DOI:10.4274/tnd.2022.24992
Turk J Neurol 2022;28:162-168

Original Article / Özgün Araştırma

Evaluation of Short-term Memory, Working Memory, and Executive Functions in Patients with Relapsing-remitting Multiple Sclerosis

Relapsing-remitting Multipl Sklerozlu Hastaların Kısa Süreli Bellek, Çalışma Belleği ve Yönetici İşlevlerinin Değerlendirilmesi

Furkan Duman[1], Handan Can[2], Alev Leventoğlu[3]

[1]Ufuk University Faculty of Arts and Sciences, Department of Psychology, Ankara, Turkey

[2]Bursa Uludag University Faculty of Arts and Sciences, Department of Psychology, Bursa, Turkey

[3]Ufuk University Faculty of Medicine, Department of Neurology, Ankara, Turkey

Abstract

Objective: To compare patients with relapsing-remitting multiple sclerosis (RRMS) and healthy individuals in terms of short-term memory (STM), working memory (WM) and executive functions.

Materials and Methods: The sample consisted of 33 patients with RRMS and 26 healthy participants. The groups were matched in terms of age, gender, level of education and hand dominance. The socio-demographic characteristics of the participants were recorded; and they were evaluated with Beck depression inventory and state/trait anxiety inventory. Visual aural digit span test B form, Wisconsin card sorting test, backward digit span task, stroop test T-BAG form, Wechsler memory scale: Revised form visual memory span subtest (WMS-R/VMS) and trail making test (TMT) for cognitive functions.

Results: There was no statistically significant difference between groups in terms of depression and anxiety scores (p>0.05). Backward visual memory span calculated from WMS-R/VMS was significantly lower (p<0.05) in the RRMS group. However, there was no significant difference between groups in WMS-R/VMS and TMT scores (p>0.05).

Conclusion: Results of this study indicate that patients with RRMS have lower visuo-spatial sketchpad capacity in their WM. However, there was no significant difference between patients with RRMS and healthy controls in terms of verbal and visuo-spatial STM capacity, phonological loop capacity in WM, perseveration, conceptualization, inhibition and set shifting skills.

Keywords: Relapsing-remitting multiple sclerosis, cognitive impairment, short-term memory, working memory, executive functions

Öz

Amaç: Relapsing-remitting multipl sklerozlu (RRMS) hastalar ile sağlıklı bireyleri kısa süreli bellek, çalışma belleği ve yönetici işlevler açısından karşılaştırmaktır.

Gereç ve Yöntem: Araştırmaya RRMS tanısı alan 33 hasta (RRMS grubu) ile yaş, cinsiyet, eğitim düzeyi ve el tercihi bakımından eşleştirilen 26 sağlıklı katılımcı (kontrol grubu) dahil edilmiştir. Katılımcıların sosyo-demografik özellikleri kaydedilmiştir ve katılımcılara Beck depresyon envanteri ile durumluk/sürekli kaygı envanteri uygulanmıştır. Katılımcılar bilişsel işlevler görsel-işitsel sayı dizisi testi B formu (GİSD-B), Wisconsin kart eşleme testi (WKET), geriye doğru sayı dizisi görevi (GDSD), stroop testi T-BAG formu, Wechsler bellek ölçeği geliştirilmiş formunun (WBÖGF) alt testlerinden biri olan görsel bellek uzamı alt testi (GBU) ve iz sürme testi (İST) kullanılarak değerlendirilmiştir.

Bulgular: Gruplar arasında depresyon ve kaygı puanları açısından istatistiksel olarak anlamlı bir fark bulunmamıştır (p>0,05). RRMS grubunun WBÖGF'nin GBU alt testinden hesaplanan ters görsel bellek uzamı daha düşüktür (p<0,05). Gruplar arasında GİSD-B, WKET, GDSD, WBÖGF'nin GBU alt testinden hesaplanan düz görsel bellek uzamı ve İST puanları açısından anlamlı bir fark bulunmamıştır (p>0,05).

Sonuç: Mevcut araştırmada RRMS'li hastaların çalışma belleğindeki görsel-mekansal kopyalama (sözel olmayan bilgi) kapasitesinin düşük olduğu saptanmıştır. Sözel olan ve olmayan kısa süreli bellek kapasitesi, çalışma belleğindeki fonolojik döngü (sözel bilgi) kapasitesi ile yönetici işlevlerden perseverasyon yapma eğilimi, kavramsallaştırma/irdeleme, inhibisyon (bozucu etkiye karşı koyma) ve set değiştirme becerileri açısından RRMS grubu ile kontrol grubu arasında istatistiksel olarak anlamlı bir farklılık olmadığı saptanmıştır.

