Published online: June 30, 2020

Short Communication

Computerized cognitive rehabilitation for treatment of cognitive impairment in multiple sclerosis: an explorative study

Irini Vilou[1,†], Christos Bakirtzis[2,†,*], Artemios Artemiadis[3], Panagiotis Ioannidis[2], Malamati Papadimitriou[4], Eleni Konstantinopoulou[1], Eleni Aretouli[1], Lambros Messinis[5], Grigorios Nasios[6], Efthimios Dardiotis[7], Mary Helen Kosmidis[1] and Nikolaos Grigoriadis[2]

[1]*Lab of Cognitive Neuroscience, School of Psychology, Aristotle University of Thessaloniki, Thessaloniki, 54124, Greece*

[2]*The Multiple Sclerosis Center, 2nd Department of Neurology, AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, 54621, Greece*

[3]*Medical School, University of Cyprus, Nicosia, 1678, Cyprus*

[4]*Department of Neurology, Inselspital, University Hospital, Bern, 3010, Switzerland*

[5]*Neuropsychology Section, Departments of Neurology and Psychiatry, University Hospital of Patras and University of Patras Medical School, Patras, 26504, Greece*

[6]*Department of Speech and Language Therapy, School of Health Sciences, University of Ioannina, Ioannina, 45100, Greece*

[7]*Department of Neurology, University of Thessaly, University Hospital of Larissa, Larissa, 41334, Greece*

*Correspondence: bakirtzischristos@yahoo.gr (Christos Bakirtzis)
†These authors contributed equally.

DOI:10.31083/j.jin.2020.02.35

In this explorative study, forty-seven patients with relapsing-remitting multiple sclerosis were randomized to a custom 6-week cognitive rehabilitation intervention (n = 23) using the BrainHQ^{TM} web-based platform and to a control group condition (n = 24). Cognitive rehabilitation intervention consisted of two 40-minute sessions per week. All patients were tested with the Brief International Cognitive Assessment for Multiple Sclerosis battery, the Stroop Color-Word Test, and the trail making test, while the Beck Depression Inventory - Fast Screen questionnaire was used as a measure of mood and the cognitive reserve index as a measure of cognitive reserve. We used the reliable change index, to calculate clinically meaningful changes of performance, and to discriminate between responders and non-responders of this intervention. Statistically significant improvement of the group receiving treatment was observed mainly on measures of verbal and non-verbal episodic memory and, to a lesser extent, on reading speed, selective attention/response inhibition, and visual attention. Verbal memory and visual attention improvements remained significant after considering the corrected for multiple comparisons level of significance. According to reliable change index scores, 12/23 (52.2%) of patients in the intervention group presented meaningful improvement in at least one measure (Greek Verbal Learning Test: 26%, Brief Visuospatial Memory Test-Revised: 17.4%, Stroop-Words test: 13%). This explorative study provides evidence that, at least in the short term, cognitive rehabilitation may improve the cognitive performance of multiple sclerosis patients.

Keywords

Multiple sclerosis; cognitive rehabilitation; cognition; neurobehavior; neuropsychology

1. Introduction

A vast number of people with multiple sclerosis (PwMS) present cognitive deficits (Langdon, 2015). Cognitive impairment may interfere with patient's ability to cope with everyday life activities (Weber et al., 2019) and tends to progress during the disease (Amato et al., 2001). Treatment of cognitive impairment in multiple sclerosis (MS) is challenging with clinicians suggesting that a brief assessment of cognitive functions should be implemented in everyday clinical practice to accurately evaluate disease severity (Bakirtzis et al., 2018; Saccà et al., 2017).

Pharmaceutical agents and supplements used in dementia have not proven to be efficacious in MS (Amato et al., 2013; He et al., 2013) while there is limited evidence to support that disease-modifying drugs may have an impact on cognitive functions in MS (Niccolai et al., 2017). It has been suggested that physical exercise may be an alternate approach since, at least in the healthy population, there is some evidence of beneficial effects on cognitive functions (Feinstein, 2011; Sandroff, 2015). Nevertheless, the beneficial effects of physical exercise on cognition in PwMS remain inconclusive (Sandroff et al., 2016). Considering this phe-

Journal of Integrative Neuroscience

nomenon, together with the fact that intellectual enrichment may protect from cognitive decline (Sumowski, 2015; Sumowski et al., 2010), current research has focused on cognitive training strategies.

Cognitive rehabilitation (CR) has been suggested as a potential therapeutic option for PwMS with cognitive deficits. CR is a neurobehavioral approach aimed at improving patient cognition, as well as assisting patients and their families in improving everyday functionality (Sandry et al., 2016). Previous studies have suggested that CR should be performed early in the disease course to enable the reorganization of cognitive circuits (Penner et al., 2007; Schoonheim et al., 2010). Recent work by Messinis et al. (2020) showed that CR might also improve cognitive functions even in the later stages of the disease. Yet CR studies in MS failed to provide robust evidence of efficacy and were therefore treated with skepticism (Rosti-Otajärvi and Hämäläinen, 2014). Recent randomized clinical trials, with better methodological approaches, have provided some evidence that at least in the short-term, CR may improve cognitive performance in PwMS, especially on memory (Chiaravalloti et al., 2013, 2019; Lincoln et al., 2019; Mousavi et al., 2018). It seems that by focusing on techniques that have been proven efficacious, a positive effect of CR in cognitive functions may be demonstrated (McCabe et al., 2016).

