

**Title:** A high-density ERP study reveals latency, amplitude, and topographical differences in multiple sclerosis patients versus controls.

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## **ABSTRACT**

**Objective.** To quantify latency, amplitude and topographical differences in event-related potential (ERP) components between multiple sclerosis (MS) patients and controls and to compare ERP findings with results from the paced auditory serial addition test (PASAT).

**Methods.** Fifty-four subjects (17 relapsing remitting (RRMS) patients, 16 secondary progressive (SPMS) patients, and 21 controls) completed visual and auditory oddball tasks while data were recorded from 134 EEG channels. Latency and amplitude differences, calculated using composite mean amplitude measures, were tested using an ANOVA. Topographical differences were tested using statistical parametric mapping (SPM).

**Results.** In the visual modality, P2, P3 amplitudes and N2 latency were significantly different across groups. In the auditory modality, P2, N2, and P3 latencies and N1 amplitude were significantly different across groups. There were no significant differences between RRMS and SPMS patients on any ERP component. There were topographical differences between MS patients and controls for both early and late components for the visual modality, but only in the early components for the auditory modality. PASAT score correlated significantly with auditory P3 latency for MS patients.

**Conclusions.** There were significant ERP differences between MS patients and controls.

**Significance.** The present study indicated that both early sensory and later cognitive ERP components are impaired in MS patients relative to controls.

# 1. Introduction

## 1.1. Measuring cognitive impairment in MS

Cognitive impairment (CI) may occur in up to 65% of multiple sclerosis (MS) patients and can occur in the absence of physical disability (Hoffmann et al., 2007). The Paced Auditory Serial Addition Test (PASAT; a difficult test of attention and working memory) is the chosen task for cognitive assessment in the MS Functional Composite (Cutter et al., 1999). Such neuropsychological tests can be adversely affected by practice effects (Barker-Collo 2005), anxiety and motor delay of speech and/or hand movement. The relationship between brain structure and function and subtle CI – in particular as measured by PASAT score – is complex, and no one MRI measure (lesion load, lesion location, atrophy, etc.) has been shown to correlate highly with subtle CI (Ranjeva et al., 2006).

Cognitive electrophysiological measures are not dependent on physical ability, which is impaired in MS (Leocani et al., 2000). The typical *oddball* task, in which occasional target stimuli have to be detected in a train of frequent irrelevant standard stimuli, evokes a number of event-related potential (ERP) components; the early components – P1, N1, P2 – and the late components N2 and P3. P3 timing is independent of behavioral reaction time and is therefore a suitable paradigm for subjects with potential impaired motor ability (Polich 2004). P3 latency and amplitude are sensitive to neural degenerative conditions and several types of dementia and psychiatric diseases (Polich 2004).

## *1.2. ERPs in MS*

Previous electrophysiological studies of cognition in MS have reported varying results in ERP differences between MS patients and controls, particularly regarding early sensory components (P1, N1, and P2). Some studies have reported impaired auditory P3 amplitude in MS patients relative to controls (Aminoff and Goodin 2001; Ellger et al., 2002; Gil et al., 1993; Piras et al., 2003; Sailer et al., 2001). Several studies have reported delays in the latency of the auditory N1, P2, N2, and P3 components (Aminoff and Goodin 2001); delay only in the latency of P2, N2, and P3 (Gil et al., 1993); no changes in any of these components (Gerschlager et al., 2000); a latency increase of P3 (Ellger et al., 2002; Sailer et al., 2001); a latency increase and an amplitude decrease in P3 (Polich et al., 1992); and no changes in P3 latency (Sailer et al., 2001). Previous studies of visual (oddball) ERP (Piras et al., 2003) reported that visual early components of ERPs were normal and that visual N2 and P3 latencies were significantly increased. Lower P300 amplitudes were also found with respect to an age-matched control group and longer P3 latencies were reported in a visual task for MS patients (Ellger et al., 2002). Some studies (Sailer et al., 2001), however, did not report any differences in P3 visual latencies and/or amplitudes for MS patients, both secondary progressive (SPMS) and relapsing remitting (RRMS), in comparison to controls.

