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Functional and structural connectivity substrates of cognitive performance in relapsing remitting multiple sclerosis with mild disability

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ABSTRACT

Multiple Sclerosis (MS) is the most common chronic inflammatory and neurodegenerative disease of the central nervous system (CNS), which can lead to severe cognitive impairment over time. Magnetic resonance imaging (MRI) is currently the best available biomarker to track MS pathophysiology *in vivo* and examine the link to clinical disability. However, conventional MRI metrics have limited sensitivity and specificity to detect direct associations between symptoms and their underlying CNS substrates. In this study, we aimed to investigate structural and resting state functional connectomes and subnetworks associated with neuropsychological (NP) performance using a graph theoretical approach. A comprehensive NP test battery was administered in a sample of patients with relapsing remitting MS (RRMS) and mild disability [n = 33, F/M = 20/13, age = 40.9 ± 9.7, median [Expanded Disability Status Scale] (EDSS) = 2, range =0–4] and compared to healthy controls (HC) [n = 29, F/M = 19/10, age = 41.0 ± 8.5] closely matched for age, sex, and level of education. The NP battery comprised the most relevant domains of cognitive dysfunction in MS including attention, processing speed, verbal and spatial learning and memory, and executive function. While standard MRI metrics showed good correlations with TAP Alertness test, disease duration and neurological exams, structural networks showed closer associations with 9-hole peg test and cognitive performances. Decreased graph strength was associated with two out of the 5 NP tests in the spatial learning and memory domain specified by BVMT [Sum 1–3] and BVMT [Recall], and with also SDMT which is one out of the 9 NP tests in the attention/processing speed domain, while no correlation was found between these scores and functional connectivity. Nodal strength was decreased in all subnetworks based on Yeo atlas in patients compared to HC; however, no difference was observed in nodal level of functional connectivity between the groups. The difference in structural and functional nodal connectivity between the groups was also observed in the relationship between structural and functional connectivity within the groups; the relationship between nodal degree and nodal strength was reversed in patients but positive in controls. On a nodal level, structural and functional networks (mainly the default mode network) were correlated with more than one cognitive domain rather than one specific network for each domain within patients. Interestingly, poorer cognitive performance was mostly correlated with increased functional connectivity but decreased structural connectivity in patients. Increased functional connectivity in the default mode network had both positive as well as negative associations with verbal and spatial learning and memory, possibly indicating adaptive and maladaptive mechanisms. In conclusion, our results suggest that cognitive performance, even in patients with RRMS and very mild disability, may reflect a loss of structural connectivity. In contrast, widespread increases in functional connectivity may be the result of maladaptive processes.

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1. Introduction

Multiple Sclerosis (MS) is the most common chronic inflammatory and neurodegenerative disease of the central nervous system (CNS), characterized by an accumulation of inflammatory and demyelinating lesions in the brain and spinal cord (Filippi et al., 2018). Cognitive dysfunction has been documented extensively even at the onset of disease (Amato et al., 2010) and during the earliest stages of relapsing-remitting MS (RRMS) (Deloire et al., 2005) and has a substantial negative impact on quality of life.

Currently, magnetic resonance imaging (MRI), one of the best techniques for noninvasive whole brain investigation, is widely used to evaluate MS (Reich et al., 2018) and standard MRI metrics (e.g. lesion load volume, global atrophy) are routinely employed to track disease activity and progression. However, it is becoming increasingly clear that these markers are poorly correlated with clinical symptoms (Wattjes et al., 2015). In contrast, network mapping may reflect neuropsychological symptoms, cognitive or social dysfunctions much more accurately (Fox, 2018). For example, in some cases, it is seen that relatively small lesions cause broader neuropsychological effects than expected by their lesion size or location (Warren et al., 2014). This might be explained by anterograde and retrograde neurodegeneration spreading in the whole network as nicely demonstrated for the visual system in MS (Balk et al., 2014). Therefore, analyzing connectivity or integrity of brain networks might better reflect non-localized pathology and take the fundamental topological organization of the brain into account (Liu et al., 2017). However, it is still an unresolved issue whether or not cognitive dysfunction in MS can be mapped to a global connection model or could better be explained by a complex system of distributed connection schemes (Zimmermann et al., 2018).

Graph theoretical approaches can be used to extract information on networks of interacting brain regions and to provide insight into the pathophysiological network changes underlying neurologic and psychiatric symptoms (Fox, 2018). Previous studies have successfully utilized structural and/or functional connectome analyses to interrogate MS pathophysiology (Filippi et al., 2013; Fleischer et al., 2017; Hardmeier et al., 2012; Hawellek et al., 2011; He et al., 2009; Li et al., 2013; Pagani et al., 2019; Rocca et al., 2016; Schoonheim et al., 2013; Shu et al., 2016, 2011, 2018; Stam, 2014; Stellmann et al., 2017; Tewarie et al., 2015). Some of these cross-sectional studies have shown that network analysis is capable of characterizing neuropsychological impairment and physical disability in MS (Hawellek et al., 2011; Pagani et al., 2019; Pardini et al., 2015; Rocca et al., 2016; Shu et al., 2018, 2016; Stam, 2014; Stellmann et al., 2017). However, there is still substantial inconsistency between clinical disabilities and findings on brain networks. For example, some investigators suggest that decreased structural (charalambous et al., 2018; Llufriu et al., 2018; Stellmann et al., 2017) and/or functional connectivity is correlated with lower performance in several clinical tests and functions in MS (Rocca et al., 2016). In contrast, other studies have indicated that increased functional connectivity in certain networks is associated with poorer performance in cognitive tests (Hawellek et al., 2011; Meijer et al., 2017; Schoonheim et al., 2015).

Whether alterations in functional connectivity represent an adaptive or maladaptive process in the context of MS, however, is hotly debated in the field (Rocca and Filippi, 2017) (Penner and Aktas, 2017). Part of the inconsistencies in the literature may be caused by the temporal kinetics of such alterations during disease evolution and progression (Schoonheim et al., 2015). In addition, some might stem from the limited clinical assessments typically done in such studies, where cognition is often measured with just a few screening tests such as the Symbol Digit Modalities Test (SDMT) or Paced Auditory Serial Addition Test (PASAT). Moreover, only few studies have combined measures of both structural and functional connectivity with comprehensive quantification of cognitive function in MS. Although there are some studies that related several cognition domains to both structural and functional connectivity (Hawellek et al., 2011; Meijer et al., 2017), the relationship between a wide range of cognitive domains and functional as well as structural brain networks remains incompletely understood.

Therefore, in this study, we provide a comprehensive exploration of the association between neuropsychological performance and both structural and functional networks in mildly disabled RRMS patients compared to healthy controls (HC). To this end, we compared network metrics of functional and structural networks first on a global level, i.e. graph theoretical summary metrics for the whole network, and second on a nodal level representing region wise and subnetwork analyses including seven main functional networks.

2. Material and methods

2.1. Subjects

We recruited thirty-three patients and twenty-nine age-, sex-, and education matched HC. For the MS group, the following exclusion/inclusion criteria were applied: (1) RRMS according to McDonald criteria 2017 (Thompson et al., 2018) (2) no relapse or steroid treatments for at least 3 months; (3) no change in disease-modifying therapies within the last 3 months; (4) within the range of Expanded Disability Status Scale (EDSS) = 0–4.

Additional criteria for all participants were (1) no evidence of medical illness or substance abuse that may affect cognitive functioning; (2) no psychiatric or neurological diseases (based on medical history and neurological exam). All subjects underwent neurological exam, comprehensive neuropsychological assessment, and neuroimaging within one week.

2.2. Neuropsychological and neurological examinations

For this study, we administered a comprehensive neuropsychological test battery. 20 different NP tests were categorized into 4 domains as attention and processing speed, verbal learning and memory, spatial learning and memory and executive functioning. Since the processing speed, sustained, divided and selective attention have been involved in a domain of the complex attention (Islas and Ciampi, 2019), we merged the attention and processing speed as an only domain. To assess attention/processing speed, we used the Test battery of Attentional Performance (TAP; (Zimmermann et al., 2004)), the Paced Auditory Serial Addition Test (PASAT 3″; (Gronwall and Sampson, 1974)), and the Symbol Digit Modalities Test (SDMT; (Smith, 1982)). To measure verbal learning and memory functions we used the Verbal Learning and Memory Task (VLMT; (Helmstaedter and Durwen, 1990)). For spatial learning and memory the Block Tapping Task of the Wechsler Memory scale (WMS; (Wechsler, 1997)) and the Brief Visuospatial Memory Test (BVMT)) were used. Executive function was measured by the Regensburger Word Fluency Task (RWT; (Aschenbrenner et al., 2000)).

