Title: A Comparison of the Effectiveness of Computer-Based, Manual-Based, and Combined Cognitive Rehabilitation on Cognitive Functions in Relapsing-Remitting Multiple Sclerosis

Running Title: Cognitive Rehabilitation in Multiple Sclerosis

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ABSTRACT

Introduction: This study aimed to compare the effectiveness of computer-based, manual-based, and combined cognitive rehabilitation to improve cognitive functions among patients with relapsing-remitting multiple sclerosis.

Methods: In the quasi-experimental design with the , posttest, and 2-month follow up, sixty female patients with relapsing-remitting multiple sclerosis were selected by convenience sampling and randomly assigned to three experimental groups (computer-based, manual-based, and combined cognitive rehabilitation, each group including 12 patients), a sham (12 patients) and a control group (12 patients). The interventions were conducted in 21 sessions for experimental groups during 5 months. The sham group as physical rehabilitation intervention and the control group received no intervention. Participants were assessed by Psychiatric-Neurological Profile, Mini-Mental State Examination Inventory, Kurtzke Expanded Disability Status Scale, Stroop Color and Word Test, Wisconsin Card Sorting Test, and Paced Auditory Serial Addition Test. Data were analyzed by repeated measures multivariate analysis of variance with SPSS-22 software.

Results: The effect of group factor is not significant (η2=0.129), but the effect of time (η2=0.884) and interaction effect of time and group (η2=0.295) are significant (P<0.05). There is no significant difference between the effects of all three rehabilitation interventions (P>0.05). In posttest totally and in follow up partially, all comparisons among three experimental groups with control and sham groups were statistically significant (P<0.05).

Conclusion: Cognitive rehabilitation is effective to improve cognitive functions in patients with relapsing-remitting multiple sclerosis. So, these cognitive rehabilitation protocol are recommended for application along with other treatment protocols to improve cognitive functions of relapsing-remitting multiple sclerosis in clinical settings.

Key Words: Cognitive rehabilitation, executive functions, working memory, selective attention, multiple sclerosis

1. INTRODUCTION

Multiple Sclerosis (MS) is a demyelinating disease of the Central Nervous System (CNS) that causes the deterioration of nerve cells (Lemus et al, 2018). Studies have shown that women are more likely
than men, apt to MS (Leray et al., 2016). Although the primary cause of the disease remains unknown, the main hypothesis is based on the activity of regulatory T cells in an autoimmune process (Bittner et al., 2017). Genetic, immunological factors and environmental factors are involved in the incidence of this multi-factorial disease. The most prevalent signs of the disease include paresthesia or numbness, diplopia, weakness, fatigue, and dizziness (Hampshire-Araújo et al., 2017). The four pathological courses that have been recognized in MS including: (1) clinically isolated, (2) relapsing-remitting, (3) secondary progressive, and (4) primary progressive (Lemus et al., 2018; Leray et al., 2016; Hampshire-Araújo et al., 2017) Relapsing-remitting MS (RRMS) is the most common types of MS, which included more than 80% of the cases. In the early stages of the disease, attacks are unpredictable and symptoms suddenly appear at any time. The patients will continue a few days or a few weeks and will disappear again. It seems that there is no MS progression between attacks, and it is possible the patients be asymptomatic for many years (Burks et al., 2009). In the present study, we examined the cognitive problems in relapsing-remitting MS that are among the problems that patients might experience. Based on the neuropsychological tests, most patients with MS suffer from cognitive impairments that can affect the personal and professional life (Hämäläinen & Rosti-Otajärvi, 2016; Ferreira, 2010; Mollison et al., 2017). It seems that cognitive impairments are very diverse among MS patients. In this regard, working memory, information processing speed, executive function, and attention are the most common functions which are at risk in MS (Fuso et al., 2010).

