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Cognitive speed and white matter integrity in secondary progressive multiple sclerosis

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Abstract

Background. Processing speed (PS) deficits have been consistently observed in secondary progressive multiple sclerosis (SPMS). However, the underlying neural correlates have not been clarified yet. The present study aimed to investigate the relationship between macrostructural and microstructural white matter (WM) integrity and performance on different cognitive measures with prominent PS load.

Methods. Thirty-one patients with SPMS were recruited and underwent neurological, neuropsychological, and MRI assessments. The associations between a composite index of PS abilities and scores on various tests with prominent PS load and T1-weighted and diffusion tensor image parameters were tested. Analyses were carried out using voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS).

Results. VBM results showed that only the semantic fluency task correlated with the volume of different grey matter (GM) volume in a range of cortical and subcortical areas bilaterally as well as the corpus callosum and the superior longitudinal fasciculus. TBSS analysis revealed consistent results across all the cognitive measures investigated, showing a prominent role of commissural and frontal associative WM tracts in supporting PS-demanding cognitive operations.

Conclusions. In patients with SPMS, PS abilities are mainly dependent on the degree of both macrostructural and microstructural WM integrity. Preservation of associative WM tracts that support information integration seems crucial to sustain performance in tasks requiring fast cognitive processes.

Keywords

Cognition; processing speed; voxel based morphometry; diffusion tensor imaging; MRI;

Hightlights

- Processing speed deficits are common in secondary progressive multiple sclerosis
- Little is known about the neural correlates of this function in this disease
- Frontal white matter integrity supports this function in this disease
- Associative and callosal tracts with information integration roles are involved
- These white matter tracts are crucial to support fast cognitive computations

1. Introduction

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system characterized by demyelination and axonal loss [1]. Cognitive impairment has been increasingly recognised as one of the common symptoms observed in 40% to 70% of patients [2]. Processing speed (PS) appears to be one of the cognitive functions more consistently affected by this pathology [3,4], even in the absence of any significant motor slowing [5].

PS is defined as either the time required to process a given amount of information or the amount of information processed in a time unit [6]. The first signs of PS decline can be detected in pre-symptomatic patients at the radiologically isolated syndrome stage of this illness [7], although the most severe deficits are usually observed in patients with secondary progressive MS (SPMS) [8]. Slowed PS has broader repercussions on performance in other cognitive domains [9-15]. Moreover, PS deficits negatively influence patients' quality of life [16] and the anxiety and depressive symptoms experienced by their caregivers [17].

Advancements in neuroimaging studies have highlighted how demyelinating lesions are increasingly detected in grey matter (GM) [18,19], and the association between regional GM loss and functional disability has become a well-established feature of MS [20]. However, the structural neural correlates of specific cognitive symptoms commonly observed in MS have not been completely clarified especially in the progressive phenotypes of this disease [21].

Most published studies investigated structural differences between cognitively impaired and unimpaired patients with either relapsing-remitting MS (RRMS) or other MS phenotypes indistinctly grouped [22,23]. Such studies have two major flows. Firstly, the operational definition of cognitive impairment in MS varies considerably across studies [24]. Secondly, patients are usually diagnosed as being cognitively impaired only on the basis of a set number of failed tests without discriminating which specific function. However, recently different profiles of cognitive decline have been detected among people with RRMS [25]. Therefore, grouping together individuals who may present deficits in different cognitive domains may lead to potentially confounding results. In those studies that looked at the correlations between cognitive performance and voxel-based brain morphometric measures, only global indices of GM atrophy were analyzed [26-28]. Similarly, those studies that focused more specifically on PS performance in patients with SPMS only investigated the relationship with the global volume of regions of interest [29,30].

Diffusion tensor imaging (DTI) studies in SPMS comparing patients with and without cognitive impairment observed diffuse reductions of white matter (WM) microstructural integrity in cognitively impaired patients [31,32]. Moreover, Rocca et al. [33] found that PS abilities of patients with SPMS correlated with average WM microstructural integrity in the corpus callosum and the fornix. To our knowledge, there are no published studies that have investigated the correlation between PS abilities of patients with SPMS and voxel-based measures of GM and WM structural integrity.

Considering the severe cognitive impairment seen in patients with SPMS, and the paucity of published neuroimaging studies focusing on the neural underpinning of PS impairments in this patient population, the aim of the present study was to investigate, at both macrostructural and

microstructural levels, the neural correlates of PS-demanding cognitive performance of patients affected by SPMS.

2. Methods

2.1. Sample

Thirty-one patients (16 females) with SPMS meeting the clinical diagnostic criteria by Lublin et al. [34] who reported subjective cognitive complaints and who had been relapse-free for at least 3 months were consecutively recruited at the MS clinic of the IRCCS Fondazione Ospedale San Camillo (Venice, Italy). To be included in this study, patients had to show preserved global cognitive status screened by means of the Raven's Coloured Progressive Matrices [35] and absence of other neurological or psychiatric comorbidities. All participants underwent a detailed neurological examination and were assigned scores on the Expanded Disability Status Scale (EDSS) [36].

This study was carried out according to the Declaration of Helsinki and was approved by the Institutional Review Board of the aforementioned institution (Protocol N. 11/09 version 2). Written informed consent was obtained from each study participant.

2.2. Neuropsychological assessment

Patients' cognitive performance was assessed by means of a neuropsychological battery of selected tests:

- *Raven's Coloured Progressive Matrices* [37]. Thirty-six figures missing a part are to be completed with a piece selected among a choice of six (maximum execution time of 10

minutes). This test measures abstract reasoning skills and absence of major intellectual deficits is indexed by an adjusted score > 17.5.

