Drakulic et al., J Mult Scler (Foster City) 2018, 5:2
DOI: 10.4172/2376-0389.1000220

Journal of Multiple Sclerosis
ISSN: 2376-0389

Research Article Open Access

# Event Related Brain Potentials (ERP) Could Not Assess the Risk of Cognitive Impairment in Relapse-Remitting Multiple Sclerosis (RRMS)

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## Abstract

**Objectives:** The first objective of our study was to determine differences between groups of patients receiving disease modifying therapy (DMTs) (INFβ-1a and INFβ-1b), patients without DMTs and a control group, in terms of neuropsychological tests and event-related brain potentials (ERP). The second objective was to determine factors that may serve to assess the risk of cognitive impairment in patients with relapsing remitting multiple sclerosis (RRMS).

**Methods:** A total of 81 RRMS patients (mean age 41.09 ± 8.71 years old, 51 women, mean disease duration 133.05 ± 76.56 months) and 32 healthy controls participated in the study. Cognitive functions were evaluated using a standard PASAT-3, the symbol digit modality test (SDMT) and ERP.

**Results:** There were statistically significant differences between the mean values for parietal (Pz) ($p \leq 0.05$) and central (Cz) latency ($p<0.05$) between the four groups of study participants. RRMS increased the risk of cognitive impairment approximately 3.5 fold. Each year of age raised the risk of cognitive impairment by 6.0%. Each unit increase in level of education reduced the risk of cognitive impairment approximately 2.5 fold. Increase in reaction time (RT) Cz by 1 ms elevated the risk of cognitive impairment by 0.5%.

**Conclusions:** There were statistically significant differences between the mean values of Pz and Cz latency between the four groups of study participants. Factors that may be used to assess the risk of developing cognitive impairment in patients with RRMS include age, education level, and RT Cz. However, ERP (latency and amplitude) did not independently assess the risk of cognitive impairment in RRMS patients.

**Keywords:** Event related brain potentials; Cognitive impairment; Multiple sclerosis; PASAT; SDMT; INFβ

## Introduction

Cognitive problems in patients with multiple sclerosis (MS) occur widely in up to 62% of cases, especially concerning executive functions, processing speed, attention, short-term memory and verbal fluency [1].

The use of disease modifying therapies (DMTs), such as interferon beta-1a (INFβ-1a) and interferon beta-1b (INFβ-1b) is considered to affect the cognitive performance of patients with relapsing-remitting multiple sclerosis (RRMS) [2-4], although there are opposite opinions [5].

Cognitive assessment is performed using a battery of neuropsychological tests, such as the Paced Auditory Serial Addition Test 3 (PASAT-3) [6], and Symbol Digit Modalities Test (SDMT) [7-11]. In some studies with a small number of patients, p300 event-related brain potentials (ERP) are considered to be an indicator of objective neuropsychological cognitive functioning for measuring cognitive function in patients with MS [12].

The first objective of our study was to determine whether there are differences between groups of patients receiving therapy, patients without therapy and a control group, in terms of neuropsychological test results and ERP. The second objective was to determine factors that may serve to assess the risk of cognitive impairment in patients with RRMS.

## Materials and Methods

### Participants

In the period from 01.05.2016 to 01.07.2016 in the Department of Neurology of the Clinical Center Kragujevac and the Faculty of medical Sciences, University of Kragujevac, Kragujevac, Serbia, we examined a total of 81 patients with RRMS (71.7%) and 32 healthy controls (28.3%). We tested all patients from our center with RRMS who were on DMTs.

The aims of our study were explained to them and informed consent was signed by all participants and approved by the Ethics Committee of the Clinical Center, Kragujevac.

Diagnosis of definitive RRMS was made using the 2010 revisions to the McDonald criteria [13]. All patients fulfilled the inclusion criteria, i.e. they had RRMS without disability in a functional system that would prevent testing. The exclusion criteria for the group of patients were presence of other neurological diseases and psychiatric disorders, use of neuroleptics, anticholinergics, antidepressants and antiepileptic drugs, relapse and use of corticosteroid therapy in the last month before the tests. The inclusion criteria for the control group were absence of: neurological disease, psychiatric diagnoses, use of any drugs. The RRMS group and the control group were matched by age, gender and education.

