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Cognitive and brain reserve in multiple sclerosis—A cross-sectional study

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ABSTRACT

Background: Cognitive impairment (CI) is detected in 40–70% of multiple sclerosis (MS) patients, but only 33–50% of the CI variance is explained by the disease burden assessed by MRI. The cognitive reserve (CR) hypothesis has been postulated to account for this discrepancy. So far, most previous studies have confirmed the CR hypothesis in MS but failed to examine CR indices collectively or use clinically relevant neuropsychological assessments. The aim of this study was to replicate previous findings for the effect of CR (and its counterpart; brain reserve-BR) in MS by considering these caveats.

Methods: 128 RRMS and 13 SPMS patients were recruited in this cross-sectional study (mean age 43.5 ± 10.4 years old, 73% females, mean disease duration 153.7 ± 89.4). CR was assessed by the Cognitive Reserve Index questionnaire (CRIq) and BR by the intracranial volume. Neuropsychological assessment was made by using the recommended for clinicians Brief International Cognitive Assessment for MS (BICAMS) tool. Other measurements included clinical characteristics, psychological status, fatigue, and MRI volumetric imaging parameters. Multiple linear regression models were implemented to ascertain the putative moderating role (i.e. interaction terms) of CR and BR in cognition.

Results: Exploratory univariate analyses revealed significant negative correlations between both disability and depression with cognitive scores (rho = −0.382, $p < 0.001$, rho = −0.278, $p = 0.001$, respectively), only. After controlling for gender, disability and depression, a significant moderating protective effect of CR on the associations between both grey and peripheral grey matter volumes with verbal memory was found (beta = 1.834, $p = 0.045$, beta = 1.936, $p = 0.04$ for the interaction terms, respectively). Also, BR moderated the effect of the total brain volume on verbal memory (beta = 1.516, $p = 0.043$).

Conclusion: This study showed that by using composite measures of CR and simple, clinically-orientated neuropsychological assessments, the protective role of CR and BR is mostly restricted to memory function. Future research should embark on investigating interventions that will aim to enhance CR for the prevention of CI in MS.

1. Introduction

Cognitive impairment (CI) is detected in 40–70% of MS patients, with information processing speed, attention, executive function and visuospatial skill being most frequently affected (Chiaravalloti and DeLuca, 2008). CI has been associated with brain damage caused by demyelinative lesions and neurodegeneration in MS (Chiaravalloti and DeLuca, 2008). However, only 33–50% of the CI variance is explained by the disease burden assessed by MRI (Benedict and Zivadinov, 2011). The cognitive reserve (CR) hypothesis has been postulated to account for this discrepancy. In fact, the construct of CR has been built upon the observation that cognitive dysfunction is not consistent with the degree

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of brain pathology (Stern, 2002). In other words, CR acts as a moderator of the relationship between brain damage and cognitive phenotype, meaning that given the same degree of brain pathology, higher CR would ameliorate cognitive decline. The validity of the CR theory has been confirmed in diseases such as Alzheimer's disease (Stern, 2002), Parkinson's disease (Hindle et al., 2014) and traumatic brain injury (Alosco et al., 2017).

Although the measurement of CR is not standard, vocabulary, literacy, intelligence, education, work and engagement in cognitive enriching leisure activities have all been considered as significant proxies (Ghaffar et al., 2012; Scarmeas and Stern, 2003; Stern, 2009). On the other hand, Stern has defined two counterparts of cognitive reserve; a. the passive reserve (also brain reserve, BR), that is attained during the critical periods of the human development and refers to structural characteristics (e.g. brain size, number of neurons or synapses, assessed by intracranial volume, ICV, or maximal lifetime brain growth, MLBG) and b. the active reserve, (or CR described above) that denotes how efficiently a person has managed to use his/her BR to counteract cognitive dysfunction (Stern, 2009).

There are several published studies examining the role of CR and less frequently BR, in MS (Sumowski and Leavitt, 2013). Sumowski et al. have showed that CR and BR are significant moderators of the relationship between disease burden (as ascertained by MRI pathology) and cognitive dysfunction in MS, both cross-sectionally and longitudinally (Sumowski et al., 2016b; Sumowski et al., 2016, 2014, 2013, 2010). The crucial role of CR, rather than BR, in memory and hippocampal volume has also been particularly outlined in their studies (Sumowski et al., 2016b; Sumowski et al., 2016, 2013). Interestingly, however, higher BR predicted lower risk of disease progression (Sumowski et al., 2016a). CR has also been attested as a significant moderator of cognitive impairment in secondary progressive MS patients (Sumowski et al., 2012), albeit other studies evince that the effect of CR may wane across time, with the accumulated structural brain damage being a more important determinant for cognitive function (Amato et al., 2013; Rimkus et al., 2018; Rocca et al., 2019). In general, the moderating role of CR or BR in the brain pathology-cognition association has been replicated by several subsequent studies (Della Corte et al., 2018; Martins Da Silva et al., 2015; Modica et al., 2016; Rimkus et al., 2018; Santangelo et al., 2018), whilst negative results, especially for BR, have been published (Barbu et al., 2018; Modica et al., 2016; Santangelo et al., 2018).

