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RESEARCH ARTICLE

Effect of Telerehabilitation on Verbal and Visual Memory in Multiple Sclerosis Patients: A 12-month Follow-up Study

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Abstract

Objective: Conditions such as chronic fatigue or physical disability, particularly regular work, limit the treatment options that require continuous participation in multiple sclerosis (MS) patients. The pandemic period highlighted the importance of home health services and increased interest in the current cognitive telerehabilitation (TR) applications. This study aims to determine the short and long-term effects of TR and the factors that influence it.

Materials and Methods: This study included 61 MS patients. During 6 months, 32 patients (mean age =41.21±11.57; females =23 and males =9) received structured TR, and 29 patients (mean age =37.62±6.95; females =20 and males =9) received unstructured mental exercises. After the 6-month intervention period, another evaluation was conducted at the end of the 6-month silent period to evaluate the protective effect of the exercises. The participants were administered with Rao's Brief Repeatable Battery of neuropsychological tests at the beginning of the study and at the 6th and 12th months. The repeated measures analysis of variance was used to evaluate performance changes over time, and the repeated measures ANCOVA test was used to assess the factors affecting these changes.

Results: On average, most participants (59.4%) used the TR application for less than 4 h each week. TR and unstructured exercises positively affected Spatial Recall Test-Total Learning/Con and Paced Auditory Serial Addition Test performances, and the total number of relapses affected these results. The total verbal learning Selective Reminding Test-Total Learning (SRT-TL), long-term storage (SRT-LTS), and delayed recall (SRT-DR) skills of all participants decreased at the end of the silent period. The factors affecting this deterioration are the duration of the disease, the total number of relapses, and the age of onset of the disease.

Conclusion: Our findings showed that TR and unstructured exercises had no differential effect on cognitive performance. In addition, the decrease in verbal memory performances in the silent period showed that the age of onset of the disease and the total number of relapses could be important evaluation criteria for cognitive involvement.

Keywords: Follow-up, multiple sclerosis, telerehabilitation, verbal memory, visual memory

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, degenerative disease of the central nervous system that causes demyelination and axonal transection (1). It is most often diagnosed in the early stages of life (between the ages of 20 and 30), and 20% of patients develop into the progressive phase of increased physical disability within an average of 15 years (2). In addition, approximately 50-60% of patients experience cognitive decline (3), which negatively affects many aspects of everyday life, including the ability to participate in society and maintain employment (4,5). Although there are several pharmacological treatment options for treating or reducing sensory and motor symptoms, there is no such method for treating cognitive impairments (6).

Telerehabilitation (TR) is the provision of therapy and rehabilitation services using various telecommunication mediums, most notably the Internet and computer networks. TR has the potential to reduce time and money and increase access and treatment adherence in groups with high or increasing disability (7,8). The advantages of TR include providing therapy

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to rural areas, expanding rehabilitation opportunities with computer-assisted systems, indirectly increasing the quality of life, and reducing medical expenses and travel time (9). According to Kairy et al., (10), a meta-analysis of the effects of TR on 28 studies, clinical outcomes after the intervention were typically positive, and clinical processes, such as participation and compliance, continued uninterrupted. In addition, it was observed that the consultation period was longer, but the satisfaction remained high and was also cost-effective.

Physical, neurogenic, or cognitive disorders, such as motor weakness, spasticity, ataxia, fatigue, and amnesia, are common in MS patients. Long-term multidisciplinary management is recommended for MS patients due to the cumulative effects of these symptoms (11,12). Patients often lack access to MS management advances due to limited mobility, fatigue, and high travel costs. TR is viewed as a potential tool for improving health services by reducing care costs (13). This study aims to evaluate the effects of a structured rehabilitation application that has been shown to affect a specific population in the MS clinic (14) when used remotely on cognitive functions. The study also evaluated the potential protective effect of TR at the end of the non-intervention (silent) period.

Materials and Methods

University of Health Sciences Turkey, Hamidiye Clinical Research Ethics Committee approved the study protocol (approval number: 20-60, date: 28.09.2020). All participants provided their written consent after being fully informed.

Participants

The study included 61 patients with MS according to McDonald's criteria (15). The ages of these participants were between 23 and 65 years, the disease duration ranged from 2 to 38 years, and their EDSS score ranged from 1 to 5.5. In addition, the age of onset of the disease varies between 10 and 55. The study included participants who were at least primary school graduates, actively using mobile devices, had no relapse in the last 3 months, or had not received corticosteroid treatment in the previous 1 month. Symbol Digit Modalities Test (SDMT) (<37.25±12.98) and PASAT (<34.51±12.47) scores were used to identify MS patients with cognitive impairment (16).

