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Memory rehabilitation for the working memory of patients with multiple sclerosis (MS)

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ABSTRACT

Objective: The main cognitive impairments in multiple sclerosis (MS) affect the working memory, processing speed, and performances that are in close interaction with one another. Cognitive problems in MS are influenced to a lesser degree by disease recovery medications or treatments, but cognitive rehabilitation is considered one of the promising methods for cure. There is evidence regarding the effectiveness of cognitive rehabilitation for MS patients in various stages of the disease. Since the impairment in working memory is one of the main MS deficits, a particular training that affects this cognitive domain can be of a great value. This study aims to determine the effectiveness of memory rehabilitation on the working memory performance of MS patients.

Method: Sixty MS patients with cognitive impairment and similar in terms of demographic characteristics, duration of disease, neurological problems, and mental health were randomly assigned to three groups: namely, experimental, placebo, and control. Patients' cognitive evaluation incorporated baseline assessments immediately post-intervention and 5 weeks post-intervention. The experimental group received a cognitive rehabilitation program in one-hour sessions on a weekly basis for 8 weeks. The placebo group received relaxation techniques on a weekly basis; the control group received no intervention.

Results: The results of this study showed that the cognitive rehabilitation program had a positive effect on the working memory performance of patients with MS in the experimental group. These results were achieved in immediate evaluation (post-test) and follow-up 5 weeks after intervention. There was no significant difference in working memory performance between the placebo group and the control group.

Conclusions: According to the study, there is evidence for the effectiveness of a memory rehabilitation program for the working memory of patients with MS. Cognitive rehabilitation can improve working memory disorders and have a positive effect on the working memory performance of these patients.

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1. Introduction

Cognitive disorders are considered the prevalent symptoms in multiple sclerosis (MS), and they have been reported to have influenced almost half of patients with MS (Amato, Zipoli, & Portaccio, 2006). In MS, cognitive impairments incorporate numerous areas, such as attention deficit (Amato, Zipoli, & Portaccio, 2008; Engle, Greim, & Zettl, 2007), memory and learning disorders (Calabrese, 2006; Chiaravalloti & Deluca, 2008), information processing speed slackness (Bergendal, Fredrikson, & Almkvist, 2007; Henry & Beatty, 2006), executive performance (Denney, Sworowski, & Lynch, 2005; Drew, Tippett, Starkey, & Isler, 2008), and working memory problems (Amato et al., 2010; Benedict et al., 2006; Sfagos et al., 2003). Information processing speed has been reportedly the most vulnerable cognitive ability in MS patients, and it is found associated with information retention capability in working memory (Parmenter, Shucard, & Shucard, 2007). The studies performed on a great number of MS patients indicate that the disorder substantially deteriorates the information processing speed, especially in relapsing–remitting MS patients, to an extent more than the working memory (Deluca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004). There is also some evidence that information processing speed impairments might be warning signs indicating working memory deficits in MS patients (Genova, Lengenfelder, Chiaravalloti, Moore, & Deluca, 2012; Leavitt, Lengenfelder, Moore, Chiaravalloti, & Deluca, 2011).

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Baddeley substituted the short-term memory with the working memory system, which includes four components: central executive agent, phonological loop (retains the information based on their phones), visuospatial sketch pad (assigned with decrypting the visual-spatial information), and episodic buffer (integrates and coordinates the information from numerous sources) (Baddeley, 2012). In patients with MS, working memory impairment has been reported in both relapsing–remitting type (Fuso, Callegearo, Pompeias, & Bueno, 2010) and progressive type MS patients. Also, disorders are found in both the secondary and the central executive systems (Archibald & Fisk, 2000). Since cognitive problems are less influenced by medication (Whyte, 2008), cognitive rehabilitation is suggested as a treatment method. Cognitive rehabilitation includes nonmedication interventions performed in line with improving the cognitive performances and supporting the affected individual in managing and accepting the remaining cognitive deficits (Prigatano, 2005).

Many of the studies concerned with the cognitive training and rehabilitation of MS patients are constrained by a plethora of methodological limitations (Das Nair, Ferguson, Stark, & Lincoln, 2012; Rosti-Otajarvi & Hamalainen, 2011).

