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Functional connectivity impairment of postcentral gyrus in relapsing-remitting multiple sclerosis with somatosensory disorder

Jialiang Fu, Xiaoya Chen, Yao Gu, Min Xie, Qiao Zheng, Jingjie Wang, Chun Zeng, Yongmei Li*

Department of Radiology, The First Affiliated Hospital of Chongqing Medical University, No. 1 Youyi Road, Yuzhong District, Chongqing, 400016, China

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ABSTRACT

Purpose: To characterize the spatial patterns of functional connectivity(FC) changes of whole brain in RRMS with somatosensory disorder(RRMS-SS) and to investigate the correlation between abnormal FC and clinical scores.

Methods: Twenty-six RRMS-SS patients and 23 healthy controls(HC) underwent resting-state functional magnetic resonance imaging(RS-fMRI) scanning. The clinical scores were collected including Expanded Disability Status Scores(EDSS), Disease Duration and Somatosensory Evaluation by the Fugl-Meyer sensory score(FMSS). With the voxel-wise methods, RS-fMRI data were analyzed using REST software, to assess the FC of the postcentral gyrus(PoCG). Correlation between clinical variables and the strength of FC was analyzed.

Results: Compared with HC, the left postcentral-based FC showed decreased FC of the right cerebellum_8, lingual lobe and Rolandic operculum gyrus, and increased FC of the left middle frontal lobe. The right postcentral-based FC revealed decreased FC with the right Heschl's gyrus lobule, and increased FC with bilateral middle frontal lobe ($p < 0.001$, AlphaSim corrected). Correlation analysis revealed that the FC of altered brain regions was associated with FMSS, EDSS and disease duration.

Conclusion: The functional connectivity of PoCG at RS-fMRI has multi-network changes in patients with RRMS-SS. This suggests a complex pattern of abnormal connections between the somatosensory network regions and the whole brain. Moreover, the correlation between the FC and the FMSS, such as the left middle frontal lobe and the right PoCG, indicate that these two brain regions play an important role in RRMS-SS.

1. Introduction

Multiple sclerosis is a chronic demyelinating and neurodegenerative disease associated with abnormal somatosensory and reduced stabilization [1]. Paresthesia is a common symptom, present in more than 80% of patients with relapsing-remitting multiple sclerosis (RRMS), which interferes with independent performance of activities such as dressing and working, even standing [2,3]. The somatosensory network is typically engaged in daily activities, therefore maintaining its own function is necessary for the quality of life. However, researchers have not paid enough attention to the patients of RRMS with somatosensory disorder(RRMS-SS).

Resting-state functional connectivity (FC) is a data-driven approach to analyze the temporal correlation of the intrinsic blood oxygen level dependent (BOLD) activities in various regions of the brain, thus highly-connected brain regions were identified to form a specific functional network [4,5]. Using this method, multiple networks can be identified, including somatosensory networks. In healthy adults, the somatosensory network mainly includes bilateral postcentral gyrus, precentral gyrus, middle frontal gyrus, cuneus, insular and middle occipital lobe. The postcentral gyrus(PoCG) has a high degree of integration in this network, which is called hub [6].

Previous fMRI studies used FC throughout the brain to describe complex patterns of abnormal connections between the sensorimotor network regions, as well as additional higher-order and multimodal integration areas [7–9]. However,these researches did not take into account patients with pure somatosensory disorder without motor impairment. Moreover, a 20-year longitudinal follow-up clinical study found that pure somatosensory disorder is common symptom and the most common sequelae in RRMS patients [10]. Therefore, in this study, we employed predefined PoCG to explore changes of FC in RRMS-SS.

The aims of the study are two-fold: first, to characterize the spatial patterns of FC changes of whole brain in RRMS-SS using a voxel-wise approach; and second, to investigate the correlation between abnormal FC and clinical scores to provide more evidences for the understanding of RRMS-SS.

* Corresponding author.
E-mail address: lymzhang70@aliyun.com (Y. Li).

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2. Material and methods

2.1. Subject group

Twenty-six RRMS patients and Twenty-three gender- and age-matched healthy control(HC) participated in this study. All tests are performed at our hospital and this research was approved by the biomedical ethics committee of our hospital. In addition, all participants provided written informed consent prior to participation in this investigation. The study period is from April 2015 to December 2017.

