

Lesion symptom map of cognitive–postural interference in multiple sclerosis

Serena Ruggieri, Fulvia Fanelli, Letizia Castelli, Nikolaos Petsas, Laura De Giglio and Luca Prosperini

Abstract

Objective: To investigate the disease-altered structure–function relationship underlying the cognitive–postural interference (CPI) phenomenon in multiple sclerosis (MS).

Methods: We measured postural sway of 96 patients and 48 sex-/age-matched healthy controls by force platform in quiet standing (single-task (ST)) while performing the Stroop test (dual-task (DT)) to estimate the dual-task cost (DTC) of balance. In patient group, binary T2 and T1 lesion masks and their corresponding lesion volumes were obtained from magnetic resonance imaging (MRI) of brain. Normalized brain volume (NBV) was also estimated by SIENAX. Correlations between DTC and lesion location were determined by voxel-based lesion symptom mapping (VLSM) analyses.

Results: Patients had greater DTC than controls ($p < 0.001$). Among whole brain MRI metrics, only T1 lesion volume correlated with DTC ($r = -0.27$; $p < 0.01$). However, VLSM analysis did not reveal any association with DTC using T1 lesion masks. By contrast, we found clusters of T2 lesions in distinct anatomical regions (anterior and superior corona radiata, bilaterally) to be correlated with DTC ($p < 0.01$ false discovery rate (FDR)-corrected). A multivariable stepwise regression model confirmed findings from VLSM analysis. NBV did not contribute to fit the model.

Conclusion: Our findings suggest that the CPI phenomenon in MS can be explained by disconnection along specific areas implicated in task-switching abilities and divided attention.

Keywords: Multiple sclerosis, MRI, T2 lesions, atrophy, cognitive–motor interference, balance

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Introduction

The so-called dual-task (DT) situations (e.g. walking while talking on a cell phone) are considered rather unproblematic in general population.¹ By contrast, older people and subjects affected by neurological diseases, including multiple sclerosis (MS), present slower short-distance speed, worse gait performance, deteriorated standing balance, and increased risk of falls in DT situations.^{2–4} This phenomenon, the so-called cognitive–motor interference (CMI), can be purposely investigated by means of DT paradigm experiments, that is, a study design aimed at assessing change in motor performance under conditions of cognitive distraction and vice versa.

Emerging evidence also supports the notion that two simultaneously performed tasks may compete for common brain network resources in MS patients, thus leading to a deterioration in standing balance during a

concurrent cognitive task.⁵ This cognitive–posture interference (CPI) phenomenon has been recently described in force platform-based experiments conducted on MS people without any overt cognitive impairment, suggesting that DT paradigms may unmask even subtle neurological deficits.^{6–8}

While investigation about the anatomical correlates of CPI in MS is still lacking, data on other neurological populations showed (a) an association between subcortical white matter hyperintensities and DT interference;⁹ (b) reduced activation at DT functional magnetic resonance imaging (MRI) in brain regions responsible for resolving interference, including pre-frontal areas, supplementary motor areas, and cerebellum.^{10,11}

Assessing the pathological mechanisms underlying CPI can lead to development of new strategies to

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reduce the risk of falls and daily activity curtailment due to MS-related deterioration of DT abilities.^{12,13} Current literature data indicate that, when considered separately, cognitive and motor impairments due to MS are more related with brain atrophy and diffuse damage rather than with focal lesions.¹⁴ On the other hand, measures of both lesioned and normal-appearing white matter support the possibility of an underlying disconnection syndrome that causes specific clinical symptoms.^{15,16} Functional reorganization and brain reserve may further obfuscate the direct clinical manifestation of MS-related damage.¹⁷

Therefore, here we aimed to unravel the behavior–structure relationship underlying the CPI phenomenon in MS, by assessing the relative contribution of strategic lesion location and brain atrophy on deterioration of standing balance observed during DT paradigm experiments.

Methods

Participants

In this independent, cross-sectional study, we collected behavioral and MRI data of patients regularly attending the MS Centre of Department of Neurology and Psychiatry, Sapienza University, Rome, Italy and consecutively enrolled in previously published clinical studies.^{5,6,13} Sex- and age-matched healthy individuals were also recruited in a 1:2 ratio among the university hospital personnel (stretcher bearers, technicians, students, residents, nurses, physiotherapists, and doctors) to serve as controls in DT experiment, but they did not underwent the brain MRI assessment.