In a recent meta-analysis of 18 primary studies and 1903 MS patients (1400 with relapsing-remitting MS, 93 with primary progressive MS and 205 with secondary progressive MS, 38 with clinically isolated syndrome) with a mean duration of disease between 6.4 and 13.4 years, researchers found significant moderate association between CR and attention, processing speed, verbal memory, spatial memory and inhibitory control (Santangelo et al., 2019a). Interestingly in the same study, disease duration, MS phenotype, disability and CR proxy did not moderate the relationship between CR and cognition. In another, more relevant to the moderating role of CR, meta-analysis, education moderated the effect of gray matter on verbal fluency, whereas vocabulary knowledge moderated the relationship between lesion load and verbal fluency (Santangelo et al., 2019b).

However, an in-depth scrutinization of the published literature on the matter, reveals several caveats that need to be addressed. Firstly, CR assessments differ substantially amongst studies, with education, vocabulary and premorbid intelligence being used more often and interchangeably as proxies for CR (Sumowski et al., 2016b; Sumowski et al., 2016, 2014, 2013, 2010). Notably, although work and leisure activities have been widely appreciated as cardinal CR indices (Luerding et al., 2016), none of the previous studies looked into their overall contribution to the composite CR. Secondly, cognitive assessments were mostly performed with complex or time-consuming tests, that have small applicability to everyday clinical practice. Moreover, some studies did not manage to adjust their statistical analyses for important confounders such as disease duration, type of disease, drugs etc. In specific, confounders such as depression or fatigue were not addressed, although there are findings emphasizing their role in CR and especially in leisure activities (Cadden et al., 2018; Patel et al., 2018).

Table 1
Characteristics of the study sample of multiple sclerosis patients ($N = 141$).

Characteristic	Mean ± SD	Categories	N (%)
Age	43.5 ± 10.4	–	–
Gender	–	Females	103 (73)
MS type	–	RRMS	128 (90.8)
	–	SPMS	13 (9.2)
MS duration (months)	153.7 ± 89.4	–	–
DMTs	–	Yes	105 (74.5)
SDT	–	Yes	98 (69.5)
ZSDMT	−0.24 ± 1.06	–	–
ZCVLT-II	−0.63 ± 1.62	–	–
ZBVMT-R	−0.05 ± 1.20	–	–
Total ZCognitive Score	−0.30 ± 0.95	–	–
DASS-D	5.6 ± 5.1	–	–
DASS-A	5.8 ± 5.1	–	–
DASS-S	7.8 ± 5.1	–	–
Fatigue (mm)	36.4 ± 25.1	–	–
Total CRI	103.6 ± 13.3	–	–
aNBV (ml)	1433.6 ± 167.4	–	–
aNGM (ml)	688.7 ± 140.7	–	–
aNWM (ml)	745.2 ± 172.5	–	–
aNPGM (ml)	527.9 ± 111.7	–	–
aNTHAL-R (ml)	10.2 ± 3.4	–	–
aNTHAL-L (ml)	10.6 ± 3.4	–	–
aTVW (mm)	4.3 ± 2.2	–	–
aCCI	0.35 ± 0.07	–	–
LV (ml)	24.5 ± 19.1	–	–
SF	1.25 ± 0.27	–	–

a: age-adjusted values, BVMT-R: Brief Visuospatial Memory Test-Revised, CCI: Corpus Callosum Index, CRI: Cognitive Reserve Index, CVLT-II: California Verbal Learning Test-II, DASS: Depression Anxiety Stress Scale (D: Depression, A: Anxiety, S: Stress), DMT: Disease Modifying Therapy, LV: Lesion Volume, NBV: Normalized Brain Volume, NGM: Normalized Gray Matter, NPGM: Normalized Peripheral Gray Matter, NTHAL: Normalized Thalamic (R: Right, L: Left), RRMS: Relapsing-Remitting Multiple Sclerosis, SD: Standard Deviation, SDMT: Symbol Digit Modalities Test, SDT: Symptomatic Drug Treatment, SF: Scaling Factor, SPMS: Secondary Progressive Multiple Sclerosis, TVW: Third Ventricle Width, z: z scores.

