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Evaluation of Patients with Multiple Sclerosis in Terms of Memory, Attention, Executive Functions, Fine Motor Movement and the Association thereof with Magnetic Resonance Imaging Results

Multiple Sklerozlu Hastaların Bellek, Dikkat, Yürütücü İşlevler, İnce Motor Hareket Yönünden Değerlendirilmesi ve Bunların Manyetik Rezonans Görüntüleme Bulguları ile İlişkisi

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ABSTRACT

Aim: This study aimed to review cognitive function and fine motor skills in patients with multiple sclerosis (MS) and investigate the association with magnetic resonance imaging (MRI) results.
Material and Methods: The study included 22 patients diagnosed with relapsing-remitting MS and 22 controls. Participants underwent neuropsychological tests, including the Stroop test, Rey auditory verbal learning test (RAVLT), line bisection test (LBT), serial reaction time test (SRTT), and finger tapping test (FTT). The relationship between severity of disease, MRI, and test performance was investigated.
Results: It was determined that the patients were lateralized to the right in the LBT data, while the control group was lateralized to the left (p=0.024). On cognitive tests, there was no significant difference in Stroop test results (p=0.134), but the mean overall RAVLT of the patient group was significantly lower than that of the control group (p<0.001). Patients had significantly longer reaction times in SRTT (p=0.038). A positive correlation was found between the expanded disability status scale (EDSS) score and LBT results (r=0.326, p=0.031), and a negative correlation between RAVLT results and EDSS score. For fine motor skills, a negative correlation was observed between FTT results and the number of MS plaques in the left hemisphere (r=-0.431, p=0.045), and a positive correlation between the number of SRTT error and the number of plaques in the juxtacortical regions (r=0.461, p=0.031).
Conclusion: This study shows that the impairment of cognitive functions in MS disease is associated with both the course and severity of the disease and MRI findings.
Keywords: Multiple sclerosis; cognitive functions; neuroanatomical localization; fine motor skills.

ÖZ

Amaç: Bu çalışmada multipl skleroz (MS) hastalarının bilişsel işlevleri ve ince motor becerilerinin gözden geçirilmesi ve bunların manyetik rezonans görüntüleme (MRG) sonuçları ile ilişkisinin araştırılması amaçlandı.
Gereç ve Yöntemler: Çalışmaya relaps-remisyon tipi MS tanısı alan 22 hasta ve 22 kontrol grubu dahil edildi. Katılımcılara Stroop testi, Rey işitsel sözel öğrenme testi (Rey auditory verbal learning test, RAVLT), çizgi bölme testi (ÇBT), seri seçim reaksiyon testi (SSRT) ve parmak vuru testi (PVT) dahil olmak üzere nöropsikolojik testler uygulandı. Hastalık şiddeti ve MRG ile test performansı arasındaki ilişki de incelendi.
Bulgular: Elde edilen sonuçlara göre ÇBT verilerinde hastaların sağa lateralize olduğu, kontrol grubunun ise sola lateralize olduğu tespit edildi (p=0,024). Bilişsel testlerde, Stroop testi sonuçları arasında anlamlı bir fark bulunmazken (p=0,134), hasta grubunun genel RAVLT ortalaması kontrol grubuna göre anlamlı derecede düşüktü (p<0,001). Hastaların SRTT'deki ortalama reaksiyon süresi anlamlı derecede daha uzundu (p=0,038). Genişletilmiş engellilik durumu ölçeği (expanded disability status scale, EDSS) skoru ile ÇBT sonuçları arasında pozitif bir korelasyon (r=0,326; p=0,031) ve RAVLT sonuçları ile EDSS skoru arasında negatif bir korelasyon belirlendi. İnce motor becerilerde, sağ el PVT sonuçları ile sol hemisferdeki MS plağı sayısı arasında negatif bir korelasyon (r=-0,431; p=0,045) ve SSRT hata sayısı ile jukstakortikal bölgelerdeki plak sayısı arasında pozitif bir korelasyon (p=0.031) tespit edildi.
Sonuç: Bu çalışma, MS hastalığında bilişsel işlevlerdeki bozulmanın hem hastalığın seyri ve şiddetiyle hem de MR bulgularıyla ilişkili olduğunu göstermiştir.
Anahtar kelimeler: Multipl skleroz; bilişsel işlevler; nöroanatomik lokalizasyon; ince motor beceri.