Anahtar Kelimeler: Relapsing-remitting multipl skleroz, bilişsel bozukluk, kısa süreli bellek, çalışma belleği, yönetici işlevler

Address for Correspondence/Yazışma Adresi: Furkan Duman Research Assistant, Ufuk University Faculty of Arts and Sciences, Department of Psychology, Ankara, Turkey
Phone: +90 312 586 74 21 E-mail: dumanfurkan74@gmail.com ORCID: orcid.org/0000-0002-7849-6806
Received/Geliş Tarihi: 09.02.2022 **Accepted/Kabul Tarihi:** 05.06.2022

Introduction

Multiple sclerosis (MS) is a chronic, autoimmune neurological disorder that causes deterioration in the central nervous system due to myelin damage (1,2). MS patients present with clinical findings such as changes in motor skills, body sensation and vision, spinal cord symptoms, psychiatric disorders, mental problems, and cognitive impairments. Approximately 40% to 70% of MS patients have impairments in attention, information processing, memory, and executive functions (EFs) (3,4).

There are contradictory or poorly explained findings in studies evaluating short-term memory (STM), working memory (WM) and EFs of patients with MS. While STM is responsible for storing a limited amount of information for a short time, WM is responsible for both storing and manipulating it (5). Span tasks that require forward retrieving of information are used in the evaluation of STM whereas information that needs to be reversed in the mind and retrieved backwards are processed by WM; thus those kind of span tests should be used for evaluating the WM (6). When STM is evaluated with WM tasks the aforementioned inconsistencies occur (4,7,8). Furthermore, STM and WM are evaluated using either verbal or non-verbal (visuo-spatial) information; as a result, STM and WM performances of patients with MS differ depending on the type of information used in these tasks (9,10,11). Also, some studies in the literature generalize their findings regarding verbal or non-verbal STM and WM performances of patients with MS leading to contradictory results (8,12). In addition, the results regarding which component of WM is impaired in patients with MS are also contradictory (13,14).

The results of specific cognitive functions under EFs are ascribed to all EFs, which is another explanation for the conflicting results in the literature (7). "Executive functions" are broad phrase encompassing a wide range of sophisticated cognitive abilities such as inhibition, set shifting, and perseveration (15). Neuropsychological tests used to assess EFs, on the other hand, may not include all of the complex cognitive abilities that make up EFs (16). Furthermore, despite the fact that certain neuropsychological tests evaluating EFs have identical names, there are various versions of these tests, and the differences in their scoring systems lead to various inconsistencies (10,17,18).

The aim of this study was to evaluate STM and WM capacities in patients with relapsing-remitting multiple sclerosis (RRMS) and healthy individuals using tests and tasks based on verbal and non-verbal information and to evaluate and compare EFs (perseveration, conceptualization, inhibition, and set shifting) using standard, valid, and reliable neuropsychological tests that were adapted to Turkish.

Materials and Methods

Subjects

The study included 37 patients with RRMS who were followed up at Ufuk University, Faculty of Medicine, Neurology Clinic and/or were members of the Ankara Branch of Multiple Sclerosis Association of Turkey. The inclusion criteria were; age >18 years, having at least five years of education, not having a physical and/or mental disability that would prevent subjects from performing the tests and tasks, not having any neurological and/or severe psychiatric disorder (such as schizophrenia) other than RRMS, and not having uncorrected visual and/or hearing impairment. Four patients with RRMS were excluded for not fulfilling the inclusion criteria. Thus, the RRMS group of the study consisted of 33 participants. The control group consisted of 26 healthy participants matched with RRMS patients in terms of age, gender, level of education and hand dominance.

Socio-demographic Characteristics and Assessment of Clinical Variables

The socio-demographic assessment form was used to register general health status information, physiological and socio-demographic characteristics of the participants. The Beck depression inventory (BDI) was used to assess the participants' depression levels. Reliability and validity study of the Turkish version of this test was conducted previously (19,20). Anxiety level was evaluated with the state/trait anxiety inventory (STAI) using a 4-point Likert-type scale, each consisting of 20 items and consisting of two subscales, the state anxiety inventory (SAI) and the trait anxiety inventory (TAI). Reliability and validity study of the Turkish version of STAI was conducted previously (21).

Assessment of Cognitive Functions

The visual aural digit span test B form (VADS-B) consists of four subtests in which verbal (AV) and written (AW) responses to aurally presented digit spans and also verbal (VV) and written (VW) responses to visually presented digit spans are evaluated. Eleven scores including 4 basic scores, 6 composite scores and 1 total score are calculated (22,23). In this study, the points of auditory stimulation (AS=AV+AW), visual stimulation (VS=VV+VW), verbal expression (VE=AV+VV) and written expression (WE=AW+VW) were calculated through VADS-B. The VADS-B was used to assess STM capacity based on verbal information.

