Original Article

The Effectiveness of Cognitive Rehabilitation on Cognitive Flexibility, Response Inhibition, and Selective Attention in Patients with Multiple Sclerosis: A Quasi-Experimental Study

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Abstract

***Background & Aims*:**Multiple sclerosis (MS) is the most common cause of disability with cognitive impairments. The current study aimed to investigate the effect of cognitive rehabilitation (CR) on cognitive flexibility, response inhibition, and selective attention in patients with MS.

Materials and Methods: The current quasi-experimental study with a pretest-posttest plot and a control group was conducted on 32 patients in the Urmia MS Society, Iran. They were selected through the purposive sampling method and were divided into intervention (n=16) and control groups (n=16) by the simple random method. The patients in the intervention group participated in the cognitive rehabilitation for 12 sessions, individually. The scores of cognitive flexibility were obtained by the Wisconsin Card Sorting Test (WCST), selective attention by the Stroop Color and Word Test (SCWT), and the response inhibition by Go/No-go task. Results were analyzed using descriptive statistics (mean and standard deviation) and inferential statistics (repeated measures analysis of variance).

Results: The results of the current study showed a significant preservation error in the interaction between group and time ($p<0.05$). Also, there was a significant difference between the groups in terms of the error of committing ($p<0.05$). Nevertheless, no significant difference was observed in the responses of inhibition scores at pre-test, post-test, and follow-up between the two groups. Thus, significant differences observed in cognitive flexibility and selective attention at follow-up and post-test in intervention and control groups.

Conclusion: Cognitive rehabilitation is likely to affect cognitive flexibility and selective attention in patients with MS.

Keywords: multiple sclerosis, cognitive flexibility, selective attention, response inhibition

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Introduction

Multiple sclerosis (MS) is an autoimmune disease with neurological damage to the central nervous system (1), affecting the nerves in the brain and spinal cord (2). MS symptoms may include motor performance, as well as emotional, verbal (3), and memory and thinking impairments (5). Scientific findings indicated that cognitive impairment in patients with MS is about 44%

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to 70% (4). The most vulnerable cognitive domains in MS include attention, learning and memory, planning, problem solving, cognitive flexibility, mental speed and word finding. MS patients can experience difficulty in Flexible thinking (5).

Cognitive flexibility is one of the subsets of the executive functions of the brain and researchers acknowledge the crucial role of frontal and prefrontal lobes in this skill (6). Cognitive flexibility is the ability to abstract and change cognitive strategies in response to the environmental feedback that requires planning, organized investigation, and the ability to use the cognitive set shifting due to environmental feedback (7). The lack of flexibility also refers to dysexecutive syndrome (8) and the preservation of the individual in a pattern (9).

The inhibition of response is a self-control process that resists the temptations and actuators (10). Scientific findings show more errors and higher impulsivity response in inhibition tests in patients with MS than in healthy subjects (11). The inhibition becomes important when it is necessary to select the appropriate stimuli and reject inappropriate ones (12).

For the efficient functioning and adaptive ability, paying attention selectively to significant information resources and, at the same time, ignoring irrelevant information are critical requirements of every living creature (13). Based on the study by Sohlberg and Mateer, the concept of selective attention refers to the ability to maintain a behavior or cognitive set confronting the intruder (8).

The treatments of cognitive disorders are generally conducted by pharmacological and non-pharmacological methods. Few evidence exist about the efficacy of medicines, particularly in view of the negative side effects on the recurrence of attacks and the mood of the patients (14&15). CR is a set of non-pharmacological intervention strategies for the consistency, control, and reduction of cognitive deficits in MS subjects (16). Sawami et al. (2017) compared two different treatment methods for cognitive disorders in patients with Alzheimer's disease. They showed that non-pharmacological treatments often promote a positive mood, and strengthen the brain reward system to continue working, and improve cognitive function to keep cognitive function (17). The findings of Yamamoto et al. emphasized the effectiveness of cognitive rehabilitation on attention deficit in elderly people with cognitive impairment (18). Rilo et al. (2018) showed that cognitive rehabilitation might improve cognitive impairments in patients with MS (19). Also Mani et al., (2018) showed that group-based CR has a significant effect on improving cognitive impairment in patients with MS, including processing speed, attention, and executive function (20). Covey and Shucard (2018) showed that CR can improve the WM, processing speed, selective attention, and abstract reasoning in patients with MS (21).

