Stimuli were 0.02 ms duration square-wave voltage pulses delivered at 1 Hz. The short stimulus duration was chosen to minimize stimulus artefact. The active recording electrode was a 0.5 mm diameter silver ball electrode placed on the left dorsal column at the level of the S4 DREZ. The reference electrode was a 0.2 mm diameter platinum wire electrode placed on the left paravertebral tissues at the same level as the active recording electrode. The distance between the stimulating cathode and the active recording electrode was always 16 mm. A maximal response was obtained in the normal control at a stimulus intensity of about 0.25 V. Cutting the left L3–L6 dorsal roots had no effect on the response. When the right dorsal spinal cord was cut 3 mm caudal to the stimulating cathode or 2 mm rostral to the active recording electrode, the response amplitude was reduced by 50%. Cutting the left dorsal spinal cord at the same level abolished the remaining response. These effects confirmed that the recorded response was transmitted through the dorsal columns.

Cerebral somatosensory evoked potentials (SSEPs). A craniectomy extending from 1 mm anterior to the bregma to 5 mm posterior to the bregma and from 1 mm lateral to the midline to 5 mm lateral to the midline was performed. A pool was made with the skin flaps. The dura was opened and, after rinsing with Hartmann's solution, paraffin oil was added to the pool. The exposed sciatic nerve was stimulated in the same site as for the DREZ recordings, with 0.1 ms square-wave voltage pulses delivered at 0 2 Hz. The active recording electrode was a 0.5 mm diameter silver ball electrode positioned on the exposed cerebral

cortex 3 mm lateral and 1 mm posterior to the bregma, as this site was found to yield the maximal response. The reference electrode was a 0.2 mm diameter platinum wire placed on the cranium at the bregma. The bandwidth was limited to 30–10 000 Hz. The signal was fed from the preamplifier to an NL106 a.c.-d.c. amplifier (Digitimer Ltd) and thence to a Digitimer Neurolog NL750 signal averager before display on an oscilloscope; 32 sweeps were averaged

M wave and H reflex recordings. The left sciatic nerve was stimulated as for the DREZ recordings except that the polarity of the stimulating electrodes was reversed. Recordings were made with a 25 gauge needle electrode in the belly of the fourth dorsal interosseus muscle and with a reference 25 gauge needle electrode subcutaneously in the plantar aspect of the distal fourth digit of the left hindfoot.

Statistical analysis. To compare the recordings from normal control rats with those from rats at each of the different stages of chronic relapsing EAE, parametric analysis of variance was used except for the comparison of the amplitudes of the cerebral somatosensory evoked potentials. For the latter the Kruskal-Wallis test was used because the data in 2 of the groups were not normally distributed.

RESULTS

Clinical findings

The clinical course in this model of chronic relapsing EAE has previously been described in detail (Pender *et al.*, 1990). Tail weakness commenced 11–16 DPI. Over the next 2 days the tail usually became completely paralysed and hindlimb weakness developed. Most of the affected animals recovered from this episode and had minimal or no residual deficit by 18–22 DPI. Of those that recovered, 85% had a second episode usually commencing 19–26 DPI. The pattern, severity and temporal profile of the neurological signs in the second episode were similar to those in the first episode. Clinical recovery from the second episode was usually complete 26–34 DPI. Of these rats, 60% had a third episode usually commencing 28–34 DPI and had recovered from this episode 33–39 DPI. The clinical profile of a rat studied electrophysiologically in the second episode is shown in fig. 1A. Some of the rats (25%) recovered incompletely or not at all from the first episode and had a chronic persistent or chronic progressive clinical course, although partial exacerbations and remissions often punctuated the course. Neurological signs persisted up to 48 DPI in some of these animals and then resolved.

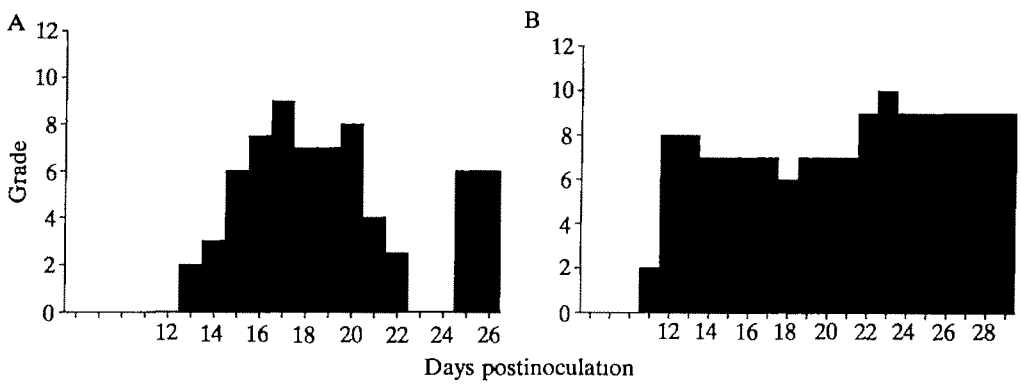

FIG 1. Clinical profiles of a rat studied electrophysiologically in the second episode of EAE 26 DPI (A) and of a rat with a chronic persistent course studied electrophysiologically 29 DPI (B).

The clinical profile of a rat which had a chronic persistent course and which was studied electrophysiologically is shown in fig. 1B.

Electrophysiological studies were performed on rats during the first episode (12–16 DPI), the first remission (18–20 DPI), the second episode (22–26 DPI), chronic persistent EAE (29–34 DPI) and well-established late (second or third) remission (50–64 DPI). The rats in the chronic persistent EAE group were studied at the usual time of the third episode (29–34 DPI). Two of these rats had a chronic persistent course with a clinical score > 6 from the first episode onwards; the other 3 had 3 episodes but either the first or the second remission was incomplete.

Lumbar DREZ recordings

Conduction through the PNS afferent pathway from the peripheral nerve to the spinal cord was studied in 17 normal controls and in 26 animals with chronic relapsing EAE (Table 1, figs 2, 3). The clinical scores for each group at the time of study also are shown in fig. 3. The normal L4 DREZ response to sciatic nerve stimulation consists of a biphasic wave (positive, negative) representing the afferent volley, and a late slow negative wave, the N wave, which is a field potential due to synaptic currents in the second order dorsal horn neurons excited mainly by low threshold cutaneous afferents (Pender and Sears, 1986) (fig. 2A).

First and second episodes. During the first and second episodes of chronic relapsing EAE the peak-to-peak amplitude and conduction velocity of the peak of the negativity of the maximal afferent volley potential were significantly reduced without temporal dispersion, and the peak of the maximal N wave was significantly reduced in amplitude and prolonged in latency (Table 1, figs 2, 3). These findings indicate failure of excitation or conduction block of the large diameter afferent fibres.

First and late remissions. During the first remission the afferent volley potential amplitude and velocity and the N wave amplitude and latency were significantly different from those of normal controls (Table 1). However, during the first remission the abnormalities were less severe than in animals studied during the first episode, although the differences between the parameters measured during the first episode and the first remission were statistically significant only for the N wave amplitudes and latencies (Table 1, fig. 3). As the animals studied during the first remission had had clinical episodes similar in severity to those of the animals studied during the first episode, these findings indicate restoration of conduction in some afferent fibres during the first remission.

During late remission the abnormalities of the afferent volley potential amplitude and velocity and of the N wave latency were significantly less severe than in animals studied during the second episode (Table 1, fig. 3). The velocity of the afferent volley and the N wave latency were now normal but the amplitudes of the afferent volley and N wave were significantly lower than in normal controls. As rats studied during late remission had had a similar clinical course to those studied during the second episode, these findings indicate restoration of conduction in many afferent fibres. The return to normal afferent volley conduction velocity indicates that at this stage there was no detectable conduction slowing. The decreased amplitude of the afferent volley without temporal dispersion suggests persistent conduction failure in other fibres.

TABLE 1 LUMBAR DREZ RECORDINGS

	Controls (*n* = 17)	*First episode* (*n* = 7)	*First remission* (*n* = 4)	*Second episode* (*n* = 6)	*Chronic persistent* (*n* = 5)	*Late remission* (*n* = 4)	*Analysis of variance. Value and significance of F*
DPI		12–16	19–20	22–26	29–34	50–64	
Maximal afferent volley							
		n s		$P < 0.025$			
Peak-to-peak amplitude (μV) Mean ± SD	1215 ± 275	497 ± 365 *$P < 0.001$	561 ± 167 $P < 0.001$	485 ± 411 $P < 0.001$	540 ± 195 $P < 0.001$	736 ± 216 $P < 0.001$	$F = 10.85$ $P < 0.001$
		n s		$P < 0.001$			
Conduction velocity to the peak of negativity ($m \cdot s^{-1}$)	55.6 ± 4.7	48.1 ± 6.7 $P < 0.001$	49.5 ± 2.6 $P < 0.001$	49.9 ± 1.7 $P < 0.001$	50.0 ± 6.3 $P < 0.001$	57.6 ± 2.3 n s	$F = 3.95$ $P < 0.01$
Maximal N wave							
		$P < 0.005$			$P < 0.001$		
Latency of peak (ms)	2.4 ± 0.23	3.0 ± 0.39 $P < 0.001$	2.7 ± 0.15 $P < 0.001$	2.9 ± 0.32 $P < 0.001$	2.8 ± 0.38 $P < 0.001$	2.5 ± 0.08 n s	$F = 5.81$ $P < 0.001$
		$P < 0.025$			n s.		
Amplitude of peak (μV)	1331 ± 294	774 ± 363 $P < 0.001$	1039 ± 393 $P < 0.001$	904 ± 322 $P < 0.001$	759 ± 337 $P < 0.001$	954 ± 254 $P < 0.001$	$F = 4.80$ $P < 0.01$

* The significance under each mean refers to the comparison with the control mean, n s = not significant.

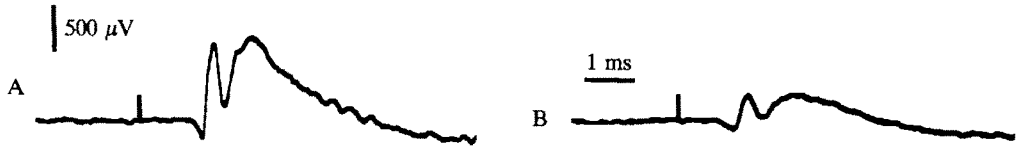

FIG 2 Volume conductor recordings of the L4 DREZ maximal afferent volley evoked by sciatic nerve stimulation in a normal control rat (A) and in a rat during the first episode of EAE (B) In these and all subsequent recordings the onset of the stimulus is indicated by a vertical line

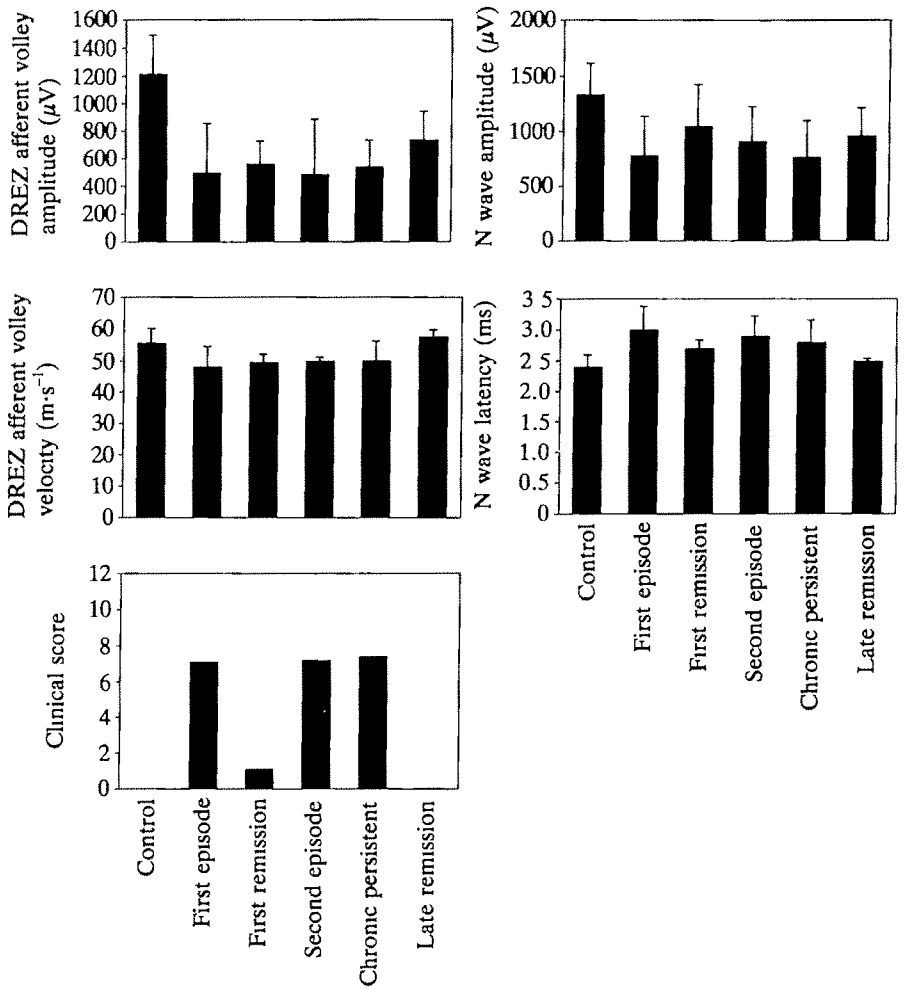

FIG. 3. L4 DREZ recordings and total clinical scores during chronic relapsing EAE.

Chronic persistent EAE. In rats with chronic persistent EAE the afferent volley potential amplitude and velocity were significantly decreased and the N wave was significantly decreased in amplitude and prolonged in latency compared with normal controls

(Table 1, fig. 3). The mean N wave latency of rats with chronic persistent EAE was significantly shorter than that of rats studied during the first episode ($P < 0.05$). Temporal dispersion, indicating slowing of conduction, of the afferent volley was observed in 2 rats with chronic persistent EAE. As the degree of temporal dispersion was insufficient to account solely for the reduced amplitude in these 2 rats and as temporal dispersion was absent in the other 3 rats, these findings also indicate failure of excitation or conduction block in large diameter afferents.

Effects of repetitive stimulation and temperature on DREZ recordings

As demyelinated fibres have an impaired ability to transmit trains of impulses (McDonald and Sears, 1970) and as conduction in demyelinated fibres is abnormally susceptible to temperature changes (Rasminsky, 1973), the effects of repetitive stimulation and temperature on afferent conduction from the peripheral nerve to the spinal cord were studied. The effects of repetitive supramaximal sciatic nerve stimulation on the peak-to-peak amplitude of the L4 DREZ afferent volley potential were assessed in 7 normal control animals and in 11 animals with chronic relapsing EAE (fig. 4, Table 2). In normal control rats, stimulation at 10 Hz for 60 s had no effect; however, stimulation at 100 Hz for 10 s resulted in a mean amplitude reduction of 24 ± 12(SD)% (fig. 4, Table 2). In rats studied during the first remission and second episode both tests of repetitive stimulation reduced the amplitude more than in normal controls (but F values were not significant) while repetitive stimulation had no greater effect in the rat studied during the first episode and in rats studied during late remission and chronic persistent EAE than in normal controls (fig. 4, Table 2). The effects of repetitive stimulation were fully reversible when stimulation at 1 Hz was resumed after a period of no stimulation. As supramaximal stimulation was used, these findings indicate rate-dependent block rather than a failure of excitation.

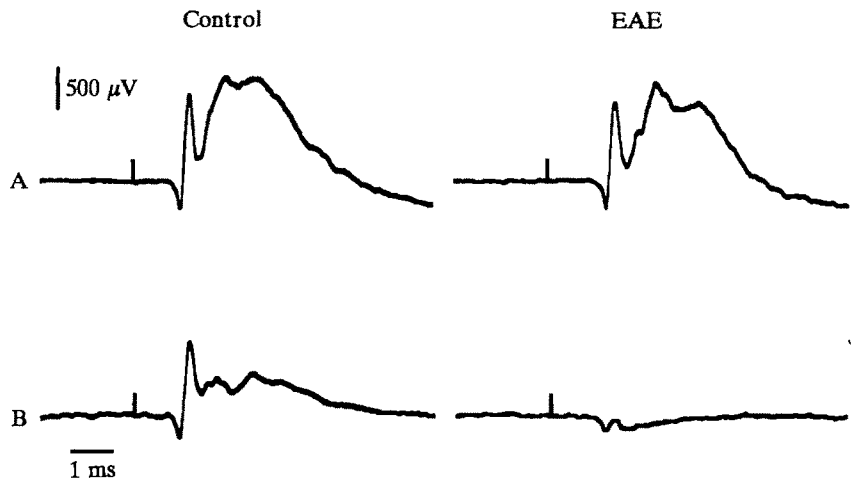

FIG. 4. Volume conductor recordings of the L4 DREZ afferent volley evoked by supramaximal stimulation of the sciatic nerve at 1 Hz (A) and immediately after a period of stimulation at 100 Hz for 10 s (B) in a normal control rat and in a rat during the second episode of EAE

TABLE 2 EFFECT OF REPETITIVE STIMULATION ON LUMBAR DREZ RECORDINGS

	Controls (n = 7)	*First episode (n = 1)*	*First remission (n = 2)*	*Second episode (n = 3)*	*Chronic persistent (n = 3)*	*Late remission (n = 2)*	*Analysis of variance Value and significance of F*
DPI		15	20	22–26	30–33	50–63	
Maximal afferent volley % reduction in peak-to-peak amplitude compared with value at 1 Hz after							
10 Hz for 60 s	0	0	13±13	8±8	0	3±4	$F = 2.49$
Mean±SD		*n.s.	$P < 0.001$	$P < 0.001$	n.s.	n.s.	n.s.
100 Hz for 10 s	24±12	16	43±11	55±27	20±5	23±3	$F = 2.88$
		n.s.	$P < 0.005$	$P < 0.001$	n.s.	n.s.	n.s.

* The significance under each mean refers to the comparison with the control mean; n.s. = not significant

TABLE 3 EFFECT OF TEMPERATURE ON LUMBAR DREZ RECORDINGS

	Controls ($n = 4$)	*First episode* ($n = 1$)	*First remission* ($n = 1$)	*Second episode* ($n = 1$)	*Chronic persistent* ($n = 4$)	*Late remission* ($n = 2$)	*Analysis of variance Value and significance of F*
DPI		15	20	23	30–34	50–63	
Maximal afferent volley % of mean peak-to-peak amplitude at 37° C Mean ± SD							
37° C	100	100	100	100	100	100	
40° C	90 ± 7	85 *n.s.	87 n.s.	95 n.s.	85 ± 8 n.s.	91 ± 7 n.s.	$F = 0.43$ n.s.
37° C	100 ± 0	100	100	100	100 ± 0	100 ± 0	
30° C	121 ± 16	114 n.s.	113 n.s.	200 $P < 0.001$	129 ± 29[a] n.s.	117 ± 2 n.s.	$F = 3.08$ n.s.
37° C	100 ± 0	100	100	100	100 ± 0	100 ± 0	

* The significance under each mean refers to the comparison with the control mean, n.s. = not significant, [a] $n = 3$.

The effect of temperature on the peak-to-peak amplitude of the maximal L4 DREZ afferent volley potential was studied in 4 normal controls and in 9 rats with chronic relapsing EAE (Table 3). In 1 rat in the second episode, lowering the laminectomy pool temperature from 37° C to 30° C increased the amplitude by 100% compared with a mean increase of $21 \pm 16\%$ in normal controls (fig. 5). After warming to 37° C the amplitude returned to the original value. This indicates that lowering the temperature reversed conduction block in some demyelinated fibres. Increasing the temperature from 37° C to 40° C did not significantly alter the amplitude. In rats in other stages of EAE, increasing or decreasing the temperature had no significant effect compared with normal controls, although in 1 rat with chronic persistent EAE cooling from 37° C to 30° C increased the amplitude by 57%.

Dorsal column recordings

To study conduction through afferent fibres in the CNS the spinal cord dorsal column compound action potential was recorded at the S4 level when the dorsal column was stimulated at the L3 level. These recordings were performed in 5 normal controls and in 16 rats with chronic relapsing EAE (Table 4, figs 6, 7). The clinical scores for each

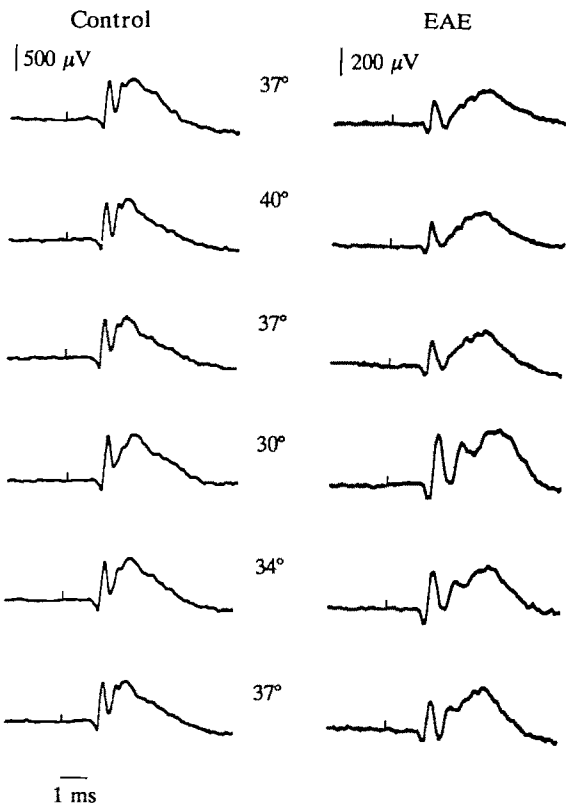

FIG. 5. Effects of laminectomy pool temperature on the L4 DREZ maximal afferent volley evoked by sciatic nerve stimulation in a normal control rat and in a rat during the second episode of EAE

TABLE 4 DORSAL COLUMN RECORDINGS

	Controls ($n = 5$)	*First episode* ($n = 3$)	*First remission* ($n = 3$)	*Second episode* ($n = 2$)	*Chronic persistent* ($n = 5$)	*Late remission* ($n = 3$)	*Analysis of variance. Value and significance of F*
DPI		12–15	20	22	29–34	50–64	
		┌ $P < 0.05$ ┐			┌ $P < 0.005$ ┐		
Peak-to-peak amplitude (μV) Mean ± SD	249 ± 100	48 ± 84 *$P < 0.001$	180 ± 53 $P < 0.025$	0 $P < 0.001$	43 ± 60 $P < 0.001$	123 ± 64 $P < 0.001$	$F = 6.44$ $P < 0.005$
		┌ n.s. ┐					
Latency-to-peak of negativity (ms)	0.42 ± 0.02	0.42[a] n.s.	0.46 ± 0.09 n.s.	–	0.50 ± 0.07[b] $P < 0.05$	0.50 ± 0.15 $P < 0.05$	$F = 0.55$ n.s.

* The significance under each mean refers to the comparison with the control mean; n.s. = not significant, [a] $n = 1$, as response absent in other 2 rats; [b] $n = 2$, as response absent in other 3 rats

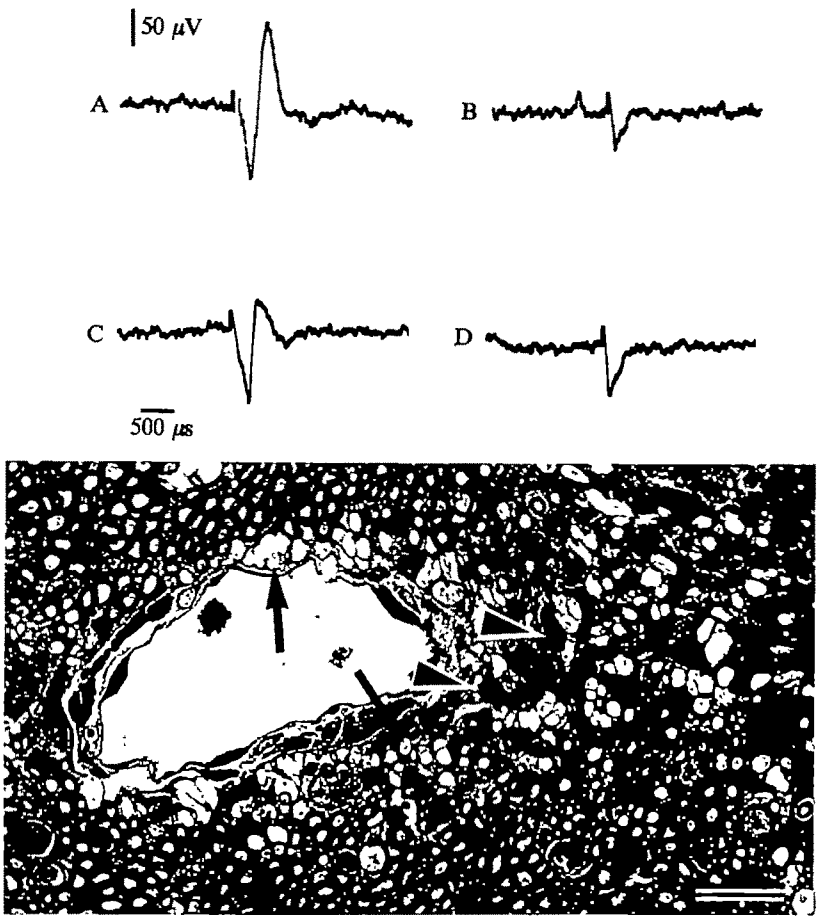

FIG. 6. Volume conductor recordings of the dorsal column maximal compound action potential in a normal control rat (A) and in rats with EAE during the first episode (B), first remission (C) and chronic persistent course (D). *Below.* Transverse section through the dorsal columns of the L6 spinal cord of the same rat as for D. Demyelinated axons (arrows) and inflammatory cells (arrowheads) can be seen. HistoResin section stained with cresyl fast violet. Bar = 25 μm.

group at the time of study also are shown in fig. 7. In the normal control the dorsal column compound action potential consisted of a biphasic wave (positive, negative) sometimes followed by a late low amplitude negativity (fig. 6A).

First and second episodes. During the first and second episodes there were statistically significant marked reductions in the peak-to-peak amplitude of the maximal dorsal column compound action potential without temporal dispersion (Table 4, figs 6, 7). This indicates failure of excitation or conduction block in a high proportion of large diameter dorsal column fibres.

First and late remissions. During the first and late remissions the amplitudes of the maximal dorsal column compound action potential were significantly higher than in animals studied during the first and second episodes, respectively, but were still

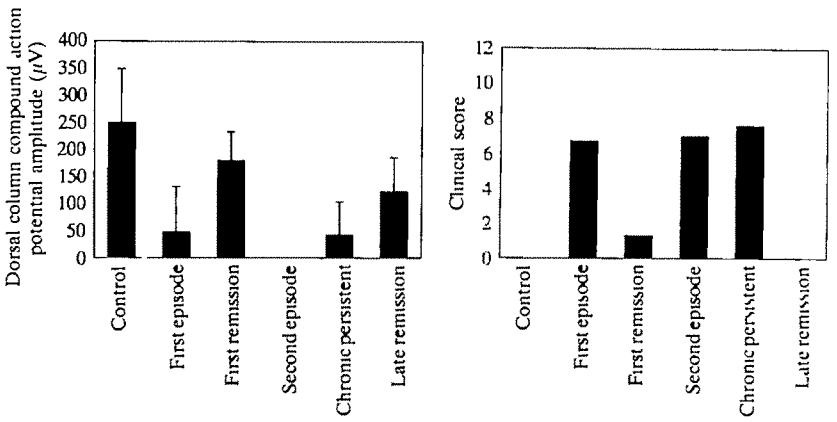

FIG. 7 Dorsal column compound action potential amplitudes and total clinical scores during chronic relapsing EAE

significantly less than in normal controls (Table 4, figs 6, 7). As the animals studied in the first and late remissions had had clinical courses similar in severity to those of the rats studied during the first and second episodes respectively, these findings indicate restoration of conduction in a high proportion of large diameter dorsal column fibres during the first and late remissions. During late remission the latency of the peak of the negativity of the dorsal column compound action potential was considerably prolonged compared with that in normal controls, although F was not significant (Table 4).

Chronic persistent EAE. In rats with chronic persistent EAE the maximal dorsal column compound action potential was markedly reduced in amplitude, without temporal dispersion, and prolonged in latency compared with normal controls (Table 4, figs 6, 7). These findings indicate a failure of excitation or conduction block in a high proportion of large diameter dorsal column fibres. Fig. 6 illustrates the conduction abnormalities and the histological findings in the dorsal column of a rat with chronic persistent EAE that was perfused through the left ventricle with fixative at the end of the electrophysiological studies. Histological examination revealed inflammation, primary demyelination, remyelination and axonal degeneration in the lumbosacral dorsal columns of this rat.

Effects of repetitive stimulation and ouabain on dorsal column recordings

The effects of repetitive supramaximal dorsal column stimulation were assessed in 4 normal control rats and in 6 rats with chronic relapsing EAE (Table 5, fig. 8). In normal control rats, stimulation at 100 Hz for 10 s resulted in a mean amplitude reduction of $6 \pm 2\%$. Compared with the effect in normal control rats, such repetitive stimulation had a greater effect in rats studied during the first remission or during chronic persistent EAE (but F was not significant). It had no significant effect in 1 rat during the first episode and in 1 rat during late remission. The effects of repetitive stimulation were fully reversible when stimulation at 1 Hz was resumed after a period of no stimulation.

It has recently been shown that ouabain, a specific inhibitor of the electrogenic sodium

TABLE 5 EFFECT OF REPETITIVE STIMULATION ON DORSAL COLUMN RECORDINGS

	Controls ($n = 4$)	*First episode* ($n = 1$)	*First remission* ($n = 2$)	*Second episode*	*Chronic persistent* ($n = 2$)	*Late remission* ($n = 1$)	*Analysis of variance. Value and significance of F*
DPI		15	20		30–33	50	
% reduction in peak-to-peak amplitude compared with value at 1 Hz after 100 Hz for 10 s							
Mean ± SD	6 ± 2	0	28 ± 29	–	36 ± 22	15	$F = 1.57$
		*n.s.	$P < 0.05$		$P < 0.01$	n.s.	n.s

* The significance under each mean refers to the comparison with the control mean, n s = not significant.

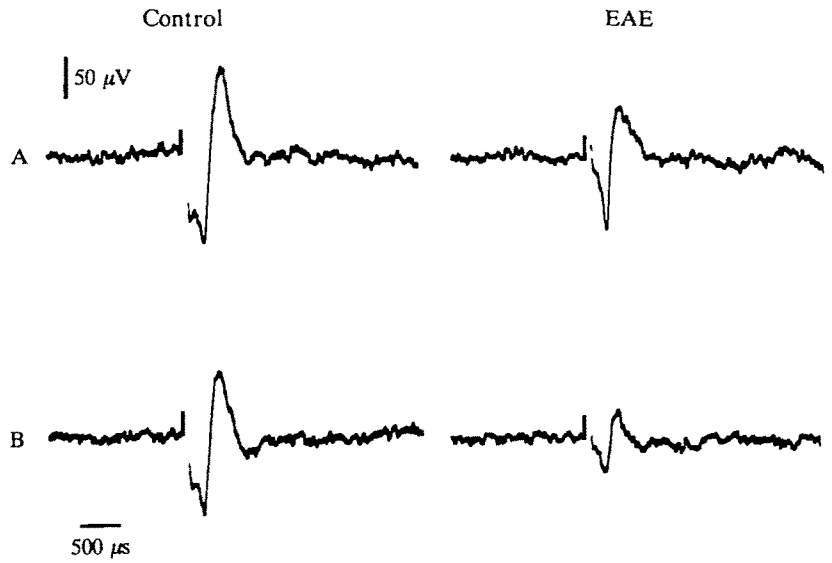

FIG. 8. Volume conductor recordings of the dorsal column compound action potential evoked by supramaximal stimulation at 1 Hz (A) and immediately after a period of stimulation at 100 Hz for 10 s (B) in a normal control rat and in a rat during the first remission of EAE

pump, reverses conduction block in single demyelinated fibres by reducing the threshold for transmission (Kaji and Sumner, 1989). We therefore assessed the effect of i.p. ouabain on the dorsal column compound action potential (at 1 Hz stimulation) in 3 rats with chronic persistent EAE. In 1 rat with a markedly reduced dorsal column compound action potential, 0.2 mg (1.5 mg/kg) ouabain i.p. increased the response to 145 μV (58% of the mean in normal controls) 15 min after administration (fig. 9). Administration of a further 0.2 mg ouabain i.p. 95 min after the first dose did not increase the amplitude further. In the other 2 rats the amplitude increased by 42% and 14% 25 min after the i.p. administration of 0.4 mg (2.9 and 2.7 mg/kg, respectively) ouabain. In the latter the response increased by 46% of the baseline value 25 min after a further 0.4 mg ouabain was given i.p., 45 min after the first injection. These findings indicate restoration of conduction in many dorsal column fibres by ouabain.

Cerebral SSEPs

To study conduction along the whole length of the PNS and CNS afferent pathway, the maximal right cerebral cortical somatosensory potential evoked by sciatic nerve stimulation was recorded in 8 normal control rats and in 21 rats with chronic relapsing EAE (Table 6, figs 10, 11, 12). The clinical scores for each group at the time of study also are shown in fig. 12. In the normal control, the averaged cerebral SSEP consisted of a biphasic wave (positive, negative) (fig. 10A).

First and second episodes. During the first and second episodes the mean peak-to-peak amplitude of the maximal cerebral SSEP did not differ significantly from that in normal control rats (Table 6). However, in these episodes the distribution of the amplitudes

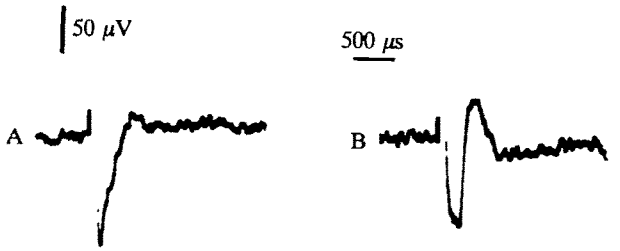

FIG 9 Volume conductor recordings of the dorsal column maximal compound action potential in a rat with chronic persistent EAE before (A) and 15 min after the i p. administration of 0 2 mg ouabain (B).

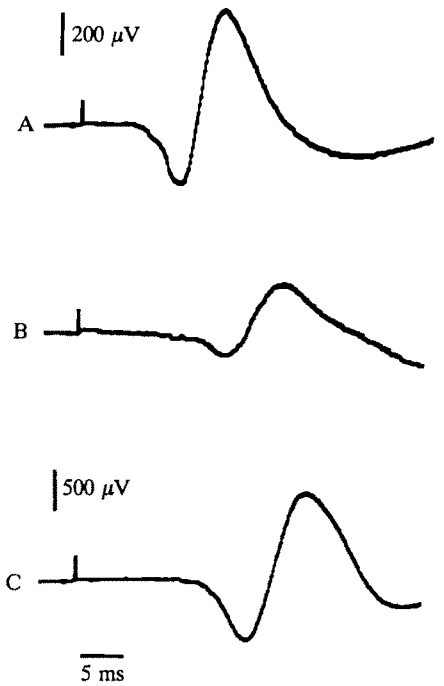

FIG 10. Volume conductor recordings of the averaged maximal right cerebral somatosensory potential evoked by left sciatic nerve stimulation in a normal control rat (A) and in rats with EAE during the first episode (B) and second episode (C). Note that the gain is lower in c

was bimodal (fig. 11). In 1 rat during the first episode and in 1 during the second episode the amplitude of the maximal cerebral SSEP was 4 and 5 SDs, respectively, above the normal mean (figs 10c, 11). In the other 6 animals the maximal cerebral SSEP amplitude was lower than the normal mean (figs 10B, 11); in 2 animals in the first episode it was 2 SDs below the normal mean and in 1 animal in the second episode it was absent. The latency to the peak of the positivity of the maximal cerebral SSEP was significantly prolonged in rats during the first and second episodes (Table 6, figs 10, 12). It was prolonged for both the high amplitude and low amplitude responses.

TABLE 6 CEREBRAL SSEPs

	Controls ($n = 8$)	*First episode* ($n = 4$)	*First remission* ($n = 4$)	*Second episode* ($n = 4$)	*Chronic persistent* ($n = 5$)	*Late remission* ($n = 4$)	*Kruskal-Wallis test and analysis of variance Value and significance of K and F*
DPI		12–15	19–20	22–26	29–34	50–64	
		n.s.		n.s.			
Peak-to-peak amplitude (μV) Mean ± SD	782 ± 207	707 ± 637 *n.s.	412 ± 168 $P < 0.05$	757 ± 763 n.s.	255 ± 170 $P < 0.01$	256 ± 167 $P < 0.01$	$K = 12.6$ $P < 0.05$
		n.s.		n.s.			
Latency-to-peak of positivity (ms)	13.8 ± 1.1	15.6 ± 2.1 $P < 0.05$	14.6 ± 1.6 n.s.	17.8 ± 2.2[a] $P < 0.001$	22.0 ± 5.3[b] $P < 0.001$	17.0 ± 2.5 $P < 0.001$	$F = 5.99$ $P < 0.005$

* The significance under each mean refers to the comparison with the control mean; n.s. = not significant, [a] $n = 3$, as absent in other rat, [b] $n = 4$, as absent in other rat

First and late remissions. In the first and late remissions the mean cerebral SSEP amplitudes were reduced, but not significantly, compared with those in rats during the first and second episodes, respectively, and were significantly reduced compared with that in normal controls (Table 6). The latencies were shorter in the first and late remissions than in the first and second episodes, respectively, but the differences were not significant (Table 6, fig. 12). Compared with that in normal controls the mean latency was not significantly prolonged during the first remission and was significantly prolonged during late remission.

Chronic persistent EAE. In rats with chronic persistent EAE the cerebral SSEP was significantly decreased in amplitude and prolonged in latency compared with that in normal controls (Table 6, fig. 12). The latency was particularly prolonged. In one rat the cerebral SSEP was absent.

M wave and H reflex studies

To assess transmission from peripheral nerve to muscle and through the monosynaptic reflex pathway, the M wave and H reflex were studied in 9 normal control rats and 22 rats with chronic relapsing EAE (Table 7, fig. 13). In normal control rats an M wave and a longer latency H reflex were recorded from the fourth dorsal interosseus muscle of the hindfoot when the ipsilateral sciatic nerve was stimulated (fig. 13A). The M wave is due to direct activation of motor fibres in the sciatic nerve while the H reflex is a monosynaptic reflex mediated by the L5 dorsal root and L5 and L6 ventral roots (Pender, 1988*a*). As the amplitude of the H reflex was greater after a period of no stimulation for several seconds, the maximal H reflex was usually recorded as the response to the first stimulus after a 5 s period of no stimulation. The ratio of the peak-to-peak amplitude of the maximal H reflex to that of the maximal M wave serves as a reliable indicator of the integrity of the monosynaptic reflex arc. The M-H latency is the difference

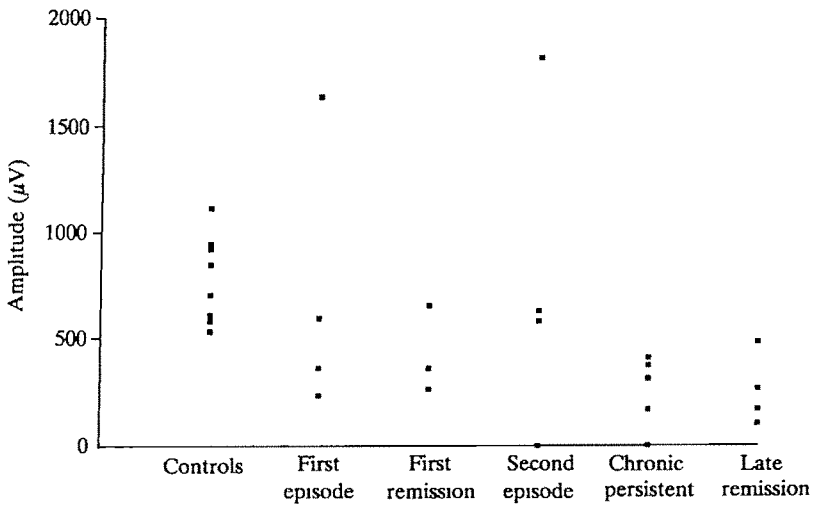

FIG. 11 Amplitudes of the averaged maximal right cerebral somatosensory potential evoked by left sciatic nerve stimulation in chronic relapsing EAE

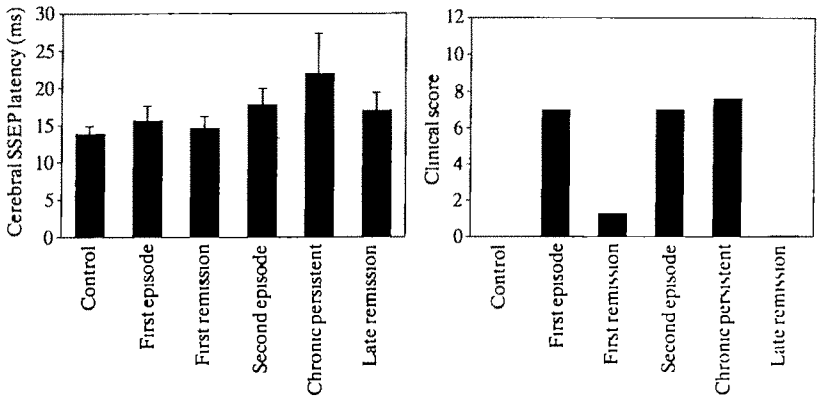

FIG 12 Cerebral somatosensory evoked potential latencies and total clinical scores during chronic relapsing EAE.

between the latency to the onset of the H reflex and the latency to the onset of the M wave and is the time for transmission through the monosynaptic reflex arc from the sciatic nerve back to the sciatic nerve at 37° C.

First and second episodes. During the first and second episodes the peak-to-peak amplitude of the maximal M wave and the latency to the onset of the M wave were normal, indicating normal peripheral nerve motor conduction (Table 7, fig. 13B). However, the mean H/M ratios were significantly reduced in both the first and second episodes compared with that in normal controls (Table 7, fig. 13B), although F was not significant. The mean M-H latency was prolonged in the first and second episodes but the difference from the normal mean reached statistical significance in the first episode only and F was not significant (Table 7). These findings indicate interruption of the monosynaptic reflex arc.

First and late remissions. In the first and late remissions the mean H/M ratios were higher than those in the first and second episodes, respectively, but only the difference between late remission and the second episode was significant (Table 7, fig. 13). The mean M-H latency during the first remission was shorter than that during the first episode but the difference was not statistically significant; this latency was also not significantly different from the normal mean. As the animals studied in the first and late remissions had had clinical courses similar in severity to those of the rats studied in the first and second episodes, respectively, these findings are consistent with restoration of conduction in the monosynaptic reflex pathway.

Chronic persistent EAE. In rats with chronic persistent EAE the mean H/M ratio was reduced compared with that in normal controls but the difference was not statistically significant (Table 7). The H/M ratio was normal in 3 rats with chronic persistent EAE but the H reflex was absent in the other.

Cyclosporin A (CyA) controls

Three rats which had been treated with CyA but not inoculated were studied electrophysiologically 26, 27 and 29 days after initiation of CyA treatment. Recordings

TABLE 7. M WAVE AND H REFLEX RECORDINGS

	Controls ($n = 9$)	*First episode* ($n = 5$)	*First remission* ($n = 5$)	*Second episode* ($n = 4$)	*Chronic persistent* ($n = 4$)	*Late remission* ($n = 4$)	*Analysis of variance Value and significance of F*
DPI		12–16	18–20	22–26	29–34	50–64	
		n s		n.s.			
M peak-to-peak amplitude (mV) Mean ± SD	4.7 ± 0.83	4.2 ± 1 26 *n s	4.8 ± 0 99 n s	4 4 ± 0.43 n.s.	5.8 ± 3.2 $P < 0$ 05	4 7 ± 2.1 n.s	$F = 0$ 49 n.s
		n s		$P < 0$ 05			
H/M ratio	0.46 ± 0.05	0.34 ± 0.14 $P < 0.01$	0.39 ± 0 20 n.s.	0 32 ± 0.20 $P < 0.005$	0 37 ± 0.26 n.s.	0.55 ± 0.09 n s	$F = 1$ 37 n s
		n.s.		n.s			
M latency to onset (ms)	2.5 ± 0.24	2 6 ± 0 14 n s	2 6 ± 0 31 n.s	2.6 ± 0 05 n.s.	2.7 ± 0.12 $P < 0.005$	2.8 ± 0 22 $P < 0.001$	$F = 1.21$ n.s.
		n s.		n s			
M-H latency (ms)	4 6 ± 0 28	5 2 ± 1 1 $P < 0$ 001	4 8 ± 0 25 n s.	4 9 ± 0 46 n.s.	4 6 ± 0.40[a] n.s	4 5 ± 0 30 n s	$F = 1.13$ n.s

* The significance under each mean refers to the comparison with the control mean, n s = not significant, [a] $n = 3$, as H reflex absent in 1 rat

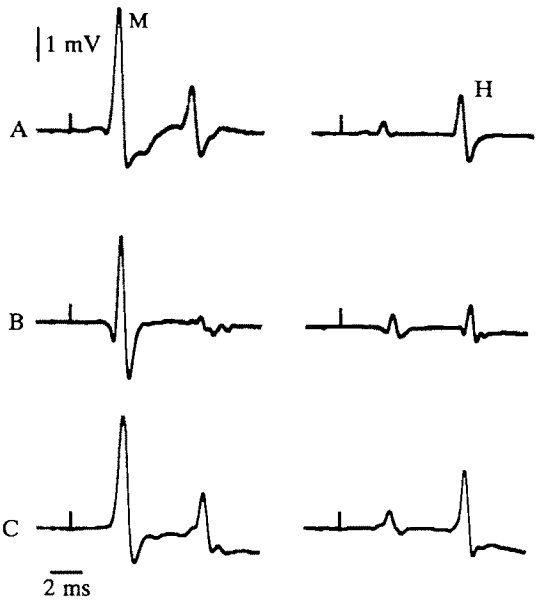

FIG 13 Maximal M wave (M) and maximal H reflex (H) elicited in the fourth dorsal interosseus muscle by sciatic nerve stimulation in a normal control rat (A) and in rats with EAE during the second episode (B) and late remission (C)

of the M wave, H reflex, lumbar DREZ response, dorsal column compound action potential and cerebral SSEP were normal in these animals, indicating that, in the dose given, CyA itself did not affect transmission in the PNS or CNS.

DISCUSSION

The present study has demonstrated a failure of excitation or conduction block in the PNS afferent pathway and in the spinal cord dorsal columns of rats with clinical episodes of chronic relapsing EAE. A failure of excitation is a feature of axonal degeneration while conduction block is typical of primary demyelination. The following observations indicate that the conduction failure was mainly due to demyelination-induced conduction block: (1) the occurrence of rate-dependent block in the PNS and CNS; (2) the restoration of PNS conduction by cooling; (3) the restoration of CNS conduction by the administration of ouabain; (4) the presence of temporal dispersion indicating conduction slowing due to demyelination in the PNS in chronic persistent EAE; (5) histological evidence of marked primary demyelination in the dorsal root ganglia, dorsal roots and dorsal columns (Pender *et al.*, 1990); and (6) the temporal association of restoration of conduction with remyelination (*see below*). However, failure of excitation due to axonal degeneration is also likely to contribute to the conduction failure, as axonal degeneration was observed in the PNS and in the dorsal columns (Pender *et al.*, 1990).

The reduction in amplitude and prolongation of latency of the cerebral SSEP during clinical episodes of chronic relapsing EAE are likely to be due to conduction abnormalities in both the PNS and CNS. As the sciatic nerve-L4 DREZ pathway constitutes part of the afferent pathway from the sciatic nerve to the cerebral cortex, the contribution of

the PNS lesions to the SSEP abnormalities is obvious. In the spinal cord the dorsal and dorsolateral columns are the primary pathways mediating the SSEP (Cohen *et al.*, 1981; York, 1985). While fibres generating the dorsal column compound action potential (from the S4 and coccygeal segments) in the present study did not contribute to the sciatic nerve-cerebral cortex afferent pathway, the marked conduction abnormalities in the lumbosacral dorsal columns indicate the likelihood of similar conduction abnormalities due to the demyelination and axonal degeneration we have observed in the thoracic and cervical spinal cord dorsal columns (Pender *et al.*, 1990). Lesions in the dorsolateral column of the spinal cord and in the brainstem and cerebral white matter are also likely to contribute to the SSEP abnormalities. The absence of cerebral SSEPs in 2 rats in which DREZ responses were present, although reduced in amplitude, is evidence of the contribution of CNS lesions to the SSEP abnormalities. The increased amplitude of the cerebral SSEP observed in 2 rats may be due to demyelination-induced conduction block of descending CNS pathways that inhibit synaptic transmission through the afferent pathway (*see* McIntyre *et al.*, 1989).

The interruption of the lumbar monosynaptic reflex arc can be explained mainly by conduction block due to the demonstrated demyelination in the dorsal root ganglion, dorsal root, dorsal root entry zone, L5 and L6 spinal cord segments, ventral root exit zones and ventral roots (Pender *et al.*, 1990). Lesions of descending pathways in the brainstem and spinal cord may also have affected the H reflex by increasing or decreasing excitability of the motor neuron pool.

CNS conduction abnormalities

This study demonstrates conduction block in CNS tracts in EAE by direct recordings from surgically exposed tracts. Direct stimulation of, and recording from, the exposed dorsal columns allowed conduction to be assessed in pathways that were restricted to the CNS and that did not have any intervening synapses. Conduction block in the dorsal columns was found in the first episode, as early as 14–15 DPI, and also in the later stages of chronic relapsing EAE. Pender (1986*a*, 1988*a*) demonstrated conduction block in the CNS part of the ventral root exit zone of the spinal cord in whole spinal cord-induced acute EAE in the Lewis rat; however, this region is a CNS-PNS transitional zone along the lower motor neuron pathway and is not a long fibre tract of the CNS. Others have used somatosensory, visual or auditory evoked potentials to assess CNS neurotransmission in acute and chronic relapsing EAE (Lumsden *et al.*, 1975; Lidsky *et al.*, 1980; Hayreh *et al.*, 1981; Wiśniewski *et al.*, 1982; Bilbool *et al.*, 1983; Heininger *et al.*, 1989); however, these recordings assessed transmission through pathways involving one or more synapses. Recordings of responses relayed through synapses are difficult to interpret because it is unknown whether the abnormalities are the direct effect of impaired axonal transmission or whether they are due to altered synaptic transmission. In the case of the cerebral SSEPs, lesions may have opposite effects on synaptic transmission, according to whether the lesions affect facilitatory or inhibitory pathways. In the only previous electrophysiological studies on chronic relapsing EAE, visual and auditory evoked potentials were recorded from guinea-pigs (Lidsky *et al.*, 1980; Wiśniewski *et al.*, 1982). Lidsky *et al.* (1980) found that the visual evoked potentials were reduced in amplitude and prolonged in latency during clinical episodes.

The finding of marked conduction abnormalities due to demyelination in the spinal

cord during the first episode of EAE as well as during later episodes indicates that CNS demyelination is an important cause of neurological dysfunction in the first and later episodes of chronic relapsing EAE, as it is in whole spinal cord-induced acute EAE in the Lewis rat although the distribution of CNS lesions may vary (Pender, 1986*a*, 1988*a*). This supports the concept that acute and chronic relapsing EAE are essentially part of the same disease process, as indicated by the conversion of acute EAE to chronic relapsing EAE by treatment with low dose cyclosporin A (Polman *et al.*, 1988; Pender *et al.*, 1990).

PNS conduction abnormalities

This study demonstrates conduction abnormalities in the PNS in chronic relapsing EAE. The conduction abnormalities in the afferent pathway from the peripheral nerve to the spinal cord are explained mainly by demyelination in the dorsal root ganglia and dorsal roots, and are similar in nature to those previously described in rabbits with acute EAE (Pender and Sears, 1982, 1984, 1985) and in Lewis rats with whole spinal cord-induced acute EAE (Pender and Sears, 1986), although less severe than in the former and more severe than in the latter. The greater severity of these abnormalities in the first episode of chronic relapsing EAE than in acute EAE in the Lewis rat may be due to the different sexes of the animals studied, to differences in the amount of spinal cord tissue and adjuvants in the inocula, to the administration of cyclosporin A or to a combination of these factors.

Our histological studies have revealed that in rats with clinically active disease studied $\geq$ 29 DPI, there is little active PNS demyelination in contrast to prominent active CNS demyelination (Pender *et al.*, 1990). This difference in disease activity in the PNS and CNS in later stages may be reflected in some of the electrophysiological findings. Rats with chronic persistent EAE (29–34 DPI) had similar afferent volley conduction velocities and N wave latencies but considerably prolonged cerebral SSEP latencies compared with rats in the second episode (22–26 DPI). This suggests progression of CNS disease but not PNS disease in the later stages of chronic relapsing EAE. In rats with chronic persistent EAE (30–33 DPI) there was no evidence of rate-dependent block in the PNS but prominent rate-dependent block in the CNS. Rate-dependent block indicates insecure high frequency transmission in fibres that are able to conduct signals at lower frequencies. Such fibres are likely to be either in the process of being demyelinated or in the early stages of remyelination. Demyelination of the PNS has been reported in other models of chronic EAE but the functional significance of these lesions has not been assessed (Raine *et al.*, 1969; Madrid and Wiśniewski, 1978; Lassmann *et al.*, 1980*a*; Brown *et al.*, 1982).

Restoration of conduction during remission

During the first and late clinical remissions there was evidence of restoration of conduction in the PNS and in the CNS. This can be explained by the observed remyelination by Schwann cells and oligodendrocytes, respectively (Pender *et al.*, 1990). There is evidence from studies on noninflammatory models of PNS demyelination that nerve conduction may be restored in demyelinated fibres in the early stages of repair before the formation of compact myelin lamellae (Bostock and Sears, 1978; Smith and Hall, 1980; Smith *et al.*, 1982). In the lysophosphatidyl choline model, restoration of

conduction occurred when demyelinated fibres became closely associated with debris-free Schwann cells (Smith and Hall, 1980; Smith *et al.*, 1982). As the rats studied electrophysiologically during the first remission had only recently recovered from the first episode, some of the PNS and CNS fibres in which conduction had been restored may have still been demyelinated but invested by Schwann cells and oligodendrocytes, respectively, as has been suggested to occur during early recovery from acute EAE (Pender, 1989; Pender *et al.*, 1989). The rate-dependent block observed in the PNS and CNS during the first remission may have been occurring in such invested demyelinated fibres. In the rats studied electrophysiologically during late remission, only a small proportion, if any, of the fibres in which conduction had been restored were still demyelinated, as these rats were studied in late second or third remission at which stage there were very few demyelinated fibres and remyelination was well established in the PNS and CNS (Pender *et al.*, 1990).

Conduction slowing would be expected during the early stages of restoration of conduction by remyelination. The only definite evidence of conduction slowing was temporal dispersion of the afferent volley potential in chronic persistent EAE. However, it is likely that conduction slowing contributed to the reduced afferent volley conduction velocities and the prolonged N wave, dorsal column compound action potential and cerebral SSEP latencies during the first remission and at all subsequent stages of disease. During late remission the afferent volley conduction velocity and the N wave latency returned to normal, which is consistent with the histological findings of well-established PNS remyelination.

Residual conduction abnormalities during late remission

While there was evidence of restoration of conduction in the PNS and CNS in late remission, the recovery was incomplete. There was a persistent significant reduction in the amplitude of the dorsal root entry zone afferent volley potential with normal conduction velocity and without temporal dispersion. The dorsal column compound action potential was persistently reduced in amplitude, without temporal dispersion, and prolonged in latency. These findings indicate persistent conduction failure in the PNS and CNS during late remission. This can be explained by the observed axonal degeneration in the PNS and particularly in the CNS (Pender *et al.*, 1990). Slowing of conduction in thinly remyelinated CNS fibres may have contributed to the prolonged latency of the dorsal column compound action potential although axonal degeneration of the fastest fibres could also account for this. Axonal degeneration in the PNS and CNS and conduction slowing in thinly remyelinated CNS fibres may explain the persistently reduced amplitude and prolonged latency of the cerebral SSEP during late remission. Axonal damage and degeneration are well-recognized features of hyperacute EAE (Lampert, 1967; Hansen and Pender, 1989), acute EAE (Lampert and Kies, 1967; Pender, 1989) and chronic relapsing EAE (Lassmann *et al.*, 1980*b*; Brown *et al.*, 1982; Pender *et al.*, 1990).

CONCLUSION

In conclusion the present study has demonstrated conduction failure in both the CNS and PNS during the early and later stages of chronic relapsing EAE. Conduction was restored in some CNS and PNS fibres during remission but conduction abnormalities

persisted in animals that were in late remission and had no neurological signs. The reversible conduction abnormalities are explained by demyelination followed by remyelination in the CNS and PNS. The persistent conduction failure in late remission is mainly due to axonal degeneration. These findings may have implications for the human demyelinating disease, multiple sclerosis.

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HEREDITARY MOTOR AND SENSORY NEUROPATHY OF NEURONAL TYPE WITH ONSET IN EARLY CHILDHOOD

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SUMMARY

Eighteen cases of a chronic progressive motor and sensory neuropathy of neuronal type with early onset are described. Based on the presented data and literature reports a condition is distinguished, which is in clinical, genetic and morphological aspects different from autosomal dominant HMSN type II. The condition corresponds to that described by Ouvrier *et al.* (1981). It shows a congenital or early childhood onset and causes a severe disability usually with wheelchair dependency already in puberty or later in adult life. The condition is probably transmitted by an autosomal recessive gene. Morphological features of biopsied nerves are an extensive loss of large diameter fibres with a shift to smaller diameters in the histogram. Regenerative features are almost absent in contrast to the distinct cluster formation in autosomal dominant HMSN type II. A maturation disturbance of peripheral motor and sensory neurons with a concomitant or secondary process of chronic neuronal degeneration is suggested. One dominantly inherited case in our group with an infantile onset exhibits clinical and morphological features consistent with an autosomal dominant HMSN type II.

INTRODUCTION

The hereditary motor and sensory neuropathies (HMSN) are a heterogeneous group of disorders, which have been classified on clinical, genetic, electrophysiological and morphological criteria (Dyck *et al.*, 1968*a*, *b*; Thomas *et al.*, 1974; Dyck, 1975). HMSN type I is characterized by severely reduced nerve conduction velocities and is associated morphologically with segmental de- and remyelination with onion-bulb formation and axonal loss. HMSN type II usually shows normal or modestly reduced nerve conduction velocities, and is associated morphologically with loss of large diameter fibres due to axonal degeneration and regeneration with the formation of clusters of small myelinated fibres. Segmental demyelination and onion-bulb formation are inconspicuous. The mode of inheritance in both forms usually is autosomal dominant, although autosomal recessive inheritance also has been described (Harding and Thomas, 1980*a*). The age of onset in autosomal dominant HMSN type II most often is in the second decade, but a considerable proportion develop symptoms later. Recessive type II cases have an earlier age of onset and seem to be more severely disabled than the dominant cases (Brust *et al.*, 1978; Dubowitz, 1978; Harding and Thomas, 1980*b*).

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In 1981, Ouvrier *et al.* described 11 cases of a severe motor and sensory neuropathy of neuronal type, with onset in early childhood. The condition was sporadic or transmitted by an autosomal recessive gene. Only in 1 case was dominant inheritance encountered. They noted this condition to be more severe than autosomal dominant motor and sensory neuropathy type II.

We describe a further 18 cases of a neuronal motor and sensory neuropathy with an early childhood onset, in which histological and morphometric studies of sural nerve biopsies were performed. In a follow-up study the progress of clinical severity has been assessed. From clinical, genetic and morphological data the differences of this condition from autosomal dominant HMSN type II are discussed.

PATIENTS AND METHODS

Patients

In a retrospective study of the congenital and early childhood cases of chronic peripheral neuropathy with nerve biopsies investigated during the past 20 yrs we have encountered 18 cases with a neuronal form of motor and sensory neuropathy. Selective criteria for our study were the following: (1) chronic progressive motor and sensory neuropathy without CNS involvement or pyramidal features, (2) infantile onset of (motor) symptoms manifested by congenital hypotonia, delayed walking (> 18 mos) or early complaints about motor performance (< 4 yrs), (3) electrophysiological examination of motor and sensory nerves compatible with a process of axonal degeneration, (4) sural nerve morphology consistent with chronic axonal degeneration without appreciable signs of demyelination or onion-bulb formation.

Electrophysiological techniques

Nerve conduction velocity was examined according to a standardized protocol. Motor conduction velocities of the median and peroneal nerves were recorded using surface electrodes. Sensory action potentials were recorded from the median nerve at the wrist on stimulating the index finger with ring electrodes. Skin temperature was at least 30° C. A general EMG investigation was performed according to a standardized protocol with concentric needle electrodes.

Histological techniques

Whole sural nerve biopsy was performed at midcalf level and prepared for light and electron microscopic examination, including teased fibres studies, using standard techniques. In 10 cases a soleus muscle biopsy was taken at the same session and prepared routinely. In Cases 1, 3, 4, 7 and 12, fascicular biopsy proximal to the lateral malleolus was performed. In Case 18, a biopsy of the lateral antebrachial nerve was taken because of severe vascular disturbances in the legs.

The total transverse fascicular area (TTFA) was determined with the aid of a planimeter on photographic enlargements of semithin sections of the whole nerve. Electron microscopic photographs (×1700) covering approximately 10% of the TTFA were used for morphometric analysis. The density and diameter distribution of myelinated fibres were determined using a Zeiss TGZ particle size analyser. Higher magnification electron microscopic photographs (×4000) were used for the determination of diameter distribution of myelinated axons in Case 6. A cluster ratio, defined as the quotient of cluster density and fibre density $\times 10^3$, was determined by counting the number of clusters (3 or more closely packed small myelinated fibres (Behse *et al.*, 1975)) at light microscopic level at a magnification of ×1000 over an area of 0.5 mm^2 of the nerve or, if TTFA was less, over the whole transverse area of the nerve. It must be noted that identifying clusters was difficult in cases with a markedly increased density of small myelinated fibres. In cases with normal or decreased densities, counting of clusters was easy and reliable. For comparison, the cluster ratio was also determined in 8 noninfantile dominantly inherited HMSN type II cases. From 13 nerve biopsies about 50 myelinated fibres were teased in each and classified according to Dyck (1975) for paranodal demyelination, segmenal de- and remyelination and linear myelin ovoids (axonal degeneration).

