Individualized Neuropsychological Rehabilitation Program in Greek Patients with Multiple Sclerosis. A pilot case study that supports its efficacy.

Dimou I[1,2,3], Liaptsi E[2], Karafyles G[2], Papadopoulou K[3], Jobst R[2], Deretzi G[1].

1. Memory Clinic, Papageorgiou General Hospital, Thessaloniki Greece
2. Neurology Department, Papageorgiou General Hospital, Thessaloniki Greece
3. City College, University of York Europe Campus

Abstract: Cognitive insufficiencies affect 40-70% of patients with multiple sclerosis throughout the course of the disease or even before the appearance of other clinical symptoms. Therefore, there has been an explosion in interest to diagnose and manage cognitive symptoms that affect the individual's quality of life, social interactions, productivity at work, independence, and functionality in daily living. Besides the pharmacological treatment and based on personalized medicine, a crucial aspect of the treatment plan is individualized neuropsychological rehabilitation programs to improve patients' strengths, compensate for the cognitive and/or mood insufficiencies and learn how to manage them. Existing evidence is quite promising for the efficacy of neuropsychological rehabilitation programs applied to individuals with multiple sclerosis. In this line, the present paper presents the efficiency of two individualized neuropsychological rehabilitation programs applied to two female patients with relapsing-remitting MS whose language background is Greek. This is the first attempt to apply individualized neuropsychological rehabilitation programs to Greek patients with multiple sclerosis.

Key words: multiple sclerosis; cognitive insufficiencies; individualized cognitive rehabilitation programs

Introduction

Multiple Sclerosis (MS) is a chronic, inflammatory, and demyelinating neurological condition of the central nervous system (CNS) which primarily affects young individuals. Even though MS is a physically disabling disease, it is often accompanied with behavioral and cognitive insufficiencies that affect social, professional, and emotional functioning (Lassmann et al., 2007; Rao, 2004; Schulz et al., 2006). Recent research suggests that cognitive impairment is present in 40-70% of MS patients throughout their lifetimes (Clough et al., 2018; Macías Islas & Ciampi, 2019; Rao, 2023). Despite the wide range of different clinical symptoms in MS, cognitive insufficiencies are considered the most common and disabling outcomes (Matias-Guiu et al., 2020). In some cases, it is hypothesized that cognitive symptoms may appear at an early stage of the disease. For this reason, other than the neurological examination which is of vital significance, neuroimaging and neuropsychological assessment are also incorporated as primary diagnostic tools in clinical settings (Casaletto & Heaton, 2017; Matias-Guiu et al., 2020; Rao, 2004).

Typical cognitive functions affected in MS patients are attention, information processing speed, working memory, visual memory, and abstract reasoning (Al-Falaki et al., 2021; Chiang et al., 2022; Matias-Guiu et al., 2020). In contrast, language and intellectual functions remain preserved throughout the course of the disease in most individuals (Schulz et al., 2006). The degree of cognitive

impairment in MS patients has been related to the extent of topographically specific neuronal loss and tissue damage in white and grey matter, resulting in cortical and subcortical alterations. Additionally, functional connectivity changes affecting brain networks are linked to cognitive insufficiencies and cognitive rehabilitation provides meaningful cognitive stimulation (Filippi et al., 2013).

Age, education, clinical subtypes of MS, disease course and duration, fatigue, medication, depression, as well as vascular comorbidities are confounding factors that may affect the degree of MS-related cognitive dysfunction (Rogers & Panegyres, 2007, Planche et al., 2015,). Moreover, educational background can determine the degree of cognitive impairment because individuals with a higher educational level have less severe cognitive insufficiencies (Planche et al., 2015).