Despite the studies confirming the effectiveness of CR, a number of studies, especially studies of Cochrane, are contrary to the assumption and the need to continue the studies is underscored (22 & 23). Cochrane's study suggest that the available documentation is not sufficient to conclude the effectiveness of cognitive rehabilitation and that further studies are required to evaluate the effectiveness of cognitive rehabilitation (24).

In general, the two factors including young people in a community and dimensions of disability, on one hand, and the impact of these defects on the everyday quality of life, social activities, dependence on others, and the economic burden on families and society, on the other hand, put MS in the spotlight. Due to the limited number of basic and applied studies in the field of cognitive rehabilitation and cognitive deficits in patients with MS in Iran and also the increasing prevalence of MS in Iran

and inconsistent research results regarding the effectiveness of non-pharmacological treatment in cognitive disorders, researchers decided to conduct this study The purpose of this study was to investigate the possible effect of CR on cognitive flexibility, response inhibition, abstract reasoning, and selective attention in patients with MS. The results can genralizable and also useful for international researchers in future to reduce the cognitive deficits in all patients with cognitive impairments.

Patients and Methods:

The subjects of the current study were selected by Urmia University of Medical Sciences and the study protocol was approved by the Ethics Committee of the same University (code: Ir.umsu.rec.1396.191).

Patients:

The participants included all patients referred to the Urmia MS Society, Iran, October 2016 to March 2017,they were diagnosed with relapsing-remitting MS based on the medical records. Researchers considered the following inclusion and exclusion criteria for study subjects.

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) ≤17
- 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
- willing 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
- 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 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 3-month of follow-up. Both groups were evaluated by means of the research, 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 (SCWT, WCST, and go/no-go task) by the subjects.
Twelve intervention sessions	Individual interventions in the intervention group through Attentive Rehabilitation of Attention and Memory (ARAM) program (12 sessions, 60 minutes each session), three times a week (documented through photography, video recording, and also registered self-reports of the 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 the 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 was repeated until the patient reacheed the desired level.
Time 2 (Posttest)	**Posttest**: Replay the neuropsychological tests on the subjects in the intervention group (posttest was simultaneously carried out in control group). - 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 was carried out 12 weeks after the rehabilitation.
Data analysis	The results of the assessment tests of the two groups (pre-test, post-test, 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:

Wisconsin Card Sorting Test (WCST) :

The neuropsychological test was designed by Grant & Berg (1948) as an indicator of the frontal lobe damage (25) and for the assessment of cognitive flexibility and abstract reasoning. It consists of 64 states with images which are different from each other in terms of color (red, yellow, blue, and green), shape (cross, circle, triangle, and star), and number (one to four). Imaging of the brain shows the connections between the frontal activities and Wisconsin test. The reported reliability of the cognitive impairment test was more than 86%, and its reliability in the Iranian samples on retest was 85% (26). Shahgholian et al. (2014) analyzed the produced psychometric indices and demonstrated its desirable reliability in Iranian subjects (27).

Stroop Color and Word Test (SCWT):

SCWT is a measurement scale to assess frontal lobe, selective attention, and executive functions, including three steps. The first and the second steps consist of coordinated efforts while the third step, named as the uncoordinated or conflicting efforts, include the names of four primary colors appeared on a computer screen; the participants should press the keys on the keyboard accordingly as soon as possible and by the words' ink color. For example, the word "red" is written with another color (e g, green). The subject should determine the ink color. This required more time to do(28). The Stroop test reliability was estimated 0.01, 0.83, and 0.90

through test-retest method for all three trials, respectively (29).

Go/No-Go Task:

This test measures sustained attention and response inhibition. In the test, the person is in two positions of Go (run or move steps) and do not go (inhibit or stop motion) that are randomly assigned. Ability to inhibit the response in the second position is an index of response inhibition. The test reliability was reported as 87% by Ghadiri et al. (2006, quoted by (30).