RESULTS

Clinical features

The clinical features of the 18 patients are listed in Table 1. Two patients had limp feet at birth. Some patients started to walk at a normal age, but in most it was delayed. At first examination, all patients showed weakness of dorsiflexion of the feet, atrophy of distal lower limbs and, with the exception of some young patients, weakness and atrophy of hand muscles. Weakness of proximal lower limbs was present in several patients from the beginning of the second decade on. Proximal weakness of the arms was sometimes present, but prominent in only the oldest case, a severely affected patient (Case 18). Four patients showed a conspicuous shoulder amyotrophy and one of them (Case 10) also had facial weakness and atrophy. Eight patients showed some asymmetry in the motor manifestations. Most patients showed distal loss of vibration and position sense and 2 patients had also slight loss of pain sensation in distal lower limbs. In the very young patients sensory function could not be tested reliably. Five patients did not show sensory changes, but sensory involvement was evident from electrophysiological investigation. Ankle jerks were absent; total tendon areflexia was present in one-third of the patients. Three patients had optic atrophy and 1 (Case 10) had slight sensorineural hearing loss. Acrocyanosis of the legs was present in severely affected patients. Pes cavus was not uncommon. Scoliosis was seen only in 3 patients. Most patients showed slight sensory ataxia. Clinically enlarged nerves were not present. Two patients had borderline or mildly retarded intelligence (Cases 13, 17).

Routine blood and urine investigations were normal. In 6 of 10 patients in whom it was examined, serum creatine kinase (CK) was elevated up to three times the normal value (Table 2). Cerebrospinal fluid (CSF) protein content, investigated in 10 patients, was normal in all. Appropriate studies excluded endocrinological and immunological conditions, chronic infectious diseases, deficiencies and disorders caused by toxic agents.

Electrophysiological studies (Table 2)

Median motor nerve conduction velocity was unobtainable in 2 patients, low normal for age in the 9-mos-old girl, markedly slowed in 2 and normal or mildly slowed in the others. Conduction along the peroneal nerve was delayed in 4 patients, in 10 patients no muscle action potential could be evoked. Recording of sensory action potentials from the median nerve was attempted in 13 patients. They were absent in 5 patients, reduced in amplitude in 6 and borderline with an increased latency in 1 patient. Sural nerve action potentials were absent in all 11 patients in whom recordings were attempted. Electromyography in 10 patients was suggestive of denervation in 9, showing spontaneous fibrillation and positive spikes.

Family investigation

Parents were examined clinically and electrophysiologically in most cases. No consanguinity was known to the parents in any family. Case 1 is an adopted child. The parents of Case 18 and the father of Case 17 could not be examined, but were said to be normal. Case 18 had normal children. Autosomal recessive inheritance seemed likely in 4 patients, each having 1 similarly affected sibling and normal parents (Cases 4, 11, 12, 16). Autosomal dominant inheritance was present in Case 15, of whom the father, a paternal uncle and his son suffered from the neuronal form of HMSN.

TABLE 1 CLINICAL SIGNS AND SYMPTOMS

Case	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
Age	9 mos	4 yrs	4 5 yrs	6 5 yrs	7 yrs	7 yrs	7 5 yrs	12 yrs	13 yrs	13 5 yrs	14 yrs	14 yrs	14 yrs	16 yrs	16 yrs	26 yrs	38 yrs	41 yrs
Sex	F	F	F	M	M	F	M	F	F	M	F	M	M	M	F	F	F	M
Onset	6 mos	6 mos	12 mos	18 mos	6 mos	12 mos	3 yrs	6 mos	Birth	<1 yr	4 yrs	18 mos	9 mos		<1 yr	4 yrs		Birth
Age of walking	–	2 5 yrs	18 mos	18 mos	18 mos	18 mos	18 mos	13 mos	2 5 yrs	3 yrs	12 mos	2 yrs	2 yrs	2 5 yrs	3 yrs	14 mos	>2 yrs	2 yrs
Pes cavus	–	+	–	–	–	–	–	+	+	+	–	+	–	+	+	–	+	+
Claw hands	–	+	–	–	+	–	–	±	–	–	–	–	+	+	–	+	–	+
Scoliosis	–	–	–	–	–	–	–	–	–	+	–	–	–	+	–	–	+	–
Clinical asymmetry	–	+	+	–	+	+	+	+	–	–	–	–	–	+	+	–	–	–
Muscle weakness																		
Distal leg	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Distal arm	–	+	–	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Proximal leg	–	–	–	–	–	–	–	+	±	–	–	–	±	–	–	+	–	+
Proximal arm	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Muscle atrophy																		
Distal leg	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Distal arm	–	+	–	–	+	+	–	+	+	+	+	+	+	+	–	+	+	+
Areflexia																		
Ankle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Total	–	–	–	+	–	+	–	–	+	+	–	–	–	+	–	–	–	+
Sensation impairment																		
Vibration/position	?	?	–	–	–	+	+	+	+	–	+	+	–	+	+	+	+	+
Pain/temperature	?	?	–	–	–	–	–	±	–	–	–	–	–	–	–	–	–	±
Cranial nerve involvement	–	–	–	–	–	–	–	–	–	+	+	–	–	+	–	–	–	+

– = absent, ± = slight, + = marked

TABLE 2 LABORATORY FINDINGS

Case	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
Age	9 mos	4 yrs	4 5 yrs	6 5 yrs	7 yrs	7 yrs	7 5 yrs	12 yrs	13 yrs	13 5 yrs	14 yrs	14 yrs	14 yrs	16 yrs	16 yrs	26 yrs	38 yrs	41 yrs
Motor nerve CV ($m \cdot s^{-1}$)																		
Median	22	40	42	47	35	27	52	63	42	35	59	–	0	27	39	49	47	0
Peroneal	0	30	–	0	–	0	0	38	–	38	0	35	0	0	0	0	0	–
Sensory conduction																		
Median																		
Latency (ms)				2.5		4 4	4 0	4 2							2 6	4 5	2 8	
Amplitude (μV)	–	–	–	5	–	2	1 5	10	0	0	0	–	0	0	8	<2	4	0
Sural																		
Amplitude (μV)	–	0	0	0	0	–	0	0	–	–	0	–	–	–	0	0	0	0
EMG denervation	+	+	–	–	–	–	+	–	+	+	–	0	+	+	+	–	+	–
CK (+ = elevated)	–	–	–	–	+	n	–	+	–	+	+	+	n	+	n	–	–	n
CSF protein	n	n	–	–	n	n	–	n	–	n	n	–	–	n	–	n	–	n

0 = no response, – = not investigated, n = normal

TABLE 3 FOLLOW-UP

Case	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
Age at first investigation	9 mos	4 yrs	4 5 yrs	6 5 yrs	7 yrs	7 yrs	7 5 yrs	12 yrs	13 yrs	13 5 yrs	14 yrs	14 yrs	14 5 yrs	16 yrs	16 yrs	26 yrs	38 yrs	41 yrs
Age at last investigation	3 yrs	18 yrs	17 yrs	7 yrs	19 yrs	15 yrs	7 5 yrs	16 yrs	27 yrs	30 5 yrs	19 yrs	24 yrs	20 yrs	32 yrs	27 yrs	41 yrs	45 yrs	53 yrs
Follow-up in years	2 5	14	12 5	0 5	12	8	0	4	14	17	5	10	5 5	16	11	15	7	12
Progression of																		
Muscle weakness	>>	>>	>>	>	>>	>	0	>>	>>	>>	>	>>	>>	>	>	>	>	>
Muscle atrophy	>	>>	>>	0	>>	>	0	>>	>	>	>	>>	>	>	>	>	>	>
Sensory deficit	0	>	>>	0	>	>	0	>	>	>	>	>	0	>	>	>	>	>
Wheelchair dependent	–	+	+	–	+	–	–	+	+	+	–	–	+	–	–	+	–	+
at age (yrs)		10	14		13			14	27	28			20			35		11
Maximum walking distance (km)		–	–		–	3		–	–	–	0 5	<0 5	–	0 5	4–5	–	3	–

Progression 0 = absent, > = slight, >> = obvious

Follow-up (Table 3)

The duration of the follow-up was 0–17 (mean 9.2) yrs. Case 1 started to walk at age 24 mos. Progression was slow in most cases. Some patients experienced a clear progression over a short period, followed by an apparently stable condition for years. In adult life most patients were severely handicapped and wheelchair dependent. Those patients still ambulant had to use orthopaedic footwear and braces or crutches. Only Case 15 with a dominantly inherited disorder and Case 17 were fairly well ambulant as adults. Hand function was severely impaired in most adult patients. Weakness of proximal upper limbs was evident in some, but pronounced only in Case 18. Acrocyanosis was present in distal lower limbs of several adults. Case 3 developed scoliosis during puberty. Patients were of normal stature in adult life.

Light microscopy

The number of myelinated fibres was grossly reduced. Large diameter fibres were almost totally lacking (fig. 1). This was practically the only abnormality observed in most nerves. Active axonal degeneration was very exceptional. There was no evidence of demyelination or onion-bulb formation. Clusters of small myelinated fibres were hardly ever present, except in Case 15 (fig. 1D). In addition, single teased fibres rarely showed any abnormalities. Only sporadically was a demyelinated segment or a degenerating fibre seen. In 8 of 13 cases, one or several fibres showed lengthening of the nodal gap or paranodal demyelination, occasionally of more than one node per fibre. Internodal length, although not measured systematically, appeared to be normal in relation to fibre diameter. No abnormalities were seen in the blood vessels or perineurium. Endoneurial connective tissue was increased in several cases in which severe fibre loss had occurred. Muscle biopsy was performed in 10 patients and in all cases showed the characteristic signs of neurogenic muscular atrophy.

Morphometry (Table 4)

The density of myelinated fibres was diminished in 14 nerves, ranging from 12% to 89% of normal values. In 4 cases, the density was normal or increased. TTFA was diminished or low normal in several nerves. Only Case 14 showed a slight increase in TTFA. The diameter histogram was unimodal in all cases with a near total loss of fibres > 8 μm. The peak of the histogram was situated between 2 and 3 μm in nearly all cases (fig. 1). The cluster ratio ranged from 0 to 1.5 (mean 0.5) in the sporadic or autosomal recessive cases but was 8.1 in the dominantly inherited case. The cluster ratio determined in 8 autosomal dominantly inherited HMSN type II cases (aged 15–76 yrs, mean age 43.5 yrs) ranged from 2.4 to 35.2 (mean 10.3). In the same way we could calculate cluster ratios of neuronal HMSN cases from literature reports. According to the data of Madrid *et al.* (1977) the cluster ratio in the sural nerve ranged from 0 (sporadic early childhood case) to 24.7; for Gherardi *et al.* (1983) in the superficial peroneal nerve from 7.8 to 36.1; and for Berciano *et al.* (1986) in the sural nerve from 18.4 to 18.9 and in several lower limb nerves from 30.4 (sciatic nerve) to 0 (terminal branches of deep peroneal nerve).

TABLE 4 MORPHOMETRY

Case	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
Age at biopsy	9 mos	4 yrs	4 5 yrs	6 5 yrs	7 yrs	7 yrs	7 5 yrs	12 yrs	13 yrs	13 5 yrs	14 yrs	14 yrs	14 yrs	16 yrs	16 yrs	26 yrs	38 yrs	41 yrs
Fibre size histogram																		
% > 6 μm	0	3	0 5	6.5	3 5	0	7	0	<0 5	1 5	<0 5	1 5	6	0	8	2	14	(1)
% > 8 μm*	0	0	0	0 5	<0 5	0	0	0	0	0	0	0	<0 5	0	2	<0 5	3	(0)
Max diameter (μm)	5	8	8	9	9	3	8	6	7	8	7	7	9	5	10	9	11	(7)
Peak (μm)	2–3	2–3	2–3	2–3	2–3	1–2	3–4	2–3	2–3	3–4	2–3	2–3	2–3	2–3	2–3	2–3	2–3	(2–3)
TTFA (mm^2)**	–	0 3	–	–	0 7	0 2	–	0.4	0 5	0 5	1 1	–	0 8	1 6	1 2	0 9	0 3	–
Density (no /mm^2)	12990	12740	8260	15720	7420	3930	5450	2380	11090	8930	7650	6820	15550	1230	6920	2440	11510	(3510)
% normal for age***	77	90	58	126	56	30	41	24	110	89	76	68	155	12	69	24	118	
Cluster ratio	0	0	1 2	0	0	0	0	0 8	0	1 1	0	0	0 2	1 0	8 1	0	1 0	(9 4)

* Mean of age-matched controls 5 (0–1 yr, n = 6), 15 (2–6 yrs, n = 7), 17 (6–11 yrs, n = 11), 25 (11–30 yrs, n = 10), 24 (31–50 yrs, n = 5) ** Mean of age-matched controls 0 6 (0–1 yr, n = 4), 0 6 (2–6 yrs, n = 4), 0 7 (6–11 yrs, n = 5), 0 9 (11–30 yrs, n = 5), 1 2 (31–50 yrs, n = 3) *** Mean of age-matched controls 16860 (0–1 yr, n = 6), 14170 (2–6 yrs, n = 6), 13180 (6–11 yrs, n = 11), 10060 (11–30 yrs, n = 10), 9760 (31–50 yrs, n = 5) Numbers in parentheses are for the lateral antebrachial nerve for which normal values are not available

Electron microscopy

The loss of large diameter fibres was confirmed on ultrastructural examination. Active axonal degeneration occurred exceptionally. Abnormalities of axonal organelles were not present. There were no demyelinated fibres. An occasional small onion-bulb was present in Cases 3 and 15. Clusters of small myelinated fibres were not seen or were encountered only infrequently, except in Case 15 and in the more proximally taken biopsy of an upper limb nerve of Case 18. Case 6 exhibited extremely small, yet myelinated axons (fig. 2). A diameter histogram of myelinated axons in Case 6 showed axon diameters of 0.6−1.8 μm, being fully within the range for unmyelinated axons (Ochoa and Mair, 1969; 0.4−2.4 μm).

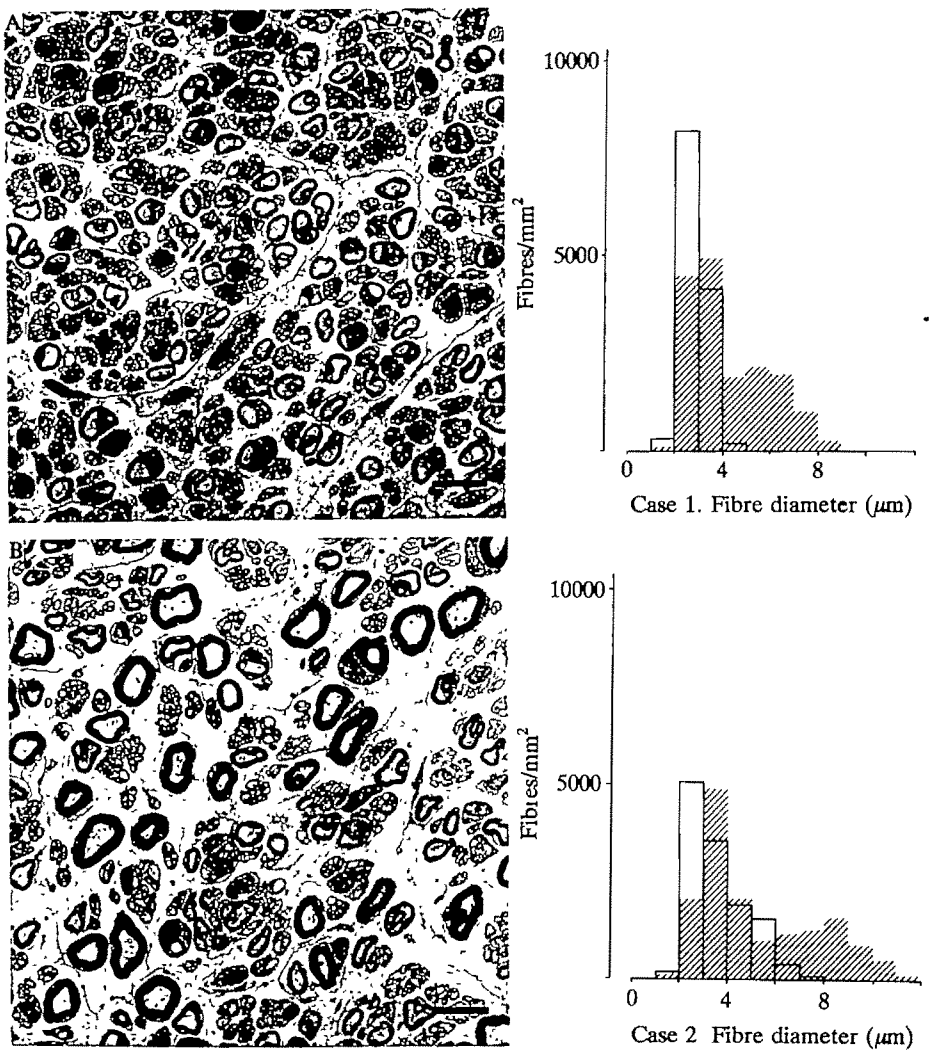

FIG 1A and B.

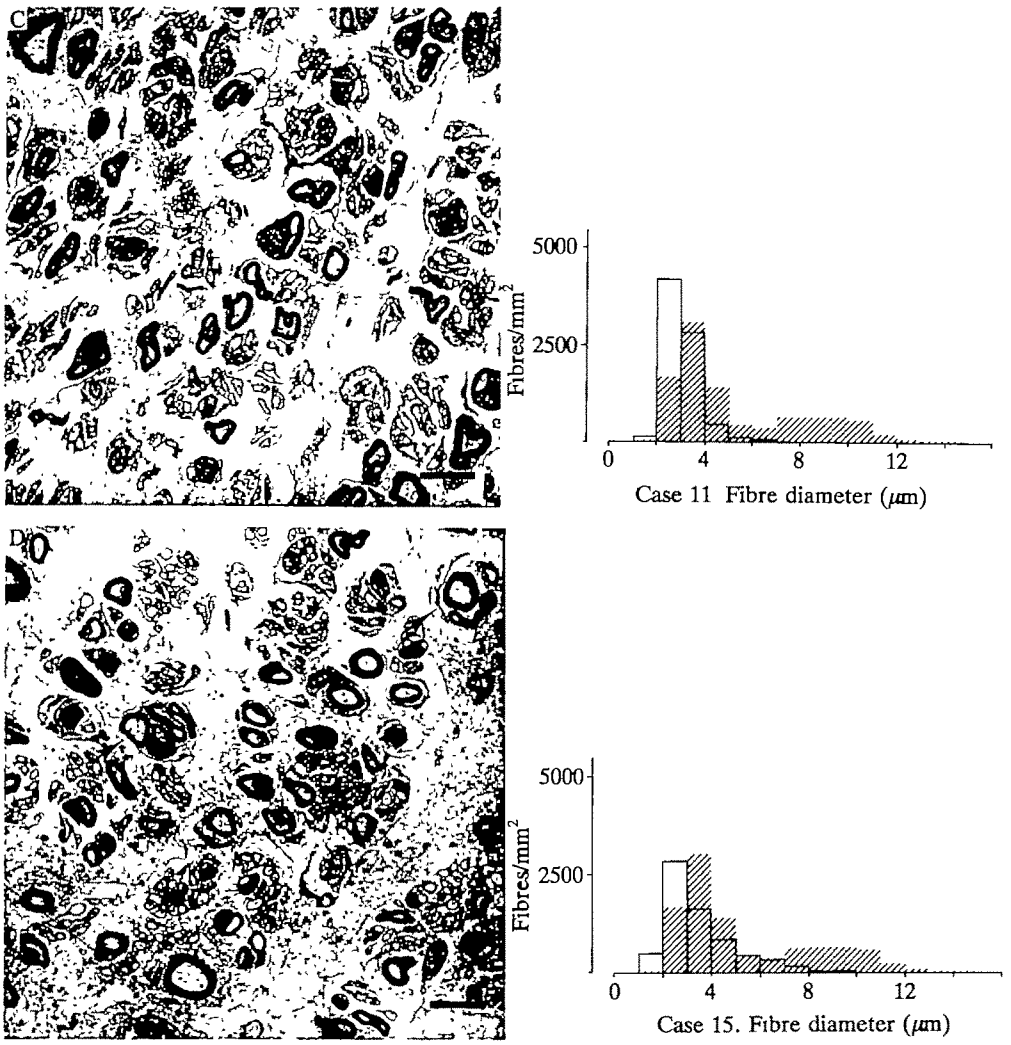

FIG 1 *Left*. low power electron microscopic pictures of cross-sections of sural nerve biopsies. A, *Case 1* (aged 9 mos); B, *Case 2* (aged 4 yrs); C, *Case 11* (aged 14 yrs), D, *Case 15* (aged 16 yrs), autosomal dominant case with cluster formation (↑) Bars = 10 μm *Right*. diameter histograms of myelinated fibres for the same 4 cases (white areas) in comparison with age-matched controls (hatched areas).

Bands of Büngner were present in all the biopsied nerves in varying numbers and complexity (fig. 3). In some cases, unmyelinated fibre pathology might have been present as judged by the occurrence of miniature axon sprouts or empty parallel Schwann cell stacks (Ochoa, 1978). However, in longstanding cases, complex Schwann cell bands with many nonmyelinated axons occurred, in which it was not possible to decide whether these axons represented regenerated but not yet myelinated axons or genuine unmyelinated axons (Behse *et al.*, 1975; Ochoa, 1978). The occasional coexistence of apparently normal

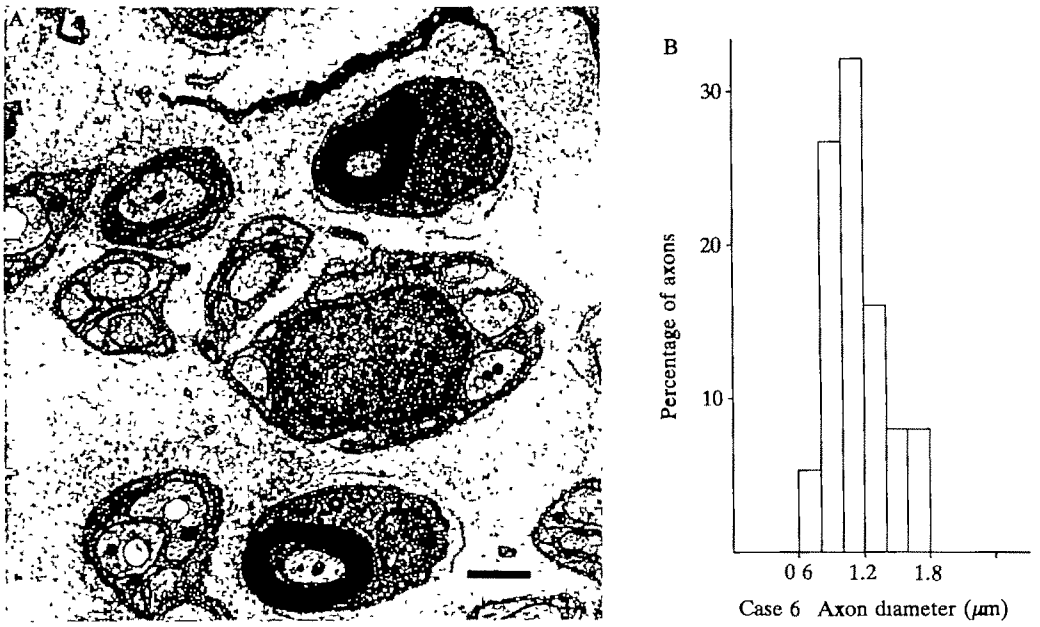

FIG 2 A, two extremely small myelinated axons, smaller in diameter than many nonmyelinated axons (*Case 6*) Bar = 1 μm B, diameter histogram of myelinated axons in *Case 6* The diameter of myelinated axons (0 6−1 8 μm) is within the range of unmyelinated axons (Ochoa and Mair, 1969; 0.4−2.4 μm)

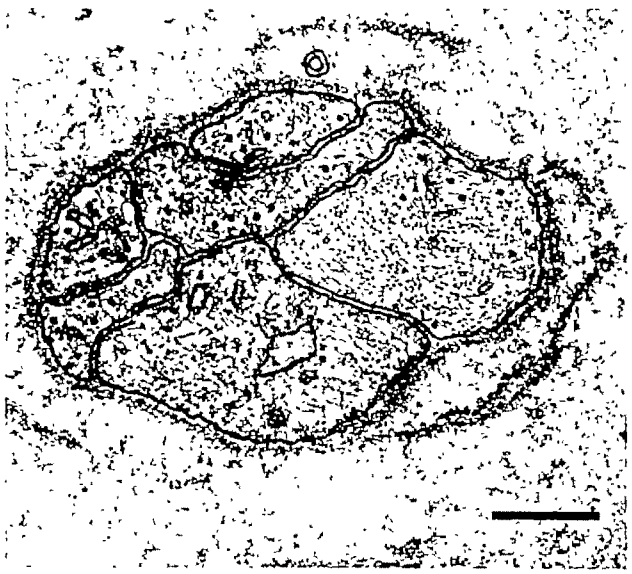

FIG 3 Band of Bungner (*Case 10*). Bar = 0.5 μm.

unmyelinated axons next to complex Schwann cell structures with many nonmyelinated axons and the severe loss of large myelinated fibres might favour the impression that these nonmyelinated fibres were regenerating, not yet myelinated axons. An increase of endoneurial collagen fibres was evident in several long-standing cases and areas of densely packed collagen fibres were often embraced by fibroblast processes.

DISCUSSION

The patients described in this paper had a chronic progressive neuronal motor and sensory neuropathy with an onset in early childhood. Ouvrier *et al.* (1981) were the first to recognize this condition as a neuronal sensorimotor neuropathy with an earlier onset and clinically and morphologically of greater severity than HMSN type II. In addition, there are a few incidental reports of an early onset neuronal motor and sensory neuropathy. Reference will be made only to cases with reliable clinical, electrophysiological or morphological information and without central nervous system involvement. Two siblings reported by Kalyanaraman *et al.* (1970) might have had a neuronal type of infantile neuropathy as was suspected by Ouvrier *et al.* (1981), although the authors had interpreted their histological findings as being suggesive of a hypertrophic neuropathy. Goebel *et al.* (1976) described a 3-yr-old girl with a congenital progressive neuropathy and slightly to moderately reduced motor nerve conduction velocities and no sensory responses. Absence of large myelinated fibres was seen in sural nerve biopsy. A neuronal type of motor and sensory neuropathy seems likely. Brust *et al.* (1978) mentioned an early onset of neuronal HMSN in a patient from a consanguinous marriage and in 2 sibs, all with unaffected parents. Madrid *et al.* (1977) described a sporadic neuronal sensorimotor case with onset in early childhood. Dubowitz (1978) reported 2 children from healthy consanguinous parents and Colomer *et al.* (1983) described 1 dominantly inherited and 4 sporadic cases with an infantile neuronal motor and sensory neuropathy. Both reports lack nerve biopsy studies. The morphological description of the childhood HMSN type II cases of Hagberg and Westerberg (1983) is limited and not published in detail to the best of our knowledge. Moreover, the normal sensory nerve recordings in 27 of their 30 patients raise doubts about the sensory involvement in all but 3, 1 sporadic and 2 autosomal dominant cases. Four of the early onset cases of Rossi *et al.* (1983) are difficult to reconcile with neuronal HMSN because of normal sensory nerve responses and 'an almost normal fibre spectrum with no or only minor loss of axons'. Only 1 sporadic case presented a severe loss of large diameter fibres. The infantile X-linked neuronal HMSN cases with deafness and mental retardation of Cowchock *et al.* (1985) were attributed to a distinct genetic disorder. Lütschg *et al.* (1985) described an infantile onset in a sporadic case of neuronal HMSN. The cases of Julien *et al.* (1988) showed dominant inheritance.

In our patients the disease followed a slow progressive course with sometimes apparently stable periods, but resulting in severe disability. Most patients became wheelchair dependent during adolescence or in adult life and had a marked impairment of hand function. Others were only poorly ambulant in adult life. Only the autosomal dominant Case 15 and the sporadic Case 17 could still manage to walk several kilometres. Nearly half the number of patients showed slight asymmetry in motor dysfunction. An

asymmetric peroneal amyotrophy was observed also by Charcot and Marie (1886), by Buchthal and Behse (1977) in 20% of their neuronal HMSN cases and by Berciano *et al.* (1986) in an HMSN type II case. Conspicuous shoulder amyotrophy was apparent in 4 cases, resembling scapuloperoneal atrophy or Davidenkow's syndrome (Davidenkow, 1939). The presence of this syndrome in neuronal HMSN cases has been described previously (Schwartz and Swash, 1975; Serratrice *et al.*, 1984). Cranial nerve involvement was seen in some of our patients. Although some authors consider the association to represent a separate syndrome (Dyck, 1975; Sommer and Schröder, 1989), others have accepted these additional features in HMSN (Harding and Thomas, 1980*a*; Ouvrier *et al.*, 1981). Two of our patients had borderline reduced intelligence to mild mental retardation. Mental retardation, neuronal HMSN and deafness was described by Cowchock *et al.* (1985) as an X-linked disorder, but our patients with mental retardation (1 female, 1 male) showed no sensorineural deafness. The CSF protein content was normal in our cases in which it was examined. This is in agreement with the early onset neuronal cases in the literature, in which, if investigated, normal CSF protein content was reported (Kalyanaraman *et al.*, 1970; Ouvrier *et al.*, 1981; Rossi *et al.*, 1983; Lütschg *et al.*, 1985). Slightly elevated serum CK values, which were demonstrated in 6 out of 10 patients, have been reported previously in cases of neurogenic muscular atrophy (Goto *et al.*, 1967).

Of our cases, 13 were sporadic. In 4 cases a similarly affected sibling and normal parents were suggestive of autosomal recessive inheritance. Only in 1 family was there a dominant inheritance pattern. Early onset neuronal HMSN cases mostly occur sporadically or are of autosomal recessive inheritance. Autosomal dominant inheritance for early onset cases was found in a family described by Ouvrier *et al.* (1981), in 1 infantile case each described by Colomer *et al.* (1983) and Hagberg and Westerberg (1983), in the family described by Julien *et al.* (1988) and in Case 15 of the present report. Only the dominant cases of Ouvrier *et al.* (1981) showed a clinical severity uncommon for autosomal dominant HMSN type II. On the other hand, convincing reports of autosomal recessive inheritance (healthy consanguinous parents and an affected child or healthy parents and affected children) of neuronal HMSN cases reported by Brust *et al.* (1978), Dubowitz (1978), Harding and Thomas (1980*b*) and Ouvrier *et al.* (1981), all showed an earlier onset and greater clinical severity than usually seen in dominant HMSN type II. It might even be reasonable to assume that autosomal recessive HMSN type II, of which a definite example has been described by Harding and Thomas (1980*b*), is identical to the currently described condition. It must be noted that in our sporadic patients there may be examples of autosomal dominant HMSN type II such as Case 15. Case 17 could be a representative because of less prominent clinical and morphological features.

Median nerve motor conduction velocity was normal or mildly reduced; however, in 3 cases it fell below 35 $m \cdot s^{-1}$. Separation of hereditary motor and sensory neuropathy in hypertrophic HMSN type I and neuronal HMSN type II cases without confirmation by biopsy is often based on a median motor nerve conduction velocity of 35–38 $m \cdot s^{-1}$ (Thomas and Calne, 1974; Brust *et al.*, 1978; Harding and Thomas, 1980*a*). From studies with fairly large groups of morphologically confirmed HMSN type I and II cases it has been assumed that overlap in motor conduction between HMSN type I and type II exists (Buchthal and Behse, 1977). Some histologically classified

neuronal sensorimotor neuropathy cases showed median motor nerve conduction velocities between 25 and 35 $m \cdot s^{-1}$ (Ben Hamida *et al.*, 1981; Gherardi *et al.*, 1983). Our Cases 6 and 14 showed slowing of motor nerve conduction velocity along the median nerve to 27 $m \cdot s^{-1}$. Loss of large fibres was also most evident in these cases: fibres with a diameter > 5 μm were absent in the sural nerve. Abnormally small fibre diameter, suggestive of a maturational deficit, as seemed particularly evident in Case 6 (fig. 2), could be an additional factor contributing to slow motor nerve conduction velocity.

Loss of large diameter fibres in our cases was more pronounced as compared with the cases classified as autosomal dominant HMSN type II (Dyck, 1975; Behse and Buchthal, 1977; McLeod and Low, 1977; Madrid *et al.*, 1977; Gherardi *et al.*, 1983). There was a near total loss of fibres > 8 μm in diameter; even fibres > 6 μm were almost completely absent in half the number of cases. The peak of the fibre size histogram was shifted to the left and located between 2 and 3 μm in most cases. This shift to smaller fibre diameters is usually not observed in HMSN type II (Behse and Buchthal, 1977; McLeod and Low, 1977; Gherardi *et al.*, 1983; Berciano *et al.*, 1986).

TTFA was diminished or low to normal in half the number of biopsies in which it was determined. Although this small TTFA could be attributed to incomplete nerve biopsies (Madrid *et al.*, 1977), this seems unlikely. Small TTFA is an unusual finding in our experience, but occurred in 50% of our infantile neuronal cases, especially of those biopsied at a younger age. Small TTFA may be attributed to the extensive lack of large diameter fibres already present early in life. Moreover, a small TTFA implies that total fibre loss is more extensive than deduced from fibre density only. Increase of endoneurial collagen fibres was evident in several long-standing cases with severe fibre loss.

One of the morphological hallmarks of HMSN type II is the presence of many clusters of small myelinated fibres (Behse and Buchthal, 1977; Madrid *et al.*, 1977; Gherardi *et al.*, 1983; Berciano *et al.*, 1986). In our early onset neuronal HMSN cases this regenerative feature was almost entirely lacking, as it was in those cases biopsied after childhood. Only in the single dominantly inherited case, a cluster ratio in the range of HMSN type II was present in the sural nerve. This absence of cluster formation was also observed by Madrid *et al.* (1977) in a sporadic early childhood case and seems likely from the morphological descriptions of illustrations in the reports of Goebel *et al.* (1976), Rossi *et al.* (1983) ('atypical neuronal case') and Lütschg *et al.* (1985). Ouvrier *et al.* (1981) mentioned some early cluster formation in 2 cases, but clusters of myelinated fibres were not shown.

Some unmyelinated fibre pathology may be present in our cases, but it was not possible even to estimate the extent of such involvement because it was not feasible to decide if nonmyelinated axons within complex Schwann cell structures represented genuine unmyelinated axons or sprouts from myelinated axons.

With respect to the pathogenetic mechanisms, the extensive lack of large diameter fibres and small TTFA already present in the youngest patients without appreciable signs of fibre degeneration or axonal atrophy, together with a shift to smaller fibre diameters and no clear cluster formation, could be explained by an early, even prenatal, disturbance in maturation of peripheral motor and sensory neurons of small and large diameter fibres. The finding of extremely small yet myelinated axons observed in Case 6 is an additional argument for a maturational deficit. A concomitant or secondary process of chronic

neuronal degeneration leading via sequential stages to distal degeneration firstly of large myelinated fibres (Dyck *et al.*, 1981), as suggested for autosomal dominant HMSN type II (Dyck, 1975), could also be present. But the axonal degeneration in our cases might follow a more aggressive course than usually seen in autosomal dominant HMSN type II as nerve biopsies showed hardly any regenerative clusters in a distal lower limb nerve and only a few clusters in a proximal upper limb nerve. The observation that paranodal demyelination was relatively frequent in our cases, whereas segmental demyelination was absent or rare, might indicate that paranodal demyelination in our cases should be considered as a stage in axonal degeneration and need not be explained as a consequence of axonal atrophy (Ochoa, 1974).

The patients in this report are suffering from an early childhood chronic progressive motor and sensory neuropathy of neuronal type as described earlier by Ouvrier *et al.* (1981). Based on data from the literature and the findings in the present report, this condition differs in clinical, genetic and morphological aspects from autosomal dominant HMSN type II. (1) The condition shows an early childhood onset in contrast to HMSN type II, in which symptoms most often begin in the second decade, but can be clinically delayed to later decades (Harding and Thomas, 1980*a*). (2) The condition is clinically more severe than HMSN type II. In adult life most patients are severely disabled and wheelchair bound. Atrophy and weakness of hand muscles is present from the end of the first decade. Total areflexia is more common and sensory disturbances are more pronounced. (3) The condition is probably transmitted by an autosomal recessive gene, while HMSN type II usually is dominantly inherited. (4) The morphological features are different from HMSN type II, especially in their quantitative aspects. TTFA is small. Loss of large diameter fibres is severe with a shift of the fibre size histogram to smaller diameters. Lack of regenerative clusters derived from myelinated fibres is a striking difference from autosomal dominant HMSN type II. A maturation disturbance of peripheral motor and sensory neurons with a concomitant or secondary process of chronic neuronal degeneration is suggested.

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PAIN-RELATED SOMATOSENSORY EVOKED POTENTIALS IN SYRINGOMYELIA

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SUMMARY

Pain-related somatosensory evoked potentials following CO_2 laser stimulation (pain SEPs) and conventional electrically-stimulated SEPs (electric SEPs) were examined in 8 patients with syringomyelia who showed various forms of dissociated sensory loss. Unlike clinical examination using a pin or needle, pain SEP is considered to be an objective and quantitative test to investigate functions of peripheral and central sensory pathways responsible for pain-temperature sensation (Aδ fibres and the spinothalamic tract). Pain SEPs were abnormal in all patients The results were generally compatible with the degree of a clinical impairment of pain-temperature sensation. Subclinical abnormality was detected in 3 patients. Electric median nerve SEPs using the scalp reference (Fz) were normal in 6 out of 8 patients. However, anterior and posterior cervical responses using a noncephalic reference were absent or small in 7 patients. Electric SEPs following tibial nerve stimulation were normal in 7 patients. These findings suggest that the function of the ascending fibres through the dorsal columns is intact in most patients, whereas the dorsal horn, where a fixed cervical potential is generated, is impaired. Pain SEPs combined with electric SEPs therefore appear to be extremely useful for investigating physiological function in the sensory pathways in patients who show 'dissociated sensory loss' such as in syringomyelia.

INTRODUCTION

Syringomyelia is characterized by 'segmental dissociated sensory loss' in which pain and temperature sensation is impaired segmentally. Tactile and deep sensation is preserved as the syrinx occupies the central portion of the spinal cord where the fibres concerned with pain and temperature sensation cross the midline.

Somatosensory evoked potentials (SEPs) are usually recorded following electrical stimulation of peripheral nerves (electric SEPs). It is accepted that electric SEP findings are related to impairment of deep sensation and that their ascending signals are carried by large myelinated fibres in the peripheral nerve and the dorsal columns of the spinal cord (Halliday and Wakefield, 1963). Conventional electric SEPs were therefore believed to be inappropriate for investigating an impairment of pain-temperature sensation or for detecting lesions in the grey matter of the spinal cord. However, Desmedt and his colleagues (1981, 1984) have produced convincing arguments that cervical potentials with a noncephalic reference reflected the activity of a segmental horizontal dipole in

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the cervical cord and attributed this activity to the postsynaptic response of dorsal horn neurons. This finding was confirmed by Emerson *et al.* (1984), Kaji and Sumner (1987), Urasaki *et al.* (1988) and Sonoo *et al.* (1990). SEPs with a noncephalic reference might therefore be useful for the detection of lesions in syringomyelia.

A low power and long wavelength CO_2 laser beam induces pain or heat sensation when applied to the skin, and several reports including ours (Carmon *et al.*, 1976, 1980; Kenton *et al.*, 1980; Bromm and Treede, 1984, 1987; Treede *et al.*, 1988*a*, *b*; Kakigi *et al.*, 1989, 1990, 1991; Kakigi and Shibasaki, 1991) have reported SEPs induced by CO_2 laser stimulation (pain SEPs). From these studies in normal subjects and in patients showing various types of sensory impairment, it is now established that CO_2 laser stimuli cause excitation of nociceptive receptors in the skin and that their ascending signals travel through small myelinated fibres (Aδ) of peripheral nerves and probably are mediated through the spinothalamic tract.

It therefore seems possible to detect physiological impairment of sensory function in patients with syringomyelia by pain SEPs combined with electric SEPs. The object of this paper is to establish the clinical usefulness of pain SEPs in syringomyelia by investigating correlations with sensory impairment as well as with magnetic resonance imaging (MRI).

MATERIAL AND METHODS

Eight patients, 4 females and 4 males, with syringomyelia were examined Their clinical profiles are summarized in Table 1. A diagnosis of syringomyelia was established by both MRI and myelography combined with computed tomography (CT). CT was examined just after the myelography and repeated 24 h later (delayed CT). No patient had a history of injury or tumour which could have caused a syrinx.

The severity of sensory impairment was classified into 5 categories: none (0), mild (1), moderate (2), marked (3) and complete loss (4). Position sense was examined by passively moving the index finger or the big toe by the examiner's finger Vibration sense was examined by placing a vibrating tuning fork (128 Hz) on the styloid process of the radius at the wrist or on the lateral malleolus at the ankle. Tactile sense was examined by gently stroking the skin surface with the soft pad of tissue paper Pain sense was examined by using a sharp needle. Sensory function was examined by at least 2 neurologists.

TABLE 1 CLINICAL AND RADIOLOGICAL PROFILES OF 8 PATIENTS WITH SYRINGOMYELIA

Case	*Sex*	*Age (yrs)*	*Sensory impairment**		*Syrinx*	*Other findings*
			Deep and touch	*Pain-temperature*		
1	F	55	(0)	R C7–T2 (2)	C2–T1	ACM 1
2	F	50	(0)	R C3–C6 (2)	C2–C4	ACM 1
3	F	62	L C5–C7 (1)	L C5–C7 (2)	C5–C6	(–)
4	M	34	(0)	(0)	C3–T9	ACM 2
5	M	55	R C3–S5 (1)	R C3–T5 (4) R T5–S5 (2)	C2–T10	(–)
6	M	57	Bilat. C3–S5 (1)	Bilat C3–S5 (4)	C2–T12	(–)
7	F	48	R C3–T1 (4) R T2–S5 (3) L C3–T1 (2)	R C3–T1 (4) R T1–S5 (2) L C3–T1 (2)	C4–T9	(–)
8	M	17	(0)	R C4–T3 (2)	C2–T1	ACM 1

* Severity of sensory impairment is classified into 5 grades: none (0), mild (1), moderate (2), marked (3), and complete loss (4). Impaired areas are described by dermatome. ACM 1 and 2 = Arnold-Chiari malformation types 1 and 2 (–) = no other additional finding.

The distribution of sensory impairment was described by dermatome (cervical, C, thoracic, T, lumbar, L, or sacral, S). Deep and tactile sensation was intact or only mildly impaired in all patients except Case 7. Pain-temperature sensation was impaired segmentally to various degrees in all patients except Case 4 who showed only lower motor neuron signs and had never noticed sensory dysfunction. All patients apart from Case 6 showed asymmetric sensory dysfunction, although radiographically the syrinx appeared to occupy a central position with no asymmetry.

In addition to the conventional method using pin prick, pain sense was evaluated by a specially designed dolorimeter using a CO_2 laser beam. Its stimulus condition will be described in the section on methods for pain SEPs. During the application of a stimulus of increasing power (every 1 mJ/mm^2) applied to various areas of the skin, subjects were requested to tell the examiner when they felt a distinct sharp pain 'like a pin prick' The test was repeated at least 3 times and the lowest threshold was adopted. When the skin area stimulated was cold, it was warmed by a heater; skin temperature was kept at over 25° C, monitored by a thermistor.

Pain SEPs were recorded by a special CO_2 laser stimulator (Nippon Infrared Industries Co. Ltd, Kawasaki, Japan) Its maximum power was 23 W, but an attenuator limited the output to approximately 12.5 W for reasons of safety. Laser wavelength was 10 6 μm, and the diameter of the irradiation beam was approximately 2 mm. Stimulus duration was 10 ms and stimulus interval 3 s. Stimulus intensity was approximately 18 mJ/mm^2 which elicited a sharp pain that normal subjects described as a tolerable 'pin-prick-like' sensation. The laser beam was applied to the dorsum of hand and foot in all patients, but various other areas were also stimulated depending on the patient's clinical and radiological findings. The eyes were protected by putting swimming goggles over the face

Silver disc electrodes (1 cm diameter) were attached to the skin with collodion and filled with electrode jelly, impedance was maintained at less than 3 KΩ. As peripheral and spinal responses of pain SEPs could not be clearly recorded (Kakigi *et al.*, 1989), only scalp responses were investigated. As pain SEPs were most prominent around the vertex (Kakigi *et al.*, 1989), exploring electrodes were placed at Cz (International 10−20 System), and FCz, CPz, CP3 and CP4 which were midway between Fz and Cz, Cz and Pz, C3 and P3, and C4 and P4, respectively. Linked earlobes (A1+A2) were used as the reference. Amplifier frequency response was 0.5−30 Hz (−3 dB). In 1 session, 15−20 responses were averaged, and at least 4 sessions were performed for each subject. After confirming consistency of waveforms, all averages were added together and the group-averaged waveforms recorded at Cz were analysed (fig. 1). As the positive component, P340 in hand-stimulated SEPs and P400 in foot-stimulated SEPs was largest and more stable as compared with the preceding negative peaks in normal individuals (Kakigi *et al.*, 1989; Kakigi and Shibasaki, 1991), these positive components were mainly analysed in this paper. Analysis time was 1.5 s after stimulation. Detailed methods were described in our previous papers (Kakigi *et al.*, 1989, 1990, 1991, Kakigi and Shibasaki, 1991).

Electric SEPs were also recorded in all patients. The electrical stimulus was a constant voltage square-wave pulse lasting 0.2 ms delivered to the median nerve at the wrist or to the tibial nerve at the ankle. The ulnar nerve at the wrist was also stimulated in Cases 1, 3 and 8. Stimulus intensity was sufficient to produce a definite twitch of the thumb or big toe; 300−400 responses were averaged in 1 session, and at least 3 sessions were undertaken. Analysis window depended on clinical findings of each patient, but principally 3−33 ms and 5−65 ms were employed for median or ulnar nerve SEPs and tibial nerve SEPs, respectively The frequency response of the amplifier was 15−3000 Hz. The sampling rate was 2.9 ms, 0.06 ms and 0.12 ms, for pain SEPs, median nerve electric SEPs, and tibial nerve electric SEPs, respectively.

The following electrode derivations were used for recording electric SEPs following upper limb stimulation in all patients: (1) Erb's point-Fz (International 10-20 System) or noncephalic site (NC, hand or Erb's point contralateral to the stimulated nerve); (2) anterior neck around the supraglottal site (ant. neck)-NC; (3) seventh cervical vertebra (Cv7)-Fz; (4) Cv7-NC; (5) second cervical vertebra (Cv2)-Fz; (6) Cv2-NC; (7) contralateral hand sensory area of the scalp (2 cm behind C3 or C4 of the International 10-20 System, C3′ or C4′-Fz or linked earlobes (A1+A2); and (8) C3′ or C4′-NC. The normal waveforms and the nomenclature of each component are shown in fig. 2.

The electrode derivations for tibial nerve stimulation were (1) Cz-Fz, (2) Cz-(A1+A2), (3) Cz′ (2 cm behind Cz)-Fz, and (4) Cz′-(A1+A2). As it was difficult to record clear spinal potentials in most patients, only scalp potentials were investigated. Principally, the first cortical component, P37, recorded in the Cz′-Fz derivation was analysed.

Relative positivity at grid 1 resulted in a downward deflection in all records. Peak latency and amplitude

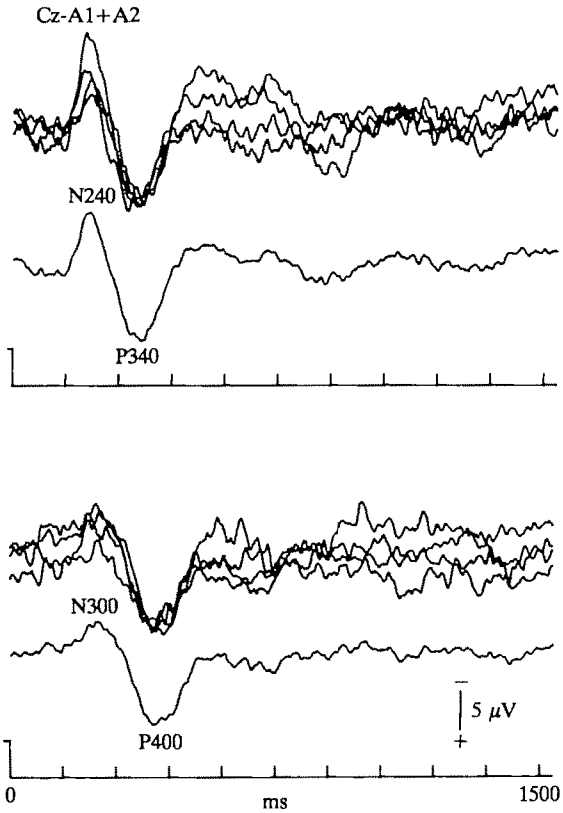


FIG. 1 Pain SEPs following stimulation of the dorsum of the left hand (*top*) and foot (*bottom*) in a normal subject The *upper* trace in each figure is a superimposition of 4 averages and the *lower* one is their summed averaged waveform. Analysis windows and amplitude scales are the same in each figure The exploring electrode is placed at Cz and the reference is the linked earlobes in this figure and the following figures of pain SEPs Relative positivity at grid 1 is shown as a downward deflection in this and all of the following figures (reproduced with permission from Kakigi and Shibasaki, 1991)

were measured for each recognizable component, and each component was named by its polarity and peak latency. Amplitude was measured from the preceding peak of the opposite polarity

Forty volunteers, aged 17–65 yrs, served as normal controls. Their heights ranged from 149 to 178 cm (mean ± SD = 158.2 ± 12.1). Some of their SEP results were previously reported by us (Kakigi, 1987, 1989; Kakigi *et al.*, 1989, 1990, 1991; Kakigi and Shibasaki, 1991). The correlation coefficient (r) between peak latencies of the recognizable components and heights was calculated and $P < 0.01$ was judged to be significant. The regression line between peak latencies or interpeak latencies of the recognizable components and body heights was calculated according to the following equation: $Y = aX+b$, where Y is latency in ms, X is height in cm and a and b are constants. When the peak latency of a component showed a significant correlation with height, the latency in each normal subject was normalized using 158 cm (mean height) as the standard height and by using the following equation: corrected latency (Y′) = $Y+a(158-X)$. After calculating mean and SD of the corrected latencies, its mean plus 2.5 SD was adopted as the upper limit of normal range. Results of each patient were also normalized by the same method by using 158 cm as the standard height, and its abnormality was judged This method was described in more detail in our previous report (Kakigi, 1989).

All patients and normal volunteers gave informed consent.

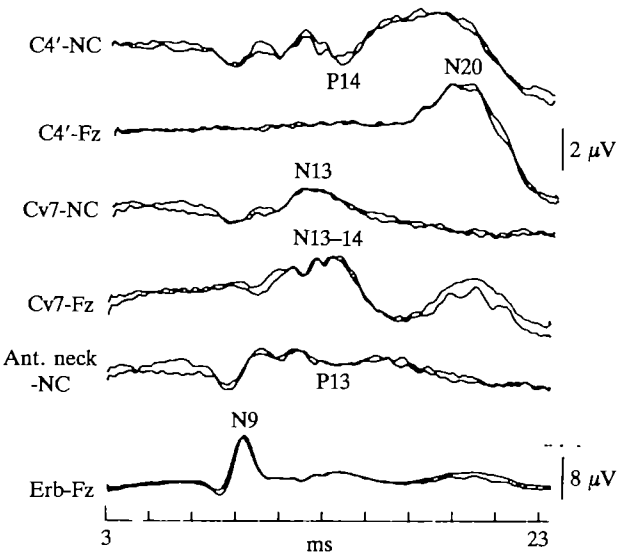


FIG 2 Waveforms and nomenclature of each component in electric SEPs following stimulation of the left median nerve in a normal subject In order to make the identification of each peak easier, only the early part of the analysis window (3−23 ms) is shown, and waveforms recorded at the second cervical vertebra are not included in this figure. NC = noncephalic site (the right hand in this record), Ant neck = anterior neck around supraglottal area, Cv7 = seventh cervical vertebra, C4′ = 2 cm behind C4 of the International 10-20 System

RESULTS

Pain SEPs and electric SEPs in normal subjects

Results of pain SEPs and pain thresholds in normal subjects are shown in Table 2. A large positive response could be clearly recorded following stimulation of the C3, C6 and C8 dermatomes in all subjects examined, but that following foot stimulation could not consistently be found in 2 out of 36 subjects examined because of insufficient cooperation. Peak latency of pain SEPs in normal subjects showed no significant correlation with the subject's height. As interindividual differences of amplitudes were very large (*see* Table 2), a lower limit for the normal range was not set. Differences of peak latencies and amplitudes between left and right stimulation were relatively small and the pain threshold showed no left-right difference. Therefore, when the left-right difference of the latency and amplitude exceeded the mean+2.5 SD, it was judged to be abnormal. When the left-right difference of the pain threshold was 1 mJ/mm^2, it was judged to be equivocally abnormal, and when it was 2 mJ/mm^2 or above, it was judged to be abnormal.

Results of electric SEPs following the right median and the right tibial nerve stimulation in normal subjects are shown in Table 3. Peak latencies of all potentials showed a significant correlation with height, but the interpeak latency between N13-14 recorded in the Cv7-Fz derivation and N20 in the C3′-Fz derivation (central conduction time) did not. An abnormality of each peak latency in patients was therefore judged by using the method described in Material and Methods. As the left-right difference of each peak

TABLE 2 MEAN ± SD OF THE PAIN SEPs AND PAIN THRESHOLDS IN NORMAL CONTROLS

Stimulus site (dermatome)	*n*	*Latency (ms)*	*Amplitude (μV)*	*Pain threshold (mJ/mm²)*
R C3	12	272.1 ± 18.2	5 5 ± 4 2	13 3 ± 0.9
L C3	12	270 5 ± 18 4	5 3 ± 4 1	13.3 ± 0.9
L-R difference		5 1 ± 4.2	1 1 ± 0 7	0
R C6	40	337 9 ± 20 1	8 6 ± 5 1	13 1 ± 0 8
L C6	40	336 0 ± 20 4	8 8 ± 5 3	13 1 ± 0 8
L-R difference		5 6 ± 4.4	1 1 ± 0 7	0
R C8	40	339.6 ± 20 2	8 2 ± 5.0	13.1 ± 0.8
L C8	40	340.5 ± 19.8	8 4 ± 5.3	13.1 ± 0 8
L-R difference		5.2 ± 4.1	1 2 ± 0.8	0
R foot	34	400.1 ± 22.3	6 0 ± 4.4	13 7 ± 1 0
L foot	34	398 4 ± 22.6	6.1 ± 4.3	13.7 ± 1.0
L-R difference		5 9 ± 4.0	1 0 ± 0.8	0

n = number of subjects studied C3 = over the clavicle; C6 and C8 = approximately 3 cm distal to the wrist joint over the radial and ulnar aspects on the dorsum of the hand, respectively, foot = approximately 4 cm distal to the ankle joint over the midline dorsum of the foot corresponding to L4-5 dermatome

latency was less than 1.5 ms in median nerve SEPs in every subject, 1.5 ms was set as its upper limit; similarly 2.0 ms was adopted for tibial nerve SEPs.

Patients with syringomyelia

Results of pain SEPs and pain thresholds in patients are shown in Table 4. Pain SEPs showed at least some abnormality in all 8 patients. Generally, pain SEPs were abnormal when the disturbed site for pain-temperature sensation was stimulated. In Cases 1, 4 and 5, however, pain SEPs were abnormal even though pain-temperature sensation was judged to be normal clinically (subclinical abnormality). In Cases 4 and 5, the pain threshold was more sensitive than pin prick testing for the detection of an impairment of pain-temperature sensation, and its finding almost paralleled those of pain SEPs.

Electric median nerve SEPs with Fz reference were normal in 6 out of 8 patients (Table 5). These findings almost paralleled an impairment of deep and tactile sensations of the hand. In contrast, posterior and/or anterior cervical potentials with the noncephalic reference (N13 and P13, respectively) could not be consistently identified in 7 patients whose pain-temperature sensation of the hand was impaired. Central conduction time was within the normal range in 7 patients except for Case 7, whose N13 − 14 and N20 could not be recorded. The P37 peak of the tibial nerve SEPs was also normal in 7 patients except in Case 7. Results of representative patients will be shown below in detail.

Case 1

This woman, aged 55 yrs, presented with only a moderate impairment of pain-temperature sensation in the right upper extremity (C7-T2 dermatome), but a large syrinx was found extending from C2 to T1 on MRI (fig. 3A). The pain threshold study was consistent with clinical examination. The pain SEP P340 could not be identified when the right C8 area was stimulated, and its peak latency was very close to the upper limit when the left C6, left C8 and the right C6 areas were stimulated (fig. 3B). P400 was of normal latency and amplitude when the right and left feet were stimulated, but that following right foot stimulation was significantly longer than that following stimulation of the left foot (Table 4, fig. 3B). Electric median

TABLE 3 RESULTS OF ELECTRIC SEPs FOLLOWING THE RIGHT MEDIAN AND TIBIAL NERVE STIMULATION IN 40 NORMAL CONTROLS

Potential	*Electrode derivations*	*Latency (mean ± SD in ms)*	*Amplitude (μV)*
N9	Erb-Fz	8.9±0 7 Y = 0 042X+2 27*	6 4±3 4
P13	Anterior neck-NC	12.2±1 4 Y = 0 054X+3.47*	0 8±0.5
N13-14	Cv7-Fz	12 2±1 1 Y = 0 063X+2.29*	2 0±1.1
N13-14	Cv2-Fz	12 3±1 1 Y = 0 061X+2 44*	2 1±1 3
N13	Cv7-NC	12.0±1 3 Y = 0.058X+2.84*	0 7±0 5
N13	Cv2-NC	12 2±1 3 Y = 0 059X+2 88*	0 8±0 5
P14	C3′-NC	12.7±1 1 Y = 0.064X+2.59*	1 1±0.6
N20	C3′-Fz	18 1±1.0 Y = 0 063X+8 56*	2.6±1 2
N20	C3′-NC	17 9±1 0 Y = 0 062X+8 10*	3.2±1 4
Interpeak latency between N13-14 (Cv7-Fz) and N20 (C3′-Fz)· (central conduction time) mean ± SD = 5.9±0.5 regression line Y = −0.002X+6.18			
P37	Cz′-Fz	36 3±2.6 Y = 0 132X+15 44	2 1±1.0

* Regression line between latency and height (Y = latency in ms, X = height in (cm) Cv7 and Cv2 = seventh and second cervical vertebrae, NC = noncephalic reference (L Erb's point), C3′ and Cz′ = 2 cm behind C3 and Cz of the International 10-20 System; Fz = midfrontal site of the International 10-20 System

and ulnar nerve SEPs with Fz reference appeared normal. With the noncephalic (NC) reference recording, however, posterior and anterior cervical responses (N13/P13) could not be recorded, although the scalp far-field potential, P14, was of normal latency (fig. 3c).

A syringosubarachnoid shunt operation was performed after the electrophysiological examination. Muscle strength and the sensory disturbances in the right hand were significantly improved, and the syrinx was substantially reduced on MRI (fig. 3A). Pain SEPs following right C8 area stimulation was clearly recorded after the operation, though its peak latency was still very close to the upper limit of the normal range (Table 4, fig. 3B). Pain SEPs following stimulation of other areas of the hand also returned to normal after the operation but they were also very close to the upper limit of the normal range. Left-right differences in pain SEP following foot stimulation were within the normal range after the operation. Electric SEPs showed no remarkable change after the operation. These results suggested the following. (1) The central grey matter including the dorsal horn was impaired segmentally particularly on the right. As pain SEPs reappeared along with clinical improvement after the operation, compression by the syrinx must have been a more important factor than the direct invasion. Although there was no clinical deficit in the left upper limb, fibres from the left might also have been impaired (subclinical abnormality). (2) The dorsal columns and the spinothalamic tracts were intact. The latter findings were not expected from the quite large and long syrinx demonstrated by MRI before the operation, but they were in conformity with the clinical findings. An explanation for the left-right difference of pain SEPs following foot stimulation before the operation cannot be provided.

