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Changes of resting cerebral activities in subacute ischemic stroke patients

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Abstract
This study aimed to detect the difference in resting cerebral activities between ischemic stroke patients and healthy participants, define the abnormal site, and provide new evidence for pathological mechanisms, clinical diagnosis, prognosis prediction and efficacy evaluation of ischemic stroke. At present, the majority of functional magnetic resonance imaging studies focus on the motor dysfunction and the acute stage of ischemic stroke. This study recruited 15 right-handed ischemic stroke patients at subacute stage (15 days to 11.5 weeks) and 15 age-matched healthy participants. A resting-state functional magnetic resonance imaging scan was performed on each subject to detect cerebral activity. Regional homogeneity analysis was used to investigate the difference in cerebral activities between ischemic stroke patients and healthy participants. The results showed that the ischemic stroke patients had lower regional homogeneity in anterior cingulate and left cerebrum and higher regional homogeneity in cerebellum, left precuneus and left frontal lobe, compared with healthy participants. The experimental findings demonstrate that the areas in which regional homogeneity was different between ischemic stroke patients and healthy participants are in the cerebellum, left precuneus, left triangle inferior frontal gyrus, left inferior temporal gyrus and anterior cingulate. These locations, related to the motor, sensory and emotion areas, are likely potential targets for the neural regeneration of subacute ischemic stroke patients.

***Key Words:** nerve regeneration; brain injury; neuroimaging; functional magnetic resonance imaging; regional homogeneity; apoplexy; subacute; ischemia; participants; healthy; volunteers; brain activity; NSFC grants; neural regeneration*

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Introduction
Stroke is an acute cerebrovascular disease with high prevalence, high deformity rate, high death rate and low cure rate. According to the World Stroke Campaign of the World Stroke Organization, one in six people will have a stroke in their lifetime (Kaste, 2013). Stroke can be classified into two categories: ischemic and hemorrhagic cerebrovascular disease (Wang et al., 2014; Xiao et al., 2014). It is estimated that about 80% of stroke pertains to ischemic, whereas 20% is due to primary hemorrhage (Rothwell, 2012; Traylor et al., 2012). The clinical staging of stroke (Cramer, 2008; Rehme et al., 2012; Zhao et al., 2014) is generally accepted as follows: the first 2 weeks are defined as the acute stage; 3–11 weeks post-stroke is termed the subacute stage in which most changes occur; 12–24 weeks post-stroke is the early chronic stage; and more than 24 weeks post-stroke is the chronic stage.

In the last two decades, the use of functional neuroimaging techniques to explore pathological changes, predict outcomes and evaluate the treatment efficacy of stroke has attracted numerous investigators. Being a valuable method for analyzing local features of resting-state functional magnetic resonance imaging (fMRI) signals (Zang et al., 2004; Tian et al., 2012), regional homogeneity can measure the temporal synchronization of the time series of nearest neighbors, requires no a priori definition of region of interest (ROI), and can provide information about the local activity of separate brain regions, so it is a useful tool for identifying cerebral activity changes.

However, the majority of existing studies focus on motor dysfunction and the acute stage of ischemic stroke, while scant attention is paid to the sensory and emotional areas and the subacute stage of stroke. The present study aims to investigate the difference in the resting brain activities, particularly in the sensory and emotional areas between ischemic stroke patients in the subacute stage and healthy participants. We used fMRI and the regional homogeneity method to observe cerebral activity changes in ischemic stroke patients at the subacute stage, in a broader attempt to provide new evidence for clinical diagnosis, predicting prognosis and evaluating therapy responses in ischemic stroke.

Subjects and Methods

Subjects

Fifteen ischemic stroke patients were recruited from the Inpatient and Outpatient Department at the First Teaching Hospital of Chengdu University of Traditional Chinese Medicine (Chengdu, Sichuan Province, China) from January 2011 to May 2013.

Inclusion criteria

(1) Cases diagnosed with ischemic stroke based on CT or MRI; (2) having first onset and with a course of disease within 2 weeks to 3 months; (3) right-handed, aged 35–85 years; (4) conscious without indication of dementia, aphasia or mental disorders by the Mini-Mental State Examination (MMSE) assessment.

