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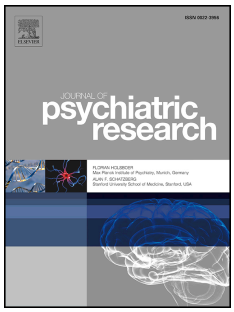

The left dorsolateral prefrontal cortex volume is reduced in adults reporting childhood trauma independent of depression diagnosis

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Abstract

Both major depressive disorder (MDD) and childhood trauma have been linked with brain structural changes. As childhood trauma is more highly prevalent in MDD patients, previous morphometric findings in MDD therefore might have been confounded by childhood trauma. This study aimed to differentiate the impact of childhood trauma from the influence of MDD diagnosis on gray matter volume (GMV). Seventy-eight subjects were recruited into four study groups (n = 16, MDD patients with childhood trauma exposures, CTE/MDD; n = 14, MDD patients without CTE, non-CTE/MDD; n = 24, healthy controls with CTE, CTE/HC; and n = 24, HCs without CTE, non-CTE/HC). All participants underwent high-resolution structural magnetic resonance scans. Voxel-based morphometry was used to investigate GM alterations, and a 2×2 analysis of variance was performed to identify the main effects of diagnosis, childhood trauma, and their interactions. The main effects of diagnosis displayed abnormal GMV located in the left superior parietal lobule (MDD < HC) and right middle occipital gyrus (MDD > HC). While the left dorsolateral prefrontal cortex (DLPFC) volume revealed a significant main effect of childhood trauma, as shown by decreased GMV of the left DLPFC in subjects with CTE, regardless of diagnosis. A negative correlation was also found between the left DLPFC volume and emotional neglect in individuals reporting CTE. The present findings suggest that decreased GMV of the left DLPFC is a function of childhood trauma rather than MDD, which may represent the biological risk for developing MDD.

Key words: *Major depressive disorder; childhood trauma; gray matter; dorsolateral prefrontal cortex*

Title Page

The left dorsolateral prefrontal cortex volume is reduced in adults reporting childhood trauma independent of depression diagnosis

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1 Introduction

Major depressive disorder (MDD) is one of the most debilitating psychiatric condition worldwide, which is also correlated with increased suicidality, mortality, and healthcare cost, imposing a serious social and economic burden in public health (Gilman et al. , 2017, Vos T et al. , 2017). Unfortunately, due to our insufficient knowledge of the pathophysiology of MDD, the current evidence-based treatment options are quite limited, especially for pediatric populations (Neavin et al. , 2018). In this context, it is important for us to elucidate a more detailed understanding of the etiology and the neurobiological mechanisms of MDD.

Over the past decades, the application of magnetic resonance imaging (MRI) has made persistent efforts to reveal the pathophysiological mechanisms underlying mental disorders. In particular, a large body of neuroimaging studies have identified several neuroanatomical changes in MDD patients. Brain structural alterations associated with MDD have been reported in the hippocampus, temporal lobes, amygdala, frontal cortex, anterior cingulate cortex, and striatum (Lorenzetti et al. , 2009), regions that are extensively interconnected within the limbic-cortical-striatal-thalamic circuitry (Sheline, 2000). Furthermore, gray matter volume (GMV) changes in the parietal and occipital lobe have been observed in patients with MDD as well (Inkster et al. , 2011, Shen et al. , 2016). However, previous findings often vary significantly across studies. Given the heterogeneity of MDD, it is acknowledged that one important issue is to investigate the impacts of key clinical and demographic features on the findings across different brain regions (Lorenzetti, Allen, 2009). Of note, childhood trauma, a significant risk factor for MDD, may contribute to the inconsistent findings (Lu et al. , 2013a).

