Title: Impaired information processing speed and attention allocation in multiple sclerosis patients versus controls: A high-density EEG study.

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Abstract

Background: The no-go P3a is a variant of the P300 event-related potential (ERP) that indexes speed of information processing and attention allocation. The aim of this study was to compare ERP findings with results from the paced auditory serial addition test (PASAT) and quantify latency, amplitude and topographical differences in P3a ERP components between multiple sclerosis (MS) patients and controls.

Patients and Methods: Seventy-four subjects (20 relapsing remitting (RRMS) patients, 20 secondary progressive (SPMS) patients and 34 controls) completed a three-stimulus oddball paradigm (target, standard, nontarget). Subjects participated in separate visual and auditory tasks while data were recorded from 134 EEG channels. Latency differences were tested using an ANCOVA. Topographical differences were tested using statistical parametric mapping.

Results: Visual P3a amplitude correlated with PASAT score in all MS patients over frontal and parietal areas. There were significant differences in latency, amplitude, and topography between MS patients and controls in the visual condition. RRMS and SPMS patients differed in visual P3a latency and amplitude at frontal and parietal scalp regions. In the auditory condition, there were latency differences between MS patients and controls only over the parietal region.

Conclusion: The present results demonstrate that information processing speed and attention allocation are impaired in MS.

1. Introduction

Cognitive impairment (CI) may occur in up to 65% of multiple sclerosis (MS) patients and can occur in the absence of physical disability(1). Deficient attention and reduced speed of information processing are often observed in MS patients(2) and impact on daily life(3). CI can vary across MS subtypes (4) and is typically more frequent and severe in secondary progressive (SPMS) than in relapsing remitting (RRMS)(5). The Paced Auditory Serial Addition Test (PASAT), a difficult test requiring both rapid information processing and simultaneous allocation of attention to two tasks, is the chosen task for cognitive assessment in the MS Functional Composite(6). Such neuropsychological tests can be adversely affected by practice effects(7), 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, cortical atrophy, etc.) has been shown to correlate highly with subtle CI(8).

Cognitive electrophysiological measures are not dependent on physical ability, which is often impaired in MS(9), and therefore have potential to measure CI in MS. Several previous studies (10) have examined the relationship between CI, event-related potentials (ERPs) and MS by employing a two-stimulus oddball task. In this task, occasional target stimuli have to be detected in a train of frequent irrelevant standard stimuli: a P3b ERP component is typically evoked approximately 300 ms after a stimulus with maximal amplitude over the parietal scalp region. The P3b is thought to be a reflection of context updating(11) or categorization of task relevant

events(12). Differences in P3b amplitude and latency between MS patients and controls are often, although not always, detected. Lower P3b amplitudes and longer P3b latencies were reported in a visual task for MS patients (13). Some studies(14), however, did not report any differences in P3 visual latencies and/or amplitudes for MS patients (both RRMS and SPMS) in comparison to controls.

A variant of the P300 – the P3a – can be produced by using a three-stimulus oddball paradigm, the additional stimulus being an infrequent non-target stimulus: the subject should withhold responding to this stimulus. There are a number of different types of P3a, with the latency, amplitude and topography varying according to the difficulty of the standard/target discrimination and the perceptual distinctiveness of the non-target stimulus. A *no-go* P3a is elicited when the non-targets are non-novel repeated stimuli. If the standard and target stimuli are difficult to discriminate, then the P3a is observed over frontal and central areas, with shorter latency in frontal areas and longer latencies in parietal areas. Auditory P3a latencies are typically shorter than visual P3a latencies(15).

The P3a is thought to signal the engagement of attention mechanisms(11). In contrast to the P3b, which seems to be mainly affected by temporoparietal junction disruptive lesions, P3a responses are compromised in patients with a variety of disruptive lesion sites, including the medial temporal, frontal, and parietal lobes(16). Therefore, the P3a may be more suitable than the P3b for detecting CI in MS, in which patients typically have widespread lesions.