Working memory is one of the major disruption in this disease that it is mild or inconsiderable in the early stages of the disease (Vacchi et al., 2017). Working memory is defined as brain function that temporarily stores information and manages them to carry out activities (Sohlberg & Mateer, 2017; Costa et al., 2017). Ferreira (2010) found that damage in frontal lobe can reduce the performance of working memory.
The decline in the information processing speed is a key flaw in MS and it can be seen in 20-30% of patients. Information processing efficacy is the brain's ability to maintain and manipulate information in the shortest time. The deficits in speed of processing are related to the slowness of nerve activity due to demyelination of axons that may affect an MS patient's ability to complete tasks and also deal with hard works (Covey et al., 2011). Executive functions are cognitive abilities, including, planning, organizing, reasoning, and abstract conceptualization that is necessary for coping with environmental changes (Ferreira, 2010; Lincoln et al., 2015). Patients with MS compared with the control group are faced with some problems in the tasks related to executive functions such as sorting cards assignments (Lincoln et al., 2015).

Patients with MS have also problems with selective attention which has an important function for activities of executive systems (Güçlü Altun et al., 2015). Many MS patients with deficits in executive functions have major difficulties in complex functions such as selective attention, failure in careful concentration on special stimulus, and discovering complicated stimuli with emotional tasks (Mattioli et al., 2012; Nejati, Shahidi, & Helmi, 2016; Rilo et al., 2018).

The measurement and intervention in cognitive functions in patients with MS are undoubtedly an important issue. Mini-Mental State Examination Inventory (MMSE) assess cognitive functions such as orientation, language, attention and concentration, calculation, recall, and perception (Folstein, Folstein & McHuge, 1975). The Stroop Color and Word Test (SCWT) as a classical test in four stages was applied for assessment of frontal lobe and selective attention and executive control (Stroop, 1935). The Wisconsin Card Sorting Test (WCST) assess the frontal lobe executive functions such as solution skills and decision-making (Grant & Berg; 1948; DeRosnay, 2008). Paced Auditory Serial Addition Test (PASAT) assess working memory and information processing speed of MS patients (Tombaugh, 2006). The standard PAST test consists of 61 numbers which broadcast auditory at 3-second intervals (Negels et al., 2005). Furthermore, the neurological impairment tests such as the Kurtzke Expanded
Disability Status Scale (EDSS) quantify disability and neurologic impairment in MS (Kurtzke, 1983). EDSS is a criterion with 8 options (pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral, and others) on the basis of illness stages and levels of neurological disability in patients with MS.

Cognitive rehabilitation, as an attempt to restore lost cognitive capacities by training and provide targeted incentives for accepting, aims to improve individual performance in the implementation of activities (Kellay & O'Sullivan, 2015). Cognitive rehabilitation is a treatment mainly set to improve deficiencies and cognitive performance, such as memory, executive function, social perception, attention, problem-solving, and judgment as well as disorders of cognitive, mental, motor, and behavioral skills in patients (Bonavita et al., 2015; Amato et al., 2014; Hancock et al., 2015).

The interventions in this study implemented using the Pars Cognitive Rehabilitation Package and Captain's Log Computerized Cognitive Training System. Pars Cognitive Rehabilitation Package consists programs for Neurocognitive Joyful Attentive Training, which was developed by Nejati et al. (2016) in the Cognitive Neuroscience Center at Shahid Beheshti University, and it includes strengthening attention exercises and working memory. The manual Cognitive Rehabilitation Protocol was designed based on cognitive rehabilitation guideline by Kellay and O'Sullivan (Kellay & O'Sullivan, 2015), Pars Cognitive Rehabilitation Package by Nejati, Shahidi and Helmi (2016) as Neurocognitive Joyful Attentive Training and Hierarchical model of cognitive rehabilitation by Sohlberg and Mateer (Sohlberg & Mateer, 2017). The computer-based cognitive rehabilitation protocol was designed based on the Captain's Log Computerized Cognitive Training System (Sandford, Browne,& Turner, 1996). The first version of the Captain's Log Computerized Cognitive Training System developed in 2001 by Brain Train Company to improve cognitive functions and processes. The cognitive functions including attention and concentration, working memory, instant memory, and short-term visual and audio memory, visual and auditory processing speed, auditory and visual
perception, sensorimotor coordination, improve hand-eye coordination, visual processing and micro-motion control, problem-solving skills, executive function, and speed of response (Sandford, Browne, & Turner, 1996).