Neuropsychological Assessment

Rao's Brief Repeatable Battery of neuropsychological tests (BRB-N) (17) was used to evaluate the changes in the cognitive profiles of the participants at the beginning of the TR application and at the sixth and 12th months. The BRB-N consists of five subtests: the Selective Reminding Test (SRT), which measures immediate (SRT-IML) and total learning (SRT-TL), delayed recall (SRT-DR), long-term storage (SRT-LTS), and controlled retrieval (SRT-CLTR) skills. 10/36 Spatial Recall Test measures immediate (SPART-IML) and total learning (SPART-TL), delayed recall (SPART-DR), and confabulations (SPART-TL/Con and SPART-DR/Con). The SDMT, which measures the speed of information processing, and the Paced Auditory Serial Addition Test (PASAT 3"), which measures attention and multitasking abilities. Finally, the Controlled Oral Word Association Test (COWAT) assesses verbal fluency categorically (COWAT-Animal) and lexically (COWAT-KAS). In addition to this battery, the Stroop test was used to evaluate participants' interference abilities (STROOP D), and the Beck Depression Inventory (BDI) was used to evaluate their mood.

Telerehabilitation Application and Intervention Protocols

In the study, the participants were divided into two groups - telerehabilitation intervention group (TR) and unstructured intervention group (nTR) - and two periods - intervention period and silent period. During the intervention period, 32 patients were given NOROSOFT, and 29 patients were given a home-based task. The NOROSOFT program was used for the TR application. The protocol has been described in a previous study (14). In addition to the protocol, the weekly usage times of the participants in the current study were determined using the interface of the NOROSOFT application. Moreover, the control group received no TR and was required to solve SUDOKU for at least 1 h a day for 6 months. However, the exercise frequency of the control group was not included in the research data because it was based only on their verbal statements.

Statistical Analysis

The SPSS program (Version 24.0, IBM Corp., Armonk, New York) was used to analyze the obtained data. Kolmogorov-Smirnov test was used to evaluate whether the data fit the normal distribution. Parametric tests were used because the data were normally distributed (p>0.05). The data are presented as percentage, mean, and standard deviation. The study used the repeated measures analysis of variance (ANOVA) method to understand the change in cognitive performance in intervention and the silent period. Repeated measures ANCOVA test was used to understand the effect of numerical variables on cognitive performances that changed during the intervention and silent periods. P-values of less than 0.05 were considered as significant.

Results

Demographic Features

The nominal and ordinal demographic characteristics of 61 participants with TR and without TR (nTR) are shown in Table 1. Although the independent sample t-test results were insignificant (p>0.05), the mean age of the TR group was 41.21±11.57, and the mean age of the nTR group was 37.62±6.95. The duration of disease in the TR group was 11.46±8.28, the age at onset of disease was 29.71±10.11, and the mean total relapse number was 6.96±4.41, whereas the

duration of disease in the nTR group was 9.68±5.06, the age of onset was 27.93±6.67, and the mean total number of relapses was 5.20±2.48. The weekly duration of the patients participating in the TR application ranges from 0.3 to 7 days. On average, the weekly attendance was 1.88±2.44 days.

In the present study, the distribution of factors, such as education level, disease progression, and depression level, which are known to affect cognitive performance, was evaluated between the TR and nTR groups. However, neither education level, disease progression, nor depression levels were shown to be significantly different across the groups (p>0.05).

The Effects of The Intervention Period on Cognitive Performance: Possible Benefits

Changes in neuropsychological tests administered to the patients before and 6 months after the application were evaluated with repeated measures ANOVA. Accordingly, there was no significant change in verbal and visual immediate learning (SRT-IML and SPART-IML), total learning (SRT-TL and SPART-TL), delayed recall (SRT-DR and SPART-DR), verbal long-term storage (SRT-LTS) and retrieval (SRT-CLTR) abilities (Table 2). In addition, when the errors made in total visual learning (SPART-TL/Con) were evaluated, a significant improvement was found within 6 months [F(1, 59)=4,713, p=0.034]. There was a decrease in errors made during visual learning in both groups. Table 2 shows that this significant change was at the trend level between the groups [F(1, 59)=3,660, p=0.061; Figure 1].