EDSS (Kurtzke, 1983), the 9-Hole Peg Test (NHPT) (Backman et al., 1992; Chan, 2000), and the Timed-25 food walk (T25FW) were used for neurological assessment.

For the analyses in this study, test scores were inverted if needed so that for all domains, higher values indicate better performance. This study was approved by the appropriate ethics committee of the Hamburg Chamber of Physicians (Registration Number PV4356) and all participants provided written informed consent prior to enrolment.

2.3. MRI data acquisition

All subjects underwent neuroimaging using a 3T MRI Scanner equipped with 32-channel head coil (Skyra, Siemens Medical Systems, Erlangen, Germany). All participants received the same protocol including diffusion tensor imaging (DTI), resting state (RS) functional MRI (fMRI) and conventional MR imaging.

DTI scans were collected using a single-shell with 32 independent

directions with non-collinear diffusion gradients (b = 1000s/mm^2) and 1 non-diffusion-weighted (b = 0 s/mm^2) (TR/TE = 7200 ms/90 ms; voxel size 1.9 × 1.9 × 2.0 mm, FOV 240 mm, matrix 128×128, 54 axial sections, without intersection gap).

For RS fMRI, a T2*-weighted (W) BOLD-sensitized echo planer imaging (EPI) sequence (TR/TE = 2500 ms/25 ms; TI = 900 ms; 40 slices, voxel size 2.7 × 2.7 × 3.0 mm, without intersection gap, matrix = 256×256, FOV = 250 mm, FA = 90°, number of volumes = 250) was acquired for 10 min while subjects were asked to stay motionless, keeping eyes open and fixating on a cross during scanning.

3D T1-W high resolution magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequences (TR/TE = 2500 ms/2.12 ms; TI = 1100 ms; 256 slices, voxel size 0.8 × 0.8 × 0.9 mm, no intersection gap, matrix = 288×288, FOV = 240 mm) and T2-W (TR/TE = 2800 ms/90 ms; 43 slices, voxel size 0.5 × 0.5 × 3.0 mm, no intersection gap, matrix = 256×256, FOV = 240 mm) were also obtained from each subject.

2.4. Processing of MRI data

Processing of MR images included the following steps: In order to obtain lesion maps, first, T1-W images were registered to T2-W images after performing the standard space reorientation for each sequence using functional imaging software library (FSL, version 5.0, www.fmrib.ox.ac.uk). Then, T1-hypo- and T2-hyper intensities were specified with Analyze 11.0 software (AnalyzeDirect, www.analyzedirect.com). Before volumetric post-processing, lesion filling on T1 images was done to avoid segmentation errors. Following lesion masking, we calculated total lesion volume.

An automated procedure for volume and thickness measurements was performed for each subject using FreeSurfer (https://surfer.nmr.mgh.harvard.edu) as described in (Fischl et al., 2002). The automated algorithm included removal of non-brain tissue (skull, eyeballs and skin) to successfully segment the whole brain. Cortical surface reconstruction methods were included to obtain regional measures of cortical volumes as well. Destrieux atlas was registered to each subject using spherical registration following the removal of white matter residual as included in autorecon processing stages in Freesurfer (https://surfer.nmr.mgh.harvard.edu/fswiki/recon-all).

To normalize the calculated parenchymal fraction, white matter and gray matter volume, each measurement was divided by total intracranial volume of each subject. In addition, brain masks and gray/white matter segmentations were manually corrected for each subjects. Finally, gray-matter parcellation of 80 regions (total: 160) for each hemisphere was determined based on the Destrieux atlas (2009) (Destrieux et al., 2010) to perform structural and functional connectivity analysis. The location of each node in one of seven functional networks (Yeo atlas) was determined on the FreeSurfer fsaverage subject (Yeo et al., 2011). Seven networks in Yeo atlas were default mode (involved 44 nodes), visual (27 nodes), somatomotor (22 nodes), frontoparietal (9 nodes), dorsal attention (15 nodes), ventral attention (14 nodes) and limbic (16 nodes) network.

2.5. Structural connectivity

Individual structural networks were formed based on whole brain probabilistic fiber tracking using MRtrix3 (www.mrtrix.org) in subject space as described in Besson et al. (2014a). Briefly, in order to compute the fractional anisotropy (FA) and mean diffusivity maps, diffusion tensor fitting was applied to DTI data following correction for head motion and eddy currents and skull stripping procedures using the diffusion toolbox of FSL (Behrens et al., 2007).

To get accurate estimation of the fiber orientation distribution (FOD) while performing constrained spherical deconvolution, the response function was determined by FOD at the FA values of higher than 0.7 (Tournier et al., 2007). Then, to build the fibers, we used probabilistic tractography algorithms (Behrens et al., 2003) which generated 150,000 fibers with a minimum length threshold of 20 mm (default parameters: step size: 0.2 mm, minimum radius of curvature: 1 mm, FOD cut-off: 0.1). Seeds were specified by all voxels of 1 mm dilated white matter masks. Then, the tracking of seeds were limited by the edge of mask and pre-defined FA or FOD threshold. We then calculated the average FA for each fiber following the estimation of the FA values at each point of the fiber.

2.6. Functional connectivity

Individual functional networks were built as described (Wirsich et al., 2016). First, we performed preprocessing of the RS fMRI data including motion distortion and slice timing correction and coregistration with T1 volume and regional parcellation using SPM12. Then, all voxels of each region and time points were averaged after applying the regression procedure for head movement, cerebrospinal fluid signals, white matter signals, and global mean signal. After the preprocessing step, output data acquired from averaged region-time series was used to perform wavelet analysis (frequency band range: 0.1 Hz - 0.05 Hz, TR = 2.5 s) (Achard et al., 2012) using the brainwaver package in R. To compute raw functional connectivity, we calculated absolute Pearson-correlations between the wavelet coefficient time series of each region. For better comparability of networks, the top 15% of connections defined the connectivity matrices (Achard et al., 2012).

2.7. Global and nodal graph metrics

The global parameters of structural networks (G^{struc}) were global strength (i.e. the sum of edge weights in each network), average shortest path length (APL) between all nodes and global clustering coefficient using the arithmetic mean method. In addition, we also computed global degree (i.e. the sum of connections per node in each network), APL and clustering coefficient for functional networks (G^{func}). Moreover, we calculated the nodal strength and degree for structural and functional networks, respectively, as nodal graph metrics.

2.8. Statistics

According to the nature of the data, we performed descriptive statistics as mean with standard deviation or as median with range. Group differences between patients and HC were assessed by Student *t*-test for continuous data and Fisher's exact-test for categorical data. To investigate associations between graph metrics and clinical data, we computed Pearson correlation coefficients. After applying false discovery rate corrections, p-values below 0.05 were considered statistically significant. The analyses were performed with statistics in R 3.2.3, including the igraph (Csárdi and Nepusz, n.d.) and tnet (Opsahl, 2009) packages.

4. Results

4.1. Neurological and neuropsychological characteristics of the cohort

Descriptive statistics are presented in Table 1. Due to the close matching, patients with RRMS (n = 33) and HC (n = 29) did not differ with respect to age (p = 0.991) sex distribution (p = 0.794), or level of education. Patient's median EDSS was 2 with 3 patients scoring 0 on the scale. Patients' mean disease duration since first symptoms (approx. 10 years) and a median EDSS of 2 indicated mild to moderate disability. As excepted, global brain volume (p = 0.031) and white matter volume (p = 0.014) were significantly lower in MS patients compared to HC. However, no significant differences were found in both groups concerning walking abilities (T25FW) and hand function (NHPT).

The neuropsychological profile of MS patients showed worse

Table 1
Descriptive statistics.