To be included in the aforementioned studies, patients must have age between 18 and 55 years, Expanded Disability Status Scale (EDSS) score between 0 and 6.5 (inclusive),¹⁸ ability to stand independently in upright position for ≥ 180 seconds, capability to accomplish all study requirements. General exclusion criteria encompassed severe visual impairment, occurrence of relapses in the previous 3 months, current steroid intake, initiation of disease-modifying or symptomatic treatments or any medication change occurring over the previous month, clinically relevant depression defined as a Beck Depression Inventory-II score ≥ 13 ;¹⁹ overt cognitive impairment defined as a Mini-Mental State Examination score ≤ 24 ,²⁰ any psychiatric illness including history drug or alcohol abuse/addiction, any other clinically relevant major medical illness potentially interfering with the study protocol.

DT experiment

Patients and controls underwent the Stroop test²¹ and were tested by means of static posturography under single-task (ST) and DT conditions,^{5,6,13} using a laboratory-grade force platform (ProKin PK-254P, TecnoBody, Bergamo, Italy; <http://www.tecnobody.it>) by two experienced operators (LC and LDG), according to standardized procedures.

The Stroop test consists of word reading and color naming (without conflicting stimuli), and then naming the ink color of words indicating conflicting colors as quickly as possible so that higher scores indicate better performance.²¹ The Stroop performance was first assessed without the interference of postural task as number of correct items in 30 seconds at the Stroop color-word test (SCWT). Participants were then instructed to maintain their balance for 30 seconds as steady as possible under eyes opened (ST condition) while performing the SCWT (DT condition) presented on a printout located 2 meters from the force platform, as described elsewhere.^{5,6,13}

The SCWT explores two processes of executive function, that is, visual selective attention and inhibition, and it is believed to be measuring both mental flexibility and the ability to inhibit a dominant response.²² Although there is no consensus on which cognitive task optimally creates the appropriate interference in MS, we choose this test as concurrent cognitive task in DT condition for several reasons: (a) executive function plays a key role in DT coordination;²³ (b) postural control and resolution of conflicting stimuli require partially overlapped brain resources, as visual network (postural stability and performing the SCWT) and cerebellum (maintenance of balance and modulation of conflict-induced behavioral adjustment);²⁴ (c) the SCWT has been recently proposed as the most suitable concurrent cognitive task to unmask the MS-related CPI phenomenon when compared to other tests, such as Word List Generation and Symbol Digit Modalities Test.⁵

We did not report data on dual-task cost (DTC) of cognition, that is, the effect of DT performance on SCWT, since it has been observed that dual-tasking deteriorated the balance, but not the cognition in MS people.⁵

The instant positions of the body's center of pressure (COP) in ST and DT conditions were measured to estimate the postural swayST and postural sway^{DT}, that is, the sum of the displacements (path) of COP in millimeters, with larger sway indicating worse balance. We calculated the DTC of balance using the following

formula: $-DTC (\%) = -(\text{postural sway}^{DT} - \text{postural sway}^{ST}) / (\text{postural sway}^{ST}) \times 100\%$; ²⁵ by convention, negative DTC values indicate the performance deterioration in DT relative to ST condition.

Image acquisition

We analyzed brain images of patients who were scanned in the same outpatient center using a superconducting 1.5-Tesla magnet (GE Signa Excite) according to published guidelines.²⁶

To be included in our analysis, brain MRI scans must have been acquired in a span of 1 month from the DT experiment. Data of patients presenting gadolinium-enhancing lesions were also excluded from analysis because MRI activity may cause a diffuse impairment of cerebral connectivity with a negative impact on cognitive functioning.²⁷

MRI was performed using eight-channel receive-only neurovascular head coil with the following protocols: dual-echo proton density (PD)-T2-weighted images (repetition time (TR)=2000–4000ms; echo time (TE)=14–20/80–108ms), with axial 4.0mm thickness, gap 0.4mm, matrix=512×512, field of view (FOV)=250×250mm, and 64 interleaved slices; fast fluid-attenuated inversion-recovery (FLAIR) (TR=8002ms, TE=98ms, inversion time (TI)=2000ms) with axial 4.0mm-thickness, gap 0.4mm, matrix=512×512, FOV=250×250mm, and 32 contiguous slices. Post-contrast T1-weighted spin-echo images after gadolinium-DTPA double-dose injection (0.2mmol/kg) (TR=520ms; TE=21ms; axial 4.0mm-thick slices with axial 4.0mm-thickness, gap 0.4mm, matrix=512×512, FOV=250×250mm, 32 contiguous slices) were also obtained.

