Pre-COVID brain structures prospectively differentiate post-traumatic stress symptoms and post-traumatic growth during the COVID-19 pandemic

Running title: Distinct brain structures in PTSS and PTG

Authors: Huan Lan[1,2,3], Xueling Suo[1,2,3], Chao Zuo[1,2,3], Nanfang Pan[1,2,3], Xun Zhang[1,2,3], Graham J Kemp[4], Song Wang[1,2,3], Qiyong Gong[1,5].

Affiliations:

[1] Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, Chengdu, Sichuan, China

[2] Research Unit of Psychoradiology, Chinese Academy of Medical Sciences, Chengdu, Sichuan, China

[3] Functional and Molecular Imaging Key Laboratory of Sichuan Province, West China Hospital of Sichuan University, Chengdu, Sichuan, China

[4] Liverpool Magnetic Resonance Imaging Centre (LiMRIC) and Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, United Kingdom

[5] Department of Radiology, West China Xiamen Hospital of Sichuan University, Xiamen, Fujian, China

Corresponding Authors: Song Wang or Qiyong Gong, Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, No. 37 Guo Xue Xiang, Chengdu 610041, PR China. **Tel**: 086-028 81812593; **Fax**: 086-028 85423503. **E-mail**: wangs_psych@163.com (Song Wang) or qiyonggong@hmrrc.org.cn (Qiyong Gong).

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Conflict of interest

The authors declare no competing interests.

Data availability statement

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Abstract

Posttraumatic stress symptoms (PTSS) and posttraumatic growth (PTG) are common co-occurring psychological responses following exposure to traumatic events (such as the COVID-19 pandemic), and their mutual relationship remains unclear. This study aimed to explore this relationship from a neuroscience perspective by examining the shared and/or distinct brain structural markers between PTSS and PTG. Structural magnetic resonance imaging scans were performed on 115 general college students before the COVID-19 pandemic, and follow-up PTSS and PTG measurements were collected during the period of community-level outbreaks. Behavioral correlation analyses found no significant relationship between PTSS and PTG. Importantly, whole-brain correlation analysis and predictive analysis revealed that higher PTSS was positively associated with increased gray matter volume (GMV) in the medial prefrontal cortex/dorsal anterior cingulate cortex; in contrast, higher PTG was negatively associated with decreased GMV in the left dorsolateral prefrontal cortex; these findings persisted even when controlling for each other (i.e., PTG/PTSS). This study advances our understanding of the neurobiological basis of PTSS and PTG, and suggests that they are be distinct psychological constructs with different neuroanatomical features. This may have implications for targeted brain interventions to reduce PTSS and increase PTG during life-stressful events.

Keywords: COVID-19, posttraumatic stress symptoms, posttraumatic growth, voxel-based morphometry, prefrontal cortex.

Introduction

The COVID-19 pandemic has been a serious global health emergency with a profound impact on public mental health (Holmes et al., 2020; Pfefferbaum & North, 2020; T. Wu et al., 2021). It can be considered a traumatic 'event' implying a threat of death or severe injury and evokes many psychological reactions, such as fear, anxiety and depression (Murata et al., 2021; Shanahan et al., 2022). As a common and negative psychological reaction following the pandemic (Vindegaard & Benros, 2020), posttraumatic stress symptoms/disorder (PTSS/PTSD) is characterized by intrusions, avoidance, hyperarousal and emotional numbing (*Diagnostic and Statistical Manual of Mental Disorders: DSM-5™, 5th ed*, 2013). There is increasing evidence of PTSS/PTSD not only in those facing higher levels of exposure to the disease, such as survivors of COVID-19 or healthcare workers (Carmassi et al., 2020; Tu et al., 2021), but also in the general population (Rossi et al., 2020; C. Wang et al., 2020), which has important implications for public mental health (Brooks et al., 2020). Nevertheless, similar to many other traumatic events, the COVID-19 pandemic can also lead to positive psychological reactions such as posttraumatic growth (PTG) (Chi et al., 2020; Mo et al., 2021), which refers to the experience of positive psychological change resulting from the struggle with challenging life crises or stressful events (Richard G. Tedeschi & Calhoun, 2004b).

