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Alterations in hippocampal subfield and amygdala subregion volumes in posttraumatic subjects with and without posttraumatic stress disorder

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Abstract

The hippocampus and amygdala are important structures in the posttraumatic stress disorder (PTSD); however, the exact relationship between these structures and stress or PTSD remains unclear. Moreover, they consist of several functionally distinct subfields/subregions that may serve different roles in the neuropathophysiology of PTSD. Here we present a subregional profile of the hippocampus and amygdala in 145 survivors of a major earthquake and 56 non-traumatized healthy controls (HCs). We found that the bilateral hippocampus and left amygdala were significantly smaller in survivors than in HCs, and there was no difference between survivors with ($n = 69$) and without PTSD (trauma-exposed controls [TCs], $n = 76$). Analyses revealed similar results in most subfields/subregions, except that the right hippocampal body (in a head-body-tail segmentation scheme), right presubiculum, and left amygdala medial nuclei (Me) were significantly larger in PTSD patients than in TCs but smaller than in HCs. Larger hippocampal body were associated with the time since trauma in PTSD patients. The volume of the right cortical nucleus (Co) was negatively correlated with the severity of symptoms in the PTSD group but positively correlated with the same measurement in the TC group. This correlation between symptom severity and Co volume was significantly different between the PTSD and TCs. Together, we demonstrated that generalized smaller volumes in the hippocampus and amygdala were more likely to be trauma-related than PTSD-specific, and their subfields/subregions were distinctively affected. Notably, larger left Me, right hippocampal body and presubiculum were PTSD-specific; these could be preexisting factors for PTSD or reflect rapid posttraumatic reshaping.

KEYWORDS
Hippocampus, posttic disorder, psychoradiology, stress, trauma, trauma amygdala

1 | INTRODUCTION

Posttraumatic stress disorder (PTSD) is a highly disabling disorder that develops in some people who have experienced or witnessed traumatizing events. Fearful memories formed from the traumatic events are the core symptoms, and dysregulation in this fearful memory process (e.g., failed fear extinction, increased fear memory incubation, generalized fear learning) could lead to PTSD (Careaga, Girardi, & Suchecki, 2016). An extensive number of studies have emphasized the importance of the hippocampus and amygdala in PTSD for their well-recognized functions in memory and fear learning that are critical in this disorder. Moreover, both the amygdala and hippocampal neurons are plastic to stress events and could inversely regulate adaptive responses in individuals to cope with the stress (McEwen, Nasca, & Gray, 2016). Dysregulation in a normal adaption to stress could also contribute to the development of PTSD (McEwen, 2004).

Numerous neuroimaging studies have identified anatomic alterations in the hippocampus and amygdala in PTSD. Volume decreases in these structures have commonly been reported in patients with PTSD, but the underlying causation between PTSD and volume loss in these structures remains controversial. Although Early studies have suggested that smaller volumes of the hippocampus are preexisting risk factors for developing PTSD or at least associated with the presence of the disorder (Bremner et al., 2003; Gilbertson et al., 2002; Gurvits et al., 1996; van Rooij et al., 2015), these studies are limited by their small sample sizes. Others have suggested that smaller hippocampal volumes could be a result of different factors: (a) there are absence findings on hippocampal volume alteration in the PTSD population when compared with trauma-exposed control (TC) subjects (Luo et al., 2016; Winter & Irle, 2004), including one of our previous report (Li et al., 2016); (b) the hippocampal volume was significantly smaller even in TCs when compared with nontraumatized subjects, as suggested by a recent meta-analysis of 89 structural MRI studies in PTSD (Bromis, Calem, Reinders, Williams, & Kempton, 2018); (c) The long illness duration of PTSD could also result in confounding factors in most neuroimaging studies since medication, insomnia, smoking, and alcohol dependence could all lead to volume reductions in the hippocampus (Kuhn et al., 2014; Neylan et al., 2010); and (d) the volume reduction of the hippocampus is commonly reported in many psychiatric disorders, including schizophrenia (Hu et al., 2020), unipolar and bipolar depression (Mathew et al., 2014; Zhang et al., 2019) and even obsessive–compulsive disorder (Hu et al., 2019).

Inconsistent reports have also been seen in amygdala studies: a smaller amygdala was observed in PTSD patients including the ENIGMA study (Logue et al., 2018) and a recent meta-analysis (Bromis et al., 2018), but negative findings were also reported in another meta-analysis (Woon & Hedges, 2009). These discrepancies could be explained by the aforementioned causation question and confounds. Hence, studying recent-onset PTSD patients and traumatized individuals who underwent similar stressors at the same time could help clarify the causality of anatomic features of the hippocampus/amygdala in PTSD.

Moreover, the hippocampus and amygdala have functionally distinct subfields/subregions that may play different roles in the development of PTSD. For example, the CA3 subfield of the hippocampus is important in forming new memories (associative learning) (Rebola, Carta, & Mulle, 2017). Neurons in dentate gyrus (DG) are sensitive to the toxic effect of hyperactivity in the hypothalamus-pituitary–adrenal (HPA) axis and retrieve memory through cues (pattern separation), whose impairment could lead to the inability to distinguish cues that is, fear generalization in PTSD (Knierim & Neunuebel, 2016). The basolateral subregion of the amygdala (BLA), which consists of the basal, lateral, and accessory basal nuclei, is crucial for fear learning, and the central nucleus of the amygdala (CeA) is responsible for correcting outdated learned associations (LeDoux, 2003; LeDoux, 2007). Hence, either an overactive BLA (which could lead to strong fear memory) or a dysfunctional CeA (which could lead to inability to remove an outdated fear memory) could result in PTSD symptoms. Overall, it is necessary to build an anatomical profile of the hippocampus and amygdala in PTSD on the subfield/subregional level that is useful for understanding pathology of this disorder, and contribute to "psychoradiology" (https://radiopeadia.org/articles/psychoradiology) the growing intersection between the field of psychiatry and radiology (Gong Q, 2020, Huang et al., 2019).

