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Clinical study

The therapeutic effect of treatment with RehaCom software on verbal performance in patients with multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is characterized by central nervous system lesions that lead to neurological dysfunctions including fatigue, depression and anxiety. MS is affecting almost 2.3 million people around the world, with the significant highest prevalence in the North America. MS also affects different cognitive abilities, such as attention, memory and executive functions. Furthermore, a significant impairment in verbal fluency and naming abilities in patients with MS has been reported. RehaCom, is a software that has improvement effects on cognitive functions. The goal of this research is to investigate the effect of treatment with RehaCom on verbal performance in patients with MS. To select the participants, 60 patients with MS who referred to our clinic were chosen randomly and divided into Control (n = 30) and Experimental (n = 30) groups. The participants in the experimental group were treated by RehaCom software for 10 sessions during 5 weeks (2 sessions per week and each session was 1 h). Controlled Oral Word Association Test (COWAT) and California Verbal Learning Test – Second Edition (CVLT-II), were used to assess verbal performance (verbal fluency, and verbal learning and memory) at weeks 0 (baseline), 5 (post-test) and 10 (follow-up). The results showed that, treatment with RehaCom improved verbal performance in patient with MS, at both post-test and follow-up stages. In conclusion, treatment with RehaCom cognitive rehabilitation software can improve verbal fluency, and verbal learning and memory in patient with MS, possibly by affecting the brain regions involved in language performance.

1. Introduction

Multiple sclerosis (MS) is characterized by central nervous system lesions that lead to neurologic dysfunctions including fatigue, depression and anxiety [1]. MS onset is most common in individuals between 20 and 40 years old, with more prevalence in women [2]. It has been reported that, MS is affecting almost 2.3 million people around the world, with the significant highest prevalence in the North America (140 cases per 100,000) and European countries (108 cases per 100,000) [3]. Patients with MS are often grouped in three clinical stages: primary progressive MS (PPMS), relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS) that develops from RRMS [4]. MS induces severe demyelination and axonal degeneration, that cause patients with MS experience a progressive loss in various cognitive functions [5]. Furthermore, MS affects different cognitive abilities, such as attention, memory and executive functions [6,7]. However, the evidence for language deficits, especially in the early stages of MS, is inconsistent [8,9]. It has been revealed that, language function is relatively preserved in patients with MS, primarily of the relapsing-remitting subtype [10]; while other reports have shown a significant impairment in verbal fluency and naming abilities in all MS subtypes [11–13]. Furthermore, in the progressive types of MS, patients show weaker performance in most cognitive and linguistic tests than RRMS patients [8,12]. Taken together, speech and language processes are relatively less studied in MS patients [14].

RehaCom, is a software which has improvement effects on cognitive functions [15]. Furthermore, RehaCom is a computerized

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presentation which can provide an special cognitive training to rehabilitate patients [16]. Many studies have reported the therapeutic effect of treatment with RehaCom in various diseases. For example, a recent study has shown the improvement effect of RehaCom on executive functions in patients with schizophrenia [17]. Furthermore, RehaCom improves attention and memory performance in patients with acquired brain damage [18]. Additionally, effectiveness of treatment with RehaCom in patients with MS has been observed in some studies [19,20].

According to the mentioned findings, the goal of this study is to investigate the effect of treatment with RehaCom cognitive rehabilitation software on verbal performance in patients with MS.

2. Material and method

2.1. Participants

60 patients with MS who referred to our clinic (*Brain and Cognition Clinic*) were chosen randomly to participate in the research. All the participants were divided into Control (n = 30) and Experimental (n = 30) groups. Only patients in the experimental group were treated with RehaCom cognitive rehabilitation software. This study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. Age, sexuality and educational status of patients have been provided in Tables 1–3, respectively.

2.2. Sample selection criteria

The criteria for entry was: Patients must be between 18 and 65 years old and have not sensory aphasia, impaired speech comprehension, hemianopia, visual disturbances and hands' mechanical/neuromuscular disorders. By evaluating the speed of hands reaction, mechanical or nervous deficit in the hands was assessed. The participants who had not meet one of the entry criteria were excluded from the study.