Because PTSS and PTG often coexist in individuals experiencing trauma (Dekel, Ein-Dor, & Solomon, 2012; Pietrzak, Tsai, & Southwick, 2021; Z. Wu, Xu, & Sui, 2016; Zhen & Zhou, 2022), studies have attempted to elucidate the relationships between

them. These have yielded inconsistent and heterogeneous results: some studies report a positive correlation between PTG and PTSS (Groarke et al., 2017; Jin, Xu, & Liu, 2014; Solomon & Dekel, 2007), some a negative correlation (K. Wu, Zhang, Liu, Zhou, & Wei, 2015; Z. Wu et al., 2016), and others find no correlation (Cordova, Cunningham, Carlson, & Andrykowski, 2001; Shand, Cowlishaw, Brooker, Burney, & Ricciardelli, 2015; Wei, Han, Zhang, Hannak, & Liu, 2017); there is some evidence for an inverted "U" association, suggesting that there may be an optimal intermediate level of PTSS that strengthens PTG (Levine, Laufer, Hamama-Raz, Stein, & Solomon, 2008; Shakespeare-Finch & Lurie-Beck, 2014; Tsai, El-Gabalawy, Sledge, Southwick, & Pietrzak, 2015). These inconsistent findings may be caused by factors such as diverse sample characteristics, heterogeneity with regard to trauma type and severity, and different measurements and study methods (Chen et al., 2019; Marziliano, Tuman, & Moyer, 2020; Shakespeare-Finch & Lurie-Beck, 2014; Shand et al., 2015). A more general factor is the limited reproducibility of current psychological science (Nosek et al., 2022) and in particular the proneness of behavioral self-reported tests to methodological bias (Podsakoff, MacKenzie, Lee, & Podsakoff, 2003). Potential clarity may result from neuroscience approaches, in which brain data are used to explore the underlying neurobiological substrates of individual differences in human cognitions, affects and behaviors (Foulkes & Blakemore, 2018; Genon, Eickhoff, & Kharabian, 2022). We sought to elucidate the relationship of PTSS and PTG from a neuroscience perspective by examining the common and/or specific neuroanatomical markers, based on structural magnetic resonance imaging (SMRI), between PTSS and PTG related to

COVID-19 pandemic

Previous structural neuroimaging studies have offered insights into the neural mechanisms underlying PTSD/PTSS, implicating particularly prefrontal-limbic circuitry. Numerous meta-analyses of PTSD have found gray matter alterations in regions of prefrontal cortex (PFC) including the medial PFC (MPFC), anterior cingulate cortex (ACC) and superior frontal gyrus (SFG) (Bromis, Calem, Reinders, Williams, & Kempton, 2018; Kühn & Gallinat, 2013; Li et al., 2014; Li, Zhang, et al., 2022; Meng et al., 2016; Serra-Blasco et al., 2021). Also reported in PTSD are abnormalities of limbic structures, such as smaller volume in hippocampus and amygdala (Bromis et al., 2018; Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005; Logue et al., 2018). Furthermore, these prefrontal-limbic structural alterations are predictive for differences and severity of PTSS among different populations (Balters et al., 2021; Carrion, Weems, Richert, Hoffman, & Reiss, 2010; Karl et al., 2006), suggesting that PTSS may be a nonclinical manifestation of PTSD.

The neuroanatomy of PTG is less well studied. To our knowledge, only one study has examined links with brain structure, finding that in individuals who experienced the East Japan Great Earthquake, PTG levels were positively associated with increased gray matter volume (GMV) in the right dorsolateral prefrontal cortex (DLPFC) relative to measurements made 3 months pre-earthquake (Nakagawa et al., 2016). A functional near-infrared spectroscopy study using an ‘emotional’ picture stimulus found that individuals with higher PTG showed increased activation in the left DLPFC (Wei, Han, Zhang, Hannak, Dai, et al., 2017). A resting-state functional magnetic resonance

imaging study based on independent component analysis reported a positive association of PTG with the DLPFC spontaneous activity (Fujisawa et al., 2015).