The explorative study makes use of computer programs that are usually designed by clinical neuropsychologists who implement various techniques or use dedicated software for computerized CR, which contain a multitude of activities for several cognitive domains (Dardiotis et al., 2018). The use of home-based CR interventions has been gaining ground in recent years (Wilms, 2020). This approach of rehabilitation has been shown to help patients understand their deficits, as it provides them with immediate feedback on their difficulties. Furthermore, the cost is low, and patients may perform the activities even when they are located at a distance from a rehabilitation unit (Bonavita et al., 2015). However, partial assistance by a therapist may be needed so that patients understand the purposes of the program; a therapist may guide how the program works (De Giglio et al., 2015). Since subjects are required to perform activities with graduated difficulty, periodic optimization of the related training could be performed to enhance the efficacy of the intervention (Messinis et al., 2017). Also, patients may experience anger or disappointment because of their performance in the program. Therefore, a therapist may help them manage these first frustrations (Stuifbergen et al., 2011); otherwise, they may drop out of the intervention (Shatil et al., 2010).

Information processing speed, various aspects of memory, and to a lesser extend attention and executive functions are the cognitive domains more often found impaired in PwMS (Bakirtzis et al., 2018). Although this pattern of cognitive impairment is widely accepted, there is no consensus yet, on how to design and perform a CR intervention to this patient group. Therefore, we aim to evaluate the efficacy of a 6-week semi-assisted home-based cognitive rehabilitation program in patients with relapsing-remitting multiple sclerosis (RRMS). We focus on multiple domains frequently found impaired in MS, and the outcome was a change of performance on cognitive measures of participants. We design a custom CR intervention, tailored to this patient group, that could easily be implemented in clinical practice. This study was approved by the Ethics Committee of the Aristotle University of Thessaloniki (2/27. 2. 2019). It was performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments.

2. Materials and Methods

2.1 Participants

Patients with RRMS diagnosed with the 2017 revised McDonald criteria (Thompson et al., 2018) were included. All participants were recruited from the outpatient clinic and provided written informed consent before their inclusion in this research. Patients were adults diagnosed with RRMS, clinically and radiologically stable for at least 3 months before the inclusion, who performed 1.5 Standard Deviation (SD) units below average on at least one of the neuropsychological measures administered and were not diagnosed with a psychiatric condition. Normative scores used in this explorative study derived from tests' original manuals (Symbol Digit Modalities Test, SDMT; Smith (1982), Brief Visuospatial Memory Test-Revised, BVMT-R; Benedict (1997), or normative studies for the Greek population (Greek Verbal Learning Test, GVLT; (Vlachou et al., 2013), Trail Making Test parts A and B, TMT-A, TMT-B; Kosmidis et al. (2006); Zalonis et al. (2008), Stroop Color-Word Test). Patients were randomized into the intervention group (n = 23) and the control group (n = 24) by an automated randomization software. Participants' demographic, disease characteristics, and baseline performances on testing are presented in Table 1.

2.2 Evaluations

A neurological examination was performed by a certified Expanded Disability Status Scale (EDSS; Kurtzke (1983)) rater. Neuropsychological assessment was performed by an experienced neuropsychologist who was blinded to the patient's group allocation and was carried out in a quiet room with no distractions at the neuropsychology laboratory of the clinic. The assessment included the Greek adaptation of the brief international cognitive assessment for multiple sclerosis (BICAMS) battery (Polychroniadou et al., 2016). This battery includes the GVLT (Vlachou et al., 2013) as a measure of verbal episodic memory, BVMT-R (Benedict, 1997) as a measure of visuospatial memory and the oral version of the SDMT (Smith, 1982) as a measure of information processing speed. Furthermore, trail making test (see, e.g., Zalonis et al. (2008)) was used to evaluate visual attention (TMT-A) as well as divided attention, set-shifting (task switching) and cognitive flexibility (TMT-B; see, e.g., Lezak et al. (2012)). Stroop Color-Word Test (see, e.g., Golden (1978); Kosmidis et al. (2006)) was used to evaluate reading speed (Color test), selective attention, and response inhibition (Color-Word test, Lezak et al. (2012)). Both groups were re-examined within 5 days from the end of training with alternate forms of the tests, where available (SDMT; Smith (1982), BVMT-R; Benedict (1997), GVLT; Vlachou et al. (2013)). Also, in the baseline assessment, the Beck depression inventory fast screen (Beck et al., 2003) was administered as a measure of mood. The cognitive reserve index (CRI) (see Maiovis et al. (2016)) was used to quantify the cognitive reserve of patients based on their level of education, vocational status, and leisure activities.