Attentive Rehabilitation of Attention and Memory (ARAM):

ARAM is a software application that is a part of Neurocognitive Joyful Attentive Training Intervention as cognitive rehabilitation intervention. In the ARAM, four joyful computer-based tasks were presented to participants. These tasks were graded and increased in the level of difficulty based on the responses. Grading was based on the number of flanker stimuli, velocity of presented stimuli, 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 acts based on one property designated by the given rule. In other words, the cognitive demand of these tasks is inhibition of unrelated properties and selectively attending to related one (32).

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) Hierarchical organization that is more difficult based on user response

2) Performing the task correctly involving the immediate reward

3) Designing based on various aspects

4) Refreshing and reinforcing 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 (31).

Statistical analysis:

All statistical analyses were performed with SPSS version 23, and p values <0.05 were considered statistically significant. Repeated measures analysis of variance (GLMRM) was used to compare the results of 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. Box's M test can also be avoided, since the two groups have equal sample size (N=15 in both groups). However, Wilks Lambda statistic can be used when the assumptions mentioned above are not present. Mauchly's Test of Sphericity is the only and the main assumption for the 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. When the significance level of the Mauchly's Test of Sphericity is more than 0.001, the sphericity assumption will be 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.

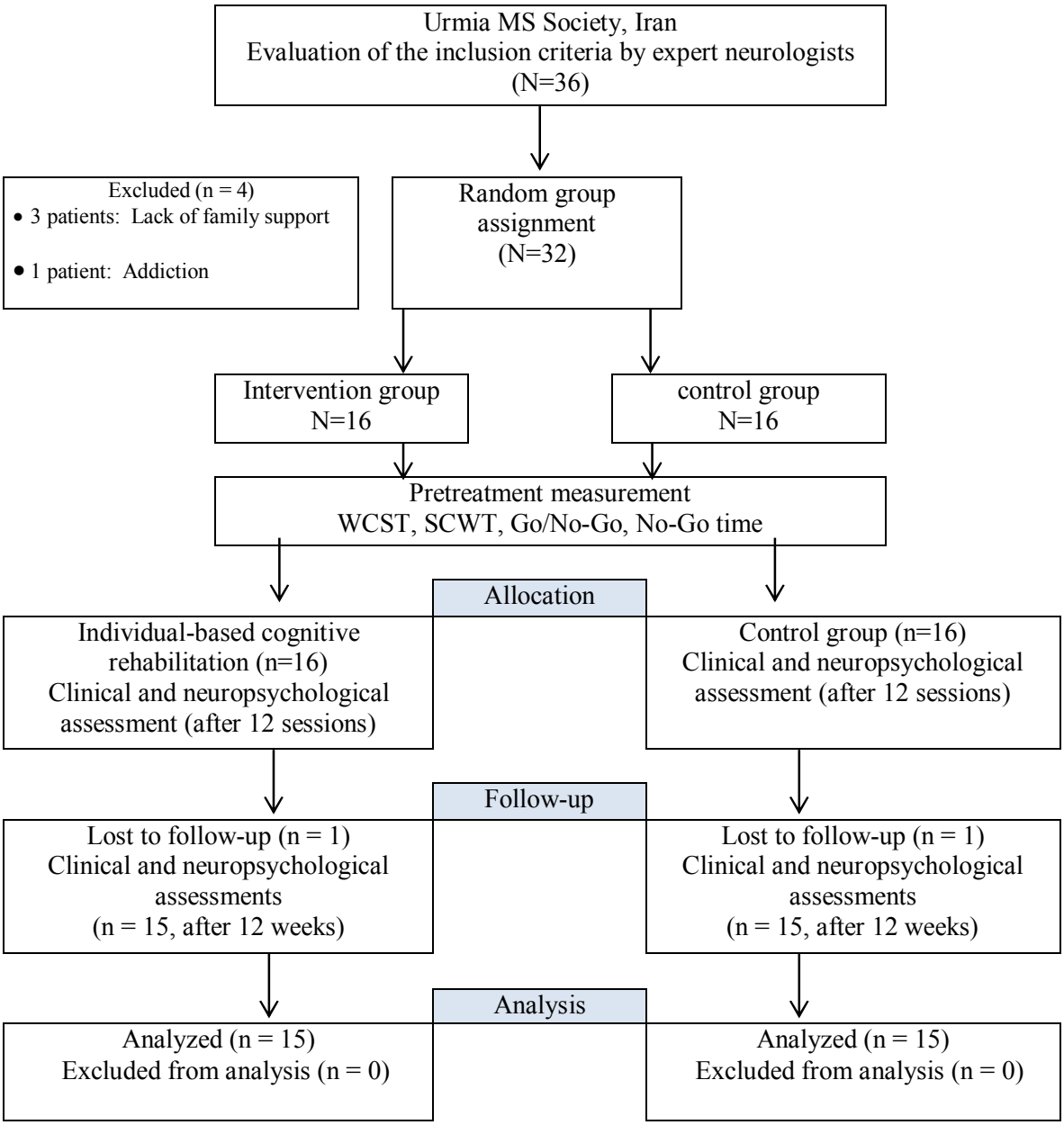


Figure 1. CONSORT flowchart of the study population

Results

The intervention group included 8 females (53.33%) and 7 males (46.66%); 9 were unmarried (60%), and 6 (40%) were married, with an average age of 23.84 years. Nine of them had a diploma or lower degrees (60%) and 6 of them (40%) had Bachelor's degree. 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. Ten patients had a diploma or lower degrees (66.66%) and 5 of them (33.33%) had Bachelor's degree, 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 experimental groups are shown in Table 1.

