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Detection of Cognitive Impairment in Multiple Sclerosis Based on P300 Event-Related Potential

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Abstract

Objective: To investigate whether P300 event-related potential (ERP) is associated with cognitive impairments in early multiple sclerosis (MS).

Methods: 72 subjects with MS participated in this prospective case-control study. 56 (78%) had a disease duration of less than 3 years and 16 (12%) had significant, previously-established cognitive deficits. For all participants, P300 ERPs were examined using the odd-ball, paradigm and cognitive assessments were conducted using the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) and the clock-drawing test (CDT).

Results: Of the 56 participants with early-stage MS, 61.5% had cognitive impairments, as defined by sub-normal scores on at least two cognitive subtests of the BRB-N or the CDT. Significant cognitive impairments were encountered in the following domains: verbal fluency (88.6%) assessed by the Word List Generation (WLG) test, short-term memory (70.5%) assessed by the Selective Reminding Test (SRT), visual-spatial learning (59.1%) assessed by the 10/36 Spatial Recall Test (10/36 SRT), CDT (45.5%), and sustained attention (29.5%) assessed by the Paced Auditory Serial Addition Test (PASAT). Significantly prolonged P300 latencies were recorded at Fz in the cognitive impairment group. None of the cognitive tests were found to be correlated with P300 latency at Fz in the early MS group. When participants with well-established cognitive impairments were included, P300 latency at Fz was correlated with WLG score, which assesses associative verbal fluency, a component of frontal lobe-associated executive functioning.

Conclusions: The present study showed that P300 latency at Fz might be useful in the detection of cognitive impairments in early stage MS. Moreover, in patients with MS who have severe cognitive impairments, P300 latency at Fz might detect impaired executive functions as assessed by the WLG test.

Keywords: Multiple sclerosis; Early MS; Cognitive impairment; P300 event-related potential (ERP); Executive functions; Frontal lobe; Word list generation (WLG)

Introduction

Cognitive dysfunction frequently occurs in individuals with multiple sclerosis (MS) and is considered a negative predictor of psycho-social functioning. Amato et al. [1] estimated that 45%-65% of MS patients have cognitive impairments. Other studies [2,3] have indicated that while cognitive impairments might have an early onset in the evolution of the disease, they might not be recognizable using common clinical tests. It is now evident that axonal injury caused by inflammation and neurodegenerative processes occurs in the earliest stages of MS. New techniques [4], such as the application of double inversion recovery (DIR) sequences in MRI examinations, have convincingly demonstrated that cortical lesions are frequent in patients with MS, even at the earliest clinical stages. Concurrently, it has been shown that patients who have cognitive deficits during the early stages of MS show more cortical lesions and more severe cortical atrophy than do cognitively preserved patients [5,6].

Cognitive domains such as attention, language, and memory may behave as interconnected neural networks that contain anatomically separate channels for transferring information [7]. Focal lesions or diffuse alteration of axons may interrupt these networks. The pathological characteristics of MS, a combination of multiple discrete lesions of the myelin and diffuse axonal pathology, are likely to explain the frequent occurrence of cognitive dysfunction associated with the disease. Various cognitive deficits, mainly affecting memory and attention, have been reported in up to 60% of patients with MS [8]. Although some previous studies suggest that cognitive impairments are more prevalent at later stages of the disease [9,10], some have detected such impairments at initial presentation [11] or during the early phase of the disease [12]. Achiron et al. [13] performed a study examining frequency and extent of cognitive deficits in patients with MS, revealing a 20.9% prevalence of cognitive impairments over a five-year period.

Electrophysiological recording of the P300 event-related potential (ERP) is often used in clinical practice [14] to determine cognitive involvement. Due to ease of recording and reliability, the P300 has become the most studied cerebral wave in the evaluation of cerebral

information processing during the course of various neurological diseases. Particularly in psychiatric disorders and dementia [15], the P300 wave has proven to be clinically useful as an index of cognitive function [16]. Among the primary reasons for its popularity is the fact that it can be reliably elicited with relatively simple paradigms, without a behavioral response. P300 latency has been shown to be more sensitive to subtle changes in cognitive processing than reaction time measures. Changes in amplitude may reflect underlying structural and/or functional brain changes. As such, in combination with functional brain imaging, P300 may serve as an early indicator for dementia [15,17]. These recorded endogenous ERPs have also been specifically linked to cognitive and dementia-associated symptoms in MS [18].

