

The Effects of Cognitive Rehabilitation on Relapsing Remitting Multiple Sclerosis Patients

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ABSTRACT

Introduction: The aims of this study were to determine the severity of cognitive impairment with Brief Repeatable Battery Neuropsychology (BRB-N) and to show the benefits of cognitive rehabilitation programs to develop coping strategies for the retardation of cognitive losses in relapsing remitting multiple sclerosis (RRMS) patients.

Methods: The cognitive screening with BRB-N was performed in RRMS patients who had applied to the MS outpatient clinic of Bakırköy Psychiatric and Neurological Diseases Hospital, had an Expanded Disability Status Scale (EDSS) score between 1.0 and 5.5, and had no other cognitive disease or used drugs that effected the cognitive status. Thirty two patients with cognitive impairment underwent consecutive computer-assisted cognitive rehabilitation program once a week for 8 weeks conducted by psychologists. The effects of the program were evaluated with the tests repeated every 4 weeks.

Results: The mean age of the patients was 36.09±7.19 years. Their initial and control test scores were found to be paced auditory serial addition test (PASAT) 29.21±17.97; 42.43±15.43, Selective Reminding Test-Total

Learning (SRT-TL) 8.03±2.36; 10.09±1.77, Selective Reminding Test-Long-term Memory (SRT-DR) 6.72±2.74; 9±2.29, Spatial Recall Test-Total Learning (SPART-TL) 4.72±2.02; 4.22±1.74, Spatial Recall Test-Long-term Memory (SPART-DR) 5.94±2.54; 5.16±2.23, Symbol Digit Modalities Test (SDMT) 40.44±17.04; 46.47±17.94, Word Fluency Test (WLG) 32.88±9.87; 40.44±9.95 respectively. There was no significant statistical difference between Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ) and SPART values of preface, 1st control and 2nd control (p>0.05). There was significant statistical difference between PASAT, WLG, SDMT, SRT-TL, SRT-DR values of Preface, 1st control, and 2nd control (p=0.0001).

Conclusion: It was determined that on distinctive improvement on sustaining attention, working memory and information processing speed, and verbal fluency and verbal learning with cognitive rehabilitation, no changes were observed on visuospatial learning. This approach is hopeful and further comprehensive studies are needed.

Keywords: Multiple sclerosis, cognitive impairment, cognitive rehabilitation

INTRODUCTION

Cognitive disorder is an important and common symptom in multiple sclerosis (MS) patients with effects on the quality of life, social life, and career (1,2). With reported prevalence of 43–70%, cognitive disorder is observed from the early stages of the disease and even in clinically isolated syndrome (3). Age, level of education, disease duration, course type, and disability level are parameters that are associated with cognitive disorders. Gender has been reported to be unrelated to cognitive functions. Data on Expanded Disability Status Scale (EDSS) to cognitive disorder relationship are unclear (4,5,6,7). Cognitive functions that are mostly affected in MS patients are information processing speed, visual learning, and long-term memory (8). Simple attention and basic verbal skills are usually maintained until the late phases (9). Reduced participation in social activities, higher unemployment rate, greater difficulty in performing routine housework, and consequently, a higher risk of psychiatric disorders have been demonstrated for MS patients in parallel with cognitive effects (9).

The limits of pharmacologic therapy in the symptomatic treatment of MS-related cognitive disorders redirected the interest towards cognitive rehabilitation. Cognitive rehabilitation has been in use for years for treating cognitive disorders that are due to head trauma, stroke, and operated central nervous system tumors (10). Rehabilitative practices in the treatment of cognitive disorder in MS patients have recently gained popularity, with positive results being reported from an increasing number of studies (11). The studies performed include computer-aided systems, as well as home-based training programs, which may or may not include compact discs (CDs). Studies particularly on correcting attention, memory, and executive functions are more prevalent. Improvement was demonstrated mostly for learning and memory functions.