Patients were divided into three subgroups: those who were not receiving DMTs, patients on INF β-1a and patients on INFβ-1b. Some patients were not receiving DMTs for economic (financial) reasons in Serbia. They had not been given other types of DMTs earlier.

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**Received** May 13, 2018; **Accepted** June 12, 2018; **Published** June 19, 2018

**Citation:** Drakulic SM, Vujic A, Arsic AA, Lazarevic S, Jevdjic J, et al. (2018) Event Related Brain Potentials (ERP) Could Not Assess the Risk of Cognitive Impairment in Relapse-Remitting Multiple Sclerosis (RRMS). J Mult Scler (Foster City) 5: 220. doi: 10.4172/2376-0389.1000220

## Clinical and neuropsychological evaluation

Neurological disability was evaluated according to the Expanded Disability Status Scale (EDSS), by the same experienced EDSS certified neurologists [14].

Cognitive functions were evaluated using a standard PASAT 3 (form A and B) and SDMT. Means with standard deviation were calculated for SDMT and standard deviations ≤ 1.5 below the mean value of correct responses for the SDMT by the control group was used as the threshold value separating cognitively preserved (CP) and cognitively impaired (CI) MS patients [10].

## Objective cognitive testing

ERP were determined for all patients and control subjects. ERP were registered from the scalp during the morning in the same sound-proofed room. Participants listened to auditory stimuli through a headset and responded by pressing a button with their dominant hand. Bioelectrical activity of the brain was registered by monopolar electrodes placed on the center line of the frontal region (Fz), central region (Cz) and parietal region (Pz) using "Keypoint® Software ver. 3.00 with three dual-channels (Ag¬AgCl). Inactive electrodes were placed on the mastoid process, and the ground electrode was on the forearm of the subjects. Impedance was kept below 5 Ω after detailed preparation of the place where they were put. The resulting signals were amplified, filtered and sampled in the time frame of 1000 ms. We used the "oddball" paradigm with two tones: a "standard" tone of 90 dB and 1000 Hz and an "expecting" tone of 90 dB and 2000 Hz. These were presented binaurally at irregular intervals and in incorrect order through a special headset. Participants were ordered to ignore low "standard" tones, and to react as quickly as possible by pressing the key with the dominant hand, every time they heard the "expecting" high tone. About 260 attempts were registered with the ratio "standard" 80%-"expecting" 20%. Processing ERP included individual identification of the highest positive wave in the window of 220 to 450 ms for each electrode and determination of the amplitude and latency of the p300 wave. Reaction time (RT) was also registered (time elapsed from the occurrence of the stimulus to the response of the patient by pressing the button).

## Statistical analysis

Descriptive data are presented as medians with percentages. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test for normality of distribution of numerical data. For differences in parametric variables Student's t-test and for nonparametric variables the Mann-Whitney U test was employed. Categorical variables were compared using the Chi-square test. Spearman's test was used to determine correlations between variables for data that did not follow a normal distribution. ANOVA was employed to examine differences in latency and amplitude and RT of ERP between the groups of participants in the study. Univariate and multivariate logistic regression was performed to examine which factors influence the occurrence of cognitive impairment in patients with RRMS. Multivariate binary logistic regression allows creation of a model for assessing the risk of cognitive impairment. A model showing the influence of factors affecting the occurrence of cognitive impairment was made based on the significant factors obtained in the univariate and multivariate logistic regression analysis. Probability (P) values<0.05 were considered statistically significant. All statistical analyses were processed in the SPSS v.20 program.

