




RESEARCH ARTICLE

Preserved network functional connectivity underlies cognitive reserve in multiple sclerosis

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Abstract

Cognitive reserve is one's mental resilience or resistance to the effects of structural brain damage. Reserve effects are well established in people with multiple sclerosis (PwMS) and Alzheimer's disease, but the neural basis of this phenomenon is unclear. We aimed to investigate whether preservation of functional connectivity explains cognitive reserve. Seventy-four PwMS and 29 HCs underwent neuropsychological assessment and 3 T MRI. Structural damage measures included gray matter (GM) atrophy and network white matter (WM) tract disruption between pairs of GM regions. Resting-state functional connectivity was also assessed. PwMS exhibited significantly impaired cognitive processing speed ($t = 2.14$, $p = .037$) and visual/spatial memory ($t = 2.72$, $p = .008$), and had significantly greater variance in functional connectivity relative to HCs within relevant networks ($p < .001$, $p < .001$, $p = .016$). Higher premorbid verbal intelligence, a proxy for cognitive reserve, predicted relative preservation of functional connectivity despite accumulation of GM atrophy (standardized- $\beta = .301$, $p = .021$). Furthermore, preservation of functional connectivity attenuated the impact of structural network WM tract disruption on cognition ($\beta = -.513$, $p = .001$, for cognitive processing speed; $\beta = -.209$, $p = .066$, for visual/spatial memory). The data suggests that preserved functional connectivity explains cognitive reserve in PwMS, helping to maintain cognitive capacity despite structural damage.

KEYWORDS

cognition, disease, disconnection, gray matter, white matter, MRI, multiple sclerosis, cognitive reserve, network analysis, structural connectivity, functional connectivity

1 | INTRODUCTION

Cognitive impairment is common in people with multiple sclerosis (PwMS; Benedict & Zivadinov, 2011). However, despite accrual of

structural brain pathology in the white matter (WM) and gray matter (GM), cognition is unimpaired in some PwMS (Sumowski & Leavitt, 2013). This ability of individuals to cope with advancing brain pathology is known as cognitive reserve and is associated with lifetime

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intellectual enrichment, leisure activities, and physical activity (Stern, 2002). This phenomenon has been observed in a number of diseases, including Alzheimer's disease as well as in MS (Hindle, Martyr, & Clare, 2014; Kesler, Adams, Blasey, & Bigler, 2003; Modica et al., 2015; Sumowski et al., 2014). Nonetheless, the underlying physiological substrates of cognitive reserve are not fully elucidated.

Functional connectivity, measured with resting-state fMRI (rs-fMRI), is an excellent candidate for exploring the neural basis of cognitive reserve (Steffener & Stern, 2012). It correlates with cognitive function in PwMS and reflects the coordinated activation patterns between functionally connected GM regions (Hawellek, Hipp, Lewis, Corbetta, & Engel, 2011; Schoonheim et al., 2015). In addition, although increased structural damage correlates with greater aberrations in functional connectivity (Rocca et al., 2002), a substantial proportion of functional connectivity remains unexplained by currently available structural measures. More may therefore be learned about cognition and cognitive reserve by considering the interaction between structural network disruption and preservation of functional connectivity.

To investigate this potential neural basis of cognitive reserve, we used a two-stage approach. First, we sought to determine whether established proxies for cognitive reserve moderate the relationship between structural pathology and preservation of functional connectivity. We hypothesized that individuals with higher cognitive reserve would exhibit preserved functional connectivity despite comparable accumulation of GM atrophy. For this analysis, premorbid verbal intelligence was used as a proxy for cognitive reserve. Second, we aimed to determine whether relative preservation of functional connectivity helps explain the gap between structural damage and cognition. For this, we applied network-based measures to account for the network organization of the brain (Zalesky, Fornito, & Bullmore, 2010a) and the overlap between structural WM tract disruption and preservation of functional connectivity within networks associated with each cognitive domain. We hypothesized that the relationship between structural network damage and cognition would be attenuated for people with preserved functional connectivity. For a diagrammatic illustration of our hypotheses, see Figure 1.

2 | METHODS

2.1 | Subjects

We studied 74 PwMS who completed cognitive assessment and both functional and structural MRI as part of a case-control cardiovascular, environmental, and genetic (CEG) study (Kappus et al., 2015; Zivadinov et al., 2016). Disease course and disease duration were determined by clinical assessment. Twenty-nine age- and sex-matched HCs were also included.

Inclusion/exclusion criteria for PwMS in the study were (a) diagnosis of MS according to the 2010 McDonald criteria (Polman et al., 2011), (b) neurologic/physical examination within 30 days from the standardized MRI, (c) English language fluency, (d) able to provide informed consent to all procedures, (e) no substance dependence/abuse past or present, (f) no neurological/psychiatric diseases other than MS, (g) no

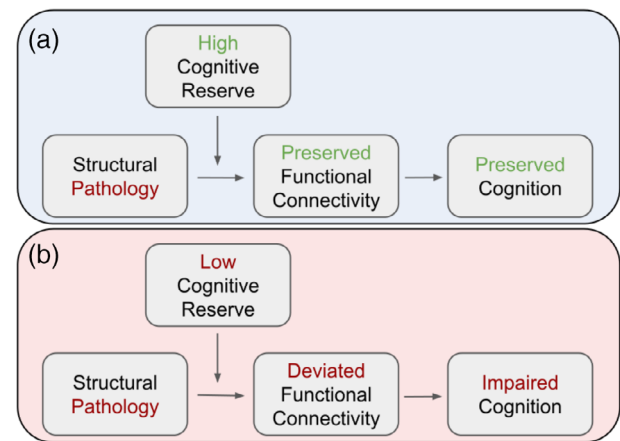


FIGURE 1 Cognitive reserve in PwMS. We hypothesize that PwMS with higher cognitive reserve (a) will exhibit preserved functional connectivity and cognition despite accumulation of structural damage. In contrast, for PwMS with low cognitive reserve (b), we propose that structural damage will be associated with greater deviations in functional connectivity and cognitive impairment. PwMS, people with multiple sclerosis [Color figure can be viewed at wileyonlinelibrary.com]

relapse/acute corticosteroid treatment within 1 month of testing, and (h) no motor or sensory defect that might interfere with cognitive test performance. The inclusion/exclusion of HCs followed the same criteria, with the exception of diagnosis of MS. The study protocol was approved by the University at Buffalo Institutional Ethics Review Board. All subjects provided written informed consent before participation.

