◆ Human Brain Mapping 35:1154–1166 (2014) ◆

Overlapping and Segregated Resting-State Functional Connectivity in Patients with Major Depressive Disorder With and Without Childhood Neglect

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Abstract: Many studies have suggested that childhood maltreatment increase risk of adulthood major depressive disorder (MDD) and predict its unfavorable treatment outcome, yet the neural underpinnings associated with childhood maltreatment in MDD remain poorly understood. Here, we seek to investigate the whole-brain functional connectivity patterns in MDD patients with childhood maltreatment. Resting-state functional magnetic resonance imaging was used to explore intrinsic or spontaneous functional connectivity networks of 18 MDD patients with childhood neglect, 20 MDD patients without childhood neglect, and 20 healthy controls. Whole-brain functional networks were constructed by measuring the temporal correlations of every pairs of brain voxels and were further analyzed by using graph-theory approaches. Relative to the healthy control group, the two MDD patient groups showed overlapping reduced functional connectivity strength in bilateral ventral medial prefrontal cortex/ventral anterior cingulate cortex. However, compared with MDD patients without a history of childhood maltreatment, those patients with such a history displayed widespread reduction of func-

Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: National Natural Science Foundation of China; Contract grant numbers: 30830046, 91232714, 81171286, 81030028, 31221003; Contract grant sponsor: National 973 Program of China; Contract grant number: 2009CB918303; Contract grant sponsor: Program of Chinese Ministry of Education; Contract grant number: 20090162110011; Contract grant sponsor: National High Technology Research and Development Program of China (The National 863 Program); Contract grant number: 2008AA022603.

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Received for publication 1 August 2012; Revised 26 October 2012; Accepted 19 November 2012

DOI: 10.1002/hbm.22241

Published online 13 February 2013 in Wiley Online Library (wileyonlinelibrary.com).

tional connectivity strength primarily in brain regions within the prefrontal-limbic-thalamic-cerebellar circuitry, and these reductions significantly correlated with measures of childhood neglect. Together, we showed that the MDD groups with and without childhood neglect exhibited overlapping and segregated functional connectivity patterns in the whole-brain networks, providing empirical evidence for the contribution of early life stress to the pathophysiology of MDD. *Hum Brain Mapp 35:1154–1166, 2014.*

Key words: MDD; childhood maltreatment; resting-state fMRI; functional connectivity; connectome

INTRODUCTION

Major depressive disorder (MDD) is one of the most common mental disorders with a lifetime prevalence of 16% [Kessler et al., 2003]. Core symptoms of MDD include persistent and pervasive depressed mood, anhedonia, irritability, difficulties in concentrating, and abnormalities in appetite and sleep [Nestler et al., 2002]. The chronic and festering nature of depression lends substantially to the global burden of disease and disability. The World Health Organization has ranked depression as the fourth contributor to the global burden of disease in the year 2000 and predicted that it would become the second leading contributor by 2020 [WHO, 2001].

The current view of the etiology of depression is best summarized as the interaction of genetic susceptibility and environmental factors. Twin and family studies have demonstrated that while $\sim$ 30–40% of the risk for the development of depression is genetic, the remaining variability is imparted by the environment [Sullivan et al., 2000]. Childhood maltreatment, a major public-health and social-welfare problem, is one of the major means whereby the environment influences the development of depression. A corpus of preclinical and clinical studies has firmly established that early life neglect or abuse is associated with dramatic increase in the risk to develop depression [Chapman et al., 2004; Heim and Nemeroff, 2001; Hill et al., 2001; Spatz Widom et al., 2007]. Moreover, early life stress can also have influence on nearly all aspects of the disease process including manifestation of symptoms, frequency of recurrence or relapse after a period of remission, and responses to pharmacotherapy [Angst et al., 2011; Klein et al., 2009; Miniati et al., 2010; Nanni et al., 2012].

An expanding body of evidence from rodent, primate, and human research suggests that early stressors promote a cascade of long-term changes in multiple brain circuits from neurohumoral to structural and functional aspects [De Bellis, 2005; Heim and Nemeroff, 2001; Hill et al., 2001]. Specifically, neurobiological alterations associated with stress in early life closely parallel established features of major depression, including sensitization of the neuroendocrine stress response, dysfunction of noradrenergic, and serotonergic systems, as well as structural and/or functional changes in neuronal circuitries relevant to stress and emotion [Heim et al., 2004]. By exploring the relationship between exposure to childhood maltreatment and gray matter morphology, several structural imaging studies have implicated widespread involvement in various brain regions including prefrontal, limbic regions, and cerebellum even in subjects without psychiatric diagnoses [Bauer et al., 2009; Cohen et al., 2006; Dannlowski et al., 2012; Edmiston et al., 2011]. Specially, Vythilingam et al. [2002] observed that the depressed patients with childhood trauma had smaller hippocampal volume than those without a history of childhood trauma. Using functional MRI, Grant et al. [2011] found that the depressed patients with a history of early life trauma showed enhanced amygdale response to negative stimuli but not those without such a history. Hence, it is theorized that many of the neurobiological changes thought to be characteristic of depression may, in fact, be due to early life stress and represent risk to develop depression, while depression in the absence of early life stress is not associated with such alterations [Heim et al., 2010]. Thus, it is conceivable that, in the current research realm of depression, one of the major challenges is to understand the underlying biological mechanisms, by which adverse experience during critical phases of development influences neural networks, leading to the pattern of neurobiological and behavioral expression that is the clinical phenotype of depression [Heim et al., 2004].

