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Social support modulates the association between PTSD diagnosis and medial frontal volume in Chinese adults who lost their only child

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ABSTRACT

Losing an only child is a devastating life event that a parent can experience and may lead to post-traumatic stress disorder (PTSD). Social support could buffer against the negative influence of this trauma, but the neural mechanism underlying this alleviation effect remains poorly understood. In this study, voxel-based morphometry was conducted on brain MRI of 220 Han Chinese adults who had lost their only child. We performed multiple regression analysis to investigate the associations between social support scores – along with PTSD diagnosis, age, sex, body mass index (BMI) – and brain grey matter (GM) volumes in these bereaved parents. For all trauma-exposed adults, social support-by-diagnosis interaction was significantly associated with medial prefrontal volume (multiple comparisons corrected $P < 0.05$), where positive correlation was found in adults with PTSD but not in those without PTSD. Besides, PTSD diagnosis was associated with decreased GM volume in medial and middle frontal gyri ($P < 0.001$, uncorrected); older age was associated with widespread GM volume deficits; male sex was associated with lower GM volume in rolandic operculum, insular, postcentral gyrus (corrected $P < 0.05$), and lower GM in thalamus but greater GM in parahippocampus ($P < 0.001$, uncorrected); higher BMI was associated with GM deficits in occipital gyrus (corrected $P < 0.05$) and precuneus ($P < 0.001$, uncorrected). In conclusions, social support modulates the association between PTSD diagnosis and medial frontal volume, which may play an important role in the emotional disturbance in PTSD development in adults who lost their only child.

1. Introduction

The death of a child – especially an only child – is a devastating life event that a parent may experience, which can cause pronounced psychological consequences, including long-term grief, anxiety, depression, and post-traumatic stress disorder (PTSD) (Song, 2014; Wei et al., 2016; Zheng et al., 2017). In China, as implementation of the 'One-Child Policy' had lasted more than 30 years (Basten and Jiang, 2014; Hesketh et al., 2005) – the number of parents who lost their only child at a time when they were aged and unable to have another was more than 1 million (Song, 2014; Zheng et al., 2017). Losing one's only child has become a significant public health concern as well as a major challenge for those childless families (Song, 2014; Wei et al., 2016; Zheng et al., 2017).

Social support plays an important role in maintaining one's physical and mental health (Sherman et al., 2016), and these protective effects have been termed as a 'buffering model' (Cohen and Hoberman, 1983; Dean and Lin, 1977). There is consistent evidence showing that social support could help in relieving psychological and emotional burdens in bereaved parents (Bartone et al., 2019; Thuen, 1997; Zheng et al., 2017). The beneficial effects of social support have been reported to be at least partially mediated by the neuropeptides oxytocin and

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vasopressin, which may inhibit the hypothalamic-pituitary-adrenal axis (HPA axis, an important pathway for stress response) reactivity to stress, and also promote social behavior (Olff, 2012; Ozbay et al., 2008). Thuen et al. (Thuen, 1997) demonstrated that the support from neighbors and professionally trained healthcare providers was associated with better psychological adaptation in parents whose infant child had died. Also, peer support was found to be helpful to bereaved parents in terms of validating the normalcy of their reactions, reducing grief symptoms, and increasing well-being and positive meaning in life (Bartone et al., 2019). Lack of social support has been considered as one of the risk factors of PTSD development (Brewin et al., 2000; Trickey et al., 2012). However, the underlying neural substrates of social support on the mental health of these bereaved parents remain poorly understood.

One way to explore the mechanism by which social support influences the mental health of trauma-exposed subjects is to examine its modulatory effect on the brain. Neuroimaging evidence suggests that high social support is associated with less threat-related neural activation in the anterior cingulate cortex, posterior cingulate, supramarginal gyrus, and postcentral gyrus (Coan et al., 2006) – regions involved in emotional and behavioral threat responses. High levels of social support are also associated with greater grey matter volume in the frontal gyrus and hippocampus (Holz et al., 2020) – regions which inhibit HPA axis, while also presenting mixed findings of volume (greater (Sato et al., 2016) or smaller (Sherman et al., 2016)) in the amygdala which excites the HPA axis. However, to the best of our knowledge, there are currently no neuroimaging studies that have directly investigated the neurological impact of social support on the brain of trauma-exposed subjects.

