Altered resting-state functional connectivity of thalamus in earthquake-induced posttraumatic stress disorder: A functional magnetic resonance imaging study

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ARTICLE INFO

Article history:
Accepted 6 July 2011
Available online 18 July 2011

Keywords:
Posttraumatic stress disorder
Thalamus
Magnetic resonance imaging
Functional connectivity
Resting-state

ABSTRACT

Background: Thalamic dysfunction has been found in patients with posttraumatic stress disorder (PTSD), suggesting that the thalamus may be implicated in the etiology of PTSD. However, no studies have explored the functional connectivity between the thalamus and other brain regions during resting-state. The objective of the present study was to investigate the resting-state functional connectivity of the thalamus in recent onset medication-naive PTSD sufferers who went through an earthquake in the Sichuan province of China. Methods: Fifty-four participants with PTSD and seventy-two age and gender matched traumatized controls without PTSD recruited from the 2008 Sichuan earthquake were scanned by 3 T functional magnetic resonance imaging (fMRI) in resting state. Region of interest (ROI)-based functional connectivity analysis was employed to identify the...
potential differences in the functional connectivity of the thalamus between the two groups. Results: In the PTSD group, the thalamus-ROIs showed decreased positive functional connectivity to particular brain regions including right medial frontal gyrus and left anterior cingulate cortex. Importantly, we also found increased positive functional connectivity of thalamus-ROIs with bilateral inferior frontal and left middle frontal gyri, left inferior parietal lobule as well as right precuneus in the PTSD participants when compared to traumatized controls without PTSD. Conclusion: The results provide evidence that abnormal resting state functional connections linking the thalamus to cortical regions may be involved in the underlying pathology in PTSD.

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1. Introduction

Posttraumatic stress disorder (PTSD) is one of the most common psychiatric disorders (Yehuda, 2002) which develops following exposure to a traumatic and life-threatening life event. The condition is characterized by three symptom clusters: reexperiencing, avoidance and hyperarousal symptoms (Boehnlein, 1989; Paige et al., 1990), along with a high rate of dissociative symptoms (Bremner et al., 1992).

Considerable evidence has increased the understanding of the underlying neuropsychological mechanism for PTSD. Researchers have proposed that PTSD is featured by exaggerated fear responses and absence of extinction of conditioned fear responses (Orr et al., 2000; Rothbaum et al., 2001). Animal and human neuroimaging studies have indicated that the amygdala is critically involved in conditioned fear and related memories (Armony and LeDoux, 1997; Buchel and Dolan, 2000; LaBar et al., 1998). Another important related structure is the medial prefrontal cortex (mPFC) consisting of the anterior cingulate cortex (ACC), the medial frontal gyrus, and the subcallosal cortex (Shin et al., 2006). This site is involved in the modulation and the extinction of conditioned fear responses. It was thus assumed that the mPFC may be comprised, while the amygdala may be overactive in PTSD (Shin et al., 2006). Based on neuroimaging research, mPFC was more consistently implicated in the mPFC-amygdala circuit of the conditioning fear model than the amygdala itself, which showed disagreement of activation in PTSD (Lanius et al., 2003).

At a more congregated level, the neural network involved in PTSD probably includes functionally connected regions such as the thalamus (hypothesized gateway for sensory inputs to cortex) (Yingling and Skinner, 1976), the amygdala, and the subregions of mPFC (Nemeroff et al., 2006). The thalamus is generally believed to act as a relay center between a variety of subcortical areas and the cerebral cortex, subserving both sensory and motor mechanisms (Herrero et al., 2002). It is also implicated in memory (Bremner et al., 1995; Johnson and Ojemann, 2000) which can be influenced by stress (Bremner et al., 1995). Moreover, the area also exerts regulation of consciousness, sleep and alertness which may be altered in PTSD patients. In fact, data from functional magnetic resonance imaging (fMRI), cerebral blood flow (rCBF) in the thalamus (Bremner et al., 1999a; Kim et al., 2007; Lanius et al., 2001, 2003; Liberzon et al., 1996). For example, Lanius et al. (2001) examined the neural correlates of PTSD using script-driven imagery with fMRI. Their results suggested that, compared with control participants, PTSD patients showed significantly less activation of the thalamus and the anterior cingulate gyrus (BA 32) at the time of internally generated memories of the traumatic experience (Lanius et al., 2003). In addition, Duggal (2002) reported a thalamic infarct resulting in the onset of PTSD with reexperience and reawakening of old traumatic memories. Less activation or decreased rCBF in the thalamus may induce lesion of the sensory areas, resulting in symptoms such as dissociation and flashback in PTSD (Lanius et al., 2001). Liberzon et al. (1996), using SPECT to examine a single PTSD case, proposed that corticothalamic dysfunction may play a role in the symptom of flashbacks.

