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Original Article

The Effectiveness of Cognitive Rehabilitation on Processing Speed, Working Memory Capacity, Executive Function, and Quality of Life in Multiple Sclerosis Patients: A Quasi-experimental Study

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Abstract

Background & Aims: Multiple sclerosis (MS) is a neurological disease that is the most common cause of disability and may be associated with cognitive impairment. Despite the implementation of cognitive rehabilitation (CR) studies in patients with MS, there are still no clear and conclusive results. This study aimed to investigate the effectiveness of CR on speed and WM capacity, executive function, and quality of life (QOL) in MS patients.

Materials & Methods: The current quasi-experimental study (with a pretest-posttest plot and a control group) was conducted on 32 patients of the ….. MS Society, Iran. Participants were selected through the purposive sampling method and were divided into intervention (n=16) and waitlist groups (n=16) by the simple random method. The patients in the intervention group participated in cognitive rehabilitation for 12 sessions, individually. The scores for speed and working memory (WM) capacity, executive function, and QOL in both the groups were determined using N-Back test, Wechsler Adult Intelligence Scale (WAIS-IV) Digit Span subtest, Wisconsin Card Sorting (WCST), and Quality of Life Questionnaire of MS patients (MSQOL-54). The scores were analyzed using descriptive statistics (mean and standard deviation) and inferential statistics (repeated measures ANOVA).

Results: The results showed that, apart from the physical domain of quality of life (QOL), the average scores in WCST and Digit Span Memory, response time in N-Beck test, and emotional QOL, differed over time and in both the intervention and waitlist groups($P<0.05$). Thus, in the intervention group, the performance in speed and capacity of WM, executive function, and emotional QOL showed a significant improvement ($P<0.05$) in the post-test and on follow-up compared to the waitlist group.

Conclusion: Cognitive rehabilitation, based on these findings, is likely to be effective in improving the speed and capacity of working memory, executive function, and quality of life of MS patients.

Keywords: cognitive rehabilitation, working memory, executive function, quality of life, multiple sclerosis

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Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system caused by an immune system induced neurological damage (1). In this disease, the autoimmune system is overactive and may attack the components of the nervous system

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considering them as foreign objects (2). Symptoms of MS include myelin pod collapse, alteration of motor function and sensory perception (blindness), lack of physical control (urine and stool), cognitive deficits, and depression (3).

Cognitive performance may be damaged in 44%–70% of patients with MS (4, 5). The most common disorders include impairment in working memory (WM) , attention, information processing speed, abstract reasoning, and executive function (6, 7). WM is a subjective system responsible for the accumulation and temporary processing of information to perform a series of tasks such as complex cognitive understanding, thinking, calculating, reasoning, and learning (8). Executive dysfunction and reduced speed of information processing have been proposed as the core aspects of many cognitive disorders including MS (9). Executive functions include mental abilities such as starting function (starting any activity quickly and easily), inhibition (thinking before acting and emotional inhibition), planning, organizing, self-directing, etc. (10). Impairment of cognitive functions covers many aspects of everyday life including the ability to manage family, full participation in the society, the maintenance of employment, and the overall QOL (4, 11). This is especially problematic in young patients who need to learn and remember large volumes of information. The cognitive deficits even disrupt the person's social and family relations, leading to reduced confidence and increased feelings of anger in patients (3).

The results of the recent studies demonstrate a significant and inverse relationship between the severity of cognitive impairment in MS patients and their QOL (12).

The treatments of cognitive disorders are generally conducted by pharmacological and non-pharmacological methods. Evidence confirming the efficacy of medicines, particularly because of the negative side effects on the recurrence of attacks and the mood of the patients, is very limited (13). There is supportive evidence on the effectiveness of the medication, especially regarding the few negative side effects of drugs on cognitive impairment in patients with MS(14). The results of a recent study showed that cognitive function did not improve after the initiation of natalizumab treatment (a humanized monoclonal antibody) over one year (15). CR is one of the non-pharmacological interventions aimed at stability, control, and reduction of cognitive deficits in the patients (16). Several studies showed the effectiveness of CR in improving the cognitive functions and the QOL of MS patients (17, 18).

Covey and Shucard (2018) showed that CR can improve the WM, processing speed, selective attention, and abstract reasoning in patients with MS (6). The recent integrative, group-based, CR studies in 2018 (19, 20) and individual-based CR studies indicated the effectiveness of CR in improving cognitive functions, processing speed, memory, and attention as well as the successful accomplishment of daily life activities (21, 22). However, recent reviews of the literature regarding the efficacy of CR in patients with MS emphasized the failure to verify the effectiveness of CR due to the small number of unacceptable and preliminary scientific studies conducted in this field (23-27). Sumowski et al. (2018) concluded that the present evidence is inadequate and it is difficult to draw any conclusions (23).