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INTRODUCTION

Multiple sclerosis (MS) is a chronic, demyelinating, and degenerative disease of the central nervous system associated with an inflammatory and immune process primarily targeting myelin, which is prevalent in young adults (1). The pathophysiology of MS is a process involving a dynamic interaction of damage and repair mechanisms. The aforementioned interaction is considered to play an important role in determining the clinical course of the disease (2). The regions, where plaques most prevalently occur, include the area around the lateral ventricle (especially between the nucleus caudate and corpus callosum), the floor and roof of the 4^{th} ventricle, optic nerve, pons, around the aqueduct, and medulla spinalis (1).

Demyelination is an acute process and is usually reversible within a few days, yet recovery is associated with remission of the lesion and surrounding edema and acute inflammatory changes. Remyelination is a slow and partial process that can induce functional effects, including slowing of nerve conduction in the central nervous system. MS symptoms may manifest as motor, sensory, visual, cerebellar, sphincter, fatigue, and cognitive disorders associated with demyelination (2,3). Although fatigue and cognitive impairment have been attached less importance compared to other symptoms, they may prove to be the most significant complaint for certain patients (2). Cognitive impairment is a condition that significantly affects the quality of life of patients with MS and is associated with decreased functionality (4). At the same time, it was reported that the decrease in attention and verbal memory performance over time decreases the possibility of finding and retaining a job (5,6). Although all types of cognitive impairment can occur in MS, it is well-established that it mostly involves information processing speed, memory, attention, executive functions, and visuospatial functions (7).

Fine motor movements are defined as movements performed by small muscle groups cooperating in a concerted manner. There is a limited number of comprehensive studies, which investigated slowing in fine motor movement in patients with MS. The results of previous studies reported impairment in fine motor skills in patients with MS (8-11).

The present study aimed to investigate the impairment in cognitive functions and changes in fine motor skills of patients with MS by means of specific tests. It also aimed to investigate the contribution of plaque localization to possible cognitive impairments by correlating test results with magnetic resonance imaging (MRI) results. This work can help researchers better understand the clinical aspects of MS and improve strategies for the management of the disease.

MATERIAL AND METHODS

This study includes patients aged between 18 and 50 years previously diagnosed with relapsing-remitting multiple sclerosis (RRMS) at the Neurology outpatient clinic of Kırıkkale University Faculty of Medicine, with an expanded disability status scale (EDSS) score below 4, and healthy controls matched in age, gender, and educational level. Access to the healthy control group was achieved through random selection from a community-based sample. Participants were informed about the study beforehand and consent forms were obtained.

Participants underwent neuropsychological tests such as the finger tapping test (FTT), serial reaction time test (SRTT), Stroop test, Rey auditory verbal learning test (RAVLT), and line bisection test (LBT), in addition to Beck's depression and anxiety inventories, and hand preference determination tests. The study included a total of 44 participants, comprising 22 RRMS patients and 22 healthy controls. Individuals who had experienced optic neuritis attacks and those with active psychiatric, neurological, visual, or auditory disabilities that could affect test results were excluded. The primary endpoint was the differential performance in neuropsychological tests between MS patients and the control group. The secondary endpoint was the correlation of MS patients' test results with their MRI and EDSS scores. The sample size was determined based on the prevalence of RRMS and the availability of eligible participants during the specified period. This sample size is considered to provide sufficient statistical power to detect clinically significant differences and associations. This study was conducted in accordance with the principles of the Declaration of Helsinki, following the approval from the ethics committee of Kırıkkale University Faculty of Medicine dated February 4^{th}, 2013, and numbered 02/02.

Tests Used in the Study

Stroop Test: This is a three-part cognitive function assessment test developed by J. R. Stroop in 1935. For the first part of the test, the subjects are provided with color names and asked to read them as fast as possible. For the second part, the subjects are asked to say the colors of the dot clusters printed in colored ink as fast as possible; whereas for the third part, the subjects are asked to read the words written in ink of a different color than the name of the presented color as fast and loudly as possible. The importance of this test in terms of cognitive assessment is based on the fact that visual perception predominates when there is a conflict between visual perception and symbolic-semantic perception (12). The Stroop test is a neuropsychological frontal region test used to assess functional impairments associated with brain injury. It is generally believed that the Stroop test measures the ability to resist interference (the ability to maintain attention despite interference).

