Local functional connectivity of patients with acute and remitting multiple sclerosis

A Kendal’s coefficient of concordance- and coherence-regional homogeneity study

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Abstract

Using Kendall’s coefficient of concordance (KCC-) and Coherence (Cohe-) regional homogeneity (ReHo) to explore the alterations of brain local functional connectivity in acute and remitting relapsing-remitting multiple sclerosis (RRMS), and its clinical relevance. 18 acute RRMS, 26 remitting RRMS and 20 healthy controls received resting-state functional magnetic resonance imaging scanning. After data preprocessing and ReHo (KCC-ReHo and Cohe-ReHo) calculation, analysis of variance and followed post hoc analysis was used to compare the KCC-ReHo or Cohe-ReHo maps across groups.

Further correlation analysis showed disease duration was negatively correlated with the KCC-ReHo (when K = 7, 19) of left SFG (r = -0.633, P = .006; r = -0.620, P = .008), left MeFG (r = -0.608, P = .010; r = -0.555, P = .022), the KCC-ReHo (when K = 27) of left and right SFG (r = -0.551, P = .022; r = -0.603, P = .010), and the Cohe-ReHo of right MeFG (r = -0.608, P = .010) in acute RRMS; meanwhile, the KCC-ReHo (when K = 7, 19) of right SFG (r = -0.590, P = .013; r = -0.599, P = .011) was negatively related to expanded disability status scale scores in the acute RRMS.

Both acute and remitting RRMS patients has disease-related brain dysfunction, interestingly, relative to remitting RRMS, the acute RRMS patients mobilized more brain regions involving visual information processing in an attempt to maintain functional stability. In addition, our results also provide a methodological consideration for future ReHo analysis.

Abbreviations: ANOVA = analysis of variance, Cohe = Coherence, FOV = field of view, HCs = healthy controls, KCC = Kendall’s coefficient of concordance, MeFG = medial frontal gyrus, MOG = middle occipital gyrus, MRI = magnetic resonance imaging, MS = Multiple sclerosis, PASAT-3 = paced auditory serial addition test 3s, ReHo = regional homogeneity, RRMS = relapsing-remitting multiple sclerosis, Rs-fMRI = resting-state functional magnetic resonance imaging, SFG = superior frontal gyrus, TE = echo time, TR = repetition time.
Keywords: acute relapsing-remitting multiple sclerosis, Kendall’s coefficient of concordance- and Coherence- regional homogeneity, Remitting relapsing-remitting multiple sclerosis

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease with characterized by extensive and diffuse inflammatory demyelination in the central nervous,[11] relapsing-remitting multiple sclerosis (RRMS) is the most common type. The clinical symptoms of MS are complex and varied, the common symptoms including the cognitive deterioration, visual and sensorimotor impairment.[2–4] Meanwhile, higher order visual processing and perception is 1 of the most frequently affected cognitive characteristics in MS,[5] even in patients without severe cognitive deterioration or significant visual problems.[6,7] It is widely believed that the neurocognitive and visual information processing problems were caused by diffuse brain lesions. Conventional magnetic resonance imaging (MRI) currently serves as an important tool to detect the MS-related lesions, however the ability to predict clinical status is low and difficulty show the gray matter lesions.[8]

With the developing of MRI, multimodal MRI studies have capability to reveal abnormalities that can’t be detected by conventional MRI in normal-appearing white matter, cortex, and deep gray matter nuclei at the earliest stages of MS.[9] These advanced MRI technologies play a leading role in the diagnosing and assessing MS, contributing to our further understanding of the underlying the abnormal functional and structural alter that cause the neurological symptoms of MS.[10,11]

Recently, resting-state functional MRI (rs-fMRI) has become a best-studied tool for measuring the intrinsic dynamics of the human brain of physiological and pathological conditions.[12] In rs-fMRI, functional connectivity is widely used to reflect the neuronal intrinsic activity level in functional communication between regions. Previous studies had shown the MS patients’ impairment of the integrity in inter-network coupling and intranetwork functional connectivity in the salience network,[13] default mode network,[14,15] sensorimotor network,[16,17] and visual network.[18] Another study[19] revealed that different immune pathogenic processes occur as the disease stage changes, which may lead to different cognitive impairment. Moreover, a previous rs-fMRI study[20] observed the several regions with significant reductions in gray matter density in MS patients with acute lesion compared to the MS patients with chronic lesion. Together these studies revealed the changes in MS at different stages from pathology and imaging perspectives.