Case 2

This women, aged 50 yrs, had moderate weakness and moderate impairment of pain-temperature sensation in the right upper limb in the C3−C5 (and equivocally C6) dermatomes. A syrinx was found between C2−C4 on MRI (fig. 4A). Pain SEPs following stimulation of either hand (C8) were normal in latency

TABLE 4 PAIN SEPs AND PAIN THRESHOLDS IN PATIENTS WITH SYRINGOMYELIA

Case	*Stimulus site*	*Latency (ms)*	*Amplitude (μV)*	*Pain threshold (mJ/mm²)*
1	R C6 (postop.)	381	7.3	14
		380	7.4	14
	L C6 (postop.)	390	8 2	14
		382	7 5	14
	R C8 (postop)	?		>20
		381	8.0	15
	L C8 (postop.)	390	5.3	14
		380	7.2	14
	R foot (postop.)	420	12.4	15
		407	12 6	15
	L foot (postop)	393	12.0	15
		394	11.0	15
2	R C3 (postop)	?		19
		336	13.6	15
	L C3 (postop)	408	7.5	16
		378	17.8	15
	R C8 (postop)	348	7.7	13
		353	13.0	13
	L C8 (postop.)	357	6 3	13
		353	16.5	13
	R foot (postop)	?		17
		405	6 7	15
	L foot (postop.)	?		17
		411	7 9	15
3	R C3	304	14.0	13
	L C3	309	15.8	13
	R C6	332	13.9	14
	L C6	332	8.8	18
	R C8	353	14.5	14
	L C8	353	16 5	14
	R foot	412	11 8	15
	L foot	405	12 6	15
4	R C6	?		18
	L C6	?		18
	R C8	?		18
	L C8	?		18
	R foot	?		19
	L foot	?		19
5	R C6	?		>20
	L C6	?		18
	R C8	?		>20
	L C8	?		18
	R foot	?		19
	L foot	710	4.5	18
6	R C8	?		>20
	L C8	?		>20
	R foot	?		>20
	L foot	?		>20

Case	Stimulus site	Latency (ms)	Amplitude (μV)	Pain threshold (mJ/mm^2)
7	R C8	?		>20
	L C8	408	3 1	15
	R foot	?		>20
	L foot	408	3 2	15
8	R C6	?		>20
	L C6	333	12.0	12
	R C8	?		>20
	L C8	342	6.0	12
	R foot	360	6.5	13
	L foot*	374	3 5	15

? = the potential was absent or could not be recorded consistently * Sensation on the left foot was slightly disturbed because of burning The underlined results are abnormal

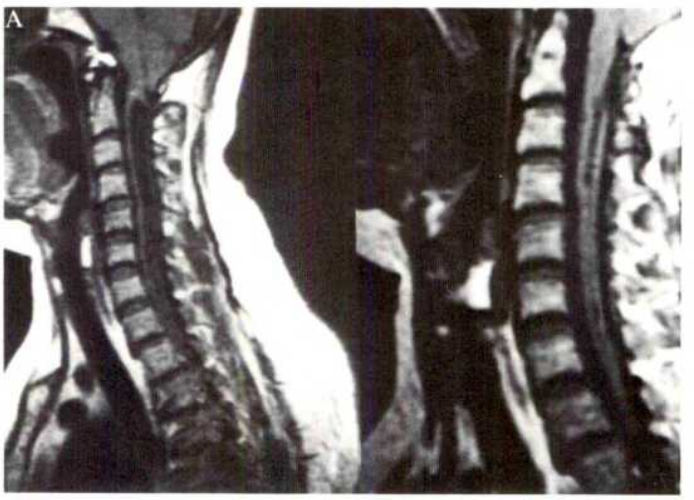
TABLE 5 ELECTRIC SEPs IN PATIENTS WITH SYRINGOMYELIA

		Median nerve stimulation							
		Fz reference			Noncephalic reference				Tibial
Case	Side	N9	N13-14	N20	N13	P13	P14	N20	P37
1*	R	N	N	N	—	—	N	N	N
	L	N	N	N	—	—	N	N	N
2*	R	N	N	N	N	—	N	N	N
	L	N	N	N	N	N	N	N	N
3	R	N	N	N	N	N	N	N	N
	L	N	N	N	N	N	N	N	N
4	R	N	—	N	—	—	N	N	N
	L	N	—	N	—	—	N	N	N
5	R	N	N	N	—	—	N	N	N
	L	N	N	N	—	—	N	N	N
6	R	N	N	N	—	—	N	N	N
	L	N	N	N	—	—	N	N	N
7	R	N	—	—	—	—	—	—	—
	L	N	—	—	—	—	—	—	—
8	R	N	N	N	—	—	N	N	N
	L	N	N	N	—	—	N	N	N

As peak latencies for all components showed a significant assessment correlation with the subject's height, only the final assessment of the data based on our normal controls is shown instead of the raw measurements. N = normal latency and amplitude; — = the response could not be identified consistently; * SEPs were studied also after a syringosubarachnoid shunt was performed. No change could be found in Case 1, but in Case 2, anterior neck P13 on right median nerve stimulation could be clearly identified after the operation (*see* fig. 4c)

and amplitude, but those following right C3 area stimulation over the clavicle were not identified, and those following left C3 stimulation were of significantly increased latency (Table 4, fig. 4B). Pain SEPs following foot stimulation could not be recorded, although impairment of pain-temperature sensation was not recognized on clinical examination (subclinical abnormality) In the right median nerve electric SEPs,

components with an Fz reference appeared normal, and upper cervical N13 and scalp P14 with an NC reference were normal, but the anterior cervical component, P13, with an NC reference was not consistent (fig. 4c). The left median and bilateral tibial nerve SEPs were normal in latency and amplitude. These clinical and electrophysiological findings suggested the following. (1) The central grey matter, including the dorsal horn around C3–C5, was impaired segmentally, predominantly on the right side. (2) The dorsal columns were intact. (3) The outer layers of the spinothalamic tracts were impaired bilaterally, because pain SEPs following foot stimulation could not be clearly identified, but pain SEPs following C8 area stimulation were normal. By considering a lamination of the spinothalamic tract, two hypotheses could be considered. The first is that the spinothalamic tracts were compressed not by the syrinx but by an extramedullary mechanism such as the Arnold-Chiari malformation shown to be present (*see* Table 1).



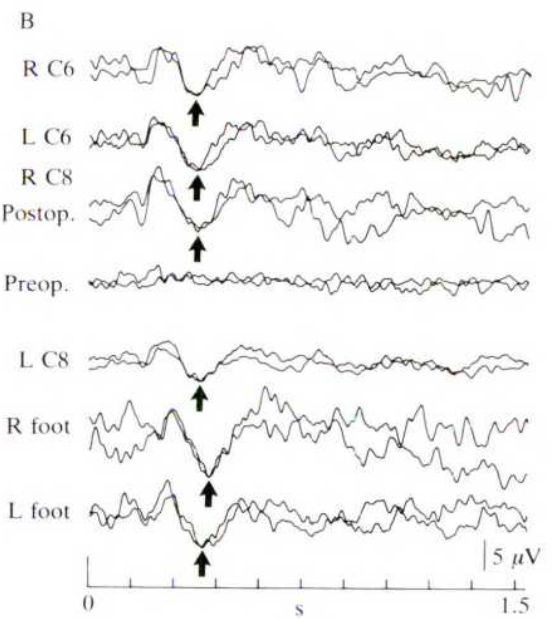


FIG. 3A and B.

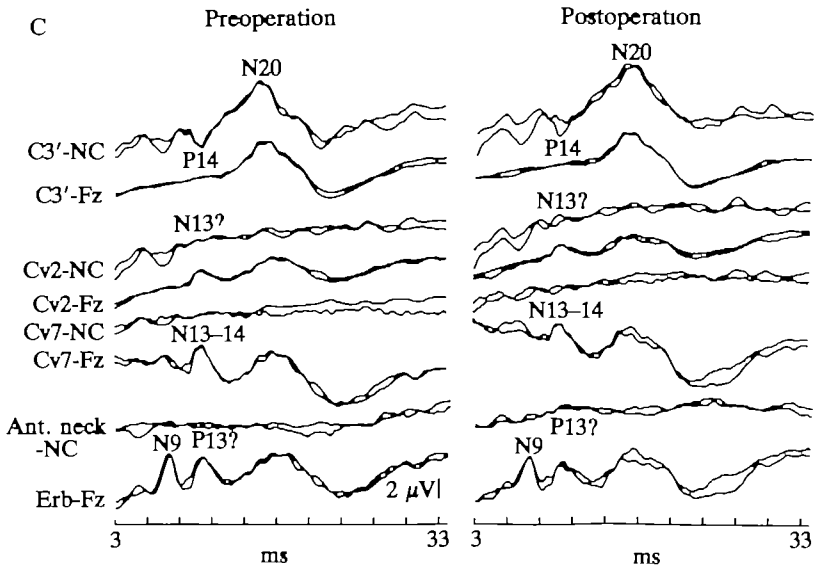


FIG. 3. A, MRI in *Case 1* A large syrinx which was seen from C2 to T1 before treatment (*left*) was considerably reduced in size after a syringosubarachnoid shunt operation (*right*) B, pain SEPs in *Case 1* Before treatment (preop.), P340 following stimulation of the right C8 dermatome was absent and that following right C6, left C6 and left C8 dermatomes was of prolonged peak latency, or was very close to the upper limit of the normal range P400 following stimulation of each foot was of normal latency and amplitude After operation (postop), P340 following right C8 stimulation could be clearly recorded C, electric SEPs following stimulation of the right median nerve in *Case 1* before and after a syringosubarachnoid shunt Anterior as well as posterior cervical components with noncephalic (NC) reference could not be recorded (?), although cervical N13−14 with Fz reference and scalp far-field P14 potential with NC reference were clearly recorded These findings did not change after operation

The second is that the outer layers of the spinothalamic tract was more vulnerable to compression by the syrinx in this particular case

Pain and electric SEPs were studied again approximately 1 month after the syringosubarachnoid shunt operation. The syrinx was significantly reduced in size (fig. 4A) and weakness and sensory impairment in the upper limbs were significantly improved. Pain SEPs following right C3 area stimulation was clearly identified, although its peak latency was significantly increased (fig. 4B). Pain SEPs following stimulation of both feet were also clearly identified with normal peak latencies (fig 4B) As for electric SEPs, the anterior cervical P13 with an NC reference could then be clearly recorded (fig 4C). These findings were compatible with the clinical improvement after the operation and indicated that abnormal clinical and electrophysiological findings before the operation were mainly because of compression rather than direct invasion by the syrinx

Case 3

This woman, aged 62 yrs, had moderate weakness and atrophy in the left upper limb and mild impairment of pain-temperature sensation in the left C5−C7 dermatomes. The pain threshold in the left C6 dermatome was significantly increased compared with normal values in the other areas (Table 4). A very small syrinx extending from C5 to C6 was seen on MRI (fig. 5A), but it was confirmed by myelography with delayed CT Pain SEPs following C3, C6, C8 and foot stimulation were normal bilaterally in latency and in amplitude However, there was a significant left-right difference in the amplitude of pain SEPs following the C6 stimulation (fig. 5B). This finding was consistent with the patient's clinical and pain threshold examination.

Electric SEPs following median nerve stimulation with Fz as well as NC references were normal in latency and amplitude. This particular finding was recognized only in Case 3 amongst the present patients.

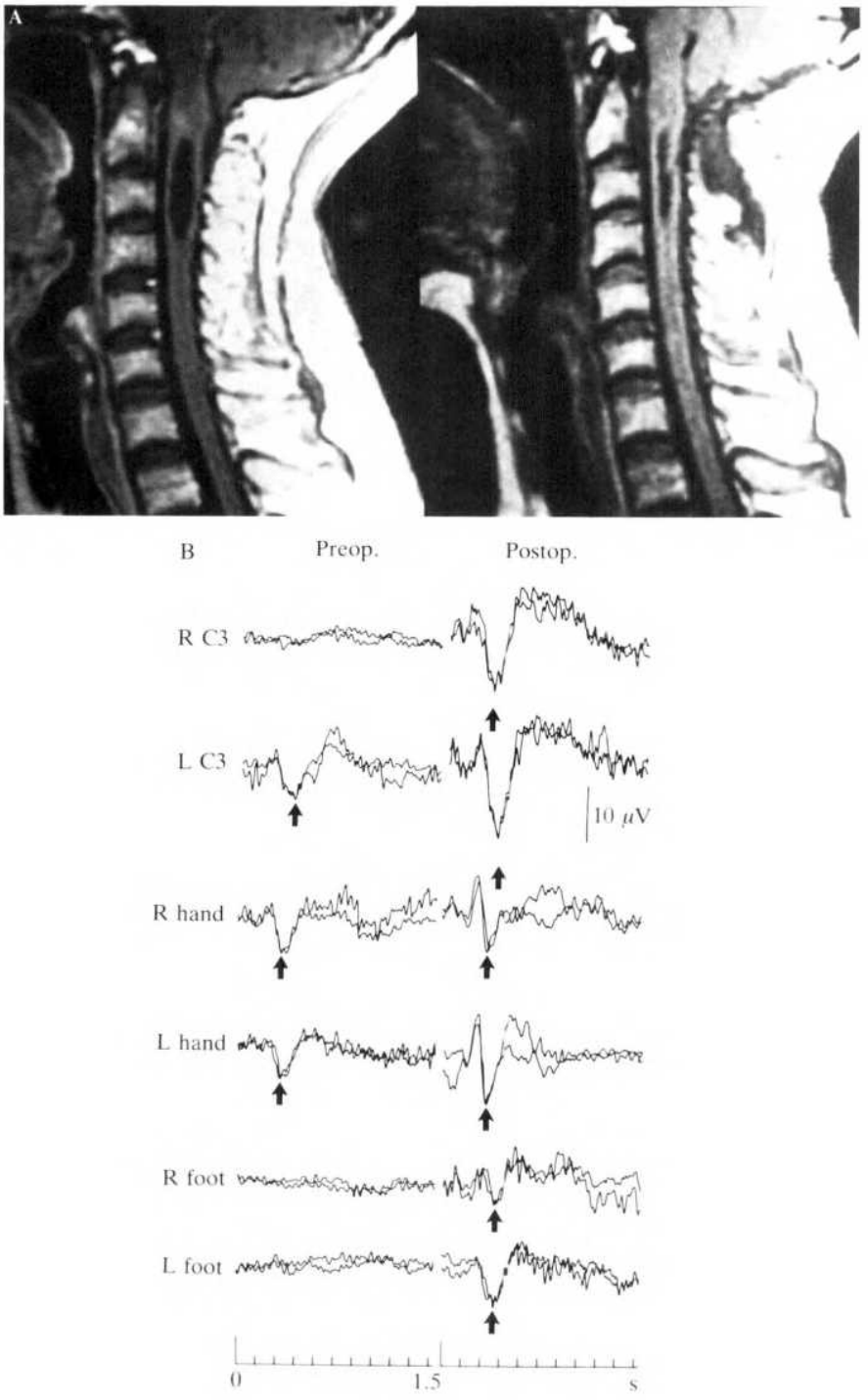


FIG. 4A and B.

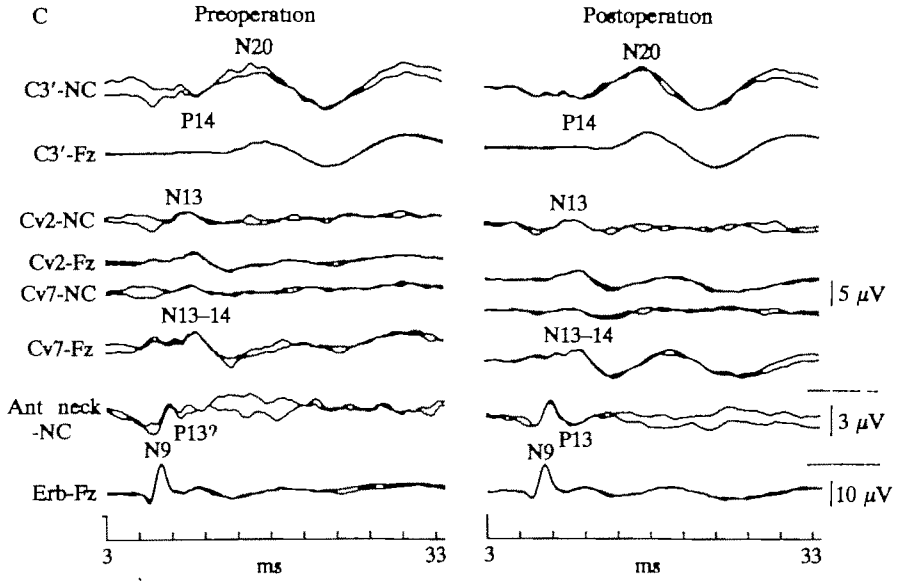


FIG 4. A, MRI in *Case 2* The syrinx seen from C2 to C4 before treatment (*left*) was considerably reduced in size after a syringosubarachnoid shunt operation (*right*) B, pain SEPs before and after the operation in *Case 2* Before the operation, no significant responses could be identified following stimulation of the right C3 dermatome (over the clavicle), or right or left feet, and the response following left C3 stimulation was present with significantly prolonged latency. After the operation, the responses following stimulation of those areas were clearly identified, though the peak latencies following C3 stimulation on either side were still significantly increased. C, electric SEPs following right median nerve stimulation in *Case 2* before and after a syringosubarachnoid shunt operation. All peaks were of normal latency and amplitude except that the P13 potential at the anterior neck with noncephalic (NC) reference was absent (?) before the operation P13 was, however, consistently recorded after the operation

Electric SEPs following tibial nerve stimulation were also normal in latency and amplitude. These clinical and electrophysiological findings suggested the following. (1) The dorsal columns, spinothalamic tracts and dorsal horns were functionally intact. (2) The small syrinx invaded the left anterior horn segmentally. (3) The syrinx mildly involved the crossing fibres segmentally.

Case 4

This man, aged 34 yrs, had marked weakness, atrophy and fasciculation in the upper limbs bilaterally, but there was no sensory disturbance, although MRI disclosed a large syrinx between C3 and T9 (fig. 6A). A syringosubarachnoid shunt operation was performed 8 yrs before the test without any definite clinical improvement. Pain thresholds on the hands and feet were, however, above the upper limit of the normal range bilaterally (Table 4). Pain SEPs following hand and foot stimulation were absent (Table 4) As for electric median nerve SEPs with Fz reference, cervical N13−14 potentials could not be identified consistently, but the cortical N20 was normal. In noncephalic reference recordings, both posterior cervical N13 and anterior cervical P13 could not be clearly recorded, but the scalp P14 was normal (fig. 6B). Tibial nerve SEPs were normal in latency, but their amplitude following left-sided stimulation (0.5 μV) was relatively smaller compared with that following right-sided stimulation (1.3 μV) The following deductions were therefore made. (1) Subclinical impairment of the crossing fibres was detected by pain threshold studies as well as by pain SEPs. (2) The dorsal columns were probably intact, but might be compressed by the syrinx or externally to a slight extent (3) The spinothalamic tracts were impaired bilaterally due either to compression or invasion by the syrinx or to extramedullary compression. These findings were consistent with the radiological findings but not with those obtained clinically.

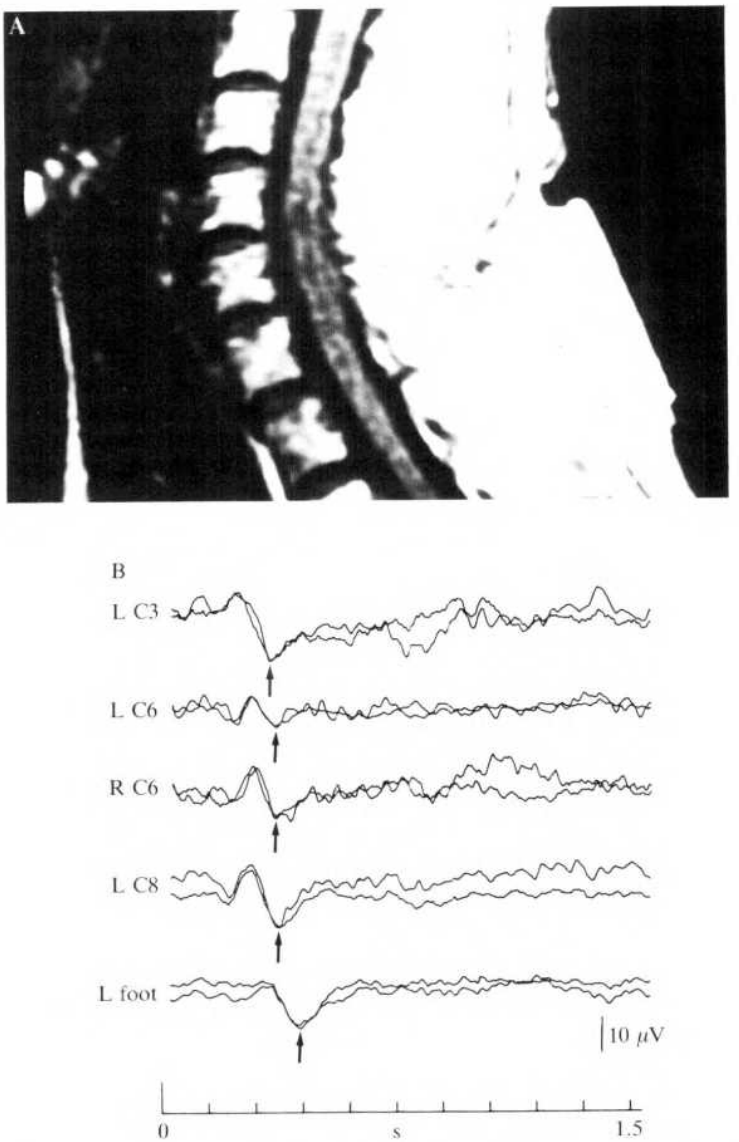


FIG. 5. A, MRI in *Case 3*. A small syrinx was identified from C5 to C6. B, pain SEPs in *Case 3*. The responses following stimulation of C3, C6 and C8 dermatomes and the foot were normal in latency, but that following left C6 stimulation was of relatively smaller amplitude compared with the others.

DISCUSSION

As clinical evaluation of pain-temperature sensation by pin prick testing is neither objective nor quantitative, there have been several attempts to record SEPs relating to pain-temperature sensation, such as following needle stimulation of the skin (Nakanishi *et al.*, 1974; Kakigi and Shibasaki, 1984) and electrical stimulation of pain spots in

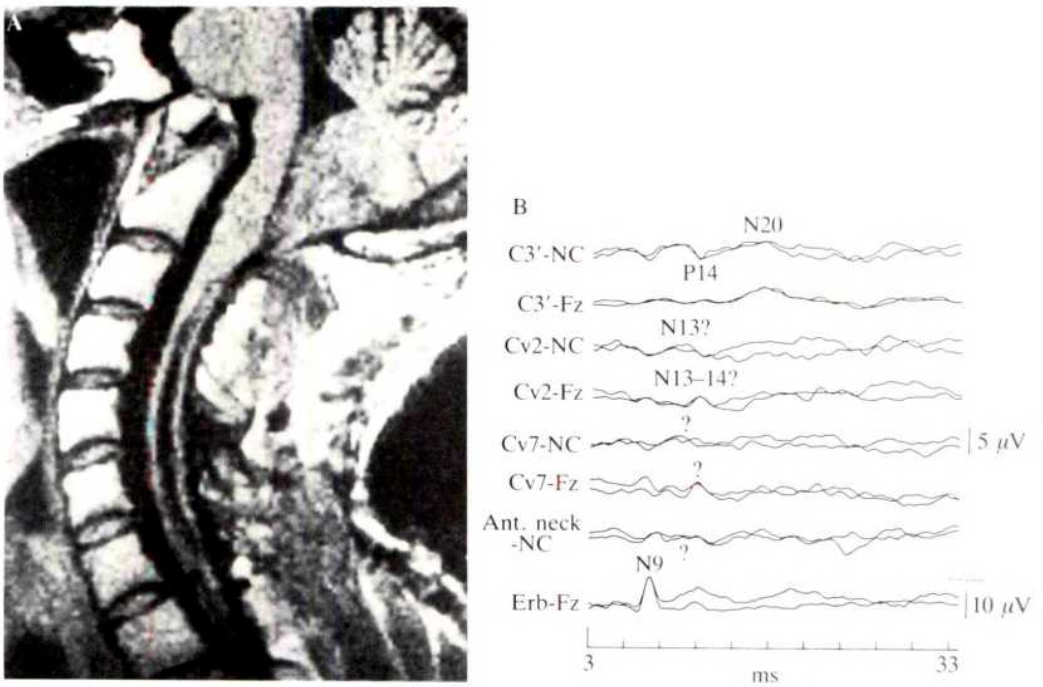


FIG. 6. A, MRI in *Case 4*. A syrinx was present extending from C3 to the thoracic cord (the lower limit was at T9). B, electric SEPs following stimulation of the right median nerve in *Case 4*. The cervical components with Fz reference (N13-14) as well as with noncephalic reference (NC) (N13 and P13) were not consistently identified. The far-field P14 and cortical N20 were normal.

skin (Yamauchi *et al.*, 1980), but none of them successfully isolated excitation of nociceptive receptors from that of tactile mechanoreceptors. In addition, it has been difficult to find an appropriate method to give heat or pain stimuli which can trigger the computer and reduce the temporal delay between the onset of averaging and the effective stimulus time to less than several milliseconds at most.

The CO_2 laser beam can solve all the problems listed above. In our previous papers (Kakigi *et al.*, 1989, 1991), we proposed that ascending signals caused by a CO_2 laser beam ascend through small diameter fibres, probably Aδ fibres, based on the following results. (1) In normal subjects, lidocaine injection to produce an anaesthetic nerve block resulted in loss of pain SEPs, but the potential was relatively well preserved during an ischaemic nerve block. (2) In patients with neuropathies, changes of pain SEPs paralleled an impairment of pain-temperature sensation and a decrease in the density of small diameter fibres in the sural nerve (Kenton *et al.*, 1980). However, there were no reports of pain SEPs in patients with myelopathy except for a brief report in 1 patient with tabes dorsalis (Treede *et al.*, 1988*b*). This is, therefore, the first systematic study reporting the results of pain SEPs in myelopathy.

Syringomyelia is considered to be one of the best indications for pain SEPs, because pain-temperature sensation is selectively affected in most patients with this disease. In

the present study, pain SEPs were either absent, or of reduced amplitude and/or of prolonged peak latency when a laser stimulus was applied to the dermatome where pain-temperature sensation was impaired, and the degree of abnormality generally paralleled the degree of sensory impairment. In 3 patients (Cases 1, 2, 4), however, pain SEPs were abnormal when the laser stimulus was applied to the areas where pain-temperature sensation was judged to be normal on clinical examination using pin prick. Pain SEPs, therefore, could possibly detect subclinical sensory abnormalities. Pain threshold results obtained in the present study also support the view that pain SEPs are more sensitive than clinical examination in evaluating the degree of impairment of pain-temperature sensation.

Evaluation of an impairment of spinothalamic tract function depends on the findings from pain SEPs following stimulation of the dermatomes below the most caudal segment of the syrinx. In Case 1, for example, foot pain SEPs were normal but hand pain SEPs were significantly prolonged. The spinothalamic tract was therefore considered to be intact in this particular patient.

MRI is extremely useful in detecting syringomyelia, but the impairment of physiological function was not consistent with the radiological findings in some patients such as Case 1 in the present investigation. In contrast, pain SEP results were generally in parallel with the clinical impairment of pain-temperature sensation except for Case 4. The pain SEP is therefore considered to be one of the most useful methods for the evaluation of clinical abnormalities in patients with syringomyelia.

There have been more than 10 publications reporting electric SEP findings in patients with syringomyelia (Mastaglia *et al.*, 1978; Small *et al.*, 1978; Green and McLeod, 1979; Riffel *et al.*, 1982; Stöhr *et al.*, 1982; Stockard and Iragui, 1984; Anderson *et al.*, 1986; Emerson and Pedley, 1986; Veilleux and Stevens, 1987; Whittle *et al.*, 1987; Kaplan *et al.*, 1988; Urasaki *et al.*, 1988; Sonoo *et al.*, 1990), but most included only a few patients with syringomyelia among their patients with various myelopathies. Anderson *et al.* (1986) reported 9 patients whose characteristic findings were reduced amplitude or absent cervical potentials and an abnormal central conduction time. In general, observations reported by other reports were compatible with these 2 findings, although the abnormalities were mild because the dorsal columns are usually intact in syringomyelia. However, if we use Fz as the reference as in most previous papers, the component recorded at the posterior neck (N13−14) is a composite of a near-field cervical negative potential and a relatively large far-field P14 potential. The generator of P14 is considered to be at the cervicomedullary junction or in the medial lemniscus (Mauguière and Courjon, 1981; Mauguière and Ibañez, 1985; Urasaki *et al.*, 1988; Sonoo *et al.*, 1990).

By using a noncephalic (NC) reference, Desmedt and his colleagues (1981, 1984) demonstrated that the cervical response was a composite of 2 components arising from different generators; an action potential ascending through the dorsal columns and a fixed potential whose generator is situated in the dorsal horn. Due to the horizontal orientation of a dipole generating the latter potential, a negativity is recorded at the posterior neck corresponding to our cervical N13 with a hand reference, and a positivity recorded at the anterior neck corresponding to our cervical P13. Subsequent papers (Emerson *et al.*, 1984; Kaji and Sumner, 1987; Urasaki *et al.*, 1988; Sonoo *et al.*, 1990) supported their hypothesis and, therefore, when examining cervical myelopathy caused

by an intramedullary lesion such as syringomyelia, recording with a noncephalic reference is necessary to detect a lesion in the dorsal horn. However, it has not yet been established to what sensory modalities the impairment of N13/P13 is related.

In the present investigation, median nerve SEPs with an Fz reference were normal in latency and amplitude in 6 patients, but cortical and/or cervical responses were absent in 2 patients. These results were compatible with mild or no impairment of deep sensation in most of the present patients. However, posterior and/or anterior cervical responses were absent in 6 out of 8 patients. These findings were compatible with the previous studies (Emerson and Pedley, 1986; Urasaki *et al.*, 1988). These findings were also similar to the results of pain SEPs following hand stimulation and generally in conformity with the impairment of pain-temperature sensation in the present investigation. Therefore, as the present results appear to suggest the N13/P13 were generated close to an area which is important for pain-temperature sensation, probably the posterior horn of the grey matter, N13/P13 with an NC reference also appears to be useful for detecting lesions in syringomyelia such as pain SEPs. However, compared with N13/P13 with an NC reference, examination of pain SEPs has the following advantages. (1) Pain SEPs can also study the function of the spinothalamic tract. (2) Pain SEPs allow an exploration of the cord segments which are not accessible to conventional electric SEPs.

Tibial nerve SEPs were normal in latency and amplitude in 6 patients, relatively small in 1, and absent in the remaining patient (Case 7) who showed a moderate to marked impairment of deep sensation in the lower limbs. As tibial nerve SEPs only reflect function in fibres ascending through the dorsal columns, these findings indicate that the syrinx usually does not invade or compress the dorsal columns.

SEP studies were done before and after a syringosubarachnoid shunt operation in 2 patients. The syrinx was substantially reduced in size in both patients, and pain SEP findings also changed appreciably in both. By comparing the results before and after the operation, an abnormality due to compression is expected to be improved while one produced by direct invasion is not. It therefore seems that SEP studies can differentiate whether an impairment is the result of compression or direct invasion.

In conclusion, pain SEPs appear to be very useful for investigating the physiological function of the dorsal horns and crossing fibres in the spinal cord, as well as the spinothalamic tracts, which are all responsible for pain-temperature sensation. Electric median nerve SEPs recorded with an NC reference can supplement the functional investigation of the cervical dorsal horn, although the N13/P13 thus recorded may not be directly related to pain-temperature sensation.

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NEW OBSERVATIONS ON THE NORMAL AUDITORY STARTLE REFLEX IN MAN

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SUMMARY

The latency and pattern of muscle recruitment in the startle response elicited by unexpected auditory stimulation was determined in 12 healthy subjects. Reflex EMG activity was recorded first in orbicularis oculi. This was of similar latency to the normal auditory blink reflex and, unlike the generalized startle response, persisted despite the frequent presentation of the test stimulus. It is argued that this early latency activity in orbicularis oculi represents a normal auditory blink reflex and is not part of the generalized auditory startle reflex. With the exception of this early latency activity in orbicularis oculi, the relative latencies of both cranial and distal muscles in the auditory startle response increased with the distance of their respective segmental innervations from the caudal brainstem. Thus the earliest EMG activity was recorded in sternocleidomastoid. The recruitment of caudal muscles was relatively slow and the latencies of the intrinsic hand muscles were disproportionately long. The pattern of recruitment of cranial muscles suggests a brainstem origin for the normal startle response. Studies on the auditory startle reflex in animals are reviewed in the light of this finding.

INTRODUCTION

Previous studies on the normal startle response in man have considered the first event in the auditory startle reflex to be the blink (Landis and Hunt, 1939; Suhren *et al.*, 1966; Gogan, 1970; Fox, 1978; Wilkins *et al.*, 1986). We present evidence that the initial activity in orbicularis oculi is an auditory blink reflex, and not part of the subsequent true startle response. Previous investigations also have given insufficient information on the distribution and latency of the true startle response in different muscles to deduce its site of origin and the characteristics of its efferent pathways (Jones and Kennedy, 1951; Suhren *et al.*, 1966; Rossignol, 1975; Wilkins *et al.*, 1986). We define the EMG pattern of the normal auditory startle response in man; it has a quite distinct timing and distribution in different muscles. The activity responsible for the startle response originates in the caudal brainstem and is conducted up the brainstem and down the spinal cord by a relatively slowly conducting efferent pathway.

METHODS

The startle reaction was recorded in 12 healthy subjects (mean age 37.1 yrs, range 18–80 yrs) following their informed consent. Auditory stimuli were presented randomly about once every 20 min, while the subject sat relaxed in a chair. The stimulus was a standardized auditory tone burst of 1000 Hz frequency,

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50 ms duration and 124 dB presented binaurally through earphones. (The intensity of the stimulus used exceeded safety standards for continuous acoustic stimulation, and the authors would recommend caution in the use of similar stimulus intensities in future experimentation.) Electromyographic (EMG) recordings were made using bipolar silver/silver chloride electrodes placed 2 cm apart longitudinally over the muscle bellies. Records were collected as single sweeps triggered at the start of the auditory stimulus The sampling rate was 1500 Hz per channel The latency to onset of reflex EMG activity was measured by visual inspection of single trials on a computer display. The latency of the initial voltage sustained above the background level of EMG activity was taken to be the start of reflex EMG activity.

The latency and duration of the auditory blink reflex to the same stimulus was also investigated. For this, auditory stimuli were presented randomly about every minute, and the responses to the first 5 stimuli were discarded to avoid recording a startle response.

Medians and ranges were recorded. Statistical analysis was performed using the Mann-Whitney U test for unpaired data and Wilcoxon signed-ranks test for paired data.

RESULTS

The most generalized startle response to the standard sound stimulus employed consisted of eye closure, grimacing, neck flexion, trunk flexion, slight abduction of the arms, flexion of the elbows and pronation of the forearms. There was considerable variation in the degree to which this response was expressed, and in some subjects only eye closure and flexion of the neck was apparent.

There was also considerable variation in the latency to onset of the EMG activity in individual muscles during the startle response (Table 1). However, although the range of latencies was wide, most responses occurred with early latencies. The variation in

TABLE 1 THE LATENCY TO ONSET OF EMG ACTIVITY IN THE NORMAL STARTLE RESPONSE TO SOUND*

		Range (ms)		
Muscle	*Median*	*Lowest*	*Highest*	*n*
R orbicularis oculi	36.7	25.0	69.0	70
R masseter	59.0	39 4	122.2	29
R sternocleidomastoid	58.3	40 4	136.0	53
R C4 paraspinal muscles	60 2	47 9	120.0	23
L biceps	68.9	59 8	91 7	10
R biceps	76.2	67.0	146 5	21
R triceps	71.0	53.2	147.8	12
R forearm extensors	73 2	61.9	172 8	24
R forearm flexors	81 9	60.1	199 9	27
R APB	98 6	74 5	178.9	26
R FDI	98.8	71.7	175.5	26
R ADM	95 9	76.3	104 0	6
R rectus abdominis	82.3	76.6	98 8	11

* The startle responses were elicited in 12 healthy sitting subjects by a 1000 Hz 124 dB tone of 50 ms duration delivered to both ears randomly, up to 3 times an hour Muscle activity was approximately synchronous bilaterally EMG activity was recorded in masseter significantly later ($P < 0.001$, Wilcoxon signed-ranks test) than in sternocleidomastoid The latencies of the intrinsic hand muscles were disproportionately long. Activity in tibialis anterior (110 7 ms, range 103 5–122.0 ms, $n = 6$) and in soleus (120 8 ms range 105 5–122 0 ms, $n = 5$) was only present in 1 subject. Abbreviations: right (R) and left (L) abductor pollicis brevis (APB), first dorsal interosseous (FDI) and abductor digiti minimi (ADM)

the latency of EMG activity in sternocleidomastoid is shown in fig. 1. The latencies of other muscles showed similar skewed distributions.

Despite the variation in latency, the overall pattern of the response to sound was distinctive. A blink reflex was always seen, regardless of the presence of a more generalized startle response. The latency to onset of this blink reflex (median 36.7 ms, range 25–69 ms) was much shorter than that of the startle response in sternocleidomastoid (58.3 ms, range 40.4–136 ms). The blink reflex persisted despite the repetition of the auditory stimulus every minute. In contrast, the startle response habituated within 2 to 6 trials, despite the random presentation of the stimulus about every 20 min.

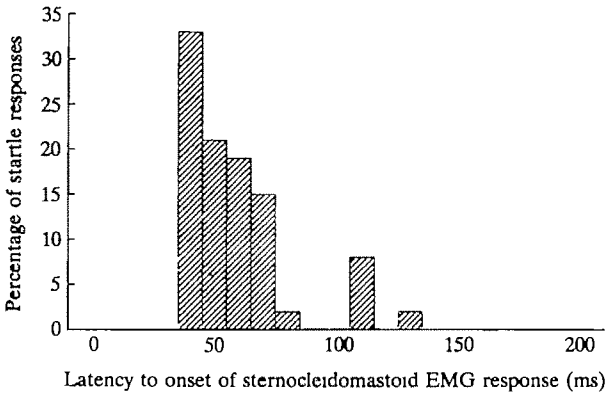

FIG 1 The latencies to onset of EMG activity in the sternocleidomastoid muscle in individual auditory startle responses (n = 53) in normal subjects (n = 12).

The auditory blink reflex could be studied in isolation, in the absence of a startle response, by delivering the standard sound stimulus every minute (fig. 2A). Under these conditions the latency of the reflex response in orbicularis oculi (median 32.3 ms, range 19.3–68.6 ms, n = 60) was similar to that seen in the auditory startle response, but the duration of the auditory blink reflex was brief (range 63.3–149.2 ms, n = 72). In the presence of a startle response, the duration of the EMG activity in orbicularis oculi was much longer and more variable (range 108 to over 400 ms, n = 70). In 36% of such trials two distinct components were visible in the response of orbicularis oculi (fig. 2B).

The earliest EMG activity recorded after the normal auditory blink reflex was in sternocleidomastoid (Table 1). This was the most consistently recorded feature of the startle response and was usually the last component to habituate. In 4 out of the 12 subjects it was the only feature of the startle response, other than a blink, to be recorded under the experimental conditions used.

When a more generalized startle response was recorded (Table 1) the EMG activity in masseter started later than in sternocleidomastoid. The difference between the median latencies to onset of EMG activity in sternocleidomastoid and masseter was 0.7 ms ($P < 0.001$, Wilcoxon signed-ranks test), when all trials were averaged. However, the median difference in latency to onset of EMG activity between sternocleidomastoid

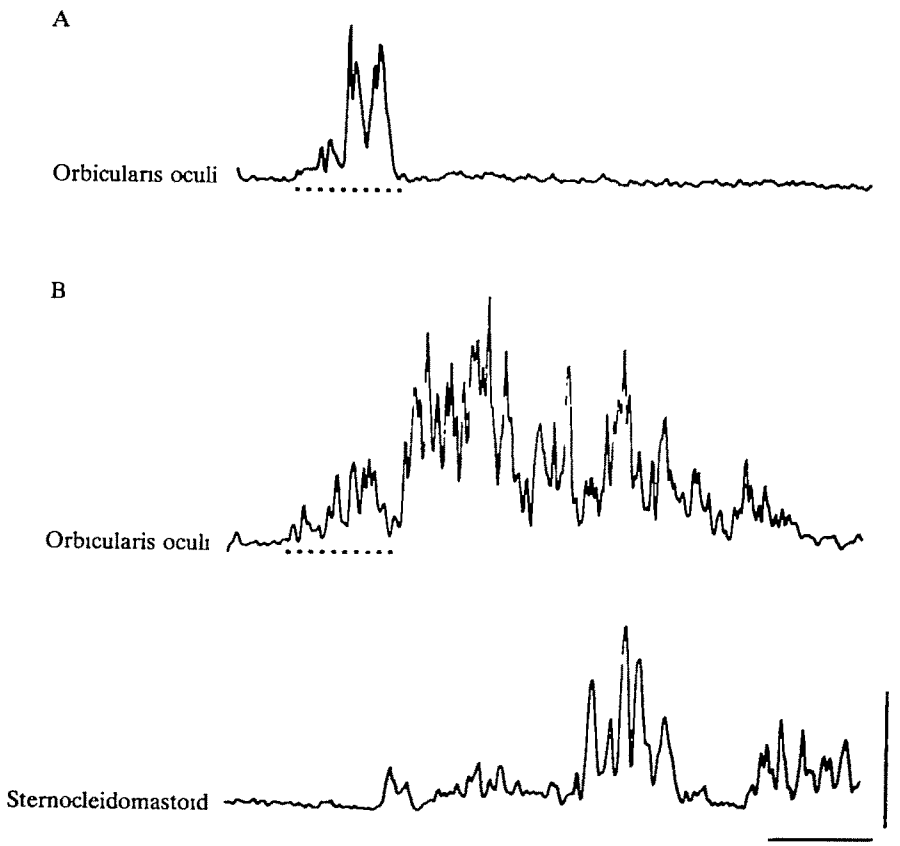

FIG. 2 A, average of 5 auditory blink reflexes (marked by dotted line) recorded in the same normal subject to a 124 dB tone of 50 ms duration, delivered randomly about every 60 s B, average of 5 startle responses recorded in the same normal subject to an unexpected 124 dB tone of 50 ms duration, delivered randomly about every 20 min. Two components may be distinguished in orbicularis oculi The first is a normal latency auditory blink reflex (marked by dotted line). The second component consists of EMG activity attributable to the true startle response and can be seen to follow EMG activity in sternocleidomastoid Rectified EMG records are shown. The horizontal and vertical calibration lines represent 50 ms and 0.1 mV, respectively.

and masseter measured in those single trials in which EMG activity was evident in both muscles, was 3.6 ms (range −4.0−15.2 ms, n = 30). In the startle responses of 1 subject, the latency of EMG activity in mentalis (51.0 ms, range 48−53.5 ms) was compared with that in masseter (56.9 ms, range 51.5−62.4 ms), and sternocleidomastoid (43.6 ms, range 38.6−45 ms, n = 7 for each muscle). The EMG activity in mentalis followed that in sternocleidomastoid significantly later ($P = 0.01$, paired Wilcoxon signed-ranks test), but preceded that in masseter ($P = 0.01$). Thus the latency of EMG activity in the cranial muscles (with the exception of orbicularis oculi, where an auditory blink reflex was recorded at 29.7 ms, range 22.8−32.7 ms, n = 7) increased with the distance of their segmental innervations from the lower brainstem (fig. 3).

The latencies of trunk and limb muscles in the auditory startle response also increased with the distance of their respective segmental innervations from the caudal brainstem

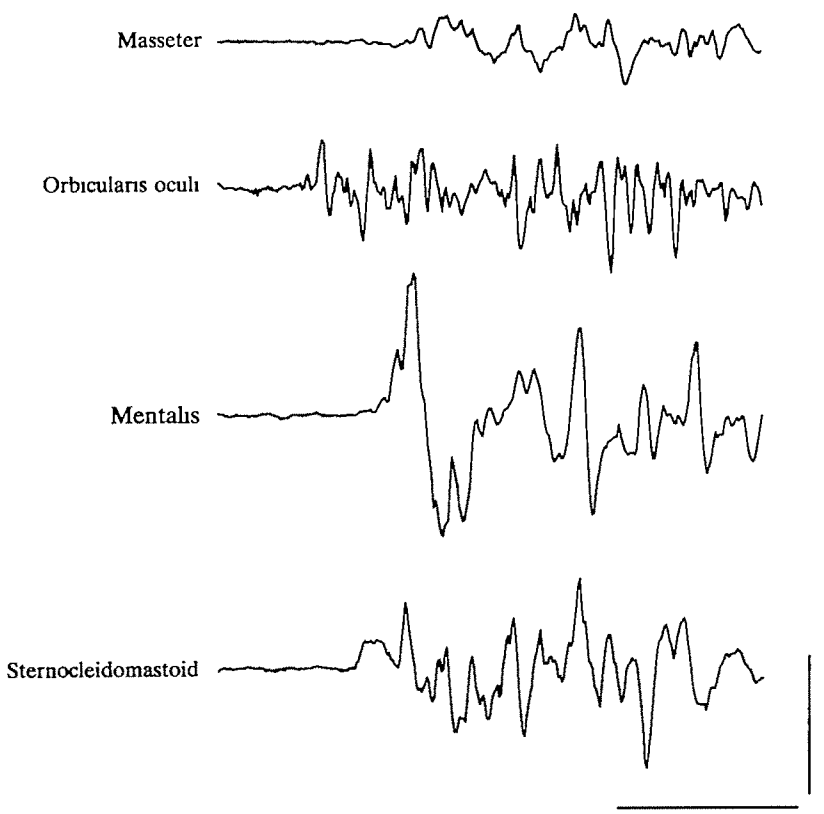

FIG. 3. Unrectified EMG record of a single startle response recorded in a normal individual A 124 dB tone of 50 ms duration was delivered to both ears at the start of the trace Excluding the auditory blink reflex, the first EMG activity is recorded in sternocleidomastoid and is followed later by mentalis then masseter The horizontal and vertical calibration lines represent 50 ms and 0.5 mV, respectively

(fig. 4, Table 1). Proximal arm muscles were activated before those of the hand. The cervical paraspinal muscles were activated before the abdominal recti. Responses in the legs were seen in only 1 of 12 subjects, and were at longer latency than those of the arms. No EMG activity was recorded in the intrinsic foot muscles of this or any other subject. The difference in latency to onset of EMG activity between sternocleidomastoid and rectus abdominis was relatively long (24.0 ms).

A distinctive feature of the pattern of muscle activation in the normal startle response to sound was the disproportionately long latencies of the intrinsic hand muscles (fig. 4, Table 2). The EMG activity in abductor pollicis brevis and first dorsal interosseous occurred 25.4 ms ($P < 0.001$) and 25.6 ms ($P < 0.001$) after that in the forearm extensors.

DISCUSSION

The normal startle response to a standardized auditory stimulus was determined in 12 healthy subjects. The general pattern of the response was consistent with previous

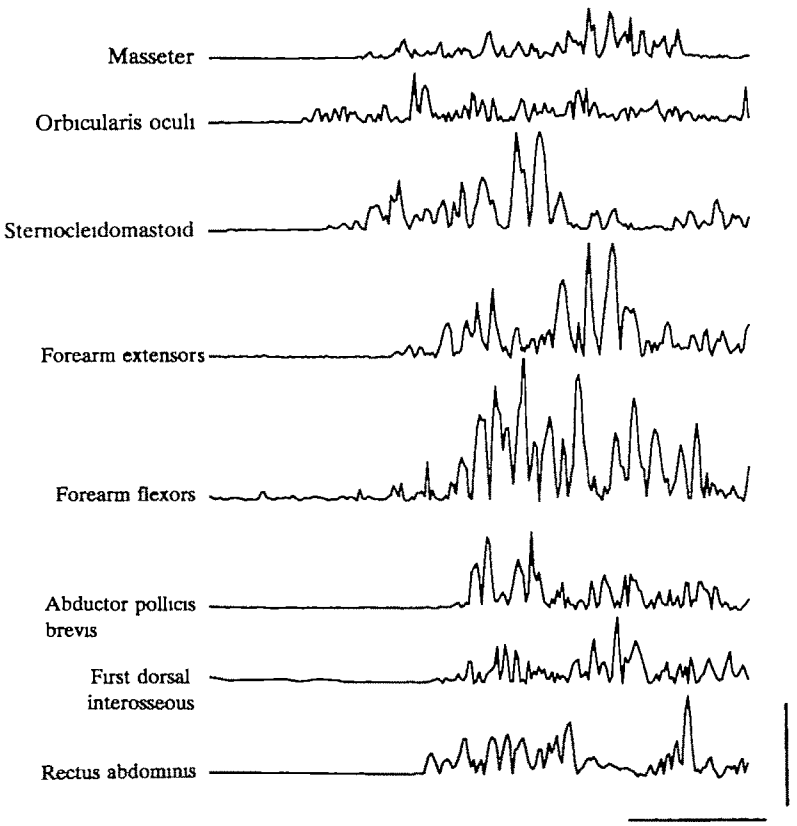

FIG. 4. Rectified EMG record of a single startle response recorded in a healthy individual. A 124 dB tone of 50 ms duration was delivered to both ears at the start of the trace. Excluding the auditory blink reflex, the first EMG activity is recorded in sternocleidomastoid and followed later by masseter. There is a disproportionately long latency to abductor pollicis brevis and the first dorsal interosseous. The horizontal and vertical calibration lines represent 50 ms and 0 5 mV, respectively.

reports. Thus the startle reflex consisted of a generalized flexion response (Landis and Hunt, 1939; Wilkins *et al.*, 1986), although EMG activity was recorded in both flexor and extensor muscles. The startle reaction was most prominent around the face, neck and shoulders, and less marked in the lower half of the body (Strauss, 1929). The minimum response, beyond a blink of the eyes, was activity in sternocleidomastoid (Jones and Kennedy, 1951). The latter was often the last component of the generalized startle reflex to disappear with repeated presentation of the stimulus (Jones and Kennedy, 1951). This habituation of the response was rapid, usually occurring within 2 to 6 trials, although the blink reflex persisted (Landis and Hunt, 1939; Wilkins *et al.*, 1986).

Previous reports have stressed that the latency of the normal startle response is relatively long and very variable (Landis and Hunt, 1939; Wilkins *et al.*, 1986). Most authors, however, report either the range (Wilkins *et al.*, 1986), or the mean of reflex latencies (Landis and Hunt, 1939; Suhren *et al.*, 1966; Rossignol, 1975). We found that the latencies to onset of any given muscle in the startle reflex were not normally distributed.

TABLE 2 A COMPARISON OF THE EFFERENT PATHWAYS SUBSERVING THE NORMAL AUDITORY STARTLE REFLEX WITH CORTICOBULBAR AND PYRAMIDAL PATHWAYS IN MAN*

	Auditory startle reflex	*Magnetic stimulation of motor cortex*
Excess latency of masseter over SCM	0.7 ms	−2 9 ms (masseter precedes SCM)
Excess latency of RA over SCM	24.0 ms	8.0 ms
Excess latency of APB over biceps	22 4 ms	10.5 ms

* The differences in the latencies to onset of EMG activity between individual muscles in the normal auditory startle reflex are calculated from the median latencies given in Table 1 The differences in the latency to onset of EMG activity between masseter and sternocleidomastoid (SCM), sternocleidomastoid and rectus abdominis (RA), and between biceps and abductor pollicis brevis (APB), following magnetic stimulation of the motor cortex, are calculated from the mean latencies reported by Cruccu *et al* (1989) and Thompson (1991) in normal subjects. The pattern of recruitment of cranial nerves seen following magnetic stimulation of the motor cortex is reversed in the normal auditory startle reflex The differences in latency to onset of EMG activity between sternocleidomastoid and rectus abdominis, and between biceps and abductor pollicis brevis, is longer in the auditory startle reflex than following magnetic stimulation of the motor cortex.

Although the range of latencies was large, most responses were of short latency. Calculation of the mean latency of an individual muscle is therefore inappropriate and misleading (calculation of the mean latency to onset of EMG activity in sternocleidomastoid from the present results gives a value 5.1 ms in excess of the median).

The distinction between the auditory blink reflex and the startle response in orbicularis oculi

The presence of a short latency blink reflex of brief duration to auditory stimulation in normal subjects has been established (Rushworth, 1962). Lesioning experiments suggest that a central circuit involving the inferior colliculus and the midbrain reticular formation underlies this auditory blink reflex (Hori *et al.*, 1986). Projections between the midbrain reticular formation and the facial nucleus exist (Hinrichsen and Watson, 1983). This mesencephalic circuit for the auditory blink reflex is in contrast to the bulbopontine origin proposed for the auditory startle response (Szabó and Hazafi, 1965; Davis *et al.*, 1982).

The auditory blink reflex has been considered to be an integral part of the normal startle response (Landis and Hunt, 1939; Suhren *et al.*, 1966; Gogan, 1970; Fox, 1978; Wilkins *et al.*, 1986). However, the auditory blink reflex may be seen without any other manifestation of the startle response and, unlike the normal startle response, it does not readily habituate. Reflex EMG activity in muscles other than orbicularis oculi was no longer recorded after 2 to 6 repetitions of the auditory stimulus every 20 min. In contrast, reflex EMG activity was recorded in orbicularis oculi with repetition of the same auditory stimulus every minute. The amplitude of the auditory blink reflex does habituate with briefer interstimulus intervals (Fox, 1978).

When seen in the context of a startle response the latency of the blink reflex is much shorter than the latency of onset of EMG activity in other cranial muscles. In 1 subject, the latency of mentalis in the startle response was determined. This muscle has a similar innervation and peripheral efferent conduction time to orbicularis oculi (Møller and Jannetta, 1986; Benecke *et al.*, 1988). The EMG startle activity in mentalis was recorded about 21 ms after the blink reflex in orbicularis oculi in the auditory startle response. When a true startle response is elicited by unexpected auditory stimulation, the duration of the EMG activity in orbicularis oculi is much longer, and it is sometimes possible to distinguish two separate components in the EMG response in orbicularis oculi. It is therefore suggested that the early latency auditory blink reflex is physiologically separate from the generalized startle response. In contrast, the true startle response in orbicularis oculi is of longer latency and is often seen grafted on to the end of the normal auditory blink reflex. The EMG response in orbicularis oculi may also show two components in the pathological auditory startle response (Colebatch *et al.*, 1990; Brown *et al.*, 1991).

Efferent pathways of the normal auditory startle reflex in man

The earliest recorded EMG activity in the true generalized startle response was in sternocleidomastoid (innervated by the eleventh cranial nerve). EMG activity in masseter (innervated by the fifth cranial nerve) occurred significantly later (*see* Table 2). This is the reverse of the rostrocaudal pattern of activation of cranial nerve innervated muscles seen in cortical reflex myoclonus (Hallett *et al.*, 1979). Similarly, with magnetic stimulation of the motor cortex, activity in masseter occurs about 2.9 ms before that in sternocleidomastoid (Cruccu *et al.*, 1989; Thompson, 1991). The latency of the true startle response in orbicularis oculi (innervated by the seventh cranial nerve) was difficult to define exactly as its onset was usually obscured by EMG activity attributable to the normal auditory blink reflex. EMG activity in mentalis, however, (also innervated by the seventh cranial nerve) occurred significantly later than that in sternocleidomastoid and before that in masseter. Given the approximately similar peripheral efferent conduction delays to masseter, orbicularis oculi, mentalis and sternocleidomastoid (Møller and Jannetta, 1986; Benecke *et al.*, 1988), the overall pattern of muscle recruitment in the physiological startle response to auditory stimulation suggests that in man, as in animals, the auditory startle response originates in the caudal brainstem, with propagation rostrally to the seventh then fifth cranial nerve nuclei. A similar pattern of activation of cranial nerve innervated muscles is seen in reticular reflex myoclonus, where myoclonic activity is propagated rostrally from a myoclonic generator in the caudal brainstem (Hallett *et al.*, 1977).

The latencies of the startle response in trunk and limb muscles also increase with the distance of their segmental innervation from the caudal brainstem. The proximal arm muscles were activated before those of the hand, and the cervical paraspinal muscles were activated before the abdominal recti. Responses in the legs were seen in only 1 of 12 subjects (when sitting relaxed) and were at longer latency than those of the arms.

The difference in latency of onset of EMG activity between sternocleidomastoid and rectus abdominis (24.0 ms) is about 16 ms longer than the difference in latency between these muscles when they are activated by magnetic stimulation of the motor cortex (Table 2). This suggests that the conduction velocity in the spinal efferent pathways utilized by the normal startle response is relatively slow. The latency to onset of EMG

activity in the intrinsic hand muscles is disproportionately long (Table 2), even when allowance is made for the slowness of conduction in spinal efferent pathways. The slowness of the spinal efferent pathways and the disproportionate latencies of the intrinsic hand muscles distinguishes the normal auditory startle reflex from cortical and brainstem reflex myoclonus (Hallett *et al.*, 1977, 1979).

In summary, the electrophysiological evidence suggests that the physiological auditory startle reflex in man is mediated by an efferent system with its origin in the caudal brainstem. The spinal projections of this system are relatively slowly conducting and distributed predominantly to axial muscles. The pattern of muscle recruitment in the normal auditory startle is then determined by the distance of each segmental level from the caudal brainstem, with two exceptions. First, an auditory blink reflex precedes the auditory startle reflex in orbicularis oculi. Secondly, the latencies of the intrinsic hand muscles are disproportionately delayed (Table 2), suggesting that the pathways responsible for activation of these muscles differ, at least in part, from those underlying the rest of the startle reflex. An alternative hypothesis is that the relative latencies of the many muscles involved in the startle reflex represent activity in multiple central circuits with differing central processing times.

The physiology of the normal startle response

Studies in animals also suggest that the startle response originates in the caudal brainstem. The short latency startle responses to sound persist after decerebration (Forbes and Sherrington, 1914; Szabó and Hazafi, 1965). Lesioning experiments in the rat have implicated the medial bulbopontine reticular formation (Szabó and Hazafi, 1965), particularly the nucleus reticularis pontis caudalis (Hammond, 1973; Leitner *et al.*, 1980; Davis *et al.*, 1982) as the primary centre subserving the acoustic startle reflex. Electrical stimulation of the nucleus reticularis pontis caudalis (Davis *et al.*, 1982; Yeomans *et al.*, 1989), but not the nucleus reticularis gigantocellularis (Davis *et al.*, 1982), elicits short latency startle-like responses in the rat. In the cat the area of the medial reticular formation involved in the auditory startle reflex may extend more caudally, into the medulla (Wright and Barnes, 1972; Wu *et al.*, 1988). If the medial pontomedullary reticular formation is the primary centre subserving the acoustic startle reflex, then the efferent limb of the reflex may be provided by the bulbobulbar (Scheibel and Scheibel, 1958) and reticulospinal (Torvik and Brodal, 1957) pathways originating in this area. In particular, Shimamura and Livingston (1963) have identified a spinobulbospinal reflex system relayed in the medial medullary reticular formation in cats, the efferent limb of which is formed by moderately slowly conducting descending spinal pathways. This efferent system may also form the basis of the chloralose jerk (Shimamura and Yamauchi, 1967) and the audiospinal reflex responses recorded in decerebrate and chloralose anaesthetized cats (Wright and Barnes, 1972). The spinobulbospinal reflex has also been identified in dogs and monkeys (Shimamura *et al.*, 1964) and, tentatively, in man (Shimamura *et al.*, 1964; Meier-Ewert *et al.*, 1972; Shimamura, 1973).

The present results suggest that the system subserving the motor limb of the startle reflex in man originates, as in animals, in the caudal brainstem. The observation that the startle reflex exists in anencephalic infants (Edinger and Fisher, 1913) would support this hypothesis. The descending spinal efferent pathways in the normal auditory startle reflex in man are slowly conducting and this might suggest the involvement of pathways

similar to the efferent limb of the spinobulbospinal reflex. The study of patients with abnormal startle responses to both somaesthetic and auditory stimuli has provided further evidence linking the startle reflex to the spinobulbospinal reflex (Brown *et al.*, 1991).

Both the pattern of muscle recruitment in man and studies in animals therefore suggest that the system subserving the motor limb of the auditory startle reflex originates in the bulbopontine brainstem in man, possibly in the medial reticular formation. This system may be activated by auditory afferent inputs at the subcortical level as suggested by animal experiments, either directly from the lateral lemniscus (Davis *et al.*, 1982) or via the inferior colliculus (Wright and Barnes, 1972). Alternatively, the afferent limb of the startle reflex may involve a cortical relay. Several authors have reported a lack of an overt startle response to unexpected sounds in patients with bitemporal cortical damage (Woods *et al.*, 1984; Ho *et al.*, 1987). In addition, Liegeois-Chauvel *et al.* (1989) reported that the facilitation of the spinal monosynaptic reflex by auditory stimulation, considered to be related to the startle reaction, is selectively depressed by lesions of the caudal part of the superior temporal gyrus.

It is most likely that the auditory cortex acts to facilitate subcortical reflex loops (Ascher *et al.*, 1963). In the chloralose anaesthetized cat strychnization of the primary auditory cortex facilitates the generalized reflex response to sound, but complete bilateral neodecortication does not abolish the reflex response (Ascher *et al.*, 1963). Such cortical facilitation could involve corticopontine tracts (Brodal, 1969) or the projection from the auditory cortex to the inferior colliculus (Andersen *et al.*, 1980*a*, *b*).

In conclusion, it is suggested that the motor response in the normal auditory startle response in man is organized in the caudal brainstem, probably in the medial reticular formation. This site may be activated by subcortically or cortically relayed afferent inputs, or by a combination of these influences.

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THE HYPEREKPLEXIAS AND THEIR RELATIONSHIP TO THE NORMAL STARTLE REFLEX

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SUMMARY

The startle response to unexpected auditory and somaesthetic stimulation was studied in 8 patients with hereditary or symptomatic hyperekplexia. It was abnormal in its resistance to habituation and in its exaggerated motor response. Both noise and taps to the face and head elicited a normal early blink response, separate from the subsequent true startle reflex. The earliest reflex EMG activity recorded after the blink was in sternocleidomastoid. EMG activity in masseter, and trunk and limb muscles followed later. This pattern of muscle recruitment suggests a brainstem origin for the abnormal startle responses. In addition, the abnormal startle responses exhibited disproportionately long latencies to the intrinsic hand and foot muscles and relatively slow recruitment of caudal muscles. The pattern of muscle recruitment was similar between patients, irrespective of the absolute latency of the response, and regardless of whether stimulation was auditory or somaesthetic. This suggests that auditory and somaesthetic afferents converge on a common brainstem efferent system, and that this system forms the final common pathway for abnormal startle responses of differing latency. The characteristics of this efferent system differ from those previously described in brainstem reticular reflex myoclonus, but are similar to those described in the normal auditory startle reflex in man. This suggests that the abnormal startle response in hyperekplexia, and the normal startle reflex represent pathological and physiological activity in the same brainstem efferent system.

INTRODUCTION

There is a syndrome characterized by an exaggerated motor response to auditory and, sometimes, somaesthetic and visual stimuli. Typically, the patients 'jump' in response to a loud unexpected noise, a tap to the body, or a visual stimulus and, if standing, may fall and injure themselves. The 'jump' characteristically consists of a blink, contortion of the face, flexion of neck and trunk, and abduction and flexion of the arms. We will call this the Startle Syndrome. It can be caused by a variety of conditions (*see* Table 1). One of these has been termed hereditary hyperekplexia, which is inherited as an autosomal dominant trait and often presents in childhood with hypertonia, hyperreflexia and falls.

The pathophysiology of the various causes of the startle syndrome is debated. In particular, there is controversy as to whether they are due to exaggeration of the normal startle reflex or to the emergence of some other pathological reflex. For example, hereditary hyperekplexia has been attributed to overactivity of the normal startle response (Andermann *et al.*, 1980), or considered quite distinct from the normal startle reflex

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(Wilkins *et al.*, 1986). Some of those who attribute pathological startles to a mechanism separate from the normal startle reflex have drawn analogies to the pathophysiological mechanisms involved in cortical (Markand *et al.*, 1984) and brainstem reticular reflex myoclonus (Wilkins *et al.*, 1986).

This confusion over the origins of pathological startles has been compounded by uncertainty about the genesis and pattern of the normal startle response in man. In the preceding paper (Brown *et al.*, 1991*a*) we presented evidence that the normal noise-induced startle reflex in man originates in the caudal brainstem, and uses relatively slowly conducting spinal efferent pathways to recruit trunk and limb muscles. Here we examine 8 patients with pathological startles, 4 from 2 families with hereditary hyperekplexia, and 4 other sporadic cases (1 with presumed multiple sclerosis, 1 with sarcoidosis, 1 with presumed encephalomyelitis, and 1 with anoxic brain damage). The pathophysiology of the noise-induced startles was the same in all 8 patients, consisting of exaggeration of the normal auditory startle response. In addition, 7 of the 8 patients exhibited abnormal jerks to somaesthetic stimuli, particularly to the mantle (face, head and upper trunk) region. These reflex jerks resembled the noise-induced startles, and had a similar pathophysiology.

As a result of these observations we propose that the term hyperekplexia is reserved to describe patients with a startle syndrome due, pathophysiologically, to an exaggerated normal startle reflex. Other causes of the startle syndrome may have different underlying pathophysiological mechanisms, and in Table 1 the causes of the startle syndrome are classified according to their physiological basis into three categories: (1) hyperekplexia (an exaggerated normal startle reflex, characterized by its slow spinal efferent pathway); (2) brainstem reticular reflex myoclonus (distinguished from the exaggerated normal startle reflex by the occurrence of spontaneous jerks, and by fast rather than slow spinal efferent conduction velocities); and (3) of unknown pathological causation.