Resting-state functional MRI (R-fMRI) is a promising imaging technique which allows researchers to observe manifestations of spontaneous neuronal activity [Biswal et al., 1995]. A growing body of studies have utilized R-fMRI to reveal abnormal functional connectivity in neurological and psychiatric disorders [Anand et al., 2005; Buckner et al., 2009; Lui et al., 2009]. Relating to depression, several studies have demonstrated reduced resting-state functional connectivity between anterior cingulate cortex (ACC) and limbic regions [Anand et al., 2005], between ACC and bilateral dorsomedial thalamus [Anand et al., 2009], and between prefrontal and limbic networks [Lui et al., 2011]. In contrast, increased functional connectivity was also detected in depression between the ACC and the left anterior insula [Horn et al., 2010], between ACC and thalamus [Greicius et al., 2007], and between an area of the dorsomedial prefrontal cortex termed "dorsal nexus" with the dorsolateral prefrontal cortex (dlPFC), the ventral medial prefrontal cortex (vmPFC), and the ACC [Sheline

TABLE I. Demographic and clinical characteristics of participants

	Controls ($N = 20$)		MDD-WoCN ($N = 20$)		MDD-WCN ($N = 18$)	
Measure	*N*	%	*N*	%	*N*	%
Female	11	55.0	8	40.0	10	55.6
SSRIs			17	85.0	15	83.3
	Mean	SD	Mean	SD	Mean	SD
Age (years)	27.9	4.4	28.2	8.7	28.3	6.2
Education (years)	15.0	3.2	13.1	3.5	11.1	2.4
Duration (months)			24.5	20.2	20.2	23.1
HAMD			27.1	6.7	27.0	7.7
CTQ-EN	8.2	3.0	9.7	1.3	15.2	3.8
CTQ-PN	6.8	1.4	6.5	1.1	11.4	3.3

SSRIs, Selective Serotonin Inhibitors, patients were either taking a typical, selective serotonin inhibitor or with a typical serotonin-norepinephrine re-uptake inhibitor; HAMD, Hamilton Depression Rating Scale; CTQ, Childhood Trauma Questionnaire; EN, emotional neglect; PN, physical neglect; MDD-WoCN, major depressive disorder without child neglect; MDD-WCN, major depressive disorder with child neglect.

et al., 2010]. However, no study reported alterations of R-fMRI functional connectivity associated with childhood neglect or abuse in depression.

Here, we have used R-fMRI to investigate whole-brain functional connectivity patterns in MDD patients with a history of early life stress and without such a history. The whole-brain functional networks were constructed by measuring temporal correlations of every pairs of voxels in the brain and were analyzed by using graph-theory approaches. Given that many previous R-fMRI studies showed abnormal functional integration in the ACC in MDD patients [Anand et al., 2005, 2009; Greicius et al., 2007; Horn et al., 2010; Sheline et al., 2010], we hypothesize that two MDD groups would show overlapping functional connectivity disruption in this region. More importantly, based on previous findings regarding persistent effects of early life trauma on focal gray matter morphology in the prefrontal-limbic-cerebellar system [Bauer et al., 2009; Cohen et al., 2006; Dannlowski et al., 2011; Edmiston et al., 2011], we hypothesize that the two patient groups would show segregated functional connectivity patterns in this neuronal circuitry.

