ORIGINAL RESEARCH

Altered intra- and interregional synchronization in relapsing–remitting multiple sclerosis: a resting-state fMRI study

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Background and purpose: Neuroimaging studies of relapsing–remitting multiple sclerosis (RRMS) have found structural disconnection and large-scale neural network dysfunction. However, few studies have explored the local brain activity of RRMS patients in the resting state.

Patients and methods: In this study, regional homogeneity (ReHo) and resting-state functional connectivity (FC) were used to investigate intra- and interregional synchronized activity in 22 patients with RRMS and 22 matched healthy controls (HCs).

Results: Compared with HCs, patients with RRMS showed significantly decreased ReHo in the left insula and right caudate. Through further seed-based FC analysis, we found decreased FC between the left insula and left precentral gyrus in patients with RRMS compared with HCs, as well as increased FC between the right caudate and right dorsolateral prefrontal cortex. Pearson's correlation analysis showed that a decreased ReHo value in the left insula was associated with an increased total white matter lesion loads (TWMLL) score (r=−0.594, P=0.004) or a worsened paced auditory serial addition test score (r=0.536, P=0.010). No other significant correlations were observed between the FC value (left insula − left precentral gyrus) and clinical scores (P=0.246–0.982). The ReHo value of the right caudate was negatively correlated with disease duration (r=−0.526, P=0.012) and with the TWMLL score (r=−0.596, P=0.003). Moreover, a positive correlation was observed between the FC value (right caudate − right dorsolateral prefrontal cortex) and the TWMLL score (r=0.523, P=0.012) or the modified fatigue impact scale-5 score (r=0.608, P=0.003).

Conclusion: Together, these findings suggest that the insula with regional dysfunction involves disconnection with sensorimotor regions, and demyelinating lesion-related intra- and interregional dysfunction in the caudate is associated with the impact of fatigue on cognitive control functions. Abnormal synchronization of intra- and interregional activity in the insula and caudate may play important roles in the pathology of RRMS.

Keywords: relapsing–remitting multiple sclerosis, functional MRI, resting state, regional homogeneity, functional connectivity, caudate, insula

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and neurodegenerative disease of the central nervous system which is a common cause of progressive neurological deficits in young adults.[1] Moreover, neurological symptoms including sensorimotor deficits, cognitive impairment, and fatigue[2–4] in patients with MS affect a range of daily activities such as working, driving, and social integration.[5] Nevertheless, the mechanisms of MS-related neurocognitive deficits and psychological health issues remain unknown. Diffuse white matter and gray matter lesions are widely believed to

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account for these neurocognitive problems and disabilities. Conventional magnetic resonance imaging (MRI) currently serves as an important diagnostic tool for MS, but it possesses shortcomings, including low sensitivity to gray matter lesions and diffuse white matter involvement, and a low ability to predict clinical status.[6]

Over the past two decades, advanced MRI techniques have enriched our understanding of the mechanisms underlying the structural and functional abnormalities that cause the neurological symptoms of MS. Together, cross-sectional and longitudinal studies have shown that gray matter atrophy occurs in the early stages of the disease,[7] and is associated with clinical disability[8] and cognitive deterioration.[9,10] These studies have also shown that cortical atrophy preferentially affects the frontotemporal area in patients with relapsing–remitting MS (RRMS).[11] In addition to the white matter abnormalities identified by conventional MRI, structural studies utilizing diffusion-tensor MRI have revealed abnormalities in normal-appearing white matter, cortex, and deep gray matter nuclei, particularly in the frontal and temporal regions, the motor strip, and the basal ganglia at the earliest stages of MS.[12,13] These studies reported that these abnormalities had a more pronounced association with increased disease duration and neurologic impairments.[12,13] Studies of resting-state functional MRI (rs-fMRI) have demonstrated the integrity of intra-network functional connectivity (FC) and changes in inter-network coupling in MS patients in the default mode network,[14–16] sensorimotor network,[17,18] and visual network.[19] These findings suggest that functional disconnection parallels both structural damage and clinical impairment.

