Title: Preliminary Evidence for Correlation Between PASAT Performance and P3a and P3b amplitudes in progressive multiple sclerosis.

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Abstract.

Background. The no-go P3a event-related potential (ERP) is a measure of attentional engagement and the P3b is a measure of context updating. The aim of this study was to compare ERP topographies 1) to Paced Auditory Serial Addition Test (PASAT) results, 2) of visual and auditory P3a and P3b of PPMS patients vs. SPMS patients and 3) of both progressive subtypes to healthy controls.

Methods. 30 subjects (10 PPMS, 10 SPMS and 10 age-matched controls) completed visual and auditory no-go P3a and P3b tasks while data were recorded from a 128-scalp channel EEG array. Data from scalp channels were converted into continuous interpolated images (incorporating the entire scalp and time). Topographical differences and correlations were then tested using statistical parametric mapping (SPM).

Results. For the MS patients, PASAT score correlated significantly with parietal regions in the auditory P3b, auditory P3a and visual P3b conditions, and with central regions in the visual P3a condition. PPMS patients had significantly lower amplitude than SPMS patients in the auditory P3b condition over the parietal area. The control group had greater amplitude than the MS patients in all the P3 tasks, with the exception of the auditory P3b.

Conclusions. These data suggest that PASAT performance and P3 ERPs correlate for MS progressive subtypes and that PPMS and SPMS in electrophysiologic responses differ during auditory P3b tasks.

Introduction.

Cognitive impairment (CI) is common in multiple sclerosis (MS). CI in MS is often measured with the Paced Auditory Serial Attention Test (PASAT), a test of attention and working memory (1). Primary progressive MS (PPMS) patients experience disease progression from onset without major relapses or remission. Patients with secondary-progressive MS (SPMS) have initially relapsing-remitting disease course followed by disease progression. Some studies have found significant neuropsychological differences between the PPMS and SPMS (eg. (2) but some have found none (e.g., (3). Both subtypes perform worse on the PASAT in comparison to controls (2).

In a two-stimulus *oddball* task, occasional target stimuli have to be detected in a train of frequent irrelevant standard stimuli: a P3b event-related potential (ERP) component is typically observed, reflecting context updating. A *no-go* P3a can be elicited when third – non-novel repeated – stimulus is presented, signalling the engagement of attention (4). In a previous study, there was no difference in visual P3b amplitude between PPMS and SPMS patients. However, only one electrode was used, making topographical analyses impossible (5). We previously employed a high-density EEG array (6-7) and reported significant differences between relapsing remitting (RRMS) and SPMS patients versus controls in both auditory and visual P3b and P3a. RRMS and SPMS patients differed only in visual P3a latency.

The aim of this study was to investigate the topography of PASAT score and P3 amplitude correlations by employing 128 scalp electrodes. We also compared P3 ERPs for PPMS versus SPMS, and for both subtypes versus age-matched controls. SPMS patients were employed as a control group because RRMS patients are typically younger than PPMS patients, and the P3 component changes with age. We hypothesized that P3 amplitude would correlate with PASAT score, that PPMS patients would have reduced P3 amplitude in comparison to SPMS patients and that both subtypes would have reduced P3 amplitude versus controls.

Methods.

Subjects, procedure and data analysis.

Ten PPMS patients satisfying the revised McDonald criteria for MS (8) were recruited. They were age, sex and education matched with 10 SPMS patients and with 10 healthy controls (Table 1).

Exclusion criteria are described in (6-7). One PPMS patient was excluded from the auditory tasks, and one PPMS patient from visual P3b task. Ethical approval was obtained from St. Vincent's University Hospital Ethics Committee. All subjects provided informed consent.

****Insert Table1 approximately here****

All subjects completed the 3-second PASAT (1). ERP data were recorded from 128 scalp electrodes. The ERP recording procedure, P3b and P3a paradigms, and ERP analysis method are described in detail in (6-7). SPM8 (Statistical Parametric Mapping 8, <http://www.fil.ion.ucl.ac.uk/spm>) was employed to test for topographical differences in ERP amplitude across the entire scalp and from 250-500 ms. The significance level was set to $p < 0.005$ which was further restrained by only retaining scalp areas in which at least 500 contiguous voxels were significant. Disease duration was entered as a nuisance variable for comparisons involving only MS patients.

Results.

The control group had significantly better PASAT scores compared to both patient groups (see Table 1) ($F(2,27)=7.92$, $p=0.002$). The patient groups did not differ in PASAT score ($p > 0.05$). The PASAT/P3 correlations for the PPMS and SPMS ($p < 0.005$) groups are displayed in Figure 1. This correlation was also significant when controls were included (Supplemental figure 1, online only).

PPMS patients had lower amplitude than SPMS patients in the auditory P3b condition over the left parietal region from 356-438 ms, and the right parietal area from 250-305 ms ($p < 0.005$) (Supplemental figure 2, online only). The control group had greater amplitude than the MS groups in all the P3 ERPs (except in auditory P3b) ($p < 0.005$) (Supplemental figure 3, online only), when testing the contrast that controls would have greater activation than either MS group, and that MS groups would not differ from each other. Activity related only to ERPs depicted in supplemental figure 4 (online only).

****Insert Figure1 approximately here****

Discussion.

The present study is the first to examine 1) ERP components in PPMS using a high density EEG array (cf. (5)), and 2) and the no-go P3a in PPMS. Furthermore, both visual and auditory tasks were employed and PPMS patients were compared to age-matched SPMS patients and controls. It is possible the previous differences (5) between RRMS and PPMS were partly due to age differences. PASAT score correlated with P3 amplitude in all P3 tasks, suggesting that the P3 may be a surrogate marker of CI in MS. PPMS patients had decreased amplitude vs. SPMS patients only in the auditory P3b task. The control group had greater amplitude than the patients in all the tasks, except in the auditory P3b task. The auditory P3b task is typically easier than the visual P3b and the no-go P3a tasks in either modality. It is possible that all conditions – with the exception of the auditory P3b – were too difficult for the MS patients. Future research comparing PPMS and SPMS using ERP tasks should be cognisant that task difficulty may obscure differences between these groups. The present study provided preliminary evidence that PASAT performance and P3 ERPs correlate for MS progressive subtypes and that there are subtle differences between PPMS and SPMS in electrophysiologic responses during an auditory P3b task.

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Figure legends:

Table 1. Demographic and behavioural data of PPMS, SPMS and controls. (RT=reaction time)

Figure 1. Significant correlation ($p < 0.005$) of the amplitudes of P3 ERPs and PASAT in MS patients. The correlation (Pearson's r) between the voxel of maximum intensity and the PASAT is also displayed.

Supplemental figure 1. Significant correlation ($p < 0.005$) of the amplitudes of P3 ERPs and PASAT in MS patients and controls. The correlation (Pearson's r) between the voxel of maximum intensity and the PASAT is displayed in each subfigure.

Supplemental figure 2. SPMS patients have significantly ($p < 0.005$) larger amplitude compared to PPMS patients in the auditory P3b condition.

Supplemental figure 3. Controls have significantly ($p < 0.005$) larger amplitude compared to MS patients in visual and auditory P3b and visual P3a. This comparison tested the contrast that controls would have greater activation than either MS group and that MS groups would not differ from each other.

Supplemental figure 4. Butterfly plots showing responses for all electrodes across all modalities and groups. Scalp maps showing topography of the response (to target stimulus in P3b tasks, and to distracter stimulus in P3a tasks) at particular latencies are displayed above the butterfly plots.

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