Exclusion criteria

(1) Cases with contraindications of fMRI scan and other intracranial lesions; (2) cases suffered serious complications such as respiratory insufficiency, heart failure, acute myocardial infarction, renal failure, hepatalgia, serious lung infection and cancer.

Meanwhile, we recruited 16 gender- and age-matched healthy volunteers *via* advertisement as the healthy participant group.

All participants gave written informed consent prior to experimentation. The present study was approved by the Ethics Committee of Chengdu University of Traditional Chinese Medicine (Chengdu, Sichuan Province, China; No. 2011KL-002).

Clinical evaluation

The nervous functional deficiency scale (Chen et al., 2009), the Fugl-Meyer assessment (Gladstone et al., 2002) and the modified barthel index (Welmer et al., 2006) were used to evaluate symptom severity and quality of life.

The nervous functional deficiency scale, based on the Scandinavian Stroke Scale, can assess patients' neurological function in terms of consciousness, muscle strength of upper and lower limb, and ambulation. The maximum score of nervous functional deficiency scale is 30 points. A lower score indicates milder neurological impairments.

The Fugl-Meyer assessment can investigate upper and lower limb motor functions after stroke. The maximum Fugl-Meyer assessment score is 100 points. A higher score indicates milder impairment of motor functions.

The modified barthel index is a daily life index and is commonly used to evaluate the daily living ability in 10 areas including feeding, grooming, bathing, and dressing. The maximum score of modified barthel index is 85 points. A higher score indicates a better daily living ability.

fMRI scan

Dataset

Head motion of more than 2.0 mm maximum displacement in any of the *X*, *Y*, or *Z* directions or 2.5 degrees of any angular motion were not included (see Data analysis). All images were acquired on a SIEMENS 3.0 T Trio scanner (Siemens Medical Solutions, Erlangen, Germany) in Huaxi MR Research Center, West China Hospital of Sichuan University (China). Foam pads were used to prevent head movement. Functional images were obtained using an echo-planar imaging sequence with the following parameters: 33 axial slices, thickness/gap = 3.0/0.6 mm, in-plane resolution = 64 × 64, repetition time = 2,000 ms, echo time = 30 ms, flip angle = 90°, field of view = 200 × 200 mm^2. Participants who performed in the resting-state session were instructed to try to hold still, not think systematically, and not fall asleep.

fMRI data preprocessing

The first 10 functional volumes were discarded for signal equilibrium and participants' adaptation to the scanning noise. Image preprocessing was performed with the Data Processing Assistant for Resting-State fMRI (DPARSF) V1.0 software package (http://restfmri.net/forum/DPARSF; Yan and Zang, 2010), which is a convenient software plug-in based on SPM (http://www.fil.ion.ucl.ac.uk/spm), and the Resting-State fMRI Data Analysis Toolkit (http://www.rest-fmri.net).

Functional data preprocessing included slice timing correction, motion correction and spatial normalization. Neither head motion of more than 2.0 mm maximum displacement in any of the *X*, *Y*, or *Z* directions nor 2.5 degrees of any angular motion throughout the course of a scan were found in any participant. Finally, we used DPARSF to remove the linear trend of the time course and for temporal band-pass filtering (0.01–0.08 Hz) (Biswal et al., 1995; Lowe et al., 1998).

Regional homogeneity calculation

Regional homogeneity analysis was performed using DPARSF software. The detailed procedure for regional homogeneity computation has been described previously (Zang et al., 2004). In brief, based on the assumption that the hemodynamic characteristics of every voxel are similar within a functional cluster, individual regional homogeneity maps were generated by assigning to each voxel a value for Kendall's coefficient of concordance (Kendall and Gibbons, 1990), which measures the similarity between the time series of a given voxel and those of its nearest neighbors (26 voxels). Then, all regional homogeneity maps were smoothed with a Gaussian filter with a 6 mm full-width half-maximum kernel (Kendall and Gibbons, 1990; Zang et al., 2004).