Inclusion criteria: all patients met the 2016 MAGNIMS diagnostic criteria [11]; the age between 18 and 59 years; right-handed; walk 100 m independently without any support and assistance; Extended disability status scale (EDSS) from 0 to 5.5. Exclusion criteria: exercise score of EDSS > 1; relapse of multiple sclerosis within the three months prior to study; a history of other neuropsychiatric symptoms; hypertension and/or diabetes; a history of previous head trauma; MRI contraindications.

Eligible patients underwent MR imaging immediately after the clinical physical examination and the scale test, and the HC underwent the same assessment and MR imaging protocol.

2.2. MR imaging acquisition

Imaging was acquired using GE Signa HDxt 3.0 T scanner(General Electric Medical Systems, USA) with 8-channel head coil. During the scan, subjects were asked to relax and remain still with their eyes closed but not to fall asleep. Skull MRI: Conventional axial T1WI (TR 250 ms, TE 2.86 ms, flip angle 90°, FOV 240 mm × 240 mm, matrix 224 × 224, layer thickness 5 mm, a total of 20 layers), T2WI(TR 3 600 ms, TE 120 ms, flip angle 90°, FOV 240 mm × 240 mm, matrix 256 × 256, layer thickness 5 mm, a total of 20 layers), T2W FLAIR sequence (TR 8 000 ms, TE 120 ms, flip angle 90°, FOV 240 mm × 240 mm, matrix 224 × 224, layer thickness 5 mm, a total of 20 layers). The resting-state BOLD sequence was acquired by GRE-EPI serial axial scanning (TR 2000 ms, TE 30 ms, flip angle 90°, FOV 240 mm × 240 mm, matrix 64 × 64, layer thickness 3 mm, a total of 33 layers, 240 time point). The scan range included the region from the calvarial vertex down to foramen magnum.

2.3. Somatosensory and neurologic testing

All study subjects underwent a comprehensive neurological examination and scale assessment by two experienced neurologists: EDSS, Disease Duration and Fugl-Meyer sensory score(FMSS). The FMSS includes a total of 12 items, each item range from 0 to 2. The final score was standardized (defined as the subtraction of 24 minus original FMSS), and the final score was greater than 0 indicated somatosensory impairment.

2.4. Resting-state functional MR imaging processing

For subjects, functional images were preprocessed using Data Processing Assistant for Resting-State fMRI software (DPABI, V3.1) (http://www.restfmri.net/forum/DPABI) [12]. The steps were as follows: First, the first 10 time points were discarded to exclude the subjects' adaptation and the impact of in-homogeneous magnetic field. Second: the slice timing and head motion correction were performed. No subjects were excluded by exceeding 2.0 mm of maximal displacement and 2.0 of maximal rotation in any direction. Third, the remaining fMRI data was normalized to the standard Montreal Neurological Institute (MNI) template by applying the EPI template at a 3 × 3 × 3 mm3 resolution. Fourth, the normalized BOLD image is smoothed by a Gaussian filter with a full width at half maximum (FWHM) of 4 mm. Fifth, the smoothed BOLD image is de-linearized Drift at 0. 01 ˜ 0.08 Hz filtering band. Sixth, Covariates such as the twenty-four head parameters, cerebrospinal fluid, gray matter and white matter signal artifacts were removed.

2.5. FC analysis

FC values were calculated by voxel-based analysis in REST V1.8 (http://www.restfmri.net/). The region of interest (ROI), defined as the bilateral PoCG (AAL57 and 58), was generated from the Automated Anatomical Labeling (AAL) atlas using the software REST. The correlation coefficients between the whole brain voxel and the seed points were calculated to obtain the correlation map. And then, Fisher transform was used to transform the correlation coefficient into z value to improve its normality and obtain the z-value map of functional connectivity for each subject.

2.6. Statistical analysis

Differences in demographic data and clinical scores between RRMS-SS and HC were analyzed using a two-sample *t*-test in the SPSS for Windows (version22.0; SPSS, Chicago, IL, USA).

To investigate differences in FC of PoCG between the two groups, two-sample t-tests were performed using REST. AlphaSim, a program based on Monte Carlo simulation and implemented in Analysis of Functional Neuro Images (http://afni.nimh.nih.gov), was used for multiple comparison correction. According to Monte Carlo simulations, a corrected *p*-value less than 0.05 had obtained a combination criterion of voxels with a *p*-value < 0.001 and a cluster size > 66(Left), a cluster size > 72(Right) with whole brain mask, respectively.