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Received: 19.09.2013 **Accepted:** 14.04.2014

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Experience related to cognitive rehabilitation for MS patients in Turkey is quite limited. The present study is one of the first and here, we have investigated the effects of an 8-week computer-aided cognitive rehabilitation application in RRMS patients.

METHODS

Patients being followed-up and treated by the MS and Demyelinating Diseases Polyclinic of Bakırköy Psychiatric Hospital were reviewed using Rao's BRB cognitive test battery, and cognitive rehabilitation was recommended to patients who performed below 5 percentile in at least two tests.

Patients who provided informed consents were evaluated for inclusion in the study. Approval of the hospital's ethics board was granted for the study. The inclusion criteria were confirmed as MS diagnosis as per the 2005 Revised McDonald criteria, relapsing remitting multiple sclerosis (RRMS) clinical form, patients of both sexes aged 18–45 years, ability to read and write, Expanded Disability Status Scale (EDSS) ≤ 5.5 , Beck Depression Scale score ≤ 17 , being episode-free or not having received steroid treatment for the past one month and absence of alcohol, substance and psychotropic drugs use for the past 3 months. The exclusion criteria were the presence of progressive (secondary progressive and primary progressive subtypes) multiple sclerosis, experiencing an attack or receiving steroid treatment over the past one month, presence of an acute psychiatric condition or a non-MS neurological condition that may affect the cognitive status, use of any drugs that may affect the cognitive status, EDSS > 5.5 , and Beck Depression Scale score > 17 . Thirty-two patients meeting the inclusion and exclusion criteria were included in the computer-aided cognitive rehabilitation program, which was supervised by an experienced clinical psychologist and lasted 1 h/week for 8 successive weeks between March 2010 and March 2011. The patients were assessed using the BRB cognitive battery before cognitive rehabilitation and at the end of weeks 4 and 8 to evaluate the effects of rehabilitation.

The following tests, in addition to the tests performed at baseline and at weeks 4 and 8, were also performed: paced auditory serial addition test (PASAT), Spatial Recall test I, Selective Reminding test, Spatial Recall test II, Symbol Digit Modalities test, Spatial Recall test III, and Verbal Fluency test. The tests and rehabilitation program were performed in a dedicated, quiet room, which was isolated from the external stimulants to the highest possible extent.

Rehabilitation exercises focused on attention, sustainable attention, information processing speed, and verbal and visual memory. Visual pattern, letter, and digit recall studies were performed on the attention screen. Time management and math problem solving exercises were performed on the information processing speed screen. Memory exercise screen included object identifying, cause identifying, problem solving, and deduction exercises. Identifying antonyms and synonyms, word association, word recall, and sentence completion exercises were performed on the verbal memory screen. Visual image identification, image confirmation, and finding similar and dissimilar image exercises were conducted on the visual memory screen.

Expanded Disability Status Scale was used to evaluate clinical status. Beck Depression Inventory was performed for depression assessment for all patients. The patients' quality of life was evaluated with Functional Assessment of Multiple Sclerosis (FAMS). The patients' cognitive status was evaluated with Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) patient form and Brief Repeatable Battery (BRB).

Beck Depression Inventory included four choices for each of the 21 symptom category. The patient is asked to select the sentence that best

corresponds how he/she felt during the last week including the day the inventory was completed. Each item is given a score from 0 to 3. Scores 17 and above from this inventory is considered to indicate the presence of depression.

Functional Assessment of Multiple Sclerosis is a self-reported form commonly used to assess the quality of life in MS patients. FAMS contains six scales (mobility, symptoms, emotional status, overall status, and familial/social status). Forty-four of the 59 statements in total are used for scoring and the patient is expected to give a score from 0 to 4 based on how a statement corresponds to his/her condition (12).

The Multiple Sclerosis Neuropsychological Questionnaire screening test includes patient and caregiver forms. In this self-reported test of 15 questions, the responses are scored from 0 to 4 (13). MSNQ patient form was used in the present study and, based on the normative data obtained from healthy individuals in Turkey, scores above 22 were considered to indicate pathology.

