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Stress-related cognitive style is related to volumetric change of the hippocampus and FK506 binding protein 5 polymorphism in post-traumatic stress disorder

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Original Article

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Abstract

Background. Patients with post-traumatic stress disorder (PTSD) show a different stress-related cognitive style compared with healthy controls (HC). The *FK506 binding protein 5* gene (*FKBP5*), one of the PTSD known risk factors, is involved in the stress response through the hypothalamic-pituitary-adrenal axis and brain volumetric alterations. The present study aimed to uncover the neural correlates of stress-related cognitive styles through the analysis of the regional brain volumes and *FKBP5* genotype in patients with PTSD compared with HC.
Methods. In this study, 51 patients with PTSD and 94 HC were assessed for stress-related cognitive styles, PTSD symptoms severity, and genotype of *FKBP5* single nucleotide polymorphisms, and underwent T1-weighted structural magnetic resonance imaging. Diagnosis-by-genotype interaction for regional brain volumes was examined in 16 brain regions of interest.
Results. Patients with PTSD showed significantly higher levels of catastrophizing, ruminative response, and repression, and reduced distress aversion and positive reappraisal compared with HC ($p < 0.001$). Significant diagnosis-by-genotype interactions for regional brain volumes were observed for bilateral hippocampi and left frontal operculum. A significant positive correlation between the severity of the repression and left hippocampal volume was found in a subgroup of patients with PTSD with *FKBP5* rs3800373 (AA genotype) or rs1360780 (CC genotype).
Conclusions. The present study showed the influences of *FKBP5* genotype on the distorted cognitive styles in PTSD by measuring the volumetric alteration of hippocampal regions, providing a possible role of the hippocampus and left frontal operculum as significant neurobiological correlates of PTSD.

Relevance statement

The present study, with neuroimaging and genotyped data of 51 PTSD patients and 94 healthy controls (HC), is the first to unravel the influences of *FKBP5* genotype for the stress-related cognitive styles including the repression (experiential avoidance) and positive reappraisal (cognitive-emotional regulation) in PTSD, by way of the altered regional brain volumes of hippocampus. Our work showed neurobiological evidence for the hippocampus as possible targets of neuromodulation aiming for the improvement of stress-related cognitive styles in a subset of patients with PTSD homozygous for the risk alleles of *FKBP5*-associated single nucleotide polymorphisms (SNPs).

Introduction

Globally, more than 70% of the adult population are exposed to traumatic events in their lifetime (Benjet et al., 2016). Notably, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition(DSM-5) highlights the importance of stress-related cognitive style in post-traumatic stress disorder (PTSD) (Shalev, Liberzon, & Marmar, 2017), including catastrophizing (Gellatly & Beck, 2016), rumination (Nolen-Hoeksema & Morrow, 1991; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008), self-denigration, emotional dysregulation, negative viewpoint of the environment and future, and related experiential avoidance (Chawla & Ostafin, 2007; Hayes, Wilson, Gifford, Follette, & Strosahl, 1996). When healthy people encounter a situation that is beyond their abilities of control, they may use emotion-focused coping strategies such as positive reappraisal instead of problem-solving skills

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(Ghasemi, Kordi, Asgharipour, Esmaeili, & Amirian, 2017). However, in PTSD, the positive reappraisal is not usually utilized, and is thus considered a possible predictor of the later reduction in experiential avoidance in these patients (Fitzgerald et al., 2018).

Parts of the inter-individual differences of vulnerability for getting PTSD after a traumatic event (especially interpersonal assaultive trauma) have been attributed to genetic factors (Stein, Jang, Taylor, Vernon, & Livesley, 2002). Heritability of proneness to PTSD has been estimated at 40–50% (Afifi, Asmundson, Taylor, & Jang, 2010), and epigenetic mechanisms such as methylation also partly contribute to vulnerability and resilience to PTSD (Lappalainen & Greally, 2017). In addition, several SNPs of the *FK506 binding protein 5* gene (*FKBP5*; encoding for the FKBP51 protein which is related to the intracellular trafficking of hetero-oligomeric forms of glucocorticoid receptors) have been suggested as risk factors for PTSD or are associated with PTSD symptom severity (Carvalho, Coimbra, Ota, Mello, & Belangero, 2017). Indeed, a decreased expression of *FKBP5* in postmortem brain samples, revealing an abnormal glucocorticoid functioning, was reported in patients with PTSD, compared with HC (Holmes et al., 2017). Furthermore, in the study by Binder et al. (2008) on subjects with a history of child abuse, various FKBP5 polymorphisms (AA, GG, CC, or CC homozygote genotypes of rs3800373, rs9296158, rs1360780, and rs9470080, respectively) were reported to be protective genotypes to traumatic stress in patients with PTSD.

Previous research has shown smaller hippocampal volumes, increased functional activation of limbic area, and decreased functional activation of prefrontal regions during task-free resting status and in response to negatively valenced emotional stimuli in patients with PTSD, compared with HC (Marin et al., 2016; Musazzi, Tornese, Sala, & Popoli, 2018). Furthermore, altered neural circuitries have been previously described in PTSD for fear learning (amygdala sub-regions) (Fanselow & LeDoux, 1999), threat detection (dorsal anterior cingulate, orbitofrontal, and anterior insular cortices) (Seeley et al., 2007; Tovote, Fadok, & Lüthi, 2015), context processing (hippocampal-medial prefrontal-thalamic circuitry) (Garfinkel et al., 2014; Liberzon & Abelson James, 2016), reward processing (striatum) (Elman et al., 2009; Loureiro, Kramar, Renard, Rosen, & Laviolette, 2016), valence representation (basolateral amygdala and nucleus accumbens) (Namburi, Al-Hasani, Calhoon, Bruchas, & Tye, 2016), and executive functioning and emotional regulation (frontoparietal and amygdala regions) (King et al., 2016; Shou et al., 2017). Also, *FKBP5* risk alleles have been associated with increased functional activation of the amygdala, altered functioning and decreased regional volume of the hippocampus, and reduced white matter integrity of the cingulum bundle (Fani et al., 2014). However, few studies have aimed to unravel the *FKBP5* genotype-related neural underpinning of stress-related cognitive style in PTSD.

Therefore, the present study first examined the altered stress-related cognitive styles for PTSD patients compared with HC and subsequently uncovered the neural correlates of these cognitive styles among the brain volumes of cortical-subcortical regions that demonstrated significant interactions of diagnosis-by-*FKBP5* SNP genotype for regional brain volumes. We hypothesized that the presence of risk alleles for *FKBP5*-related SNPs might differently affect brain volumes in regions related to the processing of contextual information (i.e. hippocampal-medial prefrontal-thalamic circuitry) (Garfinkel et al., 2014; Liberzon & Abelson James, 2016) of patients with PTSD and HC. Moreover, regional volumes of these contextual processing-related brain regions may be associated with the severity of stress-related cognitive style in patients with PTSD homozygous for the risk alleles of *FKBP5* SNPs.