There have been few previous hippocampal subfield studies of PTSD, and a smaller CA3-DG volume has been commonly reported when comparing military veterans with and without PTSD (Chen et al., 2018; Hayes et al., 2017; Wang, Neylan et al. 2010). One study reported smaller CA1 in PTSD veterans than in TCs. Only one study recruited PTSD, TC, and healthy control (HC) subjects at the same time and compared hippocampal subfield volumes among them (Luo et al., 2017). In that study, no significant differences between patients with PTSD and TCs were found (Luo et al., 2017). As for subregional-level volumetric analysis of the amygdala, one recent study reported smaller lateral and paralaminar nuclei but larger central, medial and cortical nuclei in military veterans with PTSD than in veterans without PTSD (Morey et al., 2020). Two other studies reported morphometric alterations corresponding to the basolateral subregion and the central amygdala (Akiki et al., 2017; Veer et al., 2015). Again, none of them recruited never-traumatized HCs as normal reference. In Table S1, we summarize the characteristics and main finding of the existing subfield/subregional level studies of hippocampus/amygdala in PTSD.

In the current study, we aimed to build a comprehensive anatomical profile of volumetric alterations in the hippocampus and amygdala after a traumatic event and to find PTSD-specific and trauma-related alterations. For that purpose, we recruited a large sample of survivors of a magnitude 8.0 (Richter scale) earthquake that occurred on May 12, 2008 in Wenchuan, a city in Sichuan Province, China. The earthquake resulted in 69,146 confirmed deaths, 374,131 serious injuries, and 17,516 missing individuals. HC subjects who had not experienced the earthquake were also included and served as a normal reference group. We hypothesize that volumetric alterations in both hippocampus and amygdala would be a result of mixed effects of PTSD symptoms and trauma exposure in the PTSD patients, whereas the effect

of trauma would be more prominent in the hippocampus, and disease itself would contribute to alteration in both BLA and CeA.

2 | SUBJECTS AND METHODS

2.1 | Participants

The study was approved by the Research Ethics Committee of the West China Hospital, Sichuan University, and informed written consent was obtained prior to study participation. Between January 2009 and August 2009, the participants were screened and selected from 4,200 earthquake survivors for direct exposure to major destruction, medical injury, and death from the earthquake. The inclusion criteria for survivors included: (a) physically experiencing the earthquake, (b) no personal medical injury, and (c) personally witnessing death, serious injury, or the collapse of buildings. The participants were initially evaluated by trained earthquake support psychologists who used the clinician-administered PTSD Scale (CAPS) in diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV), and participants were further evaluated by a psychiatrist with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders IV Axis I disorders (SCID) to determine the presence or absence of PTSD and other psychiatric diagnoses. Finally, a total of 145 survivors were enrolled and assigned to the PTSD patient group ($n = 69$) and trauma-exposed (TC) control group ($n = 76$, Table 1). All participants were right-handed and native Han Chinese.

The exclusion criteria were as follows: (a) a self-reported history of psychiatric disorder before the earthquake; (b) pregnancy; (c) current comorbid psychiatric disorders; (d) head injury or any other significant medical or neurologic conditions; (e) drug dependence; and (f) systemic medical illness thought to interfere with brain function.

To evaluate trauma-related brain changes, we obtained brain imaging data from 56 age- and sex-matched HC subjects from our data set collected before the earthquake. These HCs were recruited from the local area using poster advertisements and were screened using the SCID (nonpatient version) to confirm the absence of any history of affective, psychotic, or anxiety disorder. The HCs reported no known history of psychiatric illness among their first-degree relatives.

2.2 | Structural MRI data acquisition

MRI data were acquired using a 3.0 T MRI system and an eight-channel phase array head coil (EXCITE, General Electric, Milwaukee, WI). A high-resolution T1-weighted 3D spoiled gradient recall (SPGR) sequence was used (repetition time (TR) = 8.5 ms, echo time (TE) = 3.4 ms, flip angle = 12°, slice thickness = 1.0 mm). The field of view was 240×240 mm^2 with an acquisition matrix = 256×256, which yields an actual voxel size = $0.93 \times 0.93 \times 1$ mm^3. Foam padding and earplugs were used to reduce head motion and scanner noise.

2.3 | Volumetric analysis

Anatomic images were automatically segmented using FreeSurfer software (V. 6.0) (http://surfer.nmr.mgh.harvard.edu/). The recon-all FreeSurfer analysis pipeline was applied. Briefly, T1-weighted images were transformed into Talairach space, and normalization and skull-strip procedures were performed (Fischl et al., 2002; Reuter, Rosas, & Fischl, 2010; Segonne et al., 2004; Sled, Zijdenbos, & Evans, 1998). The intracranial volume (ICV) of each subject was collected.

Amygdala subregion and hippocampal subfield segmentation were performed using a special purpose module in FreeSurfer software (V. 6.0, development version), which employs a tetrahedral mesh-based probabilistic atlas built from manually delineated amygdala/hippocampus in in vivo and ex vivo data (Iglesias et al., 2015; Saygin et al., 2017). Using this algorithm, the overall volumes of the bilateral hippocampus and amygdala and their subfields/subregions were obtained. In the hippocampus, two sets of segmentations with different levels of hierarchy were generated: (a) head, body, and tail; (b) CA1, CA3 (which contains CA2), CA4, the molecular, and granule cell layers of the dentate gyrus (GC-ML-DG), the molecular layer, subiculum, presubiculum, parasubiculum, fimbria, fissure, and hippocampal-amygdala transition area (HATA). Nine subregions in the amygdala were also obtained, including seven nuclei [lateral nucleus (La), basal nucleus (Ba), accessory basal nucleus (AB), CeA, medial nucleus (Me), cortical nucleus (Co) and paralaminal nucleus] and two transition areas [anterior amygdaloid area (AAA) and corticoamygdaloid transition area (CAT)]. An example of the segmentation for a healthy subject is shown in Figure 1. All segmentation was visually verified following a quality control protocol that is similar to