There are several possible reasons for the variability of previous MS ERP findings. Cognitive impairment is more frequent and severe in SPMS

than in RRMS (Zakzanis 2000) and therefore the composition of the MS study group may affect results. Previous studies have employed electrode numbers ranging from 1 (Ellger et al., 2002) to 30 (Piras et al., 2003); 128 electrodes are required to optimally sample the topography of the human EEG (Srinivasan et al., 1998). Employing low numbers of electrodes means that there may not be sufficient scalp coverage to detect activity from the early ERP components, which are generated across a number of subcortical regions, and are observed over widespread scalp regions.

Neuropsychological studies of CI in MS have provided mixed evidence of modality-specific impairments (i.e., if impairment is more pronounced in one modality than in the other, or is common across modalities (Foong et al., 1997; Sperling et al., 2001). It is possible that there is a modality-specific effect on ERP latency in MS because of differing neuronal pathways (King and Nelken 2009).

The aims of the present study were to determine 1) differences in latency, amplitude, and topography between RRMS and SPMS patients and also between MS patients and controls, 2) ERP differences with respect to modality, 3) evidence of a correlation between the PASAT and auditory P3 amplitude and latency.

## **2. Methods**

### *2.1. Subjects*

Seventeen right-handed RRMS patients and sixteen right-handed SPMS patients satisfying the revised McDonald criteria for MS (Polman et al., 2005) were recruited. Twenty-one control patients also participated. Exclusion criteria included current use of benzodiazepines or neuroleptics, a history of alcohol or drug misuse, head injury, stroke, or recent relapse. One RRMS patient was unable to complete the visual task, and one SPMS patient and one control subject were unable to complete the auditory task. Table 1 displays the demographic data of the subjects from whom EEG data were collected. Ethical approval was obtained from St. Vincent's University Hospital Ethics Committee. Informed consent was obtained from all subjects.

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Insert Table 1 about here  
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## *2.2. Procedure*

All subjects completed the standard Paced Auditory Serial Addition Test PASAT (Tombaugh 2006) approximately one hour prior to ERP recording. The subjects sat with the examiner in a quiet room, and were asked to add consecutive single-digit numbers as they were presented on a compact disk and to respond orally with the accurate sum. The standard PASAT form, consisting of 61 single digits with a 3 second inter-stimulus interval, was used. PASAT score was based on the total number of correct responses from a maximum of 60 correct answers. Subjects were asked to perform calculations silently, without writing or using fingers, and a practice sequence was administered prior to the test.

ERP data were recorded in a soundproofed room using the ActiveTwo Biosemi™ electrode system from 134 electrodes (128 scalp electrodes) organized according to the 10-5 system; (Oostenveld and Praamstra 2001) digitized at 512 Hz. The vertical and horizontal electro-oculograms were recorded bilaterally from approximately 3 cm below the eye and from the outer canthi respectively. The visual P3 paradigm consisted of blue circles, separated by an inter-stimulus interval of 2 seconds, presented for 205 trials in a pseudorandom order. Frequent non-target (80%) and infrequent target (20%) circles were 2 cm or 4 cm in diameter, respectively. The auditory P3 paradigm consisted of tones, separated by an inter-stimulus interval of 2 seconds, presented binaurally for 205 trials in a pseudorandom order. Frequent non-target (80%) and infrequent target (20%) tones were presented at 500 Hz and 1000 Hz respectively. Subjects were instructed to press a button as quickly as possible following a target stimulus. Order of modality and task were counterbalanced across subjects.

### *2.3. Data analysis*

Correlations involving level of education and Expanded Disability Status Scale (EDSS) were conducted using a non-parametric test (Spearman's Rho) as both of these measures were on ordinal scales (primary, secondary and tertiary for education and 0-10 for EDSS). Correlations involving age and years since beginning of symptoms were tested using a parametric test (Pearson's  $r$ ).

EEGLAB (Delorme and Makeig 2004) was used for all ERP analyses. The EEG data were bandpass filtered between 1–90 Hz, bandstopped

between 48-52 Hz, average referenced across all scalp electrodes (appropriate when using a high-density EEG array), epoched and baseline corrected (100 ms before baseline). Epochs with large, obvious artifacts (e.g., muscle twitch) were first rejected manually. Independent components analysis, using the infomax algorithm, was used to identify artifacts, which were subsequently removed (see Delorme et al., 2007). Ocular artifacts were removed by identifying the components that correlated most highly with the EOG channels (minimum correlation of 0.5). Visual inspection of the EOG channel before and after removal of the component was performed in order to ensure that the ocular artifacts were removed. A 99% confidence interval was calculated across all channels for mean amplitude and variance: any channel falling outside the confidence interval was interpolated.