Nevertheless, previous most studies of MS focused on the impairment in the remission phase of RRMS, it’s little know whether the local property of intrinsic brain activity is different between acute phase and remitting phase of RRMS, and how spontaneous brain activity evolves from acute RRMS to Remitting RRMS.

Regional homogeneity (ReHo) is a sensitive method to measure the local functional connectivity of a given voxel and its neighboring voxels in different conditions.[21] This method is more reliable in test–retest analysis and less affected by global nuisances compared with other method, such as amplitude of low-frequency fluctuation.[22] Therefore, we hypothesize that the local property of intrinsic brain activity of MS in 2 disease stage (acute and remitting phase) would be different, and this discrepancy would explain the different clinical manifestation varying from different disease status. In order to confirm this hypothesis, first, 2 ReHo methods for rs-fMRI based on Kendall’s coefficient of concordance (KCC) and coherence (Cohe), proposed by Zang et al[23] and Liu et al[21] respectively, were used to explore the differences of regional spontaneous activity in the whole brain among the healthy controls (HCS), acute RRMS and remitting RRMS group. Another reason to use both parameters is that Cohe-ReHo is superior to KCC-ReHo,[21] but Cohe-ReHo has not been exploring the neurological mechanism of MS. Secondly, a post hoc analysis was performed to compare the ReHo index between each paired of groups. Finally, associations between ReHo and clinical variables were evaluated. This study may enrich our understanding of the possible imaging mechanisms that MS patients with different disease states accompany by different clinical manifestations.

2. Materials and methods

This study was approved by the Medical Research Ethics Committee and the Institutional Review Board of the First Affiliated Hospital of Nanchang University. All participants provided an informed consent form.

2.1. Participants

We recruited 44 patients with clinically definite MS at the First Affiliated Hospital of Nanchang University according to 2017 revision of the McDonald’s criteria.[24] Subsequently, we divided the MS patient group into acute phase and remission phase. The acute MS patients mainly met the several criteria: the first acute attack or functional impairment, lasting at least 24 hours. The remitting MS patients met the criteria:

1. the Expanded Disability Status Scale (EDSS) score < 2.5, which reflecting a relatively minimally disabled stage[25];
2. had not experienced a relapse and no disease-modifying medications (eg, corticosteroids or immune suppressants) treatment in the 3 months preceding the MRI measurement.

Neurological or psychiatric symptoms not attributable to MS were defined as exclusion criteria. Well-matched (age and gender) HC were enrolled from the local community. Healthy subjects had no history of neurological or psychiatric disease. Finally, a total of 18 acute RRMS, 26 remitting RRMS and 20 HC participated in the study (Table 1). Both acute and remitting RRMS underwent clinical assessments, which included EDSSs and the Paced Auditory Serial Addition Test 3s (PASAT-3).

2.2. MR imaging acquisition

A Trio 3.0-Tesla Siemens scanner (Siemens, Munich, Germany) was used to gather the MRI data. All subjects were instructed to lay down on the bench with foam pads, wear earplugs and put their heads to the head coil. During this process, they were asked to keep their eyes closed and awake. Each participant obtained
Table 1

Demographics and clinical characteristics of healthy controls and RRMS patients.

|                          | Acute RRMS (n = 18) | Remitting RRMS (n = 26) | HC (n = 20) | P-values |
|--------------------------|----------------------|-------------------------|------------|----------|
| Gender(M/F)              | 7/11                 | 10/16                   | 11/9       | .507     |
| Age(years) (mean±SD)     | 43.67±11.76          | 40.65±10.60             | 40±6.29    | .38      |
| EDSS (median)            | 3                    | 1.75                    | /          | <.001    |
| PASAT-3 (mean±SD)        | 38.67±4.67           | 44.85±6.27              | /          | <.001    |
| Disease duration (months) (mean±SD) | 29.28±29.03       | 27.32±31.36             | /          | .832     |

EDSS = expanded disability status scale, F = female, M = male, PASAT-3 = paced auditory serial addition test 3 s, / = no data, RRMS = relapsing-remitting multiple sclerosis, SD = standard deviation.