METHODS

Neurophysiological studies included routine electroencephalography (EEG), polymyography, back-averaging of the EEG activity preceding jerks, somatosensory evoked potentials (SEPs) and blink reflexes. Electromyographic (EMG) recordings were made using bipolar silver/silver chloride electrodes placed 2 cm apart longitudinally over the muscle bellies.

Patients and normal subjects gave their informed oral consent to the neurophysiological studies. Cases 1, 3, 6 and 7 continued their normal medication (outlined in the case histories) during investigation Case 5 discontinued treatment for 24 h before the investigation of his tonic spasms Cases 2, 4 and 8 were taking no regular medication. Patients were examined while sitting relaxed in a chair. Muscle jerks were elicited by a variety of stimuli, and were recorded by triggering the computer at the time of delivery of the stimulus. The stimuli used consisted of electrical stimulation of peripheral mixed and sensory nerves, taps to the body with a tendon hammer equipped with a microswitch, and auditory tone bursts of 1000 Hz frequency, 50 ms duration and 124 dB presented binaurally through earphones. (The intensity of the stimulus used exceeded safety standards for continuous acoustic stimulation, and the authors would recommend caution in the use of similar stimulus intensities in future experimentation.) Reflex latencies are measured by the visual inspection of single trials on a computer display. The sampling rate was 1500 Hz per channel.

Conditioning curves were determined for auditory stimuli by following a conditioning auditory or somaesthetic stimulus with a test auditory stimulus at different intervals. Conditioning and test stimuli were presented in pairs every 5 min. Each interval between conditioning and test stimulus was repeated at least 6 times. Conditioning and test auditory stimuli were identical (1000 Hz, 124 dB tones of 50 ms duration).

TABLE 1. THE AETIOLOGY OF THE STARTLE SYNDROME

Pathological exaggeration of the normal startle reflex

Hereditary hyperekplexia (Suhren *et al.*, 1966, Andermann *et al* , 1980)

Symptomatic hyperekplexia
- Static encephalopathies
  - Static perinatal encephalopathy without tonic spasms (Shimamura, 1973)[1]
  - Postanoxic encephalopathy (Case 8)
  - Posttraumatic encephalopathy (Duensing, 1952)[1]
- Brainstem encephalitis
  - Sarcoidosis (Case 6)
  - Viral encephalomyelitis (Fenzi *et al* , 1988)[1]
  - Encephalomyelitis with rigidity (Case 7; Leigh *et al.*, 1980)[1]
  - ? Multiple sclerosis (Case 5)
  - Paraneoplastic (Duensing, 1952)[1]
- Structural
  - Brainstem haemorrhage/infarct (Duensing, 1952, Kohara *et al.*, 1988, Shibasaki *et al* , 1988)[1]
  - Cerebral abscess (Duensing, 1952)[1]

Idiopathic (Gastaut and Villeneuve, 1967; Brown *et al.*, 1991*a*)[1]

Brainstem reticular reflex myoclonus

Postanoxic encephalopathy (Hallett *et al* , 1977; Colebatch *et al.*, 1990)

Unknown physiology

Hexosaminidase A deficiency (Gastaut and Tassinari, 1966)

Static perinatal encephalopathy with epileptic tonic spasms (startle epilepsy, Alajouanine and Gastaut, 1955)

Gilles de la Tourette syndrome (Murray, 1978, Lees *et al* , 1984)[2]

Jumping, Latah and Myriachit (Stevens, 1965, Andermann and Andermann, 1986)[3]

Hysterical jumps (Colebatch *et al* , 1990*b*)

[1] As a result of the observations described in the present paper, these conditions can now be assigned as causes of symptomatic hyperekplexia [2] Tics in Gilles de la Tourette syndrome usually are spontaneous, but sometimes may be triggered by external stimuli and have the appearance of an exaggerated startle response. The physiology of these startle tics is unknown and they are not considered further here. [3] The origin of these exaggerated startle syndromes has been widely debated. Their physiology is unknown and they are not considered further here.

SEPs were recorded following stimulation of the median nerve at the wrist with constant voltage rectangular pulse of 0.2 ms duration at intensities just above motor threshold. SEPs were the average of 256–512 stimuli Their amplitude was measured from the first major cortical positive peak following the stimulus (conventionally known as the P25, here termed P1) to the second major negative peak (the N33, here termed N2). In controls (14 healthy subjects, aged 18–60 yrs, mean age 33 yrs), the latency to the first major cortical negative peak (the N20, here termed N1) was 18.8 ms (range 17.0–20.3 ms), the mean N1 amplitude was 1.5 μV (range 0.8–2.4 μV) and the mean P1N2 amplitude was 1.8 μV (range 0.4–3.4 μV).

The EEG was recorded from silver/silver chloride electrodes fixed to the scalp with collodion and referred to linked earlobe electrodes. The signals were bandpass filtered at 2.5 kHz with a time constant of 1.0 s. The EEG recording sites were standard positions of the 10–20 system with additional electrodes used between these sites for the localization of focal cerebral activity, as necessary. In the EEG records shown positivity is downward.

Blink reflexes were measured by percutaneous electrical stimulation of the supraorbital branch of the trigeminal nerve at intensities that elicited a stable and just maximal reflex response. Surface recording electrodes were placed over the inferior and lateral portions of orbicularis oculi.

Magnetic stimulation of the cortex or spinal roots (Ugawa *et al.*, 1989) was performed with a 9 cm diameter stimulator coil using a Novametrix Magstim 200

Medians and ranges were recorded for all measures, except the electrically-induced blink reflex for which means were recorded. Statistical analysis was performed using the Mann-Whitney U test for unpaired data and the Wilcoxon signed-ranks test for paired data.

PATIENTS

Eight patients with pathological startle responses were studied. Their clinical details are first presented briefly, and then the physiological findings are considered as a group.

Hereditary hyperekplexia

Case 1

An educationally subnormal woman aged 30 yrs had a history of sudden jerks and falls in response to unexpected stimuli Unexpected sounds and less commonly taps to the body or visual events would cause a brief shock-like generalized jerk. More rarely, such unexpected stimuli were followed by a more sustained posture lasting several seconds, and consisting of adduction of the arms across the chest, flexion of the elbows and extension of the legs. She remained fully conscious throughout these attacks. When erect the longer attacks would cause her to topple stiffly to the floor, unable to move her arms or legs to take any protective action as she fell. She had injured herself on many occasions, and had in the past fractured her right wrist and patella and broken several teeth. At times the falls were so frequent and disabling that she remained indoors and took to crawling on all fours. She reported occasional jerks on going off to sleep.

She was born 2 wks prematurely and suffered several apnoeic attacks during the first few days after delivery. She was noted to be a stiff baby Her developmental milestones were all delayed: she smiled at 4 mos, sat unaided at 18 mos, and walked unaided and spoke 2-word sentences at 3 yrs. From the time she first started walking she was prone to frequent falls and jumps in response to unexpected sounds. This led her to adopt a tentative wide-based gait. From the age of 16 yrs she had held a variety of unskilled jobs. At the age of 26 yrs she had 2 major seizures. There was a strong family history of excessive startle responses (fig. 1).

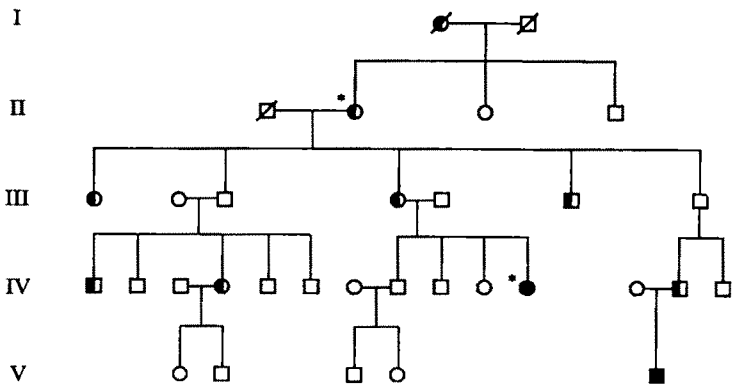

FIG. 1. Pedigrees of *Cases 1 and 2*. Case 1 (IV11) and her nephew (V5) have an abnormal startle response with falls (filled symbols) Eight other family members, including Case 2 (II2), have a history of an abnormal startle response without falls, or excessive hypnic jerks (half-filled symbols) Those family members studied electrophysiologically are marked with an asterisk

The patient's jerks and falls were well controlled with carbamazepine 1200 mg daily and clobazam 20 mg daily. Sodium valproate and levodopa-carbidopa had been tried unsuccessfully in the past.

General examination was normal. She walked with a moderately wide-based gait The cranial nerves, muscle tone, strength and coordination were normal. The tendon reflexes were generally brisk and the plantar responses were flexor. Sensation was normal. Unexpected sounds, visual stimuli or taps to the body would cause a shock-like generalized jerk. This consisted of a blink, lower facial grimace, shoulder abduction, and neck, elbow and trunk flexion.

Her full-scale IQ (WAIS) was 64. EEG studies and computerized tomography (CT) of the brain were normal.

Case 2

The grandmother of Case 1, aged 77 yrs, had a lifelong history of sudden jerks to unexpected sounds, visual events or taps to the body. However, she had never fallen as a result of unexpected stimuli and was otherwise well. Her early development had been normal. There was no relevant past medical history. In particular there was no history of gait disturbance or excessive hypnic jerks. Details of the family history are given in fig. 1.

General and neurological examination was unremarkable except for sudden jerks of the upper half of the body to unexpected noises or taps to the body. Each jerk consisted of a blink, flexion of the neck, elevation of the shoulders (more pronounced on the left), and flexion of the elbows. Taps were most effective when delivered to the upper half of the body, including the face and head.

Case 3

A girl aged 19 yrs presented with a 6 yr history of sudden jerks and falls to unexpected stimuli. Unexpected sounds, and more rarely taps to the body or visual stimuli, would cause a brief generalized jerk or a more prolonged spasm lasting up to 30 s. During a spasm, she would abduct her arms and extend her legs. She remained fully conscious but unable to move during these attacks. If they occurred when erect, she would topple stiffly to the ground, unable to initiate any protective movement of the arms or legs She frequently injured herself in these falls. During the first 3 yrs of her illness she had been unable to walk outside without holding onto someone for fear of falling during a stimulus-induced spasm. At the time of presentation such spasms occurred up to five times a day.

She also gave a 16 mo. history of spontaneous spasms at night on going to sleep. These spasms were occasionally complicated by urinary incontinence, but were otherwise similar in nature to the stimulus-induced spasms occurring during the day. The nocturnal spasms were often provoked by dreaming about a sudden stimulus, such as a dog barking.

The patient was the product of a normal pregnancy and delivery, and her early developmental milestones were normal. As a child she walked normally. At the age of 15 yrs she suffered two episodes of generalized shaking lasting 45 min, during which she remained conscious Her brother (Case 4) had a history of jerks, but not falls, to unexpected stimuli. There was no other family history of excessive startle or neurological disease.

Treatment with phenytoin 350 mg daily and carbamazepine 350 mg daily reduced the number of falls. Sodium valproate and clonazepam were tried unsuccessfully.

General and neurological examination was normal, except for the response to unexpected auditory stimulation. The latter would usually elicit a brief generalized jerk in which she would blink, grimace, elevate her shoulders, abduct her arms, flex her elbows, hips and knees. On two occasions unexpected noises elicited a prolonged spasm lasting 6–12 s, during which she would abduct and extend her arms, extend her legs and plantar flex her feet (fig. 2A). She remained fully conscious during these spasms.

A CT brain scan was normal. Her EEG was abnormal with central sharp waves.

Case 4

A man aged 21 yrs, the brother of Case 3, gave a 6 yr history of excessive jerks to unexpected noises, visual stimuli, and touches or taps around the face and head. The jerks were brief and usually involved the upper half of the body, but were occasionally generalized. They never caused him to fall. Unexpected stimuli did not elicit prolonged attacks, although 3 yrs previously, at a time of stress, he suffered several spontaneous spasms occurring while going to sleep and lasting up to 10 s These attacks consisted of involuntary extension of the arms and legs, during which he remained conscious. He also complained of

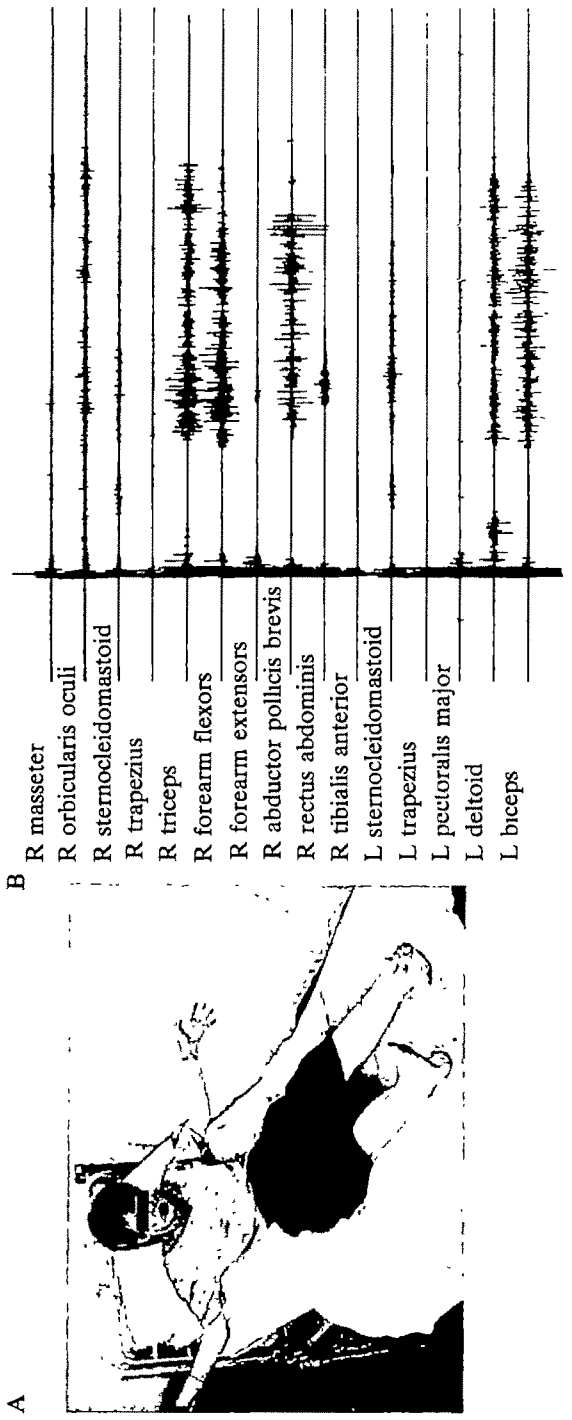

FIG. 2. A, photograph of the tonic spasm elicited by an unexpected noise in *Case 3*. The shoulders are abducted, the elbows and knees extended, and the feet plantar flexed. The tonic spasm lasted 15 s, during which consciousness was retained. B, EMG record of the tonic spasms occurring after an unexpected sound in *Case 5*. The tonic spasm starts about 4 s after the stimulus (124 dB, 1 kHz tone of 50 ms duration delivered 1.9 s after the start of the trace), and is clearly separate from the very rapid and brief initial startle response to sound. Horizontal and vertical calibration lines represent 2 s and 0.5 V, respectively

excessive hypnic jerks, but was otherwise well. There was no history of major seizures or other neurological symptoms. His early development had been normal, with no problems in walking. He had received no medication.

General and neurological examination was normal except for the response to unexpected auditory stimulation or a tap to the nose. These stimuli elicited a brief generalized jerk in which he would blink, grimace, elevate his shoulders, abduct his arms and flex his elbows, hips and knees. Unexpected stimuli did not elicit more prolonged spasms.

An EEG was unremarkable.

Sporadic hyperekplexia

Case 5

A man aged 31 yrs presented with a 5 yr history of sudden jumps and falls in response to unexpected stimuli. Unexpected sounds, visual stimuli, taps and touches to the body evoked a brief jerk of his arms and shoulders. Less often the same stimuli caused more prolonged extension of the legs and flexion of the elbows, with adduction of the shoulders so that his arms would cross his chest. This posture was sustained for several seconds, during which time he was fully conscious but unable to make any voluntary movement. If these attacks occurred while standing he would fall to the ground locked in this position and unable to take any protective action. During these falls he frequently injured himself and over the course of 5 yrs he had dislocated his elbow and fractured his jaw on several occasions. Untreated he experienced about 2 such falls a month, and about 4 minor jerks a day. He also reported excessive jerks in his sleep. He was otherwise well and there was no history of major seizures or other neurological symptoms. His early development had been normal, with no problems in walking. There was no family history of excessive startle or other neurological disease.

General examination was normal. Examination of his gait, fundi, cranial nerves, muscle tone, strength and limb coordination was unremarkable. The tendon reflexes were abnormally brisk and the right plantar response was extensor. Sensation was normal. Unexpected taps, particularly to the face and head, visual stimuli or loud noises would cause a generalized shock-like jerk. This consisted of a blink, grimace, shoulder abduction, elbow flexion, forearm pronation, neck extension, trunk flexion and leg extension.

Chest radiography, auditory and visual evoked responses and CT scan of the brain were normal. EEG was also normal and the sudden myoclonic jerks elicited by loud noises were not associated with any abnormal cortical discharges. Cerebrospinal fluid (CSF) examination revealed 4 oligoclonal bands, no white cells and a normal glucose and protein concentration. MRI of the brain showed a few scattered discrete areas of increased signal intensity in the periventricular white matter and central pons on T_2 weighted images (fig. 3). The clinical diagnosis was of laboratory supported probable multiple sclerosis.

Treatment with clonazepam 8 mg daily led to a 50% improvement in his jerks. The addition of sodium

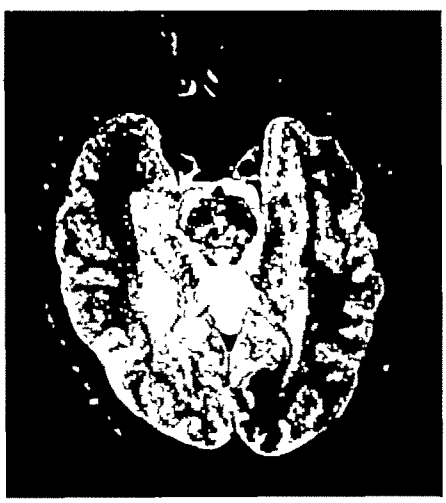

FIG. 3. Magnetic resonance imaging of the pons in *Case 5* (T_2 weighted image, TR 2500, TE 80) showing focal increased signal intensity in the central pons.

valproate 1.25 g daily and carbamazepine 1 g daily led to further but more modest improvement. Piracetam 16.8 g daily was unhelpful.

Case 6

A man aged 39 yrs developed a sharp stabbing pain at the back of the neck when eating solids. This was followed after a few days by nausea, retching, and a sensation of enlargement of the tongue and of constriction in the throat. These symptoms were associated with dysphagia and dysarthria. Two weeks later he noticed a shock-like jerk of his body in response to unexpected auditory and visual stimuli, and touch to his face, particularly his nose. Over the ensuing 2 mos the dysphagia, dysarthria, retching and sensory disturbances abated, but he developed a persistent pyrexia. The reflex jerking worsened and he developed brief and infrequent tonic spasms of extension of the arms and legs, and laryngeal spasm During these he would be initially fully conscious, but in prolonged attacks he would become severely hypoxic and lose consciousness. There was no history of weakness, diplopia, vertigo or visual or hearing disturbance

The patient had a history of congenital strabismus with corrective surgery as a child. At the age of 29 yrs pernicious anaemia was diagnosed. There was no relevant family history.

General examination 3 mos after the onset of his illness was normal. His gait was ataxic. The optic fundi were normal. There was a bilateral divergent squint and tongue movements were slow. Muscle tone and strength were normal. The tendon reflexes were brisk and both plantar responses were extensor Sensation was normal. Very light touches to the face, neck and upper chest, taps with a tendon hammer to widespread areas of the body, and loud noise elicited a shock-like generalized jerk. This consisted of extension of the neck, and flexion of the elbows, hips and knees. Light touch to the limbs was ineffective. There were no spontaneous myoclonic jerks.

Treatment with clonazepam 6 mg daily led to a modest improvement in the frequency of the reflex jerks. The addition of sodium valproate 1.5 g daily led to a marked improvement

Extensive haematological, serological and biochemical investigations were normal. Chest radiography, repeated examinations of CSF and MRI studies of the brain were also unremarkable The EEG was abnormal with a paradoxical change to frontal slow wave activity on alerting. There were no epileptiform phenomena. A bone marrow trephine revealed noncaseating granulomas and a Kveim test for sarcoidosis was positive. The clinical diagnosis, therefore, was neurosarcoidosis.

He made a slow recovery and after 4 mos convalescence he was well, although jerks persisted on touching the nose and upper lip.

Case 7

A woman aged 50 yrs presented with a 3 yr history of continuous and painful truncal stiffness. This began in the neck and progressed over 18 mos to involve all of the back, making bending almost impossible. One year after the onset of her illness she developed diplopia The latter gradually improved over the next 6 mos. Two years after the onset of her illness she developed lightening-like jerks of the body, usually in response to a touch to the face. Less commonly, unexpected visual or auditory stimuli elicited reflex jerks. Nine months later paroxysms of repetitive generalized jerks developed. Each paroxysm could last several hours and could be alleviated by parenteral diazepam or chlormethiazole. Consciousness was preserved throughout the attacks of jerking. She had a 6 yr history of hypothyroidism, but her past medical and family history was otherwise unremarkable.

On examination there was a marked thoracic kyphoscoliosis and lumbar lordosis, with continuous spasm of the paraspinal and abdominal muscles. The shoulders were elevated and movements of the cervical, thoracic and lumbosacral spine were greatly limited. There was limitation of visual pursuit to the right and upwards. This was correctable with the doll's head manoeuvre. Saccades were hypometric to the right, and slow. Convergence was absent and there was no nystagmus. The remainder of the cranial nerves were normal, as were muscle tone and strength in the limbs. There was generalized tendon areflexia. Both plantar responses were flexor. Sensation was normal. Brisk taps with a tendon hammer over the mantle area, light touch or pin prick to the face or unexpected noises would cause a generalized shock-like jerk. This consisted of a blink, facial grimace, neck extension, shoulder elevation and adduction and trunk, elbow and hip flexion.

On investigation, high titres of gastric parietal, thyroid thyroglobulin, thyroid microsomal and anti-GAD antibodies were present in the blood. The blood glucose level was normal. The CSF glucose, protein and cell content was normal. However, both oligoclonal bands and anti-GAD antibodies were detected in the

CSF. The EEG and brainstem auditory evoked potentials were normal, as was a full length myelogram. CT brain scan and MRI scan of the head and spine showed enlargement of the basal cisterns and prominence of the cerebellar folia. The clinical diagnosis was encephalomyelitis with rigidity (the 'jerking stiff-person syndrome' reported by Leigh *et al.*, 1980).

Both the painful axial stiffness and the stimulus-sensitive myoclonus partially improved with diazepam, 25 mg daily. The latter also abolished the spontaneous paroxysms of myoclonus.

Case 8

A woman aged 47 yrs gave a 6 yr history of involuntary jerks. These developed following resuscitation from an asthmatic cardiorespiratory arrest. The jerks took two forms. In the first her limbs would jerk on action These jerks were only frequent and disabling around the time of menstruation. The second form of jerking occurred in response to unexpected flashes of light, loud sounds, or taps to the body. These jerks would be generalized and were not related in frequency or severity to the timing of menstruation. She had never fallen in response to an unexpected stimulus and there was no history of seizures.

She had been blind for several months following the cardiorespiratory arrest, although her vision subsequently improved. There was a 25 yr history of asthma, but no other relevant personal or family history. In particular there was no family history of excessive startle responses. She was reluctant to take medication, but past trials of clonazepam and piracetam had been successful in diminishing the jerks on action.

On examination she had multifocal action myoclonus. The face and voice were spared. In addition, unexpected loud sounds, taps to the body or visual menace would elicit an exaggerated startle reaction in which she would blink, grimace, flex her neck, abduct her arms, flex her elbows, pronate her forearms and flex her trunk, hips and knees. There were no other abnormalities on examination.

Her WAIS (Wechsler Adult Intelligence Scale) performance IQ (105) and verbal IQ (112) contrasted with her reading ability (National Adult Reading Test) which was consistent with a superior level of premorbid intelligence. The resting EEG was normal and the jerks were not associated with any change in the EEG record. Visual and brainstem evoked responses were normal. A CT scan of the brain was also normal. The clinical diagnosis was of a static post-anoxic encephalopathy.

PHYSIOLOGICAL STUDIES

Unexpected auditory stimulation elicited reflex jerks in all 8 patients. Unexpected visual stimulation (a sudden thrust of the hand before the eyes) elicited reflex jerks in Cases 1, 5 and 8, although all the patients reported that unexpected visual stimuli had elicited jerks in the past. Somaesthetic stimuli also elicited reflex jerks in all patients except Case 3, who reported that unexpected taps and touches had elicited reflex jerks in the past. Such somaesthetic stimuli were most effective when applied to the mantle area (head and upper trunk), with the face and nose being particularly sensitive. Light touch and pin prick in all the patients, except Case 3, and taps with a tendon hammer in Cases 5 and 7, were only effective stimuli when applied within this area.

Electrical stimulation of peripheral nerves could also elicit reflex jerks in some patients. Cases, 1, 5, 6 and 7 had jerks to stimulation of the supraorbital nerve at intensities above the threshold for the blink reflex, and after stimulation of the median nerve at intensities above motor threshold.

The EMG pattern in jerks following auditory stimulation

In the previous paper (Brown *et al.*, 1991*a*) we have shown that the auditory blink reflex is not part of the true startle response. In Cases 1, 3, 4, 5, 7 and 8 there was a normal latency blink reflex to sound (Table 2). The auditory blink reflex was late in Case 2 (47 ms, range 38–55 ms), who was aged 77 yrs, and Case 6 (44 ms, range 34–53 ms), who had evidence of brainstem pathology.

The auditory blink reflex was followed by a generalized reflex response in each case.

TABLE 2. BLINK REFLEX LATENCIES

	*Auditory blink reflexes** *Latency in right orbicularis oculi to auditory stimulation median and range (ms)*			*Electrical blink reflexes*** *Electrical stimulation left supraorbital nerve mean ± SEM (ms)*				*Electrical stimulation right supraorbital nerve mean ± SEM (ms)*			
Case	*Median*	*Range*	*n*	*Left R1*	*Left R2*	*Right R2*	*n*	*Right R1*	*Right R2*	*Left R2*	*n*
1	39	32–48	8	10 7±0 3	38 5±1 2	38 6±2 0	9	11 4±0 2	38 4±1.0	40 6±1 0	10
2	47	38–55	10		N/A				N/A		
3	35	30–42	10	12 0±1 0	30 2±1 7	28 1±1 6	6	10.6±1 2	28 0±1 3	31 5±1.7	5
4	32	29–34	11	10 1±0 2	30.1±0 8	29 0±0 5	9	10.2±0 5	31 5±0.9	31.5±1 0	9
5	32	28–39	11	12 0±0 4	41 0±0.6	38 9±1 0	7	11 0±0 2	37 8±0 5	40 1±1.0	14
6	44	34–53	9	17 5±0.4	absent	absent	11	25 2±0 3	55.7±0.7	55 7±0 7	12
7	30	20–38	19	11 6±1.9	37 5±2 4	36 2±1.9	7	11 1±0 1	36.4±1.6	42.2±1 8	8
8	36	25–55	11		N/A				N/A		

* The latency to onset of EMG activity in orbicularis oculi following auditory stimulation was similar to that of the normal auditory blink reflex (32.3 ms, range 19–69 ms, n = 60), except in Cases 2 and 6 in whom it was significantly delayed ($P < 0.05$, Mann-Whitney U test) ** The electrical blink reflexes were abnormal in Case 6 The normal range (±2 5 SD) of the electrical blink reflex determined in 10 healthy subjects was R1 9 3±3 2 ms, ipsilateral R2 33 1±11 1 ms and consensual R2 35 0±12.7 ms N/A = not available

The onset latency of this reflex jerk varied considerably between patients, but the order of muscle recruitment was very similar in all individuals. An example is shown from one patient in fig. 4, and the data from all subjects is summarized in Table 3. The earliest EMG activity in the generalized jerk was recorded in sternocleidomastoid (except in Case 2, in whom EMG activity in sternocleidomastoid was not recorded). EMG activity in masseter occurred after that in sternocleidomastoid, except in Case 6 in whom it occurred at about the same time (Table 3). In Cases 3, 4 and 7, in whom EMG activity in mentalis (innervated by the seventh cranial nerve) was recorded, activity in mentalis followed that in sternocleidomastoid by 2.0, 2.0 and 8.5 ms, respectively. It also followed that due to the auditory blink reflex in orbicularis oculi (also innervated by the seventh cranial nerve) by 21.2, 18.6 and 9.5 ms, respectively.

The latencies of trunk and limb muscles increased with the distance of their respective segmental innervations from the caudal brainstem (fig. 4). The difference in latency between sternocleidomastoid and distal lower limb muscles was relatively long (*see* Table 3), in comparison with the latency difference between these muscles following magnetic stimulation of the motor cortex. In addition, the difference between the latency to onset of EMG activity in biceps and the intrinsic hand muscles, and between tibialis anterior and the intrinsic foot muscles, was disproportionately long, even when allowance was made for the slow descending motor conduction (Table 3).

These three features of (1) caudorostral activation of the cranial nerve innervated muscles, (2) slow descending motor conduction, and (3) disproportionate delay to the intrinsic muscles of the hands and feet, were common to the reflex responses of all the cases, despite differences in the absolute latencies of the responses between patients (Table 3).

Unlike the normal auditory startle (Brown *et al.*, 1991*a*), the auditory startle responses in the patients did not readily habituate. A test auditory stimulus would still elicit a jerk if repeated as little as 10, 30, 60, 60, 20, 1 and 20 s after a conditioning auditory stimulus in Cases 1–5, 7 and 8, respectively (this feature was not examined in Case 6). The pathological startle response rapidly habituated with shorter stimulus intervals than these.

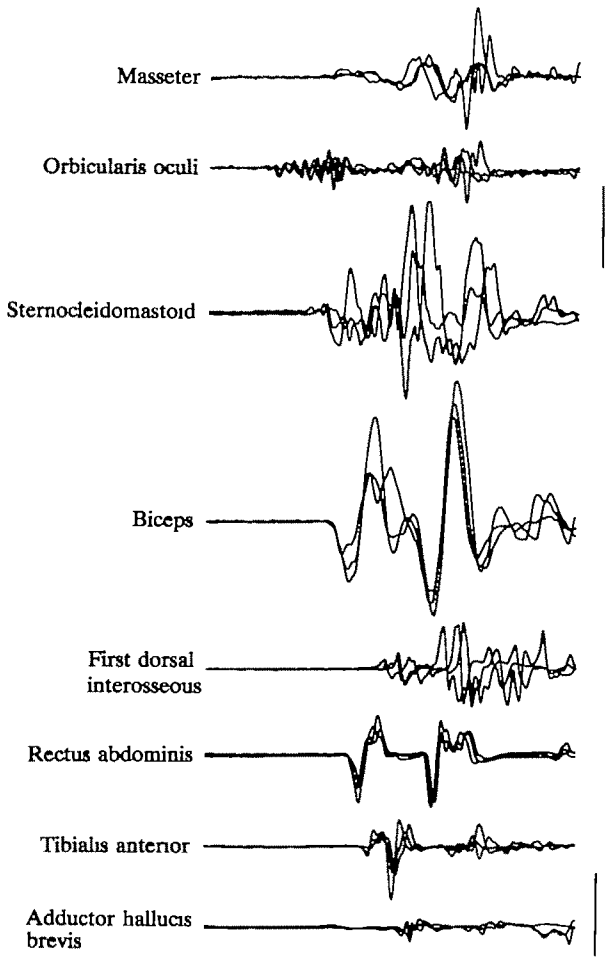

FIG. 4. EMG records of the abnormal startle response elicited by auditory stimulation in *Case 5* Three unrectified single trials are superimposed. Each trial was started at the point of presentation of a 124 dB tone of 50 ms duration to both ears Following the normal auditory blink reflex, EMG activity was recorded first in sternocleidomastoid and then later in masseter and trunk and limb muscles. The latencies to the intrinsic muscles of the hand and foot were disproportionately long. The horizontal calibration line represents 20 ms. The vertical calibration line represents 0.5 and 4.0 mV for the upper 3 channels, and the lower 5 channels, respectively

The EMG pattern in jerks following somaesthetic stimulation

The response to taps was studied in all patients except Case 8. A tap to the mantle area elicited a generalized reflex jerk in Cases 1, 2 and 4–7, and a focal jerk localized to the face and sternocleidomastoid in Case 3. The jerks began with a blink reflex in orbicularis oculi, with median latencies ranging from 9.0 to 17.3 ms for taps to the vertex, nose or jaw. Responses at similar latencies (11.9–22.9 ms) were recorded in 9 normal subjects after taps to the vertex. This blink reflex was followed in the patients by a pattern of EMG activity (fig. 5) very similar to that seen following auditory stimuli. The muscle to be recruited first after the blink reflex was sternocleidomastoid (except

TABLE 3. LATENCY TO ONSET OF EMG ACTIVITY FOLLOWING AUDITORY STIMULATION*

Latency to onset of EMG activity in the cranial nerves

	Latency of sternocleidomastoid (ms)			*Excess latency of masseter over sternocleidomastoid (ms)*		
Case	*Median*	*Range*	*n*	*Median*	*Range*	*n*
1	58	43–74	9	5	0–8	9
2		N/A			N/A	
3	54	48–68	10	27	17–32	3
4	49	40–61	11	15	9–17	5
5	57	48–62	9	4	−2–6	10
6	79	48–84	9	−2	−6–13	10
7	31	28–36	20	13	5–20	13
8	85	56–188	21	9	0–42	17

Difference in latency to onset of EMG activity between rostral and caudal muscles

		Difference in reflex jerks (ms)			*Difference with magnetic stimulation of cortex (ms) (in normal subjects)***
Case	*Muscles*	*Median*	*Range*	*n*	
1	SCM to TA	45	26–53	9	21 9
2	Biceps to Quad	25	0–43	5	11 3
3	SCM to TA	40	30–55	9	21.9
4	SCM to RA	27	18–43	6	8 0
5	SCM to TA	29	14–33	18	21.9
6	SCM to Soleus	28	13–67	9	21 9
7	SCM to TA	33	23–40	19	21 9
8	SCM to TA	51	28–78	19	21 9

Difference in latency to onset of EMG activity between biceps and the intrinsic hand muscles, and between tibialis anterior and the intrinsic foot muscles

		Difference in reflex jerks (ms)			*Difference with magnetic stimulation of cortex (ms) (in normal subjects)***
Case	*Muscles*	*Median*	*Range*	*n*	
1	Biceps to APB	22	12–39	10	10.5
2	Biceps to APB	39	19–46	8	10 5
3	F.Flex to APB	7	0–16	10	7 5
	TA to EDB	28	16–42	9	8.9
4	Biceps to APB		N/A		
5	Biceps to APB	21	18–53	9	10 9
	TA to EDB	19	17–21	8	8 9
6	Biceps to APB		N/A		
7	Biceps to APB	32	17–47	11	10 5
	TA to EDB	14	4–31	19	8 9
8	Biceps to APB	35	20–64	17	10 5
	TA to EDB	16	7–60	7	8.9

* A standard 1000 Hz, 124 dB tone of 50 ms duration was the auditory stimulus in each case. ** Calculated from Thompson (1991). N/A = not available, SCM = sternocleidomastoid, F.Flex = forearm flexors, APB = abductor pollicis brevis, RA = rectus abdominis, Quad = quadriceps, TA = tibialis anterior, EDB = extensor digitorum brevis.

in Case 7, in whom reflex EMG activity in orbicularis oculi was recorded at the same time as that in sternocleidomastoid). EMG activity in masseter, and trunk and limb muscles occurred later (Table 4, fig. 5). As with auditory evoked jerks, the difference

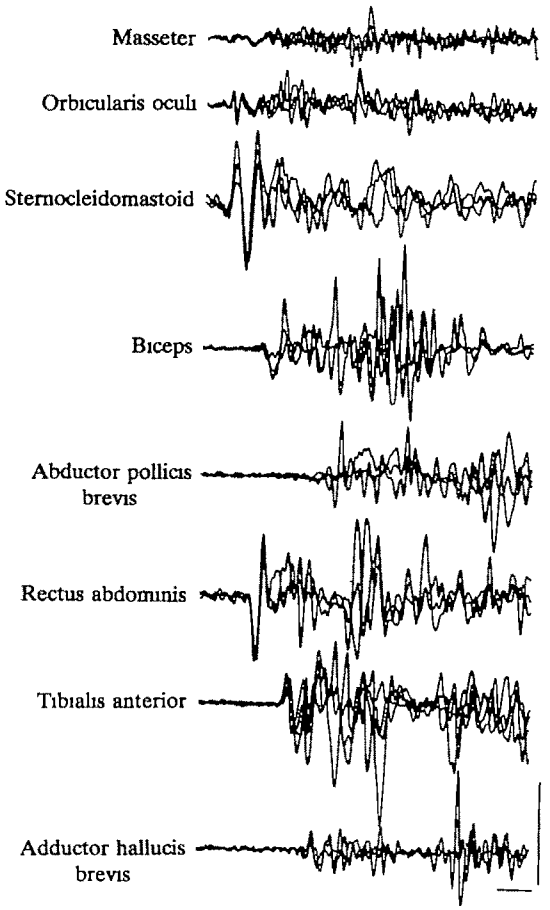

FIG 5. EMG record of the abnormal startle response elicited by a tap to the vertex delivered at the beginning of the trace in *Case 7*. Three unrectified single trials are superimposed Each trial was started at the point of contact of the tendon hammer with the vertex. EMG activity was recorded first in sternocleidomastoid and orbicularis oculi (where a R_1 reflex response is clearly visible, as in normal subjects), and then later in masseter and trunk and limb muscles. The latency to onset of EMG activity in sternocleidomastoid was very short (14 3 ms) The latency of the oligosynaptic stretch reflex in this muscle is about 8 ms. The horizontal and vertical calibration lines represent 20 ms and 0.5 mV, respectively.

in latency between sternocleidomastoid and more distal muscles was relatively long compared with the latency differences between these muscles following magnetic stimulation of the motor cortex (Table 4). The latency to onset of EMG activity in the intrinsic hand and foot muscles was also disproportionately long (Table 4).

In 2 cases it was possible to estimate the conduction velocity of the peripheral afferents mediating the jerks in response to somaesthetic stimulation. Cases 5 and 7 had generalized jerks following electrical stimulation of the median nerve. The threshold for evoking the jerks was about three times that for sensory perception. Stimulation of the median nerve at the wrist and elbow gave values for the conduction velocity in the peripheral

TABLE 4 THE LATENCY TO ONSET OF EMG ACTIVITY FOLLOWING TAPS WITH A TENDON HAMMER

The latency to onset of EMG activity in the cranial nerves following taps to the mantle area

Case	Site of stimulation	Latency of sternocleidomastoid (ms)			Excess latency of masseter over sternocleidomastoid (ms)		
		Median	Range	n	Median	Range	n
1	Vertex	19	16–30	9		N/A	
2	Clavicle	106	61–122	7	10	4–19	10
3	Sternum	15	12–17	6		N/A	
4	Nose	47	30–57	11	13	4–26	13
5	Vertex	17	13–18	15	4	0–5	10
6	Jaw	19	16–23	20		N/A	
7	Vertex	14	10–23	20	21	10–28	19
8	N/A						

Brisk taps to the vertex elicited reflex EMG activity in sternocleidomastoid in 4 out of 9 normal subjects at 28 3 ms (range 24.7–29 0 ms). No reflex EMG activity was recorded in masseter in normal subjects

Difference in latency to onset of EMG activity between rostral and caudal muscles

Case	Site of stimulation	Muscles	Difference in reflex jerks (ms)			Difference with magnetic stimulation of cortex (ms) (in normal subjects)*
			Median	Range	n	
1	Knee	SCM to TA	54	46–62	6	21.9
2	Clavicle	Bic to Quad	20	9–30	4	11.3
3	N/A					
4	Nose	SCM to TA	38	28–47	6	21 9
5	Forehead	SCM to TA	46	39–48	15	21.9
6	Jaw	SCM to Soleus	28	25–31	15	21.9
7	Vertex	SCM to TA	33	27–82	18	21 9
8	N/A					

Difference in latency to onset of EMG activity between biceps and the intrinsic hand muscles, and between tibialis anterior and the intrinsic foot muscles

Case	Site of stimulation	Muscles	Difference in reflex jerks (ms)			Difference with magnetic stimulation of cortex (ms) (in normal subjects)*
			Median	Range	n	
1	N/A					
2	Clavicle	Bic to APB	40	32–52	4	10 5
3	N/A					
4	Nose	Bic to FDI	17	4–33	12	10.1
5	Forehead	Bic to APB	37	28–43	14	10 5
	Vertex	TA to EDB	20	17–22	9	8.9
6	N/A					
7	Vertex	Bic to FDI	24	18–29	4	10.1
	Vertex	TA to EDB	12	−2–19	13	8.9
8	N/A					

* Calculated from Thompson (1991). N/A = not available, SCM = sternocleidomastoid, Bic = biceps, APB = abductor pollicis brevis, FDI = first dorsal interrosseous, Quad = quadriceps, TA = tibialis anterior, AHB = adductor hallucis brevis

afferents involved in the jerks of 33 and 36 $m \cdot s^{-1}$ in Cases 5 and 7, respectively. The peripheral nerve motor conduction velocities (which are slightly slower than the fastest sensory conduction velocities) were 55 and 54 $m \cdot s^{-1}$, respectively.

Cross-conditioning of auditory and somaesthetic stimulation

The pattern of muscle recruitment in the reflex jerks to auditory and somaesthetic stimulation suggests that they were evoked by activity in the same slowly conducting spinal efferent system. This hypothesis was supported by experiments in which cross-conditioning of the two modes of stimulation was used. In Cases 1, 5 and 7 a conditioning tap to the mantle area had the same effect on an auditory test stimulus as an auditory conditioning stimulus. Thus there was no response to an auditory test stimulus when this was preceded, by as little as 200 ms, by either a conditioning tap or an auditory stimulus. The response to the auditory test stimulus recovered when the interval between the test stimulus and the conditioning tap or sound exceeded 10, 20 and 1 s in Cases 1, 5 and 7, respectively. A conditioning tap to the patellar tendon had similar effects on an auditory test stimulus in Case 1.

Tonic spasms

In addition to the brief jerks elicited by unexpected noises or touches, Cases 1, 3, 4, 5 and 6 reported a second type of attack. This could be spontaneous (Case 4), stimulus-sensitive (Cases 1, 5) or both spontaneous and stimulus-sensitive (Cases 3, 6). In Cases 1 and 5 the attack consisted of a tonic spasm of adduction and flexion of the arms, and extension of the legs. In Cases 3, 4 and 6 the attack consisted of a tonic spasm of abduction and extension of the arms, and extension of the legs (fig. 2A). The spasms usually lasted 3–15 s, and consciousness was preserved throughout.

In Case 3 a spontaneous tonic spasm was recorded by videotelemetry. This was identical in appearance to the stimulus-induced spasms. It was preceded by a sharp and slow wave complex with phase reversal at the vertex in the EEG. The spasm itself was accompanied by central rhythmic activity of varying frequency. Following the spasm there was a marked increase in the central sharp and slow wave activity seen in the resting EEG in this patient.

On one occasion Case 5 was studied following the withdrawal of all medication for 24 h. Under these circumstances the standard 124 dB binaural tone would at times elicit an involuntary tonic muscle contraction (fig. 2B) leading to a sustained posture of extension of the legs, flexion of the elbows and adduction of the shoulders so that the arms were held across the chest. The tonic spasm would start about 2 s after the noise and last 4–5 s. The spasm was quite separate from the short latency and brief reflex response to sound which it followed. The patient reported that this tonic spasm was indistinguishable from those spasms leading to abrupt falls, often with injury.

Electrical blink reflexes

The electrical blink reflexes were normal in Cases 1, 3, 4, 5 and 7, but markedly abnormal in Case 6 (Table 2). In this patient the R1 was delayed (17.5 ± 0.4 ms) and both the ipsilateral and consensual R2 were absent following electrical stimulation of the left supraorbital nerve. With stimulation of the right supraorbital nerve the R1 (25.2 ± 0.3 ms), ipsilateral R2 (55.7 ± 0.7 ms) and consensual R2 (55.7 ± 0.7 ms) were all delayed.

Central motor conduction times

In Case 5 the central motor conduction time (CMCT) (to magnetic stimulation of the motor cortex) was prolonged to the left tibialis anterior (23.8 ms), but normal

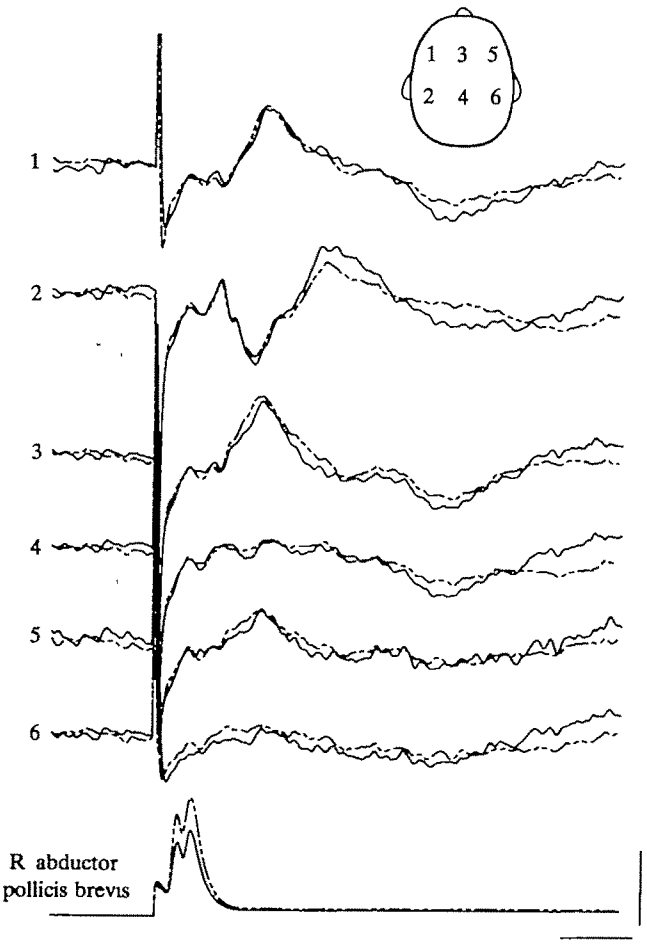

FIG 6. Enlarged cortical SEP (*see* text) following electrical stimulation of the right median nerve at the wrist in *Case 1* The averages of 2 trials, of 256 stimuli each, have been superimposed. No C reflex is seen in abductor pollicis brevis The positions of the scalp electrodes (linked to ear reference) are shown in the inset Stimulus artefact marks the delivery of the median nerve shock 30 ms after the start of each trace The horizontal calibration line represents 20 ms. The vertical calibration line represents 200 mV and 20 μV for EMG and SEP channels, respectively

(Thompson, 1991) to right (5.1 ms) and left (4.2 ms) biceps, right (8.2 ms) and left (7.7 ms) abductor pollicis brevis, and right tibialis anterior (15.2 ms). In Case 6 CMCT was prolonged bilaterally (14.4 ms, 25.2 ms and 22.8 ms for both biceps and left and right quadriceps, respectively). CMCT was normal on the right in Case 7 (biceps 6.3 ms, abductor pollicis brevis 8.6 ms and tibialis anterior 13.0 ms. Left-sided muscles were not tested).

Cortical SEPs

In Case 1 (fig. 6) these were of normal latency (N1 at 18 ms bilaterally), but of very large amplitude (N1 of 7 and 9 μV, and P1N2 of 19 and 20 μV following electrical stimulation of the left and right median nerve at the wrist, respectively). Despite this,

the long latency component of the stretch reflex was not exaggerated following step torque disturbances applied to the forearm flexors and flexor pollicis longus.

The cortical SEP following stimulation of the right median nerve at the wrist was of normal latency (N1 at 18.8 ms), but of enlarged amplitude (P1N2 of 5.4 μV) in Case 3. In Case 5 the cortical SEPs to median nerve stimulation at the wrist were delayed. The N1 was recorded at 27 ms bilaterally (the cervical cord potential was recorded at 16.8 ms, giving a central sensory conduction time of 10.2 ms). The later components of the cortical SEP were not enlarged (P1N2 2.5 and 0.9 μV following electrical stimulation of the left and right median nerve at the wrist, respectively). In Case 6 the cortical SEP following stimulation of the right median nerve at the wrist was of normal latency (N1 at 18.1 ms), but of small amplitude (P1N2 of 0.3 μV). The latency and amplitude of the cortical SEPs were normal in Case 8 (N1 at 18.9 and 20.3 ms, and P1N2 of 2.6 and 3.2 μV following electrical stimulation of the left and right median nerve at the wrist, respectively). SEPs were not recorded in Cases 2, 4 and 7.

Additional observations

In addition to the findings reported above, Case 7 was unique in having continuous EMG activity in the cervical, thoracic and lumbar paraspinal muscles at rest. The cutaneomuscular reflexes following a train of electrical pulses delivered to the right posterior tibial nerve at the ankle were normal.

Case 8 had two types of jerk. Multifocal jerks occurring on action were recorded around the time of menstruation. These differed from the generalized reflex jerks of the startle response. The duration of the EMG activity in the jerks on action was brief (25−100 ms). In the startle responses elicited by unexpected auditory stimuli the duration of EMG activity was much longer (150−400 ms). The differences in latency between the EMG activity in the muscles of the upper limb recorded in the jerks on action were short (the average difference in latencies between the forearm extensors and abductor pollicis brevis was 6.9 ms), in contrast to those recorded in the startle response (Table 3). Back-averaging of the EEG activity occurring before the action myoclonus recorded from abductor pollicis brevis revealed a lateralized positive cortical wave occurring about 23 ms before the onset of EMG activity in this muscle.

DISCUSSION

The 8 patients described were found, on physiological assessment, to have hyperekplexia (defined as an exaggerated normal startle reflex). They had different causes for their hyperekplexia. Cases 1 and 2 had the same diseases, namely hereditary hyperekplexia, with a family history suggesting autosomal dominant inheritance. Case 1 had the typical features of the major form of hereditary hyperekplexia, with stiffness as a baby, hypnagogic myoclonic jerks, hyperreflexia, and generalized stiffness in response to unexpected stimuli, frequently culminating in a fall, without loss of consciousness (Suhren *et al.*, 1966; Andermann *et al.*, 1980). A hesitant wide based gait (Suhren *et al.*, 1966), apnoeic attacks as a baby (Kurczynski, 1983), epilepsy (Suhren *et al.*, 1966; Sáenz-Lope *et al.*, 1984) and low intelligence (Andermann *et al.*, 1980; Sáenz-Lope *et al.*, 1984) also have been noted in hereditary hyperekplexia. Case 2, the grandmother of Case 1, represented the minor form of hyperekplexia (Andermann *et al.*, 1980). Thus she experienced excessive startle reactions to unexpected auditory

stimuli, although she never fell as a result. There were no other neurological abnormalities. Excessive startle reactions or hypnic jerks were also reported in relatives from 3 additional generations of the same family.

Cases 3 and 4, who were sibs, both had exaggerated startle responses to unexpected stimuli, and had suffered spontaneous or stimulus-sensitive episodes of generalized stiffness without loss of consciousness. Early motor development, however, was normal, without stiffness as babies, and on examination both cases were of normal intelligence and had normal tendon reflexes. This form of familial hyperekplexia therefore differs in some respects from classical hereditary hyperekplexia as described by Suhren *et al.* (1966) and Andermann *et al.* (1980). Case 3 had epileptiform EEG abnormalities both interictally and during episodes of generalized stiffness, but was not considered to suffer from startle epilepsy. The latter condition is not familial, and is associated with focal brain lesions, usually perinatal in origin (Alajouanine and Gastaut, 1955; Bancaud *et al.*, 1967).

Cases 5, 6, 7 and 8 had symptomatic hyperekplexia. Case 5 had laboratory-supported probable multiple sclerosis, with oligoclonal IgG bands in the CSF, and discrete areas of increased signal intensity in the pons and periventricular cerebral white matter on MRI. Case 6 had a brainstem encephalitic illness with a positive Kveim test and noncaseating granulomas on bone marrow histology, suggesting sarcoidosis. In Case 7, the combination of progressive muscular rigidity with continuous muscle fibre activity at rest, and stimulus sensitive myoclonus, resembles the entity previously reported under the title of 'jerking stiff-man' (Leigh *et al.*, 1980). The presence of anti-GAD antibodies in the serum and CSF of this case suggests that this combination of features may represent a variant of the stiff person syndrome. Case 8 had a postanoxic encephalopathy with, in addition to hyperekplexia, cortical action myoclonus. A short latency time-locked EEG correlate preceded the focal jerks on action, confirming their cortical origin (Hallett *et al.*, 1979).

Andermann and Andermann (1986) considered both familial and sporadic forms of hyperekplexia a single genetically determined disorder. Cases 5, 6, 7 and 8 suggest that hyperekplexia is not always genetically determined, but also may be symptomatic of central nervous system pathology.

The major (Cases 1, 3, 4) and minor (Case 2) forms of hereditary hyperekplexia shared some pathophysiological features, in particular those of the efferent pathways, but differed in two important respects: the absolute latencies to onset of their reflex responses and the presence or absence of tonic spasms. The cases of symptomatic hyperekplexia also were similar in regard to the characteristics of the efferent components of their pathological startle responses, but differed in that the latencies to onset of the reflex responses were short in Cases 5, 6 and 7, and long in Case 8. Also, Cases 5 and 6 exhibited tonic spasms, while Cases 7 and 8 did not. Each of these three aspects of pathophysiology, the efferent system, the afferent inputs and the tonic spasms deserve separate consideration.

The efferent system responsible for the pathological startle response in hyperekplexia

Irrespective of the afferent and central delay to auditory or somaesthetic stimulation, the characteristics of the efferent output system in the pathological startle response were

similar in all the patients with hereditary hyperekplexia (Cases 1, 2, 3, 4), and in all 4 patients with symptomatic hyperekplexia (Cases 5, 6, 7, 8).

In all 8 patients the reflex jerks to auditory or somaesthetic stimuli involved many muscles, both proximal and distal, bilaterally and synchronously to produce a sudden shock-like movement usually involving a grimace, abduction of the arms, and flexion of the neck, trunk, elbows, hips and knees. In Cases 5 and 7 the neck and knees extended rather than flexed. Thus the reflex jerks resembled the normal startle reaction in general character (Brown *et al.*, 1991*a*) although, clinically, they were greatly exaggerated in amplitude and more extensive in distribution. In addition, the reflex jerks differed from the normal startle reaction in that they habituated poorly.

The auditory blink reflex is not an integral part of the auditory startle response (Brown *et al.*, 1991*a*). This conclusion is supported, in the present study, by the difference in latency to onset of EMG activity between orbicularis oculi and mentalis following auditory stimulation in Cases 3, 4 and 7. EMG activity due to the startle response in mentalis occurred 9.5–21.2 ms after EMG activity in orbicularis oculi, despite the similar innervation (the seventh cranial nerve) and peripheral efferent conduction time between the 2 muscles (Benecke *et al.*, 1988). Similarly, the cutaneous blink reflex to taps to the mantle area is not an integral part of the startle response to somaesthetic stimulation. Such a cutaneous blink reflex was elicited in both the hyperekplectic patients studied, and in normal subjects, in whom no generalized startle reflex was elicited. In Case 2, where the startle responses to sound and tap were relatively late, 2 components were visible in the EMG activity in orbicularis oculi: the first attributable to the auditory or cutaneous blink reflex, the second attributable to the generalized startle response. Colebatch *et al.* (1990*a*) have reported similar findings in a case of idiopathic exaggeration startle disease.

The earliest muscle activity in the true generalized startle response was recorded in sternocleidomastoid. EMG activity in mentalis, masseter and in trunk and limb muscles followed later. The difference in latency between rostral and caudal muscles in both jerks to auditory and somaesthetic stimulation was greater than that seen after magnetic stimulation of the motor cortex, suggesting a moderately slowly conducting spinal efferent pathway (*see* Tables 3 and 4). In addition, the responses to both auditory and somaesthetic stimulation were characterized by disproportionately long reflex latencies to the intrinsic hand and foot muscles (*see* Tables 3 and 4). The fact that the pattern of reflex response following somaesthetic stimulation closely resembles that following auditory stimulation suggests that afferents for both modalities converge on a single reflex centre. The latter conclusion is supported by the way in which somaesthetic stimuli were able to condition the reflex response to auditory stimulation in Cases 1, 5 and 7. It is, however, possible that the conditioning somaesthetic stimulus served to alert the subject to the following auditory stimulus, which might itself have had a nonspecific effect on the reflex response to the auditory test stimulus.

The site of origin of the efferent system responsible for the pathological startle response in hyperekplexia

The clinical features in Cases 6 (facial sensory disturbance, dysphagia, dysarthria and an ataxic gait) and 7 (disordered eye movements) suggested that the major pathological processes were occurring in the brainstem. Imaging and electrophysiological studies

also implicated the brainstem in Cases 5 and 6. In Case 5, MRI revealed a discrete area of increased signal intensity in the central pons, in addition to similar areas in the periventricular cerebral white matter. The delay in the electrical blink reflexes seen in Case 6 was highly suggestive of a bulbopontine lesion (Kimura, 1973; Namerow, 1973). The delayed CMCTs in Cases 5 and 6, and the delayed central sensory conduction time in Case 5 were also consistent with a lesion at this site. Many of the previously reported cases of acquired startle disease have involved brainstem pathology (Table 1). In particular, Fenzi *et al.* (1988) reported a postmortem study of a case of symptomatic hyperekplexia, in which marked lymphocytic infiltrates, microglial proliferation and evidence of neuronophagia were found in the brainstem, with sparing of the cerebral cortex.

The pattern of muscle activity in the reflex responses to auditory and somaesthetic stimulation in the present cases also implicates the lower brainstem as the generator for the observed reflex responses. Thus the earliest recorded EMG activity (excluding the blink reflex to sound and taps to the head and face) in the reflex response to either stimulus modality was recorded in sternocleidomastoid. EMG activity in masseter and trunk and limb muscles followed later. Given the approximately similar peripheral efferent conduction delays to masseter and sternocleidomastoid (Benecke *et al.*, 1988), the overall pattern of muscle recruitment in the reflex responses to auditory and somaesthetic stimuli suggests that motor activity begins in the caudal brainstem and then spreads rostrally up to the brainstem and caudally down to the spinal cord. The reverse pattern is seen in cortical myoclonus, where EMG activity is recorded first in masseter, and then in orbicularis oculi and sternocleidomastoid (Hallett *et al.*, 1979).

The latency to onset of EMG activity in sternocleidomastoid following taps to the head, face or sternum in Cases 1, 3, 5, 6 and 7 was very short (*see* Table 4), and also suggests a brainstem origin for the reflex response to somaesthetic stimuli. The minimum delay in a cortical reflex loop would approximately equal the sum of the latency of the primary cortical response to peripheral trigeminal stimulation (14 ms: Drechsler, 1980) and the latency to onset of EMG activity in sternocleidomastoid following magnetic stimulation of the motor cortex (8.8 ms: Thompson, 1991). This minimum delay in a cortical reflex loop of 22.8 ms exceeds the latency of the reflex responses in sternocleidomastoid to a tap to the mantle area (range 14–19 ms) in Cases 1, 3, 5, 6 and 7. The reflex response in sternocleidomastoid in these 5 patients was also at least 9 ms earlier than the earliest EMG activity elicited in sternocleidomastoid by a tap to the vertex in normal subjects.

The probable convergence of the afferents of more than one sensory modality upon the one reflex centre suggests that, within the lower brainstem, the pathological startle response in hyperekplexia is most likely to originate in the medial bulbopontine reticular formation. This area receives afferent input from the body via the spinoreticular tracts (Rossi and Brodal, 1957), from the face via secondary sensory fibres from the spinal trigeminal tract (Carpenter and Hanna, 1961), and auditory (Davis *et al.*, 1982) and visual (Rasmussen, 1936; Valverde, 1962) afferent input. Leitner *et al.* (1980) have shown that lesions in the medial bulbopontine reticular formation abolish or diminish the startle response to both sound and foot shock in the rat, and Groves *et al.* (1973) have found neurons responding to the combination of tactile, auditory and visual stimuli in the rat medial bulbopontine reticular formation.

The relationship between the efferent systems responsible for the pathological startle responses in hyperekplexia and the normal startle reflex

Thus clinical, electrophysiological and pathological evidence implicates the lower brainstem as the site of origin of the pathological startle response in hyperekplexia. Animal experiments (Szabó and Hazafi, 1965; Wright and Barnes, 1972; Davis *et al.*, 1982) and electrophysiological evidence in man (Brown *et al.*, 1991*a*) indicate that the physiological startle reflex also originates in the lower brainstem, probably in the bulbopontine reticular formation. The normal auditory startle reflex in man, like the pathological startle reflex, is characterized by the relatively slow recruitment of caudal muscles, implying a moderately slow conduction velocity in spinal efferent pathways, and by a disproportionately long reflex latency to the intrinsic hand muscles (Brown *et al.*, 1991*a*). This common pattern of reflex response suggests that a single efferent system, originating in the caudal brainstem, may be responsible for both the normal startle reflex and the pathological startle response in hyperekplexia.

The relationship of the efferent system responsible for the normal and exaggerated startle responses in man to the spinobulbospinal reflex in animals

The pathways forming the basis of the normal and pathologically exaggerated startle reflex in hyperekplexia bear some similarities to those subserving the spinobulbospinal reflex identified in animals (Shimimura and Livingston, 1963) and, tentatively, in man (Shimamura *et al.*, 1964; Meier-Ewert *et al.*, 1972). This reflex is most effectively elicited by stimulation of cutaneous afferents (Shimamura and Akert, 1965). The efferent pathways originate in the medial reticular formation of the lower brainstem (Shimamura and Livingston, 1963), and are relatively slowly conducting (Shimamura *et al.*, 1964), as in Cases 1–8. The same efferent pathways form the basis of the audiospinal reflex response, believed to underlie the auditory startle reflex in animals (Wright and Barnes, 1972).