	RRMS, n = 33		HC, n = 29		P
	Female	Male	Female	Male	
Sex n	20	13	19	10	0.794
	>12 years	**<12 years**	**> 12 years**	**<12 years**	
Education n	21	12	18	11	0.524
	Mean (SD)		**Mean (SD)**		
Age *years*	40.9 (9.7)		41.0 (8.5)		0.991
Disease Duration *years*	10.4 (8.1)		–		
EDSS *median (range)*	2 (0 – 4)		–		–
Timed 25-Foot Walk sec	4.7 (0.8)		4.4 (0.7)		0.096
9-Hole Peg Test sec	19.5 (2.6)		18.4 (2.0)		0.073
Brain volume mm^3	1,463,208 (151,402)		1,533,153 (88,911)		**0.031**
White matter volume mm^3	665,651 (74,313)		705,454 (44,869)		**0.014**
Gray matter volume mm^3	797,557 (84,619)		827,698 (56,682)		0.107
T2 lesion volume mm^3 *(log)*	3.98 (4.04)		–		–
T1 lesion volume mm^3 *(log)*	4.61 (5.18)		–		

Abbreviations: RRMS = Relapsing Remitting Multiple Sclerosis; HC = Healthy Control; (disease duration since first symptoms, tissue and lesion volumes normalized based on SIENAX results); EDSS = Expanded Disability Status Scale, log = Logarithmic.
Data presented as mean (SD) or median (range). Except from sex (Fisher's exact test), group differences were compared with the Student t-test.

performance in several subtests including the following domains: Verbal learning and memory, spatial learning and memory, and executive functioning (Table 2) (Fig. 1). Specifically, compared to HC, the patients had poorer results in short term memory (p = 0.006) and verbal learning (p < 0.001) as measured by VLMT, in visual short-term memory and learning assessed by the forward Block-Tapping-Task (p = 0.008) and the BVMT learning trials (p = 0.014) as well as in executive functioning measured by lexical category change in the RWT (p < 0.001). Except for BVMT, all of these remained significant after FDR correction.

In the TAP, patients' reaction time was significantly longer than HC for alertness without warning tone (p = 0.047) and covert shift of attention (invalid) (p = 0.024). However, these findings were not significant after FDR-correction. There were no significant differences in regarding performances in other neuropsychological tests.

Association between MRI volumes, neurological exams and neuropsychological tests

First, we investigated the associations of conventional MRI metrics with neurological ratings and / or neuropsychological tests. We found that T1 lesion, gray matter and total brain volume (p = 0.04, FDR

Table 2
Summary of neuropsychological test results.

Cognitive functions	Test	RRMS (n = 33) Mean	SD	HC (n = 29) Mean	SD	p-value
Attention/Information processing						
Selective attention and working memory	PASAT (points)	49.1	9.5	51.9	6.9	0.198
Processing speed and attention	SDMT (points)	56.9	14.3	63	11.9	0.076
Tonic alertness	TAP [tonic Alertness] (ms)	261.1	41.6	243.3	24.9	0.047[a]
Phasic alertness	TAP [phasic Alertness (ms)	256.8	40.3	242.7	24.5	0.102
Shifted attention	TAP [CSA valid] (ms)	309.8	49.1	297.1	45.3	0.302
Shifted attention	TAP [CSA invalid] (ms)	361.2	50.3	331.1	50.1	0.024[a]
Incompatibility attention	TAP [compatible] (ms)	464.4	83.5	447.8	55.9	0.365
Incompatibility attention	TAP [incompatible] (ms)	509.2	83.5	502.2	62.8	0.712
Incompatibility total attention	TAP [total] (ms)	485.7	80.8	472.1	51.1	0.432
Verbal learning and memory						
Verbal short term memory	VLMT [STM] (points)	7.3	2.6	9	2	**0.006**[a,b]
Verbal learning	VLMT [VL] (points)	52.4	10.5	61	6.1	**<0.001**[a,b]
Verbal memory	VLMT [VM] (points)	1.1	1.9	0.4	1.5	0.179
Spatial learning and memory						
Visuo-spatial short term memory	Block-Tapping Task [FWD] (points)	8.3	1.6	9.6	1.9	**0.008**[a,b]
Visuo-spatial working memory	Block-Tapping Task [BWD] (points)	7.8	1.9	8.8	1.9	0.063
Total learning	BVMT [Sum 1–3] (points)	21.8	7.4	26	5.3	0.014[a]
Delayed recall	BVMT [recall] (points)	8.8	2.6	9.8	2.0	0.077
Recognition	BVMT [recognition] (points)	5.8	1.1	5.9	2.2	0.308
Executive functioning						
Word fluency	RWT [VF] (percentile rank)	55.8	30	63.7	27.1	0.292
Lexical category change	RWT [CC] (percentile rank)	34.5	27.7	59.1	26.5	**0.001**[a,b]
Word fluency	RWT [categories] (percentile rank)	48.4	32.5	59.9	26	0.135

Test Abbreviations: PASAT = Paced Auditory Serial Addition Test; SDMT = Symbol Digit Modalities Test; VLMT = verbal learning memory test; RWT = Regensburger Word Fluency Task; TAP = Test Battery of attentional performance; BVMT = Brief Visuospatial Memory Test.
Abbreviations: STM = short term memory, VL = verbal learning, VM = verbal memory, FWD = forward, BWD = backward, VF = verbal fluency, CC = category change, CSA = Covert Shift of Attention, incomp total = incompatibility total.
Data presented as mean and SD, group differences were compared with the Student t-test.
[a] p values below 0.05.
[b] False discovery rate–corrected p values below 0.05.