Each ERP component was identified by two of the authors according to its polarity, latency and topography. A component was deemed to be not identifiable if the morphology of the ERP was not clear to both assessors. Next, the maximum (or minimum where appropriate) amplitude was automatically calculated for all electrodes using the manually identified component as a guide to define the temporal window. If there was no peak inside a temporal window for a component at a particular electrode then data at that electrode for that component were recorded as missing. The early components were determined for P1 (visual only), N1 and P2 for trials that followed presentation of the standard stimulus. The N2 and P3 components were calculated for trials that followed presentation of the target stimulus.

ERP descriptors often identify electrodes where maximum amplitudes are typically observed and differ according to modality. Electrode groups



(regions of interest: ROIs) were generated and are displayed in Table 2. We used composite mean amplitude measures (i.e., the mean value of the electrodes in the ROI) computed from groups of electrodes where the peak of interest was maximal.

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Insert Table 2 about here  
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SPM 8 (<http://www.fil.ion.ucl.ac.uk/spm>) was used to create statistic parametric maps in order to test for topographical differences in ERP amplitude across the entire scalp and across time. Data from each subject were transformed into two-dimensional sensor-space (interpolated from 128 channels) and in peri-stimulus times from 0-250 ms for responses to the standard condition and from 230-600 ms for responses in the target condition. This transformation produced a three-dimensional spatiotemporal characterization of the ERP, which was then compared between groups. The significance level was set at  $p < .001$  and this was further restrained by only retaining scalp areas in which at least 100 contiguous voxels were significant (see Figure 3 ). Furthermore, a stringent family-wise threshold was implemented separately, thus showing only significant voxels following correction for multiple comparisons.

### **3. Results**

The mean percentage of retained epochs was 86%, 84%, and 82% for the control, RRMS, and SPMS groups, respectively. Overall, 18% of independent components were identified as noise and removed. All statistical

analyses were completed using SPSS 16 (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA). There were no significant reaction time differences between the groups for either auditory or visual modalities. A one-way ANOVA comparing PASAT score across groups was significant ( $F(2, 46) = 3.21, p = .49$ ). A Tukey post-hoc test showed that there was a significant difference between the SPMS and Controls groups on PASAT score. Level of education was not significantly different between MS patients and controls.

### *3.1. ERP Latency and Amplitude*

Figure 1 displays a butterfly plot showing all channels simultaneously for all groups and modalities. Scalp maps of the ERP activity are also displayed. Two dependant measures were extracted for each ERP component within a ROI: the peak amplitude and the latency at the peak amplitude. Tables 3 and 4 display the descriptive and inferential results for each component. In the visual modality, P2, P3 Central and P3 Parietal amplitudes and N2 latency were significantly different across groups. In the auditory modality, P2, N2, and P3 latencies and N1 amplitude were significantly different across groups. Post-hoc tests indicated that there were no significant differences between RRMS and SPMS patients on any ERP component.

There were no significant correlations between the PASAT vs. education, EDSS, age or years since beginning of symptoms ( $p > .05$ ). Auditory P3 latency in both central and parietal regions was correlated with age in MS patients ( $r = .412, p = .019$  and  $r = .441, p = .011$ , respectively) but not with

EDSS, level of education or years since beginning of symptoms ( $p > .05$ ).

Visual amplitude and latency, and auditory amplitude did not correlate with age, EDSS, years since beginning of symptoms, or level of education ( $p > .05$ ).

A partial correlation, controlling for age, between auditory P3 latency and the PASAT (an auditory test of cognition), across all MS subjects was significant at central and parietal ROIs ( $r_{\text{partial}} = -.483$ ,  $p = .006$ ,  $r_{\text{partial}} = -.384$ ,  $p = .033$ , respectively). PASAT score did not correlate significantly with latency of any early P3 component ( $p > .05$ ). P3 auditory amplitude was not significant ( $p > .05$ ) in either ROI. The partial correlation between PASAT score and visual P3 latency across all MS subjects approached significance at Central and Parietal sites ( $r_{\text{partial}} = -.362$ ,  $p = .069$  and  $r_{\text{partial}} = -.370$ ,  $p = .063$ , respectively).