In principle there is a gap between the theory and the current knowledge about the effectiveness of non-pharmacological interventions. Also, because of the rising prevalence of the MS in Iran, this study aimed to investigate the effectiveness of CR in improving the processing speed and capacity of brain, executive functions, and also the QOL of patients with MS.

The results of the current randomized controlled study have practical and theoretical implications and can open the door to later descriptive and intervention studies about the decline in cognitive damage of patients. Wellbeing and QOL of these patients can be enhanced through an applied occupational level and provided appropriate rehabilitation cognitive programs, and at a theoretical level, the richness of cognition theory and various aspects of QOL can be added, and even a new chapter in the field of cognitive deficits and other diseases associated with cognitive impairments can be opened.

Patients and Methods:

The study protocol was approved by the Ethics Committee of the same University (code: Ir…….rec.1396.191).

Patients:

All the patients who were referred to the ….. MS Society of Iran from October 2016 to March 2017 and were diagnosed with relapsing-remitting MS based on the medical records were included in the study. The following inclusion and exclusion criteria were considered.

Inclusion criteria were as follows:

- Diagnosis of MS, relapsing-remitting for at least 6 months, by an expert neurologist,
- Age between 18 to 45 years for both sexes,
- Literate and able to read and write,
- Lack of impairment in the use of the dominant hand,
- Expanded disability status scale (EDSS) ≤ 5.5,
- Beck Depression Inventory score (BDI) ≤ 21,
- No consumption of alcohol, narcotics, and psychotropic drugs during at least the last 3 months
- The absence of psychotic illness and symptoms of forgetfulness in daily affairs, and
- Willingness to provide informed consent to participate in the study (in accordance with the code of ethics in research[5]).

The exclusion criteria included:

- Relapse of symptoms,
- Failure during the study, and
- Unwillingness to participate in the study

Sampling Method:

The sampling method was objective-based and the sample size was set to 32 subjects considering dropouts ratio; the subjects were randomly divided into two groups of intervention (n = 16) and control (n = 16). One participant from each group (female) was removed during the research due to medical reasons and failure to meet the inclusion criteria, and the sample size became 30.

Method

The present study was a quasi-experimental research with a pretest-posttest plot and follow-up phase with a control group. CR was an independent variable of the study which was provided to the intervention group whereas the control group did not receive any cognitive intervention. The dependent variables of the study were speed and capacity of working memory, executive function, and QOL of patients with MS before and after the implementation of the independent variable and after a 3-month of follow-up. Both groups were evaluated and the changes were analyzed.

Study protocol:

[5] Ir.umsu.rec.1396.191.

Table 1. The Overall Content of Treatment Sessions

Sessions	Objectives and Content
Time 1 (Pretest)	Introducing the research to the subjects, explaining the objectives and stages of research, agreement with the subject and gathering demographic information. Pretest: Performance of neuropsychological tests (N-Back, WAIS Digit Span subtest, and Wisconsin test) by the subjects and providing them a QOL questionnaire as pencil-paper (if patients' questions have been read without any manipulation by the researcher).
Sixteen intervention sessions	Individual interventions in the intervention group through Attentive Rehabilitation of Attention and Memory (ARAM) program during 12 sessions of 60 minutes, three times a week (documented through photography, video recording, and also registered self-reports of patients). It is designed based on the Sohlberg and Mateer componential model of attention and involves sustained, selective, alternating and divided attention as well as the Baddeley working memory model. The timing of interventions was based on the protocol and workshop of Dr. Vahid Nejati (conducted by the Neuroscience Research Center of the Shahid Beheshti University of Medical Sciences) and can be repeated until the patient reaches the desired level.
Time 2 (Posttest)	Posttest: Replay the neuropsychological tests on the subjects in the intervention group (posttest was carried out in control group simultaneously). - Obtaining feedback from the intervention group for the CR exercises carried out. Some patients wrote their comments about the phase.
Time 3 (Follow-up)	Follow-up: The implementation of the third stage of evaluation 12 weeks after rehabilitation.
Data analysis	The results of the assessment tests of the two groups in three steps, pretest, posttest, and after three months follow up, were analyzed using repeated measures analysis of variance. Measurement error was determined at a rate of 0.05.

Measuring tools:

Wechsler Adult Intelligence Scale (WAIS) Digit Span subtest:

To evaluate the function of WM, we used the Digit Span Subtest. The participants must remember auditory number information that a tester reads. At first, the information should be carefully received in the subscales which require attention and encoding. Those who are easily distracted have a problem at this stage. Second, participants must remember the information and recollect the correct sequence and express it. Those who cannot possibly receive information correctly have difficulty at this stage because they cannot recall (memory) adequately. Figures which are displayed upside down are a much more difficult assignment and quite sensitive to brain damage. Test-retest reliability coefficients of 83% have been reported for these subscales (28).

