High-field MRI reveals an acute impact on brain function in survivors of the magnitude 8.0 earthquake in China

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Besides the enormous medical and economic consequences, national disasters, such as the Wenchuan 8.0 earthquake, also pose a risk to the mental health of survivors. In this context, a better understanding is needed of how functional brain systems adapt to severe emotional stress. Previous animal studies have demonstrated the importance of limbic, paralimbic, striatal, and prefrontal structures in stress and fear responses. Human studies, which have focused primarily on patients with clinically established posttraumatic stress disorders, have reported abnormalities in similar brain structures. At present, little is known about potential alterations of brain function in trauma survivors shortly after traumatic events. Here, we show alteration of brain function in a cohort of healthy survivors within 25 days after the Wenchuan earthquake by a recently discovered method known as ''resting-state'' functional MRI. The current investigation demonstrates that regional activity in frontolimbic and striatal areas increased significantly and connectivity among limbic and striatal networks was attenuated in our participants who had recently experienced severe emotional trauma. Trauma victims also had a reduced temporal synchronization within the ''default mode'' of resting-state brain function, which has been characterized in humans and other species. Taken together, our findings provide evidence that significant alterations in brain function, similar in many ways to those observed in posttraumatic stress disorders, can be seen shortly after major traumatic experiences, highlighting the need for early evaluation and intervention for trauma survivors.

neuroimaging | stress | anxiety | depression | posttraumatic stress disorder

In the afternoon on May 12, 2008, the epicenter of a devastating earthquake occurred in Wenchuan, in the Sichuan Province of China. It measured 8.0 on the Richter scale. The most severely affected geographical regions were Yingxiu, Wenchuan, Dujiangyan, and Shifang, where 45 million people were directly affected. Among them, 69,146 people were confirmed dead, 374,131 were seriously injured, and 17,516 are missing. A significant proportion of the survivors (≈20%) (1) are likely to develop stress-related disorders, such as acute stress disorder (ASD) and posttraumatic stress disorder (PTSD). Given the serious and persistent impact of these highly prevalent psychiatric disorders, it is vital to develop a better understanding of the alterations of cerebral function evident in the early stages of adaptation to trauma. Such knowledge may lead to a better understanding of posttraumatic responses and the development of more effective early interventions.

Studies of animal models of acute and chronic stress have provided evidence of physiological and morphological changes in several brain regions, including the amygdala, hippocampus, and prefrontal cortex (2, 3). Human studies (4–12) have focused primarily on patients who already have an established psychiatric disorder, such as ASD and PTSD. Despite some inconsistencies (6, 7, 9–11), findings from clinical studies also implicate limbic, paralimbic, striatal, and prefrontal structures in the pathophysiology of stress-related psychiatric disorders. However, because the majority of these studies were performed with victims of trauma that took place years or even decades earlier, it is not clear whether this represents a slowly evolving pattern of brain alteration or one that emerges shortly after traumatic experiences. No study has yet investigated alterations in cerebral function in survivors soon after a massive widespread disaster, such as an earthquake.

We applied a recently discovered method known as "resting-state" functional MRI (fMRI) to assess brain function in a cohort of healthy survivors after the Wenchuan earthquake. "Resting-state" fMRI not only avoids performance confounds (13), but in the context of clinical studies to assess resting-state brain physiology it is easier to implement than positron emission tomography (PET)/single photon emission computed tomography (SPECT) because of its lower cost, greater availability, and noninvasiveness (14). Low-frequency (0.01–0.08 Hz) fluctuations of the blood-oxygenation-level-dependent (BOLD) signal in resting state fMRI data are thought to reflect spontaneous neural activity in nonhumans (15, 16) and humans (17, 18). In addition to regional amplitude of low-frequency (0.01–0.08 Hz) fluctuations (ALFF), resting-state fMRI provides data about functional connectivity. Although ALFF provides information about synchronous regional cerebral activity, analysis of cross-correlations between spatially remote regions allows the integrity of distributed brain networks to be examined.

