The role of cognitive reserve in multiple sclerosis: A cross-sectional study in 526 patients

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ABSTRACT

Background: Cognitive impairment (CI) affects about 40–70% of multiple sclerosis (MS) patients. Brain MRI explains about 33–50% of the CI variance in MS. The cognitive reserve (CR) hypothesis has been postulated to identify other factors that can account for more variance in this outcome. The objective of this study was to explore the impact of CR on cognitive performance in MS patients.

Methods: A total of 526 MS outpatients were recruited (70.9% females, 41.7 ± 11.1 years old). CR was cross-sectionally assessed by the CR Index questionnaire (CRIq). Cognitive assessment was performed using the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) tool to evaluate information processing speed, verbal memory and visuospatial memory. The role of CRIq in MS cognition was investigated by using multiple linear regression models to account for possible confounders.

Results: In total 202 (38.4%) patients were found with CI (i.e. failure in at least one of the three cognitive tests used based on normative data from 212 healthy controls). The CRIq score of CI patients was lower than that of non-CI patients (p < 0.001). CRIq score was significantly correlated with information processing speed (rho = 0.364, p < 0.001), verbal memory (rho = 0.237, p < 0.001) and visuospatial memory (rho = 0.331, p < 0.001), having adjusted for age and sex. CRIq was also significantly associated with disability (rho = -0.188, p < 0.001) and depressive symptoms (rho = -0.220, p < 0.001). Roughly, CRIq, disability and depressive symptoms significantly explained 12.2–23.7% of cognitive performance in MS. A significant interaction between CRIq and disability was also found for information processing speed.

Conclusion: CR has a protective role in MS-related cognitive dysfunction. The differential effect of CR on distinct cognitive domains is supported. Interventions targeting CR to prevent cognitive impairment in MS patients are warranted by the study findings.

1. Introduction

Cognitive impairment (CI) affects about 40–70% of multiple sclerosis (MS) patients and has an adverse impact on the patients’ social life, employability and overall quality of life or well-being (Fischer et al., 2014). Information processing speed, attention, executive function and visuospatial skills are frequently found impaired (Fischer et al., 2014). However, only 33–50% of the CI can be explained by MS-related brain lesions and atrophy (Benedict and Zivadinov, 2011). To account for more CI variance, the cognitive reserve (CR) hypothesis has been put forward. Indeed, MS studies have lent credence to this hypothesis by showing that CR moderates the association between gray matter atrophy or lesion load with verbal memory or verbal fluency (Ifantopoulou et al., 2019; Santangelo et al., 2018; Sumowski et al., 2013).

CR is a counterpart of one’s education, intelligence, work and leisure activities. The cognitive reserve (CR) hypothesis states that a high CR buffers cognitive decline due to brain insult of any cause (Stern, 2002). More specifically,
the theoretical fundament of CR connotes that there are actually two types of reserves: the passive or brain reserve and the active or CR. The former is attained during the critical developmental periods and represents mainly brain size or neuronal counts. The principle behind brain reserve is that larger brains can sustain more insult before a critical and universal threshold is reached, after which CI emerges. On the other hand, active CR reflects the active deployment of cognitive processes and/or compensatory neural mechanisms in order to counteract cognitive decline. Active CR does not entail critical thresholds but assumes that existing or compensatory neural networks are used to serve the cognitive function “under threat” (Stern, 2009). Collectively, active CR refers to compensatory processes at the level of brain networks, while brain reserve accounts for the quantity of available neural substrate.

CI has been associated with many different clinical characteristics such as disease duration, MS type, disability etc. (Brochet and Ruet, 2019). However in a recent cross-sectional study, age and CR were the only significant predictors of CI (Amato et al., 2019). In other MS studies, CR has been substantiated as the strongest predictor of CI, after adjusting for multiple confounders (Benedict et al., 2010; Nunnari et al., 2016). More importantly, in a recent meta-analysis of 18 studies and 1903 MS patients, the weighted effect sizes between CR and different cognitive domains were found to be significant and moderate (Santangelo et al., 2019). In this meta-analysis, higher age and the female sex characteristics augmented these effect sizes, but no significant moderating role of disease duration, MS phenotype and disability (assessed by Expanded Disability Status Scale, EDSS) was documented. In conclusion, current evidence supports that CR is a strong independent predictor of cognitive performance in MS.