N-back Test:

N-back test is a valid instrument for measuring the processing speed of memory (29), especially in patients with MS (30) and is one of the most widely used non-cultural tools. The test suite consists of hundreds of serial inline images that appear on the screen, and the person must respond with varying load conditions on the active memory. At low load conditions, for each stimulus, the target key should be pressed in case of similarity of the stimulus with the previous stimulus. At high load conditions, one must compare each stimulus with the two previous stimuli and press the corresponding key in case of similarity (31). This task requires constant monitoring and updating of information in the WM, which is used in validation studies to measure the speed of information processing (29, 30).

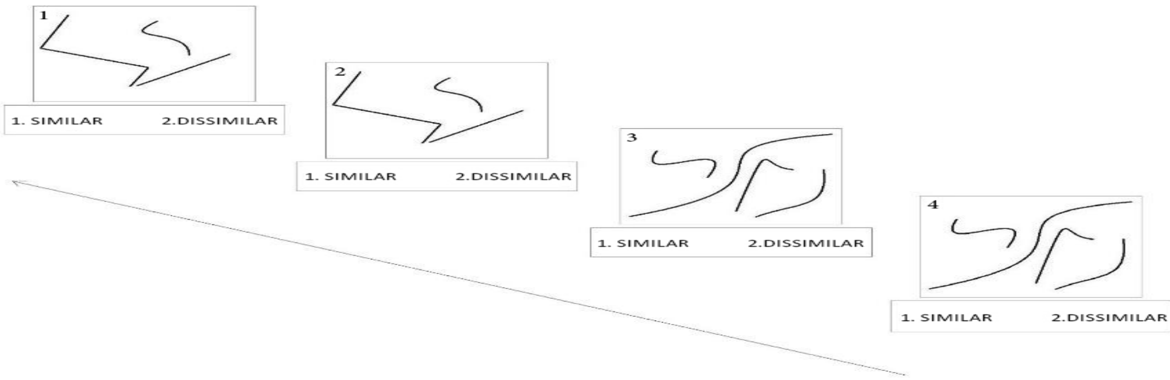

Image 1. The N-back Test

Wisconsin Card Sorting Test (WCST) :

In this study, executive function was assessed by the WCST. It is a computerized card sorting test that is widely used to assess executive functions. Imaging of the brain shows the connections between the frontal activities and the WCST test. The reported reliability of the cognitive impairment test was more than 86%, and its reliability in the Iranian samples on retest was 85% (32). Shahgholian et al. (2014) analyzed the produced psychometric indices and demonstrated its desirable reliability in Iranian subjects (33).

Multiple Sclerosis quality of life-54 (MSQOL-54):

The questionnaire contains 54 two- to seven-choice Likert questions. The scores for QOL is determined by a combination of "physical health" and "mental health." Scores from 0 to 100 and higher indicate better conditions (34). The reliability of the instrument was established with an alpha= 0.821 (35).

Attentive Rehabilitation of Attention and Memory (ARAM):

ARAM is a software application that is a part of Neurocognitive Joyful Attentive Training Intervention as a cognitive rehabilitation intervention. In the ARAM, four joyful computer-based tasks were presented to participants. These tasks were graded and increased in level of difficulty based on responses. Grading was based on the number of flanker stimuli, the velocity of presented stimuli, the number of goal stimuli, and changing task rule. For example, in one task, a subject should arrange faces in different categories based on a given rule and three properties: emotional expression (sad, angry, and neutral), hair color (green, white, and black), and skin color (yellow, white, and black). Each face had one property from each category, and the subject should assign it to just one category based on the property specified by the given rule. Thus, in each set of tasks, the subject should inhibit two properties and act based on one property designated by the given rule. In other words, the cognitive demand of these tasks is the inhibition of unrelated properties and selectively attending to related one (36).

The program includes a group of tasks hierarchically organized to strengthen the various aspects of attention (selective, stable, transmission, and distribution) and memory.

The basic principles of assignments should include:

1) The hierarchical organization that is more difficult based on user response

2) Performing the task correctly involving the immediate reward

3) Designed based on various aspects

4) Refreshing and reinforce the patient motivation

5) Repeatable to achieve the patient's desired level

6) Making progress based on the efficiency of the patient and the therapist is required to improve the task (37).