Image data analysis

The processing pipeline started with brain lesions on T2- and T1-weighted images being outlined by a semi-automated edge contour technique (Jim 7.0 software, Xinapse System, Leicester, UK) to obtain T2 and T1 lesion masks and their corresponding lesion volumes (T2-LV and T1-LV). T1 lesion masks were obtained on the T1-weighted post-gadolinium images to avoid the inclusion of acute black holes in the analysis. T2 and T1 lesion masks were binarized and subsequently co-registered to standard space using the following procedure: (a) T1 images were linearly registered to the MNI152 template (FLIRT, part of FSL, FMRIB Centre, Oxford, UK) in order to get the affine transformation matrix (12-parameter model and tri-linear interpolation); (b) T1 images where non-linearly registered to the MNI152

template (FNIRT, part of FSL, FMRIB Centre, Oxford, UK) including the default Jacobian constraint; (c) T2 images were linearly registered to the corresponding T1 images; (d) T1 and T2 lesion masks were eventually non linearly co-registered to MNI152 template using the spline coefficients and affine transform derived from previous steps.

Whole brain atrophy was measured as normalized brain volume (NBV) on T1-weighted images using SIENAX.²⁸ To avoid tissue misclassifications, we corrected the impact of white matter lesions by lesion filling according to standardized procedures.²⁹

Image data processing was performed by two operators (SR and FF), both blinded to clinical data, who independently checked the registration quality and output of every single step. Discrepancies between the two operators were resolved by a senior researcher (NP).

Voxel-based lesion symptom mapping

To provide an overview of radiological disease burden across all patients, T2 and T1 lesion overlaps were calculated to create two color-coded overlay maps of voxels containing T2 and T1 lesion masks.

Correlations between behavioral data from the DT experiment (i.e. DTC of balance) and lesion location was determined by entering individual binary T2 and T1 lesion masks into voxel-based lesion symptom mapping (VLSM) analyses using a non-parametric permutation-based mapping (NPM) software from MRICron package (www.people.cas.sc.edu/rorden/mricron/index.html). The non-parametric Brunner-Munzel rank-order test was used to compare continuous patient behavioral data derived from DT experiment on a voxel-by-voxel basis, providing *z*-statistics for VLSM analyses. The Brunner-Munzel test has some advantage over the *t*-test, since it is assumption-free and provides robust statistical power even in situations where there are many ties, and when data are not normally distributed and/or based on ordinal scale.³⁰ To avoid inflated Brunner-Munzel test scores, only voxels affected in at least in 10 patients were tested.³¹ All resulting maps were corrected for multiple comparisons using a 1% false discovery rate (FDR) threshold (1000 permutations).³²

Specifically, we ran two separate VLSM analyses to explore the structure–function relationship underlying the CPI phenomenon by correlating the probability of lesion occurrence with DTC of balance in each of the two lesion maps (T2 and T1-weighted).

We also estimated individual VLSM scores representing, for each patient, the proportion of voxels included within the brain regions corresponding to the VLSM analysis of DTC of balance. As a result of this procedure, the VLSM score was higher when the patient's lesion mask was localized in brain regions more closely correlated with DTC of balance. This step allowed us to explore, in a multivariable model, the contribution of VLSM analysis to CPI phenomenon after adjusting for demographic characteristics, clinical variables, and other MRI metrics (T2-LV, T1-LV, and NBV).

General statistical analysis

Data are expressed as mean (standard deviation) or median (range), as appropriate. All variables were checked for normality by the Kolmogorov–Smirnov test and for outliers by the Tukey method. Non-normal variables were transformed to result in a normal distribution.

Differences between patients and controls were tested using the unpaired Student *t*-test and Chi-square test with Yate's correction, as appropriate. A two-way analysis of the variance (ANOVA) with a 2 × 2 design was carried out to evaluate the condition effect (ST versus DT) and group effect (patients versus controls) on postural sway.

Pearson's correlations were performed to investigate the relationships between all variables and to determine which variables to enter in the next multivariable model, including demographic characteristics (age, body mass index (BMI), and length of formal education), clinical variables (time since first symptom, EDSS score, SCWT, and postural swayST), and brain MRI metrics (T2-LV, T1-LV, and NBV).

A stepwise linear regression model (for inclusion: $F \geq 1$ and $p \leq 0.01$; for exclusion: $F < 1$ and $p > 0.05$) was then run in patient group to assess whether there were demographic, clinical, and MRI variables associated with DTC of balance (dependent variable).