MS-related memory insufficiencies affect verbal, long-term and working memory, although, short-term memory is often unimpaired in most patients. Deficiencies are mostly observed in long-term free/cued recall, even though in cued recall, MS patients tend to perform better than in free recall and recognition tasks. The neuropsychological processes for memory impairment in MS is a debatable topic because some suggest that MS-related memory insufficiencies result from impaired selective retrieval from long-term memory, while others claim that encoding deficits result in MS-related memory failures (Matias-Guiu et al., 2020; Schulz et al., 2006). Recent investigations reveal that MS patients require more learning trials to reach the same level of storage with healthy individuals but, once this is achieved performance in recall and recognition tasks is in the normal/average range (Matias-Guiu et al., 2020). Working memory insufficiencies are also common in MS patients. More specifically, research reveals that performance on tasks based on the phonological loop (e.g., digit/word recall, non-word recall tasks) and the central executive (e.g., backwards digit/word recall, listening recall) are the most impaired ones (Grigsby et al., 1993; Kouvatsou et al., 2019; Lengenfelder et al., 2003). Additionally, two cognitive areas which are affected in MS individuals are attention and information processing speed. Studies have shown that MS patients require longer reaction times and visual-information processing speeds. Neuropsychological assessment in MS patients suggests that insufficiencies are mostly observed in focused, divided, and sustained attention (Portaccio & Amato, 2022; Rao, 2023). Lastly, there is poor performance on executive function tasks including abstract reasoning, planning, problem solving, mental flexibility, and verbal fluency (Clough et al., 2018).

In recent years, a lot of research has been conducted on the efficacy of cognitive rehabilitation for individuals with MS, given the fact that cognition is affected in 40% to 70% of patients with the specific neurological condition (Jiménez-Morales et al., 2021; Klein et al., 2017). Some studies have focused on computerized cognitive rehabilitation programs which prove to be beneficial for some adults with progressive MS (Baroni et al., 2021; Lampit et al., 2019; Messinis et al., 2017; Nauta et al., 2017), while others focus on paper and pencil cognitive rehabilitation programs which are proven efficient for patients with MS of different age groups and MS type.

The Individualized Neuropsychological Rehabilitation program is a personalized program, which considers the patient's characteristics (Sharbafshaaer et al., 2022; Tacchino et al., 2023). The primary goal of this program is to help individuals learn how to compensate for cognitive insufficiencies, strengthen their existing cognitive skills, and improve overall cognitive performance. Moreover, the program focuses on improving the patient's communication with family members. The present pilot study centers on the efficacy of individualized cognitive rehabilitation programs on the two MS patients. Until now, there is no literature concerning the efficacy of individualized neuropsychological rehabilitation programs for Greek individuals with MS. Hence, this is an initial attempt to observe how this treatment plan is applied, how it works, and whether it benefits the individual's mood and daily living.

Cases

Two patients, with relapsing/remitting MS, GV, a 36-year-old right-handed female, housewife, mother of a 5-year-old boy diagnosed with autism, and SS, a 58-year-old right-handed female, physical education teacher, mother of a 28-year-old man, were referred by their neurologists for a holistic neuropsychological assessment. Afterwards, given their performance on the cognitive areas assessed individualized neuropsychological rehabilitation programs were designed considering their cognitive, psychological, emotional level of functioning, as well as their daily needs which were completely different.

Methods

Intervention Strategies of individualized neuropsychological rehabilitation were performed, based on a holistic approach including both cognitive retraining and psychological tactics "*The therapeutic milieu approach"* (Goldstein & McNeil, 2004; Domensino et al., 2021; Nehra et al.,

2014).

The following interventions were utilized based on the structure of the initial neuropsychological assessment.