Methods and materials

Participants and clinical assessment

A total of 145 participants ($N = 94$ HC, $N = 51$ PTSD; male/female = 36/109; all Asian) aged 19–55 years and without a prior history of head trauma were recruited from the Inje University Ilsan Paik Hospital (PTSD group) or the local community using advertisements (HC group). A diagnosis of current PTSD was based on a clinical evaluation by trained psychiatrists using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) (Weathers et al., 2013a). Among the patients with PTSD, 29 (57%) were taking psychotropic medications at the time of the brain imaging acquisition. The HC did not satisfy the DSM-IV-based lifetime diagnostic criteria for any major psychiatric disorders as screened by the SCID-I Non-Patient Edition (SCID-NP). Additional clinical characteristics and lifetime exposure to trauma for both groups were measured using the following self-report questionnaires: PTSD Checklist for DSM-5 (PCL-5) (Weathers et al., 2013c), Hospital Anxiety and Depression Scale (HADS) (Oh, Min, & Park, 1999; Zigmond & Snaith, 1983), Beck Scale for Suicidal Ideation (SSI) (Beck & Kovacs, 1979; Shin, Park, Oh, & Kim, 1990), and Life Events Checklist for DSM-5 (LEC-5) (Weathers et al., 2013b).

Stress-related cognitive styles were measured using self-report questionnaires: the Ruminative Response Scale (RRS) (Kim et al., 2013; Nolen-Hoeksema, 1991), the Multidimensional Experiential Avoidance Questionnaire (MEAQ) (Gamez, Chmielewski, Kotov, Ruggero, & Watson, 2011; Park, 2013), and the Cognitive Emotion Regulation Questionnaire (CERQ) (Garnefski & Kraaij, 2007; Kim, 2004). The RRS comprises a total of 22 items on a four-point Likert Scale and measures two aspects of ruminative responses including brooding and reflective pondering (Nolen-Hoeksema, 1991; Treynor, Gonzalez, & Nolen-Hoeksema, 2003); higher total scores indicate more intense ruminative responses (Kim, Kim, & Youn, 2010). The MEAQ uses a six-point Likert Scale and measures diverse facets of experiential avoidance such as behavioral avoidance, distress aversion, repression, denial, and distress endurance; these are considered efforts to avoid distressing thoughts, feelings, memories, and other private experiences (Gamez et al., 2011; Park, 2013). The CERQ comprises 36 items on a five-point Likert Scale to measure diverse cognitive-emotion regulation strategies, such as self-blame, rumination, catastrophizing, acceptance, and positive reappraisal, in response to stressful life events (Garnefski & Kraaij, 2007; Kim, 2004).

This study complies with the ethical standards of the Institutional Review Board (IRB no. 2015-07-025) at Inje University Ilsan Paik Hospital on human experimentation and with the Declaration of Helsinki, as revised in 2008. Written informed consent was obtained from all participants before study enrollment.

Image acquisition, processing, and extraction of regional brain volumes

Whole-brain anatomy was measured for all participants using high-resolution T1-weighted, 3D magnetic resonance imaging (MRI; TR = 1900 ms; TE = 3.42 ms; FOV = 210 mm × 250 mm; FA = 15°; acquisition matrix = 227 × 384; voxel size = 0.9 × 0.7 ×

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1.2 mm^3) scans on a 1.5-Tesla scanner (Magneton Avanto, Siemens).

Image pre-processing procedures were as follows: (1) setting the T1-weighted MR images at the anterior commissure (AC); (2) approximating alignment by way of the mutual information affine registration with SPM12 tissue probability maps; (3) affine regularization with an ICBM space East Asian brain template; (4) spatial normalization using the high-dimensional DARTEL registration algorithm; (5) tissue segmentation of brain images into gray matter, white matter, and cerebrospinal fluid; and (6) modulation of normalized tissue intensities using the Jacobian-transformed tissue probability maps were conducted using the Computational Anatomy Toolbox for SPM (http://www.neuro.uni-jena.de/cat/) implemented in SPM12 (https://www.fil.ion.ucl.ac.uk/spm) software and MATLAB (https://kr.mathworks.com) platforms (Chen, Chen, Dong, Liu, & Yu, 2018; Kim et al., 2018). Finally, regional brain gray matter volumes for the 114 regions-of-interest (ROIs) defined according to the Neuromorphometric Atlas (http://Neuromorphometrics.com; from the original set of 142 ROIs, 118 regions of brain white matter, ventricles, and cerebellar sub-regions were excluded) were estimated.

For examination of the diagnosis-by-genotype interaction for regional brain volumes, in line with our study hypothesis and previous studies (Fanselow & LeDoux, 1999; Garfinkel et al., 2014; King et al., 2016; Liberzon & Abelson James, 2016; Seeley et al., 2007; Shou et al., 2017; Tovote et al., 2015), we selected the following 16 ROIs: amygdala, hippocampus, thalamus, frontal operculum, anterior cingulate gyrus, medial frontal cortex, inferior temporal gyrus, and medial orbital gyrus of both hemispheres.

DNA collection, extraction, and genotyping

In this study, we extracted four *FKBP5* SNPs (rs9296158, rs3800373, rs1360780, and rs9470080) that have been suggested as relevant predictors of stress vulnerability and risk factors for psychiatric disorders in the adult population for candidate gene analyses (Scheuer et al., 2016; Tamman et al., 2017). Genomic DNA, extracted from peripheral blood provided by participants, underwent quality check using NanoDrop® ND-1000 UV-Vis Spectrophotometer. Genotyping was conducted using polymerase chain reaction (PCR) amplification and allelic discrimination using TaqMan® SNP Genotyping Assays obtained from Applied Biosystems and ABI PRISM 7900HT Real-Time PCR system (Applied Biosystems; Foster City, CA, USA) (Schleinitz, DiStefano, & Kovacs, 2011).

Statistical analyses

Between-group differences in sex ratio were analyzed using χ^2 tests (Table 1). Differences of age, education years, clinical characteristics (illness duration for PTSD, four sub-scores of the PCL-5, anxiety and depression sub-scores of the HADS, total score of the SSI, and the 'happened to me' sub-score on the LEC-5), and stress-related cognitive characteristics (total score of the RRS, seven sub-scores on the MEAQ, and nine sub-scores on the CERQ) between the PTSD and HC were calculated using independent *t* tests (Table 1).

