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Effects of Neurocognitive Rehabilitation on the Levels of Neurotransmitters and Memory Proteins in Patients with Multiple Sclerosis*

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ABSTRACT

Objective: This study aimed to investigate the role of neurotrophic factors and neurotransmitters in the neurocognitive impairments observed in Multiple Sclerosis (MS) patients, explore potential biomarkers, and evaluate the impact of computer-assisted cognitive rehabilitation (CCR) on these biomarkers.

Materials and Methods: The study included 20 healthy volunteers and 23 relapsing-remitting MS patients with a beck depression inventory score below 17, who could use computers and had no attack in the last 6 months. Serum levels of brain-derived neurotrophic factor (BDNF), cAMP response element-binding protein (CREB), melatonin, and orexin-A were measured using enzyme-linked immunosorbent assay (ELISA) and compared between patients and controls. MS patients underwent assessment using the brief repeatable battery of neuropsychological tests (BRB-N) before (baseline) and after (sixth month) CCR their biomarker levels were measured again, along with administering neuropsychological tests.

Results: Results showed lower levels of BDNF, CREB, melatonin, and orexin-A in MS patients compared to healthy controls before neurorehabilitation. Among the measured cognition-related proteins in the MS group, only BDNF was insignificantly decreased after neurorehabilitation. No significant differences were found in orexin-A, melatonin, and CREB levels before and after neurorehabilitation. Although, correlation analysis revealed no significant correlation between biomarkers and clinical parameters, paced auditory serial addition test and stroop tests which pointed to sustaining attention, information processing speed, verbal fluency, and categorical reasoning were found meaningful after CCR.

Conclusions: CCR may have beneficial effects on cognitive functions, particularly executive functions. However, the four examined molecules did not reflect cognitive changes in MS and cannot be used as biomarkers. Further investigation of other molecules related to CREB and BDNF pathways may shed light on cognitive impairment in MS.

Keywords: Multiple Sclerosis, CCR, BDNF, CREB, melatonin, orexin-A

INTRODUCTION

Multiple Sclerosis (MS) is a chronic, inflammatory, and degenerative disease of the central nervous system, characterized by recurrent or progressive demyelination and axon damage in the white matter (1). The signs and symptoms of MS can be divided into three groups: primary symptoms related to demyelination are paresis, spasticity, sensory disorders, neuropathic pain, problems with balance, bladder-intestinal problems, fatigue, sexual dysfunctions, motor disorders, and cognitive dysfunctions; secondary symptoms are the complications of primary manifestations and include contractures, urinary tract infections, megacolon, pressure sores, and muscle atrophies; and tertiary symptoms are psychological, occupational, and social problems accompanying the remaining findings.

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Cognitive impairment, which is common in patients with MS, is an important symptom that affects the quality of life and social and working lives of patients. The prevalence of cognitive impairment in adults with MS reaches 70% in evaluations performed with neuropsychological tests (2). The accurate definition and diagnosis of cognitive dysfunction early in MS is of paramount importance since it can be a useful predictor of the efficacy of preventive measures or a predictor of disease progression. In MS, the most affected areas are attention, information processing speed, memory, executive functions, and visuospatial functions (3). First, information processing speed and executive functions deteriorate, and this is followed by memory and attention deficits. The cortical areas (gnosis and praxis) are usually intact until the later stages of the disease.

Two test batteries are widely used in international studies evaluating patients with MS: the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) and the Minimal Assessment of Cognitive Function in MS (MACFIMS) (4). One of the coactivators accompanying transcription factors in the learning process is the cAMP response element-binding protein (CREB) and the protein that binds it, the cytoplasmic polyadenylation element binding protein. CREB, also a histone acetylase, results in the remodeling of chromatin. It is now well known that CREB controls neuronal plasticity (5, 6). It has been shown that the brain-derived neurotrophic factor (BDNF) molecule shares the same pathways as CREB, is activated together, has a low level in neurodegenerative diseases, and its level increases with treatment methods that stop its destruction. It is known that melatonin and orexin-A, which are associated with the regulation of sleep functions, activate CREB and BDNF molecules and regulate cognitive functions, synaptic plasticity, and neuroprotective functions (7, 8). Melatonin also suppresses inflammation and inhibits myelin breakdown. BDNF, orexin-A, and melatonin have known effects on cognitive functions through the activation of CREB and decrease during MS (9).

