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Event related potential and response time give evidence for a physiological reserve in cognitive functioning in relapsing–remitting multiple sclerosis

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ABSTRACT

Cognitive dysfunction is common in multiple sclerosis (MS). Different factors may moderate the degree of cognitive deficit. The aim of the present study was to distinguish different mechanisms for cognitive reserve in relapsing–remitting MS (RRMS). The effects of clinical variables (physical disability, depression), premorbid intelligence (years of education, vocabulary knowledge), visual event-related potential measures (P300) and response time (RT) were studied in RRMS patients (n = 71) and healthy subjects (n = 89). Patients with high P300 amplitude and short RT had better cognitive performance. This effect was significantly weaker in controls. High P300 and short RT may be physiological markers of a cognitive reserve in RRMS. In contrast, the association between cognitive scores and premorbid intelligence was similar in patients and in control subjects. The effects of physiological reserve and clinical variables were studied in a hierarchical linear regression model of cognitive performance in RRMS. P300 amplitude and RT explained a considerable amount of variance in global cognitive performance (34%, $p < 0.001$). The effects of P300 and RT were not moderated by premorbid intelligence. Physical disability and depression added significantly to explained variance, and the final model accounted for 44% ($p < 0.001$) of the variation. We conclude that physiological reserve is the strongest moderator of cognitive impairment in RRMS.

1. Introduction

Cognitive impairment is common in multiple sclerosis (MS) and not restricted to advanced stages or progressive subtypes of the disease [1]. The prevalence has been estimated to be 22–40% in relapsing–remitting MS (RRMS) [1–3]. It correlates with physical disability [2–4] and depression [3,5–7], but not with self-reported fatigue when controlling for concomitant depression [3,8,9]. Furthermore, cognitive impairment correlates with brain magnetic resonance imaging (MRI), especially measures of brain atrophy, but the explained variance remains moderate [10]. Thus the correlation between disease burden and cognitive status is often modest. This is not unique for MS and it has foremost been described in Alzheimer's disease (AD) [11]. Higher levels of premorbid verbal intelligence and educational attainment are associated with a slower deterioration in AD [11]. This has been attributed to a larger cognitive reserve in subjects with higher premorbid intelligence, attenuating the effects of the disease process on cognitive functioning. Recent cross-sectional studies in populations of mixed sub-groups of MS have reported a moderating effect of premorbid intelligence on the cognitive dysfunction related to MRI indices of MS pathology [12–14].

Formal education and vocabulary knowledge are commonly used as surrogate markers for premorbid intelligence in studies of cognitive reserve [15,16]. However, when using education as a marker for premorbid intelligence it is important to recognize the pervasive effect of education on neuropsychological test performance seen both in healthy individuals and patients [17]. To support the reserve hypothesis the correlation between education (or vocabulary knowledge) and cognitive performance needs to be significantly stronger among patients than in healthy controls [18–20]. The cognitive reserve model as proposed by Stern accounts for the physiological variability in synaptic organization or relative utilization of different brain regions. We have previously studied event-related potentials (ERP) and response time (RT) in patients with RRMS [21]. Parietal and central P300 amplitude and RT were normal in RRMS, but patients with low P300 amplitude and long RT had a deficit in cognitive performance. The association between cognitive performance and these physiological parameters was significantly stronger in the patient population than in the healthy controls. This association indicated that high P300 amplitude and fast RT may be protective against cognitive impairment in the RRMS subgroup.

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The objectives of the present study were to distinguish different mechanisms for cognitive reserve in RRMS:

- Is cognitive impairment in RRMS influenced by premorbid intelligence?
- How much of the variance in cognitive function is explained by clinical and physiological predictors of cognitive impairment?
- Are the associations of P300 amplitude and RT with cognitive performance moderated by premorbid intelligence?

2. Methods

2.1. Patients

Clinical data, cognitive test scores, P300 amplitude and RT data in RRMS-patients (n = 72) and healthy control subjects (n = 89), were obtained from previously published data sets [3,21]. All patients were diagnosed with RRMS and they were recruited at the Department of Neurology at the Karolinska University Hospital in Stockholm/Solna. Healthy control individuals were randomly selected with the aid of the Swedish population registry. The protocol was approved by the regional ethics committee (Regionala etikprövningsnämnden i Stockholm), and the study was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Patient and control groups were similar for sex, age and education (Table 1). Premorbid intelligence was estimated by education (number of years in school and higher education) and vocabulary knowledge (performance in Vocabulary, SRB:1) [22,23].

2.2. Neuropsychological tests and clinical instruments

The neuropsychological tests and the cognitive domains are listed in Table 2.