The combined protocol of cognitive rehabilitation was constructed based on the Captain's Log Computerized Cognitive Training System and Pars Cognitive Rehabilitation Package (Sandford, Browne, & Turner, 1996; Nejati, Shahidi, & Helmi, 2016). The Pars Cognitive Rehabilitation Package, based on the hierarchical model is a series of pen-paper program for improvement executive functions and consists a hierarchically organized group of assignments that reinforce different aspects of executive functions (Nejati, Shahidi, & Helmi, 2016). In this model, the effects of interventions on cognitive domains such as conceptualizing, planning, and memory through frequent exercises and skills training was evaluated. Through this program, assignments are designed in a hierarchy and their difficulties increase based on user response beyond sessions. Assignments are organized based on various functions of attention, working memory, and inhibition. These assignments can be repeated until the patient reaches the desired level. The decision for the development of the program is based on the efficiency of the patient. Through this program, the presence of a therapist is needed to improve the assignment level (Sohlberg, 2017).

The study in psych-neurological interventions introduces two cognitive rehabilitation protocols, and compares the effectiveness of them for improving cognitive performance in patients with MS. No survey was carried out in this field and in this viewpoint, it considered as an applied research. The recent research aimed to compare the effectiveness of computer-based, manual-based and combined cognitive rehabilitation in the cognitive functional improvement of female patients with relapsing-remitting MS and identify the difference of these rehabilitation methods in cognitive function improvement of these patients.
2. Methods

2.1. Study design

The study is a quasi-experimental design with pretest, posttest, 2-months follow up accompanied by a sham and a control group.

2.2. Participants

The population of this study is all patients with relapsing-remitting multiple sclerosis in Arak, the capital city of Markazi Province, Iran from July 2016 to March 2017. Sixty female patients with relapsing-remitting multiple sclerosis were selected by a convenience sampling method and then randomly assigned to five groups of 12 persons, including three experimental groups (computer-based, manual-based, mixed cognitive rehabilitation training, respectively) and one sham group as physical rehabilitation intervention and one control group that it received no intervention. Inclusion criteria included age between 18 and 45 years, EDSS≤3.5, MMSE between 10 and 20 and moderate and higher literacy. In addition, exclusion criteria were including pregnancy during the period of study or decision of pregnancy at the beginning of the study, the lack of regular medical checkup or follow up treatment, and MS attack one past month and during the study, comorbidity with psychotic/major psychopathologies, comorbidity with major medical disease and hearing or speaking difficulties. To control confounding factors, the type of medication, dosage, and duration of drug consumption was controlled by controlling the drug type and matched by conditions of drug consumption for all patients. In addition, the severity of the disease at the onset and during the study was controlled by a neurologist. Matching on demographic variables is not performed because of sample size limitations and fairly balanced and the partly the same proportion of demographics in the groups. All three cognitive rehabilitation interventions were implemented by three MSc in clinical psychology that had already been trained and supervised by the researcher in Arak Payam Noor University Counseling
Center. Physical rehabilitation intervention in the sham group was carried out by a specialist in sports and health in Arak City.

2.3. Instruments

In this study, the Psychiatric-Neurological Profile (neurologist diagnosis, signs, symptoms, physical and clinical examination and results of paraclinical examinations such as MRI for diagnose MS), MMSE and EDSS were conducted at the initial screening for recording background characteristics and to consider inclusion/exclusion criteria. The reliability of the MMSE is acceptable and the validity of original test-retest, within 24 hours among patients with dementia was 0.89. In the study by Folstein et al.(1975) the validity of test-retest with an interval of 4 weeks in patients with dementia gained as 0.99. In addition, the SCWT, the WCST, and the PASAT as neuropsychological measurements were applied to collect the outcome data on cognitive functions at the pretest, posttest and follow up assessments. In the present computer-based study, SCWT was divided into three stages: a) at the first level, that is the level of coordinated trials, names of four main colors with black color appear in the center of the computer screen, and patient should as quickly as possible push one of the blue, red, yellow, or green keys according to their names; b) At the second level, names of four colors with their colors appear on the computer screen and the patient should as quickly as possible push the keys according to their colors; and C) the third step is the level of inconsistency or interference trails. Through these levels, the names and colors appear with different color and patient should as quickly as possible push the keys. The validity of the Wisconsin Card Sorting Test to assess cognitive impairment and the reliability of this test is high (Kohli& Kour, 2006). Studies have shown that the results of tests of memory in MS patients are significantly correlated (Tombaugh, 2006).

