

## Abnormal baseline brain activity in posttraumatic stress disorder: A resting-state functional magnetic resonance imaging study

Yan Yin<sup>a</sup>, Lingjiang Li<sup>a,\*</sup>, Changfeng Jin<sup>a</sup>, Xiaolei Hu<sup>a</sup>, Lian Duan<sup>a</sup>, Lisa T. Eyler<sup>b,c</sup>, Qiyong Gong<sup>d</sup>, Ming Song<sup>e</sup>, Tianzi Jiang<sup>e</sup>, Mei Liao<sup>a</sup>, Yan Zhang<sup>a</sup>, Weihui Li<sup>a</sup>

<sup>a</sup> Mental Health Institute, The Second Xiangya Hospital of Central South University, 139# Renmin Zhong Road, Changsha 410011, Hunan, PR China

<sup>b</sup> Department of Psychiatry, University of California, San Diego School of Medicine, 3350 La Jolla Village Dr(MC-116A), San Diego, CA, USA

<sup>c</sup> VA San Diego Healthcare System, 3350 La Jolla Village Dr(MC-116A), San Diego, CA, USA

<sup>d</sup> Huaxi MR Research Center, Department of Radiology, West China Hospital of Sichuan University, 37# Wainanguoxue Lane, Chengdu, Sichuan, China

<sup>e</sup> National Laboratory of Pattern Recognition, Automation Institute, 95# Zhongguancun Dong Road, Chinese Academy of Sciences, Beijing, China

### ARTICLE INFO

#### Article history:

Received 9 February 2011

Accepted 24 February 2011

#### Keywords:

Posttraumatic stress disorder  
Functional magnetic resonance imaging  
Amplitude of low-frequency fluctuation  
Resting-state

### ABSTRACT

Little is known about how spontaneous brain activity during the resting state may be altered in post-traumatic stress disorder (PTSD) compared to traumatized individuals. In the current study, we used a measure of amplitude of low-frequency (0.01–0.08 Hz) fluctuation (ALFF) to investigate the regional baseline brain function of this disorder. Fifty-four medication-naïve PTSD patients and seventy-two matched traumatized comparison subjects who experienced the Sichuan major earthquake participated in a functional magnetic resonance imaging (fMRI) scan. We analyzed the difference between the PTSD and comparison groups during a resting state using ALFF. PTSD patients showed decreased ALFF values in right lingual gyrus, cuneus, middle occipital gyrus, insula, and cerebellum, and increased ALFF values in right medial and middle frontal gyri, relative to traumatized individuals without PTSD. The ALFF value in the right medial frontal gyrus was positively correlated with severity of the disorder. Our findings show that abnormality of intrinsic brain activity exists under resting conditions in PTSD patients exposed to a major earthquake. Altered ALFF in predominantly right hemisphere cortical and subcortical regions and in cerebellum potentially contribute to the neural mechanisms underlying traumatic memory and symptoms in PTSD.

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Posttraumatic stress disorder (PTSD) is a debilitating anxiety condition that develops after encountering life-threatening mental trauma, and is characterized by unremitting distressing re-experiencing of the traumatic event, avoidance, and hyperarousal which are thought of as direct or indirect effects of altered memory processing.

Functional neuroimaging techniques have been utilized to explore the biological mechanism underlying PTSD, mainly including single photon emission computed tomography (SPECT), positron emission tomography (PET) and blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI). However, the nature of cerebral functional alterations is inconsistent between studies. For example, medial prefrontal cortex (mPFC,

including medial frontal gyrus and anterior cingulate cortex) has been suggested to play a critical role in pathogenesis of PTSD [36]. Studies have reported decreased activation of the mPFC in PTSD [8,42], or increased activation [10,45] or even no activation [28]. The complex patterns of findings may be due to the different cognitive challenges, to differences in the severity of the PTSD groups examined, or to the nature of the comparison group used.

Recently, the spontaneous low-frequency (0.01–0.08 Hz) fluctuation (LFF) of BOLD in resting state fMRI has been measured to investigate intrinsic functional baseline activity of the brain [31]. During a resting state scan, the absence of demanding cognitive activities and instructions makes it more straightforward to compare brain activity across groups that may differ in motivation or cognitive abilities. Thus, resting fMRI may be helpful to further understand abnormalities of brain activity in participants with brain disorders.