Two-way analysis of covariance (ANCOVA; with the covariates of age, sex, education and total intracranial volume adjusted) examined the main effect of diagnostic groups, main effect of *FKBP5* genotype (four *FKBP5* SNPs including the rs9296158 [GG and (AG + AA)], rs3800373 [AA and (AC + CC)], rs1360780 [CC and (CT + TT)], and rs9470080 [CC and (CT + TT)]), and the interaction of diagnosis-by-genotype (each SNP separately) for the regional brain gray matter volumes in 16 cortical and subcortical ROIs. All analyses were corrected for multiple comparisons using a false discovery rate (FDR) threshold of $p < 0.05$ based on the Benjamini–Hochberg (BH) procedure (Afifi et al., 2010).

Among these 16 cortical and subcortical ROIs, those showing statistically significant diagnosis-by-genotype interactions were subjected to the partial correlation coefficients calculation (adjusted for age, sex, education, and total intracranial volume) with stress-related cognitive styles for which significant differences found between HC and PTSD groups. Issues of multiple correlation testing were statistically adjusted with a 5000-bootstrap resampling technique for HC and PTSD separately (Haukoos & Lewis, 2005; Pernet, Wilcox, & Rousselet, 2013; Ruscio, 2008). Statistical analyses were conducted using IBM SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Demographic and clinical characteristics

A summary of demographics, clinical characteristics, and stress-related cognitive styles for PTSD and HC groups is provided in Table 1. Compared with HC, patients with PTSD reported more previous exposure to stressful life events (LEC-5: 'happened to me') and demonstrated more severe psychiatric symptoms scored using the PCL-5 (intrusion symptoms, avoidance, negative alterations in cognitions and mood, alterations in arousal and reactivity), more severe anxiety-depressive mood (sub-scores of HADS) as well as suicidal ideation (total score of SSI). Notably, patients with PTSD reported more ruminative response (total score of the RSS) and experiential avoidance (MEAQ sub-scores of distress aversion and repression) in stressful events confrontation. Patients with PTSD demonstrated a stronger tendency of catastrophizing and weaker positive reappraisal when attempting to create reason of the stressful events (CERQ sub-scores).

Diagnosis-by-FKBP5 genotype interactions for gray matter volumes

The minor allele frequencies of four *FKBP5*-related SNPs were greater than 5% in both groups. Additionally, the genotypic distributions of the four *FKBP5* SNPs did not deviate from the Hardy–Weinberg equilibrium for both groups (all $ps > 0.05$; online Supplementary Table S1). Two-way ANCOVA was calculated to examine the effects of PTSD diagnosis and FKBP5 SNPs genotype on the regional brain volumes. Among the two-way ANCOVA results in Table 2, only for those with statistically significant diagnosis-by-genotype interactions [$p < 0.05$ (FDR-corrected)], simple main effects of diagnosis and genotype for regional brain volumes were examined [with statistical significance of $p < 0.025$ (Bonferroni-corrected)] as described below.

FKBP5 SNP rs3800373 genotype and left hippocampal volume

A two-way ANCOVA showed statistically significant diagnosis-by-rs3800373 genotype interaction on the regional volume of the left hippocampus [$F = 11.153$, $p = 0.016$ (FDR-corrected); Table 2 and Fig. 1a]. First, the effect of PTSD diagnosis was significant for the rs3800383 AC or CC genotype ($F = 10.176$, $p = 0.002$) but not for the AA genotype ($F = 1.278$, $p = 0.260$). With the rs3800373 AC or CC genotype, left

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Table 1. Demographic, trauma-related, cognitive, and clinical characteristics

Variables	HC ($N = 94$)	PTSD ($N = 51$)	t/χ^2	df	p value
Age, years	40.9 (12.1)	39.3 (11.1)	0.783	143	0.435
Sex, M/F	28/66	8/43	3.522	1	0.071
Education, years	14.2 (2.5)	13.2 (2.4)	2.521	142	0.013
Illness duration for PTSD, months	NA	102.6 (125.7)	NA	NA	NA
Clinical characteristics					
PTSD Check List-5 (PCL-5)					
Cluster B: intrusion symptoms	4.7 (4.0)	12.8 (4.2)	−11.502	142	**<0.001*** **
Cluster C: avoidance	2.5 (2.2)	5.5 (2.0)	−7.898	142	**<0.001*** **
Cluster D: negative alterations in cognitions and mood	5.9 (5.3)	15.5 (6.7)	−9.476	142	**<0.001*** **
Cluster E: alterations in arousal and reactivity	4.6 (4.3)	13.3 (5.3)	−10.068	86.008	**<0.001*** **
Hospital Anxiety and Depression Scale (HADS)					
Anxiety	6.2 (3.5)	12.6 (4.4)	−8.991	85.336	**<0.001*** **
Depression	6.9 (3.7)	11.2 (3.8)	−6.621	143	**<0.001*** **
Beck Scale for Suicidal Ideation (SSI)***	5.6 (6.3)	12.1 (8.1)	−5.028	83.007	**<0.001*** **
Life Events Checklist for DSM-5 (LEC-5): Happened to me	3.1 (2.4)	4.8 (2.4)	−4.143	143	**<0.001*** **
Cognitive style					
Ruminative Response Scale (RRS)	40.4 (12.3)	56.1 (11.0)	−7.634	143	**<0.001*** **
Multidimensional Experiential Avoidance Questionnaire (MEAQ)					
Behavioral avoidance	40.2 (8.5)	44.5 (8.4)	−2.919	143	0.004
Distress aversion	40.8 (10.9)	30.3 (9.6)	5.8	143	**<0.001*** **
Procrastination	25.2 (5.9)	28.2 (5.3)	−3.014	143	0.003
Distraction and suppression	31.2 (7.9)	33.9 (7.5)	−2.026	143	0.045
Repression	24.5 (6.0)	29.9 (7.6)	−4.353	84.783	**<0.001*** **
Denial	11.1 (4.3)	12.6 (4.3)	−2.048	143	0.042
Distress endurance	56.0 (9.2)	54.0 (10.8)	−1.172	143	0.243
Cognitive Emotion Regulation Questionnaire (CERQ)					
Self-blame	10.8 (3.3)	11.7 (4.6)	−1.183	78.531	0.24
Acceptance	13.5 (3.0)	13.0 (3.5)	0.958	143	0.34
Rumination	11.6 (3.0)	13.4 (4.1)	−2.867	80.239	0.005
Positive refocusing	12.8 (3.7)	10.5 (4.2)	3.33	143	0.001
Refocus on planning	15.0 (3.0)	13.3 (3.7)	2.8	86.033	0.006
Positive reappraisal	14.0 (3.5)	10.7 (4.1)	4.887	90.136	**<0.001*** **
Putting into perspective	13.6 (2.9)	11.7 (3.8)	3.177	82.008	0.002
Catastrophizing	8.2 (3.2)	13.4 (4.5)	−7.249	78.336	**<0.001*** **
Blaming others	9.1 (3.5)	11.4 (4.5)	−3.104	83.128	0.003

*** $P < 0.001$

hippocampal volume was larger in HC than PTSD ($p = 0.002$). Second, the effect of rs3800373 genotype was significant in HC ($F = 10.315$, $p = 0.002$) but not in PTSD ($F = 3.651$, $p = 0.058$). For HC, left hippocampal volume was larger in the rs3800373 AC or CC than in the AA genotype ($p = 0.002$).