2.4. Procedure
Participants in all groups were tested in pretest phase before the start of the study. The study was conducted over 21 sessions of cognitive rehabilitation for intervention groups (5 months). Finally, all groups were tested in the posttest. In addition, two months after intervention all groups were tested in follow up assessment. All three cognitive rehabilitation interventions (the manual Cognitive Rehabilitation, the computer-based cognitive rehabilitation and the combined cognitive rehabilitation) were implemented at one-hour period once a week in twenty-one sessions. The contents of the sessions in three interventions include: Memory (immediate or working memory; short-term memory; remote or long-term memory or type of remembered information, including verbal; spatial; and motor skills), Information processing speed (formulate an appropriate response, processing sentences and making sense of conversations, processing of visual information in a short distance, processing auditory, and processing of incoming information), Attention (selective attention, divided attention, alternating attention, and sustained attention), Executive functions (planning and organizing sequencing such as completing complex tasks, flexible thinking, motivation/drive, self-monitoring, problem-solving, self-correction, diminished abstract reasoning, poorer decision making, and distractibility). In addition, these protocols include related psycho-neurological skills, including linguistic functions and visual-perceptual functions. The process of cognitive rehabilitative programs contains main four steps: 1. Remediation: retraining of disturbed functions, 2. Substitution: reorganizing functions, 3. Accommodation: promoting the use of preserved functions, and 4. Assimilation: learning compensation strategies.

2.5. Ethical considerations

The study was reviewed and approved by the Institutional Review Board (IRB) in the Higher Education Center of Semnan University with the Code 235/95/98 (May 2016). According to the ethical
standards of for human experimentation based on the Helsinki Declaration, the rights, and welfare of participants are protected during this study. The study was conducted with regard to the professional ethics in research on human, including confidentiality, the probability for leave the study and protection of well-being of the participants. In addition, informed written consent was obtained from participants at the beginning of the study.

2.6. Statistical analysis

Statistical analyses were performed with repeated measures multivariate analysis of variance (Repeated measures MANOVA) by SPSS-22 software. Repeated measures multivariate analysis of variance was applied to study the effects of cognitive rehabilitation interventions assigned to working memory, selective attention, executive function, and information processing speed at three-time intervals. Initially, according to the assumptions of the statistical analysis, the results showed that the sphericity of all variables is rejected. To evaluate the Pillai’s effect, the size and corrected values of Huynh–Feldt were used. The homogeneity of the assumed variances was studied according to Levine’s Test and found that the assumption in 0.01 levels is true in all variants in all steps of pretest, posttest, and follow up. In this analysis, the statistical significance level was used to test the hypotheses was p<0.05.

3. Results

Participants are within an age range of 18 to 45 years with mean age±standard deviation 29.65±7.47. The mean and standard deviation of age in the computer-based intervention, the manual-based intervention the combined intervention, the sham, and the control groups were 30.166±7.20, 29.41±5.48, 27.83±8.49, 31.16±8.42, and 29.70±7.79, respectively. According to the educational level, the participants were divided into 8 categories: Elementary literacy (16.7%), High school
literacy (16.7%), Diploma (10%), Associate degree (23.3%), Undergraduate (20.3%), MSc degree (8.3%), and Ph.D. degree (5%). Moreover, 53.3% and 46.7% of the women were single and married, respectively. The women studied in this group were suffering multiple sclerosis for 2 to 7 years. Interferon beta-1a (interferon beta 1-alpha) was the only drug used for patients.

The mean and standard deviation of working memory, selective attention, executive function, and information processing speed in the pretest, posttest, and follow up for all five groups were reported in Table 1.