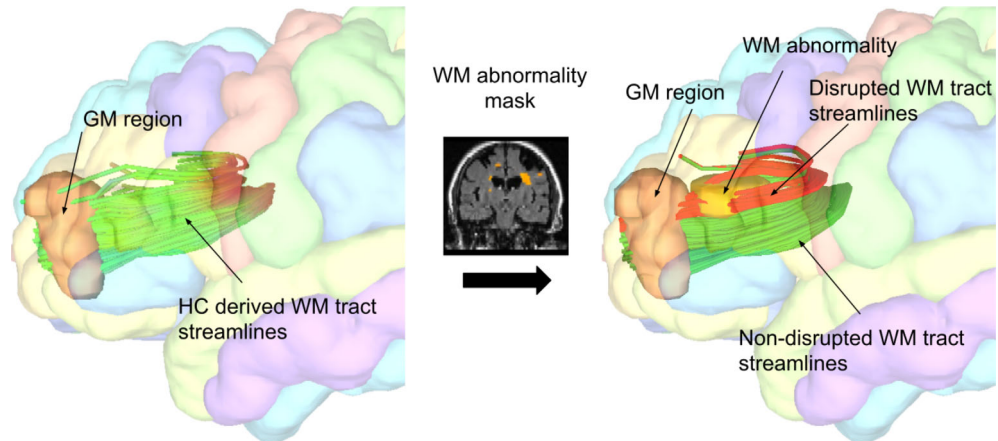
2.2 | Psychometric assessment

Cognitive testing was performed by research assistants under the supervision of a board-certified neuropsychologist (RHBB) blinded to other findings. Testing consisted of assessments recommended for the Brief International Cognitive Assessment for MS (BICAMS; Langdon et al., 2012; Benedict et al., 2012). Cognitive processing speed was assessed with the Symbol Digit Modalities Test (SDMT; Smith, 1982). Visual/spatial memory was assessed with the Brief Visuospatial Memory Test Revised (BVMTR; Benedict, 1997). Verbal memory was assessed with the California Verbal Learning Test II (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000). The relevant subscale for the BVMTR and CVLT-II in our analyses, as recommended for BICAMS, was total learning. Premorbid verbal intelligence, an established proxy for cognitive reserve in MS, was assessed using the North American Adult Reading Test (NAART; Benedict, Morrow, & Guttman, 2010; Blair & Spreen, 1989).

2.3 | MR image acquisition

MRI data were collected from a 3T GE scanner. Imaging included a 3D T1-weighted (IR-FSPGR, repetition time (TR) 5.9 ms, echo time (TE) 2.8 ms, inversion time (TI) 900 ms, flip angle (FA) 10°, field-of-view (FOV) 25.6 × 19.2 cm² [256 × 256 matrix with phase FOV 0.75], 1 × 1 mm², 180 slices of 1 mm) and a 2D T2-FLAIR scan (TR 8,500 ms, TE 120 ms, TI 2100 ms, FA 90°, echo train length

FIGURE 2 The network modification tool: A WM abnormality mask is registered to the Montreal neurological institute standard space. Then, an in-software database of HC tractogram is referenced to determine the proportion of streamlines in a WM tract bundle, connecting a pair of GM regions, which are disrupted by WM abnormalities. GM, gray matter; HC, healthy control; WM, white matter [Color figure can be viewed at wileyonlinelibrary.com]



24, FOV $25.6 \times 19.2 \text{ cm}^2$ (256×256 matrix with phase FOV 0.75), $1 \times 1 \text{ mm}^2$, 48 slices of 3 mm without gap). For resting-state fMRI, 240 volumes of gradient-echo echo-planar images were acquired (TR 2,500 ms, TE 35 ms, FA 90°), $3.75 \times 3.75 \times 4.00\text{-mm}$ voxels, and 4 mm slice thickness. During the scan, subjects were instructed to lie awake with their eyes closed and to think of nothing in particular.

2.4 | MR image processing, structural

N4 bias field correction was applied to all T1w and T2-FLAIR images. Images were pre-processed using a lesion-filling tool to minimize the impact of T1 hypointensities (Gelineau-Morel et al., 2012). Then brain extraction and the SIENAX cross-sectional software tool was applied (version 2.6; Smith et al., 2002) to obtain a global volumetric measure of GM volume (GMV), WM volume (WMV), and whole-brain volume (WBV), normalized for head size. Then FreeSurfer processing suite (Version 5.3) was applied to generate structural parcellation/segmentation maps of the 86 brain regions in the FreeSurfer atlas (<http://surfer.nmr.mgh.harvard.edu/>; Dale, Fischl, & Sereno, 1999). For quality control, manual corrections (e.g., brain extraction, control points, white matter edits) were applied when needed.

T2-FLAIR WM lesion masks and measures of T2 lesion volume (T2LV) were obtained using a semiautomated edge detection contouring/thresholding technique, described previously (Zivadinov et al., 2012). Using ANTs (Avants et al., 2011), the T2-FLAIR images were rigidly registered to the high-resolution T1 weighted images. Then, the high-resolution T1 weighted images were registered into the Montreal Neurological Institute (MNI) space nonlinearly. The same transforms were then applied to the corresponding T2-FLAIR WM lesion masks with nearest-neighbor interpolation.