The P value for gender distribution in the 3 groups was obtained by chi-square test.

The P value for age distribution in the 3 groups was obtained by 1-way analysis of variance test.

The P value for difference of EDSS between the 2 groups was obtained by Mann-Whitney U test.

The P value for difference of PASAT-3 and disease duration between the 2 groups was obtained by 2-sample t test.

Table 1

Demographics and clinical characteristics of healthy controls and RRMS patients.

- The 3D-T1-weighted images, rs-fMRI images and T2-weighted images using the following sequences:
  - (1) High-resolution 3D-T1-weighted images: repetition time (TR)/echo time (TE) = 1900 ms/2.26 ms, field of view (FOV) = 215 mm × 230 mm, matrix = 240 × 256, thickness/gap = 1.0/0.0 mm and 176 sagittal slices.
  - (2) rs-fMRI scanning using an echo planar imaging sequence with the following parameters: TR/TE = 2000/30 ms, matrix = 64 × 64, FOV = 210 × 210 mm, 30 interleaved axial slices with a slice thickness of 4 mm, slice thickness = 1.2 mm, and 240 time points which lasted about 8 min.
  - (3) T2-weighted turbo spin-echo imaging: TR/TE = 5100/117 ms, number of excitations = 3, echo train length = 11, matrix = 416 × 416, FOV = 240 × 240 mm, slice = 22, slice thickness = 6.5 mm, orientation = axial.

2.3. Data preprocessing

Rs-fMRI data preprocessing was conducted using the Data Processing and Analysis of Brain Imaging (DPABI v4.2, http://rfmri.org/dpabi) toolbox, running on the MATLAB platform (The MathWorks Inc., Natick, MA). The main preprocessing steps included: the first ten volumes were discarded for signal equilibrium and subjects' adaptation, the remaining 230 time points were left for further analysis. Then slice timing, head realignment. After head motion correction, the rs-fMRI data were spatially normalized to standard Montreal Neurological Institute template along with resampling to 3 × 3 × 3 mm³ isotropic voxels. During scanning, if the head motion of the participant was over 2.0 mm maximum translation in any direction (x,y,z) or over 1.0 degree of maximum rotation about 3 axes, the subjects would be excluded. Meanwhile, linear detrending, nuisance linear regression with the 6 head movement parameters, the white matter and the cerebrospinal fluid signals and temporal bandpass filtering (0.01–0.08 Hz) were conducted on fMRI data.

2.4. ReHo analysis

(1) The KCC-ReHo Analysis: the procedures for KCC-ReHo analysis were performed by DPABI using the rs-fMRI data. KCC was calculated to measure the local synchronization of a given voxel to its nearest neighbor voxels (6, 18, 26) in a voxel-wise way with the Eq. (1). [25]

\[ W = \frac{1}{K^2} \sum_{i=1}^{n} (R_i)^2 - n(R)^2 \]  

where W is the KCC for a given voxel, ranging from 0 to 1, a higher ReHo index correlates to greater similarity between the local activity of a given voxel and that of its neighbors; Ri is the sum rank of ith time point; R = (n+1)K/2 represent the mean for RIs; K is the number of voxels (1 center voxel plus the number of its neighbors) within measured cluster, which represent different neighboring states between voxels. Voxels are adjacent to each other in 3 ways: vertices, edges or faces, that is, the number of voxels around the center voxel may be 26, 18 or 6, so K = 27,19 or 7. Different neighboring states between voxels may result in different time series in the minimum volume unit for calculating ReHo, hence, in consideration of the effect of different K values on ReHo results, in our study, we select 3 values of K (K = 7, 19, 27) to generated different ReHo maps; n is the number of ranks (here n = 240 time points). The calculated KCC value was assigned to the center voxel of this cluster.