To avoid underestimating the true α -error, p values ≤ 0.01 in either direction were considered as significant.³³ Statistical analyses were carried out using the Statistical Package for Social Sciences, version 16.0 (IBM SPSS, Chicago, IL, USA).

Results

DT experiment

A total of 152 eligible patients with MS underwent the DT experiment from November 2013 to September

2015. Of them, 56 were excluded from the analysis for the following reasons: acquisition of brain MRI over the 1-month span ($n=45$), presence of gadolinium-enhancing lesions at brain MRI scan ($n=11$).

There were no demographic and clinical differences between the 96 patients included in the analysis and the 56 patients who were excluded ($p > 0.3$).

Data of 96 patients and 48 sex- and age-matched controls are shown in Table 1. As expected, patients had larger postural sway than controls regardless of ST or DT condition, as well as greater DTC ($p < 0.001$). The two-way ANOVA, being the assumption of sphericity satisfied, showed significant effects of condition ($F(1, 142)=201.1$), group ($F(1, 142)=42.3$), and condition by group interaction ($F(1, 142)=38.7$) on postural sway ($p < 0.001$).

Correlation analysis

All demographic and clinical variables, as well as the NBV, were normally distributed ($D < 1$, $p > 0.05$), while remaining MRI metrics became normal after \log_{10} transform. The DTC of balance (dependent variable) became normal after cubic root transform. Correlations among demographic, clinical, and MRI variables considered in this study are shown in Table 2. All correlations among demographic and clinical variables were weak to moderate, ranging between -0.27 and 0.53 ($p < 0.01$), except for BMI which did not correlate with any other variable. Among MRI metrics, only T1-LV correlated with the DTC of balance ($r=0.27$, $p=0.008$). We found strong correlations between T2-LV and T1-LV ($r=0.71$, $p < 0.001$), as well as between T1-LV and T1:T2 ratio ($r=0.67$, $p < 0.001$). NBV was inversely related with both T2-LV and T1-LV ($r=-0.34$ and $r=-0.36$, respectively; $p < 0.001$). There was no association of sex and length of formal education with other variables, including the DTC of balance ($p > 0.1$ by the Student *t*-test) (Table 2).

Voxel-based lesion symptom maps

Probabilistic spatial distribution of T2 lesions showed the highest occurrence of clusters in the bilateral periventricular white matter of both hemispheres, followed by infratentorial clusters in brainstem and middle cerebellar peduncles (Figure 1(a)). Probabilistic spatial distribution of T1 lesions showed the highest occurrence of clusters in the bilateral periventricular white matter of both hemispheres and superior corona radiata, bilaterally (Figure 1(b)).

We found clusters of T2 lesions in distinct anatomical regions, that is, superior and anterior corona radiata,

Table 1. Characteristics of the two study samples.

	Patients	Controls	<i>p</i>
<i>N</i>	96	48	–
Sex (female:male)	64:32	32:16	1.00
Age (years)	41.8 (10.6)	40.7 (8.6)	0.53
Body mass index (kg/m ²)	23.1 (4.0)	23.5 (3.7)	0.61
Length of formal education, ≤13 years:>13 years	63:33	29:19	0.54
Time since first symptom (years)	13.3 (7.9)	N/A	–
Expanded Disability Status Scale score, median (range)	3.0 (1.0–6.0)	N/A	–
Stroop test	20.1 (6.3)	27.8 (7.9)	<0.001
Postural sway ST (mm)	308 (127)	198 (63)	<0.001
Postural sway ^{DT} (mm)	427 (173)	245 (72)	<0.001
Dual-task cost (%), median (range)	–38.5 (–6 to –94)	–24.5 (–2 to –47)	<0.001
T2 lesion volume (cm ³), median (range)	11.17 (0.37–96.72)	N/A	–
T1 lesion volume (cm ³), median (range)	0.87 (0.03–10.20)	N/A	–
T1 to T2 lesion volume ratio, median (range)	0.09 (0.01–0.53)	N/A	–
Normalized brain volume (cm ³)	1521.2 (83.07)	N/A	–

DT: dual-task; N/A: not applicable; ST: single-task.
All values are mean (standard deviation), unless indicated otherwise. Significant *p*-values are shown in bold.

Table 2. Pearson correlations in patient sample (*n*=96).