So far, few studies have investigated the brain activation of PTSD patients using fMRI during the resting state [5,22]. These studies have compared women with early life trauma to healthy women or examined the relationship between resting state coordinated activity and PTSD symptoms within an acutely traumatized sample.

**Abbreviations:** ALFF, amplitude of low-frequency fluctuation; mPFC, medial prefrontal cortex; LFF, low-frequency fluctuation; PCL, PTSD checklist; dlPFC, dorsal lateral prefrontal cortex; FFT, fast Fourier transform; rCBF, regional cerebral blood flow.

\* Corresponding author. Tel.: +86 731 85550413; fax: +86 731 85360086.

E-mail address: [llj2920@163.com](mailto:llj2920@163.com) (L. Li).

No study has yet examined resting state activity of a large sample of PTSD patients compared to individuals with similar traumatic exposure. Furthermore, previous resting state studies in PTSD have measured 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, regional brain responses during resting state fMRI studies is to examine amplitude of LFF (ALFF) of the BOLD signal [44]. The ALFF is reported higher in gray matter than in white matter [3] and is associated with field potential activity in local brain region [24]. Moreover, the amplitude of activation can be used as an index to evaluate changes of brain function [26]. In this case, the ALFF are considered to be the reflection of regional spontaneous neuronal activity [21] and physiological states of the brain [43].

The purpose of the present study was to explore the possibility of altered resting state brain activity in treatment-naïve subjects with PTSD using ALFF, and to examine possible clinical correlates of ALFF measures. To avoid treatment-elicited changes in brain function and possible changes related to chronic course, we only recruited recently traumatized and treatment-naïve PTSD patients into the study. To isolate the effects of PTSD, relative to possible effects of trauma exposure itself, we used identically traumatized comparison participants. We hypothesized that (1) PTSD patients may show different ALFF in some brain areas compared with control subjects and (2) ALFF of the BOLD response in these discrepant areas may be correlated to PTSD symptom severity.

On May 12th, 2008, an 8.0-magnitude earthquake hit Sichuan Province of China, 15 million people directly affected, hundreds of thousands of people dead, injured or missing, and exerted a wide and tremendous range of mental influence on survivors. All subjects for the current study were drawn from a large-scale PTSD survey in those post-earthquake survivors. Investigation was carried out in two most devastated regions 8 months after the earthquake. A total of 3100 survivors in Hanwang town were interviewed and screened with the PTSD checklist (PCL) [41]. Survivors scoring  $\geq 35$  points were given the Clinician-Administered PTSD Scale (CAPS) [4] by psychiatrists to confirm the PTSD diagnosis. A total of 1100 survivors in Beichuan county were interviewed and screened with the PCL. Survivors scoring  $\geq 45$  points were given the CAPS to confirm the PTSD diagnosis. From these pools of PTSD subjects identified with the above procedure, 415 with PTSD diagnosis were further selected as eligible for the current functional MRI study. In addition, 109 non-PTSD controls with PCL scores below 30 points and eligibility for MRI were selected as a comparison group.

These subjects were further assessed with the Structured Clinical Interview for DSM-IV (SCID) [15] to exclude any psychiatric co-morbidities. The exclusion criteria for PTSD group were: a history of psychosis, head trauma or loss of consciousness and any other significant medical or neurological conditions, current other psychiatric disorders based on SCID as well as ageing  $\geq 60$  years. Control subjects were excluded if they had any of the above-mentioned criteria. Patients with CAPS score of  $< 50$  points were also excluded. Finally, 72 PTSD and 86 non-PTSD subjects participated the subsequent fMRI scans from 9 months to 15 months post-earthquake and their data were preprocessed. Informed consent was obtained from all subjects after reviewing detailed written information about the study, which was approved by the Ethical Committee of the Second Xiangya Hospital and the Central South of University.

Magnetic Resonance Imaging was executed on a 3-T MR imaging system (EXCITE; General Electric) using a gradient echo-planar imaging (EPI) sequence: repetition time 2 s, echo time 30 ms; flip angle  $90^\circ$ ; slice thickness 3 mm slice with 1 mm gap; matrix  $64 \times 64$ ; field of view  $220 \text{ mm} \times 220 \text{ mm}$ . Each brain volume was comprising of 30 axial slices, and each functional run contained

200 image volumes. During scanning, all participants were asked to relax, not to focus their minds on anything in particular, eyes closed and motionless.