The present study aimed to investigate whether the P300 ERP can be used to identify cognitive deficits during the early stage of MS. The hypothesis was that patients with early-stage MS would show discernible cognitive deficits associated with abnormal P300 ERPs.

Methods

Participants

The study group included 56 participants (mean age 33 ± 10.3 years, range 16-61 years, 37 females) with clinically definite recent onset MS, who were consecutively recruited at random from the outpatient clinic of the Neuro-Immunology and Multiple Sclerosis Center at Sheba Medical Center, Tel-Hashomer, Israel. Pre-assigned inclusion criteria were definite MS according to McDonald Criteria [19] and disease duration of less than three years. Participants with history of impaired hearing function, diagnosed psychiatric disorder, or cognitive impairment prior to MS diagnosis were excluded.

At a later stage, 16 additional participants with clinically definite MS and significant, previously-established cognitive impairments were recruited randomly and in succession from the same outpatient clinic. This group was included after a non-significant positive trend between the electrodiagnostic findings and cognitive impairment was found in early stage MS. It was assumed that including a study sample with increased overall cognitive difficulties would make the detection of a significant association more likely.

The study was approved by the Sheba Medical Center Ethics Committee. Written informed consent was obtained from all participants.

Procedure

All participants underwent ERP P300 examination and a neuropsychological assessment. The two procedures were performed with no more than three days between them.

P300 ERP

Recording conditions: ERPs were recorded in a silent electrodiagnostic laboratory. Electroencephalographic activity was recorded at Fz, Cz, and Pz electrode sites, according to the International 10-20 System, referenced to linked ears, with a forehead ground. Impedance was kept at 5 KΩ or less. Standard Ag/AgCl electrodes were used and affixed with electrode paste and glue after skin abrasion. An EOG electrode (Ag/AgCl) was placed to the left of the upper canthus of the right eye. Trials in which EOG activity exceeded +70 μV were automatically rejected. Bio-Logic Systems Corp. equipment was utilized with band-pass filter setting between 1 and 30 Hz and analysis time setting at 1024 msec with a 100 msec pre-stimulus base-line record.

Stimuli and procedures: P300 was elicited using an auditory "oddball" paradigm. Subjects were presented with two tones *via* headphones. The tone bursts varied in pitch and frequency of occurrence: one was a frequent or background tone presented at 1000 Hz, the other was infrequent and unpredictable (the "target" or the "oddball" tone) presented at 2000 Hz. The tones occurred at the rate of 1/sec, at a ratio of 1:4 at 50 dB above the patient's hearing threshold, with a 10 msec rise/fall time and 40 msec duration. Subjects were instructed to keep a mental count of all "target" tones with their eyes closed. After a brief demonstration, two tests were performed, each continuing until 100 artifact-free infrequent stimuli responses were collected, and then averaged.

The electrodiagnostic examination was repeated at least twice in order to confirm reproducible wave form consistency.

P300 waveform analysis: P300 amplitude was determined as the highest positive post-stimulus deflection between 250 and 600 msec, measured from pre-stimulus baseline to peak. Latency values were obtained from the intersection of extrapolated lines from ascending and descending slopes of each peak.

Neuropsychological assessment

Cognitive status was assessed using one cognitive battery that is particularly relevant for and validated in MS, and widely used in both clinical practice and research: the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) for MS [20] and the clock-drawing test (CDT) [21].

BRB-N: The BRB-N, which comprises five subtests, was administered and scored according to published procedures [22].

The Word List Generation (WLG) subtest measures associative verbal fluency. Participants were given 60 sec to say as many words as possible beginning with a particular letter. Overall number of words was counted and recorded.

The Selective Reminding Test (SRT) measures verbal learning and delayed recall through a multiple-trial list learning paradigm. Participants received a list of 12 words in the first trial. In each of five subsequent learning trials, only those items that were not recalled in the previous trial were selectively presented. After each trial the participant was instructed to recall all 12 words. Recall was also assessed after a delay of 11 minutes. Long-term storage scores were counted and used for assessment.