Rey Auditory Verbal Learning Test (RAVLT): The original form of the RAVLT comprised of word lists was developed by Rey in 1964. The RAVLT is a multi-aspect test of information processing of verbal material. These processes include verbal learning, immediate memory span, retroactive interference, free recall, and recognition memory. This test can make a quantitative assessment of both memory-related parameters and parameters determined by experimental psychological studies (13). The importance of instruments such as the RAVLT is based on the fact that they allow for a valid assessment of memory functioning.

Line Bisection Test (LBT): LBT is a test used to investigate neglect in neglect syndrome that is associated with brain injuries and "pseudoneglect" defined as neglect of the right hemisphere in healthy individuals (14). The LBT used in this study was developed by Nalçacı et al (15).

The test-retest reliability of the hardcopy form of the test was investigated in young adults by Güneş et al. (14). The mean both hand results of the tested subjects indicated that the lines presented in the left field were divided significantly to the left of the midpoint. This is called as physiological neglect. In the present study, papers with 8 cm, 14 cm, and 20 cm lines, including four lines each, were given and the participants were asked to make a mark that would divide these lines exactly in the middle. Subsequently, the average of the length group was taken separately and the deviation to the right or left (deviation in the left direction was negative, deviation in the right direction was positive) and the distance away from the center were calculated for each group, and the resultant data were statistically evaluated.

Serial Reaction Time Test (SRTT): Frequently used as a simple reaction test in studies, especially in the last 20 years, SRTT is a test characterized by responding appropriately to a stimulus after a stimulus is presented on a computer screen. The stimulus appears on the computer screen for varied durations. In the present study, the time between stimuli varied between 1 and 2 seconds. Therefore, by preventing the individual's temporal adaptation to the arrival of stimuli, it was aimed to make the preparation of the individual for the stimulus and direct attention dominant. The stimulus appears to the right or left of the focal point on the display. Depending on the side the stimulus appears, it is asked to press the button of the mouse on that side as quickly as possible. The next stimulus appears after the individual presses the button. Therefore, this test measures both the attention by capturing the appropriate response to the stimulus and the response time to the stimulus and therefore, the visuomotor performance (16).

Finger Tapping Test (FTT): FTT is a test that has been used since the 19th century aimed to assess fine motor performance. It was reported to be correlated with high levels of intelligence and high neuropsychological test scores, and it is a characteristic test, especially in assessing the motor performance of the upper extremity (17). In the present study, the computer mouse was used to repeatedly hit the right and left buttons as fast as possible for 15 seconds. The FTT value was determined as the number of button hits in 15 seconds.

Statistical Analysis

Repeated measures analysis of variance was conducted, where the amount of deviation in millimeters in the LBT was taken as the dependent variable, and line length and group were taken as independent variables. Considering the number of taps in the FTT as the dependent variable, a repeated measures analysis of variance was conducted for hand and group. Assumptions of normality were verified using the Shapiro-Wilk test. Test scores of the groups were compared by t-test. EDSS values and test scores were evaluated with Pearson correlation analysis to assess the correlation between severity of disease and test performances. The number of MS plaques and test scores were evaluated by Pearson correlation analysis to assess the correlation between MRI results and test performance. All statistical assessments were conducted using SPSS v.16.0 (SPSS Inc., Chicago, IL, USA) software, with two-tailed tests and a p-value of <0.05 considered statistically significant.

RESULTS

The study involved 22 (15 females and 7 males) MS patients and a matched control group of 22 (15 females and 7 males) healthy individuals, with no significant differences in age, gender, and educational level. The mean age of the MS group was 32.5±6.6 years, while the mean age was 32.0±6.6 years in the control group. The dependent variable for the groups in terms of their LBT performance was taken as the deviation in millimeters from the center. Accordingly, the group main effect was investigated ($f_{(1,4)}$=5.515, p=0.024). The results suggested that the patient group exhibited right lateralization, whereas the control group showed left lateralization. In the LBT measurements, it was observed that the patient group exhibited average deviations of 0.018, 0.091, and 0.468 mm for LBT 8, 14, and 20 cm, respectively, while the control group showed -0.318, -0.555, and -0.791 mm for the same measurements. There was no significant difference in the main effect of line length and group effect of line length (p=0.696, p=0.053).