In the present investigation, we applied resting-state fMRI to examine both regional cerebral function and functional brain connectivity in physically healthy trauma survivors shortly (13–25 days) after a massive psychological trauma. We hypothesized that survivors would show: (*i*) altered brain function shortly after the earthquake, especially in brain regions known to be important for emotion processing; and (*ii*) that alterations in brain function would be associated with survivors' reports of emotional distress.

Results

We acquired whole-brain resting-state fMRI in 44 healthy survivors and 32 healthy controls during resting state on a 3-T

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Table 1. Demographic information for physically healthy trauma survivors and healthy controls

Characteristics	Survivors ± SD (n = 44)	Controls ± SD (n = 32)	P
Female to male, no.	17:27	12:20	0.90
Mean age, y	37 ± 10.6	34.6 ± 11.0	0.34
Years of education	8.6 ± 4.1	9.3 ± 4.2	0.42
Days after earthquake	21.2 ± 3.3	—	—
SAS scores	48.4 ± 11.4	—	—
SDS scores	46.8 ± 10.8	—	—

MR system. Age, sex, height, weight, and years of education were matched between the two groups ($P > 0.05$; Table 1). Head translation movement of all participants was <0.5 mm, and rotation was <0.5°, and there was no significant difference in the magnitude of motion correction parameters between the two participant groups ($P > 0.05$).

To explore the alteration of regional activity in the survivor group, we examined the ALFF (0.01–0.08 Hz) of BOLD signals. ALFF maps in the survivor and control groups were compared on a voxelwise basis by using a two sample t tests in Statistical Parametric Mapping software (SPM2; Wellcome Department of Imaging Neuroscience; www.fil.ion.ucl.ac.uk). All of the analyses of whole-brain image data kept experimentwise type I error rates protected at $P < 0.05$, with a familywise error (FWE) correction procedure that considers the intercorrelation of the data structure. The whole-brain analysis indicated that, compared with controls, survivors showed significantly increased ALFF in the left prefrontal cortex and the left precentral gyrus, extending medially to the left presupplementary motor area (pre-SMA; $P < 0.05$; Fig. 1 and Table 2). In addition, region of interest (ROI) analyses revealed significantly increased ALFF in bilateral insula and caudate and the left putamen in the survivor group relative to the control group [$P < 0.05$, corrected at a cluster level after small volume correction (SVC); Table 2]. ALFF in the four core areas of default mode (19), including medial prefrontal cortex (MPF), posterior cingulate (PCC), and bilateral lateral parietal areas, did not differ between groups. There were no regions where ALFF was significantly decreased in survivors compared with controls.

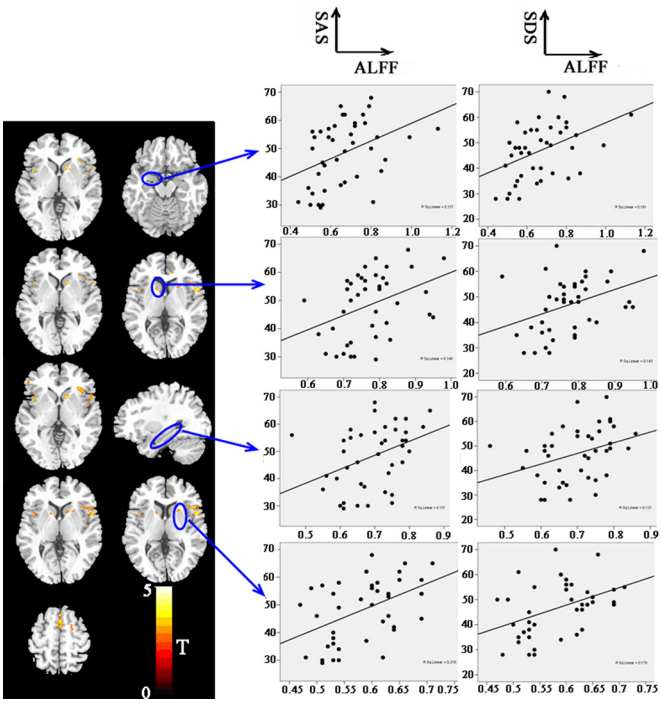

Fig. 1. Regions showing increased ALFF in survivors (red areas in blue circles) compared with controls ($P < 0.05$ corrected). Scatter plots show significant positive correlations between regional ALFF (the structures in the blue circles) and the SDS and SAS scores in the survivor group ($P < 0.05$).