2.3 Intervention

The 6-week CR intervention was performed using the web-based BrainHQ^{TM} platform (BrainHQ, Posit Sciences, `https:`

Table 1. Baseline Demographical and Clinical Data of participants.

	Intervention Group (N = 23)	Control Group (N = 24)	*P*-value[1]
Age (years)	33.5 (16)	37.8 (19)	0.183
Females	20 (87)	20 (83.3)	1
Duration since diagnosis (years)	8.3 (10.3)	10 (8.5)	0.675
Duration since onset (years)	9.9 (10.5)	12.5 (6.8)	0.39
EDSS	2.9 (1.5)	3.5 (2.5)	0.064
SDMT	49.1 (19)	46.1 (13)	0.388
GVLT	54.2 (26)	56.5 (14)	0.93
BVMT-R	22.6 (14)	22.8 (11)	0.717
TMT-A	51.5 (23)	46.5 (22)	0.907
TMT-B	105.9 (62)	100.8 (54)	0.898
STROOP COLOR	58.7 (27)	56.9 (19)	0.662
STROOP COLOR-WORD	38 (13)	36.7 (8)	0.482
CRI	95 (7)	98.7 (10)	0.064
BDI-FS	4.5 (6)	3.8 (5)	0.379

BDI-FS: Beck Depression Inventory-Fast Screen

Values represent mean values interquartile ranges and frequencies N (%)

[1]Mann-Whitney U tests for numerical characteristics and Fisher's exact test for gender

//www.brainhq.com). BrainHQ^{TM} has been successfully used in various populations such as patients with schizophrenia (Fisher et al., 2014; Surti et al., 2011), healthy older adults (Smith et al., 2009) and patients with MS (Charvet et al., 2017) amongst others. BrainHQ^{TM} enables clinicians to design a custom-made CR program using a variety of training modules. The superiority of the training tests included in this platform over other cognitive exercises has been previously demonstrated (Tennstedt and Unverzagt, 2013). We used this platform since it enables clinicians to determine the participants' level of engagement (Harvey et al., 2019) and allows remote cognitive training. For this explorative study, participants in the intervention group were trained on episodic memory (Memory Grid, Rhythm Recall, and To-Do List Training modules), attention (Divided Attention, Double Decision, Mixed Signals, and Freeze Frame modules) and processing speed (Eye for Detail, Hawk-Eye, Visual Sweeps and Sound Sweeps modules).

CR was home-based and was performed in the patients' native language. Participants were asked to enter the platform twice a week. Patients were trained individually for the use of the platform by a neuropsychologist. The activities were set in advance and were given to patients in printed form (a complete list of the activities is listed in Table S1). Each day of practice, patients had to work on two scheduled activities, dedicating 20 minutes to each one. A trained neuropsychologist got in contact with the participants weekly and assisted them in CR when needed. Also, scheduled visits were performed every 2 weeks, to review and optimize the levels of difficulty in each activity, according to patients' performance.

2.4 Statistical analysis

Baseline demographical and outcome data were presented as means and interquartile ranges and frequencies. Between-group differences were calculated with the non-parametric Mann-Whitney U test due to the small study sample. All within-group differences were computed by using the Wilcoxon test. The effect sizes (r) for the outcome score changes within the intervention group were assessed by the following formula: $r = Z/\sqrt{N}$, where r is the effect size (i.e., < 0.3 small, 0.3-0.5 moderate and > 0.5 large effect size), Z is the score of each Mann-Whitney U test and N is the study sample. To ascertain meaningful changes of outcomes, the Reliable Change Index (RCI) was computed for each participant as previously described (Jacobson and Truax, 1991; Temkin et al., 1999), after controlling for the practice effect by subtracting the difference of mean scores in the control group from the individual score differences in the intervention group. An RCI higher than 1.65, or lower than -1.65, based on the directionality of improvement for each outcome, allowed us to ascertain responders and non-responders for this specific outcome. The role of hours spent in the system and the levels reached in the BrainHQ^{TM} web-based platform were compared between responders and non-responders with the Mann-Whitney U test. The level of significance was set at 0.05. The Bonferroni corrected for multiple comparisons level of significance was 0.007. The data were analyzed with SPSS v22.0 for Windows (Armonk, NY: IBM Corp).

3. Results

The sample consisted of 23 MS patients (mean age 33.5 years old, 87% females) in the intervention group, and 24 patients (mean age 37.8, 83.3% females) in the control group. There were no dropouts. The two groups were not significantly different with respect to disease duration and disability. Also, there were no significant group differences at baseline with respect to neuropsychological assessments and the putative confounders of the cognitive reserve as measured by the CRI ($P = 0.064$) and depressive symptoms as measured by the BDI-FS ($P = 0.379$; Table 1).

Within-group comparisons revealed significant improvements in verbal learning (GVLT, $P < 0.001$), visuospatial memory (BVMT-R, $P = 0.001$), visual attention (TMT-A, $P < 0.001$), task switching (TMT-B, $P < 0.001$), reading speed and response inhibition (Stroop tests, $P = 0.002$) within the intervention group. Surprisingly, a significant improvement in task switching (TMT-

Table 2. Within Group Changes for Study Outcomes.

