ROLE OF COGNITIVE RESERVE ON COGNITIVE FUNCTION AND REGIONAL BRAIN ATROPHY IN MULTIPLE SCLEROSIS: A TWO-YEAR LONGITUDINAL STUDY

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INTRODUCTION and PURPOSE

The cognitive reserve (CR) hypothesis states that enriching experiences protect against the onset of dementia and cognitive decline [1].

In MS patients, high CR (higher educational level, greater intellectual enrichment and leisure activities) reduces the negative effect of the disease on cognitive performance [2, 3]. At present, the protective role of CR against cognitive decline over time in these patients is still controversial. Some longitudinal studies have highlighted the role of CR in attenuating the negative relationship between a disease-related variables and a cognitive outcomes [4, 5], whereas another study found that the protective effect of CR would be neutralized by the progression of brain atrophy [6]. MRI studies in MS have shown that a significant component of MS-related damage is located in the grey matter (GM) [1-3].

Aim of this work is to assess the role of CR on cognitive impairment and its progression over time in MS patients and explore the neuroanatomical bases that are modifiable from CR.

METHODS

Subjects

- Seventy-six MS patients and 20 age- and sex-matched healthy controls (HC) underwent clinical and MRI evaluation at baseline and after a median follow-up (FU) of 2.3 years (median FU duration= 2.4 years, range=1.1-5.4 years in MS patients and 2.1 years, range1.0-5.5 years in HC, p=0.4).
- Patients underwent neurologic examination, with rating of the EDSS score and the Brief Repeatable Battery of neuropsychological tests (BRB-N) (two different versions, A at baseline and B at FU) [7]. BRB-N includes tests of verbal memory (selective reminding test [SRT]), visuo-spatial memory (10/36 spatial recall test [SPART]), information processing speed (IPS) (Symbol Digit Modality Test [SDMT]) and attention (Paced Auditory Serial Attention Test [PASAT]), and verbal fluency (word list generation [WLG]).
- Evolution of cognitive performance was assessed on each test using the Reliable Change Index (RCI) [6].
- At baseline, in MS patients a CR Index (CRI) was derived, by combining educational level (years of education), premorbid IQ, estimated through the Italian version of the National Adult Reading Test and the participation on cognitive leisure activities during the patient's early 20s before the onset of MS [6].

MRI acquisition (3.0 Tesla scanner)

- Axial dual-echo (DE) TSE;
- 3D T1-weighted fast field echo (FFE).

Image analysis

- Quantification of T2 lesion volumes (LV) (Jim 6, Xinapse Systems Ltd., Northants, UK);
- Segmentation of T1 hypointense lesions on 3D FFE images, previously coregistered to the DE scans;
- Measurement of normalized brain volumes (NBV), WM volume (WMV) and GM volumes (GMV) on 3D FFE images, using the SIENAx software [8];
- Calculation of the percentage brain volume change (PBVC) between baseline and FU (SIENA software).

Mapping changes of GM and WM structures

VBM analysis (baseline) (SPM12 software)

- Refilling of T1-hypointense lesions with values randomly extracted from a gaussian distribution with mean and SD estimated from the normal appearing WM [9];
- Segmentation in GM and WM, using the standard unified model;
- Normalization to the population templates generated from the complete study dataset (DARTEL registration method); modulation and smoothing with a 8 mm Gaussian kernel; affine registration to the MNI space.
- Binarized mask from T2 lesions were coregistered to the 3D FFE images, normalized to the GM template, and averaged to obtain T2 lesion probability maps (LPMs).

TBM analysis (longitudinal) (SPM12 software)

Warping of FU to baseline, calculation of volume changes, and normalization to atlas.

Statistical analysis

- Between-group comparisons of demographic, clinical and conventional MRI variables: parametric and not parametric tests, as appropriate (SPSS software) (p<0.05);
- Within-group assessment of CRI, neuropsychological and MRI variables: univariate and multiple regression analysis, controlling for sex, age, EDSS, and disease duration (SPSS software) (p<0.05);
- VBM and TBM (SPM12): T-test and multiple regression models for correlations with CRI including sex, age, ICV (VBM) and years of FU (TBM) as covariates (p<0.001 uncorrected).

RESULTS

Clinical and conventional MRI findings

Table 1 summarizes the main clinical and conventional MRI characteristics of HC and MS patients at baseline. Compared to HC, MS patients had lower NBV (p<0.001), WMV (p=0.003), GMV (p<0.001).