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  $3 \text{ mm} \times 3 \text{ mm} \times 3 \text{ mm}$ . Then, the functional images were spatially smoothed with a 4 mm full width at half maximum Gaussian kernel. Head motion parameters of all participants were examined. A conservative inclusion criterion of translation movement was  $< 1.0 \text{ mm}$ , and rotation was  $< 1.0^\circ$ . The data of 18 subjects with PTSD and 14 traumatized controls were discarded due to excessive head motion.

REST V1.5 software (<http://www.restfmri.net/forum/REST>) was used to calculate the ALFF. After data linearly detrended and temporally band-pass filtered (0.01–0.08 Hz) [3], the filtered time series was transformed to a frequency domain with a fast Fourier transform (FFT) (parameters: taper percent = 0, FFT length = shortest) and the power spectrum was obtained. Since the power of a given frequency is proportional to the square of the amplitude of this frequency component of the original time series in the time domain, the power spectrum obtained by FFT was square-rooted and then averaged across 0.01–0.08 Hz at each voxel. This averaged square root was taken as the ALFF. For standardization purposes, the ALFF of each voxel was divided by the global mean ALFF value. The standardized ALFF of each voxel should have a value of about 1 and this standardization procedure is analogous to that used in PET studies [30]. Thus, the global mean ALFF was calculated only within the brain, with the background and tissues outside the brain removed.

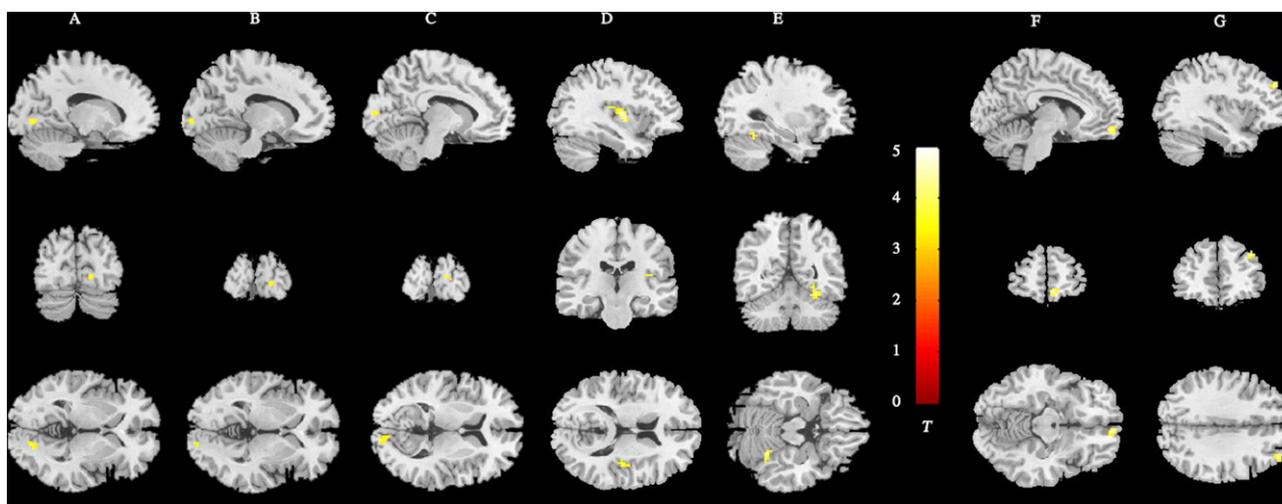
Two-sample *t*-tests were applied to assess the differences in age and years of education between the patient and comparison groups and Pearson's Chi-square test was used to compare gender ratios using SPSS 11.5. To investigate the ALFF difference between the PTSD group and control group, a two-sample *t*-test was executed on the individual normalized ALFF 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 the two-sample *t*-test were created using a combined threshold of  $P < 0.001$  and a minimum cluster size of 10 voxels ( $270 \text{ mm}^3$ ), yielding a corrected threshold of  $P < 0.01$ . Linear correlations were calculated between the CAPS scores and mean ALFF values across all voxels in the abnormal areas in PTSD group.

Group comparisons were based on 54 patients and 72 comparison subjects after discarding data from subjects with excessive head motion. Age, gender distribution, and years of education were matched between the two groups. The CAPS score of PTSD group was  $64.09 \pm 9.68$ .