	Dual-task cost	Age	Body mass index	Time since first symptom	EDSS score	Stroop test	Postural sway ST	T2 lesion volume	T1 lesion volume	T1:T2 ratio	Normalized brain volume
Dual-task cost	1.00										
Age	–0.19	1.00									
Body mass index	0.13	0.11	1.00								
Time since first symptom	–0.10	0.51**	–0.12	1.00							
EDSS score	–0.13	0.43**	–0.02	0.52**	1.00						
Stroop test	0.06	–0.26*	–0.04	–0.19	–0.37**	1.00					
Postural sway ST	0.17	0.19	–0.08	0.34*	0.48**	–0.29*	1.00				
T2 lesion volume	–0.24	0.15	–0.16	0.38**	0.32*	–0.21	0.25	1.00			
T1 lesion volume	–0.27*	0.42**	–0.11	0.52**	0.53**	–0.31*	0.28*	0.71**	1.00		
T1:T2 ratio	–0.08	0.38**	0.04	0.29*	0.41**	–0.28*	0.14	0.03	0.67**	1.00	
Normalized brain volume	0.19	–0.34**	–0.03	–0.42**	–0.26*	0.12	0.18	–0.34**	–0.36**	–0.09	1.00

EDSS: Expanded Disability Status Scale; ST: single-task; T1:T2 ratio: T1 to T2 volume ratio.
Dual-task cost was transformed as cubic root; T2 and T1 lesion volumes, T1 to T2 lesion volume ratio and third ventricle width were transformed as log₁₀ because of violation of normality assumption. Significant *p*-values are shown in bold.
p*<0.01; *p*<0.001.

bilaterally (including the anterior thalamic radiations), to be correlated with DTC of balance (FDR-corrected *p*<0.01; Figure 2). Mean (standard deviation (SD)) VLSM score^{T2} was 0.132 (0.071), ranging from 0.005 to 0.395.

The VLSM did not reveal any significant association with behavioral data using T1 lesion masks, even after adopting a less conservative 5%-FDR threshold. As a result, we did not estimate VLSM scores^{T1}.

Lastly, to confirm that the pattern of damage shown in Figure 2 was specific for DTC of balance, further VLSM analyses were re-run with EDSS score, postural swayST and Stroop test as dependent variables. These additional VLSM analyses revealed patterns of damage different from that of DTC of balance (Figure 3).

Multivariable analysis

Preliminary analyses showed that the assumptions of normality, linearity, homoscedasticity, and independ-

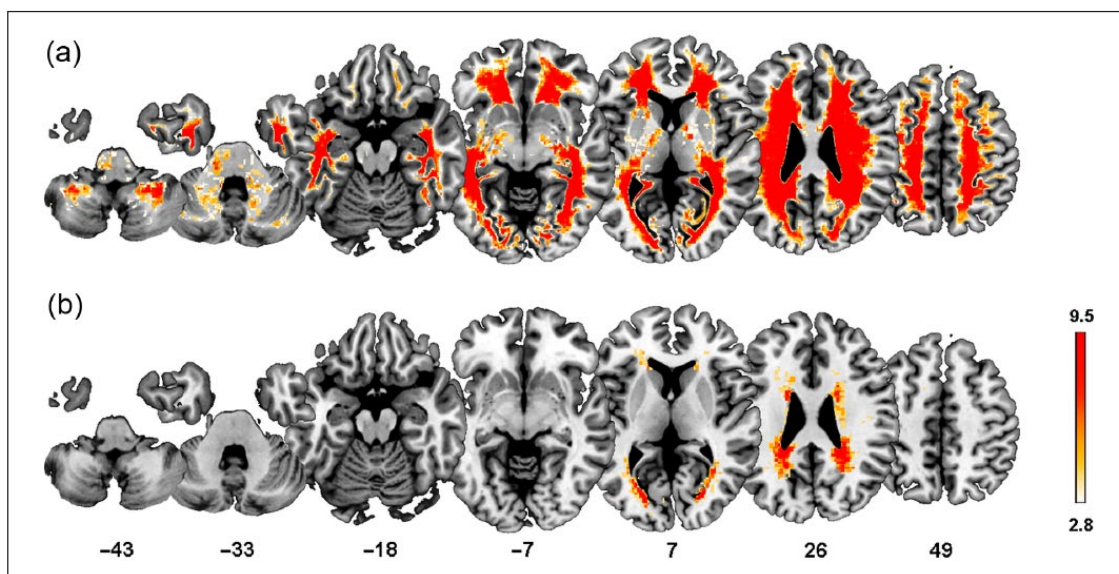


Figure 1. Overlay of (a) all T2-hyperintense lesions (a) and (b) all T1-hyperintense lesions superimposed onto a high-resolution axial standard template. Neurological Institute (MNI) coordinates on axial plane are reported at the bottom of each figure (neurological convention).