To explore the association between regional ALFF and reported levels of emotional distress, Self-Rating Anxiety Scale (SAS) (20) and Self-Rating Depression Scale (SDS) (21) scores in survivors were correlated with ALFF values extracted from ROIs that were selected either because they expressed ALFF alterations in the present investigation and/or were previously associated with altered emotion processing or episodic memory in patients with posttraumatic disorders (5). ALFF values in left putamen, right amygdala, right caudate, and right hippocampus had a significant positive correlation with SAS and SDS scores ($P < 0.05$ after Bonferroni correction for multiple comparisons; Fig. 1 and Table 3). Thus, alterations in these areas may contribute to or reflect the ongoing emotional distress experienced by some trauma survivors. The correlations between SAS and SDS scores and ALFF values in other regions were not significant (Fig. 1 and Table 3).

To characterize the alteration of neural networks involving brain areas associated with emotion processing and memory (5) and the core areas of the default mode (19), functional connectivity analysis was performed by using a seed voxel correlation approach (see *Materials and Methods*). Connectivity maps were compared across survivors and controls by using a two-sample t test in SPM2. Analysis of the combined sample of survivors and controls showed a significant positive association among seed regions, mainly involving the bilateral amygdala, hippocampus, caudate, putamen, insula, parahippocampus, prefrontal cortex, cingulate cortex, and cerebellum ($P < 0.05$). However, comparison of the two groups revealed that survivors had decreased functional connectivity compared with controls within a distributed network that included the bilateral amygdala, hippocampus, caudate, putamen, insula, anterior cingulate cortex, and cerebellum ($P < 0.05$; Fig. 2). Functional connectivity involving default-mode areas was also decreased significantly in the survivor relative to the control group. No increased functional connectivity was found in the survivors relative to the controls in any seed region. These results suggest that the survivors expressed decreased temporal synchronization of resting neurophysiological activity among limbic and striatal areas, as well as within components supporting default-mode function.

We also examined (*i*) the relationship between regional hyperactivation and decreased connectivity and (*ii*) the relationship between connectivity and the level of emotional distress as measured by SAS and SDS scores. These analyses revealed no significant correlations between decreased connectivity and increased regional ALFF values, or between connectivity and level of emotional distress ($P > 0.05$).

Discussion

This study characterizes the alteration of distributed brain function at rest in a cohort of survivors of the Wenchuan earthquake in China within 25 days (range 13–25 days; mean ± SD: 21 ± 3) after the initial seismic event. Compared with controls, survivors showed hyperactivity of prefrontal-limbic and striatal systems, including left prefrontal cortex, pre-SMA, bilateral insula, bilateral caudate, and left putamen, as well as attenuated functional connectivity involving limbic-striatal areas and default-mode areas. The increased regional activity and reduced functional connectivity in frontolimbic and striatal regions occurred in areas known to be important for emotion processing (22). Atypical function in these areas has been implicated in previous studies of patients with chronic stress-

Table 2. Voxel-based analysis of global ALFF in trauma survivors and healthy controls

Location	Talairach			Voxel size, mm³	*P*
	x	*y*	*z*		
Left hemisphere: survivors > controls					
Precentral gyrus*	−56	12	5	2646	<0.001†
Prefrontal cortex	−3	12	63	1890	0.0015†
Caudate	−12	14	−3	243	0.026‡
Insula	−39	14	−11	270	0.039‡
Putamen	−15	14	−3	378	0.009‡
Right hemisphere: survivors > controls					
Caudate	12	12	8	243	0.045‡
Insula	42	9	2	351	0.013‡