In this cross-sectional study, we conducted a voxel-based morphometry (VBM) analysis to investigate the association between social support and brain structure in Han Chinese adults who had lost their only child. A voxel-wise multiple regression statistical model was used to determine the association of social support with regional grey matter (GM) volume differences. PTSD diagnosis, age, sex, body mass index (BMI) were also input into this general linear model, as all these variances have been previously reported to be related to GM changes (Ritchie et al., 2018; Sekiguchi et al., 2013; Takahashi et al., 2011). Similar analyses have been performed in previous neuroimaging studies (Klabunde et al., 2017; Liu et al., 2018), including in our prior publications (Ho et al., 2010; Raji et al., 2010). Besides, recent findings have demonstrated that lack of social support (Brewin et al., 2000; Trickey et al., 2012) and being female (Brewin et al., 2000; Tang et al., 2017; Trickey et al., 2012) are factors which increase the risk of PTSD development. They may modulate structural brain changes in PTSD, and thus we further included the social support-by-PTSD diagnosis and sex-by-PTSD diagnosis interactions in the model (Klabunde et al., 2017). We hypothesized that social support may be positively associated with greater regional GM volumes – especially for the prefrontal-amygdala pathway, where abnormalities are related to dysfunctions of emotional processing or cognitive control in contemporary PTSD model (Etkin and Wager, 2007; Hayes et al., 2012) – in adults who suffered the loss of their only child. As for the PTSD model, converging evidence has suggested prefrontal-limbic imbalance along with a hypoactive (prefrontal) – hyperactive (limbic) gradient in PTSD patients (Etkin and Wager, 2007). Also, the cognitive-affective imbalance theory (Hayes et al., 2012; Morey et al., 2008) was propounded, where brain executive system (experiencing under-activated) and emotional processing system (experiencing over-activated) are differentially affected by PTSD.

2. Material and methods

2.1. Participants

All participants in this study provided written informed consent. This study was approved by the Medical Research Ethics Committee of Jiangsu University. Between September 2016 and March 2017, a PTSD survey was conducted in Jiangsu Province, China, for Han Chinese adults who had experienced the loss of an only child. A total of 334 adults who have lost their only child were initially contacted by telephone. However, not all were able to participate in this study, the main reasons for that being: no response, refusal to participate, and travel inconveniences due to working or living in other places. Eventually, 237 participants who lost their only child – and not found to have other major traumatic exposures – were successfully interviewed and screened with the clinician-administered PTSD scale (CAPS). For all 237 adults, the causes of death of their only child were summarized as follows: traffic accident, n = 71; malignant tumors, n = 37; suicide, n = 23; other reasons/unprovided causes, n = 106. We performed a structured clinical interview for DSM-IV (SCID) (First et al., 2002) to confirm the diagnoses of PTSD and other potential psychiatric comorbidities. Participants who were diagnosed with other psychiatric disorders but did not meet criteria for PTSD were then excluded from the present study. Out of all 237 bereaved adults, 57 were diagnosed with PTSD (19 of 57 PTSD adults had comorbid major depressive disorder [MDD], 3 had comorbid generalized anxiety disorder [GAD], and one was comorbid for both MDD and GAD.); 10 were diagnosed with other psychiatric disorders (major depression, n = 5; generalized anxiety disorder, n = 4; both depression and anxiety, n = 1) and were ruled out from this study; while the remaining 170 adults did not meet diagnostic criteria for any mental illness. The prevalence of PTSD in this surveyed sample was 24.1%, which is very close to the finding of a recent study in Chinese bereaved parents (reported PTSD prevalence = 23.78%) (Wang et al., 2019b).

Exclusion criteria for the following high-resolution MRI head scans were as follows: any current or history of brain injury or other major medical or neurological conditions (being excluded for having cerebral infarction or ischemia, n = 4; having a history of major depressive disorder and underwent antidepressant drug therapy, n = 1); MRI contraindication (n = 0); and left-handedness (n = 0).

2.2. Measures

The Chinese Social Support Rating Scale (SSRS) – developed by Prof. Shuiyuan Xiao (Xiao and Yang, 1987) from XiangYa School of Public Health, Central South University, Changsha – was applied in this study to assess the social support level for these bereaved parents. The SSRS has been widely successful in its application on participants within the Chinese population (Ma et al., 2011; Xu and Ou, 2014) and proven to have high reliability and validity (Xiao and Yang, 1987). This rating scale examines three dimensions of social support: (1) subjective support (which refers to the perceived interpersonal network that a person can rely on, such as: “Most of my colleagues care about me”); (2) objective support (which refers to the actual support that a person gained, such as: “I often live with my family members”); and (3) the utility of support (the pattern of behavior that a person utilized when seeking support, such as: “I often seek assistance proactively when I have some difficulties”). The total social support score is calculated as the sum of all three dimensions of support (ranging from 12 to 66), where higher total scores indicate stronger social support. In addition to that, each bereaved adult was also assessed using Hamilton Depression (HAMD) (Hamilton, 1960) and Hamilton Anxiety (HAMA) (Hamilton, 1959) rating scales.