Correlation analysis was performed between the total score of FMSS, EDSS, disease duration and mean FC. The threshold of statistical significance was set at *p*-value < 0.05, controlling for the effect of age, gender, education.

3. Results

3.1. Demographic and clinical data

The demographics and clinical scores are shown in Table 1. There were 10 males and 16 females in the patient group, with a mean age of 38.8 years, a rang from 1 to 24 years and mean disease duration of 6.6 years, a range from 1.0 to 5.5 and mean EDSS of 2.19; the control group had 13 men and 10 women, with a mean age of 37.5 years. There was no significant difference in education between the two groups. In the patient group, the disease-related score was significantly higher than in the control group($p < 0.001$).

3.2. Functional MR imaging characteristics

Compared with the control group, the left postcenrtal-based FC showed decreased FC of the right cerebellum_8, lingual lobe and Rolandic operculum gyrus(extending to PoCG, superior temporal gyrus), and increased FC of the left middle frontal lobe. The right postcentral-based FC revealed decreased FC of the right Heschl's gyrus lobule(extending to Rolandic operculum gyrus, superior temporal gyrus and PoCG), and increased FC of bilateral middle frontal lobe(*p* <

Table 1
Demographics of the subjects with RRMS and healthy controls.

	Patient group	Control group	P-value
Age(mean(SD),years)	38.8(12.02)	35.7(12.80)	0.210
Sex(M/F)	10/16	13/10	0.508
Education(mean(SD),years)	12.23(3.922)	12.57(4.775)	0.137
Disease duration(Median(range),years)	6.6(1–24)	–	0.000
EDSS(Median(range))	2.19(1.0–5.5)	–	0.000
Fugl-Meyer(Median(range))	2.8(1–8)	–	0.000

