Journal of the Neurological Sciences 293 (2010) 45–50

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

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

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ARTICLE INFO

Article history:
Received 18 December 2009
Received in revised form 10 March 2010
Accepted 11 March 2010

Keywords:
Multiple sclerosis
Event-related potentials, auditory
Event-related potentials, visual
Neuropsychology
Cognition
Attention

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 to 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, and non-target). 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-

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doi:10.1016/j.jns.2010.03.010

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 et al. [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 a difference in auditory P3a latency or amplitude between MS patients and controls. Jung et al. [17] employed an auditory mismatch 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) the 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.

Table 1
Subject demographic data. RRMS: relapsing remitting multiple sclerosis. SPMS: secondary progressive multiple sclerosis. PASAT: paced auditory serial addition test. EDSS: expanded disability status scale. SD: standard deviation. IQR: interquartile range.

	RRMS		SPMS		Control	
N	20		20		34	
Male/female	7/13		14/7		19/15	
	Mean	SD	Mean	SD	Mean	SD
Age	37.81	9.13	51.04	8.92	40.11	9.92
PASAT	74.93	28.19	64.98	21.13	85.86	12.66
Yrs symp	7.95	5.90	24.95	11.15	N/A	N/A
	Median	IQR	Median	IQR	Median	IQR
EDSS	1.75	1.88	6.5	2.25	N/A	N/A
Interferon beta-1a	6		4		N/A	
Interferon beta-1b	6		4		N/A	
Natalizumab	7		0		N/A	
Fingolimod	1		0		N/A	
No current tx	0		12		N/A	

2.2. Procedure

All subjects completed the standard PASAT [19] approximately 1 h 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 s, 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 s, 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 electro-oculogram (EOG) channels (minimum correlation of .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′, and AF1′; Central: Cz, Cz′, CPz, CCP2h, FCC2h, FC2′, FCz, FCC1h, FC1′, and CCP1h; Parietal: CPz′, CPP1h, P1, PPO3h, PO3h, Pz, Pz′, POz, CPP2h, P2, PPO4h, and 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