When the effect of the exercises performed for 6 months was evaluated on working memory and ability to maintain attention (PASAT 3"), a significant improvement was observed [F(1, 59)=21,202, p=0.000). However, as seen in Table 2, this

Table 1. Demographic features of patients

n		TR		nTR	
		%	n	%	
Sex	Female	23	71.9	20	69.0
	Male	9	28.1	9	31.0
Education	Primary	8	25.0	8	27.6
	Secondary	0	0.0	2	6.9
	High	7	21.9	9	31.0
	Undergraduate	16	50.0	8	27.6
	Graduate	1	3.1	2	6.9
MS type	RRMS	26	81.3	24	82.8
	SPMS	5	15.6	4	13.8
	CIS	1	3.1	1	3.4
Duration of TR usage (hr/weekly)	<4	19	59.4		
	≥4	13	40.6		

TR: Telerehabilitation intervention, nTR: No telerehabilitation intervention, RRMS: Relapsing-remitting multiple sclerosis, SPMS: Secondary progressive multiple sclerosis, CIS: Clinically isolated syndrome

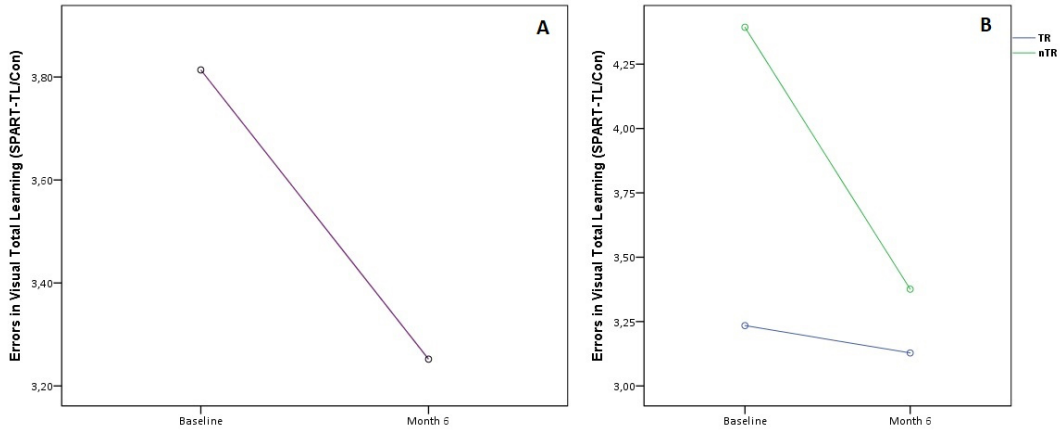

Figure 1. Change in 10/36 SPART-TL confabulation scores after the intervention period. (a) Within-subject effect: repeated measures ANOVA results of score change before splitting in the telerehabilitation (TR) and unstructured exercise (nTR) groups. (b) Between-subject effect: repeated measures ANOVA results of previous score change dividing those in the telerehabilitation (TR) and unstructured exercise (nTR) groups

significant change was not observed between the groups [F(1, 59)=1,078, p=0.303; Figure 2].

In addition, it was observed that information processing speed, categorical and lexical verbal fluency, or interference skills did not change significantly within the 6 months or between the groups (p>0.05, Table 2).

Factors Affecting Cognitive Improvement After the Intervention Period

SPART-TL/Con and PASAT 3" scores were evaluated with repeated measures of the ANCOVA test. According to these results, it can be said that the total number of relapses of the patients [F(1, 55)=6.257, p=0.015) is effective on the errors made in total