We performed SMRI scanning on each participant before the COVID-19 pandemic, and then collected the COVID-related PTSS and PTG data after the onset of epidemic outbreak. An optimized and standardized voxel-based morphometry (VBM) approach was employed to estimate regional GMV (Ashburner & Friston, 2000), a well-validated and popular parameter characterizing the gray matter morphology, which has been widely used to investigate the neurobiological bases of human cognitions, affects, personalities and behaviors (Kanai & Rees, 2011; X. Liu et al., 2021; Pan et al., 2021). First, behavioral correlation analyses were conducted to explore the relations between PTSS and PTG during the COVID-19 pandemic. Then whole-brain correlation analyses and prediction analyses were performed to identify the brain regions whose GMV linked with PTSS and PTG respectively. Considering the literature, we hypothesised that PTSS would be linked with GMV in the prefrontal-limbic brain regions (e.g., MPFC, ACC, SFG, hippocampus and amygdala), while DLPFC volume might predict individual differences in PTG. Because no study has yet examined the neural link between PTSS and PTG, our conjunction analyses were exploratory.

Methods

Participants

A total of 151 general individuals who had no history of psychiatric or neurological diseases were recruited from a larger project aimed at investigating the neuropsychology of personality and mental health (Lai et al., 2022; Suo et al., 2022).

These participants had completed pre-pandemic brain scanning from October 2019 to January 2020 (T1, prior to the declaration of emergency state and nationwide lockdown in China). All participants were re-contacted for the second stage of posttraumatic behavioral evaluations during the initial outbreak and the peak from February to April 2020 (T2, the most severe pandemic period in China), and 127 participants responded and completed the examinations. Among them, 12 participants were excluded for failing to pass the bogus items that are either obvious or ridiculous. Thus, 115 participants (66 females, mean age = 22.37, standard deviation = 2.08) were included in the subsequent data analyses. Notably, no participants tested positive on COVID-19 PCR testing at T2. The study protocol was approved by the local research ethics committee of West China Hospital of Sichuan University and written informed consent was obtained from each participant for each stage in accordance with the Declaration of Helsinki.

Behavioral measures

Impact of Event Scale-Revised (IES-R). To evaluate individuals' levels of PTSS we used the IES-R, a widely used instrument for assessing subjective distress caused by traumatic events (Creamer, Bell, & Failla, 2003). The IES-R contains 22 items and three subscales (8 items for intrusions, 8 for avoidance, and 6 for hyperarousal). Each participant was asked to identify a specific stressful life event (in this case the COVID-19 pandemic) and indicate how much they were distressed or bothered by each difficulty listed. Items are rated on a 5-point Likert scale ranging from 1 ("not at all") to 5 ("extremely"), with a higher score representing more severe PTSS. The Chinese

version of the IES-R has been well-validated and widely used for investigating pandemic-specific PTSS (Peng et al., 2020; C. Wang et al., 2020). In the present sample, Cronbach's α for IES-R was 0.89, indicating satisfactory internal reliability.

Post-traumatic Growth Inventory (PTGI). To measure individual differences in PTG we adopted the Chinese version (Ho, Chan, & Ho, 2004) of PTGI (R. G. Tedeschi & Calhoun, 1996). The PTGI is a multidimensional measurement with 21 items across 5 aspects, including new possibilities (5 items), relating to others (7 items), personal strength (4 items), spiritual change (2 items), and appreciation of life (3 items), and uses a 6-point Likert scale with response format ranging from 1 to 6. The total score of all items represents the PTGI score, a higher score indicating a higher level of PTG. The Chinese version of the PTGI exhibits good reliability and validity for assessing PTG related to COVID-19 (Li, Mao, et al., 2022; Yan et al., 2021). In the present sample Cronbach's α for PTGI was 0.97, indicating excellent internal reliability .

MRI data acquisition and preprocessing

Data acquisition. The SMRI data was acquired using a 3.0 T Siemens-Trio Erlangen scanner with a 12-channel head coil. High-resolution T1-weighted anatomical images were obtained by a rapid gradient-echo planar imaging sequence with the following parameters: 176 slices, voxel size 1 × 1 × 1 mm^3, matrix size 256 × 256, slice thickness 1 mm, flip angle 9 degrees, inversion time 900 ms, repetition time 1900 ms, echo time 2.26 ms.