TABLE 1 Demographic data, clinical ratings, and intracranial volume of PTSD, TC, and healthy controls (HC)

	PTSD ($n = 69$) mean (SD)	TC ($n = 76$) mean (SD)	HC ($n = 57$) mean (SD)	p-value
Age	42.52 (10.0)	43.87 (9.4)	39.74 (11.7)	.072
Gender (male/female)	22/47	20/56	23/33	.200
Education (years)	6.86 (2.8)	7.08 (3.3)	n.a.	.666
Time since trauma (months)	10.38 (2.0)	10.80 (2.3)	n.a.	.248
CAPS	61.58 (10.4)	20.63 (11.1)	n.a.	<.001
Intracranial volume	1,364,594 (126113)	1,355,133 (138025)	1,447,580 (151533)	<.001

Abbreviations: CAPS, clinician-administered PTSD scale; HC, healthy controls; PTSD, posttraumatic stress disorder; TC, trauma-exposed control.
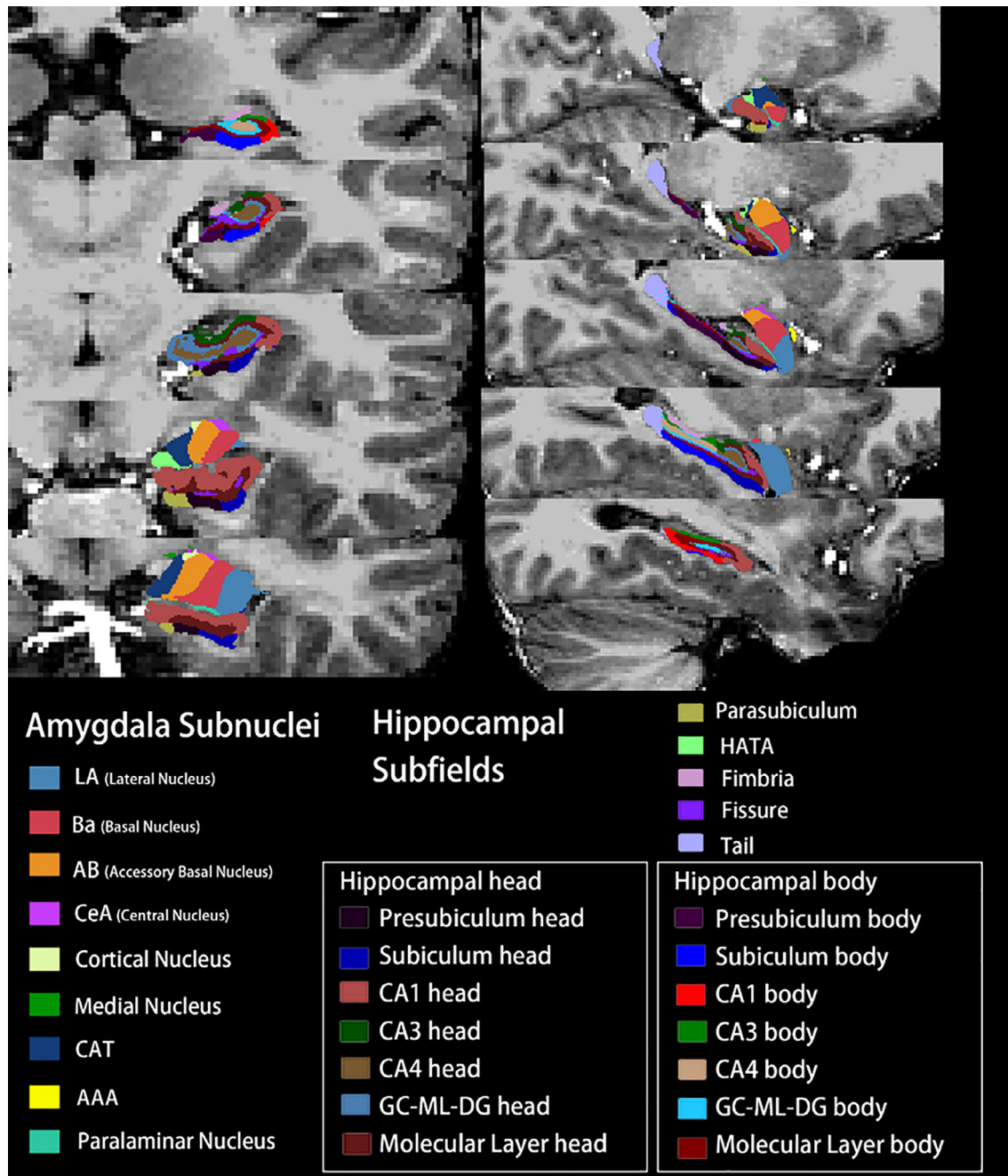
Amygdala Subnuclei
- LA (Lateral Nucleus)
- Ba (Basal Nucleus)
- AB (Accessory Basal Nucleus)
- CeA (Central Nucleus)
- Cortical Nucleus
- Medial Nucleus
- CAT
- AAA
- Paralaminar Nucleus

Hippocampal Subfields
- Parasubiculum
- HATA
- Fimbria
- Fissure
- Tail

Hippocampal head
- Presubiculum head
- Subiculum head
- CA1 head
- CA3 head
- CA4 head
- GC-ML-DG head
- Molecular Layer head

Hippocampal body
- Presubiculum body
- Subiculum body
- CA1 body
- CA3 body
- CA4 body
- GC-ML-DG body
- Molecular Layer body

FIGURE 1 An example of segmentation in a healthy subject

the ENIGMA protocol (http://enigma.ini.usc.edu/). In brief, the segmentation of each subject was independently visually checked by two coauthors (LZ and XH), and subject with segmentation results judged to be incorrect (e.g., majority of the hippocampus/amygdala was cut off, or the mask shifted from the structure) were excluded. None of the subjects showed segmentation failure.