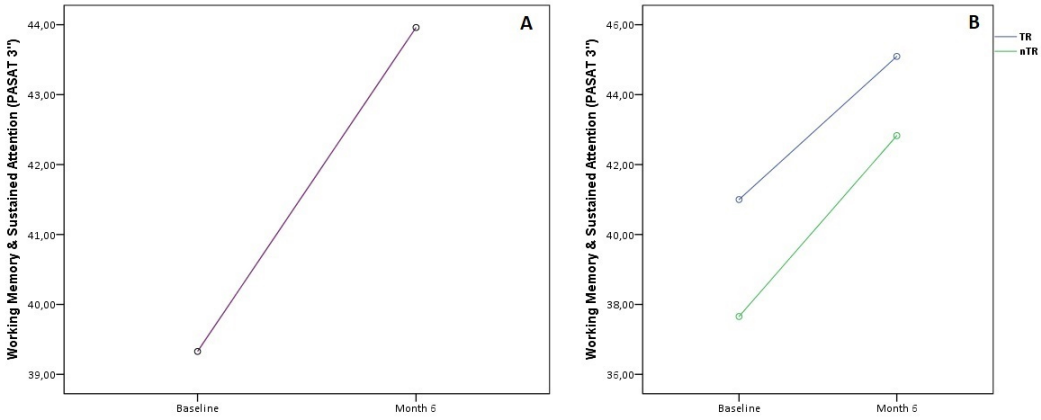

Figure 2. Change in PASAT 3" scores after the intervention period. (a) Within-subject effect: repeated measures ANOVA results of score change before splitting in the telerehabilitation (TR) and unstructured exercise (nTR) groups. (b) Between-subject effect: repeated measures ANOVA results of previous score change dividing those in the telerehabilitation (TR) and unstructured exercise (nTR) groups

Table 2. The effects of the ıntervention period (baseline to month 6)

	TR (n=32)		nTR (n=29)		p**	F***	p***
	Baseline*	Month 6	Baseline	Month 6			
SRT-IML	4.75±1.29	5.34±1.51	5.72±1.50	4.96±1.20	0.660	0.963	0.330
SRT-TL	7.73±1.46	7.92±1.47	7.95±1.20	7.83±1.18	0.848	0.055	0.816
SRT-LTS	38.21±12.84	38.90±14.18	36.44±11.66	39.37±11.29	0.329	0.060	0.808
SRT-CLTR	28.93±12.94	29.00±16.22	25.82±10.35	28.44±12.99	0.454	0.391	0.534
SRT-Int	0.43±1.01	0.43±0.80	0.17±0.46	0.31±0.84	0.636	1,710	0.196
SRT-DR	7.56±2.72	7.46±2.79	6.75±2.42	7.34±2.36	0.360	0.580	0.449
SPART-IML	3.75±1.60	3.71±1.59	4.27±1.99	3.72±2.15	0.327	0.519	0.474
SPART-TL	4.54±1.44	4.80±1.53	5.20±1.55	4.67±1.58	0.567	0.712	0.402
SPART-TL/Con	3.23±1.93	3.12±1.61	4.39±1.36	3.37±2.01	0.034	3,660	0.061
SPART-DR	4.43±1.72	4.93±1.88	5.17±2.61	4.17±2.31	0.483	0.001	0.972
SPART-DR/Con	4.03±2.68	3.59±2.06	4.31±2.31	4.48±3.08	0.720	1,159	0.286
PASAT 3"	41.00±10.57	45.09±10.33	37.65±12.27	42.82±11.84	0.000	1,078	0.303
SDMT	35.65±14.02	37.62±14.78	37.62±13.02	34.75±12.15	0.578	0.018	0.895
COWAT-Animal	20.81±4.66	22.46±5.17	22.31±4.01	20.37±5.22	0.840	0.083	0.775
COWAT-KAS	31.96±14.35	37.43±15.22	32.72±14.44	31.86±13.19	0.055	0.478	0.492
COWAT-Total	53.09±16.86	59.28±18.49	54.34±18.00	52.93±17.14	0.090	0.351	0.556
STROOP D	45.55±30.48	41.86±25.43	47.20±28.30	56.74±38.22	0.327	1,269	0.264
BDI	11.25±9.72	10.62±9.24	12.68±6.86	11.13±6.25	0.254	0.268	0.607

TR: Telerehabilitation intervention, nTR: No telerehabilitation intervention, *mean ± standart deviation, **p-value of within-subjects effect, ***F and p-value of between subject effect, SRT-IML: Selective reminding test-immediate learning, SRT-TL: Selective reminding test-total learning, SRT-LTS: Selective reminding test-long term storage, SRT-CLTR: Selective reminding test-controlled long term retrieval, SRT-Int: Selective reminding test-intrusion, SRT-DR: Selective reminding test-delayed recall, SPART-IML: Spatial recall test-immediate learning, SPART-TL: Spatial recall test-total learning, SPART-TL/Con: Spatial Recall test-total learning confabulations, SPART-DR: Spatial recall test-delayed recall, SPART-DR/Con: Spatial Recall test-delayed recall confabulations, PASAT: Paced auditory serial addition test, SDMT: Symbol digit modalities test, COWAT: Controlled oral word association test, BDI: Beck depression inventory

visual learning (SPART-TL/Con). Age, duration of disease, and age of onset of disease did not have any effect on this change. None of these covariates affected the improvement in working memory and ability to maintain attention (PASAT 3", p>0.05).