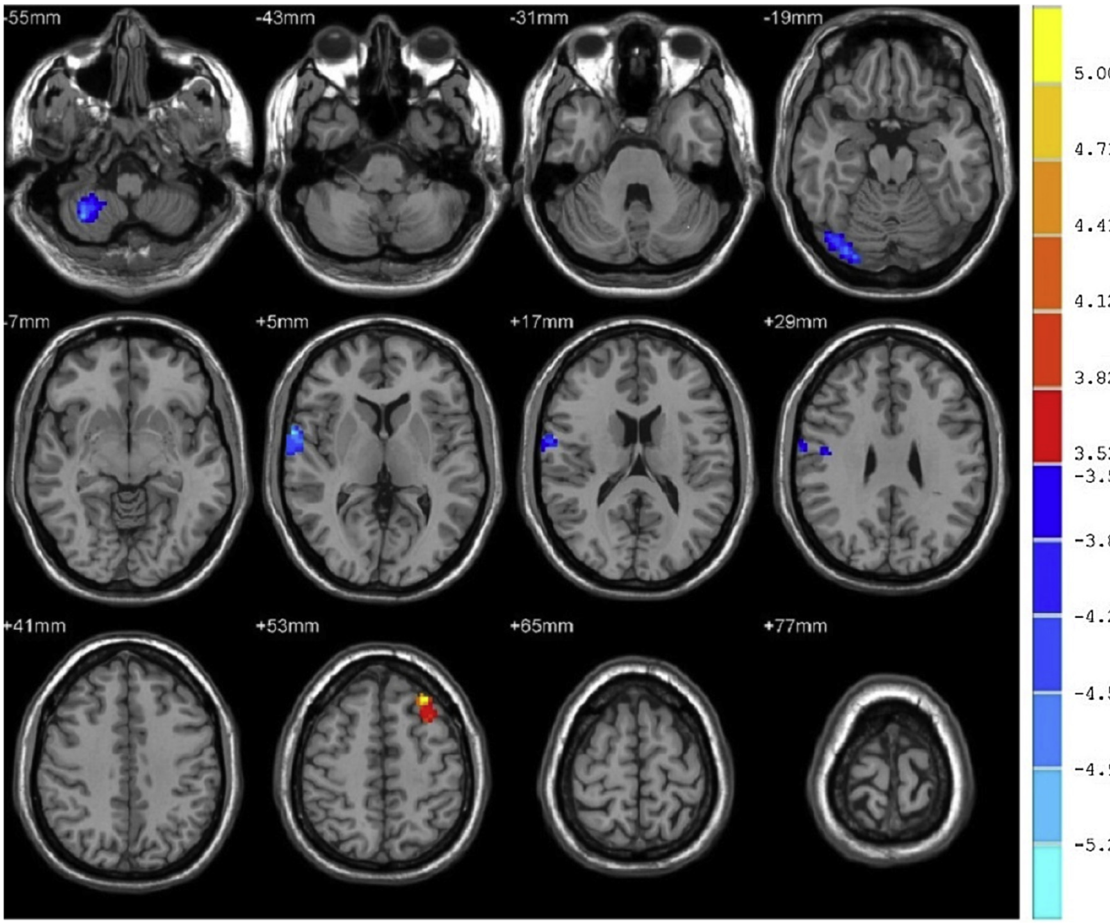

Fig. 1. FC: RED = RRMS > HC; BLUE = HC > RRMS. Notes: the blue brain regions include the right cerebellum_8, lingual lobe and Rolandic operculum gyrus (extending to PoCG, superior temporal gyrus); the red brain regions include the left middle frontal lobe ($p < 0.001$, AlphaSim corrected). The left side of the image corresponds to the right side of the anatomy. Abbreviations: FC, functional connectivity; HC, healthy control; PoCG, postcentral gyrus; RRMS, relapsing-remitting multiple sclerosis.

0.001, AlphaSim corrected), as shown in the Figs. 1 and 2 and Table 2.

3.3. Correlation between MRI data and clinical scores

We examined the relationship between FMSS, EDSS, disease duration and altered FC. The connections of the right PoCG, the left middle frontal lobe were significantly associated with FMSS in RRMS-SS. The right PoCG showed positive correlation between FC and FMSS. The left middle frontal lobe presented negative relationship between FC and FMSS.

The significantly positive correlation between the decreased FC of the right PoCG and EDSS was only found.

The abnormal FC of the right cerebellum_8, superior temporal lobe, and the right Rolandic operculum, were positively correlated with disease duration. The abnormal FC of the left middle frontal lobe was negatively correlated with disease duration. The results of correlation analysis is shown in the Fig. 3a, b and Table 3.

4. Discussion

Paresthesia is the most common clinical symptom of RRMS, which seriously affects people's daily activities, so maintaining its own somatosensory function is essential for quality of life. This research is the first study to explore FC impairment of PoCG in RRMS-SS by using a voxel-wise approach of resting-state fMRI.

In the present study, we used the bilateral postcentral-based FC to compare the differences in the connectivity patterns between RRMS-SS patients and HC. These areas were involved in default mode network, somatosensory network, visual network, and cerebellum hub network. Compared with HC, the regions showed decreased FC, including the right cerebellum_8, lingual lobe, Heschl's gyrus and Rolandic operculum gyrus, and increased FC including the bilateral frontal lobe. Additionally, the altered FC of most brain regions was associated with FMSS, EDSS and disease duration.

We found there was a decrease in FC between the left PoCG and the right cerebellum. Also, Tona revealed that the FC between the cerebellar dentate nucleus and the PoCG was decreased by using the cerebellum dentate nucleus as a seed point in MS patients with balance disorder [13]. Through animal electrophysiological experiments, the researchers found that there is a indirect connection between PoCG and cerebellum through thalamus [14–16]. An fMRI study showed that in MS patients with movement disorder, more activation of the PoCG occurred in the low lesion load group, while activation of the PoCG was reduced in the high lesion load group [17]. This result indicated that as disease processes and lesion load increases, the ability of the PoCG to regulate movement is further attenuated. So, we put forward a hypothesis that the somatosensory impairment may lead to heavier movement disorder. However, this study is a cross-sectional study after all. Longitudinal follow-up study is needed to confirm this hypothesis.

To our best knowledge, the frontotemporal lobe is the most advanced regions of brain and an important part of the default mode network, and it is also the most vulnerable [18]. Many researchers have used advanced MRI technology to discover that functional and structural damage occur in both the frontal and temporal lobes. A TBSS

