

impairment in pediatric multiple sclerosis

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ABSTRACT

Objective: We combined structural and functional MRI to better understand the mechanisms responsible for cognitive impairment in pediatric patients with multiple sclerosis (MS).

Methods: Brain dual-echo, diffusion tensor, 3D T1-weighted, and resting-state (RS) fMRI scans were acquired from 35 consecutive pediatric patients with MS and 16 sex- and age-matched healthy controls. Patients with abnormalities in ≥ 2 neuropsychological tests were classified as cognitively impaired. The regional distribution of white matter (WM) and gray matter (GM) damage was assessed using voxel-wise analyses. Default mode network (DMN) RS functional connectivity (FC) was also measured.

Results: Sixteen patients (45%) were classified as cognitively impaired. Compared to cognitively preserved (CP) patients, cognitively impaired patients with MS had higher occurrence of T2 lesions as well as more severe damage to the WM and GM, as measured by atrophy and diffusivity abnormalities, in the posterior regions of the parietal lobes close to the midline (precuneus, posterior cingulum, and corpus callosum). Compared to the other study groups, they also showed reduced RS FC of the precuneus, whereas CP patients experienced an increased RS FC of the anterior cingulate cortex. A multivariable model identified diffusivity abnormalities of the cingulum and corpus callosum and RS FC of the precuneus as the covariates more strongly associated with cognitive impairment (C-index = 0.99).

Conclusions: In pediatric patients with MS, cognitive dysfunction is associated with structural and functional abnormalities of the posterior core regions of the DMN. WM structural abnormalities co-occurring at this level are likely to be the substrate of such modifications. *Neurology*® 2014;82:1314-1321

GLOSSARY

ACC = anterior cingulate cortex; **BNBC** = Brief Neuropsychological Battery for Children; **CC** = corpus callosum; **CP** = cognitively preserved; **DMN** = default mode network; **DT** = diffusion tensor; **EDSS** = Expanded Disability Status Scale; **EPI** = echoplanar imaging; **FA** = fractional anisotropy; **FC** = functional connectivity; **FFE** = fast field echo; **GM** = gray matter; **HC** = healthy controls; **ICV** = intracranial volume; **ILF** = inferior longitudinal fasciculus; **L** = left; **LPM** = lesion probability map; **LV** = lesion volume; **MD** = mean diffusivity; **MNI** = Montreal Neurological Institute; **MS** = multiple sclerosis; **MTG** = middle temporal gyrus; **R** = right; **RD** = radial diffusivity; **RF** = random forest; **RRMS** = relapsing-remitting multiple sclerosis; **RS** = resting state; **SE** = spin echo; **SLF** = superior longitudinal fasciculus; **SPART** = Spatial Recall Test; **SRT** = Selective Reminding Test; **TBSS** = Tract-Based Spatial Statistics; **TMT** = Trail Making Test; **WM** = white matter.

Up to 10% of patients with multiple sclerosis (MS) experience their first attack during childhood.¹ The transition to a secondary progressive course and accumulation of permanent disability is more gradual and takes longer in these patients than in those with adult-onset MS.² The relatively limited disease-related damage³ with preservation of structural^{4,5} and functional⁶ integrity of the brain gray matter (GM) has been considered among the factors responsible for the course of pediatric MS.

A large proportion of pediatric patients with MS experience cognitive deficits, with a prominent involvement of linguistic abilities in addition to memory, attention, and executive

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functions.⁷ The factors associated with cognitive impairment remain largely unexplored. More severe atrophy of the thalamus and corpus callosum (CC) has been found in cognitively impaired than in cognitively preserved (CP) pediatric patients with MS.⁸ Executive deficits have been correlated with atrophy of the thalamus and frontal lobes,⁹ while reduced cognitive speed¹⁰ and math performance¹¹ were correlated with CC damage.