FKBP5 SNP rs3800373 genotype and right hippocampal volume

In addition, another statistically significant diagnosis-by-rs3800373 genotype interaction was found in the regional volume of the right hippocampus [$F = 8.381$, $p = 0.032$ (FDR-corrected); Table 2 and Fig. 1b]. First, the effect of diagnosis was significant for the rs3800383 AC or CC genotype ($F = 8.748$, $p = 0.004$) but not for the rs3800373 AA genotype ($F = 0.462$, $p = 0.498$). Specifically, for the rs3800373 AC or CC genotype, right hippocampal volume was larger in HC than in PTSD ($p = 0.004$). Second, the effect of rs3800373 genotype for the right hippocampal volume was not significant both in HC ($F = 4.159$, $p = 0.043$) and PTSD ($F = 4.544$, $p = 0.035$).

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Table 2. PTSD diagnosis-by-*FKBP5* genotype interactions (adjusted for age, sex, education years, and intracranial volume) for regional brain volumes

	Diagnosis-by-genotype											
	rs9296158			rs3800373			rs1360780			rs9470080		
	F	*p*	*p*FDR	*F*	*p*	*p*FDR	*F*	*p*	*p*FDR	*F*	*p*	*p*FDR
L Amygdala	3.197	0.076	0.243	5.677	0.019	0.076	5.586	0.02	0.064	2.492	0.117	0.374
R Amygdala	1.693	0.195	0.356	1.078	0.301	0.401	1.486	0.225	0.327	0.966	0.327	0.581
L Hippocampus	6.663	0.011	0.058	11.153	0.001	0.016*	11.241	0.001	0.016*	5.744	0.018	0.144
R Hippocampus	8.703	0.004	0.04*	8.381	0.004	0.032*	7.827	0.006	0.048*	8.093	0.005	0.08
L Thalamus	1.365	0.245	0.356	1.637	0.203	0.318	1.713	0.193	0.308	1.745	0.189	0.48
R Thalamus	1.077	0.301	0.401	0.607	0.437	0.499	0.7	0.404	0.461	1.584	0.21	0.48
L Frontal operculum	8.175	0.005	0.04*	1.749	0.188	0.318	3.314	0.071	0.178	3.273	0.073	0.332
R Frontal operculum	2.429	0.121	0.276	1.526	0.219	0.318	1.277	0.26	0.346	0.29	0.591	0.725
L Anterior cingulate gyrus	4.722	0.032	0.128	5.569	0.02	0.076	6.487	0.012	0.052	1.005	0.318	0.581
R Anterior cingulate gyrus	0.689	0.408	0.466	2.769	0.098	0.214	2.277	0.134	0.256	0.174	0.677	0.725
L Medial frontal cortex	1.393	0.24	0.356	0.241	0.625	0.666	0.345	0.558	0.595	0.103	0.749	0.749
R Medial frontal cortex	1.578	0.211	0.356	0.826	0.365	0.449	0.71	0.401	0.461	0.182	0.671	0.725
L Inferior frontal gyrus	0.027	0.869	0.922	0.025	0.875	0.875	0.082	0.775	0.775	0.68	0.411	0.597
R Inferior frontal gyrus	2.679	0.104	0.276	5.243	0.024	0.076	6.305	0.013	0.052	3.053	0.083	0.332
L Medial orbital gyrus	0.895	0.346	0.425	3.735	0.055	0.146	3.143	0.078	0.178	0.766	0.383	0.597
R Medial orbital gyrus	0.01	0.922	0.922	2.64	0.107	0.214	2.157	0.144	0.256	0.17	0.68	0.725

*$p < 0.05$ (FDR-corrected).