	HC	MS	p
Number of subjects	20	76	
Women/men	9/11	49/27	0.13*
Mean age (SD) [yrs]	37.8 (11.8)	43.0 (10.8)	0.06**
Mean disease duration (SD) [yrs]	-	13 (7.5)	
Median EDSS (range)	-	2 (1.0-8.0)	
Mean T2 LV (SD) [ml]	-	10.6 (10.3)	
Mean T1 LV (SD) [ml]	-	7.6 (8.2)	
Mean NBV (SD) [ml]	1585 (103)	1485 (95)	<0.001***
Mean WMV (SD) [ml]	737 (6)	672 (64)	<0.001***
Mean GMV (SD) [ml]	848 (54)	813 (43)	0.003***

At baseline MS patients failed mainly on tests assessing verbal memory, visuo-spatial memory, IPS, complex attention and verbal fluency.

At FU, cognitive performances worsened with a higher frequency of deterioration (at least 10%) in visuo-spatial memory, verbal short-term and long-term memory and IPS functions.

Compared to HC, MS patients had higher PBVC (p=0.008).

Cognitive reserve impact on cognitive functions and brain damage

At baseline, MS patients had significant correlation between CRI and performances at SRTlts (p=0.001), SRTcltr (p<0.001), SRTd (p=0.002), SDMT (p=0.026), PASAT2 (p=0.006), and WLG (p=0.003).

Controlling for global and regional atrophy, an effect of CRI was found on verbal memory (SRTlts: R^2=0.39, β=0.43, p=0.001; SRTcltr: R^2=0.27, β=0.52, p<0.001; SRTd: R^2=0.36, β=0.39, p=0.002), attention (PASAT2 R^2=0.32, β=0.24, p=0.05) and verbal fluency (WLG R^2=0.37, β=0.37, p=0.003) (Table 2).

Considering the interaction between CRI and regional GM/WM volumes, performance at the majority of the tests was explained by such an interaction (Table 2).

Lower CRI correlated with higher T2 LV (R^2=0.41; p=0.02), higher T1 LV (R^2=0.38, p=0.03) and L lingual gyrus atrophy (R^2=0.12; p=0.006).

At FU no effect of CRI was found on cognitive worsening.

GM atrophy of the L cerebellum, R MFG and L precuneus predicted worsening of short-term verbal memory (R^2=0.21; p<0.001), long-term verbal memory (R^2=0.12; p=0.006) and IPS (R^2=0.17; p<0.001).

Table 2. Effect of CR and brain damage on cognitive performance at baseline in MS patients.

Dependent variables	Predictors	R^2	B	p*
SRTlts	CRI*L Inferior longitudinal fasciculus	0.32	0.48	<0.001
SRTcltr	CRI	0.27	0.52	<0.001
SRTd	CRI	0.36	0.39	0.002
SPART	T1 LV	0.14	-0.31	0.04
SPARTd	Splenium of CC	0.28	0.33	0.001
SDMT	GMV	0.30	0.39	0.002
	CRI*R Heschl gyrus		0.32	0.01
PASAT3	R insula anterior part	0.22	0.33	0.01
PASAT2	GMV	0.33	0.37	0.003
	L Cerebellum (crusVIII)		0.27	0.02
	CRI*R Middle frontal gyrus		0.26	0.03
WLG	CRI*R Superior frontal gyrus	0.38	0.38	0.002

*=interaction between CRI and MRI variables.

LPMs

Figure 1 shows the distribution of T2 lesions in MS patients.

At FU, higher frequency of T2 lesions was found in several WM regions including the bilateral (B) anterior thalamic radiation, R inferior longitudinal fasciculus, L superior longitudinal fasciculus, B inferior-fronto-occipital fasciculus, B superior corona radiata, R posterior corona radiata, B cortical spinal tract and L cingulum (Figure 2B).

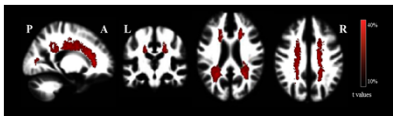


Figure 1. T2 LPM at baseline in MS patients.

Distribution of GM and WM atrophy at baseline in MS patients (VBM)

Compared to HC, MS patients showed atrophy of several GM and WM regions, including the B thalamus, cortical regions located in the frontal, parietal, temporal and occipital lobes, B corpus callosum (CC), R cingulum, R external capsule and B fornix (Figure 2A).

Progression of GM and WM atrophy during the FU (TBM)

During the FU, compared to HC, MS patients showed significant atrophy of the R thalamus, L prefrontal cortex, R superior and middle frontal gyrus, L inferior frontal gyrus, L insula, L inferior parietal lobe, B frontal gyrus, L parietal lobe, L insula, L lingual gyrus, B cerebellum, pons, R CC, L forceps minor, L superior longitudinal fasciculus and R corticospinal tract (Figure 2).