Five tests were specifically selected to assess cognitive performance with prominent PS demands either in terms of time to complete a task or the amount of information processed per unit of time:

- Trail Making Test part A (TMT-A) and part B (TMT-B) [38]. In TMT-A participants are instructed to connect as fast as they can numbers from 1 to 25 on a paper sheet drawing straight lines and without raising the pen from the paper. TMT B is analogous but participants have to alternate both numbers (1-13) and letters (A-L). The PS measure is the time in seconds needed for a participant to complete the TMT A [39], while the difference between part B and part A (TMT B-A) provides an index of executive task-switching abilities [40];
- Stroop Test [41]. Participants have to complete three sequential trials of word reading, colour naming and word-colour interference inhibition. The PS measure is calculated as the average of the time in seconds required to complete the first two trials [10], while the difference between the time on the third trial and the average time on the first two is used to quantify the executive ability to inhibit automatic responses [41];
- Digit Cancellation Test (DCT) [42]. Three arrays of digits are presented to participants that have to scan each line from left to right and cancel out as fast as they can one, two and three given digits respectively. The sum of all the correct items detected within 45 seconds is considered a measure of PS;
- Phonemic Fluency (PF) [43]. Participants are given the letters P, L, and F (one at a time) and asked to say as many words starting with each letter that they can think of in one

minute, excluding proper names of people and names of places. The sum of all the correct items reported is the PS-dependent variable investigated [44];

- Semantic Fluency (SF) [43]. Participants are given the categories cities, animals, and fruits (one at a time) and asked to say as many items from each category that they can think of in one minute. The sum of all the correct items reported is the PS-dependent variable investigated [44].

Scores obtained by patients on three timed tests that enable the evaluation of different types of cognitive speed (i.e. TMT-A, Stroop speed and number of items detected on the DCT) were z-transformed and averaged to calculate a composite index (PS_{CI}) as a measure of PS function. Before calculating the composite index, the score on the DCT had to be converted in a format that quantified PS abilities analogously to the other two tests, i.e. the higher the score the worse PS performance. The PS_{CI} was calculated by combining three simple tests routinely used in clinical practice but nonetheless characterised by a substantial cognitive component (more complex than in simple reaction time tasks) in order to minimise possible confounding effects of peripheral motor impairments on test results. Indeed, it is difficult, if not almost impossible, to disentangle completely the assessment of sensory, cognitive, and motor components in PS tasks [45]. Moreover, raw scores on the TMT B-A, Stroop inhibition, PF and SF tests were used to investigate cognitive abilities characterised by substantial PS load.

2.3. MRI acquisition

Patients were scanned on a 1.5 T Philips Medical Systems Achieva scanner (Best, the Netherlands) with a standard head coil. The MRI protocol included a structural three-dimensional

T1-weighted scan acquired using the following parameters: 280 sagittal slices; repetition time (TR) = 7.4 ms; echo time (TE) = 3.4 ms; voxel dimension = 1.1 mm × 1.1 mm × 0.6 mm. A Diffusion Tensor Imaging (DTI) scan was also acquired using the following parameters: 32 diffusion-weighted directions; 45 axial slices; TR = 8280 ms; TE = 70 ms; voxel dimension = 1.67 mm × 1.67 mm × 3 mm. Additionally a Fluid-Attenuated Inversion Recovery (FLAIR) scan was acquired: 30 coronal slices; TR = 8000 ms; TE = 125 ms; voxel dimension = 0.75 mm x 0.75 mm x 4.5 mm.

2.4. WM lesion segmentation

First T1-weighted and FLAIR scans were reoriented to the Anterior Commissure-Posterior Commissure line to optimize subsequent preprocessing steps. Second WM lesions were segmented on the reoriented T1-weighted and FLAIR images by the lesion growth algorithm as implemented in the Lesion Segmentation Toolbox (LST) v1.2.3 (www.statisticalmodelling.de/lst.html) developed for SPM8 and tested on a sample of 53 people with MS by Schmidt et al. [46]. The initial threshold to produce lesion maps was set at k = 0.3, value that has been observed by the authors to provide the closest quantification of total lesion volume (TLV) to that obtained using manual segmentation, considered as the gold standard. TLV in millilitres was automatically extracted by the toolbox.

After visually inspecting all individual lesion probability maps generated by LST to ensure no errors of lesion tissue classification had occurred, the maps were binarised and normalised to the standard ICBM template by using SPM8. Subsequently the individual maps were averaged by using the SPM8 toolbox ImCalc in order to obtain a group-specific lesion probability map [47].

2.5. VBM preprocessing

VBM analysis was carried out using Statistical Parametric Mapping software (SPM8, Wellcome Trust Centre for Neuroimaging, London, UK, http//www.fil.ion.ucl.ac.uk/spm) running on MATLAB R2008a, version 7.6.0 (The Mathworks, Natick, Massachusetts, USA).

First to avoid possible biases in VBM analysis, T1-weighted images underwent a lesion-filling process implemented in the LST toolbox using the previously segmented lesion maps [48,49]. Second the images were segmented into three tissue classes, i.e. GM, WM, and cerebrospinal fluid (CSF). Tissue maps saved in the native space were used to extract global volumes of each tissue by using the "get_totals" script (http://www0.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m) and total intracranial volume (TIV) was calculated as the sum of GM, WM, and CSF volumes. Finally, GM and WM images, bias-corrected for MR field inhomogeneities and normalised to the MNI template, were smoothed applying an isotropic Gaussian kernel of 8 mm.

2.6. TBSS preprocessing

TBSS analysis was carried out on DTI scans using the FMRIB Software Library v5.0.8 (FSL, http://www.fmrib.ox.ac.uk/fsl).