Intervention Group (N = 23)			
	Before	After	*P*-value[1]
SDMT	49.1 (19)	50 (12)	0.251
GVLT	54.2 (26)	63.7 (17)	< 0.001**
BVMT-R	22.6 (14)	27.5 (10)	0.001**
TMT-A	51.5 (23)	38.2 (20)	< 0.001**
TMT-B	105.9 (62)	73.4 (27)	< 0.001**
STROOP COLOR	58.7 (27)	65.2 (18)	0.002**
STROOP COLOR-WORD	38 (13)	44 (16)	0.002**
Control Group (N = 24)			
	Before	After	*P*-value[1]
SDMT	46.1 (13)	44.5 (13)	0.135
GVLT	56.5 (14)	54.4 (14)	0.13
BVMT-R	22.8 (11)	22.5 (9)	0.867
TMT-A	46.5 (22)	43.4 (21)	0.485
TMT-B	100.8 (54)	82.5 (24)	0.006**
STROOP COLOR	56.9 (19)	57.5 (23)	0.518
STROOP COLOR-WORD	36.7 (8)	38.8 (9)	0.213

Values represent mean raw scores (interquartile ranges) and frequencies N (%)

[1]Wilcoxon signed-rank test

*$P \leq$ 0.05, ** $PC \leq$ 0.007 (Bonferroni corrected level of significance)

Table 3. Between Group Comparisons for Outcome Changes and Effect Sizes.

	Intervention Group (N = 23)	Control Group (N = 24)	*P*-value[1]	Effect Size
SDMT	1.8 (-10, 14)	1.7 (-14, 16)	0.073	0.26
GVLT	9 (-6, 24)	-2.2 (-19, 15)	< 0.001**	0.6
BVMT-R	5 (-6, 15)	-0.3 (-13, 12)	0.01*	0.38
TMT-A	-13.3 (-131, 0)	-2.6 (-45, 22)	0.005**	0.15
TMT-B	-30.6 (-114, 11)	-18.3 (-79, 17)	0.099	0.24
STROOP COLOR	6.5 (-8, 26)	0.6 (-33, 27)	0.038*	0.3
STROOP COLOR-WORD	6.1 (-21, 24)	2 (-16, 30)	0.03*	0.32

Values represent mean raw scores across follow-up (minimum, maximum)

[1]Mann-Whitney U tests

*$P \leq$ 0.05,**$PC \leq$ 0.007 (Bonferroni corrected level of significance)

B, P = 0.006) was noted in the control group (Table 2). When group comparisons were tested by considering individual score changes across follow-up, significantly beneficial effect sizes of the intervention were noted for verbal learning (GVLT, large effect size), visuospatial memory (BVMT-R, moderate effect size), reading speed and response inhibition (Stroop tests, moderate effect size) and visual attention (TMT-A, small effect size; Table 3). Verbal learning and visual attention remained significant after considering the Bonferroni corrected P-value of significance.

More importantly, based on the RCI scores, a total of 12 (52.2%) out of the 23 patients in the intervention group showed meaningful improvement in at least one outcome (Table 4). There were no responders in the control group. Among responders, three patients improved in three tests, two in two tests and seven in one test. Most responders showed improvements in verbal memory (GVLT, 26%), followed by visuospatial memory (BVMT-R, 17.4%) and response inhibition (13% for Stroop Color-Word test), which is consistent with the observed effect sizes. About half of the participants (12/23, 52.1%) were compliant with the study protocol. Responders spent more time in the intervention sessions than non-responders (mean $\pm$ IQR: 4.3 $\pm$ 5.7 vs. 2.3 $\pm$ 2.2 hours), but the difference was not significant (P = 0.412) (Table 5). However, responders reached a significantly higher level of memory than non-responders (mean $\pm$ IQR: 36.6 $\pm$ 65 vs. 12 $\pm$ 11, P = 0.016), which further substantiates the beneficial effect of the intervention for the memory function (Table 5).

Finally, there were no significant differences between responders and non-responders with respect to age (P = 0.608), sex (P = 0.59), disease duration since diagnosis (P = 0.748) or onset (P = 0.652), EDSS (P = 0.76), and baseline SDMT (P = 0.347), GVLT (P = 0.217), BVMT-R (P = 0.069), TMT-A (P = 0.525), TMT-B (P = 0.976), Stroop Color (P = 0.695), Stroop Color-Word (P = 0.449), CRI (P = 0.088) and BDI-FS (P = 0.288).

Table 4. Reliable Change Index Values and Number of Responders to the Intervention for each Study Outcome.

	Mean RCI (IQR) for Intervention	Responders
SDMT	-0.14 (1.11)	2 (8.7)
GVLT	0.99 (0.95)	6 (26%)
BVMT-R	0.77 (0.92)	4 (17.4)
TMT-A	-0.24 (0.52)	1 (4.3)
TMT-B	-0.41 (1.15)	2 (8.7)
STROOP COLOR	0.7 (0.92)	2 (8.7)
STROOP COLOR-WORD	0.38 (0.99)	3 (13)

IQR: Interquartile Range

Table 5. Hours of exercise and levels reached among responders and non-responders.