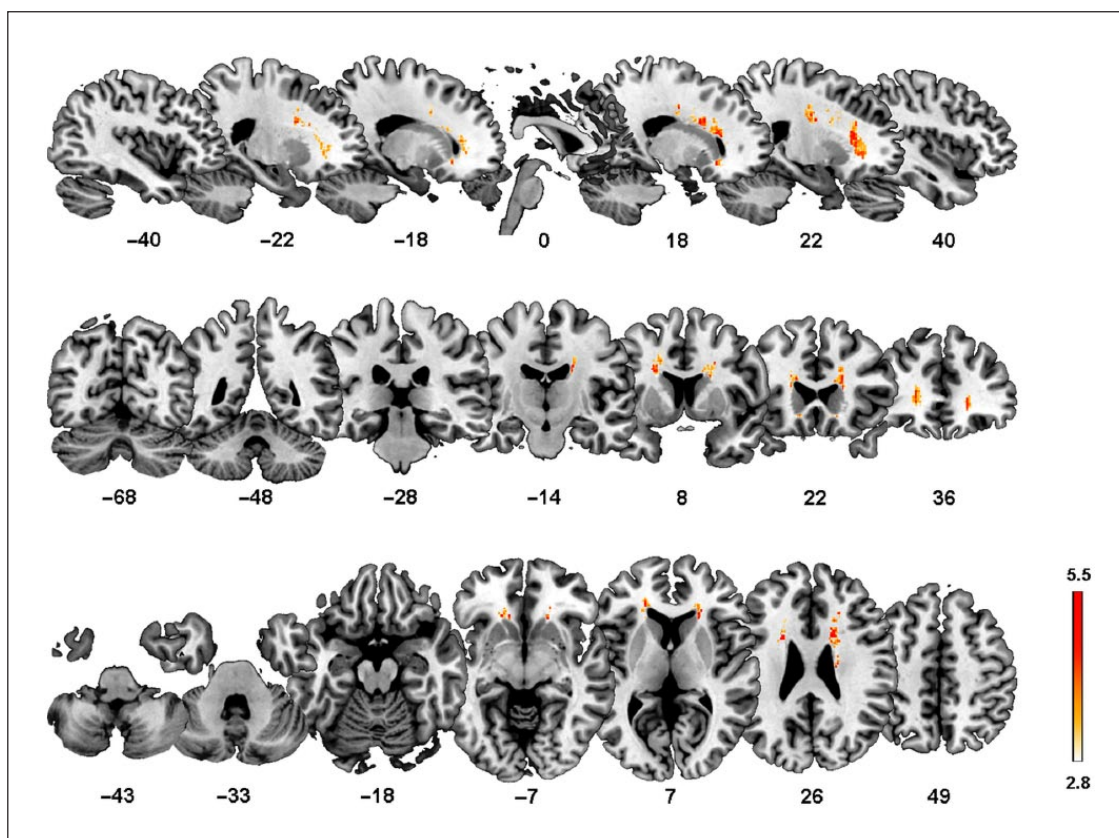


Figure 2. Colored voxel-based lesion symptom maps for T2-hyperintense lesions representing the Brunner-Munzel z-statistics for correlations with dual-task cost of balance. Only statistically significant voxels surviving the 1%-FDR threshold ($z > 2.8$) were displayed and overlaid onto a high-resolution standard template. Montreal Neurological Institute (MNI) coordinates on axial, sagittal, and coronal planes are reported at the bottom of each figure (neurological convention).