Regional homogeneity (ReHo) provides an approach to investigate the local synchronization of spontaneous activity within neighboring voxels in the resting state.[20] Previous studies have demonstrated that ReHo has high test–retest reliability and neurobiological relevance, and it could serve as a neuroimaging marker to investigate the human brain function.[21,22] ReHo analysis has been successfully used to detect brain dysfunction in many diseases, such as neuromyelitis optica,[23] schizophrenia,[24] depression,[25] and autism.[26] Dogonowski et al[27] have shown a link between impaired regional integration in the cerebellum and general disability or ataxia using the ReHo method in MS. To the best of our knowledge, little is known about local functional homogeneity across the brain in MS. Furthermore, it is unclear whether such changes simply imply an abnormal local synchronization of low-frequency blood oxygenation level dependent (BOLD) signals reflective of abnormal metabolic activity or a successive relationship. FC is provided as a statistical correlation coefficient of BOLD signal coherence between remote brain regions and can help to further clarify this issue.

In this study, we hypothesized that regional function and subserving interregional connectivity networks would be affected by abnormal local functional homogeneity in RRMS. To test this hypothesis, we collected rs-fMRI data from patients with RRMS and compared the data from the RRMS group with data from healthy controls (HCs) to examine both intraregional synchronized activity (ie, ReHo) and interregional synchronized activity (ie, FC) within the whole brain in RRMS. We also predicted that RRMS patients would show abnormal brain activity associated with clinical marks. This study may enrich our understanding of the neural underpinnings of RRMS.

Materials and methods
Participants

Twenty-two MS patients (9 males, 13 females; mean age: 44.6 [range: 21–57] years) were recruited from the Department of Neurology of the First Affiliated Hospital of Nanchang University, according to McDonald's criteria.[28] The inclusion criteria for the patients were as follows: 1) presenting with a relapsing–remitting course[29] and 2) no clinical relapse symptoms occurring during scanning. The exclusion criteria were as follows: 1) an Expanded Disability Status Scale score >2.5 (corresponding to minimal disability),[30] 2) treatment with immunomodulatory medication, and 3) any brain lesions attributed to tumor or stroke, as assessed on the basis of medical history or MRI.

In addition, we recruited 22 age- and sex-matched healthy subjects to form a control group. All of the subjects self-reported as right-handed. This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the First Affiliated Hospital of Nanchang University. Written informed consent was obtained from each subject prior to the study.

Data acquisition

All MR images were obtained on a 3.0 T MR scanner (Trio Tim; Siemens Medical Systems, Erlangen, Germany). Foam pads and earplugs were used to reduce head motion and scanner noise, respectively. T2-weighted images, three-dimensional T1-weighted images, and rs-fMRI images were acquired using the following sequences: 1) T2-weighted turbo spin-echo imaging (repetition time [TR]/echo time [TE] =5,100/117 ms, number of excitations =3, echo train length =11, matrix =416×416, field of view

[FOV] =240×240 mm, slice =22, slice thickness =6.5 mm, orientation = axial); 2) three-dimensional T1-weighted imaging (TR/TE =1,900/2.26 ms, number of excitations =1, matrix =240×256, FOV =215×230 mm, slices =176, slice thickness =1.0 mm, orientation = sagittal); and 3) rs-fMRI scan using a standard T2*-weighted gradient echo sequence with the following parameters: TR/TE =2,000/30 ms, flip angle =90°, FOV =200×200 mm, matrix =64×64, 30 interleaved axial slices with 4 mm thickness with an interslice gap of 1.2 mm, number of time points =240. During the fMRI scanning, subjects were instructed to keep their eyes closed, not to think about anything in particular, and not to fall asleep.

Data preprocessing

All rs-fMRI data were processed using Statistical Parametric Mapping (SPM8, Welcome Trust Centre for Neuroimaging, London, UK) and Data Processing Assistant for Resting-State fMRI Advanced Edition V2.2 (DPARSFA; Chinese Academy of Sciences, Beijing, People's Republic of China). For each subject, we discarded the first ten volumes to avoid the possible effects of scanner instability and the adaptation of subjects to the scanner environment. The preprocessing steps included slice timing to correct within-scan acquisition time differences between slices, realignment to the first volume to correct head motion (a six-parameter spatial transformation), spatial normalization to the Montreal Neurological Institute template using a six-parameter spatial transformation, and resampling images into a spatial resolution of 3×3×3 mm³. We then performed signal linear detrending and voxelwise temporal bandpass filtering (0.01–0.08 Hz), and subsequently regressed out the nuisance covariates, including eight covariates (ie, signals from white matter and CSF, as well as six head motion parameters).