The Diffusion Toolbox was used to correct the scans for eddy currents and head motion. Then the Brain Extraction Tool deleted the non-brain tissue from the corrected images by applying a fractional intensity threshold of 0.5 to delineate the brain outline. A binary brain mask was generated and used to fit the diffusion tensor model at each voxel of the DTI images. The obtained FA images were fed into the 4-step TBSS procedure (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS/UserGuide). Firstly, FA images were eroded in order

to prevent outliers to be included in the diffusion tensor fitting step. Secondly, the most representative subject of the sample was identified as a target template for subsequent non-linear alignment. Finally, images were registered to the MNI152 standard space and a threshold of 0.2 was applied to FA to exclude GM and CSF voxels.

2.7. Statistical analysis

All the statistical analyses on cognitive and clinical data were carried out using IBM SPSS Statistics Version 21 (IBM, Chicago, IL, USA).

Normality of distribution for all cognitive variables was tested using the Shapiro-Wilk test. Subsequently, correlations between the PS_{CI}, Stroop test and fluency tasks were tested by using the Pearson's r (two-tailed $\alpha = 0.01$). The Spearman's ρ was used for the TMT-B-A because performance on this test was not normally distributed. In addition, the relationship between all the cognitive variables, WM TLV and fatigue severity was investigated. A correlational approach [50] was also adopted in the neuroimaging analyses and the same linear regression model was applied to both VBM and TBSS with three covariates: age, education, and TIV as a proxy measure of brain reserve [51]. The VBM analysis was used to correlate cognitive performance with regional WM and GM volumes. TBSS, instead, allowed the parallel investigation of the relationship between PS function and WM microstructural integrity. Additionally, to investigate whether associations with MRI variables were specifically dependent on PS load, the correlational analyses for all the cognitive tests (TMT B-A, Stroop inhibition, PF and SF) were subsequently repeated controlling for the PS_{CI}.

In the VBM analysis, clusters were considered as significant if they survived statistical correction for multiple comparisons at a family wise error (FWE) threshold of $p < 0.05$. The brain areas included in the significant GM clusters were identified by means of the Talairach Daemon

(http://www.talairach.org/daemon.html). Similarly, the randomise FSL tool was used to perform non-parametric TBSS analysis on DTI data and 5000 permutations were carried out for each model. Significant results were reported by threshold-free cluster enhanced (TFCE) images.[52] Raw result images were masked with significant ($p < 0.05$) voxels from TFCE images and both peak and cluster data in MNI152 standard space were extracted from the resulting images. Finally, WM tracts were identified using the JHU ICBM-DTI-81 White-Matter Labels atlas [53].

3. Results

3.1. Behavioural results

The clinical, cognitive and volumetric characteristics of the patients recruited in this study are summarised in Table 1. The correlational analysis showed that the PS_{CI} was strongly associated with performance on all tests apart from TMT B-A: semantic fluency ($r = -0.52$, $p < 0.01$), phonemic fluency ($r = -0.51$, $p < 0.01$) and Stroop inhibition ($r = 0.38$, $p < 0.05$). However, when the impact of TLV on cognition was investigated, only scores on the SF task were found to be negatively associated with the amount of WM damage ($r = -0.39$, $p < 0.05$). Moreover, the correlational analysis between FSS scores and cognitive data (Pearson's r for PS_{CI}, Stroop and fluency tests and Spearman's ρ for the TMT-B-A) found that only the PS_{CI} resulted significantly correlated with fatigue severity: $r = 0.483$, $p = 0.013$.

[Add Table 1]

3.2. VBM results

The highest peaks of WM lesion probability were detected mainly in the superior corona radiata, containing both projection and associative tracts, periventricular WM and occipital WM (Figure 1).

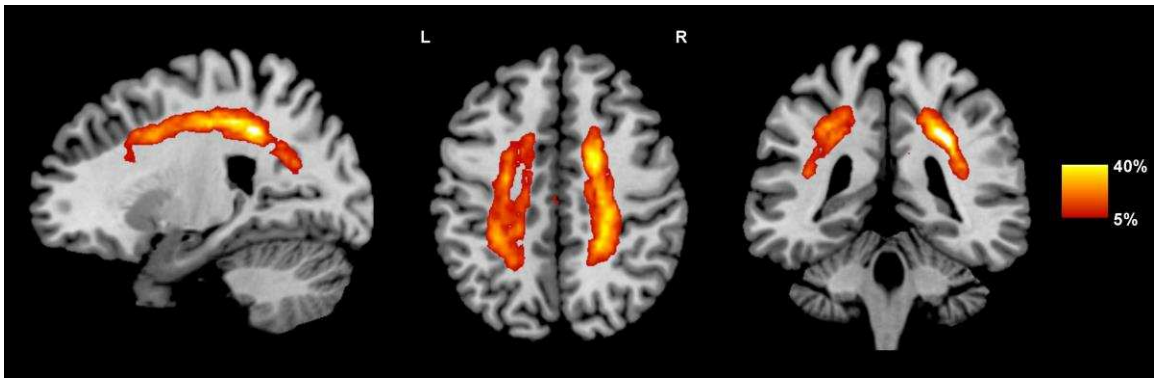

Figure 1 Lesion probability map created as an average of individual lesion maps

Scores on the semantic fluency task were found to correlate with regional volumes of bilateral WM clusters mainly involving the superior longitudinal fasciculus, the corpus callosum and the anterior thalamic radiations (Figure 2). The same WM tracts retained significant associations after controlling for PS abilities, but in much smaller clusters (Table 2). Instead, no significant correlations were found between WM regional volume and the PS_{CI} score or scores on other cognitive tests.