However, there are several caveats in the literature that have been previously enunciated and need to be addressed (Santangelo et al., 2019). Those that stand-out are firstly, the methodological heterogeneity of CR and cognitive assessment and secondly, the lack of adjustment for multiple putative confounders, such as disease type, duration, treatment, depression etc. In this cross-sectional study, we aimed to further validate the role of CR in cognitive function of MS patients by using the Cognitive Reserve Index questionnaire (CRIq) developed by Nucci et al., to collectively account for education, work and leisure activities (Nucci et al., 2012). By using CRIq instead of different CR proxies (e.g. education alone), we aimed to limit the unexplained variance of the CR construct, rather than delve into the CR theory. Also, cognitive performance was assessed by BICAMS (Brief International Cognitive Assessment for Multiple Sclerosis), a highly recommended clinical neuropsychological tool that obviates the time-and cost-related barriers of extensive neuropsychological testing in MS (Langdon et al., 2012). In other words, this study tried to replicate the contribution of CR to cognitive performance by using a large sample of MS patients and clinically relevant neuropsychological tools, in order to further address the needs of everyday clinical practice and pertinent future clinical research.

2. Materials and methods

2.1. Study design and settings

This is a cross-sectional study of 526 MS outpatients from two MS referral hospitals: the NIMTS (Army Share Fund Hospital) in Athens and the AHEPA University hospital in Thessaloniki, Greece. Outpatients were recruited, twice per week, between October 2015 and June 2017. All patients gave their written informed consent and the study protocol was approved by the involved hospitals’ Ethical committees, as it was found consistent with the Declaration of Helsinki.

2.2. Participants

Inclusion criteria were the following: clinically definite MS according to the 2011 revised McDonald criteria (Polman et al., 2011), age over 18 years old, Greek fluency and written informed consent. Exclusion criteria were the following: MS relapse or use of corticosteroids in the previous 30 days, non-response to disease modifying therapy (DMT) according to the modified Rio-Score criteria (Sormani et al., 2013), presence of physical disability interfering with neuropsychological testing (e.g. visual acuity problems, severe motor disability etc.) assessed by an experienced neurologist at site, official diagnosis of major psychiatric disease, illicit drug abuse and participation in another study.

2.3. Assessments

2.3.1. Clinical characteristics

These included the type of MS (i.e. remitting-relapsing, RRMS; secondary progressive, SPMS; primary progressive MS, PPMS), disease duration (in years), disability assessed by the EDSS (Kurtzke, 1983) and DMTs.

2.3.2. Neuropsychological assessment

Cognitive performance was assessed by BICAMS comprised by the Symbol Digits Modalities Test (SDMT) for attention and information processing speed, the California Verbal Learning Test II (CVLT-II) for verbal learning and memory and the Brief Visuospatial Memory Test Revised (BVMT-R) for visuospatial learning and memory, all validated in Greek language (Langdon et al., 2012; Polychroniadou et al., 2016). Age- and sex-corrected cognitive scores were calculated. Higher scores denote higher cognitive performance.

Cognitive impairment was ascertained by using age- and sex-adjusted residuals of 212 healthy controls (mean age 36.8 ± 8.6 years old, 60.4% females). All healthy controls were recruited through researchers’ network of family, friends or colleagues in the community. Healthy controls with outlier ages compared to patients were excluded. In specific, linear regression models with each cognitive score as dependent variable and sex and age as independent were applied. The resulting equation was used to predict scores for the MS patients. Observed minus the predicted scores were divided by the models’ standard deviations of residuals. According to previous recommendations, CI was defined as a standardized residual lower than ± 1.65, in at least one (out of the three) cognitive test (Benedict, 2009).

2.3.3. Cognitive reserve

CR was assessed by the CRIq questionnaire (CRIq), a 20-item tool which addresses: a. both formal and informal education years, b. years of working activity experience in professions categorized in five different levels according to the degree of responsibility and cognitive demands and c. leisure activity, with information about the frequency of several activities (such as reading, housekeeping, driving, hobbies, travelling etc.) in a weekly, monthly, yearly or stable basis (Nucci et al., 2012). Experienced health professionals conducted semi-structured interviews to gather pertinent information. None of the patients had significant cognitive impairment to hinder the evaluation process, whilst a well-informed family member was present most of the times to support patients’ answers. Total scores were age-adjusted by default and higher scores denoted higher CR. Although there was no effect of sex on CRIq (p = 0.848), further adjustment was made. The tool has been adapted to the Greek language (Maiovìs et al., 2016).