Childhood trauma generally refers to the traumatic experiences during early lifetime, including abuse of child, neglect of child, as well as trauma in child's household environment (Brown et al. , 2009). To date, numerous epidemiologic and clinical studies have provided compelling evidence for a strong relationship between various forms of childhood trauma and depressive symptoms or disorders (Heim and Binder, 2012). Interestingly, anatomical MRI studies have found that brain structural abnormality may be one major mediator provoking childhood trauma to MDD (Opel et al. , 2014, Vythilingam et al. , 2002). Childhood trauma also impacts key brain regions that are implicated in MDD. Hippocampal volume reductions have been repeatedly

detected in subjects affected by childhood trauma (Buss et al. , 2007). Other findings include decreased GMVs in the medial prefrontal cortex (mPFC) (van Harmelen et al. , 2010), reduced orbital-frontal cortical volume (Pollak et al. , 2010), and increased amygdala volume (Tottenham et al. , 2010) in subjects with early life stress. In two preceding studies, childhood trauma was demonstrated to be associated with widespread corticostriatal-limbic GMV reductions both in healthy adolescents (Edmiston et al. , 2011) and in adults (Dannlowski et al. , 2012).

As listed above, both MDD and childhood trauma have been linked with brain structural changes. Moreover, they often share overlapping findings. As the prevalence of childhood trauma is highly elevated in patients with MDD (Scott et al. , 2012, Young et al. , 1997), previous morphometric findings in MDD therefore might have been confounded by childhood trauma. Further designs which investigate brain structural changes in both MDD patients and normal subjects should carefully stratify groups by childhood trauma. Thus, the aim of the present study was to examine the effects of MDD and childhood trauma on GMV respectively by using whole-brain analysis, and specifically, to differentiate the impact of childhood trauma from the influence of MDD diagnosis on GMV. To the best of our knowledge, until now, only one study has conducted a similar design, which found that structural abnormalities in the fronto-limbic regions were the psychopathological consequence of childhood trauma rather than MDD (Yang et al. , 2017). However, some limitations that may influence the results should have been avoided in that study, for example, the usage of antidepressant in MDD patients when scanning, comorbidity of anxiety disorders in MDD, and relatively tiny proportion of maltreated subjects in the control group. By contrast, these confounding factors were well controlled in our study.

2 Methods

2.1 Participants

The present study recruited 78 individuals (male/female, 35/43), aged 18-39 years, including 16 MDD patients with childhood trauma exposures (CTE/MDD), 14 MDD patients without CTE (non-CTE/MDD), 24 healthy controls with CTE (CTE/HC), and 24 healthy controls without CTE (non-CTE/HC). For assignment to the CTE group, individuals must have had experienced chronic

moderate-severe trauma exposures (abuse and/or neglect) before the age of 16. MDD patients were recruited from the psychiatric clinic of the Second Xiangya Hospital of Central South University, Changsha, Hunan, P.R. China. The inclusion criteria were as follows: 1) met the Diagnostic and Statistical Manual of Mental Disorders, IV Edition (DSM- IV) criteria for current unipolar MDD episode which was assessed using Structured Clinical Interview for DSM-IV (SCID) by two professional psychiatrists; 2) free of treatment for at least 2 weeks; 3) right handedness; 4) at least junior middle school level of education; 5) the Han ethnicity. Age- and sex-matched healthy volunteers were recruited from local universities and communities via advertisements and they responded with no direct reference to childhood trauma as a key variable in this study. General exclusion criteria were as follows: 1) significant medical illness; 2) with any other psychiatric axis-I or axis-II disorders (except MDD in patients) after SCID screening; 3) alcohol or substance abuse; 4) with a family history of bipolar disorder; 5) with a history of loss of consciousness; 6) woman with pregnancy or in lactation period; 7) with a history of seizures or with a family history of epilepsy; 8) intake of any psychotropic medication or hormone, and 9) contraindications to MRI scan, including metallic implants, retractors or braces, and claustrophobia. All participants were asked for general information and were evaluated with psychological questionnaires such as Zung's Self-rating Depression Scale (SDS) (Zung et al. , 1965) and 24-item Hamilton Depression Scale (HAMD) (Hamilton, 1967). Written informed consent was obtained and this study was approved by the ethic committee of the Second Xiangya Hospital of Central South University.

