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FULL PAPER

Structural abnormalities and altered regional brain activity in multiple sclerosis with simple spinal cord involvement

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Objective: To assess the changes of the structural and functional abnormalities in multiple sclerosis with simple spinal cord involvement (MS-SSCI) by using resting-state functional MRI (RS-fMRI), voxel based morphology (VBM) and diffusion tensor tractography.

Methods: The amplitude of low-frequency fluctuation (ALFF) of 22 patients with MS-SSCI and 22 healthy controls (HCs) matched for age, gender and education were compared by using RS-fMRI. We also compared the volume, fractional anisotropy (FA) and apparent diffusion coefficient of the brain regions in baseline brain activity by using VBM and diffusion tensor imaging. The relationships between the expanded disability states scale (EDSS) scores, changed parameters of structure and function were further explored.

Results: (1) Compared with HCs, the ALFF of the bilateral hippocampus and right middle temporal gyrus in MS-SSCI decreased significantly. However, patients

exhibited increased ALFF in the left middle frontal gyrus, left posterior cingulate gyrus and right middle occipital gyrus (two-sample *t*-test, after AlphaSim correction, $p < 0.01$, voxel size > 40). The volume of right middle frontal gyrus reduced significantly ($p < 0.01$). The FA and ADC of right hippocampus, the FA of left hippocampus and right middle temporal gyrus were significantly different. (2) A significant correlation between EDSS scores and ALFF was noted only in the left posterior cingulate gyrus.

Conclusion: Our results detected structural and functional abnormalities in MS-SSCI and functional parameters were associated with clinical abnormalities. Multimodal imaging plays an important role in detecting structural and functional abnormalities in MS-SSCI.

Advances in knowledge: This is the first time to apply RS-fMRI, VBM and diffusion tensor tractography to study the structural and functional abnormalities in MS-SSCI, and to explore its correlation with EDSS score.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system, and is the main cause of non-traumatic neurological disability in young adults. Besides cerebrum and cerebellum, the spinal cord is also a site of predilection for MS lesions, which often occur separately or ahead of brain lesions and can also merge with brain lesions.¹ MS with simple spinal cord involvement (MS-SSCI) is a subtype of MS, which is characterized by the selective involvement of the spinal cord when clinical defined MS. Of course, the lesions can also be present in brain with the development of the disease. So, MS with spinal cord lesions is just only a stage of this disease course.

In Asia and Latin America, there is relative high incidence. The clinical manifestations of MS-SSCI are diversities, including physical disability, backache, abnormal sensation, a longitudinally extensive disease and relapse, can seriously influence patient's quality of life. Amplitude of low-frequency fluctuation (ALFF) is an index developed by Zang et al to assess the amplitude of resting-state spontaneous brain activity by calculating the square root of the power spectrum in a low-frequency range (0.01–0.08 Hz).^{1,2} Voxel-based morphology (VBM) is a fully automated technique used to assess the density of brain tissues at a voxel level and has been applied to assess the regional distribution of both grey matter (GM) and white matter (WM).^{3–8}

Diffusion tensor tractography can reflect the brain structure of white matter tracts and direction. Researches have shown the abnormalities of fractional anisotropy (FA) and apparent diffusion coefficient (ADC) in MS patients by using diffusion tensor imaging (DTI).^{9,10} A number of researches have shown that MS patients have structural changes^{11–14} and functional abnormalities.^{10, 15–17}

Although MS-SSCI is relatively common in Asia, no research has been conducted on both the baseline brain activity and structure of MS-SSCI. To the best of our knowledge, this is the first time to applied resting-state functional MRI (RS-fMRI), VBM and diffusion tensor tractography to study the structural and functional abnormalities in MS-SSCI, and to explore its correlation with EDSS score may exist. In the present study, we aim to investigate MS-SSCI-related alterations of brain activities and anatomy using ALFF, FA, ADC and the volume of regions of interest (ROIs) and their correlations with clinical features. We hypothesized that (1) the activity and structure of brain would be altered in MS-SSCI, which arises ahead of visible brain lesions in T_2 weighted images (T2WI), and that (2) the changes of activity and structure in these areas may be correlated with expanded disability status scale (EDSS) scores.