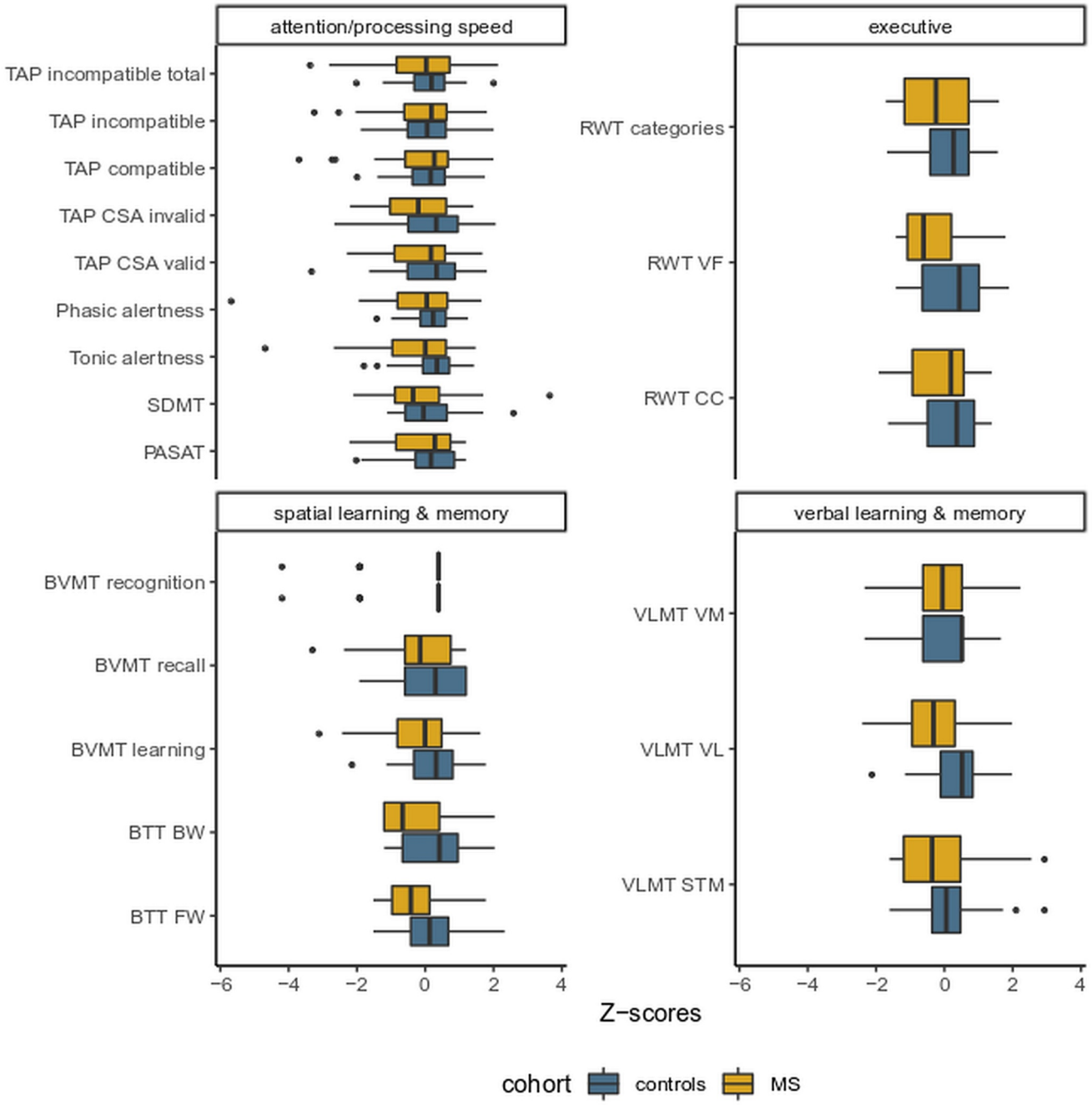

Fig. 1. Figure indicates the effect of the cognitive data presented by Z-scores in Relapsing Remitting Multiple Sclerosis (yellow) and Healthy Controls (blue). Abbreviations: PASAT = Paced Auditory Serial Addition Test; SDMT= Symbol Digit Modalities Test; VLMT = verbal learning memory test; RWT = Regensburger Word Fluency Task; TAP = Test Battery of attentional performance; BVMT= Brief Visuospatial Memory Test. STM = short term memory, VL = verbal learning, VM = verbal memory, FWD = forward, BWD = backward, VF = verbal fluency, CC= category change, CSA = Covert Shift of Attention, incomp total = incompatibility total.(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

corrected) was related with only one of the attention/processing speed functioning tests (TAP [Alertness w/o W]) in patients. There was no relationship between the other MRI volumes and neuropsychological tests (see Supplementary Table S1). In contrast, disease duration, EDSS and Timed 25-food- walk test were strongly correlated with both gray matter (p_{DD}=0.001, p_{EDSS} = 0,003, p_{T25FW} <0,001, FDR corrected) and total brain (p_{DD}=0.001, p_{EDSS} = 0,004, p_{T25FW} =0,001, FDR corrected) volume.

4.2. Structural and functional global network organizations

First, we explored if global network alterations can be detected in MS and whether they might be associated with cognitive performance. For structural networks, we computed global strength (indicating total connectivity in a network) for each individual and detected a lower total connectivity ($p < 0.001$) in patients compared to HC. Structural average path length and clustering, however, were not significantly

Table 3
Global graph metrics.

Structural weighted networks	RRMS G^{struc} n = 33	HC G^{struc} n = 29	RRMS vs. HC P
Graph strength	6447.407 (672.545)	7095.314 (356.813)	**<0.001** [a,b]
Average shortest path length	1.207 (0.043)	1.190 (0.025)	0.057
Clustering coefficient	0.796 (0.027)	0.805 (0.025)	0.172
Functional binary networks	**$G^{func}n$ = 30**	**$G^{func}n$ = 29**	**P**
Degree	3560.933 (2424.748)	3339.655 (2342.273)	0.723
Average shortest path length	2.733 (0.840)	2.870 (0.977)	0.568
Clustering coefficient	0.533 (0.081)	0.529 (0.074)	0.849

Abbreviation: G^{struc} = weighted structural networks; G^{func} = binary functional networks; RRMS = Relapsing Remitting Multiple Sclerosis; HC = Healthy Controls.
Data presented as mean (SD). Comparison of cohorts by Student t-test.
[a] p values below 0.05.
[b] False discovery rate–corrected p values below 0.05.

different between patients and HC (p = 0.057, p = 0.057 and p = 0.172, respectively) as shown in Table 3. In addition, we observed no significant differences between patients and HC for global functional network metrics including degree, average shortest path length and clustering coefficient.

4.3. Global network alterations related with MRI volumes, neurological examinations and neuropsychological tests

To elucidate the relation between structural and functional global networks and cognitive performance, we explored the association between the graph metrics and MRI volumes, neurological examinations and neuropsychological tests in patients and healthy controls separately (see Table 4 in patients: Supplementary Table S2 in HC). For the association between the MRI volumes and structural networks, larger T2 lesion volume in patients was inversely correlated with the global strength (r = −0.52, p = 0.002) while there was a positive correlation between larger gray matter volume and the increased global strength (r = 0.46, p = 0.007). In addition, higher global strength was correlated with better performance in NHPT (r = −0.42, p = 0.014) and there was an inverse relationship between the global strength in structural networks and disease duration (r = −0.52, p = 0.002).

We observed strong associations with global graph strength for structural networks in the domain attention/processing speed specified by SDMT (r = 0.46, p = 0.007) and spatial learning and memory functioning specified by BVMT [Sum 1–3] (r = 0.55, p = 0.001) and BVMT [recall] (r = 0.53, p = 0.002) (Table 4).

Notably, attentional capacities measured by TAP were highly correlated with almost all global graph metrics in HC (seen in Supplementary Table S2). None of these associations were seen in patients. In contrast, we were not able to find any relationship between the global functional graph metrics and any other neurological examinations, MRI volumes or neuropsychological tests neither in patients nor in HC.

Table 4
Correlations between structural global graph strength and MRI volumes, neurological ratings data and neuropsychological tests in patients (only significant correlations are demonstrated). [a] p Values below 0.05.[b] False discovery rate–-corrected p values below 0.05.

	Graph strength R	P
Disease Duration	**−0.52**	**0.002** [a,b]
Gray matter volume	**0.46**	**0.007** [a,b]
T2 lesion volume	**−0.52**	**0.002** [a,b]
NHPT [mean]	**−0.42**	**0.014** [a,b]
Attention/Information processing		
SDMT	**0.46**	**0.007** [a,b]
Spatial learning and memory		
BVMT [Sum 1–3]	**0.55**	**0.001** [a,b]
BVMT [recall]	**0.53**	**0.002** [a,b]

Abbreviations: SDMT= Symbol Digit Modalities Test; VLMT = verbal learning memory test; BVMT= Brief Visuospatial Memory Test.

The association between local graph strength/degree and neuropsychological tests

As global graph metrics do not reflect the local functional organization of the human brain, we also investigated the association between cognitive tasks on a nodal level and in context of their location in one of seven functional networks as defined by Yeo et al. (2011). We observed decreased structural connectivity in all subnetworks (p<0.001) in patients compared to HC (Fig. 2A). However, functional connectivity did not differ between the groups (Fig. 2B). Exploring the association between structure and function, we found a significant correlation for 30 nodes either in patients or controls, mainly in the default mode and visual network (Fig. 2C). Interestingly, the relationships between nodal strength and nodal degree were quite homogeneous (i.e. higher strength indicated higher degree) in controls; however, these relationships were mostly reversed in patients.

To focus on altered connectivity, the findings obtained within the patients are summarized for four cognitive domains of attention/processing speed, verbal learning and memory, spatial learning and memory and executive function.

Attention/Processing speed: In the domain of attention/processing speed, better SDMT performance was associated with higher connectivity of nearly all nodes in structural networks (see Fig. 3A). While the SDMT showed a wide association pattern over all yeo networks, further associations were mainly located in the default mode network (Fig. 3D). On a functional level, we observed no association with SDMT. Notably, poorer performances of TAP CSA valid and phasic alertness tests were correlated with better functional connectivity (Fig. 3A) in default mode network, while PASAT had positive correlation with functional connectivity in limbic network (Fig. 3A and D).

Verbal Learning and Memory: A relationship in all Yeo networks was observed between better performance in verbal learning and memory and structural connectivity (Fig. 4A, B and D). The default mode network was seen here again in a lead role followed by the limbic network (Fig. 4B and D). Again, associations with nodal degree in functional networks were fewer with most of them in the default mode network.

Spatial Learning and Memory: In structural networks, BVMT showed a similar wide spread association pattern as the SDMT (Fig. 5A, B and D). Better performance was correlated with higher structural connectivity in almost all nodes (Fig. 5A). For functional connectivity, we observed a reduced association pattern with a predominance in the default mode and visual network.