*Including the pre-SMA.
†Type I error rate protected at $P < 0.05$ with FWE correction.
‡Type I error rate corrected by using SVC.

related disorders (5, 6, 8, 12, 23) and was related to the reported level of emotional distress in our sample. Thus, the present investigation expands understanding of stress-related changes of brain function in humans in two important ways. First, our study demonstrates that brain function in trauma survivors is altered within 25 days of a significant traumatic event. Second, our study provides evidence that alterations in brain function are not limited to focal changes in brain activity, but are also expressed at the level of altered functional integration within distributed limbic-striatal and default-mode networks. Furthermore, the decreased functional connectivity was not significantly related to regional ALFF alteration or level of emotional distress, suggesting that it may be related to different neurophysiological alterations and potentially may have a different functional impact.

Prefrontal-limbic and striatal systems and, more recently, the pre-SMA, have been recognized to be involved in affective processing (24) and decision making (25). Functional neuroimaging studies have provided direct evidence that prefrontal-limbic and striatal systems play a critical role in anxiety disorders, including the recollection of traumatic memories and the processing of fear and pain (6, 26), whereas striatum and pre-SMA are activated when making decisions under time pressure (25). Studies in both humans (27, 28) and animals (29) also indicate the roles of these systems in regulation of stress-induced activation of the hypothalamic–pituitary–adrenal axis. Overactivity within these systems has been reported with PTSD patients in several fMRI studies using a range of experimental tasks (5, 6, 12, 26), and also with PET/SPECT studies at resting state (5).

Table 3. Relationship of ALFF values with anxiety (SAS) and depression (SDS) scores of earthquake trauma survivors

Regions	SAS, *r* (*P*)	SDS, *r* (*P*)
Left		
Amygdala	0.28 (0.07)	0.24 (0.12)
Caudate	0.23 (0.15)	0.23 (0.14)
Hippocampus	0.24 (0.13)	0.19 (0.22)
Insula	0.25 (0.11)	0.15 (0.33)
Putamen	0.47 (0.002)*	0.42 (0.005)*
Prefrontal	0.03 (0.86)	−0.08 (0.62)
Precentral gyrus	0.11 (0.49)	0.16 (0.32)
Right		
Amygdala	0.40 (0.009)*	0.44 (0.004)*
Caudate	0.37 (0.013)*	0.38 (0.013)*
Hippocampus	0.39 (0.011)*	0.35 (0.024)*
Insula	0.10 (0.52)	0.08 (0.63)
Putamen	0.29 (0.059)	0.25 (0.12)

*$P < 0.05$ with Bonferroni correction.

Our findings in the survivor group showing increased activity in the resting state in the same set of areas support our hypothesis that regional cerebral function can be affected in trauma survivors shortly after they experience severe traumatic events. This is an important finding because it indicates that changes observed in patients with chronic stress-related disorders do not only reflect slowly progressive alterations or secondary effects of chronic distress and disability. Rather, dysfunction in clinically relevant brain circuitry seems to be already manifested shortly after massive traumatic events. Consistent with this idea, studies based on animal models have revealed that cortical GABA neurons can be modulated by allopregnanolone soon (3–4 weeks) after subjecting animals to experimental fearful stimuli (30). The increased GABA tone could increase regionally synchronized neuronal activity (31) and activity in γ-band power (32), which has been found to be correlated with ALFF (15).