2.3.4. Depressive symptoms

Symptoms of depression was assessed by the seven Likert-type items of the Depression Anxiety and Stress-21 tool (DASS-21) (Lovibond and Lovibond, 1995). Scores ranged from 0–21; higher scores reflect more symptoms of depression. The scale has been adapted in the Greek population (Lyrakos et al., 2011). A significant positive correlation was found between depressive symptoms and age (rho = 0.10, p = 0.028). Age- and sex-corrected scores were produced, albeit the effect of sex
was non-significant \( (p = 0.795) \).

### 2.4. Statistical analyses

Descriptive statistics included means, standard deviations, range, medians, interquartile range and frequencies. Univariate associations were checked with Pearson's rho correlations (after inspecting graphs for outliers), or Student's t-test. Predictors of cognitive performance were explored by linear regression models. In the first step, all putative predictors (i.e. disease duration, disease type, DMT and depressive symptoms) of cognition were investigated and subsequently selected using the backward elimination method. Age and sex were not selected, since all scores were age- and sex-adjusted. In the second step, CRIq was entered and R-square \( (\Delta R^2) \) changes were assessed for their significance. Finally, the interaction terms of CRIq with other significant predictors were checked separately for their contribution to cognitive performance variance. B coefficients, standardized beta coefficients and adjusted R-square values, along with significance was set at 0.05. Analysis was performed using SPSS for Windows, version 22.0 (NY: IBM Corp.).

### 3. Results

#### 3.1. Characteristics of the study sample

The study sample consisted of 526 patients (70.9% females, mean age 41.7 \( \pm \) 11.1 years old). Most of the patients (78.5%) had RRMS; 11.4% patients had SPMS and 10.1% PPMS. Mean disease duration was about 10 years with a wide range from 1 month to 40 years. The median EDSS score was 3.0 points, with a wide range from 0 to 8.5 points. Most patients (93.5%) were receiving DMT. In total, 207 patients (39.4%) were of primary or secondary education level (i.e. 12 or less years of formal education), whilst the rest 319 patients (60.6%) were of tertiary education level. Raw cognitive, CRIq and depressive symptoms scores are presented in Table 1.

CI was detected in 202 (38.4%) patients. More specifically, 135 patients (25.7%) failed in one cognitive domain, 44 patients (8.4%) in two and 23 patients (4.4%) in all three cognitive domains assessed by the BICAMS tool. With respect to disease type, CI prevalence was significantly lower in RRMS (i.e. 136/413, 32.9%), than in SPMS (35/60, 58.3%) or PPMS (31/53, 58.5%) patients \( (p < 0.001) \). CI patients had longer disease duration (CI: 11.3 \( \pm \) 7.8 vs. non-CI: 9.6 \( \pm \) 7.7 years, \( p = 0.016 \)), higher EDSS (CI: 4.0 \( \pm \) 1.8 vs. non-CI: 2.7 \( \pm \) 1.5 points, \( p < 0.001 \)) and more depressive symptoms (CI: 5.7 \( \pm \) 5.7 vs. non-CI: 4.4 \( \pm \) 4.4, \( p = 0.004 \)) than non-CI patients.

#### 3.2. Univariate associations of CRIq

There was a significant correlation between adjusted CRIq score and information processing speed (rho = 0.364, \( p < 0.001 \)), verbal memory (rho = 0.237, \( p < 0.001 \)) and visuospatial memory (rho = 0.331, \( p < 0.001 \)) scores; increase in CRIq score was correlated with increase in cognitive performance, irrespective of age or sex. Higher CRIq was also associated with lower disability (rho = -0.188, \( p < 0.001 \)) and depressive symptoms (rho = -0.220, \( p < 0.001 \)). The CRIq score was lower in CI patients than in non-CI patients (CI: 94.8 \( \pm \) 11.6 vs. non-CI: 102.2 \( \pm \) 14.1, \( p < 0.001 \)). CRIq was not associated with disease duration (rho = 0.095).