Executive functions: Few significant relationships were observed between performance in executive function and structural connectivity

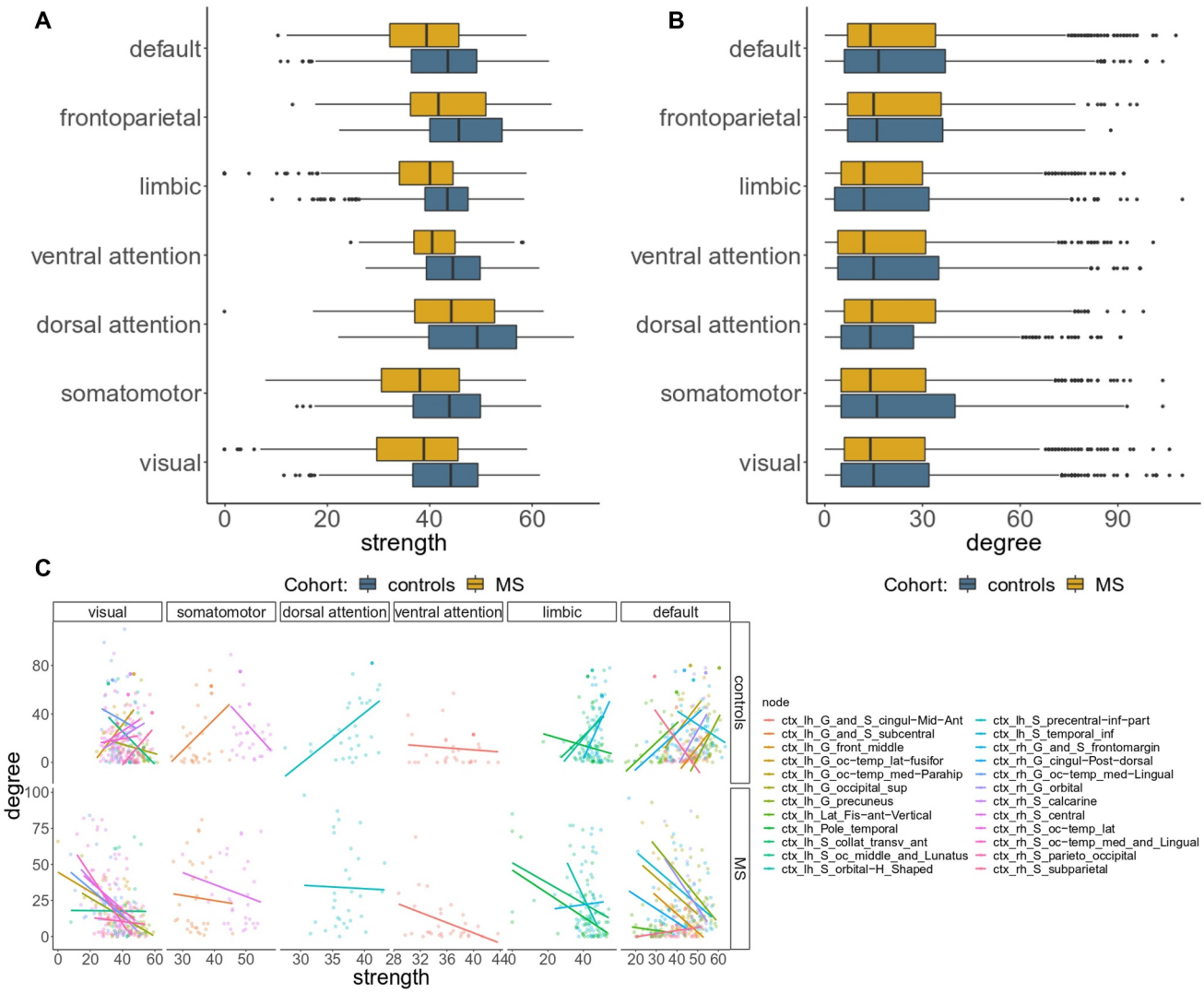

Fig. 2. Structural (A) and functional (B) connectivity for each one of seven subnetworks based on the Yeo atlas in patients (yellow) and healthy controls (blue). The correlation of structural (based on the strength) and functional (based on the degree) connectivity for all nodes in each subnetwork (C) in controls (upper side of C) and in patients (lower side of C).(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(Fig. 6). For functional connectivity, there was only one node located in the limbic network.

Direct and inverse associations with the overall cognitive performance

Next, we wanted to explore if correlation of functional connectivity might indicate an adaptive or rather maladaptive phenomenon. To address this aim, we extracted significant correlation coefficients for all nodes, which were related to at least one cognitive test. As shown in Fig. 7, structural connectivity always had a positive correlation with the task (with one exception) ($r >= 0.4$, FDR corrected), whereas functional connectivity had mostly negative correlations. However, in addition to limbic and somatomotor networks, mainly the default mode network had also a few direct or possible adaptive associations.

5. Discussion

We utilized an approach combining DTI, RS fMRI data and graph theory to characterize the relation between cognitive profiles and global and local network features in RRMS patients with mild to moderate disability. We observed a closer association of structural network metrics with cognitive abilities compared to standard MS MRI outcomes and an interesting pattern of associations with a slight predominance of nodes located in the default mode network. While structural connectivity always showed a positive correlation with performance, the number of functional connections of nodes was mostly negatively correlated.

It has previously been shown that loss of structural connectivity follows the topological organization of brain networks, with specific patterns and seems to be associated with neurological and neuropsychological impairment in MS (Charalambous et al., 2018; Pardini et al., 2015; Stellmann et al., 2017). The closer association between the disrupted structural connectivity and neurological examinations, lesion load and gray matter atrophy in our present study are consistent with this notion and extend the evidence by applying a wider range of clinical tests (He et al., 2009; Shu et al., 2018, 2011). In addition to the robustness, the sensitivity of our approach is reflected by the absence of correlations between standard MRI metrics and cognitive tasks.

Unlike the relatively consistent findings with regard to structural networks in MS, discordant results with both decreased and increased functional connectivity have been reported in previous studies (Faivre et al., 2012; Pantano et al., 2015; Rocca et al., 2012, 2018; Tewarie et al., 2015). Here, we observed no associations between functional connectivity and cognition on a global level and no