The associations between reported affective distress and ALFF values in limbic and striatal areas indicate that alterations in these areas may contribute to or reflect the ongoing emotional distress experienced by some trauma survivors. In fact, animal studies provide evidence that prefrontal-limbic and striatal systems play an important role in the regulation of stress responses. Such studies reveal that 30 to 60 min after the onset

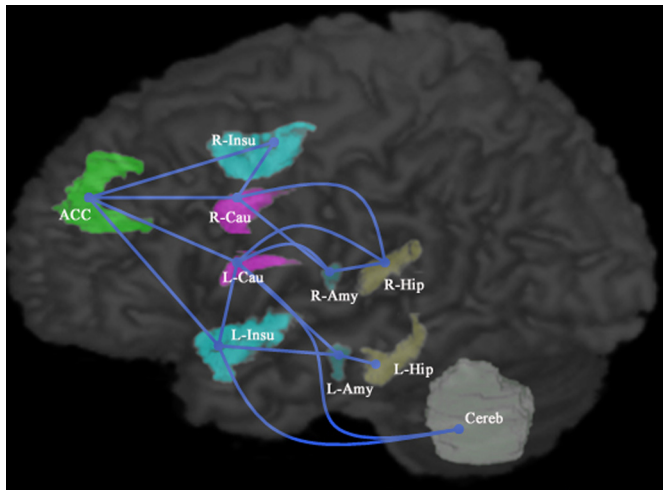

Fig. 2. Decreased functional connectivity (blue line) mainly involving limbic-striatal areas and cerebellum in the survivor group compared with the control group ($P < 0.05$, corrected with FWE correction). ACC, anterior cingulate cortex; R-Insu, right insula; L-Insu, left insula; R-Cau, right caudate; L-Cau, left caudate; R-Amy, right amygdala; L-Amy, left amygdala; R-Hip, right hippocampus; L-Hip, left hippocampus; Cereb, cerebellum.

of a stressor, molecular markers of neural activity in multiple structures are increased (e.g., cFos, nerve-growth factor-induced protein A), suggesting a stimulating effect of stress on neural activity (33, 34). In human beings, associations between neurobiological alternations in limbic areas and clinical symptoms have been reported previously in a number of psychological disorders, such as PTSD (8), social anxiety disorder (35), specific phobia (35), and depression (36).

In addition, our study identified decreased functional connectivity among distributed limbic-striatal and default-mode networks in the survivor group, reflecting functional disconnections across the brain (37). The alterations of limbic-striatal networks may be related to the bias in episodic memory and emotional processing that is typically found in survivors of traumatic events (26, 38). In fact, in a recent animal study using FG-7142 to model the effects of stress, Stevenson et al. (39) also observed decreased interactions involving limbic networks and suggested these to be relevant for alterations in the processing of sensory information associated with stressors.

The default-mode network is thought to be associated with a monitoring of internal thoughts and feelings (40) and is vulnerable in different conditions, including Alzheimer's disease (41), schizophrenia (42), and PTSD (43). A recent study (43) found that alterations in default-mode network connectivity were associated with PTSD symptom severity. The present investigation provides evidence that integration within the default-mode network may be attenuated at a very early stage in trauma survivors. These findings indicate a diffuse impact on widely distributed neural networks from trauma experiences and suggest that trauma victims have a reduced temporal synchronization across regions that comprise the default-mode system, which has been established as a component of resting-state brain function in humans (44, 45) and other species (46).

Two issues should also be considered when interpreting the present results. First, it cannot be determined with certainty that the trauma survivors did not focus on traumatic scenes during MRI. Although we instructed them not to focus on anything in particular during the resting state, and they did not report reflecting on trauma-related experiences when asked after the scan, it is not possible to exclude this possibility. Second, whether the altered neural activity we observed is compensatory in nature, changes dynamically over the months and years after trauma in some individuals, or reflects changes relevant to the later emergence of stress-related psychiatric disorders remains to be determined through longitudinal studies.

Taken together, the current results demonstrate that individuals experiencing severe emotional trauma showed hyperactivity in prefrontal-limbic and striatal brain systems and pre-SMA, and decreased functional connectivity in limbic-striatal and default-mode networks, shortly after the massively traumatic sequelae of the Wenchuan earthquake. In particular, the findings indicate that traumatic experiences affect not only regional function but also dynamic interactions within brain networks. The emergence of altered brain function in trauma survivors associated with emotional symptoms may identify those needing early treatment that might reduce long-term psychological disability in trauma survivors of national disasters, military conflict, and other causes of severe emotional distress. Longitudinal studies of trauma survivors may provide further insight into how alterations in brain function evolve over time after severe trauma, as well as their relation to the potential later emergence of stress-related disorders.

