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**Research Report**
**Brain responses to symptom provocation and trauma-related short-term memory recall in coal mining accident survivors with acute severe PTSD**
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**ABSTRACT**

Functional neuroimaging studies have largely been performed in patients with longstanding chronic posttraumatic stress disorder (PTSD). Additionally, memory function of PTSD patients has been proved to be impaired. We sought to characterize the brain responses of patients with acute PTSD and implemented a trauma-related short-term memory recall paradigm. Individuals with acute severe PTSD ( $n=10$ ) resulting from a mining accident and 7 men exposed to the mining accident without PTSD underwent functional magnetic resonance imaging (fMRI) while performing the symptom provocation and trauma-related short-term memory recall paradigms. During symptom provocation paradigm, PTSD subjects showed diminished responses in right anterior cingulate gyrus, left inferior frontal gyrus and bilateral middle frontal gyrus and enhanced left parahippocampal gyrus response compared with controls. During the short-term memory recall paradigm, PTSD group showed diminished responses in right inferior frontal gyrus, right middle frontal and left middle occipital gyrus in comparison with controls. PTSD group exhibited diminished right parahippocampal gyrus response during the memory recall task as compared to the symptom provocation task. Our findings suggest that neurophysiological alterations and memory performance deficit have developed in acute severe PTSD.

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## 1. Introduction

Exposure to trauma can precipitate the development of post-traumatic stress disorder (PTSD), a complex syndrome comprising re-experiencing symptoms, hyperarousal symptoms, numbing symptoms and avoidance symptoms in addition to poor concentration and difficulty explicitly recalling aspects of the traumatic event (DSM-IV, *American Psychiatry Association, 2000*).

Functional and structural neuroimaging studies continue to investigate potential correlates of PTSD and have looked at the regions of fear system, mainly the anterior cingulate cortex (ACC), the amygdala and the hippocampus (*Hull 2002; Shin et al., 2006*). The ACC is a component of the frontal lobes that is thought to be involved in the processing of both cognitive and emotional information and to have inhibitory projections to the amygdala (*Bush et al., 2000; Allman et al., 2001; Phillips et al., 2003*). Many researches investigated the ACC responses in individuals with chronic PTSD. Some studies (*Bremner et al., 1999a,b, 2004; Lanius et al., 2003; Shin et al., 2001; Yang et al., 2004*) observed a decreased function in the ACC when cued with emotional stimuli in comparison with control participants, while other studies (*Liberzon et al., 1999; Rauch et al., 2000; Shin et al., 1997; Lanius et al., 2002*) got the opposite results, namely PTSD patients exhibiting an equal or greater activation of the ACC in PTSD patients compared with control subjects. One study (*Gilboa et al., 2004*) investigated the functional connectivity of the amygdala and the ACC in a functional magnetic resonance imaging (fMRI) study and found no evidence supporting the notion of top-down inhibition by the ACC over the amygdala activity. Morphometric MRI studies demonstrated smaller volume of the ACC (*Rauch et al., 2003; Yamasue et al., 2003*) in comparison to non-PTSD subjects. A meta-analysis found significantly smaller ACC in PTSD (*Karl et al., 2006*).

Memory function of PTSD patients has been proved to be impaired, and functional and structural imaging techniques have identified abnormalities in the brains of patients with PTSD in regions known to be important for memory functioning. Specifically, papers found the brain areas concluding the frontal lobes, the hippocampus and the amygdala were examined in relation to the hypothesized memory functions (*Isaac et al., 2006*).

Additionally, the bulk of previous researches have been performed in victims with longstanding chronic PTSD, which is usually associated with significant psychiatric comorbidity and pharmacological treatment and may act as confounding factors for observed results to some extent. There have been only a study (*Armony et al., 2005*) focusing on acute PTSD to our knowledge which used fMRI to investigate amygdala response to emotional expressions but not symptom provocation, and the study had no control participations. Whether the neural correlates of PTSD could be observed in the acute severe PTSD has been investigated very little.