Few studies have examined the P3a component in MS. Sailer and colleagues(14) employed a novelty P3a paradigm (in which the majority of tones were novel, rather than repeated) with an easy standard/target discrimination, but did not report that a difference in auditory P3a latency or amplitude between MS patients and controls. Jung et al.(17) employed an auditory mistmatch negativity (MMN) paradigm, which also results in a P3a component, and reported that P3a waveforms were impaired in MS, relative to healthy controls. However, to our knowledge, no study has employed a no-go P3a oddball paradigm with MS patients. Such research would provide a measure of the electrophysiological functioning of MS patients during an attention-demanding task that involving the frontal lobe. The inclusion of both auditory and visual tasks would facilitate comparison of the differential effects of modality on the P3a.

The aims of the present study were to determine 1) differences in P3a latency, amplitude, and topography between the two groups of RRMS and SPMS patients and also between MS patients and controls, 2) P3a ERP differences with respect to modality and, 3) the relationship between the PASAT and P3 latency, amplitude, and topography.

2. Methods

2.1. Subjects

Twenty RRMS patients and 20 SPMS patients (satisfying the revised McDonald criteria for MS(18) and 34 control patients were recruited. Exclusion criteria were: 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. Ethical approval was obtained from St. Vincent's University Hospital Ethics Committee. Informed consent was obtained from all subjects.

2.2. Procedure

All subjects completed the standard PASAT(19) 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 the 10-5 system(20) 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 P3a paradigm consisted of stimuli separated by an inter-stimulus interval of 2 seconds, presented for 410 trials in a pseudorandom order across two separate runs of 205 trials each. Frequent standard (80%) and infrequent target (10.24%) circles were 3.5 cm or 4 cm in diameter, respectively. The

non-target stimulus was a checkerboard (9.76%) which was 5.25 cm per side. The auditory P3a paradigm consisted stimuli separated by an inter-stimulus interval of 2 seconds, presented binaurally for 410 trials in a pseudorandom order across two separate runs of 205 trials each. Frequent standard (80%) and infrequent target (10.24%) tones were presented at 900 Hz and 1000 Hz respectively. The non-target (9.76%) stimulus was a white noise burst. 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

EEGLAB(21) was used to preprocess the EEG data. 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 (22). Ocular artifacts were removed by identifying the components that correlated most highly with the electrooculogram (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.

Three regions of interest (ROIs) were generated by using composite mean amplitude measures (i.e., the mean value of the electrodes in the ROI). The electrodes used in each ROI are as follows (electrode sites are labeled according to the 10-5 system). Frontal: F2',F2,AF2',AFz, AFz', Fz, Fz', F1,F1',AF1'; Central: Cz, Cz', CPz, CCP2h, FCC2h, FC2', FCz, FCC1h, FC1', CCP1h; Parietal: CPz', CPP1h, P1, PPO3h, PO3h, Pz, Pz', POz, CPP2h, P2, PPO4h, PO4h. The peak of the P3a was found by fitting a parametric function to the ERP in the ROI using a Gaussian profile and determining the delay at the peak amplitude (23) between 250-600 ms for the visual modality and between 200-600 ms for the auditory modality. Age has been shown previously(24) to correlate with P3 latency: therefore, latencies were compared using an analysis of covariance (ANCOVA), controlling for age.

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 smoothed, full-width half-maximum 6:6:4 a.u.) and in peri-stimulus times from 200-600 ms for responses to the non-target stimulus (voxel size = 2.1 mm x 2.7 mm x 3.9 ms). This transformation produced a three-dimensional spatiotemporal characterization of the ERP, which was then compared between groups. The significance level was set at $p<.001$ for the between-group comparisons, and this was further restrained by only retaining scalp areas in which at least 500 contiguous voxels were significant. Furthermore, a stringent family-wise threshold implemented separately, thus showing only significant voxels following correction for multiple comparisons.

The significance level was set at p<.005 for the correlation between the PASAT and ERP amplitude (due to the greater sample size and the lower probability of a type-1 error), and this was further restrained by only retaining scalp areas in which at least 500 contiguous voxels were significant. The effects of age were entered as a nuisance covariate in the PASAT/ERP correlation.