MATERIALS AND METHODS

Participants

A total of 60 subjects participated in this study, including 21 MDD patients without childhood neglect (MDD-WoCN), 19 MDD patients with childhood neglect (MDD-WCN), and 20 healthy controls (HC) (Table I). Patients were recruited from inpatient or outpatient Departments of Psychiatry, the Second Xiangya Hospital, Central South University, China. The diagnosis of MDD was made by two well-trained clinical psychiatrists according to the structured clinical interview for DSM-IV (SCID) [First et al., 1997]. Severity of depression was measured with both the 17-item Hamilton Depression Rating Scale (HAMD) [Williams, 1988] and the Self-rating Depression Scale [Zung, 1965]. Several previous studies have suggested that different types of childhood trauma may have different effects on the neurobiological systems [Edmiston et al., 2011; Manly et al., 2001]. Moreover, researchers have demonstrated that in the modern society, childhood neglect accounts for about 60% of child maltreatment cases and it has been regarded as damaging or perhaps even more damaging to an individual than frequently focused sexual or physical abuse [Gilbert et al., 2009; Watts-English et al., 2006]. On the basis of these considerations, we thus restricted our inclusion criteria to childhood neglect only (including physical neglect and emotional neglect. These two categories of childhood trauma were assessed through the Childhood Trauma Questionnaire (CTQ) [Bernstein et al., 1994, 2003; Fu and Yao, 2005], in which each subscale was measured in five items and rated on a five-point Likert scale. Cutoff scores for moderate-severe exposure ($\geq$ 15 for emotional neglect; $\geq$ 10 for physical neglect) were used to classify patients as positive for a history of childhood neglect [Bernstein et al., 2003]. Being identified as "positive" corresponds to endorsing a large number of experiences as "often true." The reliability and validity of the CTQ have been established, including measures of convergent and discriminate validity from structured interviews, stability over time, and corroboration using independent data [Bernstein et al., 2003; Fu and Yao, 2005]. Exclusion criteria of the patients included other Axis I or Axis II disorders, histories of other forms of childhood trauma, electroconvulsive therapy, neurological disorders, loss of consciousness, perinatal or neonatal complications, substance dependence, and any contraindications for MRI. Two patients were excluded because of excessive head motion during fMRI scanning (see Data Preprocessing). All patients were receiving antidepressant medications, either with a typical, selective serotonin inhibitor (17 patients with MDD-WoCN and 15 patients with MDD-WCN) or with a typical serotonin-norepinephrine re-uptake inhibitor (three patients with MDD-WoCN and three patients with MDD-WCN). Healthy controls were recruited from the local area through poster advertisements, and were screened using the non-patient edition of the SCID, scales of HAMD, and CTQ to confirm the lifetime absence of psychiatric or neurological illness and any history of childhood maltreatment. They were also interviewed to exclude any family history of psychiatric illness, and histories of severe or unstable clinical illness, loss of consciousness, perinatal or neonatal complications or any contraindications for MRI. All the controls were not taking any medications. The detailed demographics and clinical characteristics of all participants were presented in Table I. The study was approved by the ethics committee of the Second Xiangya

Hospital, Central South University, and written informed consent was obtained from each participant.

Data Acquisition

The imaging data were obtained on a 3T Philips Achieva scanner at the Second Xiangya Hospital, Central South University. Participants were fitted with soft earplugs and positioned carefully in the coil with comfortable support. During the scan, participants were asked to lie still with their eyes closed and to avoid falling asleep. After this, a simple questionnaire indicated that no participants had fallen asleep. A total of 180 volumes of echo planar images were obtained axially (repetition time, 3,000 ms; echo time, 30 ms; slices, 36; thickness, 4 mm, no slice gap; field of view, 240 × 240 mm^2; resolution, 64 × 64; flip angle, 90°).

Data Preprocessing

Image preprocessing was carried out using Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and Data Processing Assistant for Resting-State fMRI (DPARSF) [Yan and Zang, 2010]. The first five volumes were discarded for scanner stabilization and participants' adaption to the circumstances. The remaining functional scans were first corrected for within-scan acquisition time differences between slices and further realigned to the first volume to correct for interscan head motions. Data of two subjects from each patient group were discarded because they had head motion of more than 3 mm of translation or 3 degrees of rotation in any direction. The head motion profiles were matched among the three groups ($P > 0.21$ in any direction). Subsequently, the motion-corrected functional volumes were spatially normalized into the stereotaxic space [Talairach and Tournoux, 1988] using an optimum, 12-parameter affine transformation and nonlinear deformation [Ashburner and Friston, 1999], and then resampled to 3 mm isotropic voxels. Further preprocessing included linear de-trend and temporal band-pass filtering (0.01–0.08 Hz), which were used to reduce the effects of low-frequency drift and high-frequency physiological noise. Finally, the nuisance signals involving six head motion parameters, global mean signal, cerebrospinal fluid signal, and white matter signal were regressed out from the data. Given that the removal of global signal introduced a shift in the distribution of correlation coefficients (mainly the presence of negative correlations) and made biological interpretation ambiguous [Murphy et al., 2009; Weissenbacher et al., 2009], we, therefore, restricted our explorations to positive correlations, as in previous studies [Buckner et al., 2009].