2.2 Assessment of childhood trauma

Childhood trauma was quantified with the 28-item Childhood Trauma Questionnaire (CTQ), which evaluates five types of negative childhood experiences: emotional abuse, emotional neglect, sexual abuse, physical abuse, and physical neglect. Every sub-scale has 5 items and each item scores as 1 = never true, 2 = rarely true, 3 = sometimes true, 4 = often true, 5 = very often true. Scores ranged from 5 to 25 for each sub-scale, with high scores indicating strong and chronic exposures to childhood trauma. Individuals who score higher than the moderate-severe threshold of a sub-scale are treated as existence of corresponding CTE. The cutoffs of each

sub-scale are 1) emotional abuse ≥ 13, 2) emotional neglect ≥ 15, 3) sexual abuse ≥ 8, 4) physical abuse ≥ 10, and 5) physical neglect ≥ 10, which have provided good sensitivity and specificity for confirmed abuse or neglect (Bernstein and Fink, 1998). The Chinese version of CTQ was used in our study, which was revealed to have good internal consistency (Cronbach's α) for the CTQ total score (0.77) and the five sub-scales (0.41~0.78) in a Chinese sample (Zhao et al. , 2005).

2.3 Image acquisition

Imaging data were acquired in the Magnetic Resonance Center belonging to the Second Xiangya Hospital of Central South University with a Philips 3.0-T scanner (Philips, Best, The Netherlands). Subjects were asked to lie on the scanner and keep eyes closed. A standard birdcage head coil was used, and the restraining foam pads were placed on two sides of the head to minimize head motion while cotton plug was used with the purpose of reducing the noise. For each participant, T1-weighted high-resolution anatomical images were obtained using a 3-dimensional rapid acquisition gradient echo sequence. Images of the whole brain were acquired in a sagittal orientation with the following parameters: slice thickness = 1 mm, gap = 0 mm, repetition time = 7.6 ms, echo time = 3.7 ms, inversion time = 795 ms, field of view = 256 x 256 mm^2, flip angle = 8°, matrix size = 256 x 256, resolution = 1.0 x 1.0 x 1.0, slices = 180, scan time = 2'58''.

2.4 Voxel-based Morphometry (VBM) analysis

All T1-weighted high-resolution anatomical data were preprocessed by using the previous method (Zhang et al. , 2012). Image analyses were performed using the Statistical Parametric Mapping 8 (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm) in a Matlab (R2008a) environment. The VBM8 Toolbox (http://dbm.neuro.uni-jena.de/vbm.html) was used for preprocessing the structural images in SPM8 with default parameters. The data was bias-corrected, tissue classified, and normalized to Montreal Neurological Institute space using linear (12-parameter affine) and non-linear transformations within a unified model (Ashburner and Friston, 2005). Then data analyses were performed on GM segment which was multiplied by the non-linear components derived from the normalization matrix in order to preserve actual

GM value locally (modulated GMV). Finally, the modulated GMV was smoothed with a Gaussian kernel of 8 mm full width at half maximum (FWHM).

2.5 Statistical analysis

Statistical analyses were conducted using Statistical Package for the Social Sciences version 16.0 (SPSS Inc., Chicago, IL, USA). Chi-square tests (χ^2) were calculated to compare groups on non-parametric data. Analyses of variance (ANOVAs) were used to compare means of demographic and clinical characteristics. Values were given as mean ± standard deviation. The level of two-tailed statistical significance was set at $p < 0.05$ for all tests.

For GMV, a voxel-by-voxel general linear model with a 2 (diagnosis: MDD *vs* HCs) × 2 (childhood trauma: CTE *vs* non-CTE) comparison, controlling for age, sex, and educational level was performed to determine the main effect of diagnosis (MDD > or < HCs), the main effect of childhood trauma (CTE > or < non-CTE), and the diagnosis-by-maltreatment interaction effect. The significance level was set at $p < 0.001$ corrected by multiple comparisons using Gaussian Random Field (GRF) theory (min $z > 3.291$, cluster significance: $p < 0.001$). Furthermore, the mean values of the clusters that had shown differences in VBM analysis were extracted by using region of interest (ROI) analyses. Correlation analyses of abnormal GMVs with clinical features were conducted using Pearson's product moment.

3 Results

3.1 Sample characteristics

As indicated in **Table 1**, no significant difference among four groups was observed for age, sex, and educational level. The two groups of MDD patients did not differ significantly in distributions of disease course and HAMD scores. As we would expect, univariate ANOVAs revealed that the experimental groups differed on scores of SDS and CTQ. Specifically, MDD patients with CTE showed higher levels of emotional abuse and CTQ total scores compared with healthy controls with CTE. In maltreated subjects, the most common aspect of childhood trauma experience was

emotional neglect, the proportions of multiple exposures (at least two forms of CTE) in MDD patients with CTE and healthy individuals with CTE were 75.0% and 62.5%, respectively.