The correlations across modalities were analyzed for all MS subjects for both amplitude and latency at Central and Parietal scalp locations. Visual Parietal amplitude correlated significantly auditory Parietal P3 amplitude ( $\rho = .507$ ,  $p = .008$ ). There were no other significant correlations for amplitude, nor for latency across modalities.

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Insert Tables 3 and 4 about here  
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### 3.2. ERP Topography

Figure 2 displays the ERP following presentation of the target stimulus from all 128 channels for both modalities. A comparison of RRMS and SPMS patients did not yield any suprathreshold voxels for early or late components in either the visual or auditory modalities (this was the case when the significance level was relaxed to  $p < .001$ ). Figure 3 displays the statistic

parametric maps of significantly different ERP activity between all MS patients and controls. In the visual modality, there was greater activity for controls from 121-156 ms over the parietal area and from 218-277 ms over the left central area following presentation of the standard stimulus and there was greater activity for controls from 235-289 ms over the frontal area and from 277-570 ms over the central and parietal areas following presentation of the target stimulus. There was greater activity for controls over the frontal area from 82-148 ms and over a region of the left central area from 219-250 ms following presentation of the standard stimulus. There were no suprathreshold voxels following presentation of the target stimulus in the auditory condition. Table 5 summarizes the results of the SPM analysis.

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Insert Figures 2 and 3 about here  
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### *3.3 Summary of results*

These results indicate that there are impairments in both ERP amplitude and latency for MS patients, in comparison to healthy control subjects, for both early and late ERP components. There were no significant differences between RRMS and SPMS patients, in latency, amplitude or topography. A topographical analysis indicated that both early and late visual components were significantly reduced for MS patients in comparison to controls. In particular, the P3 visual amplitude was significantly different across the cento-parietal scalp area. The auditory topography was significant only for the frontal area from 82-148 ms. The PASAT significantly correlated with P3 latency at Central and Parietal P3 ROIs.

## **4. Discussion**

### *4.1. The results of this study*

The present study represents an advance over previous research in that a high-density EEG array was used with a large number of subjects with MS and controls (total n=54) across both visual and auditory modalities. Impairments were present in both sensory (N1, P2) and cognitive components (N2 and P3). Visual P3 amplitudes were significantly impaired in RRMS and SPMS patients when compared to control subjects. Auditory P3 latencies were significantly impaired in SPMS patients when compared to control subjects. The relatively large sample size in the present study facilitated the comparison between RRMS and SPMS patients. There were no instances in which RRMS patients differed significantly from SPMS patients on either latency or amplitude. A correlation between PASAT score and auditory P3 latencies for all MS patients was significant for the central and parietal ROIs.

A statistical parametric approach was used to examine scalp areas that differed significantly between groups. This approach has the benefit that multiple comparisons across scalp regions are corrected without the need to make a priori assumptions about topographical differences between groups. Statistical parametric maps between MS patients and controls showed that visual P3 amplitude was significantly different over almost the entire parietal scalp region whereas auditory P3 amplitude was not significantly different between the groups. The SPM analysis also showed deficits in the early ERP components for both modalities, a finding that suggests impaired P3

components, often observed in MS, are at least be partly due to deficits earlier in the processing pathway.

#### *4.2. Comparison with previous studies*

The ROIs in the present study were identified using data from previous research with healthy subjects. However, the statistical parametric maps showed widespread regions with significantly different amplitude or latencies between groups for the early sensory components. For example, in the present study, there were significant amplitude differences between patients and controls in over much of the centro-parietal scalp region for the visual P3 component, with greater activation over the left side. Atypical topographical distributions may be a reflection of the disease process (e.g. lesions in processing pathways) and consequently patient topographies may not be in the predicted areas. A high-density EEG array is therefore useful in identifying differences between the groups because the entire scalp area can be covered. Some studies have not reported impaired early ERP components in MS (Ellger et al., 2002; Gerschlagler et al., 2000), and some have reported no difference in P3 latency or amplitude (Sailer et al., 2001). Some studies have reported a trend, but not significance, towards a reduction of visual amplitude in early components (e.g., Piras et al., 2003). It is possible these studies did not have the statistical power or sufficient electrode coverage to detect such differences.

