Working memory impairment in early multiple sclerosis
Evidence from an event-related potential study of patients with clinically isolated myelopathy

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Summary
Auditory and visual event-related potentials were recorded during a short-term memory task in 24 patients who had recently presented with symptomatically and clinically isolated spinal cord syndromes suspected to be due to multiple sclerosis and in 24 matched control subjects. Event-related potentials (ERPs) were recorded during two sequential components of the working memory task, first the temporary active memorizing of sets of digits and secondly, their subsequent manipulation, namely digit-probe recognition and matching. The patients’ reaction times were slower and showed larger increments than those of the control subjects as the number of items to be memorized was increased. The patients’ ERPs during both memorizing and probe matching/recognition phases differed significantly from control subjects for both auditory and visual presentations. The more marked changes were seen in a subgroup of eight patients who had the lowest levels of performance on a battery of general tests of memory and who also made significantly more errors in the working memory task as the memory load increased. In this subgroup, the abnormalities of the ERPs during recognition and matching tests occurred in the component of the response that has been shown to be sensitive to memory loading in healthy control subjects. This study provides objective evidence of subclinical working memory dysfunction in patients at an early stage of demyelinating disease, i.e. when they first present with clinically isolated spinal cord lesions and before they have developed symptoms of cognitive or memory dysfunction. The defect at this early stage is either restricted to processes involved in the formation of a memory trace or, more probably, involves both trace formation and the mechanisms that underly recognition (‘retrieval’) and matching of memory traces in working memory.

Keywords: event-related potentials; isolated lesions; memorizing; multiple sclerosis; working memory

Abbreviations: ERP = event-related potential; MAP = mean amplitude period; M-ERP = memorizing ERP; MIS = memory index score; MIS-A = abnormal memory index scores; MIS-N = normal memory index scores; MMA = multiple mean amplitude; MPW = major positive wave; PR-ERP = probe-related ERP; WAIS = Wechsler Adult Intelligence Scale

Introduction
Working memory can be defined as a ‘brain system that provides [mechanisms for] temporary storage and manipulation of the information necessary for such complex tasks as language comprehension, learning and reasoning’ (Baddeley, 1992). Studies in non-human primates (Fuster, 1993; Goldman-Rakic et al., 1993) have suggested that working memory is a function of a distributed network of interconnected neuronal assemblies. The focus of activity shifts in time within the network depending upon successive needs for representation and processing (Bressler et al., 1993;
working memory (Paulesu 'phonological and articulatory loop' subserving verbal MRI) studies in humans have identified a speech-based proposed by Baddeley (1992), PET and fMRI (functional 1993). In agreement with the model of working memory association cortex and ultimately the motor cortex (Fuster, 1995) and a possible frontal localization for a 'central executive' controlling these peripheral systems (D’Esposito et al., 1995). Whereas the anatomical components of working memory can be established by identifying the metabolically activated regions with PET or fMRI, the neurophysiological basis and, in particular, the temporal sequence of events can only be studied objectively using event-related potentials (ERPs).

Several ERP studies of short-term memory function have used various modifications of a paradigm described by Sternberg (1966, 1975) to investigate changes specifically associated with temporary storage, 'memory scanning' or retrieval of memorized items in working memory (Okita et al., 1985; Ruchkin et al., 1990, Lang et al., 1992; Pelosi et al., 1992, 1995; Starr et al., 1996). ERP abnormalities have been demonstrated using this paradigm in patients with epilepsy (Grippo et al., 1994, 1996a) and, with a similar memory-specific paradigm, in established multiple sclerosis (Ruchkin et al., 1994).

Memory dysfunction has been extensively documented in patients with definite multiple sclerosis (Beatty and Gange, 1977; Beatty, 1993; Rao et al., 1984, 1989a; Heaton et al., 1985; Huber et al., 1987; Litvan et al., 1988a, b; Grafman et al., 1990; Ron et al., 1991; Ron and Feinstein, 1992; De Luca et al., 1994; Grigsby et al., 1994; Grossman et al., 1994; Ruchkin et al., 1994), but controversy exists on various aspects of the nature of the memory disorder. Conflicting reports concern the relative role of impaired acquisition or retrieval mechanisms and the preservation or otherwise of short-term memory. Grant et al. (1984) found evidence of abnormalities of retention of items in short-term memory, whereas other investigators have reported that immediate memory span is intact (Jambor, 1969; Rao et al., 1984, 1989a; Heaton et al., 1985). Recent investigations have suggested that memory impairment results from defective retrieval from long-term memory storage, whereas encoding, storage capacity and short-term memory are preserved (Rao et al., 1989a,b). However, other studies have shown or suggested impaired verbal working memory (Litvan et al., 1988b, 1989b; Ruchkin et al., 1994) and inadequate initial learning (van den Burg et al., 1987; DeLuca et al., 1994). Litvan et al. (1988b) proposed that verbal memory abnormalities in multiple sclerosis were primarily due to deficits of processing in a component of working memory at the level of the articulatory loop. Abnormalities of working memory have been demonstrated in patients with chronic progressive multiple sclerosis in whom measures of short-term memory were significantly correlated with central processing capacity (Grigsby et al., 1994). In these patients a decrease in the speed and capacity of central information processing was considered to be the fundamental deficit in the early stages of the disease. The authors considered that a study of the

<table>
<thead>
<tr>
<th>Table 1 Clinical characteristics of patient groups</th>
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<tr>
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<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Multiple sclerosis diagnosis following neurological investigation</td>
</tr>
<tr>
<td>LSD multiple sclerosis</td>
</tr>
<tr>
<td>CP multiple sclerosis</td>
</tr>
<tr>
<td>Progressive possible*</td>
</tr>
<tr>
<td>Mean duration of symptoms in months (range)</td>
</tr>
<tr>
<td>Mean EDSS score (range)</td>
</tr>
<tr>
<td>Ambulation Index† (range)</td>
</tr>
<tr>
<td>MRI abnormal</td>
</tr>
<tr>
<td>EP abnormal</td>
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<tr>
<td>OB positive</td>
</tr>
</tbody>
</table>

None of these differences between groups were significant. MIS-N = normal memory index scores; MIS-A = abnormal memory index scores; EDSS = Expanded Disability Status Score (Kurtzke, 1983); MRI = magnetic resonance imaging; OB = oligoclonal bands in CSF; EP = evoked potentials; LSD = laboratory supported definite (criteria of Poser et al., 1983); CP = clinically probable (criteria of Poser et al., 1983); McDonald and Halliday (1977) criteria. * McDonald and Halliday (1983) criteria.
working memory system would help to clarify the nature of
the memory disorder in multiple sclerosis.