Whole-Brain Functional Connectivity Analysis

We performed whole-brain functional connectivity analysis as follows. First, we computed the Pearson's correlations between the time series of all pairs of brain voxels and obtained a whole-brain functional connectivity matrix for each participant. The computation was constrained within a gray-matter mask ($N_{voxels} = 67{,}632$) which was generated by thresholding (a threshold of 0.2) a prior gray-matter probability map in SPM8. Then, for a given gray-matter voxel, we computed its functional connectivity strength (FCS) using the following equation:

$$S_{voxel}(i) = \frac{1}{N}\sum_{j \neq i} z_{ij} \quad r_{ij} > r_0 \tag{1}$$

where r_{ij} was the correlation coefficient between voxel i and voxel j, r_0 was a threshold that was set to eliminate weak correlations possibly arising from signal noise ($r_0 = 0.2$ in this study), and r_{ij} was converted to z_{ij} using Fisher's Z-transformation when calculating FCS. Notably, such a FCS metric is referred to as the "degree centrality" of weighted networks in terms of graph theory [Buckner et al., 2009; Dai et al., 2012; He et al., 2009; Zuo et al., 2012]. The brain voxels with higher FCS values usually indicate their central roles in the functional integrity of the whole-brain networks.

Statistical Analysis

Group differences

Before statistical analysis, all individual FCS maps were spatially smoothed with a Gaussian kernel (full width at half-maximum = 6 mm). Statistical tests on the FCS maps across groups were performed using a voxel-based, one-way analysis of covariance (ANCOVA) with age, gender, and education level as covariates followed by post hoc, two-sample t-tests. Correction for multiple comparisons was performed by Monte Carlo simulations [Ledberg et al., 1998] using the AFNI AlphaSim program (http://afni.nih.gov/afni/docpdf/AlphaSim.pdf). A corrected significance level of 0.05 was obtained with a combined $P < 0.05$ and cluster size > 4,860 mm^3 for the ANCOVA analysis, and, a combined $P < 0.05$ and cluster size > 1,728mm^3 for post hoc, two-sample t-tests analysis (which was conducted within a mask showing group FCS differences from the ANCOVA analysis).

Brain–behavioral relationship

To determine the relationship between FCS and clinical variables (physical and emotional neglect), a voxel-based multiple linear regression analysis was separately conducted in the MDD-WCN and MDD-WoCN groups within regions showing significant FCS differences in comparisons with the control group. Age, gender, and education were considered unconcerned, confounding factors. Multiple comparisons were corrected again using Monte Carlo simulations.

Validations: Reproducibility

To further evaluate the reproducibility of our results, we conducted the following procedures.

The effects of different correlation thresholds

While computing FCS, we used a single correlation coefficient threshold of 0.2 to eliminate weak correlations possibly arising from signal noise. To determine whether our main results depended on the choices of different correlation thresholds, we recomputed FCS maps using three different correlation thresholds (i.e., 0, 0.1, and 0.3) and performed statistical analysis.

The effects of head motion

Recent literature has suggested that head motion has a confounding effect on resting-state functional connectivity [Power et al., 2012; Satterthwaite et al., 2012; Van Dijk et al., 2012]. In this study, we did not find significant differences in head motion among the three groups (all $P > 0.21$ in any direction). Nonetheless, to exclude any possible effects of head motion, we still reanalyzed our data with head motion (the root mean squares of both overall head motion displacement and rotation) as an extra covariate in the statistical models.

The effects of different preprocessing choices

In the preprocessing of R-fMRI data, whether global signal needs to be regressed out is currently a controversial step. Several R-fMRI studies have suggested that global signal is associated with respiration-induced fMRI signal [Birn et al., 2006; Chang and Glover, 2009] and should be removed to reduce the effect of the physiological artifacts [Fox et al., 2005, 2009; Fransson, 2005]. However, this processing has been criticized because it introduces widespread negative functional connectivity and thus alters intrinsic correlation structure of the brain networks [Murphy et al., 2009; Weissenbacher et al., 2009]. Notably, a recent fMRI study suggests that the global signal is correlated with an oscillatory neuronal signal, suggesting that the global signal might be biologically meaningful [Schölvinck et al., 2010]. To explore the reproducibility of our results, in this study, we reanalyzed our data without regressing out global signal.

RESULTS

Table I summarizes participants' clinical and demographic characteristics. There were no group differences ($P > 0.5$) in age and gender, but the groups did differ in the years of education ($P = 0.001$). For the two patient groups, both illness duration and the severity of depression (HAMD scores) did not differ significantly ($P > 0.8$): the MDD-WoCN group had an average of 24.5 months of illness duration (range = 1–62 months; SD = 20.2) and an average HAMD score of 27.1 (range = 18–37; SD = 6.7), and the MDD-WCN group had an average of 20.2 months of illness duration (range = 1–78 months; SD = 23.1) and an average HAMD score of 27.0 (range = 18–40; SD = 7.7). There were also no significant differences in the classes of medications the patients were taking ($P = 0.89$). Notably, the two patient groups showed significantly different emotional neglect and physical neglect subscale scores ($P < 0.0001$): the MDD-WoCN group had an average score of 9.7 of emotional neglect (range = 6–11; SD = 1.3) and an average score of 6.5 of physical neglect (range = 5–8; SD = 1.1), whereas the MDD-WCN group had an average score of 15.2 (range = 9–23; SD = 3.8) and an average score of 11.4 (range = 5–19; SD = 3.3). When compared with the HC group, there were no significant differences in emotional and physical neglect subscale scores for the MDD-WoCN group, but there were significant differences for the MDD-WCN group.