- *Orientation Training* was the first step of the rehabilitation sessions so that patients could regain awareness of oneself and the ability to accurately describe time, place, and situation. For this reason, patients were asked to buy a calendar and they were then taught on how to use it to find the details (Samuel, 2008).
- *Goal Management Training (GMT)* was incorporated in the rehabilitation sessions to reduce disorganized/impulsive behaviors and maintain attention for longer time periods by organizing step-by-step daily activities in a structured way, executing these activities, and involving in problem solving (Gillen, 2009; Krasny-Pacini et al., 2014; Wilson, 2009).
- *External compensatory strategies* were additionally used to educate the patients on how to reduce distractors in their environment in order to stay focused when at home performing everyday tasks that require multitasking skills (Wilson et al., 2009).
- *Recall: Mnemonic strategies, Cueing, & Chunking*: were used for the improvement of verbal memory. An example is giving the patient a list of words and asking for as many words as possible to be repeated (Kelly & O'Sullivan, 2015; Vallat et al., 2005).
- *Cognitive remediation strategies (CRS)* were utilized in the attempt to restore lost memory capacity, provide compensatory techniques, and improve working memory (Carpenter, 2001; Ptak et al., 2010). From the first session, G.V. and S.S. were asked to buy an agenda and start writing a diary daily so that they will remember their daily activities (Lincoln et al., 2015).
- *Spatial retrieval or expanding rehearsal*, beneficial for memory of object location and prospective memory assignment was used to enhance visuo-spatial/visuo-constructional abilities and visual memory (Clare & Jones, 2008). Patients were asked to copy specific designs and then to immediately recall them. The delayed recall task was introduced when performance in the copying and immediate recall conditions had significantly improved.
- *Spaced retrieval strategy (SRS)* was used to progressively increase time intervals so as to improve memory capacity and knowledge retention in time (Brush & Camp, 1998).

- *Retraining and Compensatory strategies for attention training*, aimed to restore the impairment per cognitive domain and increase neuroplasticity by systematically repeating paper-and-pencil exercises and cognitive stimulation tasks (Sohlberg & Mateer, 1987; 2001).
- *Internal compensatory strategies* and specifically, *errorless learning* was used to help patients avoid mistakes and prevent impulsivity (Goldstein & McNeil, 2004; Wilson et al., 2009). For example, providing cues during the learning process when patients were not able to complete a task encouraged the storage and retrieval of information in long-term memory (Clare & Jones, 2008).
- *Self-monitoring techniques (stop and check):* were used to learn how to give self-instructions, reduce impulsive behaviors, expand the attention span and apply effective coping strategies (Sohleberg & Mateer, 2001). Improvement was monitored in a hierarchical order in all the exercises.
- *Fluency training* was used for the improvement of language and frontal lobe functions. Patients were asked to produce lists of words from specific categories (animals/fruits/objects) and letters X, S, and A (phonemic part). Fluency and attention training was enhanced by presenting to patients a list of words in color who were asked to read the words and/or colors as fast as they could (Kelly & O'Sullivan, 2015).
- *Errorless learning and procedural memory training* which prioritize the avoidance of errors was the primary technique applied for the facilitation of executive function difficulties (Kelly & O'Sullivan, 2015; Middleton & Schwartz, 2012). The GMT was used to develop a systematic approach to problem solving, goal management, and execution (Levine et al., 2000; Wilson, 2009).

The rehabilitation program of G.V. included 27 sessions which lasted 30 hours in total, while the rehabilitation program of S.S. included 14 sessions with a total of 14 hours because of the less severe cognitive insufficiencies present in the initial neuropsychological assessment of S.S. For both patients, the sessions were programmed twice a week and each session lasted approximately 50 minutes, always taking into consideration their fatigue levels. Every session included verbal/visual/working memory tasks, attention, visuospatial/visuo-constructional, language, and executive function tasks. Performance (omissions, time needed to complete each task, errors) was recorded at the end of the sessions by the patients to improve self-awareness and self-monitoring abilities. This technique of Monitoring Progress

was introduced after the first four sessions to avoid disappointment (*The therapeutic milieu*, Goldstein & McNeil, 2004). From the very first session each activity was timed, and a record of the errors made was kept by the clinical neuropsychologist who was performing the sessions. Monitoring of Progress was performed upon meeting the criterion of 80% accuracy in each of the applied rehabilitation exercises to gradually increase the difficulty. G.V. made great progress even from the first month of cognitive rehabilitation in all targeted cognitive areas, and S.S. was able to make progress from the first couple of weeks given the fact that her cognitive insufficiencies were not as severe as in the case of G.V. In the last sessions, both patients could complete the tasks in half the time they needed in the first sessions. They were able to apply the knowledge they had gained to execute daily tasks and the feeling of success had significantly altered their self-confidence levels and mental well-being (Sohlberg & Mateer, 2001; Wilson, 2013).