The afferent inputs responsible for the pathological startle response in hyperekplexia

All 8 patients complained of jerks in response to unexpected visual, auditory and somaesthetic stimuli. On examination, reflex jerks were elicited by unexpected visual stimulation in 3 (Cases 1, 5, 8), and by unexpected auditory stimulation in all 8 cases. Somaesthetic stimulation was also effective in 7 out of the 8 patients. In Case 3, somaesthetic stimulation did not elicit a reflex jerk during the electrophysiological studies, although the patient reported that unexpected taps and touches had elicited jerks in the past. In the other cases somaesthetic stimuli were most effective when applied to the mantle area. In particular, light touch and pin prick were only effective in eliciting a jerk when applied within this area. The face and nose were especially sensitive to the latter stimuli. In Cases 5 and 7, the effectiveness of taps in eliciting a reflex jerk was also restricted to the mantle area, and somaesthetic stimulation over the lower trunk and legs was ineffective. Similar patterns of stimulus sensitivity confined to the mantle area have been previously reported in some forms of brainstem reflex myoclonus (Niedermeyer *et al.*, 1977; Leigh *et al.*, 1980), and in hereditary hyperekplexia. Tactile stimulation, particularly touch or taps to the forehead (Gastaut and Villeneuve, 1967; Andermann *et al.*, 1980), glabella (Suhren *et al.*, 1966; Andermann *et al.*, 1980), vertex

(Gastaut and Villeneuve, 1967) and nose (Morley *et al.*, 1982; Kurczynski, 1983) have been reported to elicit startle responses in hereditary hyperekplexia. Kurczynski (1983) reported 2 cases from the same family where, in addition to unexpected noises, only touch to the tip of the nose would elicit a startle response.

Electrical stimulation of the supraorbital nerve at intensities above the threshold for the blink reflex, and electrical stimulation of the median nerve at intensities above motor threshold, also elicited generalized jerks in Cases 1, 5, 6 and 7. In Cases 5 and 7 the conduction velocity of the peripheral afferents subserving the reflex response (33 and 36 $m \cdot s^{-1}$) made it unlikely that Ia and Ib afferents were involved, despite the responsiveness to tendon taps.

The characteristics of the stimulus sensitivity in the pathological startle response are consistent with the results of animal studies, which indicate that reticular neurons receive input from a wide variety of afferents. These include visual inputs (Rasmussen, 1936; Valverde, 1962), auditory inputs (Buser *et al.*, 1966; Brodal, 1969), and inputs from cutaneous and deep receptors and from high threshold muscle afferents (Segundo *et al.*, 1967; Casey, 1969). Reticular neurons do not receive input from muscle spindle primary receptors or Golgi tendon organs (Pompeiano and Swett, 1963*a*, *b*). The dominance of the face and adjacent areas in the receptive fields of bulbar reticular neurons (Segundo *et al.*, 1967) might underlie the peculiar sensitivity of the mantle area.

Although the overall pattern of the reflex jerks was similar in all 8 cases, the absolute latencies of the reflex jerks differed between patients. The exact timing of the reflex discharge of the brainstem centre responsible for the pathological startle response will depend on the delays in the afferent limb of the reflex response and, perhaps, on the level of facilitatory influences on this centre. Given that the medial bulbopontine reticular formation probably receives visual, auditory and somaesthetic afferent inputs from subcortical (Rasmussen, 1936; Rossi and Brodal, 1957; Buser *et al.*, 1966) and cortical (Valverde, 1962; Brodal, 1969) levels, and that it is under complex cortical facilitatory influences (Ascher *et al.*, 1963; Liegeois-Chauvel *et al.*, 1989), it is possible that, under differing pathological circumstances, this centre may generate reflex responses of different latency.

Alternative theories as to the origin of the pathological startle response in hereditary hyperekplexia

Case 1 had giant cortical SEPs on electrical stimulation of peripheral nerves. In Case 3 the cortical SEPs were modestly enlarged. Markand *et al.* (1984) reported pathologically enlarged cortical SEPs in 7 members of a family with hyperekplexia. They also found enhanced C responses in 6 of these patients and suggested that the basic pathophysiological mechanism responsible for hyperekplexia was the release of cortical long-loop reflexes. However, not all hyperekplectics have enlarged SEPs (Andermann and Andermann, 1986) and no cortical correlate has been found on back-averaging the EEG activity before the startle responses (Morley *et al.*, 1982; Markand *et al.*, 1984). Despite the presence of enlarged cortical SEPs, there was no enhancement of the C response on electrical stimulation of the median nerve in Cases 1 and 3, and stretch reflexes showed a normal long latency component in Case 1. The long-loop reflexes reported by Markand *et al.* may have a reticular origin (Shimamura *et al.*, 1964). It is of interest that one of their cases showed a bilaterally synchronous C response. If the brainstem reticular formation

were the primary site of pathology in hyperekplexia then its influence on the central transmission of sensory impulses (Halliday, 1975) might explain the occasional finding of enlarged cortical SEPs in this condition.

Several authors (Andermann and Andermann, 1983; Wilkins *et al.*, 1986) have commented on the similarities between familial hyperekplexia and brainstem reticular reflex myoclonus. However, certain clinical and electrophysiological distinctions exist between brainstem reticular reflex myoclonus and hyperekplexia. In the former spontaneous myoclonus continues in between reflex jerks, leading to a different clinical presentation (Hallett *et al.*, 1977; Brown *et al.*, 1991*b*). Stimulus sensitivity is greatest over the limbs, and does not show a mantle distribution (Hallett *et al.*, 1977; Brown *et al.*, 1991*b*). The conduction velocities of the peripheral afferents subserving reticular reflex myoclonus are rapid (Hallett *et al.*, 1977). Although the motor responses in both reticular reflex myoclonus and hyperekplexia arise in the lower brainstem, the conduction velocities in the descending spinal efferent pathways are rapidly conducting in reticular reflex myoclonus (Hallett *et al.*, 1977; Brown *et al.*, 1991*b*), and moderately slowly conducting in hyperekplexia. Finally, in reticular reflex myoclonus the relative latencies of the intrinsic hand and foot muscles are not disproportionately prolonged (Hallett *et al.*, 1977).

The tonic spasms of hyperekplexia

Cases 1, 3, 4, 5 and 6 suffered from a second form of startle phenomenon, quite distinct from the brief startle reflex itself. In addition to the latter, these patients also sometimes experienced a generalized stiffening, lasting a few seconds, either spontaneously or in response to unexpected somaesthetic or acoustic stimuli. During these tonic spasms the patients were unable to take any protective action and, if erect, would fall stiffly to the ground, without losing consciousness. Identical attacks have been previously reported in hereditary (Suhren *et al.*, 1966; Andermann *et al.*, 1980; Morley *et al.*, 1982; Sáenz-Lope *et al.*, 1984) and sporadic (Gastaut and Villeneuve, 1967) hyperekplexia. It is during these tonic attacks that patients suffer the injuries that occur recurrently in hyperekplexia. These tonic episodes are quite different to the brief generalized startle reflexes seen in these patients and occur less frequently than the latter. In Case 5 the tonic response to an unexpected sound was delayed and separate from the earlier startle response. These tonic responses do not resemble the tonic spasms of multiple sclerosis, which are usually painful, unilateral and rarely stimulus sensitive.

The tonic spasms of hyperekplexia do bear certain similarities to the startle epilepsy described by Alajouanine and Gastaut (1955). The latter presents in childhood or adolescence, with tonic spasms. The spasms may last up to 30 ms, with preservation of consciousness, and are elicited by unexpected auditory, visual or somaesthetic stimulation. Bancaud *et al.* (1967), using depth electrodes, correlated the onset of these seizures with a discharging focus in the supplementary motor area of the cortex. The ictal EEG changes may resemble those recorded in Case 3 (Gastaut and Tassinari, 1966). The difficulty in distinguishing hyperekplexia from startle epilepsy is compounded by the frequency of epilepsy in hereditary hyperekplexia (Suhren *et al.*, 1966; Sáenz-Lope *et al.*, 1984), and by the presence of a pathological startle reflex in those patients with startle epilepsy (Bancaud *et al.*, 1975; Giménez-Roldán and Martín, 1979). Indeed the tonic spasms of hyperekplexia and startle epilepsy may be found to share a common

pathophysiology. Until this latter point is resolved the term startle epilepsy is most usefully used to describe those patients, who form at least a clinical entity, with infantile hemiparesis or, rarely, diplegia, in whom tonic spasms are most commonly asymmetric or unilateral (Alajouanine and Gastaut, 1955; Andermann and Andermann, 1986).

In summary, hyperekplexia is characterized by two abnormal forms of response to unexpected auditory, visual and somaesthetic stimuli: the sustained tonic spasm and the briefer pathological startle reflex. It is proposed that the pathological and normal startle reflex are the result of activity in a common reflex centre in the lower brainstem. Afferent inputs may be relayed subcortically or cortically to activate this bulbopontine reflex system, with variable afferent delays. The spinal efferent pathway originating in this lower brainstem centre is characterized by the relatively slow recruitment of caudal muscles, and by disproportionate delays to the intrinsic hand and foot muscles. The efferent system of the normal and pathological startle may be that of the spinobulbospinal reflex, but this remains to be proved.

Our conclusions only apply to the types of startle syndrome we have studied, namely hereditary hyperekplexia and some examples of symptomatic sporadic hyperekplexia. There are other causes of the startle syndrome which do not employ the pathology of a pathologically exaggerated normal startle reflex described in the material presented here. For example, we have encountered several cases of hysterical startle in which the pathways involved were quite different, namely those employed for willed movement (Colebatch *et al.*, 1991). Another pathophysiological mechanism in some cases of the startle syndrome is brainstem reticular reflex myoclonus. Whether other types of symptomatic or idiopathic sporadic startle syndrome are based on a true pathological startle response requires further investigation. Likewise, it would be interesting to study the startles in Gilles de la Tourette disease, and in the various Jumpers described with similar techniques.

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VULNERABILITY OF NERVE FIBRES TO ISCHAEMIA

A QUANTITATIVE LIGHT AND ELECTRON MICROSCOPE STUDY

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SUMMARY

In order to learn more about the vulnerability of nerve fibres to ischaemia, a quantitative study of nerve fibre abnormalities was performed on biopsy specimens of the superficial branch of the peroneal nerve from 26 patients with vasculitic neuropathy: 20 had necrotizing arteritis, 5 a lymphocytic, and 1 a leucocytoclastic vasculitis on nerve and/or muscle biopsy. The density of myelinated fibres ranged from 25 to 7880 per mm^2 ($n = 8470 \pm 706$ (SD)). There was a marked inequality in the density of nerve fibres between the fascicles of individual nerves with a mean coefficient of variation of 41 ± 37 (SD) % versus 7.4 ± 3.0% in controls Loss of myelinated fibres, which was greater for fibres larger than 7 μm in diameter, was more severe than that for unmyelinated axons. Regeneration, which was assessed by the number of clustered axons, decreased when the density of myelinated fibres decreased, suggesting that severe nerve ischaemia precludes axonal regeneration. Wallerian degeneration affected on average 58% (range 5–100%) and segmental demyelination, mainly of the secondary type, on average 1.94% (range 1–10%) of teased fibres. It was concluded that (1) myelinated fibres are more vulnerable to ischaemia than unmyelinated axons; (2) large myelinated fibres are affected before the smaller ones; (3) segmental demyelination is uncommon in this context; (4) severe nerve ischaemia precludes axonal regeneration.

INTRODUCTION

In spite of the rich anastomotic vascular supply of peripheral nerves (Lundborg, 1975; Sunderland, 1978), ischaemic neuropathy is a frequent complication of vasculitis (Moore and Fauci, 1981). It is widely accepted that acute nerve ischaemic results in simultaneous degeneration of axons, with marked asymmetry between or within fascicles (Dyck *et al.*, 1972; Asbury and Johnson, 1978; Kissel *et al.*, 1985; Johnson *et al.*, 1986; Said *et al.*, 1988). These findings have been supported by studies of experimental models of acute nerve ischaemia (Korthals and Wiśniewski, 1975; Mäkitie and Teräväinen, 1977; Hess *et al.*, 1979; Parry and Brown, 1981; Nukada and Dyck, 1984). In some studies, axonal lesions predominated in small myelinated axons (Parry and Brown, 1982). These findings did not fit well with our observations in patients with vasculitic neuropathy. We thus performed a morphometric study of nerve biopsy specimens from patients with vasculitic neuropathy and various degrees of axonal loss, in order to determine the susceptibility of different subpopulations of nerve fibres to ischaemia.

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PATIENTS AND METHODS

Patients and controls

Twenty-six patients, 18 females and 8 males, were included in the study. The mean age of the patients was 61.8 ± 12.6 (range 25–79) yrs Five patients had mononeuritis, 13 had mononeuritis multiplex and 10 had a distal symmetric sensory or sensorimotor polyneuropathy, including 3 patients who had features both of mononeuritis multiplex and of distal symmetric sensorimotor polyneuropathy. One patient had no detectable neuropathy. There was no evidence of other known causes of neuropathy.

A total nerve biopsy of the superficial branch of the peroneal nerve was combined with a biopsy of the peroneus brevis muscle in all patients (Table 1). The nerve specimen was removed at the junction of the lower and middle thirds of the leg under local anaesthesia. In 20 patients the diagnosis of necrotizing arteritis of the type observed in polyarteritis nodosa was established on the presence of necrosis of the wall of small arteries with transmural inflammatory cell infiltration, admixed with polymorphonuclear and lymphocytic cells. Five patients had pure perivascular lymphocytic infiltrates on biopsy. In 1 patient, polymorphonuclear cells with nuclear debris surrounded both arterial and venous walls with necrosis, suggesting the diagnosis of leucocytoclastic vasculitis (Winkelmann, 1980)

Control nerves were obtained from 5 patients with muscular dystrophy (mean age 63.2 ± 2.5 yrs), and the same procedure of nerve and muscle biopsy was used.

Tissue preparation

The nerve specimens were fixed in buffered 3.6% isotonic glutaraldehyde at pH 7.4. After fixation, they were divided into 3 parts. One fragment was embedded in paraffin wax and studied in serial sections stained with haematoxylin and eosin. The second fragment was embedded in Epon after postfixation in osmium tetroxide. Transverse sections (1 μm) were stained with 1% thionin and used for morphometry. Ultrathin sections were prepared with an LKB Ultrotome III and a diamond knife, stained with uranyl acetate and lead citrate and examined in an electron microscope (Siemens Elmiskop CT 150). The third fragment (at least 15 mm long) was osmicated after fixation, macerated in 66% glycerin for 48 h or longer before dissection in pure glycerin. 100 consecutive fibres were isolated and classified according to their morphology into normal fibres; fibres showing segmental abnormalities of the myelin sheath, which include paranodal demyelination, segmental demyelination, and the presence of short intercalated internodes; early stages of wallerian degeneration with continuous rows of large ovoids and balls of myelin debris; late stages of wallerian degeneration with the presence of small amounts of myelin debris and lipid droplets in Schwann cells.

Morphometric procedures

In order to evaluate any asymmetry in density of nerve fibres between fascicles of individual nerves, three different fascicles were selected in each nerve by formal randomization: the surface of the intrafascicular area of each fascicle was measured on photographs taken at low magnification. Fascicles whose cross-sectional area was greater than 0.1 mm^2 were numbered from 1 (upper left in the low power field) to the last (lower right); the first 3 fascicles were chosen when the nerve specimen contained less than 5 fascicles; the first, third and fifth fascicles when more than 5 fascicles were present. The density of myelinated fibres was determined within the whole intrafascicular area. The outer fibre diameter was measured with an objective micrometer at a magnification of ×1250 by the arithmetic mean of long and short axes, on half of the intrafascicular area. In order to evaluate the magnitude of fibre loss, we examined the correlation between the ratio of small to large myelinated fibres and the total density of myelinated fibres; in each nerve, the mean values of each density were used for this purpose

Nerve regeneration was evaluated by measuring the density per mm^2 of fibres forming clusters. These were recognized on light microscopic examination when 2 or more, usually small, myelinated fibres, were packed together and often surrounded by a common Schwann cell process, and sometimes containing myelin debris of the original fibre. The extent of axonal regeneration was evaluated by calculating the ratio of the density of clustered fibres to the total density of myelinated fibres.

The density and the size distribution of unmyelinated axons were assessed on photographs by measuring at least one-third of whole intrafascicular areas and more than 250 unmyelinated axons at a final magnification of ×9000. The respective susceptibility of myelinated and of unmyelinated axons to ischaemia was evaluated

by the correlation between the ratio of unmyelinated axons to myelinated fibres and the cumulated density of myelinated fibres and unmyelinated axons per mm^2.

Statistical analyses

All the values for statistics were treated after transformation into logarithmic values. All analyses were performed by Student's t test and by method of the least squares of linear regression. The results were expressed as r (correlation coefficient) and *P* value (significance level).

RESULTS

General neuropathological findings

Vasculitis, which was found in all cases, was present both in muscle and in nerve specimens in 14 patients, in the nerve specimens only in 7 patients and in the muscle specimens only in 5 patients (Table 1). In 15 out of the 21 patients with lesions of vasa nervorum, only epineurial vessels were affected (fig. 1). Focal lesions were found in 6 fascicles from 4 patients; in 1 fascicle the central fascicular area was affected; in the others a semilunar or wedge-shaped lesion was present (fig. 2). Mild to moderate endoneurial oedema was seen in some instances. We did not observe significantly enlarged axons.

TABLE 1 DETAILS OF PATIENTS*

Case	*Age (yrs)***	*Sex*	*Diagnosis*	*Type of neuropathy*	*Vascular lesion*	
					Muscle	*Nerve*
1	59	F	V	MM	+	Epi
2	59	F	PAN	MM	+	Epi
3	55	F	PAN	MM	+	Epi
4	73	F	PAN	MM	+	−
5	53	F	V	No neuropathy	−	Epi
6	62	F	PAN	MM	+	Epi
7	58	F	PAN	DSSN	+	Epi
8	55	M	LCV	MM	+	Epi, peri
9	74	F	PAN	MM	+	−
10	43	F	PAN	DSSN	+	Epi, peri
11	70	F	PAN	MM+DSSMN	−	Epi, peri
12	52	M	PAN	MM	+	Epi
13	57	F	PAN	M	+	Epi
14	49	F	PAN	MM	+	−
15	75	F	PAN	MM	+	Epi
16	76	M	PAN	M+DSSMN	+	Epi, peri
17	62	F	PAN	MM	+	Epi, peri
18	67	F	PAN	MM+DSSMN	−	Epi
19	25	F	PAN	DSSN	−	Epi
20	76	M	PAN	DSSMN	+	Epi
21	72	M	V	M	+	Epi, peri
22	48	M	PAN	DSSMN	+	−
23	70	M	PAN	M	−	Epi
24	76	M	PAN	DSSMN	+	−
25	79	F	V	M	−	Epi
26	62	F	V	DSSN	−	Epi

* V = lymphocytic vasculitis, PAN = polyarteritis nodosa; LCV = leucocytoclasis vasculitis, M = mononeuritis; MM = mononeuritis multiplex, DSS(M)N = distal symmetric sensory/sensorimotor neuropathy; + = present, − = absent, epi = present in the epineurium, peri = present in the perineurium ** Mean age 61.8 ± 12.6 yrs

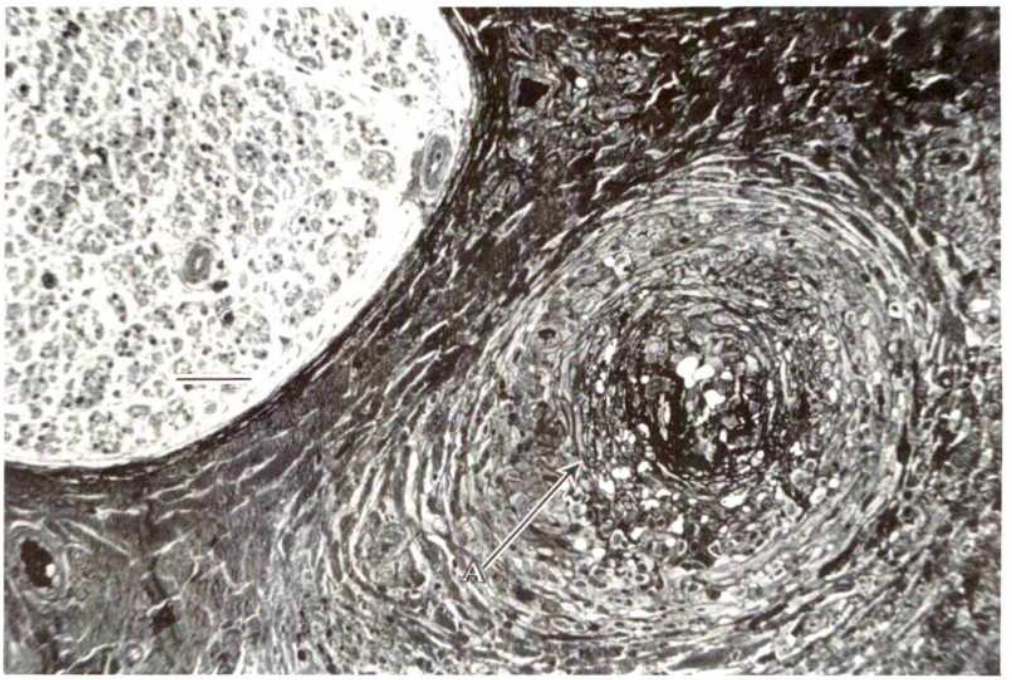

FIG. 1. Necrotizing arteries of an epineurial artery (A) associated with complete loss of myelinated fibres in *Case 18*. 1 μm section, thionin stain. Bar = 50 μm.

Teased fibre studies

Thirty-five fascicles from the 26 patients were studied (Table 2). Three patients presented no abnormality of isolated fibres. In 31 fascicles from 23 patients, wallerian degeneration affected an average of 58.1% of myelinated fibres (range 5–100%); segmental abnormalities of the myelin sheath were mainly of the secondary type, with segmental and paranodal demyelination clustered on individual fibres. They were observed in 1.94% of myelinated fibres (range 1–10%) in 19 fascicles out of 31. Substantial differences in the incidence of degenerating fibres between 2 fascicles of the same nerve specimen were observed in Cases 3, 10 and 20.

Duration of the neuropathy

Although the clinical onset of the neuropathy had been fairly clearly defined in most patients, the age of the lesions of degenerating isolated fibres did not always fit with the apparent duration of the neuropathy. For example, (1) fibres at an early stage of wallerian degeneration were isolated from nerve specimens of 9 patients sampled more than 3 wks or more after the first symptoms of neuropathy; (2) degenerating fibres were still present more than a year after the initial symptoms in 2 patients; and (3) fibres at a late stage of wallerian degeneration were found in nerve specimens of 4 patients with a neuropathy of 2 wks duration or less. Numerous clusters of regenerating myelinated fibres were seen in 3 specimens from patients with a history of neuropathy of less than

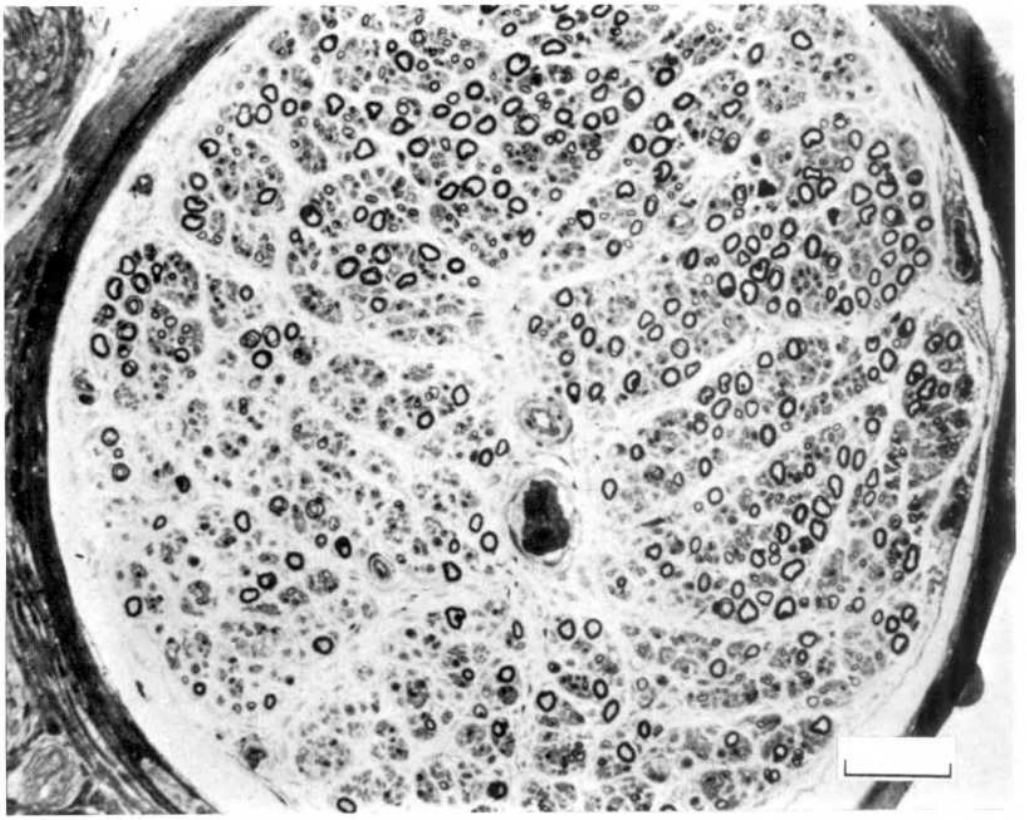

FIG. 2. Nonuniform fibre loss within a fascicle (*Case 10*). 1 μm section, thionin stain. Bar = 50 μm.

4 wks duration. In Cases 13, 22 and 23, all the isolated fibres seemed at the same stage of wallerian degeneration.

Myelinated fibres (figs 3, 4)

The density of myelinated fibres per mm^2 was 8470 ± 706 (SD) in controls. The point of separation between small and large myelinated fibres fell at 7.0 μm. The densities of small and large myelinated fibres per mm^2 were 6190 ± 758 and 2280 ± 512, respectively. In the patients, the density of myelinated fibres varied from 25 to 7910 per mm^2, with large differences between the fascicles of individual nerves. The mean coefficient of variation in each nerve was $41 \pm 37\%$ (SD), versus $7.4 \pm 3.0\%$ in controls. The ratio of small to large myelinated fibres showed a significant negative correlation with the total density of myelinated fibres ($r = -0.566$, $P < 0.005$), indicating that axon loss predominated on larger fibres when total density of myelinated fibres decreased (fig. 4, Table 3).

Clusters of regenerating myelinated fibres were present in nearly all the fascicles studied (Table 4) and their incidence in the different fascicles was positively correlated with the total density of myelinated fibres ($r = 0.840$, $P < 0.001$) (fig. 5).

TABLE 2. RESULTS OF TEASED FIBRE STUDIES*

Case	Duration (wks)	Normal	Demyelination/ remyelination	Wallerian degeneration	
				Early stage	Late stage
1	1	4	10	66	20
		4	0	4	92
2	1	5	0	0	95
3	1	2	0	0	98
		22	1	0	77
4	2	25	4	8	63
5	–	99	0	1	0
6	3	34	3	0	63
7	3	13	0	87	0
8	4	78	3	9	10
9	4	20	3	0	77
10	4	10	3	0	87
		92	2	0	6
11	6	21	5	2	72
12	6	3	4	62	31
13	6	2	0	0	98
		4	1	0	95
14	8	10	0	90	0
15	8	8	1	0	91
16	12	65	0	2	33
17	14	5	2	60	33
		6	2	72	20
18	16	0	0	0	100
19	16	100	0	0	0
20	16	35	0	3	62
		5	2	0	93
21	20	92	3	5	0
22	26	54	0	0	46
		72	3	0	25
23	34	88	0	0	12
		86	0	0	14
24	52	47	4	0	49
25	208	76	6	0	18
26	?	99	1	0	0
		98	2	0	0
Mean ± SD:			1.94 ± 1.89%	58.1 ± 36.0%	

* 100 consecutive myelinated fibres were isolated and categorized according to their morphology. In Cases 1, 3, 10, 13, 17, 20, 22, 23 and 26, the incidence of degenerating fibres was compared between two contiguous fascicles. Duration = time elapsed between the first symptoms of neuropathy and performance of the nerve biopsy.

Unmyelinated axons (figs 3, 6, 7)

The density of unmyelinated fibres per mm^2 of intrafascicular area was 35 700 ± 4700 (SD) in controls; their median size was between 0.6 and 0.8 μm. Fifteen out of the 26 patients were evaluated by electron microscopic examination for the unmyelinated axons; in the specimens from Cases 11, 12, 15, 18 and 20, the density of unmyelinated axons was below 10 000 per mm^2. In addition, it was sometimes difficult to differentiate unmyelinated axon sprouts from Schwann cell processes. However, the increased proportion of unmyelinated axons smaller than 0.8 μm diameter observed in such cases may reflect the presence of axon sprouts (fig. 3 Table 4).

The relationship between alterations of myelinated fibres and unmyelinated axons was analysed in 15 patients. The ratio of unmyelinated to myelinated axons was significantly

correlated with the cumulated density of myelinated and unmyelinated axons ($r = -0.619$, $P < 0.02$), showing that loss of myelinated fibres were more marked than that of unmyelinated axons when the cumulated density of fibres decreased (fig. 7).

DISCUSSION

In ischaemic neuropathies, the distribution of nerve damage has been well studied in human (Dyck *et al.*, 1972; Kissel *et al.*, 1985) and in experimental conditions (Korthals *et al.*, 1975; Parry and Brown, 1981, 1982). In humans, the regions the most susceptible

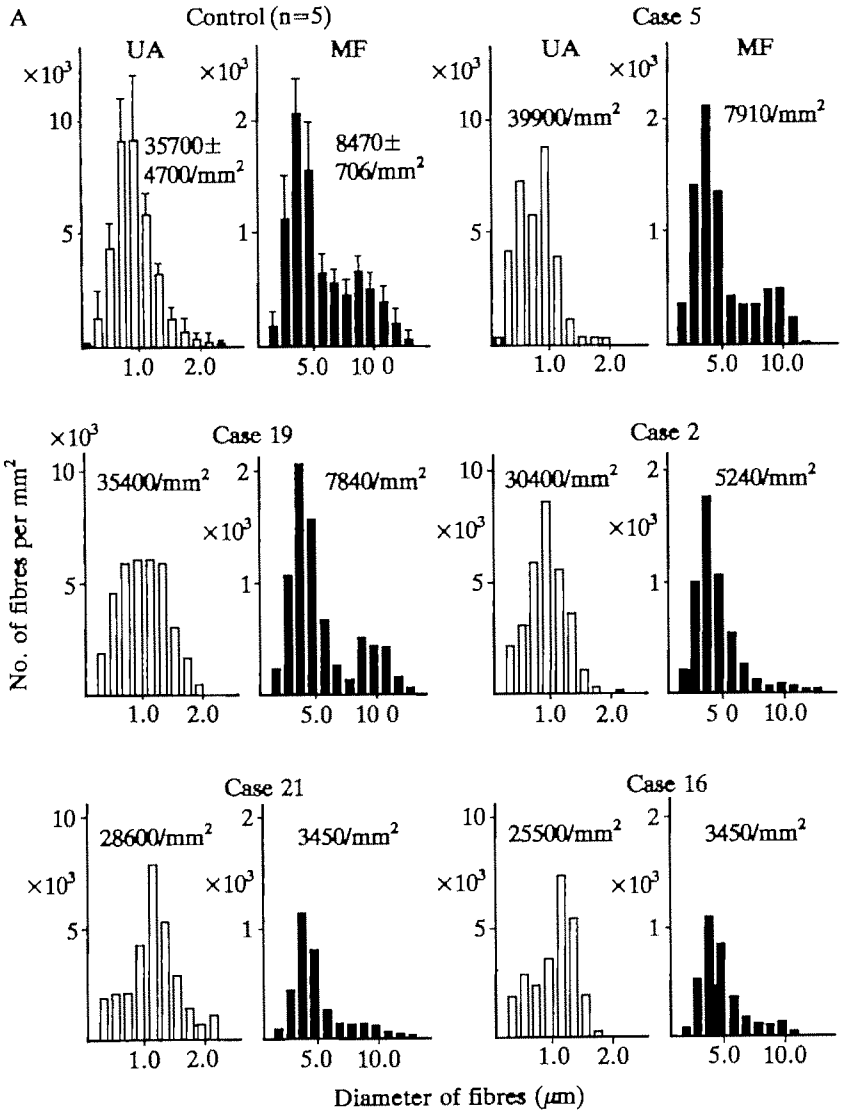

FIG 3A.

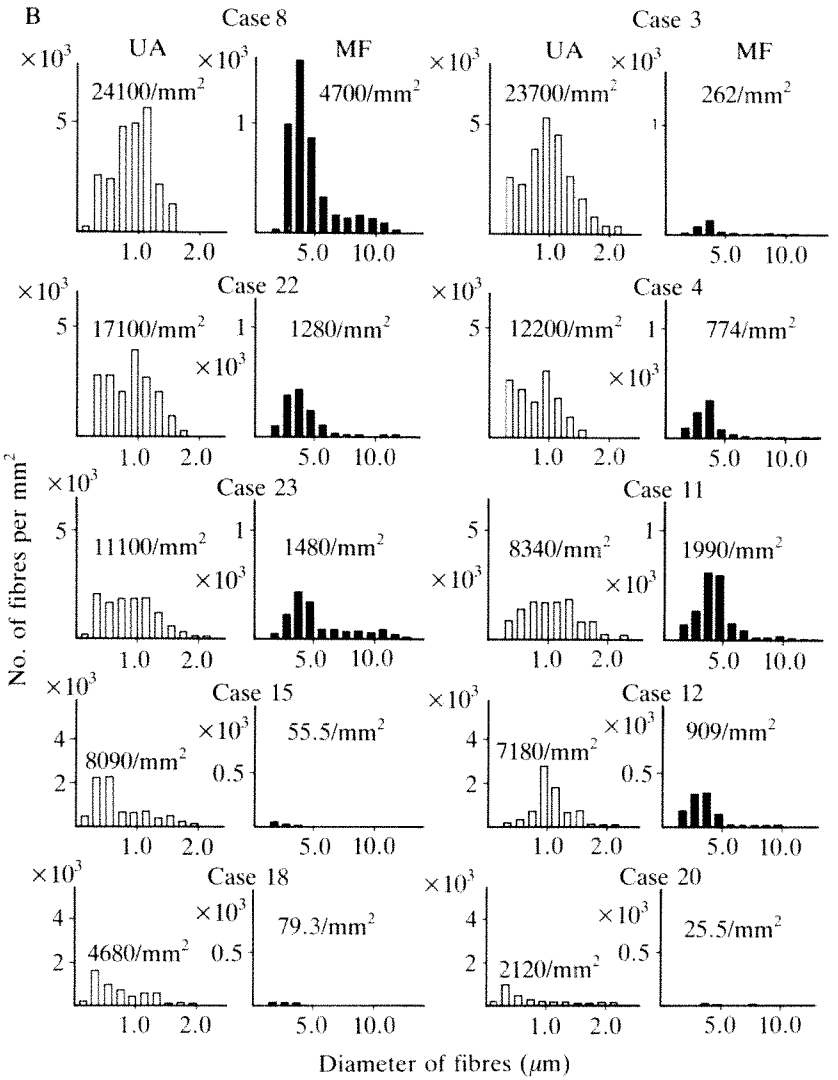

FIG. 3. A, B, histograms of myelinated fibres and unmyelinated axons in patients and controls. Each column of the histograms represents the mean value for 3 fascicles. There is a greater loss of myelinated fibres, especially the larger, than of unmyelinated axons.

to ischaemia lie in the upper arm and at midthigh, where central fascicular necrotic lesions are admixed with spared fascicles, while nerve abnormalities tend to be more diffuse and homogeneous distally. In our observations, even when marked asymmetry of fibre loss between and within fascicles was found, none of the fascicles was spared. Teased fibre preparations revealed massive axonal degeneration with fibres at different stages of wallerian degeneration in most cases. The presence of fibres at different stages of wallerian degeneration in some specimens suggests that the abnormalities found in

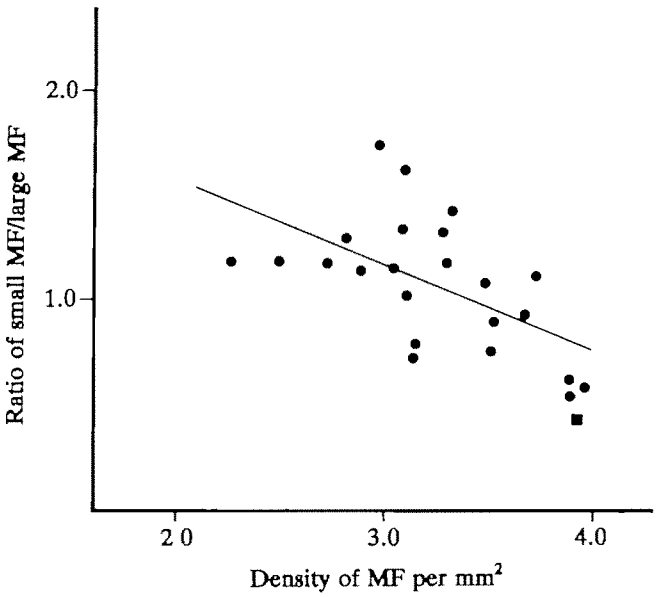

FIG. 4. Fibre depletion of subpopulations of myelinated fibres (MF) was examined by the correlation between the ratio of small to large myelinated fibres and total density of myelinated fibres. A greater degree of depletion in large than in small myelinated fibres was demonstrated ($P < 0\ 005$). The values for both axes are log transformations. Filled Square = mean value for controls.

nerve biopsy specimens result from the summation of lesions of different age (Asbury and Johnson, 1978) spread along the nerve length, rather than from a single, acute, lesion. In other nerve specimens however, the vast majority of nerve fibres were at the same stage of wallerian degeneration, which fits well with acute nerve ischaemia. The increased number of clusters of regenerating myelinated fibres often admixed with fibres at an early stage of axonal degeneration also favours this opinion. In experimental models, such clusters of regenerating fibres have been identified in the necrotic zone 3–10 wks after the ischaemic procedure (Korthals and Wiśniewski, 1975; Hess *et al.*, 1979; Nukada and Dyck, 1984). It is also important to note that a predominantly demyelinative neuropathy is virtually never induced by nerve ischaemia.

We have found that large myelinated fibres were more vulnerable to ischaemia than the smaller ones, as already observed, to a lesser degree, however, in chronic occlusive arterial disease (Garven *et al.*, 1962). Conversely, different studies of acute or transient ischaemia found equal (Ohnishi *et al.*, 1975; Mäkitie and Teräväinen, 1977; Hess *et al.*, 1979) or variable vulnerability (Vital and Vital, 1985) of different types of fibres. Selective lesions of small myelinated fibres have been observed in only one study (Parry and Brown, 1982). All these studies have been performed on a small number of cases, mostly by comparison of the pattern of the histograms of diameters. In addition, axonal swelling present at the acute phase of nerve degeneration after ischaemia may induce a bias in morphometric studies (Korthals and Wiśniewski, 1975). We explored the possibility that greater depletion in large myelinated fibres could be related to an increased

TABLE 3 MORPHOMETRIC STUDIES*

Controls	*MF*	*CV*	*SMF*	*LMF*	*S/L*
Mean ± SD	8470 ± 507	7.4 ± 3.0	6170 ± 758	2300 ± 512	2 68 ± 0 90
Range	7600–9670	5 0–11 4	4970–7010	1710–2970	1 67–3 81
Case					
1	1240	15 5	1180	55 7	21.2
2	5240	19 3	4850	382	12.7
3	262	79.9	236	26 5	8 9
4	774	72.2	744	30.8	24 2
5	7910	7.1	6280	1630	3 9
6	1910	56.8	1830	83 1	22 0
7	3190	10 1	2900	282	10 3
8	4700	16 6	4240	505	8 4
9	1370	35.4	1250	118	10.6
10	1830	87.3	1560	264	5.9
11	1990	29.1	1880	113	16 6
12	909	2 8	897	12.8	70 1
13	538	23 2	498	39.9	12 5
14	2200	17 7	2120	84 4	25 1
15	55 5	57 9	55 5	0	–
16	3450	15 6	3060	389	7 9
17	335	32.7	311	23.2	13.4
18	25 5	147.0	25.5	0	–
19	7840	2.8	6100	1740	3 5
20	79.3	93.7	79.3	0	–
21	3450	13 5	2930	516	5 7
22	1280	14 4	1240	31 6	39.2
23	1480	43 7	1190	287	4.2
24	812	31.3	757	54 7	13 8
25	668	21.7	634	33.5	18 9
26	9310	–	7320	1990	3 7

* MF = density of myelinated fibres/mm^2 of endoneurial area; CV = coefficient of variation of the density of myelinated fibres between three fascicles of the same nerve, LMF = myelinated fibres larger than 7 μm diameter; SMF = myelinated fibres smaller than 7 μm diameter, S/L = ratio of small to large myelinated fibres.

number of regenerating small myelinated fibres (Schröder, 1975), but found it unlikely after approximation of the original density of small myelinated fibres by the regression line of the ratio of small to large myelinated fibres.

There was no selective susceptibility of the different subclasses of unmyelinated axons in our study, although a relative increase in unmyelinated axons smaller than 0.8 μm diameter was present in some cases (Behse *et al.*, 1975; Hess *et al.*, 1979; Pagès and Pagès, 1984), which did not result from a more extensive regeneration of unmyelinated axons as compared with myelinated fibres.

Quantitation of clusters of myelinated fibres provided a useful approximation of the total extent of the intensity of the regenerating process (Schröder, 1975). This method showed that intense nerve ischaemia may preclude the regenerative process, perhaps by destroying Schwann cells necessary to guide axon sprouts.

Teased fibre studies confirmed that axonal degeneration was much more common than segmental demyelination in ischaemic neuropathy (Conn and Dyck, 1984; Vital and Vital, 1985). When segmental demyelination occurs, demyelinated internodes are usually clustered on individual fibres suggesting that demyelination is secondary to axonal lesions (Dyck *et al.*, 1971; Said and Landrieu, 1978).

TABLE 4 MORPHOMETRIC STUDIES*

Controls	*Clusters*	*UA*	*U/M*
Mean ± SD	18.6 ± 13 4	35 700 ± 4700	4.17 ± 0 35
Range	6.1 − 35 6	31 780 − 40 870	3 93 − 4.58
Case			
1	37.4	nd	nd
2	211.8	30 400	5.80
3	11.1	23 700	90.46
4	12.0	12 200	15.76
5	57.6	39 900	5.06
6	41 2	nd	nd
7	40.6	nd	nd
8	43.9	24 100	5.13
9	68.3	nd	nd
10	38 7	nd	nd
11	24 5	8340	4.19
12	37 0	7180	7.90
13	17 7	nd	nd
14	42 4	nd	nd
15	5.4	8090	145.77
16	86 4	25 500	7.39
17	11 0	nd	nd
18	7 6	2120	25.50
19	36.2	35 400	4.52
20	7.2	4680	59.02
21	98.7	28 600	8.29
22	71.0	17 100	13.36
23	29.1	11 100	7.50
24	39 6	nd	nd
25	33 5	nd	nd
26	84 0	nd	nd

* Clusters = density of clustered myelinated fibres, UA = density of unmyelinated axons/mm^2 of endoneurial area; U/M = ratio of unmyelinated to myelinated axons/mm^2 of endoneurial area; nd = not done. All values are mean values obtained from three fascicles from each nerve specimen.

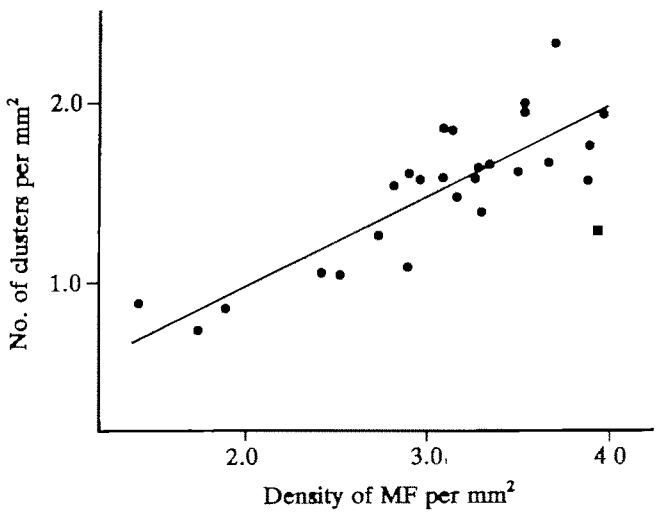

FIG. 5. Percentage number of clusters of regenerating myelinated fibres (MF) was correlated with the total density of myelinated fibres ($P < 0\ 001$). Filled square = mean value in controls. The values for both axes are log transformations

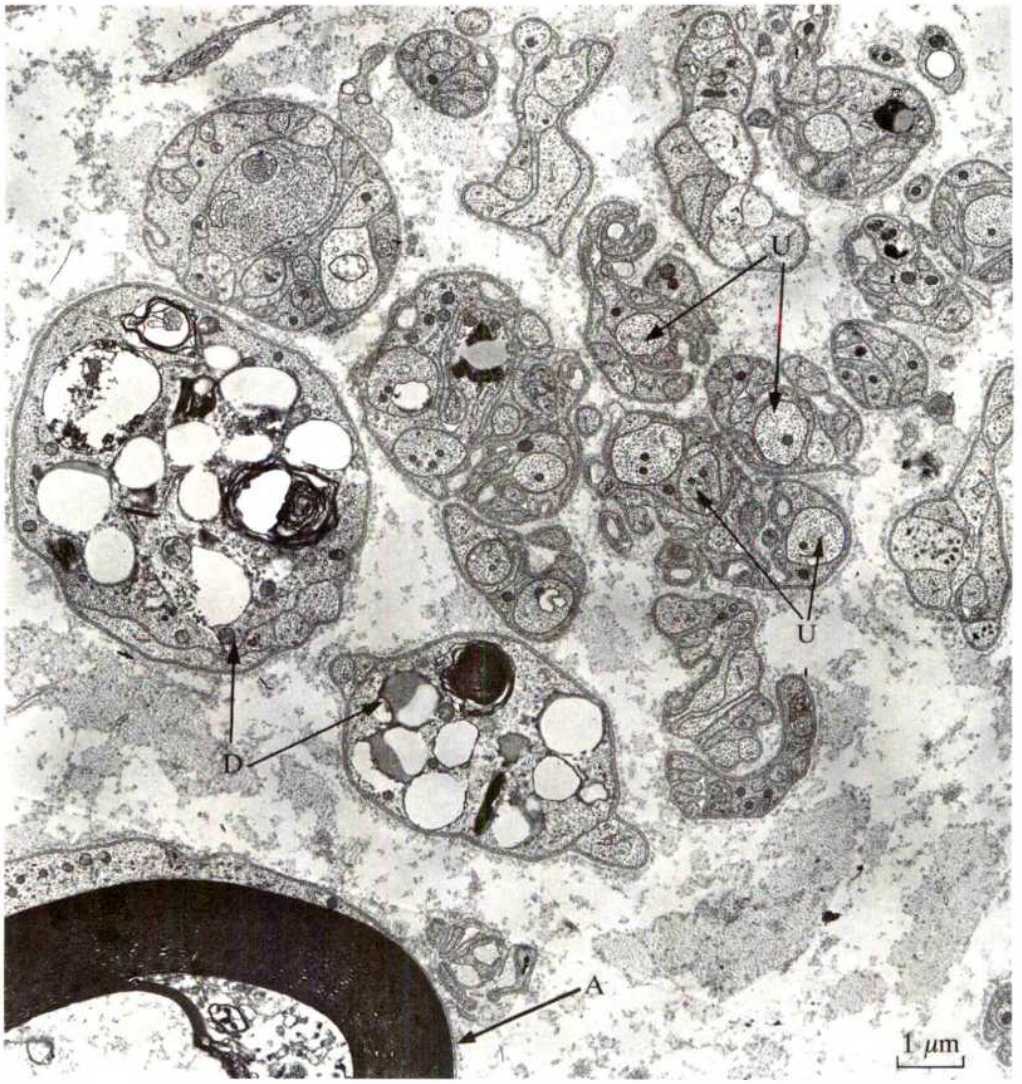

FIG. 6. Electron micrograph of the nerve specimen from *Case 3*, showing degeneration of myelinated fibres with preservation of a number of unmyelinated axons (U) in this area. D = myelin debris corresponding to a late stage of wallerian degeneration in Schwann cells. The myelinated fibre A is also degenerating. Uranyl acetate and lead citrate. Bar = 1 μm.

In conclusion, ischaemic nerve lesions observed in vasculitic neuropathy are characterized by inequality of fibre loss between and within nerve fascicles. Fibre loss, which predominates for large myelinated fibres, is likely to result in many cases from multiple lesions of different age spread along the nerves. The unmyelinated axons are affected in the most damaged nerves. Occlusion of vasa nervorum induces axonal degeneration of the majority of nerve fibres with little or no segmental demyelination.

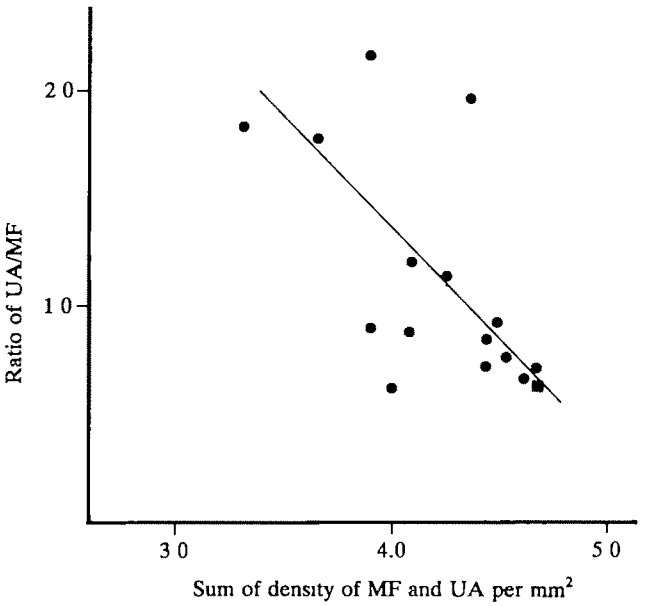

FIG 7 The different degree of fibre depletion in myelinated fibres (MF) and unmyelinated axons (UA) was examined by the correlation between the ratio of unmyelinated axons to myelinated fibres and the cumulative density of myelinated and unmyelinated axons. A greater depletion in myelinated fibres than in unmyelinated axons was demonstrated ($P < 0\ 02$).The numbers on both axes are log transformation Filled square = mean value in controls

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THROUGH A LOOKING GLASS. A NEW TECHNIQUE TO DEMONSTRATE DIRECTIONAL HYPOKINESIA IN UNILATERAL NEGLECT

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SUMMARY

A line cancellation task was performed by right brain-damaged patients with neglect in two response conditions. The task was presented either in normal view or through a 90° angle mirror with direct view prevented. The latter decouples the direction of visual attention and of arm movement. In the mirror condition, 4 of 18 patients cancelled lines only in right hemispace which means that they directed their visual attention to the left but failed to execute movements towards contralateral hemispace—what has been termed directional hypokinesia. In contrast, 10 patients cancelled lines only in left hemispace in the mirror condition, which accords better with attention-representation deficit hypotheses. Our results support a division of the neglect syndrome according to whether perceptual or premotor deficits are predominant

INTRODUCTION

Unilateral spatial neglect designates a condition where brain-damaged patients fail to respond normally to stimuli on the side opposite to the lesion. Severe unilateral neglect is most common after right parietal injury (De Renzi, 1982; Heilman *et al.*, 1983). The condition is commonly regarded as heterogeneous, but partition has proved difficult. Several recent studies, however, have attempted to differentiate between intentional and attentional-representational deficits. The former concerns processes closer to the output side, premotor, and is described by the directional hypokinesia (DH) hypothesis, according to which subjects with neglect are impaired in the initiation or execution of movements into contralateral hemispace (Watson *et al.*, 1978). Heilman *et al.* (1985) demonstrated that right brain-damaged (RBD) patients with hemispatial neglect initiated responses toward left hemispace slower than toward right hemispace. Also, subjects with neglect generate hypometric saccades when they attempt to direct their gaze into the neglected hemispace (Heilman *et al.*, 1980; Girotti *et al.*, 1983).

Attentional and representational hypotheses describe deficits closer to perception. According to the representational hypothesis the neglect syndrome is due to degradation of an inner (sensory) representation of hemispace (Bisiach *et al.*, 1979). Neglect may alternatively be due to an impaired ability to attend to stimuli in contralateral hemispace or to the contralateral side of an internal representation (Heilman and Valenstein, 1979).

Several experiments have been designed to demonstrate directional hypokinesia. On a line bisection task RBD patients showed more neglect in a 'motor' condition where the subjects marked the midpoint of a line than in a 'perceptual' condition where the

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examiner moved the tip of a pen along the line and the patient stated when the midpoint was reached (Reuter-Lorenz and Posner, 1990).

A different paradigm was used by Coslett *et al.* (1990), who tested 4 subjects with neglect on a line bisection task where direct view was prevented and the lines were instead seen on a video monitor positioned in left or right hemispace. This means that they disconnected the side of hand performance and the side to which visual attention was directed. The authors concluded that their data supported both the directional hypokinesia and the representational-attentional theories. However, as pointed out by Bisiach *et al.* (1990), they did not decouple arm movement and the direction of the image on the video monitor. Their results may therefore reflect differences in visual and somatosensory representation of space rather than in perceptual and premotor processes.

In order to decouple the direction of a visual stimulus and the direction of hand movement, Bisiach *et al.* (1990) used a line bisection task, where the midpoint was indicated by a pointer, which could be made to move in the same or in the opposite direction to that of the patient's hand. The authors claimed that their results 'demonstrate that the perceptual/premotor dichotomy of unilateral neglect exists'.

In the present investigation, arm movement and direction of visual attention were also decoupled, but we used a different experimental design and a cancellation task instead of line bisection. The advantage of our design is that there is no spatial cueing, which was a confounding factor with the line bisection tasks described above.

METHODS

Subjects

The study comprised a continuous series of 18 RBD patients with unilateral neglect, 10 RBD patients without neglect, and 13 left brain-damaged (LBD) patients without neglect. Clinical data for patients with neglect are summarized in Table 1. All patients had unilateral lesions due to cerebrovascular events. They were all right handed. Motor and somatosensory impairment and visual field defects were assessed from a standard procedure (Bisiach *et al.*, 1986). The presence of neglect was determined from a random letter cancellation test (Weintraub and Mesulam, 1987), line bisection, and a reading task. Line bisection was assessed by presenting 2 mm wide black lines, ranging in length from 25 to 200 mm, on separate sheets of white paper; data from 200 mm lines are shown in Table 1. Neglect dyslexia was tested with 10 sentences of 4 words each, presented one at a time; the number of sentences with neglect omissions is shown in Table 1.

Mean age of the groups were: RBD with neglect 61.6 ± 15.7 y, RBD without neglect 67.9 ± 8.4 y, and LBD 64.3 ± 11.7 y (mean $\pm$ SD).

Patients without neglect had distinct neurological deficits in the form of aphasia, visual field defect, hemiparesis, and sensory loss. They were examined 4–28 days after their stroke.

Cancellation test

A version of Albert's test was used with 40 lines (25 mm long, 0.5 mm wide) scattered pseudorandomly on a 297×210 mm sheet of white paper (Albert, 1973). The 4 central lines are not included in the data presentation. Two response conditions were used, both with the central lines positioned in the sagittal midplane of the subject's trunk. First, the cancellation task was performed with normal viewing, with a viewing distance of about 50 cm. Next, the sheet of paper was positioned between the patient and a 90° angle mirror made of 2 mirrors of 45×22 cm each (fig. 1). The viewing distance was about 65 cm. Direct view was precluded by placing the sheet of paper beneath a wooden bench. The lateral ends of the mirrors were covered with white cardboard so that only the midline image of the cancellation task was visible. RBD patients used the right arm, while all but 1 LBD patient used the left arm The same

TABLE 1 AGE, SEX, AND CLINICAL DATA OF PATIENTS WITH UNILATERAL NEGLECT

Case	Age (y)/sex	Lesion, duration poststroke	VFD	P	S	Neglect test R	CA	LB
1	50, F	PT, 12 d	+	+	+	10/10	49/60	25
2	54, M	FPTD, 17 d	+	+	+	ND	59/60	5
3	61, M	FPT, 8 d	+	+	+	0/10	53/60	9
4	74, M	PT, 11 d	+	+	+	ND	31/60	55
5	45, M	0, 9 d	+	−	−	9/10	53/60	71
6	51, F	PTD, 22 d	+	+	+	7/10	55/60	3
7	82, M	O, 8 d	+	−	−	0/10	4/60	36
8	73, F	FPT, 9 d	−	+	+	0/10	26/60	ND
9	20, F	FP, 7 d	−	+	+	0/10	23/60	3
10	75, F	D, 15 d	−	+	+	6/10	54/60	12
11	62, F	PD, 12 d	−	−	−	ND	34/60	51
12	49, M	FPTD, 20 d	+	+	+	0/10	34/60	7
13	76, M	FPT, 40 d	+	+	+	7/10	ND	23
14	74, M	PT, 74 d	+	+	+	10/10	ND	78
15	78, M	PT, 16 d	+	+	+	5/10	ND	30
16	67, M	O, 10 d	+	+	+	ND	16/60	61
17	69, M	P, 10 d	+	−	+	7/10	ND	65
18	67, F	D, 17 d	−	+	+	4/10	ND	32

F = frontal, P = parietal; T = temporal, O = occipital, D = deep, VFD = visual field defect; P = hemiparesis, S = sensory loss; R = number of errors on reading test, CA = number of omissions on letter cancellation test, LB = rightward error (in mm) on bisection of 200 mm line, ND = not done

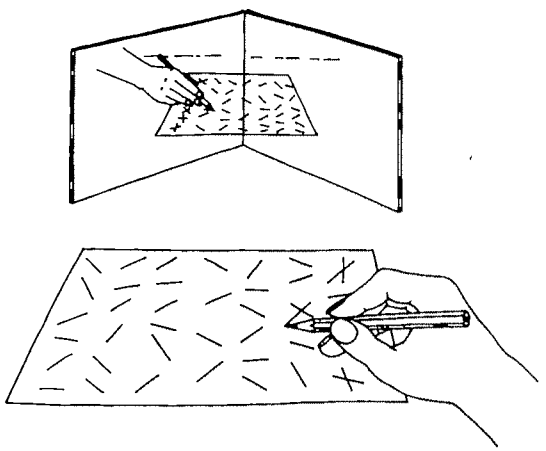

FIG. 1. Cancellation task in mirror view condition

instruction was used with both response conditions: 'Mark all lines that you see one at a time'. No time limit was used If the subject paused for more than 15 s, he was asked if he had finished the task. If he answered 'no' he was allowed to continue, if 'yes' he was asked if he was aware of any lines that were left unmarked.

Eight patients with neglect were reexamined with an interval of 4–7 days, and Case 5 was examined repeatedly up to 4 months poststroke.

The choice of a cancellation task instead of line bisection was partly based on the limitations of the experimental instrument: (1) it would only be possible to present lines in either hemispace and not in the midline position, (2) only lines of less than about 100 mm could be used, and (3) it requires good motor performance so that few patients would be available for examination.

RESULTS

During normal presentation, 12 of 18 patients with neglect omitted left-sided lines (Table 2). The number of omissions increased markedly in the mirror view condition where the minimum number of omissions on first examination was 10 of 36 lines.

TABLE 2 NUMBER OF LINES CANCELLED BY NEGLECT PATIENTS

	Normal view		*Mirror view*	
Case	*L*	*R*	*L*	*R*
1a	0	14	16	3
1b	18	18	16	6
2a	0	18	0	6
2b	7	18	0	5
3a*	0	18	2	5
3b	0	18	6	17
3c	0	17	11	13
4	17	18	5	0
5a	0	14	3	0
5b	0	12	5	0
5c	10	17	13	0
5d	18	18	18	18
6a	0	17	17	0
6b	15	18	18	3
7	0	18	7	0
8a	18	18	0	8
8b	18	18	0	4
9a	18	18	8	18
9b**	7	30	4	19
10a	0	14	0	10
10b	0	9	0	5
11	17	17	12	1
12*	15	18	0	1
13*	0	17	2	4
14	0	6	2	0
15	18	18	15	0
16	18	18	17	0
17	18	18	5	0
18*	18	18	2	9

L and R refer to actual line position Small letters refer to order of examination within patients. * Cancelled central lines ** Letter cancellation task

Fourteen patients showed a typical neglect behaviour with a vertical boundary between marked and unmarked lines, but with two different patterns. Fig. 2 shows records from 2 of 10 patients who cancelled lines in right hemispace during normal viewing and lines in left hemispace during mirror viewing. This means that they directed their visual attention to the right in both response conditions. This contrasts with the behaviour of 4 patients, who only cancelled lines in right hemispace in both response conditions (fig. 3). Thus in the mirror condition they directed visual attention to the left but made no movement into left hemispace.

Table 2 also shows that no patient changed pattern on repeated examination. Four patients with neglect behaved differently and only cancelled central lines. During normal viewing only 3 patients marked the same line more than once, while during mirror viewing 15 patients showed perseveration (figs 2 and 3).

Patients without neglect omitted fewer lines and the omissions were not lateralized (Table 3). Not shown is that many of these patients performed poorly, drawing many lines beside the targets and sometimes scribbling all over the sheet of paper.