Brief Repeatable Battery is the most commonly used battery of neuropsychological test for cognitive status assessment in MS patients with high specificity and sensitivity. It takes about 30 min to complete the tests. Previous studies have found a sensitivity of 71% and a specificity of 94% (14). It includes PASAT, Selective Reminding test, Spatial Recall test, Symbol-Digit Modalities test, and Verbal Fluency tests (14,15).

Paced Auditory Serial Addition test (PASAT) has two forms and the subject is asked to sum up the last two numbers, which are uttered successively. It assesses sustainable attention and information processing speed. A maximum of 60 correct responses may be given (16).

Selective Reminding test (SRT) assesses verbal learning and recalling. The rater reads the 12 words in the list and the patient is asked to remember these words and then repeat them. At the second attempt, the patient is told only the words he/she could not remember during the previous attempt and is asked to recite the complete list. This continues up to 6 attempts and the number of all words remembered at the sixth attempt is summed up (17).

In the Spatial Recall test (SPART), also known as the 10/36 test, the patient is asked to memorize the locations of 10 round marks placed in a checkerboard design of 6×6 squares and to remember them later. Three learning attempts and delayed recall phase at 25 min are performed. Visuospatial learning and long-term memory are assessed (15).

In Symbol-Digit Modalities, the patient is given a key comprising symbols numbered from 1 to 9. A score is given for each correct matching in 90 s. The maximum score is 60. Attention, visual/spatial information processing speed, and working memory are assessed (18).

In the verbal fluency test, the patient is asked to say as many words as possible for 1 min. In the two alternative forms, the patient is asked to list fruits and vegetables in form A and animals in form B (18).

Statistical Analysis

Statistical analyses in this study were performed using Number Cruncher Statistical System (NCSS) 2007 Statistical Software (Utah, USA) package. Descriptive statistics (mean, standard deviation) as well as the following were used for data evaluation: one-way variance analysis for inter-group comparisons, Tukey multiple comparison test for subgroup comparisons, paired variance analysis for follow-up comparisons of groups, Newman

Table 1. Distribution of age and disease duration by gender (percentage, mean, standard deviation)

	Gender distribution		Age		Disease duration (years)	
	n	%*	Mean	SD (±)	Mean	SD (±)
Female	24	75.0	35.58	7.35	9.70	7.29
Male	8	25.0	37.62	6.92	8.12	8.70
Total	32	100.0	36.09	7.19	9.31	7.55

*Column percentage used. SD: standard deviation

Keuls multiple comparison test for subgroup comparisons, and Pearson correlation analysis to determine the inter-association of the data.

RESULTS

Thirty-two patients meeting the study criteria were studied during the study period.

Patients' ages ranged from 24 to 45 years, with a mean age [\pm standard deviation (SD)] of 36.09 ± 7.19 years. Of the patients, 75% ($n=24$) were females and 25% ($n=8$) were males. The disease duration ranged from 1 to 24 years, with a mean duration (\pm SD) of 9.31 ± 7.55 years (Table 1).

Of the patients, 46.88 ($n=15$) were graduated from primary school, 43.75% ($n=14$) from secondary or high school, and 9.37% ($n=3$) had university degree or above. FAMS scores ranged from 27 to 173, with a mean (\pm SD) score of 69.5 ± 30.27 . Beck Depression Inventory scores ranged from 4 to 17, with a mean (\pm SD) score of 12.97 ± 3.81 . EDSS scores ranged from 1 to 4, with a mean (\pm SD) score of 2.08 ± 0.99 .

Multiple Sclerosis Neuropsychological Screening Questionnaire, SPART I, SPART II, and SPART III tests did not differ significantly between baseline, follow-up 1, and follow 2 ($p > 0.05$).