Effects of the Silent Period on Cognitive Performance: Possible Protective Effect

Positive or negative cognitive differences after TR or exercise were evaluated with repeated measures ANOVA. Accordingly, no changes were observed in visual immediate learning (SPART-IML), total learning (SPART-TL), delayed recall (SPART-DR), errors in total learning and delayed recall (SPART-TL/Con and SPART-DR/Con), maintaining attention (PASAT 3"), information processing (SDMT), verbal fluency (COWAT), interference (STROOP D), or mood (BDI) (p>0.05). However, when verbal total learning (SRT-TL; F(1, 59)=4,860, p=0.031), long-term storage [SRT-LTS; F(1, 59)=9.37, p=0.003], retrieval [SRT-CLTR; F(1, 59)=8,576, p=0.005], and delayed recall [F(1, 59)=3,947, p=0.052] skills were evaluated, significant deterioration were observed in both groups. As shown in Table 3, it can be said that the verbal learning and recording capacities of both the TR group and the nTR group were not preserved after the 6-month exercise period.

Factors Affecting Cognitive Deterioration After a Silent Period

The factors affecting the performance decline of the patients at the end of the silent period were evaluated with the repeated measures ANCOVA test. Accordingly, it was observed that patients' age [F(1, 55)=3,943, p=0.052] and a total number of relapses [F(1, 55)=5.269, p=0.026) affected the decrease in long-term verbal storage. In addition, disease duration [F(1, 55)=3,943, p=0.052), age of disease onset [F(1, 55)=4,079, p=0.048), and patient's age [F(1, 55)=4,145, p=0.047) were found to be effective on delayed recall of verbal information (Figure 3).

Discussion

The present study showed that TR and unstructured mental exercises had no differential effect on cognitive performance at the end of the 6-month intervention period. At the end of this period, it was observed that the patient's capacity to maintain attention (PASAT 3") increased and the errors made while scanning visual information (SPART-TL/Con) decreased. However, these developments did not differ between groups. In addition, a decrease in verbal memory performance was observed at the end of the 6-month silent period after the intervention. In particular, learning verbal information (SRT-TL), long-term storage (SRT-LTS), and recall (SRT-DR) skills have decreased. However, the decline in these skills did not differ between the intervention groups. In addition, it was observed that the improvement after the intervention period varied according to the number of relapses of the patients. It was found that factors, such as current age, disease duration, or disease onset age, did not affect this development. Contrary to these findings, the problems experienced in restoring verbal information at the end of the silent period are related to the duration of the disease and the age of onset of the disease.

There are few studies in which home-based cognitive TR practices have been applied to MS patients (18,19). These studies include fatigue, balance control, and strengthening exercises (20,21). In a randomized and double-blind study by Charvet et al. (19), the information processing (SDMT) and visual memory (BVMT-R) skills of the intervention group (adaptive cognitive remediation) improved. The reason for the difference in our results may be that the control group of this study was also semistructured. According to a TR meta-analysis by Di Tella et al. (18), the integrated TR approach mainly reduces physical problems and has little effect on cognitive impairments. It is noteworthy that most of the studies were conducted with populations other than MS, such as Alzheimer's disease, mild

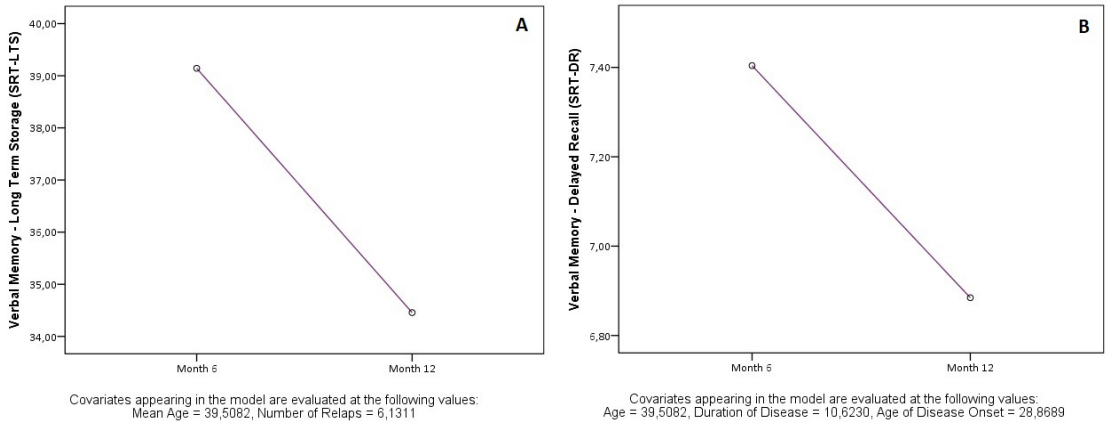

Figure 3. Change in SRT-LTS and SRT-DR scores after a silent period. (a) Repeated measures ANCOVA results of the factors affecting the long-term storage of information in verbal memory after the silent period. (b) Repeated measures ANCOVA results of the factors affecting the delayed recall score change of stored data after the silent period