Table 1. Descriptive statistics of the variables

		pre-test	post-test	Follow up
		Mean ± Standard division	Mean ± Standard division	Mean ± Standard division
(WCST) Preservation error	Control group	16.27 ± 4.743	14.93 ± 3.751	13.67 ± 5.665
	Intervention group	16.33 ± 8.372	10.33 ± 5.178	8.40 ± 5.853
(SCWT) Commission error	Control group	87.73 ± 12.510	88.93 ± 9.004	89.60 ± 8.322
	Intervention group	88.53 ± 11.501	98.40 ± 2.530	99.20 ± 1.656
(SCWT) Reaction time	Control group	3.1019 ± 4.1905	1.1596 ± 1.525	1.9076 ± 1.024
	Intervention group	2.2088 ± 1.6695	1.4469 ± 0.470	1.2941 ± 0.361
No-go errors	Control group	3.27 ± 1.751	3.27 ± 2.086	2.60 ± 2.414
	Intervention group	3.47 ± 2.416	3.33 ± 3.716	2.53 ± 4.422
No-Go reaction time	Control group	0.68 ± 0.323	0.75 ± 0.327	0.60 ± 0.454
	Intervention group	0.65 ± 0.302	0.61 ± 0.638	0.45 ± 0.788

Table 2 shows the intergroup and intragroup effects and covariance between the variables. The significance level of Mauchly's Test with or without sphericity assumption shows the use of Greenhouse-Geisser correction for the difference of the 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) Preservation error	Time	437.422	2	218.711	15.963	0.000	0.363
	Group	240.100	1	240.100	3.311	0.080	0.106
(SCWT) Commission error	Time	704.267	1.270	554.474	11.379	0.001	0.289
	Group	986.711	1	986.711	6.082	0.020	0.178
(SCWT) Reaction time	Time	18.791	1.026	18.308	2.819	0.103	0.091
	Group	12.313	1	12.313	2.292	0.141	0.076
No-go errors	Time	11.822	1.577	7.494	1.707	0.198	0.057
	Group	0.100	1	0.100	0.005	0.943	0.000
No-Go reaction time	Time	0.432	2	0.216	1.681	0.196	0.057
	Group	0.247	1	0.247	0.482	0.493	0.017

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

The findings show that the changes were significant for the preservation error in the experimental group during three phases of pre-test, post-test and follow-up for cognitive flexibility (p <0.05) while they were not

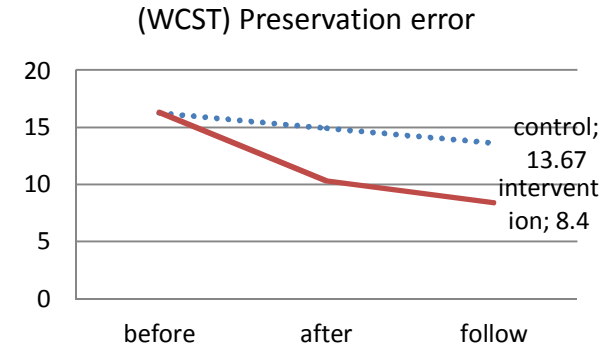
significant in the control group at three phases the pre-test, post-test and follow-up (p> 0.05).