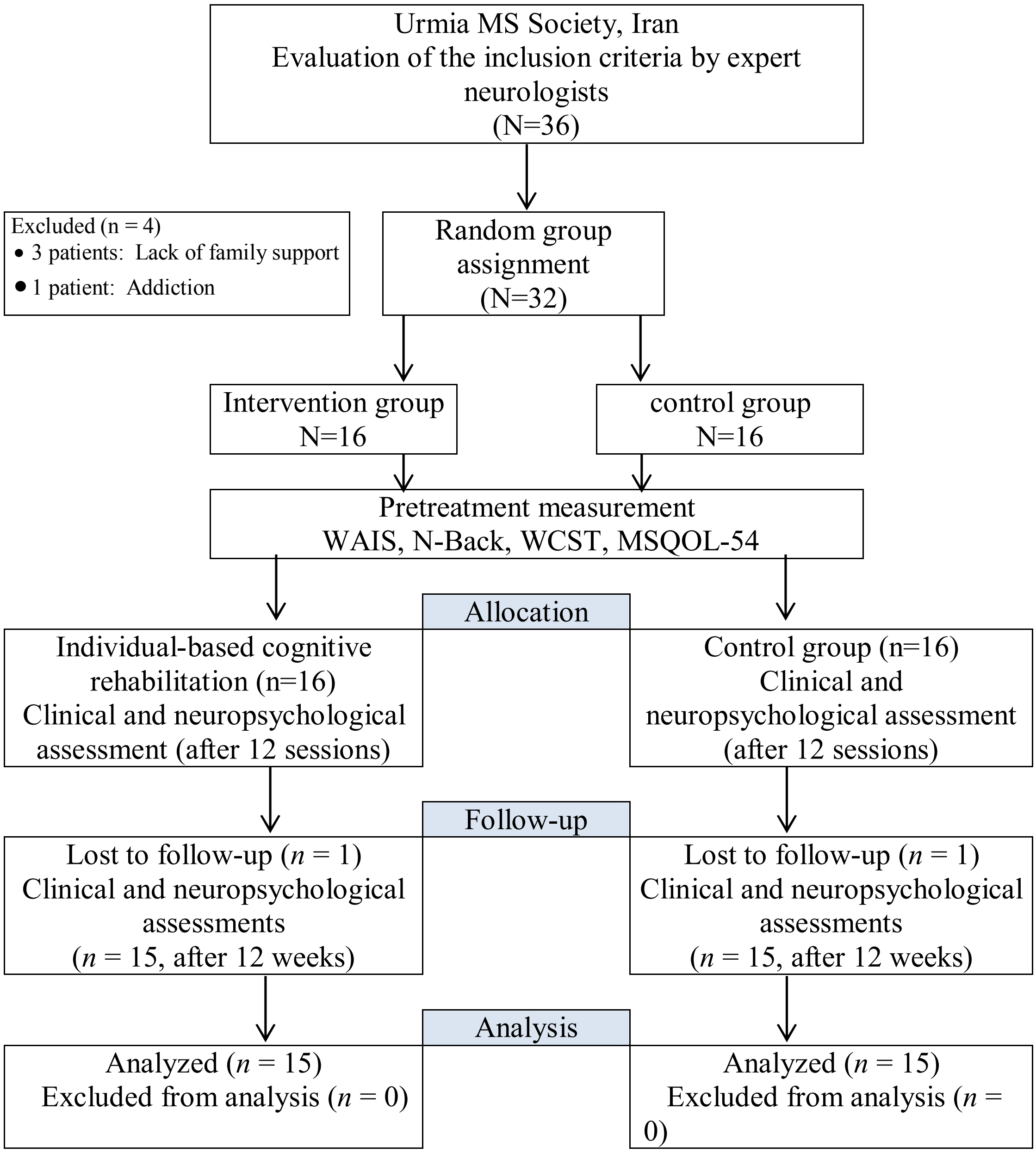

Figure 1. CONSORT flowchart of the study population

Statistical analysis: All statistical analyses were performed with SPSS version 23 software, and P values <.05 were considered statistically significant. Repeated measures analysis of variance (GLMRM) was used to compare the two groups at three different times. This test is flexible, and more conservative statistics can be used with degrees of freedom. Repeated measures analysis of variance is resistant to the normality of the distribution of the data and does not change the test results in the absence of a part of the data. The average pretest in both groups showed no significant difference due to the cloning of both waitlist and intervention groups. Controlling the effect of pretest (as the variety variable) is not recommended because improper control leads to unfair results due to the interaction of the variable. Since the two groups have an equal sample size (both 15), Box's M test can also be avoided. However, Wilks Lambda statistic can be used in the absence of the assumptions mentioned above. Mauchly's Test of Sphericity is the main assumption of repeated measures analysis of variance. The distribution of data at different levels must be normal and so-called spherical. The sphericity concerns the similarity of the relationship between the dependent and independent variables in a repeated measures design. If the significance level of the Mauchly's Test of Sphericity is more than 0.001, the sphericity assumption has been fulfilled; otherwise, three epsilon corrected by adjusting the degree of freedom will be used. The three tests are Greenhouse-Geisser, Huynh-Feldt, and Lower-bound. Usually, the test with epsilon less than 0.75 is used.

Results

The intervention group included 8 females (53.33%) and 7 male patients (46.66%); 9 were unmarried (60%), and 6 (40%) were married, with an average age of 23.84 years. The control group consisted of 7 females (46.66%) and 8 males (53.33%); 11 (73.33%) were unmarried, and 4 (26.66%) were married, with an average age of 22.25 years.