To measure changes in structural connectivity caused by damage to WM tracts, the transformed WM lesion masks were processed with the Network Modification (NeMo) tool (Kuceyeski, Maruta, Relkin, & Raj, 2013). Our use of this approach has been previously described (Fuchs et al., 2018). In short, this tool infers changes to the structural connectivity network resulting from the WM lesion mask by referencing a within-software database of 73 healthy control tractograms. The proportion of WM tract disruption between each pair of GM regions is

calculated as the proportion of tract streamlines connecting those regions which pass through the given lesion mask and are therefore considered disrupted. This was done for all possible pairs of structurally connected GM regions in the 86 region FreeSurfer brain atlas (Dale et al., 1999). This resulted in the generation of 86×86 structural connectivity matrices which account for the proportion of WM tract disruption between each pair of connected GM regions. For additional explanation regarding our measure of WM tract disruption, see Figure 2.

2.5 | MR image processing, resting-state functional preprocessing

Resting-state fMRI data were processed with FSL tools (Smith et al., 2004). Preprocessing steps included removal of volumes 1–2, slice-time correction, motion correction, intensity normalization, high-pass temporal filtering (2,000 s), brain extraction, fieldmap unwarping, and 4 mm spatial smoothing. These data were nonlinearly registered to the corresponding T1w structural images using ANTs (Avants et al., 2011). Independent component analysis, hand-classification, and removal of noise components were completed using FSL MELODIC according to recently published guidelines (Griffanti et al., 2017). Although this method of denoising requires considerable additional labor, we chose this option in an effort to increase the fidelity of our data, excluding noise components which are not removed by more automated methods (e.g., MRI-related artifacts and physiological noise). Mean CSF signal, mean WM signal, and motion parameters were regressed out of the data.

2.6 | MR image processing, preservation of functional connectivity

Next, we sought to produce a summary measure of preservation of functional connectivity for each MS subject. Though conventional summary measures are common for structural pathology (e.g., GM atrophy) such measures are less common for functional connectivity. However, a previously employed summary measure relating to mean deviations in functional connectivity relative to HCs has been applied with moderate success in predicting cognitive function in PwMS

(Meijer et al., 2018). We followed a similar process to produce a summary metric of functional network preservation. First, 86×86 functional connectivity matrices were generated using Nilearn (Abraham et al., 2014). Specifically, we measured functional connectivity between pairs of GM regions using the inverse covariance function (akin to partial correlations) to control for global signal fluctuations. Then to measure preservation in functional connectivity for each MS subject, the mean and standard deviation of the functional connectivity matrix was generated from the age- and sex-matched HCs for comparison. Subsequently, an 86×86 z-score matrix was generated

for each MS subject, representing the change in functional connectivity relative to the HC group. Because the direction of deviations in functional connectivity can vary depending on the region-pair under investigation, the absolute value of the matrix was taken as the final value. Thus, lower values reflect greater preservation of functional connectivity within normal ranges (similar to HCs) and higher values reflect lower preservation (greater deviation from the HC distribution). Finally, we calculated the mean from these 86×86 matrices for each of the PwMS. For an illustration of these stages of processing, see Figure 3.

