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·Original Article·

Altered regional homogeneity in post-traumatic stress disorder: a resting-state functional magnetic resonance imaging study

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Abstract: Objective Little is known about the brain systems that contribute to vulnerability to post-traumatic stress disorder (PTSD). Comparison of the resting-state patterns of intrinsic functional synchronization, as measured by functional magnetic resonance imaging (fMRI), between groups with and without PTSD following a traumatic event can help identify the neural mechanisms of the disorder and targets for intervention. **Methods** Fifty-four PTSD patients and 72 matched traumatized subjects who experienced the 2008 Sichuan earthquake were imaged with blood oxygen level-dependent (BOLD) fMRI and analyzed using the measure of regional homogeneity (ReHo) during the resting state. **Results** PTSD patients presented enhanced ReHo in the left inferior parietal lobule and right superior frontal gyrus, and reduced ReHo in the right middle temporal gyrus and lingual gyrus, relative to traumatized individuals without PTSD. **Conclusion** Our findings showed that abnormal brain activity exists under resting conditions in PTSD patients who had been exposed to a major earthquake. Alterations in the local functional connectivity of cortical regions are likely to contribute to the neural mechanisms underlying PTSD.

Keywords: functional magnetic resonance imaging; post-traumatic stress disorder; regional homogeneity; resting-state

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1 Introduction

Post-traumatic stress disorder (PTSD) is a common psychiatric disorder that develops after people are exposed

to catastrophic mental trauma[1]. The condition features the core symptoms of re-experiencing, avoidance and hyperarousal[2,3], in tandem with a high rate of dissociative experience[4]. However, the pathogenesis of PTSD remains unclear. Non-radioactive functional magnetic resonance imaging (fMRI) studies have provided invaluable information about PTSD, but most of them were task-related and difficult for subjects to perform.

Recently, resting-state fMRI has been used to investigate the intrinsic functional organization of the brain[5]. Blood oxygen level-dependent (BOLD) fMRI is used to explore brain activation during the resting state. The method detects the functional neuronal activity of unified networks by measuring the relationships among regions in the degree of fluctuation in blood oxygenation across time. The so-called default-mode network appears to be important for self-reflection and is often deactivated during a cognitively challenging task. During a resting-state scan, participants only need to keep their eyes closed, remain relaxed and motionless, and allow the mind to wander[6], in the absence of external stimuli and cognitive processing demands. The absence of demanding cognitive activity and instructions makes it more straightforward to compare brain activity across groups that may differ in motivation or cognitive abilities. In addition, measuring the coordinated activity of networks may be more sensitive to pathophysiological mechanisms than isolated, regional activity. Thus, resting fMRI may be helpful to further understand the abnormalities of brain activity in patients with brain disorders.

To date, only a few studies have used fMRI during the resting state to investigate brain activation in PTSD patients. For example, two studies compared women with early-life trauma to healthy women[6] and examined the relationship between coordinated activity in the resting state and PTSD symptoms in an acutely traumatized sample[7]. No study has yet examined the resting state activity in a large sample of PTSD patients compared to individuals with similar traumatic exposure. Furthermore, previous resting-state studies in PTSD have measured the correlated activity of the default mode using a seed-point method. This method may be biased by the particular seed region chosen and focuses on long-distance patterns of connectivity.

An alternative way of measuring intrinsic, temporally-coordinated brain responses during resting-state fMRI studies is to assess the regional homogeneity (ReHo) of the BOLD signal[8]. The ReHo method is based on the theory that the similarity of BOLD signal fluctuations in a local brain region may reflect homogeneity of neuronal activity at the same frequency. Brain activity is more likely to develop in spatially contiguous voxels rather than in a single voxel. Accordingly, the ReHo approach assumes that a given voxel is temporally similar to those of its neighbors. Kendall's coefficient of concordance (KCC)[9] is used to measure the ReHo of a given voxel and its neighbors in the time series. KCC values are given to the voxels and individual KCC maps (i.e., ReHo maps) are obtained. ReHo reflects the temporal homogeneity of each voxel's BOLD signal in the regional brain area and presumably is an index of the efficiency of the local coordinated response. Higher ReHo values may indicate greater temporal homogeneity and synchrony, while lower ReHo values may reflect temporal disorder of local neurons.