There was a significant difference in the scores of PASAT, SRT I, SRT II, SDMT, and WLG tests between baseline and follow-up 1 and follow-up 2 tests ($p=0.0001$). Advanced analysis demonstrated that the difference was originating from the baseline test results, where the values were significantly low, and that there was a significant increase in the results of tests 1 and 2 performed during the rehabilitation.

No significant relationship was observed between age and improvements in PASAT, SPART I, SPART II, WLG, SDMT, SRT I, or SRT II ($p > 0.05$).

The mean scores of primary school, secondary/high school, and university groups from PASAT, SPART I, SPART II, SPART III, WLG, SRT I, and SRT II were not significantly different ($p > 0.05$).

The mean SDMT scores of primary school, secondary/high school, and university groups were statistically significantly different ($p=0.042$).

In conclusion, there was a marked improvement with cognitive rehabilitation in maintaining attention, working memory and information processing speed, verbal fluency, and verbal learning whereas there was no impact on visuospatial learning visuospatial (Table 2).

DISCUSSION

Cognitive effects have a direct impact on the daily life activities of MS patients (19). The quality of life of these patients is correlated with physical disability, psychiatric symptoms, disease duration as well as cognitive functions. There has been an increase in the number of the studies inves-

tigating the ways to correct or prevent cognitive disorder, which is of such vital importance for and common among these patients.

Although there are some studies on the effects of the attempted pharmacological treatments on cognitive impairment in MS patients, conclusive data is currently unavailable (20). It has been demonstrated that disease-modifying drugs reduce the inflammatory process and may protect against the development of new brain lesions and progressive brain atrophy and that they may thus be beneficial from the cognitive perspective in MS patients (21).

Several pharmacological agents such as cholinesterase inhibitors and memantine were tried in the treatment of cognitive disorder in MS but the results have not been satisfactory (22,23,24). In a study by Krupp et al. (23), donepezil, an acetylcholinesterase inhibitor, resulted in significant improvement in verbal learning and memory tests and some improvement in attention tests, although the studies are inadequate (23). A 36-week, randomized, double-blind, placebo-controlled study with a 12-week follow-up period with rivastigmine, another acetylcholinesterase inhibitor has, likewise, unclear results (24).

Having drawn recent attention, rehabilitation programs' efficacy was demonstrated in several studies (11). Although cognitive rehabilitation studies performed for cognitive disorder that developed following brain damage such as head trauma and stroke achieved A, B, and C level of evidence, there is a need for studies that are well-designed in terms of patient selection and treatment standardization (10). Available studies on MS examined rehabilitations for the correction of attention, memory, and executive function in particular. Learning and memory functions were those in which best recovery was achieved. The intention is to increase patients' cognitive performance with the help of certain techniques (association, positioning) given as part of rehabilitation (25).

Of the patients included in our study, 75% ($n=24$) were females and 25% ($n=8$) were males, which was not consistent with literature data (26,27). This could be explained by the fact that there was a limited number of subjects in the study, that the study required continued participation, and that male patients failed to maintain participation due to their occupations. Patients' ages ranged from 24 and 45 years and the mean age was 36.09 ± 7.2 years. There was no significant relationship between patient age and level of improvements in cognitive tests.

Mean scores from the tests excluding SDMT did not differ statistically significantly by patients' education levels in this study. These results are not consistent with the relevant literature and this was attributed to the difference in the number of subjects in the two groups and absence of a control group (28). In a study by Tesar et al. (29), the two groups were comparable with regards to clinical and sociodemographic data and basic intelligence level.