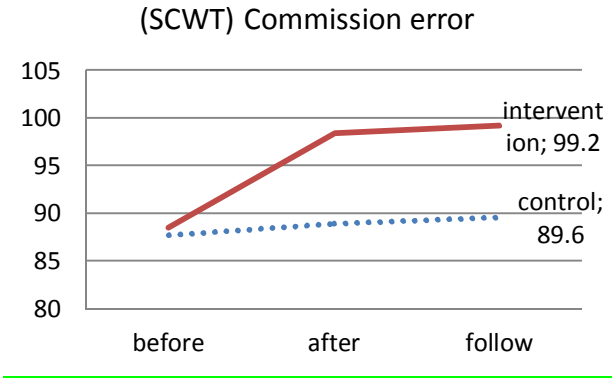
In selective attention, with regard to the number of correct answers in the third stage of the Stroop test, significant differences were observed in both control and experimental groups (F = 6.082, df = 1, p = 0.020) in addition to significant changes that occured over time (F = 11.379, df = 1.270, p = 0.001). For cognitive reaction time (the third stage of the Stroop test), the changes showed no significant difference neither over time (F = 2.819, df = 1.026, p = 0.103), nor among the groups (F = 2.292, df = 1, p = 0.141). The changes over time (F = 1.707, df = 1.577, p = 0.198) were not significant for response inhibition in error variable NO GO. There was no significant difference between the control and experimental groups (F = 0.005, df = 1, p = 0.943). For reaction time in NO GO, the change was not significant neither over time (F = 1.681, df = 2, p = 0.196) nor for the two groups (F = 0.482, df = 1, p = 0.493).

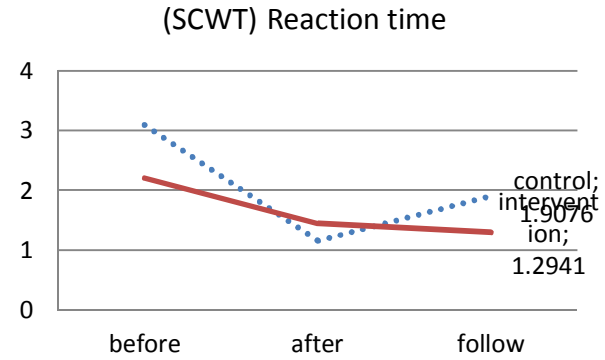
Table 3. Pairwise comparison of two interferences in the research variables

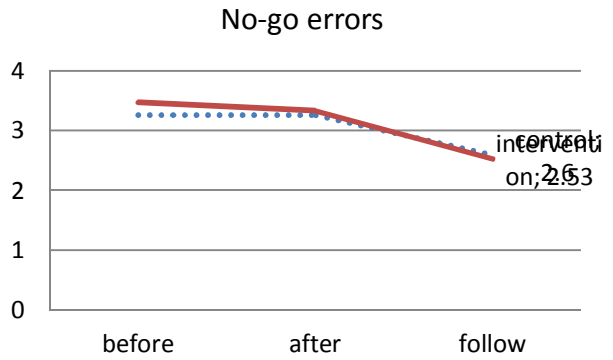
		pre-test	post-test	Follow-up	pre-test and post-test	pre-test and follow-up	post-test and follow-up
(WCST) Preservation error	Control	16.27	14.93	13.67	P=0.070	P=0.126	P=0.349
	Intervention	16.33	10.33	8.40	P=0.003	P=0.000	P=0.021
	Group comparison	P=0.979	P=0.009	P=0.018			
(SCWT) Commission error	Control	87.73	88.93	89.60	P=0.489	P=0.250	P=0.632
	Intervention	88.53	98.40	99.20	P=0.006	P=0.002	P=0.082
	Group comparison	P=0.857	P=0.001	P=0.001			
(SCWT) Cognitive reaction time	Control	3.1019	1.1596	1.9076	P=0.397	P=0.279	P=0.094
	Intervention	2.2088	1.4469	1.2941	P=0.094	P=0.047	P=0.026
	Group comparison	P=0.450	P=0.095	P=0.037			
No-go errors	Control	3.27	3.27	2.60	P=1.000	P=0.182	P=0.012
	Intervention	3.47	3.33	2.53	P=0.855	P=0.174	P=0.120
	Group comparison	P=0.797	P=0.952	P=0.960			
No-Go reaction time	Control	0.68	0.75	0.60	P=0.371	P=0.215	P=0.158
	Intervention	0.65	0.61	0.45	P=0.790	P=0.304	P=0.347
	Group comparison	P=0.788	P=0.468	P=0.539			