To improve our understanding of the mechanisms responsible for the presence and severity of cognitive impairment in pediatric patients with MS, we applied a voxel-wise analysis of advanced structural MRI techniques to determine the patterns of regional involvement of the white matter (WM) and GM according to their cognitive profile. We also quantified resting-state (RS) functional connectivity (FC) of the default mode network (DMN), since this is the most robust network identified by RS studies of the human brain, and its disruption has been associated with cognitive deficits in elderly individuals¹² and adult patients with MS.^{13–15}

METHODS Patients. We studied 35 consecutive right-handed pediatric patients with relapsing-remitting MS (RRMS) referred to specialized MS centers and 16 sex- and age-matched right-handed healthy controls (HC) (table 1). Patients with acute disseminated encephalomyelitis were excluded according to published operational criteria.¹⁶ Patients had to be relapse- and steroid-free for at least 3 months. Exclusion criteria were concomitant therapy with antidepressants, psychoactive drugs, or a history of major medical, neurologic, or psychiatric disorders.

Standard protocol approvals, registrations, and patient consents. *Ethics committee approval.* Approval was received from the local ethical standards committee on human experimentation, and written informed consent was obtained from all subjects' parents prior to study enrollment.

Clinical and neuropsychological evaluation. All patients underwent a neurologic examination with rating of the Expanded Disability Status Scale (EDSS), and a neuropsychological assessment using the Brief Neuropsychological Battery for Children (BNBC), which has been standardized and validated for Italian pediatric patients with MS.¹⁷ Both assessments were performed within 3 days of the MRI study by an experienced observer blinded to the clinical and MRI results. The BNBC includes the following: (1) global cognitive functioning with IQ; (2) verbal learning and delayed recall with the Selective Reminding Test (SRT, SRT-Delayed); (3) visuospatial learning and delayed recall with the Spatial Recall Test (SPART, SPART-Delayed); (4) sustained attention and concentration with the Symbol Digit Modalities Test and the Trail Making Test (TMT-A and TMT-B); (5) abstract reasoning through the Modified Card Sorting Test; (6) expressive language through a Semantic and Phonemic verbal fluency test and an Oral Denomination test; and (7) receptive language using the Token Test, the Indication of Pictures from the Neuropsychological Examination for Aphasia, and the Phrase Comprehension test from the Battery for the Analysis of Aphasic Deficits. The 5th or 95th percentile of the corrected scores of the normative data were used as the cutoff for determining failure at a given test. Patients with an abnormal performance in ≥ 2 tests were classified as cognitively impaired.¹⁷

MRI acquisition. The e-Methods on the *Neurology*[®] Web site at Neurology.org provide a detailed description of the MRI acquisition and analysis protocol. Using a 3.0-T scanner, the following brain sequences were acquired, in the following order: T2*-weighted single-shot echoplanar imaging (EPI) sequence for RS fMRI; dual-echo turbo spin echo (SE); 3D T1-weighted fast field echo (FFE); and pulsed-gradient SE EPI with diffusion gradients applied in 35 noncollinear directions. The total acquisition duration was around 35 minutes.

MRI postprocessing and statistical analysis. MRI analyses were performed by an experienced observer blinded to the clinical and neuropsychological results. T2 lesion volumes (LV) were

Table 1 Main demographic, clinical, and conventional MRI characteristics of the subjects enrolled in the study

	Pediatric healthy controls	Pediatric patients with RRMS		
		All	Cognitively preserved	Cognitively impaired
Number of subjects	16	35	19	16
Girls/boys	9/7	21/14	13/6	9/7
Mean (range) age, y	14.3 (8–18)	15.3 (7–18)	15.4 (11–18)	15.2 (7–18)
Mean (SD) education, y	9.2 (4.0)	8.9 (2.3)	8.9 (2.3)	8.9 (2.3)
Median (range) EDSS score	—	1.5 (0–3.5)	1.5 (0–3.0)	1.5 (0–3.5)
Mean (range) disease duration, y	—	2.1 (0.2–8.1)	1.7 (0.3–5.1)	2.8 (0.2–8.1)
Therapy: none/IFN- β 1a/glatiramer acetate/natalizumab/mitoxantrone	—	6/19/4/5/1	4/10/3/2/0	2/9/1/3/1
Mean (SD) T2 LV, mL	—	5.4 (6.9)	3.5 (1.8)	7.7 (9.8)
Mean (SD) T1 LV, mL	—	3.4 (5.2)	1.9 (5.2)	5.2 (7.3)
Mean (SD) ICV, mL	1,450 (108)	1,392 (113)	1,379 (113)	1,403 (115)

Abbreviations: EDSS = Expanded Disability Status Scale; ICV = intracranial volume; IFN- β = interferon- β ; LV = lesion volume; RRMS = relapsing-remitting multiple sclerosis.

quantified using a local thresholding segmentation technique (Jim 5, Xinapse Systems Ltd., Northants, UK). T1 hypointense lesions were identified and segmented on the 3D FFE images, which were previously coregistered and resliced to match the T2-weighted scans.