Wisconsin card sorting test (WCST) consists of 4 stimulus and 128 response cards. This test assesses EFs by asking participants to match response cards to stimulus cards based on a variety of characteristics. In this study, EFs, perseverance and conceptualization skills were assessed with WCST. The validity and reliability study of its Turkish version was conducted (REF) (22).

The Backward digit span task (BDS) was developed in the tests and tasks used to assess WM (6). The material is scored similar to the VADS-B in BDS, however unlike VADS-B, participants must remember the presented digit spans in reverse order. In the current study, the scores of auditory stimulation (AS=AV+AW), visual stimulation (VS=VV+VW), verbal expression (VE=AV+VV) and written expression (WE=AW+VW) were calculated from the scores of through BDS. The BDS was used to assess the capacity of the phonological loop which is based on verbal knowledge in WM.

Although there are several variations of the Stroop task, this task focuses on the interference of pronouncing colors on reading colors (24). The stroop test TBAG form (stroop TBAG) was adapted to Turkish using the Victoria form as a model. This test is assessing EFs, attention, and information processing speed, and consists of five subtests totaling 15 points, including time, error, and correction score for each subtest (22,25,26). In this study, all stroop TBAG scores were measured. However, only the 5th part completion time score, which assesses blocking ability, was included in the analyses.

Wechsler Memory Scale: Revised form (WMS-R) assesses visual memory, verbal memory, instant and delayed recall, learning, attention and concentration; therefore, it is one of the most comprehensive tests for assessing memory (16,22,27). One of the subtests of WMS-R, visual memory span (WMS-R-WMS) subtest consists of two trials, forward and backward. During these trials, the tester first taps the squares in various spots on the cards, and then the participant is instructed to tap the same squares in turn. In the forward trial, the participants are asked to tap the presented squares in the same order, while in the backward trial, they are asked to tap the presented squares in reverse order. In the present study, the maximum amount of span recalled in the forward trial for the STM capacity based on non-verbal knowledge, and the maximum amount of span recalled in the backward trial for the visuo-spatial sketchpad capacity in the WM were assessed (28).

The trail making test (TMT) is a test that consists of two parts, A and B, and assesses EFs such as information speed, mental flexibility, planning and set shifting (29,30). The completion time of parts A and B, as well as the number of errors committed in these parts, are used to calculate the test scores. In the current study, the completion time of the A part (A time), the completion time of the B part (B time) and the difference between these times (B-A time) were assessed to measure the skill of set shifting.

Procedure

After ethical approval, (Ufuk University Faculty of Medicine Non-Interventional Clinical Research Evaluation Commission, ref: 20171101-2), data were collected. All participants gave a written informed consent form before study enrolment. Psychologists who were trained in conducting, scoring, and interpreting neuropsychological assessments implemented the tests. The tests were given in two separate sessions, each lasting 45 minutes. The socio-demographic form, BDI, STAI, VADS-B, and WCST were completed in the first session, whereas BDS, stroop TBAG, WMS-R/VMS, and TMT were implemented in the second session.

Statistical Analysis

SPSS 22.0 was used in data analysis. The t-test was used for intergroup comparisons of normally distributed quantitative data with independent samples; the Mann-Whitney U test was used for intergroup comparisons of non-normally distributed quantitative data with independent samples; and the chi-square test was used for intergroup comparisons of qualitative data with independent samples.

Results

There was no statistically significant difference between the RRMS and control groups in terms of confounding variables such as age, gender, level of education, and hand dominance, that might affect cognitive performance (Table 1). As a result, it was assumed that the groups were equivalent in terms of age, gender, education level and hand dominance. The mean BDI scores of the RRMS and control groups were 12.0±8.9 and 9.3±6.7, respectively. There was no statistically significant difference in BDI scores between the groups (U=345.000, Z=-1.112, p=0.266). The mean SAI subscale score was 31.8±9.4 and the mean TAI subscale score was 42.7±10.6 in the RRMS group. These scores were 30.6±6.8 and 40.7±7.6, respectively in the control group. There was no statistically significant difference between the groups in terms of the total scores obtained from the SAI and TAI subscales of the STAI (respectively, U=373,000, Z=-0.068, p=0.946, U=336,000, Z=-0.692, p=0.489). As a result, it was concluded that depression and anxiety had no confounding effect on cognitive function performance between the 2 groups (Table 2). Furthermore, patients' disease duration ranged from 5 to 468 months [mean: 140.97, standard deviation (SD): 117.14, median: 96.00], the amount of attacks ranged from 1 to 17 (mean: 5.15, SD: 4.70, median: 3.00), and disability scores ranged from 1 to 5 (mean: 2.21, SD: 1.19, median: 2).