Data preprocessing. Image preprocessing was performed in MATLAB (r2013b) using the automated Computational Anatomy Toolbox (CAT12, http://dbm. neuro.uni-

jena.de/cat12/) based on Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neuroscience, London, UK). Images were reoriented to the anterior commissure in SPM12 for better registration, then segmented into gray matter, white matter, cerebrospinal fluid probability maps and background using the ICBM Tissue Probabilistic Atlases in SPM12. Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) in SPM12 was used to perform morphological and anatomical registration, normalization, and modulation analysis (Ashburner, 2007). Gray matter images were aligned and resampled to 1.5 × 1.5 × 1.5 mm^3 and then normalized to Montreal Neurological Institute (MNI152) space; the inverse Jacobian matrix of the local transformation was used to modulate the segmented gray matter to retain the volume measurement. Finally, an 8-mm full-width at half-maximum Gaussian kernel was used to smooth the modulated GMV images.

Statistical analyses

Behavioral analyses. Using the IBM SPSS Statistics 22.0, descriptive statistics and bivariate correlation coefficients were calculated for study measures, and independent samples t-tests were conducted to examine the sex differences.

GMV-behavior correlation analyses. Whole-brain voxel-wise correlation analyses were performed to explore brain areas in which GMV was associated with PTSS and PTG. The IES-R or PTGI scores were considered the variable of interest and age, sex and total intracranial volume (TIV) controlling variables. An absolute threshold masking of 0.2 was applied to remove the edge effect near the gray and white matter boundaries. The Gaussian random field approach was used to determine the regions of

significance (Worsley, Evans, Marrett, & Neelin, 1992), taking a threshold of $p < 0.001$ at the voxel level and $p < 0.05$ at the cluster level, which is a reliable correction method for VBM data (Qiu et al., 2018; S. Wang et al., 2020).

Prediction analyses. The robustness of the association between PTSS/PTG and identified GMV was assessed using a balanced four-fold cross-validation procedure using a machine learning method (Evans et al., 2015; Lai, Wang, Zhao, Qiu, & Gong, 2020; Supekar et al., 2013). GMV data of the significant regions obtained from the whole-brain correlation analysis were extracted, then randomly divided into four subsets. A linear regression model using the data of three subsets was used to predict the fourth. Specifically, GMV of the identified cluster was entered into the linear regression model that predicted the PTSS/PTG scores to evaluate predictive ability by correlations of the predicted values with the observed values, $r_{(\text{predicted, observed})}$. Repeating this for the four different set choices yielded the mean value $r_{\text{final (predicted, observed)}}$. To check its statistical significance an established nonparametric testing procedure in MATLAB (r2013b) was conducted by generating 5000 surrogate datasets (Lai et al., 2020; Wang et al., 2018).

Results

Behavioral characteristics of PTSS and PTG during the pandemic

Table 1 shows the descriptive statistics of the study measures. There were no sex differences in PTSS ($t [113] = 1.20$, $p = 0.232$) or PTG ($t [113] = 0.05$, $p = 0.962$). Participants' age was negatively correlated with PTG ($r = -0.20$, $p = 0.029$), but not with PTSS ($r = -0.02$, $p = 0.821$). TIV was not correlated with PTG ($r = -0.06$, $p = 0.504$) or

PTSS (r = -0.10, p = 0.283). Importantly, we observed no significant association between PTSS and PTG (r = 0.10, p = 0.292), or after adjusting for sex, age and TIV (r = 0.10, p = 0.311).

Brain structures related to PTSS and PTG during the pandemic

In whole-brain correlation analysis, after controlling for sex, age and TIV, PTSS was positively associated with GMV in the left MPFC extending to dorsal ACC (MPFC/dACC; r = 0.34, p < 0.001; **Table 2 and Figure 1**); PTG was negatively associated with GMV in the left DLPFC (from middle frontal gyrus extending to superior frontal gyrus; r = -0.36, p < 0.001; **Table 2 and Figure 2**).

Checking the robustness of these relationships, PTSS was stably predicted by GMV of the left MPFC/dACC [$r_{(predicted, observed)}$ = 0.31, p < 0.001]; PTG was stably predicted by GMV of the left DLPFC [$r_{(predicted, observed)}$ = 0.32, p < 0.001], after adjusting for sex, age and TIV.