Neurocognitive rehabilitation applied with special software has been shown to lead to an improvement in memory functions, parallel to which the levels of memory proteins, neurotrophic factors, and neurotransmitters in the peripheral blood change (10, 11). However, in the literature, there are very few studies on the preventive effect of neurocognitive rehabilitation on cognitive deterioration and changes in the expression of molecules in patients with MS.

In this study, we aimed to reveal the role of neurotrophic factors and neurotransmitters in neurocognitive involvement observed in MS disease, identify possible new biomarkers, and determine whether these biomarker candidates were affected by computer-assisted cognitive rehabilitation (CCR).

MATERIALS AND METHODS

The study included 23 patients with MS followed up at the Neurology Clinic of the University of Health Sciences Haydarpasa Numune Training and Research Hospital. All the patients met the McDonald criteria for classical MS in terms of their clinical and radiological findings. In the selection of patients, attention was paid to ensure that they were able to use computers and that their beck depression inventory (BDI) scores were below 17 because of ruling out the negative impact of depression on neuropsychological tests. Patients who have experienced attacks in the last 6 months and received corticosteroid treatment were not included in the study due to the potential of altering the levels of the proteins under investigation. No criterion was applied concerning the disease duration and the expanded disability status scale (EDSS) scores of the patients.

The study was approved by the Haydarpasa Numune Training and Research Hospital clinical research local ethics committee (dated 28.11.2016 and approved by HNEAH-KAEK2016/KK/114), and eligible patients signed voluntary informed consent forms.

For all patients with MS, data on age, gender, age at disease onset, disease duration, EDSS scores, education year, and progression index (EDSS/duration of disease) were recorded (Table 1). Healthy individuals were selected from the patients who were presented to the outpatient clinic with a headache but were found to have normal neurological and systemic examination results and unremarkable cranial magnetic resonance imaging, complete blood count, and extensive biochemistry examination findings.

Human BDNF (Abbkine), human CREB (Abbkine), human orexin-A (Shanghai Yehuda Biological Technology), and human melatonin (Abbkine) levels were measured from the serum samples of the patients according to the manufacturer's instructions. The serum samples were stored at -80 °C until analysis.

Neuropsychological Evaluation

The participants underwent assessment using the BRB-N before (baseline) and after (sixth month) CCR. The BRB-N,

Table 1. Clinical and demographic features of MS and healthy controls.

	MS	Healthy Controls
Sex (F/M)	17/6	9/11
Age, years, mean±SD	39.3 ± 11	36.0 ± 9.0
Duration of MS, years, mean±SD	13.0 ± 5.0	-
Academic year, mean±SD	11.5 ± 4.2	11.0 ± 3.4
EDSS, mean±SD	3.2 ± 1.3	-
BDI scores, mean±SD	9.0 ± 5.0	7.0 ± 4.0

Abbreviations: F, female; M, male; EDSS, expanded disability status scale; BDI, beck depression inventory.

developed by Rao et al., consists of a series of tests designed to evaluate MS-specific disorders (12). These tests include measures of verbal memory acquisition [selective reminding test - total learning (SRT-TL)], delayed verbal learning (SRT-DL), visual memory acquisition (SPART-TL), delayed visual learning (SPART-DL), sustained attention and processing speed