For these reasons, we have designed a cross-sectional study aiming to replicate previous findings for the effect of both CR and BR in the MS-related brain pathology and cognitive function relationship, by considering the aforementioned caveats. In specific, we used the Cognitive Reserve Index questionnaire (CRIq) developed by Nucci et al., that considers education, work and leisure activity and generates a composite CR score (Nucci et al., 2012). To our knowledge, there are only two studies using this instrument in MS. In Nunnari et al. study the CR hypothesis was not confirmed, although CRIq was found to be associated with cognitive function (Nunnari et al., 2016). In another study by Chillemi et al., CRIq was associated with cognitive function, but only univariate tests are provided by the authors (Chillemi et al., 2015). Furthermore, our study examined cognitive function using BICAMS (Brief International Cognitive Assessment for Multiple Sclerosis) (Langdon et al., 2012), a highly recommended clinical assessment for cognitive function in MS, that overcomes the time- and/or cost-related barriers of other complex neuropsychological tests. Finally, several confounding factors such as fatigue, depression, drugs etc. were adjusted for in our analyses.

2. Materials and methods

2.1. Study design, settings and participants

This cross-sectional study recruited 141 MS outpatients from two

Table 2
Significant correlations (Spearman's rho, *p* value) for cognitive function scores in multiple sclerosis patients ($N = 141$).

	SDMT	CVLT-II	BVMT-R	Total cognitive score
EDSS	−0.340, <0.001	−0.349, <0.001	−0.225, 0.008	−0.382, <0.001
DASS-D	−0.181,0.033	−0.309, <0.001	−0.175, 0.04	−0.278, 0.001
DASS-A	n.s.	−0.209, 0.013	−0.265, 0.002	−0.237, 0.005
DASS-S	n.s.	−0.202, 0.019	−0.174, 0.043	−0.194, 0.024

a: age-adjusted values, BVMT-R: Brief Visuospatial Memory Test-Revised, CVLT-II: California Verbal Learning Test-II, DASS: Depression Anxiety Stress Scale (D: Depression, A: Anxiety, S: Stress), SDMT: Symbol Digit Modalities Test.
n.s. non-significant.

tertiary referral hospitals in Greece; the NIMTS (Army Share Fund Hospital) in Athens and the AHEPA university hospital in Thessaloniki. Patients were recruited in the study between October 2015 and June 2017. Recruitment was performed by a researcher and took place once or twice per week during scheduled consultations in the outpatient clinics. Recruitment was terminated as soon as the adequate sample size was reached (see below). First, all patients were informed about the goals and the procedures of the study and if eligible, they were asked to provide their written informed consent. All patients had clinically definite MS according to the 2011 revised McDonald criteria (Polman et al., 2011). The inclusion criteria were: age over 18 years old, perfectly writing and speaking Greek and Expanded Disability Status Scale (EDSS, Kurtzke, 1983) of 6.0 or less. Exclusion criteria were: primary progressive MS, MS relapse or use of corticosteroids in the previous 30 days, officially diagnosed major psychiatric disease, illicit drug abuse and denial to participate in the study. The study protocol was approved by the hospitals' Ethical committees, as it was found consistent with the declaration of Helsinki.

2.2. Assessments

General characteristics: Demographic and MS-related variables included age, gender, type of MS (i.e. remitting-relapsing, RRMS, secondary progressive, SPMS), disease duration (in months), EDSS, disease modifying therapy (DMT) or other therapies (e.g. anti-depressants etc.).

Neuropsychological assessment: Cognitive performance was assessed by the Brief International Cognitive Assessment for MS (BICAMS), a brief 15-minute screening tool comprised of the Symbol Digits Modalities Test (SDMT), the California Verbal Learning Test II (CVLT-II) and the Brief Visuospatial Memory Test Revised (BVMT-R) (Langdon et al., 2012). The tool has been validated in Greece (Polychroniadou et al., 2016). SDMT assesses attention and information processing speed, the CVLT-II is a measure of verbal learning and memory and the BVMT-R evaluates visuospatial learning and memory as previously described (Langdon et al., 2012; Polychroniadou et al., 2016). Age corrected values were computed by using the residuals of a linear regression model with age as an independent factor and cognitive scores as dependent. The z scores were calculated by using the age adjusted means and standard deviations (SDs) in a sample of 207 healthy individuals (mean age 36.8 ± 9 years old, 49.3% women). The age adjusted means and SDs for this sample were the following: SDMT 53 ± 13.7, CVLT-II 63.1 ± 9.0, BVMT-R 28.9 ± 5.7. A total cognitive score was calculated, based on the mean z scores of the three cognitive domains of BICAMS.