Recent studies[31–33] have indicated that head motion can significantly influence the results derived from rs-fMRI. So, we computed the voxel-specific framewise displacement (FDvox) for each subject by using the DPARSF toolbox as described in a previous study.[34] Using two-sample t-tests, we estimated the mean FDvox across all subjects and found no significant group difference (report in Table 1). In this study, we excluded subjects for further analysis if the translation or rotation of head movement was greater than 2 mm or 2° in any direction.

ReHo analysis

rs-fMRI data without spatial smoothing were used for ReHo analysis with DPARSFA.[35] Kendall's coefficient of concordance was calculated to measure the local synchronization of 27 nearest neighboring voxels with Equation 1,[20] and the ReHo value was assigned to the central voxel. Then, a ReHo map was obtained in a voxelwise manner. Thus, each individual ReHo map was generated. A standardized ReHo map was created by dividing every individual ReHo map by each participant's global mean Kendall's coefficient concordance value within the brain mask. Finally, the standardized ReHo maps were spatially smoothed using a Gaussian kernel (full width at half maximum) of 4 mm. Notably, spatial smoothing before ReHo calculation dramatically increased the ReHo value.[35]

$$W = \frac{\sum (R_i)^2 - n(\acute{R})^2}{\frac{1}{12} K^2 (n^3 - n)}, \text{ where } \acute{R} = \frac{1}{n}\sum_{i=1}^{n} R_i \quad (1)$$

Where W is the Kendall's coefficient concordance for a given voxel, ranging from 0 to 1; R_i is the sum rank of the ith time point; K is the number of time series within a measured cluster (27, one given voxel plus the number of its neighbors); n is the number of ranks (n=230 time points).

FC analysis

A seed-based correlation approach was used for FC analysis. The seed was defined in the difference regions of the ReHo

Table 1 Demographics and clinical characteristics of healthy controls and RRMS patients

	RRMS patients (n=22)	Healthy controls (n=22)	P-values
Sex (M/F)	9/13	9/13	>0.99
Mean age (range) (years)	44.6 (21–57)	40.1 (24–58)	0.86
Mean disease duration (range) (months)	34.1 (2–150)	–	–
Mean TWMLL* (range) (mL) (normalized)	15.9 (0.43–47.2)	–	–
Median EDSS (range)	1.8 (1–2.5)	0	–
Mean PASAT (range)	85.3 (70–108)	101.9 (79–119)	0.000
Mean MFIS-5 (range)	11.2 (6–17)	0.7 (0–4)	0.000
Head motion (mean ± standard deviation)	0.04±0.013	0.02±0.014	0.122

Note: *The measurement procedures for TWMLL in the RRMS patients were described previously by Shu et al.[36]
Abbreviations: EDSS, Expanded Disability Status Scale; F, female; M, male; MFIS-5, modified fatigue impact scale-5; PASAT, paced auditory serial addition test; RRMS, relapsing–remitting multiple sclerosis; TWMLL, total white matter lesion load.

analysis. FC analysis was performed using the data resulting from preprocessing. We calculated the temporal correlation between the seed region and every other voxel within the brain. We used eight nuisance covariates: the six head motion parameters, a white matter time course, and a cerebrospinal fluid time course. Fisher's z transformation was used to improve the normality of the correlation coefficients, and the resulting correlation coefficients were transformed into z values. All of the above procedures were executed using DPARSFA software.