2.4 | Statistical analysis

First, an analysis of variance (ANOVA) test was used to test whether ICV differed across the PTSD, TC, and HC groups. Then, a multivariate analysis of covariance (MANCOVA) test was used to test for overall amygdala/hippocampal volume differences between groups with age, sex, and ICV as covariates, and Fisher's least significant difference (LSD) method was used for post hoc analysis if the overall p value reached statistical significance.

Another MANCOVA test was employed to determine whether subfield or subregional volumes of the hippocampus and amygdala differed across the three groups with subfields/subregions entered as dependent variables, and the false discovery rate (FDR) method was used to correct multiple hypothesis testing issues. For subfields/subregions that showed significance after FDR correction, post hoc tests (using LSD) were employed to determine where the difference

TABLE 2 Volume differences in hippocampal and amygdala volumes across posttraumatic stress disorder patients (PTSD), trauma-exposed controls (TC), and healthy controls (HC)

	Volume difference					Post hoc		
	PTSD	TC	F	Effect size	Adjusted p-value	PTSD vs. HC	TC vs. HC	PTSD vs. TC
Hippocampus								
Left								
Overall volume	↓	↓↓	3.453	0.034	.034	0.056	0.010	0.478
Head	↓	↓↓	0.843	0.009	.432			
Body	↓	↓↓	4.003	0.039	.030	0.031	0.007	0.543
Tail	↓	↓↓	6.363	0.061	.006	0.058	<0.001	0.072
CA1	↑	↓	0.088	0.001	.916			
CA3	↓↓	↓	5.271	0.051	.022	0.004	0.005	0.916
CA4	↓	↓↓	4.983	0.049	.022	0.014	0.003	0.538
GC-ML-DG	↓	↓↓	4.007	0.039	.037	0.020	0.008	0.746
Molecular layer	↓	↓↓	1.355	0.014	.347			
Subiculum	↓	↓↓	1.037	0.011	.428			
Presubiculum	↓↓	↓	9.407	0.088	<.001	<0.001	<0.001	0.740
Parasubiculum	↓↓	↓	0.634	0.006	.580			
Fimbria	↑	↑↑	4.759	0.047	.022	0.010	0.004	0.794
Fissure	↓↓	↓	2.159	0.022	.177			
HATA	↓	↓↓	5.390	0.052	.022	0.007	0.002	0.695
Right								
Overall volume	↓	↓↓	9.180	0.086	<.001	0.001	<0.001	0.319
Head	↓	↓↓	2.185	0.022	.115			
Body	↓	↓↓	15.441	0.137	<.001	<0.001	<0.001	0.037
Tail	↓	↓↓	11.950	0.109	<.001	<0.001	<0.001	0.298
CA1	↓↓	↓	0.559	0.006	.630			
CA3	↓	↓↓	10.087	0.094	<.001	0.001	<0.001	0.395
CA4	↓	↓↓	13.732	0.123	<.001	<0.001	<0.001	0.323
GC-ML-DG	↓	↓↓	11.602	0.106	<.001	<0.001	<0.001	0.365
Molecular layer	↓	↓↓	4.310	0.042	.025	0.045	0.004	0.331
Subiculum	↓	↓↓	4.393	0.043	.025	0.049	0.004	0.297
Presubiculum	↓	↓↓	9.026	0.085	<.001	0.016	<0.001	0.049
Parasubiculum	↓	↓↓	1.168	0.012	.383			
Fimbria	↑	↑↑	0.142	0.001	.868			
Fissure	↓	↓↓	4.230	0.042	.025	0.022	0.006	0.601
HATA	↓↓	↓	3.115	0.031	.064			
Amygdala								
Left								
Overall volume	↓	↓↓	2.696	0.027	.045	0.223	0.022	0.234
La	↑↑	↑	2.044	0.021	.198			
Ba	↓	↓↓	1.270	0.013	.364			
AB	↓	↓↓	14.059	0.126	<.001	<0.001	<0.001	0.218
AAA	↑	↓	0.769	0.008	.465			
CeA	↓	↓↓	12.418	0.113	<.001	<0.001	<0.001	0.794
Me	↓	↓↓	23.018	0.191	<.001	<0.001	<0.001	0.015
Co	↓	↓↓	21.402	0.180	<.001	<0.001	<0.001	0.088
CAT	↓	↓↓	5.608	0.054	.007	0.042	0.001	0.159
Paralaminar	↓	↓↓	0.902	0.009	.458			

TABLE 2 (Continued)

	Volume difference					Post hoc		
	PTSD	TC	F	Effect size	Adjusted *p*-value	PTSD vs. HC	TC vs. HC	PTSD vs. TC
Right								
Overall volume	↓	↓↓	5.267	0.051	**.006**	**0.007**	**0.003**	0.767
La	↓↓	↓	1.177	0.012	.465			
Ba	↓	↓↓	4.844	0.047	**.016**	**0.011**	**0.004**	0.689
AB	↓	↓↓	15.227	0.135	**<.001**	**<0.001**	**<0.001**	0.500
AAA	↓↓	↓	0.689	0.007	.503			
CeA	↓↓	↓	8.197	0.078	**<.001**	**<0.001**	**0.001**	0.813
Me	↓	↓↓	8.897	0.084	**<.001**	**0.002**	**<0.001**	0.248
Co	↓	↓↓	21.427	0.180	**<.001**	**<0.001**	**<0.001**	0.319
CAT	↓	↓↓	0.705	0.007	.503			
Paralaminar	↓	↓↓	0.736	0.007	.503			

Notes: Multivariate analyses of covariance with age, gender, and total brain volume as covariates. Volume differences were compared with HCs, ↓ indicates smaller than HCs and ↑ indicates larger than HC. *p*-values across all groups were adjusted for false discovery rate (FDR), bold indicates significance. Effect size was determined by partial eta squared (η^2).

Abbreviations: AB, accessory basal nucleus; Ba, basal nucleus; CAT, corticoamygdaloid transition area.; CeA, central nucleus; GC-ML-DG, the molecular and granule cell layers of the dentate gyrus; HATA, hippocampal-amygdala transaction area; La, lateral nucleus; Me, medial nucleus, Co, cortical nucleus, AAA, anterior amygdaloid area; N.S., nonsignificant.

between groups was. Partial eta squared (η^2) was calculated to estimate effect sizes.