Results

Performance on cognitive tasks before and after treatment are shown in Tables 1 and 2.

Table 1. G.V.'s cognitive performance before and after individualized neuropsychological rehabilitation sessions.

Baseline Neuropsychological Assessment		Follow-up Assessment (After 3 months)
Cognitive Areas	Results	Results
Verbal Fluency[1] Semantic	**31** Mild to moderate insufficiencies	**52** Very Good Performance
Verbal Fluency Phonemic	**15** Moderate to severe insufficiencies	**28** Very Good Performance
Naming[2]	**15** Excellent Performance	**15** Excellent Performance
New Learning & Memory[3] Trials 1-5	**13** Severe insufficiencies	**29** Mild insufficiencies

Short delay free recall	**2** Severe insufficiencies	**5** Mild to moderate insufficiencies
Short delay cued recall	**6** Severe insufficiencies	**8** Mild to moderate insufficiencies
Long delay free recall	**0** Severe insufficiencies	**3** Mild to moderate insufficiencies
Long delay cued recall	**2** Severe insufficiencies	**6** Mild to moderate insufficiencies
Auditory Working Memory[4] Story A	**12/50** Severe Insufficiencies	**33/50** Mild to moderate insufficiencies
Visuospatial/ Visuoconstructive Functions[5] Copy	**6** Severe insufficiencies	**32** Mild insufficiencies
Immediate Recall	**0** Severe insufficiencies	**4** Moderate to severe insufficiencies
Delayed Recall	**0** Severe insufficiencies	**4** Moderate to severe insufficiencies
Recognition	**0** Severe insufficiencies	**15** Mild to moderate insufficiencies
Focused & Sustained Attention[6]	**7** Mild to moderate insufficiencies	**11** Mild insufficiencies
Complex & Sustained Attention[7]	**17** Severe insufficiencies	**23** Moderate to severe insufficiencies
Visual Detection Speed & Execution[8]	**75 secs** Severe insufficiencies	**56 secs** Mild to moderate insufficiencies
Alternative & Complex Sustained Attention[9]	**189 secs** Severe insufficiencies	**118 secs** Mild insufficiencies
Selective Attention, Vulnerability to instructions, inhibition[10] Word	**36** Severe insufficiencies	**72** Moderate to severe insufficiencies
Color	**31** Severe insufficiencies	**38** Moderate to severe insufficiencies
Word-Color	**15** Moderate to severe insufficiencies	**25** Mild insufficiencies
Executive Functions[11] Rule Shifting	**2** Very Good Performance	**0** Excellent Performance

Key Search	**5** Moderate to severe insufficiencies	**8** Mild to moderate insufficiencies
Zoo Map	**-4** Severe insufficiencies	**10** Mild to moderate insufficiencies
Mood[12]	**38** Indication of severe depressive disorder	**18** Indication of mild depressive disorder

Table 2. S.S.'s cognitive performance before and after individualized neuropsychological rehabilitation sessions.

Baseline Neuropsychological Assessment		Follow-up Assessment (After 3 months)
Cognitive Areas	Results	Results
Verbal Fluency[1] Semantic	**39** Mild insufficiencies	**60** Very Good Performance
Verbal Fluency Phonemic	**27** Very Good Performance	**36** Excellent Performance
Naming[2]	**15** Excellent Performance	**15** Excellent Performance
New Learning & Memory[3] Trials 1-5	**27** Mild to moderate insufficiencies	**74** Excellent Performance
Short delay free recall	**6** Mild to moderate insufficiencies	**14** Very Good Performance
Short delay cued recall	**10** Mild to moderate insufficiencies	**16** Excellent Performance
Long delay free recall	**5** Mild to moderate insufficiencies	**13** Very Good Performance
Long delay cued recall	**8** Mild to moderate insufficiencies	**16** Excellent Performance
Auditory Working Memory[4] Story A	**35/50** Mild to moderate insufficiencies	**47/50** Very Good Performance
Visuospatial/ Visuoconstructive Functions[5] Copy	**29** Severe insufficiencies	**32** Mild insufficiencies
Immediate Recall	**19** Very Good Performance	**29** Excellent Performance
Delayed Recall	**13.5** Mild insufficiencies	**21.5** Very Good Performance
Recognition	**21** Very Good Performance	**23** Excellent Performance
Focused & Sustained Attention[6]	**13** Very Good Performance	**16** Very Good Performance

