Working memory deficits in multiple sclerosis: a controlled study with auditory P600 correlates

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Cognitive impairment is a common clinical feature of multiple sclerosis (MS), occurring in up to 65% of patients with this disorder.1,2 Repeatedly, it has been suggested that the cognitive impairment in MS patients is strongly associated with limitations in work and social activities.3

Recent neuropsychological studies provided evidence indicating that working memory (WM) deficits may be involved in MS.3,4 However, brain mechanisms underlying these deficits continue to be a subject of ongoing investigation, as their pattern and specificity still remain unclear. This is particularly evident in psychophysiological research. The existing evidence indicates that the multifocal demyelination of MS leads to a disruption of the multiple interconnected brain areas, which form the substrate of the working memory.5,6

Event related potentials (ERPs) provide a valuable means for studying brain-behaviour relations.6 Pelosi et al., recording both auditory and visual ERPs during the memorising as well as the recognition and matching of digits of a short-term memory paradigm, found that early MS patients as compared with healthy controls displayed a delay of the N270/N290 waves and a decreased amplitude of the major positivities (P400/P560).7 Although these abnormalities have been referred to with regard to both modalities, abnormal changes were more noticeable in the auditory modality. The delay of the negative waves has been interpreted as “an index of slowed processing between stimulus presentation and motor response selection”, while the reduction of the amplitudes as “a manifestation of either the allocation of attentional resources to cope with the increasing task demands or a desynchronization of decision making and/or response selection and execution”. It should be noted that in this study only three leads were used, namely Fz, Cz, and Pz.

The P600 component of ERPs or late positive potentials (elicited between 500 and 800 ms or later after warning stimuli) is accepted as reflecting the completion of any synchronised operation immediately after target detection. In other words, it signals “the second pass parsing processes” of information processing. Specifically, its amplitude is considered as an index of the cost of reprocessing, while its latency as a function of onset and duration of parsing processes.8 Furthermore, it has been suggested that the P600 component may be related to WM.9

Contemporary neuropsychological views define working memory as the capacity to keep information on line as necessary for an ongoing task.10 According to this prospect WM comprises those functional components of cognition that allow humans to comprehend and mentally represent their immediate environment, to retain information about their past experience, to support the acquisition of new knowledge, to solve a problem, as well as to formulate, relate, and act on current goals. In other words WM is not for “memorising” in itself. It is rather in the service of complex cognitive activities, such as reasoning, problem solving, and decision making.11

Consequently, for a neural mechanism underlying the generation of P600, intracranial recordings suggest that P600 is associated with activity in wide ranged brain structures including frontal, temporal, and superior parietal regions, which are believed to contribute significantly to some aspect of information processing during recognition memory.12 Additionally, the results of more recent research indicate that the P600 waveform is generated and/or...
Table 1  Sample characteristics: demographic variables (age, education, duration of illness), clinical characteristics from the EDSS, as well as memory performance (mean (SD) and statistical significance)*

<table>
<thead>
<tr>
<th></th>
<th>MSP (n=22)</th>
<th>Controls (n=2)</th>
<th>p t test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>40.77 9.38</td>
<td>38.7 7.1</td>
<td>NS</td>
</tr>
<tr>
<td>Education (y)</td>
<td>13.36 2.53</td>
<td>12.85 2.15</td>
<td></td>
</tr>
<tr>
<td>Duration of illness (y)</td>
<td>9.31 9.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory performance</td>
<td>21.31 21.30</td>
<td>67.4 6.7 0.002</td>
<td></td>
</tr>
<tr>
<td>Duration of illness</td>
<td>9.31 9.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyramidal function</td>
<td>2.77 1.44</td>
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<td></td>
</tr>
<tr>
<td>Cerebellar function</td>
<td>1.77</td>
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<td></td>
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<tr>
<td>Brain stem function</td>
<td>0.95 1.29</td>
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<td></td>
</tr>
<tr>
<td>Mental function</td>
<td>0.54 0.73</td>
<td></td>
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<tr>
<td>Sensory function</td>
<td>1.54 1.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary bladder function</td>
<td>0.36 0.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual-optic function</td>
<td>0.40 1.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>4.29 1.92</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05.