Materials and Methods

Participants. A total of 44 healthy trauma survivors (17 women, ages 37 ± 10.6 years, 8.6 ± 4.1 years of education) and 32 healthy controls (12 women, ages 34.6 ± 11.0 years, 9.3 ± 4.2 years of education) were recruited. This study was approved by the local ethics committee, and all participants gave written informed consent to their participation. All survivors were recruited within 25 days (range 13–25 days; mean ± SD: 21 ± 3) after the start of the Wenchuan earthquake from the most affected regions, where seismic intensity ranged from 9 to 11 on the Mercalli intensity scale. In these regions, thousands of people were buried and dead under collapsed buildings, and survivors were still afraid of intense aftershocks. The inclusion criteria for survivors included: (*i*) physically experiencing the earthquake, (*ii*) no personal medical injury, and (*iii*) personally witnessing death, serious injury, or the collapse of buildings. Participants underwent Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders-IV* (SCID) interview to rule out a current diagnosis of psychiatric disorder. All participants were told that they were being recruited for an ongoing, large-scale imaging project investigating human brain function, and they did not know that the investigation was related to the earthquake at any point during the study. Healthy controls were recruited from Chengdu, within 50 miles from the epicenter, by poster advertisement and were scanned shortly before the earthquake for another study (47). All controls were also screened by using SCID-nonpatient version to confirm the lifetime absence of psychiatric illness. Clinical assessments were performed by two experienced clinical psychiatrists before the MRI examination. Levels of anxiety and depression were evaluated by using the SAS (21) and the SDS (20). The following exclusion criteria applied to both groups: the existence of organic brain disorder, any psychiatric disorders, any recent medications thought to affect brain function, alcohol or drug abuse, pregnancy, or any physical illness, such as hepatitis, brain tumor, or epilepsy. Brain MR images (i.e., T1- and T2-weighted images) were inspected by an experienced neuroradiologist, and no gross abnormalities were observed for any participant.

Data Acquisition. MR images sensitized to changes in BOLD signal levels were obtained by using a 3-T MR imaging system (EXCITE; General Electric) with a gradient-echo echo-planar imaging sequence: repetition time/echo time (TR/TE), 2,000/30 ms; flip angle, 90°; slice thickness, 5 mm (no slice gap); matrix, 64×64; FOV, 240×240 mm^2; and voxel size, $3.75 \times 3.75 \times 5$ mm^3. Each brain volume comprised 30 axial slices, and each functional run contained 200 image volumes preceded by five dummy volumes, resulting in a total scan time of 410 s. All participants were instructed not to focus their thoughts on anything in particular and to keep their eyes closed during the resting-state MR acquisition. All participants reported that they complied with these instructions. However, because such reports are potentially biased by participants wanting to appear compliant with instructions, it is not possible to know for certain what participants were thinking or feeling during scans.

Data Preprocessing. Functional image preprocessing and statistical analyses were carried out by using SPM2. For each participant, echo-planar imaging (EPI) images were slice-time-corrected, realigned to the first image, and unwarped to correct for susceptibility-by-movement interaction. All of the realigned images were spatially normalized to the Montreal Neurological Institute template, and each voxel was resampled to $3 \times 3 \times 3$ mm^3 without spatial filtering.

ALFF Calculation. ALFF values were calculated by using REST (State Key Laboratory of Cognitive Neuroscience and Learning in Beijing Normal University; http://resting-fmri.sourceforge.net) with a procedure similar to that used in our earlier study (48). In brief, after bandpass filtering (0.01–0.08 Hz) (49) and linear-trend removal, the time series was transformed to the frequency domain by using fast Fourier transform (FFT; parameters: taper percent = 0, FFT length = shortest), and the power spectrum was obtained. Then, the power spectrum obtained by FFT was square root-transformed and averaged across 0.01–0.08 Hz at each voxel. The averaged square root of activity in this frequency band was taken as the ALFF. For standardization purposes, the ALFF of each voxel was divided by the global mean ALFF values, which were not statistically different between survivors and controls ($P > 0.05$) (44).