2.3. MRI data acquisition

High-resolution structural MRI data were acquired on a 3.0T Philips MR scanner (Achieva 3.0 TTX; Amsterdam, the Netherlands). Foam pads were applied to minimize head motion during image acquisition. Three-dimensional T_1-weighted structural brain images were acquired in the sagittal orientation using the turbo fast echo (3D-T_1TFE)

sequence: repetition time (msec)/echo time (msec) = 9.7/4.6; flip angle = 9°; matrix size = 256 × 256; field of view = 256 × 256 mm^2; slice thickness = 1 mm; number of slices = 160.

2.4. Data preprocessing

T_1-weighted structural brain images were preprocessed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm) and the voxel-based morphometry (VBM) toolbox CAT12 (http://dbm.neuro.uni-jena.de/cat12/). We applied most default parameters just as stated in the CAT12 manual, with the exception that in the template option we used affine regularization with the International Consortium for Brain Mapping template for East Asian brains (Liu et al., 2019). The structural images were then bias-field-corrected, tissue-classified, and spatially normalized using the DARTEL algorithm. The images were subsequently segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF). The tissue deformations were performed to modulate participants' segmented GM images. Finally, the normalized and modulated GM images were smoothed using a Gaussian filter (8 mm full width at half maximum, FWHM).

2.5. Quality control

All segmented GM images were visually checked for artifacts. Also, before image preprocessing, a weighted imaging quality rating (IQR) – an index that takes image resolution, noise, and bias into account – was automatically computed by CAT12 for each participant. The weighted IQR of all individuals in this study was good–excellent (individual procentaged rating point > 80) according to the quality assurance criterion of CAT12 (http://www.neuro.uni-jena.de/cat/). After the image preprocessing, the mean correlation – calculating the mean overall correlation value between one data with all other data – was assessed to check the homogeneity of the segmented GM tissues. Two participants were excluded as outliers for having mean correlation values below 2 standard deviations. Thus, the smoothed GM maps of the remaining 220 adults (PTSD, n = 57; non-PTSD, n = 163) were used for the final statistical analysis (Table 1).

2.6. Statistical analysis

The demographic data were analyzed with SPSS, version 25 (IBM Corp, Armonk, NY, USA). For GM data, similar to previous studies (Ho et al., 2010; Klabunde et al., 2017; Raji et al., 2010), a voxel-wise multiple regression analysis was performed using SPM12 to explore the association of social support score – along with diagnosis, age, sex (male vs. female), BMI, social support × diagnosis interaction, and sex × diagnosis interaction – with brain GM volumes. Total intracranial volume (TIV), educational level, and time duration since losing the child were included in this multiple regression model as confounding variables to adjust for their effects. To better understand how the associations between different variables and GM volume differences were distributed in PTSD and non-PTSD groups separately, the same multiple regression model – except for having no variables of diagnosis or interactions – was conducted after dividing participants into the diagnostic groups of PTSD and non-PTSD. Besides, we used the SSRS subscale instead of total SSRS in the same multiple regression model to further examine the associations between GM volume and each of the SRRS scales. All results were corrected by using a Gaussian random field (GRF) (Worsley et al., 2004) cluster level threshold of $P < 0.05$, which corresponded to a voxel-wise $P < 0.001$ and cluster-wise $P < 0.05$. To show the results more comprehensively, we also displayed the results thresholded at a more liberal threshold of $P < 0.001$, uncorrected (defined as results which survived the height threshold of voxel-wise $P < 0.001$ but not the extent threshold of cluster-wise $P < 0.05$), and at a more stringent standard for multiple testing correction by applying a voxel-wise false discovery rate (FDR) correction at $P < 0.05$ (see detailed results in the online **Supplementary Material**).

Table 1
Demographics of Han Chinese adults who lost an only child.

Protocols	Adults with PTSD (n = 57)	Adults without PTSD (n = 163)	*P* value
Age (± SD), y	57.57 ± 5.48	58.87 ± 5.53	0.13[a]
Sex (F/M)	40/17	72/91	0.001[b]
Education, y	6.42 ± 4.12	6.70 ± 3.54	0.63[a]
SSRS_total	39.81 ± 7.27	39.90 ± 6.49	0.93[a]
Objective support	12.53 ± 2.77	12.74 ± 2.64	0.61[a]
Subjective support	21.58 ± 3.95	21.64 ± 3.88	0.92[a]
Utility of support	5.70 ± 2.04	5.53 ± 1.92	0.56[a]
BMI	24.34 ± 2.44	24.24 ± 2.89	0.80
HAMD	15.93 ± 6.61	5.89 ± 4.23	<0.001[a]
HAMA	12.65 ± 6.52	4.56 ± 3.42	<0.001[a]
Duration since trauma, month	59.35 ± 48.44	108.15 ± 71.38	< 0.001[a]
CAPS_total	47.65 ± 12.84	16.14 ± 9.96	<0.001[a]

Values are expressed as mean ± SD. PTSD = post-traumatic stress disorder; SSRS = social support rating scale; BMI = body mass index; HAMD = Hamilton Depression; HAMA = Hamilton Anxiety; CAPS = clinician-administered PTSD scale.
[a] The *P* value for the difference between the two trauma-exposed groups was obtained by two-sample *t*-test.
[b] The *P* value for gender distribution between the two trauma-exposed groups was obtained by the chi-square test.