(2) The Cohe-ReHo Analysis: the data analysis was performed using the Resting-State fMRI Data Analysis Toolkit plus V1.2 (REST plus V1.2, http://restfmri.net/forum/RESTplusV1.2), and the specific process of algorithm for calculating Cohe-ReHo was described in the previous study. [21] In brief, included 3 following steps. Firstly, Welch’s modified periodogram averaging methods were utilized to estimate the power spectrums and cross spectrum for any 2 times series in a given cluster. Secondly, the coherence of the 2 times series above-mentioned across low-frequency (0.01–0.08 Hz) band with their band-averaged estimates of the cross spectrum and power spectrums was evaluated. Finally, the given cluster’s Cohe-ReHo was calculated by averaging coherence coefficient of the cluster.

Through calculating the KCC-ReHo and Cohe-ReHo value of every voxel in the whole brain, an individual KCC-ReHo and Cohe-ReHo map was obtained for each subject in a voxel-wise way. Then, the standardized KCC-ReHo and Cohe-ReHo maps were generated via Fisher’s r-to-z standardization within a whole brain mask. Finally, the spatial smoothing was performed using a 6-mm full-width at half maximum Gaussian filter on the standardization KCC-ReHo and Cohe-ReHo maps.

2.5. Statistical analysis

For each KCC- or Cohe-ReHo map, 1-way analysis of variance (ANOVA) was conducted to explore the group differences across the 3 groups using statistical analysis of DPABI base on SPM12. The resultant F value map was corrected using Gaussian random field theory (2-tailed, voxel-wise P < .01, cluster-level P < .05). If different result was presented, the regions showed significant among-group differences at ANOVA were considered as regions of interest (ROIs). Additionally, the KCC- and Cohe-ReHo
values were extracted from these ROIs within each subject. Subsequently, a post hoc test (P < .001, Bonferroni correction) of these quantitative KCC- and Cohe-ReHo values was performed using SPSS 13.0 (SPSS Inc., Chicago, IL) to investigate the differences between paired subgroups (acute RRMS vs HCs, remitting RRMS vs HCs and acute RRMS vs remitting RRMS).

To examine the clinical correlation, we conducted a partial correlation analysis with age and gender as covariates (P < .05) to evaluate the relationship between ReHo value (KCC-ReHo or CoHe-ReHo value) extracted from the regions with significant group differences and clinical variables (EDSS, PASAT-3 and disease duration) of acute and remitting RRMS by using SPSS software.

3. Results

3.1. Demographic and clinical data

Demographics and clinical data for MS patients and healthy subjects were summarized in Table 1. There were no significant differences in gender (P = .507) and age (P = .38) among the 3 groups. The EDSS and PASAT-3 scores between the acute RRMS and remitting RRMS showed significant difference (P < .01). The difference of the disease duration between the 2 patient groups didn’t reach the statistical significance (P = .837).

3.2. KCC-ReHo or Cohe-ReHo differences among the 3 groups

ANOVA was used to determine the regions in which the KCC-ReHo or Cohe-ReHo index was significantly altered among the acute RRMS, remitting RRMS and HCs. Regions with significant differences among the 3 groups detected by the 2 ReHo analyses were overlapped (Table 2 and Fig. 1A-D), these overlapped regions located in: the left superior frontal gyrus (SFG), the right SFG, the left cuneus and the right middle occipital gyrus (MOG). The inconsistently altered region detected by 2 ReHo methods are detailed in the Table 2 (P < .01, Gaussian random field correction).

3.3. KCC-ReHo or Cohe-ReHo differences between each pair of groups

We employed the post hoc analysis to revealed the detailed KCC-ReHo or Cohe-ReHo alterations between each pair of groups (acute RRMS vs HCs, remitting RRMS vs HCs and acute RRMS vs remitting RRMS), and details were as follows:

(1) compared to HCs, the alterations were only detect in acute RRMS instead of remitting RRMS: the increased KCC-ReHo (when K = 7, 19, 27) (Fig. 2A-C) and Cohe-ReHo values (Fig. 2D) of acute RRMS were detected in the left cuneus and right MOG (P < .001);

(2) compared to HCs, the similar alterations were detect in acute and remitting RRMS patients: both KCC ReHo (when K = 7, 19, 27) (Fig. 2A-C) and Cohe-ReHo analysis (Fig. 2D) reported that the acute and remitting RRMS similarly exhibited the decrease ReHo values in the left and right SFG (P < .001). Additionally, the acute and remitting RRMS both exhibited the decreased KCC-ReHo (when K = 7, 19) in the left medial frontal gyrus (MeFG) (P < .001) (Fig. 2A-B) and decreased Cohe-ReHo in the right MeFG (P < .001) (Fig. 2D).