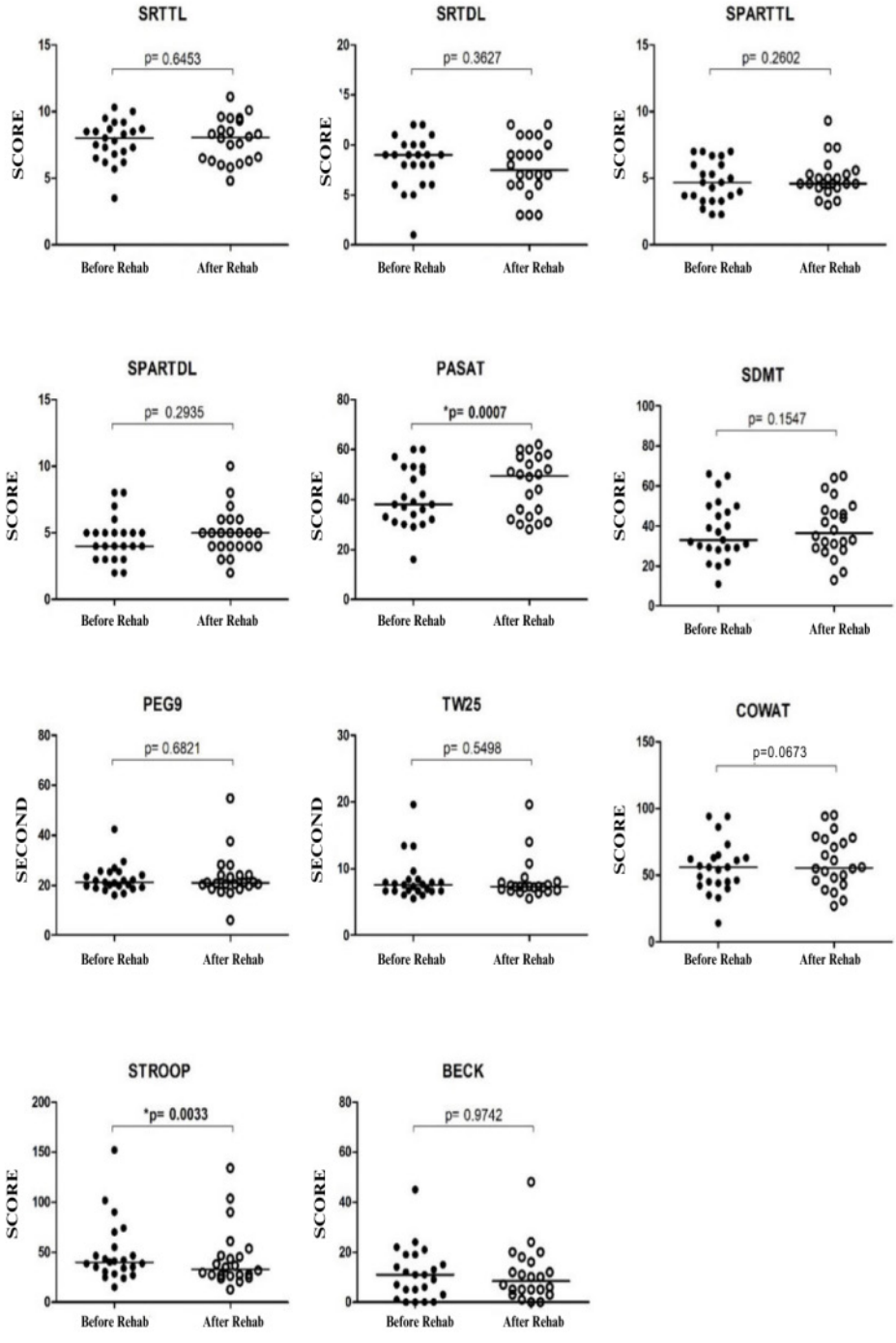

Figure 1. Comparison of the neuropsychological assessment scores before and after rehabilitation. Rehab, rehabilitation.

[paced auditory serial addition test-3 (PASAT-3)], symbol digit modalities test and verbal fluency and categorical reasoning (controlled oral word association test: COWAT). Additionally, executive functions were evaluated using the stroop color and word test, motor functions were assessed using the nine-hole peg and 25-foot walking tests, and mood changes were evaluated using the BDI scores.

Cognitive Rehabilitation

In this study, the CCR utilized the NoroSOFT mental exercise program, which consisted of five modules: attention, memory, reasoning, visual tasks, and verbal tasks. The patients were instructed to engage in 50 minutes of exercise, five days a week. Each session included a 20-minute daily exercise where patients performed tasks from each module, along with a 30-minute personalized training session tailored to their individual BRB-N scores. The patients received weekly follow-up and supervision through the program's institutional interface. Monthly evaluations were conducted for each patient to track their progress.