## Result

Demographic, clinical and neuropsychological characteristics for RRMS patients compared to the control group are presented in Table 1. There were negative correlations between EDSS and the results of PASAT A (r=-0.289, p=0.010) and PASAT B (r=-0.319, p<0.001). The results of the SDMT were influenced by gender (women performed better p<0.05), age (p<0.05, r=-0.217), duration of education (p<0.01, r=0.460), educational level (people with a university degree performed better than those with secondary (p<0.05) and primary school education only (p<0.01). There was a significant negative correlation between SDMT and EDSS (r=-0.387, p=0.001). When patients were divided into groups of CP and CI participants, in the RRMS group the relative number with cognitive impairment was 53.2%. The difference between the mean values of EDSS between these groups was statistically significant (CP=2.2 ± 1.5, CI=2.6 ± 1.4, p<0.05). The differences in mean values for PASAT A (CP=45.8 ± 11.1, CI=37.4 ± 10.8, p<0.05) and PASAT B (CP=49.5 ± 9.5, CI=40.4 ± 11.5, p<0.01) between these two groups were statistically significant. CP was related to the level of education (p<0.05).

Our study showed that therapy did not affect performance in PASAT A and PASAT B (PASAT A: INFβ-1b *vs.* without DMTs p=0.739; INFβ-1a *vs.* without DMTs p=0.776; PASAT B: INFβ-1b *vs.* without DMTs p=0.243, INFβ-1a *vs.* without DMTs p=0.844). Moreover, no differences between the groups on DMTs and patients without DMTs (INFβ-1b *vs.* no DMTs p=1.000; INFβ-1a *vs.* no DMTs p=0.676) or between the two groups receiving DMTs (INFβ-1b *vs.* INFβ-1a p=1.000) were found. There was also no significant difference in relation to DMTs between the CP and CI groups ($\chi^{2=}$6.876, p=0.076).

Comparison of ERP latency (ANOVA) between four groups of participants is presented in Figure 1. There were significant differences

| Measures | Patients with RRMS | | | Control group | p value |
|---|---|---|---|---|---|
| | INFb1b | INFB1a | Without DMTs | | |
| **Male/female (number)** | 4/9 | 43391 | 43417 | 16/16 | (p=0.420) |
| **Age (mean ± SD) (years)** | 40.3 ± 8.4 | 38.9 ± 9.1 | 44.5 ± 8.0 | 38.8 ± 9.3 | (p=0.076) |
| **Duration of education (mean ± SD) (years)** | 13 ± 2.7 | 13.4 ± 2.9 | 12.3 ± 3.4 | 14.4 ± 4.4 | (p=0.157) |
| **Education level (number) Primary/Secondary/Higher/ University** | 1/20/2/6 | 1/19/2/6 | 4/13/5/2 | 2/18/5/7 | (p=0.377) |
| **Duration of illness (mean ± SD) (months)** | 143.6 ± 87.9 | 132 ± 64.3 | 121 ± 76.4 | - | (p=0.575) |
| **EDSS (mediana, IQR)** | 2 (1.5-3.0) | 1.5 (1.125-2.375) | 3 (1.5-5.5) | - | **p<0.05** |
| **PASAT A-3 (mean ± SD)** | 42.0 ± 11.1 | 42.0 ± 11.8 | 37.2 ± 11.6 | 48.6 ± 10.0 | **p<0.05** |
| **PASAT B-3 (mean ± SD)** | 46.7 ± 9.9 | 44.2 ± 11.9 | 40.5 ± 11.9 | 51.8 ± 8.7 | **p<0.05** |
| **SDMT (mean ± SD)** | 37.8 ± 10.9 | 38.8 ± 13.0 | 32.8 ± 16.7 | 50.3 ± 12.5 | **p<0.01** |
| RRMS: Relapsing-Remitting Multiple Sclerosis; SD: Standard Deviation; EDSS: Expanded Disability Status Scale; IQR: Interquartile Rang; PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modalities Test | | | | | |

**Table 1:** Demographic, clinical and neuropsychological characteristics for RRMS patients compared to control group.

between the mean values of Pz ($p<0.05$) and Cz latency ($p<0.05$) between the four groups of study participants. Thus, Cz latency for the control group diverged from that for patients without DMTs ($p<0.05$), while Pz latency for the control group diverged from that for patients on INFβ-1b ($p<0.01$) (Figure 1).