#### 3.3. Multi-variable tests

EDSS and depressive symptoms were the only significant negative predictors of information processing speed and verbal memory, meaning that higher disability and depressive symptoms were
associated with worse information processing speed and verbal memory. On the other hand, EDSS was the sole significant negative predictor of visuospatial memory. Disease duration, MS type and DMT status characteristics were backward eliminated as non-significant in all models. Based on the standardized betas values, EDSS was a more potent predictor of cognitive scores than depressive symptoms. In total, both EDSS and depressive symptoms explained about 9.8–14.9% of the cognitive performance variance.

Adding CRIq in the models increased the explained variance by 7.9%, 2.4% and 3.7% of SDMT, CVLT-II and BVMT-R scores, respectively. Based on standardized betas values, EDSS was the second stronger predictor of cognitive performance after EDSS. Notably, after inclusion of the CRIq variable, depressive symptoms remained significant only in the verbal memory model.

A significant interaction term of CRIq by EDSS in the information processing speed model was found. In order to interpret this interaction, a line plot of EDSS and SDMT was constructed, considering low and high CRIq based on the 25th and 75th percentile (Fig. 1). As evidenced, high CR exerts a moderating role in the negative association of disability with information processing speed. Among patients with high disability, those with high CR have better information processing speed than those with low CR.

4. Discussion

This large cross-sectional study focused mainly on the role of CR in the cognitive performance of MS patients. In total, this study showed that disability and CR were important independent predictors of MS-related cognitive performance explaining up to 23.7% of its variance, compared to the 33–50% variance explained by brain MRI alone as reported in MS literature (Benedict and Zivadinov, 2011). Even though we used a convenience clinical sample, the patients’ characteristics (Table 1), along with the observed CI prevalence (i.e. 38.4%) rendered our findings generalizable to the MS population (Fischer et al., 2014).

Table 2

The CRIq score was found to be significantly correlated with cognitive performance, implying that patients with higher CRIq score had better information processing speed, verbal and visuospatial memory performance compared to patients with lower CRIq scores. Likewise, CI patients had lower CRIq scores than non-CI patients. The association between CR and cognitive performance has been well-substantiated by previous research in MS using the CRIq (Chillemi et al., 2015; Nunnari et al., 2016) but also in other neurological diseases or even in healthy subjects (Santangelo et al., 2019; Stern, 2002). This is in accordance with the active CR hypothesis whereby, it is suggested, compensation for brain damage occurs through existing or, in some cases, new neural networks. Individuals with higher CR are thus more resilient to cognitive impairment than those with lower CR, after a brain damage (Stern, 2009).

Patients with low CRIq score had higher disability and depressive symptoms than patients with high CRIq scores. The link between disability and depression in MS has been previously well-documented and

Fig. 1. Correlation of Expanded Disability Status Scale (EDSS) and Symbol Digit Modalities Test (SDMT), for high and low cognitive reserve based on the 25th and 75th percentiles. A negative correlation between disability and information processing speed was noted in all patients. Cognitive reserve moderated this correlation, meaning that with increasing disability, the information processing speed impairment is less pronounced in patients with high cognitive reserve.
Table 2
Linear Regression Models Exploring the Predictors of Cognitive Performance in Multiple Sclerosis Patients (N = 526).

<table>
<thead>
<tr>
<th>Symbol Digit Modality Test Model 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>California Verbal Learning Test Model 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Brief Visuospatial Memory Test Model 1&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td><strong>EDSS</strong></td>
<td>b (± SE)</td>
<td>Beta</td>
</tr>
<tr>
<td></td>
<td>(0.32)</td>
<td>−2.71</td>
</tr>
<tr>
<td><strong>Depressive Symptoms</strong></td>
<td>b (± SE)</td>
<td>−0.33</td>
</tr>
<tr>
<td></td>
<td>(0.11)</td>
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</table>