These apparently conflicting conclusions may result from
differences in methodology and the heterogeneity of the
multiple sclerosis cohorts, in which patients with varying
levels of disability and disease durations have been studied.
Generalizations across such groups are unlikely to be
appropriate given the widely differing patterns of memory
dysfunction reported in recent studies (Beatty et al., 1996).
There have been few attempts to study patients either early
in the disease, or classified by disease course. Patients
presenting with clinically isolated lesions characteristic of
multiple sclerosis may provide the best chance of
understanding the mechanisms underlying memory deficits
before damage accumulates and the cognitive disability
becomes diffuse and complicated. Nevertheless, there have
been few reports of memory function in these patients. In
one study, 67% of patients with optic neuritis were thought
to have evidence of memory impairment on the Wechsler
Memory Scale (Lyon-Caen et al., 1989). In the other report,
patients with clinically isolated syndromes of optic nerve,
brainstem or spinal cord were found to have intact recognition
patients with clinically isolated syndromes of optic nerve,
abnormalities on cerebral MRI, even at their first presentation
that 74% of patients have evidence of multiple white matter
(cortical and subcortical areas would be highly likely, given
widely distributed neural network of multiple interconnected
isolated lesions characteristic of early multiple sclerosis. Our
memory, or of any type of ERPs, in patients presenting with
isolated to the spinal cord—a characteristic presentation of
patients with multiple sclerosis—and in whom there
were no complaints of memory deficits or cognitive
impairment; (ii) the presence of abnormalities of memorizing
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impairment; (ii) the presence of abnormalities of memorizing

### Table 2 Demography of patients and matched control subjects by group

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Sex (M/F)</th>
<th>Age (years)</th>
<th>Handedness (R/L)</th>
<th>Education (years)</th>
<th>MIS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (24)</td>
<td>5/19</td>
<td>42.4 ± 10.7</td>
<td>24/0</td>
<td>12.0 ± 2.4</td>
<td>2.4 ± 2.2*</td>
</tr>
<tr>
<td>All control subjects (24)</td>
<td>8/16</td>
<td>42.4 ± 12.7</td>
<td>23/1</td>
<td>12.7 ± 2.7</td>
<td>1.1 ± 0.9</td>
</tr>
<tr>
<td>MIS-N patients (16)</td>
<td>4/12</td>
<td>41.3 ± 11.6</td>
<td>16/0</td>
<td>12.0 ± 2.1</td>
<td>1.1 ± 0.9</td>
</tr>
<tr>
<td>Controls for MIS-N group (16)</td>
<td>4/12</td>
<td>40.8 ± 13.6</td>
<td>15/1</td>
<td>12.9 ± 2.8</td>
<td>1.0 ± 0.9</td>
</tr>
<tr>
<td>MIS-A patients (8)</td>
<td>1/7</td>
<td>44.7 ± 8.8</td>
<td>8/0</td>
<td>12.0 ± 3.1</td>
<td>5.0 ± 1.6**</td>
</tr>
<tr>
<td>Controls for MIS-A group (8)</td>
<td>4/4</td>
<td>45.6 ± 10.6</td>
<td>8/0</td>
<td>12.2 ± 2.5</td>
<td>1.1 ± 1.2</td>
</tr>
</tbody>
</table>

M/F = males/females; MIS = memory index score; MIS-N = normal memory index scores; MIS-
A = abnormal memory index scores. * P < 0.05 and ** P < 0.001: significant differences between
patient group and matched control subjects. †Means ± SDs are given.

**Methods**

### Patients and healthy control subjects

Twenty-four patients from a multiple sclerosis research clinic
were studied. They were randomly selected from a prospective
study of 69 patients (Blumhardt et al., 1995a, b) who
presented with an isolated, non-familial, non-compressive
myelogram-negative myelopathy for which other causes had
been excluded, and in whom a diagnosis of demyelinating
disease was either confirmed or suspected. By definition, no
patient had symptoms or signs of higher cerebral function
disorder or cranial nerve abnormalities. Vision and hearing
were clinically normal. The course of the myelopathy was
slowly progressive after an insidious onset in 15 of the 24
(63%), progressive with superimposed relapses in seven
(29%) and acute and monophasic in two (8%).

After diagnostic workup, including MRI and CSF
examination (intrathecal immunoglobulin synthesis and
oligoclonal bands) and a battery of tests of exclusion
(including full blood count, erythrocyte sedimentation rate,
syphilis serology, thyroid function, B12 and folate, HTLV-I
virus serology and long chain fatty acids), nine patients
(37%) were classified on the Washington Committee criteria
(Poser et al., 1983) as ‘laboratory supported definite multiple
sclerosis’ and 10 patients (42%) as ‘clinically probable
multiple sclerosis’. Five patients (21%) were classifiable as
‘progressive possible multiple sclerosis’ on the McDonald
and Halliday (1977) criteria (Table 1). On routine neurological
assessment, none of the patients had symptoms or clinical
evidence of abnormal cognition or memory function.

Twenty-four healthy subjects, with no history of CNS
Table 3  Scores of patients and control groups on psychological tests and their significance