Descriptive statistics of the variables in the three phases, before, after, and on follow-up, in both control and intervention groups are shown in Table 1.

Table 1. Descriptive statistics of the variables

		Before intervention	After intervention	Follow-up
		Mean (Standard deviation)	Mean (Standard deviation)	Mean (Standard deviation)
(WCST) Overall time	Control group	368.7906 ± 150.814	364.1345± 115.488	327.7378±138.584
	Intervention group	290.0931 ± 254.726	226.7257± 172.466	186.513 ± 83.346
(WCST) number of categories	Control group	3.20 ± 0.941	3.27 ± 1.100	3.33 ± 0.900
	Intervention group	3.47 ± 0.990	4.33 ± 0.816	4.27 ± 0.961
(WCST) Preservation error	Control group	16.27 ± 4.743	14.93 ± 3.751	13.67 ± 5.665
	Intervention l group	16.33 ± 8.372	10.33 ± 5.178	8.40 ± 5.853
(WAIS) Digit span forward	Control group	5.13 ± 1.125	5.20 ± 1.424	5.13 ± 1.356
	Intervention group	5.33 ± 0.724	6.60 ± 0.986	6.47 ± 1.125
(WAIS) Digit span backward	Control group	3.93 ± 1.100	4.00 ± 1.195	4.00 ± 1.134
	Intervention group	4.20 ± 0.775	5.53 ± 1.187	5.20 ± 1.373
(N-Back) Processing speed	Control group	224.81 ± 82.24	211.34 ± 63.67	204.31 ± 77.28
	Intervention group	173.23 ± 78.81	143.66 ± 62.01	124.13 ± 39.11
(MSQOL-54) Combined physical health	Control group	48.36 ± 9.877	48.10 ± 10.715	47.13 ± 10.517
	Intervention group	49.12 ± 7.368	51.83 ± 9.454	52.37 ± 9.763
(MSQOL-54) Combined mental health	Control group	54.03 ± 12.222	53.16 ± 12.573	54.74 ± 12.172
	Intervention group	56.86 ± 9.068	65.53 ± 10.712	68.33 ± 11.537

The current study findings showed that the changes differed between the two groups during the three phases in digit forward Wechsler memory test (WMT) mean scores for working memory capacity (df=2, F=9.015, P=0.000, α=0.05). Also, the differences were reported for both groups and over time in digit forward (df=1, F=6.968, P=0.013, α=0.05). The changes between the two groups and over time were also reported differently for reverse memory. The mean scores of the variables in digit backward (WMT) for the control group during the three phases (df=2, F=13.885, P=0.000, α=0.05) and for the intervention group were significantly different (df=1, F=6.753, P=0.015, α=0.05). Based on the average scores for the speed of information processing in the control (df=1.367, F=5.137, P=0.020, α=0.05) and intervention groups (df=1, F=10.672, P=0.003, α=0.05), the two variables showed significant differences for processing speed in N-back test over time and between the groups.

Wisconsin card sorting test mean scores for executive functioning for the whole time showed significant differences in both groups in the post-test (df=28, t=-2.564, P=0.016) and follow-up (df=28, t=-3.382, P=0.002, α=0.05), and the differences were significant over time and no significant differences were reported between after phase and follow-up in experimental group. The WCST number of categories of both intervention and control groups in the post-test (df=28, t=3.016, P=0.005, α=0.05) and follow-up (df=28, t=2.746, P=0.010, α=0.05) showed significant differences; the differences were significant over time and no significant differences were reported between after phase and follow-up in the experimental group**.** The intervention group showed significant changes in preservation error based on the Wisconsin test in three phases of before, after, and follow-up (df=2, F=15.963, P=0.000 α=0.05).

The changes in pretest, posttest, and follow-up phases were not significant in physical health combination, both in the control and intervention groups (df=2, F=2.203, P=0.120, α=0.05) (and not between the groups) (df=1, F=0.020, P=0.889). But, due to changes in the control and intervention groups the results showed significant changes in the mental health dimension over time (df=1.332, F=16.420, P=0.000, α=0.05) and also between the two groups (df=1, F=5.780, P=0.023, α=0.05).

Table 2 shows the intergroup and intragroup effects and covariance between the variables. The significance level of Mauchly's Test with sphericity assumption or no assumption shows the Greenhouse-Geisser correction for the different changes.