Depression Anxiety and Stress Scale-21 (DASS-21): In this scale responders declare the frequency of depressive (D-DASS), anxiety (A-DASS) or stress (S-DASS) symptoms in a 4-point Likert-type scale (0 = did not apply to me at all, 3 = applied to me very much, or most of the time) (Lovibond and Lovibond, 1995). Scores are produced by summing up the 7 items of each of the three subscales (theoretical range 0–21). Higher scores denote higher frequency of symptoms. The scale has been adapted in the Greek population (Lyrakos et al., 2011). In this study the Cronbach's alphas for internal reliability were good; 0.889 for D-DASS, 0.893 for A-DASS and 0.891 for S-DASS.

Physical fatigue: A visual analogue scale for physical fatigue (VAS-PF) was used. Each participant declared his/her level of fatigue during the last week by drawing a single point in a 100-mm line (from 0 no fatigue to 100 mm very much fatigue). Scores were derived by measuring the distance (in mm) from 0 to the point indicated. VAS scales for fatigue have been previously found reliable in MS patients (Kos et al., 2017).

Cognitive Reserve Index questionnaire (CRIq): This tool quantifies the amount of cognitive reserve based on education (years of formal and informal education), working activity (years and level of professional occupation) and leisure time (years of frequent attainment of various activities), producing three scores for each category (Nucci et al., 2012). Scores correspond to years spent for these three activities. A total CRI score is derived by averaging the three subscales (CRI-total). The full description of this tool and its age-adjusted scoring can be found elsewhere (Nucci et al., 2012). The tool has been adapted in the Greek language (Maiovis et al., 2016).

Neuroimaging assessments: Conventional MRI scans acquired within the last 6 months before the study were used. All brain MRIs were performed at 3.0T devices in multiple centers using the same acquisition MRI protocol: T1-weighted 3D high resolution magnetization-prepared rapid acquisition with gradient echo (3D MP-RAGE) sequence, axial T2-weighted fluid attenuated inversion recovery (FLAIR) sequence and axial proton density-weighted images. All scans were examined by an experienced observer. On FLAIR images, lesions were identified and quantified (white matter lesion volume, WMLV) using a semi-automated local threshold technique as part of the Medical Images Processing Analysis and Visualization (MIPAV) software (https://mipav.cit.nih.gov/). Third ventricle volume width (TVW) and corpus callosum index (CCI) were computed as previously described (Artemiadis et al., 2018; Butzkueven et al., 2008). Volumetric analyses of the brain was also conducted using axial 3D MP-RAGE images and FMRI Software Library (FSL) (Smith et al., 2004). Brain tissue volume, normalized for subject head size, was estimated with Structural Image Evaluation using Normalization of Atrophy Cross-sectional (SIENAX) method (Smith, 2002). From this procedure normalized brain volume (NBV), normalized white matter volume (NWM), normalized grey matter (NGM) and normalized peripheral grey matter (NPGM) were obtained. We also calculated the regional thalamic volumes, normalized by multiplying the estimated volumes by the scaling factors derived from SIENAX (Patenaude et al., 2011).

Finally, we estimated the MLBG or BR by using ICV as an estimate, since during development brain growth is associated with increased ICV. For this reason, we employed the scaling factor within SIENAX, which is a measurement of ICV and thus, an estimate of MLBG. Values higher than one are obtained in small ICVs (i.e. lower BR), whereas values lower than one for larger ICVs (i.e. higher BR). The rationale and characteristics of this estimate have been previously elaborated in pertinent studies (Sumowski et al., 2016a, 2014, 2013). All MRI data (except lesion volume and scaling factor) were age-adjusted by using the residuals of linear regression models with age as independent factor and each volumetric measure as dependent.

Table 3
Multivariate linear regression models showing the statistically significant moderating role of cognitive and brain reserve in the MRI vs. cognitive function association in multiple sclerosis patients ($N = 141$).

CVLT-II						Total cognitive score			
Gender[1]	0.272, 0.002*	Gender[1]	0.274, 0.002*	Gender[1]	0.257, 0.006*	Gender[1]	0.186, 0.029*	Gender[1]	0.236, 0.011*
EDSS	−0.271, 0.002*	EDSS	−0.266, 0.002*	EDSS	−0.247, 0.006*	EDSS	−0.289, 0.001*	EDSS	−0.271, 0.003*
DASS-D	−0.246, 0.006*	DASS-D	−0.254, 0.004*	DASS-D	−0.293, 0.001*	DASS-D	−0.184, 0.034*	DASS-D	−0.251, 0.005*
CRI	−0.713, 0.103	CRI	−0.732, 0.096	SF	−1.128, 0.045*	CRI	0.567, 0.193	SF	−1.331, 0.018*
aNGM	−1.414, 0.057	aNPGM	−1.5, 0.05*	aNBV	−0.337, 0.213	aNGM	−1.377, 0.062	aNBV	−0.155, 0.566
CRI × aNGM	1.834, 0.045*	CRI × aNPGM	1.936, 0.041*	SF × aNBV	1.516, 0.043*	CRI × aNGM	1.777, 0.05*	SF × aNBV	1.528, 0.041*
Adjusted $R^2 = 25.6\%$		Adjusted $R^2 = 25.5\%$		Adjusted $R^2 = 24.2\%$		Adjusted $R^2 = 27.6\%$		Adjusted $R^2 = 24.6\%$	