Table 3. Effects of silent period (month 6 to month 12)

	TR (n=32)		nTR (n=29)		p**	F***	p***
	Month 6*	Month 12	Month 6	Month 12			
SRT-IML	5.34±1.51	5.65±1.57	4.96±1.20	5.00±1.36	0.369	2.737	0.103
SRT-TL	7.92±1.47	7.66±1.62	7.83±1.81	7.36±1.55	0.031	0.444	0.508
SRT-LTS	38.90±14.18	34.25±15.91	39.37±11.29	34.72±13.73	0.003	0.021	0.885
SRT-CLTR	29.00±16.22	24.96±14.89	28.44±12.99	24.31±14.04	0.005	0.030	0.863
SRT-Int	0.43±0.80	0.34±0.70	0.31±0.84	1.10±1.44	0.060	3.310	0.074
SRT-DR	7.46±2.79	6.87±2.88	7.34±2.36	6.89±2.25	0.052	0.007	0.934
SPART-IML	3.71±1.59	4.28±1.98	3.72±2.15	4.13±1.80	0.091	0.031	0.861
SPART-TL	4.80±1.53	4.67±1.58	5.25±1.82	5.00±1.84	0.098	0.256	0.615
SPART-TL/Con	3.12±1.61	3.09±1.90	3.37±2.10	3.22±2.22	0.678	0.175	0.677
SPART-DR	4.93±1.88	5.25±2.06	4.17±2.31	5.02±2.17	0.105	1.465	0.231
SPART-DR/Con	3.59±2.06	3.62±2.25	4.48±3.08	3.72±2.96	0.278	0.725	0.398
PASAT 3"	45.09±10.33	43.87±11.16	42.82±11.84	43.34±11.34	0.758	0.283	0.597
SDMT	37.62±14.78	36.71±12.09	34.75±12.15	35.34±12.95	0.901	0.468	0.496
COWAT-Animal	22.46±5.17	21.65±4.81	20.37±5.22	20.44±4.93	0.571	2.187	0.144
COWAT-KAS	37.43±15.22	35.93±14.32	31.86±13.19	29.44±11.88	0.131	3.360	0.072
COWAT-Total	59.28±18.49	57.90±17.76	52.93±17.14	49.55±15.50	0.118	3.099	0.084
STROOP D	41.86±25.43	41.19±27.85	56.74±38.22	55.27±36.75	0.691	3.424	0.069
BDI	10.62±9.24	10.75±7.70	11.13±6.25	9.96±6.85	0.626	0.007	0.934

TR: Telerehabilitation intervention, nTR: No telerehabilitation ınterventıon, *mean ± standart deviation, **p-value of within-subjects effect, ***F and p-value of between subject effect, SRT-IML: Selective reminding test-immediate learning, SRT-TL: Selective reminding test-total learning, SRT-LTS: Selective reminding test-long term storage, SRT-CLTR: Selective reminding test-controlled long term retrieval, SRT-Int: Selective reminding test-intrusion, SRT-DR: Selective reminding test-delayed recall, SPART-IML: Spatial recall test-immediate learning, SPART-TL: Spatial recall test-total learning, SPART-TL/Con: Spatial recall test-total learning confabulations, SPART-DR: Spatial recall test-delayed recall, SPART-DR/Con: Spatial recall test-delayed recall confabulations, PASAT: Paced auditory serial addition test, SDMT: Symbol digit modalities test, COWAT: Controlled Oral Word Association Test, BDI: Beck depression inventory

cognitive impairment, and primary progressive aphasia. According to a meta-analysis by Cotelli et al. (22), the effects of cognitive rehabilitation are relatively limited, and the quality of the method needs to be improved. In addition, unlike our results, cognitive TR applied in neurodegenerative diseases is more effective than traditional face-to-face methods, but these results do not appear to be valid for MS disease for now.