Recent studies using ReHo have identified disturbances in brain regions during the resting state in patients with depression[10,11], schizophrenia[12,13], obsessive-compulsive disorder[14], autism[15,16], Alzheimer's disease[17], attention deficit hyperactivity disorder[18], and Parkinson's disease[19]. The goal of the present study was to explore the possibility of altered resting-state brain activation in subjects with PTSD using ReHo. Because this method differs from those previously used to study functional activity in PTSD, we did not have any predictions for the directions or locations of changes in this exploratory study.

2 Methods

2.1 Subjects We drew subjects from a large-scale PTSD survey of earthquake survivors in Sichuan Province, China, which was hit by an 8.0-magnitude earthquake on May 12th, 2008. As previously reported[20], 3 100 survivors were screened with the PTSD checklist[21]. Then the clinician-administered PTSD scale (CAPS)[22] and structured clinical

interview for DSM-IV[23] were used to confirm the PTSD diagnosis and to rule out comorbidities. The subjects were 18 to 59 years old and had no previous psychiatric diagnosis, no history of brain trauma, and no significant medical or neurological conditions. Finally, MRI data were collected from 72 PTSD (CAPS score ≥50) and 86 non-PTSD subjects. All subjects gave informed written consent as approved by the Ethics Committee of the Second Xiangya Hospital and Central South University.

2.2 Data acquisition Images were acquired on a 3-T MR scanner (Excite; General Electric) using a gradient echo-planar imaging (EPI) sequence (repetition time 2 s, echo time 30 ms, flip angle 90°, slice thickness 3 mm, slice gap 1 mm, matrix 64 × 64, field of view 220 × 220 mm^2). Thirty axial slices were acquired across the whole brain, and each functional run contained 200 image volumes. Participants were instructed to close their eyes and not to focus their minds on anything in particular during the scan.

2.3 Data preprocessing Image preprocessing and statistical analyses were conducted using SPM2 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm2/). For each participant, the functional scans were slice-time-corrected and realigned to the first volume to correct for inter-scan movements. Next, the functional scans were spatially normalized to a standard EPI template and resampled to the voxel size of 3 × 3 × 3 mm^3. The head motion parameters of all participants were determined. The conservative inclusion criterion of translational movement was <1.0 mm, and rotation <1.0°. According to this standard, the data from 18 subjects with PTSD and 14 traumatized controls were discarded due to excessive head motion. Following this, the fMRI data were linearly de-trended and temporally band-pass filtered (0.01–0.08 Hz) to reduce the effect of low-frequency drifts and physiological high-frequency noise[24] with REST V1.5 software (http://www.restfmri.net/forum/REST). We evaluated four metrics of the head motion of the two groups: mean motion, maximum motion, number of movements and rotation[25]. Suppose the time point is L, then we get the translation parameters: x(i), y(i), z(i), phi(i), theta(i), and psi(i), where i is 1 to L-1. When DIS, displacement, is also a vector,

DIS(i) = square root ((x(i) – x(i–1))^2 + ((y(i) – y(i–1))^2 + ((z(i) – z(i–1))^2),

x(0) = 0, y(0) = 0, z(0) = 0.

"Mean motion" and "max motion" are measures of DIS. Mean motion = 1/(L–1)*sum(DIS), max motion = max(DIS). "Number of movements" = length (find(DIS>0.1)). The rotation is: ROT(i) = arccos ((cos (phi(i) – phi(i–1)) cos (theta(i) – theta(i–1)) + cos (psi(i) – psi(i–1)) cos (theta(i) – theta(i–1)) + cos (phi(i) – phi(i–1)) cos (psi(i) – psi(i-1)) + sin (phi(i) – phi(i–1)) sin (theta(i) – theta(i–1)) sin (psi(i) – psi(i-1)) – 1)/2), phi(0) = 0 , theta(0) = 0, psi(0) = 0; rotation = mean(ROT(i)).