3. Results

3.1. Sample demographics

There were no significant differences between PTSD and non-PTSD groups in social support scores (total or subscales), age, or educational level (all $P > 0.05$). However, the PTSD group showed higher CAPS, HAMA and HAMD scores, lower male to female ratio, and shorter time duration since losing the child, relative to the non-PTSD group (Table 1).

3.2. Imaging results

For the total social support score, in the combined group of all bereaved adults, support scale itself did not display significant association with GM volume. However, support-by-diagnosis interaction was significantly associated with medial prefrontal gyrus (MFG) volume (GRF corrected $P < 0.05$), where higher social support was associated with higher MFG volume in PTSD but not in the non-PTSD group (interaction *t* value = 2.22, *P* value = 0.03) (Fig. 1). Furthermore, when examining SSRS subscales, the associations between support subscale-by-diagnosis interaction and brain volume were significant in MFG for subjective support (GRF corrected $P < 0.05$), and in MFG for utility of support ($P = 0.0001$, uncorrected), but not found across the brain for objective support (Fig. 1). Results for other variables in the multiple regression model using SSRS subscales were almost the same as using the SSRS total scale (data not shown).

As for other variables, PTSD diagnosis was associated (survived the height threshold of multiple testing correction – $P < 0.001$, uncorrected) with lower GM volume in MFG ($P = 0.0009$, uncorrected) and right middle frontal cortex (MFC) ($P = 0.0008$, uncorrected); older age was significantly associated with widespread GM volume deficits in frontal, temporal, parietal, occipital lobes, and basal ganglia regions; males were found to have lower GM volume in bilateral rolandic operculum, insular, postcentral gyri (GRF corrected $P < 0.05$), and associated with lower GM volume in bilateral thalami (right thalamus, $P = 0.0008$, uncorrected; left thalamus, $P = 0.0009$, uncorrected) and MFG ($P = 0.0008$, uncorrected), but greater GM volume in bilateral parahippocampus ($P = 0.00001$ for both sides, uncorrected); higher