METHODS AND MATERIALS

Subjects

We studied 22 patients with MS-SSCI (9 males, 13 females; median age 37.5 years, age range 22 to 50 years, median EDSS 3.5, range 1.0 to 7.5) and 22 age- and gender-matched healthy controls (HCs, 9 males, 13 females; median age 36.0 years, age range 24 to 51 years). Patients were recruited from the Department of Neurology, and normal volunteers were recruited from Chongqing Medical University and the surrounding communities. The subjects were all right-handed, as assessed by the Edinburgh Inventory.¹⁸ All subjects were assessed clinically by an experienced neurologist who was unaware of the MRI results. Inclusion criteria for the patients included those experiencing at least two attacks, objective clinical evidence of at least two lesions or objective clinical evidence of one lesion with reasonable historical evidence of a prior attack (the McDonald 2010 criteria¹⁹) and underwent a thorough physical examination on the day of the MRI examination. None of the recruited patients had neuromyelitis optica (NMO)-IgG positive or other neurological diseases or psychiatric problems, such as cerebrovascular disorders, hydrocephalus, an intracranial mass, psychiatric hospitalization, substance abuse, or traumatic brain injury and other myelopathy diseases.²⁰

All HCs from local community were matched to the patients individually for age, sex and school education, who were free of neurological or psychiatric diseases as assessed by a neurologist. None of the subjects in the control group received psychotropic medications.

This study was approved by the local Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. Written informed consent was obtained from all subjects.

Data acquisitions

All MRI was performed on a 3.0 T MR GE imaging System (Waukesha, WI) using an eight-channel phased-array head coil. The RS-fMRI data were recorded axially using an echoplanar imaging (EPI) sequence with the following parameters: repetition time (TR)/echo time (TE) = 2000/40 ms, flip angle = 90°, 33 slices, slice thickness/gap = 4.0/0.0 mm, voxel size (mm) = 3.75 × 3.75 × 4.0, matrix (cm) = 64 × 64, and field of view = 240 × 240 mm. A three-dimensional T_1 weighted fast-spoiled gradient echo sequence was acquired to determine anatomy in axial sections [TR/TE = 8300/3.3 ms, flip angle = 12°, matrix (cm) = 256 × 256, slice thickness/gap = 1.0/0.0 mm, slice number = 156]. DTI was performed using an echoplanar spin echo diffusion sequence [TR/TE = 15000/86.8 ms, field of view = 24 × 24 cm, matrix (cm) = 128 × 128, slice thickness/gap = 2.4/0.0 mm, slice number = 53, $b = 0$ and 30 directions for $b = 1000$].

The fMRI scanning was performed in darkness, and the participants were explicitly instructed to relax, close their eyes, and not fall asleep (confirmed by subjects immediately after the experiment) during the resting-state MR acquisition. Ear plugs were used to reduce scanner noise, and head motion was minimized by stabilizing the head with cushions. The subject's compliance was confirmed after the scanning was completed. All subjects completed the scans without reporting discomfort during or after the procedure. No subjects fell asleep during scanning. No obvious structural brain damage was found in any subject based on conventional MRI scans that were examined by two experienced radiologists.

Functional data preprocessing

Functional data preprocessing was performed using the Data Processing Assistant for RS-fMRI (DPARSF2.1, <http://www.restfmri.net>) based on the platform of Matrix Laboratory (MATLAB)7.9 (R2010a) (Mathworks, Natick, MA, USA). The first 10 sets of functional images were discarded due to lack of signal equilibrium and participants' adaptation to scanning noise. The remaining EPI images were then preprocessed using the following steps: slice timing, motion correction, spatial normalization to the standard Montreal Neurological Institute EPI template in Statistical Parametric Mapping (SPM8, <http://www.fil.ion.ucl.ac.uk>) and resampling to 3 × 3 × 3 mm, followed by spatial smoothing with a 6 mm full-width at half-maximum Gaussian kernel. According to the record of head motions in each fMRI run, all participants had a maximum displacement of less than 1 mm in the x , y , or z plane and less than 1° of angular rotation about each axis. RS-fMRI Data Analysis Toolkit (<http://restfmri.net/forum/rest>) was then used for removing the linear trend of time courses and for temporally band-pass filtering (0.01–0.08 Hz).