3.2 Alterations in GMVs

The whole brain analysis revealed significant diagnosis main effects in the left superior parietal lobule (SPL) and right middle occipital gyrus (MOG) (**Table 2** and **Figure 1**), with reduced GMV in the left SPL while increased GMV in the right MOG in MDD patients compared to healthy subjects. In addition, the left dorsolateral prefrontal cortex (DLPFC) GMV revealed a significant main effect of childhood trauma (**Table 2** and **Figure 2**), as shown by decreased GMV of the left DLPFC in subjects with CTE compared to individuals without CTE. However, no diagnosis-by-maltreatment interaction effect was observed in the present analysis.

The mean cluster values of the regions that showed significant differences in the above VBM analysis were extracted from each subject. Correlation analyses further showed that GMV in the left SPL was negatively associated with disease course (r = -0.408, p = 0.034) and HAMD scores (r = -0.573, p = 0.002) in patients with MDD, and that GMV in the left DLPFC was negatively correlated with scores of emotional neglect (r = -0.330, p = 0.046) in subjects with CTE.

4 Discussion

Using a whole-brain VBM approach, the present study investigated the influence of MDD and childhood trauma on GMV changes, respectively. Our results demonstrated that decreased GMV in the left SPL and increased GMV in the right MOG were associated with MDD. More importantly, we also confirmed that reduced GMV of the left DLPFC, which was usually recognized as psychopathology of MDD, was associated with childhood trauma independent of MDD diagnosis. Therefore, these findings highlight the importance of investigations that focus on the effect of childhood trauma on GMV changes in MDD and may provide new insights and implications into the pathophysiology and treatment of MDD experiencing childhood trauma.

In this study, the main effect of MDD diagnosis was identified on the parietal-occipital regions, with decreased GMV in the left SPL and increased GMV in the right MOG. The SPL is

considered as a crucial brain region involved in top-town control, or value-driven or allocation of attention (Corbetta and Shulman, 2002). Moreover, the important role of SPL is also widely tied to executive function, especially working memory (Koenigs et al. , 2009). GMV loss of the SPL has been consistently reported in MDD patients when comparing to healthy controls (Abe et al. , 2010). Recently, a study investigated brain structural alterations in first-episode, drug-naïve MDD patients by using magnetization transfer imaging (MTI), a MR technique with the potential for providing more early neuropathological changes than volumetric MRI and found that the left SPL might be involved in the early neurobiology of depression, as reflected by microstructural GM changes before volume loss in the parietal cortex (Chen et al. , 2016). Our current result is in line with these prior research findings and we speculate that GMV reduction in the left SPL may be related to the attentional and cognitive dysfunction in MDD patients.

Alteration of GMV in the right MOG was also detected to be associated with MDD in our study. The MOG is one of key brain regions that form visual recognition network (Tao et al. , 2013). The visual recognition network is involved in emotional facial processing, which is crucial for social interactions (Fusar-Poli et al. , 2009). Previous studies have revealed structural and functional abnormalities of the visual processing regions in MDD patients, suggesting the involvement of the visual recognition network in the pathogenesis of MDD (Zhao et al. , 2017). Our finding is congruent with a report in a group of early adult onset MDD patients showing increased GMV in the right MOG and it is speculated that increased GMV of the right MOG in MDD may be morphological compensations for the GMV reductions in other brain regions (Shen, Cheng, 2016). In addition, our result is also comparable with two previous structural MRI findings demonstrating a greater thickness and increased surface area in the right lateral occipital cortex (Zhao, Chen, 2017, Zorlu et al. , 2017).