2.4 ReHo analysis Individual ReHo maps were generated by calculating the KCC (also called the ReHo value) which measures the regional homogeneity of the time series of a given voxel and its nearest 26 voxels on a voxel-wise basis. This procedure was implemented with REST software. The method of computing the KCC value has been specified in previous studies[8,12]. The intracranial voxels were extracted to make a mask[26]. For standardization purposes, each individual ReHo map was divided by its own mean ReHo within the mask. Subsequently, the functional images were spatially smoothed with a 4-mm full-width at half-maximum Gaussian kernel to reduce noise and residual differences in gyral anatomy.

2.5 Statistics analysis To investigate ReHo differences between the PTSD group and traumatized control group, a second-level random-effects two-sample *t*-test was executed on the individual normalized ReHo maps in a voxel-by-voxel manner. Multiple comparisons correction was performed using the AlphaSim program in the AFNI software determined by Monte Carlo simulations. Statistical maps of two-sample *t*-tests were set at a combined threshold of P <0.001 and a minimum cluster size of 10 voxels (270 mm^3), yielding a corrected threshold of P <0.01. We also evaluated the head motion differences between the two groups by two-sample *t*-tests.

3 Results

3.1 Demographic data Group comparisons were based on 54 patients and 72 control subjects after discarding data

from subjects with excessive head motion. Age, gender distribution, and years of education were matched between the two groups. The mean CAPS score of the PTSD group was 64.09 ± 9.68.

3.2 ReHo: PTSD patients *versus* traumatized controls Compared to the control group, the PTSD group displayed enhanced ReHo in clusters within the left inferior parietal lobule and the right superior frontal gyrus, and decreased ReHo in the right middle temporal gyrus and lingual gyrus ($P < 0.01$, corrected; Table 1, Fig. 1).

To investigate the relationship between the altered ReHo in different areas and the severity of clinical symptoms, the average ReHo values of all voxels showing significant group differences were extracted. Significant positive correlations were found between ReHo values in the left inferior parietal lobule and the right superior frontal gyrus in the PTSD group ($r = 0.356$, $P = 0.008$). However, no correlation was found between the CAPS scores and these regions.

3.3 Head motion No significant difference was found in head motion between the two groups in terms of mean motion (control 0.060 ± 0.058 mm and PTSD 0.057 ± 0.040 mm, $t = 0.42$, d.f. = 124, $P = 0.68$), maximum motion (control 0.261 ± 0.196 mm and PTSD 0.262 ± 0.189 mm, $t = –0.05$, d.f. = 124, $P = 0.96$), number of movements (control 31.0 ± 44.3 and PTSD 30.6 ± 43.5, $t = 0.05$, d.f. = 124, $P = 0.96$) or rotation (control 0.001 ± 0.000 mm and PTSD 0.001 ± 0.000 mm, $t = 0.12$, d.f. = 124, $P = 0.90$).

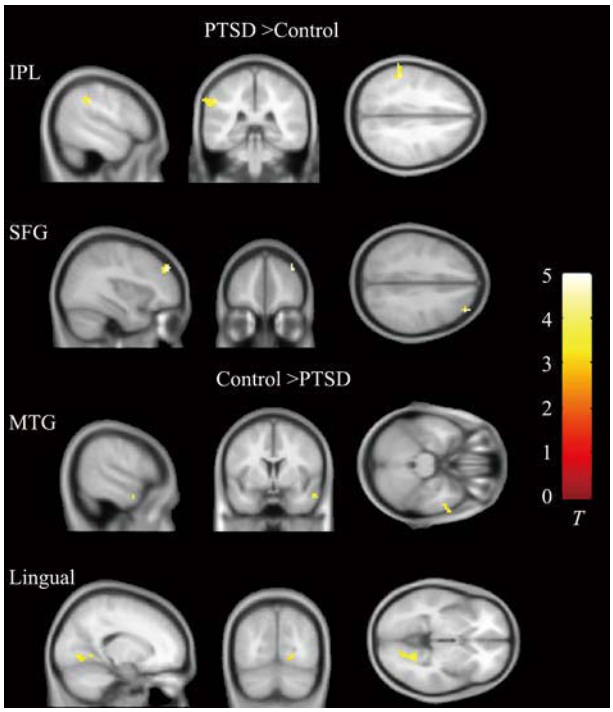

Fig. 1. Brain areas with altered regional homogeneity (ReHo) in PTSD subjects. Upper six panels: brain areas with greater ReHo in PTSD than control. Lower six panels: areas with greater ReHo in control than PTSD. Threshold was set at $P < 0.01$ (corrected). IPL, inferior parietal lobule; MTG, middle temporal gyrus; PTSD, post-traumatic stress disorder; SFG, superior frontal gyrus; *T*, *t*-value.