<table>
<thead>
<tr>
<th>Test</th>
<th>Patients $(n = 24)^{\dagger}$</th>
<th>Control subjects $(n = 24)^{\dagger}$</th>
<th>$F$(1,46) (ANOVA)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full scale IQ</td>
<td>106.4 ± 11.7</td>
<td>113.6 ± 8.9</td>
<td>6.78</td>
<td>0.012</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>104.5 ± 11.1</td>
<td>112.2 ± 12.1</td>
<td>5.24</td>
<td>0.027</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>107.8 ± 11.1</td>
<td>114.2 ± 8.1</td>
<td>5.29</td>
<td>0.026</td>
</tr>
<tr>
<td>Verbal subtests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arithmetic</td>
<td>10.4 ± 2.7</td>
<td>11.4 ± 2.2</td>
<td>2.16</td>
<td>0.149</td>
</tr>
<tr>
<td>Similarities</td>
<td>11.1 ± 1.9</td>
<td>12.4 ± 2.1</td>
<td>4.76</td>
<td>0.034</td>
</tr>
<tr>
<td>Digit span</td>
<td>11.1 ± 3.2</td>
<td>12.2 ± 3.0</td>
<td>1.53</td>
<td>0.223</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>10.5 ± 1.5</td>
<td>12.0 ± 2.0</td>
<td>7.83</td>
<td>0.008</td>
</tr>
<tr>
<td>Performance subtests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit symbol</td>
<td>11.8 ± 2.7</td>
<td>13.8 ± 2.1</td>
<td>8.06</td>
<td>0.007</td>
</tr>
<tr>
<td>Picture completion</td>
<td>10.1 ± 1.5</td>
<td>11.0 ± 1.9</td>
<td>3.71</td>
<td>0.060</td>
</tr>
<tr>
<td>Block design</td>
<td>12.1 ± 2.7</td>
<td>12.9 ± 2.7</td>
<td>0.95</td>
<td>0.334</td>
</tr>
<tr>
<td>Picture arrangement</td>
<td>11.1 ± 2.5</td>
<td>11.7 ± 2.8</td>
<td>0.66</td>
<td>0.419</td>
</tr>
<tr>
<td>Wechsler Memory Scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>9.8 ± 2.7</td>
<td>11.4 ± 3.1</td>
<td>3.57</td>
<td>0.065</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>6.0 ± 2.4*</td>
<td>8.6 ± 3.2*</td>
<td>10.42*</td>
<td>0.002*</td>
</tr>
<tr>
<td>Paired associate Learning</td>
<td>12.5 ± 3.7</td>
<td>15.6 ± 3.4</td>
<td>8.71</td>
<td>0.005</td>
</tr>
<tr>
<td>Digit span forwards</td>
<td>6.71 ± 1.5</td>
<td>7.3 ± 1.5</td>
<td>1.81</td>
<td>0.185</td>
</tr>
<tr>
<td>Digit span backwards</td>
<td>4.71 ± 1.4</td>
<td>5.1 ± 1.3</td>
<td>0.94</td>
<td>0.338</td>
</tr>
<tr>
<td>Recognition Memory Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Words</td>
<td>45.7 ± 4.5</td>
<td>47.8 ± 3.1</td>
<td>3.49</td>
<td>0.068</td>
</tr>
<tr>
<td>Faces</td>
<td>43.1 ± 4.6</td>
<td>44.2 ± 4.2</td>
<td>0.71</td>
<td>0.404</td>
</tr>
<tr>
<td>Benton Visual Retention Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benton errors</td>
<td>5.0 ± 2.7</td>
<td>3.2 ± 2.5</td>
<td>5.34</td>
<td>0.025</td>
</tr>
<tr>
<td>Benton correct</td>
<td>6.7 ± 1.6</td>
<td>7.5 ± 1.6</td>
<td>3.15</td>
<td>0.082</td>
</tr>
</tbody>
</table>

*MIS-N = normal memory index scores; MIS-A = abnormal memory index scores; WAIS = Wechsler Adult Intelligence Scale. The only results which were significant after Bonferroni correction for the number of comparisons. Means ± SDs are given.

damage, psychiatric illness or memory disorder, who were either staff in the neurology unit or friends or relatives of staff, were recruited as healthy control subjects. They were matched with the patients for age and education years (Table 2). All patients and control subjects gave informed consent to participate in the study, which was approved by the South Sefton Research Ethics Committee.

**Psychological tests and memory index scores**

Tests of intellect from the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955) included four verbal (Vocabulary, Similarities, Arithmetic and Digit Span) and four performance (Digit Symbol, Block Design, Picture Arrangement and Picture Completion) subtests. The verbal IQ, performance IQ and full scale IQ were calculated from the scores of these subtests. Memory tests included Immediate Logical Memory, Delayed Logical Memory and Paired Associate Learning from the Wechsler Memory Scale (Wechsler, 1945), Digit Span Backwards and Forwards from the WAIS (Wechsler, 1955) and the Benton Visual Retention and Recognition Memory tests for Words and Faces (Warrington, 1984). The complete battery of tests was administered to all patients and healthy control subjects (Table 3).

Our 'Memory Index Score' (MIS) was derived from the performance of the healthy control subjects on the above memory tests in order to obtain a sensitive index of memory dysfunction. This method is similar to that used by Callanan et al. (1989) to detect subtle reductions of cognition in a similar cohort of patients with isolated demyelinating lesions. It allows the combination of scores from tests using different units of measurement and does not assume independence of the individual tests. A graded scoring system (0–2) was devised for each test: for the subtests 'Digit Span Backwards' and 'Digit Span Forwards', 'Immediate Logical Memory', 'Delayed Logical Memory' and 'Paired Associate Learning', the patients’ performance was compared with the normative data (for the appropriate age group) (Wechsler, 1945) and scored according to the following system: 0, if within 1 SD of the mean; 1, if between 1 and 2 SD; 2, if above 2 SD. The criteria for the 'Benton Correct' and 'Benton Errors' were: 0, if scores were within two points below (correct) and three points above (error) the expected score according to IQ and age; 1, for scores three points below and four points...
above the expected scores; 2, for scores four points or more below and five or more above the expected scores. For the Recognition Memory tests, 0 was given for scaled scores of 10 ± 3 (<1 SD), 1 for scaled scores between 7 and 4 (between 1 and 2 SD) and 2 for scaled scores below 4 (>2 SD). However, for patients whose IQ was above average, scores between 10 and 7 were classified as 1, and scores of 7 or below were classified as 2. The MIS was obtained by adding the scores from each memory test. The upper limit of the normal range of the MIS was set at 3 (mean ± 2 SD = 2.9). None of the 24 control subjects exceeded this value (control subject mean 1.1 ± 0.9, range 0–3; patient mean 2.4 ± 2.2, range 0–8). The defined upper limit of the MIS separated the patients into two groups, eight with
abnormal MIS (MIS-A) (MIS > 3) and 16 with normal MIS (MIS < 3). The two patient groups did not differ significantly for any clinical parameter (Tables 1 and 2).

The memory paradigm
The paradigm was modified from the original version described by Sternberg (1966). The subjects were presented with sets (‘memory sets’) of one, three or five digits to be memorized. A single probe digit was presented 3 s after the end of each memory set. Subjects were required to indicate whether the probe was either present in, or absent from, the preceding memory set (by pressing a button in the dominant or non-dominant hand, respectively). Probe digits which were present in, or absent from the preceding set are referred to as positive or negative probes, respectively. The probability that the probe was a member of the preceding memory set was 0.5. The digits contained in each trial were randomly selected with the restriction that no particular digit could occur as a probe in two consecutive trials and no more than three consecutive positive or negative probes occurred in sequence (pseudorandom sequence). The proportions of positive probes related to each possible position of the matching digit in the preceding string (first, second or third in the three digit sets and first, second, third, fourth or fifth in the five digit sets) were adjusted to be approximately

![Fig. 2](image-url)
equal. Each trial commenced with a warning signal (the word ‘start’), followed 0.85 s later by the first item of the memory set. The onset-to-onset intervals between digits in the memory sets was 1.2 s. The word ‘start’ and the digits 1–9 were presented either aurally, through a loudspeaker using a microcomputer fitted with a speech synthesizer chip, or visually, by a sequential display on a monitor. Memory-set items and digit probes were always presented in the same modality, i.e. visual probes for visual memory sets and auditory probes for auditory memory sets. For each response, the interval between the onset of the probe digit and the button press was measured as the reaction time. The accuracy of probe identification was also recorded, including incorrect responses (‘button-press errors’) and failure to press a button within 3 s (‘time out’). Precipitate responses in which the reaction time was less than 200 ms (‘false alarms’) were excluded from the analysis. Forty trials were performed for each memory set in two runs, each of 20 trials.