Recently, the results of a systematic review encompassing 20 studies have indicated that there is low-level evidence for the positive effects of rehabilitation in MS (Rosti-Otajarvi & Hamalainen, 2011). However, data meta-analyses have shown positive rehabilitative effects in 18 studies. The researchers came to the conclusion that cognitive training improves the memory span and working memory, and, when it is accompanied by other rehabilitation methods such as compensatory strategies, it can be of great use in elevating the immediate verbal memory and the delayed memory.

The study by Hildbrandt et al. (2007) demonstrated the significant effects of computer-aided training on the working memory and verbal memory of individuals with MS. But it was also shown that such training has no influence on exhaustion and quality of life. Also, computer-aided training with the use of Brainstim software has been shown to improve healthy individuals' working memory (Penner, Kobel, & Opwis, 2006).The aforesaid software was designed based on a fake model of the working memory, and it targets three indicators, namely phonetic, visual, and central executive. The software has been designed to be applied in such a manner so as to ensure that the training takes place based on developmental strategies, not practice and repetition.

Vogt et al. (2008) used the software for MS patients. The results indicated that the working memory performance has been improved post-training. In later studies, the researchers (Vogt et al., 2009) compared the same training method but with different intensities (high intensity = 16 sessions in 4 weeks; distributed intensity = 16 sessions in 8 weeks). The results were suggestive of similar effects on exhaustion, working memory, and processing speed in both of the groups. In the meantime, it was shown that distributed training has more promising effects on working memory in healthy individuals (Penner et al., 2012).

There is a scarcity of studies regarding cognitive training and rehabilitation effects on MS patients' working memory. Therefore, the present study is aimed at determining the effectiveness of cognitive rehabilitation on MS patients' working memory; it runs a rehabilitation program on MS patients in a randomized controlled study.

2. Method

2.1. Participants

In a double-blind randomized controlled trial, 60 patients with MS were selected as study participants on the basis of the following inclusion scales: age 18–69 years, the ability to read and write, MSNQ ≤ 27, earn 2 standard deviations lower than the healthy people on the scale of BRBN (Lincoln et al., 2015), EDSS < 4, GHQ < 22, and not having medical and severe psychiatric problems at the same time. Testees were compared in three groups according to demographic characteristics and duration of the disease; and, finally, they were randomly assigned to three groups—namely, experimental (n = 20), placebo (n = 20), and control (n = 20)—with the help of randomized software.

All the patients were selected from Isfahan's center for MS, and the preliminary examinations were carried out through cognitive screening tests so as to identify the individuals with memory problems. Patients' screening was conducted via MSNQ and BRBN tests, and individuals who were found qualified to be included in the study and announced their willingness for doing so were assigned to three groups—namely experimental, control, and placebo. At this stage, the Wechsler memory scale–III (WMS–III) (Wechsler, 1997) (third edition) was administered to the participants so as to evaluate their working memory performance baseline.

The number of female and male participants was 35 (58%) and 25 (42%), respectively. The age range of the

Table 1. Specifications of the statistical population.

Groups	Mean age (years)	Mean duration of disease (years)
Experimental	40.55	6.20
Placebo	41.25	7.55
Control	40.65	6.80

participants was 33–48 years, and their mean age was 40.81. The mean age of the experimental group was 40.55; those of the placebo and control groups were 41.25 and 40.65, respectively. The mean duration of disease in the experimental group was 6.20, and in the placebo and control group 7.55 and 6.80, respectively (Table 1).

The experimental group received the memory rehabilitation program for 8 weeks (an hour a week) in four-people groups. The placebo group received body relaxation techniques during weekly sessions, and the control group was given ordinary information regarding cognitive problems in MS. Post-tests immediately followed the termination of training sessions, and follow-up tests were provided five weeks after the training sessions termination to determine the immediate and delayed effects of the intervention, respectively. The present study was undertaken during the period from August 2015 to December 2016. Control and placebo group patients (who declared their interest) received a rehabilitation program after going through all the stages. It is worth mentioning that both participants and the statistics analyzer were blind to the purposes of the study.

2.2. Instruments

The test used in this study include the following:

The Multiple sclerosis neuropsychological screening questionnaire (MSNQ) (Benedict et al., 2003) and the brief repeatable battery of neuropsychological test (BRBN) (Rao, 1990), for the initial assessment of cognitive problems; and the General health Questionnaire 28 (GHQ) (Goldberg & Williams, 1991), the expanded disability status scale (EDSS) (Kurtzke, 1983), and the Wechsler Memory Scale–III (WMS–III) (Wechsler, 1997), for assessment baseline and intervention.