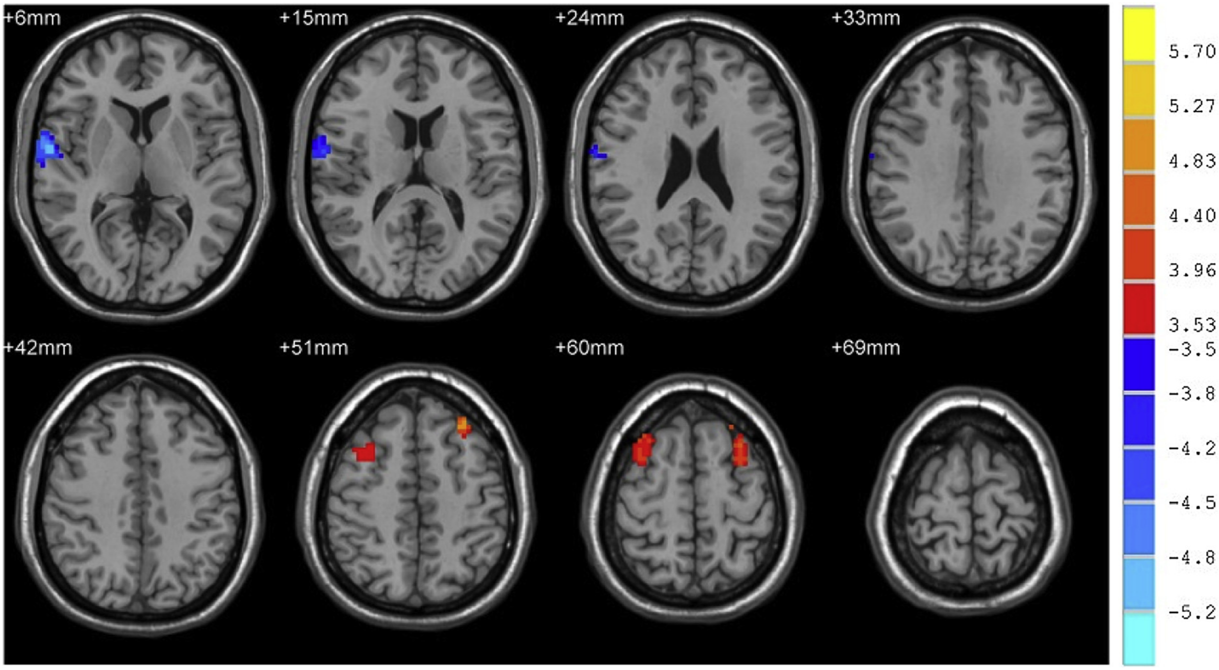

Fig. 2. FC: RED = RRMS > HC; BLUE = HC > RRMS. Notes: the blue brain regions include the right Heschl's gyrus lobule(extending to Rolandic operculum gyrus, superior temporal gyrus and PoCG); the red brain regions include the bilateral middle frontal lobe ($p < 0.001$, AlphaSim corrected). The left side of the image corresponds to the right side of the anatomy. Abbreviations: FC, functional connectivity; HC, healthy control; PoCG, postcentral gyrus; RRMS, relapsing-remitting multiple sclerosis.

Table 2
Brain areas showing significant FC differences of the bilateral postcentral gyrus between RRMS and healthy controls ($p < 0.001$, AlphaSim corrected).

Regions of interest	Brain Area	Peak MNI Coordinates			Cluster Size	T-score
		x	y	z		
Left postcentral gyrus	Cerebellum_8_R	33	−60	−57	75	−5.4268
	Lingual_R	33	−87	−18	75	−4.7089
	Rolandic_Oper_R	66	3	6	174	−5.4565
	Frontal_Mid_L	−27	30	51	91	5.2029
Right postcentral gyrus	Heschl_R	63	−3	6	148	−5.0697
	Frontal_Mid_R	39	9	54	82	4.2954
	Frontal_Mid_L	−30	30	54	73	6.1384

T-scores > 0 represent increased FC brain regions; T-scores < 0 represent decreased FC brain regions regions.

study showed that several regions exhibited increased axial diffusivity (AD), such as inferior temporal and frontal gyrus [19]. Berg et al discovered that depressed MS patients had a significantly larger temporal lesion load than non-depressed MS patients, especially on the right side. A trend of difference was detected for lesions of the right frontal lobe [20]. Also, we found a common pattern of significantly decreased FC in some frontal and temporal lobe(the right Heschl's gyrus, Rolandic operculum, and superior temporal lobe).

Contrary to previous studies [21–23], in our study the decreased FC of these impaired brain areas were positively associated with the FMSS ie the more severe the somatosensory disturbance in RRMS the higher the connectivity of these regions with bilateral PoCG. On the other hand, the less FC drops, the more severe the clinical symptoms are. Although there were other brain regions that may compensate for the damaged brain regions, the underlying mechanism of this strange and interesting phenomenon remains unclear. Several factors,including clinical subtypes and methodological differences and course of disease of MS, may help to explain differences between studies.