Correlations of ERP with demographic characteristics, neuropsychological tests and EDSS in the RRMS group are shown in Table 2.

Univariate binary logistic regression and multivariate binary logistic regression indicated factors that have an impact on the occurrence of cognitive impairment (Table 3).

RRMS increased the risk of cognitive impairment by approximately 3.5 times. Each year of age raised the risk of cognitive impairment by 6.0%. Unit increase in level of education reduced the risk of cognitive impairment approximately 2.5 fold. Increase in the variable RT Cz by 1 ms elevated the risk of cognitive impairment by 0.5%. Multivariate binary logistic regression allowed creation of a model for assessing the risk of cognitive impairment. The model is a new variable calculated as follows:

$$\text{Model} = e^{sum}/(1 + e^{sum}) \cdot 100$$

$$sum = 1.278*MS + 0.058*age - 0.913*level\ of\ education + 0.005*RT\ Cz - 3.291.$$

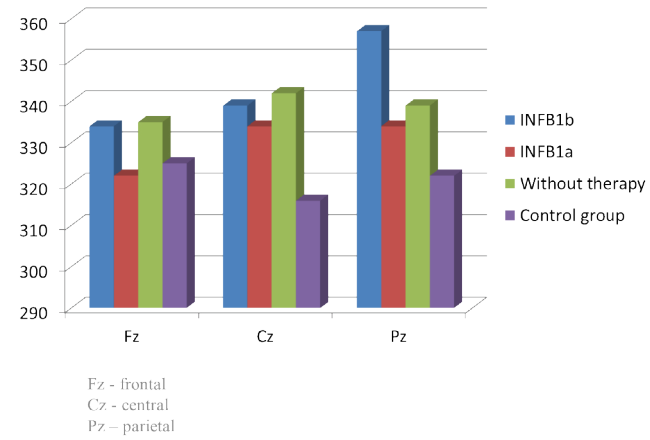


**Figure 1:** The comparison of event related potentials latency, in milliseconds, between 4 groups of participants, from Fz, Cz and Pz electrode.

