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Do Secondary Progressive Multiple Sclerosis patients benefit from Computer- based cognitive neurorehabilitation? A randomized sham controlled trial

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ABSTRACT

Background

Cognitive impairment is common in multiple sclerosis (MS), but deficits tend to be more pronounced in progressive MS, negatively impacting daily functional capacity. Despite this, most cognitive rehabilitation (CR) interventions to date have focused on relapsing-remitting MS (RRMS). Moreover, information on the efficacy of CR in progressive MS is limited and controversial. The present study investigated the efficacy of a home based, computer assisted cognitive rehabilitation (HBCACR) intervention (RehaCom^{TM} software) exclusively in a Secondary Progressive Multiple Sclerosis (SPMS) sample.

Methods

This was a randomized, multi site, sham controlled trial. Thirty six (36) individuals with SPMS, naïve to the RehaCom software, with cognitive deficits were randomized to the treatment (IG; n= 19) or control group condition (CG; n=17). Treatment with the RehaCom modules consisted of 24 domain and task specific, 45 minute session's over an 8-week period, three sessions per week, applied by each patient at home. The CG completed non specific computer based activities at home with the same frequency and duration. Primary cognitive outcome measures included the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery, and secondary outcome measures for depression (BDI-FS), fatigue (MFIS), and quality of life (EuroQol EQ-5D) visual analogue scale (VAS).

Results

The two groups were well matched on demographic and clinical characteristics, cognitive reserve and severity of cognitive deficits at baseline assessment. At post treatment assessment the IG group showed significant improvements with large effect sizes; in verbal learning [z = -4.759, p <.0005, g = 2.898], visuospatial memory [z = -3.940, p <.0005, g = 1.699] and information processing speed [z= -4.792, p <.0005, g = 2.980], compared with the sham control group. We also found significant between group differences on physical [z=-3.308, p = .001, g= -.604], cognitive [z = -4.011, p <.0005, g = -1.654], psychosocial [z= 3.308, p = .010, g = -.940], and general fatigue impact [z= -2.623, p = .008, g = -.519], depression severity [z = -2.730, p = .006, g = -.519], and quality of life [z= -4.239, p <.0005, g = -1.885] in favor of the treated group.

Conclusion

These data provide the first evidence supporting the efficacy of computer based restorative cognitive rehabilitation applied at home exclusively in SPMS patients, suggesting that adaptive neuroplasticity may occur after functional cognitive training in progressive MS. Improved cognitive functioning in combination with mood augmentation appear to have ameliorated fatigue, which impacted daily functioning activity and culminated in improved health related quality of life.

Introduction

Cognitive impairment is a common feature affecting between 45-70% of multiple sclerosis (MS) patients overall (Chiaravalloti and DeLuca, 2008), but prevalence rates of cognitive deficits in individuals with secondary progressive MS (SPMS) are much higher (Doshi et al., 2016) and may even reach 80% (Papathanasiou et al., 2014). Although there is significant variation among individuals, the most prevalent cognitive impairments have been reported in the domains of visual and verbal learning / episodic memory, complex attention and information processing speed (Langdon, 2011; Ntoskou et al., 2018). These deficits limit the individual's capacity in terms of employment status, social relationships, and may even compromise activities of daily living such as driving (Ryan et al., 2009), finances (Goverover, 2016) and quality of life (Kargiotis et al., 2010; Messinis et al., 2019). Further, individuals with SPMS consistently present with lower cognitive performance than those with relapsing-remitting MS (RRMS), possibly due to their older age, longer duration of illness, or more severe physical disability (Ntoskou et al., 2018; Brochet and Ruet, 2019).

The treatment of MS has made significant progress in the last decade. The utilization of disease modifying therapies in RRMS patients reduces the number of relapses and slows down the disease course, but still require the proper balancing of efficacy and safety (Auricchio et al., 2017; Comi et al., 2017). Cognitive impairment poses a considerable burden in terms of everyday functioning ability, but no effective pharmacological therapies have been approved to treat these debilitating symptoms (Feinstein, 2017), with studies reporting only modest efficacy (Roy et al., 2016). The evidence to date for non-pharmacological interventions such as cognitive rehabilitation (CR) is also incomplete on whether they might improve or stabilize cognitive impairment, but especially whether gains obtained on neuropsychological testing translate into meaningful long term changes in MS patients' everyday functioning (Mitolo et al., 2015; Miller et al., 2018; Messinis et al., 2018). Furthermore, validated and widely accepted clinical procedures for CR are lacking (Sokolov et al., 2018). Despite this general consensus, several studies have reported the efficacy of pharmacological agents (Mokhber et al., 2014) and cognitive rehabilitation (Messinis et al., 2017; Rosti-Otajarvi et al., 2014; Dardiotis et al., 2018) in alleviating MS associated cognitive deficits, predominantly in RRMS patients. Moreover, f-MRI studies documenting alterations in cortical activation associated with CR raise the intriguing possibility that compensatory cerebral reorganization may underlie the benefits observed in these patients (Fillipi et al. 2012; Chiaravalotti et al. 2015).