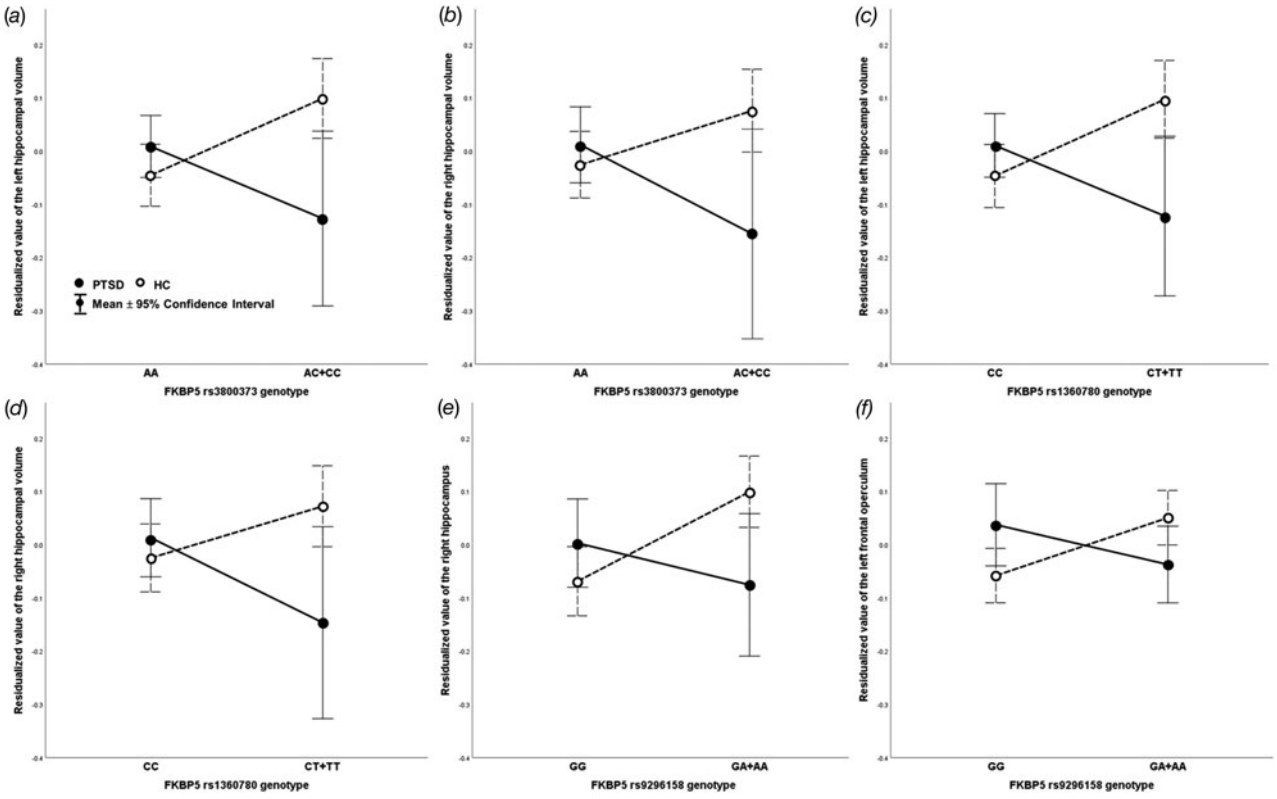

Fig. 1. Interactions between the post-traumatic stress disorder (PTSD) diagnosis and FKBP5 single nucleotide polymorphism (SNP) genotype for regional brain volumes. (*a*) FKBP5 rs3800373 and left hippocampus: with the rs3800373 genotype of AC or CC, left hippocampal volume was larger in healthy controls (HC) than in PTSD. In HC, left hippocampal volume was larger for the rs3800373 AC or CC genotype than for the rs3800373 AA genotype. (*b*) FKBP5 rs3800373 and right hippocampus: with the rs3800373 AC or CC genotype, right hippocampal volume was larger in HC compared to PTSD. (*c*) FKBP5 rs1360780 genotype and left hippocampus: with the rs1360780 CT or TT genotype, the left hippocampal volume was larger in HC compared to PTSD. In HC, the left hippocampal volume was larger for the rs1360780 CT or TT genotype than for the CC genotype. (*d*) FKBP5 rs1360780 genotype and right hippocampus: for the rs1360780 genotype of CT or TT, the right hippocampal volume was larger in HC than in PTSD. (*e*) FKBP5 rs9296158 genotype and right hippocampus: for the rs9296158 genotypes of GA or AA, the right hippocampal volume was larger in HC compared to PTSD. In HC, the right hippocampal volume was larger for the rs9296158 GA or AA genotype than for GG genotype. (*f*) FKBP5 rs9296158 genotype and left frontal operculum: for HC, left frontal operculum volume was larger in the rs9296158 GA or AA genotype compared to the rs9296158 GG genotype. *Y* scale depicts residual of regional brain volume (*y*-axis) calculated by regressing the covariates (age, sex, education years, and total intracranial volume) out.

FKBP5 SNP rs1360780 genotype and left hippocampal volume

For the rs1380780 genotype, a statistically significant diagnosis-by-genotype interaction on the regional volume of the left hippocampus [$F = 11.241$, $p = 0.016$ (FDR-corrected); Table 2 and Fig. 1c] was found. First, the effect of diagnosis was significant with the rs1360780 CT or TT genotype ($F = 10.157$, $p = 0.002$) but not with the rs1360780 CC genotype ($F = 1.389$, $p = 0.241$). For the rs1360780 CT or TT, the left hippocampal volume was larger in HC than PTSD ($p = 0.002$). Second, the effect of rs1360780 genotype in the left hippocampal volume was significant in HC ($F = 10.253$, $p = 0.002$) but not in PTSD ($F = 3.625$, $p = 0.059$). The left hippocampal volume in HC was larger for the rs1360780 CT or TT genotype than for CC genotype ($p = 0.002$).

FKBP5 SNP rs1360780 genotype and right hippocampal volume

Moreover, diagnosis-by-rs1360780 genotype interaction was also statistically significant for the right hippocampal volume [$F = 7.827$, $p = 0.048$ (FDR-corrected); Table 2 and Fig. 1d]. First, the effect of diagnosis was significant for the rs1360780 CT or TT genotype ($F = 8.233$, $p = 0.005$) but not for the rs1360780 CC genotype ($F = 0.449$, $p = 0.504$). With the rs1360780 CT or TT genotype, right hippocampal volume was larger in HC than in PTSD ($p = 0.005$). Second, the effect of rs1360780 genotype for the right hippocampal volume was not significant both in HC ($F = 3.750$, $p = 0.055$) and in PTSD ($F = 4.277$, $p = 0.041$).

FKBP5 SNP rs9296158 genotype and right hippocampal volume

In terms of the rs9296158 genotype, diagnosis-by-genotype interaction was statistically significant for the right hippocampal volume [$F = 8.703$, $p = 0.040$ (FDR-corrected); Table 2 and Fig. 1e]. First, the effect of PTSD diagnosis was significant for the rs9296158 GA or AA genotype ($F = 7.583$, $p = 0.007$) but not for the rs9296158 GG genotype ($F = 1.560$, $p = 0.214$). Specifically, for the rs9296158 GA or AA, the right hippocampal volume was larger in HC than in PTSD ($p = 0.007$). Second, the effect of rs9296158 genotype for the right hippocampal volume was significant in HC ($F = 11.937$, $p = 0.001$) but not in PTSD ($F = 1.275$, $p = 0.261$). In HC, the right hippocampal volume was larger for the rs9296158 GA or AA genotype than for GG genotype ($p = 0.001$).

FKBP5 SNP rs9296158 genotype and volume of the left frontal operculum

Further, another significant diagnosis-by-rs9296158 genotype interaction was found for the regional volume of the left frontal operculum [$F = 8.175$, $p = 0.040$ (FDR-corrected); Table 2 and

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Fig. 1f]. First, the effect of diagnosis for the regional volume of left frontal operculum was not significant with the rs9296158 GA or AA genotype ($F = 3.053$, $p = 0.083$) and also with the rs9296158 GG genotype ($F = 5.097$, $p = 0.026$). Second, the effect of rs9296158 genotype for the left frontal operculum volume was significant in HC ($F = 8.587$, $p = 0.041$) but not in PTSD ($F = 1.948$, $p = 0.165$). For HC, the left frontal operculum volume was larger in the rs9296158 GA or AA genotype than for GG genotype ($p = 0.004$).

FKBP5 SNP rs9470080 genotype

For the rs9470080 genotype, no statistically significant diagnosis-by-genotype interactions of regional brain volumes were found (all $p > 0.05$; Table 2).

Correlations between the regional brain volumes and stress-related cognitive styles

Partial correlation coefficients (adjusted for age, sex, education, and total intracranial volume) between five stress-related cognitive styles (ruminative response, distress aversion, repression, positive reappraisal, catastrophizing) with significant between-group (HC and PTSD) differences and three brain regions with significant diagnosis-by-genotype interactions for regional brain volumes [left hippocampus (rs3800373 and rs1360780), right hippocampus (rs9296158, rs3800373, and rs1360780), and left frontal operculum (rs9296158)] were calculated for each subgroup segregated according to the diagnosis-by-*FKBP5* SNP genotypes.