The results of neuropsychological tests assessing STM, WM, and EFs were analyzed using the Mann-Whitney U test. There was a statistically significant difference between the RRMS and the control groups in terms of backward visual memory span calculated from WMS-R/VMS (U=240.000, Z=-2.549, p=0.011). The RRMS group's backward visual memory span (median: 4.5) was lower than the control group (median: 5.0). However, it was observed that the groups did not differ statistically from each other in terms of plain visual memory span calculated from WMS-R/VMS, VADS-B, WCST, BDS, stroop TBAG and TMT (Tables 3, 4, 5).

Table 1. Comparison of the RRMS and control groups in terms of control variables

		RRMS group	Control group	Statistical test	p
Age (mean ± SD)		41.24±10.84	41.15±12.71	t(57)=-0.029	0.977*
Gender	Female (n)	23 (69.7%)	19 (73.1%)	χ^2 (1)=0.081	0.776**
	Male (n)	10 (30.3%)	7 (26.9%)		
Level of education	Primary/secondary school (n)	4 (12.1%)	4 (15.4%)	χ^2 (2)=0.133	0.936**
	High school (n)	12 (36.4%)	9 (34.6%)		
	Collage and above (n)	17 (51.5%)	13 (50.0%)		
Hand dominance	Right (n)	31 (93.9%)	25 (96.2%)	χ^2 (2)=0.148	0.701**
	Left (n)	2 (6.1%)	1 (3.8%)		

*Independent samples t-test; **chi-square test, RRMS: Relapsing-remitting multiple sclerosis, SD: Standard deviation

Discussion

With verbal and non-verbal information-based neuropsychological tests and tasks, the presented study aimed to compare the STM and WM capacities of the RRMS group with the control group. We also aimed to compare the groups in terms of EFs such as perseveration, conceptualization, inhibition, and set shifting. Firstly, the backward visual memory span obtained from the WMS-R/VMS, where the visuo-spatial sketchpad was assessed, was found to be lower in patients with RRMS than in healthy. Furthermore, the scores obtained from the BDS, which assesses phonological loop, did not show a statistically significant difference between the 2 groups. In fact, while the notion that WM is impaired is widely emphasized in the literature, it is not known where the deterioration occurs; the phonological loop or the visuo-spatial sketchpad of WM (13,14,31,32). Our results support the notion that the visuo-spatial sketchpad is impaired in WM but they contradict the notion that only the phonological loop is impaired (7,8,11,13). However, there are also arguments that the impairment in the phonological loop in patients with MS is actually caused by the deterioration in articulatory rehearsal. This phenomenon is explained by the impairment in articulatory rehearsal caused by motor speech disorder (dysarthria) or slowing in information processing speed, which is common in MS (31). Although patients with MS and healthy controls did not differ in their performance on backward digit span tasks, MS patients

Table 2. Comparison of depression, state anxiety and trait anxiety scores of the RRMS and control groups with Mann-Whitney U test

	RRMS group Mean ± SD (median)	n	Control group Mean ± SD (median)	n	U	Z	p
BDI	12.08±8.94 (9.95)	32	9.34±6.78 (6.50)	26	345.000	-1.112	0.266
SAI	31.89±9.42 (29.00)	29	30.8-69±6.84 (29.16)	26	373.000	-0.068	0.946
TAI	42.79±10.67 (40.28)	29	48.78±7.61 (42.08)	26	336.000	-0.692	0.489

BDI: Beck depression inventory total score, SAI: State/trait anxiety inventory state anxiety subtest total score, TAI: State/trait anxiety inventory trait anxiety subtest total score, RRMS: Relapsing-remitting multiple sclerosis, SD: Standard deviation

Table 3. Comparison of STM capacities of the RRMS and control groups with Mann-Whitney U test

	RRMS group Mean ± SD (median)	n	Control group Mean ± SD (median)	n	U	Z	p	r
VADS-B								
Auditory stimulation	10.27±1.94 (10.00)	33	11.31±2.53 (11.00)	26	331.500	-1.503	0.133	-0.20
Visual stimulation	11.00±2.88 (11.00)	32	11.77±3.08 (11.00)	26	373.500	-0.670	0.503	-0.09
Verbal expression	10.56±2.39 (11.00)	32	11.27±2.60 (11.00)	26	364.000	-0.822	0.411	-0.11
Written expression	10.66±2.29 (10.00)	32	11.77±2.92 (12.00)	26	330.500	-1.348	0.178	-0.18
WMS-R/VMS								
Forward visual memory span	5.30±1.21 (5.00)	30	5.85±1.19 (6.00)	26	287.000	-1.752	0.080	-0.23