| **EDSS**                                      | b (± SE) | Beta | Sig. | Adj. R², (sig.) | Adj. R², (sig.) | Adj. R², (sig.) | b (± SE) | Beta | Sig. | Adj. R², (sig.) | Adj. R², (sig.) | Adj. R², (sig.) |
|                                              | (0.31)   | −2.36| −0.31| <0.001<sup>*</sup> | 22.8% (<0.001<sup>a</sup>) | ΔR² = +7.9% | (0.28) | −1.40| −0.21| <0.001<sup>*</sup> | 12.2% (<0.001<sup>a</sup>) | ΔR² = +2.4% | (0.20) | −1.71| −0.35| <0.001<sup>*</sup> | 18.1% (<0.001<sup>a</sup>) | ΔR² = +3.7% |
| **Depressive Symptoms**                       | b (± SE) | −0.07| 0.092 | (0.11) | −0.33 | −0.14 | 0.001<sup>*</sup> |
|                                              |         |      |      |            |      |      |            |
| **CRI**                                       | b (± SE) | 0.31 | 0.29 | <0.001<sup>a</sup> | 0.15 (0.04) | 0.17 | <0.001<sup>*</sup> | 0.13 (0.01) | 0.20 | <0.001<sup>*</sup> |
|                                              | (0.04) |      |      |            |      |      |            |

<table>
<thead>
<tr>
<th>Symbol Digit Modality Test Models 3 and 4&lt;sup&gt;b&lt;/sup&gt;</th>
<th>California Verbal Learning Test Models 3 and 4&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Brief Visuospatial Memory Test Models 3 and 4&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRI × EDSS (Model 3)</strong></td>
<td>b (± SE)</td>
<td>Beta</td>
</tr>
<tr>
<td></td>
<td>(0.03)</td>
<td>−0.07</td>
</tr>
<tr>
<td><strong>CRI × Depressive Symptoms (Model 4)</strong></td>
<td>b (± SE)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<sup>a</sup> Disease duration, MS type and treatment status were not found to be significant predictors of cognitive performance in the first step of the multi-variable analyses (i.e. backward elimination method) and were removed from the next steps of the analysis.

<sup>b</sup> ΔR² changes refer to changes from model 1 to model 2 due to the inclusion of the CRI.

<sup>c</sup> Model 3 was produced by inclusion of the interaction term CRI × EDSS in model 2. Model 4 was produced by inclusion of the interaction term CRI × depression in model 2. ΔR² are reported.

<sup>*</sup> p < 0.05, CRI: Cognitive Reserve Index, EDSS: Expanded Disability Status Scale.
possibly explains the significant association of CR with both (Mattioli et al., 2011).

However, in a previous study by Nunnari et al. also using the CRiq, this was not associated with disability (Nunnari et al., 2016). The CRiq entails items about leisure activities such as driving, sports and other hobbies requiring physical exertion. Furthermore, although patients were asked to indicate the number of years and the frequency of these activities throughout their lives, questions do not distinguish the pre-morbid from the MS time-period. Inevitably thus, disability may interfere with CRiq scoring. In the Nunnari et al. study the sample was relatively small (N = 66) and patients had shorter disease duration (mean = 6.3 years) and disability (mean EDSS = 2.5) compared to the present study. Thus, the significant effect of disability on CRiq might be missed in this small study. Nonetheless, in our study disease duration was not associated with CRiq score, which agrees with the Nunnari et al. findings.

With regards to depression, patients with higher depressive symptoms may tend to underreport positive events such as leisure or social activities (Dalgleish and Werner-Seidler, 2014). However, most patients in this study had relatively low depressive symptoms scores (mean 4.9–5.0, median 3.0, theoretical range 0–21) which most likely minimizes such an effect.

In the multi-variable analyses, we found that EDSS and depressive symptoms explained 9.8–14.9% of cognitive performance variance. Although disability is associated with depressive symptoms (Mattioli et al., 2011), no multi-collinearity problems were detected in the regression analyses. This means that depressive symptoms are predictors of cognitive performance, independently from disability, at least for information processing speed and verbal memory.

Similar neural networks sub-serving physical, psychological and cognitive functioning most likely account for the above findings (Rocca et al., 2018). On the other hand, the lack of a significant association between depressive symptoms and visuospatial memory could be presumably accounted by the more frontal brain networks implicated for emotion compared to the more dorsal networks (i.e. parahippocampal- retrosplenial) involved in spatial memory (Catani et al., 2013).