Our study also evaluated in terms of mood levels. One study (23) has stated that depression affects cognitive performance, but no study has been found to evaluate its effect on TR. Unlike our study, most studies evaluated fatigue and quality of life (24).

Study Limitations

Some points should be evaluated in further research. The information obtained on the nTR group depended only on the verbal statement of the participant, and the absence of weekly follow-up interviews over the phone is an important shortcoming of this study. In addition, there are studies in which the intervention and silent period are kept shorter because assessing the rehabilitation effect is difficult (25,26). The follow-up of the intervals between neuropsychological assessments may be determined differently in further studies. One of the data not included in the study is the drugs used by the participants and the duration of use of these drugs. Although studies are showing that interferon and natalizumab treatments did not provide a significant improvement in sustained attention, delayed recall, or information processing skills in both the treatment group and placebo group, it would be useful to include data on the drugs used in the study (27,28).

Conclusion

The present study found that the long-term effects of home-based TR are not discriminating between groups. In addition, the errors made during visual learning decreased and the attention span increased in all groups. However, this development was not observed in the silent period; conversely, regression was shown in the verbal learning processes independently of the groups. In our study, there was a difference between benign MS patients and RRMS patients, which used face-to-face rehabilitation software, although there was a need for improvements in remote application. Furthermore, the difference between these results is due to the evaluation intervals, the adequacy of the practitioner interface, and the lack of structuring of the control exercises.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Hamidiye Clinical Research Ethics Committee approved the study protocol (approval number: 20-60, date: 28.09.2020).

Informed Consent: All participants provided their written consent after being fully informed.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.P., R.T., Concept: E.T., R.T., Design: E.A., E.T., R.T., Data Collection or Processing: E.A., Analysis or Interpretation: E.A., Literature Search: E.A., S.P., Writing: E.A.