**ERP recording**

During the recording sessions, the subjects sat in a comfortable armchair in a semi-darkened room. Recordings were obtained from 10 mm Ag/AgCl electrodes (inter-electrode impedance $<$5000 Ω) at Fz, Cz and Pz (10–20 International System) using linked ears as the common reference. Electrooculography was monitored via electrodes positioned above and below the left eye.

For all studies, we analysed a 960-ms epoch which included the 120-ms period prior to (and the 840 ms which followed) the presentation of the first item of each memory set (M-ERPs) or a probe digit (PR-ERPs). For M-ERPs the analysis was restricted to the first item of each ‘memory set’ regardless of the number of items. Only M-ERPs and PR-ERPs which were associated with correctly identified probes were analysed.

There were 256 samples per sweep. ERPs were sorted and averaged separately according to the task (memorizing of set items or probe identification/matching), the stimulus modality (auditory or visual), the memory-set size (one, three or five digits) and, for the PR-ERPs, the type of probe (positive or negative). A preliminary analysis showed no significant differences between the M-ERPs associated with positive and negative probes (because subjects could not anticipate the type of probe which would follow a memory set in any particular trial due to randomization) so that all subsequent analyses combined the M-ERPs from tasks associated with either a positive or a negative probe.
The time constant was 3 s. Waveforms were digitally filtered with a high frequency cut off at 44 Hz. The response to each trial was stored on floppy disk for analysis. ERPs from individual trials were visually inspected and selected for averaging only if uncontaminated by marked muscle or eye movement artefact (i.e. EOG deviations from baseline <100 µV). A minimum of 15 artefact-free correct responses were required for an average to be accepted into the analysis.

Following inspection of the responses to single trials, there were 24 and 22 patients with sufficient, technically adequate auditory and visual responses, respectively (to both probe types). The much smaller responses to item memorizing were frequently contaminated by EOG artefacts, which left 20 and 15 technically satisfactory cases for visual and auditory averaging, respectively.

**ERP analysis**

After averaging, the analysis of the PR-ERPs was carried out by two methods, a conventional method of ‘component analysis’ based on component identification according to polarity and latency and an objective method of ‘multiple mean amplitude’ (MMA) analysis based on computer-determined mean amplitudes for short epochs. MMA analysis was the sole method used for the analysis of the M-ERPs, as explained below.

**Component analysis**

The group average waveforms of healthy subjects were used to identify the major components according to their polarity (P for positive and N for negative) and mean latencies. The major components defined from the group averages were identified in the individual responses using latency criteria (Fig. 1). For the auditory ERPs, the early part of the response was made up of four components, the P100, N170, P250 and N290 waves, which were clearly seen for all conditions (Fig. 1A). The later part of the response varied according to the memory-set size and the recording site. In the responses to sets of single digits there was a single major positive component (P400) at Fz and Cz, whereas at Pz, two positive peaks (P400 and P560) were frequently seen in this region of the waveform (Fig. 1A). The P560 was the dominant positivity in the responses to sets of three and five digits (Fig. 1A).

For visual ERPs, the early response was made up of two main components (P145 and N220) and a series of less consistent smaller waves (N190, P240 and N270). The first
Multiple mean amplitude (MMA) analysis
Component identification was difficult in some patients, particularly in the small amplitude M-ERPs and in the probe responses concerning the larger memory sets. In these situations, analogous waves were either ‘missing’, or difficult to identify with confidence, in both patients and control subjects. For the initial comparison of all 24 patients and control subjects we used both component analysis and the objective MMA method, but for the patient subgroups and for all M-ERP analyses, we used only the objective MMA method of data analysis. With this technique, the 840 ms which followed probe presentation was subdivided into 16 epochs or ‘mean amplitude periods’ (MAPs 1–16), each of 52.5 ms (‘50-ms epochs’). A computer program calculated a single mean amplitude (relative to the prestimulus baseline) from the amplitudes of all the individual ordinates within each epoch.

Statistical analysis
As some of the data deviated from a normal distribution, we used non-parametric tests from the SPSS-X statistical package (mainframe version, release 3).

Psychological data
Group means were compared with a one-way ANOVA, and Bonferroni correction was used for multiple comparisons.

Behavioural data
The effects on reaction times and button-press errors of the between-subject factor Group (patients and matched control subjects) and the within-subject factors Modality (two levels; auditory and visual), Probe (two levels; positive and negative) and Set Size (three levels; one, three and five digits) were analysed by multiple analysis of variance (MANOVA) with repeated measures (see below).

ERPs
The effects on the latency and amplitude of components and on the MAPs of the between-subject factor Group and the within-subject factors Set Size, Probe and Electrode (three levels; Fz, Cz and Pz) were analysed by MANOVA with repeated measures using the Greenhouse–Geisser correction for sphericity. The conservative Scheffé test was used for post hoc analyses.

Results
All patients versus all control subjects
Psychological tests
The patients’ mean scores were lower than those of control subjects on all psychological tests and particularly for the Wechsler Memory Scale subtests ‘Delayed Recall’, ‘Paired Associate Learning’ and the ‘Benton Visual Retention Test’ as well as full scale IQ, visual IQ, performance IQ and the WAIS subtests ‘Digit Symbol’, ‘Vocabulary’ and ‘Similarities’ (Table 3). However, only the patients’ performance on ‘Delayed Recall’ was significantly worse than that of control subjects after statistical corrections for the number of comparisons (Table 3).

Performance on psychological tests did not correlate with disease duration, disability level, or the presence or absence of MRI abnormalities on T2-weighted spin echo images.

Behavioural data
Reaction time. The patients’ reaction times were consistently slower than those of control subjects [Auditory: $F(1,46) = 14.2, P < 0.001$; Visual: $F(1,42) = 16.9, P < 0.001$] (Fig. 2A) and showed a greater increase with increasing
Fig. 5 Multiple mean amplitude (MMA) plots of auditory and visual PR-ERPs, during the first 16 (50-ms) epochs, for all patients (closed circles, n = 24 and 22, respectively) and control subjects (open triangles, n = 24 and 22, respectively). Effects of recording site, set size and probe type are pooled.