Regarding the efficacy of computer based training in CR interventions, a recent systematic review reported a moderate overall cognitive effect and small to moderate effect sizes for attention/processing speed, executive functions, and verbal/visuospatial memory. The authors, however, raised concerns regarding the efficacy of such interventions in progressive forms of MS and whether the performance gains on neuropsychological measures actually transfer to daily functioning capacity (Lampit et al., 2019).

Considering that SPMS patients show gradual accumulation of disability resulting mainly from atrophy and neurodegeneration, and rarely inflammatory lesion activity (Ontaneda et al., 2017), available pharmacological treatments have minimum effectiveness on these progressive patients cognitive ability. Exceptions to this are the findings of two recent studies. The first by Chan et al., (2017), noted a significant treatment effect of high-dose simvastatin after 24 months on a measure of frontal lobe functions (FAB), but verbal and non-verbal memory declined further during this treatment period. In the second study, a clinically meaningful positive effect for the pharmaceutical substance siponimod on mental processing speed was reported in relapsing and non relapsing SPMS patients, but not on visual/ spatial episodic memory (Benedict et al., 2018).

Thus, for individuals with SPMS, there appears to be no pharmacological treatment available at present to slow down overall cognitive impairment or frequently affected cognitive domains such as verbal or visual episodic memory, visuospatial perception, or social cognition. Moreover, as SPMS patients have increased motor and other disabilities, attending rehabilitation interventions in outpatient settings frequently, as is usually required, is a major burden. In the absence of effective pharmacological therapies, and the complexity and heterogeneity of cognitive impairment in SPMS patients, the search for appropriate non-pharmacological interventions, which can be applied in the home setting, has become a priority. Furthermore, to our knowledge, the effectiveness of cognitive rehabilitation interventions in MS have been investigated only in mixed MS populations.

With this background, the present study sought to 1) objectively evaluate the efficacy of a neurobehavioral, home based, computer assisted cognitive rehabilitation (HBCACR) intervention in SPMS patients on cognitive / neuropsychological measures of verbal learning – episodic memory, visuospatial memory, and information processing speed / working memory, (2) increase the generalizability of the HBCACR procedure by assessing outcome on measures of depression, fatigue and quality of life

Section snippets

Participants

Forty four patients diagnosed with SPMS attending the outpatient neurology clinic at the University Hospital of Patras in Greece or the Multiple Sclerosis center at AHEPA University hospital in Thessaloniki, took part in the study. These patients reported cognitive difficulties or were judged by clinical neurological evaluation to have cognitive deficits and were referred for specialist neuropsychological assessment and rehabilitation to the outpatient memory and neuropsychological units of the

Comparison of demographic and clinical characteristics at baseline

A total of 44 patients with SPMS were screened. Eight patients did not meet the eligibility criteria (see figure 1).

We did not find statistically significant differences between the two groups on baseline assessment for any of the demographic or clinical variables (see Table 1 for a detailed description of demographic and clinical characteristics at baseline and comparison).

From the above analysis, we conclude that our two groups were well matched on baseline demographic variables, premorbid

Discussion

The purpose of this study was to examine the efficacy of a home based 8-week multicenter randomized sham controlled trial by utilizing therapeutic modules from the RehaCom software in order to restore the most frequent cognitive domains affected in progressive MS patients. This is the first trial that recruited SPMS patients exclusively. Results revealed that the two SPMS groups were well matched at baseline assessment on demographic and clinical characteristics, cognitive reserve and cognitive

Limitations

Although our study has several strengths, including its multicenter randomized sham controlled design, inclusion of exclusively SPMS patients, and its home based application, it does have several potential limitations. Firstly, the potential impact of symptomatic treatment for spasticity and mood has not been taken into account. However, no treatment regimen changes or dosage alterations occurred during the study duration**.** Secondly, while improvements on measures of processing speed and verbal

Conclusions

These data provide the first evidence for efficacy of a computer based restorative cognitive rehabilitation intervention applied at home exclusively in SPMS patients. Moreover, improved cognitive functioning in combination with mood augmentation appear to have ameliorated cognitive and physical fatigue, which impacted daily functioning activity and culminated in improved health related quality of life. Given the limited pharmacological treatment options for progressive MS, further

Author Contribution

All included authors have contributed equally to this manuscript in all respects.

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Research ethics

Approval was granted by the ethic committees from each institution that provided participants or facilitated participant recruitment for this study

Declaration of Competing Interest

The authors report no conflict of interest

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