Data analysis

Data were analyzed using SPSS 17.0 software (SPSS, Chicago, IL, USA) and SPM software (http://www.fil.ion.ucl.ac. uk/spm).

fMRI data

One-sample *t*-tests were performed to identify regions significantly greater than the whole brain average within each group. Two-sample *t*-tests were performed to compare the regional homogeneity results between ischemic stroke patients and healthy participants within a mask. This mask was created by combining the voxels in both the patients

Table 2 Regions that showed significant changes in regional homogeneity between ischemic stroke patients and healthy participants

Region	Voxels	Talairach (coordinate cluster extreme point) X	Y	Z	*t* value	BA	Sign
Cerebellum	103	33	–90	–30	4.39		Increase
Cerebellum	96	–39	–78	–51	4.61		Increase
Precuneus-L	62	–6	–63	27	6.12	BA31	Increase
Frontal-Inf-Tri-L	50	–54	27	0	3.97	BA47	Increase
Temporal-Inf-L	39	–60	–27	–21	3.90		Increase
Cingulum-Post-L	33	–3	–42	9	4.48		Increase
Anterior Cingulate-L	94	12	27	9	4.09		Decrease
Cerebrum-L	34	–18	12	30	4.20	BA26, 29, 30	Decrease

"Sign" indicates whether the cerebral activities showed a signal increase (patients > controls) or decrease (patients < controls), one-sample *t*-test or two-sample *t*-test was used. R: Right; L: left; Inf: inferior; Post: posterior; Tri: triangle; BA: Brodmann area.

Table 1 Baseline information of ischemic stroke patients and healthy participants

Group	Ischemic stroke patients	Healthy participants
n	15	15
Age (year, mean ± SD)	63.4±13.2	62.1±10.1
Gender (female/male, *n*/*n*)	6/9	6/9
Nervous Functional Deficiency scores (mean ± SD)	24.6±4.2*	28.2±0.9
Fugl-Meyer assessment scores (mean ± SD)	82.7±4.5*	92.9±2.8
Modified Barthel Index scores (mean ± SD)	30.9±9.8*	84.3±1.1

*$P < 0.05$, *vs*. healthy participants. Two-sample *t*-test and chi-square test were performed to compare the age, clinical variables and gender between the ischemic stroke patients and healthy participants.

and the healthy participants, which were obtained from the one-sample *t*-test results. The *t*-map was set at a threshold of $P < 0.05$ (combined height threshold $P < 0.01$ and a minimum cluster size of 30 voxels).

Clinical variables

Two-sample *t*-tests and chi-square test were performed to compare the age, clinical variables and gender between the ischemic stroke patients and healthy participants. $P < 0.05$ was considered statistically significant.

Results

Quantitative analysis of subjects

In the healthy participant group, one healthy participant was excluded from our analysis because of his relatively large head movement during the scan, and 15 cases were in cluded in the final analysis. In total, 30 participants in the two groups entered the final analysis.

Baseline information of subjects

The locations of lesions of the ischemic stroke patients at the subacute stage were mainly in the left basal ganglia. The average duration of the stroke was 4.5 weeks (from 15 days to 11.5 weeks). There was no significant difference in age and gender distribution between ischemic stroke patients and healthy participants ($P > 0.05$). The ischemic stroke patients were clearly conscious and the MMSE scores were more than 20 points, except for 19 points in one case (receiving no education). The nervous functional deficiency, Fugl-Meyer assessment and modified barthel index scores in ischemic stroke patients were lower than that in healthy participants ($P < 0.05$, **Table 1**).

Difference of regional homogeneity in the resting-state brain regions of ischemic stroke patients and healthy participants

Compared with healthy participants, the ischemic stroke patients had a lower regional homogeneity in anterior cingulate and left cerebrum and a higher regional homogeneity in the cerebellum, left precuneus, left triangle inferior frontal gyrus and left inferior temporal gyrus (**Table 2**, **Figure 1**).

Discussion

This study demonstrated the different regional cerebral activities between ischemic stroke patients in subacute stage and healthy participants in the cerebellum, left precuneus, left triangle inferior frontal gyrus, left inferior temporal gyrus and left anterior cingulate. These areas are involved in motor, sensory and emotion processing, which are tightly connected with the lesions found mainly in the left basal ganglia.