A noteworthy finding of the current study was decreased GMV of the left DLPFC in subjects with CTE, regardless of MDD diagnosis. Our finding is in parallel with prior observations that have identified the DLPFC as most vulnerable to the adverse effects of childhood trauma. It has been indicated that smaller DLPFC volume is associated with a previous history of emotional abuse in unaffected first-degree relatives of patients with MDD (Carballedo et al. , 2012). Moreover, a meta-analysis which included 19 whole-brain VBM studies concluded that one of the most prominent anatomical alterations among adults with a history of childhood trauma was GMV

diminishment in the DLPFC (Paquola et al. , 2016). Thus, it seems like that decreased GMV of the left DLPFC may be secondary to childhood trauma, likely representing the biological vulnerability for developing MDD in response to early stress rather than neurobiological consequence of MDD. The DLPFC is tightly involved in plenty of mental processing, including executive functioning, attention, and emotional processing (Schmahl et al. , 2004). Structural and functional abnormalities in the DLPFC have been proved to account for cognitive and emotional dysregulations (Pechtel and Pizzagalli, 2011) that can be commonly observed in individuals with CTE (Chu et al. , 2013, Lu et al. , 2017), which may help to explain the significance of the present finding.

Previous studies have demonstrated that the effects of childhood trauma on brain structure, including altered GMV in the hippocampus and prefrontal lobe, were also integrated in the pathophysiology of MDD (Opel, Redlich, 2014, Yang, Cheng, 2017). However, our study failed to detect a diagnosis-by-maltreatment interaction effect on GMV changes. One explanation could be that the small sample size in our study might limit the power to detect the interaction effect in data analysis. Other potential factors, such as different timing and duration of CTE, differential severity of CTE, and different concomitant and subsequent psychosocial conditions might contribute to the inconsistent findings as well (Lupien et al. , 2009).

In the present study, although the two groups of MDD patients showed similar clinical manifestations, the VBM analysis demonstrated the essential difference between them. MDD patients with CTE showed decreased GMV in the left DLPFC, while this change was not existed in MDD patients without CTE. Similarly, our previous studies also indicated different alterations when investigating the hypothalamo-pituitary-adrenal (HPA) axis activity (Lu et al. , 2016) and plasma cytokine levels (Lu et al. , 2013b) in MDD patients with or without childhood trauma. Taken together, our series findings may support the view that MDD with a history of childhood trauma could be treated as a special subtype of depression with unique pathogenesis (Heim et al. , 2008). Therefore, individual differences in childhood trauma experiences should be severely taken into account in future research of MDD.

Finally, a growing bulk of evidence has revealed that in MDD patients, childhood trauma was associated with an elevated risk of developing recurrent and persistent depressive episodes, and lack of response or remission during treatment for depression (Nanni et al. , 2012). In particular,

previous studies have also proposed that a history of childhood trauma predict poor pharmacologic treatment outcomes in MDD patients (Tyrka et al. , 2013). Reported history of childhood trauma and sequelae of these experiences may be associated with treatment resistance in depressed outpatients (Kaplan and Klinetob, 2000). Hence, MDD patients with childhood trauma may require treatments that are specific to this condition. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive therapy approved for the treatment of MDD, which has been proved to be effective and safe for treatment resistant depression (TRD) as well (Gaynes et al. , 2014). rTMS for MDD most commonly targets the left DLPFC, as a modulatory cortical region of the emotional circuit affected by that disorder (Mayberg, 2007). In this context, we speculate that rTMS treatment may produce more direct effects in MDD patients with CTE than those without such experiences, since the current result demonstrates the abnormality of the left DLPFC in MDD patients with CTE, but not in depressed-only individuals. However, more clinical trails should be designed to test our hypothesis in the future.

The present study has certain limitations. First, the sample size in each group is relatively small, especially in two MDD groups. However, it should be noted that the two patient groups were homogeneous groups of treatment-free MDD patients. Second, this study was a cross-sectional design, which precluded causal inferences. Meanwhile, data on childhood trauma were corrected by a retrospective questionnaire, which might lead to recall bias. Third, due to the modest sample size and high proportion of multiple trauma exposures in our sample, we did not investigate the effects of different types of childhood trauma on GMV alterations. Finally, we have not done the corrections for the correlation analyses, so the present associations between abnormal GMVs with clinical features should only be understood as exploratory.

5 Conclusion

In summary, the present findings suggest that the effect of childhood trauma on GMV alterations should be considered in neuroimaging studies of MDD. In addition, this study also demonstrates that decreased GMV of the left DLPFC is a function of childhood trauma rather than MDD, which may represent the biological risk for developing MDD.