Table 2. Mean scores, standard deviations, and extreme values from the cognitive tests

	Test 1 results pre-rehabilitation			Test 2 results at the end of week 4			Test 3 results at the end of week 8			p*	p**
	Mean±SD	Min	Max	Mean±SD	Min	Max	Mean±SD	Min	Max		
MSNQ	19.97±8.49	0	40	19.63±8.29	3	39	17.34±7.75	3	31	>0.05	--
PASAT	29.21±17.97***	0	56	38.96±16.84***	0	60	42.43±15.43***	4	60	0.0001	0.0001
SPART I	4.72±2.02	1	9	4.31±1.80	0	9	4.22±1.74	0	8	>0.05	--
SPART II	5.63±2.09	2	10	5.28±2.05	2	10	5±1.80	2	10	>0.05	--
SPART III	5.94±2.54	1	10	5.53±2.09	1	10	5.16±2.23	1	10	>0.05	--
SRT I	8.03±2.36***	3	12	9.59±2.05	5	13	10.09±1.77	6	13	0.0001	0.0001
SRT II	6.72±2.74***	0	11	7.91±2.60	2	12	9±2.29	2	12	0.0001	0.003
SDMT	40.44±17.04***	0	69	46.41±17.26	18	82	46.47±17.94	19	82	0.001	0.003
WLG	32.88±9.87***	8	52	37.31±11.13	14	59	40.44±9.95	19	60	0.0001	0.047

Statistical significance was set at $p < 0.05$.
 *One-way variance analysis for inter-group comparisons
 **Tukey multiple comparison test for subgroup comparisons
 ***Group causing significant difference
 SD: standard deviation; Max: maximum; MSNQ: Multiple Sclerosis Neuropsychological Questionnaire; PASAT: Paced Auditory Serial Addition Test; SPART I: Spatial Recall Test I; SPART II: Spatial Recall Test II; SPART III: Spatial Recall Test III; SRT I: Selective Reminding Test I; SRT II: Selective Reminding Test II; SDMT: Symbol Digit Modalities Test; WLG: Word Fluency Test

There was no statistically significant difference between the patients' disease duration and tests. In a study by Brenk et al. (30), patients with a disease history of 3–10 years were included and comparable results were obtained.

Seven patients with Beck depression above 17 were excluded. Whether these patients had cognitive disorder accompanying depression is unknown and how cognitive disorder accompanying depression would respond to rehabilitation could not be determined. Patients with all degrees of cognitive impairment based on the BRB-N score were included in the study. However, among patients diagnosed with severe depression, a group of patients i.e., those for whom severe cognitive involvement was identified might have not been included in the study. Thus, response to cognitive rehabilitation could not be assessed in these patients.

Multiple Sclerosis Neuropsychological Questionnaire data were obtained from the forms completed by the patients themselves in this study. No statistically significant differences were observed between baseline and first and second follow-up tests. Self-reported cognitive deterioration has been identified not to be a sensitive indicator of actual deterioration (31). Although MSNQ is an effective and useful screening test in identifying cognitive disorder, it does not provide as detailed information on the type of the cognitive disorder as BRB-N. In this study, follow-up of patients who were evaluated with MSNQ and BRB-N and who were identified to have cognitive disorder were performed with BRB-N but correlations between the two tests were not studied. Previous studies indicate that MSNQ and BRB-N scores are independent (32,33).

Paced Auditory Serial Addition Test values at baseline and first and second follow-ups were not statistically significantly different. These results indicated that the cognitive rehabilitation given was quite effective on sustainable attention, working memory, and information processing speed. Measuring attention, working memory, information processing speed, and SDMT was similarly significantly different between baseline and first and second follow-ups. Previous studies have likewise determined a marked improvement in PASAT and SDMT values following cognitive rehabilitation (11,29,34,35,36).

Although a favorable effect of cognitive rehabilitation on visual memory was demonstrated in a study by Shatil et al. (37), confirmed data regarding visuospatial learning and long-term memory from other studies are lacking. There were statistically significant differences in SPART I, SPART II, and SPART III at baseline and in the first and second follow-ups. This may be attributed to the short rehabilitation duration and limited number of weekly sessions.

The impact of cognitive programs on verbal learning and verbal memory was demonstrated clearly in a study by Hildebrandt et al. (34). Our study also demonstrated a statistically significant difference in SRT I values between baseline and first and second follow-ups. There was also a statistically significant difference in SRT 2 values between baseline and first and second follow-ups. Based on these results, cognitive rehabilitation was effective on verbal fluency and verbal learning.