One patient (Case 5) was examined with a line bisection task during mirror viewing. He could only be examined with lines in the right visual hemifield in the mirror view condition. Ten lines of 100 mm were presented for each spatial position and response

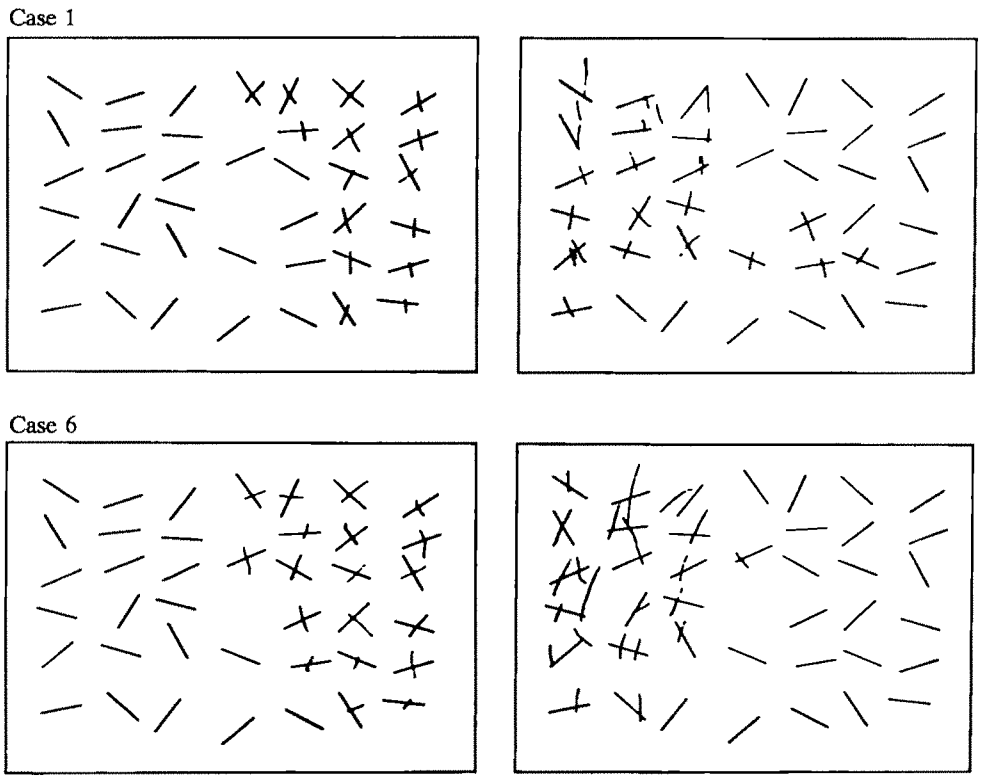

FIG 2. Examples of perceptual neglect Normal view (*left*), mirror view (*right*)

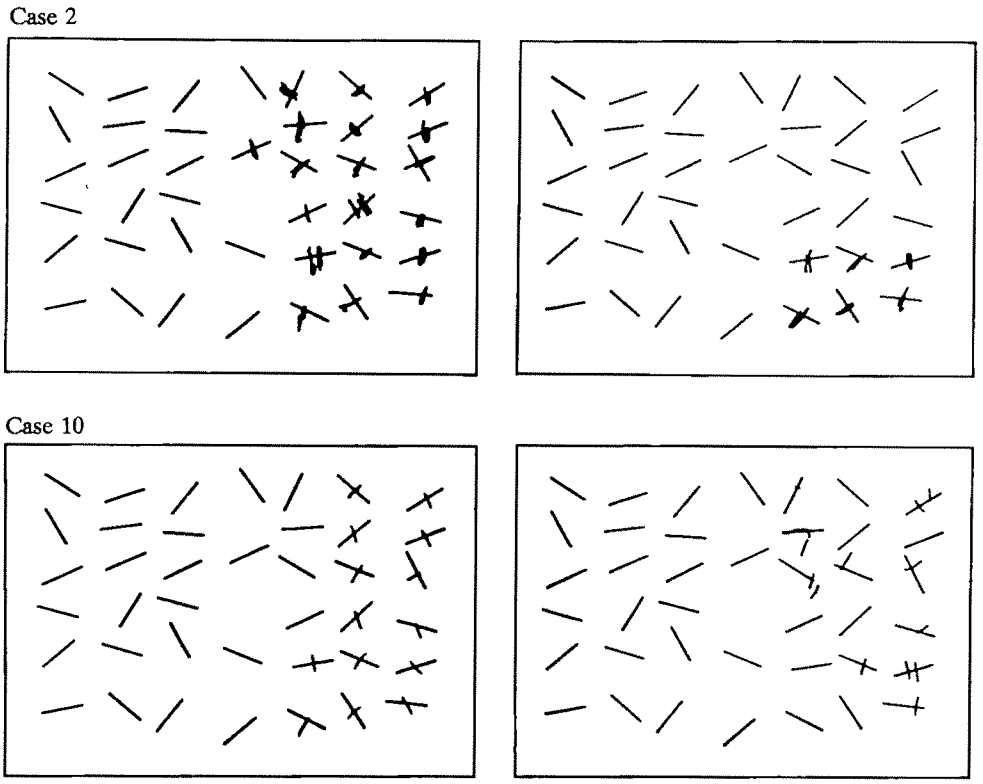

FIG 3. Examples of directional hypokinesia. Normal view (*left*), mirror view (*right*)

condition. The results are shown in Table 4. In the normal view condition he made rightward errors that increased when the line position was shifted leftwards. In the mirror view condition he made a leftward error of the same magnitude as the rightward error in right hemispace during normal viewing. There is thus no indication of directional hypokinesia, since in that case he should also have made a rightward error in mirror viewing and of the same magnitude as in left hemispace during normal viewing.

DISCUSSION

Our results support the directional hypokinesia theory (Watson *et al.*, 1978) in that some patients with neglect were impaired in their ability to make arm movements into left hemispace while they remained fully capable of attending to stimuli in their left visual hemifield. Using different experimental designs, two other studies have reached the same conclusion (Bisiach *et al.*, 1990; Coslett *et al.*, 1990).

Only 4 of 18 patients with neglect showed an unambiguous hypokinetic behaviour but in addition, 4 patients cancelled only central lines which we believe was due to a combination of premotor and perceptual deficits. In the mirror view condition, they directed their gaze to the right while making many futile attempts to move their arm

TABLE 3 NUMBER OF LINES CANCELLED IN MIRROR VIEW BY BRAIN-DAMAGED PATIENTS WITHOUT NEGLECT

	RBD		*LBD*	
Case	*L*	*R*	*L*	*R*
1	18	18	18	18
2	18	18	16	16
3	17	16	18	18
4	14	12	16	18
5	17	18	18	17
6	13	13	17	17
7	18	18	18	18
8	18	18	ND	ND
9	18	18	18	18
10	ND	ND	18	18
11			ND	ND
12			16	16
13			18	18

L and R refer to actual line position ND = task interrupted because of fatigue

TABLE 4 ERRORS (IN mm) ON LINE BISECTION

Position	*Left*	*Middle*	*Right*
Normal condition	+30.0 (1.9)	+28.8 (1 8)	+23 2 (4.3)
Mirror condition	−24 1 (4 8)	—	—

Positive sign denotes rightward error. Mean (SD).

into left hemispace until they managed to mark a few lines close to the midline. Note also that they all cancelled more lines on the right than the left side (Table 2).

Ten patients with neglect performed in accordance with representational-attentional theories. Their visual attention was directed to the right in both response conditions and they showed no difficulties in moving their arm into left hemispace. The possibility remains that (some of) these patients suffered from directional hypokinesia of eye movements but not of arm movements. This cannot be excluded by our experimental paradigm but circumstantial evidence from 3 patients makes it less plausible. On copying a drawing (fig. 4), they omitted the left half of the house while they correctly reproduced the trees on the extreme left (Gainotti *et al.*, 1986). Such a performance seems best explained by a perceptual-representational deficit.

Watson *et al.* (1978) first showed that frontal lesions in monkeys induced intentional neglect. Later Mesulam (1981) proposed that anterior lesions may be associated with intentional neglect while posterior lesions cause attentional-representational deficits. The theory has gained support from two recent studies where directional hypokinesia was associated with anterior lesions (Bisiach *et al.*, 1990; Coslett *et al.*, 1990). Our results also accord with this hypothesis. Out of 6 patients with lesions extending into the frontal lobe, 3 had directional hypokinesia and 3 showed combined perceptual/premotor deficits. Stated otherwise, of 4 patients with directional hypokinesia, 3 had frontal lesions, and 1 had a central lesion. All patients with isolated posterior lesions showed a perceptual pattern; directional hypokinesia in any of these patients would seriously have questioned

FIG 4 *Case 1.* Figure copying with neglect for central objects

the hypothesis. However, our results must be regarded with caution. The material is small, patients with directional hypokinesia tended to have larger lesions and no patients with isolated anterior lesions have been examined. More definite support would require a comparison between patients with isolated anterior and posterior lesions.

Finally, it is of interest that all patients with directional hypokinesia, after having completed the mirror condition, claimed that there were no more lines to cancel. Note that the remaining lines were all within the intact right visual hemifield. Brain-damaged patients without neglect (RBD Cases 4 and 6, and LBD Cases 2 and 12) instead declared that they saw the unmarked lines but that they could not reach them. The finding supports the previous observation that perceptual awareness may depend on response factors (Bisiach *et al.*, 1985). RBD patient correctly identified right visual stimuli when a right motor response was demanded but failed to detect 50% of them when a left motor response was required; moreover they explicitly denied that any stimulus had occurred.

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ALTERATIONS IN THE LEVELS OF IRON, FERRITIN AND OTHER TRACE METALS IN PARKINSON'S DISEASE AND OTHER NEURODEGENERATIVE DISEASES AFFECTING THE BASAL GANGLIA

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SUMMARY

Levels of iron, copper, zinc and manganese were measured by inductively coupled plasma spectroscopy in frozen postmortem brain tissue from patients with Parkinson's disease (PD), progressive supranuclear palsy (PSP), multiple system atrophy with strionigral degeneration (MSA), and Huntington's disease (HD) compared with control subjects. Total iron levels were found to be elevated in the areas of basal ganglia showing pathological change in these disorders. In particular, total iron content was increased in substantia nigra in PD, PSP and MSA, but not in HD. Total iron levels in the striatum (putamen and/or caudate nucleus) were increased in PSP, MSA and HD but not in PD. Total iron levels were decreased in the globus pallidus in PD There were no consistent alterations of manganese levels in basal ganglia structures in any of the diseases studied. Copper levels were decreased in the substantia nigra in PD, and in the cerebellum in PSP, and were elevated in the putamen and possibly substantia nigra in HD. Zinc levels were only increased in PD, in substantia nigra and in caudate nucleus and lateral putamen.

Levels of the iron binding protein ferritin were measured in the same patient groups using a radioimmunoassay technique. Increased iron levels in basal ganglia were generally associated with normal or elevated levels of ferritin immunoreactivity, for example, the substantia nigra in PSP and possibly MSA, and in putamen in MSA. The exception was PD where there was a generalized reduction in brain ferritin immunoreactivity, even in the substantia nigra.

An increase in total iron content appears to be a response to neurodegeneration in affected basal ganglia regions in a number of movement disorders. However, only in PD was there an increased total iron level, decreased ferritin content, decreased copper content, and an increased zinc concentration in substantia nigra. These findings suggest an alteration of iron handling in the substantia nigra in PD. Depending on the form in which the excess iron load exists in nigra in PD, it may contribute to the neurodegenerative process.

INTRODUCTION

The biochemical and pathological consequences of Parkinson's disease (PD), Steele-Richardson-Olszewski disease (progressive supranuclear palsy) (PSP), multiple system

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atrophy (MSA) and Huntington's disease (HD) have been described. All may cause an akinetic-rigid parkinsonian syndrome. The focus of attack in PD is on the pigmented neurons of the substantia nigra pars compacta (SNpc) with resulting striatal dopamine deficiency. In PSP extensive neuronal degeneration of SNpc also occurs but, in addition, pathology affects caudate and putamen, globus pallidus, subthalamic nucleus, brainstem and dentate nucleus. In MSA with strionigral degeneration the SNpc again is affected, but there is additional degeneration in caudate and putamen, as well as in the olives, pons, cerebellum and intermediolateral columns of the spinal cord. In HD the SNpc is less affected but there is profound degeneration of the caudate and putamen.

Little is known about the causes of cell death in these neurodegenerations. In PD there are suggestions that SNpc degeneration is associated with and may be even due to an active toxic process involving reactive oxygen species. Reactive oxygen species cause cell death, in part, by inducing lipid peroxidation. Recently, we demonstrated an increase in basal levels of malondialdehyde, a stable intermediate in lipid peroxidation, in SN in postmortem brain tissue from patients dying with PD (Dexter *et al.*, 1989*a*). This finding has recently been confirmed by the detection of increased levels of lipid hydroperoxides in the SN in PD when compared with tissue from control subjects (T. F. Slater *et al.*, unpublished observations). Such findings are compatible with a free radical attack on SN neurons occurring in PD. They receive further support from the observation in postmortem brain tissue that superoxide dismutase activity in SN is increased in PD (Marttila *et al.*, 1988; Saggu *et al.*, 1989), and by the claim that levels of reduced glutathione in SN are profoundly depleted, without any change in glutathione transferase activity (Perry *et al.*, 1982, 1986; Riederer *et al.*, 1988). These observations are compatible with the concept of toxicity induced by reactive oxygen species, including free radicals, occurring in SN in PD up to the time of death. This concept is supported by the detection of increased neuronal phagocytosis by microglia in the SN of patients dying with PD (McGeer *et al.*, 1989).

Increased levels of reactive oxygen species in SN in PD could arise through a number of different mechanisms. The discovery that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can selectively destroy SNpc to cause a parkinsonian syndrome in man and other primates (Davis *et al.*, 1979; Burns *et al.*, 1983; Langston *et al.*, 1983, 1984) has prompted a search for other environmental toxins. MPTP, via its metabolites $MPDP^+$ and MPP^+, can generate free radicals (Rossetti *et al.*, 1988), although an effect of MPP^+ on complex I of the mitochondrial respiratory chain is viewed as the major cause of nigral cell death (Singer *et al.*, 1987). Alternatively, the metabolism of endogenous dopamine in nigrostriatal neurons gives rise to reactive oxygen species, both via its catabolism and by its oxidation to neuromelanin (Graham *et al.*, 1978; Cohen, 1988). Any increase in the formation of reactive oxygen species might overwhelm protective mechanisms and induce nigral cell death. Similarly, any deficiency in cellular protective mechanisms (such as glutathione peroxidase, catalase, superoxide dismutase, α-tocopherol, ascorbic acid) might induce the same toxic events.

One factor known to stimulate the generation of radical species is free reactive iron. Recently, we and others have demonstrated excess levels of iron in SNpc of patients dying with Parkinson's disease (Earle, 1968; Dexter *et al.*, 1987, 1989*b*; Sofic *et al.*, 1988) although Uitti *et al.* (1989) were unable to find any change in formalin-fixed tissues.

Iron is implicated in many important cellular functions, for example, as part of the

cytochrome complex involved in mitochondrial respiration. However, it also facilitates decomposition of lipid peroxides and the formation of a variety of reactive oxygen species including hydroxyl and superoxide radicals and hydrogen peroxide, which can induce cellular damage (Halliwell and Gutteridge, 1986). Within the brain, relatively little iron is normally present in a free and reactive form. Most is stored as a ferritin-iron complex (Hallgren and Sourander, 1958; Octave *et al.*, 1983). In peripheral tissues it is known that iron modulates the biosynthesis of ferritin through a specific mRNA. Iron levels above the normal requirements for cellular metabolism trigger ferritin synthesis which binds and detoxifies it (Casey *et al.*, 1988). Consequently, in PD the increased iron load in SN may not be toxic if ferritin synthesis is induced. However, we recently observed that ferritin levels measured using a specific antibody to human spleen ferritin were reduced in SN and throughout the parkinsonian brain, but not in cerebrospinal fluid or plasma (Dexter *et al.*, 1990; *but see* Riederer *et al.*, 1988). This might suggest that altered iron handling occurs in PD. The form in which the excess iron is present in brain in PD is not known, but it may be able to stimulate oxidative stress resulting in cell death. The importance of the changes in iron and ferritin levels to the cause of PD depends on whether they are specific to the illness. If they merely reflect a response to neurodegenerative processes, similar changes should be evident in other basal ganglia disorders.

Other divalent trace metals, such as copper and manganese also have prooxidant capabilities (Halliwell, 1984; Halliwell and Gutteridge, 1985). Some are also implicated in neurodegenerative disorders such as copper in Wilson's disease and chronic manganese intoxication in producing parkinsonism. However, other divalent trace metals such as zinc can have antioxidant activity both in vitro and in vivo. Indeed, we previously showed a reduction in copper levels but an increase in zinc levels in substantia nigra in Parkinson's disease. How these changes relate to the disease process or to the alterations in iron levels is not known.

The object of the present study was to investigate the total iron levels (along with copper, zinc and manganese) and ferritin content in a range of basal ganglia disorders affecting SN and to compare them with our previously published data on PD (Dexter *et al.*, 1989*b*, 1990). Postmortem brain tissues have been examined from patients dying with a clinical and pathological diagnosis of PD, MSA and PSP, all of which show pathological changes in the substantia nigra, and in HD where substantia nigra is relatively unaffected.

MATERIAL AND METHODS

Brain tissue from patients dying with PD, PSP and HD and from control patients dying of non-neurological disorders was obtained from the Brain Bank of INSERM-U289, Hôpital de la Salpêtrière, Paris, and from the Parkinson's Disease Society Brain Bank, London. Additional nigral tissue from patients dying of HD was also supplied by Dr Gavin Reynolds, Department of Pathology, Queen's Medical Centre, Nottingham. Details of patients and postmortem procedures are given in Tables 1, 3, 5 and 6 The postmortem tissues used in these studies were obtained from different Brain Banks which used different procedures for brain collection and dissection. As far as possible tissues from patients with neurological disease from an individual Brain Bank were matched with control tissues handled in an identical manner from the same source. The brain areas available from the different Brain Banks, however, were not always identical so that not all brain regions could be analysed for each patient studied. In some cases, both control and patient material were obtained from different Brain Banks and the data obtained are presented in a combined form. However,

separation of the results for tissues from the individual Brain Banks showed an identical pattern of change irrespective of tissue source (data not shown). All samples from control and pathological conditions were run in parallel for each estimation to ensure comparability.

Brain tissue

In London, at autopsy brains were removed and divided midsagittally. One half brain was placed in 10% formol saline for at least 6 wks prior to neuropathological examination. The other half brain was immediately frozen at −20° C and transported on cardice to the Brain Bank. The tissue was frozen at −70° C until assayed. In Paris, the procedure was the same, except that the brainstem was first separated from the rest of the brain less than 2 h after autopsy; one hemisphere of the brain was stored at −70° C until dissection, while the other half brain was used for neuropathological examination. In England and France, the cerebellum, SN (total or zona compacta only), putamen, caudate nucleus, globus pallidus, and the cerebral cortex (Brodmann area 10) were dissected from frozen brains according to the technique previously described (Dexter *et al* , 1989*a*). Samples of each brain area were then stored at −70° C until biochemical assay

In order to minimize trace metal ion contamination during dissection the brain tissue was stored in plastic containers, dissected on a refrigerated platform covered with aluminium foil; brain tissue received minimal handling with metal instruments which were constructed of high quality stainless steel and brains were dissected in a dust-free environment. Also, since brain tissue from the 4 neurodegenerative disorders studied was not obtained from the same Brain Bank metal ion and ferritin analysis was performed on a set of control tissue for each disorder which was dissected under identical conditions

Determination of total iron, copper, manganese and zinc levels in brain tissue

Metal ions were measured in solubilized brain samples using the sensitive technique of inductively coupled plasma spectroscopy. The technique for solubilization and infusion of the samples into the spectrophotometer was scaled down for brain areas from which only small (30−50 mg) samples were available. Reagent volumes used for scaled down samples are shown in brackets after those normally employed.

Individual brain samples (30−50 mg or 100−250 mg) of SN, cerebellum, cerebral cortex (Brodmann area 10), caudate nucleus, putamen and globus pallidus were prepared according to the method of Dexter *et al.* (1989*b*) which involved freeze-drying the frozen tissue for a minimum of 16 h in an Edwards freeze dryer. Among the drying procedures usually used, freeze-drying is the method considered least susceptible to element loss (Smeyers-Verbeke, 1985). Samples were reweighed in order to obtain a dry weight. The tissue was then solubilized by heating the samples at 60° C with 1.0 ml (200 µl) of concentrated sulphuric acid (Spectrograde, BDH, UK). This was followed by the dropwise addition of 400 µl (80 µl) of 30% (w/v) hydrogen peroxide (Spectrograde, BDH, UK) to enhance tissue solubilization and to bleach the sample. The samples were gradually cooled to room temperature and the volume made up to 5 0 ml (1.0 ml) with deionized water.

During the process of tissue solubilization, samples received limited handling with metal instruments and all manipulations were conducted in plastic containers in a dust-free environment in order to minimize trace metal ion contamination. All reagents used were of spectroscopic grade. Tissues from the various neurodegenerative disorders and from controls were prepared for analysis under identical conditions.

Standard solutions of total volume 5.0 ml containing 0.78−25 nmol copper, 0.78−25 nmol maganese, 25−800 nmol iron and 3.125−1000 nmol zinc were prepared in deionized water with the addition of 1.0 ml concentrated sulphuric acid and 400 µl of 30% hydrogen peroxide All solutions, including a reagent blank and standards were then analysed on an ARL inductively coupled plasma (ICP) spectrophotometer. For the larger brain samples a flow rate of 2 0 ml/min was used through a Meinhard nebulizer with a preflush of 20 s. For the scaled down brain samples, however, the small volumes involved were infused into a Meinhard nebulizer by a Gilson peristaltic pump (Sterilin Instruments peristaltic pump tubing, 0.015 ID) at a rate of 200 µl/min. A long preflush time of 120 s was used to allow sufficient flushing of the peristaltic tubing and nebulizer with the sample.

All solutions were measured at detection wavelengths of 259.94 nm for iron, 324 754 nm for copper, 257.61 nm for manganese and 213.856 nm for zinc. Results were expressed as nmol metal ion/g dry weight of human brain The limits of sensitivity for the metal ion analysis was 1.25 nmol per tube for copper, 0.78 nmol per tube for iron, 1.25 nmol per tube for manganese and 1.56 nmol per tube for zinc. The

variability within the assay and between assays were 1.8% and 5.3%, respectively, for copper, 1.9% and 4.8% for iron, 1.5% and 6.4% for manganese and 2.8% and 5.6% for zinc

Determination of ferritin immunoreactivity in brain tissue

Frozen brain tissue (10−30 mg) was suspended in 250 μl of 0.05 M diethylmalonylurea (Prolabo, France) buffer (pH 7.4) containing 2.0 g/l bovine serum albumin (Sigma, France). The tissue was homogenized for up to 10 s using a probe sonicator. Homogenates of brain tissue were then heated at 70−75° C for 10 min in a water bath in order to precipitate some proteins (ferritin being stable under these conditions). Solutions were then centrifuged at 3000 g for 15 min. The supernatant formed containing the soluble ferritin was separated and stored at −70° C until assayed.

Ferritin immunoreactivity levels were measured by a radioimmunoassay (RIA) (Dexter *et al.*, 1990). The assay involved the dilution of the brain extracts in a standard RIA buffer consisting of 0.05 M diethylmalonylurea plus 20 g/l bovine serum albumin (pH 7.4) as follows: cerebellum and cerebral cortex 1:10, caudate nucleus 1:50, globus pallidus, putamen and substantia nigra 1.100. Aliquots (50 μl) of diluted brain extract were incubated with 300 μl of [^{125}I] human spleen ferritin (0 5 kBq per tube) (CIS-Oris, Gif-sur-Yvette, France), along with 100 μl of ferritin antibody (final dilution RIA 1:50 000) at 37° C in a water bath for between 15 and 120 min to ensure that the binding between the ferritin antibody and ferritin (antigen) was in equilibrium. The ferritin antibody used in the RIA assay was raised in rabbits using human spleen ferritin, which is mainly composed of L-isoferritin subunits as the antigen (Dexter *et al.*, 1990).

After incubation, 50 μl of precipitating antiserum (1:20) prepared from donkey serum (Wellcome Ltd, UK) was added. Solutions were again incubated at 37° C for between 15 and 120 min to achieve equilibrium. Immediately 2.0 ml of distilled water was added to all tubes followed by centrifugation at 3500 g for 15 min. The solution was discarded and the radioactivity of the precipitate was measured using a gamma counter.

A standard curve was constructed using solutions of human spleen ferritin dissolved in standard diethylmalonylurea RIA buffer in the concentration range of 5−2000 ng/ml. Aliquots (50 μl) of the standard were substituted for the brain extracts in the RIA to construct a standard curve which was linear between 0.2 and 25 ng/tube.

Results were calculated in terms of percentage of bound [^{125}I] human ferritin. Samples containing either (1) 300 μl of [^{125}I] human ferritin only (total radioactivity) or (2) 300 μl of [^{125}I] human ferritin plus 150 μl of RIA buffer (nonspecific binding) or (3) 300 μl [^{125}I] human ferritin, 100 μl ferritin antibody plus 50 μl RIA buffer (zero ferritin binding) were used to determine the specific binding component.

Results were expressed as ng ferritin/mg of tissue. The limit of sensitivity of the ferritin assay was 125 pg ferritin per tube and the variability within the assay and between assays were 4.1% and 6.2%, respectively.

Statistics

Control and neurological patient groups were compared statistically using an unpaired two-tailed Student's t test.

RESULTS

Determination of metal ions and ferritin immunoreactivity in control and Parkinson's disease brain

Patient groups. Brain tissue was obtained from 34 control patients, who did not have a neurological or psychiatric illness as a diagnosis in life or as the cause of death, and from 27 PD patients dying from natural causes or complications to the illness. PD was confirmed pathologically by a marked cell loss in the SNpc and the presence of Lewy bodies in the remaining nigral neurons. The control and PD patient groups were closely matched for age and postmortem delay. The only significant difference between the 2 patient groups' characteristics was a marked reduction in caudate nucleus dopamine concentrations found in the PD patients compared with control subjects. Full patient

characteristics and postmortem procedures are given in Table 1. These results were previously presented in Dexter *et al.* (1989*b*, 1990).

Iron levels. In control tissues the basal ganglia (globus pallidus, total SN and SNpc, putamen and caudate nucleus) showed markedly higher (2–3 times) total iron levels when compared with the cerebellum and cerebral cortex. Total iron levels in the cerebellum, putamen, caudate nucleus and cerebral cortex were not different when the control and PD patient groups were compared. In the lateral and medial portions of the globus pallidus total iron levels were found to be reduced by 29% in the PD patient groups when compared with controls (fig. 1A). However, in the SNpc and in the total SN of the PD patients there was a marked increase (by 31% and 35%, respectively) in the total levels of iron when compared with control tissue (fig. 1A).

TABLE 1 CHARACTERISTICS OF CONTROL AND PARKINSON'S DISEASE PATIENT GROUPS AND DETAILS OF POSTMORTEM PROCEDURES

	Control (*n* = 34)	*Parkinsonian* (*n* = 27)
Age (yrs)	75 5±2 7	75 4±1 5
Sex: Female	21	12
Male	13	15
Age of onset of Parkinson's disease (yrs)	–	61.4±2.03
Duration of Parkinson's disease (yrs)	–	14 4±1.8 (1–31)
L-DOPA dosage level at the time of death	–	483 1±56 mg/day (137 5–1375)
Cell loss and presence of Lewy bodies in midbrain	No	Yes
Caudate dopamine concentration (ng/g)	2480±30.3	471±120.7*
Time between death and autopsy (h)	13.0±1 6	17.2±1.7

Values are shown as the mean value ±1 SEM Figures in brackets show range of values Caudate dopamine levels were measured by standard HPLC-ECD techniques (Weller *et al.*, 1987) There were no statistical differences between parameters except for caudate dopamine content * $P < 0$ 05, Student's t test

Copper levels. In normal tissues copper levels, unlike those of iron, were not consistently higher in basal ganglia when compared with the cerebral cortex or cerebellum. In control subjects the highest levels of copper were detected in the total SN, SNpc and cerebellum (Table 2). No difference in copper levels in the cerebral cortex, caudate nucleus, putamen, globus pallidus and cerebellum was found when tissues from PD patients and tissue from controls were compared. However, total copper levels were reduced in the SNpc (by 45%) and in the total SN (by 34%) of PD patients compared with control tissue (Table 2).

Zinc levels. The distribution of zinc in normal brains was the opposite to that for iron, with the cerebellum and cerebral cortex containing higher levels than most areas of the basal ganglia. No differences in total zinc levels were observed between the PD

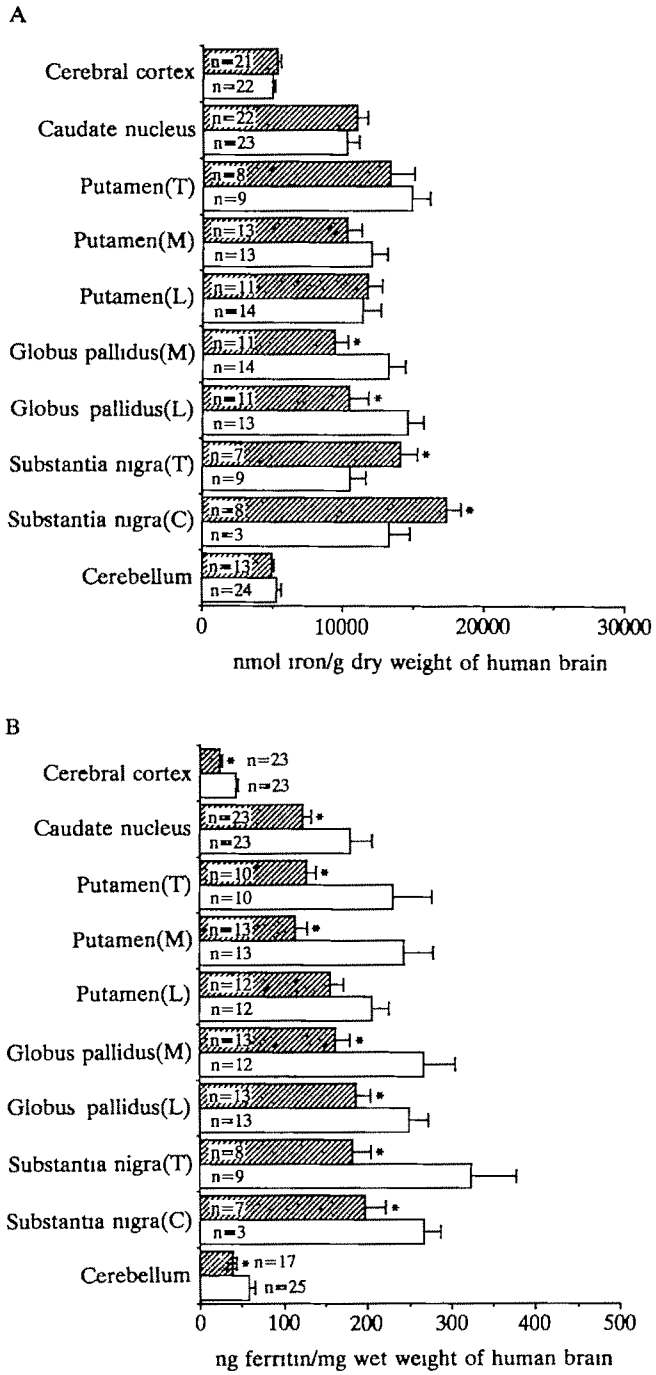

FIG 1. Total levels of (A) iron (nmol/g dry weight), and (B) ferritin immunoreactivity (ng/mg wet weight) in PD and age-matched control human autopsy brains Values represent means ± 1 SEM * $P < 0.05$ compared with controls (Student's t test). C = compacta, L = lateral, M = medial, T = total PD patients (hatched bars), controls (open bars).

and control patients in the medial or total putamen, cerebral cortex, globus pallidus and cerebellar regions of the brain (Table 2). Increases of 54% and 50% in total zinc levels were observed in the PD SNpc and total SN respectively when compared with control patients (Table 2). Total zinc levels were also increased by 35% and 18%, respectively, in the caudate nucleus and lateral putamen in the PD patients when compared with those in control tissue.

TABLE 2. TOTAL LEVELS OF COPPER AND ZINC (nmols/g DRY WEIGHT OF HUMAN BRAIN) IN PD AND AGE-MATCHED CONTROL HUMAN AUTOPSY BRAINS

	Metal ion levels (nmol/g dry weight human brain)			
	Copper		*Zinc*	
Brain region	*Control*	*PD*	*Control*	*PD*
Cerebral cortex	311±27 n = 22	266±20 n = 21	2265±260 n = 22	2150±281 n = 21
Caudate nucleus	393±28 n = 23	358±31 n = 22	1222±55 n = 23	1651±161* n = 22
Putamen (total)	491±62 n = 9	403±40 n = 8	1046±50 n = 9	964±67 n = 8
Putamen (medial)	534±49 n = 13	480±47 n = 13	984±47 n = 13	1052±57 n = 13
Putamen (lateral)	491±27 n = 14	520±47 n = 11	1002±52 n = 14	1184±35* n = 11
Globus pallidus (medial)	391±28 n = 14	306±36 n = 11	814±76 n = 14	785±78 n = 11
Globus pallidus (lateral)	401±29 n = 13	366±24 n = 11	904±56 n = 13	861±38 n = 11
Substantia nigra (total)	655±59 n = 9	435±51* n = 7	956±71 n = 9	1436±210* n = 7
Substantia nigra (compacta)	705±107 n = 3	384±64* n = 8	945±69 n = 3	1456±201* n = 8
Cerebellum	635±64 n = 24	620±57 n = 13	1343±55 n = 24	1504±68 n = 13

Values represent means ±1 SEM. * $P < 0.05$ compared with controls (Student's t test)

Manganese levels. Manganese levels were low in the normal brain; they were higher in the caudate, putamen, globus pallidus and cerebellum than in SN or cerebral cortex. No difference in total manganese levels were observed in the cerebellum, cerebral cortex, SN, globus pallidus, caudate nucleus, total or lateral putamen between the PD and control patient groups (data not shown). However, a decrease of 20% in the manganese levels was observed in the medial putamen in PD when compared with control tissue.

Ferritin immunoreactivity. In control brain the distribution of ferritin immunoreactivity was similar to that of iron, with the basal ganglia nuclei demonstrating higher ferritin immunoreactivity than the cerebellum or cerebral cortex (fig. 1B). However, in all regions (with the possible exception of the lateral portion of the putamen) of the PD brain examined there was a marked reduction (47−75% of control values) in the levels of ferritin immunoreactivity compared with control tissues (fig. 1B). The reduction in ferritin levels was more marked in the total SN and medial portion of the putamen than in other brain regions.

Determination of metal ions and ferritin immunoreactivity in brain tissue from control subjects and those with progressive supranuclear palsy

Patient groups. Brain tissue was obtained from 37 non-neurological controls and from 11 patients dying with a clinical diagnosis of PSP. Subsequently, the clinical diagnosis of PSP was confirmed pathologically by marked cell loss with characteristic neurofibrillary tangles in pallidum, subthalamic nucleus, superior colliculus, peri-aqueductal grey matter, SN and dentate nucleus (Steele *et al.*, 1964).

The mean age of the PSP patient group was lower than that of the control group. This may reflect the poor prognosis of these patients when symptoms of the disease first appear around the age of 55 yrs. The control and PSP patient groups were closely matched for the time between death and autopsy. Full patient characteristics and postmortem procedures are given in Table 3.

TABLE 3 CHARACTERISTICS OF CONTROL AND PROGRESSIVE SUPRANUCLEAR PALSY PATIENT GROUPS AND DETAILS OF POSTMORTEM PROCEDURES

	Control (n = 37)	*Progressive supranuclear palsy (PSP) (n = 11)*
Age (yrs)	81 8±1 3	70.0±2 2*
Sex. Female	23	6
Male	14	5
Cell loss in substantia nigra, globus pallidus and superior colliculus and presence of neurofibrilary tangles in the pallidum, subthalamic nucleus, midbrain and dentate nucleus	No	Yes
Time between death and autopsy (h)	8 5±1 0	11 8±2.0

Values are shown as the mean value ± 1 SEM. Mean age of patients was significantly lower in the progressive supranuclear palsy patient group when compared with controls.
* $P < 0\ 05$ Student's t test.

Iron levels. There was no difference in the total iron levels in the cerebellum, caudate nucleus or cerebral cortex when control and PSP patients were compared (fig. 2A). However, there was a marked increase in the total iron levels in the SNpc (by 70%), and a smaller increase (by 36%) in the putamen of the PSP group when compared with control tissue (fig. 2A).

Copper levels. Total copper levels in the cerebral cortex, caudate nucleus, putamen, SNpc and cerebellum from patients with PSP tended to be lower than those found in control patients. The reduction in copper levels in PSP tissues, however, only reached significance in the cerebellum (Table 4).

Zinc levels. There was no difference in zinc levels in the SNpc, putamen, cerebral cortex or cerebellum when tissues from PSP and control patients were compared (Table 4). Zinc levels in the caudate nucleus in PSP were reduced by 17% compared with values for control tissue (Table 4).

Manganese levels. Total manganese levels in the caudate nucleus, putamen, SNpc and cerebellum were similar in control and PSP tissues (data not shown). There was

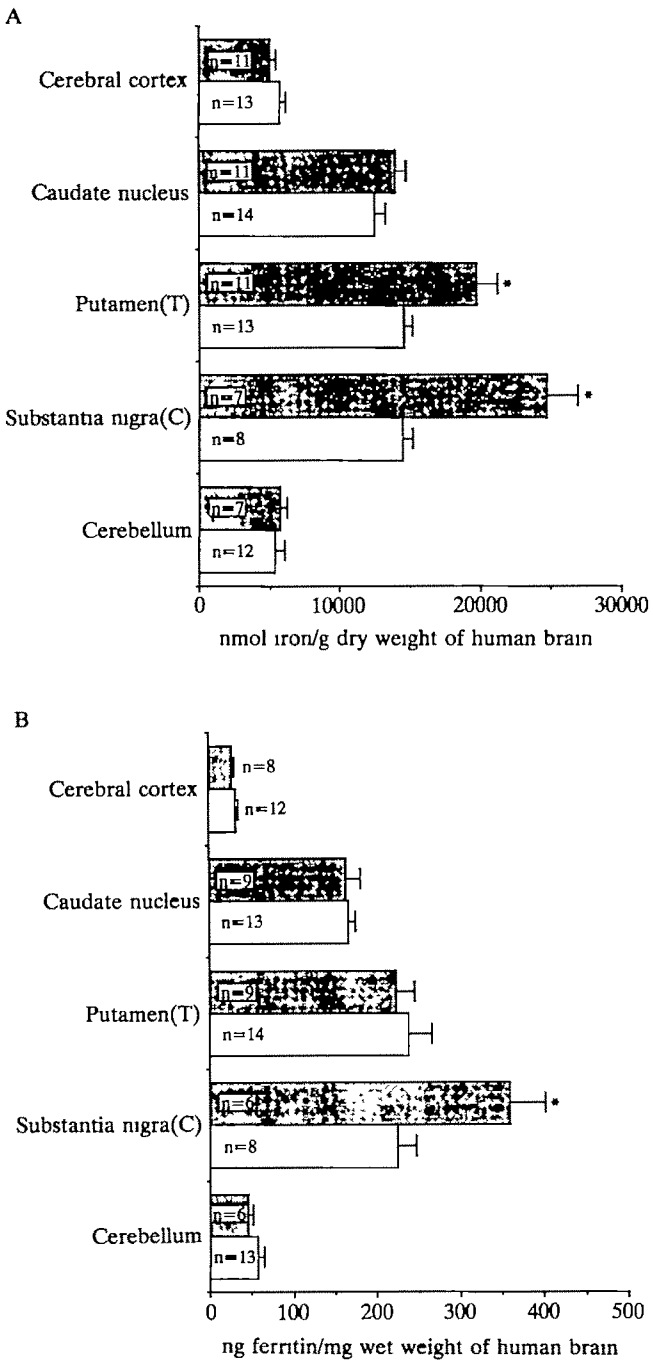

FIG. 2. Total levels of (A) iron (nmol/g dry weight), and (B) ferritin immunoreactivity (ng/mg wet weight) in progressive supranuclear palsy and control human autopsy brains. Values represent means ±1 SEM. * $P < 0.05$ compared with controls (Student's t test) C = compacta; T = total. PSP patients (closed bars), controls (open bars).

TABLE 4 TOTAL LEVELS OF COPPER AND ZINC (nmol/g DRY WEIGHT OF HUMAN BRAIN) IN PSP AND CONTROL HUMAN AUTOPSY BRAINS

	Metal ion levels (nmol/g dry weight human brain)			
	Copper		*Zinc*	
Brain region	*Control*	*PSP*	*Control*	*PSP*
Cerebral cortex	384 ± 29 n = 13	321 ± 45 n = 11	1349 ± 85 n = 14	1469 ± 124 n = 11
Caudate nucleus	412 ± 44 n = 14	358 ± 37 n = 11	1229 ± 44 n = 14	1020 ± 95* n = 11
Putamen (total)	536 ± 58 n = 13	494 ± 22 n = 11	1261 ± 55 n = 13	1332 ± 52 n = 11
Substantia nigra (compacta)	596 ± 68 n = 8	517 ± 94 n = 7	1261 ± 136 n = 8	1429 ± 205 n = 7
Cerebellum	509 ± 43 n = 12	374 ± 30* n = 7	1404 ± 92 n = 92	1219 ± 102 n = 102

Values represent means ± 1 SEM. * $P < 0.05$ compared with controls (Student's t test)

an increase (by 37%) in total levels of manganese in the cerebral cortex of PSP patients when compared with control subjects.

Ferritin immunoreactivity. There was no difference in the levels of ferritin immunoreactivity of the cerebral cortex, caudate nucleus, putamen or cerebellum when control and PSP patients were compared (fig. 2B). There was a marked increase (by 70%) in ferritin immunoreactivity in the SNpc of patients with PSP above those found in control patients (fig. 2B).

Determination of metal ions and ferritin immunoreactivity in brain tissue from control subjects and those with multiple system atrophy

Patient groups. Brain tissue was obtained from 13 control patients who did not have a neurological or psychiatric illness as a diagnosis in life or as the cause of death, and from 8 patients with a clinical diagnosis of MSA dying from natural causes or complications of MSA. MSA with strionigral degeneration was confirmed pathologically by marked cell loss with gliosis in SN, putamen and caudate nucleus. In addition, there were changes in the olives, pons, cerebellum and autonomic nuclei. The cerebral cortex was normal and there were no Lewy bodies. The two patient groups were closely matched for age and postmortem delay. Full patient characteristics and postmortem procedures are given in Table 5.

Iron levels. Total iron levels in the cerebral cortex, globus pallidus and cerebellum were not different when MSA and age-matched control patients were compared (fig. 3A). However, total iron levels were increased in the total SN (by 59%), medial putamen (by 67%) and the caudate nucleus (by 42%), in tissues from MSA patients when compared with the control group (fig. 3A). There was also a 44% increase in the total iron content of the lateral putamen in the MSA patients but this did not reach statistical significance (Fig. 3A).

Copper levels. There were no differences in the copper levels observed in any of the areas of the MSA brain examined when compared with control tissue (data not shown).

TABLE 5 CHARACTERISTICS OF CONTROL AND MULTIPLE SYSTEM ATROPHY PATIENT (MSA) GROUPS AND DETAILS OF POSTMORTEM PROCEDURES

	Control (n = 13)	*Multiple system atrophy (MSA) (n = 8)*
Age (yrs)	66±5 9	63.4±3.0
Sex: Female	6	2
Male	7	6
Age of onset of multiple system atrophy (yrs)	–	56 4±2 8 (47–72)
Duration of multiple system atrophy (yrs)	–	7±0 89 (3–10)
Cell loss in substantia nigra, putamen and caudate nucleus	No	Yes
Presence of Lewy bodies	No	No
Time between death and autopsy (h)	20.3±1.9	17.0±3 6

Values are shown as the mean value ± 1 SEM Figures in brackets show range of values
No significant difference was observed in any patient characteristics when control and MSA patients were compared

Zinc levels. No differences in total zinc levels were observed in any of the brain areas examined when tissues from control and MSA patients were compared (data not shown).

Manganese levels. No differences in total manganese levels were observed when the caudate nucleus, putamen, globus pallidus, total SN and cerebellum from the MSA patients were compared with controls (data not shown). However, in the cerebral cortex of MSA patients there was a decrease (by 34%) in manganese levels when compared with control tissue.

Ferritin immunoreactivity. Levels of ferritin immunoreactivity in the cerebral cortex, caudate nucleus, globus pallidus and cerebellum from MSA patients were not different from those observed in the control tissues (fig. 3B). Increased levels of ferritin immunoreactivity were observed in the lateral and medial putamen (by 73% and 59%, respectively). In the total SN of MSA patients levels of ferritin immunoreactivity were also increased (by 34%) but this did not reach statistical significance (fig. 3B).

Determination of metal ions and ferritin immunoreactivity in brain tissue from control subjects and those with Huntington's disease

Patient details. Brain tissue was obtained from 32 non-neurological controls dying from natural causes and from 10 HD patients dying from natural causes or complications arising from HD. The clinical diagnosis of HD was confirmed pathologically by marked neuronal cell loss with gliosis in the caudate and putamen. Less severe atrophy was also observed in the globus pallidus, thalamus and cortex. The mean age of the HD patients was lower than that of the controls. The time between death and autopsy was longer in the HD patient group than for controls. Full patient characteristics and postmortem procedures are given in Table 6.

Iron levels. There were no differences in total iron levels of the cerebral cortex, SNpc and cerebellum of control subjects and those with HD. In patients with HD total iron levels were increased in the caudate nucleus (by 56%) when compared with control

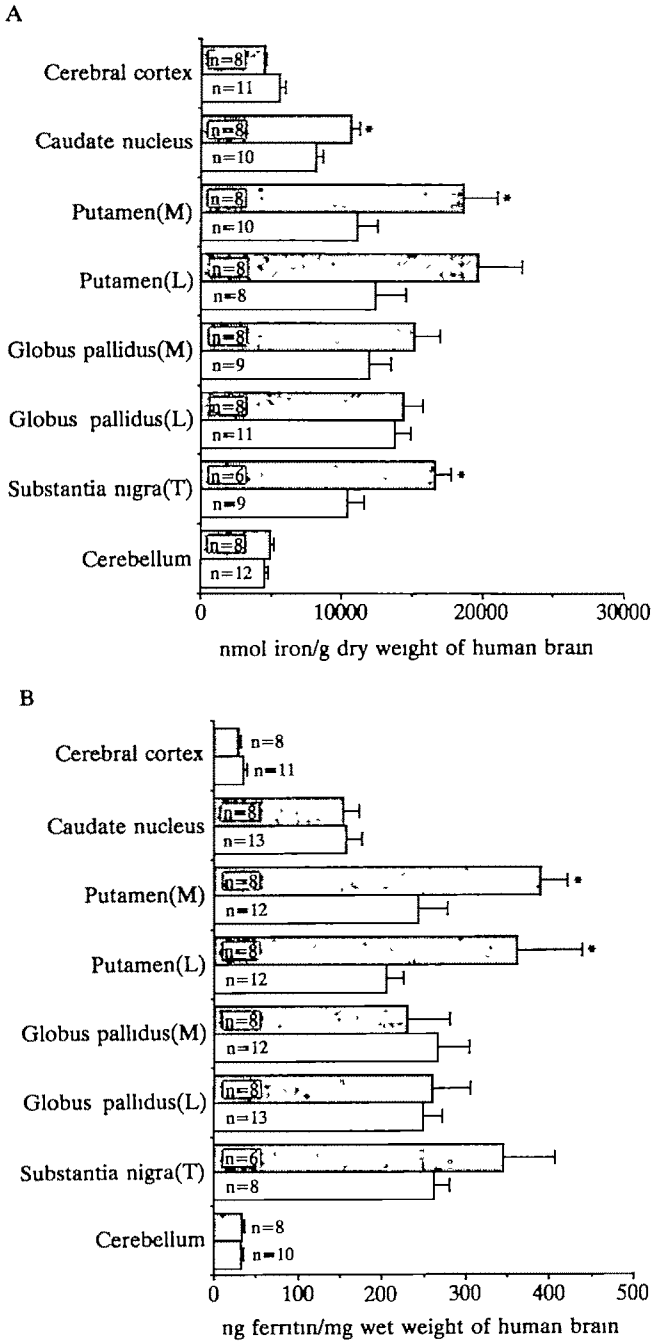

FIG. 3. Total levels of (A) iron (nmol/g dry weight), and (B) ferritin immunoreactivity (ng/mg wet weight) in multiple system atrophy and age-matched control human autopsy brains. Values represent means ± 1 SEM. * $P < 0.05$ compared with controls (Student's t test). C = compacta; L = lateral, M = medial; T = total. MSA patients (closed bars); controls (open bars).

TABLE 6 CHARACTERISTICS OF CONTROL AND HUNTINGTON'S DISEASE (HD) PATIENT GROUPS AND DETAILS OF POSTMORTEM PROCEDURES

Patient details	*Control (n = 32)*	*HD (n = 10)*
Age (yrs)	76.4±2.9	58.6±4.5*
Sex: Female	15	6
Male	17	4
Marked cell loss with gliosis in caudate and putamen	No	Yes
Time between death and autopsy (h)	13.3±1 5	32 6±7.1*

Values are shown as the mean value ±1 SEM In the HD patient group the mean age of the patients was lower than that of control patients and the time between death and autopsy was longer in the HD group when compared with controls. * $P < 0.05$ Student's t test

tissue (fig. 4A). In the putamen in HD there was a 44% increase in total iron levels but this failed to reach statistical significance.

Copper levels. Total copper levels were not different in the cerebral cortex and caudate nucleus of control tissues and those from HD (Table 7). In patients with HD total copper levels in the putamen were markedly increased (by 64%) when compared with control tissues. Also, in the SNpc from HD patients total copper levels were increased (by 68%) when compared with control patients, but this increase did not reach significance. Copper levels in the cerebellum tended to be lower in HD but tissue was only available from 2 patients (Table 7).

Zinc and manganese levels. No differences in zinc or manganese levels were found when the cerebral cortex, caudate nucleus, putamen, SNpc and cerebellum from control and HD patients were compared (Table 7). There was no difference in manganese levels between controls and HD patients (data not shown).

Ferritin immunoreactivity. In the cerebral cortex, caudate nucleus, putamen and SNpc no differences in levels of ferritin immunoreactivity were observed in any brain region when control and HD patients were compared (fig. 4B).

Effect of patient age and postmortem delay on metal ion and ferritin levels in the brain

Tissues were matched for antemortem and postmortem parameters as far as possible, but the average age of patients dying with PSP and HD was lower than that of the available control subjects. Also the postmortem delay was longer for patients dying with HD than for the control brain tissue used in this part of the study. These differences could potentially influence the results obtained. However, in the large series of control and PD brains studied (n = 27−34), there was no correlation between metal or ferritin levels and the age or postmortem delay for individual patients (data not shown).

DISCUSSION

In the studies reported in this paper the total iron levels in control brain tissue were markedly higher in the basal ganglia compared with the cerebral cortex and cerebellum. The overall distribution in rank order of total iron levels in the control brain was: globus pallidus > putamen > SN > caudate nucleus > cerebral cortex = cerebellum. This

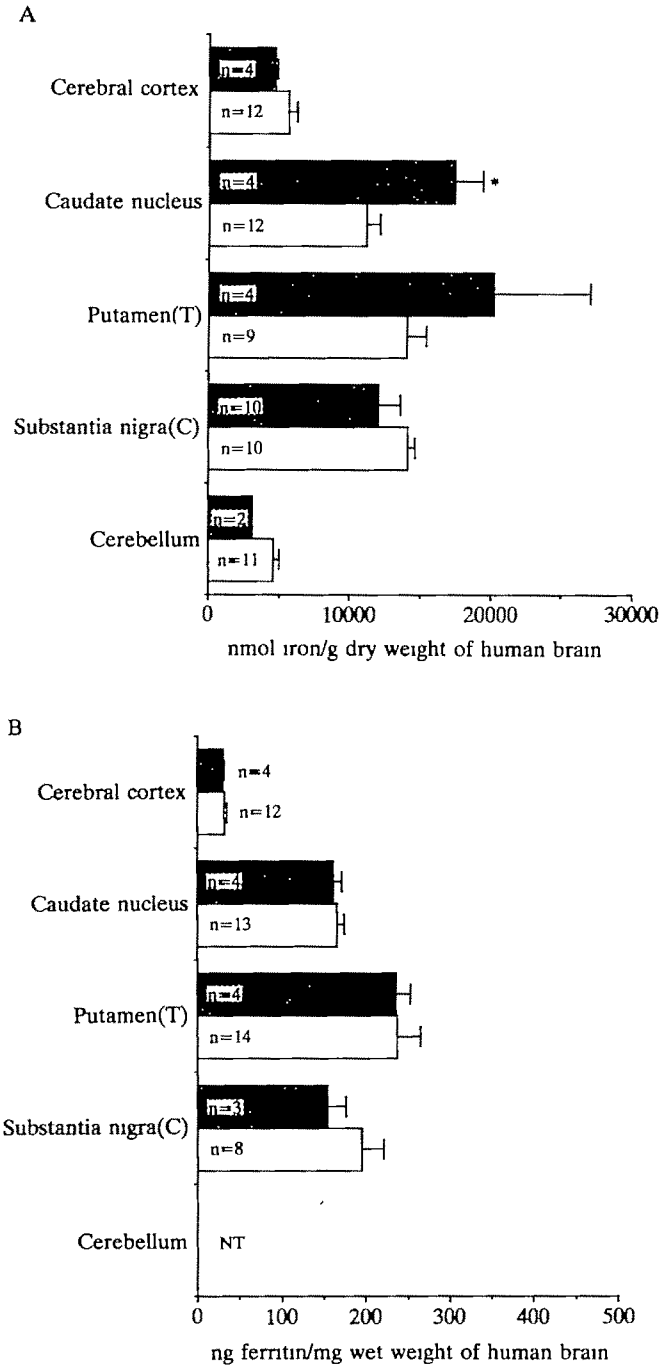

FIG. 4 Total levels of (A) iron (nmol/g dry weight), and (B) ferritin immunoreactivity (ng/mg wet weight) in Huntington's disease and control human autopsy brains. Values represent means ± 1 SEM. * $P < 0.05$ compared with controls (Student's t test). C = compacta, T = total.

TABLE 7. TOTAL LEVELS OF COPPER AND ZINC (nmol/g DRY WEIGHT OF HUMAN BRAIN) IN HD AND CONTROL HUMAN AUTOPSY BRAINS

	Metal ion levels (nmol/g dry weight human brain)			
	Copper		*Zinc*	
Brain region	*Control*	*HD*	*Control*	*HD*
Cerebral cortex	344 ± 30 n = 12	302 ± 54 n = 4	1170 ± 55 n = 12	1285 ± 167 n = 4
Caudate nucleus	448 ± 61 n = 12	414 ± 69 n = 4	1171 ± 68 n = 12	1431 ± 148 n = 4
Putamen (total)	399 ± 35 n = 9	657 ± 126* n = 4	1010 ± 27 n = 9	1086 ± 99 n = 4
Substantia nigra (compacta)	629 ± 56 n = 10	1061 ± 229 n = 10	1175 ± 108 n = 10	1130 ± 137 n = 10
Cerebellum	552 ± 60 n = 11	215 n = 2	1158 ± 51 n = 11	887 n = 2

Values represent means ± 1 SEM. * $P < 0.05$ compared with controls (Student's t test).

distribution of total iron in control brain tissue correlates well with that previously shown by histological (Spatz, 1922), chemical (Hallgren and Sourander, 1958; Harrison *et al.*, 1968; Höck *et al.*, 1975) and MR imaging (Drayer *et al.*, 1986) studies of normal human brain. Brain iron plays an essential role in learning and memory, the functioning of many oxidative and other enzymes and is required for the interaction of certain neurotransmitters to their receptors (Youdim, 1985). But why the basal ganglia contain such high levels of iron remains a mystery. Iron has an important role in normal cellular metabolism but may also be potentially toxic due to its ability to catalyse various stages of oxidative stress.

Our earlier study (Dexter *et al.*, 1987, 1989*b*) showed that iron accumulated in the SN in PD. This study was in agreement with the earlier report of Earle (1968) who showed an increase in the total iron content of midbrain from formalin-fixed brain tissue in PD. Similarly, Riederer *et al.* (1989) showed an increased total iron content of previously frozen substantia nigra in severe PD although this was not evident in mild cases. The same group proposed a shift from Fe^{2+} to Fe^{3+} to occur, so promoting toxic radical formation (Youdim *et al.*, 1989). MRI studies also support the accumulation of iron in substantia nigra in patients with idiopathic PD (Olanow *et al.*, 1989), although this is controversial.

How or why a specific increase in the total iron content of SN should occur in PD is not understood. The fetal brain contains little or no iron; brain iron levels increase in early life but little or no further deposition appears to occur in middle and late life (Hallgren and Sourander, 1958). The mechanisms by which iron accumulates in brain are not clear. Transferrin receptors have been localized on the endothelial surface of brain capillaries (Jefferies *et al.*, 1984), suggesting a means through which transferrin-bound iron can be transported from the plasma to the cells of the brain. Transferrin receptors are also located in brain but not always in those areas where iron is in highest concentration. Peripheral blood iron and ferritin content appears normal in PD (Dexter *et al.*, 1990). Accordingly, it seems likely that the increased total content of SN in PD is due to some local process.

One way of assessing the relevance of the increased accumulation of iron in SN in PD is to examine the levels of iron in other neurodegenerative disorders of the basal ganglia in which SN either is pathologically involved or spared. Total iron levels in SN were elevated, not only in PD, but also in PSP and MSA in which major pathological changes occur in SN. In contrast, there was no change in total iron levels in SN in HD. An increase in total iron content in SN thus appears to be associated with nonspecific pathological change in that region rather than with a specific disease entity. Indeed, total iron levels also were increased in the putamen in PSP, and in the caudate and putamen in MSA, where neurodegeneration also occurs. Similarly, in HD there was a trend in the small number of cases studied for increased total iron levels in both the affected caudate and putamen. The reason for these increases in total iron content in the striatum in PSP, MSA and in HD are not known. They may reflect some nonspecific effect of degeneration of striatal tissue in these conditions. At least in the putamen in MSA the increased iron is associated with an appropriate increase in ferritin levels (*see below*). Further work is required to establish the significance of these observations. Reduced iron levels were found only in PD and only in the globus pallidus. Again, the reason for this change is unknown and deserves further study. Previously increased iron levels have been found in brain in multiple sclerosis (Valberg *et al.*, 1989) and MRI studies have suggested iron accumulation in the striatum of patients with chorea, amyotrophic lateral sclerosis and Alzheimer's disease (Olanow *et al.*, 1989).

Thus, increased brain iron levels are found in a number of basal ganglia regions known to be affected in the neurodegenerative diseases studied. At first sight this makes it unlikely that such changes are a primary cause of the different pathological changes characterizing these conditions. The neurodegenerative processes involved in these different diseases are unlikely to be identical, in view of the varied distribution of their pathology and different cellular pathological markers, for example, Lewy bodies in PD and neurofibrillary tangles in PSP. Raised iron levels, however, might still contribute to the neurodegenerative changes once initiated.

Iron within the brain exists in many complex forms not all of which are capable of catalysing oxidative stress. The majority of iron is bound and inactivated by association with ferritin. Ferritin is a ubiquitous protein consisting of a spherical shell of 24 subunits surrounding an iron core. The ferritin protein consists of subunits of two types: light or L (19 000 Da) and heavy or H (21 000 Da), the proportions of which vary between tissues (Theil, 1987). The subunit composition of ferritin in peripheral tissues is known, but that of brain ferritin remains to be determined. Under normal physiological conditions its biosynthesis is controlled by iron availability, resulting in increased ferritin formation in which the L isoferritin predominates (White and Munro, 1988).

The potential toxicity of the increased iron load in the SNpc in PD will therefore be determined by the extent to which it is deactivated by binding to ferritin (and other moieties). In PD the increased total iron level in SNpc was not associated with a compensatory increase in ferritin (Dexter *et al.*, 1990); indeed, brain ferritin immunoreactivity was decreased. In contrast, the raised total iron levels in SNpc in PSP were associated with and possibly deactivated by an enhanced ferritin content, and there was a similar trend for a rise in SNpc ferritin in MSA patients. Similarly, the increased total iron levels in the putamen in MSA was associated with an elevation of ferritin immunoreactivity. However, raised total iron level in the putamen in PSP and

caudate nucleus in MSA was not associated with elevated ferritin immunoreactivity. Why this should occur is not clear but may relate to the extent to which ferritin is normally saturated by iron. Ferritin can store up to 4500 atoms of iron, but under normal conditions in peripheral tissue, it is only partially saturated (Harrison *et al.*, 1977). Excess iron, in some circumstances, may therefore be accommodated without an increase in ferritin synthesis.

As far as the SN is concerned, the increased iron load in PD may exceed the storage capacity of available ferritin, leading to excess reactive iron (*but see below*), driving free radical generation. This concept is supported by the increase in basal lipid peroxidation found in SN in PD (Dexter *et al.*, 1986).

The finding of a generalized decrease in ferritin immunoreactivity in PD, including brain areas not associated with pathological change, was unexpected. Our findings contrast with a recent report by Riederer *et al.* (1989) who reported a small increase (by 29%) in ferritin levels in the SN and a nonsignificant increase (by 37%) in the putamen of patients with PD. This discrepancy may be due to different techniques used in the two studies to measure ferritin content. A more likely explanation, however, is that the polyclonal antibody used by Riederer and colleagues differs from the antibody used in the present study in its recognition of isoferritin subunits. Alternatively, it may recognize a different configuration of the ferritin molecule, since the latter is comprised of 24 subunits of which the proportion of H and L isoferritins vary. The reduction in ferritin immunoreactivity that we have observed in PD, but not in the other disorders studied, may thus represent an alteration in the structural configuration of H and L isoferritin in the ferritin molecule, perhaps induced by alterations in the degree of saturation by iron. However, we have obtained results similar to those shown in this study on ferritin levels in PD brain using a commercially produced antibody to human spleen ferritin (data not shown).

In brain areas other than the SN in PD, the reduced levels of ferritin immunoreactivity were associated with a normal or reduced total iron content. Since lipid peroxidation was not increased in such areas (Dexter *et al.*, 1989*a*) their iron content seem to be adequately accommodated in an inactive form.

The form in which the increased total iron load, apparently inadequately deactivated by binding to ferritin, occurs in SN in PD remains unknown. It could be present as low molecular weight chelates, such as citrates, which are capable of stimulating oxidative stress (Halliwell and Gutteridge, 1985). Alternatively, it might be inactivated by binding to another iron binding protein such as haemosiderin (Wixom *et al.*, 1980). Indeed, the decreased levels of ferritin found in PD could be due to increased lysosomal breakdown of ferritin to haemosiderin (Andrews *et al.*, 1987). This might be particularly relevant if the increased iron load had been present in brain for the duration of the illness. In addition, the subcellular localization of the excess iron within SN is not known. It will be important to determine not only whether the excess iron in SN in PD is in a reactive form, but also whether it selectively occurs in surviving neurons or glial cells, and whether it is associated with Lewy bodies.

Copper levels were reduced in SNpc in PD. This may be compatible with the increase in total iron content in that site in PD. An inverse relationship between the tissue content of iron and copper has been established in the liver (Symes *et al.*, 1969). However, copper levels were normal in SN in PSP and MSA, despite increased iron content. Also,

copper levels were increased in the putamen in HD (and there was a tendency for such an increase in SN). Manganese levels were reduced in the medial putamen in PD and in the cerebral cortex in MSA, but the significance of these observations again is unknown.