Cognitive processes are typically evaluated neurophysiologically by measuring two aspects of the ERP: latency and amplitude. Differences

between RRMS patients and controls and between SPMS patients and controls in the visual modality were reflected in reduced amplitude of the P3 components. Latency of the visual N2 was delayed for the RRMS group versus controls. In the auditory modality, latencies were prolonged for the RRMS patients versus controls for the P2 and N2 components and for the SPMS patients versus controls for the Parietal P3 latency. The N1 amplitude was significantly greater for SPMS patients than for controls. An N1 amplitude increase, in conjunction with a P3 amplitude decrease, has been reported for older subjects during an auditory oddball task (Anderer et al., 1996), which has been attributed to a higher level of general attention of older adults during the oddball task. It is plausible that a similar compensatory mechanism is involved for MS subjects with respect to the auditory N1 component.

Parietal P3 amplitude correlated across modalities. However, latency was not correlated across modalities: only the auditory P3 latency was delayed in SPMS patients relative to controls. The finding that auditory ERPs were more susceptible to delay may be a consequence of the differences between visual and auditory processing pathways. More synaptic relays are involved in early auditory processing (King and Nelken 2009) in comparison to early visual processing and therefore there is more opportunity for demyelination to delay transmission (e.g., Piras et al., 2007). This study adds to the literature that suggests a modality-specific impairment in MS (cf. De Sonneville et al., 2002).

#### *4.3. Implications for future research*

It is important to identify CI as early as possible and to monitor CI frequently. Cognitive impairment may have predictive utility for disease progression (Portaccio et al., 2009). The PASAT is subject to practice effects (Barker-Collo 2005) and can be affected by educational level, anxiety and motor delay of speech; many patients dislike performing the PASAT, a consideration especially important in the context of clinical trials in which repeated testing might increase the drop-out rate (Williams et al., 2006). Although we have shown that early sensory ERP delays may contribute to the delay of the auditory P3 latency between SPMS patients and controls, a significant correlation between PASAT and auditory P3 latency was still found within the MS group. PASAT score did not correlate with latency of earlier auditory ERP components in MS patients. This indicates that auditory P3 latency is sensitive to the degree of CI for MS patients. EEG has several benefits in comparison to neuropsychological testing including high temporal resolution and the facility to measure cognitive processing independently of behavioral responding. The intra-subject test-retest correlation coefficients for the P3 compares favorably with clinical assays: .50 to .80 for amplitude and .40 to .70 for peak latency (Segalowitz and Barnes 1993). Furthermore, the P3 is not influenced by practice effects.

The relationship between lesions and neuropsychological and neurophysiological cognitive function is imprecisely defined in MS (Lazeron et al., 2005). Future studies employing ERPs could also examine abnormalities in normal-appearing white and grey matter, which may correlate with severity of CI but are often undetectable by conventional imaging (Bagert et al., 2002). In addition, a full neuropsychological battery could help to elucidate any



differences between specific cognitive domains and ERP amplitude and latency and/or MRI findings. Future work could also investigate EEG parameters, such as synchronization (Arrondo et al, 2009) across scalp regions or brain sources. Longitudinal studies of ERPs in MS are also required, in order to determine if ERPs can be used to predict the development of CI in MS.

## **5. Conclusions**

The present study shows that there are widespread deficits in sensory and cognitive processing in MS patients, in comparison to healthy controls. An SPM analysis showed that both sensory and cognitive ERP amplitudes were impaired for MS patients, relative to controls, during a visual oddball task. Only early ERP amplitudes were impaired during the auditory task. However, P2, N2 and P3 latencies were delayed for the auditory condition only. PASAT score correlated significantly with auditory P3 latency for the MS patients. The finding of no significant differences between RRMS and SPMS on any ERP measure suggests that the disease process *per se*, rather than severity or duration of the disease, impacts on ERP amplitude and latency.

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## Figure Legends

Figure 1. Butterfly plots showing responses for all electrodes across all modalities and groups. Scalp maps showing the topography of the response at particular latencies are displayed above the butterfly plots. RRMS: relapsing remitting multiple sclerosis. SPMS: secondary progressive multiple sclerosis.

Figure 2. ERPs to the target stimulus in the visual and auditory conditions. Black lines denote control subjects, gray lines denote MS subjects.

Figure 3. 3D spatiotemporal characterization of the ERP. The left top panel shows responses to the standard stimulus in the visual condition. The right top panel shows responses to the target stimulus in the visual condition. The bottom panel shows responses to the standard stimulus in the auditory condition.