Analysis of structural regional WM and GM damage. The e-Methods provides a comprehensive methodologic description of the analysis used to assess structural abnormalities of the GM and WM.

Lesion probability maps (LPMs) were produced and compared between cognitively impaired and CP patients (2-sample *t* test, SPM8).

Voxel-based morphometry was performed using SPM8 software. Between-group comparisons of GM and WM maps were assessed using analyses of covariance, including age, sex, and intracranial volume (ICV) as covariates. A conjunction analysis was run to identify atrophied areas in cognitively impaired patients vs CP patients and HC. A linear regression analysis was used to investigate the correlations between areas of regional atrophy associated with cognitive impairment vs clinical variables, neuropsychological scores, and other MRI variables (T2 and T1 LV).

Tract-Based Spatial Statistics (TBSS) analysis¹⁸ was used for voxel-wise analysis of whole brain WM diffusion tensor (DT) MRI measures. Voxel-wise differences in fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity, and radial diffusivity (RD) values between pediatric patients and controls as well as between cognitively impaired and CP patients were tested using a permutation-based inference for nonparametric statistical thresholding (“randomize” program, FSL)¹⁹ and 2-sample *t* tests, adjusting for age and T2 lesion maps. A nonparametric statistical thresholding was also used to assess the correlations between DT MRI metrics identified by the previous analysis and clinical and neuropsychological variables.

DMN RS FC analysis. A comprehensive methodologic description of the fMRI analyses is provided in the e-Methods. RS fMRI data were preprocessed using SPM8. An independent component analysis was used to decompose RS fMRI data into spatially independent maps and time courses (GIFT software).²⁰ The DMN was identified through a voxel-wise correlation with the DMN template supplied in GIFT.²¹ Between-group comparisons of RS FC were tested using factorial models, which were explicitly masked with the binarized DMN mask extracted from each one-sample *t* test using Marsbar.²² Correlations between DMN RS FC abnormalities vs clinical variables, neuropsychological scores, and other MRI variables were assessed using linear regression models.

Multimodal analysis. To integrate structural and RS functional MRI measures, multimodal prediction models were built to define which of the measures significantly different between groups predicted cognitive impairment in patients. To do this, a random forest (RF) approach (see e-Methods)²³ was used to rank the MRI variables according to their importance (ability to predict the outcome). Thereafter, for each outcome, a multivariable logistic predictive model was built, using only the most important variables detected by the RF analyses. The final predictive model was chosen according to the minimum Akaike Information Criterion. The discriminatory power was assessed by computing C-statistics.

RESULTS Clinical, neuropsychological, and conventional MRI assessment.

Age ($p = 0.24$) and sex ($p = 0.32$) did not differ between pediatric HC and patients with MS. Sixteen pediatric patients with MS (45%) were classified as cognitively impaired. Age ($p = 0.2$), disease