The results of the multivariate tests show that group factor is not statistically significant (Pillai's Trace=0.515, F_{16,220}=2.033, P>0.001, Partial Eta Square=0.1290), while the effects of time in the Partial Eta Square (Pillai's Trace=0.884, F_{8,48}=45.750, P<0.001, Eta square=0.884) and interaction of time in group Partial Eta are statistically significant (Pillai's Trace=1.036, F_{32,204}=2.228, P<0.001, Eta square=0.259). Moreover, the results of multivariate tests of within-subjects show that the effect of the time factor (Pillai's trace=19.048, F_{8,216}=19.048, P<0.001, Partial Eta Square=0.414) and the time (Pillai’s Trace=0.824, F_{32,440}=3.567, P<0.001, Partial Eta Square=0.206) is significant. For the follow up group, the univariate analysis was used and the results showed that the main effect of time (pretest, posttest, and follow up) on working memory scores (F=76.776, P<0.001, Partial Eta Square=0.583), selective attention (F=102.670, P<0.001, Partial Eta Square=0.651), executive performance (F=141.540, P<0.001, Partial Eta Square=0.720), and information processing speed (F=16.401, P<0.001, Partial Eta Square=0.230) is significant. The interaction with follow up univariate tests was performed and found that the interaction time in the working memory scores (F=10.924, P<0.001, Partial Eta Square=0.443), selective attention (F=15.012, P<0.001, Partial Eta Square=0.522), and executive performance (F=20.976, P<0.001, Partial Eta Square=0.604) is significant, but the interaction effect of time in processing speed scores (F=2.923, P>0.001, Partial Eta Square=0.175) is not
significant. The findings in comparison of differences between the control and sham groups were not statistically significant (P>0.001).

Paired comparison after the experience and adjustment was followed by the Bonferroni method (Table 2). The working memory capacity of computer-based groups and sham in posttest were significantly different (D=3.917, P<0.001). The comparison of two groups showed that the mean of sham group is less than that of the computer-based group, suggesting that computer-based cognitive rehabilitation is effective for improvement of working memory (Figure 1A). In selective attention, two computer-based rehabilitation and sham groups in posttest were significantly different (D=2.750, P<0.05). Comparing these two groups shows that the mean score of sham group is lower than that of the computer-based rehabilitation; namely, the intervention was effective in improving selective attention. In selective attention, computer-based rehabilitation and control groups in posttest were significantly different (D=3.583, P<0.01). The selective attention between manual and computer-based rehabilitation in the posttest was significantly different (D=2.917, P<0.05). Moreover, the selective attention between computer-based rehabilitation and control group at the posttest was significantly different (D=2.833, P<0.05); namely, the intervention was effective on selective attention in follow up. The mean difference between computer-based and sham groups (D=−2.833, P<0.05), computer-based and control groups (D=−2.417, P<0.05), manual and sham groups (D=−2.000, P<0.05), manual and control groups (D=−2.083, P<0.05) were statistically significant.

In posttest, all comparisons among three experimental groups with control and sham groups were statistically significant (P<0.05). In addition, in follow up, most of these comparisons were statistically significant (P<0.05).
The working memory in computer-based and sham groups (D=3.917, P<0.001), computer-based and control groups (D=3.583, P<0.01), manual and sham groups (D=2.917, P<0.05), manual and control groups (D=2.583, P<0.05), combined and sham groups (D=-3.833, P<0.01), and combined and control groups (D=3.500, P<0.01) during the posttest were significantly different, suggesting the effectiveness of the intervention in all three computer-based, manual-based, and combined cognitive rehabilitation on working memory (Figure 1-A). The effects of the intervention of three rehabilitation methods (computer-based, manual-based, and combined) with the control (D=2.833, P<0.05; D=2.917, P<0.05; D=2.833, P<0.05) and computer-based and combined intervention with sham group (D=2.750, P<0.05) on improvement of selective attention in the posttest is significant (Figure 1-B). Executive performance of computer-based and sham groups (D=-3.083, P<0.05), computer-based and control groups (D=-2.667, P<0.05), manual and control groups (D=-3.083, P<0.05), combined and sham groups (D=3.333, P<0.01), and combined and control groups (D=2.917, P<0.05) in the posttest indicate significant differences. The executive function in computer-based and sham groups (D=-2.417, P<0.05), manual and sham groups (D=-2.667, P<0.05), manual and control groups (D=-2.333, P<0.05), combined and sham groups (D=2.667, P<0.05), and combined and control groups (D=2.333, P<0.05) during the follow up were significantly different, suggesting the effectiveness of the intervention in all three computer-based, manual-based, and combined) methods of rehabilitation of executive function ((Figure 1-C). Information processing speed in computer-based and sham groups (D=-87.167, P<0.001), combined and sham groups (D=81.083, P<0.05), and the combined group and control (D=84.500, P<0.01) at posttests are significantly different. Thus, it can be suggested that the combined effect of the two methods can improve the speed of the computer and information processing (Figure 1-D).