FKBP5 SNP rs3800373 genotype

For the rs3800373 genotype, there was a significant positive correlation between repression and left hippocampal volume ($r = 0.426$, $p = 0.012$) in PTSD with rs3800373 AA genotype (Fig. 2a). On the other hand, there were no significant correlations found between the repression and left hippocampal volume in PTSD with rs3800373 C carriers ($r = -0.478$, $p = 0.231$), in HC with rs3800373 AA genotype ($r = -0.027$, $p = 0.847$), or in HC with rs3800383 C carriers ($r = -0.189$, $p = 0.285$; Table 3).

Moreover, left hippocampal volume also showed a statistically significant negative correlation with the strength of positive reappraisal in HC with rs3800373 AC or CC genotype ($r = -0.366$, $p = 0.033$; Fig. 2b) which was not evident in HC with AA genotype ($r = -0.206$, $p = 0.142$), in PTSD with AA genotype ($r = 0.327$, $p = 0.059$), nor in PTSD with AC or CC genotype ($r = -0.431$, $p = 0.286$; Table 3).

FKBP5 SNP rs1360780 genotype

Regarding the rs1360780 genotype, there was a significant positive association between the repression and left hippocampal volume in PTSD with rs1360780; CC ($r = 0.425$, $p = 0.014$; Fig. 2c). On the contrary, association between the repression and the left hippocampal volume did not show statistical significance for PTSD with rs1360780 CT or TT genotype ($r = -0.393$, $p = 0.296$), HC with rs1360780 CC genotype ($r = -0.025$, $p = 0.863$), nor HC with rs1360780 CT or TT genotype ($r = -0.181$, $p = 0.297$; Table 3).

Further, for HC with rs1360780 CT or TT genotype, regional volume of the left hippocampus and strength of positive reappraisal showed statistically significant negative association ($r = -0.361$, $p = 0.033$; Fig. 2d), which was not statistically significant in other subgroups of HC with CC genotype ($r = -0.200$, $p = 0.158$), PTSD with CC genotype ($r = 0.322$, $p = 0.067$), nor PTSD with CT or TT genotype ($r = -0.270$, $p = 0.482$; Table 3).

FKBP5 SNP rs9296158 genotype

In terms of the rs9296158 genotype, a significant positive correlation between catastrophizing and left frontal operculum volume was found in HC with rs9296158 GG genotype ($r = 0.356$, $p = 0.019$; Fig. 2e). On the contrary, associations between the catastrophizing and volume of the left frontal operculum were not statistically significant in other subgroups of HC with rs9296158 GA or AA genotype ($r = 0.025$, $p = 0.871$), PTSD with rs9296158 GG genotype ($r = 0.245$, $p = 0.227$), nor PTSD with rs9296158 GA or AA genotype ($r = 0.006$, $p = 0.983$; Table 3).

FKBP5 SNP rs9470080 genotype

As no statistically significant diagnosis-by-genotype interactions of regional brain volumes were found regarding the rs9470080 genotype (refer to the 'Diagnosis-by-FKBP5 genotype interactions for gray matter volumes' section in the 'Results' above), differential partial correlations between the stress-related cognitive styles *v.* the regional brain volumes regarding the rs8470080 genotype and PTSD diagnosis were not calculated in the current study.

Discussion

To the best of our knowledge, this is the first study that unraveled the *FKBP5* genotype-related neural underpinning of stress-related cognitive style in PTSD. In this study, patients with PTSD showed more severe catastrophizing, rumination, and repression in addition to the weaker tendencies of distress aversion and positive reappraisal compared to HC. Significant diagnosis-by-genotype interactions were found for bilateral hippocampi and left frontal operculum. Moreover, the significant positive correlations between the cognitive style (repression) and the left hippocampal volume were uncovered in patients with PTDS who had homozygous genotypes for the *FKBP5* SNPs of rs3800373 (AA genotype) or rs1360780 (CC genotype). These results suggest that stress-related cognitive style exists in neural circuitry including the hippocampus under the influence of *FKBP5* genotype in patients with PTSD.

The hippocampus has been regarded as a major region involved in the pathology of PTSD. A meta-analysis showed that hippocampal volumes were smaller in the PTSD group and trauma-exposed group without PTSD compared with those of the trauma-unexposed group (Woon, Sood, & Hedges, 2010). The significant negative correlation between the hippocampal volumes and PTSD symptomatology was shown only in PTSD patients (Nelson & Tumpap, 2017), but not in malingering subjects (Butler et al., 2018) or in HC (Logue et al., 2018). In a resting-state fMRI study, a successful distinction between patients with PTSD and HC was reported from the effective connectivity of the amygdala to the right hippocampus and of the right hippocampus to the left striatum-precuneus-insula (Rangaprakash et al., 2018). Likewise, the resting-state functional connectivity between the hippocampus and other regions – as reflected in the values of nodal efficiency and degree centrality – was elevated in patients with PTSD exposed to a major earthquake (Zhang et al., 2017).

In the current study, the regional volume of bilateral hippocampi demonstrated a significant interaction between the PTSD diagnosis and *FKBP5* genotype. This result is consistent with prior studies that reported the influence of genetic factors on the morphology of the hippocampus in patients with PTSD. Indeed, a positive correlation between the hippocampal volume and degree of methylation in the exon 1F promoter region of