To find associations between volume measurements and features of trauma (the time since trauma and CAPS scores), we combined PTSD patients and TC subjects and performed partial correlation analyses. The correlation analyses were then repeated in these groups separately. R values were transformed into z scores and subsequently compared with to test if the correlations differed between the PTSD and TC groups. *p*-values were also corrected with FDR.

3 | RESULTS

The ICV values significantly differed across groups (*p* < .001), and post hoc analyses revealed that both the PTSD (*p* = .001) and TC (*p* < .001) subjects had significantly smaller ICV than the HC subjects, while there was no significant difference between the PTSD and TC groups (*p* = .669; Table 1). The bilateral overall hippocampus (left, η^2 = .034, *p* = .034; right: η^2 = 0.086, *p* < .001) and right amygdala (η^2 = 0.051; *p* = .006) were significantly smaller in both the PTSD and TC subjects than in the HC subjects, while differences between the PTSD and TC groups were not significant (Table 2).
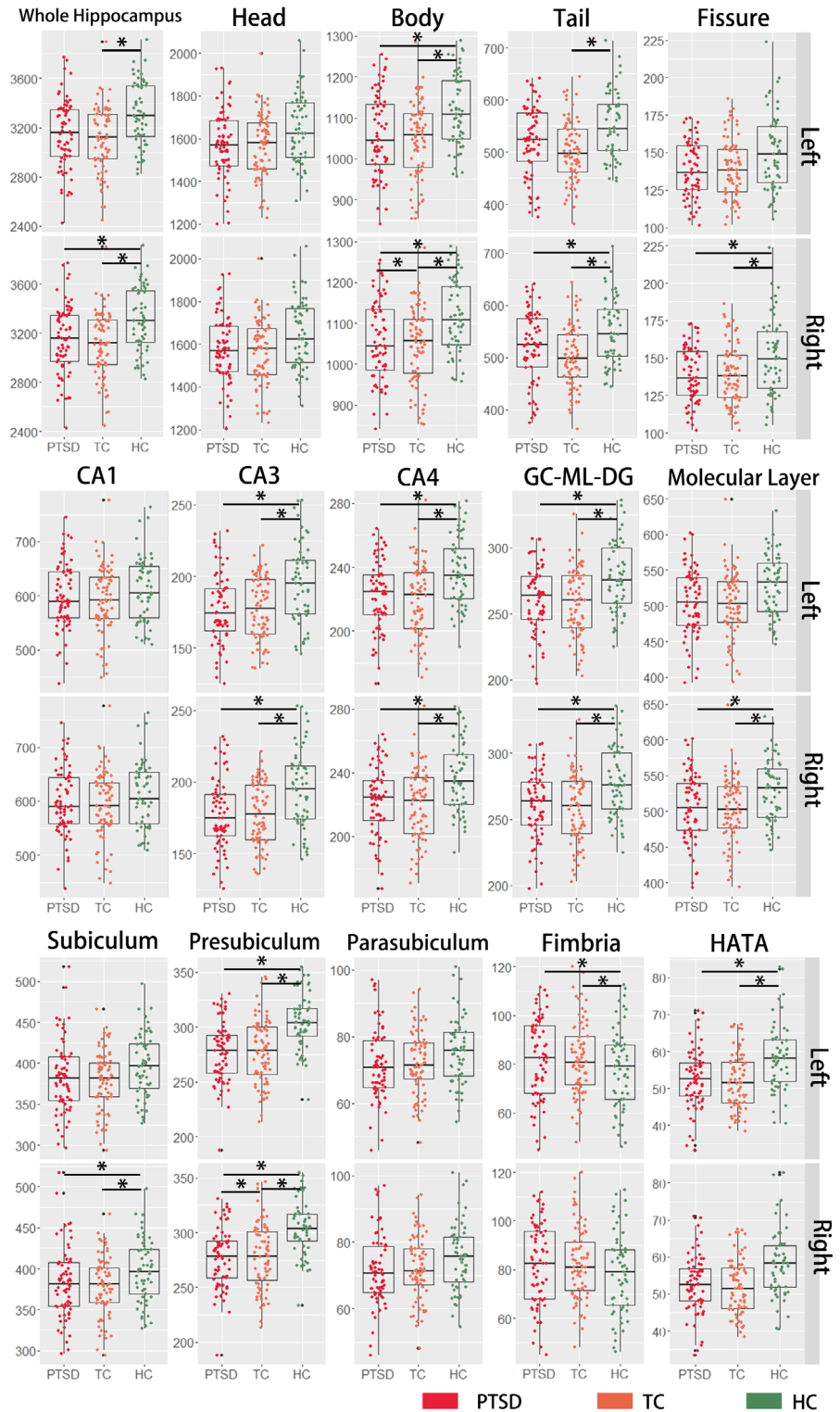
Subsequent subfield/subregional analyses revealed that most subfields in the hippocampus and subregions in the amygdala were significantly smaller in both the PTSD and TC groups than in the HC group, as shown in Table 2 and Figures 2 and 3. The right hippocampal body (*p* = .037), right presubiculum (*p* = .049) and left Me (*p* = .027) were significantly larger in the PTSD patients than in the TCs. Mean volumes of the overall hippocampus and amygdala and their subfields/subregions are shown in Table S2.

No correlations were significant in the earthquake survivors (combining PTSD patients and TCs). We repeated the correlation analysis in the PTSD and TC subjects separately and found that the volume of the left hippocampal body was correlated with the time since trauma (*r* = .446, *p* < .001, FDR corrected) in the PTSD patients (Figure 4). The CAPS scores were negatively correlated with volumes of the right AB (*r* = −.404, *p* < .001, FDR corrected) and right molecular layer (*r* = −.364, *p* = .04, FDR corrected). Moreover, the volume of the right Co was negatively correlated with the CAPS scores in the PTSD group (*r* = −.407, *p* < .001, FDR corrected) but positively correlated in the TC group (*r* = .367, *p* = .04, FDR corrected). This correlation was significantly different between the PTSD and TC subjects (Z = -4.64, *p* < .001).