In the past decade, researchers have increasingly studied the resting-state functional connectivity pattern between distributed brain regions in the psychiatric field. Alterations in functional connectivity of the thalamus have been detected using resting-state fMRI in psychiatric disorders such as depression, schizophrenia and autism (Anand et al., 2005; Cauda et al., 2009; Greicius et al., 2007; Mizuno et al., 2006; Welsh et al., 2008). As to PTSD, however, very few neuroimaging studies have addressed the functional connectivity during the resting state. Bluhm et al. (2009) examined the components of the default mode network functional connectivity in PTSD patients, revealing altered functional connectivity in the default network. In the present study, we explore the resting-state functional connectivity patterns of the thalamus in traumatized participants with and without PTSD. To avoid treatment-elicted changes in brain function (Fernandez et al., 2001) and possible changes related to chronic course, we only recruited recently traumatized and treatment-naive PTSD participants into the study. Based on the previous findings, we hypothesized that subjects with PTSD would show decreased functional connectivity of the thalamus with
mPFC, and increased functional connectivity between the thalamus and the amygdala.

2. Results

2.1. Demographic characteristics

The demographic and clinical characteristics of the 54 patients and 72 traumatized controls were summarized in Table 1. There are no significant differences in age, gender distribution and years of education between the PTSD patients and well-matched controls. The CAPS score of PTSD group was 64.09±9.68.

2.2. FMRI results

2.2.1. Functional connectivity pattern of the thalamus

In the control group, left and right thalamus-ROIs showed positive connectivity with whole brain regions including the cerebral and the subcortical structure including the cerebellum and brainstem; whereas a negative functional connectivity did not emerged in any areas of the brain. On the whole, the PTSD group showed substantially similar positive functional connectivity pattern to the controls.

2.2.2. Between-group differences of the functional connectivity pattern of the thalamus

Direct group comparisons were performed using two-sample t-tests to investigate the differences of functional connectivity of the thalamus-ROIs between the two groups. The results for the comparison of functional connectivity of the thalamus-ROIs between the two groups have yielded two clusters with significantly lower functional connectivity for the PTSD group as compared with the controls (Table 2 and Fig. 1). For the bilateral thalamus, these effects were found in right medial frontal gyrus and left rostral ACC. A few clusters showed inverse effects, that is, greater functional connectivity in the PTSD group compared to the control group (Table 2). These were seen in bilateral inferior and left middle frontal gyri, left inferior parietal lobule as well as right precuneus (Fig. 2). Both analyses for unilateral seed volumes showed roughly similar patterns of functional connectivity in the two study groups.

2.2.3. Correlation between the strength of functional connectivity and the symptom severity

Correlation analysis was performed between the connectivity strength (mean z-values) and the CAPS scores. The strength of functional connectivity of the left thalamus-ROI to right precuneus showed significant negative correlation with the CAPS scores (r=−0.33, P=0.014) in PTSD group (Fig. 3). No correlations were found in other functional connectivity of significant group differences.