2.3. Study assessment

2.3.1. Controlled Oral word Association Test (COWAT)

COWAT, is a verbal fluency test that evaluates spontaneous production of words belonging to the same category or beginning with some designated letter. In other words, COWAT is a measure of a person's ability to make verbal associations to specified letters [21]. COWAT can also discover any alterations in word association fluency found with different disorders [21]. COWAT asks participants to verbally list as many words as possible that begin with "F, A and S", as well as the category "Animals," excluding proper nouns and the same root word with different endings.

2.3.2. California Verbal Learning Test – Second Edition (CVLT-II)

CVLT-II is one of the most widely used neuropsychological tests in the North America. CVLT-II evaluates episodic verbal learning and memory and detects sensitivity to a range of clinical conditions [22]. CVLT-II consists of word lists: List "A", that contains words from different semantic categories with no words from the same category that presented consecutively within the list. List A is presented to the participant five times. On the other hand, List "B", a new list that is structured similarly to List A, is presented to the participant, after the completion of 5-times presentation of List A. Following the recall of List B, free and cued recall of List A is also evaluated. This contains the short delayed recall portion of the test. After a long delay, free and cued recall of List A is evaluated again. This is the long delayed recall portion of the test. Then, subsequent yes/no recognition trials are performed and an optional forced choice recognition component of the assessment can be administered as a measure of test effort. CVLT-II evaluates general verbal learning, response discrimination, primacy-recency effects, organization strategies, recall efficiency and acquisition rate through primary measures.

2.3.3. RehaCom cognitive rehabilitation software

RehaCom is a comprehensive system of software to rehabilitate cognitive dysfunctions [20]. RehaCom has 20 modules in English, that is also available in 21 other languages. RehaCom is auto-adaptive, so the difficulty level will rise and fall depending on the performance of the patient. Furthermore, the therapist can take into account the information obtained from the assessment of the sessions and based on it, provide modules to strengthen brain cognitive functions.

2.4. Experimental procedure

60 patients with MS were chosen and randomly divided into Control (n = 30) and Experimental (n = 30) groups. A comprehensive description of the research goals and the number of treatment sessions were given to the participants by holding an introduction meeting; then, patients were asked to participate in the treatment. After that, participants' language performance and verbal fluency were evaluated using COWAT and CVLT-II. Then, only participants in the experimental group were treated by RehaCom cognitive rehabilitation software for 10 sessions during 5 weeks (2 sessions per week and each session was 1 h). After the completion of 10 sessions, language performance and verbal fluency of all patients in both groups were assessed using COWAT and CVLT-II (post-test). For the follow-up assessment, at the week 10 (5 weeks after the post-test evaluation, during this time there was no any intervention), COWAT and CVLT-II were used to assess participants' language performance and verbal fluency in both groups. It should be noted that, 4 patients of the control group and 3 patients of the experimental group optionally dropped out of the treatment.

2.5. Statistical analysis

To assess any difference between two groups, the mean difference in change score (between baseline and each point of follow-up stages) and respective confidence intervals (95% CI)

Table 1
Distribution of gender in patients with MS in the studied groups.

Sexuality	Control group		Experimental group	
	n	%	*n*	%
Female	22	85	21	78
Male	4	15	6	22
Total	26	100	27	100

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Table 2
Distribution of age in patients with MS in the studied groups.

Age	Control group		Experimental group	
	Mean	SD	Mean	SD
	39.23	7.81	37.11	8.12

Table 3
Distribution of educational status in patients with MS in the studied groups.

Education	Control group		Experimental group	
	n	%	*n*	%
Under diploma	4	15	3	11
Diploma degree	4	15	5	19
Associate degree	6	23	7	26
Bachelor's degree	8	32	8	30
Master's degree	4	15	3	11
Ph.D. degree	0	0	1	3
Total	26	100	27	100

were calculated. The repeated-measures ANOVA was used to assess the therapeutic efficacy over time and possible interaction between time and treatment (time × treatment). All statistical analyses were done using the IBM SPSS Statistics 24.0.0 in a two-tailed approach with significance level P < 0.05.

3. Results

The results of repeated-measure ANOVA showed that, there is a significant efficacy of treatment with RehaCom for verbal learning and memory, and verbal fluency within two groups combined: CVLT-II – (F = 45.11, df = 1.26, P < 0.001) and COWAT – (F = 65.27, df = 1.29, P < 0.001). The analyses of time-treatment interactions also showed that, there is a significantly higher effectiveness for the experimental group compared with the control group in verbal learning and memory, and verbal fluency over time: CVLT-II – (F = 84.55, df = 1.26, P < 0.001) and COWAT – (F = 62.50, df = 1.29, P < 0.001). Additionally, the analyses of between subjects showed that, there is a significant difference between two groups in verbal learning and memory, and verbal fluency: CVLT-II – (F = 904.05, df = 1, P < 0.001) and COWAT – (F = 590.99, df = 1, P < 0.001) (Table 4).