To check their specificity, including PTG as an additional controlling variable, PTSS was still associated with GMV in the left MPFC/dACC (r = 0.34, p < 0.001; **Table 2**); including PTSS as an additional controlling variable, PTG was still associated with GMV in the left DLPFC (r = -0.36, p < 0.001; **Table 2**). Adjusting for PTG as well as sex, age and TIV, PTSS was still stably predicted by GMV in the left MPFC/dACC [$r_{(predicted, observed)}$ = 0.31, p < 0.001]; adjusting for PTSS, sex, age and TIV, PTG was still stably predicted by GMV in the left DLPFC [$r_{(predicted, observed)}$ = 0.32, p < 0.001].

Discussion

This prospective study investigated the relation between PTSS and PTG in the circumstances of the COVID-19 pandemic from the neuroanatomical perspective. Behaviorally, there was no significant association between PTSS and PTG. Neuroanatomically, higher PTSS was positively associated with increased GMV in the left MPFC/dACC, while higher PTG was negatively associated with decreased GMV in the left DLPFC; and each of these findings remained unchanged when controlling for the other. Our study is the first to point out that PTSS and PTG are related to, and thus presumably supported, by distinct brain structures; they seem to be relatively independent psychological constructs with different underlying neurobiology. We now discuss the implications in more detail.

The lack of behavioral association between PTSS and PTG fits with previous findings (Cordova et al., 2001; Shand et al., 2015). This relationship is known to be affected by factors such as trauma exposure levels, trauma type and age (A. N. Liu, Wang, Li, Gong, & Liu, 2017; Shakespeare-Finch & Lurie-Beck, 2014; Shand et al., 2015); for example, compared to higher levels of trauma exposure, a lower level may weaken the association of PTSS and PTG (Wei, Han, Zhang, Hannak, & Liu, 2017), which may be why it is stronger in survivors of natural disaster than in health professionals who assist trauma survivors (Shakespeare-Finch & Lurie-Beck, 2014); furthermore the association of PTSS and PTG is stronger in children than in adults (Shakespeare-Finch & Lurie-Beck, 2014). Note that our participants were healthy young adults and their trauma exposure levels were relatively low.

The positive association between PTSS and GMV in left MPFC/dACC is consistent

with studies showing increased GMV (Zhang, Zhang, Wang, & Zhang, 2018) and cortical thickness (Li, Zhang, et al., 2022) of the MPFC/dACC in PTSD patients in relative to healthy controls. As a core component of the default-mode network, MPFC/dACC is related to self-referential processing, inhibition control, and top-down emotion regulation (Alexandra Kredlow, Fenster, Laurent, Ressler, & Phelps, 2022; Patel, Spreng, Shin, & Girard, 2012). Neurocircuitry models of PTSD posit that MPFC/dACC fails to inhibit the amygdala, resulting in attentional bias to threats, increased fear responses and deficits in top-down emotion regulation (Elzinga & Bremner, 2002; Rauch, Shin, & Phelps, 2006). Functional neuroimaging studies in PTSS find *increased* activation in the MPFC/dACC during relevant tasks, suggesting a failing attempt at compensatory suppression of adverse emotional responses (Carrion, Garrett, Menon, Weems, & Reiss, 2008; Garrett et al., 2012), and our positive correlation between PTSS and left MPFC/dACC GMV may be the structural manifestation of this (Herringa, Phillips, Fournier, Kronhaus, & Germain, 2013; Jeong et al., 2021).

The negative association between PTG and GMV in left DLPFC is consistent with studies showing an association of PTG with alteration in DLPFC structure (Nakagawa et al., 2016) and function (Fujisawa et al., 2015; Wei, Han, Zhang, Hannak, Dai, et al., 2017). The DLPFC sends afferent projections to subcortical structures such as striatum, hippocampus and amygdala, and is involved in higher-order cognitive processes such as conscious decision-making and cognitive control, as well as emotional regulation (Badre & Wagner, 2004; Kanske, Heissler, Schönfelder, Bongers, & Wessa, 2011;