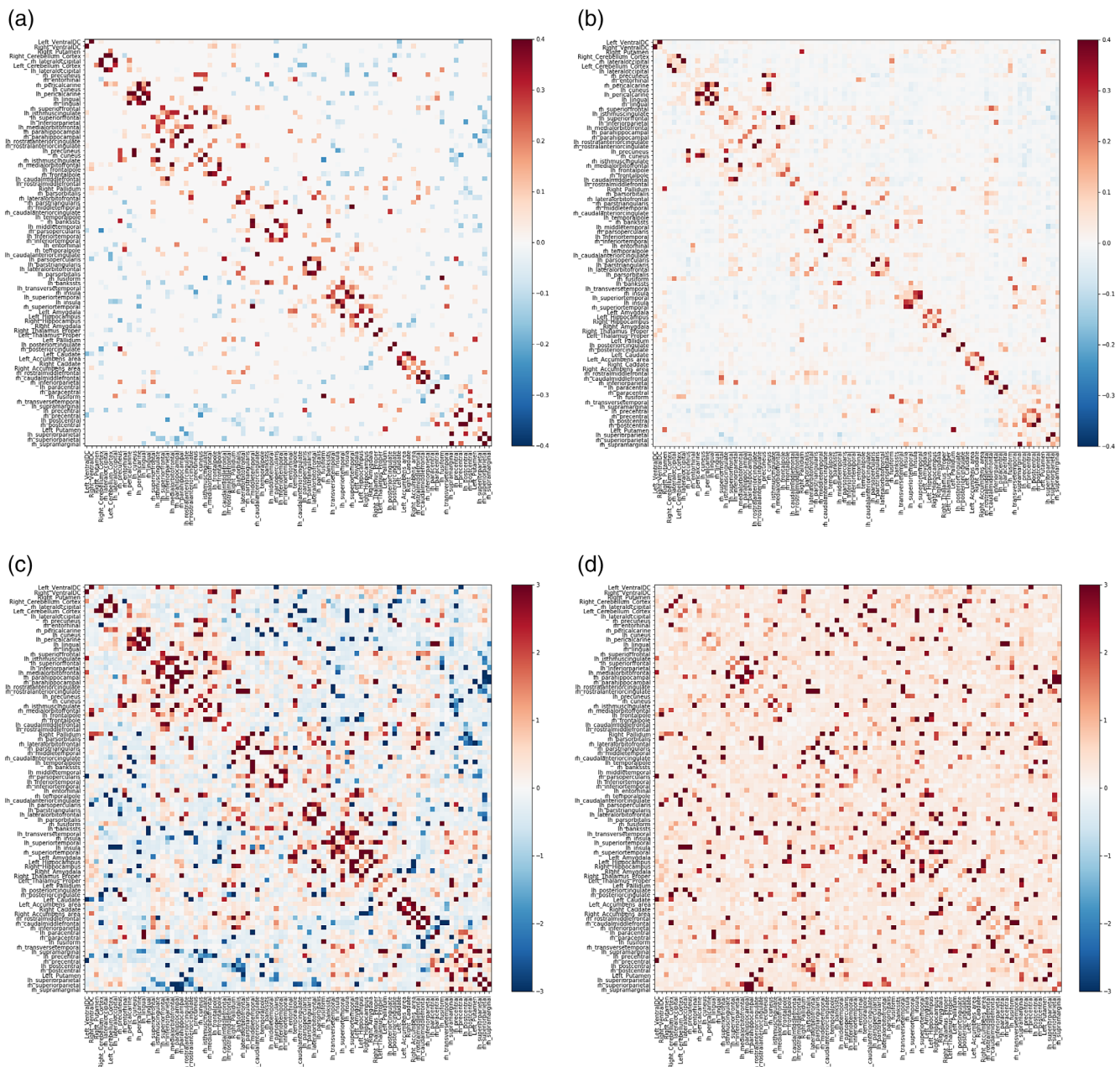


FIGURE 3 MR image processing, preservation of functional connectivity. First, we applied the Nilearn inverse covariance function to generate an 86×86 functional connectivity matrix for each MS subject (a). Then, we compared this with the average of the HCs (b) to generate a corresponding z-score matrix (c). We subsequently took the absolute value of this z-score matrix to measure the preservation of functional connectivity for each region-pair (d), where lower values reflect more preserved functional connectivity. HC, healthy control; MS, multiple sclerosis [Color figure can be viewed at wileyonlinelibrary.com]

2.7 | Statistical analysis

2.7.1 | Sample characteristics

To characterize our sample of PwMS, group comparisons were carried out relative to HCs. Fisher's exact test was applied to compare sex of MS and HCs. Independent samples *t*-tests were applied to compare both groups in terms of age, cognitive processing speed, visual/spatial memory, verbal memory, WBV, GMV, WMV, and T2LV (log-transformed).

2.7.2 | Cognitive reserve and preserved functional connectivity

Then, we sought to determine whether premorbid verbal intelligence (a proxy for cognitive reserve) moderates the relationship between structural damage and preservation of functional connectivity. To explore this, we applied a regression analysis predicting the mean preservation in functional connectivity for MS participants. Predictors in the regression included GMV, premorbid verbal intelligence, and the GMV-by-premorbid verbal intelligence interaction term. In this regression, a statistically significant interaction effect would imply that premorbid verbal intelligence, a proxy for cognitive reserve, moderates the relationship between GM atrophy and preservation of functional connectivity. This would suggest that cognitive reserve predicts preservation of normal functional connectivity, despite accumulation of GM atrophy.

2.7.3 | Preservation of functional connectivity and the structure–cognition relationship

Next, we aimed to investigate the structure–function relationship for each cognitive domain under investigation: cognitive processing speed, visual/spatial memory, and verbal memory. Our hypothesis was that preservation of functional connectivity attenuates the impact of structural network damage on cognition, similarly to the manner in which previously explored proxies of cognitive reserve moderate the structure–cognition relationship (Sumowski & Leavitt, 2013). For this, we aimed to consider each cognitive domain separately, as pertinent network damage may differ depending on the cognitive domain under investigation. This also allows us to consider the interaction between brain structure and brain function using matched spatial and neuroanatomical parameters within networks which are pertinent to each cognitive domain. As such, we first identified networks of connected GM regions whose localized WM tract disruption is significantly associated with each cognitive domain using network-based statistics (NBS; Zalesky, Fornito, & Bullmore, 2010a). Mean WM tract disruption (structural), functional connectivity, and preservation in functional connectivity (functional) within the networks identified by NBS were calculated in preparation for the subsequent steps of analysis. Variance of functional connectivity for the MS subjects within each of these networks was compared with the HCs using Bartlett's test. As well, mean preservation in functional connectivity within the networks was defined as either “preserved” or “nonpreserved” (deviated)

for each subject, depending on whether the mean preservation was below or above median.

As stated above, the step of identifying pertinent structural networks for each cognitive domain was accomplished using NBS, a method for controlling family-wise error while retaining power by accounting for network structure—and is similar to more conventional cluster statistics. Additional details can be found in a previous publication (Fuchs et al., 2018). To maximize statistical power for this step of network identification, a larger cohort of PwMS was used ($n = 137$), including individuals without fMRI. Structural connectivity/disconnectivity matrices were associated with cognitive processing speed, controlling for age, sex, and WBV. This analysis was then repeated for visual/spatial memory and verbal memory. Component size was determined according to the sum of individual edge scores with a test-statistic threshold of 3.0. Results were considered significant at an α -level of .05.

To determine whether the structure–cognition relationship is moderated by preservation of within-network functional connectivity, we applied multiple linear regression analyses. The regression model predicting cognitive processing speed contained the following covariates: Age, sex, WM tract disruption of the cognitive processing speed-associated networks, preservation of functional connectivity in the cognitive processing speed-associated networks, and the interaction term between network WM tract disruption and functional network preservation. The interaction term in this regression model was intended to address our hypothesis: Preservation of functional connectivity attenuates the impact of structural network damage on cognition. Here, a statistically significant interaction effect would suggest that individuals with preserved functional connectivity also exhibit relatively preserved cognition despite accumulation of within-network WM tract disruption. Separate but analogous multiple linear regression models were applied to predict visual/spatial memory performance and verbal memory respectively. All β coefficients reported are standardized, and R^2 values are adjusted for the number of covariates in the models. To maintain normality prior to final analysis, we applied \log_{10} transformations to the mean network WM tract disruption data.