Some of the studies involved computer-aided programs while others involved home-based training programs with or without CDs (11,29,30,35,36,37). The present study used a computer-aided rehabilitation program focusing on attention and memory functions. Favorable effects were identified with cognitive tests as a result of rehabilitation utilizing both methods.

Positive aspects of the present study were the use of BRB-N, which demonstrates the degree of cognitive impairment with very high sensitivity and specificity in MS patients and the detailed assessment of patients' depression status, quality of life, and functionality level. This was one of the first studies to use the Neurosoft software developed for the implementation of cognitive rehabilitation programs conducted for slowing down the loss of cognitive losses, which is common among MS patients, and developing strategies and achieving regeneration where possible, to correct and prevent cognitive impairment in the Turkish patient population.

The method to rule out the learning effect, which is one of the key aspects of cognitive tests, involving duplicate testing before starting rehabilitation and to document the second test was not used in this study. Instead, an

Table 3. Assessment of the cognitive rehabilitation study

Study name	Number of subjects in the patient and/or control group	Rehabilitation Method in the study	Duration and frequency of rehabilitation in the study	Study results
Tesar et al. (29)	19 (patient+ controls)	Computer aided	4 weeks 3 times/week	Marked improvement in executive functions, verbal learning and memory, sustainable attention
Brenk et al. (30)	27 patients 14 controls	House-based training program	6 weeks 1 or 5 times/ week	Marked improvement in memory, working memory and attention
Mattioli et al. (35)*	20 patients	Computer aided	3 months	Improvement in attention, information processing speed and executive functions
Hildebrandt et al. (34)	17 patients 25 controls	Computer aided	6 weeks 5 times/week	Marked improvement in verbal learning, verbal memory and working memory
Shatil et al. (37)	59 patients 48 controls	House-based training program	12 weeks 3 times/week	Improvement in memory, verbal and visual memory
Chiaravalloti et al. (11)•	29 (patients+ controls)	House-based training program	8 sessions	Positive effect on learning and memory
Lincoln et al. (28)	240 (patients+ controls)	House-based training program	4-8 months	No marked change
Solari et al. (36)*	82	Computer aided	8 weeks 2 times/week	Improvement in BRB-N of at least 20% in at least 2 tests, improvement in word list
Present study	32	Computer aided	8 weeks 1 times/week	Marked improvement in attention, information processing speed, working memory and verbal memory

*double-blind, randomized, controlled. •randomized, controlled

attempt was made to exclude this effect by performing the tests, which comprise A and B forms, by using different forms for each occasion. The absence of a control group was one of the most important limitations of the study. Despite the negative aspects of the study including the limited number of subjects and short follow-up duration, the obtained data were substantially consistent with previous reports (Table 3).

In conclusion, it is important to identify cognitive impairment, which is common in MS patients and has substantial negative effect on the quality of life, and to implement curative or inhibitory therapeutic measures at the earlier phases before the patient's status gets more complicated. Cognitive rehabilitation programs are promising in this respect. Comprehensive studies with larger samples and longer follow-up durations supported by radiological data examining this significant problem in MS patients in the Turkish population are needed.

Acknowledgements: Many thanks to psychologist Pinar Kaya and psychologist Elif Kurt for their support at the phase of rehabilitation process.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