3. Results

For the P3a visual task, the mean percentage of retained epochs was 87.47%, 82.00%, and 88.30% for the control, RRMS, and SPMS groups, respectively for the non-target stimulus. For the P3a auditory task, the mean percentage of retained epochs was 84.25%, 80.62%, and 84.57% for the control, RRMS, and SPMS groups, respectively for the non-target stimulus. All statistical analyses were completed using SPSS 16 (SPSS Inc., Chicago, IL, USA).

PASAT score did not correlate with EDSS score (rho = -.20, $p > .05$). PASAT score was significantly correlated with age (rho = -.258, $p < .05$) and consequently, all subsequent analyses involving PASAT score were conducted with age as a covariate. A one-way ANCOVA comparing PASAT score across groups was significant ($F(2, 62)= 4.51$, $p < .05$). A post-hoc test (least-significant difference) showed that there was a significant difference between the SPMS and Controls groups on PASAT score ($p<.05$) and also between RRMS versus Controls ($p< .05$).

Figure 1 displays a butterfly plot showing all channels simultaneously for all groups and modalities. Scalp maps of the ERP activity are also

displayed. Figures 2 and 3 display the latencies and significant comparisons for each group across the three locations in the visual and auditory modalities, respectively. Latencies in both auditory and visual modalities were not significantly correlated with EDSS score. Neither PASAT score nor EDSS correlated significantly with ERP latency (when the effects of age were removed). It is possible that delayed latencies in the visual condition were caused by delays in early visual processing. Therefore, the mean latencies for patients with and without optic neuritis were compared for each ROI. No comparison was significant: Frontal, $t(30) = .694$, $p = .493$; Central, $t(31) = .643$, $p = .646$; and Parietal, $t(24) = .072$, $p = .944$.

Insert Figures 1, 2, 3, and the supplemental figure about here

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The ERP following presentation of the target stimulus from all 128 channels for both modalities are displayed in supplementary material. A SPM comparison of RRMS and SPMS patients did not yield any suprathreshold voxels in either the visual or auditory modalities, and therefore the RRMS and SPMS groups were combined for subsequent analyses. Figure 4 displays the statistic parametric maps of significantly different ERP activity between all MS patients and controls in the visual modality: there was significantly greater activity for controls from 235-305 ms over the frontal area and from 344-473 ms over the parietal area following presentation of the non-target stimulus. There were no suprathreshold voxels following presentation of the non-target stimulus in the auditory condition.

SPM was used to examine scalp areas and time periods in which ERP amplitude was significantly correlated with PASAT score (see Figure 5). The visual condition was significant for a positive correlation over the frontal scalp area from 223-297 ms, over the central-parietal area from 328-375 ms, and over the lateral frontal region again from 477-594 ms. The visual condition was significant for a negative correlation over the parietal/occipital are from 231-301 ms, over the frontal region from 325-395 ms and from 414-442 ms, and over the medial parietal/occipital are from 520-594 ms. It should be noted, however, that these areas are essentially the inverse of positive correlation due to the dipolar nature of the neural sources.

Insert Figures 4 and 5 about here

These results indicate that there are impairments in both ERP amplitude and latency for MS patients, in comparison to healthy control subjects, for the visual P3a ERP component. There were significant latency differences between RRMS and SPMS patients for the visual P3a ERP component. There was a significant latency difference between controls and patients over the parietal region in the auditory condition. There were no significant differences between RRMS and SPMS patients, in latency, amplitude or topography in the auditory condition.

4. Discussion

The no-go P3a is a variant of the P300 ERP that indexes speed of information processing and attention allocation. The present study has

demonstrated that visual P3a latencies, amplitude and topography were significantly different between MS patients and controls. Amplitude differed significantly over the frontal and parietal areas in the visual condition. There were no significant amplitude differences in the auditory condition. RRMS and SPMS differed only with respect to latency differences in the visual modality. PASAT score correlated significantly with visual amplitude over a widespread area.

A reduced processing speed is the most common cognitive deficit in MS(25). It is important to identify CI as early as possible and to monitor CI frequently. CI may have predictive utility for disease progression(26) and it has been shown that neuropsychological rehabilitation can improve attention, information processing and executive functions in MS patients with low disability levels(27). The PASAT is subject to practice effects(7) 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(28). 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(29). Furthermore, the P3 is not influenced by practice effects.