Functional Connectivity Mapping

The functional connectivity strength maps are presented in Figure 1. Visual examination indicated that the spatial distributions of brain regions with high FCS were remarkably similar across the three groups in spite of some differences in strength. Those highly connected regions (i.e., higher FCS) were primarily located in several default-mode regions (mainly involving the bilateral medial frontal and parietal regions as well as lateral temporal and parietal regions), bilateral sensorimotor, and occipital regions (Fig. 1 A,B,C). Notably, these FCS maps among the three groups showed high spatial correlations ($r > 0.91$) (Supporting Information Fig. S1). Further ANCOVA analysis revealed significant group differences in FCS values mainly in the bilateral medial and lateral prefrontal regions, the medial temporal lobe, insula, and thalamus (Fig. 1D).

Compared with the HC group, the MDD-WoCN group showed significantly reduced FCS values in the bilateral ventral medial prefrontal cortex/ventral anterior cingulate cortex (vmPFC/vACC) (Fig. 2A), whereas the MDD-WCN group showed more widespread reductions of FCS mainly involving the bilateral vmPFC/vACC, dlPFC, dorsomedial prefrontal cortex (dmPFC), ventrolateral prefrontal cortex (vlPFC), insula, caudate, thalamus, parahippocampal gyrus, hippocampus, amygdala, and cerebellum (Fig. 2B). Notably, both the MDD groups showed an overlapping reduction of FCS values in the vmPFC/vACC (Fig. 2C). Furthermore, a direct comparison between the two patient groups revealed significantly reduced FCS values in the MDD-WCN group in many brain regions (Fig. 3), most of which (except the vmPFC/vACC) were identified when comparing MDD-WCN with controls. Moreover, the comparative results of two MDD groups remained little changed after taking disease duration and medication classes as covariates (Fig. 4A).