The Paced Auditory Serial Addition Task (PASAT) assesses sustained attention and concentration while a series of single digit numbers are aurally presented every 3 s. Participants were instructed to add each new number to the one presented immediately prior to it and report the result to the examiner. The percentage of correct responses was recorded.

The Symbol Digit Modality Test (SDMT) measures complex attention and concentration in a task that also requires speed and accuracy in visual search and scanning. Participants were asked to associate symbols with numbers and quickly generate the number when shown the symbol. The oral form of this test was used and the number of correct responses provided in 90 s was recorded.

The 10/36 Spatial Recall Test (10/36 SRT) assesses visual-spatial learning and delayed recall. Subjects viewed a 6 × 6 checkerboard with ten checkers on it for 10 s. They were then asked to reconstruct the pattern on a blank checkerboard. The total number of correct responses was recorded.

CDT: Each participant was given a sheet of paper with a pre-drawn circle on it and asked to draw the numbers on the clock and set the time to 10 past 11. Scoring was based on the method used by Shulman et al. [23]. Participants were defined as cognitively impaired if they performed below the normal range on at least two of the cognitive tasks, including the BRB-N subtests and the CDT.

Cognitive impairment definition: Participants were considered cognitively impaired if they had sub-normal scores on at least two cognitive subtests of the BRB-N or the CDT. The normal range was for each test was based on the relevant literature [24,25], and cut-off scores were as follows:

Word list generation: ≤ 14; Short-term memory ≤ 6; Late selective memory: ≤ 6; Paced auditory serial addition task: ≤ 80%; Symbol digit modalities test: ≤ 31; 10/36 Spatial recall test: ≤ 5 CDT: ≥ 2.

Demographic data: Demographic and disease-related data including age, gender, time since MS diagnosis, and level of disability were also collected. The Expanded Disability Status Scale (EDSS), which ranges from of 0 (normal) to 10 in increments of 0.5 [26] was used to quantify level of disability following a complete neurological examination.

Data Analysis

Demographic, clinical, neuropsychological, and electrophysiological data were analyzed using independent samples Student's t-tests and the χ^2 test (for gender distribution). Linear regression analyses were conducted to explore associations between electrophysiological and neuropsychological data. All tests were two-tailed, and p values of 0.05 or less were considered significant.

t-tests were used to compare the cognitive impairment and early MS groups with respect to P300 latencies and amplitudes at Fz, Pz and Cz.

Results

Demographic and disease-related data

Of the 56 patients with clinically definite MS and disease duration of three years, 84% were examined within the first year after diagnosis. Statistical analyses were performed on 52 patients due to missing data in the remaining 4 patients. Table 1 summarizes demographic and disease characteristics in early MS subjects with and without cognitive impairment.

Variable	Early MS group (N=52)	
	No cognitive impairments	Cognitive impairments
	n=20 (38.5%)	n=32 (61.5%)
Age (Mean ± SD)	39.8 ± 10.24	45.1 ± 10.37
Sex (%m/%f)	30/70	31.3/68.7
EDSS disability score (Mean ± SD)	2.0 ± 1.24	2.3 ± 1.24
WLG (% patholog.)	30%	84.4% p=0.000
SRT short-term memory (% patholog.)	20%	70.5% p=0.001
SRT long-term memory (% patholog.)	0%	6.3%
PASAT (% patholog.)	5%	25%
SDMT (% patholog.)	0%	6.3%
10/36 SRT (% patholog.)	20%	56.3% p=0.010
CDT (% patholog.)	0%	43.8% p=0.001

Table 1: Demographic data, disease characteristics, and cognitive task results in participants with short disease duration (Early MS) with and without cognitive impairments (WLG: Word List Generation; SRT: Serial Reminding Test; PASAT: Paced Auditory Serial Addition Task; SDMT: Symbol Digit Modality Test; 10/36 SRT: 10/36 Spatial Recall Test).