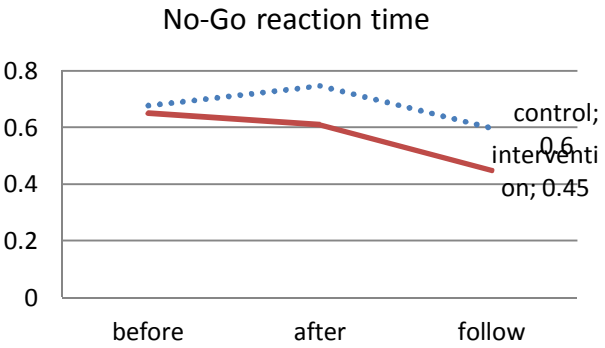
The significance level in Table 2 shows that the preservation error (cognitive flexibility) decreased over time in both groups. The significance level of the findings was confirmed except in the correct answering time at the third stage of the Stroop test (time to inhibit the responses) and inappropriate inhibition in the Go/No-go test in paired comparisons (Table 3).











Discussion and conclusion

In the current study, the repeated measures analysis using the software showed that the preservation error (cognitive flexibility) was significant in repeated measures test in paired comparisons and the number of Commission error of the Stroop test (selective attention) in paired comparisons, and there was a significant difference in terms of the grades between intervention and control groups. However, in the above cases, the difference was not significant between the post-test and follow-up of the intervention group (Figure1). The results were consistent with the findings of previous studies (17, 18, 19, 20, 21) and in contrast with the findings of some others (24, 22 & 23).

In a recent study on patients with MS, Rilo et al. (2018) investigated the efficacy of group-based CR on cognitive impairments of MS patients that received cognitive rehabilitation for three months (3 hours per week). This study supported the efficacy of group-based cognitive rehabilitation intervention for MS patients (19). Also Mani et al. (2018) investigated the effectiveness of group-based CR in patients with MS-related cognitive impairment and their results supported the effectiveness of CR for improving the cognitive

functions in patients with MS (20). Our methodology is similar to the aforementioned studies. However, each study used a different set of assessment tools and assessed different domains. Besides, interventions were group-based in the previous studies but in the present study, the interventions were performed individually. However, Goverover et al. (2018) reported no consensus in the current literature regarding the effectiveness of CR for improving the memory functions of patients with MS (33).

The improvement in cognitive function after the intervention might be due to the changes in the brain neural networks. This means that a change occurs in executive functions of patients. Several explanations are noteworthy to explain the alignment results. One of them is a strong correlation between the brain function and cognitive training. This is demonstrated with advances in cognitive neuroscience, configurability, self-repair brain-based theory of Luria, and based on neuroimaging findings in animals and humans. Studies indicated that cognitive disorders are associated with lesions in the forebrain and especially in the frontal cortex. Similar executive dysfunctions of the brain and cognitive flexibility of patients with frontal lobe brain damage can be observed in patients with MS. Therefore, it can be indicated that memory, executive function, concentration, active thinking, and reasoning indexes are related to the prefrontal areas of the brain and cognitive rehabilitation can strengthen these areas (34). The study by Stranahan et al. showed that cognitive training could increase norepinephrine and dopamine in the brain in which the neurotransmitters play a crucial role in attention, thinking, and understanding (35). Therefore, with assignments based on attention and memory, these interventions can reduce distraction and strengthen the promotion and attention, which might result in cognitive flexibility among subjects. In general, cognitive rehabilitation creates sustainable synaptic changes in accordance with the principle of self-healing ability of the brain through successive excitation of less active areas in the brain (36).

However, despite a reduction in selective attention errors, the cognitive reaction time between pre-test, post-test, and follow-up was in line with the findings of the previous studies(37) and no significant difference was observed. Based on the findings it can be concluded that after the intervention, the number of wrongs over time differed, but there was no significant interaction between group and time and in general, the research hypothesis for this index in Go/No-go test was rejected. These results were in line with some previous studies (38) while contrary to some other findings (21, 10).