Table 2. The effects within and between groups of covariance of the research variables

	Effect	Sum of squares	Degree of freedom	Mean Square	F	Sig level	Test square root
(WCST)	Time	78536.663	1.227	64027.812	5.276	0.022	0.159
Overall time	Group	319212.918	1	319212.918	5.023	0.033	0.152
(WCST)	Time	356.4	2	2.178	4.651	0.014	0.142
number of categories	Group	12.844	1	12.844	7.130	0.012	0.203
(WCST)	Time	437.422	2	218.711	15.963	0.000	0.363
Preservation error	Group	240.100	1	240.100	3.311	0.080	0.106
(WAIS)	Time	7.756	2	3.878	9.015	0.000	0.244
Digi spant forward	Group	21.511	1	21.511	6.968	0.013	0.199
(WAIS)	Time	8.022	2	4.011	13.885	0.000	0.331

Digit span backward	Group	22.500	1	22.500	6.753	0.015	0.194
(N-Back)	Time	19101.838	1.367	13971.093	5.137	0.020	0.150
Processing speed	Group	102645.635	1	102645.635	10.672	0.003	0.269
(MSQOL-54)	Time	25585	2	12.793	2.203	0.120	0.073
Combined physical health	Group	10.000	1	10.000	0.020	0.889	0.001
(MSQOL-54)	Time	569.824	1.332	427.748	16.420	0.000	0.370
Combined mental health	Group	2070.241	1	2070.241	5.780	0.023	0.171

Table 3 shows the effect of the intervention on the variables using the average comparison test of two independent and dependent groups.

Table 3. Pairwise comparison of two interferences in the research variables

		Before	After	Follow-up	Before and after	Before and follow-up	After and follow-up
(WCST) Overall time	Control	368.7906	364.1345	327.7378	P=0.501	P=0.152	P=0.147
	Intervention	290.0931	226.7257	186.5134	P=0.031	P=0.071	P=0.183
	Group comparison	P=0.312	P=0.016	P=0.002			
(WCST) number of categories	Control	3.20	3.27	3.33	P=0.806	P=0.499	P=0.751
	Intervention	3.47	4.33	4.27	P=0.004	P=0.034	P=0.751
	Group comparison	P=0.456	P=0.005	P=0.010			
(WCST) Preservation error	Control	16.27	14.93	13.67	P=0.070	P=0.126	P=0.349
	Intervention	16.33	10.33	8.40	P=0.003	P=0.000	P=0.021
	Group comparison	P=0.979	P=0.009	P=0.018			
(WAIS) Digit span forward	Control	5.13	5.20	5.13	P=0.774	P=1.000	P=0.806
	Intervention	5.33	6.60	6.47	P=0.000	P=0.002	P=0.582
	Group comparison	P=0.567	P=0.004	P=0.007			
(WAIS) Digit span backward	Control	3.93	4.00	4.00	P=0.670	P=0.582	P=1.000
	Intervention	4.20	5.53	5.20	P=0.000	P=0.002	P=0.207
	Group comparison	P=0.449	P=0.001	P=0.014			
(N-Back) Processing speed	Control	224.81	211.34	204.31	P=0.351	P=0.251	P=0.453
	Intervention	173.23	143.66	124.13	P=0.186	P=0.015	P=0.037
	Group comparison	P=0.068	P=0.006	P=0.002			
(MSQOL-54) Combined physical health	Control	48.36	48.10	47.13	P=0.722	P=0.043	P=0.049
	Intervention	49.12	51.83	52.37	P=0.031	P=0.033	P=0.424
	Group comparison	P=0.813	P=0.320	P=0.168			
(MSQOL-54) Combined mental health	Control	54.03	53.16	54.74	P=0.197	P=0.174	P=0.054
	Intervention	56.86	65.53	68.33	P=0.002	P=0.001	P=0.010
	Group comparison	P=0.478	P=0.007	P=0.004			

The significance level of the test is shown in Tables 2 and 3. Apart from the physical health composite variable, all variables were significant over time and in both experimental and control groups in terms of average differences.