Errors. There were no significant differences between patients and control subjects for the percentage of errors during the tasks (Fig. 2B).

Responses to probes (PR-ERPs): component analysis

Auditory digits. The P400 wave was reduced in the patients’ responses compared with that of control subjects [Group × Probe: F(1,35) = 4.83, P < 0.05], whereas the P250 was increased (particularly for positive probes) [Group × Probe: F(1,35) = 4.58, P < 0.05] (Fig. 3). The latency of the N290 wave was prolonged, particularly for negative probes [Group × Probe: F(1,31) = 12.19, P < 0.001] and larger set sizes [Group × Set Size: F(2,57) = 4.71, P < 0.05] (Fig. 3).

Visual digits. The P145 was delayed in the patients’ responses at Cz and Pz compared with that of control subjects [Group × Electrode: F(2,68) = 3.63, P < 0.05]. Both the patients’ P240 [F(1,18) = 18.59, P < 0.001] and N270 waves [F(1,21) = 7.37, P < 0.05] were prolonged, the latter particularly at Fz and Cz [Group × Electrode: F(2,30) = 4.33, P < 0.05] (Fig. 4).

The amplitude of the MPW was reduced in the patients compared with that of control subjects [F(1,37) = 5.6, P < 0.05]. The amplitude distribution of the N190 [Group × Electrode: F(2,57) = 3.5, P < 0.05], P240 [F(2,30) = 7.3, P < 0.01] and N270 waves [F(2,34) = 4.4, P < 0.05] were significantly altered in the patients, with the largest negative activity at Fz and Cz in the patients and at Pz in the control subjects (Fig. 4).

Responses to probes (PR-ERPs): MMA analysis

Auditory digits. The activity between 210 and 315 ms (MAPs 5 and 6) was significantly more positive in patients at Cz and Pz [Group × Electrode: F(2,92) = 4.1 and 3.9, respectively, P < 0.05]. Group differences in the positive activity between 315 and 840 ms (MAPs 7–16) were not significant (cf. component analysis) (Fig. 5).

Visual digits. The group differences in the positive activity between 262 and 840 ms (MAPs 6–16) were not significant (Fig. 5). The positive activity between 52 and 157 ms (MAPs 2 and 3) was significantly reduced in the patients [F(1,46) = 5.2 and 5.7, respectively; P < 0.01] (Fig. 5). Negative activity between 210 and 262 ms (MAP 5) was larger in the patients at Fz and Cz, and larger in the control subjects at Pz [Group × Electrode: F(2,92) = 4.5, P < 0.05].

Responses to memorizing of digits (M-ERPs): MMA analysis

Auditory digits. The activity in the five 50-ms epochs between 210 and 315 ms (MAPs 8–12) was more negative
in the patients at Fz and Cz [Group × Electrode: $F(2,92) = 5.3, 5.1, 4.0, 4.3$ and $4.4$, respectively; $P < 0.05$] (Fig. 6A).

Visual digits. There were no significant differences between patients and control subjects (Fig. 6B).

**Comparison of patient groups defined by MISs**

*Psychological tests*

The mean scores of the MIS-A patients on tests of memory were consistently worse than those of the MIS-N patients (particularly for Digit Span Backwards, Recognition Memory for Faces and to a lesser extent for Paired Associate Learning and Digit Symbol), but none of the individual test differences achieved significance after statistical correction for multiple comparisons (Table 4). The group differences for MIS were highly significant [$F(1,22) = 59.2, P < 0.0001$].

**Behavioural data**

*Reaction time.* Each group of patients had significantly slower reaction times than the matched control group [MIS-A, auditory: $F(1,14) = 4.4$, visual $F(1,12) = 5.4$, $P < 0.05$] [MIS-N, auditory: $F(1,30) = 9.8$, visual $F(1,28) = 10.7$, $P < 0.01$] (Fig. 2A). In addition, the increase in reaction time with set size in the auditory modality was significantly greater in MIS-N patients than their control subjects.
Table 4 Scores of MIS-A and MIS-N patient groups on psychological tests and their significance

<table>
<thead>
<tr>
<th>Test</th>
<th>MIS-A patients (n = 8)</th>
<th>MIS-N patients (n = 16)</th>
<th>F(1,22) (ANOVA)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAIS</td>
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</tr>
<tr>
<td>Full scale IQ</td>
<td>102.8 ± 12.9</td>
<td>108.2 ± 8.5</td>
<td>1.55</td>
<td>0.226</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>101.4 ± 11.1</td>
<td>106.1 ± 9.9</td>
<td>0.97</td>
<td>0.334</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>103.8 ± 13.7</td>
<td>109.7 ± 13.7</td>
<td>1.59</td>
<td>0.221</td>
</tr>
<tr>
<td>Verbal subtests</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arithmetic</td>
<td>9.4 ± 3.7</td>
<td>10.9 ± 1.9</td>
<td>1.85</td>
<td>0.188</td>
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<tr>
<td>Similarities</td>
<td>11.2 ± 2.9</td>
<td>11.1 ± 1.2</td>
<td>0.02</td>
<td>0.883</td>
</tr>
<tr>
<td>Digit span</td>
<td>9.5 ± 1.8</td>
<td>11.9 ± 3.5</td>
<td>3.30</td>
<td>0.083</td>
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<tr>
<td>Vocabulary</td>
<td>10.7 ± 2.2</td>
<td>10.4 ± 1.1</td>
<td>0.21</td>
<td>0.648</td>
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<tr>
<td>Performance subtests</td>
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<tr>
<td>Digit symbol</td>
<td>10.2 ± 3.1</td>
<td>12.6 ± 2.2</td>
<td>4.44</td>
<td>0.047</td>
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<tr>
<td>Picture completion</td>
<td>10.1 ± 1.8</td>
<td>10.1 ± 1.4</td>
<td>0.01</td>
<td>0.927</td>
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<tr>
<td>Block design</td>
<td>11.7 ± 3.1</td>
<td>12.3 ± 2.5</td>
<td>0.23</td>
<td>0.636</td>
</tr>
<tr>
<td>Picture arrangement</td>
<td>10.2 ± 2.9</td>
<td>11.5 ± 2.3</td>
<td>1.31</td>
<td>0.264</td>
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<tr>
<td>Wechsler Memory Scale</td>
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<tr>
<td>Immediate recall</td>
<td>8.8 ± 3.4</td>
<td>10.3 ± 2.2</td>
<td>1.81</td>
<td>0.192</td>
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<tr>
<td>Delayed recall</td>
<td>5.1 ± 2.8</td>
<td>6.5 ± 2.1</td>
<td>1.76</td>
<td>0.199</td>
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<td>Paired associate</td>
<td>10.3 ± 3.8</td>
<td>13.7 ± 3.1</td>
<td>5.29</td>
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<td>Learning</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Digit span forwards</td>
<td>5.9 ± 1.1</td>
<td>7.1 ± 1.5</td>
<td>0.22</td>
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<td>Digit span backwards</td>
<td>3.5 ± 0.9</td>
<td>5.3 ± 1.2</td>
<td>10.04</td>
<td>0.005</td>
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<tr>
<td>Recognition Memory Test</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Words</td>
<td>43.5 ± 5.5</td>
<td>46.7 ± 3.6</td>
<td>3.02</td>
<td>0.097</td>
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<tr>
<td>Faces</td>
<td>39.5 ± 5.9</td>
<td>44.9 ± 2.5</td>
<td>10.18</td>
<td>0.004</td>
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<tr>
<td>Benton Visual Retention Test</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benton errors</td>
<td>6.4 ± 3.2</td>
<td>4.3 ± 2.2</td>
<td>3.43</td>
<td>0.077</td>
</tr>
<tr>
<td>Benton correct</td>
<td>5.9 ± 1.9</td>
<td>7.1 ± 1.4</td>
<td>2.96</td>
<td>0.099</td>
</tr>
</tbody>
</table>