ALFF analysis

ALFF analyses were performed by using the RS-fMRI Data Analysis Toolkit (<http://restfmri.net/forum/rest>). The procedure for calculating ALFF is similar to that used in previous studies.^{20,21} After preprocessing, the time series for each voxel was filtered (band-pass, 0.01–0.08 Hz) to remove the effects

of very-low-frequency drift and high-frequency noise, such as respiratory and heart rhythms²². ALFF computations and further analyses were performed within a GM group mask. For standardization purposes, each individual ALFF map was divided by its own mean ALFF values within this mask.

The determination of ROIs

For further study, we used the RS-fMRI Data Analysis Toolkit (<http://restfmri.net/forum/rest>) to extract the ROIs that have a significantly different ALFF in MS-SSCI compared with normal controls.

Structural data preprocessing

Structural data preprocessing was performed using DPARSF2.1 (<http://www.restfmri.net>). The three-dimensional T_1 weighted images were preprocessed using the following steps: convert scanner images to Neuroimaging Informatics Technology Initiative format by using MRICron software (<http://www.mricron.com>; University of South Carolina, Columbia, SC, USA), segmentation, spatial normalization of the GM, WM and cerebrospinal fluid (CSF) to the standard Montreal Neurological Institute EPI template in Statistical Parametric Mapping (SPM8, <http://www.fil.ion.ucl.ac.uk>), smooth, then extract the volumes of ROIs.

Diffusion tensor tractography

Converting scanner images to Neuroimaging Informatics Technology Initiative format by using MRI conversion, viewing and analysis (<http://www.nitrc.org/projects/mricron>), then using SPM8 software to standardize these files formats and DTI track fibre tracking software to read the completed individual space transformation ROIs respectively. Finally, tracking through the WM fibre tracts of each ROI (minimum fibre length was 10 mm, minimum FA value was 0.2), importing an FA and ADC template and calculating the FA and ADC values of each individual respectively.

Measurements of spinal cord lesion volume

Visible spinal cord lesions were identified and manually extracted based on the T2WI (hyperintensity) by an experienced radiologist and compared with fluid-attenuated inversion recovery images (hyperintensity).

Statistical analysis

A two-sample *t*-test was performed to investigate the ALFF, FA, ADC and the volume of GM, WM, CSF and ROIs differences between MS-SSCI and HCs, with age treated as the covariate. Voxels with a *p*-value < 0.01 and a cluster size >1080 mm³ (40 voxels) were considered significantly different between the two groups. This yields a corrected threshold of *p* < 0.05, determined by Monte Carlo simulation using the AlphaSim program

(Parameters were: full-width at half-maximum = 6 mm, with a mask of the whole brain GM tissues). Pearson's correlative analyses were performed using SPSS v. 17 software (SPSS, Inc., Chicago, IL) to explore the relationships between the EDSS and changed structural and functional parameters in regions with significant group differences.

RESULTS

Characteristics of spinal cord lesions in conventional MRI

The spinal cord lesions of 22 MS-SSCI were commonly located in lower cervical spinal and upper thoracic spinal cord. All patients had no visible brain lesions on T2WI. Distribution of spinal lesions less than three vertebral segment sections is 91.67% (Table 1).

ALFF between MS-SSCI and HCs

The two-sample *t*-test confirmed significant differences in the ALFF values in specific brain areas of MS-SSCI compared with HCs (*p* < 0.01). In particular, significantly decreased ALFF values were observed in the bilateral hippocampus, right middle temporal gyrus of MS-SSCI. However, the ALFF values of the left middle frontal gyrus, left posterior cingulate gyrus and right middle occipital gyrus in the MS-SSCI were significantly higher than HCs (Figure 1, Table 2). A significant correlation between EDSS scores and ALFF was noted only in the left posterior cingulate gyrus (*r* = 0.595, *p* = 0.003, Figure 2).