3. Discussion

The present study found patterns of significant connectivity to the bilateral thalamus-ROIs under resting-state both in recently traumatized and treatment naïve PTSD participants and matched traumatized controls. Specifically, the comparison between the two groups exhibited different functional connectivity. In the PTSD group, there was increased positive

### Table 1 - Demographic and clinical data for PTSD and controls.

<table>
<thead>
<tr>
<th>Data</th>
<th>PTSD</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total participants</td>
<td>54</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Mean±SD age (years)</td>
<td>41.52±9.81</td>
<td>42.21±8.32</td>
<td>0.67</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>15/39</td>
<td>22/50</td>
<td>0.74*</td>
</tr>
<tr>
<td>Education (years)</td>
<td>7.56±3.32</td>
<td>7.57±2.88</td>
<td>0.98</td>
</tr>
<tr>
<td>CAPS score</td>
<td>64.09±9.68</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

M, male; F, female; SD, standard deviation; CAPS, Clinician-Administered PTSD Scale for DSM-IV. *P values were obtained using a Pearson χ² two-tailed test.

### Table 2 - Difference of functional connectivity of bilateral thalamus-ROIs between PTSD patients and traumatized controls.

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>Region</th>
<th>BA</th>
<th>Cluster</th>
<th>t-value (peak)</th>
<th>MNI coordinator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left thalamus-ROI</td>
<td>Medial frontal gyrus</td>
<td>11</td>
<td>17</td>
<td>3.70</td>
<td>3  54  -9</td>
</tr>
<tr>
<td>Controls&gt;PTSD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>Inferior frontal gyrus</td>
<td>44</td>
<td>10</td>
<td>3.86</td>
<td>-60  6  21</td>
</tr>
<tr>
<td>PTSD&gt;controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>Middle frontal gyrus</td>
<td>6</td>
<td>20</td>
<td>3.77</td>
<td>-33  -6  63</td>
</tr>
<tr>
<td>Left</td>
<td>Precuneus</td>
<td>7</td>
<td>6</td>
<td>3.58</td>
<td>21  -75  48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Right thalamus-ROI</th>
<th>Region</th>
<th>BA</th>
<th>Cluster</th>
<th>t-value (peak)</th>
<th>MNI coordinator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls&gt;PTSD</td>
<td>Anterior cingulate cortex</td>
<td>32</td>
<td>31</td>
<td>3.68</td>
<td>-3  39  15</td>
</tr>
<tr>
<td>Left</td>
<td>Medial frontal gyrus</td>
<td>11</td>
<td>17</td>
<td>3.46</td>
<td>3  54  -12</td>
</tr>
<tr>
<td>PTSD&gt;controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>Inferior frontal gyrus</td>
<td>44</td>
<td>10</td>
<td>4.63</td>
<td>-60  6  21</td>
</tr>
<tr>
<td>Left</td>
<td>Middle frontal gyrus</td>
<td>6</td>
<td>13</td>
<td>3.55</td>
<td>-27  -9  60</td>
</tr>
<tr>
<td>Right</td>
<td>Inferior frontal gyrus</td>
<td>9</td>
<td>6</td>
<td>3.50</td>
<td>63  6  24</td>
</tr>
<tr>
<td>Left</td>
<td>Inferior parietal lobule</td>
<td>40</td>
<td>10</td>
<td>3.28</td>
<td>-60  -24  27</td>
</tr>
</tbody>
</table>

BA, Brodmann area; MNI, Montreal Neurological Institute; ROI, region of interest; threshold was set at P<0.05 (corrected).
functional connectivity to the thalamus-ROIs for bilateral inferior and left middle frontal gyri, left inferior parietal lobule and right precuneus. It was also found that there was decreased positive functional connectivity to the thalamus-ROIs for right medial frontal gyrus and left rostral ACC.