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Contributors

Author Shaojia Lu designed the study and wrote the first draft of the manuscript. Authors Shaojia Lu and Zhaoguo Wei recruited the sample, authors Ruizhi Xu, Jiang Cao, Yan Yin, and Dandan Wang finished the clinical assessments, and authors Weijia Gao, Shaohua Hu, and Manli Huang conducted the statistical analyses. Authors Yi Xu and Lingjiang Li also designed the study and had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to and have approved the final manuscript.

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Table 1: Demographic and clinical characteristics for all subjects (n=78).

	MDD		HC		Analysis	*p*-values
	CTE(n=16)	non-CTE(n=14)	CTE(n=24)	non-CTE(n=24)	F/χ^2	
Age	24.4(4.79)	23.5(5.77)	21.5(3.98)	21.5(3.69)	2.002	0.121
Sex (Male/Female)	11/5	6/8	9/15	9/15	4.765	0.190
Education years	14.2(2.26)	14.5(3.30)	14.0(1.30)	14.7(1.92)	0.440	0.725
Disease course(Months)	39.1(32.4)	21.1(19.2)			3.292	0.080
SDS score	72.4(12.7)	70.6(11.9)	36.2(6.06)[a,b]	34.5(5.30)[a,b]	104.3	0.000
HAMD score	30.7(6.03)	29.5(4.99)			0.339	0.565
CTQ score						
Emotional abuse	12.1(4.61)	6.07(1.14)[a]	9.21(2.36)[a,b]	6.21(1.22)[a,c]	20.85	0.000
Physical abuse	8.63(3.05)	5.57(1.28)[a]	7.83(2.93)[b]	5.71(1.33)[a,c]	7.855	0.000
Sexual abuse	6.00(1.21)	5.36(0.63)	5.46(0.83)	5.38(0.58)	2.259	0.089
Emotional neglect	16.3(5.06)	9.50(2.41)[a]	15.2(3.28)[b]	7.38(2.65)[a,c]	32.53	0.000
Physical neglect	11.6(3.61)	6.93(10.2)[a]	10.2(2.72)[b]	5.63(0.93)[a,c]	27.91	0.000
Total	54.6(10.7)	33.4(3.39)[a]	47.9(6.08)[a,b]	30.2(4.63)[a,c]	59.10	0.000
CTE, n(%)						
Emotional abuse	6(37.5)		2(8.33)			
Physical abuse	3(18.8)		8(33.3)			
Sexual abuse	3(18.8)		0(0)			
Emotional neglect	12(75.0)		17(70.8)			
Physical neglect	11(68.8)		14(58.3)			
Single exposure	4(25.0)		9(37.5)			
Multiple exposures	12(75.0)		15(62.5)			

CTE, childhood trauma exposure; CTQ, childhood trauma questionnaires; HAMD, Hamilton depression scale; HC, health control; MDD, major depressive disorder; SAS, self-rating anxiety scale; SDS, self-rating depression scale. [a]compared with MDD/CTE, $p<0.01$, [b]compared with MDD/non-CTE, $p<0.01$, [c]compared with HC/CTE, $p<0.01$.

Table 2. Brain regions showing significant main effects of diagnosis or childhood trauma. (*p* < 0.001, *GRF corrected*)

Brain region	Hemisphere	Cluster size	*F* value	MNI coordinate		
				x	*y*	*z*
Main effect of diagnosis						
SPL	L	102	16.1	-17	-66	57
MOG	R	276	19.6	30	-78	27
Main effect of childhood trauma						
DLPFC	L	226	20.1	-39	32	24

DLPFC, dorsolateral prefrontal cortex; GRF, Gaussian Random Field; MNI, Montreal neurological institute; MOG, middle occipital gyrus; SPL, superior parietal lobule.

Figure 1 Brain regions showing significant main effect of diagnosis (*p* < 0.001, *GRF corrected*). *a)* Left superior parietal lobule (MDD < HC); *b)* Right middle occipital gyrus (MDD > HC), color scales represent *F*-values. MDD, major depressive disorder; GRF, Gaussian Random Field; HC, health control.

Figure 2 Brain regions showing significant main effect of childhood trauma (*p* < 0.001, *GRF corrected*). Statistical parametric map depicting a main effect of childhood trauma in the left dorsolateral prefrontal cortex (CTE < non-CTE), color scales represent *F*-values. CTE, childhood trauma exposure; GRF, Gaussian Random Field.