- Pelosi L, Geesken JM, Holly M, Hayward M, Blumhardt LD. Working memory impairment in early multiple sclerosis. Evidence from an event-related potential study of patients with clinically isolate myelopathy. *Brain* 1997; 120:2039-2058. [CrossRef]
- Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology* 1991; 41:685-691. [CrossRef]
- Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol* 2008; 7:1139-1151. [CrossRef]
- Randolph JJ, Arnett PA, Higginson CI. Metamemory and testing functioning in multiple sclerosis. *Clin Neuropsychol* 2001; 15:357-368. [CrossRef]
- Haase CG, Tinnefeld M, Lienemann M, Ganz RE, Faustmann PM. Depression and cognitive impairment in disability free early multiple sclerosis. *Behav Neurol* 2003; 14:39-45. [CrossRef]
- Amato MP, Ponziani G, Siracusa G, Sorbi S. Cognitive dysfunction in early-onset multiplesclerosis: a reappraisal after 10 years. *Arch Neurol* 2001; 58:1602-1606. [CrossRef]
- Dineen RA, Vilisaar J, Hlinka J, Bradshaw CM, Morgan PS, Constantinescu CS, Auer DP. Disconnection as a mechanism for cognitive dysfunction in multiple sclerosis. *Brain* 2009; 132:239-249. [CrossRef]
- Benedict RH, Cookfair D, Gavett R, Gunther M, Munschauer F, Garg N, Weinstock Guttman B. Validity of the minimal assessment of cognitive function in multiple sclerosis. *J Int Neuropsychol Soc* 2006; 12:549-558. [CrossRef]
- Rao SM, Leo GJ, Ellington L, Nauertz T, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. *Neurology* 1991; 41:692-696. [CrossRef]
- Cappa SF, Benke T, Clarke S, Rossi B, Stemmer B, van Heugten M. Task Force on Cognitive Rehabilitation; European Federation of Neurological Societies. EFNS guidelines on cognitive rehabilitation: report of an EFNS task force. *Eur J Neurol* 2005; 12:665-680. [CrossRef]
- Chiaravalloti ND, DeLuca J, Moore NB, Ricker JH. Treating learning impairments improves memory performance in multiple sclerosis: a randomized clinical trial. *Mult Scler* 2005; 11:58-68. [CrossRef]
- Fischer JS, LaRocca NG, Miller DM, Ritvo PG, Andrews H, Paty D. Recent developments in the assessment of quality of life in multiple sclerosis (MS). *Mult Scler* 1999; 5:251-259. [CrossRef]
- Benedict RH, Munschauer F, Linn R, Miller C, Murphy E, Foley F, Jacobs L. Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire. *Mult Scler* 2003; 9:95-101. [CrossRef]
- Portaccio E, Goretti B, Zipoli V, Ludice A, Pina DD, Malentacchi G.M, Sabatini S, Annunziata P, Falcini M, Mazzoni M, Pia Amato M; TuSCIMS Study Group. Reliability, practice effects and change indices for Rao's Brief Repeatable Battery. *Mult Scler* 2010; 16:611-617. [CrossRef]
- Boringa JB, Lazeron RH, Reuling IE, Ader HJ, Pfenning L, Lindeboom J, de Sonneville LM, Kalkers NF, Polman CH. The brief repeatable battery of neu-