Convergent evidence indicates that as a relay center, the thalamus has reciprocal connections with nearly all areas of the cortex. Studies from animal and human have revealed anatomically and functionally the relationship between the thalamus and spatially extensive cortical regions (Behrens et al., 2003; Selemon and Goldman-Rakic, 1988; Zhang et al., 2008, 2010), as well as between the thalamus and the subcortical structures, cerebellum, midbrain, and pons (Rubin and Safdieh, 2007; Sofroniew et al., 1985). Consistent with this thesis, we found that the thalamus corresponded functionally not only with the ipsilateral cerebral hemisphere and other brain areas, but also with the contralateral ones in both the PTSD group and the matched traumatized control group. Though most of these connectivities we found have been observed in healthy participants (Cao et al., 2009; Postuma and Dagher, 2006; Zhang et al., 2008), the comparison showed significant group effects between the PTSD group and the matched traumatized

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**Fig. 1** – Regions showing greater functional connectivity of the bilateral thalamus-ROIs in control group compared to PTSD group. A, right medial frontal gyrus (left thalamus); B, right medial frontal gyrus (right thalamus); C, left rostral anterior cingulate. Threshold was set at $P<0.05$ (corrected); $T$, t-value.

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**Fig. 2** – Regions showing greater functional connectivity of the bilateral thalamus-ROIs in PTSD group compared to control group. A, left inferior frontal gyrus (left thalamus); B, left middle frontal gyrus (left thalamus); C, right precuneus; D, left inferior frontal gyrus (right thalamus); E, left middle frontal gyrus (right thalamus); F, right inferior frontal gyrus; G, left inferior parietal lobule. Threshold was set at $P<0.05$ (corrected); $T$, t-value.
control group in the present study, indicating that the altered connectivity to thalamus-ROIs relative to the traumatized non-PTSD may be the underlying neural correlates for PTSD.

The current less connectivity to bilateral thalamus-ROIs was found in the right medial frontal gyrus and the left rostral ACC—the components of mPFC (Shin et al., 2006) in the PTSD group when compared with their matched traumatized controls. Morphometric MRI studies suggested that ACC volumes might be smaller in PTSD sufferers in comparison with trauma-exposed control groups (Rauch et al., 2003; Woodward et al., 2006). Furthermore, convergent evidence demonstrated reduced activation of the mPFC in PTSD participants compared to traumatized controls by applying different modalities (PET, fMRI) (Bremner et al., 1999b; Lanius et al., 2001, 2003; Markowitsch et al., 2000; Shin et al., 2001). Indeed, such impairments of the mPFC have been implicated in the pathology of PTSD, in which an excess of fear memory of traumatic event and a failure of expression and retention of extinction memory may be important in the persistence and reexperiencing of traumatic memories (Charney et al., 1993). The mPFC plays a critical role in emotional processing through inhibition of amygdala responsiveness and contributes to extinction of conditioned fear and extinction retention. This was made possible on the basis of its structural connection with the amygdala (McDonald et al., 1996; Rosenkranz and Grace, 2002). Individuals with dysfunction in mPFC could not respond to physiological stress adequately, which may produce inappropriate conditioned fear responses and a failure of extinction memory observed in PTSD patients (Orr et al., 2000; Rothbaum et al., 2001). Repetitive transcranial magnetic stimulations to the mPFC enhance extinction memory (Milad and Quirk, 2002) and reduced conditioned fearful responses (Milad et al., 2004). Thus, the decreased connectivity from thalamus-ROIs to the right medial frontal gyrus and the left rostral ACC may contribute to persistent excessive fear responses and failed extinction memory and extinction retention in the PTSD group. This notion is further supported by the evidence that reducing thalamic inputs to the mPFC is associated with resistance to extinction (Herry and Garcia, 2002). In line with this notion, Lanius et al. (2001, 2003) found that lower activation of the thalamus and the anterior cingulate gyrus and medial frontal gyrus arose during different script-driven imagery-induced emotional states (traumatic, sad and anxious) in PTSD patients exhibiting symptoms of flashback/revising/hyperarousal compared with traumatized non-PTSD participants. This suggested that dysfunction of these areas may be involved in the negative (including traumatic) remembrance and the altered emotion processing observed in PTSD (Lanius et al., 2001, 2003).

Our results also showed that connectivity strength was greater in PTSD patients than in the matched traumatized controls between the left thalamus and left inferior and middle frontal gyri as well as right precuneus; and between the right thalamus and bilateral inferior and left middle frontal gyri along with left inferior parietal lobule (Table 2 and Fig. 2). In other words, the PTSD patients displayed enhanced functional correlation of the thalamus with the frontal and parietal cortices. These findings are consistent with the existing evidence that both of the two structures are closely related to PTSD.