No group differences were significant after Bonferroni correction. MIS-N = normal memory index scores; MIS-A = abnormal memory index scores; WAIS = Wechsler Adult Intelligence Scale. † Means ± SDs are given.

(Group × Set Size: F(2,60) = 5.7, P < 0.05) (Fig. 2A). A similar trend in the MIS-A patients did not reach significance (Fig. 2A).

Errors. Performance accuracy did not differ significantly between either group of patients and their control subjects for either modality (Fig. 2B). In the auditory modality the MIS-A patients made significantly more errors with increasing set size [Group × Set Size: F(2,28) = 3.4, P < 0.05] (Fig. 2B).

Responses to probes (PR-ERPs)

Auditory responses: group average waveforms. The responses of the MIS-A patients showed marked waveform changes, particularly for sets of three and five digits (Fig. 1A). Immediately after the peak of the N290 wave, their waveforms diverged from those of the control subjects, due to a sustained negativity which eventually terminated in a reduced amplitude positivity (cf. the P560 wave in the control subjects) (Fig. 1A). In the responses to single digits, the P400 wave was reduced and the N290 wave delayed.

In the MIS-N patients, the amplitude of the N170 wave was slightly reduced and the P250 increased, compared with those of control subjects (Fig. 1A). In addition, the P400 in their responses to single digits and the main positivity of the responses to three digit sets, were generally smaller (Fig. 1A).

Visual responses: group average waveforms. The responses of the MIS-A patients diverged markedly from those of their control subjects, particularly for larger set sizes. The first negative wave was broadened (positive probes, sets one and three) and/or followed by a sustained negative wave which terminated with a positivity of reduced amplitude with respect to the MPW in control subjects (Fig. 1B).

In the MIS-N patients, the P145 and MPW were reduced in some conditions and the responses to memory sets of five digits showed negative-going activity superimposed on the descending slope of the MPW (Fig. 1B).
**Responses to probes (PR-ERPs): MMA analysis**

**Auditory digits.** In the MIS-A patients, the activity in the four 50-ms epochs between 315 and 525 ms (MAPs 7–10) was significantly more negative than in control subjects [Group: $F(1,14) = 5.2, 9.7, 11.0$ and $6.1$, respectively; $P < 0.05, 0.01, 0.01$ and $0.01$, respectively] (Fig. 7). With increasing set size, there was a ‘negative amplitude shift’ of the waveforms in both patients and control subjects (Fig. 8), but this was significantly more marked in patients in the three epochs between 262 and 420 ms (MAPs 6–8), particularly at Cz and Pz [Group×Set Size×Electrode: $F(4,56) = 5.8, 5.5$ and $6.2$, respectively; $P < 0.001$] (Fig. 8). There were other significant and complex interactions between Group, Electrode and Set Size between 105 and 262 ms (MAPs 3–5) and between 577 and 735 ms (MAPs 12–14).

The ERPs in the MIS-N patients differed from control subjects in the two epochs between 105 and 210 ms (MAP3 and MAP 4), where negative activity was significantly reduced [Group: $F(1,30) = 8.0, 8.0$, respectively; $P < 0.01$] (Fig. 7). Between 157 and 315 ms (MAPs 4–6), the patients’ responses were more positive at Cz and Pz [Group×Electrode: $F(2,60) = 3.9, 7.0$ and $6.0$, respectively; $P < 0.05, 0.01$ and $0.01$, respectively].

**Visual digits.** As for the auditory PR-ERPs, the most marked differences were seen in the MIS-N group. Between 262 and 840 ms (MAPs 6–16) the patients’ responses were more negative than those of control subjects (Fig. 7) with significant differences occurring between 315 and 420 ms (MAPs 7 and 8) [Group $F(1,12) = 6.7$ and $7.5$, respectively; $P < 0.05$].

Significant changes in the MIS-N patients were restricted to the early activity between 52 and 157 ms (MAPs 2 and 3), which was more negative than in control subjects [Group: $F(1,28) = 7.1$ and $8.3$, $P < 0.05$ and $0.01$, respectively] (Fig. 7), and the activity between 210 and 262 ms (MAP 5), which was more negative at Fz and Cz in patients, and at Pz in control subjects.

**Responses to memorizing of digits (M-ERPs)**

**Auditory digits.** In the two epochs between 315 and 420 ms (MAPs 7 and 8), responses were significantly more negative in MIS-A patients than in control subjects [$F(1,6) = 8.03$ and $6.02$, respectively; $P < 0.05$] (Fig. 9A), whereas MAPs 6–12 (262–630 ms) were significantly more negative in MIS-N patients than in their matched control subjects at Fz and Cz, but not at Pz [Group × Electrode: $F(2,40) = 6.27, 5.43, 8.85, 8.42, 9.00, 6.80$ and $6.40$, respectively; $P < 0.01, 0.05, 0.01, 0.01, 0.005$ and $0.05$, respectively] (Fig. 9A). With increasing task difficulty, the activity between 315 and 375 ms (MAP 7) became more positive at Cz and Pz in the MIS-A group. This positive effect was significantly less marked in both the MIS-N group and the control subjects [Group × Set Size × Electrode: $F(4,80) = 4.28$, $P < 0.05$] (Fig. 10A).