Table 1. Brain areas with ReHo changes in PTSD group relative to the control group

Anatomical region	Hemisphere	BA	Cluster size (No. voxels)	Peak *t*-value	MNI coordinates		
					X	Y	Z
PTSD >control							
Inferior parietal lobule	Left	40	47	4.46	–51	–36	36
				3.97	–60	–39	36
Superior frontal gyrus	Right	9	22	4.68	36	45	36
Control >PTSD							
Middle temporal gyrus	Right	21	11	3.72	57	3	–27
Lingual gyrus	Right	18	49	3.53	18	–72	3

BA, Brodmann area; MNI, Montreal Neurological Institute; PTSD, post-traumatic stress disorder; ReHo, regional homogeneity. Threshold set at $P < 0.01$ (corrected).

4 Discussion

In the present study, we measured locally-coordinated brain activity during the resting state using the ReHo approach in traumatized patients with or without PTSD. Altered ReHo is thought to indicate abnormal neuronal activity in a local brain area[12]. We found that ReHo was heightened in clusters within the left inferior parietal lobule and right superior frontal gyrus in subjects with PTSD relative to controls, suggesting that PTSD is characterized by increased synchronous neuronal activity in these two loci.

Consistent with our results, a prior single-photon-emission computed tomography (SPECT) study reported higher regional cerebral blood flow (rCBF) in the left inferior parietal gyrus (Brodmann area 40) in PTSD patients exposed to civilian traumatic events compared to traumatized controls at rest[27]. Increased blood flow in the inferior parietal lobule has also been reported in different paradigms such as symptom provocation[28] and cognitive activation[29] in patients suffering from PTSD. The inferior parietal cortex is involved in mediating visuospatial processing[30-33] which performs a vital function in preparation for coping with a physical threat and survival in life-threatening situations[34]. Evidence suggests that enhancement of memory, including nonverbal visual memory, for traumatic events exists in PTSD[34,35]. The inferior parietal cortex has also been hypothesized to be involved in spatial memory. Greater activity in this region potentially represents increased demands on visuospatial processing and spatial memory, which might be associated with the augmented attention or fear response to stress in PTSD patients[29,36]. As such, hyperactivity and abnormally high local connectivity in the inferior parietal lobule is presumed to be part of the neuronal substrate of the excessive vigilance observed in PTSD.

Increased activation of the right superior frontal region has been demonstrated in other PTSD neuroimaging studies[34,37]. Hyperactivation in this site in PTSD may be linked to altered emotional processing[37]. Furthermore, anatomically and functionally connected to the posterior parietal lobe[38], prefrontal cortex has also been thought to play a critical role in memory and visuospatial processing. Thus, the change we observed in the right superior frontal cortex may also be a neuronal correlate of the excessively vigilant state in PTSD[36]. In addition, previous resting electroencephalogram and fMRI studies have suggested that right frontal activation is involved in negative emotional states, increased vigilance in anxiety, and withdrawal behavior[28,39-41]. The right superior frontal cortex was also found to activate more for negative emotion in an fMRI study of generalized social phobia[42] and to be active during sustained vigilance tasks in healthy individuals[32]. The increased activation in the superior frontal cortex found in the present study might therefore be related to altered processing of negative emotions in PTSD, perhaps underlying the avoidance[43], hypervigilance and emotional numbness[37] seen in PTSD. Consistent with this, a study of resting-state functional connectivity between the posterior cingulate and other brain regions in a group of acutely traumatized adults found that the degree of connectivity with bilateral anterior cingulate region is positively associated with the severity of PTSD symptoms (i.e., the most severe cases had the greatest coordinated activity between posterior and anterior cingulate)[7].