On the morning of June 8, 2005, a devastating mining accident occurred in Zijiang Coal Mine in Hunan Province, PR China. Approximately 15.3% of the whole coal miners in the coal well lost their lives (22 people), and the other 112 people were stranded in horror and death threat for several hours and

survived in the end. Our epidemiological survey indicated that among the survivals (104 people receiving survey), 50% of them developed PTSD at 2 months follow-up. According to the median age of 37 years, the group (>37 years) had 50 coal miners in which 19 suffered from PTSD (the incidence: 38%), while the other group ( $\leq 37$  years) had 54 coal miners in which 33 suffered from PTSD (the incidence: 61.1%), the incidences between the two groups were significantly different ( $\chi^2=5.547$ ,  $P=0.019$ ) (*Cailan et al., in press*).

In the current study, we investigated the characteristics of functional abnormalities in brain responses in acute severe PTSD and implemented a trauma-related short-term memory recall paradigm to determine the neurobiological alternations. To our knowledge, none of the existing studies of coal miners has been examined the neurobiology of those with PTSD.

We studied fMRI blood oxygen-level depletion (BOLD) signal in the mining accident exposed men with and without PTSD while they viewed blocks of mining accident related pictures and neutral pictures. In the trauma-related versus neutral comparison, we predicted that participants with PTSD would exhibit diminished activation in the prefrontal regions and greater activation in amygdala compared with control participants. In addition, we predicted that PTSD group would show diminished activation in the hippocampus or frontal lobe during the memory recall paradigm.

## 2. Results

**Table 1** presents the within- and between-group findings from the whole brain analysis in the stimulus provocation paradigm.

### 2.1. Within-group analysis

In response to picture stimulus (mining accident related pictures versus neutral pictures), the PTSD group showed significant activations in the left posterior cingulate gyrus, the bilateral caudate and the right thalamus and significant deactivations in the right cingulate gyrus and the bilateral middle frontal gyrus. Control subjects showed significant activations in many brain areas (**Table 1**).

### 2.2. Between-group analysis

In response to picture stimulus, the PTSD group had significantly greater BOLD activations than controls in the left parahippocampal gyrus, and lower BOLD activations in the right anterior cingulate gyrus, left inferior frontal gyrus, bilateral middle frontal gyrus, bilateral middle temporal gyrus, left postcentral gyrus and right temporal gyrus (**Fig. 1**).

**Table 2** presents the within- and between-group findings from the whole brain analysis in the trauma-related short-term memory recall paradigm.

### 2.3. Within-group analysis

Performing short-term memory recall task (mining accident related pictures versus neutral pictures), many brain areas in control participants were activated greatly. In the PTSD group,

**Table 1 – Summary of within-group and between-group whole-brain analysis in the stimulus provocation task**

PTSD group				Control group			
Region	Voxel	Z score	Talairach x, y, z	Region	Voxel	Z score	Talairach x, y, z
<i>BOLD signal increases (within-group analysis)</i>							
Left posterior cingulate	36	2.96	–6, –48, 6	Bilateral thalamus	79	3.14	–15, –24, –6
Bilateral caudate	27	3.57	–6, 9, 9		59	3.34	21, –27, 12
	27	2.94	6, 9, 9		68	3.23	–9, –9, 15
Right thalamus	290	3.98	12, –9, 0	Left insula	24	2.74	–33, –12, 21
				Left medial frontal gyrus	45	3.05	–3, 60, 24
					24	2.73	–3, 54, 39
				Bilateral middle frontal gyrus	332	4.54	45, 18, 27
					386	3.71	–42, 33, 18
				Bilateral occipital gyrus	1282	4.97	57, –66, –15
					2197	4.66	–51, –69, 6
				Right inferior temporal gyrus	1282	4.99	48, –42, –24
					1282	4.65	54, –51, –15
				Right superior temporal gyrus	27	4.58	51, 12, –18
				Right parahippocampal gyrus	14	3.06	24, –21, –9
<i>BOLD signal decreases (within-group analysis)</i>							
Right cingulate gyrus	31	3.02	9, 33, 30	None			
Bilateral middle frontal gyrus	27	2.83	–42, 48, 15				
	8	4.09	39, 60, 12				
Right superior temporal gyrus	38	3.06	69, –18, 9				
<i>Between-group analysis</i>							
<i>PTSD group &gt; Control group</i>				<i>PTSD group &lt; Control group</i>			
Left parahippocampal gyrus	22	3.21	–24, –51, –6	Right anterior cingulate gyrus	57	2.90	3, 48, 3
				Left inferior frontal gyrus	9	3.06	–57, 21, 24
				Bilateral middle frontal gyrus	13	3.44	42, 57, 15
					38	2.89	–42, 33, 18
					5	2.86	–42, 48, 15
				Bilateral middle temporal gyrus	8	2.83	51, –78, 21
					26	2.90	–54, –45, –15
				Left postcentral gyrus	290	3.30	–33, –36, 69
				Right superior temporal gyrus	22	3.12	66, –21, 9

Abbreviations: BOLD, blood oxygenation level-dependent; PTSD, posttraumatic stress disorder.

significant activations occurred in the right posterior cingulate gyrus and the bilateral parahippocampal gyrus (Table 2).