The inclusion of CRiq scores in the multi-variable models increased significantly the explained cognitive performance variance from 9.8–14.9% to 12.2–23.7%. The largest positive effect (based on ΔR² and standardized betas) was noted for information processing speed, followed by visuospatial memory and verbal memory. This is consistent with previous studies supporting the differential protective effect of CR on cognitive function (Ifantopoulou et al., 2019; Santangelo et al., 2019). In a previous study, high CR predicted preservation of the functional brain connectivity despite gray matter atrophy and attenuated the detrimental effect of white matter disruption on information processing speed but not visuospatial memory in MS patients (Fuchs et al., 2019). In another MS study, high CR was found to selectively protect against the effect of peripheral gray matter atrophy in verbal memory, but not in other cognitive domains (Ifantopoulou et al., 2019). Finally, in a recent meta-analysis, larger effect sizes between CR and cognition were noted for most cognitive domains, except verbal fluency (Santangelo et al., 2019). The differential role of CR on cognition and the heterogeneity among studies presumably reflect diverse personal developmental and life-course trajectories leading to preferential strengthening of certain brain networks and pertinent cognitive domains (Stern, 2002).

Finally, we found a significant interaction between CRiq and EDSS in the SDMT model, implying that with increasing disability, information processing speed performance decreases more in patients with low CR than in patients with high CR. The moderating role of CR has been largely documented with respect to the effect of brain atrophy or lesions on cognitive performance (Santangelo et al., 2018). To our knowledge, this is the first study showing this finding and it actually contradicts the conclusions of a recent meta-analysis showing no moderating effect of disability on the CR and cognition relationship (Santangelo et al., 2019). We hypothesize that high physical disability as assessed by EDSS mostly reflects the integrity of subcortical structures and especially white matter in the presence of demyelinating lesions. Similarly, information processing speed performance has been recently strongly associated with the white matter and subcortical structures integrity (Ricitelli et al., 2019). Collectively, the protective effect of CR would be more prominent in patients with high disability wherein, more subcortical structures and association fibers related to cognitive neural networks are presumably impaired, rather than in patients with low disability in whom there are less demands for neural compensation.

This study had several limitations that need to be discussed. Firstly, this was a cross-sectional study; thus, no etiologic inferences can be made. Longitudinal analysis of this sample would further avail the investigation of CR in MS and especially, its differential role across time. Secondly, CRiq evaluation is subject to recall bias, thus some patients may have been misclassified with respect to the CR levels. However, a well-informed family member was present most of the times to support patients’ answers. Thirdly, we did not estimate imaging parameters such as lesion load and brain cortical and subcortical volumes or atrophy. However, the matter has been extensively investigated in previous studies revealing the protective role of CR in the effect of brain insults on cognition (Ifantopoulou et al., 2019; Santangelo et al., 2018). Also, the lack of longitudinal neuropsychological assessments imposes the theoretical risk for gathering unreliable BICAMS data, due to uncontrolled factors during testing. Finally, there can be always some residual confounders or predictors that could affect cognition in MS, such as personality traits, or environmental factors. More importantly, CR may well reflect socioeconomic status, healthcare access and medication adherence which may explain the observed relationships to cognitive performance. Also, this study did not assess the role of each CR proxy in cognition, separately. In any case, the goal of the present study was not to scrutinize the constantly evolving CR model but to estimate the contribution of CR to cognition by taking into account important CR indices simultaneously and by using a large sample of MS patients and a clinically relevant neuropsychological tool (i.e. BICAMS).

In conclusion, our findings suggest that CR is strongly associated with cognitive function in MS patients. More importantly, CR along with disability and depressive symptoms explained up to roughly 23.7% of the cognitive performance, especially of the information processing speed domain. Although, the study did not address the separate role of each CR proxy (i.e. education, working and leisure activities) in MS cognition, these findings still justify future preventive CR-targeted interventions at a healthcare, community, institutional or even governmental level to preserve or even enhance cognitive function in MS patients.

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CRediT authorship contribution statement

Artemios Artemiadis: Conceptualization, Methodology, Formal analysis, Resources, Writing - original draft, Writing - review & editing, Visualization, Project administration. Christos Bakirtzis: Conceptualization, Methodology, Investigation, Writing - review & editing, Project administration. Parthena Ifantopoulou: Methodology, Investigation. Panagiotis Zis: Validation, Writing - review & editing, Visualization. Panagiotis Bargiots: Validation, Writing - review & editing, Visualization. Nikolaos Grigoriadis: Conceptualization, Validation, Resources, Writing - review & editing, Supervision, Project administration. Georgios Hadjigeorgiou: Conceptualization, Validation, Resources, Writing - review & editing, Supervision, Project administration.
Declaration of Competing Interest

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