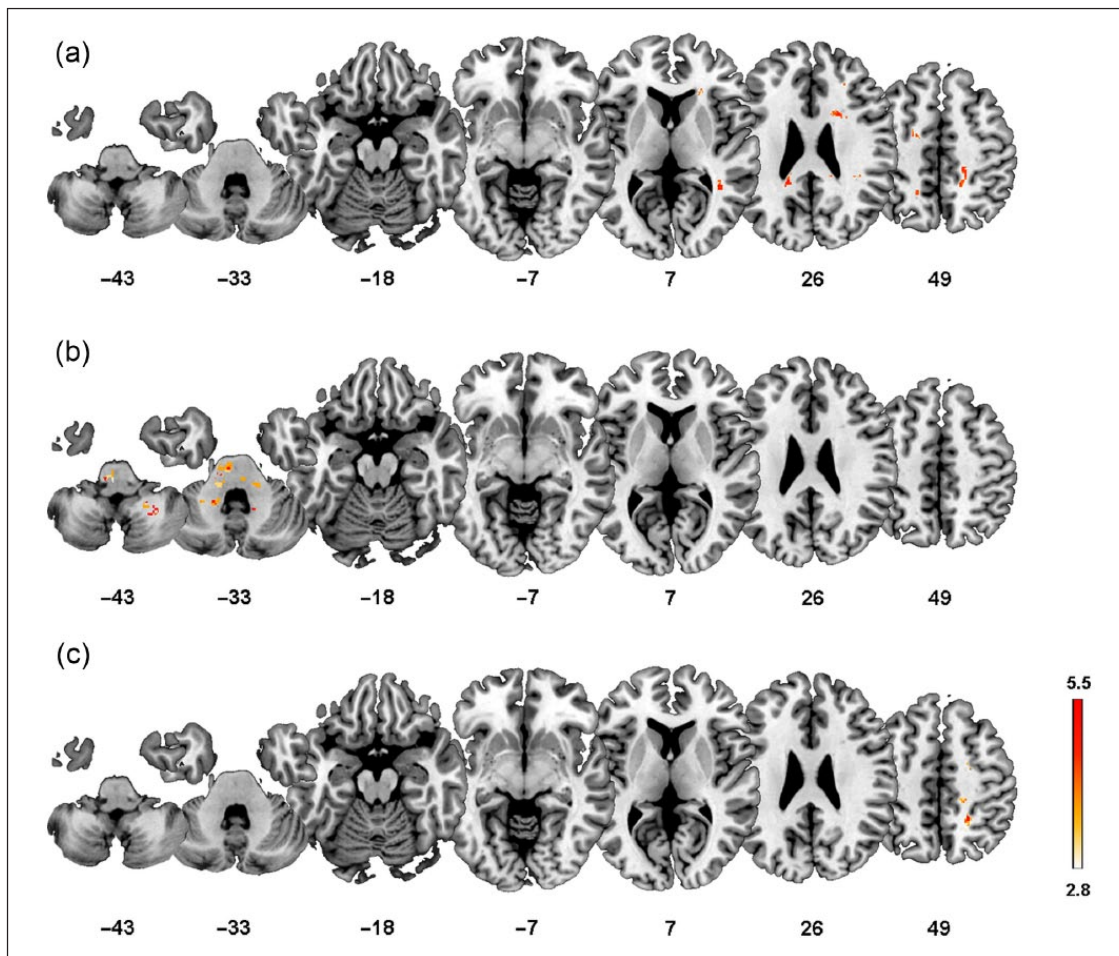


Figure 3. Colored voxel-based lesion symptom maps for T2-hyperintense lesions representing the Brunner-Munzel z-statistics for correlations with (a) Expanded Disability Status Scale, (b) postural swayST, and (c) Stroop test. Only statistically significant voxels surviving the 1%-FDR threshold ($z > 2.8$) were displayed and overlaid onto a high-resolution standard template. Montreal Neurological Institute (MNI) coordinates on axial plane are reported at the bottom of each figure (neurological convention).

ence of observation were met. There was no significant collinearity (variance inflation factors < 10).

The final stepwise linear regression model showed that DTC of balance only was associated with VLSM score^{T2} ($\beta = -4.93$, $p < 0.001$). The other demographic (sex, age, length of formal education) clinical (BMI, time since first symptom, EDSS, SCWT, and postural swayST) and MRI variable (T2-LV, T1-LV, T1:T2 ratio, and NBV) did not contribute to fit the model. This model was statistically significant ($F(1, 95) = 29.60$, $p < 0.001$) and explained 24% of variance in DTC of balance (Table 3).

Discussion

In this study, we investigated whether the CPI phenomenon, detected in patients with MS as increased

DTC of balance compared to healthy controls, might be explained by strategic lesion location rather than by global lesion volumes or whole brain atrophy. To our best knowledge, anatomical frameworks elucidating the CPI phenomenon in MS people are still lacking.⁸

The main finding of our study is clusters of T2 lesions in distinct anatomical regions (superior and anterior radiata, bilaterally) to be correlated with DTC of balance. Unlike T2 lesions, the association between T1-LV and DTC of balance seems to be not mediated by specific lesion locations. However, T1-LV did not survive the stepwise model, suggesting that disconnection along specific areas implicated in task-switching abilities and divided attention can represent one of the main reasons of pathological CPI phenomenon in MS. Yet, the final stepwise model accounted for a

Table 3. Stepwise regression model of dual-task cost of balance (cubic root-transformed; dependent variable) in patients with MS ($n=96$).