Statistical analysis

Statistical analysis was performed using the software Statistical Package for the Social Sciences Version 17.0 (SPSS Inc., Chicago, IL, USA) for demographic and clinical data and SPM8 for fMRI data. Age and sex were included as covariates in the present and following statistical analysis of functional data. An independent two-sample t-test was performed on the standardized ReHo and FC maps using SPM8 software. ReHo and FC were reported at a two-tailed voxelwise significance level threshold of $P<0.01$ and cluster level of $P<0.05$ with Gaussian Random Field (GRF) correction. We used Pearson's correlation analysis to assess the relationship between the rs-fMRI measurements (ie, ReHo values and the strength of FC from the connections indicating significant group differences) and the clinical presentation of the subjects. The statistical significance level was set at $P<0.05$ (uncorrection).

Results
Demographic and clinical data

Table 1 provides the demographic information of the RRMS patients and HCs, and demonstrates the clinical features of RRMS patients. The two groups displayed no significant differences in age, sex, or handedness.

Decreased ReHo in RRMS patients

Compared with HCs, RRMS patients showed decreased ReHo in the left insula (Brodmann Area [BA] 13) and right caudate. No significant increase in ReHo was observed. Table 2 and Figure 1 show the group differences in ReHo

between RRMS patients and HCs (voxel-level $P<0.01$, cluster-level $P<0.05$, GRF correction).

Seed-based FC of altered ReHo regions

Based on group comparison in ReHo, the left insula and right caudate were selected as seed regions of interest for FC analysis. Consequently, we found decreased FC between the left insula and left precentral gyrus (lPreCG) (BA6) in patients with RRMS compared with HCs, while we observed increased FC between the right caudate and right dorsolateral prefrontal cortex (rDLPFC) (BA9) in patients (voxel-level $P<0.01$, cluster-level $P<0.05$, GRF correction) (Table 3 and Figure 2).

Correlations between ReHo/FC and clinical variables

We found that a decreased ReHo in the left insula was negatively correlated with total white matter lesion loads (TWMLL) score (Figure 3A), while it was positively correlated with paced auditory serial addition test (PASAT) score (Figure 3B). We found that a decreased ReHo in the right caudate was negatively correlated with TWMLL score (Figure 3C) and disease duration score (Figure 3D). No other significant correlations were identified between altered ReHo and the other clinical scores assessed. A positive correlation was observed between the intensity of FC (right caudate − rDLPFC) and TWMLL score (Figure 3E) or modified fatigue impact scale-5 (MFIS-5) score (Figure 3F). No other significant correlations were identified between the intensity of FC (left insula − lPreCG) and the clinical scores assessed (Table 4).

Discussion

In this study, the RRMS group presented a specifically decreased ReHo in the left insula and right caudate. Furthermore, the left insula showed decreased FC with the lPreCG, while the right caudate showed increased FC with the dorsolateral prefrontal cortex in patients with RRMS. We also identified an association between ReHo/FC and clinical variables

Table 2 Brain regions showing a significant difference in ReHo map between RRMS patients and HCs (voxel-level $P<0.01$ and cluster-level $P<0.05$, GRF correction)

Brain regions	Brodmann areas	Talairach coordinates (MNI)			Cluster size (voxels)	t statistic
		X	**Y**	**Z**		
RRMS-HCs						
Left insula	13	−45	−18	15	61	−3.6251
Right caudate	−	15	15	9	54	−4.8591