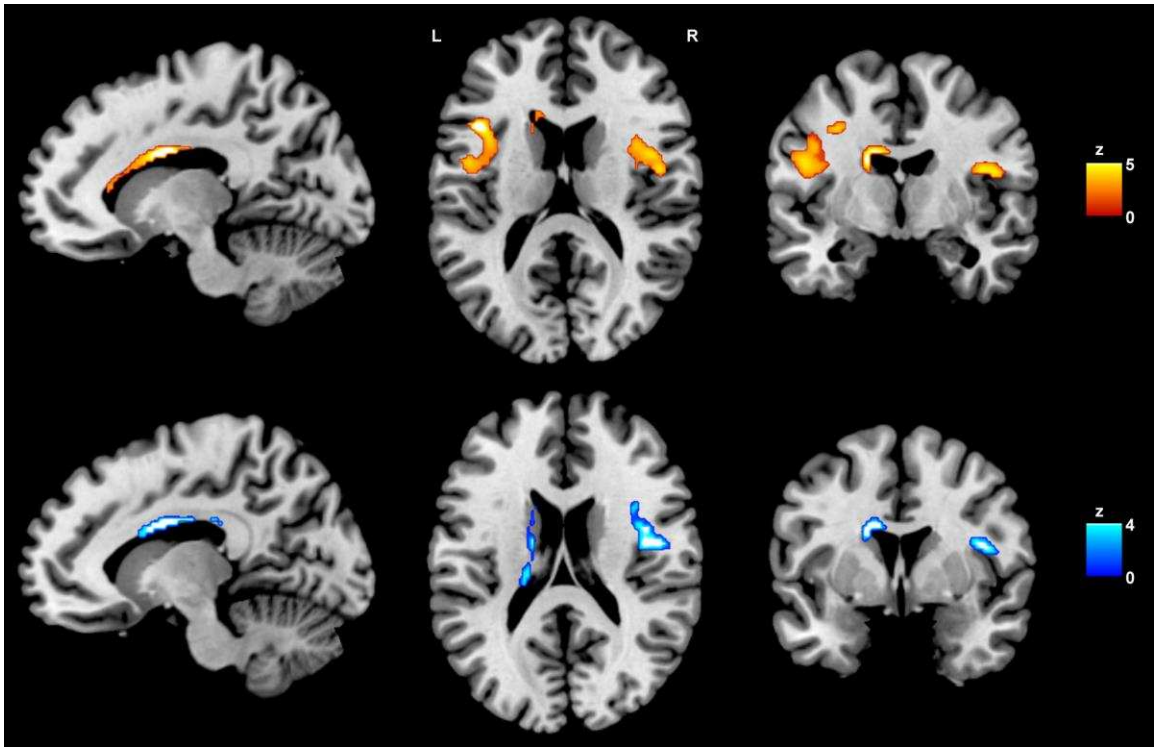

Figure 2 WM regions correlated with scores on the semantic fluency task before (red) and after (blue) correcting for PS abilities at pFWE < 0.05

Similar findings were observed in the VBM analysis on GM maps where only scores on the semantic fluency task were significantly correlated with regional GM volumes namely the occipital and temporal areas, the posterior cingulate cortex and the caudate (Figure 3). After controlling for PS performance, only occipito-temporal areas still emerged as strongly correlated with semantic fluency scores (Table 2).

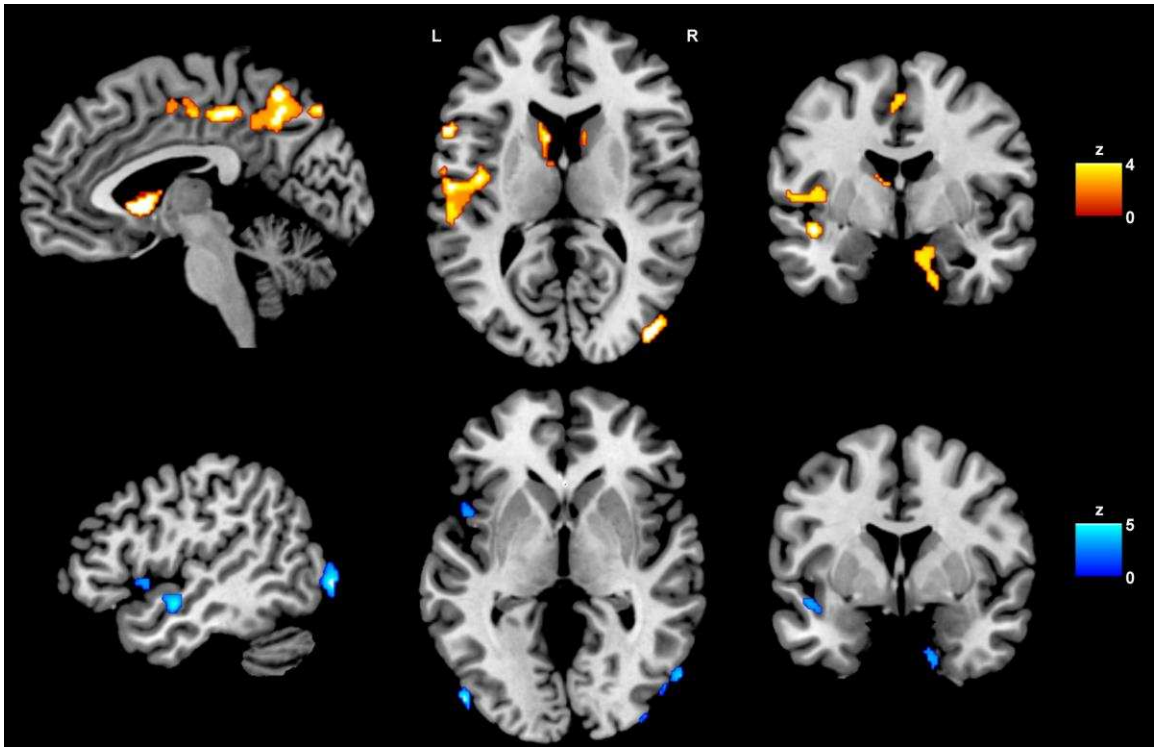

Figure 3 GM regions correlated with scores on the semantic fluency task before (red) and after (blue) correcting for PS abilities at pFWE < 0.05