2.7.4 | Supplemental processing and analyses

Because our in-house HC sample was small ($n = 29$) relative to the PwMS ($n = 74$) under investigation, we sought to replicate our findings using a larger age- and sex-matched HC sample ($n = 90$) for comparison of functional connectivity. This additional HC data was acquired from a publicly available database (http://fcon_1000.projects.nitrc.org; Biswal et al., 2010). For more information, see the Supplementary Section A. In addition, the regression analyses described in the sections above were repeated in progressive MS and relapsing–remitting MS participants separately. See Supplementary Section C for details and results. Finally, in order to account for structural damage outside of the networks under investigation, the final regressions predicting cognitive function were repeated with an added covariate for global lesion volume. See Supplementary Section D for details and results.

	MS (n = 74)	HC (n = 29)	p
Age in years (mean ± SD)	53.62 ± 10.92	49.85 ± 13.48	.144
Female/male; % female	56/18; 75.7	20/90; 69	.486
Years of education	15.02 ± 2.38	14.29 ± 2.45	.170
Disease duration (mean ± SD)	19.97 ± 10.44	–	–
Relapse remitting MS; %	48; 64.9	–	–
Primary progressive MS; %	2; 2.7	–	–
Secondary progressive MS; %	24; 32.4	–	–
EDSS (median; IQR)	3.0; 2.0–6.0	–	–
White; % white	70; 94.6	25; 86.2	–
Hispanic/Latino; %	1; 1.4	2; 6.9	–
Black/African-American; %	1; 1.4	1; 3.4	–
Asian; %	1; 1.4	1; 3.4	–

TABLE 1 Demographic & clinical characteristics of study participants

Abbreviations: EDSS, Expanded Disability Status Scale; HC, healthy control; IQR, interquartile range; MS, multiple sclerosis; SD, standard deviation.

TABLE 2 MRI and neuropsychological characteristics of study participants

	MS (n = 74)	HC (n = 29)	t	p
MRI				
Whole brain volume (ml; mean ± SD)	1,447.8 ± 88.4	1,522.6 ± 88.6	3.86	<.001
Gray matter volume (ml; mean ± SD)	735.3 ± 62.5	772.0 ± 55.4	2.77	.007
White matter volume (ml; mean ± SD)	712.5 ± 37.3	750.5 ± 45.7	4.36	<.001
T2 lesion volume (ml; mean ± SD)	14.9 ± 18.4	0.5 ± 1.2	4.18	<.001
Cognition				
Cognitive processing speed (mean ± SD)	50.9 ± 14.7	57.0 ± 12.4	2.14	.037
Visual/spatial memory (mean ± SD)	22.3 ± 8.6	26.5 ± 6.3	2.72	.008
Verbal memory (mean ± SD)	51.6 ± 12.6	54.7 ± 10.4	1.28	.207

Note. *p*-values related to significance of independent-sample *t*-test comparisons.

Abbreviations: HC, healthy control; MRI, magnetic resonance imaging; MS, multiple sclerosis; SD, standard deviation.

3 | RESULTS

3.1 | Sample characteristics

The PwMS participating in our study had a mean (SD) age and disease duration of 53.86 (11.35) and 21.07 (10.72) years, respectively. Median EDSS (IQR) for PwMS was 3.0 (2.0–6.0). The PwMS did not significantly differ from HCs by age or sex. Refer to Table 1 for additional demographic and clinical characteristics of study participants. In comparison with HCs, the PwMS exhibited significantly reduced GMV ($p = .007$) and increased T2LV ($p < .001$). Additionally, the PwMS exhibited significantly reduced cognitive processing speed ($p = .008$) and visual/spatial memory ($p = .037$), but not verbal memory ($p = .242$). Refer to Table 2 for additional information.

3.2 | Cognitive reserve and preserved functional connectivity

In the model predicting mean preservation of functional connectivity ($R^2 = .20$, $p = .001$), we observed a significant effect of GMV ($\beta = -.182$,

$p = .013$), premorbid verbal intelligence ($\beta = -.300$, $p = .014$), and the interaction term between GMV and premorbid verbal intelligence ($\beta = .301$, $p = .021$). Individuals with higher premorbid verbal intelligence, a proxy for cognitive reserve, exhibited relatively preserved functional connectivity despite accumulation of GM atrophy.

3.3 | Preservation of functional connectivity and the structure–cognition relationship

NBS analysis showed that impaired cognitive processing speed was characterized by a widespread pattern of WM tract disruption, including cortical frontoparietal pathways, cortical visual processing pathways, basal ganglia, thalamus, hypothalamus, and hippocampus (Figure 4). This pattern was observed in both the left ($p < .001$) and right ($p < .001$) hemispheres. Because many region-pairs were included in the cognitive processing speed-associated networks, details about these region-pairs as well as the strength of the relationship between each region-pair and cognitive processing speed are provided in supplemental materials (Table S1) rather than as an inline