Statistical Analyses

The serum levels of BDNF, CREB, melatonin, and orexin-A of the patients with MS and healthy controls were compared using the analysis of variance test and Tukey's post hoc test. The pre- and post-rehabilitation values of these parameters and those of neuropsychological tests were compared using paired t-test. Possible correlations between age, disease duration, age at disease onset, EDSS scores, progression index, total number of attacks, and number of attacks per year, and neuropsychological and cognitive test results or serum BDNF, CREB, melatonin, and orexin-A levels were investigated with

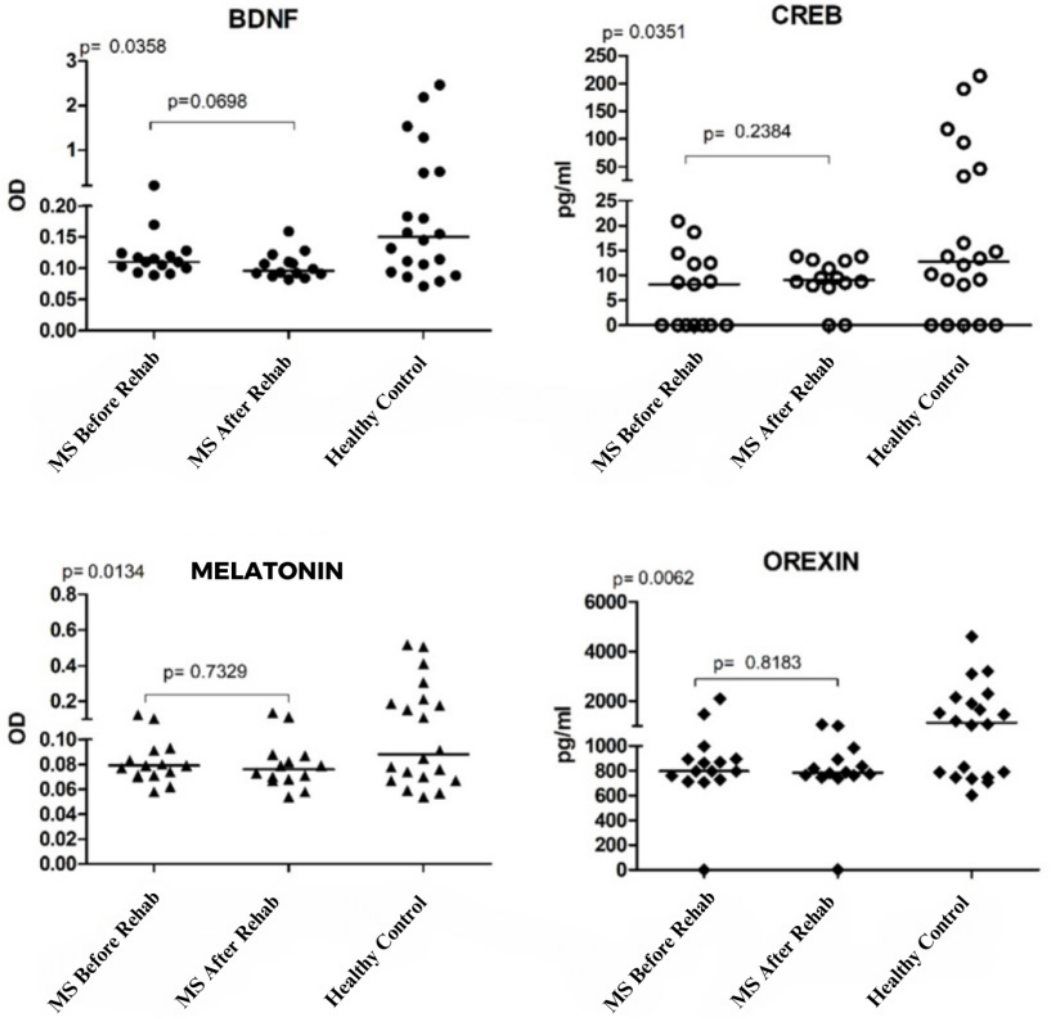

Figure 2. Serum BDNF, CREB, melatonin, and orexin-A levels in the multiple sclerosis (MS) and healthy control groups. The p values presented on the upper left corners of the panels show the results of the analysis of variance, and the p values above the horizontal lines show the results of the test scores before and after rehabilitation, as obtained from the t-test. Rehab, rehabilitation.

the Pearson test. A p-value of <0.05 was considered statistically significant.