[Add Table 2]

3.3. TBSS results

At a microstructural level, PS_{CI} scores were associated with the integrity of the corpus callosum and different frontal tracts, namely the anterior thalamic radiations and the inferior fronto-occipital fasciculus. Performance in all cognitive tests was differentially associated with FA in several WM tracts, though, for the TMT B-A, the significance threshold was increased to $p = 0.1$ to probe the strongest peaks of correlation that emerged in a cluster in the forceps minor (Figure 4). Indeed, FA in the corpus callosum was positively associated with performance on all tests,

despite widespread patterns of correlations, especially for the semantic fluency and the Stroop inhibition tasks. Nonetheless, some of the strongest associations were consistently found in the inferior fronto-occipital fasciculus as observed for the PS_{CI} (Table 3). Additionally, the superior longitudinal fasciculus also emerged as significantly involved in supporting PS-demanding cognitive performance across tests.

For semantic fluency and Stroop inhibition, a similar pattern of associations survived statistical correction for the $PS_{CI,}$ but in smaller clusters. However, a shift of the most significant peaks of association towards more posterior occipito-temporal tracts, i.e. the forceps major and the inferior longitudinal fasciculus, clearly emerged for both tests. For phonemic fluency, no significant results were observed after controlling for PS abilities.

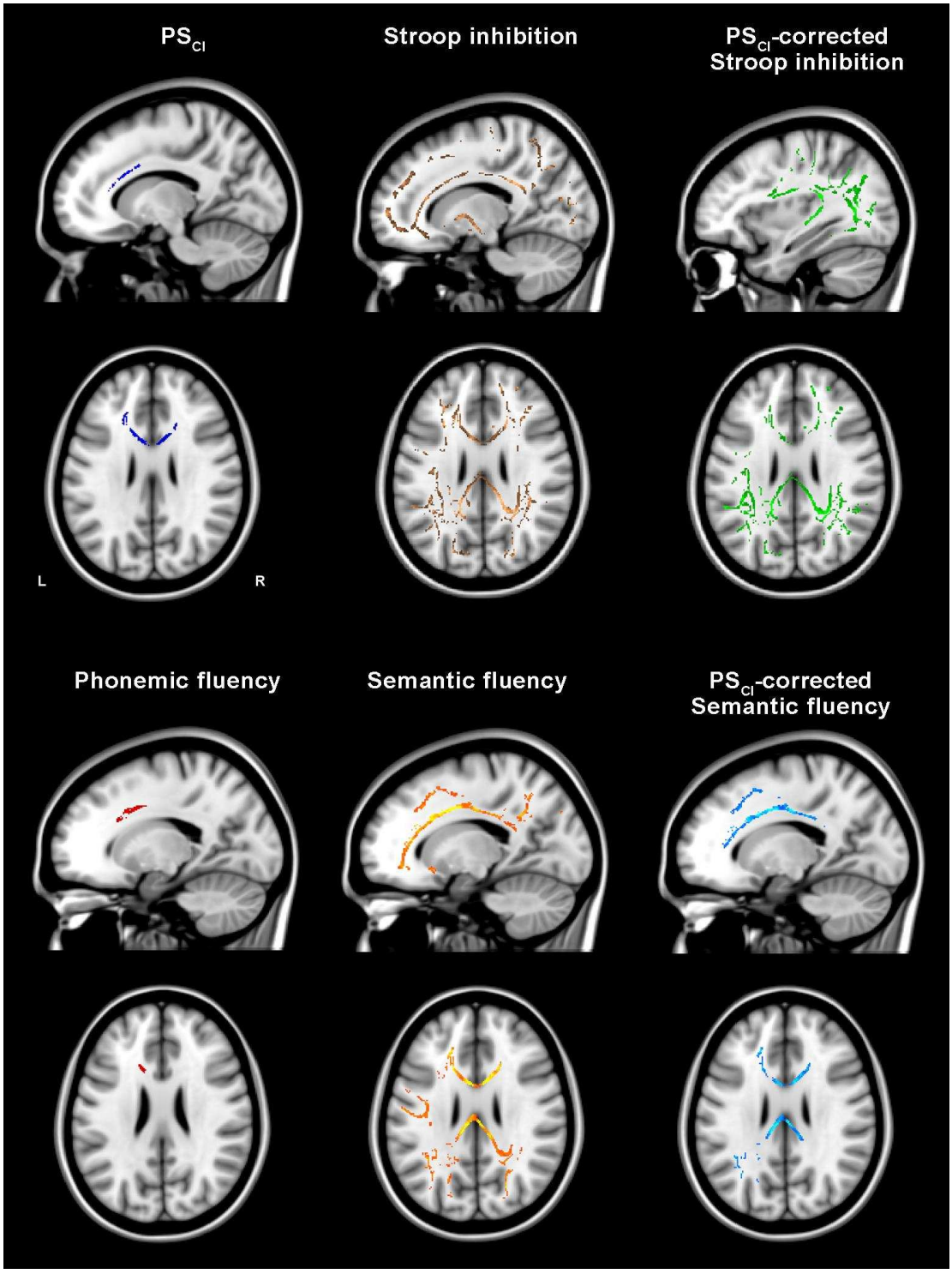
PS$_{CI}$
Stroop inhibition
PS$_{CI}$-corrected Stroop inhibition
L
R
Phonemic fluency
Semantic fluency
PS$_{CI}$-corrected Semantic fluency