Notably, in the current research, we found significantly decreased FC in the right but not the left cerebral hemisphere, which showed a partial lateralization. The possible reason for this is that our subjects are all right-handed. Gold et al discovered that only the right hippocampal volumes were smaller in the high depression versus the low depression in MS patients by using automated surface mesh modeling [24]. A functional brain network study showed that the basal ganglia hubs in HC are located in the left hemisphere, but in the right hemisphere in the MS [25]. However, the past data on the lateralization effect of brain changes may be an accidental phenomenon, lacking of clear consistent evidence. Thus, more studies on the different stages of MS are needed to exclusive the abnormal manifestations of the cerebral hemisphere and the consistency of lateralization.

In addition, we also found that the FC of the right lingual lobe, part of visual network, was decreased. Recent studies using an special optogenetically evoked BOLD fMRI revealed that the primary visual cortex responses are highly dependent on somatosensory stimuli, indicated that the somatosensory cortex has a wide range of physiological connections with the visual cortex [26,27]. Hence, when somatosensory disorder occurred, the functional connectivity of these brain regions would become abnormal.

Interestingly, at the same time as these brain region’s functional connections were decrease, we also found that in the study there were performed the increased FC of bilateral middle frontal lobes increased, and the FC of the left frontal lobe was negatively correlated with the FMSS. In other words, the higher connection between these brain