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

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References

1. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and Treatment of Multiple Sclerosis: A Review. JAMA 2021;325:765-779.
2. Cree BA, Gourraud PA, Oksenberg JR, Bevan C, Crabtree-Hartman E, Gelfand JM, Goodin DS, Graves J, Green AJ, Mowry E, Okuda DT, Pelletier D, von Büdingen HC, Zamvil SS, Agrawal A, Caillier S, Ciocca C, Gomez R, Kanner R, Lincoln R, Lizee A, Qualley P, Santaniello A, Suleiman L, Bucci M, Panara V, Papinutto N, Stern WA, Zhu AH, Cutter GR, Baranzini S, Henry RG, Hauser SL. Long-term evolution of multiple sclerosis disability in the treatment era. Ann Neurol 2016;80:499-510.
3. Langdon DW. Cognition in multiple sclerosis. Curr Opin Neurol 2011;24:244-249.
4. Glanz BI, Dégano IR, Rintell DJ, Chitnis T, Weiner HL, Healy BC. Work productivity in relapsing multiple sclerosis: associations with disability, depression, fatigue, anxiety, cognition, and health-related quality of life. Value Health 2012;15:1029-1035.
5. Rosti-Otajärvi E, Mäntynen A, Koivisto K, Huhtala H, Hämäläinen P. Patient-related factors may affect the outcome of neuropsychological rehabilitation in multiple sclerosis. J Neurol Sci 2013;334:106-111.
6. DeLuca J, Nocentini U. Neuropsychological, medical and rehabilitative management of persons with multiple sclerosis. NeuroRehabilitation 2011;29:197-219.
7. Theodoros D, Russell T, Latifi R. Telerehabilitation: Current Perspectives. In: Current Principles and Practices of Telemedicine and E-health 2008:131;191-210.
8. Hailey D, Roine R, Ohinmaa A, Dennett L. Evidence of benefit from telerehabilitation in routine care: a systematic review. J Telemed Telecare 2011;17:281-287.
9. Rogante M, Grigioni M, Cordella D, Giacomozzi C. Ten years of telerehabilitation: A literature overview of technologies and clinical applications. NeuroRehabilitation 2010;27:287-304.
10. Kairy D, Lehoux P, Vincent C, Visintin M. A systematic review of clinical outcomes, clinical process, healthcare utilization and costs associated with telerehabilitation. Disabil Rehabil 2009;31:427-447.
11. Filippi M, Amato MP, Centonze D, Gallo P, Gasperini C, Inglese M, Patti F, Pozzilli C, Preziosa P, Trojano M. Early use of high-efficacy diseasemodifying therapies makes the difference in people with multiple sclerosis: an expert opinion. J Neurol 2022;269:5382-5394.
12. Amatya B, Khan F, Galea M. Rehabilitation for people with multiple sclerosis: an overview of Cochrane Reviews. Cochrane Database Syst Rev 2019;1:CD012732.
13. Khan F, Amatya B, Kesselring J, Galea M. Telerehabilitation for persons with multiple sclerosis. Cochrane Database Syst Rev 2015;2015:CD010508.
14. Arsoy E, Tüzün E, Türkoğlu R. Effects of computer-assisted cognitive rehabilitation in benign multiple sclerosis. Turk J Med Sci 2018;48:999-1005.
15. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara K, Galetta SL, Hartung HP, Kappos L, Lublin FD, Marrie RA, Miller AE, Miller DH, Montalban X, Mowry EM, Sorensen PS, Tintoré M, Traboulsee AL, Trojano M, Uitdehaag BMJ, Vukusic S, Waubant E, Weinshenker BG, Reingold SC, Cohen JA. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162-173.
16. Ozakbas S, Turkoglu R, Tamam Y, Terzi M, Taskapilioglu O, Yucesan C, Baser HL, Gencer M, Akil E, Sen S, Turan OF, Sorgun MH, Yigit P, Turkes N. Prevalence of and risk factors for cognitive impairment in patients with relapsing-remitting multiple sclerosis: Multi-center, controlled trial. Mult Scler Relat Disord 2018;22:70-76.
17. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology 1991;41:685-691.
18. Di Tella S, Pagliari C, Blasi V, Mendozzi L, Rovaris M, Baglio F. Integrated telerehabilitation approach in multiple sclerosis: A systematic review and meta-analysis. J Telemed Telecare 2020;26:385-399.
19. Charvet LE, Yang J, Shaw MT, Sherman K, Haider L, Xu J, Krupp LB. Cognitive function in multiple sclerosis improves with telerehabilitation: Results from a randomized controlled trial. PLoS One 2017;12:e0177177.
20. Gutiérrez RO, Galán Del Río F, Cano de la Cuerda R, Alguacil Diego IM, González RA, Page JC. A telerehabilitation program by virtual reality-video games improves balance and postural control in multiple sclerosis patients. NeuroRehabilitation 2013;33:545-554.
21. Motl RW, Dlugonski D, Wójcicki TR, McAuley E, Mohr DC. Internet intervention for increasing physical activity in persons with multiple sclerosis. Mult Scler 2011;17:116-128.
22. Cotelli M, Manenti R, Brambilla M, Gobbi E, Ferrari C, Binetti G, Cappa SF. Cognitive telerehabilitation in mild cognitive impairment, Alzheimer's disease and frontotemporal dementia: A systematic review. J Telemed Telecare 2019;25:67-79.
23. Rahn K, Slusher B, Kaplin A. Cognitive impairment in multiple sclerosis: a forgotten disability remembered. Cerebrum 2012;2012:14.
24. Egner A, Phillips VL, Vora R, Wiggers E. Depression, fatigue, and health-related quality of life among people with advanced multiple sclerosis: results from an exploratory telerehabilitation study. NeuroRehabilitation 2003;18:125-133.
25. Cerasa A, Gioia MC, Valentino P, Nisticò R, Chiriaco C, Pirritano D, Tomaiuolo F, Mangone G, Trotta M, Talarico T, Bilotti G, Quattrone A. Computer-assisted cognitive rehabilitation of attention deficits for multiple sclerosis: a randomized trial with fMRI correlates. Neurorehabil Neural Repair 2013;27:284-295.
26. Amato MP, Goretti B, Viterbo RG, Portaccio E, Niccolai C, Hakiki B, Iaffaldano P, Trojano M. Computer-assisted rehabilitation of attention in patients with multiple sclerosis: results of a randomized, double-blind trial. Mult Scler 2014;20:91-98.
27. Fischer JS, Priore RL, Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, Goodkin DE, Granger CV, Simon JH, Grafman JH, Lezak MD, O'Reilly Hovey KM, Perkins KK, Barilla-Clark D, Schacter M, Shucard DW, Davidson AL, Wende KE, Bourdette DN, Kooijmans-Coutinho MF. Neuropsychological effects of interferon beta-1a in relapsing multiple sclerosis. Multiple Sclerosis Collaborative Research Group. Ann Neurol 2000;48:885-892.
28. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, Phillips JT, Lublin FD, Giovannoni G, Wajgt A, Toal M, Lynn F, Panzara MA, Sandrock AW; AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354:899-910.