FTT was conducted twice using both hands. Aside from the main effects for hand and group (p<0.001, p=0.002), no significant effects or interactions were noted. The mean FTT measurements were 72.77±15.76 and 86.46±10.49 for right1, in patient and control groups, respectively. The means were 73.96±19.09 and 85.36±10.66 for right2, 60.59±16.48 and 75.18±7.69 for left1, and 62.68±15.70 and 73.32±8.82 for left2.

The results of the Stroop test were analyzed upon calculating the Stroop interference. The analysis results showed that the average Stroop interference for the patient group was 1.067, while for the control group, it was 3.867. These findings indicate that there was no significant difference in Stroop interference between the patient and control groups (p=0.134). The SRTT reaction time results were suggestive of the fact that the reaction time in the patient group was significantly longer compared to that of the control group (p=0.038). The SRTT error results showed that there was no significant difference in the number of errors between the patient group and the control group (p=0.336). Based on the RAVLT results, there was a significant difference between the two groups in all 9 steps of the test, and the patient group could have recalled fewer words in each step (Table 1).

Table 1. Comparison of the SRTT and RAVLT results

	Patient (n=22)	Control (n=22)	p
SRTT	40.75±14.18	33.42±7.51	**0.038**
SRTT error	1.05±1.21	0.73±0.94	0.336
RAVLT 1	5.64±1.62	7.64±1.59	**<0.001**
RAVLT 2	7.68±1.91	11.00±1.83	**<0.001**
RAVLT 3	9.32±2.46	12.18±1.68	**<0.001**
RAVLT 4	10.36±2.46	13.45±1.30	**<0.001**
RAVLT 5	10.86±2.42	14.64±0.58	**<0.001**
RAVLT 6	5.18±1.59	6.36±1.36	**0.011**
RAVLT 7	8.27±2.47	13.32±1.36	**<0.001**
RAVLT 8	8.32±2.70	13.73±0.88	**<0.001**
RAVLT recognition	9.36±3.42	14.50±0.86	**<0.001**

SRTT: serial reaction time test, RAVLT: Rey auditory verbal learning test

EDSS scores and test performance results were assessed with Pearson correlation analysis to see the effect of the severity of MS disease on test performance. There was a positive correlation between the 20 cm LBT test and EDSS scores (r=0.326, p=0.031). As the EDSS score increased, the deviation from the center increased. Upon review of EDSS and FTT results, there was a negative correlation between EDSS and FTT performance. As the EDSS score increased, FTT performance decreased. There was no significant correlation between EDSS and Stroop test scores. While there was a positive correlation between EDSS and SRTT reaction time (r=0.359, p=0.017), there was no significant correlation between EDSS and SRTT error rate (r=0.117, p=0.450). An analysis of the EDSS and RAVLT correlation showed a negative correlation for all subtest results of RAVLT (Table 2).

MRI findings in MS patients were analyzed to determine the smallest lesion diameter (SLD) and largest lesion diameter (LLD). The mean SLD was 3.8±0.3 mm, and the mean LLD was 17.0±1.3 mm across all patients.

There was no significant correlation between the number of MS plaques and LBT. Upon review of the periventricular, juxtacortical, and infratentorial regions of the hemisphere (contralateral), which ensured motor control of the hand, the right-hand FTT performance decreased as the number of MS plaques in the left juxtacortical region increased (r=-0.431, p=0.045). There was no significant correlation between FTT left-hand performances and the number of MS plaques in the right hemisphere (Table 3). No significant correlation was found between Stroop interference and the number of MS plaques. While there was no significant correlation between SRTT reaction time and the number of MS plaques, there was a positive correlation between the SRTT errors and juxtacortical right and juxtacortical left (Table 4). Upon review of the subtests of the RAVLT, which assessed language skills in a very broad framework, the number of plaques in the juxtacortical region was mostly associated with RAVLT scores (Table 5). Besides, the number of plaques in the left infratentorial region was also correlated with the RAVLT subtests (Table 6).