**Visual digits.** The responses of MIS-A patients were more negative than both those of their matched control subjects and those of the MIS-N patients (Fig. 9B), with significant differences between the two groups of patients for MAP 2 [$F(1,18) = 5.01$, $P < 0.05$], MAPs 5–9 [$F(1,18) = 5.32, 10.54$, $P < 0.05$].
Fig. 8 Multiple mean amplitude (MMA) plots of auditory PR-ERPS (with effects of probe type pooled) to show effects on MIS-A patients and control subjects of memory-set size (set 1 = open circles; set 3 = open triangles; set 5 = closed circles), by recording site. 8.26, 6.76 and 5.18, respectively; $P < 0.05, 0.001, 0.01, 0.05$ and 0.05, respectively] ] and MAPs 11–13 [$F(1,18) = 6.38, 6.34$ and 7.02, respectively; $P < 0.05$]. In addition, the activity between 52 and 105 ms (MAP 2) and between 315 and 472 ms (MAPs 7–9) became more positive with increasing set size, whereas it was unchanged, or more negative, in MIS-N patients and control subjects [Group $\times$ Set Size: $F(2,36) = 5.6, 6.63, 3.98$ and 4.19, respectively; $P < 0.01, 0.01, 0.05$ and 0.05, respectively] (Figs 9B and 10B). MIS-N patients did not differ from their control subjects.

MRI
There were no significant psychological differences between patients either with, or without characteristic high signal abnormalities on their $T_2$-weighted spin echo images. On quantitative analysis, there was no correlation between the total lesion volume on $T_2$-weighted spin echo MRI and either ERP or psychological test results. The MRI analysis will be presented in detail elsewhere.

Discussion
The few published psychological studies of patients presenting with clinically isolated lesions have produced conflicting results and have not specifically addressed the question of working memory impairment (Lyon-Caen et al., 1986; Callanan et al., 1989; Ron et al., 1991; Feinstein et al., 1992a, b). One study of patients with optic neuritis reported deficits in attention and/or in speed of information processing (Feinstein et al., 1992a), but memory function was not specifically investigated. Another study which analysed patients with lesions isolated to optic nerve, brainstem or spinal cord, reported intact memory function with impaired attention and speed of information processing (Callanan et al., 1989). A subsequent investigation (Ron et al., 1991) which compared the same patients studied by Callanan et al. (1989) with patients with established multiple sclerosis, found more severe cognitive abnormalities in the latter, despite similar levels of attentional deficits. Ron et al. (1991) concluded that ‘early attention deficits which can be detected even in those with minimal neurological impairment, extend with advancing disease to involve memory and abstracting abilities’. However, the only memory tests used in these two studies were Recognition Memory for Words and Faces (Callanan et al., 1989; Ron et al., 1991). Another group reported significant impairment on the Wechsler Memory Scale in some patients with isolated optic neuritis (Lyon-Caen et al., 1986), but abnormalities of working memory
were not clearly defined. In the present study we have found abnormalities of both behavioural and ERP data generated by a short-term memory paradigm in a group of patients who were only mildly and insignificantly impaired on cognitive testing. This suggests that working memory is affected early in the course of multiple sclerosis, at a stage when any cognitive impairment remains subtle and asymptomatic.

Although our patients had clinically isolated myelopathy, their reaction times were prolonged overall compared with healthy control subjects, particularly under conditions of increasing memory load. These findings which indicate slowed information processing speed in working memory, independent of motor disability, are similar to those previously reported in working memory studies of patients with established multiple sclerosis (Rao et al., 1989b; Ruchkin et al., 1994). By contrast, the mean group reaction time to an oddball paradigm, or simple or choice reaction times (Newton et al., 1989; Feinstein et al., 1992a; Giesser et al., 1992) do not differentiate patients with established multiple sclerosis from control subjects. These results suggest that the reaction-time slowing we and others have observed is likely to be related to difficulties in working memory and not merely due to a generalized slowing of information processing. Despite their slowed reaction time, our early multiple sclerosis patients were able to cope with the demands of the task; overall they made no more errors than healthy control subjects.

ERPs were significantly altered in our patients during both memorizing and the subsequent recognition and matching of digits. Some of the changes in the probe-associated ERPs

Fig. 9 (A) Multiple mean amplitude (MMA) plots of auditory M-ERPs to show the differences between control subjects (open circles, n = 15), and MIS-N (open triangles, n = 11) and MIS-A (closed circles, n = 4) patient groups, by recording site. (B) MMA plots of visual M-ERPs to show the effects of memory-set size (set 1 = open circles; set 3 = open triangles; set 5 = closed circles) on control subjects (n = 20), MIS-N (n = 14) and MIS-A (n = 6) patient groups.
appeared similar for both modalities, namely a delay of the N270/N290 waves and a decreased amplitude of the major positivities (P400/MPW). The delay of the negative waves may be analogous to the prolonged reaction time and could be interpreted as the electrophysiological correlate of slowed processing between stimulus presentation and motor response selection. Furthermore, the amplitude distribution of the early potentials which preceded the major positivity was abnormal, as shown both by component and MMA analyses. These findings, which confirm similar findings in patients with epilepsy (Grippi et al., 1994, 1996a), suggest that the generators of these components are actively involved in the processing of this working memory task. The alternative possibility, that these alterations in patients with early multiple sclerosis merely reflect demyelination in the primary sensory pathways, is unlikely. First, the auditory P100 was normal, whereas the later auditory components were affected and, secondly, the visual P145 was abnormal in the responses to probes, but not in the ERPs to memory-set items. Finally, there was a rather low incidence of abnormalities in visual evoked responses and brainstem auditory evoked responses (20% and 19% of the patient population, respectively), the distribution of which did not correlate with the ERP abnormalities in our cohort. The reduced amplitudes of the major positive waves (P400/MPW) may result from either a superimposed negative activity (see below), or alternatively, from an increased latency jitter due to a greater desynchronization of decision making and/or response selection and execution. The patients’ ERPs to memorizing were normal for visually presented items, but the more negative centro-frontal activity (between 375 and 630 ms) for the auditory modality suggests that the task of temporary storage in working memory was accomplished by a different mechanism to that of control subjects.