Sensation-related areas

The areas associated with sensory processing are usually located in the parietal, temporal, occipital lobes and the basal ganglia. The anterior region of the parietal lobe holds the somatosensory cortex, while posterior and inferior to the somatosensory region is the inferior parietal lobe, which is thought to be the site for multisensory integration. The temporal lobe is not only a sound and language-processing region, as the middle sections of the temporal lobe also contain conceptual representations for semantic knowledge. As part of the medial posterior parietal cortex, the precuneus and the frontal lobe are engaged in sensation, and they are the key parietal nodes and connections of the network that carry this information (Gong et al., 2008; Sheng et al., 2012). The ventral precuneus is positively connected to the cingulate gyrus, as well as the right cerebellar lobule III and left cerebellar lobule X; they control awareness and conscious information processing, and along with the angular gyrus are the key parietal nodes of the default network (Margulies et al., 2009; Zhang, 2010, 2011; Loayza et al., 2011; Randy, 2012). In other words, the sensory process was not only related to the parietal, temporal, frontal and occipital lobes and the basal ganglia, but also the precuneus and cingulate areas that belong to the default network.

Increasing evidence (Schaechter et al., 2006; Laible et al., 2012) has illustrated the selective role of the somatosensory cortex in motor recovery, and the ipsilesional precentral gyrus (BA4, frontal) has been shown to be significantly related to both sensorimotor rhythm modulation skills after stroke. The ipsilesional angular gyrus and middle frontal gyrus also show a significantly positive relationship with acquired sensorimotor rhythm modulation skill.

In this study, cerebral activity changed in regions responsible for the sensory processing included anterior cingulate, left precuneus, left triangle inferior frontal gyrus, left inferior temporal gyrus. This result coincides with previous findings. The changed areas were associated with patients' clinical manifestations like sensory disturbance, and the nervous functional deficiency scores of the patients were significantly lower than those of healthy participants. The nervous functional deficiency score was related to the lesion in the left basal ganglia and the higher activity of these regions can compensate for and improve sensory dysfunction, so that patients only appear to have mild dysfunction.

To date, fewer studies have focused on the regional cerebral activities in the somatosensory region between ischemic stroke patients and healthy participants. The present study found different regional cerebral activities in anterior cingulate, left precuneus, left triangle inferior frontal gyrus, left inferior temporal gyrus, which are all involved in sensory processing, between the ischemic stroke patients and the healthy participants.

Emotion-related areas

The areas associated with emotion modulation are usually located in the limbic system, the basal ganglia, the cerebellum and the prefrontal lobes. The limbic system (Kidwell, 2012) includes cingulate gyrus, amygdala, hippocampus, parahippocampal cortex, hypothalamus. It is densely interconnected with the cortex (including ventromedial prefrontal and insular) and neocortex (including some subcortical nuclei, like the basal ganglia). It plays an important role in controlling complex cognitive, linguistic, motor, sensory and social abilities, and in regulating expression of emotion.

In this study, the cerebral activity changed in regions responsible for emotional processing, including anterior cingulate, left inferior temporal gyrus and left cerebrum (BA26, BA29, BA30), because these areas are the constituents of the cingulate, which belongs to the limbic system. Moreover, the cerebellum is no longer considered purely devoted to motor control. A wider role for the cerebellum in cognitive and affective functions is supported by anatomical, clinical and functional neuroimaging data. Meanwhile, more cognitively demanding tasks are engaged in prefrontal and parietal cortices along with cerebellar lobules VI and VII. These findings provide further support for the role of the cerebellum in both motor and cognitive tasks. In the present study, the changed cerebral activity in regions related to emotional processing was mainly located in the cerebellum. The anterior cingulate and left cerebrum (BA26, BA29, BA30), left inferior temporal gyrus and cerebellum are related to patients' clinical manifestations like depression disturbance; the nervous functional deficiency scores and the modified barthel index scores of the ischemic stroke patients were lower than that in healthy participants. The nervous functional deficiency was related to the lesion in the basal ganglia, and also lower regional homogeneity was found in the anterior cingulate and left cerebrum. At the same time, higher regional homogeneity in the left inferior temporal gyrus and cerebellum can compensate for and improve the dysfunction of emotion. That is one possible reason to explain why depression is a frequent complication after stroke, with a prevalence of up to 50%. Post-stroke depression is associated with impaired neurological recovery and increased mortality (Minnerup et al., 2012).