DISCUSSION

Cognitive impairment is a condition that is associated with significant impairment of the quality of life of patients with MS. Physical independence, ability to perform daily activities, symptom management, coping, treatment adherence, and rehabilitation are particularly affected subgroups. Fine motor movements, which are important for performing daily activities are also affected by MS. The study results showed impairment in all the tests aimed to assess cognitive functions. Furthermore, the deterioration in their test performance became more manifest upon increasing severity of MS.

Table 2. Correlation of EDDS and test performance results

	EDDS	
	r	**p**
LBT 8 cm	0.129	0.403
LBT 14 cm	0.255	0.095
LBT 20 cm	0.326	**0.031**
FTT right 1	-0.578	**<0.001**
FTT right 2	-0.487	**0.001**
FTT left 1	-0.612	**<0.001**
FTT left 2	-0.475	**<0.001**
SRTT	0.359	**0.017**
SRTT error	0.117	0.450
RAVLT 1	-0.517	**<0.001**
RAVLT 2	-0.600	**<0.001**
RAVLT 3	-0.558	**<0.001**
RAVLT 4	-0.605	**0.042**
RAVLT 5	-0.732	**<0.001**
RAVLT 6	-0.308	**<0.001**
RAVLT 7	-0.708	**<0.001**
RAVLT 8	-0.768	**<0.001**
RAVLT recognition	-0.662	**<0.001**

EDSS: expanded disability status scale, LBT: line bisection test, FTT: finger tapping test, SRTT: serial reaction time test, RAVLT: Rey auditory verbal learning test

Table 3. Correlation of FTT right-hand performance and left hemisphere MS plaque count

	FTT right 1		FTT right 2	
Left	**r**	**p**	**r**	**p**
Periventricular	-0.040	0.858	0.033	0.884
Juxtacortical	-0.396	0.068	-0.431	**0.045**
Infratentorial	-0.205	0.360	-0.126	0.575

FTT: finger tapping test, MS: multiple sclerosis

Table 4. Correlation of the number of SRTT error and the number of MS plaques

	SRTT Error	
	r	**p**
Periventricular right	0.244	0.273
Periventricular left	0.167	0.457
Juxtacortical right	0.443	**0.039**
Juxtacortical left	0.461	**0.031**
Infratentorial right	0.098	0.666
Infratentorial left	0.206	0.358

SRTT: serial reaction time test, MS: multiple sclerosis

Table 5. Correlation analysis between RAVLT subtests and juxtacortical right and juxtacortical left MS plaque count

	RAVLT 4		RAVLT 5		RAVLT 7		RAVLT 8		RAVLT recognition	
	r	**p**	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
Juxtacortical										
Right	-0.460	**0.031**	-0.495	**0.019**	-0.466	**0.029**	-0.615	**0.002**	-0.521	**0.013**
Left	-0.348	0.112	-0.408	0.059	-0.400	0.065	-0.511	**0.015**	-0.522	**0.013**

RAVLT: Rey auditory verbal learning test, MS: multiple sclerosis

Table 6. Correlation analysis between RAVLT subtests and infratentorial left MS plaque count

	RAVLT 3		RAVLT 4		RAVLT 8	
	r	**p**	**r**	**p**	**r**	**p**
Infratentorial left	-0.462	**0.030**	-0.470	**0.027**	-0.454	**0.034**

RAVLT: Rey auditory verbal learning test, MS: multiple sclerosis

The SRTT test showed a significant increase in reaction time in patients with MS. The increase in cognitive load with increasing difficulty of the task was indicative of the fact that this test was effective in assessing cognitive processing speed. Moreover, there was a positive correlation between EDSS scores and SRTT reaction times, suggestive of the fact that as the severity of the disease increased, the information processing time was prolonged. Upon error analysis, patients with MS had longer reaction times, though the number of errors was similar to the control group. This suggested that the prolongation of reaction time might be a result of an effort to reduce the rate of error. Previous studies also supported that SRTT results indicated longer reaction times in patients with MS and that this difference became further manifest with increased severity of disease (18-22).