(3) compared to remitting RRMS, the acute RRMS exhibited lower KCC-ReHo (Fig. 2A-C) and Cohe-ReHo in the right MOG (P < .001) (Fig. 2D).

3.4. Correlations between the altered KCC-ReHo or Cohe-ReHo and clinical assessments

The correlation analysis showed that there were significantly negative correlations between the disease duration and the

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Table 2

| Region               | Talairach coordinate (MNI) | Cluster size (voxels) | F statistic |
|----------------------|---------------------------|-----------------------|-------------|
| L.Cuneus (K = 7)     | 31/19                     | 18                    | 87          | 15           | 103          | 13.481       |
| R.MOG                | 39/30                     | 30                    | 72          | 21           | 95           | 9.4173       |
| L.MeFG               | 32                        | -3                    | 54          | 9            | 90           | 12.9473      |
| R.SFG                | 46                        | 15                    | 57          | 21           | 100          | 13.5275      |
| L.SFG                | 10/9                      | -27                   | 42          | 33           | 129          | 9.7072       |
| R.MOG                | 30/19                     | 30                    | 72          | 21           | 161          | 9.5492       |
| L.MeFG               | 32/24                     | -3                    | 54          | 9            | 327          | 13.1709      |
| R.SFG                | 10/9                      | 15                    | 57          | 21           | 116          | 14.9885      |
| L.SFG                | 10/9                      | -27                   | 45          | 21           | 110          | 9.5371       |
| L.Cuneus (K = 19)    | 31/19                     | -18                   | -87         | 15           | 162          | 14.7772      |
| R.MOG                | 30/19                     | 30                    | -72         | 21           | 179          | 9.4734       |
| R.SFG                | 32/24                     | 15                    | 57          | 21           | 495          | 14.9599      |
| L.SFG                | 30/19                     | -27                   | 45          | 21           | 131          | 9.947        |
| L.Cuneus (K = 27)    | 31/23                     | -15                   | -87         | 15           | 271          | 12.5021      |
| R.MOG                | 39/31                     | 18                    | -81         | 21           | 357          | 12.0897      |
| R.MeFG               | 32/24                     | 15                    | 57          | 21           | 419          | 14.169       |
| R.SFG                | 10/9                      | 27                    | 42          | 27           | 102          | 11.6083      |
| L.SFG                | 46/32                     | -27                   | 45          | 30           | 392          | 12.916       |

Cohe = Coherence, GRF = Gaussian Random Field, KCC = Kendall’s coefficient of concordance, L = left, L.SFG = left superior frontal gyrus, MeFG = medial frontal gyrus, MNI = Montreal Neurological Institute, MOG = middle occipital gyrus, R = right, ReHo = regional homogeneity, RRMS = relapsing remitting multiple sclerosis, R.SFG = right superior frontal gyrus, SFG = superior frontal gyrus.
observed between the EDSS and the KCC-ReHo (when K = 7, 19) from the regions of left SFG (r = -0.633, P = .006; r = -0.620, P = .008) (Fig. 3B) or left MeFG (r = -0.608, P = .010; r = -0.555, P = .022) (Fig. 3C); between the disease duration and the KCC-ReHo (when K = 27) from the regions of left or right SFG (r = -0.603, P = .010; r = -0.551, P = .022) (Fig. 3B); between the disease duration and the Cohe-ReHo from the regions of right MeFG (r = -0.608, P = .010) (Fig. 3C). Additionally, significantly negative correlation was observed between the EDSS and the KCC-ReHo (when K = 7, 19) from the regions of right SFG (r = -0.590, P = .013; r = -0.599, P = .011) (Fig. 3A). Briefly, correlations between abnormal ReHo values and clinical assessments only detected in acute RRMS patients when compared with HCs (Fig. 3A-C). This further indicated that the increased ReHo of the MOG and cuneus only occurred in the acute phase of MS, implying that MS has the subclinical damage in visual pathway.