RESULTS

Effect of Cognitive Rehabilitation on Neuropsychological Evaluation Results

There was no statistically significant difference between the pre- and post-rehabilitation scores of the SRT-TL, SRT-DL, SPART-TL, SPART-DL, SDMT, and COWAT tests, which primarily evaluate memory functions. Similarly, there was no significant change in the scores of the nine-hole peg and 25-foot walking tests, which measure motor functions, and the BDI, which assesses mood. A significant improvement was found in the scores of the PASAT and Stroop tests after rehabilitation (Figure 1).

ELISA and Correlation Results

The BDNF, CREB, melatonin, and orexin-A levels of the patients with MS (before and after neurorehabilitation) and those of the healthy controls were evaluated. The BDNF, CREB, melatonin, and orexin-A levels were found to be lower than those of the healthy controls (p=0.0358, p=0.0351, p=0.0134, and p=0.0062, respectively) (Figure 1). Among these proteins, which are associated with cognitive functions that are not affected by neurorehabilitation, only BDNF levels have shown trends towards decreasing, albeit at an insignificant level, following rehabilitation (p= 0.0698). There was no significant difference between the pre- and post-neurorehabilitation values of orexin-A, melatonin, and CREB (Figure 2). Lastly, the correlation analysis with the Pearson test revealed no significant correlation between the BDNF, CREB, orexin-A, and melatonin levels and the clinical parameters or neuropsychological evaluation scores of the patients with MS.

DISCUSSION

During MS, it is widely recognized that patients experience impairments in memory, attention, and frontal lobe cognitive functions (13). Cognitive impairment frequency and severity do not significantly differ between individuals with a good or poor prognosis (14). Structural damage to the brain regions connecting the cortical and subcortical areas has been associated with deficits in executive functions, processing speed, and attention (15). In line with previous studies, our study found that patients with MS exhibited deficits in various cognitive functions, including verbal and visual memory, attention, and executive functions. Our results indicate that the brain regions involved in cognitive functions are impacted in MS.

CCR has been widely used to rehabilitate cognitive dysfunction in patients with MS, as it has shown improvements in neuropsychological test scores across a broad range (10, 11). In our study, the most significant improvements were observed in the scores of the PASAT-3, and stroop tests, compared to the verbal and visual memory test scores. Notably, the stroop and PASAT test scores exhibited significant improvements after CCR, reversing the cognitive decline trend in patients with MS. Previous studies have also reported similar tendencies of CCR to enhance PASAT and stroop test performance (11, 16).

The PASAT-3, COWAT, and stroop tests are used to assess sustained attention, information processing speed, verbal fluency, and categorical reasoning, which are known to be closely linked to executive functions (17). The recovery pattern observed in CCR may be attributed to enhanced adaptive recovery activity in the brain's executive functioning regions (15), or these regions may benefit from rehabilitation more rapidly due to higher cognitive reserves. Therefore, neurocognitive rehabilitation shows promise in addressing the severe cognitive deficits experienced by patients with MS. Long-term effects of CCR and optimal cognitive rehabilitation approaches for patients with MS should be further investigated in studies with extended follow-up periods.

In the second phase of our study, we aimed to understand the mechanisms through which CCR improves cognitive processes and identify potential biomarkers that could predict patient response to CCR. To achieve this, we examined four important mediator molecules (CREB, BDNF, orexin-A, and melatonin) that have been associated not only with cognitive functions, neuroprotective effects, and synaptic plasticity but also with the pathophysiology of MS and treatment response in various neurorehabilitation studies. A noteworthy finding from previous research is that CREB and BDNF molecules share common pathways and can be activated together. Furthermore, melatonin and orexin-A, known for their involvement in sleep functions, have been found to activate CREB and BDNF molecules (7, 9).

It has been shown that there is a relationship between low levels of BDNF and cognitive decline in neurodegenerative diseases and that BDNF levels increase in parallel with the improvement in neuropsychological tests following treatments that stop the deterioration in cognitive functions (8). It is also known that repetitive transcranial magnetic stimulation, which is a frequently used neurorehabilitation method, activates neurogenesis by activating the BDNF/TrkB pathway in neuronal damage caused by ischemic cerebrovascular events (8, 18).