Previous studies on memory in patients with MS generally reported impaired memory (23-29). Miyazaki et al. (30) investigated the cognitive functions of patients with MS using the symbol digit modalities test (SDMT), California verbal learning test-second edition (CVLT-2), and brief visuospatial memory test-revised (BVMT-R). The above study investigated associations between clinical characteristics, patterns of brain volume loss, and cognitive test results. SDMT performance declined through the course of MS disease in association with brain volume loss. It was concluded that BVMT-R performance also decreased in parallel with brain volume loss, but the deterioration in CVLT-2 became more manifest, especially during the later stages of MS (30). In the present study, patients with MS had impaired memory performance in all subtests of the RAVLT. The patients with MS remembered significantly fewer words compared to the control group.

In addition, as a result of the analyses in the scope of the study, there was a negative correlation between EDSS scores and RAVLT performance. This result suggested that as the severity of the disease increased, the number of recalled words decreased. Notwithstanding the above, there was a significant negative correlation between RAVLT subtest scores and left infratentorial region, right, and left juxtacortical region, and the number of plaques. This result suggested that damage to those brain regions was associated with impaired memory performance. Various studies investigated the cognitive functions of patients with MS using different tests. In a study to evaluate the cognitive functions in patients with MS, Scherer et al. (24) reported that patients had lower performance in the digit symbol substitution test (DSST), paced auditory serial addition test (PASAT), and faces symbol test (FST). Schulz et al. (26) reported impaired processing speed and memory problems in patients with MS. Demers et al. (28) found significant differences in patients with MS, but reported that there was no linear relationship between cognitive impairment and severity of disease. Cerezo Garcia et al. (25) reported impairment in executive functions, while Hoffman et al. (31) found impairment in working memory in most participants. Sehanovic et al. (32) showed that 40-60% of patients with MS had impaired cognitive functions and that this effect became more manifest with an increase in disease duration. Consistent with the above studies, the results of the present study indicated that memory impairment in patients with MS was positively associated with disease duration, and also with disease severity. For the purposes of the present study, participants without depressive disorders were included in both the MS patient group and the control group to exclude the effect of depression on cognitive functions. Previous studies suggested that individuals with MS had impairment in complex attention tasks. This was usually associated with working memory and executive attention (33). Attention is maintained by an important neural network widely distributed across the brain. These networks include regions such as the prefrontal cortex, parietal cortex, and cingulate gyrus, which are tightly interconnected. It has been emphasized that these regions are critical in various tasks varying between motor executive functions and information encoding and planning and executive functions of attention (34,35). In the present study, there was no significant difference between the groups by Stroop test performance. This was suggestive of the fact that patients with MS might have memory impairment independent of executive functions. Furthermore, there was no significant difference between the groups upon analysis of the number of errors component of the SRTT. Nevertheless, there was a positive correlation between the number of SRTT errors and the number of MS lesions in the left and right juxtacortical regions. In other words, the participants with a higher number of SRTT errors had a higher number of MS lesions in these regions. It was likely that the above regions were located at the connections between regions critical for attentional function.

De Sonneville et al. (36) reported that patients with MS had significant impairments in all attention domains. A study by Bodling et al. (18) suggested a remarkable slowing of response time and inconsistencies and errors between the responses in patients with MS. The authors suggested that the foregoing prolongation in response time in MS primarily indicated a slowdown in the speed of information processing, but there was also an attentional impairment. In the present study, the fact that the SRTT reaction time was longer and there was no difference in the number of errors in the Stroop test and SRTT in patients with MS, indicated that there was an impairment in the information processing process rather than attention.