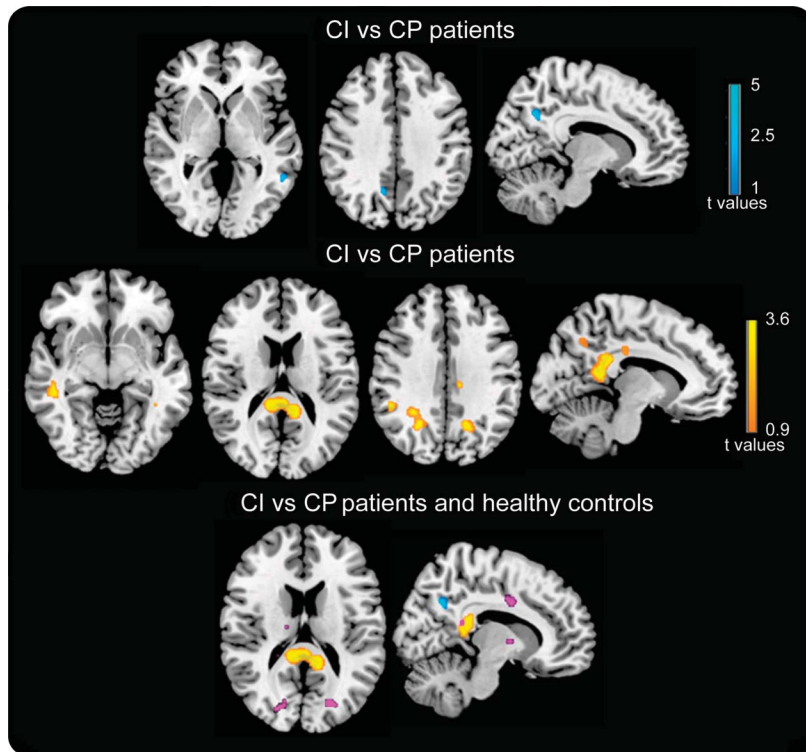
duration ($p = 0.1$), EDSS score ($p = 0.8$), T2 LV ($p = 0.1$), T1 LV ($p = 0.09$), and ICV ($p = 0.5$) did not differ between cognitively impaired and CP patients with MS. The median number of abnormal neuropsychological tests was 0 (range = 0–1, where 0 reflects no impairment) in CP patients and 3 (range = 2–9) in cognitively impaired patients. Table e-1 summarizes the performance on individual neuropsychological tests by pediatric patients with MS. Ten (31%) patients showed a low IQ²⁴ (range 70–90), including 5 (28%) CP and 5 (36%) cognitively impaired patients. The cognitive domains most frequently involved were spatial and verbal memory (17.6% of all pediatric patients with MS, 1% of CP, 37.8% of cognitively impaired patients with MS), language abilities (11.5% of all pediatric patients with MS, 6.6% of CP, 17.8% of cognitively impaired patients), and attention (8% of all pediatric patients with MS, 1% of CP, 15.3% of cognitively impaired patients).

WM LPMs. Compared to CP patients, cognitively impaired patients had an increased probability of harboring lesions in the right (R) thalamus, middle and posterior (close to the R precuneus) CC, and bilateral parieto-occipital WM ($p < 0.001$, uncorrected) (figure 1).

GM atrophy. Table e-2 summarizes regions showing significant differences of GM volume between patients with MS and HC as well as between patient subgroups ($p < 0.001$, uncorrected). Compared to CP patients, cognitively impaired patients had atrophy of the R precuneus and left (L) middle temporal gyrus (MTG) (figure 1). No GM area was more atrophied in CP vs cognitively impaired patients. The conjunction analysis showed that, compared to HC and CP patients, cognitively impaired patients had atrophy of the R precuneus (Montreal Neurological Institute [MNI] coordinates: 11, –59, 36) (figure 1).

WM atrophy. Table e-3 summarizes areas showing significant differences of WM volume between groups ($p < 0.001$, uncorrected). Compared to HC, pediatric patients with MS had atrophy of the R superior longitudinal fasciculus (SLF) and L inferior longitudinal fasciculus (ILF). Compared to HC, cognitively impaired patients had WM atrophy of the splenium of the CC, R SLF, WM close to L precuneus, and L ILF. No area of WM atrophy was identified in CP patients vs HC. Compared to CP patients, cognitively impaired patients had WM atrophy of the splenium of the CC, posterior cingulum, L parahippocampus, WM close to the precuneus, bilaterally, and bilateral SLF (figure 1). No area of WM atrophy was detected in CP vs cognitively impaired patients. The conjunction analysis showed that compared to HC and CP patients, cognitively impaired patients had WM atrophy

Figure 1 Structural regional damage in pediatric multiple sclerosis



Brain regions show significant gray matter (GM) (cyan color scale) (top row) and white matter (WM) (yellow color scale) (middle row) atrophy and higher frequency of T2 lesions (pink) (bottom row) in cognitively impaired (CI) vs cognitively preserved (CP) patients with pediatric multiple sclerosis, superimposed on a high-resolution T1-weighted template ($p < 0.001$ uncorrected, cluster extent >5 voxels). In the bottom row, the results of the conjunction analysis showing atrophied GM and WM areas in CI vs CP and healthy controls are shown. Images are presented in radiologic convention.

of the splenium of the CC, posterior cingulum, and WM close to the L precuneus (figure 1).