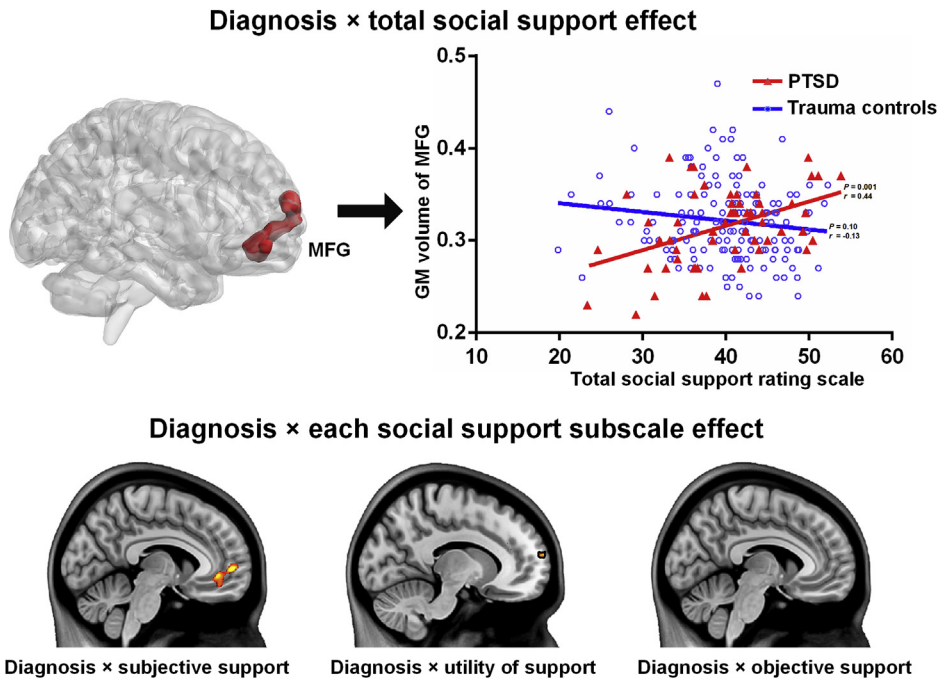

Fig. 1. Associations between social support-by-diagnosis and brain volume in all trauma-exposed adults (GRF corrected $P < 0.05$).
There is a significant association between social support × diagnosis interaction and MFG volume (GRF corrected $P < 0.05$). Subsequent correlation analyses show that higher social support is associated with higher MFG volume in PTSD but not in the non-PTSD group. When conducting the SSRS subscales, the associations between support subscale-by-diagnosis interaction and brain volume are significant in MFG for subjective support (GRF corrected $P < 0.05$), and in MFG for utility of support ($P = 0.0001$, uncorrected), but not found across the brain for objective support. Brain regions with a rim of black outline indicate results at an uncorrected threshold of $P < 0.001$.
GRF = Gaussian random field; MFG = medial prefrontal gyrus; PTSD = post-traumatic stress disorder.

BMI was significantly associated with GM deficits in left middle occipital gyrus (MOG) (GRF corrected $P < 0.05$), and associated with lower GM volume in left precuneus ($P = 0.0009$, uncorrected) and right MOG ($P = 0.0009$, uncorrected) (Fig. 2, Supplementary Table 1).

After conducting subsequent analyses separately in adults with and without PTSD, most of the findings of associations with age, sex, and BMI were replicated in both PTSD and non-PTSD groups, with the exception that the association of BMI only existed in the non-PTSD group (Fig. 3), and the association of social support was only found in the PTSD group (left MFG at x = −6, y = 54, z = 0; right middle/inferior frontal gyri at x = 42, y = 36, z = −1.5; left temporal lobe at x = −51, y = −15, z = 4.5) (Fig. 4). Besides, when thresholded at FDR $P < 0.05$, only the results for association of age and sex remained significant after multiple statistical comparisons correction in the combined sample of all trauma-exposed adults (**Supplementary Fig. 1**), **and in the divided non-PTSD group (Supplementary Fig. 2), but not in the PTSD group (the smaller sample size in PTSD group may account for the lower statistical power).**

4. Discussion

In this study, we found several important results relating social support – along with PTSD diagnosis, age, sex, and BMI – to brain structural changes in adults who had lost their only child. First, higher social support was associated with greater medial prefrontal volume in adults with PTSD but not in those without PTSD (support-by-diagnosis interaction). Second, PTSD diagnosis was associated with lower GM volume in medial and middle frontal gyri; older age was strongly associated with GM volume deficits throughout the brain; females were found to have greater volumes in rolandic operculum, postcentral gyrus, insular, thalamus, and MFG, but lower parahippocampal volume; and also, BMI was associated with brain volume deficits in middle occipital gyrus and precuneus.

4.1. Impact of social support on brain structure in trauma-exposed subjects

The most important finding in this study was the association between total social support-by-diagnosis interaction and brain volume of MFG, which was further supported by the results when PTSD and non-PTSD groups were analyzed separately. This is a new finding, which we believe has not been previously reported. There is growing evidence that demonstrates the important role of gene-by-environment interactions in the pathophysiology of PTSD (Klengel and Binder, 2015; Logue et al., 2015; Sharma and Ressler, 2019). It is generally believed that social support – an important environmental factor – can buffer the negative impact of stress (Cohen and Hoberman, 1983; Dean and Lin, 1977; Hostinar and Gunnar, 2015). High social support was reported to be associated with better quality of life (Xu and Ou, 2014), better cognitive status (Alpass et al., 2004), and less suicidal ideation (Wang et al., 2019a) in PTSD which resulted from a variety of traumatic events. A meta-analysis of risk factors for PTSD showed that the lack of social support had even stronger effects than pre-trauma factors (such as gender, race, and family psychiatric history) on PTSD (Brewin et al., 2000). Neuroimaging offers a sensitive means to explore the mechanism by which social support influences mental health in trauma-exposed subjects. In this study, although the total social support scores did not differ between PTSD and non-PTSD adults, lower social support scores were related to MFG volume deficits only in the PTSD group but not in non-PTSD group. These results suggest that the MFG volume alterations may depend on the interaction of PTSD and total social support, reflecting a possible biological correlate of PTSD symptomatology.

We also noted that within the result of support-by-diagnosis interaction, there was a subset of PTSD adults having both high total social support score and high MFG volume. This finding suggests that despite the protective role of social support, there might be other risk factors which hinder the buffering role of social support, and/or also lead to PTSD development (Breet et al., 2014). For instance, Lian et al. found that low social support under specific genotypes of the glucocorticoid receptor gene may increase the risk for PTSD (Lian et al., 2014). Also, prior twin and heritability studies have consistently demonstrated that at least one-third of the variance in PTSD risk is determined by genetic components (Sartor et al., 2011, 2012; Stein et al., 2002). Further studies – tests for social support × gene interaction effects on the brain in particular – are needed to clarify the combined influences of social support and other variables on PTSD.