#### 2.4. Between-group analysis

In the short-term memory recall paradigm, the PTSD group had significantly lower activation than controls in the right frontal gyrus, the right middle frontal gyrus, the left middle occipital gyrus and the left cuneus.

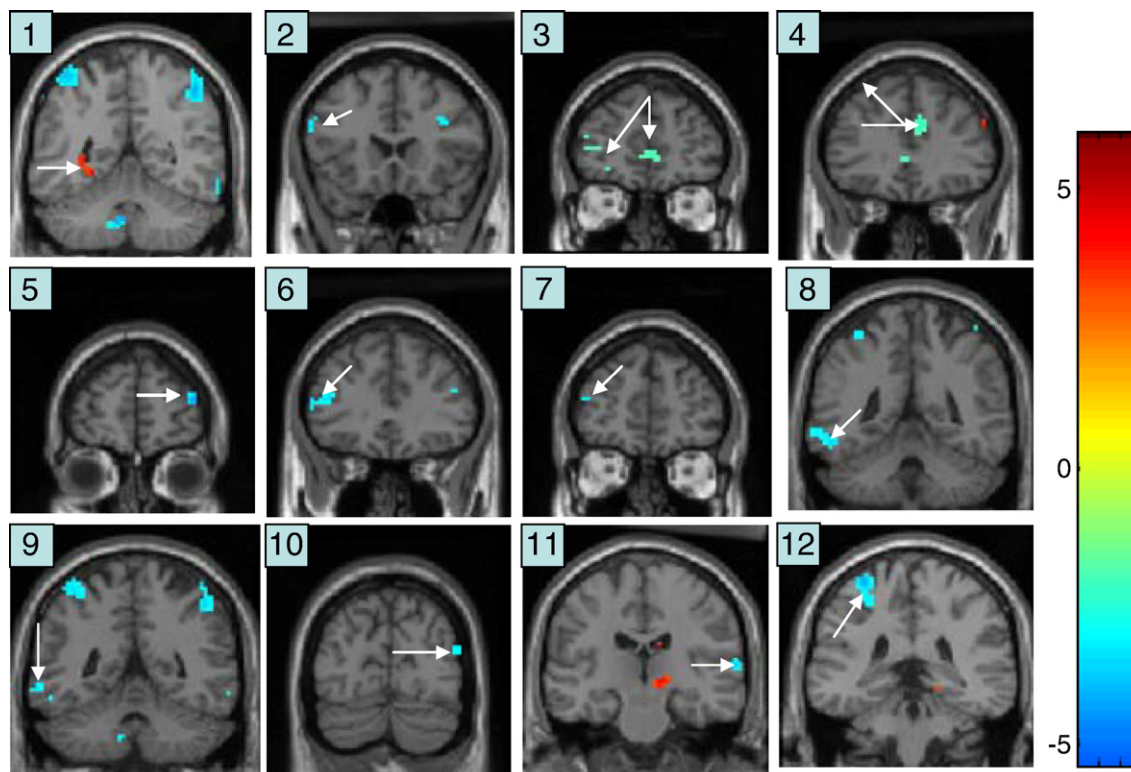
Table 3 presents the findings between the short-term memory recall task and the stimulus provocation task in the PTSD and control group.

When the two tasks were compared with each other, the control group in memory recall task had significantly greater activations in the left anterior cingulate gyrus, the right posterior cingulate gyrus, the superior frontal gyrus, the left insula, the right superior temporal gyrus, the right superior temporal gyrus, the left caudate, the right middle occipital gyrus and the cuneus than in the symptom provocation task, while the PTSD group in the trauma-related memory recall task had significantly lower activation in the right parahippocampal gyrus than in the symptom provocation task (Table 3, Fig. 2).