TBSS analysis. Compared to HC, pediatric patients with MS had a distributed pattern of decreased FA in the WM, as well as an increased RD of the splenium of the CC and posterior parieto-occipital WM. No MD or axial diffusivity abnormalities were detected (figure 2). When the 2 groups of pediatric patients with MS were analyzed separately, no DT-MRI abnormalities were detected in CP patients vs HC, while cognitively impaired patients had a diffuse pattern of decreased FA and increased RD mainly involving the CC, cingulum, fornix, and parieto-occipital WM (figure 2). Compared to CP patients, cognitively impaired patients had decreased FA and increased RD of the posterior CC and cingulum as well as decreased FA of the bilateral parieto-occipital WM (figure 2).

DMN FC analysis. Figure 3 shows the independent component with the highest squared spatial correlation ($R^2 = 0.34$, corresponding to a plain correlation coefficient of $r = 0.58$) with the DMN template.

Compared to HC, pediatric patients with MS had decreased FC of the posterior regions of the DMN (R precuneus, MNI coordinates: 24, -69, 33; $t = 3.76$, $k = 16$; and R angular gyrus, MNI coordinates: 42, -58, 42; $t = 4.76$, $k = 24$). CP patients vs HC had decreased RS FC of the R angular gyrus (MNI coordinates: 42, -58, 38; $t = 4.7$, $k = 11$), whereas cognitively impaired patients vs both HC and CP patients had decreased RS FC of the R precuneus (MNI coordinates: 24, -67, 38; $t = 3$, $k = 13$). Compared to both HC and cognitively impaired patients, CP patients experienced an increased RS FC of the R anterior cingulate cortex (ACC) (MNI coordinates: 3, 11, 46; $t = 3.3$, $k = 5$) (figure 3). No clusters of significantly increased RS FC were found in cognitively impaired vs CP patients or HC.

Analysis of correlations. Table 2 summarizes correlations ($p < 0.001$, uncorrected) between measures of regional structural and functional damage in pediatric patients with MS vs clinical, neuropsychological, and other MRI variables.

Significant correlations were found between the patterns of regional atrophy vs T2 LV, T1 LV, and global neuropsychological performance, as well as performance in individual neuropsychological tests.

Significant correlations were also found between abnormalities of RS FC vs global neuropsychological performance as well as performance on individual neuropsychological tests.

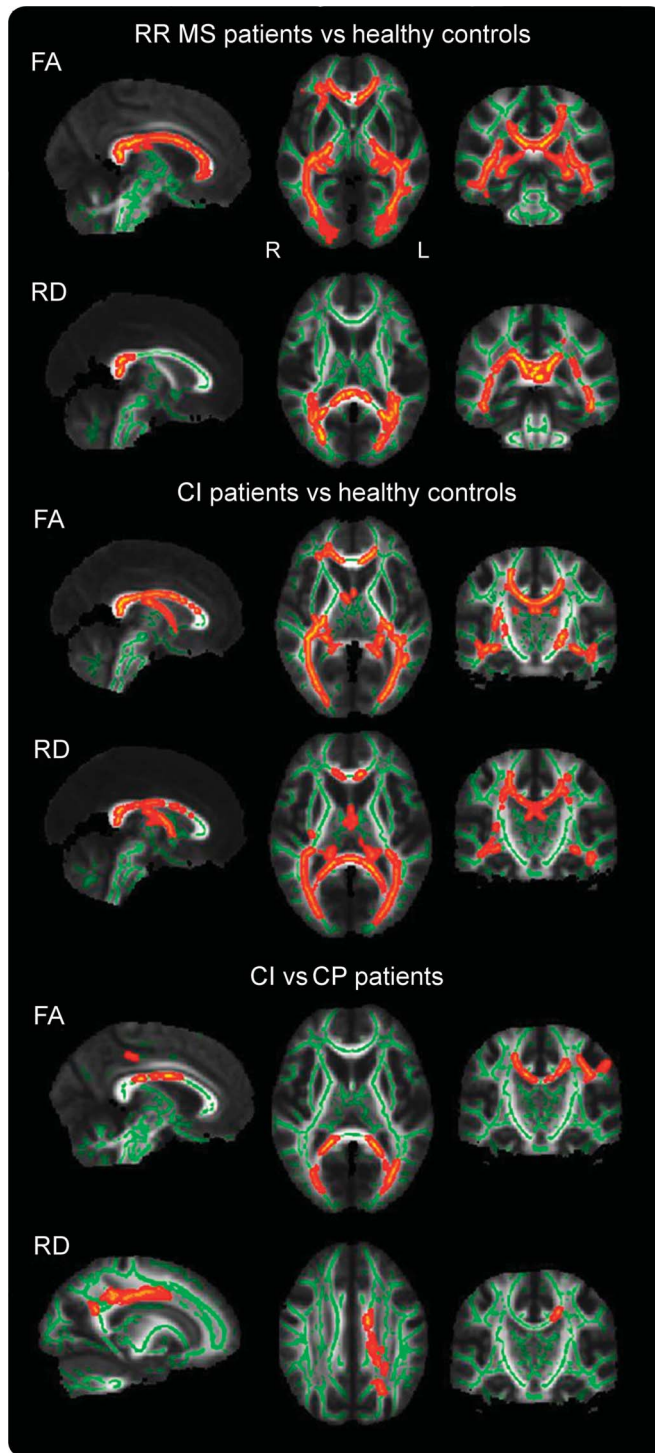
No correlation was found between regional structural or functional abnormalities and either disease duration or EDSS.