As for social support subscales, the perceived support has been shown to be a more useful index, both mediating the impact of received support (Norris and Kaniasty, 1996) and playing an important role in complex PTSD (Simon et al., 2019). In this study, SSRS subscales (subjective/perceived support, objective/received support, and the

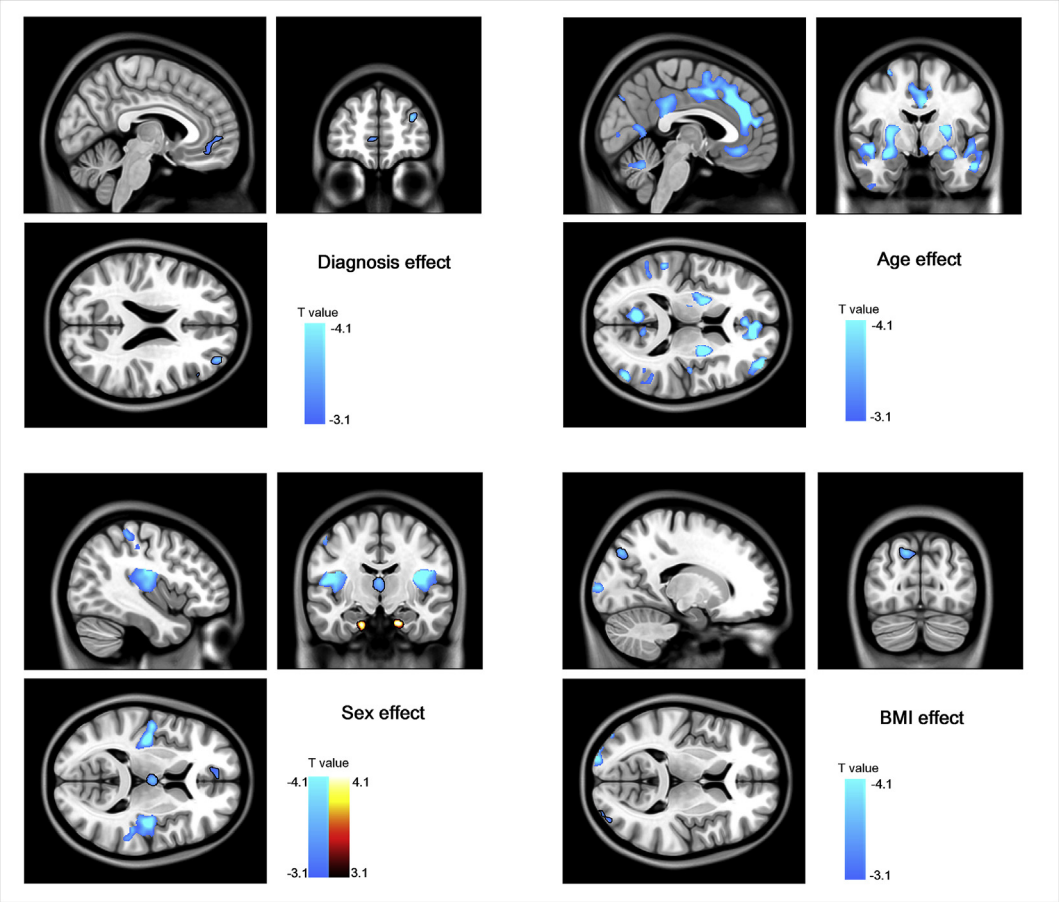

Fig. 2. Associations between PTSD diagnosis, age, sex, BMI and brain volume in all trauma-exposed adults (GRF corrected $P < 0.05$).
PTSD diagnosis is associated with lower GM volume in MFG and right MFC ($P < 0.001$, uncorrected); older age is significantly associated with widespread GM volume deficits; males are shown to have lower GM volume in bilateral rolandic operculum, insular, postcentral gyri, and associated with lower GM volume in bilateral thalami, MFG but greater GM volume in bilateral parahippocampus ($P < 0.001$, uncorrected); higher BMI was significantly associated with GM deficits in left MOG, and associated with lower GM volume in left precuneus and right MOG ($P < 0.001$, uncorrected). It should be noted that for sex effect, the negative association indicates lower values for males. Brain regions with a rim of black outline indicate results at an uncorrected threshold of $P < 0.001$. GRF = Gaussian random field; PTSD = post-traumatic stress disorder; GM = grey matter; MFG = medial prefrontal gyrus; MFC = middle frontal cortex; MOG = middle occipital gyrus; BMI = body mass index.