2.3. Rehabilitation program

The rehabilitation program included 8 one-hour sessions held once a week. The sessions consisted of the following: introducing the various types of external memory aids, compensatory strategies, and various kinds of memory aids, making use of mental reviewing methods, error-free learning, solutions to focus attention and concentration, and methods of coping with memory problems (depending on the patients' individual memory problems, as outlined during the preliminary sessions). At the end of each session, participants were given homework. After the termination of the training program, evaluation followed in terms of the degree to which the partial and total objectives of the program had been fulfilled.

2.4. Statistical analyses

Data analysis was conducted using multivariate analysis of covariance (MANCOVA), and SPSS software.

3. Results

In this study, 60 MS patients with memory deficits were selected as study participants according to the inclusion criteria. The mean working memory component in the experimental group in the pre-test was 20.10, in the placebo it was 20.25, and in the control group it was 20.75. In the post-test the mean of working memory in the experimental group was 24.55, in the placebo it was 21.70, and in the control group it was 20.85. Finally, in the follow-up stage, the mean of the working memory component in the experimental group was 22.85, in the placebo it was 20.40, and in the control group it was 20.90. Mean and standard deviation of the working memory component are shown in Table 2.

As the objective of the present study was to determine the extent to which rehabilitation is effective on the working memory of patients with multiple sclerosis (MS), the results were assessed based on covariance analysis. The use of covariance analysis entails adhering to some of the essential assumptions, including the normality of the dependent and controlling variables, variance homogeneity, and regression lines homogeneity. The present study investigated such assumptions. The scores obtained for dependent and controlling variables were evaluated and verified by Shapiro-Wilk tests, and error variance homogeneity underwent the same analysis and verification through the use of the

Table 2. Mean and standard deviation of working memory component.

Groups		Working memory		
		Pre-test	Post-test	Follow-up
Experimental	M	20.1000	24.5500	22.8500
	SD	2.35975	2.98196	3.08263
Placebo	M	20.2500	21.7000	20.4000
	SD	2.24488	3.74306	3.21837
Control	M	20.7500	20.8500	20.9000
	SD	2.09950	3.78744	3.43205

Levin test. The assumption of the regression line parallelism was also investigated, and it was shown that it holds between the groups and in terms of the working memory pretest scores.

As is shown in Table 3, once the effect of the synchronous variables on the dependent variable had been omitted and according to *F*-coefficient calculated for the current research paper, a significant difference ($p < .01$) became evident between the adjusted means of the participants' working memory scores based on group memberships (experimental group, placebo group, and control group) in both post-test and follow-up stages. Therefore it can be concluded that the memory rehabilitation training program had an effect on working memory in both post-test and follow-up stages in the experimental group. The amount of this effect in the post-test and follow-up stages was 22.4% and 13.4% respectively. A statistical power approaching unity and a significance level near zero are indicative of the adequacy of the sample size.

As is shown in Table 4, the experimental group has been able to be significantly more effective in elevating the working memory level of the individuals with multiple sclerosis (MS), in contrast with the placebo and control groups. No significant difference was observed between the control and placebo groups in post-test and follow-up stages (Table 4).

4. Discussion

The results of the present study conform to the results obtained in prior research in this regard (Hildbrandt et al., 2007; Vogt et al., 2008, 2009). Hildbrandt et al. (2007) reported the positive effects of cognitive training on the memory and working memory of RRMS patients. They concluded that treatment improves performance, on the one hand, and it neutralizes performance deterioration, on the other. Rosti-Otajarvi and Hamalainen (2011), reported few, though positive, evidences regarding the effectiveness of neurological rehabilitation on MS patients. The results of their study, using Cochran's method, indicated that the administered training program substantially influences the memory span as well as the working memory.