4 | DISCUSSION

In the current study, we recruited a relatively large sample of survivors of a major earthquake to examine anatomic alterations in the hippocampus and amygdala after severe trauma with and without PTSD. We found that (a) the overall volumes of both the hippocampus and amygdala and most of their subfields/subregions showed no differences between survivors with or without PTSD, suggesting that volume decreases of the hippocampus/amygdala were mainly trauma-related but not PTSD-specific. (b) PTSD-specific structural alterations were found in the left Me and the right hippocampal body and presubiculum, where the volume was larger in survivors with PTSD than in TCs. (c) There were significant differences in associations between volumes of the right Co nuclei of the amygdala and the CAPS scores between the PTSD and TCs, which suggested that volume reductions in this nucleus may have been caused by different
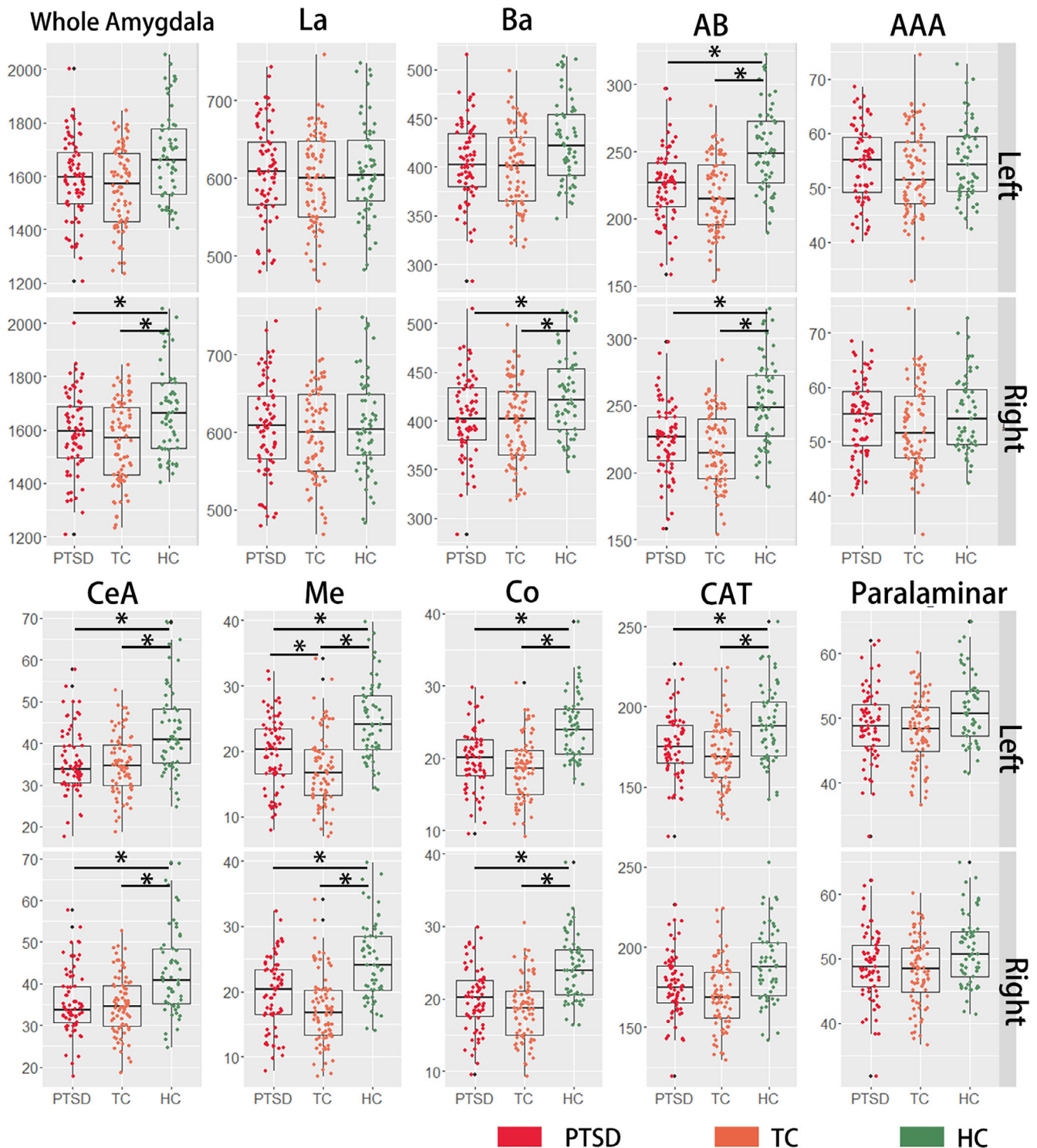
FIGURE 2 Box-plots of volumes of the hippocampal subfields in earthquake survivors with/without posttraumatic stress disorder and healthy control subjects. *indicates FDR-level significance

4.1 | Stress-related brain changes

Our results supported the notion that a smaller hippocampus is more likely to be caused by traumatic events than by PTSD itself,

underlying mechanisms that led to different psychopathology in the two groups.

and a smaller hippocampus does not appear to be a preexisting risk factor for developing PTSD due to the following reasons: (a) although the volume of the hippocampus is smaller in PTSD patients when compared with HCs, this pattern was also observed in TCs, suggesting trauma contributes to volume reduction; (b) even in the hippocampal body and presubiculum, the only subfields where PTSD-specific abnormalities were observed, the volumes of these subfields were larger in the PTSD group when compared with TCs

FIGURE 3 Box-plots of volumes of the amygdala subregions in earthquake survivors with/without posttraumatic stress disorder and healthy control subjects. *indicates FDR-level significant

(see discussion below: PTSD-specific Alterations). This result is in line with some previous studies that compared recent-onset PTSD patients with TCs (Luo et al., 2017; Winter & Irle, 2004), but not all of them (Gilbertson et al., 2002; Zhang et al., 2011). The sample size and heterogeneity of stressors could account for these discrepancies.