### 3. Discussion

In the present study, the acute severe PTSD group exhibited diminished anterior cingulate gyrus and middle frontal gyrus responses and exaggerated parahippocampal gyrus responses across presented mining accident related pictures vs neutral pictures. In addition, the PTSD group showed decreased inferior frontal gyrus and middle frontal gyrus response while performing memory performance. Finally, the PTSD patients in the memory recall task showed significantly lower activations in the right parahippocampal gyrus than in the symptom provocation task.

The anterior cingulate gyrus is an area in the medial prefrontal cortex that has been receiving abundant attention in PTSD neuroimaging research. Medial prefrontal cortex is involved in the process of extinction of fear conditioning and the retention of extinction (Maren and Quick 2004; Milad et al., 2006; Lebron et al., 2004). Extinction does not occur normally when medial prefrontal cortex is damaged (Morgan et al., 1993; Quirk et al., 2000). The finding of decreased anterior cingulate gyrus function in acute severe PTSD is consistent with previous functional imaging studies for chronic PTSD (Brem-



**Fig. 1** – Regions of activation and deactivation during trauma provocation task where control groups show greater activation than PTSD groups except left parahippocampal gyrus during coal mining accident related pictures exposure versus neutral pictures. 1. Left parahippocampal gyrus (BA 19), 2. left inferior frontal gyrus (BA 45), 3. right anterior cingulate (BA 32), 4. right cingulate gyrus (BA 32), 5. right middle frontal gyrus (BA 10), 6. left middle frontal gyrus (BA 46), 7. left middle frontal gyrus (BA 10), 8. left inferior temporal gyrus (BA 20), 9. left middle temporal gyrus (BA 21), 10. right middle temporal gyrus (BA 39), 11. right superior temporal gyrus (BA 42), 12. left postcentral gyrus (BA 1).

ner et al., 2004; Yang et al., 2004; Lanius et al., 2003; Shin et al., 2001). Additionally, it is necessary to emphasize that there was no difference in ACC volume between acute PTSD and healthy subjects but found a reduced gray matter density in the dorsal ACC in PTSD individuals in a recent study (Corbo et al., 2005). Individuals with PTSD exhibit persistent inappropriate fear responses in daily life and diminished extinction of conditioned fear responses in the laboratory (Orr et al., 2000; Rothbaum et al., 2001), leading to the hypothesis that medial prefrontal cortex may be impaired in PTSD and may be under the emotional dysregulation frequently observed in patients with PTSD. A deactivation of the anterior cingulate gyrus could explain the inability of patients with PTSD to extinguish fear reactions associated with conditioning stimulus when the unconditioning stimulus is no longer occurring.

The inferior frontal gyrus has also gotten special attention in previous fMRI studies. The anterior language area (Broca's area or BA 45) is part of the dominant inferior frontal gyrus. It is common clinical knowledge that patients with PTSD have difficulties in verbally describing and processing trauma-related experiences. Most studies spanning a variety of study populations have found the deactivation of the left inferior frontal gyrus of right-handed subjects with PTSD during symptom provocation paradigms (Shin et al., 1997, 1999, 2001; Rauch and van der Kolk, 1996; Lanius et al., 2003), but all the studies did not use control individuals. Two studies

(Lanius et al., 2003; Bremner et al., 2003) showed inconsistent results—activation of the left inferior frontal gyrus of subjects with PTSD. The inferior frontal gyrus deactivation was consistent with the common clinical observation that patients with PTSD have decreased ability to verbalize their traumatic experiences. Previous researches have showed an increase (Shin et al., 2001; Lanius et al., 2002; Bremner et al., 1999a) or a decrease (Bremner et al., 1999b; Lanius et al., 2003) in right inferior frontal gyrus activation in subjects with PTSD on trauma reminders. However, the effects of the nondominant inferior frontal gyrus to PTSD symptomatology are less uniform and require additional research.