As to the frontal cortex, researchers reported that emotional (including traumatic) memories of childhood sexual abuse were associated with greater increases in blood flow in left middle frontal gyrus in sexually abused women with PTSD than in sexually abused women without PTSD (Bremner, 2003; Bremner et al., 1999a). Middle/inferior frontal gyrus has also been implicated in encoding and retrieval of verbal memories (Tulving et al., 1994). Thus the activation of these areas may reflect the strength of traumatic recollection in patients with PTSD (Bremner et al., 1999a), with the strengthened thalamo-frontal connectivity possibly recruited according to our present findings.

Many functional aspects of parietal cortex may be implicated in neural mechanisms underlying PTSD. Previous researches have found significantly greater activation in inferior parietal lobule during different traumatic cues (script, sound and pictures) in participants with PTSD (Bremner et al., 1999b; Pagani et al., 2010). More generally, the parietal lobe is also involved in modulation of arousal (Heilman, 1997) as well as in negative emotional processing (Etkin and Wager, 2007; Pagani et al., 2010). Thus, these findings including our present ones are in accordance with the possibility that the enhanced thalamo-parietal connectivity may be involved in the traumatic memories, hyperarousal and emotions such as depression and anxiety observed in PTSD. In addition to the mPFC, further integration of the frontal cortex, the parietal cortex and the thalamus may promote deeper understanding of the neurophysiological processes of PTSD. Spatial memory and visuospatial processing are mediated by functionally connected parietal and frontal cortices that comprise of the inferior parietal gyrus, the inferior frontal and the middle frontal gyri (Jonides et al., 1993; Ricciardi et al., 2006), and play a critical role in dealing with potential life-threatening events. The establishment and maintenance of a state of alertness can keep people alert or of preparation for a stimulus (Posner and Petersen, 1990) which is associated with frontal, parietal and thalamic areas as well as the brain-stem. These regions are coactivated by alerting and orienting attentional demands. Higher activities in these regions induced by the thalamus (Van der Werf et al., 2002) may reflect increased demands of visuospatial function, and underlying exaggerated vigilance in PTSD (Bremner et al., 1999a). For the memory

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Fig. 3 – The negative correlation between the strength of left thalamus-ROI functional connectivity with right precuneus and the CAPS scores. $r = -0.33$, $P = 0.014$. CAPS, clinician-administered PTSD scale for DSM-IV; FC, functional connectivity. Black solid circles indicate the 54 PTSD subjects.
function, traumatic stress may interrupt it and its related brain areas containing the thalamus, frontal and parietal cortex (Bremner et al., 1995). On the one hand, this interruption may include enhancement of memory, including nonverbal visual memory, for traumatic events in PTSD (Bremner et al., 1999a; Southwick et al., 1997). On the other hand, it may include impairment of declarative memories of the traumatic event which would be more experienced in a sensory and non-verbal way in PTSD victims (Dalgleish et al., 2008; Lanius et al., 2004). The stimulation of the thalamus subdivisions results in a disruption of memory and language abilities because of the involvement of thalami in these two functions (Johnson and Ojemann, 2000), so the thalamus may be more critical than expected to such abnormalities. Moreover, the altered functional activation of thalamus and the connectivity to it observed in PTSD patients may subserve the abnormal phenomenology of traumatic memories in PTSD patients (Lanius et al., 2006). Bremner et al. (1999a) suggested that greater functional correlation of the thalamus with the functionally linked parietal and prefrontal zones (Bremner et al., 1999a) may mediate jointly traumatic recollection in PTSD. Therefore, in our present work, the enhanced functional correlation of the thalamus with the frontal and parietal cortices have further strengthened the critical role of the thalamus in PTSD in the context of the integrated neural network comprising of the thalamus, the frontal and the parietal lobes.