Variable	Early MS (n=52)	Cog. Imp. MS (n=16)
Age (Mean ± SD)	32.6 ± 10.3	41.1 ± 13.5, P=0.009
Sex (m%/f%)	66.1/33.9	56.3/43.8, n.s.
Disease duration	0.86 ± 0.90	9.81 ± 7.40, p=0.000
EDSS disability score	2.2 ± 1.22	5.41 ± 2.38, p=0.000
Word list generation	11.88 ± 4.41	8.31 ± 3.45, P=0.008

Short term memory	6.6 ± 1.83	5.23 ± 2.45, P=0.03
Late selective memory	10.0 ± 1.85	7.46 ± 2.63, p=0.000
PASAT	90 ± 19.8	73.46 ± 37.1, p=0.025
SDMT	46.2 ± 8.25	34.15 ± 9.96, p=0.000
10/36SRT	6.1 ± 2.23	4.15 ± 2.1, p=0.007
CDT	1.4 ± 0.73	1.92 ± 1.08, p=0.052

Table 2: Demographic data, disease characteristics, and cognitive task results in participants with short disease duration (Early MS) and established cognitive impairment (Cog. Imp. MS) regardless of disease duration (WLG: Word List Generation; SRT: Serial Reminding Test; PASAT: Paced Auditory Serial Addition Task; SDMT: Symbol Digit Modality Test; 10/36 SRT: 10/36 Spatial Recall Test).

ERP data

Table 3 summarizes the ERP results observed in participants with short disease durations.

Variable	No cognitive impairments n=20 (38.5%)	Cognitive impairments n=32 (61.5%)	Severe cognitive impairment n=16
FzP300 Latency (msec)	309.3 ± 25.76	329.6 ± 34.25 p=0.035	372.8 ± 60.92
CzP300 Latency (msec)	317.3 ± 34.95	330.2 ± 32.72	384.2 ± 59.32
PzP300 Latency (msec)	321.8 ± 32.78	338.8 ± 36.99	390.0 ± 57.26
FzP300 Amplitude (μV)	7.47 ± 3.200	7.11 ± 4.081	4.42 ± 2.590
CzP300 Amplitude (μV)	10.33 ± 2.613	8.65 ± 3.778	6.52 ± 2.824
PzP300 Amplitude (μV)	11.61 ± 3.129	18.74 ± 54.526	8.15 ± 2.984

Table 3: Summary of event-related potential (ERP) results (Mean ± SD) observed in participants with short disease duration (Early MS) with and without cognitive impairments and the participants with severe cognitive impairment and long disease duration.

Regression analyses

To examine whether it was possible to predict P300 Fz latency during early-stage MS based on the scores of the five cognitive subtests that were found to be significantly abnormal, a multiple linear regression analysis was conducted. The analysis yielded a non-significant regression equation, $F(4,43)=1.059$ ns.

Based on the results above, a group of participants with severe cognitive impairments were recruited with the aim of predicting P300 Fz latency based on a particular cognitive subtest of the two cognitive batteries. Following their inclusion, a second multiple linear regression was conducted to predict P300 Fz latency based on the five cognitive subtests in which participants with short disease duration and cognitive impairments showed significantly lower scores.

As shown in Table 2, the severe cognitive impairment group had a significantly higher number of abnormal scores on all the neuropsychological subtest categories, except for the short-term memory test.

The multiple regression analysis yielded a significant result, $F(1,64)=9.24$, $p<0.003$. Results showed that only WLG test scores, which reflect associative verbal fluency, predicted P300 latency at Fz. In accordance with this result, the mean P300 latency at Fz of participants who had scores within the normal range on the WLG test was 52.1 ms shorter than that of those who did not (Table 4).

ANOVA					
	df	SS	MS	F	Significance F
Regression	1	16979.292	16979.3	9.242	0.003
Residual	64	117577.804	16979.3		
Total	65	134557.1			
	Coefficients	Sig.	Importance		
Intercept	381.166	0			
WLG	-52.09	0.001	1		

Table 4: The results of the linear regression for FzP300 Latency.

Discussion

The current study showed that P300 latency at Fz (frontal lobe) was associated with cognitive dysfunction in patients with early-stage MS. This is in accordance with fMRI studies that have shown increased activation of the dorsolateral prefrontal cortex and the anterior cingulate cortex in the frontal lobes during performance of various cognitive tasks [27]. However, the findings of the current study

contradict those of previous studies showing that most patients with MS have P300 latencies within normal range [28-30].