utility of support) – instead of total SSRS – were further evaluated in the same regression model. We found that subjective support significantly interacted with diagnosis in MFG, the utility of support also interacted with diagnosis in MFG, but objective support did not demonstrate interaction effects with diagnosis, suggesting that there may be meaningful distinction between actually received support and perceived support. Unlike the objective support, subjective support is more about the feeling of being supported. A previous study also showed that subjective support, and support utilization, were significantly associated with the recovery from prior PTSD, while objective support did not show such association (Dai et al., 2016). Taken together, our findings about social support may provide neuroimaging evidence into understanding the mechanisms of how social support (both total scale and subscale) modulates the association between PTSD development and brain structural deficits in Chinese adults who lost their only child, pointing to the need for providing interventions that may benefit these parents – especially in efforts which encourage PTSD adults to feel assured that help would be promptly provided when needed.

4.2. Influence of other variables on brain structure in trauma-exposed subjects

Many morphometric MRI studies have reported decreased prefrontal volume in PTSD (O'Doherty et al., 2017; Sekiguchi et al., 2013; Tavanti et al., 2012), which was also associated with high re-experiencing symptom (Tavanti et al., 2012), greater hyper-arousal (Weber et al., 2013), and worse executive function (Fennema-Notestine et al., 2002). All these findings support a neurocircuitry model, which proposes that the exaggerated responsiveness of the amygdala in PTSD might be secondary to a dysfunction in top-down regulation by the MFG (Etkin and Wager, 2007).

In this study, females showed greater GM volume in rolandic operculum, insular, postcentral gyrus, thalami, MFG, but lower parahippocampal volume; most of these findings are supported by prior studies (Cosgrove et al., 2007; Kang et al., 2017; Kaufmann et al., 2001; Ritchie et al., 2018). We noted that there is little consistency regarding the sex differences in volumes of hippocampus and parahippocampus, with studies showing either increases (Filipek et al., 1994; Szabó et al., 2003), decreases (Lotze et al., 2019; Ruigrok et al., 2014), or no differences (Perlaki et al., 2014; Tan et al., 2016) in females compared to males. Heterogeneous study populations and differing approaches for structural segmentation may contribute to the mixed results. Also, race-related differences in brain shape, size, and volume were found in previous studies (Bai et al., 2012; Isamah et al., 2010; Rao et al., 2017). For the Chinese population, higher hippocampal volume in males relative to females was demonstrated in a large sample size of Han Chinese subjects (a total of 1000 subjects) (Zhang et al., 2010). Therefore, this study's finding of greater parahippocampal volume in male relative

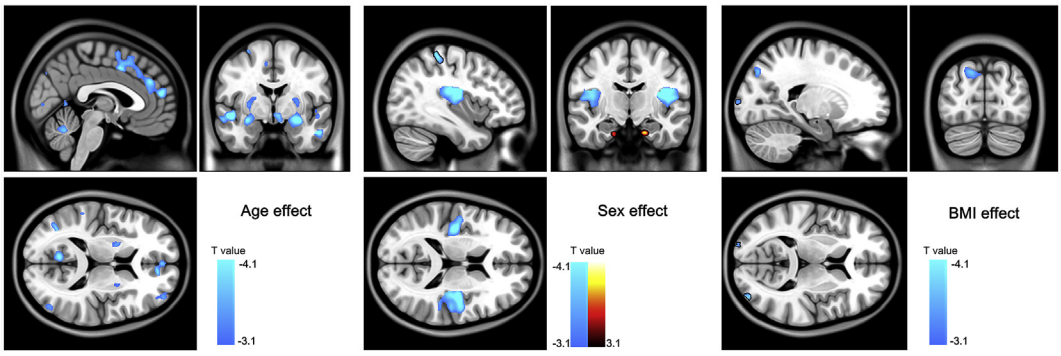

Fig. 3. Multiple regression results in non-PTSD group (GRF corrected $P < 0.05$).
Older age is significantly associated with widespread GM volume deficits; males are shown to have lower GM in bilateral rolandic operculum, insular, and associated with lower GM in postcentral gyrus but greater GM volume in bilateral parahippocampus ($P < 0.001$, uncorrected); higher BMI is significantly associated with GM deficits in left precuneus, and associated with lower GM volume in bilateral MOG ($P < 0.001$, uncorrected). It should be noted that for sex effect, the negative association indicates lower values for males. Brain regions with a rim of black outline indicate results at an uncorrected threshold of $P < 0.001$.
GRF =
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medial prefrontal gyrus; MOG =
middle occipital gyrus; BMI =
body mass index.

to female adults may support the notion that sex indeed influences the volume of hippocampus/parahippocampus in the Chinese population. Besides, we found no sex-related brain volume differences between PTSD and non-PTSD group. Only a few studies have examined sex difference in brain structure in participants with trauma histories. MD De Bellis (De Bellis and Keshavan, 2003) first reported that there were sex differences observed in the brain maturation (cerebral volumes and corpus callosum area) of boys and girls with maltreatment-related PTSD. M Klabunde et al. (2017) found that within the insula's anterior circular sulcus, boys with PTSD symptoms demonstrated larger volume and surface area than control boys, while girls with PTSD symptoms demonstrated smaller volume and surface area than control girls. Future studies are needed to address the modulatory effect of sex on brain structure in trauma-exposed subjects.