Figure 4 WM tracts in which FA positively correlated with the PS_{CI} (blue), the phonemic fluency task (red), and the semantic fluency task before (orange) and after (light blue) correcting for PS abilities ($p < 0.05$ TFCE)

[Add Table 3]

3.4. Supplementary results

Because of the heterogeneous cognitive and motor functions required by the tests used to compute the PS_{CI} , supplementary analyses were carried out on two distinct PS components: visuo-motor (combining the TMT-A and the DCT scores) and verbal (Stroop speed). While no significant associations with GM/WM volumes were found, we observed that verbal PS correlated with FA mainly in the corpus callosum, left anterior thalamic radiations and bilateral inferior fronto-occipital fasciculus. Increasing the significant threshold in TBSS analysis to $p = 0.1$, visual PS also correlated with FA in similar frontal WM tracts (Table 4). These results are consistent with those observed for the PS_{CI} and highlight how the verbal and less motor-related PS index appears more strongly correlated with WM integrity, as reflected also in the analysis of the different PS-demanding cognitive tests.

Additionally, given the finding of an association between fatigue severity and PS_{CI}, FSS scores were added as a covariate in the analyses of the neural correlates of the PS_{CI}.

No significant associations between the PS_{CI} and either GM or WM regional volumes emerged in our VBM analyses after controlling also for fatigue severity. A change in results, instead, was observed in the TBSS analysis after adding FSS scores as fourth covariate, since no significant associations between the PS_{CI} and FA remained. This result may, to some extent, be expected considering the correlation existing between the PS_{CI} measure and fatigue severity. However, in

this study the directionality of the relationship between objectively assessed PS performance and patients' self-perception of fatigue cannot be ascertained.

[Add Table 4]

4. Discussion

In this study the combination of VBM and TBSS analyses provided new insights into the association between measures of structural brain integrity and cognitive performance of patients with SPMS on tasks characterized by a substantial PS load. The investigation of WM microstructure showed that PS function is associated preferentially with the level of integrity of commissural and frontal associative WM tracts: the body of the corpus callosum, the anterior thalamic radiations and the inferior fronto-occipital fasciculus. Similar results were replicated after disentangling the visuomotor and the verbal components of the PS_{CI}. The latter, less confounded by possible deficits in motor execution, was observed to be more strongly correlated with FA in the abovementioned WM tracts than its visuomotor counterpart. Indeed, only the adoption of a less restrictive threshold in the TBSS analysis allowed the detection of significant correlations for the visuomotor PS component.

Furthermore, performance on the PS-loaded cognitive tests was associated with FA values in analogous WM tracts, especially with the corpus callosum, which resulted significantly involved in each single test, and the inferior fronto-occipital fasciculus, detected for the Stroop and the fluency tasks. Hence, these two fiber bundles, along with anterior thalamic radiations, appear to represent the structural network supporting PS-loaded cognitive performance in people affected by SPMS, in line with previous findings in ageing [54-56]. Additionally, the superior longitudinal

fasciculus was found associated only with more complex tests (Stroop and the fluency tasks), but not with the indices of PS, possibly because of their greater global cognitive load beyond PS [57,58].

After statistically controlling for PS ability, the correlation between FA and the Stroop and semantic fluency tests only survived in smaller clusters of WM mainly localised in posterior occipital (forceps major) and occipito-temporal (inferior longitudinal fasciculus) tracts involved primarily in visual perceptual processes [59]. Therefore, the PS load that characterizes these tests appears the main component driving the detection of significant correlations in more frontal and cognitively salient WM tracts.

VBM analysis was used with the aim to investigate whether regional atrophy of either WM or GM could also capture PS decline, since the secondary progressive stage of this disease is known to be heavily characterized by neurodegenerative processes [60] resulting in considerable levels of brain atrophy [61]. In our battery of tests, only the scores obtained on the semantic fluency task emerged significantly correlated with both GM and WM volumes. Moreover, this unique association was also found with TLV, thus confirming that semantic fluency may be particularly sensitive to WM damage. Indeed, semantic cognition is supported by a distributed network both for storage of semantic knowledge [62] and deployment of sematic control processes [63]. On the contrary letter fluency is a task requiring prevalently executive control processes associated with the frontal lobes that undergo macrostructural degeneration later on in the disease course [61].

The findings of this study suggest that in this clinical population fast cognitive processing is supported by structural connections that enable integration of information across each hemisphere and especially between frontal lobes and other GM structures. Indeed, these findings support the

view that MS is a disconnection syndrome [64] and the hypothesized network collapse underlying the cognitive dysfunction seen in this illness [65]. In line with the cognitive efficiency theory [66] and neuroimaging findings that support it [67,68], it could also be argued that in MS, a condition particularly characterized by PS deficits [3], the execution of PS-challenging cognitive tasks requires greater deployment of executive control processes reliant on brain networks centered on the frontal lobes. Therefore, preservation of frontal connections that allow control processes over other cognitive functions appears crucial for people affected by MS while performing PS-demanding tasks. Among the various WM tracts likely to be crucial for cognitive PS abilities, of particular interest is the IFOF whose level of microstructural integrity was found to correlate with all of PS-related tests investigated in this study. In fact, the IFOF has been found to subserve complex functions related to semantic cognition, though characterized by interhemispheric differences [69,70], and to contribute to attention orienting [71].