Regarding the amygdala, we also found that a smaller amygdala volume was mainly trauma-related, which is in line with a previous meta-analysis (O'Doherty, Chitty, Saddiqui, Bennett, & Lagopoulos, 2015). However, none of the anatomical studies of recent-onset PTSD have reported significant alterations in the overall amygdala volume (Liu, Li, Luo, Lu, & Yin, 2012; Qi et al., 2013; Wang,
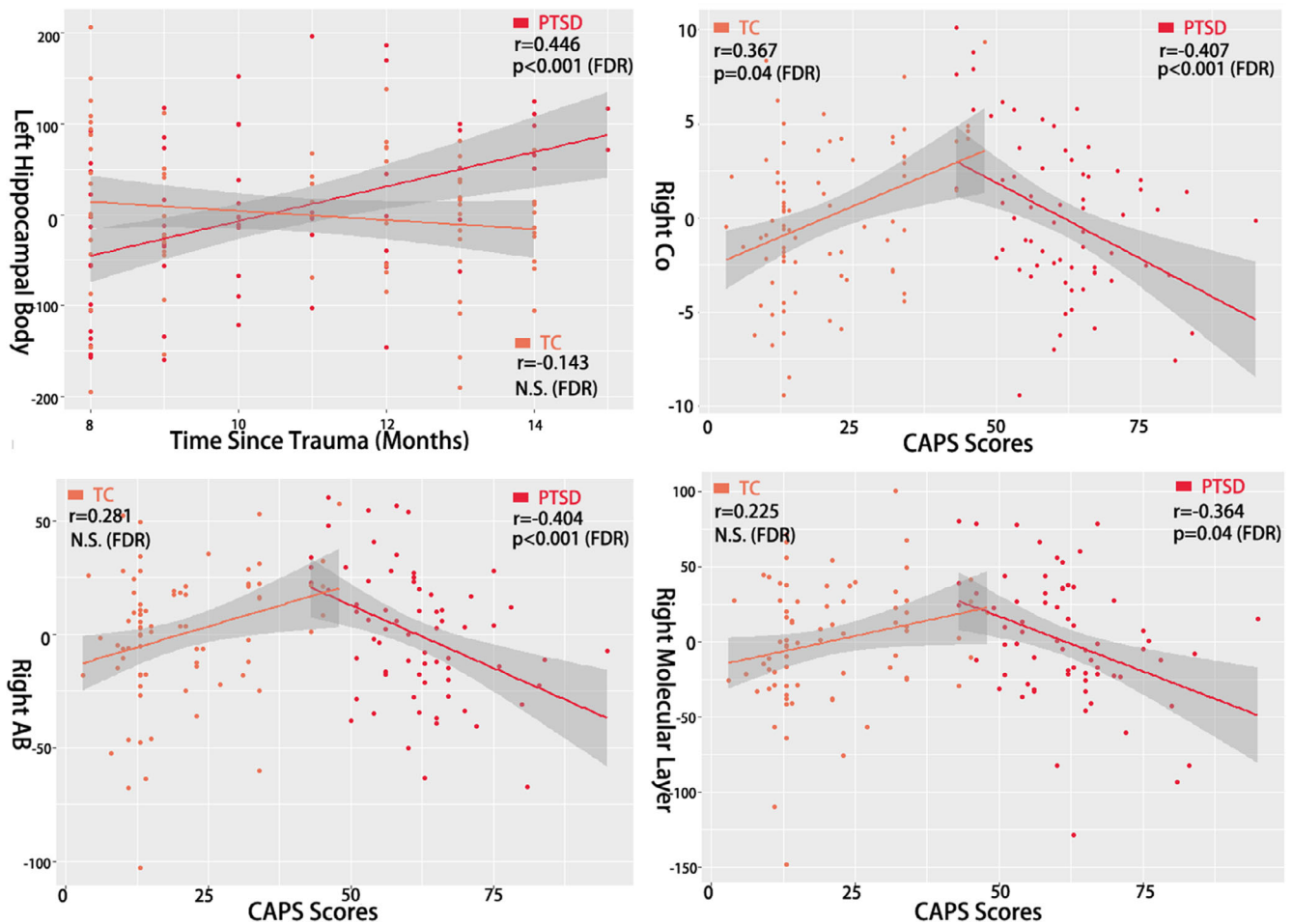
FIGURE 4 Correlations between volume measurements and CAPS scores or time since trauma. Volumes for the shown subfields/subregions were residuals adjusted for age, gender, and ICV

Zhang et al., 2010; Zhang et al., 2011). The increased statistical power (given the large sample size) and homogeneous but extreme stressors together may account for the unique observation of trauma-related volume loss in the amygdala.

Furthermore, we found that ICV was also smaller in both the PTSD and TCs than in the HCs, suggesting that extreme traumatic events such as a major earthquake could lead to brain volume loss that is not limited to stress-sensitive structures. However, this result (trauma-related smaller ICV) was contradictory to a recently published meta-analysis which reported that ICV was smaller in PTSD patients than in TCs or HCs but did not differ between TCs and HCs (Bromis et al., 2018). Because that meta-analysis included mostly chronic patients (mean time since trauma: 9 years), we speculate that this brain volume loss could have been reversed over time in TCs.

Our results suggested that subfields of the hippocampus and subregions of the amygdala are not evenly affected by trauma exposure. In the hippocampus, volume losses in the hippocampal body, tail, CA3, CA4, and GC-ML-DG reached medium effect sizes, which suggested that these subfields were more vulnerable to toxic effects of stressful events, while the hippocampal head, CA1, and parasubiculum were less affected. This specific sensitivity pattern to stress we found

across subfields of the hippocampus was similar to Luo's report, in which they reported psychological trauma caused volume loss in CA2-3, CA4-DG, and subiculum, while the CA1 was spared (Luo et al., 2017). The uneven volume loss in different subfields reflects different levels of vulnerability of these subfields to trauma exposure. For example, chronic stress could induce shrinkage of apical dendrites of pyramidal cells in the CA3 region and reduce neurogenesis in the DG, while ventral CA1 was not significantly affected in animal studies (McEwen et al., 2016; McEwen & Gianaros, 2011).