Age was associated with widespread brain volume deficits in this study, which is consistent with convergent evidence which shows that the brain shrinks with increasing age (Curiati et al., 2009; Takahashi et al., 2011). As for BMI, prior studies reported that it was associated with widespread brain volume deficits in cognitively normal elderly subjects (Raji et al., 2010), as well as in patients with mild cognitive impairment and Alzheimer's disease (Ho et al., 2010). However, in our study, BMI was only associated with brain volume deficits in limited regions, for this population of Chinese bereaved parents. One possible interpretation is that BMI might have varying degrees of impact across racial groups (Carroll et al., 2008). Further studies are needed to warrant this interpretation.

4.3. Limitations

Our study had several limitations. First, the cross-sectional design of this study could not allow us to ascertain how the modulatory effects of social support and other tested variables might influence brain volume changes over time. Second, as our study focused on Chinese adults who experienced the loss of an only child, we need to be cautious in

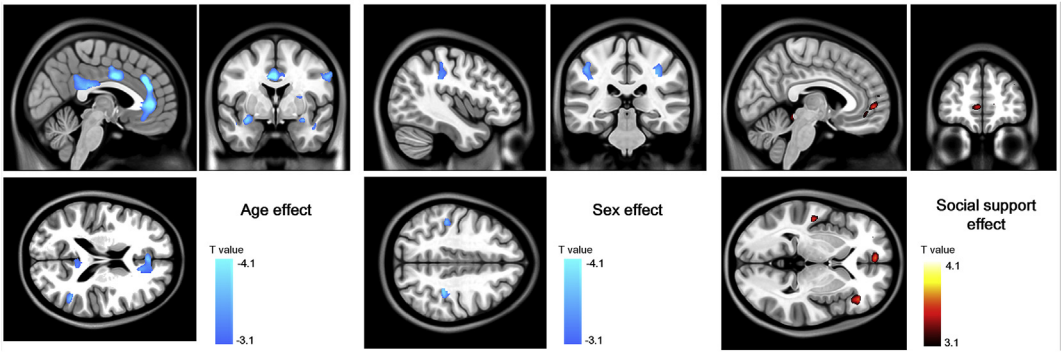

Fig. 4. Multiple regression results in PTSD group (GRF corrected $P < 0.05$). Older age is significantly associated with widespread GM volume deficits; males are shown to have decreased GM in bilateral postcentral gyri; higher social support was significantly associated with greater volume in left MFG, right middle/inferior frontal gyri, and left temporal lobe. It should be noted that for sex effect, the negative association indicates lower values for males. Brain regions with a rim of black outline indicate results at an uncorrected threshold of $P < 0.001$.
GRF =
Gaussian random field; PTSD =
post-traumatic stress disorder; GM =
grey matter; MFG =
medial prefrontal gyrus.

generalizing interpretations of these results to other demographic groups. Third, as recent evidence suggests the importance of gene-by-environment interactions during PTSD development, genetic effects on adults who lost their only child (Qi et al., 2020a, 2020b) need to be taken into account in further studies.

5. Conclusion

We found that social support modulated the association between PTSD diagnosis and medial frontal volume, which may offer preliminary evidence for the impact of social support on the emotional disturbance in PTSD development after experiencing the loss of an only child.

CRediT authorship contribution statement

Rongfeng Qi: Conceptualization, Formal analysis, Funding acquisition, Project administration, Writing - original draft. **Yifeng Luo:** Funding acquisition, Writing - original draft. **Li Zhang:** Investigation, Resources, Supervision. **Yifei Weng:** Investigation, Visualization. **Wesley Surento:** Software, Validation, Writing - review & editing. **Neda Jahanshad:** Supervision, Writing - review & editing. **Qiang Xu:** Software, Investigation. **Yan Yin:** Investigation, Resources. **Lingjiang Li:** Supervision, Resources. **Zhihong Cao:** Funding acquisition, Supervision. **Paul M. Thompson:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing. **Guang Ming Lu:** Supervision, Funding acquisition, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2020.100227.

Declaration of interest

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