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Cognitive event-related potentials in multiple sclerosis: Correlation with MRI and neuropsychological findings

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ABSTRACT

Background: Cognitive event-related potentials (ERPs) have been previously correlated with T2 lesion load (T2LL) in patients with multiple sclerosis (MS). It is currently unknown, however, whether ERPs also correlate with brain atrophy or the presence of T1 hypointense lesions ("black holes") which reflect tissue destruction and axonal loss. The primary aim of the current study is to explore the effect of neuroradiological parameters such as brain atrophy, T1 and T2 lesion load on auditory ERPs in MS patients. In addition, we correlated cognitive impairment with neurophysiological (ERP) and neuroradiological (MRI) variables and investigated whether a combination of ERP and MRI parameters is capable of distinguishing patients suffering from secondary progressive (SP), primary progressive (PP) and relapsing-remitting (RR) MS.

Materials and methods: The study sample consisted of fifty nine MS patients (mean age ± SD: 37.82 ± 1.38 years; average disease duration: 6.76 ± 5.3 years) and twenty six age-matched controls (mean age ± SD: 41.42 ± 15.39 years). The patients' EDSS and NRS scores were 3.77 ± 2.14 (range: 1–7.5) and 75.88 ± 11.99 (range: 42–94) respectively. ERPs were recorded using the auditory "odd-ball" paradigm. T1 and T2 lesions were automatically segmented using an edge-finding tool and total lesion volumes were calculated. MRI measures of brain atrophy included third ventricle width (THIRDVW) and the ratio of mid-sagittal corpus callosum area to the mid-sagittal intracranial skull surface area (CC/MISS). Statistical analysis was performed using multiple regression, principal component (PCA) and discriminant analysis.

Results: T1 lesion load emerged as the most significant predictor of P300 and N200 latency. The rest of the endogenous ERPs parameters (P300 amplitude, N200 amplitude) were not significantly correlated with the MRI variables. PCA of pooled neuroradiological and neurophysiological markers suggested that four components accounted for 64.6% of the total variability. Discriminant analysis based on ERP & $2 MRI markers classified correctly 79.63% of patients in RR, PP and SP subgroups.

Conclusion: T1 lesion load is the most significant MRI correlate of auditory ERPs in MS patients. Importantly, ERPs in combination with MRI variables can be usefully employed for distinguishing patients with different subtypes of MS.

1. Introduction

The impairment of cognitive function in multiple sclerosis (MS), particularly in the advanced stages of the disease, was first described in the 19th century by the famous neuropsychiatrist Charcot (Charcot, 1877) who noted "*there is marked enfeeblement of the memory; conceptions are formed slowly*". Recent studies provided a detailed insight of cognitive dysfunction in MS and identified attentional disorders, slowing of thought processes and memory disturbances as its' major components. These deficits occur in 30–70% of MS patients (Rao et al., 1991; Peyser et al., 1980) and are frequently compounded by psychiatric comorbidities, most notably depression.

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The pathophysiological substrate of cognitive impairment in MS has been extensively investigated with various MRI techniques as well as neurophysiological methods including cognitive event-related potentials (ERPs). A number of studies established that the latencies of N200 and P300 waves of auditory ERPs are consistently increased in MS, even in patients with a clinically isolated syndrome (Kocer et al., 2008) whereas an amplitude decrease is a less stable finding (Newton et al., 1989; Gil et al., 1993; Giesser et al., 1992; Sundgren et al., 2015). These electrophysiological abnormalities correlate with the T2 lesion load on MRI (Sánchez et al., 2008; Piras et al., 2003). The influence, however, of other neuroradiological parameters (i.e. brain atrophy and T1 hypointense lesions or "black holes") on ERPs remains unexplored. This issue is of potential importance as brain atrophy and T1 lesion load, which reflects tissue destruction and axonal loss, have been shown to correlate with cognitive impairment (Honig et al., 1992).

The main purpose of the present work is to study the impact of T1 and T2 lesion loads as well as brain atrophy markers on auditory ERPs in MS patients. In addition, we correlated cognitive impairment with ERP and MRI variables and investigated whether a combination of ERP and MRI parameters is capable of distinguishing patients suffering from SP, PP and RR MS.

2. Materials and methods

The study sample consisted of fifty nine MS patients (mean age ± SD: 37.82 ± 1.38 years; average disease duration: 6.76 ± 5.3 years) and twenty six age-matched controls (mean age ± SD: 41.42 ± 15.39 years). All participants entered the study after giving informed consent for the procedures which were approved by an institutional ethics committee and were performed in accordance with the ethical standards laid down in the Declaration of Helsinki. The patients' EDSS and NRS scores were 3.77 ± 2.14 (range: 1–7.5) and 75.88 ± 11.99 (range: 42–94), respectively. The group was divided into 3 subgroups: patients with secondary progressive (n=20), primary progressive (n=10) and relapsing remitting MS (n=29).