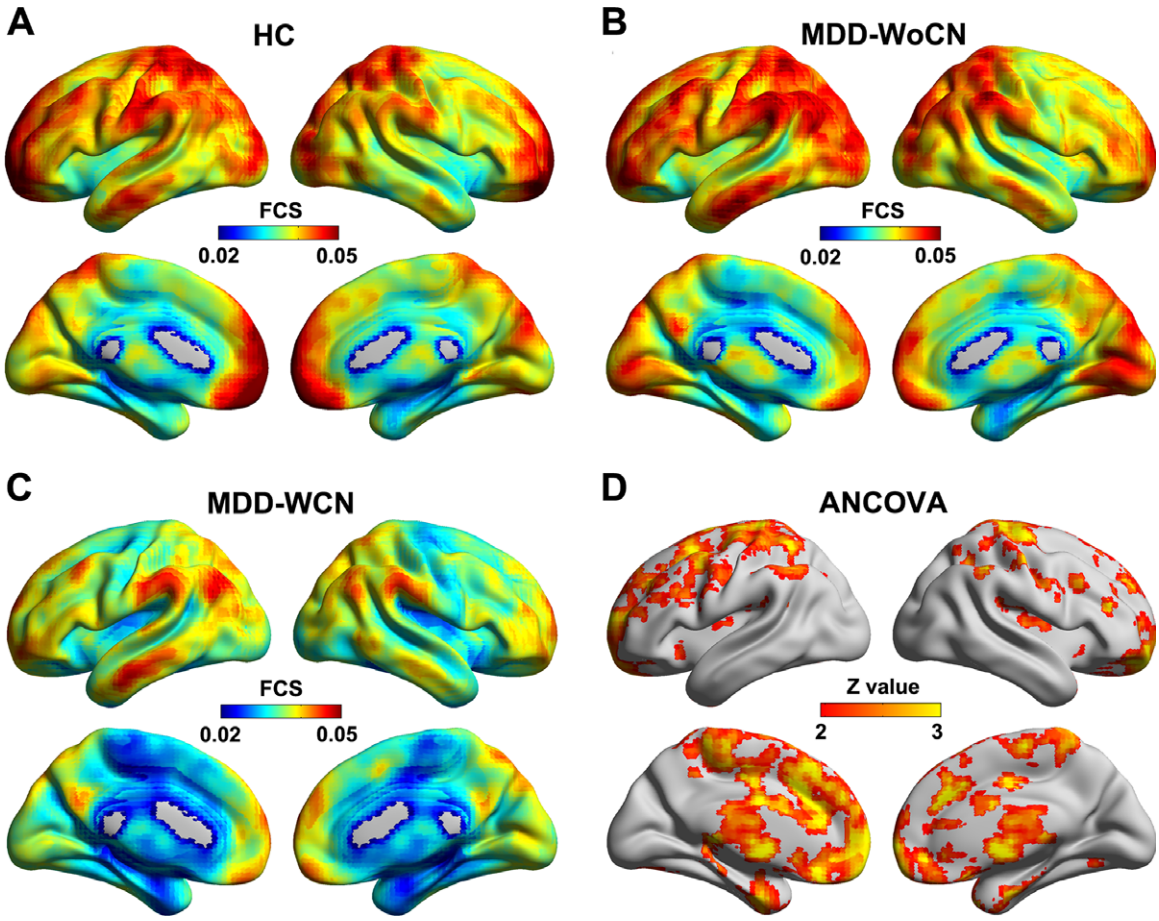

Figure 1.

Functional connectivity strength maps within groups and statistical differences across groups. Mean FCS maps within the HC group (**A**) ($N = 20$), MDD-WoCN group (**B**) ($N = 20$), MDD-WCN group (**C**) ($N = 18$). The color bars represent the strength of functional connectivity. **D**: Z-statistical difference maps across groups. The color bar indicates statistical significance threshold. Multiple comparisons were done by a combined $|z| > 1.96$ ($P < 0.05$) and cluster size $> 4{,}860$ mm^3, which corresponded to a corrected $P < 0.05$. The 3D maps were made by using the BrainNet Viewer (http://www.nitrc.org/projects/bnv/). FCS, functional connectivity strength; ANCOVA, one-way analysis of covariance; HC, healthy controls; MDD-WoCN, major depressive disorder patients without childhood neglect; MDD-WCN, major depressive disorder patients with childhood neglect. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Relationships Between Connectivity Measures and Clinical Variables

In the MDD-WCN group, we observed significant negative correlations between the emotional neglect subscale scores and regional FCS values in the bilateral thalamus, dmPFC, and dlPFC ($P < 0.05$, corrected) (Fig. 5). There were no significant correlations between the physical neglect subscale scores and regional FCS values. In the MDD-WoCN group, no significant correlations were observed between the emotional/physical neglect scores and FCS values.

Reproducibility of Our Findings

We found that our main results were reproducible after considering the effects of different correlation thresholds (Supporting Information Fig. S2), head motion (Supporting Information Fig. S3 and Fig. 4B) and without global signal removal (Supporting Information Fig. S4). It was worth mentioning that in the analysis with head motion covaried, a significant correlation was observed between physical neglect and the FCS of the lateral prefrontal cortex. Additionally, we also noticed that the differences in the FCS in the vmPFC between the MDD-WoCN patients and controls survived the height but not the extent threshold (1,350 mm^3) (Supporting Information Fig. S3). Without regressing the global signal out, we observed that the two MDD groups showed commonly decreased functional connectivity in the vmPFC/ACC, and different connectivity patterns in the insula, parahippocampal gyrus, and cerebellum (Supporting Information Fig. S4), which was consistent with those with global signal removal. However, it was noted that