Values in this table represent standardized beta coefficients and p values (beta, *p* value).
a: age-adjusted values, Cognitive Reserve Index, CVLT-II: California Verbal Learning Test-II, DASS: Depression Anxiety Stress Scale (D: Depression), NBV: Normalized Brain Volume, NGM: Normalized Gray Matter, NPGM: Normalized Peripheral Gray Matter, SF: Scaling Factor.
[1] Reference category for gender: males.
* $p \leq 0.05$.

2.3. Statistical analyses

The sample size was calculated by using the G*power 3.1.9.2 software (Faul et al., 2009). In order to be able to detect a medium effect size (i.e. $f^2 = 0.1$), with a power of 80%, an alpha error of 0.05 and including up to six predictors in the multivariate regression models, a sample of 143 patients was needed. Two patients were retrospectively found with significant motion artifacts in their MRIs and were excluded from the final analysis. Thus, the final sample consisted of 141 patients.

Descriptive statistics included means, standard deviations, absolute and relative frequencies. In order to explore the moderating role of CR and BR in the MRI-cognitive function relationship, we used several hierarchical linear regression models using the MRI evaluations as predictors of cognitive function. The moderating role of CR and BR was specifically examined by entering the interaction term of CR or BR with the MRI assessment evaluated in each model. Several univariate tests were conducted to ascertain which confounders may be more meaningful to incorporate or adjust for in a regression model. These univariate tests included simple Spearman's rho correlations (instead of Pearson's rho, to eliminate the effect of outliers) and Student's t-tests (Q–Q plots were inspected to ensure normality assumption) between cognitive scores and the other putative predictors. Predictors that were found significant were entered in the models. Gender was forced entered in all the models. Since MRI, neuropsychological and CRI were age-adjusted, age was not included. Standardized beta coefficients and p values were reported, along with the adjusted R-square values denoting the overall percentage of the variance of cognitive functions explained by predictors. All assumptions of linear models were checked (e.g. linearity, homoscedasticity, auto-correlation and multi-collinearity). Interpretation of the significant interaction terms was aided by producing line plots of the MRI (x axis) and cognitive assessments (y axis) taking into account high and low CRI and BR groups based on the 25th and 75th percentiles, respectively. The level of significance was set at 0.05. All analyses were performed using SPSS v22.0 for Windows (Chicago IL).

3. Results

3.1. Characteristics of the study sample (Table 1)

The sample consisted of 128 (90.8%) RRMS and 13 (9.2%) SPMS patients. There were 103 (73%) women and the mean age was 43.5 years old. The mean duration of disease was over 10 years old, although there were patients with more recent onset. Most patients (74.5) were on disease modifying drugs; 34.1% were receiving first line therapies and 40.4% were on second line treatments (i.e. 29.1% fingolimod, 22.7% interferons, 5.7% glatiramer acetate, 6.4% natalizumab, 5% dimethyl fumarate, 3.5% immune-suppressive, 1.4% alemtuzumab and 0.7% teriflunomide). In total, 98 (69.5%) patients were on symptomatic drugs; 32.6% psychotropic drugs (e.g. anti-depressants and anxiolytics), 29.8% symptomatic drugs e.g. spasmolytics, 25.5% over-the-counter drugs or OTCs (e.g. vitamin D etc.) and 3.5% were on memantine.

3.2. Univariate associations between cognitive scores and other characteristics and selection of confounders (Table 2)

EDSS showed a highly significant negative correlation with cognitive scores. Also, patients receiving symptomatic treatment or OTCs were more likely to have worse cognitive function than patients not receiving these drugs (total z-cognitive scores for symptomatic treatment vs. no treatment: -0.71 ± 0.87 vs. -0.12 ± 0.93, $p = 0.001$ and for OTCs vs. no OTCs: 0.02 ± 0.86 vs. -0.41 ± 0.96 $p = 0.02$). However, patients with higher EDSS were more like to take these drugs (symptomatic drugs: $p < 0.001$, OTC: $p = 0.003$), thus EDSS was selected, instead of drugs, to be entered in the multivariate models.