Functional Connectivity Analysis. Functional connectivity was examined by using a seed voxel correlation approach (47). Thirteen areas were selected as seed regions based on our ALFF findings and previous neuroimaging studies of patients with posttraumatic disorders that have revealed abnormal function in regions associated with emotional processing and episodic memory; that is, bilateral amygdala, hippocampus, caudate, putamen, insula, precentral gyrus, and medial anterior cingulate cortex (ACC) (4–12). Four other areas, including MPF, PCC, and bilateral lateral parietal areas, were also selected because they are the core areas of the default-mode network, which is preferentially activated during the resting state (19) and has been related to PTSD (43). Thus, a total of 17 areas were selected as seeds for the functional connectivity analysis, including seven bilateral areas, which included amyg-

dala, hippocampi, caudate, putamen, insula, precentral gyrus, and lateral parietal areas, and three medial areas (i.e., ACC, MPF, and PCC).

In SPM2, after bandpass filtering (0.01–0.08 Hz) (49) and linear-trend removal, a reference time series for each seed was extracted by averaging the fMRI time series of voxels within each ROI as defined in the WFU-pickatlas (Wake Forest University, Wake Forest, NC) (50, 51). Fifteen correlations were computed between each seed reference and the rest of the brain in a voxel-wise manner. Finally, the correlation coefficients in each voxel were transformed to z values by using the Fisher r-to-z transformation to improve normality before averaging data across participants. By using SPM2, we removed components with high correlation to CSF or white matter, or with low correlation to gray matter, which are thought to be associated with artifacts, such as cardiac-induced (52) or respiratory-induced variations (53), rather than representing neural activity.

Statistical Analysis. ALFF maps in the survivor and control groups were compared on a voxelwise basis by using a two-sample t test in SPM2. First, a statistical threshold of $P < 0.05$ (after FWE correction) was used for an exploratory whole-brain analysis. Second, SVC was performed to examine specific ROIs using a less conservative threshold ($P < 0.05$ at cluster level). In ROIs, selected based on prior neuroimaging studies of PTSDs (5), we applied SVC by using masks (bilateral amygdala, hippocampi, caudate, putamen, and insula, as well as medial cingulate cortex) from the WFU-pickatlas (50, 51). SVC was also used in the four core areas of the default mode (19), including MPF, PCC, and bilateral lateral parietal areas.

ROI analysis was also used to explore the association between emotional distress reflected by the SAS (20) and the SDS (21) with the average ALFF values in the areas of interest (Table 3). These were selected on the basis that they expressed ALFF alterations in the present investigation and/or were previously associated with altered emotional processing or episodic memory in patients with posttraumatic disorders (5). The average ALFF values of all voxels in these areas were extracted by using a volume of interest approach in SPM2 and were analyzed by using SPSS13.0. A multiple-correlation analysis was performed to estimate the relationship between the average ALFF values and SAS/SDS scores. Because of the lack of spatial dependency across the averaged time series from each ROI, a statistical threshold of $P < 0.05$ (two-tailed) was used, with Bonferroni correction.

To examine functional connectivity within the groups, one-sample t tests were performed on the individual z-value maps with a statistical threshold of $P < 0.05$ (after FWE correction). The z values in each voxel were compared across groups by using a two-sample t test in SPM2, again with statistical inferences being made at $P < 0.05$ (after FWE correction). Finally, ROI analysis was also performed to characterize the association between functional connectivity and averaged regional ALFF, and between connectivity indices and reported level of emotional distress (SAS and SDS scores), by using a statistical threshold of $P < 0.05$ with Bonferroni correction.

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