Vol of ROIs between MS-SSCI and HCs

We compared the volume of all ROIs, only find the right middle frontal gyrus showed significantly brain atrophy (*p* < 0.01) compared with HCs.

FA and ADC of ROIs between MS-SSCI and HCs

The FA and ADC of right hippocampus and the FA of left hippocampus and right middle temporal gyrus has a significant difference compared with HCs (Table 3). There is no significant correlation among EDSS scores and the FA and ADC values of ROIs.

DISCUSSION

In this study, abnormalities of the structure and function in brain of MS-SSCI were quantified using RS-fMRI, VBM and diffusion tensor tractography.^{16,26,27} Compared with HCs, the ALFF of the bilateral hippocampus and right middle temporal gyrus in MS-SSCI decreased significantly. However, patients exhibited increased ALFF in the left middle frontal gyrus, left posterior cingulate gyrus and right middle occipital gyrus. The volume of right middle frontal gyrus reduced significantly (*p* < 0.01). The FA and ADC of right hippocampus, the FA of left hippocampus and right middle temporal gyrus were significantly different. A

Table 1. Characteristics of spinal cord lesions in conventional MRI

Distribution	C	T	L	C5–T6	≤1	1 ~≤ 2	2 ~≤ 3	≥3
N	13	10	1	19	1	16	5	2
%	56.17%	41.67%	4.17%	79.17%	4.17%	66.67%	20.08%	8.33%

C, cervical spinal; T, chest pulp; L, lumbosacral; N, number of lesions.

Table 3. FA and ADC of ROIs

DTI parameters	MS-SSCI	HCs	T value	p value
Right hippocampus				
FA	0.379 ± 0.186	0.392 ± 0.241	2.099	0.042
ADC (×10 ⁻⁴ mm ² s ⁻¹)	11.298 ± 0.0861	10.979 ± 0.0782	-2.053	0.047
Left hippocampus				
FA	0.501 ± 0.053	0.565 ± 0.035	-4.652	0.000
ADC (×10 ⁻⁴ mm ² s ⁻¹)	8.640 ± 0.417	8.601 ± 0.336	0.343	0.733
Right middle temporal gyrus				
FA	0.381 ± 0.055	0.463 ± 0.040	-5.688	0.000
ADC (×10 ⁻⁴ mm ² s ⁻¹)	8.490 ± 0.396	8.361 ± 0.353	1.140	0.261
Left posterior cingulate gyrus				
FA	0.515 ± 0.226	0.531 ± 0.304	1.894	0.065
ADC (×10 ⁻⁴ mm ² s ⁻¹)	8.666 ± 0.304	8.515 ± 0.239	-1.937	0.073
Left middle frontal gyrus				
FA	0.389 ± 0.169	0.3999 ± 0.206	1.874	0.068
ADC (×10 ⁻⁴ mm ² s ⁻¹)	1.221 ± 0.929	1.174 ± 0.866	-1.735	0.090
Right middle occipital gyrus				
FA	0.508 ± 0.038	0.535 ± 0.051	1.992	0.053
ADC (×10 ⁻⁴ mm ² s ⁻¹)	1.090 ± 0.088	1.0539 ± 0.083	-1.409	0.166

ADC, apparent diffusion coefficient; FA, fractional anisotropy; ROI, region of interest.

significant correlation between EDSS scores and ALFF was noted only in the left posterior cingulate gyrus

We detected the ALFF values using RS-fMRI, which showed decreased ALFF values in the bilateral hippocampus, right middle temporal gyrus, while increased ALFF values in the left

middle frontal gyrus, left posterior cingulate gyrus and right middle occipital gyrus of MS-SSCI compared with the HCs. The abnormal baseline brain activity may be due to spinal cord damage or potential brain damage that could not be detected at the examined disease stage.

Figure 1. Compared with the healthy controls, the ALFF values of the bilateral hippocampus, right middle temporal gyrus were significantly decreased in MS-SSCI. However, the left middle frontal gyrus, left posterior cingulate gyrus and right middle occipital gyrus showed increased ALFF values in the MS-SSCI group.