Previous research conducted by Covey et al. [31] and Kok [32] showed associations between P300 latency and both cognitive processing speed and memory. Giesser et al. [18] demonstrated a high correlation between P300 latencies and impaired cognitive functions, such as visual and verbal memory, as well as storage and retrieval strategies. Other studies have shown that in addition to cognitive impairment, prolonged P300 latency is related to the degree of brain involvement revealed by MRI [33,34] On the other hand, a previous study [35] examining schizophrenic patients with cognitive dysfunction found no correlation between any cognitive test and P300 recorded at all standard sites.

The current attempt to reveal associations between delayed latency of the P300 component at frontal and prefrontal cortex sites and distinct cognitive impairments assessed by the two cognitive tests, BRB-N and CDT, was not successful. A significant prolongation of P300 latency was only detected at Fz. As the electrode at the P300 Fz site is located above the frontal lobe, ERPs generated in the frontal and prefrontal cortex have a dominant impact on the recording.

The attempt to localize cognitive deficits using P300 ERP examination is a sophisticated task. Beyond the general challenge of relating a specific cognitive deficit to a precise anatomical site, the P300 wave is believed to be generated in several brain regions, including the ventrolateral prefrontal cortex, the frontal and medial temporal lobe, and the hippocampus [36,37].

The incidence rate of participants with cognitive impairments in our study was 61.5%. Chiaravalloti et al. [38] demonstrated that cognitive deterioration may occur early in the clinical evolution of MS, but also that it may not be obvious. Deloire et al. [39] found that 59.7% of recently diagnosed patients with MS scored below the fifth percentile on two or more tests, compared to the normal population. In a study conducted by Glanz et al. [40], 49% of patients with clinically isolated syndrome or newly diagnosed MS showed at least one impaired cognitive measure, compared to 30% of the healthy controls. The most commonly identified impaired cognitive domains in patients with early-stage MS are attention, information processing speed, and memory.

In the current study, patients with early-stage MS who had cognitive impairments were not significantly different from those without cognitive impairments with respect to demographic and clinical variables, EDSS included.

Early-stage patients with cognitive impairments scored below normal on the WLG, the short-term memory measure of the SRT, the PASAT, and the 10/36 SRT subtests of the BRB-N, as well as on the CDT. Though prolongation of P300 latency at Fz was associated with the cognitive impairment subgroup as a whole, it was not correlated to any one of the cognitive subtests.

A P300 ERP response develops when the subject is actively engaged in the task of detecting targets. In this study, the participants' task was to respond to the presence of an auditory target stimulus. While the amplitude of the P300 component increases with lower probability and higher discriminability of the targets, its latency increases when targets are harder to discriminate, making it an attractive tool to separate the mental processes of stimulus evaluation from response selection and execution [41].

The aim of the current study was to find specific cognitive subtests that might be correlated to P300 latency at Fz. Therefore, following the initial results from the early-stage group, in which the extent of cognitive impairments was relatively low, additional subjects with definite diagnosis of MS and established severe cognitive impairments were included. The rationale was that associations between the previously detected prolonged P300 latency at Fz and impairments in specific cognitive domains would be more easily detected in a study sample with increased overall cognitive difficulties. Following the addition of these participants, as anticipated, P300 Fz latency remained significantly prolonged in the cognitively impaired subjects. Furthermore, it was found to be significantly correlated with the WLG subtest, which assesses associative verbal fluency.

The WLG or verbal fluency test is a relative simple and frequently used neuropsychological tool for the assessment of executive function. Its validity for this purpose has been keenly discussed. The WLG test has both phonemic and semantic versions. The current study used the phonemic WLG test, which requires retrieval of information from long-term memory without contextual cues. As the brain does not store information alphabetically, this retrieval process is dependent on effective search strategies, thus involving both executive and semantic functioning [42]. Troyer et al. [43] assumed that the ability to switch flexibly between different subcategories is specifically related to frontal lobe function. The WLG test requires the ability to initiate and maintain factors involved in continuous word production, such as short-term memory, strategies to avoid repetition of responses and shifting quickly from one word to the next in the selected category, and the ability to inhibit incorrect responses [44], all of which reflect executive function.