2.1. Electrophysiological study

Auditory event-related potentials were elicited using a simple discrimination task, the so-called "oddball paradigm". Briefly, a series of binaural tones at 70 dB sound pressure level (SPL) with a 10 ms rise/fall and a 100 ms plateau time was presented to all subjects. The auditory stimuli were presented in a random sequence with target tones of 2000 Hz occurring 20% of the time and standard tones of 1000 Hz occurring 80% of the time with an interstimulus interval of 2 s. The subject was required to distinguish between the two tones by responding to the target (i.e. mentally counting) and not responding to the standard. Patients were instructed to pay attention in distinguishing the tones, count the target tones silently and report the total number at the end of the exam.

EEG activity was recorded (filter bandpass: .1–50 Hz, 1 s epochs ranging from −100 to +900 ms relative to stimulus onset) from scalp AgCl electrodes at Cz and Pz sites according to the 10/20 system referred to linked earlobe electrodes, with a right hand ground. Artifacts caused by ocular movements ± 50 μV were automatically rejected. Bioelectrical activity was digitized (12 bit) in 250 Hz, 100 ms before till 900 ms after the stimulus was provided. The responses to target and non-target stimuli were averaged separately. Each patient was tested twice to ensure that waveform components are reproducible.

Latencies and amplitudes of N100, P200, N200 and P300 waves were measured after averaging of the independent waveforms. The peak of the ERP components was measured as follows: if the waveform was smooth, the maximal amplitude point was taken as a peak. Otherwise, the leading and trailing slopes of the waveform were extended, and the intersection point was determined. N100 was the waveform of maximal negativity between 80 and 160 ms and P200 wave was the waveform of maximal positivity between 150 and 250 ms. N200 wave was defined as the maximal negativity between 175 and 250 ms that appeared before the P300 wave that, in turn, was defined as the maximal positivity between 250 and 600 ms. In patients with discrete P3a and P3b waveforms, only P3b was taken into consideration[8]. For the needs of the present endogenous ERP study, amplitudes and latencies of N200 and P300 waves were studied.

2.2. Neuroradiological assessment

All patients were examined with a standard MS protocol using a 1.5T MR scanner including T1SE (with and without contrast administration), T2TSE, FLAIR and DWI sequences. No contrast-enhancing lesions were observed. The contouring of demyelinated plaques in the T1 and T2 sequences of MRI and brain atrophy measurements were performed using an image analysis software (ImageJ, 1.45, National Institute of Health, USA). The total volume of T1 (T1LL) and T2 lesions (T2LL) was calculated as the sum of the volumes of individual lesions. We defined 'black holes' as any abnormal hypointensity compared to normal-appearing white matter on a T1-weighted MRI that also appears hyperintense in the corresponding T2-weighted image (Sahraian and Radue, 2008). MRI measures of brain atrophy included the ratio of mid-sagittal corpus callosum area to the mid-sagittal intracranial skull surface area (CC/MISS) and third ventricle width (THIRDVW). The latter was measured according to the method of Benedict et al. (2004). Briefly, a line region of interest was drawn through the long axis of the ventricle, parallel to the interhemispheric fissure in the slice where the third ventricle was most visible. The width was measured by drawing a second line perpendicular to the first at its midpoint and recording its length.

2.3. Neuropsychometric evaluation

A number of neuropsychological tests that assess cognitive functions such as verbal memory, working memory, attention and abstract thought were applied in a subgroup of 26 patients. In particular, attention and concentration were assessed by the neuropsychometric tests, Stroop Test (Stroop, 1935) and Trail Making Test (Vlahou and Kosmidis, 2002). Abstract logic was tested by Raven Progressive Matrices Sets: A, B, C, D and E for adults (Raven, 1960) and Wisconsin Card Sorting Test (Heaton et al., 1993). The Paced Auditory Serial Addition Test (PASAT) was not included as test material because a subgroup of study participants had repeatedly performed the test in the context of previous studies and the resulting learning effects might act as a confounder in the analysis (Gronwall, 1977). Verbal memory was assessed by two subtests of the Wechsler Memory Scale Form II (Wechsler, 1945) (logical memory and subtest combinational memory) as well as the Verbal Fluency Test (Kosmidis et al., 2004). Z-scores of these tests were also calculated as well as the Z-score of the patients' total cognitive function.

2.4. Statistical analysis

Differences in ERP characteristics between MS patients and controls were tested with a *t*-test for independent samples and the non-parametric Mann–Whitney test, depending on normality of the variables' distribution. Normality was tested using the Shapiro–Wilk test, as well as graphical methods (Q-Q plots). The relationship between total cognitive performance and neuroradiological parameters and ERP characteristics was investigated with stepwise multiple regression analysis, whereas the correlation between neuropsychometric tests and radiological and electrophysiological parameters was performed with Spearman's correlation coefficient. In multiple regression analysis, multicollinearity was assessed with the commonly utilized variance inflation factor (VIF) and Tolerance techniques. Variables were