	Responders (N = 12)	Non-Responders (N = 11)	*P*-value[1]
Hours of exercise	4.3 (5.7)	2.3 (2.2)	0.412
Levels Attention	59.6 (89)	28 (32)	0.151
Levels Memory	36.6 (65)	12 (11)	0.016*
Levels Processing Speed	23.8 (25)	23.6 (44)	0.976
Levels total	119.5 (54)	63 (63)	0.211

Values represent means (interquartile range)

[1]Mann-Whitney U exact test

*$P \leq 0.05$

4. Discussion

Cognitive rehabilitation with the BrainHQ^{TM} web-based platform may improve cognitive functions, especially episodic memory. More specifically, there was a statistically significant improvement in patients' performance in the GVLT, BVMT-R, Stroop, and Trail Making Test tests, with GVLT and Trail Making Test-A remaining significant after considering the Bonferroni corrected level of significance in the study group comparisons. Their improvement in these measures may be attributed to the fact that through the program and their training in attention and memory tests, they learned how they could pay more attention to stimuli so that they can remember them (Temkin et al., 1999). Among the tests mentioned above, the improvement of performance was greater on the memory tests of the BICAMS battery. No statistically significant difference was observed on information processing speed as measured by the SDMT, although many exercises had focused on this cognitive domain. Research in healthy older adults using the Double Decision module has previously demonstrated a positive effect in processing speed (Tennstedt and Unverzagt, 2013). Whether this type of CR intervention may improve the information processing speed of PwMS or not, remains to be further explored, perhaps with the combined use of advanced neuroimaging techniques.

This home-based CR allowed participants to train in those hours and days that were more convenient for each participant. The type of CR activities was preselected by a neuropsychologist based on the cognitive deficits of the studied group observed on baseline assessment. Several cognitive rehabilitation studies have highlighted the importance of distance learning outcomes while showing that cognitive deficits can be improved when the program used has specific activities and objectives, in contrast to non-specific programs available on the internet (Charvet et al., 2017; Chiaravalloti et al., 2013).

The improvement of cognitive performance was greater in those who complied with the program as compared to those who did the activities but missed several of the sessions. Only 12/23 (52.1%) were consistent with the cognitive rehabilitation program despite the assistance provided by the neuropsychologist. Poor adherence is common, especially in-home based CR (Dardiotis et al., 2018); patients may not actively participate because they get frustrated by poor performance in a project and cannot manage it (McCabe et al., 2016; Stuifbergen et al., 2011). Also, during the weekly contacts, participants often reported poor adherence due to cognitive fatigue, a measure of which was not included in this explorative study and, therefore, was not quantified. Regarding the control group's performance, an improvement was only observed in the Trail Making Test Part B, probably due to their familiarity with the tests and the instructions of administration (Buck et al., 2008; Goldberg et al., 2015).

Previous studies have demonstrated that the positive effects of CR may be transient, and patients' cognitive function often returns to a previous state (Mousavi et al., 2018). This phenomenon could be attributed to the lack of modification of relevant cognitive circuits (Filippi et al., 2012). It is still questionable whether brain/cognitive training reflects an improvement in the performance in everyday cognitive activities (McCabe et al., 2016). Nevertheless, regarding MS, when memory training is focused on skills needed in everyday life, such as cooking and financial management, beneficial outcomes may be observed (Goverover et al., 2008). Although practice effects are a crucial issue in serial neuropsychological examinations (Calamia et al., 2012), we tried to overcome this by using alternate forms when available. Our results support the beneficial effects of CR on the cognitive function of MS patients.

Abbreviations

BDI-FS: Beck Depression Inventory-Fast Screen; BICAMS: brief international cognitive assessment for multiple sclerosis; BVMT-R: Brief Visuospatial Memory Test-Revised; CR: cognitive rehabilitation; CRI: cognitive reserve index; EDSS: Expanded Disability Status Scale; GVLT: Greek Verbal Learning Test; IQR: Interquartile Range; MS: multiple sclerosis; PwMS: people with multiple sclerosis; RCI: Reliable Change Index; RRMS: relapsing-remitting multiple sclerosis; SD: Standard Deviation; SDMT: Symbol Digit Modalities Test; TMT-A: Trail Making Test parts A; TMT-B: Trail Making Test parts B.

Author contributions

EK, EA, ED, NG, and MK designed the research. IV, CB, IP, and EK performed the research. AA and GN analyzed the data. MP and LM assisted in the setup of the intervention. IV, CB, AA, LM, NG wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Aristotle University of Thessaloniki (2/27. 2. 2019). It was performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments.

Acknowledgment

The authors would like to thank I. Papadimitriou, M. Ampatzoglou and A. Papadopoulou for their invaluable help in data handling.

Conflict of Interest

The authors declare no competing interests.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://jin.imrpress.com/EN/10.31083/j.jin.2020.02.35.