Complex & Sustained Attention[7]	**30** Mild to moderate insufficiencies	**38** Mild insufficiencies
Visual Detection Speed & Execution[8]	**51 secs** Mild insufficiencies	**40 secs** Very Good Performance
Alternative & Complex Sustained Attention[9]	**104 secs** Mild insufficiencies	**81 secs** Very Good Performance
Selective Attention, Vulnerability to instructions, inhibition[10] Word	**76** Mild insufficiencies	**87** Very Good Performance
Color	**54** Mild insufficiencies	**65** Very Good Performance
Word-Color	**29** Mild insufficiencies	**32** Mild insufficiencies
Executive Functions[11] Rule Shifting	**0** Excellent Performance	**0** Excellent Performance
Key Search	**11** Very Good Performance	**13** Very Good Performance
Zoo Map	**13** Very Good Performance	**15** Very Good Performance
Mood[12]	**25** Indication of moderate depressive disorder	**12** Indication of minimal depressive disorder

[1]Verbal Fluency (VF) Test was used to assess language functions.
[2]The Boston Naming Test (BNT) was used to assess naming abilities.
[3]The California Verbal Learning Test (CVLT) was used to assess new learning of information and memory.
[4]The Logical Memory subtest (WMS-IV) was used to assess auditory working memory.
[5]The Rey-Osterrieth Complex Figure Test (ROCF) was used to assess visuospatial/visuoconstructive abilities.
[6,7,8,9,10]The Digit Span Forward (DSF) and Backward (DSB), The Digit Symbol Modalities Test (DSMT), The Trail Making test A & B (TMT A & B), and the Stroop Color and Word Test (Stroop) were used for the assessment of attentional processes.
[11]The subtests of the Behavioral Assessment of the Dysexecutive Syndrome (BADS Rule Shifting, Key Search, Zoo Map) were used to assess executive functions.
[12]Beck's Depression Inventory (BDI) was used to assess mood.

As is evident from the tables above, the two individualized cognitive rehabilitation programs were highly efficient for both patients, even though, in the initial neuropsychological assessment their insufficiencies and needs were not of similar severity. These two ladies are from different age groups, cultural/educational backgrounds, occupational status, and also, their emotional states, daily routines, and needs were completely dissimilar. GV who has a 5-year-old child with autism needed a completely different therapeutic approach compared to SS whose child is an adult and has different needs. Hence,

this approach follows the rationale of personalized medicine for the greater good of the individual and not the neurological condition per se.

Discussion and Conclusions

Cognitive insufficiencies are very common among individuals with MS who are struggling to remain functional and independent in their daily life. At an existential level, serious cognitive decline can be present at the very early stages of the disorder and therefore, it has devastating effects for the individual's quality of life, self-esteem, and well-being. MS primarily affects younger individuals who are high achievers and live upon the high standards set by themselves and others. MS diagnosis accompanied by the cognitive insufficiencies presented, challenges their health and strength and makes them eventually enter a new life stage and acquire the role of a chronic patient. As it is evident in the literature, the most commonly affected areas of cognitive functioning in patients with MS are information processing speed, attention, memory (visual, long-term), and executive functioning.