Gourovitch et al. [45] showed that phonemic WLG is affected by disturbed executive function, which can be affirmed by brain-imaging studies showing involvement of the frontal lobes. Cummings [46] observed that subjects with ischemic vascular dementia and impaired WLG performance had primary involvement of the frontal white matter areas and the subcortical grey (basal ganglia and thalamus). A study of patients with MS revealed that left frontal lobe lesions may negatively affect word fluency skills [47].

A medical literature search on the topic of cognitive dysfunction and ERPs in MS revealed inconsistent results regarding the verbal fluency task. Pokryszko-Dragan et al. [48] who examined patients with more severe cognitive deficits, did not find impaired performance on the WLG test. In contrast, in a study conducted by López-Góngora et al. [49], patients with early-stage MS performed poorly on a phonetic verbal fluency task, in accordance with the current results. However, until now, no study has demonstrated a correlation between P300 latency at Fz and impaired verbal fluency in MS.

Patients with MS who have cognitive deficits may experience greater difficulties at work and during social interactions and daily activities, irrespective of their physical disability. Therefore, it is crucial to identify a tool able to detect cognitive deficits, particularly those involving executive function, as early as possible. The importance of such a tool is further supported by findings showing that early cognitive impairment in MS may predict disability outcome several years later [50].

This study supports prior research findings showing that subjects with diverse frontal lobe pathologies exhibit prolonged P300 latencies, and suggesting that ERP can be used in the assessment of impaired

executive function [51]. In contrast to the current findings, prolonged P300 latencies were found at the Pz recording site.

Our study suggests that P300 Fz latency prolongation during early-stage MS may be useful in the detection of cognitive impairment, and may be specifically linked to evolving executive dysfunction. As such, it may serve as a preliminary marker for patients who are cognitively at risk. However, it should be noted that P300 latency has also been shown to be affected by other factors, such as circadian rhythm, fatigue, sleep deprivation, drug use, age, intelligence, gender, and genetic factors [52]. Likewise, it is possible that phonetic verbal fluency tasks reflect a general reduction in processing speed rather than a specific executive deficit.

Conclusion

P300 latency at the Fz site appears to provide a nonspecific, simple, and objective index of central nervous system dysfunction in early MS. The present research supports previous study results showing that cognitive impairments may be detectable at initial presentation [27], during the early phase, and in the presence of limited physical disability [38], and that they are more prevalent at later stages of the disease [13].

The identification of cognitive impairments in MS patients at early stages of the disease has important therapeutic and prognostic implications. Early diagnosis may improve patient management and, hopefully, the patient's quality of life. Further studies should be undertaken to validate the utility of P300 component latency at Fz as an indicator of the effectiveness of neuropsychological interventions, with an emphasis on cognitive rehabilitation. Future research may also clarify if the P300 ERP examination restricted to recording latency at frontal lobe sites is sufficient for saving time and financial resources.