Instead, results on the correlation between PS performance and self-reported levels of fatigue are of difficult interpretation, since the analysis carried out in this paper cannot clarify the directionality of such association. Fatigue, in fact, represents the symptom most commonly experienced by a vast majority of patients with MS and its relationship with cognitive decline and depressive symptoms is not clear [72]. In particular, self-reported fatigue and cognition appear only weakly related and depression and fatigue were observed to explain only 6% of the variance in objectively assessed cognitive performance [73]. Consistently, deficits in PS in people with progressive MS, compared to healthy controls, have been observed also after controlling for fatigue and depression scores [74].

In conclusion, our study provides new insights into the structural correlates of PS-related cognitive performance of patients with SPMS, a clinical population whose neurocognitive profile

is still poorly studied, probably due to the relatively small number of patients experiencing this condition compared to RRMS [75]. Further investigations on the functional networks connected by the WM tracts observed in our analysis are needed to characterise more extensively the relationship between neural and cognitive changes in SPMS. Indeed, currently little is known about functional reorganization in SPMS since most investigations have focused on RRMS and the Default Mode Network [76]. Moreover, our results should encourage the investigation of specific MRI markers of cognitive decline across the spectrum of MS phenotypes. Such MRI-based markers could provide objective outcome measures for clinical trials that would be useful in testing the effects of pharmacological and non-pharmacological interventions on neurocognitive function.

Declarations of interest

The authors declare that there is no conflict of interest and that they received no financial support for the research, authorship, and/or publication of this article.

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Table 1 Clinical, cognitive and volumetric characteristics of the patient sample (n = 31)

Variable	Mean	SD	Median	Minimum	Maximum
Demographics					
Age (years)	54.80	11.54	54	29	70
Education (years)	10.32	2.78	11	5	13
Clinical characteristics					
Disease duration (years)	16.32	8.48	14	3	31
EDSS	6.48	1.20	7	3.5	8
FSS	4.94	1.22	5	2.67	7
Cognitive tests					
PS_{CI}	0.02	0.95	-0.07	-1.15	2.37
Stroop inhibition	28.27	15.02	20.50	5.50	66.00
TMT B-A	131.89	151.03	80.00	5	663
PF	28.08	11.22	31	8	48
SF	37.96	11.62	35	20	61
Neural characteristics					
GMV (ml)	578.88	58.07	587.30	482.30	715.70
WMV (ml)	433.91	65.96	426.92	312.75	655.00
TIV (ml)	1685.09	170.39	1685.58	1341.29	2044.44
TLV (ml)	23.55	18.95	21.69	0.85	81.96

EDSS: Expanded Disability Status Scale, FSS: Fatigue Status Scale, GMV: Grey matter volume, PF: Phonemic fluency, PS_{CI}: Processing speed composite index, SF: Semantic fluency, TIV: Total intracranial volume, TLV: Total lesion volume, TMT B-A: Trail Making Test part B - part A, WMV: White matter volume

Table 2 Positive association between semantic fluency scores and GM/WM regional volumes before and after controlling for the PS_{CI} (pFWE <.05)

Cognitive variable	Cluster extent	Side	Brain region	t value	MNI coordinates		
					x	y	z
			White matter tracts				
SF	364	L	ATR	6.16	-16	-2	24
		L	Corpus callosum (body)	4.32	-8	-12	28
		L	Forceps minor	3.96	-14	26	10
	1180	L	Uncinate fasciculus	5.81	-42	16	16
		L	SLF	5.30	-34	12	20
		L	SLF	4.88	-32	-4	40
	334	R	SLF	4.72	46	-6	18
		R	SLF	4.68	42	2	18
		R	SLF	4.19	42	-14	36
PS_{CI}-corrected SF	281	L	ATR	5.38	-16	-2	24
		L	Corpus callosum (body)	4.28	-12	-14	30
		L	ATR	4.20	-18	-20	24
	235	R	SLF	4.37	42	4	16
		R	SLF	4.36	48	-6	18
		R	SLF	3.99	36	12	24
			Grey matter regions				
SF	504	R	Temporal pole (BA 38)	5.99	16	14	-36
		R	PHG (BA 28)	4.21	16	-14	-38
		R	PHG (BA 34)	4.11	8	-8	-24
	456	R	MTG (BA 19)	5.48	44	-84	14
		R	IOG (BA 18)	5.46	40	-92	-12
		R	IOG (BA 19)	4.74	50	-82	-10
	272	L	Caudate	5.06	-6	12	0
		L	Caudate	4.07	-10	8	14
		L	Caudate	3.97	-10	-2	14
	718	L	Precuneus (BA 7)	4.92	-2	-56	54
		L	Precuneus (BA 7)	4.88	-2	-64	48
		L	Precuneus (BA 7)	4.42	-12	-76	52
	835	L	STG (BA 22)	4.86	-48	10	-2
		L	STG (BA 42)	4.44	-58	-14	14
		L	PreCG (BA 44)	4.34	-58	14	10
PS_{CI}-corrected SF	211	L	IOG (BA 18)	6.11	-42	-92	-12
		L	MOG (BA 19)	5.45	-50	-84	-2
	466	R	MOG (BA 19)	5.81	44	-84	12

	R	IOG (BA 18)	5.37	40	-92	-12
	R	ITG (BA 37)	4.65	58	-72	-2
223	L	STG (BA 21)	5.49	-52	-6	-12
	L	STG (BA 22)	3.92	-48	10	-2
	L	Temporal pole (BA 38)	3.65	-40	6	-16
215	R	Temporal pole (BA 38)	5.27	16	14	-36
	R	PHG (BA 36)	4.43	14	6	-40
	R	PHG (BA 35)	4.00	16	-14	-36