Note: An independent two-sample t-test was used.
Abbreviations: GRF, Gaussian Random Field; HCs, healthy controls; MNI, Montreal Neurological Institute; ReHo, regional homogeneity; RRMS, relapsing–remitting multiple sclerosis.
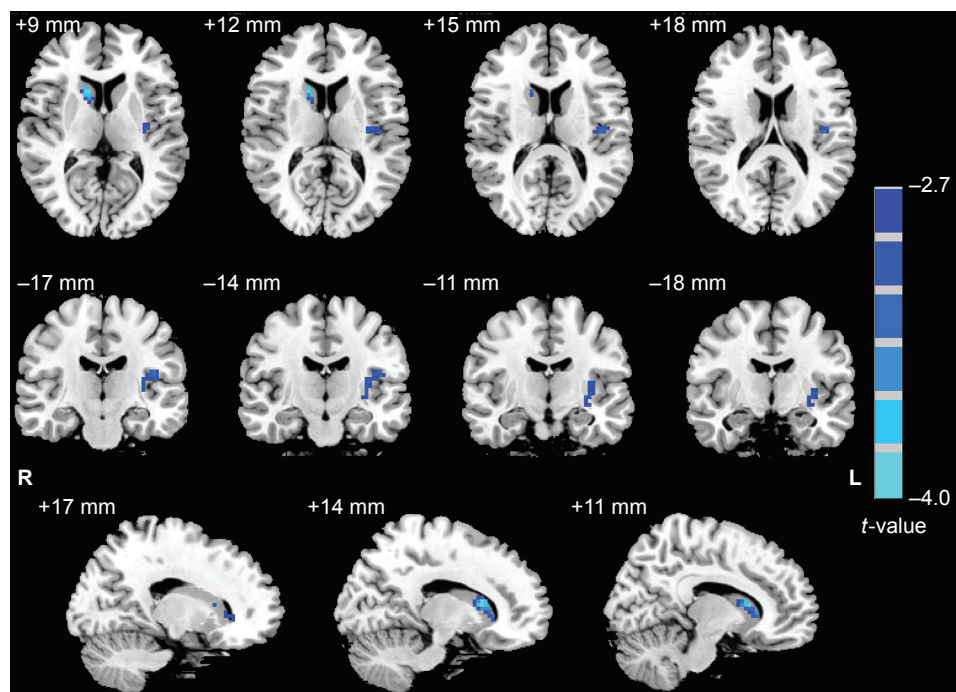
Figure 1 Group differences in ReHo between RRMS patients and HCs (voxel-level *P*<0.01, cluster-level *P*<0.05, GRF correction).
Abbreviations: GRF, Gaussian Random Field; HCs, healthy controls; ReHo, regional homogeneity; RRMS, relapsing–remitting multiple sclerosis.

Table 3 Group differences in seed-based functional connectivity in altered ReHo regions (voxel-level *P*<0.01 and cluster-level *P*<0.05, GRF correction)

Brain regions	Brodmann areas	Talairach coordinates (MNI)			Cluster size (voxels)	t statistic
		X	Y	Z		
RRMS-HCs						
Left insula seed						
lPreCG	6	−42	−12	57	50	−3.7159
Right caudate seed						
rDLPFC	9	48	9	42	32	4.0142

Note: An independent two-sample *t*-test was used.
Abbreviations: GRF, Gaussian Random Field; HCs, healthy controls; lPreCG, left precentral gyrus; MNI, Montreal Neurological Institute; rDLPFC, right dorsolateral prefrontal cortex; ReHo, regional homogeneity; RRMS, relapsing–remitting multiple sclerosis.
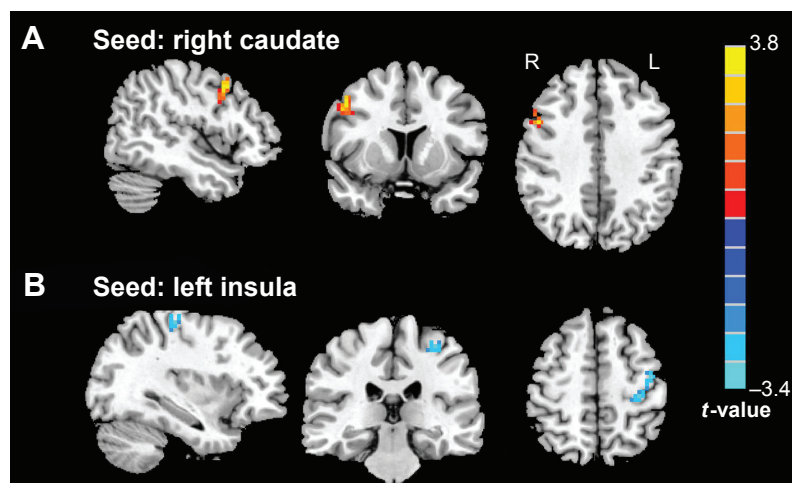