References

1. Amato MP, Zipoli V, Portaccio E (2006) Multiple sclerosis-related cognitive changes: A review of cross-sectional and longitudinal studies. J Neurol Sci 245: 41-46.
2. Schulz D, Kopp B, Kunkel A, Faiss JH (2006) Cognition in the early stage of multiple sclerosis. J Neurol 253: 1002-1010.
3. Sartori E, Edan G (2006) Assessment of cognitive dysfunction in multiple sclerosis. J Neurol Sci 245: 169-175.
4. Geurts JJ, Pouwels PJ, Uitdehaag BM, Polman CH, Barkhof F, et al. (2005) Intracortical lesions in multiple sclerosis: improved detection with 3D double inversion-recovery MR imaging. Radiology 236: 254-260.
5. Calabrese M, Agosta F, Rinaldi F, Mattisi I, Grossi P, et al. (2009) Cortical lesions and atrophy associated with cognitive impairment in relapsing-remitting multiple sclerosis. Arch Neurol 66: 1144-1150.
6. Morgen K, Sammer G, Courtney SM, Wolters T, Melchior H, et al. (2006) Evidence for a direct association between cortical atrophy and cognitive impairment in relapsing–remitting MS. Neuroimage 30: 891-898.
7. Steven PE, Sporns O (2015) Brain Networks and Cognitive Architectures. Neuron 88: 207-219.
8. Nabavi SM, Sangelaji B (2015) Cognitive dysfunction in multiple sclerosis: Usually forgotten in the clinical assessment of MS patients. J Res Med Sci 20: 533.
9. Daams M, Steenwijk MD, Schoonheim MM, Wattjes MP, Balk LJ, et al. (2016) Multi-parametric structural magnetic resonance imaging in relation to cognitive dysfunction in long-standing multiple sclerosis. Mult Scler 22: 608-619.
10. Benedict RH, Cookfair D, Gavett R, Gunther M, Munschauer F, et al. (2006) Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). J Int Neuropsychol Soc 12: 549-558.
11. Schulz D, Kopp B, Kunkel A, Faiss JH (2006) Cognition in the early stage of multiple sclerosis. J Neurol 253: 1002-1010.
12. Amato MP, Ponziani G, Siracusa G, Sorbi S (2001) Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years. Arch Neurol 58: 1602-1606.
13. Achiron A, Chapman J, Magalashvili D, Dolev M, Lavie M, et al. (2013) Modeling of cognitive impairment by disease duration in multiple sclerosis: a cross-sectional study. PLoS One 8: e71058.
14. Polich J, Herbst KL (2000) P300 as a clinical assay: rationale, evaluation, and findings. Int J Psychophysiol 38: 3-19.
15. Bonanni L, Franciotti R, Onofrj V, Anzellotti F, Mancino E, et al. (2010) Revisiting P300 cognitive studies for dementia diagnosis: Early dementia with Lewy bodies (DLB) and Alzheimer disease (AD). Neurophysiol Clin 40: 255-265.
16. Polich J (1998) P300 clinical utility and control of variability. J Clin Neurophysiol 15: 14-33.
17. Fuhr P, Kappos L (2001) Evoked potentials for evaluation of multiple sclerosis. Clin Neurophysiol 112: 2185-2189.
18. Giesser BS, Schroeder MM, LaRocca NG, Kurtzberg D, Ritter W, et al. (1992) Endogenous event-related potentials as indices of dementia in multiple sclerosis patients. Electroencephalography and clinical neurophysiology. 82: 320-329.
19. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, et al. (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 69: 292-302.
20. Boringa J, Lazeron RH, Reuling IE, Ader H, Pfennings LE, et al. (2001) The brief repeatable battery of neuropsychological tests: normative values allow application in multiple sclerosis clinical practice. Multiple Sclerosis 7: 263-267.
21. Barak Y, Lavie M, Achiron A (2002) Screening for early cognitive impairment in multiple sclerosis patients using the clock drawing test. J Clin Neurosci 9: 629-632.
22. Boringa J, Lazeron RH, Reuling IE, Ader H, Pfennings LE, et al. (2001) The brief repeatable battery of neuropsychological tests: normative values allow application in multiple sclerosis clinical practice. Multiple Sclerosis 7: 263-267.
23. Shulman KI, Pushkar Gold D, Cohen CA, Zucchero CA (1993) Clock-drawing and dementia in the community: A longitudinal study. Int J Geriatr Psychiatry 8: 487-496.
24. Rao SM, Leo GJ, Bernardin L, Unverzagt F (1991) Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology 41: 685-691.
25. Rao SM (1995) Neuropsychology of multiple sclerosis. Curr Opin Neurol 8: 216-220.
26. Kurtzke JF (1983) Rating neurologic impairment in multiple sclerosis an expanded disability status scale (EDSS). Neurol 33: 1444-1444.
27. Glanz BI, Holland CM, Gauthier SA, Amunwa EL, Liptak Z, et al. (2007) Cognitive dysfunction in patients with clinically isolated syndromes or newly diagnosed multiple sclerosis. Mult Scler 13: 1004-1010.
28. Newton MR, Barrett G, Callanan MM, Towell AD (1989) Cognitive event-related potentials in multiple sclerosis. Brain 112: 1637-1660.
29. Polich J, Romine JS, Sipe JC, Aung M, Dalessio DJ (1992) P300 in multiple sclerosis: a preliminary report. Int J Psychophysiol 12: 155-163.
30. Ruchkin DS, Grafman J, Krauss GL, Johnson R, Canoune H, et al. (1994) Event-related brain potential evidence for a verbal working memory deficit in multiple sclerosis. Brain 117: 289-305.
31. Covey TJ, Shucard JL, Shucard DW (2017) Event-related brain potential indices of cognitive function and brain resource reallocation during working memory in patients with Multiple Sclerosis. Clin Neurophysiol 128: 604-621.
32. Kok A (1997) Event-related-potential (ERP) reflections of mental resources: a review and synthesis. Biol Psychol 45: 19-56.
33. Piras MR, Magnano I, Canu ED, Paulus KS, Satta WM, et al. (2003) Longitudinal study of cognitive dysfunction in multiple sclerosis:

neuropsychological, neuroradiological, and neurophysiological findings. J Neurol Neurosurg Psychiatry 74: 878-885.