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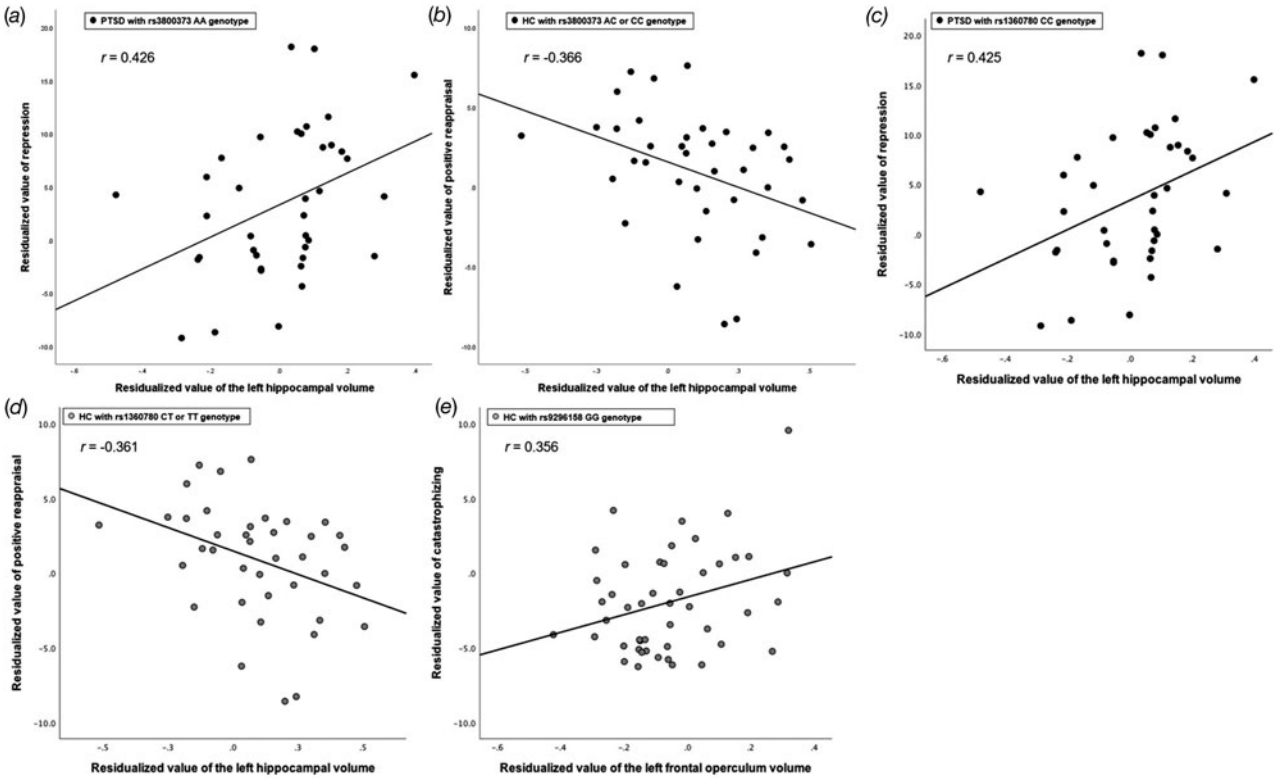

Fig. 2. Partial correlations between cognitive styles and regional brain volumes (adjusted for age, sex, education year, and total intracranial volume). (*a*) Positive correlation between repression and the left hippocampal volume ($r = 0.426$, $p = 0.012$) in post-traumatic stress disorder (PTSD) with rs3800373 AA genotype. (*b*) Negative association between the left hippocampal volume and positive reappraisal in healthy controls (HC) with rs3800373 AC or CC genotype ($r = -0.366$, $p = 0.033$). (*c*) Positive correlation between the repression and left hippocampal volume in PTSD with rs1360780 CC genotype ($r = 0.425$, $p = 0.014$). (*d*) Negative relationship between the left hippocampal volume and positive reappraisal in HC with rs1360780 CT or TT genotype ($r = -0.361$, $p = 0.033$). (*e*) Positive correlation between regional volume of the left frontal operculum and the severity of catastrophizing in HC with rs9296158 GG genotype ($r = 0.356$, $p = 0.019$). *X* and *Y* scales depict residuals of cognitive style (*y*-axis) and regional brain volume (*x*-axis) calculated by regressing the covariates (age, sex, education years, and total intracranial volume) out.

the glucocorticoid receptor gene was found in patients with PTSD (McNerney et al., 2018).

Furthermore, in the current study, positive correlations between the left hippocampal volume and severity of repression (a form of experiential avoidance) were also found in PTSD patients homozygous for *FKBP5* SNPs rs3800373 (AA genotype) or rs1360780 (CC genotype). Increased experiential avoidance was reported to be related to the decreased functional activation of the hippocampus in healthy adults in an fMRI study (Schlund, Magee, & Hudgins, 2011). Moreover, increased functional activation of the hippocampus during encoding of episodic memory is associated with re-experiencing symptoms of PTSD in these patients (Stevens et al., 2018). All these previous evidences support the validity of our results.

Previous research has shown that two FKBP5 SNPs (rs3800373 and rs1360780) interact with child abuse severity (Binder et al., 2008) or adult natural disaster (Hawn et al., 2019) as predictors of PTSD symptoms in adult age. Previous studies showed an association between the genotype of FKBP5 SNP rs1360780 and resting-state functional connectivity of the hippocampus-anterior cingulate (Fani et al., 2016) and between increased expression of FKBP5 protein, increased hippocampal volume, and clinical improvement after cognitive-behavioral therapy in patients with PTSD (Levy-Gigi, Szabo, Kelemen, & Keri, 2013).

The present study uncovered a cognitive style and brain volume in patients with PTSD. Repression is a kind of mental defense mechanism that prevents overwhelming PTSD symptoms such as flashback, and re-experience and has been considered as a secondary distorted cognitive style to abnormal neocortical and hippocampal arousal and corticosteroid and enkephalin secretion, which can induce functional, cellular, and anatomical abnormality within the hippocampus (Joseph, 1998). Hulbert, Henson, and Anderson (2016) showed that when people suppress retrieval of unwanted memory, stopping retrieval engages a suppression mechanism that is related to the hippocampal processes. A cognitive style, repression, through mediation of frontal cortex, could operate to protect the brain from stressful symptoms. Neuroimaging data revealed that trauma-exposed individuals showed reduced activation in the right middle frontal gyrus during memory suppression. Difficulty in active suppression of memories may contribute to the development of PTSD (Sullivan et al., 2019). Current study showed a positive correlation between the left hippocampal volume and severity of repression in patients with PTSD homozygous for *FKBP5* SNPs rs3800373 (AA genotype) or rs1360780 (CC genotype). We hypothesized that homozygous for *FKBP5* SNPs rs3800373 (AA genotype) or rs1360780 (CC genotype) could be protective factors for symptoms aggravation through protective cognitive style (repression) in patients with PTSD compared with other genotypes. The hypothesis is in line with the results of Binder et al. (2008) who suggested a protective genotype effect of FKBP5 toward traumatic stress.