Submitted: February 09, 2020
Revised: May 02, 2020
Accepted: May 06, 2020
Published: June 30, 2020

References

Amato, M. P., Langdon, D., Montalban, X., Bennedict, R. H., DeLuca, J., Krupp, L. B., Thompson A. J. and Comi, G. (2013) Treatment of cognitive impairment in multiple sclerosis: position paper. *Journal of Neurology* **260**, 1452-1468.

Amato, M. P., Ponziani, G., Siracusa, G. and Sorbi, S. (2001) Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years. *Archives of Neurology* **58**, 1602-1606.

Bakirtzis, C., Ioannidis, P., Messinis, L., Nasios, G., Konstantinopoulou, E., Papathanasopoulos, P. and Grigoriadis, N. (2018) The rationale for monitoring cognitive function in multiple sclerosis: Practical issues for clinicians. *Open Neurology Journal* **12**, 31-40.

Beck, A. T., Steer, R. A. and Brown, G. K. (2003) *Manual for the beck depression inventory - fast screen for medical patients*. San Antonio, CA: Psychological Corporation.

Benedict, R. H. B. (1997) *Brief visuospatial memory test - revised: professional manual*. Florida, CA: Psychological Assessment Resources.

Bonavita, S., Sacco, R., Della Corte, M., Esposito, S., Sparaco, M., d'Amprosio, A., Docimo, R., Bisecco, A., Lavorgna, L., Corbo, D., Cirillo, S., Gallo, S., Esposito, F. and Tedeschi, G. (2015) Computer-aided cognitive rehabilitation improves cognitive performances and induces brain functional connectivity changes in relapsing remitting multiple sclerosis patients: an exploratory study. *Journal of Neurology* **262**, 91-100.

Buck, K., Atkinson, T. and Ryan, J. (2008) Evidence of practice effects in variants of the trail making test during serial assessment. *Journal of Clinical and Experimental Neuropsychology* **30**, 312-318.

Calamia, M., Markon, K. and Tranel, D. (2012) Scoring higher the second time around: meta-analyses of practice effects in neuropsychological assessment. *The Clinical Neuropsychologist* **26**, 543-570.

Charvet, L. E., Yang, J., Shaw, M., Sherman, K., Haider, L., Xu, J. and Krupp, L. B. (2017) Cognitive function in multiple sclerosis improves with telerehabilitation: Results from a randomized controlled trial. *PloS one* **12**, 1-13.

Chiaravalloti, N. D., Moore, N. B. and Nikelshpur, O. M. (2013). An RCT to treat learning impairment in multiple sclerosis: The MEMREHAB trial. *Neurology* 81, 2066-2072.

Chiaravalloti, N. D., Moore, N. B., Weber, E. and DeLuca, J. (2019) The application of Strategy-based Training to Enhance Memory (STEM) in multiple sclerosis: A pilot RCT. *Neuropsycholological Rehabilitation* **21**,1-24.

Dardiotis, E., Nousia, A., Siokas, V., Tsouris, Z., Andravizou, A., Mentis, A. A., Florou, D., Messinis, L. and Nasios, G. (2018) Efficacy of computer-based cognitive training in neuropsychological performance of patients with multiple sclerosis: A systematic review and meta-analysis. *Multiple Sclerosis and Related Disorders* **20**, 58-66.

De Giglio, L., De Luca, F. and Prosperini, L. (2015) A low-cost cognitive rehabilitation with a commercial video game improves sustained attention and executive functions in multiple sclerosis: a pilot study. *Neurorehabilitation and Neural Repair* **29**, 453-461.

Feinstein, A. (2011) Multiple sclerosis, cognitive dysfunction and the potential benefits of exercise. *Multiple Sclerosis* **17**, 1032-1033.

Filippi, M., Riccitelli, G. and Mattioli, F. (2012) Multiple sclerosis: effects of cognitive rehabilitation on structural and functional MR imaging measures-an explorative study. *Radiology* **262**, 932-940.

Fisher, M., Loewy, R., Carter, C., Lee, A., Ragland, J. D., Niendam, T., Schlosser, D., Pham, L., Miskovich, T. and Vinogradov, S. (2014) Neuroplasticity-based auditory training via laptop computer improves cognition in young individuals with recent onset schizophrenia. *Schizophrenia Bulletin* **41**, 250-258.

Goldberg, T. E., Harvey, P. D., Wesnes, K. A., Snyder, P. J. and Schneider, L. S. (2015) Practice effects due to serial cognitive assessment: implications for preclinical Alzheimer's disease randomized controlled trials. *Alzheimer's & Dementia: Diagnosis Assessment & Disease Monitoring* **1**, 103-111.

Golden, C. J. (1978) *Stroop color and word test: A manual for clinical and experimental uses*. Chicago, CA: Skoelting.

Goverover, Y., Chiaravalloti, N. and DeLuca, J. (2008) Self-generation to improve learning and memory of functional activities in persons with multiple sclerosis: meal preparation and managing finances. *Archives of Physical Medicine and Rehabilitation* **89**, 1514-1521.