VADS-B: Visual aural digit span test B form, WMS-R/VMS: Wechsler memory scale: Revised form visual memory span subtest, RRMS: Relapsing-remitting multiple sclerosis, SD: Standard deviation, STM: Short-term memory

Table 4. Comparison of WM capacities of the RRMS and control groups with Mann-Whitney U test

	RRMS group Mean ± SD (median)	n	Control group Mean ± SD (median)	n	U	Z	p	r
BDS								
Auditory stimulation	8.61±2.17 (9.00)	31	9.62±2.93 (9.00)	26	330.500	-1.174	0.241	-0.16
Visual stimulation	10.73±3.11 (10.50)	30	11.42±2.97 (11.00)	26	336.500	-0.892	0.372	-0.12
Verbal expression	9.70±2.36 (9.50)	30	10.31±3.28 (10.00)	26	335.500	-0.903	0.367	-0.12
Written expression	9.63±2.76 (10.00)	30	10.23±3.20 (10.00)	26	336.000	-0.895	0.371	-0.12
WMS-R/VMS								
Backward visual memory span	4.67±1.12 (4.50)	30	5.54±1.21 (5.00)	26	240.000	-2.549	0.011*	-0.34

*p<0.05; BDS: Backward digit span task, WMS-R/VMS: Wechsler memory scale: Revised form visual memory span subtest, RRMS: Relapsing-remitting multiple sclerosis, SD: Standard deviation

Table 5. Comparison of executive functions of the RRMS and control groups with Mann-Whitney U test

	RRMS group Mean ± SD (median)	n	Control group Mean ± SD (median)	n	U	Z	p	r
WCST								
WCST4	4.17±2.00 (4.50)	30	4.96±1.46 (9.00)	25	292.500	-1.503	0.133	-0.20
WCST5	24.63±23.5 (21.50)	30	18.96±13.08 (17.00)	25	340.000	-0.592	0.554	-0.08
WCST6	22.07±18.40 (21.50)	30	17.52±11.52 (17.00)	25	327.000	-0.812	0.417	-0.11
WCST7	18.40±12.11 (17.50)	30	15.96±11.75 (13.00)	25	320.000	-0.930	0.352	-0.12
WCST8	18.41±13.59 (16.80)	30	14.93±7.78 (13.28)	25	345.500	-0.499	0.618	-0.07
WCST10	57.37±15.95 (60.00)	30	60.28±10.65 (61.00)	25	309.500	-1.112	0.266	-0.15
WCST11	54.77±15.95 (52.74)	30	61.70±19.36 (64.17)	25	298.000	-1.302	0.193	-0.18
WCST12	1.44±2.18 (1.00)	29	0.96±1.27 (1.00)	25	346.500	-0.296	0.767	-0.04
Stroop TBAG								
5th part completion time (sec)	24.18±2.18 (22.50)	28	23.96±8.00 (22.50)	26	358.500	-0.095	0.924	-0.01
TMT								
A time (sec)	37.32±20.59 (30.50)	28	29.50±13.20 (26.00)	26	262.500	-1.759	0.079	-0.24
B time (sec)	117.28±99.96 (94.00)	25	88.27±51.76 (69.00)	26	253.500	-1.348	0.178	-0.19
B-A time (sec)	79.20±84.01 (59.00)	25	58.38±42.63 (41.00)	26	275.500	-0.933	0.351	-0.13

WCST: Wisconsin card sorting test, WCST4: Completed category amount, WCST5: Total perseverative response amount, WCST6: Total perseverative error amount, WCST7: Total non-perseverative error amount, WCST8: Perseverative error percentage, WCST10: Conceptual response amount, WCST11: Conceptual response percentage, WCST12: Failure of set maintenance, Stroop TBAG: Stroop test TBAG form; TMT: Trail making test, RRMS: Relapsing-remitting multiple sclerosis, SD: Standard deviation

had lower scores on word span tasks that evaluated articulatory rehearsal (11). This result support the aforementioned phenomenon (11). This result support the aforementioned phenomenon (11). In the current study, while the amount of information stored by patients with RRMS decreased during the processing and storage of non-verbal information, the amount of information stored by them did not decrease when performing the same tasks with verbal information. On the other hand, it should not be ignored that the backward visual memory span obtained from the WMS-R/VMS, based on non-verbal information, might be more complex and difficult than the BDS, which is based on verbal information. Therefore, it should be kept in mind that the comparison between the components of the phonological loop and the visuo-spatial sketchpad may not yield healthy results owing to the difficulty in adjusting the complexity of the tests evaluating components according to modalities (33).