Increases in zinc levels were observed in patients with PD but not in the other conditions studied. The largest increase in zinc levels in PD was in SN with smaller increases occurring in the lateral putamen and caudate nucleus. Zinc, as one of its many cellular functions, can protect against oxidative stress, evidence for which has been demonstrated in vivo (Radomski and Wood, 1970; Floersheim and Floersheim, 1986) and in vitro (Chvapil *et al.*, 1972, 1974; Girotti *et al.*, 1985). The mechanism of zinc's antioxidant properties is not fully known but it may stabilize sulphydryl-containing antioxidants (Floersheim and Floersheim, 1986), interfere with NADPH dependent oxidation reactions (Chvapil *et al.*, 1976), or inhibit formation of tertiary complexes between oxygen, Fe^{2+} and the double bonds of fatty acids (Peterson *et al.*, 1981; Szebeni *et al.*, 1988). In rheumatoid arthritis and alcohol-induced liver cirrhosis, zinc protects against the decompartmentalization of iron (Willson, 1977). Whatever the mechanism by which zinc exerts its antioxidant activity, the fact that zinc levels are markedly increased in SN in PD, where iron metabolism may be altered and increased levels of lipid peroxidation are observed (Dexter *et al.*, 1989*a*), may indicate a physiological response to oxidative stress.

The alterations in copper and zinc levels observed in SN in PD were not observed in the other neurodegenerative disorders investigated, although several brain regions in these disorders demonstrated increased total iron levels. Hence it would appear that the changes in copper and zinc that occur in SN in PD are not simply due to changes in iron levels but may be related to specific disease processes which occur in PD.

The results of metal ion analysis presented in this study contrast with a recent report by Uitti *et al.* (1989) who, using atomic absorption and atomic emission spectroscopy, measured 24 metals in fixed postmortem brain tissues from a range of neurological disorders. Reduced copper levels were found in the SN in PD. However, no alterations in the levels of iron or zinc were observed in the frontal cerebral cortex, caudate nucleus, SN and cerebellum from patients with PD or HD when compared with controls. One possible explanation is that Uitti *et al.* used formalin-fixed brain material. Although the patients were matched for postmortem parameters, the process of fixation, duration of fixation and even the size of brain sample, could have marked effects on the metal ion concentrations since many metal complexes are water soluble.

The alterations in metal ion levels and ferritin levels observed in the neurodegenerative disorders studied seem unlikely to be linked to drug treatment of these conditions. Although all the PD patients in this study were receiving L-DOPA up to the time of death, Earle (1968) had demonstrated increased iron content in formalin-fixed brain samples collected between 1895 and 1964 which was prior to the use of L-DOPA in the treatment of Parkinson's disease. Also, we have previously shown that ferritin levels in serum of Parkinson's disease patients are comparable with nonneurological controls whether the parkinsonian patients were receiving L-DOPA treatment or not (Dexter *et al.*, 1990). Nevertheless, an influence of drug therapy, particularly of L-DOPA in PD, cannot be excluded. At present it is very difficult to obtain brain tissue from PD patients not taking L-DOPA, but there is a crucial observation which may settle this issue. If the changes in the SN content of iron, copper, zinc and ferritin can be found

in the brain of those with preclinical PD (i.e., incidental Lewy body disease), then the effects of L-DOPA can be excluded. Furthermore, such a finding would reinforce the view that these changes are relevant to the cause of PD and are not merely the consequences of the nigral destruction.

CONCLUSIONS

From this study the following conclusions can be drawn. (1) Increases in iron levels in SN are not specific to PD, but occur in other basal ganglia diseases with nigral destruction (PSP and MSA). Hence increased iron levels are not the primary initiator of nerve cell death in PD and may represent a secondary nonspecific response to nerve cell death. (2) Increased iron levels in SN in PSP and MSA, however, were associated with appropriate increased or normal levels of ferritin, whereas in PD ferritin levels in SN were reduced. (3) Hence the increased iron levels in the SN in PD may include a form capable of contributing to the toxic processes occurring in PD by driving the formation of reactive oxygen species to cause lipid peroxidation and other tissue damage. (4) The reduced copper levels in SN in PD (but not in MSA or PSP) may reflect this increased reactive load of iron. The increases in zinc levels in SN are selective in PD; changes in this antioxidant metal ion may be protective against the toxic effects of iron.

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PHONOLEXICAL AGRAPHIA

SUPERIMPOSITION OF ACQUIRED LEXICAL AGRAPHIA ON DEVELOPMENTAL PHONOLOGICAL DYSGRAPHIA

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SUMMARY

Study of neuropsychological sequelae of a focal acquired brain lesion may bring out and help delineate the features of a compensated developmental language disorder and its anatomical substrate. A left-handed man with a history of phonological developmental dyslexia and dysgraphia learned in early adulthood to read and write using a lexical system. Following a small posterior right parietal infarct when aged 56 yrs he developed a severe agraphia displaying features of phonological dysgraphia with impaired segmentation and features of lexical agraphia. Writing was severely impaired for all classes of word and nonword stimuli but his errors did not resemble those attributable to a deficit in the system responsible for the short-term storage of the graphemic representation of a word (graphemic output buffer). These observations imply that an acquired lexical agraphia has been superimposed on his developmental phonological dysgraphia, resulting in a combined or 'phonolexical' agraphia.

INTRODUCTION

Acquired agraphias can be broadly classified as either linguistic or motor agraphias (Roeltgen and Heilman, 1984). Linguistic agraphias have been further subdivided, on the basis of patterns of impairment, into at least two major types. Patients with phonological agraphia have difficulty spelling nonwords but have a relatively preserved ability to write phonetically irregular words. Errors tend not to be phonologically correct (Shallice, 1981). Part of speech and imageability of the target word are important determinants of spelling accuracy in this disorder. In particular, functors are written less accurately than are content words and performance is better for high than for low imagery nouns (Assal *et al.*, 1981; Bub and Kertesz, 1982; Roeltgen *et al.*, 1983*b*). Writing includes semantic or derivational errors, neologisms, mistakes with visual similarity to the intended word, and incorrect real words unrelated to the stimulus (Shallice, 1981; Bub and Kertesz, 1982; Roeltgen *et al.*, 1983*b*; Bolla-Wilson *et al.*, 1985). High frequency words are written more accurately than less frequent words (Shallice, 1981), and short words are more accurately written than long words (Shallice, 1981; Roeltgen *et al.*, 1983*b*; Temple, 1988).

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In contrast to phonologically agraphic patients, those with lexical agraphia spell irregular words poorly but have a relatively spared ability to write regular words and pronounceable nonwords. Errors tend to be phonologically correct (e.g., NEPHEW → NEFFUE; Patterson, 1982). Imageability and grammatical class do no necessarily affect writing accuracy, and functors may thus be written as well as content words (Beauvois and Dérouesné, 1981; Roeltgen and Heilman, 1984; Gonzalez Rothi *et al.*, 1987; Rapcsak *et al.*, 1988). These patients may also be impaired at spelling the correct homophone, producing, for example, PALE instead of PAIL (Hatfield and Patterson, 1983; Roeltgen and Heilman, 1984; Goodman and Caramazza, 1986).

These patterns of agraphia have contributed to the development of models of writing that include at least two routes that can be used to spell (e.g., Beauvois and Dérouesné, 1981; Nolan and Caramazza, 1983; Roeltgen and Heilman, 1984). Spellings of familiar words may be retrieved from a lexicon, whereas spellings for unfamiliar words or nonwords must be arrived at via a phonological route as no lexical entries exist for them. Irregular words could thus only be spelled using the lexical route and nonwords only phonologically or perhaps, in some cases, by analogy with real words (Shallice, 1981).

Ellis (1982) has suggested that phonological transcoding entails two functions: segmentation of words into phonemes and then conversion of phonemes into graphemes. Roeltgen *et al.* (1983*b*) found support for this model in their analysis of errors made by subjects with phonological agraphia.

Models of writing often include a graphemic output buffer responsible for short-term storage of a graphemic representation of a word. This abstract representation, which may have been generated via phonological or lexical means, can then be used to produce letter names or shapes for oral or written spelling (Morton, 1980; Newcombe and Marshall, 1980; Ellis, 1982). Several cases have been documented in which agraphia has been ascribed to damage to this graphemic buffer (Miceli *et al.*, 1985; Caramazza *et al.*, 1987; Posteraro *et al.*, 1988; Hillis and Caramazza, 1989). Graphemic buffer deficits should affect spelling in specific ways (Caramazza *et al.*, 1987; Hillis and Caramazza, 1989). Word and nonword spelling should be impaired essentially equally. Impairment should be independent of modality of input or output. Long words should be spelt more poorly than short words. Part of speech, word frequency, and imageability should not affect spelling accuracy. Although some of these criteria can apply individually to phonological or lexical agraphia, a different type of error is expected of a graphemic buffer deficit. Errors should not resemble the intended word semantically, phonologically, or morphologically. Instead, errors should consist of graphemic substitutions, transpositions, insertions and deletions. These erroneous responses often violate orthographic rules of the language and are thus unpronounceable.

Lesions causing phonological agraphia have been localized to the left supramarginal gyrus or underlying insula (Roeltgen *et al.*, 1983*b*) whereas lexical agraphia has been attributed to lesions of the left posterior angular gyrus and parieto-occipital lobule (Roeltgen and Heilman, 1984). A single case of lexical agraphia with a left precentral gyrus lesion (Rapcsak *et al.*, 1988) has also been reported. The two reports describing linguistic agraphia resulting from right hemisphere damage have documented lesions in the corresponding retrorolandic sites on the right. Thus Bolla-Wilson *et al.* (1985) reported a case of phonological agraphia in a left-handed patient with a right supramarginal

gyrus lesion, and Gonzalez Rothi *et al.* (1987) found a right posterior parieto-occipital lesion in a right hander with lexical agraphia.

Children with developmental dysgraphia have also been classified on the basis of the phonological accuracy of their misspellings. Boder (1973) used the terms dyseidetic and dysphonetic to describe children making phonologically correct and incorrect errors, respectively. Frith (1980) described two groups of poor spellers who varied in their ability to write nonwords. Temple (1986) has described children with deficits akin to phonological and lexical agraphia. Roeltgen and Tucker (1988) have divided adults with developmental dysgraphia into phonological and lexical groups with profiles of spelling ability virtually indistinguishable from those of patients with acquired agraphias. Case reports have also documented the persistence of phonological dysgraphia into adulthood (Temple, 1988; Funnell and Davison, 1989). Campbell and Butterworth (1985) have described a patient with developmental phonological dyslexia and dysgraphia who overcame her disability and became highly literate using lexical strategies.

We describe a unique subject with developmental dysgraphia and dyslexia, seemingly due to phonological impairment, who learned to read and write well in adulthood using a lexical strategy and then, after a right parietal infarct, developed a superimposed acquired agraphia. His new deficit does not resemble phonological agraphia and we argue that the best explanation for his current deficit is an acquired lexical agraphia combined with his pre-existing phonological impairment.

CASE REPORT

O.C., a left-handed man, aged 56 yrs, was examined in March, 1989, 3 mos after a stroke impaired his reading and writing. As a child he had had great difficulty learning to read and write although his speech development had been normal. His older brother was also left handed but learned to read and write without difficulty. His 3 sisters and his parents were right handed and had no literacy problems. O.C. reported that he never could 'see the sense' in sounding out words and never understood how it could be possible to 'break up words' O.C. left school at age 13 yrs with an eighth grade education. He recalled that at that time he could read and write only the letters of the alphabet and his name. At 18 he joined the Navy (he recalled that the 'written' entrance examination was read to him by a recruiter) where his captain discovered his illiteracy and assigned 3 chaplains to teach him to read and write. A trial of teaching him to sound out words was unsuccessful. The clergymen subsequently gave him lists of words each day to copy and memorize by rote By the time he left the service 3 yrs later he was literate enough to work as a machinist and rose to become a state union president by his early thirties In this capacity he wrote reports and read speeches regularly. He later worked with computers in an airplane engine factory monitoring the flow of parts and finished engines into and out of the factory. As an adult, O.C. described himself as an avid and rapid reader. He particularly enjoyed books on American labour and politics.

His medical history was unremarkable until December 1988, when he underwent cardiac catheterization for investigation of recent chest pain. Coronary angiography was normal but shortly after the procedure he experienced the sudden onset of left hand numbness and slight weakness. When asked to sign a form he found that he was unable to write intelligibly with either hand. He had begun reading a lengthy political tome just before his catheterization but was never able thereafter to progress beyond the first chapter despite repeated attempts.

Although his hand numbness and weakness disappeared completely over the next few weeks, he was disabled by his inability to read or write and was unable to return to his former employment. CT scan on the day of the stroke was normal but on the following day showed a small right parietal lucency MRI scan performed 4 mos later confirmed a small right posterior parietal lobe lesion but was otherwise normal (*see* fig. 1).

When first seen at the University of Florida Teaching Hospital 3 mos after his stroke, cranial nerve, motor, sensory, and reflex examinations were normal except for minor awkwardness of fine finger

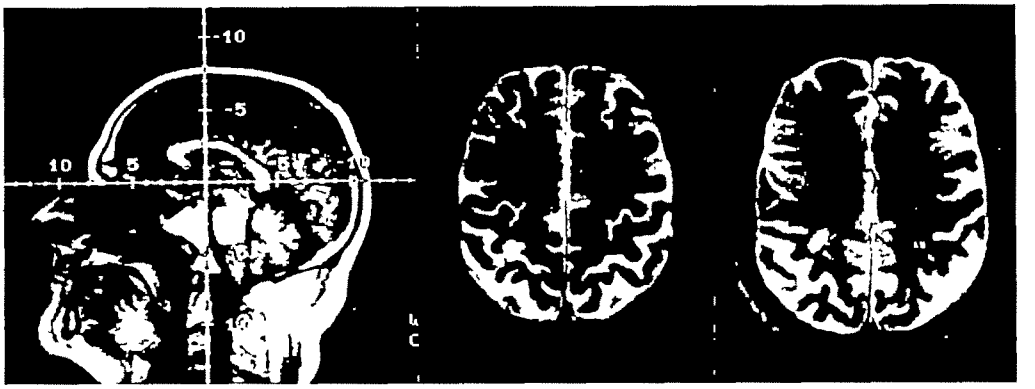

FIG. 1. MRI scan 4 mos after O C.'s stroke, showing small posterior right parietal lesion also seen on second, but not first, CT scan Centre and right are T_2 weighted axial cuts taken at 3.79 and 2.88 cm above horizontal with centimetre markings seen in T_1 weighted sagittal scout film at left.

movements on the left. He was oriented for time, place, and person. He remembered 3 of the past 5 presidents and 2 of 3 words after 3 min distraction. Digit span was five forward. He stated that an apple and a banana were both to eat and that a chair and a table were both wooden and had legs. He performed calculations well (24/24 on the Western Aphasia Battery (WAB) (Kertesz, 1982) calculation subtest). There was no right-left confusion. He was not apraxic with either hand (59/60 on the WAB praxis subtest). There was no neglect on cancellation or line bisection tasks. Drawing was unimpaired.

O.C. was not aphasic, scoring a WAB aphasia quotient of 97.7, well within the normal range. In contrast to his normal verbal communication, he was severely agraphic, unable to write even his own name without a model from which to copy. WAB reading and writing scores were 88/100 and 52.5/100, respectively An investigation of his reading and writing was thus undertaken.

RESULTS

Writing

O.C. made no errors in copying 50 written stimuli comprising letters, nonwords, and regular and irregular words. He could transcribe upper to lower case flawlessly, print to script, and vice versa. Letters were always well-formed. He preferred to print in block capitals but could produce script upon request. Samples of his handwriting revealed that he had usually written in block letters even before his stroke. O.C. always began at the left of a word and wrote it in the normal sequence, using his left hand. When asked to use his right, spelling was similarly affected but letters were not so neatly formed.

O.C. made no errors when asked to repeat aloud orally presented letters, phonemes, words, or nonwords. He could correctly write 26/26 single dictated letters and could write letters for 23/24 dictated single phonemes.

O.C. was asked to write to dictation 30 nonwords, 30 regular, and 30 irregular words (*see* Appendix) taken from the Battery of Adult Reading Functions (BARF) (L. J. G. Rothi, H. B. Coslett and K. M. Heilman, unpublished manuscript; Gonzalez Rothi *et al.*, 1987). Nonwords were constructed so as to be phonologically plausible and probable (Venezky, 1979; Kay and Marcel, 1981). The three groups of stimuli were balanced for length (mean 5.3 letters in each case) and the two groups of real words were balanced

for frequency of usage (43.3/million for regular words, 43.6/million for irregular) (Kučera and Francis, 1967). Nouns, verbs, and adjectives were equally represented on the two lists. To examine the effect of grammatical class of stimuli on spelling accuracy, O.C. was also asked to write to dictation 30 functors (mainly prepositions and adverbs) and 30 contentives (nouns, adjectives, and verbs) matched for length (mean 5.3 letters for each list) and frequency of usage (403.3/million for functors, 402.8/million for contentives). Note that, since functors tend to be very frequent words, these two lists are of higher frequency than the regular and irregular words. To ensure that any impairment was not due to a simple memory disturbance causing him to forget the stimuli, O.C. was required to repeat each stimulus both before and after attempting to write it. This he was able to do without fail. He could define the words presented. When asked immediately, he was always able to tell whether he had written a word correctly or not but was never able to make any attempt at correcting his mistakes. As shown in Table 1, O.C.'s performance on writing to dictation was severely impaired in writing nonwords and regular and irregular words, although he was better at writing contentives than functors.

To determine whether modality of output influenced his spelling accuracy, he was asked to spell aloud 30 nonwords and 30 regular and 30 irregular words taken from the Battery of Linguistic Analysis for Writing and Reading (BLAWR) (Roeltgen *et al.*, 1983*a*; Roeltgen and Heilman, 1984). These stimuli were comparable with those used for writing to dictation and are also listed in the Appendix. Mean stimulus length was 5.3 letters for all three lists. Mean frequency of usage was 43.8/million for regular and 43.7/million for irregular words. O.C.'s performance on spelling dictated words aloud is shown in Table 1. It is apparent that spelling aloud and writing to dictation are similarly affected. He is severely impaired at writing nonwords and regular and irregular words. O.C. was also asked to spell aloud 10 high and 10 low imagery nouns (mean imageability ratings 6.46 and 2.98; Paivio *et al.*, 1968) balanced for regularity, word length (mean 4.4 letters for each list), and frequency (mean 151.4 and 151.5/million, respectively). He correctly spelled six high and six low imagery nouns. Thus target word imageability does not appear to play a major role in spelling accuracy. An attempt was also made to test O.C.'s ability to assemble a dictated word using its letters printed

TABLE 1 O C 'S PERFORMANCE AT WRITING AND SPELLING ALOUD TO DICTATION

Stimulus category	*No of stimuli*	*% correct*	*% omission*	*% errors*
Writing to dictation				
Letters	26	100.0	0	0
Phonemes	24	95.8	0	4.2
Nonwords	30	10.0	0	90.0
Regular words	30	3.3	0	96.7
Irregular words	30	0	0	100 0
Functors	30	0	0	100 0
Contentives	30	23.3	0	76.7
Spelling aloud to dictation				
Nonwords	30	3.3	0	96.7
Regular words	30	10.0	3.3	86.7
Irregular words	30	3 3	13.3	83.4

on cardboard squares and randomly mixed. This was abandoned after five stimuli as O.C. found it extremely frustrating and was unable to produce any response.

To assess whether modality of stimulus input affected O.C.'s writing, he was asked to name, in writing, 15 common objects shown to him. Seven were written correctly. Later, when the same words were dictated, he performed similarly, writing six correctly.

Before examining O.C.'s error types in detail, it is important to establish, as far as possible, the nature and extent of the developmental dysgraphia from which he suffered before his stroke. Given his history, there is little doubt that his writing was severely impaired by his stroke. Support for this is found in a song he composed in 1986. The original manuscript contained one misspelling (SOON → SOONE) and one mispunctuation (LETTERS → LETTER'S). By contrast, when he was asked, after his stroke, to write his song from memory he made 18 errors in 50 words. Direct comparison of this error rate with that for the stimuli discussed above would be misleading as the song contained many short high frequency words. When provided with a correctly written copy of his song, O.C. was able to flawlessly copy it, apart from leaving out one word.

O.C.'s history suggested that he had suffered from a developmental phonological dysgraphia. He had in his possession several postcards that he had written to his family during his stint in the Navy while he was learning to read and write. These contained 147 words, of which 82% were correctly written. All letters were well-formed. All words spelled wrongly were always written in the same wrong way—there were no examples of words being written correctly in one place and incorrectly in another or of a word being misspelled in two different ways. Errors were often phonologically incorrect. He correctly spelled 88% of regular words and 76% of irregular words.

Writing samples from recent years before his stroke showed considerably fewer errors. Perusing notebooks of several hundred words, originally intended only for his own reference, we uncovered five words spelled incorrectly (ABSENTEE → ABESENTEE; THIRTY → THIRITY; THIRTY → THEREE; SEARS → SEAR; ONE → OME: HUNDRED → HUNDER). ABSENTEE appeared only once and was spelled incorrectly as shown. THIRTY was never spelled correctly on the four occasions it appeared. The other 3 words appeared more than once and were spelled both correctly and incorrectly.

Given the likelihood that O.C.'s developmental dysgraphia was phonological, we decided to examine his phonological abilities. Ellis (1982) proposed that writing a word via a phonological route includes two separable processes, segmentation of the word into phonemes and then conversion of those phonemes into graphemes. As O.C.'s conversion of single letters to phonemes and vice versa was well-preserved even after his stroke, we tested his ability to segment sounds using the Lindamood Auditory Conceptualization (LAC) Test (Lindamood and Lindamood, 1971) in which coloured tokens chosen by the subject are made to stand for single phonemes. In LAC Category I-A, the subject is asked to use a token of a given colour to represent each different phoneme uniquely in a string of separately enunciated sounds dictated to him. For example, the examiner dictates, 'Show me s/s' or 'Show me g/b/v' where the appropriate phoneme is pronounced rather than the letter name. Correct responses to these 2 examples would be 2 tokens of the same colour for the former and 3 tokens of different colours for the latter. O.C. represented 8/10 strings correctly with tokens. He quickly corrected his 2 incorrect responses after the stimuli were repeated. On the similar but more demanding LAC Category I-B, O.C. correctly formed 4/6 token strings. Again, when

the stimuli were repeated, he immediately corrected his 2 incorrect constructions saying, 'I didn't quite catch that the first time.' In contrast to his relatively spared performance on Category I, essentially a test of phoneme-symbol conversion, O.C. performed poorly on Category II where the subject is asked to represent nonwords with strings of coloured tokens, a task requiring segmentation ability. For example, when shown a string of 4 tokens of different colours and told, 'If that says "vops", show me "vaps" ', he is expected to replace the second token with one of a new colour. In this category, O.C. correctly assembled only 1/13 responses. He was clearly mystified by the requests and aimlessly moved tokens about. He commented, 'I'm not getting the breakdown of the word. I understand in theory what it is you want me to do but I know that's something I've never been able to do.'

We next attempted to determine what acquired deficit had been superimposed on O.C.'s pre-existing phonological impairment. His well-formed letters, his normal repetition and copying, and the presence of a severe deficit for all types of input or output suggested that the impairment could be no more peripheral than the graphemic output buffer. That his new difficulty was not merely a worsening of his phonological dysgraphia was apparent from his uniformly high error rates in writing nonwords and regular and irregular words. Dysfunction of the graphemic output buffer would impair all three categories of stimuli, but impairment of the lexical writing route in the presence of his developmental phonological impairment might also be expected to impair his writing in this fashion. Analysis of error types may help in distinguishing between these and other alternatives, as specific error types reflect specific patterns of impairment.

Unlike other cases of agraphia in the literature, O.C. is not now impaired by damaged function in a single component of the spelling system, and we must consider what errors are likely to result from impairment of phonological segmentation plus another central deficit. In recent years before his stroke, O.C.'s writing was marked by only very infrequent errors. He compensated well for his phonological deficit, presumably through use of the lexical route. If his stroke were to result in a defect localized to the graphemic output buffer, then the previous good performance of his lexical route should continue to supply the graphemic buffer with accurate spellings in almost every instance and his errors should predominantly be those reported as the typical result of graphemic buffer damage. In this instance, his errors should consist of graphemic deletions, substitutions, insertions, and transpositions and should often be unpronounceable combinations violating rules of English orthography. Error rates should be influenced by stimulus length but not by lexical characteristics such as word frequency or part of speech. However, if O.C.'s new deficit was related to an impairment of his lexical writing route, the resulting errors would be less predictable because he would now spell by using whatever function remains in his defective lexical and phonological systems. Although we might expect some combination of the characteristics of lexical and phonological agraphia, it is impossible to predict with certainty the precise constellation of error types that would be expected or the influence of word frequency, part of speech, or imageability. He does not appear to have complete disruption of both routes. If this were the case, he would presumably be completely unable to spell any words.

Table 2 classifies O.C.'s 224 errors made in writing and spelling aloud 240 words dictated to him. It is apparent that the great majority of his erorrs (78.6%) are phonologically incorrect neologisms and that the frequencies of different types of errors

that these errors are not at all specific for cases with graphemic buffer deficit. For example, fully 79% of the errors made by Beauvois and Dérouesné's (1981) oft-cited case of lexical agraphia are readily classifiable as 'graphemic' errors (most often single deletions) using this system. From Table 3, it is apparent that very few of O.C.'s errors are classifiable as graphemic errors attributable to impairment of the graphemic buffer.

The position of errors within a word may also be related to the type of agraphia. Hillis and Caramazza (1989) described 2 patients with graphemic buffer impairment, 1 with a left hemisphere lesion who was more accurate at writing the beginning of a word and 1 with a right hemisphere lesion who was more accurate at the end of a word. They attributed this phenomenon to hemispatial neglect of a spatially coded representation in the graphemic output buffer. To assess O.C.'s spelling accuracy as a function of letter position within a word, we used Wing and Baddeley's (1980) formula for equating letter positions in words of varying lengths. This formula was used by Caramazza *et al.* (1987) and Hillis and Caramazza (1989) to examine the spatial distribution of errors; we instead examined O.C.'s accuracy, rather than his errors, at each of the five standardized relative letter positions in response to stimuli of five letters or more (168 of the 240 words and nonwords in Table 1 were at least five letters long). Fig. 2 shows the frequency with which O.C., in writing and spelling aloud, placed the correct letters in each of these five positions. Fig. 3 shows the frequency with which the correct letters for each of these five relative positions appeared anywhere in his response, namely, in either the correct or incorrect position. The figures show that O.C. is most successful at writing the initial letter of a word and becomes progressively less accurate at later letter positions.

The effects of stimulus characteristics may also be important in distinguishing between different types of agraphia, although in O.C.'s case these are complicated by the interaction of two deficits. For the 350 words in Table 1 and in the homophone lists (*see* next paragraph), the mean length of the words correctly written or spelled aloud was 4.3 letters, significantly shorter than the mean length of the words spelled incorrectly, 5.1 letters ($P < 0.05$). For the 290 real words in Table 1 and in the homophone lists (*see below*), the mean frequency of usage of words correctly spelled was 265.5/million, significantly higher than that of words spelled incorrectly, 136.5/million ($P < 0.05$).

An important characteristic of disturbances of the lexical route in writing is a tendency to produce incorrect homophones (Hatfield and Patterson, 1983; Roeltgen and Heilman, 1984; Goodman and Caramazza, 1986; Rapcsak *et al.*, 1988). Roeltgen and Heilman's patients with lexical agraphia each produced incorrect homophones in response to about a quarter of the homophonic words dictated to them. O.C. was asked to write 36 homophonic words and to spell aloud 74. Each word was dictated to him, used in a sentence, and then repeated. He correctly spelled 22 (20.0%) of these words, 5 (13.9%) in writing and 17 (23.0%) aloud. He produced 17 (15.5%) homophone substitutions, 5 (13.9%) in writing and 12 (16.2%) aloud.

Reading

O.C. read aloud 26/26 upper-case printed letters correctly. He correctly pronounced the corresponding phoneme for 24/24 printed letters. He was asked to read aloud phonologically plausible nonwords, regular, and irregular words from the BLAWR. Each word was individually printed on a card in upper-case letters. Word length and

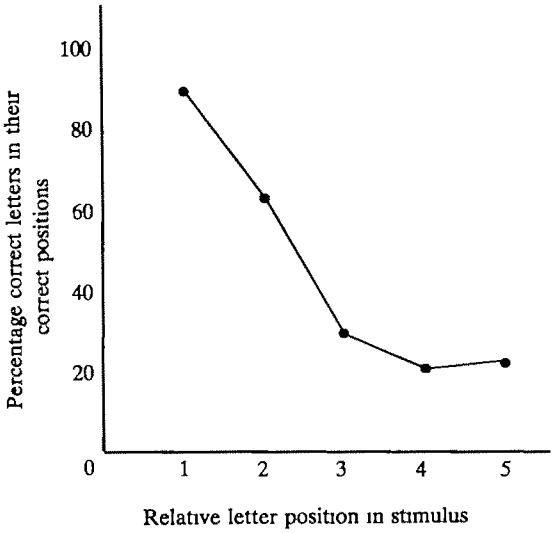

FIG. 2. Distribution of letters correctly written or spelled aloud in their correct positions by O.C as a function of letter 'position'. This figure is based on 168 word and nonword stimuli. The formula used to normalize letter positions in words of different lengths is taken from Wing and Baddeley (1980).

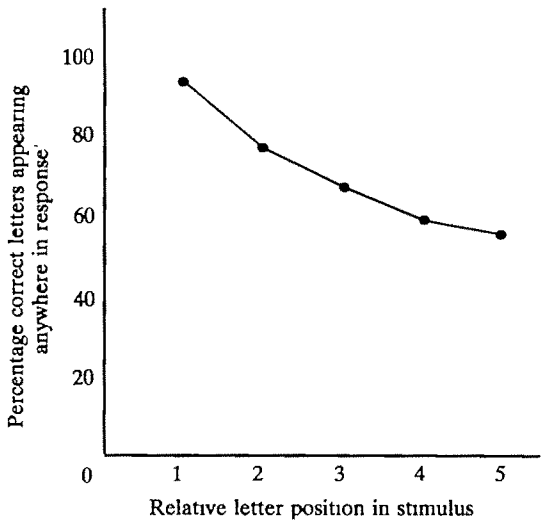

FIG. 3. Distribution, as a function of stimulus letter 'position', of letters present in O C.'s responses, whether placed in correct or incorrect positions This figure is based on responses to 168 word and nonword stimuli The letters from each position in the stimulus are here scored 'correct' if they appear anywhere in O C 's response to that stimulus.

frequency of usage were similar for the regular (means 6.4 letters and 68.7/million) and irregular (means 6.4 letters and 70.2/million) words. Even though the nonwords were shorter (mean 5.1 letters), it can be seen from Table 4 that O.C. read nonwords much more poorly than he did either class of real word. O.C. was also asked to read functors and contentive words from the BLAWR. These stimuli were matched for word length (mean 4.3 letters for each list). Although the functors were more frequently used (mean 4343.7 vs 262.6 per million) than the contentives, Table 4 shows that O.C. read the functors much more poorly than he did the contentives. We also had O.C. read lists of high and low imagery nouns balanced for regularity, length (mean 4.4 letters

TABLE 4 O C 'S READING PERFORMANCE

Stimulus category	*No. of stimuli*	*% correct*	*% omissions*	*% errors*
Letters	26	100.0	0	0
Nonwords	37	13.5	5.4	81 1
Regular words	31	77.4	12 9	9.7
Irregular words	33	69.7	21.2	9.1
Functors	40	62.5	22.5	15.0
Contentives	19	100 0	0	0
High imagery words	10	90 0	10.0	0
Low imagery words	10	80.0	10 0	10 0

each) and frequency (mean 151.4 and 151.5/million, respectively). As seen in Table 4, he performed similarly on the two groups of words.

When reading words and nonwords, errors tended to bear some orthographic similarity to the targets, that is, the two usually had several phonemes in common. Of 30 errors in reading nonwords, three were orthographically similar real words (e.g., DOP → DOPE; NUD → NUN) and 27 were neologistic nonwords with some similarity to the targets (e.g., JOFTIB → JOBBITY; ZIMNUL → ZAGLUE). In all instances but one, the correct initial phoneme was preserved in his erroneous verbal response. In reading real words, all errors were real words with some orthographic similarity to the target (e.g., EVENT → EVEN; SOVEREIGN → SOUVENIR). No semantic errors were seen (unless one accepts FABRIC → FIBRE). The only error that could be construed as derivational was ADVANTAGE → VANTAGE. Omissions were characterized by the statements, 'I don't know' or 'That's not a real word'. O.C. was never willing to hazard a guess at a real word he did not recognize although he admitted that when reading the nonwords, realizing that they were nonwords, he almost always guessed. When able to read a word correctly, O.C. could always provide a reasonable definition. When unable to read a word aloud he could not define it. If a word was incorrectly read as another word, he gave a definition corresponding to his response rather than to the stimulus.

O.C.'s difficulty reading nonwords with relative sparing of real words, both regular and irregular, his errors which orthographically resembled the stimuli, and his difficulty with functors led us to conclude that he had phonological alexia.

DISCUSSION

This left-handed subject presented after a right parietal infarct with linguistic agraphia and alexia, but not aphasia. His agraphia was not due to a memory disturbance as he could repeat a dictated word both before and after incorrectly writing it. His early history was compatible with developmental dysgraphia and dyslexia. He vividly recalled an inability to read or write phonetically and was illiterate until, as an adult, he was taught via a regimen of rote word memorization—as lexically oriented a system as one can imagine. Writing samples from this acquisition period support the hypothesis that he had a development phonological dysgraphia and learned to write lexically. Many of his errors then were phonetically incorrect, implying an impaired phonological system, and there was a remarkable tendency to repeat his errors, spelling a word in the same

incorrect way every time it appeared. In fact, in extant writing samples from this period, he never spelled a word in more than one way, suggesting a developing, but as yet imperfect lexical system with some incorrect but stable representations in the lexicon. Writing samples from recent years reflect a much greater command of written language. Rare errors that are phonologically incorrect likely reflect the lack of an effective phonological system. Campbell and Butterworth (1985) reported a subject, R.E., whose history was in many ways similar to O.C.'s before his stroke. R.E. also had developmental phonological dyslexia and dysgraphia and learned to read and write using a lexically oriented system of whole word memorization. She also achieved a high level of literacy but, like O.C., still made occasional errors which were not phonetically correct. Following his stroke, O.C.'s writing was severely impaired. With the exception of single letters, he performed extremely poorly at writing and spelling aloud all classes of stimuli. He showed neither the relative sparing of regular words and nonwords seen with lexical agraphia nor the sparing of real words typical of phonological agraphia. His letters were always well-formed, ruling out a peripheral motor disturbance as an explanation for his writing impairment. Severe impairment was seen for all output modalities tested (writing, spelling aloud, and anagram letters). Written naming was as impaired as writing to dictation. Copying was normal even when O.C. was asked to copy print as script, and upper as lower case. These characteristics effectively rule out a deficit any more peripheral in the writing system than the graphemic output buffer.

O.C.'s ability to accurately transcribe single phonemes illustrates preservation of phoneme-grapheme conversion but his extreme difficulty on LAC category II reflects a pronounced segmentation deficit, which presumably was responsible for his inability to learn to write phonetically. Following his stroke, O.C.'s writing deteriorated but did not display the typical features of phonological graphia. Thus, an acquired deficit has been superimposed on his developmental phonological dysgraphia with segmentation deficit. O.C. infrequently produced unpronounceable nonwords violating orthographic rules, a feature which is, by contrast, common in the writing of subjects with a deficit of the graphemic output buffer. Word length, frequency of usage, and part of speech all influenced O.C.'s spelling accuracy. The majority of his errors were not the graphemic deletions, substitutions, insertions, or transpositions characteristic of patients with graphemic buffer impairment. Instead, most of O.C.'s erroneous responses in writing and spelling aloud all classes of stimuli were phonologically incorrect neologisms which nevertheless often had letters in common with the stimulus. As shown in figs 2 and 3, O.C. was better at spelling the beginning of a word and became progressively less accurate as he continued towards its end. Although Hillis and Caramazza (1989) have ascribed a similar pattern (with a different error type) to graphemic buffer impairment in a subject with a *left* hemisphere lesion, this has been attributed to right hemineglect of a spatially coded representation within the buffer. If O.C.'s agraphia were due to a similar attentional mechanism, his *right* hemisphere lesion would be expected to produce, if anything, the opposite profile, with greater accuracy at the end of a word. For several reasons, it thus does not seem reasonable to attribute O.C.'s agraphia to graphemic output buffer impairment.

If O.C.'s infarct were to result in a lexical agraphia superimposed on his pre-existing phonological dysgraphia with segmentation deficit, one would also expect to see severe disruption in writing all classes of stimuli except single letters. No longer able to accurately

write using a lexical route and with no effective phonological route on which to fall back, he would be forced to rely on remaining function in these two imperfect writing routes. In arriving at spellings for words in this way, word frequency, length, and part of speech might all influence accuracy, as they do in O.C. His difficulty in writing homophones and frequent substitution of incorrect homophones has been reported as a characteristic of lexical agraphia (Hatfield and Patterson, 1983; Roeltgen and Heilman, 1984; Goodman and Caramazza, 1986).

Roeltgen *et al.* (1983*b*) and Bolla-Wilson *et al.* (1985) have shown that subjects with phonological agraphia with disruption of the segmentation component of the phonological writing route make characteristic errors. Like O.C.'s, their written productions share many letters with the targets but initial letters are much more often correct than are letters later in the word. Horowitz *et al.* (1968) suggested that the initial grapheme/phoneme of a word is its most salient, containing the most relevant discriminative information. O.C. thus made errors typical of phonological agraphia with impaired phonemic segmentation but was severely impaired at writing all classes of words, not just nonwords as in phonological agraphia. This is a pattern one would expect in a subject with phonological agraphia with segmentation deficit who has also sustained functional damage to the lexical writing route. We thus postulate that O.C. suffered from a developmental phonological dysgraphia with segmentation deficit, which he overcame by using lexical strategies localizable to his right parietal lobe. When his small right parietal infarct impaired his lexical writing route, he was forced to rely more on his ineffective phonological route, resulting in a combined phonological and lexical or 'phonolexical agraphia'.

Less can be said about the evolution of O.C.'s reading impairment as we have no prestroke examples of his reading and must rely on self-report. By history it seems most likely that he had a developmental phonological dyslexia and learned to read lexically. Testing after his stroke reveals typical characteristics of phonological alexia (Patterson, 1982). Like Campbell and Butterworth's (1985) subject, R.E., O.C. usually produces neologistic responses to nonwords and does not tend to 'lexicalize' or read nonwords as visually similar real words as is common in acquired phonological alexia (Patterson, 1982; Funnell, 1983). Patients with acquired phonological alexia may read nonwords as visually similar words because these nonwords are able to 'activate' lexical entries for similar real words, unchecked by phonological confirmation. O.C. and R.E., on the other hand, who have achieved literacy in the absence of an effective phonological route, have perhaps had to develop a more discriminating lexical reading system which does not as readily accept a word as another visually similar word, which recognizes a nonword as a nonword but, due to poor phonological functioning, can only offer an approximate nonword rendering. Although O.C. sometimes failed to recognize a real word and said that it was not a word, he always refused to guess at it while he confessed to usually guessing at nonwords. We might surmise that his alexia worsened following his stroke but, without prestroke testing, we can conclude little else.

The right posterior parietal localization of O.C.'s stroke is consistent with the location of lesions responsible for lexical agraphia in the left (Roeltgen and Heilman, 1984) and in the right hemispheres (Gonzalez Rothi *et al.*, 1987), lending support to the contention that one or the other posterior parietal lobe is essential to the lexical route in writing. No lesion is visible to explain O.C.'s developmental literacy problems. Galaburda *et al.*

(1985) have documented microscopic abnormalities predominantly affecting the left perisylvian regions of patients with developmental dyslexia and dysgraphia.

O.C.'s lack of aphasia after his right parietal stroke may reflect left hemisphere dominance for speech, or may relate instead to the small lesion size as aphasia is usual but not invariable in dextrals with agraphia or alexia after left hemisphere lesions (Dubois *et al.*, 1969; Damasio and Damasio, 1983).

This case, like that of Campbell and Butterworth (1985), illustrates that written language deficits can be overcome in at least a subtest of cases by using an alternate educational strategy, in this case lexical rather than phonetic. In O.C.'s instance, a right parietal anatomical substrate can be inferred for this acquisition. To what extent this localizing information and the characteristics of the agraphia can be generalized remains to be seen. Further cases with acquired deficits superimposed on developmental language disorders are likely to be rare but instructive.

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APPENDIX

STIMULI GIVEN TO O.C., FOLLOWED BY HIS RESPONSES

Writing to dictation

(a) Nonwords		(b) Regular words		(c) Irregular words	
TRAD	TAIRD	TRANSFER	TRAFAD	MISCHIEF	MIHCER
PABLE	PALIE	NEGLECT	+	TOMB	TOOAM
TERRIAGE	THI	MASK	MAX	HONOR	ONHAR
MANVER	NAMIFD	PITIFUL	PIFTFAL	DENY	DIERE
JISP	GIGFI	MOTOR	MONTAR	CIRCUIT	CE
BIROUGH	BARORD	SINK	CENK	HEIR	HIRE
ZILLER	ZEALID	FORGET	FORCUT	ENGINE	ENGRON
QUIM	QUMEN	HOLDER	HLOUD	BOUQUET	BOUKEY
VATTER	FITED	ADMIT	ADMAT	SHOES	SHOUE
BLIME	+	HOLY	HOLLAT	WEAPON	WIPIN
SOUD	+	INJURY	INGJRE	CHORD	CORD
CIMY	SIMAD	MAKER	MAKRE	YACHT	EYOUT
SCOMB	CONSE	FACTOR	FACTER	PALACE	PALTIST
ILLEND	ELAN	HUNGER	HUNTER	FRIEND	FOREN
TROOGE	THRUG	DAMP	DIAE	BUSY	BISEZ
CRANG	CRAG	PINCH	PINER	ISLE	IL
PHEKE	FLEGT	SUBMIT	SBMIAT	CORPS	CORE
THUSE	THGOU	CORN	CAN	ANSWER	ANCENT
SLEM	SELAM	DIVINE	DVIAN	BUOYS	BOUT
SLIG	CEGEI	HOTEL	HOLTEEL	HYMN	HIMM
TRALF	TRUCH	GRAND	GRATIN	BREAST	BRESET
STRICK	STICH	HALTER	HOTLTER	EARTH	EARS
BARCLE	BARCH	OPEN	OPTAN	MENACE	MEASET
MOFER	+	INFORM	INFROM	BOMB	BOND
ISLECK	ILET	VETERAN	VACTION	SURE	SCHURE
VYTE	VRLER	VENT	VEAT	GLACIER	GIASHR
ANDON	ANGON	STAR	STARE	MORGUE	MOBGER
INTRET	INTHER	DARN	DAMR	SUBTLE	SETRAL
THEAWAY	THAWA	STAND	SAN	AISLE	IRALE
NACE	NAIC	MATCH	MATICH	YOLK	YOKE

(d) Functors		(e) Contentives		(f) Homophones	
ALTHOUGH	ALTHUR	GENERAL	GENA	SEA	SEIE
HOWEVER	HOWEAER	MONEY	MONDAY	NIGHT	MIGAT
WHOSE	HOSER	HELP	HAEP	HAIR	HERIE
SHALL	CLERL	COLLEGE	CALGET	SLAY	SL
THUS	THART	BEST	BESTER	YOKE	(Omission)
EVER	EVERN	INTEREST	INTRESL	HOES	HOLDS
SHOULD	SHOUD	PART	PERT	CORD	SORED
UPON	UPROUN	PEOPLE	POPLITY	CLOTHES	CLAST
THOUGH	THPOW	TAKEN	TAKING	FLEE	FLED
ALREADY	ALREAD	NUMBER	NUMTER	BAWLED	BALD
ALMOST	AMOST	UNITED	UNIGHT	CAUGHT	(Omission)
MAYBE	MAYBEE	METHOD	MADFOED	SELL	SEALD
WHOM	HOME	DEEP	+	FIR	FUR
NONE	NUMER	LEADER	+	RING	RIND
NEARLY	NALER	CLUB	+	ROSE	+
ELSE	EALSE	TRIAL	TRYRALL	PANE	PAINE
ALWAYS	AWAY	LIVE	+	PAIR	PARY
AMONG	ARMOUN	POINT	PONT	SON	SUN
WHETHER	WHER	PUBLIC	PUBLEAR	SEE	SEAE
WHERE	WHARE	YEARS	YEAR	CLOSE	+
NOBODY	NOBOUY	MAJOR	MARGER	KNIGHT	NIGHT
QUITE	QU	HISTORY	HISTORE	HARE	HERE
STILL	STRAL	STATE	+	SLEIGH	SLAID
EACH	EATECH	WORK	+	YOKE	YOUE
BOTH	BOATH	LONG	LOND	HOSE	HOUSE
ONCE	OUNCE	HIGH	+	CHORD	CORE
EVERY	EVARE	SMALL	SMALE	FLEA	FLEED
THINGS	THERTIN	LOOKED	LOOK	BALD	BOULD
WITHIN	WHEIN	CHURCH	CHERE	COT	COUD
ITSELF	ITSALE	MATTER	MATLAR	CELL	SEALD
				FUR	FURD
				WRING	RING
				ROWS	ROW
				PAIN	+
				PEAR	+
				SUN	+

(g) Written naming

Stimulus	Written naming	Writing to dictation
BAND	+	+
RING	+	+
CARD	+	CORD
SPOON	SPO	SPOOLEN
BRACELET	BRACLET	BRACLET
PENCIL	PENNCEL	PINCEIL
ASHTRAY	+	+
PURSE	POT	PURESH
PAPER	PAPPER	PAPPER
WALLET	+	WAILLOTE
DOLLAR	DOLLER	+
KEY	QUTLER	QULIE
BOOK	+	BOOOK
PEN	+	+
SHIRT	TSH	+

Spelling aloud to dictation

(a) Nonwords

NID	NEID
BAP	BAT
RIN	RENG
FALKO	THUOGH
RITKON	RITCOME
BUTCHO	BUOGH
RIBBLE	RIDRON
GUDIN	GOODING
SIBWAR	SISBRY
BLUMPKIN	BUMPKEN
GIBSOG	GIBSAW
FLISHIB	FLISHBR
KROGUD	CROWER
TRAG	TRIAG
LUTCHO	LUCO
KAFMAL	CATMUOT
HANFIM	HIMFEN
TEDDLE	TIAL
BAFLOD	BIFLOC
RABZIL	RABSULD
JOFTIB	JOBIFLE
KELBON	KLBON
VAGGLE	+
NIBER	NIBBIC
OBJOL	OLBJOR
JISH	JUISE
FOSH	FROUGH
BLIB	BLUD
KOLAT	COLLLAP
FLIG	FURLINE

(b) Regular words

SELL	SILER
PATIENTS	PANC
ARTIST	ARTTESE
INSECT	INSCENCE
ABDOMEN	ADDMENT
NEWSPAPER	NEWPAPPER
PROSPERITY	PROSTTER
LIBRARY	LIBBRE
HOLE	HOLD
ARMY	ARIME
GENTLEMAN	GENTMAN
FRUIT	FRU
GRASS	GREET
ARC	ARCH
ANGER	ANGLER
EAR	EIR
ANIMAL	AN
BARE	(Omission)
BUY	BY
CHAIR	CHIR
MEET	MEAT
BALE	+
THRONE	THROUGH
LENDS	LENDSEN
BAIL	+
BUTTER	BUTER
FLESH	FL
PAIL	+
BEAST	BES
CHIEF	CHEF

(c) Irregular words

KNOT	(Omission)
MENACE	MINNES
PLUMB	PLUM
MISCHIEF	MISSCH
WRAP	WIP
WEAPON	WHEPIN
SCENE	SLEN
SIGHED	SIDE
PRESTIGE	PRESTAGER
BOROUGH	BROW
TROUBLE	TRUBELEF
EYE	(Omission)
SHOES	SHOUSE
KNOWS	KNO
HEIR	ARIE
PRAIRIE	PRE
SCENT	CENTER
PALACE	PALICE
ISLE	ILEREY
EARTH	EARGH
CHORD	CORD
SKY	SKI

(d) High imagery words

CITY	+
BOOK	+
CHAIR	CHIR
BODY	+
DRESS	+
ANIMAL	ANI
CORN	+
ARM	+
CHILD	CHI
ARMY	ARIME

(e) Low imagery words

FATE	+
LAW	+
EVENT	+
DUTY	+
HONOR	(Omission)
ADVICE	+
IDEA	ID
FACT	FAT
HOPE	+

(c) Irregular words		(e) Low Imagery words	
GUILT	GULED	TRUTH	TRUE
VILLAGE	VILGET		
HOUR	+		
OCEAN	OCEEN		
HONOR	(Omission)		
DOUGH	DO		
WEAR	(Omission)		
REIGN	RANNER		

(f) Homophones

CELL	SEAL	BOWLED	BOW
RODE	ROUD	RIGHT	+
MAIL	+	BEEN	BENN
GALE	GALER	COLONEL	(Omission)
AIL	YALE	CORPS	CORER
MEET	MEAT	KNEAD	NEED
BAIL	+	LEAD (Pb)	LED
WHERE	WHIRE	LENDS	LENDSN
GAIL	(Omission)	ACTS	ACTER
HEIR	HIRE	AWL	ALD
I'LL	IL	BASS	+
WHOLE	HOLD	BEAU	BOW
SELL	SILER	BOW (ship's)	(Omission)
MALE	MILE	BARE	(Omission)
ROAD	ROB	CHORD	CORD
ALE	+	GUILT	GULED
MEAT	+	KNEW	NEW
BALE	+	HEARD	HERD
WEAR	(Omission)	HIGHER	+
AIR	+	HYMN	HIMMER
SIGHED	SIDE	WHOLLY	HOLER
HOLE	HOLD	HOUR	+
EYE	(Omission)	KNIGHT	NIGHT
BEAT	BEEAT	CACHE	CASH
DEAR	+	CASTE	CASH
FEET	+	SIGHT	(Omission)
THRONE	THOROUGH	CLIMB	CLAME
ONE	+	MIGHT	MINET
FLEA	FLEED	KNIT	KI
PAIL	+	KNOW	+
SALE	+	NONE	NUNN
DEW	DOW	TAIL	TALE
KNOT	(Omission)	EIGHT	+
ARC	ARCH	PATIENTS	PANC
SEALING	CELN	PLUMB	PLUM
THYME	THTHME	PREY	PRA
DOUGH	DO	HARE	HIRE

Reading aloud

(a) Nonwords		(b) Regular words	
NID	+	ANIMAL	+
BAP	(Omission)	GREEN	+
BUTCHO	butʃio	INTEREST	+
BLUMPKIN	+	FREEDOM	+
FLIM	FLIN (flɪn)	FROG	(Omission)
NUD	NUN	ADVICE	+
JAF	dʒæd	HISTORY	+
HOMFIS	+	REFLEX	REFLUX
JOFTIB	dʒɒbɪt	CONTRACT	+
LODAR	lodɹ	MASTER	+
RABZIL	+	ATTITUDE	+
KAKMIN	kʌmɪn	CORNER	+
TIBBLE	tɪbɪɹ	SADNESS	+
VAGTOB	vægɑrɪn	SPEECH	+
TRAG	+	CHIN	(Omission)
BEP	BEEP	MAGNITUDE	+
KAFMAL	(Omission)	LETTER	+
GOF	gɔrdz	BOTTLE	+
KACNIM	ket	INDUSTRY	+
RIBBLE	rɪn	GARDEN	+
SIBWAR	sæf	BLANDNESS	BLINDNESS
JISH	dʒɹʃə	HARNESS	+
DOD	dub	SUNSET	+
JAD	dʒæl	LOYALTY	+
FIMKO	fipe	VICTIM	+

(a) Nonwords

PUD	pʊŋjo
VAGGLE	vædʒɪdʒɪdʒɪ
LUMRIN	lʌmbərɪnz
KOLAT	kolɛp
PISHNEP	pɪʃmɪr
KELBON	ɪlɪbon
DOP	DOPE
ZIMNUL	zɛglu
OBJOL	obɔdʒab
FLIBBIK	fɛʃɔbɪ
JOSFID	dʒɔɔsɑfɪdɪ
FLISHIB	fɛʃbɔr

(b) Regular words

BRAVERY	(Omission)
EFFORT	+
NUTMEG	(Omission)
FLASK	+
FABRIC	FIBRE
BANDIT	+

(c) Irregular words

CHIEF	+
DEATH	(Omission)
ADVANTAGE	VANTAGE
ENGINE	+
TOMB	+
CIRCUIT	+
VILLAGE	+
HEAVEN	+
JEALOUSY	(Omission)
HEALTH	(Omission)
SOVEREIGN	SOUVENIR
SWAMP	+
ANSWER	+
THOUGHT	+
BREAST	+
PLEASURE	+
LIMB	(Omission)
EARTH	+
RITUAL	+
MARRIAGE	+
JUSTICE	+
WALL	+
EDIFICE	(Omission)
BEVERAGE	+
MORGUE	MORTGAGE
KERCHIEF	+
COMRADE	+
MEADOW	+
FRIEND	+
HONOR	+
HOSTAGE	+
GLACIER	(Omission)
EPISTLE	(Omission)

(d) High imagery words

CITY	+
BOOK	+
CHAIR	+
DRESS	+
ANIMAL	+
BODY	+
CORN	(Omission)
ARM	+
CHILD	+
ARMY	+

(e) Low imagery words

FATE	(Omission)
LAW	+
EVENT	EVEN
DUTY	+
HONOR	+
ADVICE	+
IDEA	+
FACT	+
HOPE	+
TRUTH	+

(f) Functors

WHY	(Omission)
SHALL	(Omission)
THE	+
HAS	(Omission)
FROM	+
ABOUT	+
WHO	+
THESE	(Omission)
WHILE	(Omission)
SHOULD	SHOULDER
UNTIL	+
WAS	+
ALSO	+
QUITE	QUIET
MUCH	(Omission)
WITH	WIT
THOUGH	THOROUGH
AND	+
VERY	+
EVER	+
SINCE	SIN
GET	+
WHEN	+
THAT	+
USUALLY	(Omission)
HAD	+
THEN	+
WHATEVER	+

(g) Contentives

ARM	+
RIVER	+
BODY	+
WALL	+
CHAIR	+
BLOOD	+
BOY	+
GOLD	+
FRIEND	+
WORLD	+
MAN	+
BED	+
BOOK	+
WATER	+
FOOT	+
MOTHER	+
CAR	+
WOMAN	+
TOWN	+

ONCE	+
THOSE	+
WERE	+
HOW	+
NOR	(Omission)
OUGHT	OUCH
THUS	(Omission)
WHERE	+
AS	+
HOWEVER	+
ELSE	+
THIS	+

+ = correct response

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TRUNK ORIENTATION AS THE DETERMINING FACTOR OF THE 'CONTRALATERAL' DEFICIT IN THE NEGLECT SYNDROME AND AS THE PHYSICAL ANCHOR OF THE INTERNAL REPRESENTATION OF BODY ORIENTATION IN SPACE

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SUMMARY

The present study examines which egocentric coordinate system determines the border between the disturbed 'contralateral' and the normal 'ipsilateral' side in patients with hemineglect. Based on the observation of significantly longer reaction times for saccades towards stimuli presented in the left visual field (LVF) in right brain-damaged patients with hemineglect, stimuli were presented randomly to the LVF or RVF and the corresponding saccadic reaction times (SRTs) were compared. Beginning with the standard body position generally used for the investigation of neglect patients, where the midlines of head, trunk and visual field are parallel and oriented straight towards the middle of the projection screen, the spatial relation between orientation of head and trunk midlines and location of the target stimuli was systematically varied while holding the retinal projection of the stimuli constant. The deficit in SRTs towards the LVF in 4 right brain-damaged patients with left-sided hemineglect could be compensated for by turning the patients' trunk to the left, such that both LVF and RVF-stimuli were projected to the right, ipsilateral side of trunk space. The results suggest that the spatial orientation of the trunk midline divides our normal perception of space into an egocentric 'left' and an egocentric 'right' sector and seems to be the decisive factor for determining the neglected 'contralateral' part of space in patients with brain-damage. They indicate that the trunk midline constitutes the physical anchor for calculation of the internal egocentric coordinate frame for representing body position with respect to external objects. The hypothesis of Ventre *et al.* (1984) that deficient reactions to contralaterally located stimuli in neglect patients could be the result of a displacement of these egocentric coordinates towards the non-neglected, ipsilateral side is discussed.

INTRODUCTION

Regardless of whether the neglect syndrome is considered to represent an impairment of attentional systems (Mesulam, 1981, 1985; Kinsbourne, 1977, 1987; Baynes *et al.*, 1986; Gainotti *et al.*, 1986), a cognitive deficit involving the mental representation of space (De Renzi *et al.*, 1970; Bisiach *et al.*, 1979, 1981) or a result of the combined effect of several different components of disturbance (Karnath, 1988), all of these authors found the patients unable to report, recognize or respond to a stimulus on the side contralateral to the lesion as compared with the ipsilateral side.

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The present study examined which egocentric coordinate system divides the spatial field into a 'left' and a 'right' hemispace. Several studies have shown that for visual stimuli, information can even be derived to some extent from the neglected visual field (Volpe *et al.*, 1979; Karnath and Hartje, 1987; Marshall and Halligan, 1988) and that the border between the disturbed 'contralateral' and the normal 'ipsilateral' side is not determined by retinal coordinates (Gentilucci *et al.*, 1983; Rizzolatti *et al.*, 1985; Johnston and Diller, 1986; Posner *et al.*, 1987; Huber *et al.*, 1988).

Huber *et al.* (1988) investigated the eye movement behaviour of a patient with left-sided hemineglect without hemianopia while reading. They found that the return sweeps which were started from the end of a line stereotypically ended in the middle of the next line and not—as could be observed in normal readers—close to the beginning of the next line. The return sweeps were followed by silent backwards reading until a linguistically plausible continuation of the previous line was found, irrespective of the actual beginning of each line. The shortened return sweeps could not be attributed to oculomotor impairment because the patient was able to plan and to perform long saccades from the right to the left border of the text projection screen when this was requested by the investigator. Both deviant types of behaviour—shortened return sweeps (mean length: 11.5°) and saccades which were followed by the sweeps (mean length: 1.2° and 2.4°)—were planned from the current point of fixation contralaterally into the LVF. The authors therefore concluded that the reason for the different performance of the two types of leftward directed eye movements in reading cannot be attributed to the retinal border between the LVF and RVF, but must instead be influenced by the head/trunk midline which in this case was identical with the middle of the projection screen and the texts.

The present study investigated whether the midline of the trunk and/or head serves as a plane for dividing space into a 'right' and a 'left' sector in causing a neglected 'contralateral' and a normal 'ipsilateral' side in brain-damaged patients with neglect. Saccadic reaction times were observed, which had proved to be a sensitive variable for measuring differences between LVF and RVF performance in patients with hemineglect (Girotti *et al.*, 1983). In their study, the analysis of eye movements following randomly presented spots of lights 10°, 20° and 30° peripheral to the central fixation point in the LVF or RVF revealed 3 symptoms of pathological eye movement behaviour in patients with right hemisphere lesions and additional hemineglect. The authors found (1) longer saccadic reaction times for stimuli presented in the LVF when compared with those in the RVF, (2) complete absence of saccades in 25% of the trials to stimuli presented in the LVF and (3) comparable with the results of Perenin and Vighetto (1983) or Huber *et al.* (1988), a saccadic step pattern for eye movements directed leftwards caused by reduced amplitudes of saccades. Similar results in saccadic eye movement behaviour were also described in monkeys after lesions of the parieto-occipital cortex (Lynch and McLaren, 1989).

Girotti *et al.* (1983) examined their patients in the standard body position usually employed for investigations of neglect patients where the midlines of head, trunk and visual field were parallel and oriented straight towards the middle of the projection screen. In the present study the spatial relation between orientation of head and trunk midline and location of the target stimuli was systematically varied while holding the retinal projection of the stimuli constant.

METHODS

Subjects

The brain-damaged patients were selected on the basis of their CT scans and clinical signs. The neuropsychological examination of each patient included the random letter cancellation task (Mesulam, 1985), line bisection, copying of a flower, completion of a clock face, the clinical confrontation method with visual, auditory and somaesthetic stimuli, and a tachistoscopic naming task (Karnath, 1988) of randomly presented photographs of geometric figures unilaterally in the RVF or LVF or bilaterally in both visual half-fields with a presentation time of 180 ms. The tachistoscopic task proved to be a sensitive method for detecting deficits even in the recovered stage of a neglect syndrome, when any other clinical signs of a lateralized disorder are no longer apparent. Hemineglect was accepted when clinically manifest symptoms could be observed in at least 2 of the 6 different tasks.

The following additional criteria had to be fulfilled: (1) the lesion had to be circumscribed in the CT scan and restricted to one hemisphere; (2) no clinical or CT evidence for diffuse or multiple lesions was detectable; (3) the visual fields were required to be intact, as tested by Goldman perimetry with white 0.25 mm^2 and 16 mm^2 targets; (4) cases of cerebral contusion were excluded if there was clinical or CT evidence of a contre-coup injury; and (5) with the exception of antiepileptic drugs, no sedative medication was allowed.

A group consisting of 4 patients with right hemisphere lesions and clinically manifest neglect but without any visual field defects, e.g., hemianopia, were examined (Table 1). Two groups of subjects served as

TABLE 1 CLINICAL AND DEMOGRAPHIC DATA OF THE PATIENT GROUPS WITH RIGHT HEMISPHERE LESIONS (R1–R4) AND THOSE WITH LEFT HEMISPHERE LESIONS (L1–L4)

Case no.	*Age (yrs)/sex*	*Aetiology*	*Location of lesion*	*Hemineglect*	*Time since lesion (days)*
R1	47/F	Infarct	R temporoparietal	+	33
R2	40/F	Contusion	R frontolateral	+	20
R3	54/F	Haemorrhage	R basal ganglia	+	640
R4	46/M	Infarct	R temporoparietal	+	60
L1	58/M	Infarct	L frontal	–	355
L2	51/M	Infarct	L basal ganglia	–	35
L3	30/M	Haemorrhage	L fronto-occipital	–	17
L4	52/M	Infarct	L basal ganglia	–	47

controls. The performance of the neglect patients was compared with a group of 4 patients with left hemisphere lesions without neglect symptoms or visual field defects (Table 1) and a group of 13 normal subjects aged from 27 to 42 (median 32) yrs.

The performance of the patients with right hemisphere lesions in the tachistoscopic naming task is given in Table 2. Besides other typical neglect symptoms (observed with the additional tasks described above), in each of these 4 neglect patients the usual difference was detected between normal LVF and RVF performance under unilateral conditions of stimulus presentation and decreased (correct) naming performance in the contralateral LVF when the stimuli were presented bilaterally. (Under both conditions of stimulus presentation, non-brain-damaged neurological patients achieve responses between 95% and 100% correct in both visual half-fields (*cf* Karnath, 1988).)