Independent variable(s)	β (std. error)	95% confidence intervals	p	R^2
Constant	-2.75 (0.12)	-2.99 to -2.51	<0.001	0.24
VLSM score ^{T2}	-4.93 (0.91)	-6.73 to -3.12	<0.001	

VLSM: voxel-based lesion symptom mapping.
 Variables included in the model are as follows: sex, age, length of formal education, body mass index, time since first symptom, Expanded Disability Status Scale score, Stroop color-word test score, T2 lesion volume, T1 lesion volume, T1 to T2 volume ratio, normalized brain volume.

relatively moderate amount (24%) of variance in DTC of balance, thus encouraging further investigation on neuroanatomical correlates of CPI phenomenon in MS.

This study raises the hypothesis that MS-related damage might have disconnected brain circuitry at two distinct levels: (a) between cerebellum, striatum, and pre-frontal areas, connected through the anterior and superior corona radiata; (b) between frontal lobes and anterior/midline nuclear groups of thalami, connected through the anterior thalamic peduncles. These disconnections might have, in turn, impaired the integration of brain networks required to maintain adequate performance in DT situations.

This latter hypothesis is in line with functional MRI experiments on general population have demonstrated activation of specific brain areas during DT performance, that is, cerebellum, pre-frontal, and/or parietal cortex.³⁴⁻³⁶ Studies on MS populations have suggested that cortico-cerebellar loop disruption results in cognitive processing deficit.^{37,38} Our findings are also corroborated by an earlier study showing high T2 lesion load in frontal lobe of MS patients with frontal lobe deficits.³⁹ However, even if we found significant correlations in clinically plausible brain regions, VLSM analysis cannot directly detect either network disruption or diffuse damage.¹⁵ To partially overcome this well-known drawback of VLSM analysis, we also quantify NBV, a measure that is closely related with motor and cognitive disability in MS people.^{14,16} Despite this, we found no association of CPI phenomenon with NBV, suggesting that more complex features (damage to normal-appearing brain tissue, regional atrophy, and maladaptive plasticity) should be investigated.

Our study supports the rationale for exploring new treatment strategies aimed at improving performance of MS people in DT situations. Manor et al.⁴⁰ recently demonstrated that facilitation of prefrontal cortical activity via transcranial direct current stimulation reduces DTC of balance in older adults. Hence,

partially disconnected pre-frontal areas may represent a putative target for brain modulation even in MS people.⁴¹ Moreover, dopamine agonist therapy could represent a suitable treatment as most disconnected areas are innervated by dopaminergic neurons (striatum and pre-frontal cortex) which are thought to modulate DT performance.⁴²

We are aware that this study is not without limitations, mainly because its cross-sectional design and the use of two-dimensional (2D) low-resolution images (axial 4-mm slices with 0.4-mm interslice spacing) acquired with a 1.5-Tesla magnet. This latter drawback, in particular, might have increased partial volume effects, affecting both the identification of small lesions and the accuracy of normalization. Therefore, the putative relationship between CPI phenomenon and MS-related pathology deserves further efforts, possibly through advanced non-conventional MRI techniques, including functional MRI studies.⁸

In conclusion, we attempted to unravel how MS lesions affect higher-level postural control, based on the currently prevailing theory that mobility, cognitive function, and structural and functional brain integrity are closely interconnected.^{2,8,9,25} Our findings confirm and extend previously published data by our research team, further developing the hypothesis that the CPI phenomenon results from MS-related damage of partly overlapped brain networks subserving both postural control and executive functions.⁵ Further investigation is now warranted to establish the relationship between structural brain damage and functional adaptive plasticity underlying the CPI phenomenon and impaired DT performance in MS people.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Serena Ruggieri received speaking honoraria from Merck Serono and Teva. Fulvia Fanelli has nothing to disclose. Letizia Castelli received consulting fees from Almirall. Nikolaos Petsas received speaking honoraria from Biogen. Laura De Giglio received travel grants from Biogen, Novartis, and Teva. Luca Prosperini received consulting fees from Biogen, Genzyme, and Novartis; speaking honoraria from Biogen, Genzyme, Merck Serono, Novartis, and Teva; and travel grants from Biogen, Genzyme, and Teva.

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Ethical statement

This study was conducted in accordance with specific national laws and the ethical standards outlined in the 1964 Declaration of Helsinki and its later amendments. The ethical committee board of our University provided exemption of approval for non-interventional studies. An informed consent was obtained from each participant before any study procedure.

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