Previous studies of structural brain abnormalities in PTSD have focused in particular on the hippocampus, a gray matter structure in the limbic system that is critically involved in explicit (declarative) memory, working memory (Squire, 1992) and memory for episodic events (Buckner et al., 2004), the hippocampus also has an important role in the regulation of stress (Jacobson and Sapolsky, 1991). Because of its critical role in learning and memory as well as stress regulation, alterations to the etiology in the hippocampus have been proposed as contributing to the etiology of PTSD (Bremner, 2001). Activation of the left parahippocampal gyrus during symptom provocation in the present study was consistent with two studies (Niki and Luo 2002; Sakamoto et al., 2005). Functional neuroimaging studies are much mixed, with reports of both a

**Table 2 – Summary of within-group and between-group whole-brain analysis in the trauma-related short-term memory recall task**

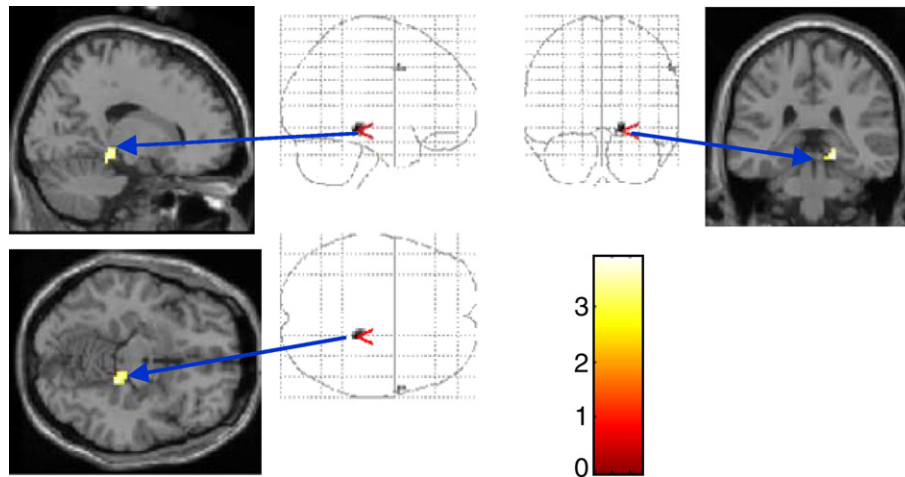
PTSD group				Control group			
Region	Voxel	Z score	Talairach x, y, z	Region	Voxel	Z score	Talairach x, y, z
<i>BOLD signal increases (within-group analysis)</i>							
Right posterior cingulate	39	3.48	6, -51, 15	Right posterior cingulate	760	3.90	3, -39, 24
Bilateral parahippocampal gyrus	10	3.25	28, -20, -18	Left medial frontal gyrus	32	3.00	-3, 60, -18
	16	3.25	-21, -24, -18		6	2.80	-3, 33, 39
				Left superior frontal gyrus	234	4.89	-12, 63, 27
					6	2.83	-21, 63, 15
				Right middle frontal gyrus	181	3.87	48, 39, 33
				Left inferior frontal gyrus	31	3.59	-51, 27, -12
				Right thalamus	57	3.02	15, -30, 12
					51	2.91	18, -15, 18
				Left middle temporal gyrus	29	2.98	-66, -42, -3
				Bilateral lentiform nucleus	5	4.04	-24, -15, 0
					23	3.13	21, -6, 3
				Bilateral caudate	51	2.97	9, 9, 6
					9	2.91	-9, 6, 6
				Right lingual gyrus	19	3.55	18, -99, -15
<i>BOLD signal decreases (within-group analysis)</i>							
None				None			
Between-group analysis							
<i>PTSD group &gt; Control group</i>				<i>PTSD group &lt; Control group</i>			
None				Right inferior frontal gyrus	8	3.57	57, 33, 15
				Right middle frontal gyrus	5	2.79	42, 57, 6
Abbreviations: BOLD, blood oxygenation level-dependent; PTSD, posttraumatic stress disorder.							

failure to activate the hippocampus during cognitive tasks and increased hippocampal activation at rest or across tasks. Across studies, greater PTSD symptom severity has been associated with elevated hippocampus/parahippocampal blood flow. In addition, the parahippocampal area that was activated in the PTSD group has been suggested to be related to episodic, spatial and contextual memory and emotional

responses. These results may be related to the clinical characteristic of PTSD, in which general ability to attend and short time memory are impaired while traumatic memories are abnormally readily recollected. In the end, there are lower activations in the right parahippocampal gyrus in PTSD patients when performing memory recall task compared with symptom provocation task. In our consideration, mem-

**Table 3 – The trauma-related short-term memory recall task and the stimulus provocation task in the PTSD and control group**