Relative to the traumatized comparisons, PTSD patients showed decreased ALFF in right insula, visual cortex (middle occipital gyrus, lingual gyrus and cuneus) and cerebellum, and greater ALFF in right frontal lobe, including right medial frontal gyrus and middle frontal gyrus (Fig. 1).

To identify the association between altered ALFF and clinical symptom severity of PTSD, the average ALFF values of all voxels in the above regions were extracted separately. Significant positive correlations were observed between ALFF values in the right medial frontal gyrus and the CAPS scores ( $r = 0.335$ ,  $P = 0.014$ ). No correlations between CAPS scores and ALFF were found in other brain loci of significant group difference.

In the present study, we found abnormal intrinsic functional activity during a resting state in PTSD patients compared to similarly traumatized individuals without the disorder. PTSD patients



**Fig. 1.** Regions showing different ALFF between control group and PTSD group. Regions showing greater ALFF in control group: A, right lingual gyrus; B, right cuneus; C, right middle occipital gyrus; D, right insula; E, right cerebellum. Regions showing greater ALFF in PTSD group: F, right medial frontal gyrus; G, right middle frontal gyrus. Threshold was set  $P < 0.01$  (corrected);  $T$ ,  $t$ -value. ALFF, amplitude of low-frequency fluctuation; PTSD, posttraumatic stress disorder.

had lower ALFF than controls in right insula, visual cortex, cerebellum and higher ALFF than controls in right frontal lobe, specifically in ventral mPFC (medial frontal gyrus) and dorsolateral prefrontal cortex (dlPFC) (middle frontal gyrus).

The insula is thought to play a role in cognition [1], especially in memory function. It has been demonstrated that activation in insula cortex correlates with complex verbal working memory tasks [38] and encoding/retrieval in episodic memory [20] in healthy subjects. A morphometric study reported reduced gray matter density in the insula in fire survivors with PTSD as compared with non-PTSD fire victims [46]. In subsequent study, the authors found insular hypofunction in PTSD subjects during declarative memory tasks [12]. Prior animal study showed insular lesions led to memory deficits in the food reward value task [29]. Insular atrophy was also found in early Alzheimer's disease patients with cognitive deficits [16]. Our result, in combination with prior findings, suggests that deactivation of insula cortex may contribute to memory deficits in PTSD. In addition, insular hypofunction in recent-onset PTSD patients in our study may indicate dysfunction at early stages of the disease, or even a liability factor (although we could not test this hypothesis directly).

The cerebellum had been suggested to have a potential association with the pathophysiology of PTSD [14]. This locus, traditionally associated with motor control, is recognized increasingly to be implicated in cognitive processing and emotion medication [34], and has been hypothesized to be related to the neuropathology of cognitive and emotional processing of PTSD patients [39]. Our finding was not in agreement, however, with a previous finding of cerebellar hyperactivation at rest [6]. The localization within the cerebellum was different, however, with the increased response found in anterior cerebellum, a region more associated with motor function. Our finding of decreased regional spontaneous activity in posterior cerebellum, which is predominantly involved in cognition regulation [2], signal processing, and storage relevant to auditory-verbal memory function [18], suggests that reduced spontaneous cerebellar activity in PTSD may subserve impairments of verbal memory in the disorder.

Visual cortex has showed relative deactivation in patients with PTSD compared with traumatized subjects without PTSD during a color stroop task [8] and traumatic stimuli [7]. Visual association cortex and cuneus are responsible for making visual associations and processing visual imagery and are also involved in the network of regions subserving verbal declarative memory [9]. Abnormal

ALFF in these regions might therefore represent a neural correlate of decreased function in visual imagery [8] and verbal memory [23] observed in patients with PTSD.

mPFC has been implicated in the processing of emotional material generated internally [17] and anxiety [11] as well as the regulation of arousal [45]. PTSD subjects exhibited increased regional cerebral blood flow (rCBF) in mPFC for processing of acoustic traumatic scripts relative to neutral conditions [32] and during combat-sound stimuli compared with normal subjects [45]. Heightened activity in mPFC has also been found during visualization of traumatic events in combat veterans with PTSD compared to traumatized controls [35]. The authors argued that mPFC activation was associated with generating mental imagery of combat-related pictures, but not with perception of those pictures. In addition, recruitment of mPFC may be involved in unconscious fear processing in PTSD patients [10]. In the current study, greater mPFC activation in PTSD individuals at rest may indicate that patients were experiencing mental images of the trauma and processing these fearful memories unconsciously during this unstructured resting condition. Alternatively or additionally, heightened intrinsic activity at rest may be a predisposing factor for over-responsiveness of this region to fearful stimuli.