- ropsychological tests: normative values allow application in multiple sclerosis clinical practice. *Mult Scler* 2001; 7:263-267. [\[CrossRef\]](#)
16. Tombaugh TN. A comprehensive review of the Paced Auditory Serial Addition Test (PASAT). *Arch Clin Neuropsychol* 2006; 21:53-76. [\[CrossRef\]](#)
 17. Ehrenreich JH. Normative data for adults on a short form of the Selective Reminding Test. *Psychol Rep* 1995; 76:387-390. [\[CrossRef\]](#)
 18. Lezak MD, Howieson DB, Loring DW. *Neuropsychological assessment*. 4th edition. New York, USA: Oxford University Press, 2004.
 19. Beatty WM, Blanco CR, Wilbanks SL. Demographic, clinical, and cognitive characteristics of multiple sclerosis patients who continue to work. *J Neurol Rehab* 1995; 9:167-173. [\[CrossRef\]](#)
 20. Patti F. Cognitive impairment in multiple sclerosis. *Mult Scler* 2009; 15:2-8. [\[CrossRef\]](#)
 21. Amato M, Portaccio E, Zipoli V. Are there protective treatments for cognitive decline in MS? *J Neurol Sci* 2006; 245:183-186. [\[CrossRef\]](#)
 22. Amato MP. Donepezil for memory impairment in multiple sclerosis. *Lancet Neurol* 2005; 4:72-73. [\[CrossRef\]](#)
 23. Krupp LB, Christodoulou C, Melville P, Scherl WF, Macallister WS, Elkins LE. Donepezil improved memory in multiple sclerosis in a randomized clinical trial. *Neurology* 2004; 63:1579-1585. [\[CrossRef\]](#)
 24. Porcel J, Montalban X. Anticholinesterasics in the treatment of cognitive impairment in multiple sclerosis. *J Neurol Sci* 2006; 245:177-181. [\[CrossRef\]](#)
 25. Basso MR, Lowery N, Ghormley C, Combs D, Johnson J. Self-generated learning in people with multiple sclerosis. *J Int Neuropsychol Soc* 2006; 12:640-648. [\[CrossRef\]](#)
 26. Koch-Henriksen N, Sørensen PS. The changing demographic pattern of multiple sclerosis epidemiology. *Lancet Neurol* 2010; 9:520-532. [\[CrossRef\]](#)
 27. Tremlett H, Zhao Y, Rieckmann P, Hutchinson M. New perspectives in the natural history of multiple sclerosis. *Neurology* 2010; 74: 2004-2015. [\[CrossRef\]](#)
 28. Lincoln NB, Dent A, Harding J, Weyman N, Nicholl C, Blumhardt L.D, Playford E.D. Evaluation of cognitive assessment and cognitive intervention for people with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2002; 72:93-98. [\[CrossRef\]](#)
 29. Tesar N, Bandion K, Baumhackl U. Efficacy of a neuropsychological training programme for patients with multiple sclerosis-a randomised controlled trial. *Wien Klin Wochenschr* 2005; 117:747-754. [\[CrossRef\]](#)
 30. Brenk A, Laun K, Haase C.G. Short-term Cognitive training improves mental efficiency and mood in patients with multiple sclerosis. *Eur Neurol* 2008; 60:304-309. [\[CrossRef\]](#)
 31. Julian L, Merluzzi NM, Mohr DC. The relationship among depression, subjective cognitive impairment, and neuropsychological performance in multiple sclerosis. *Mult Scler* 2007; 13:81-86. [\[CrossRef\]](#)
 32. Akbar N, Honarmand K, Kou N, Levine B, Rector N, Feinstein A. Validity of an Internet version of the Multiple Sclerosis Neuropsychological Questionnaire. *Mult Scler* 2010; 16:1500-1506. [\[CrossRef\]](#)
 33. Sonder JM, Mokkink LB, van der Linden FA, Polman CH, Uitdehaag BM. Validation and interpretation of the Dutch version of the Multiple Sclerosis Neuropsychological Screening Questionnaire. *J Neurol Sci* 2012; 320:91-96. [\[CrossRef\]](#)
 34. Hildebrandt H, Lanz M, Hahn HK, Hoffmann E, Schwarze B, Schwendemann G, Kraus JA. Cognitive training in MS: Effects and relation to brain atrophy. *Restor Neurol Neurosci* 2007; 25:33-43.
 35. Mattioli F, Stampatori C, Zanotti D, Parrinello G, Capra R. Efficacy and specificity of intensive cognitive rehabilitation of attention and executive functions in multiple sclerosis. *J Neurol Sci* 2010; 288:101-105. [\[CrossRef\]](#)
 36. Solari A, Motta A, Mendozzi L, Pucci E, Forni M, Mancardi G, Rozzilli C, CRIMS Trial. Computer aided retraining of memory and attention in people with multiple sclerosis, randomized, double blind controlled trial. *J Neurol Sci* 2004; 222:99-104. [\[CrossRef\]](#)
 37. Shatil E, Metzger A, Horvitz O, Millerb A. Home-based personalized cognitive training in MS patients: A study of adherence and cognitive performance. *NeuroRehabilitation* 2010; 26:143-153.