When the scores from VADS-B, which is assessing STM based on verbal knowledge, and the plain visual memory span obtained from WMS-R/VMS, which is assessing STM based on non-verbal knowledge, were compared, there was no statistically significant difference between the groups' STM performances. The current study's results on STM based on verbal knowledge are consistent with results from related reports in the literature (34,35). However, other results in studies evaluating STM, which includes non-verbal knowledge, suggest a decrease in capacity (8,11). Therefore, our results regarding STM contradict the literature. According to Rao (36), STM performance of patients with MS is not directly impaired; instead, the decrease in STM performance is caused by the ineffective use of retrieval strategies. Baseline assessments in follow-up studies also demonstrate that verbal and non-verbal STM capacities of patients with MS are equal to healthy controls (9,10). Results of the current study also show that the STM capacity of patients with RRMS are intact.

The results of STM and WM tests were evaluated holistically and it was found that the STM and phonological loop capacities of patients with RRMS did not differ from the control group. However, their visuo-spatial sketchpad capacities were lower than those of the control group. This result may be due to the fact that WM is more affected in MS than STM (37). In addition, although there was no difference between groups in non-verbal knowledge based STM in the current study, the difference found in visuo-spatial sketchpad supported the argument that STM and WM are different structures. The differences between the current study and some other studies in the literature may be due to the fact that these previous studies did not separate STM and WM commendably; in these studies, WM tasks are used to evaluate STM and vice versa. For example; erroneously, the forward digit span task is used to evaluate the phonological loop, the BDS is used to evaluate STM, and the forward tapping of Corsi Block is used to evaluate visuo-spatial sketchpad (8,11,14). Instead, forward digit span tasks should be used to evaluate verbal STM, BDS should be used to evaluate phonological loop, the forward tapping of Corsi Block should be used to evaluate non-verbal STM, and the backward tapping of Corsi Block should be used to evaluate non-verbal visuo-spatial sketchpad.

EFs are commonly impaired in MS (17,38). The WCST was used to assess perseveration, one of the EFs, and no statistically significant differences were identified between the groups.

Accordingly, it appears that RRMS does not increase perseveration. These results appear to be inconsistent with the literature (4,17). This discrepancy may be due to the subgroup of MS we have examined in this study, because perseveration is influenced by the subtype of MS (17).

Another EF assessed with the WCST is the conceptualization skill. It was shown to be similar in both groups in the presented study; conceptualizing abilities of the patients with RRMS were intact. Our results regarding the conceptualization skills also contradict with the literature (18,39). This inconsistency may be related to the inability of patients with RRMS to complete the task. Because some participants underperformed and failed to score any points, they were excluded from WCST intergroup comparisons. This may have led to our inability to interpret the effect of RRMS on conceptualization and perseveration.

The ability of inhibition, one of the EFs, was assessed using the stroop TBAG 5th part completion time score, and no statistically significant difference was observed between the 2 groups. Our results did not indicate any evidence suggesting a decrease in inhibition skill of patients with RRMS. However, there are differences between the results in the literature about the inhibition skill of patients with MS. In some studies, it has been reported that inhibition skill of patients with MS is worse than that of healthy individuals; in others, no difference is found (18,35,40,41). This disagreement with the literature might be caused by the insufficient balance in terms of level of education of the participants in the presented study. Due to the difficulty in finding patients with RRMS, the study sample largely consisted of participants with a middle or higher education level. Therefore the discrepancy with the literature might be the result of a protective effect of higher level of education on cognitive functions of the MS participants of the presented study (7,35).

In the presented study, the groups did not differ in terms of TMT B time and TMT B-A time. In other words, regardless of motor speed, there was no impairment in set shifting skills in the RRMS group. Other studies reported that patients with MS are slower in trail making tasks and have lower set shifting skills than healthy individuals (18,40). In this context, our results contradict the literature but in our opinion, other authors' explanations for this disparity are not clear enough. It is assumed that the poor performance of patients with MS in the trail making task is related to a decrease in their processing speed rather than an impairment in their set shifting skills (42). Another explanation for this situation may be that, as mentioned above, higher education level may have a protective effect on the cognitive functions of patients with RRMS.

While verbal information is assessed in the studies on STM and WM in MS, the number of studies assessing both forms of information is very limited. To our knowledge, there are no studies assessing both STM and WM with verbal and non-verbal components conducted in Turkey. In this context, the current study differs from other national studies and makes an important contribution to the literature.

Study Limitations

The present study also has some limitations. The low sample size is one of its limitations. The inclusion of solely patients with RRMS is a restriction in terms of the generalizability of the results. Another limitation of the study is the inability to control the impact of clinical characteristics of patients with MS on their cognitive functions, such as disease duration, number of attacks, medications used, and disability levels. The lack of validity, reliability and standardization of the BDS, which was designed to be used in the evaluation of the phonological loop capacity in WM, is another limitation of the current study.