The study of Barekatain et al. (2016) revealed the lack of effectiveness of cognitive rehabilitation on response inhibition of patients with mild cognitive impairment (38). This might be due to the uncertainty and lack of sufficient scientific data in response inhibition of MS patients.

Although deficits in the executive function and its cognitive effects on patients with MS are known, the response inhibition performance in such patients is less understood. Inhibitory response, defined as the ability to withhold a response, is typically preserved in patients with multiple sclerosis (MS), despite impairment in other executive functions (39).

In addition, the study of Smith et al. (2009) with magnetic imaging of the brain showed that no significant difference existed in the reaction time of MS patients in the control group and the healthy group (40).

The findings of this study showed no significant difference in cognitive or complex reaction time, (Stroop Test) as well as No-go / Stop or simple reaction time. It is worth noting that the tests that are used to measure inhibitory control are different. For instance, Go / No-go test mostly measures motor inhibitory control. No-go reaction time is the time it takes to inhibit an ongoing reaction while the Stroop test examines their selective inhibition. In other words, No-go testing,

requires less cognitive processing and just measures simple reaction or stop time. But the third stage of the Stroop test evaluates the interaction time and requires inhibition of a stimulus and response based on another inconsistent dimension. Successful performance in the third stage of the Stroop test needs attention on relevant stimuli processing and inhibit the attention to irrelevant drivers. According to the recent findings, the inferior frontal gyrus is involved in the response inhibition (41) while the bilateral dorsolateral prefrontal cortex is activated during the Stroop task (42).

Several factors might explain the absence of significant changes in reaction time, intensification and the chance of recurrence. Medication side effects might be noted due to the small size of the sample, for example changes and interventions during test execution time can greatly affect the results. In addition, the difference in the selection of the sample group in studies about the level of disability (EDSS) also seems to be one of the factors affecting the time of reaction. Myelin and axons neural pathways damage and the slow nerve flow may be a reason for the lack of effectiveness of interventions in reaction time in the Stroop test.

In order to explain the contrary findings, the difference in cognitive rehabilitation techniques, assessment tools, protocols of studies, the age of onset, and the duration of the disease in various studies can be cited. According to the results of the study by Rosti-Otajarvi and Hamalainen (43), effective communication and relationship between the patient and the therapist are also the factors affecting the outcome of treatment. In addition, a previous study (44) showed that cognitive rehabilitation workout durations (short courses) are likely to affect the results.

It is assumed in CR that cognitive function can somewhat improve after the brain damage in patients with MS by creating new experiences and in certain circumstances. The most important issue is undoubtedly whether providing training and rehabilitation affects daily functioning and quality of life in such patients. In the current study, patients in the final interviews in the intervention group (expressing themselves in writing and orally) pointed that their life expectancy and self-confidence improved in work and daily activities, and also significant positive changes happened to them. In general, the results of the current study indicated the efficacy of cognitive rehabilitation in cognitive performance and function in MS. The findings of the current study can be used by clinicians and researchers in the field. The small sample size was one of the primary limitations of this study.

Another limitation of the research was the burden of commuting for patients to attend the clinic for interventions. Among the limitations of the current study, which delayed the initiation of the implementation phase (for at least three months) was the rise in the temperature during the summer that made the researchers to postpone the intervention until autumn by doctors' recommendations due to the increased probability of recurrence with increasing temperature. In addition, despite the high motivation of patients to attend regular sessions of cognitive rehabilitation, sometimes side effects of drug therapy and chemotherapy in patients led to problems in organizing meetings and delayed the implementation of the intervention. In this regard, it is suggested that future studies be planned for appropriate weather conditions to assess MS and learn about the possible side effects of medications.

Finally, due to inconsistent results of different studies, it is suggested that subsequent studies use standardization in intervention methods and valid tests and neuroimaging as well as more precise control for confounding variables such as cognitive intelligence (IQ), perceived social support, domestic violence. In terms of cognitive rehabilitation based on the number of sessions required, it is recommended to compare the studies in different groups by the number of classified

sessions. Eventually, based on the researchers' stress (45, 46) on reiterating the findings, there is a need for multidisciplinary cooperation in the therapy of this disease.

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