In addition, the results of the effect of treatment on outcome measures over trials showed that, treatment with RehaCom software improved verbal learning and memory, and verbal fluency at week 5 (post-test): CVLT-II – (*MD*, 95% *CL*: −9.42, −16.58 to −2.27 – P < 0.05) and COWAT – (*MD*, 95% *CL*: −6.73, −10.77 to −2.69 – P < 0.01). Furthermore, this effect remained at the follow-up assessment: CVLT-II – (*MD*, 95% *CL*: −7.38, −14.51 to −0.25 – P < 0.05) and COWAT – (*MD*, 95% *CL*: −4.89, −8.70 to −1.07 – P < 0.05) (Table 5).

4. Discussion

As the results showed, treatment with RehaCom cognitive rehabilitation software enhanced verbal performance in patients with MS. In other words, training with RehaCom improved verbal learning and memory, and verbal fluency in patients with MS, at both post-test and follow-up stages. In developed countries, about 10% of people are affected by autoimmune disease [23]. MS is an autoimmune disease that affects central nervous system (CNS) and induces myelin sheath destruction and CNS plaques [24]. The pathogenesis of MS is not completely understood, but MS is described as an inflammatory demyelinating disease and CNS axonal damage correlates with inflammatory processes [25]. Studies have reported that these cognitive impairments are not related only to detrimental effects of inflammation, glial activity and subsequent demyelination, but neuroendocrine factors are also involved [26]. Neuronal dysfunctions that are induced by MS lead to different clinical problems, such as visual disturbances, ataxia, fatigue and mental problems [27]. Unfortunately, cognitive dysfunctions occur in 43–70% of patients with MS [28]. Sleep disturbances and cognitive fatigue have also been observed in patients with MS [26,29]. MS has four basic patterns: relapsing remitting, primary progressive, secondary progressive and progressive relapsing. Unfortunately, in the advance form of MS, reduced mobility, poor gait mechanics and balance, muscle weakness, and cognitive and autonomic dysfunctions are observed [30]. In general, due to the huge number of possible lesion sites in the CNS of patients with MS, symptoms are various and differ from one patients to another, including sensorial disorders, visual problems, urinary dysfunctions, fatigue, cognitive impairments, emotional disorders, anxiety and depression [31–34].

Table 4
Repeated-measure ANOVA: the effect of time, time × treatment and between subjects, between two groups on verbal performance.

Outcome	Baseline		Week 5		Week 10		Time			Time * Treatment Interaction			Between Subjects		
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*F*	*df*	*P*	*F*	*df*	*P*	*F*	*df*	*P*
CVLT-II															
Control	48.08	11.22	47.12	9.84	46.62	10.10									
Experimental	50.11	13.43	56.54	14.29	54	14.17	45.11	1.26	<0.001	84.55	1.26	<0.001	904.05	1	<0.001
COWAT															
Control	24.04	7.39	24.15	7.09	23.73	7.07									
Experimental	25.22	8.47	30.88	8.81	28.62	8.62	65.27	1.29	<0.001	62.50	1.29	<0.001	590.99	1	<0.001

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Table 5
The effect of treatment on verbal performance over the trials in both groups at week 5 (post-test) and week 10 (follow-up).

Outcome	Mean (SD) change in score		Mean difference (95% CI)	*t* (*df*)	*P*
	Control	Experimental			
CVLT-II					
Week 5	47.12 (9.84)	56.54 (14.29)	−9.42 (−16.58 to −2.27)	−2.71 (25)	<0.05
Week 10	46.62 (10.10)	54 (14.17)	−7.38 (−14.51 to −0.25)	−2.13 (25)	<0.05
COWAT					
Week 5	24.15 (7.09)	30.88 (8.81)	−6.73 (−10.77 to −2.69)	−3.43 (25)	<0.01
Week 10	23.73 (7.07)	28.62 (8.62)	−4.89 (−8.70 to −1.07)	−2.63 (25)	<0.05