PTSD group				Control group			
Region	Voxel	Z score	Talairach x, y, z	Region	Voxel	Z score	Talairach x, y, z
<i>BOLD signal increases (memory recall task &gt; symptom provocation task)</i>							
None				Left anterior cingulate	19	2.74	-3, -6, 30
				Right posterior cingulate	24	3.08	6, -36, 24
				Right superior frontal gyrus	24	2.66	3, 27, 60
				Left insula	7	3.23	-42, 0, 12
				Right superior temporal gyrus	149	3.96	42, -33, 6
				Right superior temporal gyrus	6	3.25	69, -12, 9
				Left thalamus	10	3.37	-12, -27, 15
				Right caudate	71	3.35	9, 9, 6
					71	3.27	3, 3, 3
				Right middle occipital gyrus	59	3.16	15, -90, 9
				Right cuneus	59	3.17	12, -93, 0
<i>BOLD signal decreases (memory recall task &lt; symptom provocation task)</i>							
Right parahippocampal gyrus	22	2.88	18, -33, -12	none			
Abbreviations: BOLD, blood oxygenation level-dependent; PTSD, posttraumatic stress disorder.							



**Fig. 2 – Right parahippocampal gyrus (BA 35) activation where the PTSD group in the stimulus provocation task shows greater activation than in the short-term trauma-related memory recall.**

ory recall is a kind of active working memory, while the ability of active memory recall was impaired. Future studies will be needed.

The amygdala is involved in the assessment of threat-related stimuli and/or biological ambiguity (Davis and Whalen, 2001) and animal studies have been definitely implicated in fear conditioning (Ledoux, 2000). Functional neuroimaging studies have provided evidence for amygdala hyperresponsivity in PTSD during the presentation of personalized traumatic narratives (Rauch and van der Kolk, 1996; Shin et al., 2004) and cues (Driessen et al., 2004), combat sounds (Liberzon et al., 1999; Pissioti et al., 2002), combat photographs (Hendler et al., 2003; Shin et al., 1997), and trauma-related words (Protopopescu et al., 2005), as well as during the presentation to trauma-unrelated affective material, such as fearful expressions (Rauch et al., 2000; Shin et al., 2005) and during neutral auditory oddball and continuous performance tasks (Bryant et al., 2005; Semple et al., 2000). Amygdala activation has been shown to be positively correlated with PTSD symptom severity (Rauch and van der Kolk, 1996; Shin et al., 2004; Protopopescu et al., 2005; Armony et al., 2005). Importantly, amygdala hyperresponsivity was found during acquisition of fear conditioning in abuse survivors with PTSD in a recent PET study (Bremner et al., 2005). Structural changes in the amygdala were inconsistent. Matsuoka et al. (2003) found that the total volume of the amygdala was significantly smaller in subjects with a history of intrusive recollections as compared with the control subjects. Others did not replicate it (Bremner et al., 1997; De Bellis et al., 2001; Wignall et al., 2004). In the present study, however, exaggerated amygdala responsibility was not observed in the acute phase of PTSD. Several functional neuroimaging studies have also failed to find any amygdala activation during symptomatic in PTSD (Lanius and Williamson, 2001; Shin et al., 1999; Bremner et al., 1997, 1999a,b). Failure to replicate amygdala hyperresponsivity may be due to relatively poor spatial and temporal resolution or type II error associated small sizes (Shin et al., 2006).

Many other brain areas, such as the superior temporal gyrus, the inferior parietal lobule and the thalamus, may also be contributing to PTSD symptoms. However, there are not

enough data or studies which have found equivocal results on the activation of those areas. The contribution of these areas to the neurocircuitry of PTSD remains to be elucidated in the future.

In conclusion, the present findings suggest that neurophysiological alterations and memory performance deficit have developed in acute severe PTSD. Longitudinal studies about these coal miners are needed in the future.

## 4. Experimental procedures

### 4.1. Participants

Participants were chosen from all of 104 survivors according to the severity of symptom severity and their informed consent to attend the research. As a result, 14 patients with the most severe PTSD symptoms among 52 survivors with PTSD and 14 controls with minimal or no PTSD symptoms among other 52 survivors without PTSD were enrolled into this study. Because of the great head movement during performing the stimulus tasks under fMRI, the imaging data of 4 patients and 7 controls were removed from the research. Therefore, only 17 mining accident exposed men (10 patients and 7 controls) were analyzed. Ten participants met DSM-IV diagnostic criteria for current PTSD (PTSD group), and never had PTSD (control group) according to a structured clinical interview (the Clinician-Administered PTSD Scale [CAPS]). The subjects were assessed and diagnosed for PTSD symptoms 2 months from the mining accident, and then the subjects were immediately tested for the various fMRI parameters. After fMRI tests were finished, we offered them free psychological and drug therapy. We reassessed and diagnosed for PTSD symptoms 10 months from the mining accident, and the PTSD patients who were diagnosed for the first time received fMRI tests for the second time, and the data have been managed. All participants were without a history of head injury, neurological disorders, or other major medical conditions and had never taken psychotropic at the time of the study or before the study. All participants were right-handed. After a detailed

description of the study to the subjects, written informed consent was obtained from all participants.