ATR: Anterior thalamic radiations, BA: Brodmann area, IOG: Inferior occipital gyrus, ITG: Inferior temporal gyrus, MOG: Middle occipital gyrus, MTG: Middle temporal gyrus, PHG: Parahippocampal gyrus, PreCG: Precentral gyrus, SF: Semantic fluency, SLF: Superior longitudinal fasciculus, STG: Superior temporal gyrus

Table 3 Correlation between cognitive tests and FA (pFWE <.05)

Cognitive variable	Cluster extent	Side	White matter tract	t value	MNI coordinates		
					x	y	z
PS_{CI}	1705	L	ATR	5.42	-20	27	30
		L	Corpus callosum (body)	4.78	-13	14	26
		L	ATR	4.75	-22	29	21
		L	Corpus callosum (body)	4.48	-13	7	30
		L	IFOF	4.46	-24	28	8
		L	Corpus callosum (body)	4.40	-7	7	27
Stroop inhibition	38191	R	SLF	5.91	42	-45	9
		L	IFOF	5.76	-29	-72	4
		R	Corpus callosum (body)	5.49	12	19	22
		L	ATR	5.39	-16	-10	-1
		L	Forceps major	5.31	-27	-74	4
		R	Forceps minor	5.20	11	28	13
PS_{CI}-corrected Stroop inhibition	29954	R	SLF	6.14	43	-46	8
		R	SLF	6.07	43	-46	10
		L	Forceps major	5.50	-29	-72	4
		L	Forceps major	5.12	-29	-71	6
		L	ILF	5.02	-44	-38	-7
		L	Forceps major	5.00	-27	-69	2
TMT B-A*	18	L	Forceps minor	3.85	-10	30	11
		L	Forceps minor	3.66	-8	29	10
		L	Forceps minor	3.39	-5	27	10
PF	212	L	SLF	4.71	-17	6	34
		L	SLF	4.19	-17	12	34
		L	SLF	3.93	-16	1	37
		L	Corpus callosum (body)	3.67	-15	19	25
		L	SLF	3.65	-16	9	35
		L	SLF	3.48	-17	15	32
	205	L	SLF	4.70	-29	3	7
		L	SLF	4.58	-28	3	9
		L	IFOF	3.97	-25	18	0
		L	SLF	3.91	-30	-4	11
		L	SLF	3.69	-29	-1	10
		L	IFOF	3.66	-26	14	0
SF	18771	L	SLF	7.58	-18	7	35
		L	SLF	7.37	-17	6	37
		R	Corpus callosum (body)	6.44	6	-24	28
		L	SLF	5.86	-41	11	8
		L	Corpus callosum (body)	5.86	-10	2	31

		L	SLF	5.64	-17	1	37
	144	R	IFOF	3.10	39	-27	-3
		R	IFOF	3.02	39	-28	-1
		R	IFOF	2.98	32	-21	-2
		R	IFOF	2.67	35	-28	0
		R	IFOF	2.61	37	-32	2
		R	IFOF	2.49	40	-32	-3
PS_{CI}-corrected SF	4420	L	SLF	6.74	-18	7	37
		L	SLF	6.36	-18	7	35
		R	Corpus callosum (body)	6.14	6	-24	28
		L	Corpus callosum (body)	5.77	-15	-5	36
		L	SLF	5.42	-17	-18	37
		L	SLF	5.38	-17	-16	36
	1332	L	ILF	4.27	-32	-60	24
		L	ILF	4.17	-32	-61	26
		L	IFOF	3.66	-31	-60	19
		L	IFOF	3.52	-33	-55	17
		L	ILF	3.48	-27	-59	19
		L	SLF	3.37	-37	-51	29

ATR: Anterior thalamic radiations, IFOF: Inferior fronto-occipital fasciculus, ILF: Inferior longitudinal fasciculus, PF: Phonemic fluency, PS_{CI}: Processing speed composite index, SF: Semantic fluency, SLF: Superior longitudinal fasciculus, TMT B-A: Trail Making Test part B - part A

* $p < 0.1$

Table 4 Correlation between the visuomotor and cognitive components of the PS_{CI} and FA (pFWE <.05)

Cognitive variable	Cluster extent	Side	White matter tract	t value	MNI coordinates		
					x	y	z
Visuomotor speed*	123	L	ATR	4.98	-20	27	30
		L	ATR	4.73	-22	29	21
		L	ATR	3.79	-20	22	34
		L	Forceps minor	3.33	-21	31	23
		L	ATR	3.20	-23	28	17
		L	ATR	2.99	-22	23	30
	60	L	IFOF	3.68	-24	28	8
		L	IFOF	3.64	-24	29	6
		L	IFOF	3.62	-24	32	5
		L	IFOF	3.20	-26	29	11
		L	IFOF	2.94	-24	26	12
		L	IFOF	2.84	-24	29	11
Stroop speed	18071	L	Cingulum	6.40	-17	-66	-1
		L	IFOF	5.47	-24	28	8
		L	ATR	5.29	-16	-11	-3
		L	Corpus callosum (body)	5.13	-12	16	24
		L	ATR	5.08	-18	-2	9
		L	Cingulum	4.85	-17	-65	3
	448	R	ILF	3.68	39	-25	-6
		R	ILF	3.50	43	-35	-8
		R	ILF	3.24	42	-35	-12
		R	IFOF	3.10	40	-32	-4
		R	IFOF	3.09	41	-34	-2
		R	ILF	2.97	41	-28	-1

ATR: Anterior thalamic radiations, IFOF: Inferior fronto-occipital fasciculus, ILF: Inferior longitudinal fasciculus

* $p < 0.1$