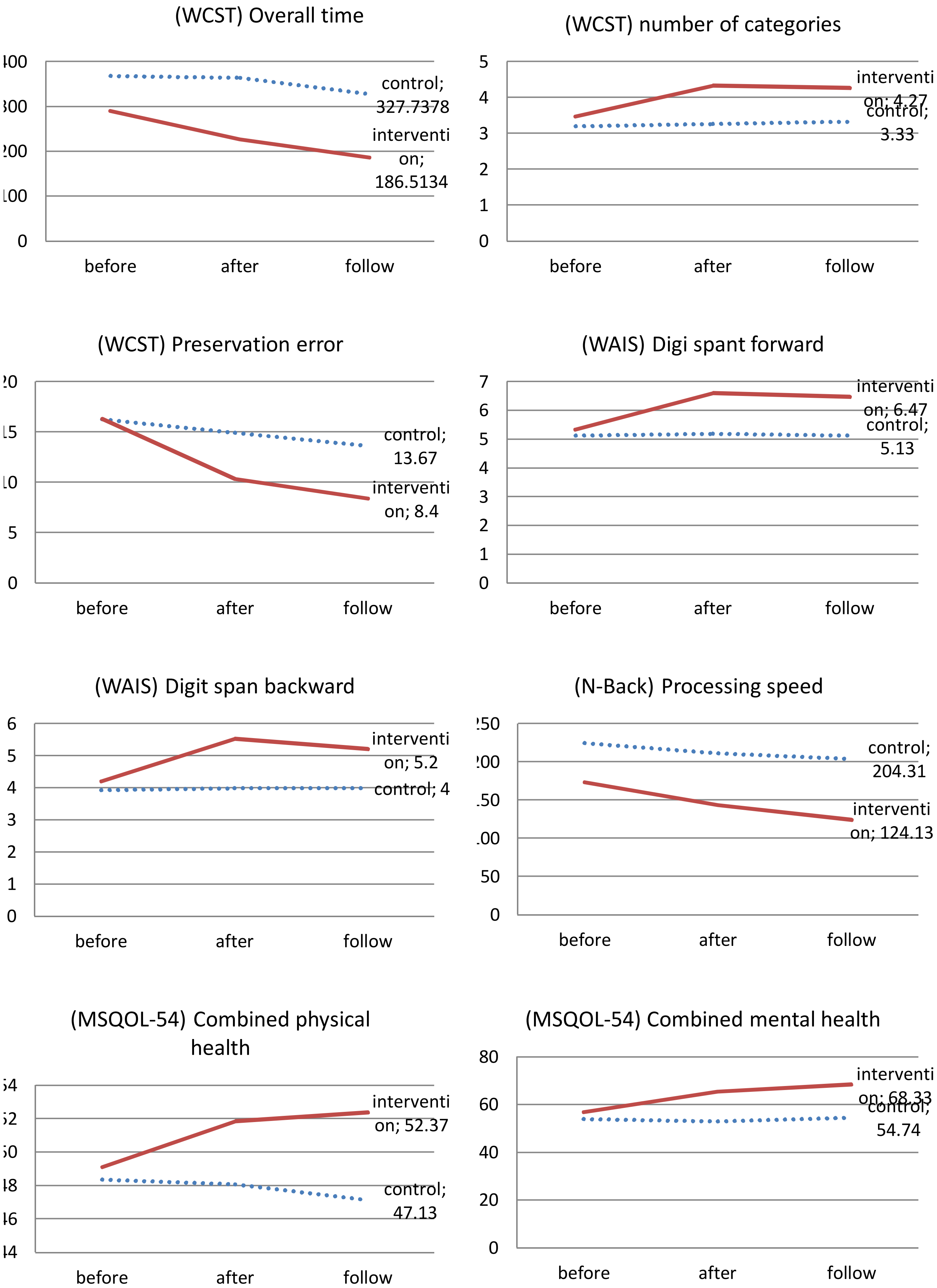

Chart 1: Study variables in the two groups at three phases

Discussion and Conclusion

Chronic diseases such as MS in combination with cognitive disorders, in addition to physical problems, result in psychological, social, occupational, family, and other problems as well. It can negatively affect the patient's daily activities and QOL. The effect of CR was evaluated on patients with MS and cognitive disorders.

Baseline characteristics, measures of cognitive performance and QOL of the study group were previously outlined. There were no significant differences at baseline in demographic characteristics, and cognitive performance functions including speed and the capacity of WM, executive functions, and QOL measures between the groups. Patients were reassessed immediately after training (time 2) and after an additional 12-week period (time 3/follow-up).

Our findings showed improvement in the variables, including speed and the capacity of WM, executive functions, and Combined mental health of patients in the CR intervention group which are in line with the findings of earlier research (6, 19-21, 27, 37, 38) and counter the findings of some other studies (24-27).

Also, at time 2 and time 3 (follow-up) there were no significant differences in speed and the capacity of WM, executive functions, and QOL outcome measures (Chart 1).

In the review of previous studies, Goverover et al. (2018) reported no consensus in the current literature regarding the efficacy of CR in improving the processing speed and WM and executive functions of patients with MS (39). Also, Das Nair et al. in a Cochrane review (2016) indicated some evidence to support the effectiveness of memory rehabilitation on memory function and QOL. Since the evidence is limited, more studies are needed (24). Conversely, Covey and Shucard (2018) examined the effect of N-back working memory training on cognitive performance and brain function in patients with MS. Participants completed approximately 20 sessions of N-back training, five days a week, for 25–30 minutes a day, on a home computer using a web browser. The results showed that CR may improve cognitive function (WM, processing speed, complex attention, and reasoning ability) in MS (6). Rilo et al. (2018) showed significant improvements in processing speed, WM, and executive functioning (19).

In addition to memory, executive function showed significant improvement in the patients of the current study receiving CR. Executive function was assessed by the WSCT. In a recent study, Mani et al. investigated the efficacy of group CR on executive function. The CR intervention in their study consisted of eight two-hour sessions of comprehensive group CR over a four-week period (20). However, Hanssen et al., (18) reported improvement in executive function in both CR and control groups, with no significant differences between the groups.