Figure 2 Group differences in seed-based functional connectivity between RRMS patients and HCs (voxel-level *P*<0.01, cluster-level *P*<0.05, GRF correction).
Notes: The right caudate seed exhibited increased FC with the right dorsolateral prefrontal cortex (**A**) and the left insula seed exhibited decreased FC with the left precentral gyrus (**B**) in patients with RRMS compared with HCs.
Abbreviations: FC, functional connectivity; GRF, Gaussian Random Field; HCs, healthy controls; RRMS, relapsing–remitting multiple sclerosis.
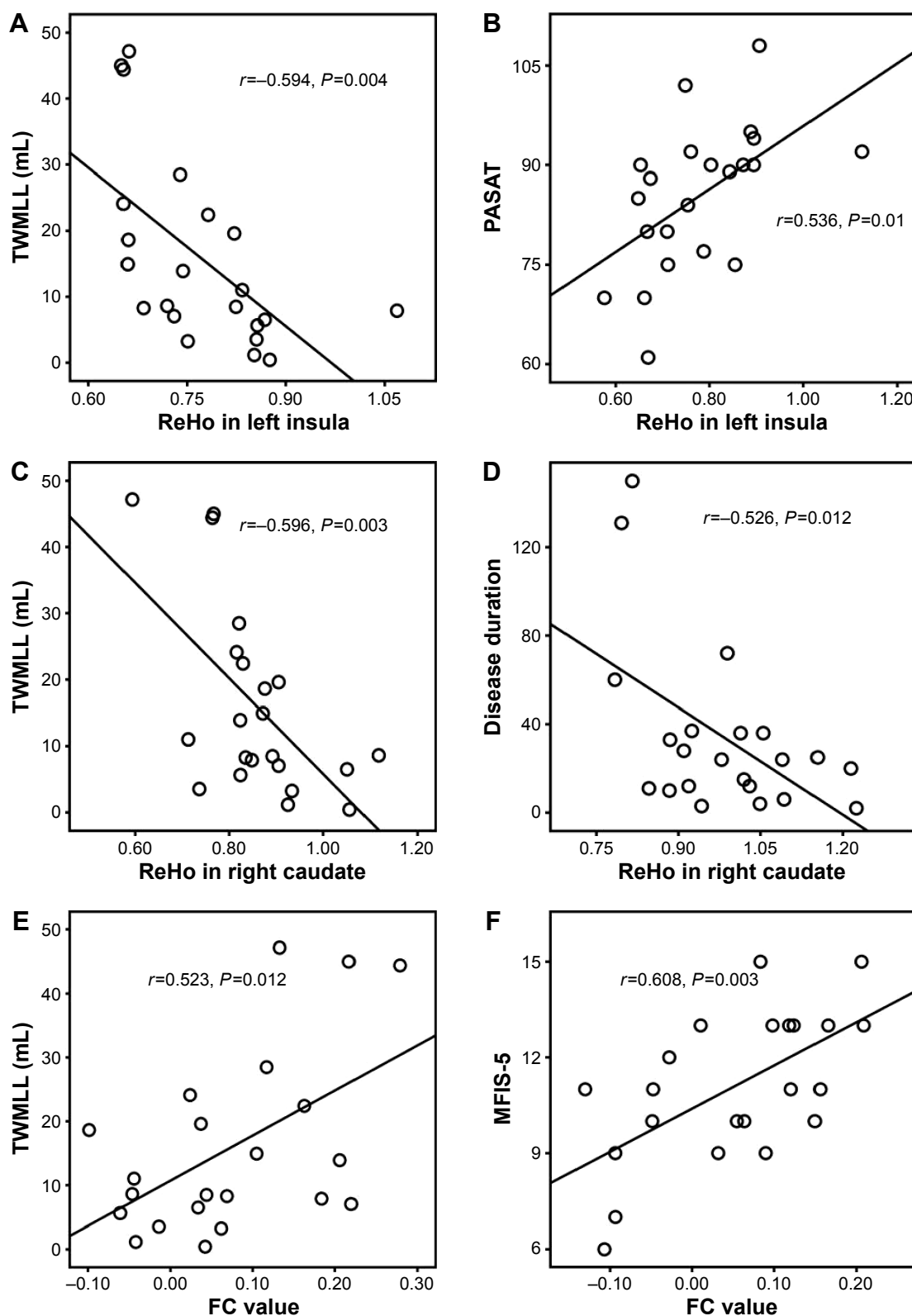
Figure 3 Correlations between ReHo/FC and clinical variables (uncorrection).
Notes: The decreased ReHo in left insula was negatively correlated with TWMLL score (**A**), while it was positively correlated with PASAT score (**B**). We found that the decrease in ReHo in the right caudate was negatively correlated with TWMLL score (**C**) and disease duration score (**D**). A positive correlation was observed between the intensity of FC (right caudate – rDLPFC) and TWMLL score (**E**) and MFIS-5 score (**F**).
Abbreviations: FC, functional connectivity; MFIS-5, modified fatigue impact scale-5; PASAT, paced auditory serial addition test; rDLPFC, right dorsolateral prefrontal cortex; ReHo, regional homogeneity; TWMLL, total white matter lesion loads.