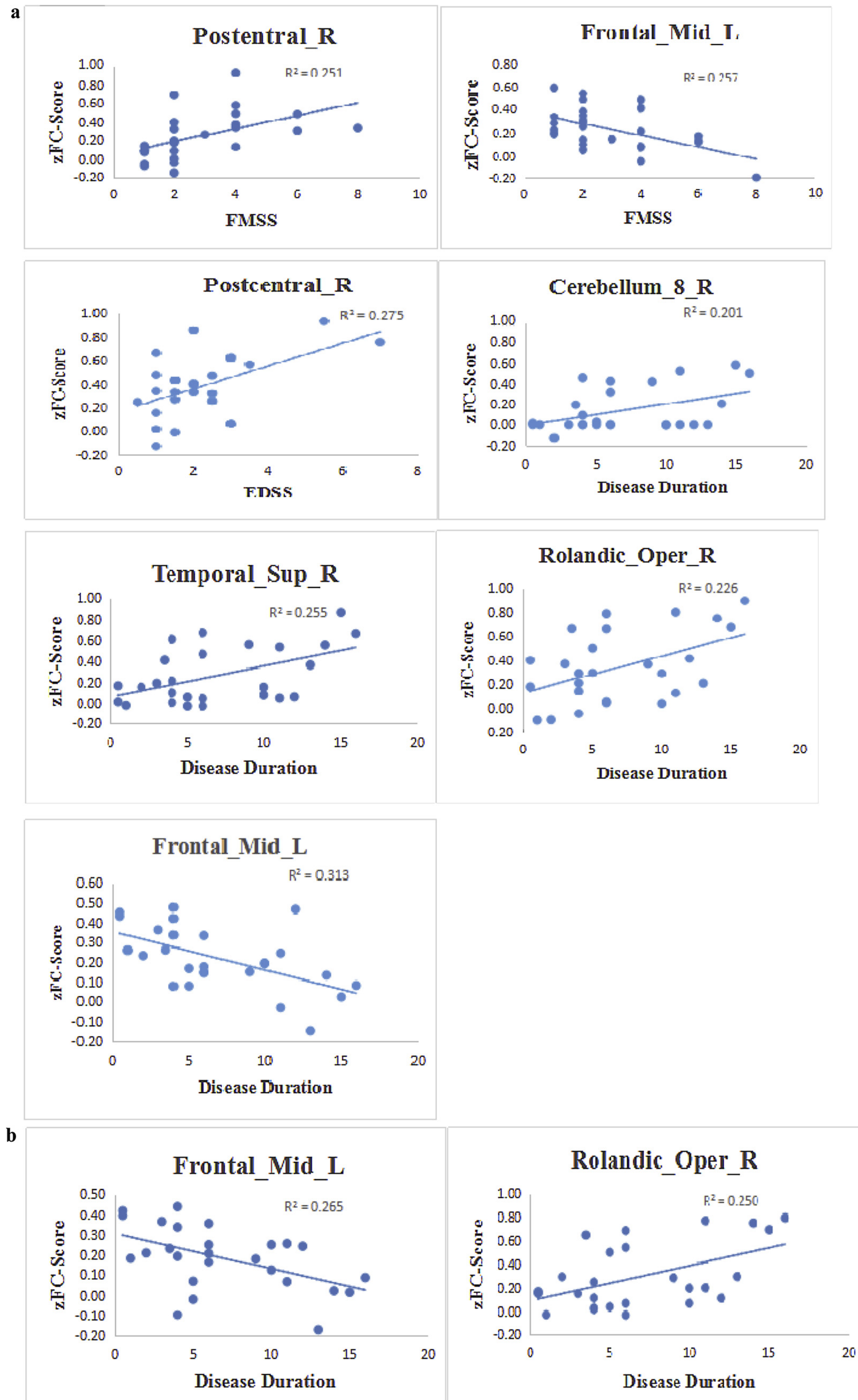

Fig. 3. a. Correlation analysis between clinical data and FC, using left PoCG as seed point. b Correlation analysis between clinical data and FC, using right PoCG as seed point.

Table 3
Correlation between disease severity scores and FC ($p < 0.05$, uncorrected).

Regions of interest	Correlation	Anatomic Area	MNI Coordinates			Cluster Size	P-value	r-value	R^2-value
			x	y	z				
Left postcentral gyrus	FMSS	Postcentral_R	69	−6	19	8	0.009	0.501	0.251
		Frontal_Mid_L	−33	24	48	8	0.036	−0.414	0.257
	EDSS	Postcentral_R	60	−9	39	20	0.006	0.525	0.275
	DD	Cerebellum_8_R	30	−60	−57	16	0.022	0.448	0.201
		Temporal_Sup_R	69	−12	6	21	0.008	0.505	0.255
		Rolandic_Oper_R	57	−6	12	10	0.014	0.4875	0.226
		Frontal_Mid_L	−30	36	51	14	0.003	−0.560	0.313
Right postcentral gyrus	DD	Frontal_Mid_L	−24	30	54	9	0.007	−0.515	0.265
		Rolandic_Oper_R	57	−3	9	14	0.009	0.500	0.250

regions, the lighter the symptoms. Based on these results, the hypothesis that increased FC as a compensatory adaptation mechanism to limit the consequences of disease-related functional impairment would be supported [28,29].

We found moderately negative correlations between the FC of the left middle frontal lobe and disease duration, suggesting a longer disease duration induced a more severe disconnection. This finding is also supported findings from previous DTI and FC studies which showed a correlation between structural and functional integrity and disease duration in MS patients [30,31]. In addition, we also observed that positive correlation between the FC and disease duration in several regions, such as the right superior temporal lobe, Rolandic operculum gyrus and cerebellum_8, suggesting the recovery of functional connections occurred in disease duration. As we expressed this kind of FC changes, the brain reorganization may be a dynamical process across the disease course. Nevertheless, it is not clear whether this dynamic change is an adaptive change or a maladaptive performance, so the further longitudinal research is needed.

There are not without limitations in this study. First, this study is a cross-sectional study; therefore, the lack of longitudinal data does not allow analyzing the cause-effect relationship. Second, this study was limited to just somatosensory scores and did not evaluate the relationship of depression and cognitive scale scores with functional connectivity of different brain regions. Third, because the sample size was small we did not include RRMS patients without somatosensory disorder. Fourth, only the functional connection method was used, we didn't study morphometric changes of the related brain regions.

5. Conclusion

Our findings showed that The functional connectivity of PoCG at RS-fMRI has multi-network changes in patients with RRMS with somatosensory disorder. This suggests a complex pattern of abnormal connections between the somatosensory network regions and the whole brain. Moreover, the correlations between the FC and Fugl-Meyer assessment score, such as the left middle frontal lobe and the right PoCG, indicate that these two brain regions play an important role in RRMS-SS. In the future, large samples of longitudinal studies should be used to obtain more specific and reliable imaging markers by combining structural and functional MRI to evaluate the pathophysiological changes of MS more comprehensively.

Declaration of Competing Interest

There is no conflict of interest in the submission of this manuscript and all authors are authorized to publish it. All the listed authors approved the manuscript.

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