The foregoing points motivated us to examine aspects of “second pass parsing” processes of information processing as are reflected by P600 elicited during a WM test in MS patients compared with those of healthy controls.

METHODS
Participants
Twenty two definite, chronic progressive MS patients (8 men, and 14 women), with recent exacerbation of their illness participated in the study. They were hospitalised in the neurology clinic of the Athens University Medical School or had been previously hospitalised and were being followed up. Patients were selected according to the Poser et al criteria for definite or probable MS, and had no history of alcohol/drug misuse, head injury, or stroke. Fourteen of the patients had a relapsing or probable MS, and had no history of alcohol/drug misuse, head injury, or stroke. Fourteen of the patients had a relapsing or probable MS, and had no history of alcohol/drug misuse, head injury, or stroke. Twelve patients had a progressive form of MS. All patients were assessed with the Kurtzke Expanded Disability Status Scale (EDSS see table 1).

Twenty controls were recruited from the hospital staff and local volunteer groups. They were free of psychiatric and physical illness. All participants were right handed as assessed by the Edinburgh Inventory; and had no history of any neurological or hearing problems. Written informed consent was obtained from both patients and control subjects.

Stimuli and procedure
Patients and controls were evaluated by a computerised version of the digit span Wechsler test. Although the digit span of the Wechsler test is considered a test of short-term memory, more recent reports emphasise its relevance to WM. The subjects sat in an anatomical chair placed inside an electromagnetically shielded room. An outline of the procedure is provided in figure 1. A single sound of either high (3000 Hz) or low frequency (500 Hz) was presented to the subjects, who were asked to memorise the numbers that followed. The warning stimulus lasted 100 ms. A one second interval followed and then the numbers to be memorised were presented. At the end of the number sequence presentation, the signal tone was repeated and subjects were asked to recall the administered numbers as quickly as possible. The numbers were recalled by the subject in the same (low frequency tone) or in the opposite order (high frequency tone) than that presented to the participant.

Before any recording of ERPs, a pre-process was performed so that the two sounds were differentiated by the subjects. According to this process, various trials have taken place until each subject understood both the different tonalities and the requirements of the test, concerning the storage and retrieval of presented numbers. After the completion of the above mentioned process, a rest period of five minutes followed, before the recording of the ERPs.

ERPs were recorded during the 1100 ms interval between the warning stimulus and the first administered number. The other auditory stimuli were given at an intensity of 65 dB sound pressure level. The evoked bio-potential signal was submitted to an analogue to digital conversion, at a sampling rate of 500 Hz, and was averaged by a computerised system. Each recording session consisted of 26 repetitions of the trial. Eye movements corresponding to EOG higher than 75 V, resulting in rejection of the recording, ranged from one to two per investigation. Thus the minimum number of artefact free trials that were averaged to produce an ERP was 24.

As the warning stimuli were of two different frequencies, one high and one low, it was not clear whether they could generate the same P600, although the P600 component is included in the array of late endogenous ERPs’ components, which normally are not modality specific. To ensure that there were no differences in the P600 waveforms caused by frequency modalities, we conducted t test series comparisons between the P600 waveforms (amplitudes and latencies) evoked by the two frequency modalities (13 high and 13 low frequencies), in all subjects. No differences were found in the P600 waveforms, by frequency, in each subject.

Figure 1  Outline of the experimental procedure.
Consequently the pooled P600 waveforms for each lead (fig 2) were used in the analysis. The following parameters were calculated:

(A) ERPs were recorded for each subject at leads Fp1, Fp2, F3, F4, C3, C4, C3-T5/2, C4-T6/2, P3, P4, O1, O2, Pz, Cz, and Fz for each of the 26 test repetition. In this context, it should be noted that the positions C3-T5/2 and C4-T6/2 are used as electrode leads, because these positions correspond to brain areas serving verbal memory and language.37 Recordings with acceptable EOG level were averaged, for each lead, by a computerised system. An algorithm was used, which identified the P600 as the most positive peak, in each averaged lead curve, between 500 and 800 ms, after the warning stimulus. Peak amplitudes were measured relative to the mean amplitude of the 100 ms prestimulus baseline period and latency measurements were computed relative to stimulus onset.

(B) The behavioural performance refers to the number of recalled digits. It should be noted that the total digits presented were 149.