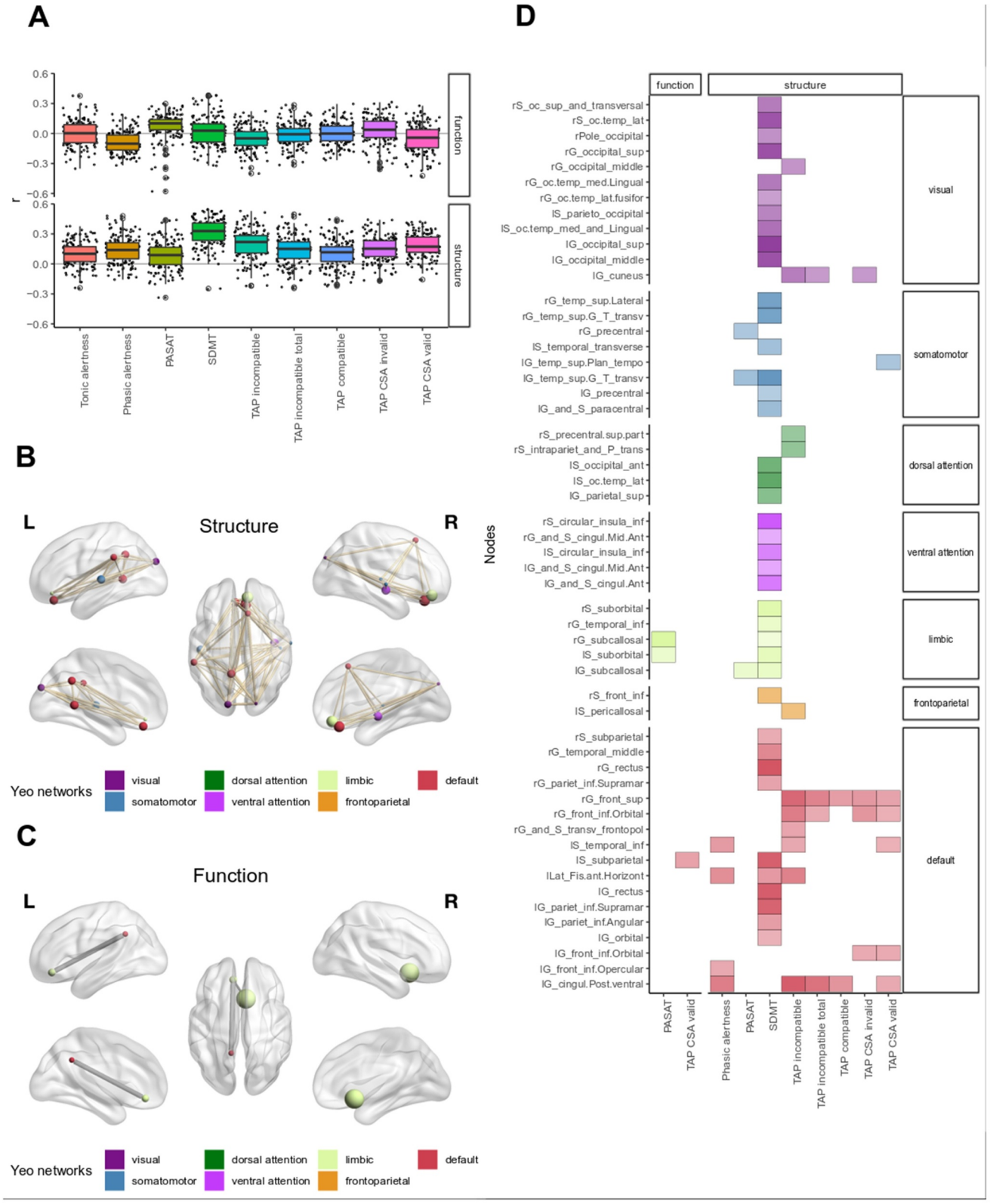

Fig. 3. The association of structural / functional networks and attention/processing speed functioning. (A) Boxplot displaying Pearson's correlation coefficients (r) for all nodes and for all tasks in the domain of attention/processing speed. (*B + C*) BrainViewer plots illustrate the localization of highly correlated ($r >= 0.4$) nodes in the brain. Size represents r, color their location in Yeo networks. (D) Correlogram of highly significant ($r >= 0.4$, $p < 0.05$ after FDR correction) nodes associated with attention/processing speed performances. Nodes are grouped by their location in seven functional networks defined by the Yeo atlas.

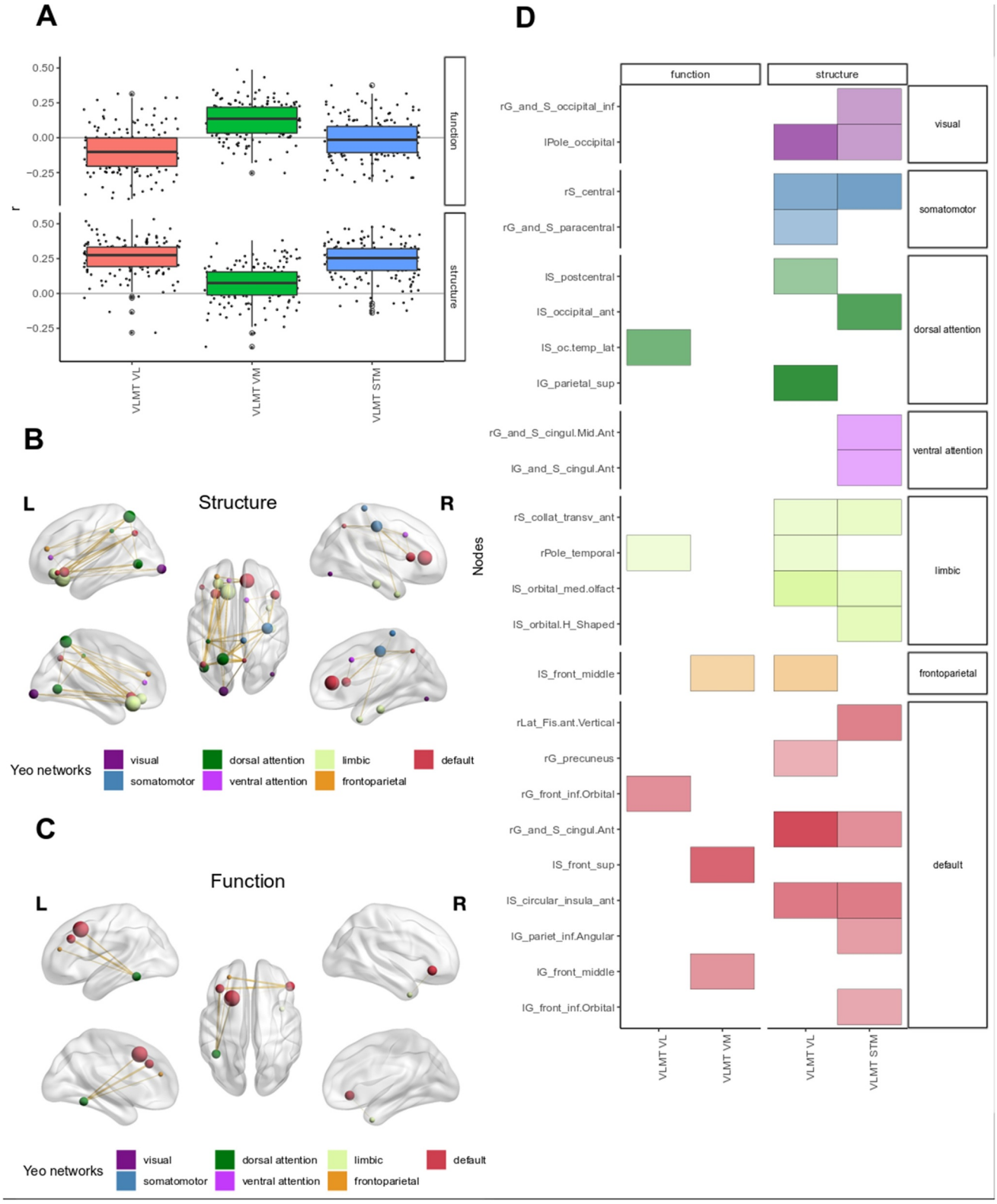

Fig. 4. The association of nodal structural / functional networks and verbal learning and memory functioning. (A) Boxplot displaying Pearson's correlation coefficients (r) for all nodes and for all tasks in the domain of verbal learning and memory. (*B + C*) BrainViewer plots illustrate the localization of highly correlated ($r >= 0.4$) nodes in the brain. Size represents r, color their location in Yeo networks. (D) Correlogram of highly significant ($r >= 0.4$, $p < 0.05$ after FDR correction) nodes associated with verbal learning and memory performances. Nodes are grouped by their location in seven functional networks defined by the Yeo atlas.