At present, few studies have focused on regional cerebral activities in the emotional regions. Our research found different regional cerebral activities between ischemic stroke patients and healthy participants. The emotional processing-related areas wherein the regional homogeneity was different between ischemic stroke patients and healthy participants included anterior cingulate and left cerebrum (BA26, BA29, BA30), left inferior temporal gyrus and cerebellum.

Motor-related areas

The areas associated with motor control are usually located in the basal ganglia, the cerebellum and the frontal lobe. The basal ganglia have been implicated in action planning and unconscious cognitive operations. Comprising the caudate nucleus and lenticular nucleus, the striatum mainly lies in the basal ganglia. The cerebellum is comprised of ten lobules, and is thought to be mainly involved in controlling fine motor movements. It can maintain body balance, control posture and gait, modulate muscle tone and coordinate the accuracy of voluntary movement (Stoodley et al., 2012). Recent studies (Habas et al., 2009; Krienen, 2009; Bernard et al., 2010; O'Reilly et al., 2010; Stoodley, 2010) have shown that overt movement can activate sensorimotor cortices along with contralateral cerebellar lobules IV–V and VIII, and the massive frontal lobe is the site for motor planning and motor output.

In this study, the cerebral activity changed in regions associated with motor regulation including the left cerebrum, cerebellum, and left triangle inferior frontal gyrus. The lesion mainly lay in the basal ganglia and was related to motor function. So, the ischemic stroke patients' regional homogeneity was lower than that of the healthy participants in left cerebrum (BA26, BA29, BA30) and higher in cerebellum and left triangle inferior frontal gyrus, because of the movement disorders caused by the basal ganglia lesions. The higher activity of the cerebellum might compensate for motor dysfunction and improve motor function. Our results coincide with previous task-fMRI and resting-state fMRI studies (Dong et al., 2007; Gerloff, 2010; Wang et al.,