4. Discussion
Although the findings showed lack of significant difference between all types of cognitive rehabilitations (computer-based, manual, and combined), but suggest the effectiveness of each of these interventions on working memory, selective attention, executive function, and information processing speed in comparison with sham and control groups. The results of this study are consistent with those results of the computer-based cognitive rehabilitation developed by Lincoln and his colleagues that could improve attention and memory in patients suffering from multiple sclerosis (Lincoln et al., 2015). In addition, a clinical trial was accomplished by Cerasa et al. (2013) for attention deficits showed improvement of intentional functions in patients with multiple sclerosis (Cerasa et al., 2013). Among recent studies, Vogt et al. (2009) in a computer-based training about executive functions including working memory in patients with MS showed the relative effectiveness of the computer rehabilitative program on processing speed, and working memory in 30 patients and 20 healthy controls during 45-minute sessions per week (Vogt et al., 2009). Also, Mattioli et al. (2010) indicate the intensive cognitive rehabilitation, including memory techniques, enhances executive function, especially memory and recall (Mattioli et al., 2010). Their work could markedly enhance the ability of patients with cognitive impairment compared with the control group. In the randomized clinical trial by Mattioli et al. (2010), new techniques were used to improve learning and memory performance of patients (MS) that results showed that memory impairment in MS can be effectively treated through a rehabilitation program memory using text and images (Mattioli et al., 2010).

In another study, Bonavita et al. (2015) tried a computer-aided cognitive rehabilitation to improve cognitive performances that showed significant improvement in the training group compared to the control group with cognitive abilities (Bonavita et al., 2015). Moreover, they showed that personal cognitive training is a practical and valuable procedure for improving cognitive abilities and reducing neurocognitive signs in relapsing-remitting MS (Bonavita et al., 2015). The results of Pusswald et al.
(2014) showed that the computer-based neuropsychological rehabilitation can significantly improve executive functions including processing speed, cognitive flexibility, visual and verbal declarative memory performance as well as the efficiency of the prefrontal cortex, administrative skills and memory in this group (Pusswald et al., 2014). Moreover, the results of the present study are consistent with those reported by Mäntynen et al. (2014) using a computer-based neuropsychological rehabilitation that the results of their study showed this intervention reduces cognitive deficits for MS patients (Mäntynen et al., 2014).

As previously noted, this study exhibited a statistically significant difference in computer-based, manual-based, and combined cognitive rehabilitation groups with the control and sham groups between pretest, posttest and follow up. According to these results, computer-based, manual-based, and combined cognitive rehabilitation was effective on working memory, selective attention, executive functions, and information processing speed. As Bonavita et al. (2015) noted computer-aided cognitive rehabilitation with cognitive training and effects on the neuropsychological mechanisms may improve memory, attention, and executive functions (Bonavita et al., 2015). It can be argued that computer-based cognitive rehabilitation, manual-based cognitive rehabilitation or combination of computer-based and manual-based cognitive rehabilitation decelerate the loss of cognitive deficits among MS patients because of cognitive plasticity toward cognitive training in these patients. Accordingly, planning strategies and treatment agenda to recover and prevent cognitive impairments is important for patients with MS. In addition, it can be concluded that cognitive functions in MS may be improved due to cognitive rehabilitation, whether computer-based or manual-based intervention impact on prefrontal and frontal functions including, cognitive problems and this treatment accompanied with cognitive remediation and reinforcement of adaptive cognitive abilities. Mattioli et al. (2010) suggested that new technologies for cognitive enhancement, including computerized cognitive training plans are objective, convenient and cost-benefit for administration by
trainers and trainees and as tailored interventions have been effective to enhance cognitive functions. Pusswald et al. (2014) argued that the cognitive rehabilitation is especially effective intervention when patients have memory impairments in moderate to severe level. In addition, with regard to the lack of significant differences between all interventions with together, it is concluded that cognitive rehabilitation is tailored intervention that it has effectiveness and efficacy unrelated to administration format and applied in the background of multidisciplinary interventions.