34. Medaglini S, Filippi M, Martinelli V, Locatelli T, Lia C, et al. (1993) Auditory P300 in multiple sclerosis (MS): Correlations with neuroradiological and neuropsychological findings. Electroencephal Clin Neurophysiol 87: S92.
35. O'Donnell BF, Vohs JL, Hetrick WP, Carroll CA, Shekhar A (2004) Auditory event-related potential abnormalities in bipolar disorder and schizophrenia. Int J Psychophysiol 53: 45-55.
36. Mecklinger A, Ullsperger P (1995) The P300 to novel and target events: a spatio-temporal dipole model analysis. NeuroReport 7: 241-245.
37. Yamaguchi S, R.T. Knight (1991) P300 generation by novel somatosensory stimuli. Electroencephal Clin Neurophysiol 78: 50-55.
38. Chiaravalloti ND, DeLuca J (2008) Cognitive impairment in multiple sclerosis. Minerva Med 7: 1139-1151.
39. Deloire MS, Bonnet M, Salort E, Arimone Y, Boudineau M, et al. (2006) How to detect cognitive dysfunction at early stages of multiple sclerosis? Mult Scler 12: 445-452.
40. Glanz BI, Holland CM, Gauthier SA, Amunwa EL, Liptak Z, et al. (2007) Cognitive dysfunction in patients with clinically isolated syndromes or newly diagnosed multiple sclerosis. Mult Scler 13: 1004-1010.
41. http://psycnet.apa.org/record/1995-98514-004.
42. Mayr U, Kliegl R (2000) Complex semantic processing in old age: Does it stay or does it go? Psychol Aging 15: 29.
43. Troyer AK, Moscovitch M, Winocur G, Alexander MP, Stuss D (1998) Clustering and switching on verbal fluency: The effects of focal frontal- and temporal-lobe lesions. Neuropsychologia 36: 499-504.
44. Monsch AU, Bondi MW, Butters N, Paulsen JS, Salmon DP, et al. (1994) A comparison of category and letter fluency in Alzheimer's disease and Huntington's disease. Neuropsychology 8: 25.
Gourovitch ML, Kirkby BS, Goldberg TE, Weinberger DR, Gold JM, et al. (2000) A comparison of rCBF patterns during letter and semantic fluency. Neuropsychology 14: 353.
45. Cummings JL (1990) Subcortical dementia. Oxford University Press.
46. Foong J, Rozewicz L, Quaghebeur G, Davie CA, Kartsounis LD, et al. (1997) Executive function in multiple sclerosis. Brain 120: 15-26.
47. Pokryszko-Dragan A, Zagrajek M, Slotwinski K, Bilinska M, Gruszka E, et al. (2016) Event-related potentials and cognitive performance in multiple sclerosis patients with fatigue. Neurol Sci: 1-12.
48. López-Góngora M, Escartín A, Martínez-Horta S, Fernández-Bobadilla R, Querol L, et al. (2015) Neurophysiological evidence of compensatory brain mechanisms in early-stage multiple sclerosis. PloS one 10: e0136786.
49. Deloire M, Ruet A, Hamel D, Bonnet M, Brochet B (2010) Early cognitive impairment in multiple sclerosis predicts disability outcome several years later. Mult Scler 16: 581-587.
50. Lai CL, Lin RT, Liou LM, Yang YH, Liu CK (2013) The role of cognitive event-related potentials in executive dysfunction. Kaohsiung J Med Sci. 29: 680-686.
51. Pfefferbaum A, Ford JM, Wenegrat BG, Roth WT, Kopell BS (1984) Clinical application of the P3 component of event-related potentials. I. Normal aging. Electroencephalogr Clin Neurophysiol 59: 85-103.