While no correlations were found between any of the clinical indices (disease duration, PASAT-3 and EDSS) and altered KCC- or Cohe-ReHo in remitting RRMS patients when compared with HCs (see Table, Supplemental Digital Content 2, http://links.lww.com/MD/F76, which illustrates the correlations between altered ReHo and clinical variables in the acute RRMS patients compared with HCs). No correlations were found between the clinical indices and altered KCC- or Cohe-ReHo in acute RRMS patients when compared with remitting RRMS (see Table, Supplemental Digital Content 3, http://links.lww.com/MD/F77, which illustrates the correlations between altered ReHo and clinical variables in the acute RRMS patients compared with remitting RRMS).

4. Discussion

In this study, we investigated the local functional connectivity property of the MS during the acute and remission phase using KCC-ReHo and Cohe-ReHo analyses. Our researches demonstrated that increased KCC-ReHo and Cohe-ReHo of the right MOG and left cuneus only occurred in the MS of acute phase rather than in the remission phase. MS patients have similar alteration in acute and remission phase: ReHo of the SFG and MeFG decreased compared with HCs. Furthermore, the correlations between ReHo (KCC-ReHo or Cohe-ReHo) and clinical variables (such as EDSS, disease duration) were only observed in acute RRMS.

4.1. More regional synchronized activity brain regions were mobilized/recruited in acute RRMS

In this research, patients with acute RRMS showed more widely spread KCC-ReHo or Cohe-ReHo values abnormalities in several brain regions, that is, the increased ReHo scores of the right MOG and left cuneus were only observed in the acute RRMS, indicating these changes are specific for acute RRMS patients. The MOG and the cuneus contributed to visual information processing and communication with the cerebral cortex, indicating that the acute RRMS mobilized/recruited more brain regions involved in visual information processing. In a previous study, a visual function impairment-associated amplitude of low-frequency fluctuations enhancement in MOG was demonstrated in RRMS patients. Another RRMS studies detected that the medial visual component functional connectivity significantly increased in left cuneus has influenced on visual processing speed in MS. Furthermore, the Optical Coherence Tomography has detected the reduced retinal nerve fiber layer thickness which was associated with visual functional dysfunction occur in the multiples sclerosis, even in the patients absence of Optic neuritis, implying that MS has the subclinical damage in visual pathway.

Taken together, it might be speculated that the acute RRMS mobilized/recruited more brain regions could be interpreted as an adaptive plasticity process, and this potential role is to compensate for the potential visual impairment of MS, to maintain functional stability. In early stages of lesion or the acute phase, axons and neurons are in part preserved, however, with maturation of the lesions and chronicity of the disease, substantial axonal loss is seen and the susceptibility of the target tissue for neurodegeneration increased. Furthermore, previous studies has observed significant heterogeneity with ReHo alterations of MS, usually, the brain lesion of MS initially causes an increase in connectivity, followed by a subsequent decrease before reaching a plateau. Hence, it should be interpreted with caution about the brain local connectivity alteration present in our study that increased ReHo of the MOG and cuneus only detected in acute RRMS rather than remitting RRMS, although related to acute RRMS, these brain regions seems to have returned to normal in remission phase, while we can’t affirm curtily that the local brain functional activity of these brain area recovery in remitting phase.
4.2. Similar alteration of regional synchronized activity in acute and remitting RRMS

In our present study, we observed the similar alterations in acute and remitting RRMS compared to HCs, that is, the acute and remitting RRMS patients both showed decreased KCC-ReHo (when \( k = 7, 19 \)) or Cohe-ReHo values in the SFG and MeFG. The bilateral prefrontal cortices regulate several cognitive processes, mainly associated with executive functions, working memory and making decision.[34,35] A previous study reported a significant hypoperfusion area was found for MS in the superior frontal gyrus, suggesting superior frontal gyrus has tissue damage.[36] The similar alteration was also reported in other previous perfusion study,[37] which showed a progressive cerebral blood flow and cerebral blood volume deficits present in the superior frontal gyrus for RRMS patients. Another study using echo planar spectroscopic imaging showed abnormal metabolite such as decreased NAA and Glx were predominantly tested in gray matter within prefrontal cortices in MS patients.[38] In addition, several study has reported that neuronal damage in the prefrontal cortices was correlates with cognitive dysfunction.[39] So we speculate that the decreased KCC-ReHo or Cohe-Reho in the present study may be attributable to brain dysfunction, such as impaired cognitive function.