Recently, there has been a great interest on how to deal with the cognitive insufficiencies presented in patients with MS because of their devastating effects on the individual and because quite often these difficulties do not allow the patient to receive the appropriate pharmacological treatment prescribed by the neurologist mainly because of their inability to follow the prescription timetables. For this reason, individualized neuropsychological rehabilitation programs are of vital significance for the patient to learn how to compensate with the cognitive difficulties, how to re-learn acquired skills that were eventually lost, and how to manage mood problems which can affect the neuropsychological profile of the individual and his/her performance at the rehabilitation sessions to a great extent. The effectiveness of neuropsychological rehabilitation has been questioned quite a lot because research findings are sometimes controversial. However, the majority of studies have found very promising results and as it was observed, the cognitive performance of individuals with different MS types, of different age groups, occupations, and gender performed better after receiving a Holistic Neuropsychological Rehabilitation treatment plan focusing on the cognitive insufficiencies but also mood which is of paramount significance in order for the rehabilitation sessions to be successful and for one's ongoing neuropsychological profile (Papadopoulou, 2020).

Personalized medicine is of great significance, nowadays, since research has shown that pharmacological treatments are not equally effective for each patient and when it comes to neurological

conditions of complex etiology like MS the focus should be on the individual and his/her singular needs in order for the treatment plan to be effective (Giovannoni, 2017; Leist, 2021). Based on this approach, individualized neuropsychological rehabilitation programs are designed to provide to each patient what he/she essentially needs. Another important aspect is that the patient has continuous personal contact with the neuropsychologist which can motivate him/her even more.

In this line, prior to the individualized neuropsychological rehabilitation sessions designed by trained Neuropsychologists, a mandatory procedure is the initial neuropsychological assessment in order to examine which cognitive areas are affected and determine the level of disability. Based on the results of the initial assessment and the clinical interview, neuropsychological rehabilitation programs are designed and executed by trained Neuropsychologists tailored to the needs of each patient, by targeting different areas of cognition, including memory, attention/concentration, executive functions, language and providing psychological support when needed (Amato et al., 2012; Brochet, 2022).

In our study, the efficiency of two individualized cognitive rehabilitation programs applied to two female patients with relapsing/remitting MS gives quite promising results about the effects of neuropsychological rehabilitation on Greek patients with the same MS type but from different cultural, educational, social, vocational, and economic backgrounds. Despite the diversity in their backgrounds and cognitive level, it is clear that after neuropsychological rehabilitation the results for both patients were impressive since all areas of cognitive functioning improved significantly. Great progress was observed in cognitive areas which were mildly affected and this is a promising sign for the efficacy of neuropsychological rehabilitation across Greek patients with the relapsing-remitting MS type. This could be a step for further investigation in relation to the efficacy of individualized neuropsychological rehabilitation programs for individuals from different language and cultural backgrounds with MS and its types. Psychoeducation and psychological support provided during the sessions have shown to have helped the patients' mood to a great extent, which then made it easier for them to continue more successfully with the cognitive part of the sessions (Domensino et al., 2021). When depressive symptoms are present, patients cannot concentrate and perform the tasks required, hence, the first aim in the rehabilitation sessions was to deal with the mood problems and then proceed to the cognitive ones (Papadopoulou, 2020).

To our knowledge, this was the first attempt to investigate the effectiveness of two individualized neuropsychological rehabilitation programs applied to two Greek female patients with relapsing-remitting MS. As was evident, neuropsychological rehabilitation was very successful for both ladies despite their age, cultural/educational background, occupational status, and levels of cognitive decline. Firstly, their overall perspective towards their condition had altered through psychoeducation, non-specific therapeutic skills and specific therapeutic alliance. The mood of both patients improved as well as their confidence and independence. Also, their self-esteem levels enhanced and they achieved a healthier relationship with their family members and friends. However, there are some possible limitations of the present study such as individualized neuropsychological rehabilitation programs should be applied to more patients in order to have more comprehensive conclusions and be able to generalize the results. Moreover, individualized neuropsychological rehabilitation programs should be applied to patients with all possible MS subtypes to ensure that they are equally effective for everyone. To this end, future research should clarify in more depth how cultural differences may affect individualized neuropsychological rehabilitation programs and more Greek patients should be able to have access to such programs.

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