Vogt et al. (2008, 2009) showed the positive effects of cognitive training on working memory in MS patients. They also applied high-intensity training and distributed training for the patients and finally concluded that the cognitive training has positive effects on the working memory in both groups. Also, they found out that the positive effect of training has nothing to do with the amount and the intensity of the training. Issues like time duration and the intensity of the intervention are of great importance in cognitive rehabilitation. Shatil, Metzer, Horvitz, and Miller (2010) reported that more tangible results can be obtained if the cognitive interventions are implemented over a far longer duration of time in order for the reorganization to take place in the brain or for more novel strategies to be devised. Their study demonstrated that compressed and home-based cognitive intervention (three sessions a week for 12 weeks) is effective on memory improvement and information processing speed—counter to the study conducted by Vogt et al. (2008), where the intervention intensity was not proved effective on positive results. In the present study, cognitive intervention was delivered to MS patients for 8 sessions on a weekly basis. In addition to in-clinic training sessions, the patients were given homework so as to be able to better memorize the session contents as well to have more practice to attain their personal goals. Furthermore, the training material

Table 3. The results of multivariate analysis of variance of the effects of group membership on working memory scores.

Dependent variable		SS	df	MS	F	*p*	η_p^2	Observed power
Post-test working memory	Contrast	175.633	2	87.817	8.104	.001	.224	0.949
	Error	606.820	56	10.836				
Follow-up working memory	Contrast	78.593	2	39.297	4.330	.018	.134	0.729
	Error	508.252	56	9.076				

Note: SS = sum of squares; MS = mean square.

Table 4. Results of pairwise comparisons.

Dependent variable	Pairwise comparison	Mean difference	SE	p
Post-test working memory	Experimental group - Placebo group	2.939	1.041	.007
	Experimental group - Control group	4.087	1.049	.000
	Placebo group - Control group	1.147	1.046	.277
Follow-up working memory	Experimental group - Placebo group	2.536	0.953	.010
	Experimental group - Control group	2.321	0.960	.019
	Placebo group - Control group	−0.215	0.957	.823

and solutions provided in previous sessions were reviewed at the beginning of every session.

Generally, in addition to the positive effects of the cognitive rehabilitation training, the patients accomplished those personal objectives they had determined in the first session. In Wilson's opinion (2009), opines that rehabilitation programs do not solely target memory in such a way that individuals are trained to perform the memory exercises or learn a list of words more effectively; rather, the goal is enabling individuals to achieve their own personal objectives. Thus, such goals should be the focus of the memory rehabilitation programs.

Among the cases in which the effectiveness of the rehabilitation program can be evaluated is the use of controlled randomized experiments, preferably under a double-blind condition. Of course, perfect implementation of such conditions is very difficult due to the nature of rehabilitation program, and the great majority of the patients gain awareness of the treatment they receive. The present study, which was carried out in double-blind format (for both the patients and the statistics analyzer), tried to keep the patients and the statistics analyzer uninformed of the program's objectives and the treatment allocation but having an independent assessor was not possible. Therefore, the obtained results can be attributed to the effectiveness of the cognitive rehabilitation program on patients' working memory performance.

All of the participants in the present study had been diagnosed with memory disorders, and they were evaluated by the use of standard tests. The patients mostly indicated weak to medium neurological disorders (EDSS < 4), and they were in the normal range (GHQ < 22) in terms of the psychological health variables. Controlling such factors can constrain the generalization of the results to the other groups of such patients featuring more severe neurological and psychological disorders. Also, such a control was accompanied by limitations regarding the size of the study sample. Finding a group of patients who, in spite of memory problems, are in a normal range in terms of neurological and psychological health faced the author of the current research paper with difficulties, and, subsequently, it was decided that a sample size of 60 would suffice. For this reason, it can be suggested that future research should consider running the rehabilitation program on groups featuring more diversity and various degrees of impairment as well as larger study sample sizes.

5. Conclusion

The results of this study showed that the cognitive rehabilitation training program had a positive effect on the working memory of patients with MS—results that have been well demonstrated in post-tests and follow-up tests. Based on the evaluations performed through relevant cognitive tests, cognitive intervention has been able to exert a significant effect on the MS patients' working memory performance. Moreover, it was found, from the evaluations undertaken, that the study objective was met. The intervention program was able to exert a significant effect on the MS patients' working memory performance, according to the current research paper. The examinations were carried out via the Wechsler Memory Scale–III (WMS–III) (Wechsler, 1997), which is a frequently used test for assessing memory function.

Disclosure statement

No potential conflict of interest was reported by the authors.

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