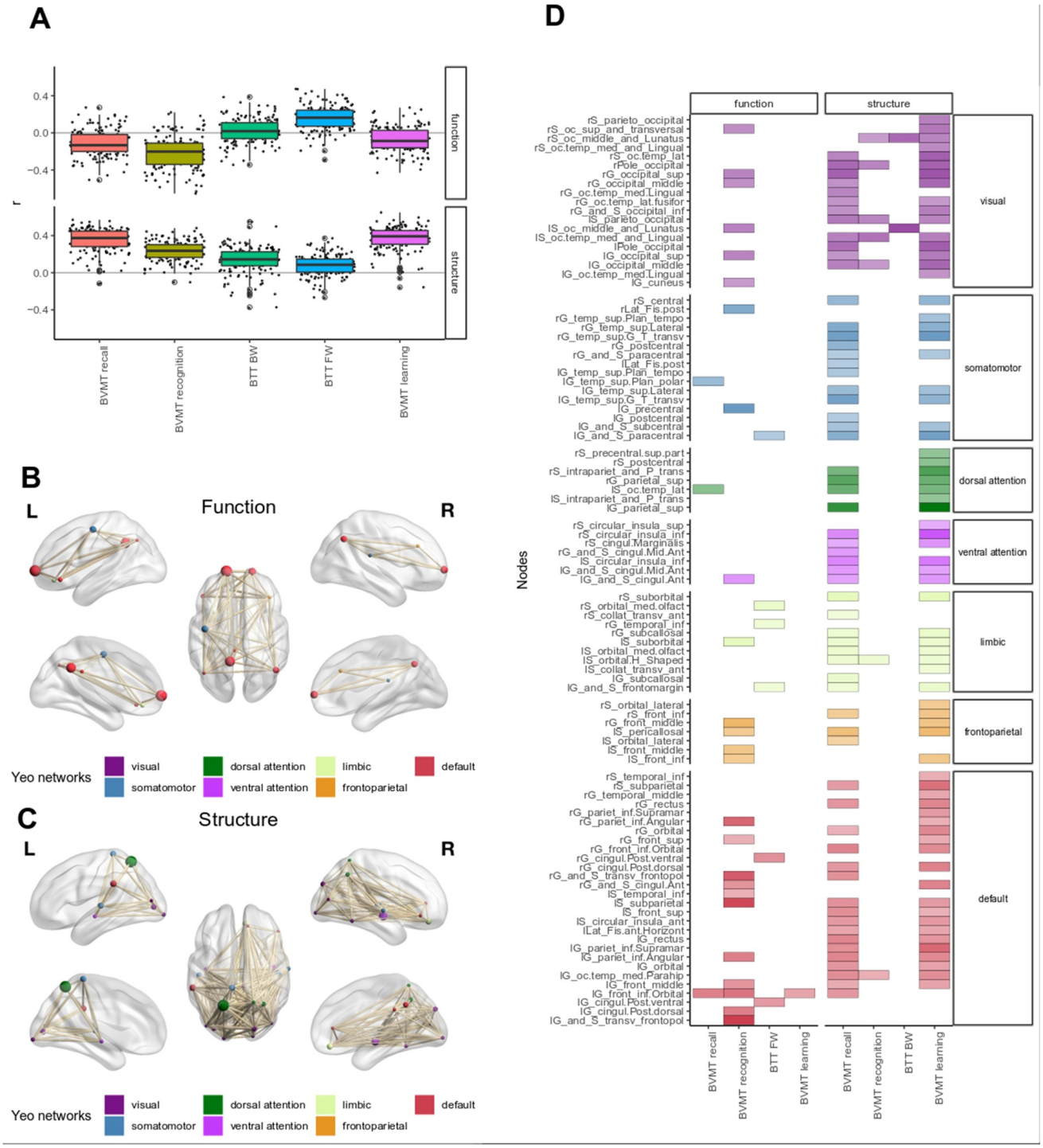

Fig. 5. The association of structural / functional networks and spatial learning and memory functioning.(A) Boxplot displaying Pearson's correlation coefficients (r) for all nodes and for all tasks in the domain of spatial learning and memory. (*B* + *C*) BrainViewer plots illustrate the localization of highly correlated ($r >= 0.4$, $p < 0.05$ after FDR correction) nodes in the brain. Size represents r, color their location in Yeo networks. (D) Correlogram of highly significant ($r >= 0.4$) nodes associated with spatial learning and memory performances. Nodes are grouped by their location in seven functional networks defined by the Yeo atlas.

differences between controls and patients. However, while functional connectivity is constrained by the structural connectome, it has also been proposed to contain information which is independent from structural connectivity (Engel et al., 2013; Mišić et al., 2016). Therefore, the absence of detectable or specific alterations in functional connectivity on a global level might result from increased functional connectivity caused by structural disconnection in concurrence with decreased plasticity in mildly disabled RRMS. This interpretation is supported by work from Patel et al. (2018), which suggested that structural disruption causes increased rather than decreased functional connectivity in MS.

On a global level, disrupted structural connectivity was predominantly associated with reduced performance in attention/processing speed and verbal learning and memory functions that are known as the most common impairments occurring in the early stage of MS (Schulz et al., 2006). Recently, Llufriu et al. demonstrated specific

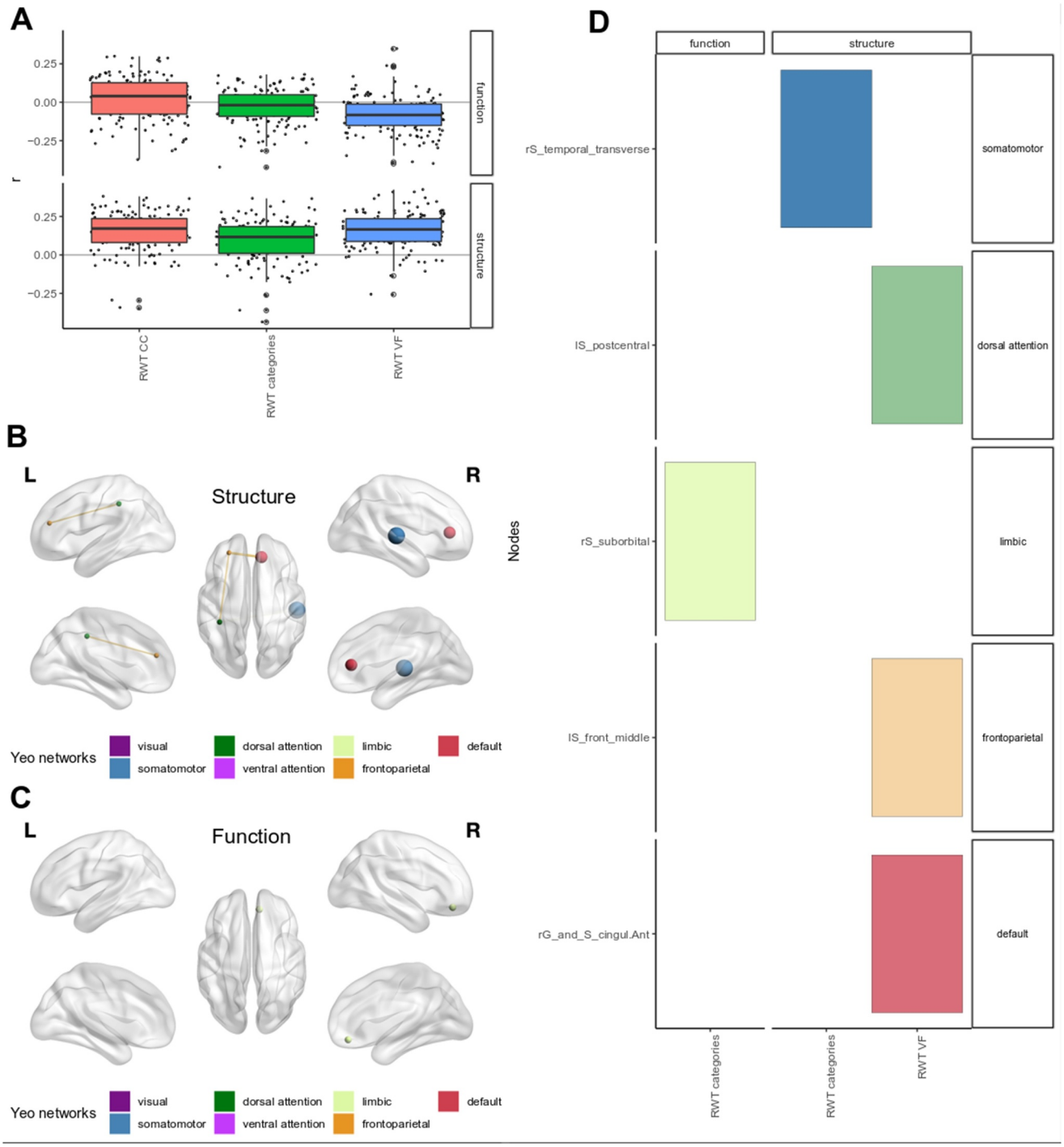

Fig. 6. The association of nodal structural / functional networks and executive functioning. (A) Boxplot displaying Pearson's correlation coefficients (r) for all nodes and for all tasks in the domain of executive functioning. (B) Correlogram of highly significant ($r >= 0.4$, $p < 0.05$ after FDR correction) nodes associated with executive functioning performances. Nodes are grouped by their location in five functional networks defined by the Yeo atlas. ($C + D$) BrainViewer plots illustrate the localization of highly correlated ($r >= 0.4$) nodes in the brain. Size represents r, color their location in Yeo networks.

structural networks like fronto-parietal networks to be involved in attention and executive function impairments in patients advanced/long standing RRMS (Llufriu et al., 2017). In addition, a correlation was shown between impaired structural connectivity and the hippocampal-related memory network in a large cohort of MS patients (Llufriu et al., 2018). However, these studies have not systematically assessed the relationship between cognitive performance and global structural networks of mildly disabled RRMS patients. Our study is supporting the relevance of structural integrity for the preservation of cognitive functions in MS and extends previous research to mild RRMS. This is in line with the concept that neurodegeneration is not a feature of long-standing MS but occurs without clinical manifestation from diseases onset (Friese et al., 2014; Stys et al., 2012).