Multimodal analysis. The multivariable model identified cingulum FA, CC MD, CC RD, and R precuneus RS FC (in this order of ranking) as covariates associated with cognitive impairment (C index = 0.99).

DISCUSSION In line with previous reports,^{7,17} which applied similar neuropsychological tests and criteria to classify patients' cognitive status, we found that a relatively high percentage of pediatric patients with MS experience cognitive impairment, with a prominent involvement of spatial and verbal memory abilities, language, attention, and concentration. All of this indicates that our sample is representative of the more general population of patients with pediatric MS.

Using voxel-wise methods, we determined the relationship between the regional distribution of damage to the WM and GM and cognitive impairment in these patients. This analysis showed that the presence and severity of cognitive impairment was associated with structural damage to a set of brain regions that form the posterior node of the DMN. These regions had a high probability of harboring

Figure 2 White matter diffusivity abnormalities in pediatric multiple sclerosis



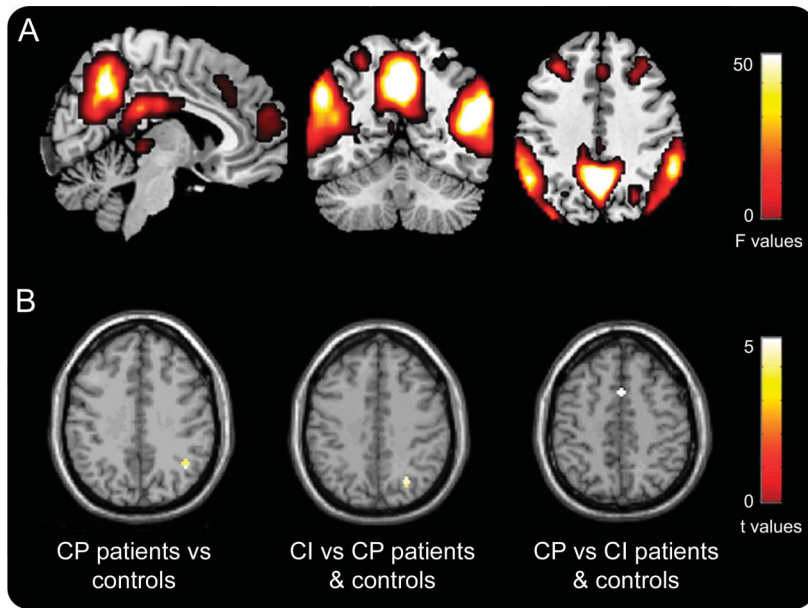
Illustrative images show in red-yellow the clusters of voxels with significantly decreased fractional anisotropy (FA) and increased radial diffusivity (RD) values among the different study groups ($p < 0.01$, family-wise error corrected). The significant regions have been thickened for better visibility. The white matter skeleton, thresholded at $FA > 0.2$, is represented in green. The background image is the mean FA map derived from all subjects. Images are presented in radiologic convention. CI = cognitively impaired; CP = cognitively preserved; RRMS = relapsing-remitting multiple sclerosis.