Verbal fluency disorders affect a variety of forms, including perseveration, the repeating of words or the formation of words that do not belong in a required category [35]. Verbal fluency impairment is an important diagnostic factor of frontal lobe dysfunction, especially frontal lobe of the left hemisphere; however, dysfunctions of the left temporal cortex and/or prefrontal cortex (PFC) are also involved in poor verbal performance [36]. In depressed patients, impaired verbal fluency may be associated with a reduced level of oxyhemoglobin around the frontal lobes [37]. Furthermore, other study has shown that poor verbal fluency may be associated with suboptimal neuronal activity around the caudate nucleus and the frontal part of the callosal gyrus in the left hemisphere of patients with depression [38]. Additionally, poor language abilities has been reported in patients with MS [39]. It's important to note that, the key role of the cerebellum in executive functions, working memory, visuo-spatial functions, attention and language performance has been also reported [40]. In fact, the cognitive role of the cerebellum is related to the existence of well-established anatomical connections in the cerebellum with a variety of high-level cortical regions [41,42]. A significant activation in the right posterior-lateral cerebellum has been observed during various language abilities, such as word generation, semantic processing, phonological processing and verbal fluency task [43]. Therefore, cerebellar damage leads to language dysfunction, and also, impaired executive functions and poor spatial cognition [42]. Interestingly, cerebellar damage is a common feature of MS patients [39]. It has been reported that, almost 30% of patients with relapsing–remitting MS have at least one lesion in their cerebellum [44]. We don't exactly know how cerebellar damages impair cognitive functions in patients with MS, but we know that cognitive dysfunctions in patients with MS who have cerebellar damages are more severe than other patients; with this explanation that, these cognitive dysfunctions mainly belong to the domains of attention and verbal fluency [45]. Furthermore, a decline of verbal fluency has been observed only in MS patients with cerebellar damages, that result in being correlated with gray matter loss in the superior temporal cortex [45]. Additionally, cerebellar damages and atrophies in the frontal and temporal cortices induce poor verbal fluency and attention [46].

The therapeutic effect of computerized cognitive rehabilitation intervention in the improvement of cognitive impairments has been revealed in patients with MS. Previous research has demonstrated that, treatment with RehaCom software enhances cognitive performance in patients with MS [20]. Furthermore, 10-week RehaCom treatment enhanced attention and processing speed scores in patients with relapsing-remitting MS [19]. RehaCom has also therapeutic effect on other diseases. Previous research has reported that, training with RehaCom improves executive functions in patients with schizophrenia [47]. Additionally, our recent research has shown that treatment with RehaCom improves activities of daily living, attention and response control in patients with chronic stroke [48]. The exact effect of RehaCom on the function of brain regions has not been completely recognized; however, it seems that treatment with RehaCom can alter the function of brain regions involved in cognitive functions. For example, previous study has shown alterations in the function of dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC) after treatment with RehaCom [20]. Alterations in the recruitment of DLPFC, PPC, anterior cingulate cortex (ACC) and inferior parietal lobule (IPL) are also observed after treatment with RehaCom [49]. Furthermore, it has been revealed that treatment with RehaCom enhances activation in the bilateral PFC in patients with MS [20]. Additionally, RehaCom improves visual and verbal memory and processing speed by the increase in the functional connectivity between PCC and inferior parietal cortex (IPC) [50]. Therefore, it seems that treatment with RehaCom by affecting the function of different brain regions and their connections, especially brain regions involved in language performance and verbal fluency, improved verbal performance in patients with MS. The results of the present study by showing the possible effect of treatment with RehaCom on the function of the cerebellum and its connections, can provide a broader understanding about the effect of RehaCom on the brain function. There is no many published papers about the effect of RehaCom on different brain regions, especially on the cerebellum. Therefore, more detailed studies with the focus on the effect of RehaCom treatment on the function of the cerebellum are needed.

5. Conclusion

The present study showed that, treatment with RehaCom for 10 sessions during 5 weeks (2 sessions per week and each session: 1 h) improved verbal learning and memory, and verbal fluency in patients with MS. Dysfunctionsk in the left temporal cortex, PFC, frontal lobes and especially the cerebellum, may lead to poor language performance in patients with MS. We suggest that, treatment with RehaCom by affecting these brain regions, improved verbal performance in patients with MS.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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