Harvey, P. D., Balzer, A. M. and Kotwicki, R. J. (2019) Training engagement, baseline cognitive functioning, and cognitive gains with computerized cognitive training: A cross-diagnostic study. *Schizophrenia research: Cognition* **19**, 100150.

He, D., Zhang, Y., Dong, S., Wang, D., Gao, X. and Zhou, H. (2013) Pharmacological treatment for memory disorder in multiple sclerosis. *Cochrane Database of Systematic Reviews* **17**, CD008876.

Jacobson, N. S. and Truax, P. (1991) Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology* **59**, 12-19.

Kosmidis, M. H., Bozikas, V. P., Zafiri, M. and Karavatos, A. (2006) Shared cognitive processes underlying performance on the wisconsin card sorting test and the stroop test in patients with schizophrenia: A measurement artifact? *Neuroscience Letters* **409**, 234-238.

Langdon, D. (2015) Cognitive assessment in MS. *Neurodegenerative Disease Management* **5**, 43-45.

Kurtzke, J. F. (1983) Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* **33**, 1444-1452.

Lezak, M., Howieson, D., Bigler, E. and Tranel, D. (2012) *Neuropsychological assessment (5th ed.)*. Northamptonshire, CA: Oxford University Press.

Lincoln, N. B., Bradshaw, L. E., Constantinescu, C. S., Day, F., Drummond, A. E., Fitzimmons, D., Harris, S., Montgomery, A. A., das Nair, R. and CRAMMS Trial Collaborative Group. (2019). Cognitive rehabilitation for attention and memory in people with multiple sclerosis: A randomized controlled trial (CRAMMS). *Clinical Rehabilitation* **26**, 269215519890378.

Maiovis, P., Ioannidis, P., Nucci, M., Gotzamani-Psarrakou, A. and Karacostas, D. (2016) Adaptation of the Cognitive Reserve Index questionnaire (CRIq) for the Greek population. *Neurological Sciences* **37**, 633-636.

McCabe, J. A., Redick, T. S. and Engle, R. W. (2016) Brain-training pessimism, but applied-memory optimism. *Psychological Science in the Public Interest* **17**, 187-191.

Messinis, L., Kosmidis, M. H., Nasios, G., Konitsiotis, S., Ntoskou, A., Bakirtzis, C., Grigoriadis, N., Patrikelis, P., Panagiotopoulos, E., Gourzis, P., Malefaki, S. and Papathanasopoulos, P. (2020) Do secondary progressive Multiple Sclerosis patients benefit from computer-based cognitive neurorehabilitation? A randomized sham-controlled trial. *Multiple Sclerosis and Related Disorders* **39**, 101932.

Messinis, L., Nasios, G., Kosmidis, M. H., Zampakis, P., Malefaki, S., Ntoskou, K., Nousia, A., Bakirtzis, C., Grigoriadis, N., Gourzis, P. and Ppathanasopoulos, P. (2017) Efficacy of a computer-assisted cognitive rehabilitation intervention in relapsing-remitting multiple sclerosis patients: A multicenter randomized controlled trial. *Behavioural Neurology* **2017**, 5919841.

Mousavi, S., Zare, H., Etemadifar, M. and Taher Neshatdoost, H. (2018) Memory rehabilitation for the working memory of patients with multiple sclerosis (MS). *Journal of Clinical and Experimental Neuropsychology* **40**, 405-410.

Mousavi, S., Zare, H. and Etemadifar, M. (2018) Evaluating the effectiveness of cognitive rehabilitation on everyday memory in multiple sclerosis patients. *Neuropsychological Rehabilitation* **24**, 1-11.

Niccolai, C., Goretti, B. and Amato, M. P. (2017) Disease modifying treatments and symptomatic drugs for cognitive impairment in multiple sclerosis: where do we stand? *Multiple Sclerosis and Demyelinating Disorders* **2**, 8.

Penner, I. K., Opwis, K. and Kappos, L. (2007) Relation between functional brain imaging, cognitive impairment and cognitive rehabilitation in patients with multiple sclerosis. *Journal of Neurology* **254**, 1153-1157.

Polychroniadou, E., Bakirtzis, C., Langdon, D., Lagoudaki, R., Kesidou, E., Theotokis, P., Tsalikakis, D., Poulatsidou, K., Kyriazis, O., Boziki, M., Papadopoulos, G., Boura, E., Sintila, L., Hatzigeorgiou, S., Ziamos, C., Ioannidis, P., Karacostas, D. and Grigoriadis, N. (2016) Validation of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) in Greek population with multiple sclerosis. *Multiple Sclerosis and Related Disorders* **9**, 68-72.

Rosti-Otajärvi, E. M. and Hämäläinen, P. I. (2014) Neuropsychological rehabilitation for multiple sclerosis. *Cochrane Database of Systematic Reviews* **2**, CD009131.

Saccà, F., Costabile, T., Carotenuto, A., Lanzillo, R., Moccia, M., Pane, C., Russo, C.V., Barbarulo, A. M., Casertano, S., Rossi, F., Signoriello, E., Lus, G. and Brescia Morra, V. (2017) The EDSS integration with the brief international cognitive assessment for Multiple Sclerosis and orientation tests. *Multiple Sclerosis Journal* **23**, 1289-1296.