Conclusion

In conclusion, patients with RRMS show lower visuo-spatial sketchpad capacity in WM but do not have lower phonological loop capacity. Furthermore, STM capacity based on both verbal and non-verbal information, and EFs including perseveration, conceptualization, inhibition, and set shifting skills are intact in patients with RRMS. These results suggest that while evaluating STM and WM in patients with MS, the type of information or modality must be taken into account. Then again putative differences depending on the modality is ignored in the evaluation of the cognitive functions of patients with RRMS in the literature. In addition, STM and WM, which are different functions, are used interchangeably in the literature, and the results related to some of the EF components are generalized to all cognitive skills under these umbrella terms leading to a confusion in interpretation of study results. The same type of conceptual ambiguity may be found in the selection of tests to be used in neuropsychological assessment. Also, the use of different versions of neuropsychological tests contributes to the ambiguity in the literature. Adopting an interdisciplinary approach in studies assessing cognitive functions in patients with MS and evaluating and interpreting the results of the study with a neuropsychologist may be considered as a valid method to pursue for preventing such imprecisions. Also, using validated and reliable neuropsychological tests with norm values determined for the Turkish society may help in solving this problem for Turkish studies. Hopefully, new rehabilitation approaches based on a better understanding of the cognitive functions impaired in MS will help patients with MS and their caregivers retain their quality of life.

Ethics

Ethics Committee Approval: Ufuk University Faculty of Medicine Non-Interventional Clinical Research Evaluation Commission (approval number: 20171101-2).

Informed Consent: All participants signed the informed consent forms.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.D., H.C., Design: F.D., H.C., A.L., Data Collection or Processing: F.D., A.L., Analysis or Interpretation: F.D., H.C., A.L., Literature Search: F.D., H.C., A.L., Writing: F.D., H.C., A.L.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Fazzito MM, Jordy SS, Tilbery CP. Psychiatric disorders in multiple sclerosis patients. Arq Neuropsiquiatr 2009;67:664-667.
2. Kornek B, Lassmann H. Neuropathology of multiple sclerosis-new concepts. Brain Res Bull 2003;61:321-326.