It was seen that the left hemisphere lesions tended not to affect spatial attention, but right hemisphere lesions might have affected attention directed to left space. This condition is known as the "neglect phenomenon" and affects the spatial awareness of the patients. Patients with neglect phenomena can focus only on the right space in visual drawings or written texts while neglecting the left space. For example, they can copy only the right side of a drawing or read only the right half of a text. A patient with left space neglect may divide the lines closer to the right, considering that they would divide the lines in the center, and as a result may leave a longer space on the left compared to the right (37). A study by Kocsis et al. (38) reported the left-sided tendency of pseudoneglect in healthy individuals, whereas it was concluded that lesions affecting the integrity of white matter pathways in patients with MS might increase the variability of spatial attentional bias. In a study by Gilad et al. (39), LBT, a random shape cancellation test was used and its correlation with brain MRI was investigated. Based on the results of LBT, significant right lateralization was observed in the MS patient group compared to the healthy controls. Furthermore, the results of the random cancellation test indicated high error rates on the left side in patients with MS. Nevertheless, there was no significant correlation upon the comparison of the test results with MRI results. In the present study, although all the participants were right-handed, participants in the control group lateralized to the left, whereas patients with MS lateralized to the right. In addition, the deviation from the center was significantly higher as the line length increased in the MS patient group. Patients with MS were significantly more distanced from the center in the 20 cm subtest of the LBT. There was a positive correlation between the LBT 20 cm test and EDSS; i.e., the deviation from the center increased with increasing disease severity in the longer lines. This suggested that although patients with MS could compensate for spatial attentional impairment in short lines and/or narrow space, the compensation mechanism was not sufficient and the impairment became more pronounced as the line got longer/space widened. Nevertheless, the results of the study indicated that there was no correlation between the number of MS plaques in any region and the performance of LBT. Therefore, the LBT data suggested that the spatial distribution of patients' attention differed from the controls (that negligence changed direction) and that disease severity made the foregoing difference more pronounced as line length increased.

Fine motor movements are the movements performed upon coordinated work of small muscle groups. A previous study reported that the primary motor area (M1) was the general main control center for simple voluntary movements and the premotor area played an auxiliary role in those movements (40). There are only a limited number of studies investigated slowing in fine motor movements in MS. Nevertheless, a study by Longstaff et al. (8) reported that patients with MS performed the task of drawing a spiral on a graphic tablet more slowly, applying less pressure, and deviating more from the ideal trajectory compared to the control group. These results were interpreted as an indicator of fine motor movement impairment in patients with MS. In the present study, there were significant differences between the groups by both FTT performance, a pure motor test, and SRTT performance, which reflected the cognitive component of fine motor movement. Patients with MS were slower, had longer SRTT reaction times, and had fewer FTT taps compared to the healthy controls. Based on these results, it was suggested that patients with MS had impaired fine motor movement performance and that this impairment was induced by both cognitive and motor processes. Besides, there was a negative correlation between EDSS scores and FTT performance and a positive correlation between SRTT reaction time and EDSS scores. In other words, as the severity of the disease increased, the number of FTT taps decreased and the SRTT reaction time increased. Therefore, it can be suggested that impairment in fine motor skills becomes more manifest as the severity of MS disease increases. Furthermore, the correlation between FTT performance and the number of MS plaques in the periventricular, juxtacortical, and infratentorial regions of the hemisphere (contralateral), which provided motor control of the hand, suggested that right-hand FTT performance decreased as the number of MS plaques in the left juxtacortical region increased. Nevertheless, there was no significant correlation between the left-hand FTT performance and the number of plaques in the right hemisphere. This result is suggestive of the fact that the motor problem due to MS plaques became more pronounced as the functional burden/responsibility became more apparent.

The results of the present study indicated impairment in cognitive domains, including spatial orientation of attention, information processing time, and verbal memory. It also suggested that fine motor skills were affected in both cognitive and motor domains. The significant correlations observed between MRI results and these impaired functions provided insight into the neuroanatomical localization of cognitive functions. The severity of the disease and the localization of the MS plaque had an impact on the prominence of this impairment. Accordingly, functional MRI or event-related monitoring during testing may not only provide information about the neuroanatomical localization of both cognitive functions and fine motor skills but also information about cognitive impairment during the disease. These results provided significant clues to better understand the effects of MS on cognitive functioning and the relationship between the severity of the disease and these effects. Nevertheless, it should be noted that further studies can help deepen our understanding of this issue.

Limitations of this study include the relatively small sample size, which may limit the generalizability of the findings, the cross-sectional design, which limits the ability to determine long-term effects, and the fact that the sample only represents a specific subgroup of MS patients. Additionally, the tests used and the MRI findings have their own limitations, which should be considered when interpreting the results.

CONCLUSION

The results indicative of the fact that the impairment in cognitive functions of patients with MS was directly proportional to the course and severity of the disease, may shed light on future studies in this field. Furthermore, the MRI results in the present study provided a more comprehensive perspective by helping us better understand the association between these cognitive impairments and neuroanatomical localization.

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