The hippocampal expression levels of the phosphorylated and non-phosphorylated CREB molecule have been reported to decrease in ischemic events presenting with neuronal damage, and this decrease has been associated with impairment in cognitive functions (19). It has been determined that CREB levels increase during neurorehabilitation procedures, parallel to which there is improvement in cognitive functions. There are studies supporting the idea that this improvement is due to the neuroprotective effects of apoptosis and oxidative stress inhibitory mechanisms induced by CREB (19, 20).

Melatonin and orexin-A, which are closely related to the regulation of sleep functions, are also known to regulate various cognitive functions, especially memory, synaptic plasticity, and neuroprotective functions. Most importantly, melatonin affects

cognitive functions by activating BDNF expression, and this molecule is also involved in the suppression of inflammation and the prevention of myelin degradation (21-25). Studies are showing that BDNF, melatonin, and orexin-A, which are molecules we identified as biomarker candidates in MS cases, have reduced levels during the disease (26-28). However, we found no study in the literature investigating the serum levels of the CREB molecule. It has been shown that cognitive dysfunction and a decrease in BDNF levels are associated with the early stages of MS. In an experimental animal model study of MS, orexin-A administration was reported to improve the clinical and immunological parameters of the disease through its anti-inflammatory effects (29).

In this study, we determined that the levels of all four molecules we determined as biomarker candidates were significantly lower in the MS group compared to the healthy controls. This finding supports previous studies suggesting that BDNF, CREB, melatonin, and orexin-A are associated with the pathogenesis of MS. In addition, the decreased levels of these molecules in patients with MS whose cognitive functions, especially memory and executive functions, are affected to a certain extent, emphasizes the role of these mediator molecules in normal cognition. The relationship between sleep disorder and the pathogenesis of MS is a well-debated issue. The detection of low levels of melatonin and orexin-A, which facilitate normal sleep functions, in patients with MS once again demonstrates the association between MS and sleep disturbances. Low levels of melatonin and orexin-A, which have immunosuppressive and neuroprotective properties, may cause the development of MS.

It is known that the CREB molecule has characteristics that suppress myelin production and increase Th17-type immune responses, which are known to be involved in the pathogenesis of MS (30). Therefore, low CREB levels detected in patients with MS can be considered as a contradictory finding. However, this change can create a compensatory corrective mechanism by preventing the destruction of myelin and the immune system's attack against myelin.

Another important finding of our study is that there was no significant difference between the pre-and post-neurorehabilitation levels of CREB, BDNF, melatonin, and orexin-A, and no correlation was observed between these molecules and the clinical parameters and neuropsychological test results of the patients with MS. These results suggest that serum levels of the four mediator molecules selected due to their association with MS and cognitive functions do not reflect the cognitive changes that occur in patients with MS, and therefore cannot be used as biomarkers for this purpose. Therefore, a more appropriate approach may be the identification of new biomarker candidates with different methodologies (e.g., the comparison of mRNA expression levels with a microarray analysis before and after rehabilitation).

The limitations of the study include the measurement of possible biomarker levels in serum rather than cerebrospinal fluid, the short follow-up period after rehabilitation, and the evaluation period not being sufficient to observe changes in expression levels. Expanding the study with a greater number of patients, incorporating neuroimaging, comparing with relapsing-remitting MS patients who have not undergone neurorehabilitation, and considering the treatments administered, can provide more information in this regard. In addition, we consider that sleep studies in patients with MS who have low melatonin and orexin-A levels can provide beneficial results by exploring possible correlations between sleep disturbances and the CREB, BDNF, orexin-A, and melatonin levels.

In conclusion, our findings showed that CCR could have beneficial effects on cognitive functions, especially executive functions. The suppression of the four evaluated cognition-related molecules in patients with MS suggests that the pathways responsible for neuroprotection and synaptic plasticity functions may play a role in the development and course of MS. The examination of the other molecules in the pathways to which CREB and BDNF belong can shed further light on cognitive impairment in MS.

Ethics Committee Approval: The study was approved by the Haydarpasa Numune Training and Research Hospital clinical research local ethics committee (dated 28.11.2016 and approved by HNEAH-KAEK2016/KK/114).

Informed Consent: Eligible patients signed voluntary informed consent forms.

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