In addition, significant diagnosis-by-genotype interactions for regional brain volumes were also found in the left frontal

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Table 3. Partial correlations between the regional brain volumes and stress-related cognitive styles (adjusted for age, sex, education years, and intracranial volume)

		Left hippocampus				Right hippocampus				Left frontal operculum			
Cognitive style	Statistics	HC		PTSD		HC		PTSD		HC		PTSD	
***rs3800373* genotype**		AA	AC + CC	AA	AC + CC	AA	AC + CC	AA	AC + CC	AA	AC + CC	AA	AC + CC
Ruminative response	Pearson's *r*	−0.032	0.072	0.172	−0.053	−0.127	0.081	0.061	0.052	–	–	–	–
	p value	0.823	0.684	0.331	0.901	0.37	0.651	0.73	0.903	–	–	–	–
Distress aversion	Pearson's *r*	0.061	0.002	0.093	0.413	0.104	−0.095	0.058	0.302	–	–	–	–
	p value	0.669	0.992	0.599	0.31	0.464	0.595	0.743	0.468	–	–	–	–
Repression	Pearson's *r*	−0.027	−0.189	**0.426**	−0.478	−0.065	−0.122	0.103	−0.311	–	–	–	–
	p value	0.847	0.285	**0.012***	0.231	0.648	0.492	0.561	0.453	–	–	–	–
Positive reappraisal	Pearson's *r*	−0.206	**−0.366**	0.327	−0.431	0.04	−0.262	0.197	−0.39	–	–	–	–
	p value	0.142	**0.033***	0.059	0.286	0.78	0.134	0.264	0.339	–	–	–	–
Catastrophizing	Pearson's *r*	0.001	−0.029	−0.025	−0.246	−0.113	0.075	0.135	−0.166	–	–	–	–
	p value	0.993	0.869	0.89	0.556	0.424	0.671	0.448	0.695	–	–	–	–
***rs1360780* genotype**		CC	CT + TT	CC	CT + TT	CC	CT + TT	CC	CT + TT	CC	CT + TT	CC	CT + TT
Ruminative response	Pearson's *r*	−0.039	0.067	0.169	0.023	−0.122	0.075	0.065	0.084	–	–	–	–
	p value	0.784	0.701	0.348	0.953	0.395	0.667	0.721	0.829	–	–	–	–
Distress aversion	Pearson's *r*	0.067	0.01	0.101	0.328	0.099	−0.084	0.054	0.264	–	–	–	–
	p value	0.638	0.952	0.575	0.388	0.49	0.63	0.766	0.492	–	–	–	–
Repression	Pearson's *r*	−0.025	−0.181	**0.425**	−0.393	−0.067	−0.115	0.104	−0.275	–	–	–	–
	p value	0.863	0.297	**0.014***	0.296	0.639	0.511	0.563	0.474	–	–	–	–
Positive reappraisal	Pearson's *r*	−0.2	**−0.361**	0.322	−0.27	0.032	−0.257	0.206	−0.303	–	–	–	–
	p value	0.158	**0.033***	0.067	0.482	0.824	0.136	0.251	0.428	–	–	–	–
Catastrophizing	Pearson's *r*	−0.009	−0.044	−0.023	−0.209	−0.106	0.057	0.134	−0.151	–	–	–	–
	p value	0.949	0.803	0.899	0.589	0.458	0.747	0.459	0.698	–	–	–	–
***rs9296158* genotype**		GG	GA + AA	GG	GA + AA	GG	GA + AA	GG	GA + AA	GG	GA + AA	GG	GA + AA
Ruminative response	Pearson's *r*	–	–	–	–	−0.25	0.089	0.112	0.093	0.252	−0.182	0.119	−0.009
	p value	–	–	–	–	0.106	0.572	0.587	0.731	0.104	0.242	0.564	0.975
Distress aversion	Pearson's *r*	–	–	–	–	0.157	−0.129	−0.032	0.262	−0.07	−0.061	−0.257	0.32
	p value	–	–	–	–	0.316	0.411	0.878	0.328	0.657	0.697	0.204	0.226
Repression	Pearson's *r*	–	–	–	–	−0.134	−0.107	0.192	−0.202	0.158	0.124	0.073	−0.291
	p value	–	–	–	–	0.392	0.496	0.348	0.454	0.311	0.429	0.723	0.275

(*Continued*)

Table 3. (*Continued.*)

Cognitive style	Statistics	Left hippocampus		Right hippocampus		Left frontal operculum			
		HC	PTSD	HC	PTSD	HC		PTSD	
Positive reappraisal	Pearson's *r*	–	–	–	0.078	−0.246	0.29	−0.305	−0.079	−0.09	0.085	0.013
	p value	–	–	–	0.617	0.111	0.15	0.251	0.614	0.566	0.679	0.961
Catastrophizing	Pearson's *r*	–	–	–	−0.272	0.127	0.272	−0.064	**0.356**	0.025	0.245	0.006
	p value	–	–	–	0.078	0.416	0.179	0.815	**0.019***	0.871	0.227	0.983
***rs9470080* genotype**		*no statistically significant diagnosis-by-genotype interactions for regional brain volumes found*										

*$p < 0.05$ (adjusted with a 5000-bootstrap resampling technique).

operculum, which showed significant correlations with cognitive style in HC. The regional grey matter volume of the left frontal operculum showed a positive association with sensitivity to negative life events as mediated by rumination (Qiao et al., 2013). Activation of the frontal operculum is positively correlated with the intensity of trait rumination (Kocsel et al., 2017) and with rewards of food intake in youth at risk for obesity (Stice, Yokum, Burger, Epstein, & Small, 2011). Likewise, different genotypes of catechol-I-methyltransferase gene are associated with functional connectivity between frontal operculum and other posterior regions (Jaspar et al., 2016). Furthermore, patients with major depressive disorder having a risk allele (T) for *FKBP5 rs1360780* SNP showed reduced activation of frontal operculum during emotional attention task compared to patients without the T allele (Tozzi et al., 2016).

Limitations

This study has some limitations. First, this study compared the HC and PTSD using the cross-sectional design and did not assess the longitudinal trajectories of regional brain volumes and stress-related cognitive styles. Accordingly, the current study results might indicate not causation but association among the PTSD diagnosis, FKBP5 genotype, regional brain volumes, and cognitive styles. Second, possible distinctive profiles of diagnosis-by-genotype interactions for cortical surface area or cortical thickness separately (Panizzon et al., 2009) were not explored.

Conclusion

Collectively, this study is the first to unravel the *FKBP5* genotype-related neural underpinning of stress-related cognitive style in PTSD. The *FKBP5* gene, one of the risk factors for PTSD development or symptoms, is involved with the hypothalamic-pituitary-adrenal axis and associated with the stress response. This study showed that the *FKBP5* genotype-by-PTSD diagnosis interaction for grey matter volumes of the hippocampus is also associated with cognitive style in PTSD, including the elevated experiential avoidance and lowered cognitive-emotional regulation. Our work shows the neurobiological support for the inclusion of the hippocampus and left frontal operculum as possible candidate brain regions of the neuromodulation of patients with PTSD homozygous for risk alleles of *FKBP5*-associated SNPs, targeting the improvement of stress-related cognitive styles in PTSD.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291720002949

Data availability. The corresponding author S.H.L. has full access to the study data. For more information regarding the request for access to the study data, please contact the corresponding author by way of e-mail: lshpss@paik.ac.kr.

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Conflict of interest. None.

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