Precuneus has been proposed to be involved in memory processing or spatial location encoding (Frings et al., 2006; Lundstrom et al., 2005). Reduced activation in precuneus has been found in PTSD patients during the retrieve of an associative learning task (Werner et al., 2009) and encoding of neutral, non-trauma related word pairs (Geuze et al., 2008) and resting state (Molina et al., 2010), suggesting the possible involvement of deactivation in the precuneus in cognitive deficit seen in PTSD. Our finding of enhanced functional connectivity of the right precuneus to the left thalamus-ROI in PTSD patients negatively correlated with symptom severity of PTSD may be a reflection of neural adaptation, that is, a compensatory strategy for the cognitive impairment in PTSD. The similar mechanism can be found in general anxiety disorder patients (Etkin et al., 2009).

Out of our expectation, however, we did not find changes in the connectivity between the thalamus and the amygdala. The potential explanation is that amygdala activation may be more easily detected during conditions evoking fear (Shin et al., 1999) rather than in resting state. This is also partially in line with some neuroimaging researches, indicating that mPFC was more consistently implicated in mPFC-amygdala circuit of the conditioning fear model than the amygdala region which showed disagreement of activation in PTSD (Lanius et al., 2003).

Our results were limited by several reasons. Firstly, we adopted the whole thalamus as seed region automatically using WFU_Pickatlas procedure instead of dividing it into subregions, which may affect our understanding of functional pathways between thalamic subdivisions and the cortex. In addition, the absence of a non-traumatized control group limited the investigation of the discrepancy between PTSD sample, healthy, and non-traumatized controls. Recently, abnormal resting state function connectivity has been detected between traumatized non-PTSD participants and non-traumatized participants (Lui et al., 2009), although it has been thought that the disorder itself contribute to the underlying biological abnormalities rather than the trauma exposure (Yehuda and McFarlane, 1995). In this case, it may be necessary to recruit non-traumatized healthy participants for more extensive research on the neurobiological basis of PTSD. Moreover, though there is no between-group difference in the extent of head motion, its effect on functional connectivity cannot be ruled out only by linear regression. Finally, the lack of pre-scan before formal resting fMRI examination in our study may lead to greater pressure in the PTSD group as compared to the control group, inducing not entirely consistent resting state between the two groups.

Overall, the present study found resting state dysfunctional connectivity patterns of bilateral thalami in PTSD patients using fMRI. The alterations in thalamo-cortical connectivity may be implicated in excessive fear recall, failure of expression and maintenance of extinction memory, and heightened traumatic remembrance which cause the characterized symptoms in PTSD. These results add to our understanding of the altered neural network organization in PTSD patients and contribute to elucidate the potential biological mechanism of PTSD.

4. Experimental procedures

4.1. Subjects

At 2:28 p.m. on 12 May 2008, an earthquake measuring 8.0-magnitude devastated the Sichuan Province of China. More than 15 million people were directly affected, leaving hundreds of thousands of people dead, injured as well as missing. The tragedy had caused tremendous mental and psychological trauma to tens of millions of survivors. A large scale survey and assessment was held to select participants among the post-earthquake survivors for the PTSD study. 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; Weathers et al., 1994). Survivors scoring ≥ 35 points were given the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995) by psychiatrists to confirm the PTSD diagnosis. A total of 1100 survivors in Beichuan county were interviewed and screened with the PCL. Survivors scoring ≥ 45 points were given the CAPS to confirm the PTSD diagnosis.

From these pools of PTSD participants identified with the above procedure, 415 fulfilling the PTSD diagnostic criteria were selected for eligibility to the current fMRI study. To exclude psychiatric co-morbidities, the Structured Clinical Interview for DSM-IV (First et al., 1995) was administered for further assessment. All participants were recruited by qualified clinicians using standardized screening criteria. The exclusion criteria for both groups include: history of psychiatric disorders, current psychiatric disorders other than PTSD, head injury, as well as any other significant medical or neurological conditions. We also excluded participants aging ≥ 60 years and PTSD patients with CAPS score of < 50 points. After exclusion by the eligibility screening, 72 PTSD individuals and 86 non-PTSD individuals participate in undergoing fMRI scans from 9 months to 15 months post-earthquake and their
data were preprocessed. Informed consent was obtained from all participants after reviewing detailed written information about the study. The research protocol was approved by the Ethical Committee of the Second Xiangya Hospital and the Ethical Committee of the Central South of University.