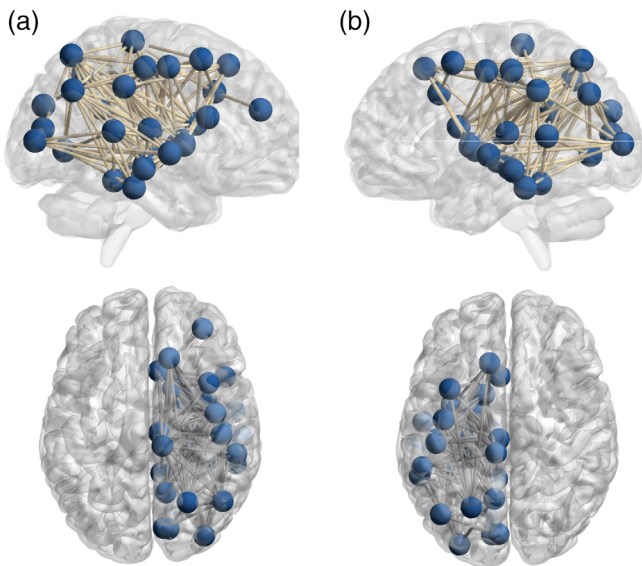


FIGURE 4 Cognitive processing speed-associated networks. A diffuse pattern of lesion-based WM tract disruption in the right (a) and left (b) hemisphere is significantly associated with slower cognitive processing speed in PwMS. Labels are omitted due to density of networks. For a list of GM region-pairs included in these networks, see Table S1. PwMS, people with multiple sclerosis; WM, white matter [Color figure can be viewed at wileyonlinelibrary.com]

table. The mean proportion of WM tract disruption within these networks were significantly greater than zero (39.0%, $t = 19.8$, $p < .001$).

Network analysis also showed that reduced visual/spatial memory was characterized by two focal patterns of WM tract disruption ($p = .029$, $p = .027$), predominantly in the right hemisphere (Figure 5). This included disruption of occipitally derived visual processing pathways in the right hemisphere, as well as in pathways connecting to hippocampus, thalamus, and basal ganglia. For details about region-pairs included in visual/spatial memory-associated networks as well as the strength of the relationship between each region pair and visual/spatial memory, see Table 3. As above, the mean proportion of WM tract disruption within these networks were significantly greater than zero (25.9%, $t = 16.9$, $p < .001$).

Finally, reduced verbal memory was significantly associated with patterns of WM tract disruption, mostly in the left hemisphere and including the hippocampus, cingulate, and thalamus. However, because the study sample was not, on average, significantly impaired on verbal memory relative to controls, these results are not included within the main text and this cognitive domain was not considered further. For additional details about these networks, see the Supplementary Section B, Supplementary Table II, and Supplementary Figure S1. Notably, a statistically significant difference was observed between MS and HCs in the variance of functional connectivity observed within each of the aforementioned networks (cognitive

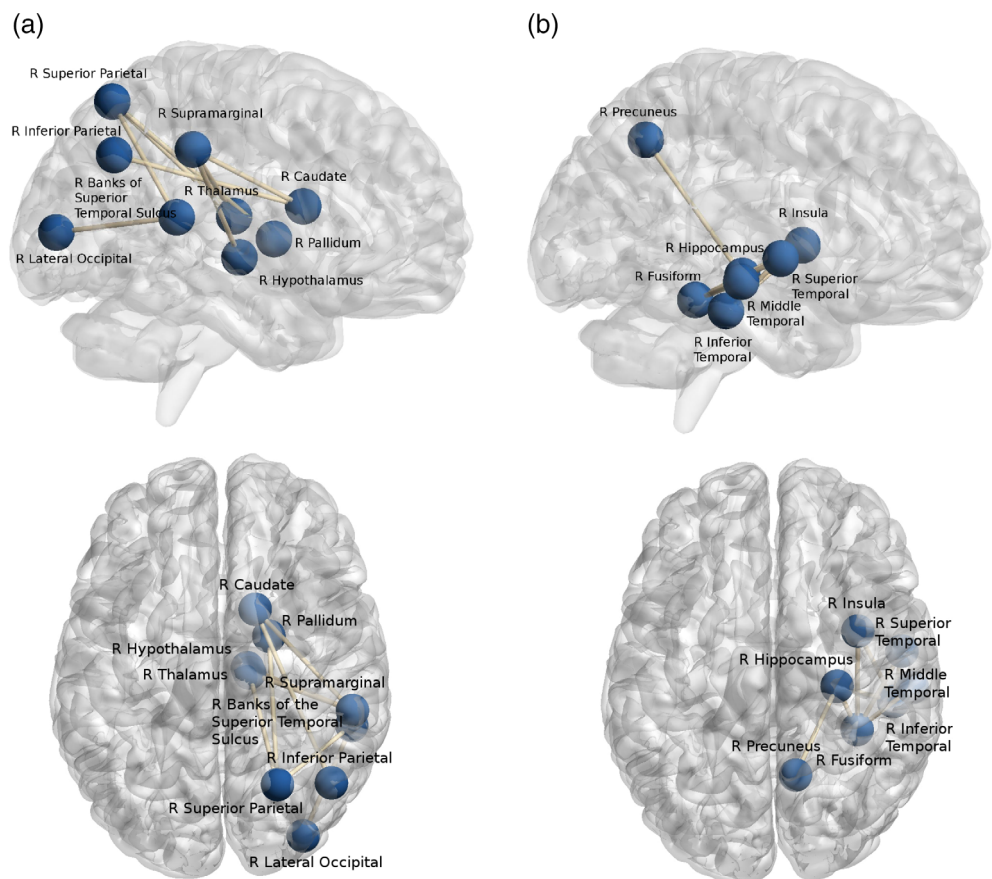


FIGURE 5 Visual/spatial memory-associated networks. Lesion-based WM tract disruption within dorsal visual processing pathways (a) and a network of hippocampal connections (b) in the right hemisphere is significantly associated with visual/spatial memory impairment in PwMS. PwMS, people with multiple sclerosis; WM, white matter [Color figure can be viewed at wileyonlinelibrary.com]

processing speed, $p < .001$; visual/spatial memory, $p < .001$; verbal memory, $p = .016$).