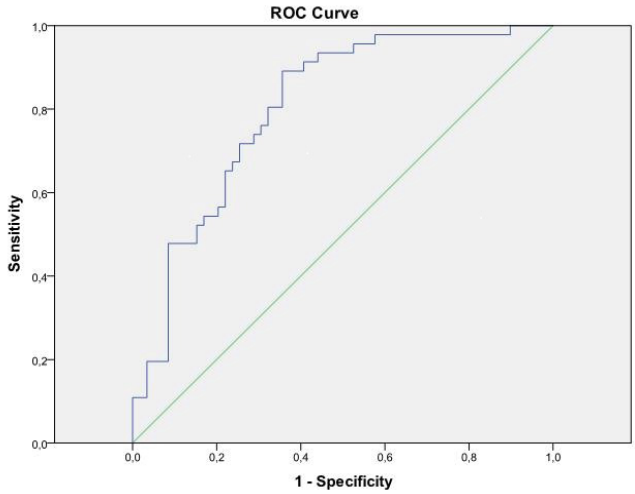


**Figure 2:** ROC curve.

| Measures | Age | Duration of education | EDSS | PASAT A-3 | PASAT B-3 | SDMT |
|---|---|---|---|---|---|---|
| **Fz latency (ms)** | r=0.249* | p=0.355 | p=0.126 | p=0.315 | p=0.402 | p=0.440 |
| **Fz amplitude (μV)** | p=0.132 | p=0.520 | p=0.561 | p=0.578 | p=0.547 | p=0.543 |
| **RT Fz (ms)** | p=0.511 | p=0.400 | p=0.283 | p=0.700 | r=-0.267* | p=0.257 |
| **Cz latency (ms)** | p=0.623 | p=0.859 | r=0.363** | p=0.892 | p=0.666 | p=0.260 |
| **Cz amplitude (μV)** | p=0.277 | p=0.481 | p=0.088 | p=0.724 | p=0.460 | p=0.649 |
| **RT Cz (ms)** | p=0.934 | p=0.286 | p=0.207 | p=0.892 | p=0.235 | p=0.110 |
| **Pz latency (ms)** | p=0.674 | p=0.599 | r=0.284* | p=0.337 | p=0.510 | p=0.663 |
| **Pz amplitude (μV)** | r=-0.313* | r=0.273* | r=-0.296** | p=0.469 | p=0.244 | p=0.171 |
| **RT Pz (ms)** | p=0.703 | p=0.233 | p=0.164 | p=0.785 | p=224 | p=0.116 |
| RRMS: Relapsing-Remitting Multiple Sclerosis; EDSS: Expanded Disability Status Scale; PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modalities Test; Fz: Frontal; ms: Milisecond; *p<0.05; μV–microvolt; **p<0.01; RT: Reaction Time; Cz: Central; Pz: Parietal | | | | | | |

**Table 2:** Correlation of P300 event-related potentials with demographic characteristics, neuropsychological tests and EDSS in the group of patients with RRMS.

| | Univariate binary regression | | Multivariate binary regression | |
|---|---|---|---|---|
| **Measures** | OR with 95% CI | p value | OR with 95% CI | p value |
| **RRMS** | 3.905 (1.505-10.1332) | p<0.01 | 3.589 (1.152–11.175) | p<0.05 |
| **Age** | 1.052 (1.006-1.101) | p<0.05 | 1.060 (1.006-1.117) | p<0.05 |
| **Education level** | 0.377 (0.212-0.673) | p<0.01 | 0.401 (0.219-0.735) | p<0.01 |
| **Duration of education** | 0.751 (0.630-0.894) | p<0.01 | | |
| **Fz latency** | 1.012 (1.000-1.024) | p<0.05 | | |
| **RT Fz** | 1.006 (1.002-1.010) | p<0.01 | | |
| **RT Cz** | 1.006 (1.002-1.010) | p<0.01 | 1.005 (1.000-1.009) | p<0.05 |
| **RT Pz** | 1.005 (1.001-1.009) | p<0.05 | | |
| OR: Odds Ratio; CI: Confidence Interval; RRMS: Relapsing-Remitting Multiple Sclerosis; RT: Reaction Time; Fz: Frontal; Cz: Central; Pz: Parietal | | | | |

**Table 3:** Univariate and Multivariate binary regression showed which factors influence the occurrence of cognitive impairment and the values of OR with 95% CI.

The ROC curve showed that this model may be a good marker to separate participants into those with cognitive impairment and those without cognitive impairment (AUROC=0.803, p<0.01) (Figure 2).

## Discussion

Cognitive impairment has been registered over a wide range of proportions of RRMS patients, i.e. from 9% to 62% [5,15-23]. In our sample of RRMS patients the percentage of CI (defined as ≤ 1.5 standard deviations below the mean value of correct responses for the SDMT by the control group) was 53.2%.

In our cross-sectional study therapy did not affect performance in PASAT A and PASAT B, while some longitudinal studies have shown that performance in PASAT improves slightly after one year of application of INFβ-1b, but not statistically significantly, while use of INFβ-1a led to a statistically significant improvement [3].

There were also marked improvements in the SDMT one year after the application of INFβ-1b and INFβ-1a [3], which was not confirmed in our cross-sectional study. Thus, no differences between the groups on DMTs and patients without DMTs or between the two groups receiving DMTs or in relation to DMTs in those with CP and with CI.

A small number of studies have aimed to investigate the effect of DMTs on latency, amplitude and RT of ERP in patients with RRMS. Thus, INFβ-1b was shown to reduce amplitude and latency [1]. In our cross-sectional study, there were no differences in amplitude and latency and RT between patients without DMTs and patients on INFβ-1a and INFβ-1b (Figure 1).