The current study differed from some previous studies of brain activity in PTSD during the resting state. A resting SPECT study found lower blood flow in the bilateral superior frontal regions in patients with PTSD than in healthy participants[44]. Bluhm *et al*.[6] found under-connectivity between the posterior cingulate and other default mode network and medial temporal regions among women with PTSD who had been exposed to early trauma. There are several possible explanations for these divergent findings. First, the studies differ in age, gender distribution, handedness, sample size, trauma type, and duration of illness, as well as the type of control group. Different types of trauma, for example, have been shown to have dissimilar influences on rCBF distribution[45]. In addition, the degree of depression is likely to have differed between studies and depression may influence superior frontal function in an opposing manner[46-48]. Finally, Lucey *et al*.[44] used SPECT modality and Bluhm *et al*.[6] used seed-point analysis, whereas we

used fMRI with the measurement of ReHo. The ReHo method focuses on measurement of local, short-distance connectivity as opposed to global activity or long-distance connectivity, which might explain the partial inconsistency between our findings and those of others.

Our study also found reduced ReHo values in the right middle temporal gyrus and lingual gyrus. A PET study discovered decreased rCBF in the middle temporal gyrus in PTSD when subjects performed a trauma script-driven imagery task; however the study lacked a control group[49]. Other PET trials found that, compared with controls, PTSD subjects show reduced blood flow in the middle temporal gyrus when applying symptom-provoking tasks (traumatic pictures, sounds, trauma-related psychological images and administration of yohimbine)[28,50,51]. The middle temporal gyrus can inhibit the function of the amygdala, facilitate the extinction of fear conditioning[52,53], and is linked to episodic memory as well as language processing[54]. Lower ReHo in the middle temporal gyrus in the PTSD patients in the current study may be associated with difficulty in the extinction of fear memory and dysfunction in verbal memory.

The lingual gyrus is a component of the visual association cortex which is responsible for visual association and the processing of visual images related closely to the formation of autobiographical memory, and is implicated in verbal declarative memory. Previous studies have reported decreased function in the visual cortex of PTSD subjects[29,34]. Less ReHo in the lingual gyrus is consistent with the hypofunction of autobiographical and declarative memory in patients with PTSD[55,56].

In addition, no correlation with CAPS score was found for any area showing group differences in ReHo values, demonstrating that ReHo cannot evaluate the symptom severity of PTSD as a quantitative indicator at this stage, even though it may be used as a qualitative marker to help locate functionally altered areas.

This study suffers from several limitations. One is that it lacks subjects who were not exposed to trauma. Although having a traumatized control group without PTSD allowed us to make inferences about the effects of PTSD above and beyond the effects of trauma, a more complete exploration could have been made with an additional group of non-traumatized individuals. There are suggestions from a recent report that traumatized non-PTSD subjects also show altered resting-state functional connectivity relative to non-traumatized subjects[57], although a prior study indicated, on the contrary, that biologic abnormalities are associated with PTSD rather than the trauma exposure *per se*[58]. An additional limitation is that we only studied PTSD participants exposed to earthquake-related trauma, which limits our ability to generalize to PTSD patients exposed to other traumatic events[59]. More extensive research will be necessary to confirm our findings in PTSD patients exposed to other uniform traumatic events. Also, pre-scanning was not performed in our study, which could lead to more stress on PTSD subjects during the formal scanning than controls, generating resting states that were not completely identical in the two groups.

In conclusion, we found heightened coordinated local activity in the left inferior parietal lobule and right superior frontal gyrus, and decreased activity in the right middle temporal gyrus and lingual gyrus at rest in PTSD relative to control traumatized subjects, using fMRI and measures of ReHo. Abnormalities of local coordinated function in these brain regions are likely to contribute to the neuronal mechanisms underlying PTSD. Treatments that aim to remedy the altered activity may be successful in reducing the symptoms of PTSD. Further work is needed to determine whether this pattern is a marker of vulnerability or disease. Measurement of ReHo during rest may be a helpful approach to understanding the changes of neuronal activation in PTSD and how these might be improved by interventions.

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