3. Donmez Keklikoglu H, Yoldas TK, Zengin O, Solak EB, Keskin S. Cognitive impairment in patients with early relapsing-remitting multiple sclerosis. Noro Psikiyatr Ars 2010;47:88-90.
4. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology 1991;41:685-691.
5. Diamond A. Executive functions. Annu Rev Psychol 2013;64:135-168.
6. Lezak MD. Neuropsychological Assessment. 3rd ed. New York: Oxford University Press, 1995.
7. Aksoy S, Timer E, Mumcu S, et al. Screening for cognitive impairment in multiple sclerosis with MOCA test. Turk J Neurol 2013;19:52-55.
8. Kouvatsou Z, Masoura E, Kiosseoglou G, Kimiskidis VK. Working memory profiles of patients with multiple sclerosis: Where does the impairment lie? J Clin Exp Neuropsychol 2019;41:832-844.
9. Bergendal G, Fredrikson S, Almkvist O. Selective decline in information processing in subgroups of multiple sclerosis: an 8-year longitudinal study. Eur Neurol 2007;57:193-202.
10. Kuscu DY, Kandemir M, Unal A, Topcular B, Kirbas D. Longitudinal study of cognitive impairment in multiple sclerosis: a 5-year follow-up. Noro Psikiyatr Ars 2012;49:29-32.
11. Nathalie E, Diana O, Amaya S, et al. Short-term memory impairment sparing the central executive in relapsing-remitting multiple sclerosis? J Neurol Neurophysiol 2014;5:3.
12. Yılmaz T. Evaluation of visual evoked potentials and cognitive iŚmpairment in relapsing-remitting multiple sclerosis patients (Specialization Thesis in Medicine). Erzurum: Atatürk University; 2013.
13. Foong J, Rozewicz L, Quaghebeur G, et al. Executive function in multiple sclerosis. The role of frontal lobe pathology. Brain 1997;120:15-26.
14. Grigsby J, Ayarbe SD, Kravcisin N, Busenbark D. Working memory impairment among persons with chronic progressive multiple sclerosis. J Neurol 1994;241:125-131.
15. Miyake A, Friedman NP. The nature and organization of individual differences in executive functions: four general conclusions. Curr Dir Psychol Sci 2012;21:8-14.
16. Öktem Ö. Nöropsikolojik testler ve nöropsikolojik değerlendirme. Turkish Journal of Psychology 1994;9:33-44.
17. Parmenter BA, Zivadinov R, Kerenyi L, et al. Validity of the Wisconsin card sorting and Delis-Kaplan executive function system (DKEFS) sorting tests in multiple sclerosis. J Clin Exp Neuropsychol 2007;29:215-223.
18. Till C, Ho C, Dudani A, et al. Magnetic resonance imaging predictors of executive functioning in patients with pediatric-onset multiple sclerosis. Arch Clin Neuropsychol 2012;27:495-509.
19. Hisli N. Beck depresyon envanterinin geçerliği üzerine bir çalışma. Turkish Journal of Psychology 1988;6:188-126.
20. Hisli N. Beck depresyon envanterinin üniversite öğrencileri için geçerliği, güvenirliği. Turkish Journal of Psychology 1989;7:3-13.
21. Öner N. Türkiye'de Kullanılan Psikolojik Testlerden Örnekler: Bir Başvuru Kaynağı. 7th ed. İstanbul: Boğaziçi Üniversitesi Yayınevi, 2012.
22. Karakaş S, Erdoğan-Bakar E, Doğutepe-Dinçer E. Nöropsikolojik Testlerin Yetişkinler İçin Araştırma ve Geliştirme Çalışmaları Bilnot-Yetişkin. 3rd ed. Konya: Eğitim Yayınevi, 2013.
23. Karakaş S, Yalın A. Görsel İşitsel Sayı Dizileri Testi B Formu Kullanım Kılavuzu. Ankara: Eryılmaz Ofset Matbaacılık Gazetecilik, 2009.
24. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935;18:643-662.
25. Karakaş S, Erdoğan E, Sak L, et al. Stroop Test TBAG Form: Standardisation for Turkish culture, reliability and validity. Turkish Journal of Clinical Psychiatry 1999;2:75-88.
26. Karakaş S, Irak M, Kurt M, Erzengin ÖU. Wisconsin card sorting test and stroop test TBAG version: comparative analysis of the measured properties. 3P Dergisi 1999;7:179-192.
27. Karakaş S, Kafadar, H, Eski R. Wechsler bellek ölçeği geliştirilmiş formunun test-tekrar test güvenirliği. Turkish Journal of Psychology 1996;11:46-52.
28. Pirkola T, Tuulio-Henriksson A, Glahn D, et al. Spatial working memory function in twins with schizophrenia and bipolar disorder. Biol Psychiatry 2005;58:930-936.
29. Cangöz B, Karakoç E, Selekler K. Standardization study of "Trail Making Test" for Turkish adults and elderly people (ages 50 and over). Turk Geriatri Derg 2007;10:73-82.
30. Strauss E, Sherman EMS, Spreen O. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. 3rd ed. New York: Oxford University Press, 2006.
31. Rao SM, Grafman J, DiGiulio D, et al. Memory dysfunction in multiple sclerosis: Its relation to working memory, semantic encoding, and implicit learning. Neuropsychology 1993;7:364-374.
32. Ruchkin DS, Grafman J, Krauss GL, et al. Event-related brain potential evidence for a verbal working memory deficit in multiple sclerosis. Brain 1994;117:289-305.
33. Diamond BJ, DeLuca J, Kim H, Kelley SM. The question of disproportionate impairments in visual and auditory information processing in multiple sclerosis. J Clin Exp Neuropsychol 1997;19:34-42.
34. Rao SM, Leo GJ, St Aubin-Faubert P. On the nature of memory disturbance in multiple sclerosis. J Clin Exp Neuropsychol 1989;11:699-712.
35. Doğan M. Multipl sklerozda kognitif etkilenmenin değerlendirilmesi (Specialization Thesis in Medicine). Isparta: Süleyman Demirel University; 2012.
36. Rao SM. Neuropsychology of multiple sclerosis: a critical review. J Clin Exp Neuropsychol 1986;8:503-542.
37. Thornton AE, Raz N. Memory impairment in multiple sclerosis: a quantitative review. Neuropsychology 1997;11:357-366.
38. Ruano L, Portaccio E, Goretti B, et al. Age and disability drive cognitive impairment in multiple sclerosis across disease subtypes. Mult Scler 2017;23:1258-1267.
39. Beatty WW, Monson N. Problem solving by patients with multiple sclerosis: comparison of performance on the Wisconsin and California Card Sorting Tests. J Int Neuropsychol Soc 1996;2:134-140.
40. Drew M, Tippett LJ, Starkey NJ, Isler RB. Executive dysfunction and cognitive impairment in a large community-based sample with Multiple Sclerosis from New Zealand: a descriptive study. Arch Clin Neuropsychol 2008;23:1-19.
41. Macniven JA, Davis C, Ho MY, et al. Stroop performance in multiple sclerosis: information processing, selective attention, or executive functioning? J Int Neuropsychol Soc 2008;14:805-814.
42. Leavitt VM, Wylie G, Krch D, et al. Does slowed processing speed account for executive deficits in multiple sclerosis? Evidence from neuropsychological performance and structural neuroimaging. Rehabil Psychol 2014;59:422-428.