4.2. Data acquisition

Magnetic resonance imaging was conducted on a 3 T MR imaging system (EXCITE; General Electric) using gradient-echo planar imaging (EPI) sequence: repetition time (TR)=2000 ms; echo time (TE)=30 ms; flip angle=90°; slice thickness=3 mm; slice gap=1 mm; matrix=64x64; field of view (FOV)=220x220 mm². Each brain volume involved 30 axial slices, and each functional run contained 200 image volumes. Foam pads and ear plugs were used to reduce head motion and scanner noise. During scanning, all participants were asked to relax and remain still, thinking of nothing in particular, with their eyes closed but not to fall asleep. All participants were observed to have acted in good conformity to the guidance.

4.3. Data preprocessing

Image preprocessing and statistical analyses were conducted using SPM2 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm2/). Firstly, for each participant, slice timing and head motion correction of the functional scans were carried out. Next, the functional scans were spatially normalized to a standard EPI template and were resampled to the voxel size of 3x3x3 mm³. Following this, the functional images were spatially smoothed with a 4 mm full width at half maximum (FWHM) Gaussian kernel. Subsequently, linear regression was used to remove the influence of head motion and linear trends (Song et al., 2008). Then, the fMRI data were temporally band-pass filtered (0.01–0.08 Hz) to reduce the effect of low-frequency drifts and high-frequency noise (Biswal et al., 1995; Greicius et al., 2003) with AFNI (http://afni.nimh.nih.gov/). Head motion parameters of all participants were examined. Exclusion criterion of translation movement was >1.0 mm, and rotation was >1.0°. The data of 18 participants with PTSD and 14 traumatized controls were discarded due to the excessive head motion according to this criterion. We further evaluated the maximum head motion and mean head motion differences between groups (Holmes and Friston, 1998; Tian et al., 2006), and no significant difference was found (P>0.05).

4.4. Definition of seed region

The left and right seed regions of the thalami were separately defined using WFU_Pickatlas (http://fmri.wfubmc.edu/cms/software) (Maldjian et al., 2003), which has been used in previous studies (Etkin and Wager, 2007; Wu et al., 2009). Then the thalami as regions of interest (ROIs) were resampled to 3x3x3 mm³ for further analysis. Following processes were conducted in left and right thalamus-ROIs separately.

4.5. Functional connectivity analyses and statistics

A seed reference time course was obtained by averaging the time courses within the ROI. Correlational analysis was carried out between the seed reference and the whole brain in a voxel-wise manner. A Fisher’s z-transform was applied to improve the normality of these correlation coefficients (Lowe et al., 1998; Press et al., 1992). Spatial maps were obtained for the value of voxels representing the strength of the connectivity with the ROIs. The individual z value was entered into a one-sample t-test in a voxel-wise manner to determine brain regions showing significant connectivity to the right and left thalami within each group. These values were also entered into a two-sample t-test in a voxel-wise manner to identify the regions showing significant differences in connectivity to the right and left thalami between the groups.

Within each group, statistical threshold was set at P<1.0×10⁻⁸. Between experimental groups, multiple comparisons correction was done by using AlphaSim program in AFNI software (Analysis of Functional NeuroImages, http://afni.nimh.nih.gov/) determined by Monte Carlo simulations. A corrected threshold of P<0.05 was utilized, with a combined threshold of P<0.001 and a minimum cluster size of 162 mm³ (6 voxels).

Linear correlations were calculated between the mean z-scores of each cluster showing significant group differences and the CAPS scores in the PTSD group to identify the relationship between the strength of functional connectivity and symptom severity. P<0.05 was taken as statistically significant.

Financial disclosures

All authors report no biomedical financial interests or potential conflicts of interest.

Acknowledgments

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: 2008AA022708 to Qiyong Gong). The authors thank Drs. Baoci Shan, Zhijun Zhang, and Feng Bai for assistance in manuscript writing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.brainres.2011.07.016.

References