In the current study, cognitive rehabilitation programs were used to investigate the effect of cognitive rehabilitation on cognitive impairment in patients with MS. CR program is designed based on the Sohlberg and. Mateer componential model of attention and involves sustained, selective, alternating, and divided attention as well as the Baddeley working memory model. It is designed from easy to difficult as hierarchical levels and all the important principles such as diversity, overload, feedback, ratings, and other learning principles are considered. ARAM program assignments include colored houses, similar windows, section images, last colors, pairing delay colors, naming titles, etc. It is used in several studies. Regarding, Luria's theory and cognitive neuroscience studies about the flexibility of the brain can be considered in explaining the findings in line. Recent studies using neurological tests as well as brain imaging have shown that by providing new experiences, changes in the growth of brain neurons, especially in the cerebral cortex neuronal connections, are increased, resulting in improved cognitive function of the individual. Xerri et al. introduced a phenomenon known as pruning, which is effective due to the changes in the environment and the desired function on the strength or weakness of synapses. Neural plasticity can occur in healthy subjects and patients with possible brain damage (40). Rehabilitation causes changes in the activity of the frontal and parietal lobes, core principle as well as changes in the density of dopamine receptors in the neuronal network plasticity involved in memory, to change the memory capacity (41). In our study, cognitive rehabilitation techniques were used by increasing the three stages of memory formation including encoding, storage, and memory and recovery focusing on memory and attention. The improvement in the working memory performance after these exercises can be explained based on a theoretical model of spurious correlation between attention and working memory (42). According to this theory, attention and concentration mechanisms are responsible for processing management and storing data in WM. Undergoing various types of training to improve attention, learning self-attention strategies, and creating positive effects can also affect memory performance.

On the other hand, the existence of a defect in the processing speed in MS is the biggest factor affecting executive functions and the high correlation between WM and executive functions (43) can be used to explain the findings of this study based on the effectiveness of the CR in improving the performance of executive functions. CR leads to changes in the activity of the frontal and parietal lobes, basal ganglia, and the density of dopamine receptors (41).

According to scientific results, it can be stated that the negative effects of cognitive impairment in everyday activities, career, social activities, and QOL of these patients are undeniable. It is clear that the restoration and improvement in executive function and memory increases the possibility of improving the QOL.

The current study showed that the changes the in pre-test, post-test, and follow-up phases were not significant ($P < 0.05$) in physical health combination both in the control and intervention groups, but the results showed significant changes ($P < 0.05$) in psychological health dimension in the intervention group. In agreement with the results of two other studies, (20, 21) it was observed that CR can improve certain domains of the psychosocial aspects of QOL in patients with MS. Chart 1 shows improvements at follow-up ($P < 0.05$); however, no significant differences between the control group changes were observed. Also, the study of Fuvesi et al. showed that MS is only effective on the mental aspect of QOL, and depression (44) is the most effective factor in the QOL of these patients. The results of the comparative study by Hindle et al. in 2018 showed the effectiveness of CR in improving memory performance compared with conventional therapy and relaxation on Parkinson's disease (45).

Several factors can explain the counter findings, including the lack of integrity in the selection of the sample group, the measuring tools, and methods as well as the lack of control for confounders including cognitive intelligence or cognitive defects that can be considered as part of the criteria for being included in the study. The physical condition, mental condition, mood, perceived level of social support, domestic violence in the sample group, and even side effects of the associated medication during the study can be considered as the other confounding factors. For example, family conflict and stress are some of the limitations of this study which may have negatively affected the mood of some patients during the study. Also, the communication skills of the clinical therapist may have affected the results. CR is supposed to create new experiences to improve cognitive function after brain damage. Certainly the most important issue is whether the provided training and rehabilitation affect the daily functioning and QOL of these patients or not.

Improved cognitive function is often referred to, especially, in connection with the daily activities. Increased confidence and life expectancy in the final interview and self-expression of the intervention group was due to the positive changes they had experienced. The experiences of the patients during the simple and important activities in life had significant changes.

Strengths and limitations:

Overall, the findings of this study indicate the efficacy of CR on memory improvement, executive function, and QOL of MS patients. These findings can be used by therapists and researchers in the field as well. Despite the high motivation of the patients to attend regular sessions of CR, some of them had problems, which form a limitation of this study, including difficulty in walking and balancing, side effects of the medications and chemotherapy, family conflict and, sometimes, lack of adequate social support which lead to irregular attendance to the meetings and the likely results.

Due to inconsistent results and findings of different studies, it is recommended to synchronize the intervention methods, such as the number of intervention sessions, using reliable and precise control for confounding variables including cognitive intelligence (IQ), perceived social support, etc., in the future studies to have comparable results. Finally, due to the emphasis on the studies (46, 47), reiterating the need for multidisciplinary cooperation in the detection of cognitive diseases, it is suggested to use interventions based on CR as a combination therapy approach and supportive applications in the therapy by professionals and researchers in the field.

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