There was a pronounced effect of modality in the present study, with more significant effects in the visual condition. Differences in stimulus characteristics may be the cause of the modality differences. A faster ERP to

the auditory stimuli may indicate that it was easier to discriminate between auditory target and non-target stimuli (P3a non-target latency increases when targets are harder to discriminate from standards). It is also possible that the white noise burst in the auditory condition was not as salient as the checkerboard in the visual condition. In general, previous studies have shown that the P3a to auditory stimuli is typically faster than the ERP to visual stimuli, and the control data in the present study are comparable to data using similar paradigms (15). This divergence in absolute magnitude of the amplitude and latency responses between visual and auditory modalities may have made statistical comparisons between groups differentially powerful. The difference in modality effects may explain why some previous studies (14) did not report significant differences in auditory P3a between MS patients and controls.

The PASAT makes demands of a number of cognitive domains, including speed of information processing and simultaneous allocation of attention to two tasks. A functional MRI (fMRI) study(30) reported that, during execution of the PASAT in RRMS patients, there was activation of the inferior and middle frontal gyrus, anterior cingulate, inferior parietal lobule, supplementary motor area, superior and middle temporal gyrus, insula, thalamus, vermis and brainstem bilaterally as well as the right superior parietal lobule and right lateral premotor area. The results of the ERP/PASAT correlation are consistent with a pattern of widespread frontal and parietal activation.

A drawback of fMRI is that it is limited in the temporal domain (resolution is in the order of seconds). In contrast, high-density EEG provides excellent temporal resolution (resolution in the order of milliseconds) and

moderate spatial resolution (in the order of centimeters). Latency differences in the present study, in particular in the visual condition, showed that MS patients had significantly longer latencies than control subjects. This was most pronounced over frontal and parietal sites. It is notable, however, that the latencies of RRMS patients were significantly longer than those of SPMS patients at the frontal ROI in the visual condition and over the parietal ROI in the auditory condition. It is possible that initial attention allocation in RRMS patients was affected to a greater degree than the SPMS patients. This may be due to aggressive damage with limited opportunity for plastic repair in the RRMS groups, in comparison to the SPMS group. For example, atrophy in the neocortex (31) may proceed rapidly in early RRMS. The differences in location between modalities may be a reflection of the relative difficulty of the standard/target discrimination. The shorter latencies in the auditory condition show that the standard/target discrimination was easier than in visual condition. It has previously been shown (15) that P3a amplitudes are likely to be higher in amplitude over anterior areas when the discrimination is difficult. Therefore, in the visual condition the differences between RRMS and SPMS were observed over the frontal ROI, whereas in the auditory condition the differences were observed over the parietal ROI (there were no significant differences among the groups at the frontal and central ROIs in the auditory condition).

The relationship between lesions and neuropsychological and neurophysiological cognitive function is imprecisely defined in MS(32). 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(33). 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. 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.

The present study shows that there are deficits in P3a latency, amplitude and topography in MS patients versus healthy controls, particularly in the visual condition. In the visual condition there were significant latency differences between controls and MS patients for frontal and parietal scalp areas. In the auditory condition, there were latency differences between MS patients and controls only over the parietal region. RRMS and SPMS patients differed in visual P3a latency at frontal and parietal scalp regions. Visual P3a amplitude correlated with PASAT score in all MS patients over frontal and parietal areas. The results of the present study suggest that the P3a may have potential as a surrogate marker for CI in MS.

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Figure Legends

Figure 1. Butterfly plots showing responses for all electrodes across all modalities and groups.

Figure 2. Latencies and significant comparisons for each group across the three locations in the visual modality.

Figure 3. Latencies and significant comparisons for each group across the three locations in the auditory modality

Figure 4. 3D spatiotemporal characterization of the ERP for all MS patients vs controls in the visual condition.

Figure 5. 3D spatiotemporal characterization of the ERP for the correlation between ERP amplitude and PASAT score.

Supplementary Figure. ERPs to the target stimulus in the visual (A) and auditory (B) conditions for all scalp channels.