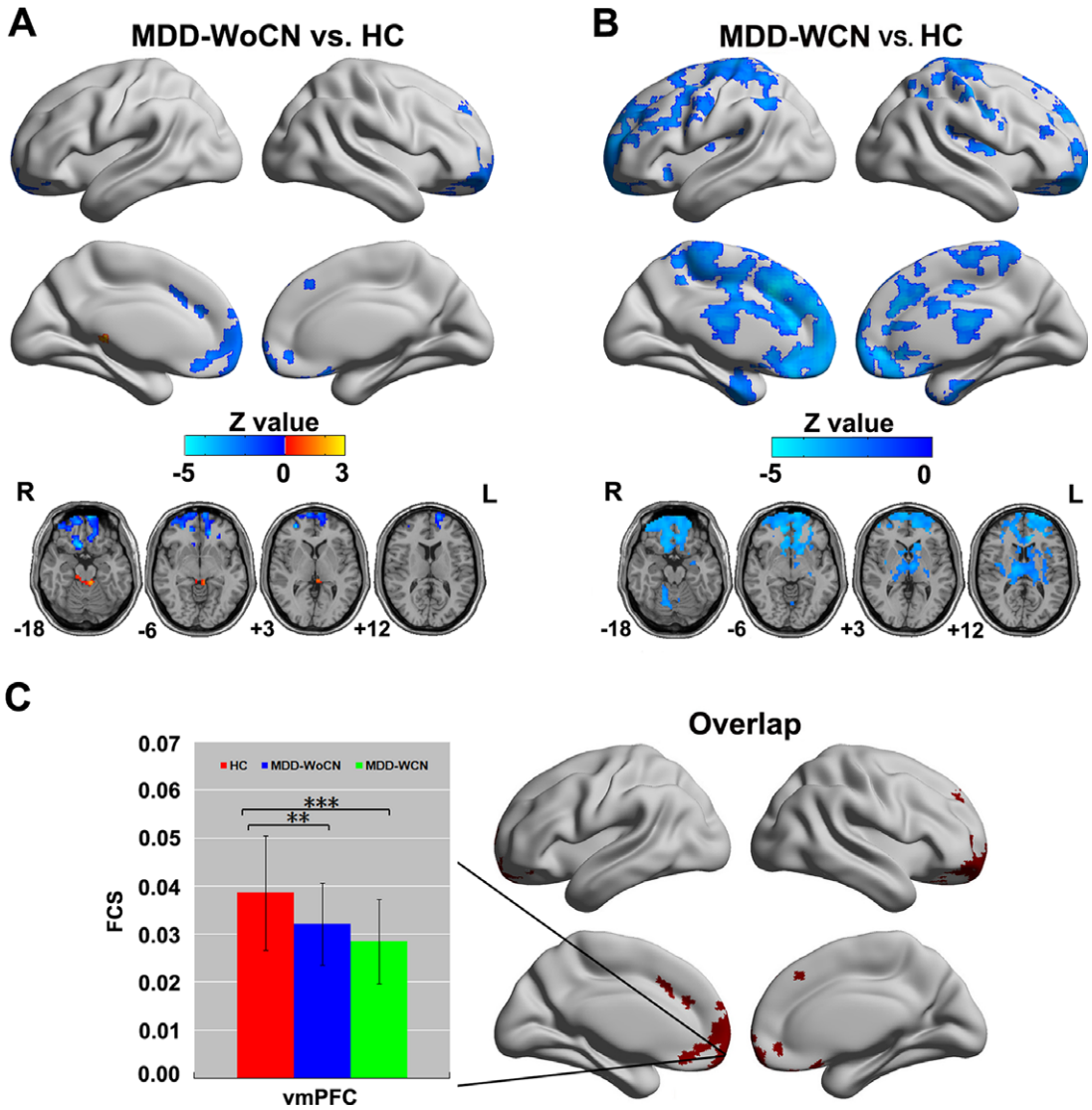

Figure 2.

Difference of functional connectivity strength maps between major depressive disorder patients and healthy controls. **A**: Z-statistical difference maps between MDD-WoCN patients and HC individuals. **B**: Z-statistical difference maps between MDD-WCN patients and HC individuals. The statistical significance threshold was set at $|z| > 1.96$ ($P < 0.05$), and cluster size $> 1{,}728$ mm^3, which corresponded to a corrected $P < 0.05$. Of note, the results of between-group comparisons were obtained within a mask showing significant differences in the ANCOVA analysis (Fig. 1D). **C**: The overlapping regions of statistical difference maps (A) and (B). The bar graph on the left represents connectivity strength values of the three groups at the peak of the ventral medial prefrontal cortex. $^{**}P < 0.01$; $^{***}P < 0.001$. HC, healthy controls; MDD-WoCN, major depressive disorder patients without childhood neglect; MDD-WCN, major depressive disorder patients with childhood neglect; R, right; L, left. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

without global signal removal, we found more widespread overlapped functional connectivity decreases in the two MDD groups and less between-group differences in FCS (Supporting Information Fig. S4 vs. Figs. 1–3).

DISCUSSION

In this study, we used R-fMRI and functional connectivity strength mapping approaches to study whole-brain networks in the MDD-WoCN and MDD-WCN groups, and in healthy controls. While the two MDD groups showed common alterations of functional connectivity in the vmPFC/vACC, we observed significant group differences as demonstrated by widespread reduction of functional connectivity strength within prefrontal-limbic-thalamic-cerebellar circuit in the MDD-WCN group. Importantly, these disrupted connections significantly correlated with childhood neglect measurements.