Based on our knowledge this quasi-experimental design with a randomized clinical trial is the first study to compare the effectiveness of computer-based, manual-based, and combined cognitive rehabilitation on improving cognitive functions of patients with relapsing-remitting multiple sclerosis. Due to the fact that the effects of the cognitive rehabilitations are very likely different in patients with diverse neuropsychological profile and distinctive severities of cognitive impairments, different rehabilitation programs, including computer-based, manual-based or combination cognitive rehabilitation may be required in MS. The benefits of computer-based cognitive rehabilitation, including convenient accessibility to the intervention, low cost in real-world application and powerfully intervention adherence are main reinforcements for greater tendency to use of computer-based cognitive rehabilitation in MS management in the future.

The implement of the tailored and curative cognitive rehabilitative programs in cognitive impairments at the onset or earlier phases of the MS before the deterioration of patient’s status is important. Cognitive rehabilitation manuals are encouraging in this respect. These results are shared in bringing about to further progression of MS rehabilitation programs and will also provide information to health care providers for providing the tailored cognitive rehabilitation services for patients with MS. Consequentially; this study overcomes the shortcomings of many studies, including no unrepresentative consequences and passive controls with the sham group. As one advantage, patients
with specific clinical features (relapsing-remitting MS) enable researchers for tailored intervention in this study.

Since the project is based on the development of a contraceptive method, and may not see the noticeable impact in a short period of time, it is needed to perform long-term follow up. In this regard, an 18-month follow up seems enough for this program, but it can be extended if longer follow up for referring the patient to the association and hospital is needed. Another limitation of this study is the inability to apply the techniques to patients in the advanced stages. The study stressed only on some cognitive functions (working memory, selective attention, executive functions, and information processing speed), thus generalizing it to other cognitive functions might not be correct. Furthermore, since this study was performed only on female patients with relapsing-remitting MS, it is suggested implementing it on broader scales on men as well as other types of MS manifestation (such as primary and secondary progressive). Due to irreversible cognitive damage in the advanced stages of the MS, it is also recommended continuing the cognitive rehabilitation programs immediately after the diagnosis along with other medications. Moreover, in the study, the socioeconomic status was not matched in the groups. The statistical sample was small compared to the population heterogeneity that results in restricted generalization. However, the evidence didn’t support socioeconomic differences in these interventions affect the interpretation of the results. Another limitation is that fatigue and depression due to controlling them were not included in this study. These symptoms are common among patients with MS that they bring about cognitive impairments. It is suggested that the psychopathological comorbidity will include in future studies.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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Author’ Contributions

Mehri Rahmani collected the data and participated in drafting the article. Isaac Rahimian Boogar contributed to study design, literature review, conceptualization, and interpretations of the study findings. Siavash Talepasand and Mostafa Nokani contributed to data analysis and interpretations of the findings. All authors were engaged in writing, revising, reviewing, and approval of the manuscript.

References


Tables:

**Table 1.** Descriptive Statistics

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Working memory M±SD</th>
<th>Selective attention M±SD</th>
<th>Executive function M±SD</th>
<th>Processing speed M±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pretest</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Computer-based</td>
<td>19.3±2.74</td>
<td>12.25±2.18</td>
<td>13.42±1.57</td>
<td>1136.42±89.95</td>
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<tr>
<td>Manual</td>
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<td>11.92±1.17</td>
<td>13.25±1.42</td>
<td>1127.83±73.48</td>
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<tr>
<td>Combined</td>
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<td>12.08±1.44</td>
<td>13.33±1.92</td>
<td>1116.25±49.02</td>
</tr>
<tr>
<td>Sham</td>
<td>19.25±3.16</td>
<td>12.00±1.48</td>
<td>13.42±2.23</td>
<td>1119.75±72.01</td>
</tr>
<tr>
<td>control</td>
<td>19.17±2.98</td>
<td>12.17±1.90</td>
<td>13.42±1.92</td>
<td>1125.58±52.04</td>
</tr>
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<td><strong>Posttest</strong></td>
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<tr>
<td>Computer-based</td>
<td>23.25±2.42</td>
<td>9.16±1.99</td>
<td>10.41±1.44</td>
<td>1033.59±35.80</td>
</tr>
<tr>
<td>Manual</td>
<td>22.25±3.10</td>
<td>9.08±1.08</td>
<td>10.00±1.41</td>
<td>1051.00±61.48</td>
</tr>
<tr>
<td>Combined</td>
<td>23.17±3.51</td>
<td>9.16±1.47</td>
<td>10.17±1.94</td>
<td>1039.67±58.57</td>
</tr>
<tr>
<td>Sham</td>
<td>19.33±3.00</td>
<td>11.91±1.38</td>
<td>13.50±2.31</td>
<td>1120.75±74.74</td>
</tr>
<tr>
<td>control</td>
<td>19.78±3.48</td>
<td>12.00±1.70</td>
<td>13.08±2.50</td>
<td>1124.17±87.30</td>
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<tr>
<td><strong>Follow up</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Computer-based</td>
<td>22.25±2.00</td>
<td>9.58±1.88</td>
<td>11.08±1.31</td>
<td>1075.91±63.22</td>
</tr>
<tr>
<td>Manual</td>
<td>20.67±2.80</td>
<td>9.91±0.90</td>
<td>10.83±1.40</td>
<td>1083.75±52.52</td>
</tr>
<tr>
<td>combined</td>
<td>22.75±3.72</td>
<td>9.83±1.64</td>
<td>10.83±1.69</td>
<td>1055.83±60.42</td>
</tr>
<tr>
<td>Sham</td>
<td>19.33±2.64</td>
<td>11.91±1.24</td>
<td>13.50±2.40</td>
<td>1117.50±71.58</td>
</tr>
<tr>
<td>control</td>
<td>19.59±4.03</td>
<td>12.00±1.41</td>
<td>13.16±2.40</td>
<td>1128.08±89.60</td>
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</tbody>
</table>
**Table 2.** Paired comparison of working memory, selective attention, executive function, and processing speed in all groups

<table>
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<tr>
<th>Variable</th>
<th>The mean difference of experimental group from control group:</th>
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<tr>
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<td>Pretest</td>
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<tr>
<td>Working Memory</td>
<td>1.250, 1.083, 0.167, 1.083, 1.000, 1.3917***, 1.5</td>
</tr>
<tr>
<td></td>
<td>5.083, 2.3, 1.67, 2.4, 0.83, 2.4</td>
</tr>
<tr>
<td></td>
<td>5.033, 3.4, 0.083, 3.5</td>
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<tr>
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<td>0.0167, 4.5, 0.0250</td>
</tr>
<tr>
<td>Selective Attention</td>
<td>1.033, 3.5, 0.250, 1.67, 3.083, 1.750*, 1.2, 2.833*, 1.4</td>
</tr>
<tr>
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<td>1.5, 0.167, 2.3, 0.83, 2.4</td>
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<tr>
<td></td>
<td>2.5, 0.083, 3.4, 0.083, 3.5, 2.750*, 3.4</td>
</tr>
<tr>
<td></td>
<td>3.5, 0.083, 4.5, 0.83</td>
</tr>
<tr>
<td>Executive Function</td>
<td>1.5, 0.167, 3.5, 0.00, 1.4, 0.00, 1.083, 1.3, 3.083*, 1.4, 2.667*, 1.4</td>
</tr>
<tr>
<td></td>
<td>1.5, 0.250, 2.3, 3.500**, 2.4</td>
</tr>
<tr>
<td></td>
<td>3.083*, 2.5, 0.167, 3.4, 0.417, 3.4</td>
</tr>
<tr>
<td></td>
<td>5.083, 4.5, 0.83</td>
</tr>
<tr>
<td>Processing Speed</td>
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<tr>
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<td>4, 10.833, 1.5, 20.167, 2</td>
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<tr>
<td></td>
<td>3.8, 0.83, 2.4, 2.250, 2.5, 11.583</td>
</tr>
<tr>
<td></td>
<td>3.4, 5.833, 3.5, 5.000, 4.5, 9.333</td>
</tr>
</tbody>
</table>
Note: computer-based group (1) manual group (2), sham group (3), control group (4), combined group (5)
Figure 1. The effect of interaction time on working memory, selective attention, executive function, and information processing speed.