4.3. Correlations between clinical indices and abnormal KCC-ReHo or Cohe-ReHo in acute RRMS

Significant correlation was only detected in the acute RRMS patients, the KCC-ReHo of the left SFG, right SFG and the left MeFG, while the Cohe-ReHo of the right MeFG was inversely correlated with the disease duration. Together, these results suggest that decreased local connectivity is associated with prolonged disease duration, in other words, MS patients with a shorter history of disease showed greater compensatory capacity in these regions compared to those with a longer history. In addition, the associations were observed between altered KCC-ReHo and the EDSS. This correlation was inconsistent with the previous published studies, as these studies reported that the EDSS is widely used instrument to evaluating the functional systems of the central nervous system, which is usually associated with sensorimotor networks.[17,40] The exact causes for these
differences were unknown, but it may be a spurious correlation that caused by the brain dysfunction.

4.4. Methodological considerations in KCC-ReHo and Cohe-ReHo

ReHo signifies the temporal synchrony of BOLD signals between an individual voxel and those of its neighboring voxels that participate in the execution of related functions in a given region. Zang and colleagues\[23\] applied the KCC ($K=7, 19, 27$) algorithms and later Liu and colleagues\[21\] applied the coherence-based algorithms to measure the local synchronization of rs-fMRI signal. In our study, a large proportion of brain regions (SFG, MOG and cuneus) of aberrant ReHo and its coordinates in MS patients detected by 2 ReHo analysis were similar, while the KCC-ReHo is more sensitive to detect the clinical relevance of ReHo than the Cohe-ReHo. Our result show different with the previous study reported by Liu et al.,\[21\] whose result suggested Cohe-ReHo is superior to KCC-ReHo owing to the Cohe-ReHo been not susceptible to random noise induced by phase delay among the time courses. In addition, previous studies mostly use KCC-ReHo (set $K=27$) to detect the abnormal spontaneous brain activity regions in all kinds of diseases,\[41,42\] and little know that what difference result will be happened compared to $K=27$ if $K=7$ or $K=19$. In present study, as for KCC-ReHo analysis, when $K=7$ or $K=19$, consistent alterations in spatial distribution were demonstrated and have the advantage to reveal more difference in the MeFG than $K=27$, suggested that $K=7$ or $19$ is superior to $K=27$ for KCC-ReHo analysis in MS patients. However, in order to deeper elucidate the sensitivity and specificity of these methods in MS patients, it’s necessary to carry out further studies.

5. Conclusions

In this study, based on 2 ReHo methods (KCC- and Cohe-ReHo), we revealed the disease-related brain local functional connectivity alterations in both acute and remitting RRMS patients, while the acute RRMS patients mobilized more brain regions in an attempt to maintain functional stability. In addition, our study also provides a methodological consideration for future ReHo analysis.

5.1. Limitations

Our study presented some limits. First, previous rs-fMRI study has demonstrated contradictory results of increased and decreased connectivity in MS, and inconsistent changes in local brain functional connectivity occurred as the disease stage changes was found in our study. In future studies, the effects of disease stages should be considered when investigating the alteration brain connectivity of MS. Second, future studies should be designed to add longitudinal data to obtain more information about the ReHo alteration trends throughout the disease cycle. Thirdly, the incidence of MS in China is low, previous study showed the national incidence of MS as 0.288 in adults per 100,000,\[43\] so the sample size collected in this study is small. This may have an impact on the reliability of our conclusions. While the subjects’ numble in this study was within the range of the sample size estimation method.\[44,45\] Finally, the population of this study was limited to RRMS patients with low EDSS scores (EDSS < 2.5), so we can recruit more remitting RRMS with higher EDSS scores to lower this limitation in further study.

Author contributions

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