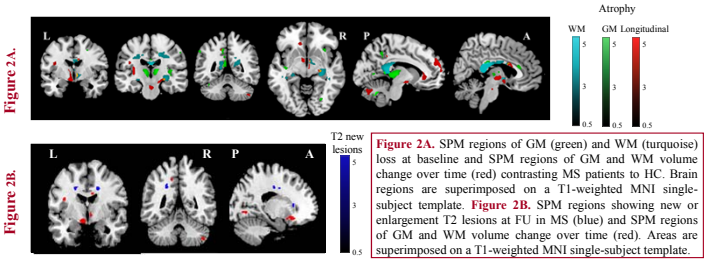


Figure 2A. SPM regions of GM (green) and WM (turquoise) loss at baseline and SPM regions of GM and WM volume change over time (red) contrasting MS patients to HC. Brain regions are superimposed on a T1-weighted MNI single-subject template. **Figure 2B.** SPM regions showing new or enlargement T2 lesions at FU in MS (blue) and SPM regions of GM and WM volume change over time (red). Areas are superimposed on a T1-weighted MNI single-subject template.

Correlation analysis in MS patients

At baseline, higher CR correlated with higher volume of the L ILF (r=0.40) and CC (r=0.48) (Figure 3A).

Significant correlation was found between higher CRI and lower progression of atrophy of the L anterior nuclear complex of the thalamus (r=0.35) (Figure 3B).

Figure 3A. Correlation betwe en higher CR vs L ILF and CC volumes at baseline.

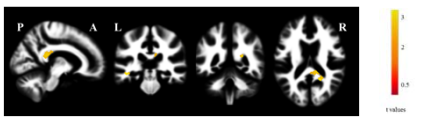
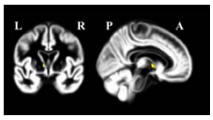


Figure 3B. Correlation between CR and progression of thalamic atrophy.



CONCLUSIONS

In this 2-year longitudinal study, regional GM/WM atrophy in MS patients progressed following a caudal-rostral trajectory, moving towards frontal regions, and volume loss appeared controlaterally in the structures that were unilaterally atrophic at baseline. This evolution of atrophy could be due to an acceleration of all processes related to normal ageing [10] and to tract maturity, resulting to a more pronounced susceptibility to injury in frontal location, since myelination proceeds along a caudo-rostral pattern until early adulthood [11, 12]. Evolution of atrophy could be also related to the presence of new/enlarged WM lesions in several WM tracts, which in turn have a negative impact on subsequent atrophy of the connected GM areas [13].

Confirming previous evidences reporting that brain volume is associated to IQ and challenging activities [14], higher CR was correlated with higher volume of the L ILF and CC, two areas correlated respectively to verbal memory and visuo-spatial memory. The association of CR with cognitive performances at baseline, but not with the worsening of cognitive functions during the FU, suggests that CR may have a protective role on cognition reducing the impact of GM and WM atrophy on cognitive performance. However, the progressive accumulation of brain damage might reduce this protective role of CR, since it is not able anymore to compensate the impact of tissue injury on cognitive processes when the burden of brain damage becomes more relevant [6].

These findings may help developing new therapeutic strategies, based on CR enhancement during the time window of its influence and identifying, through the investigation of CR, the individual level of risk in developing future impairment.

Interestingly enough, we found that even if CR loses its protective effect on cognitive performance over time, it reduced atrophy development in the anterior nuclear complex of L thalamus, suggesting that it could maintain a role on brain plasticity, which, in turn, can modulate the degree of cognitive symptoms [15] as this area has extensive connections with frontal lobe regions [16].

REFERENCES

1) Stern, J Int Neuropsychol Soc 2002
2) Sumowski et al., Neurology 2013
3) Bonnet et al., J Neurol Sci 2006
4) Sumowski et al., Neurology 2014
5) Modica et al., Mult Scler,2016
6) Amato et al., Neurology 2013
7) Amato et al., Multe Scler 2006
8) Smith et al., Radiology 2011
9) Chard et al., Radiology 2010
10) Klingbeil et al., Arch Phys Med Rehabil 2004
11) Klingberg et al., Neuroreport 1999
12) Paus et al., Trend Cogn Sci 2005
13) Bodini et al., Neurology 2016
14) Brown et al., Eur J Neurosci 2003
15) Behrens et al., Nat Neurosci 2003
16) Bisecco et al., Hum Brain Mapp 2015

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