Procedure

The possible influence a change in trunk and/or head orientation might have on the SRTs was tested systematically under 5 different test conditions. In each of the 5 conditions, the retinal projection of the target stimuli was held constant by directing the subjects' gaze towards a fixation point before presentation of a target stimulus. A peripheral target (red spot of light) appeared randomly at a horizontal eccentricity of 7° from the fixation point (white spot of light) in the LVF or RVF. The stimuli were presented on a computer monitor The size of the fixation point was 0.07°, the target size 0.30°. The temporal sequence

TABLE 2 PERCENTAGE OF CORRECT NAMING RESPONSES FOR LVF AND FOR RVF STIMULI GIVEN BY THE PATIENTS WITH RIGHT HEMISPHERE LESIONS (R1–R4)

	*Condition of presentation**			
	Unilaterally		*Bilaterally*	
Case no.	*LVF*	*RVF*	*LVF*	*RVF*
R1	77	90	0	82
R2	92	92	55	88
R3	97	98	72	92
R4	95	95	73	90

* Under each condition the maximum possible number of correct naming responses was n = 60 in each visual half-field.

of fixation point and target onset and offset is illustrated in fig. 1. A temporally overlapping presentation of the fixation point and the target was used, because in this paradigm unimodal distributions of long reaction times are usually obtained (Mayfrank *et al.*, 1986; Fischer and Breitmeyer, 1987). The subjects were instructed first to look at the central fixation point, and then to shift their gaze towards the target as soon as it appeared. Those trials in which deviations from the fixation point occurred were excluded from further analysis.

The subjects were seated on an experimental chair which was aligned with the centre of the computer monitor and the location of the fixation point. The head was stabilized by a chin rest. Both the chin rest and the seat could be fixed independently in different rotational positions. In 4 of the 5 different test conditions, either the head or the trunk was turned 15° to the left or right. The chin rest oriented the head in the desired position and a shoulder strap fixed the subject's trunk, when the seat of the chair (and consequently the trunk) was turned 15° to the right or left. The horizontal eye movements were recorded by an infrared light technique using an electric threshold detector which stopped a millisecond counter triggered by the onset of the target (Gauthier and Volle, 1975). The direction and amplitude of the saccades were determined with an oscilloscope. Thus artefacts, for example, blinks, could be excluded from the analysis. Under each test condition, the SRTs were measured for 75 saccades following LVF and 75 saccades following RVF stimuli. In addition, the frequency of 3 different error-types was recorded. (1) 'Error in direction': when the stimulus lit up in one visual half-field the subject performed a saccade to the opposite half-field. (2) 'Omissions': the subject did not react to the onset of a peripheral target within 800 ms (*see* fig. 1). (3) 'Error in amplitude': the subject did not reach the target with a single saccade and corrected it by performing further steps.

The 5 test conditions differed as to head and trunk position. In Condition I—the 'baseline condition'—trunk and head were facing the centre of the monitor straight ahead where the fixation point was presented. By turning the head or the trunk for 15° in Conditions II to V, alternating projections of the LVF and RVF target stimulus to the left or right space of the head or trunk midline were achieved (fig. 1). The 5 conditions were tested in the following order.

Condition I ('baseline condition'). The LVF-stimulus was projected to the left half of trunk space and head space, the RVF stimulus to the right half of trunk and head space.

Condition II. Both the LVF and RVF stimuli were projected to the right half of trunk space. The LVF stimulus appeared to the left of the head, the RVF stimulus to the right of the head.

Condition III. Both the LVF and RVF stimuli were projected to the left half of trunk space. The LVF stimulus appeared to the left of the head, the RVF stimulus to the right of the head.

Condition IV. Both the LVF and RVF stimuli were projected to the right half of head space. The LVF stimulus appeared to the left of the trunk, the RVF stimulus to the right of the trunk.

Condition V. Both the LVF and RVF stimuli were projected to the left half of head space. The LVF stimulus appeared to the left of the trunk, the RVF stimulus to the right of the trunk.

Statistical methods

The median SRT of each subject for LVF and for RVF stimuli under the different test conditions were used separately for further analysis. For the analysis of the SDs of the SRT distributions, of the frequencies

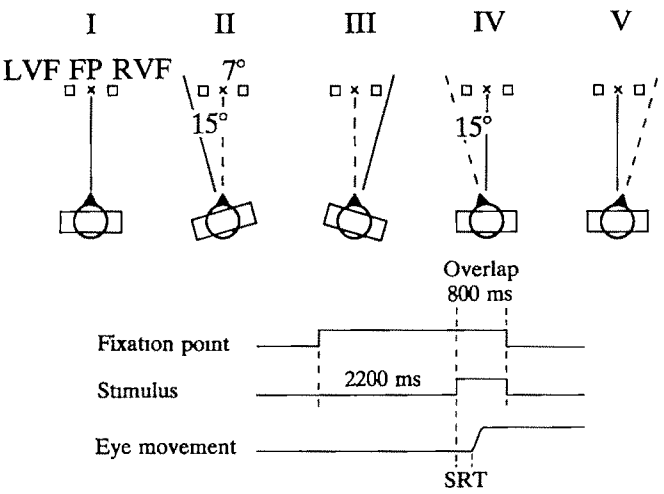

FIG. 1. The 5 different test conditions and the temporal sequence of fixation point and target onset and offset used in the examination. The central fixation point remained visible when the peripheral target appeared (overlap paradigm). SRT = saccadic reaction time. The spatial relation between the orientation of head and trunk midline and the location of the stimuli is illustrated as seen from above. The trunk is represented by a rectangle, the head by a circle. Square = target; X = fixation point (FP); broken lines = head midline; continuous line = trunk midline. In all test conditions, only 1 target was projected per trial unilaterally to the LVF or the RVF (never bilaterally).

of 'omissions', 'errors in direction' and of 'errors in amplitude', the arithmetical means were used accordingly. Because of the skewed distribution, we used a logarithmic transformation for the analysis of the SDs. For the same reason, an angular transformation (Kirk, 1968) was used to analyse the frequencies of omissions and the two other types of errors.

For all variables—SRTs, SDs of the SRT distributions, omissions, errors in direction and errors in amplitude—repeated measure analyses of variance (two-tailed, alpha-level = 0.05) were carried out, which analysed the factors 'Test Condition' (I–V) and 'direction of saccades' (LVF vs RVF) as within-subject fixed effects and the factor 'patient group' as the independent variable. In view of Hager and Westermann's (1983) proposal for post hoc comparisons, the t-test for independent samples (two-tailed) and for paired samples (two-tailed) was used. The overall alpha level of 0.05 was corrected according to the multiple-test procedure of Holm (1979).

RESULTS

Saccadic reaction times

Comparable with the data of Girotti *et al.* (1983), in Condition I (the 'baseline' condition, where the midlines of head, trunk and visual field were parallel and oriented straight towards the middle of the projection screen) the patient group with right hemisphere lesions and hemineglect produced longer SRTs to the contralateral LVF than to the RVF (fig. 2). The repeated measures analysis of variance (data of fig. 2) with factors 'patient group' and 'direction of saccades' revealed a significant interaction ($F(2,90) = 7.47$, $P = 0.004$). Post hoc comparisons yielded a significant difference between SRTs for stimuli in the RVF and LVF only for the patient group with right hemisphere lesions ($t = 4.94$, $P = 0.016$). For the patient group with left hemisphere

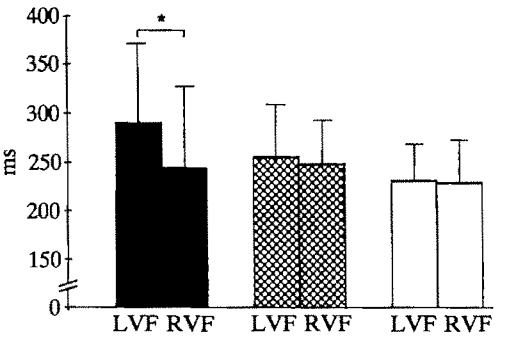

FIG. 2. Mean saccadic reaction times to LVF and RVF stimuli in test Condition I (the 'baseline condition') for the two patient groups and the group of normal subjects Filled columns = right brain-damaged patients, cross-hatched columns = left brain-damaged patients; open columns = controls. Asterisk = significant difference.

lesions and the group of normal subjects, no significant differences between SRTs to the LVF and RVF could be discerned under 'baseline' Condition I.

An overview of the average SRTs measured in all 5 test conditions for stimuli in the LVF and RVF is given in fig. 3. The repeated measure analysis of variance (data of fig. 3) revealed a significant interaction between the 3 factors 'patient group', 'test condition' and 'direction of saccades' ($F(8,180) = 6.99$, $P < 0.001$). Thus for the SRTs to the LVF and those to the RVF, two separate repeated measure analyses of variance were carried out.

The analysis for SRTs to the RVF revealed no significant result. Both main effects

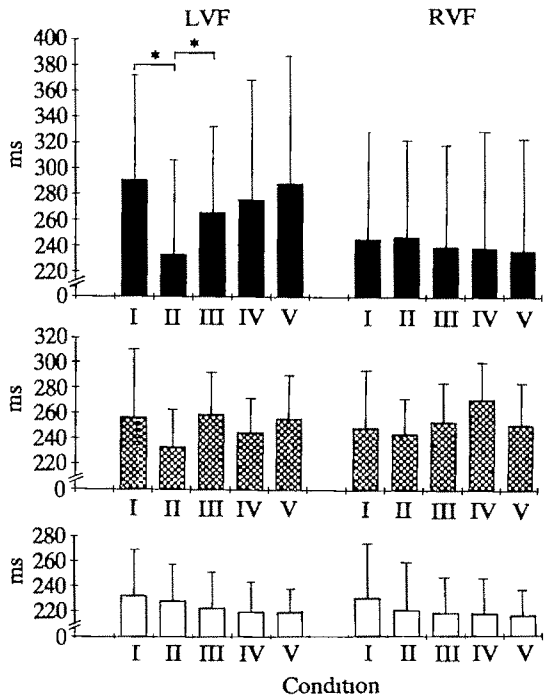

FIG 3. Overview of the mean saccadic reaction times in test Conditions I–V for the two patient groups and the group of normal subjects Symbols as in fig 2.

and the interaction were insignificant. The analysis of SRTs to the LVF, however, yielded a significant interaction ($F(8,90) = 4.75$, $P < 0.001$). In answer to the question whether the contralateral LVF deficit measured in the 'baseline' Condition I can be compensated by a rotation of the trunk or the head, in post hoc comparisons the SRTs of Conditions II–V were compared with 'baseline' Condition I for each group of patients. These post hoc comparisons of the SRTs measured for the patients with left hemisphere lesions and for the group of normal subjects revealed no significant result. A significant difference was found only in the patient group with right hemisphere lesions and hemineglect and only between 'baseline' Condition I and Condition II ($t = 5.83$, $P = 0.010$) when the trunk was turned to the left (fig. 3).

From fig. 3 it may appear that turning the trunk to the right under Condition III also improved the SRTs to the LVF of the patient group with right hemisphere lesions. Post hoc comparisons, however, did not confirm this impression. On the one hand, the comparison of 'baseline' Condition I with Condition III revealed no significant result. On the other hand, a significant difference was found between Conditions II and III ($t = 3.65$, $P = 0.035$).

The statistical analysis showed that only in Condition II, when the trunk was turned 15° to the left allowing both LVF and RVF stimuli to be projected to the ipsilateral side of trunk space, did the mean level of SRTs to LVF stimuli differ for the right brain-damaged patient group significantly from their slowed LVF performance in 'baseline' Condition I. Selectively under this test condition the LVF performance improved and reached the level that was measured for the SRTs to RVF stimuli in the 5 test conditions. Fig. 4 shows that the marked improvement of SRTs from Conditions I to II in the LVF was not only an effect of group statistics. In every neglect patient, this characteristic pattern could be observed.

Under Condition III the trunk midline of the neglect patient group was turned to the right, which allowed both target stimuli to be located on the contralateral side of the

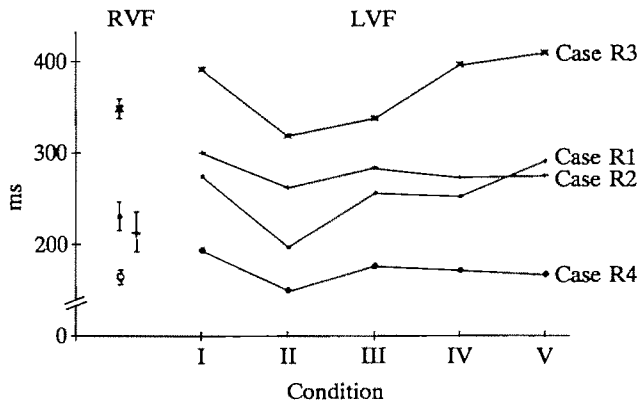

FIG. 4. Medians of saccadic reaction times to stimuli presented in the LVF in test Conditions I–V for the 4 neglect patients with right hemisphere lesions (R1–R4) To give an intraindividual comparison, the medians of the SRTs to RVF stimuli were averaged over all 5 test conditions and presented in the diagram.

trunk midline. In this position no significant differences from the mean levels of SRTs towards the LVF and the RVF stimuli obtained under 'baseline' Condition I were found. Also no significant changes from the 'baseline' SRTs could be observed when the head orientation was turned to the left and to the right under Conditions IV and V. In the left brain-damaged patient group and the group of normal subjects, the SRTs to the LVF and the SRTs to the RVF did not differ statistically under any of the 5 test conditions. This was also the case for the right brain-damaged patient group for the SRTs to the RVF. In addition, no statistical difference was found between the 3 subject groups for their SRTs toward the RVF target stimulus in any of the 5 test conditions.

Further analysis of the SRTs examined the SDs of the SRT distributions (fig. 5). The repeated measure analysis of variance of the SDs with all 3 factors revealed a significant interaction between factors 'patient group' and 'direction of saccade' ($F(2,180) = 7.33$, $P = 0.005$). Thus for the SDs of the SRT distributions to the LVF and those to the RVF, two separate repeated measures analyses of variance were carried out.

The analysis for the RVF revealed no significant result. Both main effects and the interaction were not significant. The analysis for the LVF yielded a significant main effect for factor 'patient group' ($F(2,90) = 5.16$, $P = 0.017$). The interaction with 'test conditions' was not significant. Further analysis revealed significant differences between the patient group with right hemisphere lesions and both other subject groups ($t = 12.02$ and $t = 13.25$, $P < 0.001$). The difference between the patient group with left hemisphere lesions and the group of normal subjects was not significant.

The statistical analysis showed that under all test conditions the SDs of the SRT distributions for stimuli in the LVF were significantly higher for the patient group with right hemisphere lesions than those of the 2 other subject groups. Even under Condition II, when the longer SRTs to the LVF which were performed in all other test conditions could be compensated for, a completely 'normal' SRT-pattern was not achieved by the right brain-damaged patient group (fig. 5).

Errors in direction

The repeated measure analysis of variance for the observed number of 'errors in direction' (Table 3) with all 3 factors revealed a significant main effect of factor 'patient group' ($F(2,180) = 4.48$, $P = 0.026$). All other effects were not significant. Post hoc comparisons revealed significant differences between the patient group with right hemisphere lesions and both other subject groups ($t = 5.07$ and $t = 5.95$, $P < 0.001$). The difference between the patient group with left hemisphere lesions and the group of normal subjects was not significant.

The analysis demonstrated that under all test conditions and independently of the visual half-field, the patient group with right hemisphere lesions produced significantly more 'errors in direction' than the two compared subject groups (Table 3). When stimuli were presented in one visual half-field (LVF or RVF), this patient group performed significantly more often saccades in the opposite direction.

Omissions

A significant interaction between the 3 factors ($F(8,180) = 2.33$, $P = 0.028$) was found with the repeated measures analysis of variance for this variable. Thus for omissions

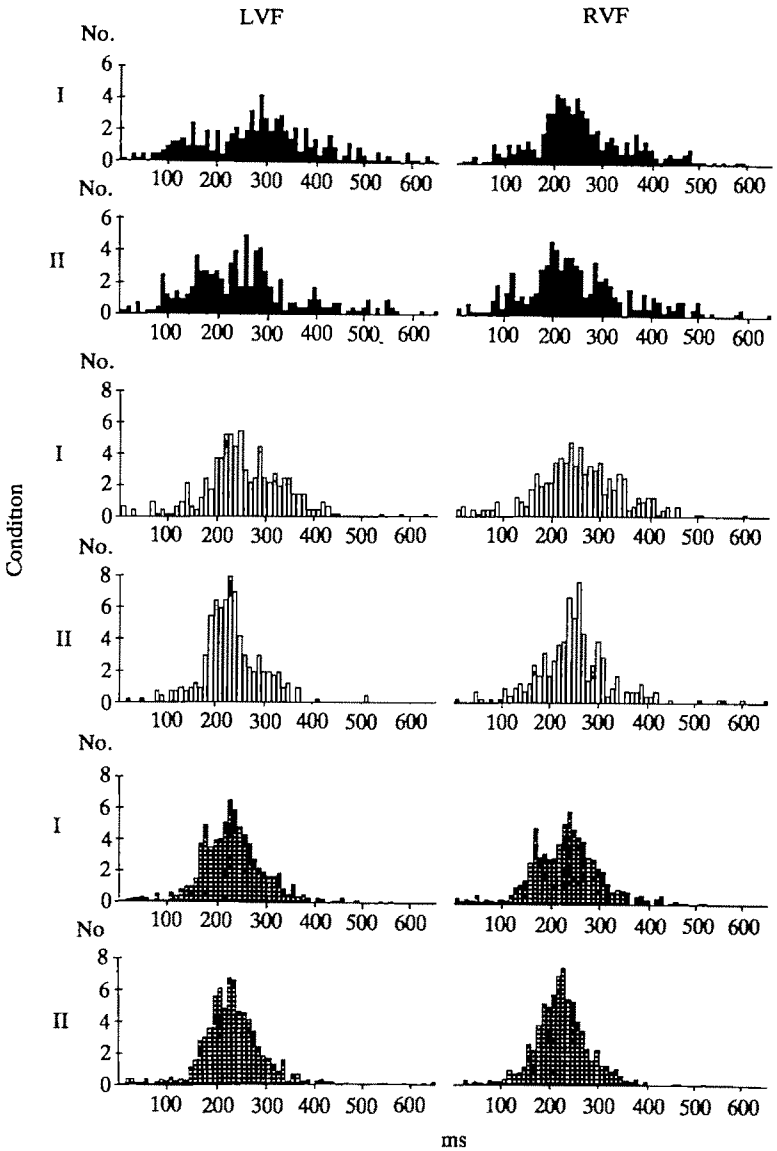

FIG. 5 Distribution of the saccadic reaction times in test Conditions I and II averaged within the two patient groups and the group of normal subjects. Filled columns = right brain-damaged patients, open columns = left brain-damaged patients, cross-hatched columns = controls.

of LVF and RVF stimuli (Table 3), two separate repeated measures analyses of variance were executed.

The analysis of omissions of RVF stimuli yielded a significant interaction of the two factors 'patient group' and 'test condition' ($F(8,90) = 2.65$, $P = 0.013$). Closer analysis of the different test conditions revealed no significant result. The analysis of omissions

TABLE 3 MEANS AND SDs OF THE PERCENTAGE OF 'ERRORS IN DIRECTION', 'OMISSIONS' AND 'ERRORS IN AMPLITUDE' FOR LVF AND RVF STIMULI (AVERAGED OVER ALL 5 TEST CONDITIONS) PERFORMED BY THE PATIENT GROUP WITH RIGHT BRAIN DAMAGE (RBD), LEFT BRAIN DAMAGE (LBD) AND NORMAL SUBJECTS (NS)

	Subject group					
	RBD		*LBD*		*NS*	
Variable	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Errors in direction						
LVF	4.0	(5 4)	0.9	(1.8)	0 6	(1.4)
RVF	2.4	(2.8)	0.5	(1.0)	0 4	(0 8)
Omissions						
LVF	4.6	(6 2)	0 7	(1.4)	0.9	(2 4)
RVF	2.1	(3 0)	2 2	(4.0)	0.3	(0 8)
Errors in amplitude						
LVF	1 2	(2 0)	2.5	(2.8)	1 4	(2 2)
RVF	3.5	(5.8)	5.2	(4 2)	1 6	(2.4)

of LVF stimuli, however, yielded a significant main effect of factor 'patient group' ($F(2.90) = 4.67$, $P = 0.023$). Post hoc comparisons showed significant differences between the patient group with right hemisphere lesions and both other subject groups ($t = 4.79$ and $t = 5.10$, $P < 0.01$). The difference between the patient group with left hemisphere lesions and the group of normal subjects was insignificant.

The analysis showed that under all test conditions the patient group with right hemisphere lesions failed to react to stimuli which appeared in the LVF within 800 ms significantly more often than the two compared subject groups (Table 3). The number of omissions of RVF stimuli, however, did not differ significantly between the three subject groups.

Errors in amplitude

The repeated measure analysis of variance with all three factors revealed a significant interaction between factors 'test condition' and 'direction of saccades' ($F(4,180) = 3.96$, $P = 0.006$). Post hoc comparisons yielded no significant differences. Thus in all test conditions, no significant differences between the three subject groups were found for the number of trials in which the subjects did not reach the target in the LVF or RVF with a single saccade and corrected it by performing further steps (Table 3).

DISCUSSION

Analysing the differential effects of the 5 test conditions, the results obtained in the 'baseline' test Condition I confirm the findings of Girotti *et al.* (1983). Comparing LVF and RVF performance, specifically the right brain-damaged patients with hemineglect showed longer SRTs to the LVF. Under this test condition the midlines of head, trunk and visual field were aligned and corresponded to the middle of the projection screen. The LVF deficit could be compensated for by solely turning the trunk of the patients

to the left while holding the orientation of all other axes constant. This test Condition II differed from the standard 'baseline' Condition I only in that the stimulus in the LVF was now projected—like the stimulus in the RVF—to the ipsilateral right side of trunk space.

Riddoch and Humphreys (1983) and Karnath (1988) observed that the deficient performance of neglect patients on their contralateral side could be compensated for by orienting their attention overtly (by eye and head movements) or covertly (by instruction to shift attention mentally, i.e., without eye and head movements) to the contralateral side. Kinsbourne (1987) argued that activation imbalance produced by brain damage or sensory stimulation determines the directional vector that will exert the predominant control on attentional orienting. It could be claimed that since the neglect patients were asked to turn left in Condition II of the present study, this directional orienting tendency was accentuated and the improvement of the LVF deficit under this test condition was simply due to the fact that the body was turned to the left.

There are two arguments against this explanation of the compensation of the LVF deficit observed under Condition II (trunk turned to the left) as a simple effect of an attentional shift to the left hemispace cued by a body movement to the left. The first argument is that turning the trunk or the head to the right side in test Conditions III and V had no decreasing effect on the SRTs measured for the stimuli presented in the RVF. There was no statistical difference under any of the 5 test conditions for SRTs to the RVF between the three subject groups. This result, however, might be due to a floor effect. The second, more powerful argument, is that turning the head to the left side in Condition IV did not have the same effect of SRT facilitation as turning the trunk to that side (Condition II). There is no theoretical or empirical evidence to assume that cueing or shifting attentional mechanisms into a given direction can only be released by trunk but not by head movements. On the contrary, Meador *et al.* (1987) reported a patient with right cerebral infarction and a neglect syndrome whose percentage of correct recall of items improved to 26% in a spatial imagination task (similar to the one used by Bisiach and Luzzatti, 1978) when the patient's head/eye orientation was directed to the neglected left hemispace, inducing an attentional shift to that side.

Alternatively, the improvement of SRTs to the LVF in the right brain-damaged patient group from 'baseline' Condition I to Condition II, might be attributed to a practice effect, which could be observed in the control group over the course of time from Conditions I to V (*see* fig. 3), or to adaptation to the postural conditions used in the experiment. Among the 5 conditions, Condition II was tested second. However, if such an explanation is assumed, comparable or even better results in the subsequent Conditions III, IV and V than those measured under Condition II would be expected. This was not the case, since the improvement from Condition I to Condition II was followed by an increase of SRTs in Conditions III, IV and V. It might be argued that this increase of SRTs in Conditions III, IV and V was due to fatigue and that for this reason the effects of practice or adaptation were merely superimposed. But as an effect of fatigue corresponding changes in SRTs for eye movements to both visual fields would be expected. This was not observed (*see* fig. 3). Furthermore, it would have to be explained why fatigue should only be observable for SRTs to the LVF in brain-damaged patients with right hemisphere lesions but not in those with left hemisphere lesions or in normal subjects.

To conclude, the results of the present study suggest that the orientation of the trunk in space, as indicated by the trunk midline, divides our normal perception of space into an egocentric 'left' and an egocentric 'right' sector. They indicate that the trunk orientation in brain-damaged patients with neglect syndrome is the decisive factor for determining the 'contralateral' part of space in which information is neglected and deficient reactions to stimuli are exhibited.

Our results are consistent with the findings of Heilman and Valenstein (1979), Bisiach *et al.* (1985) and Nichelli *et al.* (1989). The authors asked their right brain-damaged patients with left-sided hemineglect to perform a blind tactile exploration task (Bisiach *et al.*, 1985) or a line bisection task. The tasks had to be performed in different locations from the patients' trunk midline. The patients gave their best results (the lowest frequency of omissions in the left half of the display in the tactile exploration task and the smallest displacements of the mark to the right in line bisecting), when the task was located to the right of the trunk midline.

Recordings of single neurons in the inferior parietal lobule in primates (Andersen *et al.*, 1985) suggest that the brain transforms the retinotopic location of visual input into head and body-centred coordinate frames. This transformation seems to be important for many aspects of visuomotor coordination since the positions of the eyes and head—and therefore the retinotopic locations of targets—change frequently, although the spatial locations of these targets with respect to the body may not change. On the basis of the observation of asymmetric compensatory eye movements after lesions in the cat parietal cortex and superior colliculus, Ventre *et al.* (1984) hypothesized that a body reference that allows reconstruction of body position in space with respect to external objects is built as an internal representation of body midline or longitudinal axis. This internal representation was assumed to be a result of symmetric activity of associative neural structures. Unilateral lesions of these structures were supposed to produce permanent asymmetric activity inducing a displacement of the egocentric coordinates to a new position. A constant 'directional' error, which would similarly be expected according to this hypothesis after brain damage in humans, has been described by various authors (Kinsbourne, 1977; Girotti *et al.*, 1983; Huber *et al.*, 1988; De Renzi *et al.*, 1989). It has been reported, for example, in patients suffering from parietal lesions exhibiting the deviant reaching behaviour referred to as 'optic ataxia'. These patients constantly misreach for objects towards the ipsilateral side (for review, *see* Ventre *et al.*, 1984). Moreover, Heilman *et al.* (1983) reported that their 5 patients with right hemisphere lesions with left-sided neglect showed a large deviation to the ipsilateral half of space, when they were requested to point to an imaginary spot in space perpendicular to the midline of the chest with their eyes closed.

If the theoretical interpretation of lateralized deficits in the neglect syndrome is accepted as being the consequence of a displacement of the internal egocentric coordinate frame for representing body position with respect to external objects, the results of the present study imply that the physical anchor for the calculation of these egocentric coordinates is our trunk orientation in space.

Karnath (1988) proposed a three-component model to explain the deficits underlying visual neglect, consisting of two different components affecting the directionally-specific orienting of attention, which have been reported by various authors (Kinsbourne, 1977, 1987; Posner *et al.*, 1984, 1987; Mesulam, 1985; Rizzolatti *et al.*, 1985; De Renzi *et al.*, 1989), and one affecting the directionally *nonspecific* processing of information.

Component A describes the directionally-orienting specific, spontaneous and automatic orienting of attention to the ipsilateral side leading to the primary analysis of ipsilateral information. Component B represents the directionally specific deficit of voluntary orienting of attention towards the contralateral side, irrespective of the simultaneous presence or absence of information on the ipsilateral side. Component C characterizes the directionally *nonspecific* deficit of information processing caused by a general disturbance of attentional processes and/or a generally reduced capacity for processing information by sequential analysis. The combined effect of the three components is responsible for the development of the conspicuous neglect symptoms in the acute stage of symptomatology (Karnath, 1988). Perception and response to Tstimuli on the contralateral side are affected by an automatic and primary orientation of attention to the ipsilateral side (Component A) and by the deficit to voluntarily orient attentional processes from this primary focus to the contralateral side (Component B). In addition, information analysis on both sides—the contralateral *and* the ipsilateral side—is affected by a generally reduced capacity for processing information sequentially and/or generally reduced attentional resources (Component C).

According to Rizzolatti *et al.* (1987), it can be assumed that overt and covert orienting of attention are controlled by a common program and that the absence of eye movements in the case of covert orienting is a consequence of a peripheral inhibition process, which leaves the central programming unchanged (for discussion, *see* Groner and Groner, 1989). Fischer (1987) has suggested that for both a shift of the direction of attention as well as for a shift of the direction of gaze, the visual attentional system has to enter a stage of disengagement. In this stage, visual information can be received to localize a target, which then can lead to a saccade or to a covert shifting of focal attention towards the target. Thus it may be assumed that the three-component model is not restricted only to the process of covertly shifting of attention but also for overt shifts, for example, eye movements. In fact, in their neglect patients Riddoch and Humphreys (1983) were able to observe Component A in the overt act of orienting attention by fixational change. Component B was reported by Girotti *et al.* (1983) for the eye movement behaviour of their neglect patients, and could again be observed in the present study.

In recent studies it has been discussed as to whether neglect phenomena associated with unilateral brain lesions represent either an attentional disorder or are determined by 'hemispatial'/egocentric coordinates. Reuter-Lorenz *et al.* (1990) tested the predictions of the activation-orienting hypothesis of Kinsbourne (1977, 1987) in normal subjects. They found that the distribution of attention in space is biased in the direction contralateral to the stimulated hemisphere and is not dependent on the hemispatial position of the stimulus producing the activation imbalance. When Posner *et al.* (1987) investigated the effects of parietal lesions in brain-damaged patients with neglect, the authors considered the disturbed process of covert shifting of attention from the current focus in the contralesional direction to be the basic effect of parietal damage, irrespective of the visual field or hemispace involved. Thus they assumed Component B to be a disturbance occurring independently of a physical anchor represented by the spatial body orientation and of an internal representation of visual space as was proposed, for example, by Bisiach *et al.* (1979, 1985). Rizzolatti *et al.* (1985) also suggested a representational hypothesis, claiming that the contralateral part of visual space is most strongly represented in each hemisphere.

The results of the present study support the idea that these two theoretical points of

view have to be integrated for an understanding of the neglect syndrome. They suggest that in neglect patients the border between the unaffected and the disturbed part of space for Component B corresponds to the internal representation of body midline in space. On the basis of our data, we hypothesize that Component B (voluntary orienting of attention in the contralesional direction) is restricted to and observable only *within* this disturbed part of space. According to Ventre *et al.* (1984), it may be assumed that in right brain-damaged neglect patients this part includes not only the left side of the physical trunk midline/body space but also a part of its right side. The right side is assumed to be affected to the extent to which the internal representation of body midline is displaced towards the ipsilateral side. Component C of the neglect syndrome, however, seems to be a general disturbance of information processing occurring independently of the spatial trunk orientation and of an internal representation of visual space.

In two different experiments, Posner *et al.* (1987) measured manual reaction times to visual stimuli which were presented 3°, 6° and 9° peripherally from a central fixation point in the LVF and RVF. The authors observed that in neglect patients with parietal lesions, reaction times to visual stimuli located in the contralesional direction away from the current focus of attention, had a disadvantage, irrespective of the visual field involved. In their study the patients' midlines of head, trunk and visual field were parallel and oriented straight towards the screen. If the part of space in which deficient orienting of attention to the contralateral side (Component B) can be observed, is determined by an ipsilaterally displaced internal representation of body orientation in space (Ventre *et al.*, 1984), then in the study of Posner *et al.* (1987), the stimuli presented in the LVF as well as those in the RVF were located (in relation to this displaced internal representation) *within* the disturbed part of space. Thus it seems to be the patients' body position which made the authors find impaired attentional orienting in the contralesional direction in both visual half-fields.

Taking these considerations into account, in all test conditions of the present study except Condition II, the LVF stimulus was located in the disturbed part of space. The increased SRTs of the neglect patients in these conditions for eye movements which had to be performed from the central fixation point towards the contralateral side (LVF stimulus) can therefore—according to the results of Posner *et al.* (1987)—be regarded as the expression of a deficient orienting of attention from one point of fixation towards another located in the contralateral direction within the disturbed part of space.

Under Test Condition II, the trunk and thus the physical anchor for the calculation of the egocentric coordinates of the internal representation of body midline was shifted to the left side. It was only under this test condition that the mean SRT to the LVF of the neglect patients reached a level which was comparable with that measured to the RVF. It therefore may be assumed that with the shift of the anchor a shift of the LVF stimulus into the unaffected part of space was induced accordingly. Under Condition III the anchor (trunk position) was then shifted to the right side. Contrary to Condition II, a shift of both target stimuli to the disturbed part of space was induced. Under this condition the SRTs to the RVF stimulus might be expected to increase. This was not the case and on the basis of the results of Posner *et al.* (1987) would not be predicted. Both target stimuli were located within the disturbed part of space. According to their observations, in this situation reaction times to the LVF stimulus, located in the contralesional direction to the fixation point, should be longer than those to the

ipsilaterally located RVF stimulus for the neglect patients. The results obtained under test Condition III numerically confirmed this expectation. The SRTs towards RVF stimuli were faster than those towards LVF stimuli.

Compensating for the deficient eye movement behaviour of the right brain-damaged neglect patients by shifting the trunk midline to the left side could, however, not be achieved for all of the variables that were measured in the present study. Under *all* 5 test conditions the SDs of the SRT distributions for stimuli in the LVF were significantly increased for this group and they failed to react to stimuli which appeared in the LVF ('omissions') more often than the two other subject groups. Furthermore, in all test conditions the group of neglect patients reacted more often in the direction opposite to that field where the actual stimulus appeared ('errors in direction'). This happened when the stimulus was presented to the LVF as well as to the RVF. (No effect was found for the 'errors in amplitude' as was reported by Girotti *et al.* (1983). This might be due to the fact that the present study only determined whether one or more than one saccades were performed per trial. The exact number of saccades which were needed to reach the target was not recorded as had been done by Girotti *et al.* (1983).)

This generally deviant eye movement behaviour observed in all 5 test conditions for the neglect patients might be due to the directionally *nonspecific* component of visual neglect syndrome (Component C). This general disturbance of information processing occurs independently of the orientation of the trunk midline in space and does not result from displaced egocentric coordinates of the internal representation of body position in space.

A possible neurophysiological correlate of clinico-anatomical data supporting an analogue model for space representation within the nervous system in primates was discussed by Andersen *et al.* (1985) and Bisiach *et al.* (1985). As a first indication for the neurophysiological basis underlying the observed effect of trunk rotation in neglect patients, the findings of Biguer *et al.* (1988) seem to be of further importance. In the present investigation the relative deviation of the trunk midline to the left from the straight ahead head/eye orientation under Condition II led to a compensation of the increased values of left-sided SRTs. In the literature, there seems to be a general consensus that this sensory information—the head-on-trunk signal—is of proprioceptive origin and that it is derived from receptors (presumably the muscle spindles) in the neck muscles. Biguer *et al.* (1988) made the observation that the proprioceptive signals from the neck muscles are involved in the elaboration of the coordinates of visual space. The authors investigated normal subjects sitting with their head and body oriented straight ahead towards a central stationary red spot of light. During the vibration of the left posterior neck muscles, which induced the false afferent signal that these muscles had lengthened, the subjects reported an apparent motion and displacement of the stationary visual target towards the right. Furthermore, when requested to point to the target, the subjects performed a consistent error in pointing which was in the same direction as the illusory displacement. The magnitudes of both the displacement and pure motion illusions were dependent on vibration amplitude. Moreover, when the target had to be moved until the subjects perceived it as lying in their subjective midline the target was usually located left of the physical midline. These results indicate that the abnormal afferent head-on-trunk signal, released by the vibration of the left posterior neck muscles, resulted in a displacement of the egocentric midline of the body-centred representation of visual space.

It may be speculated that the lengthening of the left posterior neck muscles by turning the trunk to the left under Condition II of the present study, together with the signal of the eye-in-head position, led to a compensatory shift of the displaced egocentric coordinates of the internal representation of body position in the investigated neglect patients. An interaction of the head-on-trunk and the eye-in-head signals must be assumed, because in both Condition II (trunk turned to the left/head straight ahead) and Condition V (trunk straight ahead/head turned to the right), the left posterior neck muscles were lengthened, but only under Condition II could the compensatory effect be observed. The two test conditions differed, however, concerning the induction of different eye-in-head signals.

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BOOK REVIEWS

Cellular and Molecular Biology of Myelination. Edited by G. Jeserich, H. H. Althaus and T. V. Waehneldt. 1990. Pp. 565. NATO ASI Series H: *Cell Biology*, Volume 43. Berlin: Springer. Price DM 298.00.

This book consists of the abstracts of 37 papers presented by the participants of the NATO advanced workshop on cellular and molecular biology of myelination, held at the monastery Ohrbeck, Germany, on August 28–September 2, 1989. The book is divided into 7 chapters that cover steps in glial cell differentiation and myelinogenesis; demyelination, remyelination and glial cell transplantation; signal transduction and regulatory events in myelin forming cells; transfected cells as a tool in myelin research; phylogenetic aspects of myelination, components and structure of myelin; and the molecular biology of genes coding for myelin proteins. Although the individual papers are presented in camera-ready format, the overall standard of reproduction of the text and figures is high, including a number of electron micrographs and immunofluorescence photographs. The inevitable change in fonts between each paper of this 'camera-ready' approach highlights the fact that this volume is a collection of relatively up-to-date reviews by different authors of their own work on the cellular and/or molecular biology of myelin. However, one of the main benefits of NATO advanced research workshops, as mentioned by the editors in their introduction, is the discussion and exchange of ideas that occurs after the presentations. Neither these discussions nor an editorial critique or comment to tie the individual papers together is included. This, I think, reduces the overall interest of the book to both a general neuroscience audience and also to those who have a particular interest in the field but were not able to attend the meeting. I enjoyed reading this book and think it contains much to recommend it to those with a specialist interest in the cell and molecular biology of myelin. However, the high price, together with my previous comments, make it difficult to recommend it to the general neurologist or neuroscientist. Moreover, this volume covers a lot of similar ground to *Differentiation and Function of Glial Cells*, from the *Neurology and Neurobiology* series (Volume 55, 1990), that was recently reviewed in this journal.

DAMIAN WREN

Localization in Clinical Neurology. Second edition. By Paul W. Brzis, Joseph C. Marsdell and Jose Biller. 1990. Pp. 520. Boston and London: Littley Brown. Price £47.50.

In the review of the first edition of this book (1985) appearing in *Brain*, **109**, p. 275 in 1986, the reviewer had difficulty in recommending the textbook on account of lack of clinical perspective, difficulty in perceiving the wood from the trees, and some errors. The new edition (1990) is larger, with 520 pages and 75 illustrations, by the same three authors. They take a totally comprehensive and detailed approach to anatomical localization within the human nervous system, starting peripherally, proceeding via the spinal cord, brainstem and basal parts of the brain, to end in the cerebral hemispheres.

It would be impossible to read through this book from start to finish profitably. It might be referred to by clinicians in relation to individual clinical cases. The same lack of emphasis exists with regard to what is common and likely compared with the rare and esoteric, and the book is still not without error. Though clinical neurologists must always attempt accurate anatomical diagnosis, the volume is almost over-burdened with detail. It specifies localization more than is usually required from the clinical point of view, and possibly more confidently than can actually be achieved in day-to-day clinical practice.

I. M. S. WILKINSON

Focal Epilepsy: Clinical Use of Emission Tomography. Edited by M. Baldy-Moulinier, N. A. Lassen, J. Engel and S. Askienazy. 1990. Pp. 216. London: John Libbey. Price £28.00.

This volume consists of the proceedings of a symposium held in May 1989 on the clinical use of functional imaging in focal epilepsy. As such, the 20 chapters are largely repetitive and there is little evidence of active editing. Engel provides a useful review of terminology, the neurobiological basis of epileptogenesis, and the role of positron emission tomography in presurgical evaluation. Lassen's account of single photon emission computed tomography (SPECT) blood flow tracers is clear and readable. There are two chapters on SPECT methodology that have a significant overlap, and the account of PET methodology is superficial. There are 13 contributions relating to the clinical use of cerebral blood flow imaging in patients with partial seizures that vary in their depth, quality and degree of critical appraisal of their results. The best two chapters in this section of the book are those by Habert *et al.* and by Rowe *et al.* There are some interesting side issues presented within the main thrust, such as the report of increased blood flow in cortical motor areas at the time of a definite pseudoseizure, and a preliminary report on the effects of hyperventilation on tracer uptake in patients with partial seizures. At the end of the volume there is a very clear, concise summary and overview of the field by Lassen.

This book will be of interest to those who are planning to use SPECT with interictal and ictal blood flow imaging in the presurgical evaluation of patients with partial seizures.

JOHN S. DUNCAN

Alcohol and Seizures. Basic Mechanisms and Clinical Concepts. Edited by R. J. Porter, R. H. Mattson, J. A. Cramer and I. Diamond. 1990. Pp. 342. Philadelphia: F. A. Davis. Price £39.72.

This book arose out of the International Symposium on Alcohol and Seizures held in Washington in 1988. It is divided into 4 parts: clinical overview; basic mechanisms of alcohol-related seizures; classification and diagnosis of syndromes; and prevention and treatment of alcohol-related seizures. These are further subdivided into a total of 32 chapters, with more than 50 contributors.

The preface suggests that the book is more than a conference proceedings: the aim is to provide a comprehensive and up-to-date description of clinical investigations and current dilemmas from foremost worldwide authorities. Certainly the book contains contributions from many leading authorities, and given the time delay in compiling such a work, is reasonably up to date. Consequently, it brings together in one forum quite a range of potentially useful material. The different contributors present their own data and views, sometimes with overlap or conflict. Given the diversity of material and opinions, the summary to the book is relatively brief (3 pages), and about one-third of this is taken up with criticisms of a particular contribution.

To an outsider to the subject wishing to obtain an overview, further editorial comment might have been helpful. Specialists in the field may have been familiar with the conference, and there is an unavoidable delay in collating and publishing such material in a book.

D. R. FISH

Cranial Meningiomas: Diagnosis, Biology, Therapy. Edited by G B. Bradac, R. Ferszt and B. E. Kendall. 1990. Pp. 154. Berlin: Springer. Price DM 248.00.

This compact (154 pages) review of *Cranial Meningiomas,* their diagnosis, biology and therapy, is an authoritative up-to-date guide for all those concerned with the neurosciences.

The term 'Meningioma' was introduced by Cushing in 1922 to serve, as he later explained, as an all-embracing catchword, but has led over the years to controversial and confusing subclassifications. The true histological problem, as the authors indicate, lies in the assessment of the rate of growth and the risk of recurrence employing certain general parameters. The current WHO classification is here outlined and discussed in this framework with emphasis on atypical findings.

Radiological techniques, including plain x-ray, computed tomography, magnetic resonance imaging and angiography, their value and their general application, are reviewed in 4 separate sections. A further 6 sections consider the growth patterns of meningiomas arising in various locations, together with the role of all the investigative methods in differential diagnosis.

The controversial and ill-understood issue of peritumoural oedema is examined separately, and the various potential mechanisms discussed. The observation that white matter oedema which extends postoperatively might suggest further tumour of postsurgical complication, is perhaps the most practical outcome. The two final sections deal with treatment, which remains essentially surgical. Adjuvant therapies, including preoperative embolization and radiation, are outlined.

The editors have drawn from expertise in Turin, Berlin and London to provide this highly readable, well researched, well referenced, and elegantly illustrated slim volume. The cost at DM 248.00 may regrettably exceed the budget of some departments.

IAN ISHERWOOD

Malignant Cerebral Glioma. Neurosurgical Topics. Edited by L. J. Apuzzo. 1990. Pp. 231. Park Ridge, IL: American Association of Neurological Surgeons. No price stated.

This volume is one in a series on Neurosurgical Topics produced under the auspices of the American Association of Neurological Surgeons. It aims to provide a concise review covering not only the historical information available on the topic but also the current status of basic science and clinical aspects of malignant cerebral glioma. A novel feature is that directions for future study in most relevant areas are also indicated. The 15 chapters of the book are divided into 7 sections covering: pathology, tumour biology and immunology, neuroimaging, epidemiology, surgery, radiation treatment and chemotherapy. They have been written by over 30 acknowledged experts in their respective fields The book is relatively short and in all chapters an attempt is made to be concise and to state clearly the relevant information. In spite of this brevity, controversial points, for example on the subject of pathological classification and grading of gliomas or on the relative merits of radical or limited surgical resection, are given an airing. Adequate numbers of references to original papers or more extensive reviews are also provided so that the reader can follow up further areas which capture his interest. Most of the authors make specific predictions about the future directions their subject will take and the volume editor has added several useful commentaries within the book, highlighting the interrelationships between chapters and the practical significance of findings from one scientific discipline for others.

The book is well produced and illustrated. Malignant cerebral gliomas are a very common entity in clinical neurology and this book can be recommended as an up-to-date introductory text, not only for neurological surgeons but also for medical neurologists and oncologists, as well as to scientists interested in basic research upon cerebral gliomas.

D G. T. THOMAS

Cerebral Gliomas. Edited by G. Broggi and M. A. Gerosa. 1989. Pp. 260. Amsterdam: Excerpta Medica. No price stated.

This volume contains the collected manuscripts of papers presented at the International Workshop on Brain Tumours held in Italy in 1988. The aim of that Workshop was to present up-to-date reviews of many aspects of brain tumour research, both clinical and basic, with the hope of promoting new methods of investigation and treatment of cerebral gliomas; it is not intended as a comprehensive textbook on the subject. The conference papers are collected in 4 sections covering basic science and neuropathology, epidemiology, diagnosis—that is principally neuroimaging—and treatment by surgery, radiation and drugs. In all, 31 contributions from 85 authors are included. As in many reports of proceedings, the quality of content and presentation of individual articles vary, but generally the scientific standard is high.

The book is well produced and appropriately illustrated. It can be recommended both to experts and newcomers to neuro-oncology, whether from basic or clinical neurosciences, as an up-to-date source of information on most of those areas of the subject which are of current interest, including molecular neuropathology and experimental forms of therapy. It should find a place in the personal libraries of many who are interested in neuro-oncology, as well as in departmental libraries of neurosurgery, neurology and oncology.

D. G. T. THOMAS

Computer-aided Electromyography and Expert Systems in Diagnosis. *Clinical Neurophysiology Updates*, Volume 2. Edited by J. E. Desmedt. 1989. Pp. 320. Amsterdam: Elsevier Price Dfl. 315 00.

The initial sections in this collection of excellent papers address various aspects of harnessing computer power to the acquisition and analysis of needle and surface recorded EMG signals. The later sections describe packages of on-line help for electromyographers, using knowledge based software. These include expert system software which is intended to pilot the investigator through the various tests needed to confirm or refute a hypothesis about the cause of a clinical condition, and software consisting of more mundane collections of useful facts.

The book makes absorbing reading. The introductory paper touches on the conceptual framework of EMG, and will be of interest to the general reader as well as the dedicated professional Other topics include decomposition techniques for extracting single motor unit potentials from the interference pattern, and possibilities which flow from these such as analysis of the firing behaviour of single motor units within the interference pattern. The papers on surface recorded EMG provide an appraisal of what can be achieved by this technique, such as estimation of the propagation velocity of muscle action potentials in fatigue Some authors suggest minimum technical standards for implementing these evolving methods of acquiring data.

Any perusal of manufacturers' literature quickly confirms that new microcomputer and signal processing hardware and software are transforming the design of laboratory EMG apparatus, and this is a reference work which should help the potential user to evaluate what is on offer.

There are many books on the practical aspects of clinical electromyography, which the electromyographer may find useful in everyday practice, but for those interested in new developments and those in EMG research, there is a considerable amount of interesting material in this volume which will be difficult to find elsewhere. It is an essential reference work for every departmental library.

R. M. SHERRATT

Intervertebral Disk Diseases: Causes, Diagnosis, Treatment and Prophylaxis. Second edition. By Jürgen Krämer. 1990. Pp. 328. Stuttgart: Thieme. Price DM 148.00.

This is a second edition of a book first published in 1981. It has been expanded in length by about 25% with a fresh section, amongst others, on the new imaging techniques, percutaneous discectomy and the psychological aspects of back disease.

The author is a professor of orthopaedics and the book provides a useful review of the whole range of disc disease as seen from the point of view of the orthopaedic surgeon or the physical therapist. It is important for the neurologist or neurosurgeon to realize the limitations that this statement implies. Whilst certain topics, such as the anatomy, pathology and biomechanics of the spine are covered thoroughly, the neurosurgeon will find scant attention paid to what he may regard as key subjects. Thus the spinal cord manifestations of cervical and dorsal disc disease are scarcely mentioned, and arachnoiditis is not mentioned at all. Discussion of the anterior approach to the cervical spine is confined to the limited orthopaedic technique of anterior fusion, without any treatment of the various techniques available for entering the spinal and root canals by this route.

Much of the text is thorough but somewhat laboured. Nevertheless, the translation and general presentation are a clear improvement on the first edition and the production and numerous illustrations are of the highest quality. This volume will be a useful addition to the library of the experienced spinal surgeon who will find much of interest within it. It is perhaps of less value to the trainee or the nonspecialist who will lack the experience to pick out the nuggets of real worth from those parts of the text which are based on mere assertion.

R. S. MAURICE-WILLIAMS

Disorders of Movement: Clinical, Pharmacological and Physiological Aspects. Edited by N. P. Quinn and P. G. Jenner. 1989. Pp. 567. London: Academic Press. Price $60.00.

This book is the product of a meeting held in 1987 to give tribute to David Marsden's 15 years as foundation Professor of Neurology at Kings College Hospital and the Institute of Psychiatry. Doubtless this is the

first of many eventual volumes that will acknowledge not only his personal achievements and those of his associates but the invigorating effect he has had on encouraging the development of academic neurology in the UK. Peter Jenner and Neill Quinn have persuaded some 65 new eminent former and current collaborators to write nearly 40 chapters on a very wide range of topics, mostly of course pertaining to movement disorders. Never can so much of quality have been written in recent times on movement disorders without a certain co-author! The book is divided into sections on Parkinson's disease, dystonia, neuroleptic-induced movement disorders and a miscellaneous section covering ataxia, myoclonus, chorea, tics and tremors. Rather surprisingly there are very few books covering both clinical and scientific aspects of movement disorders and the editors have performed an important function in bringing this volume together, which still reads well despite the time lapse such is the quality of the authors. The book is a valuable source of reference and references. Most people in the movement disorders field and many others will find much of interest here and I can recommend it.

A. C. WILLIAMS

Laughing Death. The Untold Story of Kuru. By Vincent Zigas. Foreword by D. C Gadjusek 1990. Pp. 315. Clifton, NJ: Humana Press Price £25.95.

This book is not a conventional scientific text. There are no references and, although concentrating on the early research into Kuru, the book provides an intensely personal and at times philosophical account of the work of a doctor in extraordinarily difficult circumstances. The author's respect and admiration for the native people of New Guinea is clear and often moving, but his judgements on members of the colonial administration are highly critical and often extreme. There is also a disturbing account of the scientific jealousies prompted by the discovery and investigation of Kuru, with particular criticism of the Australian scientific community. Dr Zigas' resentment of the Australian medical establishment is a recurring theme and the accuracy of his recollections is brought into doubt by a carefully considered foreword by Dr D. C. Gajdusek which describes the book as 'historical fiction' and 'abstract expressionistic ironical parody'.

Kuru is not mentioned until p. 124 and the early chapters provide a chronological account of Dr Zigas' early experiences in New Guinea. The existence of cannibalism, crucial to the current interpretation of the mechanism of cross-contamination in Kuru, is supported by anecdotes, including the description of one disgruntled elderly patient who claimed to have eaten the grandfather of one of the attendant nurses. The first encounters with individuals affected by Kuru are described and the clinical descriptions are of interest. The gradual realization of the extent to which particular tribes were affected is paralleled by understandable confusion about the nature and cause of the disease. The possibility that Kuru was a hysterical disorder is raised and promptly discarded, to be followed by a range of other theories ascribing Kuru to toxic, nutritional and genetic factors. The investigation and exclusion of each possibility was achieved despite enormous practical problems, including difficulties with language and the acquisition of laboratory specimens, including postmortem material, with minimal facilities. Dr Zigas rightly credits Dr D. C. Gajdusek with the major role in the unravelling of the epidemiology of Kuru and this book provides further evidence of the extraordinary determination of resilience that this required.

The book concentrates on the first years of Kuru research and events subsequent to 1958 are covered in a cursory final chapter and epilogue. There are interesting parallels between the early years of Kuru and current attitudes to bovine spongiform encephalopathy. Following the recognition of Kuru, some authorities took an extreme view, suggesting that the affected areas of New Guinea should be surrounded by a high wall to prevent any possible spread of disease. There was also intense media coverage, described in the book as 'appalling, . . . all nonsense and awful', and it is ironic that the very title of this book is described as 'a hideous misnomer'.

This is a flawed but fascinating book. For a detailed and accurate account of early Kuru research it would be more profitable to read Dr Gajdusek's own accounts, including the volume *Correspondence on the Discovery and Original Investigations on Kuru: Smadel–Gajdusek Correspondence, 1955–1958,* (edited by D. C. Gajdusek. Bethesda, Maryland: National Institute of Neurological and Communicable Disorders, National Institutes of Health, 1975), and it is an interesting exercise to compare sources. However, Dr Zigas' personal views on the interaction between 'civilization' and the indigenous population, on the evolution

of an understanding of the cause of Kuru, and on the scientific community are all stimulating and readable One is left with the impression of an intellectually gifted and sensitive individual troubled by resentment and dissatisfaction and it is to be hoped, as is suggested in the foreword, that Dr Zigas wrote 'with more humour than bitterness'.

R. WILL

ANNOUNCEMENTS

Continuing Medical Education Symposium

The Academy of Medicine of Brooklyn, Inc. is sponsoring this symposium on the 'Management of Parkinson's Disease and Other Movement Disorders', to be held on Sunday, September 15, 1991 at the La Guardia Marriott Hotel. Registration information is available through the Academy of Medicine of Brooklyn, Inc , 1313 Bedford Avenue, Brooklyn, NY 11216, USA. (Tel: 718 467 9000).

Peter Debije-prize 1992 on Aging of the Brain

The University of Limburg at Maastricht, The Netherlands, has been given the opportunity of awarding the Peter Debije-prize This prize in the sum of 20,000 guilders is an expression of appreciation. The funds for the Peter Debije-prize are provided by the Edmond Hustinx Foundation in Maastricht. The prize is named after the physicist Peter J. W Debije (1884–1966), a native of Maastricht, who was awarded the Nobel Prize for chemistry in 1936

The prize will be awarded for the seventh time on January 10th, 1992 to a person or group of persons (three as a maximum, but preferably less than three) who are considered to have made a fundamental contribution to research in the field of Aging of the Brain, particularly with respect to the (patho)physiology, epidemiology and clinical aspects.

The jury would like to draw the attention to persons or groups of persons from any country, who might be considered for this award on the basis of their scientific work in the field indicated.

Nominations (in English) should enclose a curriculum vitae, a survey of the achievements of the candidate(s) (not exceeding 4 pages) and a list of publications Nominations, as well as questions about the award, should be addressed to the University of Limburg, att Dr E H. S. Drenthe, Secretary of the jury of the Peter Debije-prize 1992, Office of the Rector, PO Box 616, 6200 MD Maastricht, The Netherlands. Deadline for receipt of nominations is September 15th, 1991.

Blood Vessel Imaging Using Ultrasound Techniques

This intensive three-day course/workshop will be held at the Overmead Hotel, Torquay, Devon, on October 30–November 1, 1991. It is designed to cover both the basic principles of these techniques and a review of the current state of Ultrasound Arteriography and Venography Full details and registration forms are available from Mr K N Humphries, BLOOD VESSEL IMAGING COURSE, 10 Swale Drive, Chandlers Ford, Hampshire SO5 3QY, UK.

European Neurological Society

The third meeting will be held at the Palais de Beaulieu, Lausanne, Switzerland on June 27–July 1, 1992 The deadline for the receipt of abstracts is January 15, 1992. Further information may be obtained from Professor Andreas Steck, Service de Neurologie, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland

International Conference on Alzheimer's Disease and Related Disorders

The Third International Conference on Alzheimer's Disease and Related Disorders will be held at the Palazzo del Turismo, Montegrotto Terme, Padova, Italy, on July 12–17, 1992 Conference convenors: Drs M. Nicolini, K. Iqbal, B Winblad and H M. Wisniewski For further information and abstract forms contact the Conference Organizer, Dr P. Zatta, CNR-UNIT, Dipartimento di Biologia, via Trieste 75, 35131 Padova, Italy (Tel (49) 828 6361; Fax. (49) 828 6359).

First International Symposium on Brain Death

The First International Symposium on Brain Death will be held at the Havana International Conference Center, Cuba, on September 22–25, 1992. The symposium will be of interest to neurologists, neurosurgeons and specialists in transplantation, as well as lawyers, theologians, religious people and psychologists. Further information may be obtained from Dr Calixto Machado, Chairman, Organizing Committee, Instituto de Neurología y Neurocirugía, 29 y D, Vedado, Habana 4, Ciudad de La Habana 10400, Cuba (Tel: 32 7825; Fax: 22 8382).

Erratum

Brain, Volume 114, Part II, April 1991 (pp. 811–824)

CEREBRAL AKINETOPSIA
(VISUAL MOTION BLINDNESS)
A REVIEW

by S. ZEKI

Square brackets in quotations were incorrectly changed to round brackets after the author had corrected the proofs. The publishers regret any inconvenience caused. The correct quotations are reprinted below.

(p. 811, line 12 of Introduction)

strongly challenged. Here there was no MacKay (1888) to complain that 'the cases are very few in number', no Henschen (1910) to claim that his 'cortical retina' (the striate cortex) is also a retina for '[movement] impressions', no Critchley (1965) to write of '. . . a mere handful of instances of alleged [motion] agnosia, most of which are unconvincing'. Compared with the many, and conceptually seemingly powerful,

(p. 812, line 6 of Early History)

nor fixate them when they approached her quickly. The akinetopsia was linked to a 'defect of peripheral vision with retention of light perception and colour vision [and with] evidence of mental blindness and disturbance of spatial orientation'. In addition,

(p. 813, line 24)

be appreciated'. But there was an explanation for this, since 'I have always found that the acuity of vision in these [scotomatous] areas is considerably diminished . . . Further, colour vision is invariably affected in these areas'. Just as he thought that there was

(p. 814, last 2 lines, p. 815, line 1)

When Holmes (1945), in his Ferrier Lecture, spoke of the striate cortex as 'a merely perceptive centre', adding that 'The perception of colour also depends on [it] . . . there is no evidence that this is subserved by any other part of the brain', he saw no reason

(p. 815, line 19)

Korean War. Using both kinetic and static perimetry, Koerner and Teuber (1973) explained that a '. . . rather surprising feature of our present findings was the thorough going association of symptoms that we encountered: once the sensitive technique of static perimetry was taken as a baseline, regional losses as defined by kinetic perimetry [and other techniques] turned out to be essentially redundant sources of information on the status of these visual fields', leading them to the conclusion that 'There was no evidence that one could dissociate detection of moving and stationary targets.'

BIBLIOGRAPHIC REFERENCES should be limited to essential literature. They should be listed at the end of the paper in alphabetical order and not numbered. For a citation from a *journal*, the author's name in capital letters and the year of publication in brackets are followed by the title of the paper, the name of the journal *in full* and underlined for italicization, the volume number and the first and last pages of the journal. For multiple publications by the same author, those by the author alone are listed first and any with two or more co-authors listed subsequently in chronological order The names of all authors must be given up to a maximum of six. If there is more than one paper for a given year, these should be listed *a, b, c,* etc., after the year. For *books*, the author's name and year of publication in brackets are followed by the title of the book, underlined for italicization, place of publication, publisher's name and first and last page numbers. For *chapters in books*, the author's name and year of publication in brackets is followed by the title of the chapter, the title of the book (underlined), preceded by 'In:', the name(s) of the editor(s), the place of publication, the name of the publishers and the first and last pages of the chapter. *In the text*, numbered references are not used The author's name and year of publication are given in brackets If there are three or more authors, the name of the first is followed by *et al.* The punctuation, both in the Reference list and in the text, should follow the style of the journal (*see* current issue). Papers in which the reference citations do not follow this format may be returned for retyping. References to papers 'in preparation' or 'submitted' are not acceptable, if 'in press' the name of the journal or book must be given. Reference citations should not include 'personal communications' or other inaccessible information; information derived from personal communications or from unpublished work by the authors should be referred to in the text

ILLUSTRATIONS should be original line drawings or glossy prints, with their number and the author's name on the back. They should be of sufficient size to permit relettering by the publishers. The journal reserves the right to reduce the size of illustrative material. Half-tone photographs, particularly for electron micrographs or CT or MR images, must be of good quality All micrographs must carry a magnification bar (e.g., 1 μm). Colour illustrations are accepted, but the authors will be required to contribute to the cost of the reproduction. An estimate of the cost will be provided. The number of all illustrations must be kept to a minimum The desired position of figures and tables should be indicated in the typescript of the paper (e.g , fig. 1 near here, in brackets). Legends for figures should be listed on a separate sheet. All tables must bear a title. Footnotes may be used in the tables, but not in the text.

ABBREVIATIONS FOR SCIENTIFIC UNITS should conform to the Système Internationale (SI units). The statistical guidelines advocated by the International Committee of Medical Journal Editors (*Ann. Intern. Med.* **108**, 266–273, 1988) should be followed.

TRAVEL GRANTS

The Guarantors of Brain are prepared to consider applications for part or all of the costs incurred by clinical and non-clinical neuroscientists, aged under 40 and based in the United Kingdom, wishing to visit laboratories or clinical departments at home or abroad. Awards of up to £2000 may be available.

Applications will be considered for attendance at scientific meetings which relate directly to the applicants' research interests. Only exceptionally will applications to attend larger international conferences be considered. The Guarantors are unlikely to meet all of the costs of these visits and encourage applicants to seek part of their expenses from other sources.

Four copies of each application must be submitted at least two months before the planned date of departure.

The following documents are required:

1. An abbreviated curriculum vitae with a list of publications.
2. An account of the purpose of the visit.
3. The names of two referees.
4. A letter of invitation from the Host Department.
5. A statement of the costs with details of related applications.
6. A list of previous awards given by the Guarantors of Brain.

The applications should be sent to Professor Alastair Compston, Honorary Secretary and Treasurer to the Guarantors of Brain, University of Cambridge Neurology Unit, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ. (Tel. 0223 217091).

All successful applicants are expected to submit a short report of the visit on their return.

Contents continued from front cover

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