Statistical analysis
The statistical analysis used for each group of variables (amplitudes and latencies) was exclusively dictated by the normality of their distributions. Thus the Kolmogorov-Smirnov goodness of fit test shows that both the amplitudes and the latencies are consistent with a normal distribution, as well as a multivariate normal distribution, while the equality of the covariance matrices was ascertained with Box’s M test. This permitted the use of multivariate tests for the examination of the overall group differences, while group differences for each lead individually was ascertained by the corresponding univariate statistics as well as by stepdown procedures. At each step the most important leads played the part of covariates. In the case of latencies stepwise discriminant analysis was also applied to elucidate the discrimination power of the specific group of variables—that is, whether they would be able to predict group membership.

One way analysis of variance was used to assess group differences in memory performance measures. Results were considered significant at the 0.05 level. Finally, linear regression models were applied for the elucidation of the effect of clinical characteristics and the memory performance on the P600 waveforms differences.

RESULTS
Comparison of P600 in MS patients and controls
Table 2 shows the mean latencies and standard deviations in milliseconds of the P600 waveform for the two groups at each lead. Both Pillai’s and Hotelling’s trace manifested statistically significant differences between the overall means of the compared groups (p=0.021), while the value of Wilk’s η2 (0.412) shows that 58.8% of the overall variability can be attributed to group differences. Univariate F tests showed that between group variability significantly exceeded the within group variability (p<0.01) at leads Fp1, F3, and Fp2. Estimates of effect size, especially for Fp1 (η2=0.384) are quite high. Stepdown procedures reduce the number of leads where significant differences between the groups are observed to leads Fp1 and F3. Likewise stepwise discriminant analysis showed the two above mentioned leads were able to correctly classify 85.7% of the original grouped cases (16 of 20 normal subjects and 20 of 22 of the MS patients).

Table 3 shows the mean amplitudes and standard deviations in microvolts of the P600 waveform for the compared groups at each lead. It is interesting to note that neither Pillai’s nor Hotelling’s trace (0.472 and 0.893 respectively) manifested statistically significant differences between the overall means of the compared groups, while the value of Wilk’s η2 (0.528) shows that only 47.2% of the overall variability can be attributed to group differences. Nevertheless, univariate F tests showed that there are significant group differences at the 0.05 level at leads C3-T5/2, C4-F6/2, C4, O1, O2, Pz, Cz, and Fz. However, η2 values show only medium effect size, while stepdown procedures reduce the significance to only one lead, namely C3-T5/2.
The aim of this study was to investigate aspects of information processing in MS patients as reflected by P600 waveform. The results of this study should be interpreted with caution because of the following limitations: firstly, the post hoc assignment of psychological function to neurobiological activation is somewhat hypothetical and more specific techniques (for example, the inverse solution of the ERPs data to identify the underlying sources) investigating the role of a particular psychological process in the functional anatomy of MS are required. Secondly, taking into account the heterogeneity of MS patients, further studies are needed to specify the effects of illness subtypes and determine whether there is impairment in a task-specific manner or across tasks. Finally, in our sample most MS patients had long histories of drug treatment, mainly glucocorticoids. The effect of these somatic treatments on the obtained findings is unclear. Nevertheless, the obtained results could support the hypothesis that MS patients manifest abnormal aspects of “second pass parsing processes” of information as they are reflected by P600 elicited during a WM test.

### DISCUSSION

The analysis revealed that the patient group had significantly attenuated memory performance as compared with healthy controls ($t_{1,40} = 10.41, p < 0.01$).

**Correlation of P600 with the clinical characteristics and memory performance**

Stepwise regression analyses, in which the clinical characteristics and the memory performance were set as the independent variables and observed differences regarding the P600 waveforms were the dependent variable, showed: firstly, that duration of illness was positively associated with P600 latencies at F3 site ($\beta = 0.539, t_{p} = 2.860, p = 0.010$). Secondly, cerebellar clinical dimension was negatively related to P600 latencies at Fp1 site ($\beta = -0.504, t_{p} = -2.609, p = 0.017$).