Also, depression score was significantly negatively correlated with

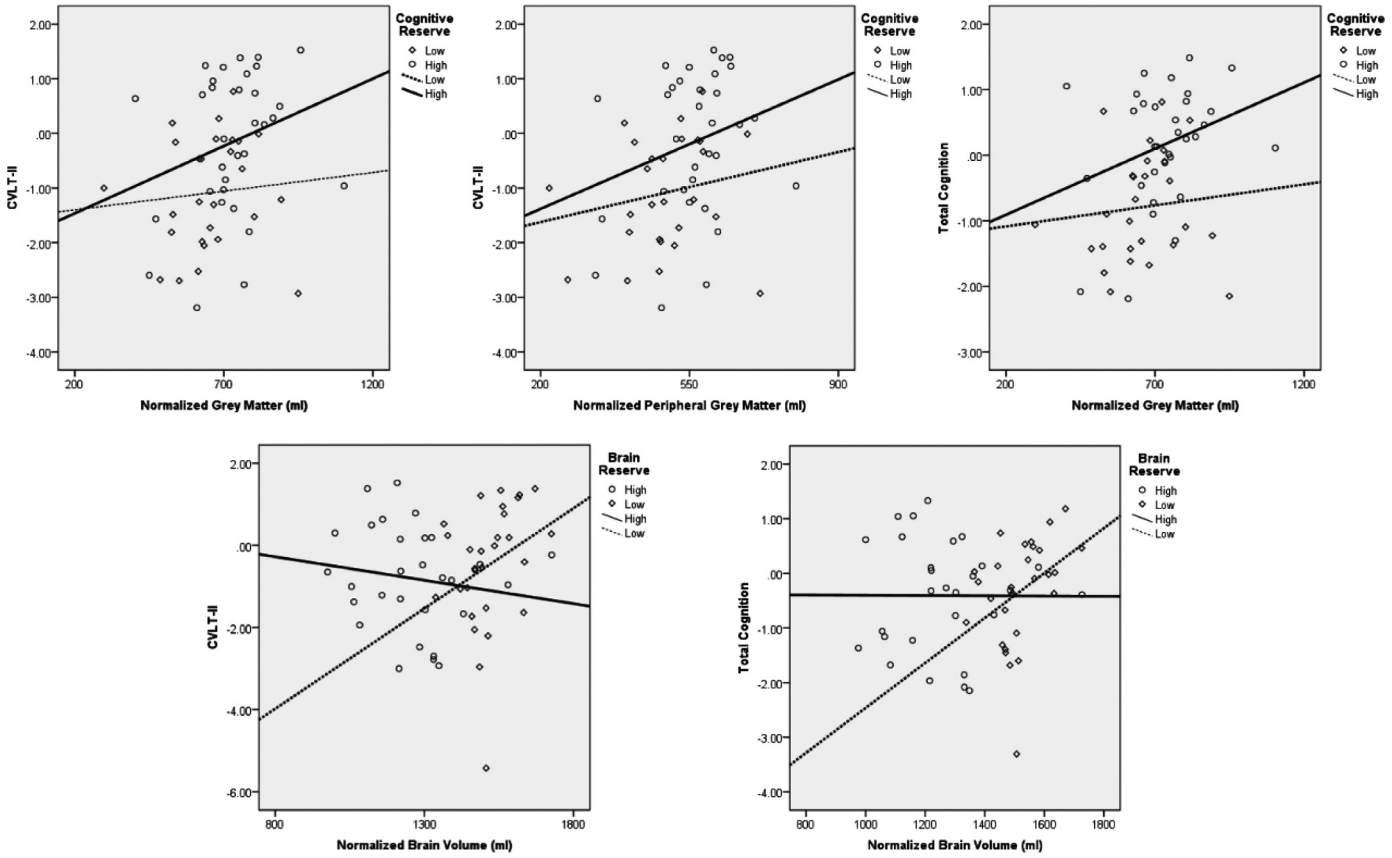

Fig. 1. Correlations of normalized grey matter, normalized peripheral grey matter and normalized brain volume with verbal memory (CVLT-II: California Verbal Learning Test) and total cognition, for high and low cognitive and brain reserve based on 25th and 75th percentiles.

cognitive function. Anxiety and stress were also significantly associated with CVLT-II, BVMT-R and total cognitive scores. Since, depression was highly correlated with both anxiety (Spearman's rho = 0.785, $p < 0.001$) and stress (Spearman's rho = 0.721, $p < 0.001$), depression was selected for further analysis to avoid multi-collinearity in the ensuing multivariate models.

We found no significant associations between disease duration, DMTs and physical fatigue with cognitive function (data not showed).