Krawczyk, 2002; MacDonald, Cohen, Stenger, & Carter, 2000). This aligns with the neurocircuitry model of PTG, which highlights the role of higher-order cognitive processing in individuals struggling with challenging life circumstances (Richard G. Tedeschi & Calhoun, 2004a). Lower PTSD symptom severity and better recovery and resilience have been linked with DLPFC activation and morphology (Aupperle et al., 2012; Lyoo et al., 2011). Repetitive transcranial magnetic stimulation of left DLPFC decreases core PTSD symptoms (avoidance and re-experiencing) and benefits mood (Boggio et al., 2010). If the DLPFC is indeed involved in positive psychological changes in individuals experiencing trauma, the negative association between between PTG and left DLPFC GMV may reflect increased myelination and synaptic pruning (Paus, 2005; Sowell, Thompson, Tessner, & Toga, 2001). This is supported by reports that the volume of left DLPFC is negatively correlated with positive psychological constructs such as 'grit' personality (Wang et al., 2018), social well-being (Kong, Hu, Xue, Song, & Liu, 2015) and elevation tendency (G. Liu et al., 2018).

Our research has several limitations. First, the subjects are normal young adults, so the results are not necessarily applicable to other populations such as children and elderly, and individuals directly exposed to the pandemic (e.g. frontline healthcare workers, or COVID-19 patients). Second, we only performed MRI scan and behavioral measures once before and during the pandemic. A longitudinal design with brain and behavioral measurements at multiple time points will be needed to test and extend our results. Third, we adopted the single index of the GMV as the measure of brain structure in the present study, and identified only one cortical region related to PTSS and PTG

respectively. Future research may explore the relationship more fully using other structural approaches (e.g. cortical surface area and cortical thickness) combined with functional methods (e.g. resting-state functional activity and connectivity).

Conclusions

In conclusion, this prospective study demonstrates that the pre-pandemic brain gray matter structures can distinguish COVID-related PTSS and PTG after the onset of the pandemic, revealing that higher PTSS is linked to larger GMV in the left MPFC/dACC, while higher PTG is linked to smaller GMV in the left DLPFC. These findings advance our understanding of the neurobiological basis of PTSS and PTG, and help to elucidate their relationship. They may also be valuable in suggesting potential brain regions for targeted interventions such as transcranial direct current stimulation (Valero-Cabré, Amengual, Stengel, Pascual-Leone, & Coubard, 2017) aimed at decreasing PTSS and increasing PTG in individuals experiencing major trauma events.

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Figure legends

Figure 1. Regional GMV related to PTSS. (A) Brain image showing that PTSS is positively linked with GMV in the left MPFC after adjusting for sex, age and TIV. (B) Scatter plots showing the correlation between PTSS and left MPFC volume. Abbreviations: GMV, gray matter volume; MPFC, medial prefrontal cortex; PTSS, post-traumatic stress symptoms