It has been suggested that the deterioration of structural connectivity leads to a loss of diversity in large-scale cortical dynamics (Hawellek et al., 2011) and is a potential biomarker for monitoring cognitive dysfunction in MS (Shu et al., 2016). As reported here, attention/processing speed, verbal and spatial learning and memory were

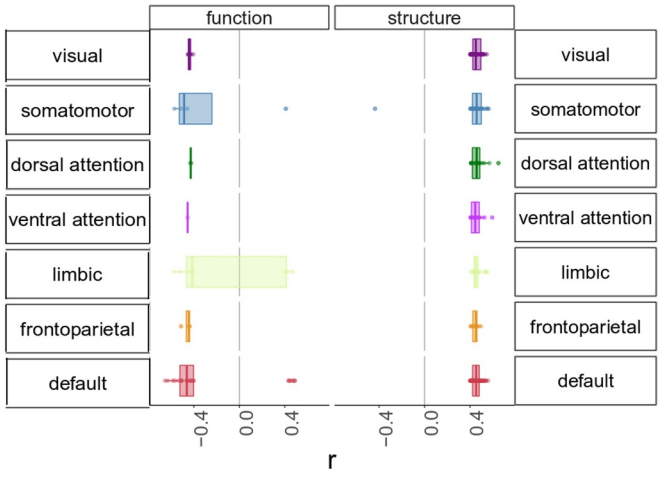

Fig. 7. Figure shows the significant correlation coefficients for all nodes, which were related to at least one cognitive test within patients. Direct ($r = 0.4$) and inverse ($r = -0.4$) associations of functional (left) and structural (right) connectivity of nodes with overall cognitive performance.

mainly related to changes in both visual and default mode networks. The broad pattern of association between cognition domains and nodal strength in different Yeo networks might indicate that cognitive performance depends rather on general structural connectivity than on the integrity of a specific sub-network in MS. This topology is not unexpected: The visual network is active at rest even when no visual task is performed and increased functional connectivity is associated with structural impairment, for example, after optic neuritis in neuromyelitis optica and MS (Backner et al., 2018; Finke et al., 2018).

The default mode network is defined as one of the functional brain networks that uses the most direct structural links (Horn et al., 2014). It is de-activated during cognitive performance, but active in the resting state, and alterations of the default mode network have shown a link with cognitive decline associated with aging, mild cognitive impairment, Alzheimer and MS (Rocca et al., 2010; Sorg et al., 2007). However, as summarized in a review paper (Schoonheim et al., 2015), there is a discrepancy in the literature as findings indicated both increased and decreased DMN connectivity as potential substrates of cognitive impairment. This might be caused by different diseases states (e.g. inflammatory vs. progressive MS) and different principles that were used for the processing of MRI data. Recently, Rocca et al. suggested that both increased and decreased functional connectivity might occur in MS and accompany a wide range of clinical manifestations (Rocca et al., 2018). Here, the misbalanced functional connectivity in DMN seems to be associated mainly with verbal learning and memory performance in RRMS. In addition, increased functional connectivity with poorer performance is in line with the previous studies (Faivre et al., 2012; Hawellek et al., 2011; Meijer et al., 2017). In light of the debate about maladaptation and adaptation, comprehensive assessment of cognitive functioning and combination of structural and functional analysis has been proposed as a means to solve the discrepancy. Although the discussion will not be concluded without longitudinal studies with sufficient sample size, in our study, increased functional connectivity in relation to worse cognitive performance appears as a possibly maladaptive response to structural damage in most cases. Our findings indicate that the discussion should probably focus more on network imbalances to better understand the complexity of heterogeneous activation patterns. Furthermore, longitudinal and task-based fMRI studies may aid in solving the misbalanced managing function within the default mode network. Several limitations of our study need to be considered. Our sample was small, MS patients mostly had mild disability, and we used a cross sectional design. Although our study includes baseline assessment and we do not routinely apply PASAT in our clinic, some patients might not have been naive to the PASAT.

There were technical limitations caused by our calculation strategies. In our study, we threshold networks to keep only the strongest 15% of connections. This increases comparability of networks according to Achard et al., 2012; Achard et al., 2006) but might have an impact on network topology. However, applying different thresholds between 1 and 50% had no major impact on the relative connectivity of the nodes (data not shown). Similarly, weighted structural network was defined by average FA along the tracts of two regions to reduce the spurious connections (Besson et al., 2014b; Buchanan et al., n.d.). However, it is still hard to accurately interpret weighted networks due to the different diffusion characteristics in WM, both relevant and irrelevant, especially seen in long range tracks (Tsai, 2018). To solve the ambiguity that limits the tractography, advanced diffusion microstructure modeling and multi-modality imaging is necessary (Maier-Hein et al., 2017). In addition, we did not use advanced graph theoretical approaches and calculated mainly strength and degree as a starting point. Since small word concept states that these networks are circular in shape and do not have modules, our findings are limited and further studies might improve the findings by advanced graph theoretical approach. Finally, our study might be limited by our statistical model that used only *t*-test for comparisons. Generalized linear models with age/sex/education as covariates were also possible; however, we observed no differences between *t*-test and general linear models. Therefore, we chose the simpler model.

In conclusion, cognitive performance in early RRMS is almost certainly related to a widespread disruption of structural connectivity. In contrast, increased functional connectivity shows overall a reverse associations with few exceptions located in the default mode and limbic networks. A longitudinal study with a wide spectrum of clinical disabilities assed by weighted networks would be helpful to see the pattern during the long term and different effect according to the degree of clinical disability in MS. In particular, assessment of dynamic change might completely explain the misbalanced associations in DMN.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: ACHS: nothing to declare; LF: nothing to declare. JP reports grants from Deutsche Rentenversicherung Bund outside the submitted work. IKP has received honoraria for speaking at scientific meetings, serving at scientific advisory boards and consulting activities from Adamas Pharma, Almirall, Bayer, Biogen, Celgene, Desitin, Genzyme, Merck, Novartis,Roche, and Teva outside the submitted work. She has received research support from the German MS Society, Celgene, Novartis and Teva. AKE receives research funding from the Deutsche Forschungsgemeinschaft, Bundesministerium für Bildung und Forschung, and the EU. CH reports grants and personal fees from Biogen, personal fees from Genzyme, grants and personal fees from Novartis, grants from Merck-Serono, outside the submitted work. SM Gold reports honoraria from Mylan GmbH, Almirall S.A., and Celgene and research grants from Biogen, outside the submitted work. He receives research funding from the Deutsche Forschungsgemeinschaft, Bundesministerium für Bildung und Forschung, the National MS Society, and the European Commission. JPS receives research funding from Deutsche Forschungsgemeinschaft and reports grants from Biogen and Genzyme outside the submitted work. He further received personal fees from Biogen and Alexion.

CRediT authorship contribution statement

Arzu Ceylan Has Silemek: Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing, Visualization. **Lukas Fischer:** Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing,

Visualization. **Jana Pöttgen:** Writing - review & editing. **Iris-Katharina Penner:** Writing - review & editing. **Andreas K. Engel:** Conceptualization, Writing - review & editing. **Christoph Heesen:** Conceptualization, Writing - review & editing. **Stefan M. Gold:** Conceptualization, Writing - review & editing. **Jan-Patrick Stellmann:** Conceptualization, Methodology, Data curation, Formal analysis, Writing - review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nicl.2020.102177.

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