In the regression model predicting cognitive processing speed ($R^2 = .253$, $p < .001$; Figure 6), a statistically significant effect was observed for age ($\beta = -.309$, $p = .004$), preservation of functional connectivity ($\beta = -.450$, $p = .002$), and the interaction between WM tract disruption and preservation of functional connectivity in the cognitive processing speed-associated networks ($\beta = -.513$, $p = .001$). Thus, the impact of network WM tract disruption on cognitive processing speed

was attenuated for individuals with preserved functional connectivity within the network.

For the regression model predicting visual/spatial memory ($R^2 = .170$, $p = .003$; Figure S2), a statistically significant effect of age ($\beta = -.390$, $p < .001$) was observed. A trending effect was also observed for the interaction between WM tract disruption and preservation of functional connectivity within the visual/spatial memory-associated networks ($\beta = -.209$, $p = .066$).

4 | DISCUSSION

The results of this study contribute to our understanding of the neural basis of cognitive reserve in PwMS. In this study, we observed that people with higher premorbid verbal intelligence, a proxy for cognitive reserve (Benedict, Morrow, Guttman, Cookfair, & Schretlen, 2010), exhibit preserved functional connectivity despite accumulation of GM atrophy. Furthermore, relative preservation of functional connectivity (more similar to HCs) attenuates the impact of structural network disruption on cognition. This interaction was observed in models predicting impairment on cognitive processing speed. A trend for a similar effect was also observed for visual/spatial memory impairment.

Our findings are comparable to results previously described, where PwMS exhibiting normal patterns of default mode network deactivation during a sustained attention task, rather than abnormally high patterns, displayed an attenuated correlation between atrophy and memory impairment (Sumowski, Wylie, Leavitt, Chiaravalloti, & DeLuca, 2013). Although through potentially different mechanisms, this phenomenon is also observed in healthy aging, where elderly people who performed better on a working memory task exhibited task-related network activation which was more similar to the network activation patterns displayed by the young (Steffener, Brickman, Rakitin, Gazes, & Stern,

TABLE 3 Strength of association between region-pair WM tract disruption and visual/spatial memory in PwMS

Network	Region-pair	t value
1	R. Supramarginal–R. thalamus proper	3.33
	R. Inferior parietal–R. caudate	3.31
	R. Supramarginal–R. caudate	3.24
	R. Superior parietal–R. Thalamus proper	3.12
	R. Bankssts–R. Lateral occipital	3.11
	R. Bankssts–R. Superior parietal	3.08
	R. Superior parietal–R. Pallidum	3.06
	R. Supramarginal–R. Hypothalamus	3.02
2	R. Inferior temporal–R. Insula	3.33
	R. Fusiform–R. Middle temporal	3.31
	R. Fusiform–R. Superior temporal	3.22
	R. Inferior temporal–R. Superior temporal	3.22
	R. Inferior temporal–R. Hippocampus	3.21
	R. Fusiform–R. Hippocampus	3.09
	R. Fusiform–R. Insula	3.07
	R. Precuneus–R. Hippocampus	3.03

Abbreviation: PwMS, people with multiple sclerosis.

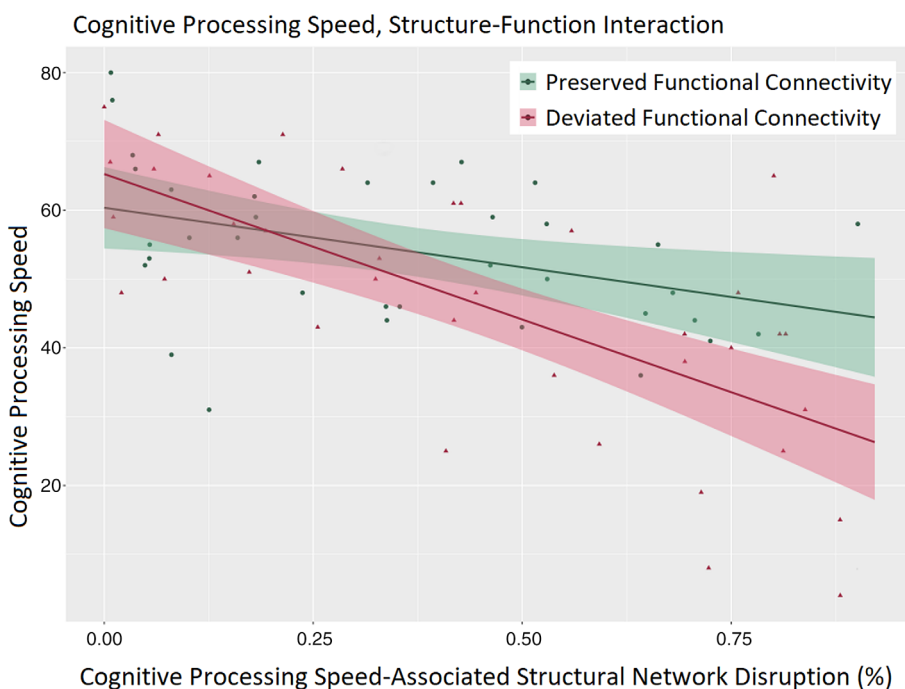


FIGURE 6 Cognition and the structure–function interaction. Individuals with preserved functional connectivity (green) within the cognitive processing speed-associated networks exhibit an attenuated correlation between structural network disruption and dysfunction of cognitive processing speed. In comparison, individuals with a high degree of deviation in functional connectivity (red) exhibit a stronger structure cognition correlation [Color figure can be viewed at wileyonlinelibrary.com]

2009). Thus, in studies of PwMS as well as in healthy aging, maintenance of normal functional activation patterns is associated with improved cognitive outcomes, despite accrual of structural damage.