### Table 3

Mean (SD) amplitudes (ms) of the P600 waveforms for the two groups at each lead

<table>
<thead>
<tr>
<th>Lead</th>
<th>MSP (n=22)</th>
<th>Controls (n=20)</th>
<th>t</th>
<th>1-40</th>
<th>$\eta^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fp1</td>
<td>-2.45</td>
<td>7.8</td>
<td>1.45 6.0 3.213 0.074</td>
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<td></td>
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<tr>
<td>F3</td>
<td>-0.34</td>
<td>5.6</td>
<td>1.30 5.1 0.972 0.024</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3-T5/2</td>
<td>1.33</td>
<td>4.2</td>
<td>5.76 4.9 9.740 0.196</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>1.85</td>
<td>3.4</td>
<td>4.24 4.9 3.312 0.072</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fp2</td>
<td>-1.81</td>
<td>6.8</td>
<td>1.13 6.1 2.158 0.051</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F4</td>
<td>-0.25</td>
<td>5.6</td>
<td>1.01 4.6 0.625 0.015</td>
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<td></td>
</tr>
<tr>
<td>C4-T6/2</td>
<td>-1.00</td>
<td>6.6</td>
<td>3.51 5.0 6.054 0.131</td>
<td></td>
<td></td>
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<tr>
<td>C1</td>
<td>1.17</td>
<td>4.4</td>
<td>4.51 4.7 5.498 0.121</td>
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<tr>
<td>C2</td>
<td>3.32</td>
<td>4.3</td>
<td>8.59 5.0 5.047 0.112</td>
<td></td>
<td></td>
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<tr>
<td>C3-T5/2</td>
<td>4.80</td>
<td>5.1</td>
<td>9.93 5.8 9.112 0.186</td>
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<tr>
<td>P3</td>
<td>4.78</td>
<td>4.5</td>
<td>7.63 5.2 3.584 0.082</td>
<td></td>
<td></td>
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<tr>
<td>F3</td>
<td>3.78</td>
<td>3.7</td>
<td>7.53 4.4 8.783 0.180</td>
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<tr>
<td>Pz</td>
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<td>5.1</td>
<td>8.919 5.7 8.275 0.171</td>
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</tr>
<tr>
<td>Cz</td>
<td>0.63</td>
<td>4.8</td>
<td>4.03 4.2 5.644 0.124</td>
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<td></td>
</tr>
<tr>
<td>Fz</td>
<td>-0.77</td>
<td>6.6</td>
<td>0.48 4.5 0.498 0.012</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

An asterisk next to the F value denotes statistically significant differences between the two groups at the 5% level, two asterisks, at the 1% level.

### Behavioural data

The analysis revealed that the patient group had significantly attenuated memory performance as compared with healthy controls ($t_{1,40} = 10.41, p < 0.01$).

Concerning the memory performance, there was a significant difference between MS patients and normal controls, indicating that patients perform worse on the digit span tests. This finding is in agreement with a series of other related studies, two of which concluded that the verbal memory functioning of MS patients is impaired.

It is worth noting that in this study no association was found between memory performance and observed differences concerning the P600 waveform. Possibly, this particular discrepancy may be credited to the ability of psychophysiological measures, such as the P600, to define the “endophenotype, ie the manifestation of a disorder via anomalies not observable by diagnostic interviews or traditional psychological measures.”

### Conclusions

The results of this study should be interpreted with caution because of the following limitations; firstly, the post hoc assignment of psychological function to neurobiological activation is somewhat hypothetical and more specific techniques (for example, the inverse solution of the ERPs data to identify the underlying sources) investigating the role of a particular psychological process in the functional anatomy of MS are required. Secondly, taking into account the heterogeneity of MS patients, further studies are needed to specify the effects of illness subtypes and determine whether there is impairment in a task-specific manner or across tasks. Finally, in our sample most MS patients had long histories of drug treatment, mainly glucocorticoids. The effect of these somatic treatments on the obtained findings is unclear. Nevertheless, the obtained results could support the hypothesis that MS patients manifest abnormal aspects of “second pass parsing processes” of information as they are reflected by P600 elicited during a WM test.

An asterisk next to the F value denotes statistically significant differences between the two groups at the 5% level, two asterisks, at the 1% level.

An asterisk next to the F value denotes statistically significant differences between the two groups at the 5% level, two asterisks, at the 1% level.
Working memory deficits in multiple sclerosis

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