Physical disability was assessed by Kurtzke Expanded Disability Status Scale (EDSS) [24], and the Multiple Sclerosis Severity Score (MSSS) [25] was used to assess disease severity. Symptoms of depression were assessed by the Beck Depression Inventory (BDI) [26] and the scale was separated into its non-somatic (BDI-NS) and somatic (BDI-S) components [3,27]. Fatigue was scored with the Fatigue Severity Scale (FSS) [28]. Seven patients and 7 control subjects had visual acuity less than 1.0, but none of these had poor vision that could interfere with the testing procedure [21].

The neurophysiological data included in the present study were P300 amplitude over the parietal and central regions, and RT in response to a visual choice reaction. These were the variables with the strongest correlation to cognitive performance in patients and controls [21].

Table 1
Demographic and clinical data of study population. EDSS, Expanded Disability Status Scale; MSSS, Multiple Sclerosis Severity Scores; BDI, Beck Depression Inventory; FSS, Fatigue Severity Scale; n.s., non-significant.

	Patients (n = 72)	Control subjects (n = 89)	p value
Female sex (%)	71.0	57.0	n.s.
Left handedness (%)	12.5	9.0	n.s.
	Mean ± SD (range)	Mean ± SD (range)	
Age (years)	37.9 ± 10.0 (22–61)	38.2 ± 11.5 (21–60)	n.s.
Education (years)	13.8 ± 2.8 (8–21)	14.1 ± 2.5 (9–21)	n.s.
Disease duration (years)	9.3 ± 6.5 (0.5–31)	–	–
EDSS (scale 0–10)	2.7 ± 1.5 (0–7.5)	–	–
MSSS (scale 0.01–9.99)	4.1 ± 2.2 (0.5–9.1)	–	–
BDI (scale 0–63)	8.8 ± 7.3 (0–44)	4.0 ± 4.2 (0–21)	<0.0001
FSS (scale 1–7)	3.9 ± 1.8 (1–7)	2.6 ± 1.0 (1–5.7)	<0.0001

Table 2
Test grouping in cognitive domains and scores in the patient population. n.s. = non-significant.

Cognitive domain	Cognitive test	z-Score
Benton Visual Retention Test[a]	Memory, visual	−0.12 (n.s.)
Vocabulary Test[b]	Verbal ability	−0.29 (p = 0.03)
Controlled Oral Word Association Test[c]		
Digit Span Test, forward[d]	Attention	−0.88 (p < 0.0001)
Digit Span Test, backwards[d]		
Digit Span Test, total[d]		
Trail Making Test, conditions 1, 2, 3 and 5[c]		
Color–Word Interference Test, conditions 1 and 2[c]		
Controlled Oral Word Association Test[c]	Executive functions	−0.92 (p < 0.0001)
Color–Word Interference Test, conditions 1–4[c]		
Trail Making Test, conditions 1–5[c]		
Digit Span Test, backwards[d]		
Benton Visual Retention Test[a]	Visual perception/ organization	−0.49 (p = 0.002)
Block Design Test[d]		
Digit Symbol Coding Test[d]		
Symbol Search Test[d]		
Digit Symbol Coding Test[d]	Processing speed	−0.64 (p < 0.0001)
Symbol Search Test[d]		
Controlled Oral Word Association Test[c]		
All tests	Global score	−0.71 (p < 0.0001)

[a] BVRT-5, Form C, Administration A [45].
[b] SRB:1 [22,23].
[c] Delis–Kaplan Executive Function System (D-KEFS) [46].
[d] Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) [47].

2.3. Statistics

Cognitive scores, P300 data and RT were adjusted for the effects of age and sex as identified in linear regression analysis of data from the healthy control subjects. Subsequently, the cognitive scores were adjusted for the effects of education [3], with some exceptions as indicated in the Results. All data were expressed as z-scores, where z = (measured value − controls' mean value) / controls' S.D. Correlation analyses were performed with parametric and/or non-parametric methods as indicated. Bonferroni corrections were performed for multiple independent comparisons. Calculations were performed with Matlab R2013b with Statistics Toolbox (MathWorks Inc.) and IBM SPSS Statistics version 20.0.

3. Results

3.1. Physical disability, depression, fatigue and cognitive function in RRMS patients

Patients were on average mildly disabled with a mean EDSS of 2.7. They had significantly more symptoms of depression and fatigue compared to controls (both p < 0.0001). Patients also had deficits in cognitive function relative to controls (global score −0.71, p < 0.0001). Executive functions, attention and processing speed were the most affected cognitive domains (Table 2). One patient was an outlier with a global score of −8.1 S.D. and was excluded from the regression analyses.

3.2. Effect of premorbid intelligence on cognitive function

The cognitive test scores (adjusted for age and sex) were plotted across years of education (Fig. 1). The global score had a positive correlation with education in patients (r = 0.102, p = 0.007) as well as in control subjects (r = 0.085, p = 0.001). When the test scores obtained in the patients had been adjusted for the effect of education as measured in the controls, there was no residual effect of education, neither on the