Sandroff, B. M. (2015) Exercise and cognition in multiple sclerosis: The importance of acute exercise for developing better interventions. *Neuroscience and Biobehavioral Reviews* **59**,173-183.

Sandroff, B. M., Motl, R. W., Scudder, M. R. and DeLuca, J. (2016) Systematic, evidence-based review of exercise, physical activity, and physical fitness effects on cognition in persons with multiple sclerosis. *Neuropsychology Review* **26**, 271-294.

Sandry, J., Akbar, N., Zuppichini, M. and DeLuca, J. (2016) Cognitive rehabilitation in multiple sclerosis. In, Sun, M. (eds.) *Research Progress in Alzheimer's Disease and Dementia (pp. 195-233)*. Hauppauge, NY: Nova Science Publishers, Inc.

Schoonheim, M. M., Geurts, J. J. and Barkhof, F. (2010) The limits of functional reorganization in multiple sclerosis. *Neurology* **74**, 1246.

Shatil, E., Metzer, A., Horvitz, O. and Miller, A. (2010) Home-based personalized cognitive training in MS patients: a study of adherence and cognitive performance. *NeuroRehabilitation* **26**, 143-153.

Smith, A. (1982) *Symbol digit modalities test: Manual*. Los Angeles, CA: Western Psychological Services.

Smith, G. E., Housen, P., Yaffe, K., Ruff, R., Kennison, R. F., Mahncke, H. W. and Zelinski, E. M. (2009) A cognitive training program based on principles of brain plasticity: Results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study. *Journal of the American Geriatrics Society* **57**, 594-603.

Stuifbergen, A., Becker, H., Morgan, S., Morrison, J. and Perez, F. (2011) Home-based computer-assisted cognitive training: feasibility and perceptions of people with multiple sclerosis. *International Journal of MS care* **13**, 189-198.

Sumowski, J. (2015) Cognitive reserve as a useful concept for early intervention research in multiple sclerosis. *Frontiers in Neurology* **6**, 176.

Sumowski, J., Wylie, G. and Chiaravalloti, N. (2010) Intellectual enrichment lessens the effect of brain atrophy on learning and memory in multiple sclerosis. *Neurology* **74**, 1942-1945.

Surti, T. S., Corbera, S., Bell, M. D. and Wexler, B. E. (2011) Successful computer-based visual training specifically predicts visual memory enhancement over verbal memory improvement in schizophrenia. *Schizophrenia Research* **132**, 131-134.

Tennstedt, S. L. and Unverzagt, F. W. (2013) The ACTIVE study: study overview and major findings. *Journal of Aging and Health* **25**, 3S-20S.

Temkin, N. R., Heaton, R. K., Grant, I. and Dikmen, S. S. (1999) Detecting significant change in neuropsychological test performance: a comparison of four models. *Journal of the International Neuropsychological Society* **5**, 357-369.

Thompson, A. J., Banwell, B. L., Barkhof, F., Carroll, W. M., Coerzee, T., Comi, G., Correale, J., Fazekas, F., Filippi, M., Freedman, M. S., Fujihara, K., Galetta, S. L., Hartung, H. P., Kappos, L., Lublin, F. D., Marrie, R. A., Miller, A. E., Miller, D. H., Montalban, X., Mowry, E. M., Sorensen, P. S., Tintore, M., Traboulsee, A. L., Trojano, M., Uitdehaag, B. M. J., Vukusic, S., Waubant, E., Weinshenker, B. G., Reingold, S. C. and Cohen, J. A. (2018) Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurology* **17**,162-173.

Vlachou, C., Kosmidis, M., Dardagani, A., Tsotsi, S., Giannakou, M., Giazkoulidou, A., Zervoudakis, E. and Pontikakis, N. (2013) Development of the Greek verbal learning test: reliability, construct validity, and normative standards. *Archives of Clinical Neuropsychology* **28**, 52-64.

Weber, E., Goverover, Y. and DeLuca, J. (2019) Beyond cognitive dysfunction: Relevance of ecological validity of neuropsychological tests in multiple sclerosis. *Multiple Sclerosis Journal* **25**, 1412-1419.

Wilms, I. L. (2020) The computerized cognitive training alliance - A proposal for a therapeutic alliance model for home-based computerized cognitive training. *Heliyon* **6**, e03254.

Zalonis, I., Kararizou, E., Triantafyllou, N. I., Kapaki, E., Papageorgiou, S., Sgouropoulos, P. and Vassilopoulos, D. (2008) A normative study of the trail making test A and B in Greek adults. *The Clinical Neuropsychologist* **22**, 842-850.

Zalonis, I., Christidi, F., Bonakis, A., Kararizou, E., Triantafyllou, N. I., Paraskevas, G., Kapaki, E. and Vasilopoulos, D. (2009) The stroop effect in Greek healthy population: normative data for the stroop neuropsychological screening test. *Archives of Clinical Neuropsychology* **24**, 81-88.