The hippocampus is closely related with the cognitive activities, study has shown that the existence of inflammatory demyelination in hippocampus of MS,²⁸ indicated that some MS-SSCI may exist spatial learning, memory and other senior activity abnormalities. Middle temporal gyrus is the high-level centre, participating in language and auditory processing and other activities. Posterior cingulate cortex is an important hub for the default mode network,²⁹ and is closely linked with the medial prefrontal cortex, temporal lobe, hippocampus, composed of the default network system. Studies have shown that the posterior cingulate gyrus plays a dominant role in complex tasks, including visual space image recognition, episodic memory, self-processing.³⁰ Our results indicated that increased ALFF and activity in the left posterior cingulate gyrus may be responsible for disrupting the default mode network and the abnormality in dealing with complex tasks in MS-SSCI. The left middle frontal gyrus has been widely involved in mental set maintaining³¹ and responds to complex tasks. This study showed the abnormal function in the left middle frontal gyrus, which may be related to the interaction or compensation of relevant brain regions caused by dysfunction of brain.

Additionally, the ALFF value of the left posterior cingulate gyrus was positively correlated with the EDSS score, indicated that the

Figure 2. A significant correlation between EDSS scores and ALFF was noted in the left posterior cingulate gyrus. ($r = .23^{.24}$, $p = .23^{.25}$).

neural activity of left posterior cingulate gyrus is still in compensatory stage. However, this remodelling is limited, it will cause structural damage when the injury is severe beyond the adaptive scope of brain. Our results suggested that the ALFF measurement of intrinsic brain activity could be useful for characterizing the physiology of MS-SSCI.

To further demonstrate the structural change of MS-SSCI, we calculated the volume of the regions where ALFF value changed. The results showed there was obvious atrophy of the right middle temporal gyrus compared with HCs, which is consistent with the results of Parisi et al.³² Middle temporal gyrus is the high-level centre, participating in language and auditory processing and other activities. Some MS-SSCI occur language abnormality and dysarthria, which may be related to the volume abnormalities of middle temporal gyrus.

Our study demonstrated the FA values of bilateral hippocampus and ADC value of right hippocampus reduced compared with HCs, which is consistent with the previous study.³³ Pathology has confirmed that the hippocampus of MS patients can occur demyelinating change,³⁴ suggesting that the bilateral hippocampus of MS-SSCI may have happened occult injury, which can be detected by DTI. Research has shown that the scope of MS lesions is far beyond the scope show in the conventional MRI, lesions can be located in cortical and GM, even normal appearing WM and GM.²³ The reduction of the FA and ADC values, prompting the myelin integrity and the number of dendrites and axons may be changed. In addition, reactive hyperplasia of microglia can also affect the diffusion of water molecules, which lead to the change of FA and ADC value.

The correlation study demonstrated that the structural parameters of right middle temporal gyrus, the FA and ADC values of right hippocampus have no significant correlation with clinical disability status. This may be related to the compensatory changes. So, we believe that the change of structure in MS-SSCI may be caused by spinal cord or the compensatory of brain, and the structural changes and clinical disability status were independent of each other.

There are some limitations in this study. Firstly, our results should be interpreted with caution because of the small sample size and cross-sectional design. Larger sample size and longitudinal studies are necessary to determine whether abnormal ALFF, FA, ADC and the volume of GM, WM, CSF values change dynamically after therapy. Secondly, we could not completely eliminate the effects of physiological noise, such as cardiac and respiratory fluctuations. Future studies should simultaneously record the cardiac and respiratory rates to address these potentially confounding variables. Lastly, we only analysed the relations between the encephalic regional changes with EDSS, a correlation with neuropsychological measures should be further considered.

In conclusion, our study demonstrated the abnormalities of structure and function in MS-SSCI using RS-fMRI, VBM, and diffusion tensor tractograph. We believe these alterations may reflect spinal cord damage or potential brain changes that cannot be detected by conventional MRI. Multimodal plays an important role in detecting structural and functional abnormalities in MS-SSCI.

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