focal T2 lesions, loss of WM and GM, as well as FA and RD abnormalities. The pattern of structural abnormalities associated with cognitive impairment in pediatric patients with RRMS differs significantly

from that described in adult patients with RRMS, in whom GM loss from the frontal, parietal, and temporal lobes, only marginally linked to the presence of focal lesions, has been reported consistently.^{25,26} A distributed pattern of WM FA abnormalities has also been detected in adult patients with MS with cognitive impairment.²⁷ The colocalization of T2 lesions, GM and WM atrophy, and DT MRI abnormalities in brain posterior regions of pediatric patients with MS suggests that degeneration of axons passing through focal lesions and areas of demyelination (as indicated by decreased FA and increased RD)²⁸ may lead to deafferentation and atrophy, pointing to a pivotal role of WM damage (lesions and microstructural abnormalities) in the pathogenesis of cognitive impairment in these patients. This hypothesis is also supported by the results of the RF analysis, which identified FA decrease of the cingulum as the best predictor of cognitive impairment. In contrast to what has been found in adult patients with MS,²⁹ focal GM lesions are likely not to have influenced our results, since they are found in less than 10% of pediatric patients with MS.⁵

In agreement with previous studies,^{30,31} the analysis of regional GM atrophy confirmed that thalamic atrophy is typically seen in pediatric MS and that it is strongly correlated with the extent of WM lesions, but not with disease duration.^{30,31} GM atrophy in our patients was not limited to the thalamus, but extended diffusely to several cortical and subcortical regions. Cognitive impairment in these patients was associated with more pronounced atrophy of the R precuneus and L MTG. Neuroimaging findings in healthy subjects suggest a central role of the precuneus in a wide spectrum of highly integrated tasks, including visuospatial imagery, episodic memory, and self-processing operations.³² Recently, global cognitive dysfunction has been associated with reduced thalamic volume in pediatric patients with MS,⁸ whereas word list learning has been correlated with hippocampal volume.³³ Differences in the analysis methods, as well as in clinical and neuropsychological characteristics of the patients enrolled in these studies, may help to explain discrepancies between our results and previous studies.^{8,33} Surprisingly, patients' global cognitive performance as well as their performance on executive tests were not associated with atrophy of frontal lobe regions. Different features of cognitive impairment in adult and pediatric patients (with prominent effects on linguistic abilities in children)^{7,17} as well as a different regional vulnerability to damage due to the variability of maturation and myelination of CNS structures might account for the discrepancies between pediatric and adult patients with MS. Indeed, age-related structural changes in GM and WM volumes and diffusivity characteristics,

Figure 3 Default mode network abnormalities in pediatric multiple sclerosis



Spatial pattern of the independent component shows the highest squared spatial correlation with the template of the default mode network (DMN) (A). Spatial pattern of the within-group differences of resting-state (RS) functional connectivity (FC) of the DMN among the study groups (B): (1) decreased RS FC of the right angular gyrus in cognitively preserved (CP) patients with multiple sclerosis (MS) vs healthy controls; (2) decreased RS FC of the right precuneus in cognitively impaired (CI) patients with MS vs both healthy controls and CP patients; (3) increased RS FC in the anterior cingulum in CP patients vs healthy controls and CI patients.

with a caudo-rostral pattern of myelination, have been demonstrated consistently through childhood and adolescence by several studies.^{34,35} Maturation of the frontal lobe WM during the second decade of life has been suggested as a possible mechanism that confers a sort of protection from MS-related damage.¹⁰ The notion of a higher susceptibility to damage in specific brain regions of pediatric patients with MS is also supported by the analysis of the regional distribution of damage to the WM, which showed atrophy and diffusivity abnormalities in the posterior CC, cingulum, and parieto-occipital WM in cognitively impaired patients.