The groups differed with regard to age (mean±SD age, 34.30±4.55 [PTSD group] versus 40.57±5.26 [control group];  $t=-2.63$ ,  $P=0.019$ ). The groups did not differ with regard to education (mean±SD, 7.90±1.60 [PTSD group] versus 8.57±1.81 years [control group];  $t=-0.81$ ,  $P=0.432$ ) and marital status (all participants were married). The control group had an average of 10.72 more years of length of service in the pit bottom of the coal mine than the PTSD group (mean±SD, 7.85±6.73 [PTSD group] versus 18.57±7.02 years [control group];  $t=-3.18$ ,  $P=0.006$ ). Relative to the control group, the PTSD group had significantly higher mean±SD scores (indicating greater symptom severity) on the following clinical measures: CAPS (83.60±8.28 [PTSD group] versus 16.29±7.83 [control group];  $Z=3.42$ ,  $P=0.000$ ); the Beck Depression Inventory (BDI) (31.70±9.91 [PTSD group] versus 12.14±8.63 [control group];  $t=4.21$ ,  $P=0.001$ ); the state anxiety subscale of State-Trait Anxiety Inventory (STAI) (65.60±7.38 [PTSD group] versus 40.29±6.32 [control group];  $t=7.36$ ,  $P=0.000$ ). Relative to the control, the PTSD group had significantly lower mean±SD scores on the following clinical measures: the trait anxiety subscale of STAI (29.30±8.78 [PTSD group] versus 40.43±2.99 [control group],  $t=-3.20$ ,  $P=0.006$ ); the Visual Recognition subtest of Wechsler Memory Scale-Revised (WMS-R) (3.20±3.33 [PTSD group] versus 9.00±3.96 [control group],  $t=-3.28$ ,  $P=0.005$ ). While the Logical Memory subtest of WMS-R (4.20±1.81 [PTSD group] versus 5.71±1.89 [control group];  $t=-1.67$ ,  $P=0.116$ ) or the Visual Reproduction subtest of WMS-R (3.90±2.03 [PTSD group] versus 4.71±2.63 [control group];  $t=-0.72$ ,  $P=0.481$ ) did not differ between the two groups.

All symptoms of PTSD were represented among the PTSD participants, although not every symptom in each case. The PTSD group's mean CAPS score represents severe PTSD symptoms, and the control group's mean CAPS score represents minimal PTSD symptoms.

The presence of other Axis I mental disorders was assessed with the structured clinical interview for DSM-IV. Neither participants in the PTSD group nor the participants in the control group met criteria for another current Axis I diagnosis. For the details of subject's clinical profile, please refer to our epidemiological reports (Cailan et al., in press).

#### 4.2. Provocation presentation

The methods used in this study were approved by the Ethical Committee of the Second Xiangya Hospital and the Ethical Committee of the Central South of University.

The participants lay in the supine position in the MRI system. They viewed images on a semi-transparent screen through a mirror in the head coil of the MRI system. The stimulus presentation software (MacStim) was run on a personal computer (IBMR52-1858-BC2, IBM Ltd) and projected onto the screen using crystal projector (LVP-2000, Mitsubishi).