Our findings build on previously reported results by demonstrating that resting-state functional connectivity is relevant to cognitive reserve, corroborating findings from studies of task-based activation. Additionally, by considering neuropathology from a network perspective we were able to characterize previously validated proxies for cognitive reserve according to the overlap/interaction between structural network disruption and functional network deviation. In short, individuals with high cognitive reserve express preserved functional connectivity despite GM atrophy and relative preservation of functional connectivity attenuates the impact of structural network tract disruption on cognition.

Functional brain activation is a complex and dynamic phenomenon. In many cases, it remains difficult to determine whether individual alterations reflect adaptive compensation (Penner & Aktas, 2017; Steffener & Stern, 2012) or pathological changes (Rocca & Filippi, 2017). It may be that differences in functional connectivity are context-dependent, and must be interpreted alongside the structural burden of disease. For some individuals, deviations in functional connectivity may be adaptive, and for others, pathological. However, our work suggests that the overall preservation of normal functional connectivity is important for maintaining normal cognition despite accumulation of structural MS damage. Although we are limited in deriving causal conclusions from these findings given the cross-sectional nature of the study, our results may imply that cognitive reserve building activities help preserve normal functional connectivity and therefore cognition. The relative preservation of healthy functional connectivity may be the result of many possible cellular and molecular mechanisms associated with cognitive reserve building, including epigenetic changes, activity-dependent gene expression, protein processing, and trafficking, neurogenesis, synaptic plasticity, synaptogenesis, gliogenesis, and angiogenesis (Nithianantharajah & Hannan, 2009). All these changes may allow for functional connectivity between pairs of GM regions that are more resilient to WM tract damage.

In addition to our major findings described above, we also identified localized patterns of WM tract disruption that explain cognitive deficits beyond what is otherwise explained by global atrophy. The networks of GM regions whose WM tract disruption was significantly associated with each cognitive domain are consistent with expectations. For example, the network of GM regions whose WM tract disruption was significantly associated with visual/spatial memory (Figure 5) was made up of region-pairs including right-hemispheric occipitotemporal as well as a right-hemispheric network of hippocampal connections. These results confirm the role of right hemispheric ventral visual pathways and hippocampal networks in visual/spatial processing and memory (De Schotten et al., 2011; Kravitz, Saleem, Baker, Ungerleider, & Mishkin, 2013; Squire, Zola-Morgan, Haist, & Musen, 1992). Impairment of cognitive processing speed as measured by SDMT was significantly related to a much more diffuse network of structurally disrupted pairs of GM regions (Figure 4), which is consistent with our understanding of SDMT as a cognitive

assessment that is highly sensitive to structural damage in PwMS (Benedict et al., 2017).

The clinical implications for our results are twofold. For one, we have provided further evidence supporting the notion that clinicians should consider the location of WM lesions and the brain networks they intersect when determining which consequent cognitive disturbances to expect. Furthermore, although our work is cross-sectional, our results suggest that beyond a particular threshold of deviation in functional connectivity, additional structural damage might result in accentuated cognitive decline. Future longitudinal work may help elucidate such a tipping point and whether rates of cognitive decline are greater for individuals whose functional connectivity is no longer preserved (more deviated from HCs). It is of particular interest to determine whether preserved functional connectivity can be maintained for longer periods of time or reaffirmed following pharmacological or behavioral interventions.

One limitation of this study was that structural network disruption measured for our analysis was derived through lesion-based methods which are independent of diffusion characteristics or diffuse WM damage for each individual subject. Nonetheless, the NeMo tool is useful for quantifying the impact of WM lesions on structural connectivity without the problems associated with diffusion and tractography through MS lesions (Reich, Ozturk, Calabresi, & Mori, 2010). We are also limited by the relatively small sample of HCs used for comparison to the PwMS under investigation. Nonetheless, we were able to reproduce our results using broader HC data from a publicly available database (see Supporting Information). As well, the acquisition time for our fMRI resting-state scans was ~11 min (TR 2,500 ms, TE 35 ms). Given that reliability of functional connectivity, results can be greatly improved by increasing the scan length to approximately 13 min (Birn et al., 2013), future work should consider longer acquisition times. Future work should also aim to utilize more automated methods of labeling and removal of noise components from the resting-state fMRI data which are trained to robustly remove known noise components (e.g., physiological noise and MRI-related artifacts). We opted to follow recently published guidelines for reliable hand-classification of noise components (Griffanti et al., 2017), but with larger training datasets, automated software might be able to make more reproducible classifications.

Future work should also explore proxies of cognitive reserve in greater detail. For this study, we relied solely on premorbid verbal intelligence (NAART) as a proxy measure. However, other factors, such as the type and duration of cognitive reserve building activities may provide additional insights as these factors are not directly addressed by the NAART. In addition, future research should explore the relationship between structure and function by also considering structural damage outside of the cognitive-domain associated networks. It is possible that damage elsewhere in the brain can also influence functional connectivity. For instance, when accounting for global lesion volume, the interaction between structural disruption and preservation of functional connectivity became borderline significant ($p = .054$ and $p = .078$) in regression models explaining cognitive function (Supplementary Materials, Section D). These preliminary results indicate the need for further investigation into this phenomenon.

Finally, although we attempted to recreate our major analyses in relapsing–remitting MS and progressive MS subjects separately (Supplementary Materials, Section C), these post hoc analyses were underpowered relative to the whole study sample and were unequal from one another. Future research should explore cognitive reserve and preservation of functional connectivity in greater detail for these subgroups separately, as the relevant pathophysiology may evolve during the disease course.

5 | CONCLUSION

Individuals with higher cognitive reserve exhibit preserved functional connectivity despite accumulation of GM atrophy. Furthermore, preservation of network functional connectivity (more similar to HCs) attenuates the impact of structural network disruption on cognition in PwMS. Taken together these results suggest that preservation of network functional connectivity underlies cognitive reserve in PwMS.

CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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