Table 4 Correlations between ReHo/FC and clinical variables

	Correlation coefficient (*P*-value)				
	Disease duration	**TWMLL**	**EDSS**	**MFIS-5**	**PASAT**
Regional ReHo					
Insula	0.154 (0.493)	−0.594 (0.004)**	−0.255 (0.253)	0.376 (0.850)	0.536 (0.010)*
Caudate	−0.526 (0.012)*	−0.596 (0.003)**	0.038 (0.868)	−0.132 (0.558)	0.036 (0.874)
Strength of FC					
Left insula – lPreCG	−0.095 (0.674)	−0.005 (0.982)	−0.013 (0.954)	0.258 (0.246)	−0.006 (0.977)
Right caudate – rDLPFC	0.017 (0.939)	0.523 (0.012)*	0.243 (0.275)	0.608 (0.003)**	−0.208 (0.353)

Note: *$P<0.05$, **$P<0.01$ (uncorrection).
Abbreviations: EDSS, Expanded Disability Status Scale; FC, functional connectivity; lPreCG, left precentral gyrus; MFIS-5, modified fatigue impact scale-5; PASAT, paced auditory serial addition test; rDLPFC, right dorsolateral prefrontal cortex; ReHo, regional homogeneity; TWMLL, total white matter lesion loads.

such as lesion load (TWMLL) and PASAT in patients with RRMS. This evidence for local functional homogeneity and interregional FC contributes to our understanding of MS-related changes under neuropsychiatric conditions.

Decreased intraregional synchronized activity (ReHo) in RRMS

Our study found decreased ReHo in the left insula and right caudate in RRMS patients. ReHo is defined by the temporal coherence or synchronization of the BOLD time series between a given voxel and its nearest neighboring voxels,[20,37] and can be interpreted as an index of network centrality to characterize the importance of the node in the human brain connectome by its local functional interactions.[37] Decreased ReHo may suggest a disease-related dysfunction caused by dysregulation over a short distance.

In this study, we observed a decreased ReHo in the left insula. The insula plays roles in sensorimotor function, emotion, and decision making[38] as well as high-level cognitive processing,[39,40] and is a hub of the salience network.[41] The insula comprises anterior and posterior sections: the anterior insula is specifically sensitive to salient environmental events,[41] while the posterior insula is involved in somatosensory–vestibular interactions.[42,43] Moreover, decreased ReHo in left insula was positively correlated with PASAT score, which provides further evidence supporting a role for insula in high-level cognitive processing. Charil et al[44] have found that a relationship between TWMLL score and cortical loss in the insula was present in MS patients. Brain structure is considered to be the basis of function; our results show that decreased ReHo in the left insula is negatively correlated with TWMLL score, which corroborates this dogma.