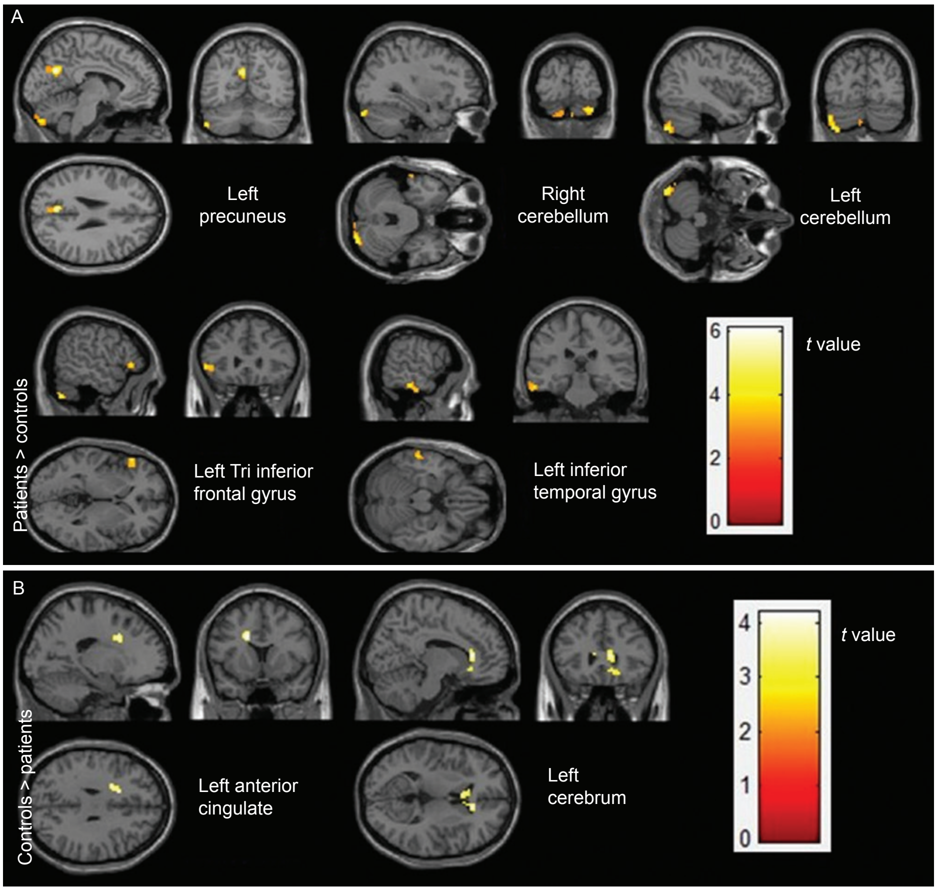

Figure 1 Regional homogeneity map of statistically significant differences by two-sample *t*-test between ischemic stroke patients and healthy participants.
Each significant region was shown in axial, coronal and sagittal planes (color bar, *t* value of group analysis). (A) Patients > controls, higher regional homogeneity in left precuneus, cerebellum, left triangle inferior frontal gyrus, and left inferior temporal gyrus. (B) Patients < controls, lower regional homogeneity in left anterior cingulate and left cerebrum (BA26, BA29, BA30).

2010; Park et al., 2011); the cerebellum may relate to motor recovery in the subacute stage. Second, because of the basal ganglia lesions causing disorders in movement and language, the higher activity of the frontal lobe (left triangle inferior frontal gyrus, BA47) compensates for and improves the dysfunction of motor and language. The results are also coincident with previous studies (Grefkes et al., 2008; Rehme et al., 2011; Richard et al., 2011; Stinear et al., 2012). Therefore our research showed regional homogeneity's reliability, sensitivity and practicability in detecting local brain function. In addition, we found that the changed areas were related to patients' clinical manifestations such as hemiplegia and language handicap. The Fugl-Meyer assessment scores and modified barthel index scores of the ischemic stroke patients were lower than those in healthy participants. The impairments in motor functions were related to the lesions in the basal ganglia, and the higher regional homogeneity in cerebellum and left triangle inferior frontal gyrus could compensate for the dysfunction of the motor system, with mild dysfunction shown in the patients. Thus, the areas in which the regional homogeneity was different between the ischemic stroke patients and healthy participants in left cerebrum, cerebellum, and left triangle inferior frontal gyrus were related to motor processing.

In this study, patients' lesions were mainly localized in the left basal ganglia, which, among other things, maintains the normal functional coordination of muscles and body posture. The left brain as the dominant hemisphere is closely related to sensation and to emotions. Injury to these areas will result in functional obstacles in movement, speech, sensation and consciousness, but fewer studies have focused on the changes in sensation and consciousness after ischemic stroke. In our study, the different regional homogeneity between the ischemic stroke patients and the healthy participants was found in anterior cingulate, left cerebrum, cerebellum, left precuneus, left inferior temporal gyrus, and left triangle inferior frontal gyrus, which are related to default network areas and the limbic system (Schaechter et al., 2006; Laible et al., 2012; Minnerup et al., 2012). These areas are involved in motor, sensation and emotion processing and provide new evidence for clinical diagnosis, prognosis prediction and therapy evaluation after ischemic stroke. Meanwhile, clinical manifestations of stroke patients include hemiplegia, depression, aphasia and sensory disturbance.

In conclusion, we analyzed the different regional cerebral activities between ischemic stroke patients in the subacute stage and healthy participants using resting-state fMRI and the regional homogeneity method. The different regional cerebral activities are related to the location of the lesion and the time post-stroke, and are also related to clinical manifestations and predicting the prognosis of stroke patients. Meanwhile we can make sure that the pathological mechanism is related to anterior cingulate, cerebellum, left precuneus, left inferior temporal gyrus, and left triangle inferior frontal gyrus in stroke patients. These regions that are related to the motor, sensory and emotional areas might be potential targets for the neural regeneration of stroke.

The main limitations of the present study are as follows.

First, the sample size in this study is relatively small. Second, this study could not observe dynamic changes in the pattern of regional homogeneity following stroke. A longitudinal study is needed to determine whether specific regional homogeneity patterns predict clinical outcome during stroke recovery.

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