Participants performed two 5-min functional imaging runs which consisted of the symptom provocation paradigm and trauma-related short-term memory recall paradigm during fMRI data acquisition. The block-design in both runs was +N-C-N-C+ (+rest, C—coal mining accident related pictures, N—neutral pictures). Two sets of pictures were used for visual

stimulation in each run. The first set consisted of 20 pictures of coal mining accident damage occurring in Zijiang Coal Mine. The second set consisted of 20 pictures of neutral and affectively innocuous scenery unrelated to coal mining accidents which was taken as control stimulus. Two resting states (each of 30 s) were added before and after the picture stimulus for the stability of the MRI signal and the adaptation of subjects to the circumstance. The two sets of pictures were balanced for color, luminance and complexity. The neutrality of neutral pictures and balance of color, luminance and complexity between the two sets of pictures were evaluated visually by consensus of three researchers. The trauma-related pictures were presented to the subjects the day before fMRI tests, and the heart rates were recorded when they see the pictures. The heart rates differed significantly (mean±SD, 86.60±6.19 [PTSD group] versus 75.14±8.57 [control group];  $t=-3.21$ ,  $P=0.006$ ). Moreover, some PTSD patients behaved very nervously, shivering or weeping while seeing the pictures. Each picture was presented for 6 s and each run lasted for 5 min.

In the second run, the previous two sets of pictures were also used, but half of the pictures were replaced by new pictures including 10 new coal mining accident related pictures and 10 new neutral pictures that the subjects had never seen in the first run. Subjects responded using a keypad consisting of four horizontally arranged buttons that represented the numbers 1, 2, 3 and 4 from left to right. Subjects were instructed to button-press with their left and right thumbs before the experiment. During the experiment, they were asked to press button 1 on the response pad if they had seen the picture in the first run, and if otherwise, to press button 4. By analyzing the performance data, we found that the dropping rate of choosing in PTSD group was 6.67%, while in the control group was 1.43%. The numbers of correct performance differed significantly (mean±SD, 20.44±2.07 [PTSD group] versus 24.14±2.41 [control group];  $t=-3.30$ ,  $P=0.005$ ), while the rate of correct performance had no significant difference (mean±SD, 0.55±0.07 [PTSD group] versus 0.61±0.07 [control group];  $t=-1.83$ ,  $P=0.09$ ).

#### 4.3. Functional MRI procedures

##### 4.3.1. Data acquisition

All the images were acquired with a Sigma 1.5 T Scanner (GE signal 1.5 T Twinspeed, Milwaukee, Wisconsin, USA) fitted with a standard quadrature head coil. Blood oxygenation level-dependent (BOLD) contrast image (time of repletion (TR)=3000 ms, single-shot echo-planar image, echo time (TE)=60 ms, flip angle=90°, matrix=64×64, field of view (FOV)=24 cm) was used to scan the whole brain repeatedly for 100 times in each session. Eighteen axial noncontiguous slices of 5 mm thickness (5 mm interslice gap) were measured, positioned parallel to the intercommisural (anterior commissure–posterior commissure [AC-PC]) line. These slices covered the whole cerebrum providing whole-brain coverage.

#### 4.4. Data analysis

The first and last 10 image acquisitions of the resting state were excluded from the analysis. The remaining fMRI data were first preprocessed using statistical parametric mapping

(SPM2; Wellcome Department of Cognitive Neurology, London, UK) with standard procedures, i.e. motion realignment, spatial normalization and smoothing (FWHM=4 mm). Then the activation profiles were analyzed with SPM2 using a general linear model approach. A square wave function convolved with a standard hemodynamic response function was used to estimate contrast of interest. Voxel-by-voxel hypotheses were tested with a *t* statistic (which were then transformed to *Z* scores) to provide statistical parametric maps.

#### 4.5. Within task analysis

For each of the two tasks (the stimulus provocation task and the trauma-related short-term memory recall task), firstly, the contrast images of PTSD patients and controls were respectively entered into a random-effect one-sample *t* test to determine the brain regions showing significant activations to the picture stimuli (coal mining accident related pictures versus neural pictures) within each group. The contrast images of PTSD patients and controls were also entered into a random-effect two-sample *t* test to determine the brain regions showing significantly different activations between the two groups.

#### 4.6. Between task analysis

For the PTSD patients, the contrast images of the two tasks were entered into a random-effect two-sample *t* test to determine the brain regions showing significantly different activations between the two task paradigms. This analysis was also performed for the control group. Especially to emphasize, PTSD may be accompanied by some problems with attention and working memory (Vasterling et al., 2002). In the present study, we intended to add the short-term memory recall task in order to investigate the brain responses while subjects perform the task, as well as to compare the activation patterns between the two tasks by subtracting activation for the brain responses performing working memory and attention excluding the influence of trauma exposure.

A level of  $P < 0.005$  (uncorrected for multiple comparisons) was chosen for the significant threshold. All data were analyzed at the Medical Imaging and Computing Group, National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing 100080, PR China.

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