The caudate is an important region involved in movement planning and execution[45] and is the main input node of the basal ganglia circuitry that receives glutamatergic fibers from

the sensorimotor cortex.[46] Moreover, the caudate is linked to the neural networks underlying affective and cognitive function.[45,47] In the current study, we detected decreased ReHo in the right caudate in patients with RRMS. These findings are consistent with previous reports that found abnormalities in caudate structure[48,49] and function[50,51] in patients with MS. In this study, abnormal ReHo in the caudate might reflect changes in somatosensory, motor, and cognitive functions in RRMS patients. Moreover, the ReHo of the right caudate was negatively correlated with RRMS duration and TWMLL score, indicating that the state of the right caudate may be a marker for the progression of RRMS. The decreased regional coherence in the left insula and right caudate is consistent with the reduced functional activation and structural abnormality reported in previous literature.[38–51]

Abnormal interregional synchronized activity (FC) in RRMS

To clarify how regional coherence affects interregional connectivity, we investigated the FC between regions with altered ReHo (left insula and right caudate) and other brain regions.

We observed decreased FC between the left insula and the lPreCG in patients with RRMS, which suggested dysfunction in the insula-related motor network. Structural studies have demonstrated that the insula plays the role of the so-called "rich club" within the connectomes to form the basis of its central communication.[52–54] Rs-fMRI studies also found that connections between the insula cortex and both the pre- and post-central cortex were mainly associated with the functional integration of somatosensory, motor, and auditory information.[55,56] He et al[57] suggest that the decreased network efficiency in MS might reflect the disrupted functional neuronal organization of spatially distributed cortical regions as well as disruptions in the integrity of large-scale interconnected brain systems. In our study, the FC value between the

left insula and lPreCG was found to be unassociated with clinical variables. Therefore, our interpretation of the current abnormal FC data in RRMS is cautious.

Connectivity between the rDLPFC and right caudate has been associated with increased restricted and repetitive behaviors that involve frontostriatal circuitry.[58] Also, few studies have found that increased FC might represent a neural mechanism to compensate for disease-induced dysfunction.[59,60] In the current study, we found that increased FC between the right caudate and rDLPFC positively correlated with TWMLL or MFIS-5 score. MS lesions are predominantly located in the white matter and, therefore, mainly affect axonal conduction. We suggest that FC between the right caudate and rDLPFC may be affected by MS lesions. The fatigue-related MFIS-5 scale is an abbreviated version used to assess the impact of fatigue on physical, cognitive, and psychosocial functioning. Finke et al[61] found that fatigue severity was correlated with FC of basal ganglia nuclei (ie, reduction in caudate volume) with medial prefrontal cortex, precuneus, and motor cortex. Fatigue is associated with distinct alterations of basal ganglia FC independent of overall disability. In our view, the association of the caudate with interregional hyperconnectivity acts to compensate for fatigue on cognitive control functions.

Interestingly, we observed a laterality alteration in interregional FC with altered ReHo regions (left insula and right caudate). There are two possible explanations: 1) disruption of anatomic connectivity of the corpus callosum in MS may affect the interhemispheric functional connecting interactions[62] and 2) compensatory functional reorganization ensues in both subcortical and cortical synchronization in the absence of corpus callosum.[63] In our study, we speculate that increased FC between the right caudate and rDLPFC may present compensatory function. In addition, compensatory functional reorganization as a complex and slow evolutionary fashion remains in need of further study to evaluate a specific functional pathway to explain decreased FC between the left insula and lPreCG.

Limitations
Certain MS lesions disrupted corresponding white matter pathways, which likely resulted in altered FC between gray matter regions and caused clinical impairment. However, cortical reorganization could improve the clinical symptoms caused by structural damage.[60] In future studies, the effects of lesion location should be considered when investigating the functional–structural–clinical relationships involved in MS. Second, decreased FC between the insula and PreCG

subserving sensorimotor dysfunction in RRMS was found in our study. Future studies should be designed to include a scale to measure motor function in order to obtain more information about the mechanism of motor impairment. Our study involved Pearson's correlation analysis for correlations between clinical data and neurocognitive metrics rather than multiple comparisons analysis, which should be applied in further studies.

Conclusion
This study suggests that RRMS patients present regional dysfunctions in the insula and caudate and decreased FC of the insula subserving sensorimotor dysfunction, and demyelinating lesion-related intra- and interregional dysfunction in the caudate is associated with the impact of fatigue on cognitive control functions. The alteration of intra- and interregional activity in the insula and caudate may play an important role in the pathology of RRMS.

Disclosure
The authors report no conflicts of interest in this work.

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