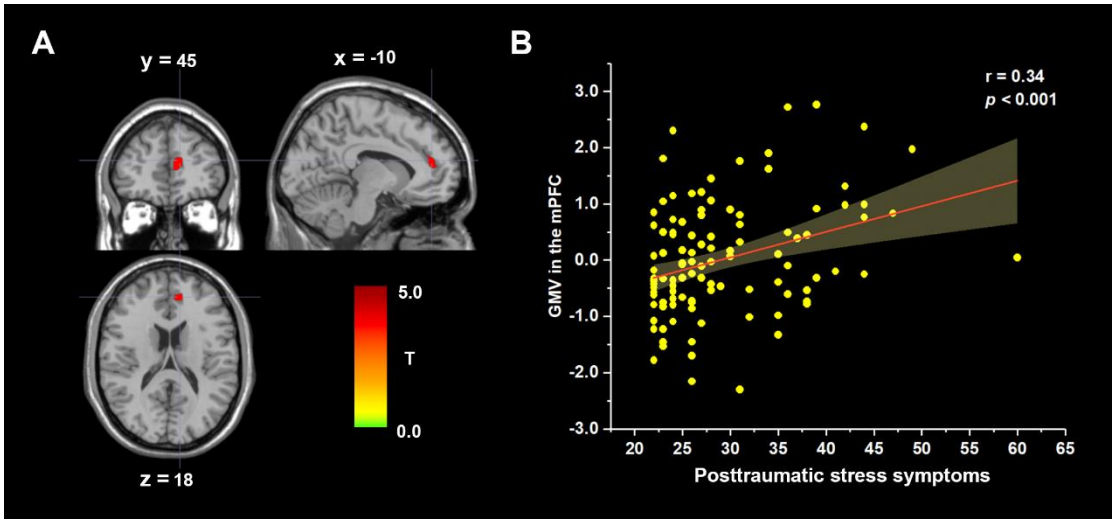

Figure 2. Regional GMV related to PTG. (A) Brain image showing that PTG is negatively linked with GMV in the left DLPFC after adjusting for sex, age and TIV. (B) Scatter plots depicting the correlation between PTG and left DLPFC volume. Abbreviations: DLPFC, dorsolateral prefrontal cortex; GMV, gray matter volume; PTG, post-traumatic growth.

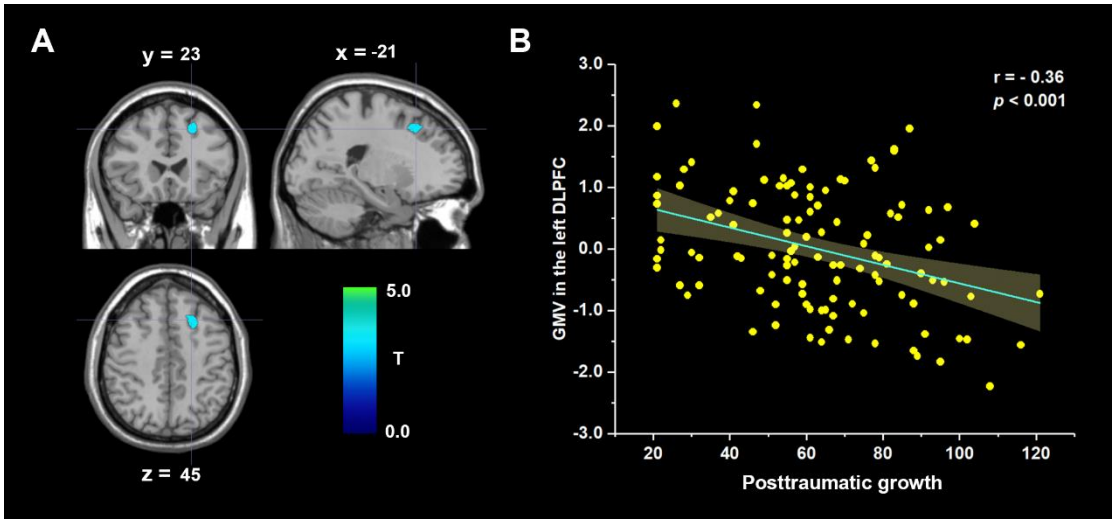

Table 1. Study variables (N =115; 66 female, 49 male)

Variable	Mean	SD	Minimum	Maximum
Age (y)	22.4	2.1	19	27
TIV (ml)	1478	123	1251	1778
PTSS	28.9	7.3	22	60
PTG	62.8	23.3	21	121

Abbreviations: N = number; PTSS = post-traumatic stress symptoms; PTG = post-traumatic growth; TIV = total intracranial volume.

Table 2. Brain regions where gray matter volume is significantly related to PTSS and PTG

Posttraumatic response	Controlling variables	Brain region	No. of voxels	BA	Peak t score	Peak MNI coordinates		
						X	Y	Z
PTSS	Age, sex and TIV	Left MPFC	203	BA6/32	3.75	-10	45	18
	Age, sex, TIV and PTG	Left MPFC	222	BA6/32	3.76	-11	45	18
PTG	Age, sex and TIV	Left DLPFC	248	BA8/9	- 4.31	-21	23	45
	Age, sex, TIV and PTSS	Left DLPFC	234	BA8/9	- 4.27	-21	23	45

Abbreviations: BA, Brodmann area; DLPFC, dorsolateral prefrontal cortex; MPFC, medial prefrontal cortex; MNI, Montreal Neurological Institute; PTG, post-traumatic growth; PTSS, post-traumatic stress symptoms; TIV, total intracranial volume.