We report that trauma-related volume loss was observed in the bilateral corticomedial group (consisting of Co, Me, and CeA) with a medium effect size. In the BLA group, both AB (bilateral) and Ba (right) were also affected, but not La. The relationship between stress-related neural architecture remodeling in the amygdala and volume changes observed in MRI is complicated. In rodents, exposure to traumatic stressors led to anxiety and increased spine density on BLA neurons (Mitra, Jadhav, McEwen, Vyas, & Chattarji, 2005). In patients, receiving chronic corticosteroid therapy leads to a smaller overall amygdala volume (Brown, Woolston, & Frol, 2008). The observed volume loss in the amygdala in the current study could be explained by water loss or a reduced number/size of astrocytes caused by the

elevated corticosteroid levels after trauma (Brown et al., 2008). Further studies are needed to fully clarify this relationship.

4.2 | PTSD-specific alterations

In this study, we found that the left Me, right hippocampal body and presubiculum were the only regions with significantly larger volumes in earthquake survivors who developed PTSD than in TCs. The finding of larger Me in PTSD group as compared with TCs is in line with a recent published amygdala subregion study (Morey et al., 2020). Interestingly, the volumes of these regions in both the PTSD patients and TCs were significantly smaller than those in HCs, suggesting that a traumatic event may cause volume loss in these regions in both groups. We propose two possible explanations for this observation. First, a larger Me of the amygdala, hippocampal body or presubiculum could be the preexisting risk factor for PTSD, which means volumes of these regions were larger before the earthquake in these survivors who later developed PTSD. For example, it has been demonstrated in rodents that the Me plays a critical role in fear memory incubation—the increase in fear memory over time following a traumatic event—though the neuropeptide tuberoinfundibular peptide of 39 residues (TIP39) signaling process (Tsuda, Yeung, Kuo, & Usdin, 2015). In PTSD patients, TIP39 signaling in the Me could be more active than that in TCs, as represented by larger size; this might cause overactive fear memory incubation that finally led to PTSD symptoms.

Second, the trauma-related neuroendocrine process could be different in these regions between PTSD patients and TCs. Stress-triggered responses are not always destructive to individuals; for example, Rao and colleagues demonstrated in rats that the presence of elevated levels of corticosterone at the time of acute stress actually protected them against the delayed effects of stress on BLA synaptic connectivity and anxiety-like behavior (Rao, Anilkumar, McEwen, & Chattarji, 2012). In patients, lower glucocorticoid levels at the time of trauma related to a higher probability of PTSD symptoms(Schelling, Roozendaal, & De Quervain, 2004; Yehuda, McFarlane, & Shalev, 1998), while the administration of glucocorticoids immediately after trauma could reduce subsequent PTSD symptoms (Zohar et al., 2011). Considering that the hippocampus is a structure regulating the stress response and is heavily affected by the stress itself at the same time (McEwen, 2004; McEwen et al., 2016), we propose that a smaller hippocampal body or presubiculum volume in TCs represents a normal response toward stress in these subfields and could trigger adaptive responses that help individuals deal with traumatic events; however, this normal stress-related response was reduced in the patients with PTSD, which led to insufficient adaptive behavior.

Another observation that distinguished the PTSD patients from the TCs was the relationship between volume measurements and CAPS scores. First, smaller volumes of the AB in the amygdala were related to higher CAPS scores only in the PTSD patients but not the TCs. The AB, also known as the basomedial amygdala, has been reported to mediate top-down control of anxiety and fear with the medial prefrontal cortex (Adhikari et al., 2015). It is not surprising to find this relationship.

Second, we found reduced volumes in the Co of the amygdala associated with higher CAPS scores in the PTSD patients but lower scores in the TCs. These observations are in line with the inverted U-shaped dose-time response (toward stress) concept, which suggests that synaptic function could be enhanced with an increase in the amount/frequency of stress, but once the amount/frequency exceeds a limit, synaptic functions are suppressed or even destroyed by the stress (McEwen et al., 2016). In the circumstances of the current study, the volumes of Co could have increased to compensate for the trauma-related change in the TCs, but in the PTSD patients, trauma-related damage may have exceeded ability to adapt.

There are limitations that need to be considered in interpreting the findings of the present study. First, we used a sample of survivors from the same traumatic event, that is, a major earthquake, and used strict inclusion criterion that removed patients with comorbid depression/anxiety. While this approach had advantages for controlling confounders and identifying PTSD-specific alterations, it remains uncertain whether our findings extend to the general PTSD population, especially those with repeated stress events. Second, although we found associations between symptom severity and anatomic features of the amygdala and hippocampus, the effects were not large. We used FDR to control the false discovery rate in the correlation analyses, but the results still should be interpreted with caution. Third, although both patients with PTSD and TCs experienced homogeneous stressors, level of trauma exposure during childhood and adulthood (aside from the earthquake) in each of the groups were not measured. With the above limitations, as the confounds were controlled for by recruiting recent-onset (mean time since trauma: 10–11 months) and nonmedicated patients, our study still provided important information for the understanding of the contribution of the hippocampus and amygdala in the stressful population who developed PTSD and those who did not.

In conclusion, our findings support the view that smaller volumes in most parts of the hippocampus and amygdala was more likely to be trauma-related then a preexisting risk factor in patients with PTSD. We identified that the right hippocampal body, presubiculum and left medial nucleus of the amygdala are critical for developing PTSD, possibly by increased fear memory incubation or failure in triggering adaptive responses. Furthermore, we found that associations between the CAPS scores and anatomical features of the amygdala differed between PTSD patients and TCs. A possible explanation of this finding could be that structural remodeling responses to stress in the amygdala differ between the two groups. Further animal model or postmortem studies are warranted to clarify the underlying mechanism.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

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