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**Fig. 10** (A) Auditory M-ERPs (group averages), by memory-set size and recording site, for control subjects and patient groups. (B) Visual M-ERPs (group averages), by set size and recording site, for control subjects and patient groups. Note that, in both auditory (A) and visual (B) M-ERPs, significant effects of memory-set size occurred only in the MIS-A group.
Although psychological studies have shown that cognition is impaired in the earliest stages of multiple sclerosis, there have been no reported ERP studies of patients at their first presentation with a clinically isolated lesion. All previous ERP investigations have involved cohorts of patients with predominantly established multiple sclerosis of long duration. All but one of these studies have used the P300 wave evoked by the oddball paradigm rather than a task specific to memory. A latency increase of the auditory P300 wave, combined in two studies with a prolongation of an N200 component (Newton et al., 1989; Gil et al., 1993), has been the most frequently reported abnormality (Tourtellotte et al., 1984; Hautecoeur et al., 1989; Gieser et al., 1992). ERP amplitude changes have seldom been reported (Newton et al., 1989) and correlations between neuropsychological tests and P300 latency changes have been inconsistent. In one study, more than half the patients with normal performance on psychological tests had abnormalities of the P300 wave and 40% of patients with abnormal psychological tests had normal P300 waves (Newton et al., 1989). These results suggest that the oddball P300 waves and the psychological tests used in these studies may reflect different cognitive functions. As it is still a matter of debate whether the ‘oddball P300’ reflects any aspect of memory function (Onofrj et al., 1991, 1992; Rugg et al., 1991; O’Donnell et al., 1993), further comparisons between our results and earlier P300 studies in multiple sclerosis may be inappropriate.

There has been one previous study of memory function in multiple sclerosis in which ERPs were recorded during the performance of phonological and visuo-spatial working memory tests in 10 patients with clinically definite or probable multiple sclerosis and heterogeneous clinical presentations (Ruchkin et al., 1994). The significant changes which were found, particularly for verbal material, were attributed to disruption of the fibre networks connecting regions involved in verbal working memory (anterior articulatory loop and posterior phonological store) such as the superior longitudinal fasciculus. Again, comparisons with our data are probably inappropriate, since there are substantial methodological differences, including the type of patient, the paradigm, stimulus type, recording sites and analysis times. Nevertheless, it is of interest that the ‘P300’ elicited by the memory paradigm used in this study was not affected.

Although our classification of patients was based on a MIS compiled from tests that were not specific to working memory function, it revealed significant differences which might have been overlooked if we had studied only the entire cohort. The patients with abnormal MIS made significantly more mistakes than patients with normal MIS as the load in working memory was increased. In addition, most of the significant changes in the N270/N290–P400/MPW region of the ERPs can be attributed to the group with abnormal MIS. These patients showed an abnormal increase in the surface negative activity in this latency range, which is the section of the waveform previously identified as sensitive to memory load in healthy subjects (Pelosi et al., 1992, 1995). In addition, the effects of memory loading in this region were significantly more marked in patients with poor memory performance, at least for the auditory modality. In healthy subjects, a ‘negative amplitude shift’ in this region with memory loading has been interpreted as part of a ‘processing negativity’ which reflects the allocation of attentional resources to cope with the increasing task demands (Okita et al., 1985; Pelosi et al., 1992, 1995). The exaggeration of these ‘negative effects’ in our patients with abnormal memory may therefore reflect the extra resources required to compensate for deficits in working memory, in order to accomplish the task successfully. This conclusion is supported by the behavioural data, as despite these patients’ higher error rates, their ERPs were associated with correctly identified probes.

The changes in the ‘memory-sensitive’ section of ERPs in patients with abnormal memory are consistent with the results of a previous study of patients with temporal lobe epilepsy (Grippo et al., 1996a). These observations confirm the sensitivity of the Sternberg ERPs to poor memory performance due to widely varying pathological processes. As our method of classifying patients was based on tests of both long- and short-term memory, the reduced performance and altered ERPs during a working memory task implies either that working memory dysfunction accounts for at least some secondary memory dysfunction in multiple sclerosis, as others have suggested (Litvan et al., 1988b; Grafman et al., 1990), or that our patients had deficits of both short- and long-term memory.

Our MIS-N patients also showed significant ERP alterations, but these affected earlier ERPs (for the auditory responses in the region of the N170–N290 and for the visual responses, the P145–N270 waves). These changes may reflect the attentional deficits which have been described in patients with clinically isolated lesions due to multiple sclerosis (Callanan et al., 1989), since the first negativity, at least for other cognitive paradigms, is thought to reflect mainly attentional processes ( Näätänen and Picton, 1987). Although the ERPs associated with the acquisition and retention of items in auditory working memory (‘memorizing ERPs’, M-ERPs) were significantly altered in both patient groups, the changes in the MIS-A group were more marked. On the other hand, the visual M-ERPs were altered only in the group with the poorer memory performance. This apparent dissociation parallels the behavioural changes (reaction times and error scores) which were more marked in the auditory modality, perhaps providing some support for the hypothesis that verbal memory is more affected than visual memory in multiple sclerosis (Litvan et al., 1988b; Ruchkin et al., 1994).

In our ‘memorizing’ experiments, we made a decision to study only the ERPs associated with the first item in each memory set. This is because our data from control experiments show quite unequivocally that the first item is the most difficult to recognize and/or match correctly, due to a strong recency effect in working memory (Grippo et al., 1996b). Therefore, the M-ERPs to the first item should be the most
sensitive to processing deficits during the ‘memorizing’ stage. We found no significant differences between control subjects and the subgroup of MIS-N patients, but for both auditory and visual modalities, the MIS-A patients showed significant M-ERP changes with increasing memory load. This could suggest changes in strategy to cope with the anticipated increase in the number of items to retain in a defective working memory system, e.g. perhaps of reduced storage capacity. In our block design experiments, the size of the memory set within each block was fixed, so that the subject was always aware in advance of the demands of each trial.

In conclusion, we have found alterations of electrical brain activity in patients with no symptoms of memory dysfunction, during both ‘memorizing’ (ie in this context the active temporary storage of items in working memory) and the subsequent recognition or matching of digits in working memory, demonstrating that the cognitive processing of a short-term memory task in these patients differs from that in healthy control subjects. This ERP evidence of working memory impairment, which correlates with a subtle abnormality of performance that is beyond the range of most individual psychological tests, suggests that the cognitive abnormalities in these patients are not restricted to attentional deficits as previously reported (Callanan et al., 1989; Ron et al., 1991; Feinstein et al., 1992a). Functional imaging has revealed that working memory involves a network of multiple interconnected brain areas (Grasby et al., 1993; Jonides et al., 1993; Paulesu et al., 1993; D’Esposito et al., 1995; Smith and Jonides, 1995), a system which is likely to be highly vulnerable to a disease characterized by multifocal demyelination. As to the nature of the working memory disorder in early multiple sclerosis, our results suggest either that the primary defect involves the temporary ‘acquisition or storage’ of memory traces in working memory or, as is likely in such a diffuse, essentially subcortical pathology, that both these and the subsequent recognition/matching processes may be affected. Finally, although we found evidence for involvement of both auditory and visual ERPs, the changes were more marked in the auditory modality, at least for some tests, perhaps suggesting that impairments of verbal memory may dominate in the early stages of demyelinating disease.

References


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