3.3. The moderating role of CR and BR in the MRI-cognitive function association (Table 3)

We conducted 72 linear regression models for CR; for each of the 9 MRI assessments used as predictors, four models were produced with cognitive scores (SDMT, CVLT-II, BVMT-R and total cognitive scores) as dependent factors. The process was reiterated for BR assessed by the scaling factor derived from SIENAX method, as explained before. Gender was forced entered in all models as predictor, along with EDSS and depression that were found significant in the univariate tests. For the sake of brevity, only the models showing a statistically significant moderation effect are presented inTable 3.

A significant moderating effect of CRI was found for NGM volume in the CVLT-II model ($p = 0.045$). Higher CRI moderated/increased the positive effect of NGM on verbal memory (Fig. 1). The same significant moderating pattern was also noticed in the CVLT-II model for NPGM volume and in the total cognition model for NGM (Fig. 1). With regards to SF which is a surrogate marker for BR (i.e. lower SF denotes higher BR), a significant moderating effect was found in the CVLT-II model for NBV ($p = 0.043$). Higher brain reserve was associated with better verbal memory at least for NBV volumes below about 1400–1500 ml (Fig. 1). Above this cut-off, there were few patients with high BR, thus the slopes in Fig. 1 should be interpreted with caution. The same pattern was also noticed for the total cognition model. It should be noted that since total cognition was derived from the composite BICAMS score and no other significant moderating effect was found except for CVLT-II, the effects for total cognition reflect those in the CVLT-II models. Finally, males, and patients with higher depression or EDSS had significantly worse cognition in all the models presented in Table 3, than females or patients with less depression and disability.

The analysis was repeated after excluding SPMS patients ($N = 13$). In the resulting sample of 128 RRMS patients the CRI was found to be a significant moderator for the effect of age-adjusted NPGM (standardized beta = 2.392, $p = 0.046$) on CVLT-II, only. Negative results were found on the effect of CRI on the NGM and CVLT-II association (standardized beta = 1.671, $p = 0.09$) and on the effect of brain reserve (i.e. SF) on NBV and CVLT-II association (standardized beta = 0.911, $p = 0.251$). No other significant moderating effect was found either for cognitive (i.e. CRI) or brain reserve. It should be noted that SPMS patients did not significantly differ from RRMS patients in characteristics not included in the model due to lack of significant association with cognition, such as disease duration (RRMS: 153.4 ± 91.7 months, SPMS: 156.9 ± 66 months, Mann–Whitney $Z = 0.445$, $p = 0.656$), fatigue (RRMS: 36.3 ± 25.2, SPMS: 37.1 ± 25.3, Mann–Whitney $Z = 0.196$, $p = 0.845$) and disease modifying drugs ($F = 1.18$, $p = 0.555$). As such, the confounding effect of including SPMS patients in the original analysis is minimized. On the other hand, it should be stressed that having a sample of 128 patients the power to capture an adjusted variance of 9% ($f^2 = 0.1$) is 74.5%, 5.5% below the desired power of 80% used in this study. Notwithstanding, the role of cognitive reserve in the effect of peripheral grey matter on verbal memory remained significant.

4. Discussion

Higher CR moderated the effect of grey matter and especially peripheral grey matter on verbal memory. Also, BR moderated the effect of brain volume on verbal memory, but this became non-significant after excluding SPMS patients. The results of this study are indicative of a cognitive modality-specific role of CR/BR, at least in the context of the neuropsychological assessment performed by a clinically-orientated tool such as BICAMS and by considering three CR indices (i.e. education, work, leisure activities) simultaneously. In general, this study corroborates and specifies more, previous findings on the role of CR in cognition in MS (Santangelo et al., 2019a; Sumowski et al., 2016b; Sumowski et al., 2016, 2014, 2013, 2010).

Our findings contradict those reported by Nunnari et al., who also used CRIq and a similar to ours statistical approach (Nunnari et al., 2016). In their multivariate models, the interaction term of CR × normalized cortical volume was not found significant for any of the neuropsychological tests, including the Selective Reminding Test-D for verbal memory (Nunnari et al., 2016). To explain this discrepancy, firstly, their sample consisted of nearly half the patients compared to ours, hence, the power to detect significance is smaller than the present study. Most importantly, age was the only confounder in their models (compared to gender, EDSS and depression and adjustment of our cognitive and MRI evaluations by age in this study), thus there is always the chance that significant associations have been missed. Finally, in another study by Chillemi et al., also using CRIq, CR was associated with information processing speed, but only univariate tests are provided by the authors and no MRI evaluations took place, thus their results should be interpreted with caution (Chillemi et al., 2015).