It has been reported that emotional (including traumatic) memories of childhood sexual abuse may be related to increased rCBF in dlPFC (middle frontal gyrus) in sexually abused women with PTSD relative to sexually abused women comparisons [7]. In an early work on verbal working memory, PTSD patients showed decreased activity in the left dlPFC, but increased activity in the right dlPFC [13]. Other working memory studies show that left dlPFC is associated with encoding and retrieval of verbal stimuli [37], while right or bilateral frontal regions are more involved in nonverbal memory [37]. These findings are congruent with the proposal that PTSD patients have increased dependence on nonverbal working memory areas as a strategy for coping with decreased verbal memory abilities [13], so the activation of the right dlPFC in PTSD at rest may relate to the strength of traumatic recollection in patients with PTSD [7]. Additionally, middle frontal gyrus is thought to be a component of a neural network that shows increased activation when processing visuospatial memory and planning to cope with potentially life-threatening events in excessively vigilant PTSD patients [7].

Our correlation analysis linked ALFF values in the mPFC to symptom severity of PTSD, such that higher ALFF values in mPFC

were found in the most severely symptomatic PTSD patients. The result is consistent with prior studies in which increased rCBF to the mPFC correlated at trend levels with stress responsiveness in PTSD patients [45]. Activity of the mPFC was also correlated with enhancement of anxiety by injected yohimbine in healthy subjects [11]. These findings suggest that altered baseline mPFC activation may be associated with levels of subjective distress and anxious emotion seen in PTSD.

In the present study, all altered ALFF values were lateralized to the right side in subjects with PTSD. The right hemisphere is involved in emotions and the processing and integration of trauma recall [27,33]. Prior studies have reported that right hemisphere brain regions are predominantly affected in PTSD [32]. Right laterality of abnormalities in the present work may also be associated with predominant non-verbal memory of traumatic events along with poor verbal memory performance in PTSD subjects [23], although we did not have measures of memory ability in these participants to test this directly. We found both reduced and increased ALFF in right hemisphere regions. Right middle occipital gyrus and cuneus were regions with lower ALFF in PTSD, and have been more implicated in memory tasks than in symptom provocation [19]. We found resting overactivation in right frontal regions, where activation has been associated with depression, anxiety and autonomic arousal [40], symptoms that are closely related to symptomatic manifestation of PTSD. Taken together, these findings have underlined the role of right hemisphere in the recollection of traumatic memory and in symptoms that are often related to this memory dysfunction in PTSD subjects.

Methodological limitation should be considered when interpreting the results. We used a relatively low sampling rate (repetition time = 2 s) which may have led to aliasing of heart pulsation in modeling the LFF (0.01–0.08 Hz)[25]. Future studies should record cardiac rate to deal with this potential confound.

Our findings of abnormalities in PTSD subjects are consistent with previous reports that used different challenge stimuli. This resting-state fMRI study thus suggests that abnormal spontaneous activity of right hemisphere cortical, subcortical and cerebellar regions is a feature of recent-onset PTSD. In addition, mPFC intrinsic activity is directly related to symptom severity and may therefore be of particular relevance to the underlying the pathophysiology of the disorder.

## Financial disclosures

All authors report no conflicts of interest.

## Acknowledgements

This work was supported by the National Natural Science Foundation of China (30830046 to Lingjiang Li; 30625024 and 81030027 to Qiyong Gong), the National Science and Technology Program of China (2007BAI17B02 to lingjiang Li), the National 973 Program of China (2009CB918303 to Lingjiang Li); the Program of Chinese Ministry of Education (20090162110011 to Lingjiang Li); and the National High-Tech Research and Development Program of China (863 program: 2008AA022603 to Lingjiang Li; 863 program:2008AA022408 to Qiyong Gong). Authors thank Drs. Rongfeng Qi and Li Zhang for the assistance for data analysis.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neulet.2011.02.069.

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