The analysis of RS FC of the DMN disclosed that functional abnormalities of the posterior regions of the network (in particular the precuneus) paralleled abnormalities detected by structural MRI in pediatric patients with cognitive impairment. On the other hand, CP patients experienced an increased RS FC of the ACC. The DMN is a medial cortical network involving several brain regions structurally connected throughout 2 large intrahemispheric and interhemispheric WM tracts (the CC and cingulum).^{36,37} Also, for the analysis of RS FC, the pattern of abnormalities we found in pediatric patients with MS with cognitive impairment differs from that described in adult patients, in whom a consistent reduced RS FC of the anterior regions of the DMN^{13,15} and an enhanced RS FC of the posterior ones have been described.^{13,38} As previously argued for the regional distribution of structural abnormalities, maturation effects might influence a different functional reorganization in adult vs pediatric patients with MS. Indeed, the long-range connections between the posterior cingulate cortex and the anterior prefrontal cortex have been shown to mature with age (being immature in 7-year-old children),^{39,40} and to be associated with the development of cognitive abilities.³⁴ Importantly, the multimodal prediction model that integrated structural and functional MRI measures showed that cognitive impairment was highly associated with the extent of structural damage and reduced RS FC of the posterior node of the DMN. Localized structural damage to this node was the main factor associated with cognitive impairment. Therefore, it is tempting to speculate that abnormalities of RS FC might be secondary to the occurrence of WM damage in the same region of pediatric patients with MS.

Our study is not without limitations. First, it is cross-sectional and therefore does not allow testing for cause-effect relationships between structural and functional abnormalities. Second, the number of patients enrolled is relatively small, particularly when considering the 2 groups of patients separately. Third,

Table 2 Correlations (r values) between measures of regional structural and functional damage in pediatric patients with multiple sclerosis vs clinical, neuropsychological, and other MRI variables ($p < 0.001$ uncorrected)

	T2 LV	T1 LV	Number of abnormal neuropsychological tests	TMT-B	SRT-LTS	SPART	SPART-D
Left thalamus volume	-0.65	-0.70	—	—	—	—	—
Right precuneus volume	—	—	-0.49	—	—	—	—
White matter close to the left precuneus volume	—	—	-0.51	-0.47	0.49	0.51	0.50
Splenium of the CC volume	-0.56	-0.56	—	-0.42	0.50	—	0.54
Right precuneus resting-state functional connectivity	—	—	-0.65	—	—	—	—
Right angular gyrus resting-state functional connectivity	—	—	—	0.63	—	—	—

Abbreviations: CC = corpus callosum; LV = lesion volume; SPART = 10/36 Spatial Recall Test; SPART-D = 10/36 Spatial Recall Test-Delayed; SRT-LTS = Selective Reminding Test-Long-Term Storage; TMT = Trail Making Test.

disease duration of the cohort was relatively short and their EDSS score relatively low, thus potentially influencing our correlation analyses. Finally, we did not perform a neuropsychological evaluation (including assessment of global IQ) in controls.

AUTHOR CONTRIBUTIONS

Maria A. Rocca contributed to drafting/revising the manuscript, statistical analysis, and obtaining funding. Martina Absinta contributed to MRI data postprocessing and statistical analysis. Maria Pia Amato contributed to patients' enrollment and analysis of the data. Lucia Moiola contributed to patients' enrollment and analysis of the data. Angelo Ghezzi contributed to patients' enrollment and analysis of the data. Pierangelo Veggiotti contributed to patients' enrollment and analysis of the data. Ruggero Capra contributed to patients' enrollment and analysis of the data. Emilio Portaccio contributed to patients' neuropsychological assessment and analysis of the data. Agnese Fiorino contributed to patients' neuropsychological assessment and analysis of the data. Lorena Pippolo contributed to patients' neuropsychological assessment and analysis of the data. Maria Carmela Pera contributed to patients' neuropsychological assessment and analysis of the data. Mark A. Horsfield contributed to drafting/revising the manuscript and interpretation of the data. Andrea Falini contributed to MRI acquisitions and analysis of the data. Giancarlo Comi contributed to the study concept. Massimo Filippi contributed to drafting/revising the manuscript, study concept, and analysis and interpretation of the data. He also acted as study supervisor. All authors approved the current version of the manuscript.

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