Direct comparison with other previous studies is cumbersome, since there is significant heterogeneity. Different sample sizes, patients' characteristics, confounders, statistical analyses, CR and neuropsychological assessments account largely for inconsistencies between research findings, albeit most of the studies substantiated the moderating role of CR, as in this study (Della Corte et al., 2018; Martins Da Silva et al., 2015; Modica et al., 2016; Rimkus et al., 2018; Santangelo et al., 2018). However, a study by Amato et al., showed that after considering different CR counterparts (i.e. education, leisure activities and IQ), CR moderated the effect of cortical volume on verbal memory, which is in complete accordance with this study (Amato et al., 2013). Furthermore, the moderating role of CR in memory has been enunciated also in longitudinal studies (Rocca et al., 2019; Sumowski et al., 2014). More in-depth research has also disclosed that CR moderates the effect of subcortical grey matter and hippocampi atrophy on processing speed and memory, respectively (Modica et al., 2016; Sumowski et al., 2016b; Sumowski et al., 2016). In the present cross-sectional study, only thalamus was examined based on the established role of thalamic atrophy in cognition, thus no direct comparison can be made (Rojas et al., 2018).

Other studies support the significant role of CR in different cognitive modalities, but it should be emphasized that these studies did not take MRI assessment and their interactions with CR into account in the multivariate models (Della Corte et al., 2018; Martins Da Silva et al., 2015). In a recent meta-analysis by Santangelo et al., CR was significantly associated with multiple cognitive domains, but the moderating role of CR in the effect of disease burden on cognition was not included in the study's aims (Santangelo et al., 2019a). However, what is important in this meta-analysis in view of the present study, was that disease duration, phenotype and disability did not moderate the relationship between CRI and cognition. This substantiates our results further, since SPMS patients were also included in the analysis. Still, after removing these patients and likely putative confounders related to disease phenotype, the CRI role in the peripheral grey matter and verbal memory relationship remained significant, despite the lower power to detect significant differences.

In another meta-analysis that fills the gap of examining the specific moderating role of CR on the effect brain damage on cognition, education reliably moderated the effect of gray matter on verbal fluency, whereas vocabulary knowledge moderated the relationship between lesion load and verbal fluency (Santangelo et al., 2019b). Although the latter was supported only in three studies in the meta-analysis, altogether, there seems to be a converging moderating role of different CR indices in the effect of cortical atrophy on verbal fluency. Our study utilized a single CR index, which likely yields more reliable associations than by examining different CR indices separately. This may explain the negative results for verbal memory in this meta-analysis that used studies examining single CR indices. Also, the present study did not assess verbal fluency, since we chose to implement a widely used clinical neurophysiology tool (i.e. BICAMS). Notwithstanding, we consider our results in close resemblance to this meta-analysis, since apart for the common finding for the role of gray matter, verbal memory and verbal fluency share quite similar brain functional networks (Pirmoradi et al., 2016).

Regarding BR, our study presented data in favor of its moderating role on the effect of brain volume on verbal memory. Our results partially diverge from previous studies that used the same estimates of ICV (Modica et al., 2016; Santangelo et al., 2018; Sumowski et al., 2014, 2013). Sumowsky et al. work posit a protective role of ICV on the effect of lesion load and brain atrophy on cognition and especially cognition efficiency and not memory (Sumowski et al., 2014, 2013). However, negative results have also been reported (Modica et al., 2016; Santangelo et al., 2018). Again, methodological differences can account for these inconsistencies.

This study has several limitations. Firstly, the cross-sectional design does not allow etiological inferences, albeit the established knowledge and the theory behind CR/BR, leave no space for chronological misinterpretations. Longitudinal studies, have certainly a value for addressing the differential moderating role of CR across MS span, as previously reported (Rimkus et al., 2018; Rocca et al., 2019; Sumowski et al., 2014). Furthermore, we did not assess regional brain volumes, which might be more crucial for specific cognitive domains. Besides that, generalization of our results is mainly restricted to RRMS patients, since there were only 13 SPMS patients. The role of CR/BR in progressive MS should be considered separately in future studies (Sumowski et al., 2012). Finally, cognition is a versatile brain function, hence there is always the chance that other factors (e.g. lifestyle, diet etc.) may influence our results.

In a nutshell, CR and BR have a cognitive modality-specific moderating role in the effect of disease burden as assessed with MRI on cognition, in MS. Herein, we presented data that point out the role of CR/BR on verbal memory, by using a neuropsychological assessment that is highly pertinent to everyday clinical practice. This has several clinical implications. Identification of patients with increased risk of CI should urge clinicians for a more frequent or even astute neuropsychological assessment, lending more attention to memory problems. Also, since CR is a modifiable characteristic, this study supports the implementation of early interventions for the prevention of CI in MS. Future research is strongly encouraged to focus on such interventions aiming to enhance CR in MS patients.

Declaration of Competing Interest

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