Others have recorded significantly higher EDSS in CI patients [20,24], which was also the case in our group of participants. Cognitive assessment using PASAT-3 indicated better performance by our control group than the RRMS group (Table 1), in accordance with earlier findings [25,26].

Parmenter and Borghi showed high sensitivity and specificity of the SDMT demonstrating its efficiency as a screening test for cognitive impairment in patients with MS [15,27]. Thus our control group also achieved better results on SDMT than our patients, confirming the findings of others [25]. In our group of participants, women achieved better scores in the SDMT. According to our knowledge, no other study has demonstrated a difference in SDMT between the genders.

SDMT negatively correlated with EDSS during the entire follow-up of patients in Brochet's study [7,25], similarly to our group of patients (p<0.01, rho=-0.363).

We have found that performance of neuropsychological tests is significantly affected by education level, in accordance with Luerding's conclusion that cognitive reserve is the greatest among the highly educated. He found an especially strong relation of educational background to memory and executive functions [28].

The two main neuropsychological markers of cognitive functioning are ERP latency and ERP amplitude. Prolonged latency indicates a long information processing time [29]. Some research has confirmed a connection between ERP and cognitive impairment, defined by neuropsychological tests in MS patients [12,30-32] but this correlation is stronger in patients with Alzheimer's disease where the cortical dementia concept is dominant [33-35]. The correlation between multifocal white-matter and gray-matter lesions in cognitive dysfunction pathology has laid the foundations of the theory of multiple disconnection. Disconnection occurs between cortical and subcortical regions. MS patients with CI manifested more cortical lesions than patients who were CP. The multiple disconnection syndrome means that more than one cognitive domain can be interrupted, producing a variety of neuropsychological deficits [36]. As far as we know there is no study connecting ERP and multiple disconnection syndrome.

Duration of education in our RRMS patients significantly correlated with Pz amplitude. Sundgren stated that half of the variance of cognitive functioning in patients with RRMS is explained by variations in ERP amplitude and RT, together with EDSS, but there are different opinions [30,31]. Positive correlations of EDSS with Cz and Pz latency, and a negative one with Pz amplitude, were also observed in our patients with RRMS. Others have shown that changes in ERP correlate significantly with changes in PASAT during a one year follow-up [37]. While Sundgren found that success in neuropsychological tests correlates with ERP from the parietal region, and not from the frontal region in patients with RRMS [31] we only obtained correlation of PASAT B and RT Fz (Table 2).

The risk of cognitive impairment was calculated in percentages, with a formula that includes factors of importance for the assessment of cognitive risk: the diagnosis of RRMS, age, education level and RT Cz. For example, participant number 38 without a diagnosis of RRMS, was 32 years old, has finished university, and his RT Cz was 414 ms. Our model calculated that the relative risk of cognitive impairment for this participant was 10.87%. This subject had no cognitive impairment. Participant number 41 had an RRMS diagnosis, was 43 years old, finished secondary school and his RT Cz was 674 ms. The risk of cognitive impairment for this individual was high, 88.34% and he did manifest cognitive impairment. In the model the significant factors for assessing cognitive impairment in RRMS patients did not include either latency or amplitude from ERP, so we conclude that ERP is not a reliable indicator of cognitive impairment in these patients.

The advantages of our research are the size of the sample of patients with RRMS, who were receiving DMTs, and who were tested for ERP. We are the first to form a model that calculates an adequate assessment of the risk of cognitive impairment for each RRMS patient. A limitation of this study is that some patients were not receiving DMTs for economic reasons in Serbia.

## Conclusion

There were a significant differences between the mean values for Pz (p<0.05) and Cz latency (p<0.05) between four groups of study participants. Thus, Cz latency for the control group differed from that for patients without DMTs (p<0.05), while Pz latency for the control group differed from that for patients on INFβ-1b (p<0.01). Factors that can be used to assess the risk of developing cognitive impairment in patients with RRMS are age, education level, RT Cz. However, ERP (latency and amplitude) did not independently assess the risk of cognitive impairment in RRMS patients.

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