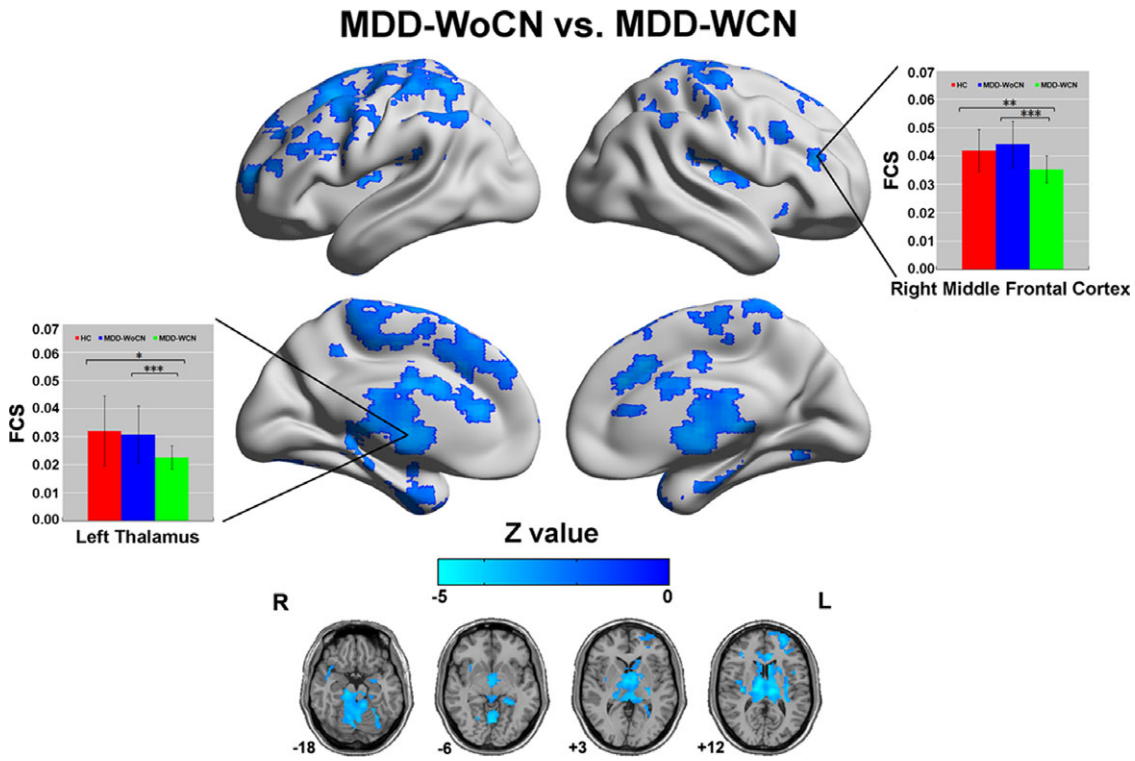

Figure 3.

Difference of functional connectivity strength maps between major depressive disorder patients with and without childhood neglect. *Z*-statistical difference maps between MDD-WoCN patients and MDD-WCN patients. The statistical significance threshold was set at $|z| > 1.96$ ($P < 0.05$), and cluster size $>$ 1,728 mm^3, which corresponded to a corrected $P < 0.05$. Of note, the results of between-group comparisons were obtained within a mask showing significant differences in the ANCOVA analysis (Fig. 1D). The two bar graphs demonstrate connectivity strength values of the three groups at the peak of the left thalamus and the right middle prefrontal cortex. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. HC, healthy controls; MDD-WoCN, major depressive disorder patients without childhood neglect; MDD-WCN, major depressive disorder patients with childhood neglect; R, right; L, left. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Both the MDD-WoCN and the MDD-WCN groups demonstrated decreased functional connectivity in the vmPFC/vACC. Accumulating research aimed at exploring the pathophysiological underpinnings of MDD and convergent evidence from neuroimaging, neuropathological, and lesion analysis studies suggests that neural circuits associated with vmPFC/vACC are centrally implicated in the pathophysiology of MDD [Phillips et al., 2003b; Price and Drevets, 2010). The vmPFC/vACC has extensive connectivity to many cortical and subcortical regions and the disregulation of these connectivities contributes to the disturbances of emotion, behavior, and cognition in depression [Myers-Schulz and Koenigs, 2012]. Our findings of reduced FCS in the vmPFC/vACC in both depressed patients further confirm that functional impairments in this region may be at the root of the pathogenesis of MDD.

Importantly, we showed the MDD-WCN patients are associated with reductions in FCS in prefrontal-limbic-cerebellar system when compared with the MDD-WoCN patients. Extensive, decreased functional connectivity in prefrontal cortex, especially in the dmPFC, vlPFC and in the dlPFC in MDD-WCN patients, are prominent findings in this study. In line with our study, previous structural imaging studies have shown prefrontal volume decreases in the MDD patients with a history of childhood neglect [Frodl et al., 2010a,b]. Furthermore, Gatt et al. [2010] found that exposure to childhood neglect, combined with genetic risks, predicted reduced gray matter volume in the lateral prefrontal cortex. The dlPFC is known to perform a variety of cognitive functions, such as the maintenance and manipulation of information in working memory, intention formation, goal-directed action, abstract reasoning, decision-making, and attentional control [Miller and Cohen, 2001]. Recent studies also suggest that dlPFC-mediated cognitive control functions may also pertain to emotion [Ray and Zald, 2012]. Specifically, functional imaging studies demonstrate the recruitment of dlPFC during the regulation of negative emotion through reappraisal/suppression strategies [Levesque et al., 2003; Ochsner et al., 2002; Phan et al.,

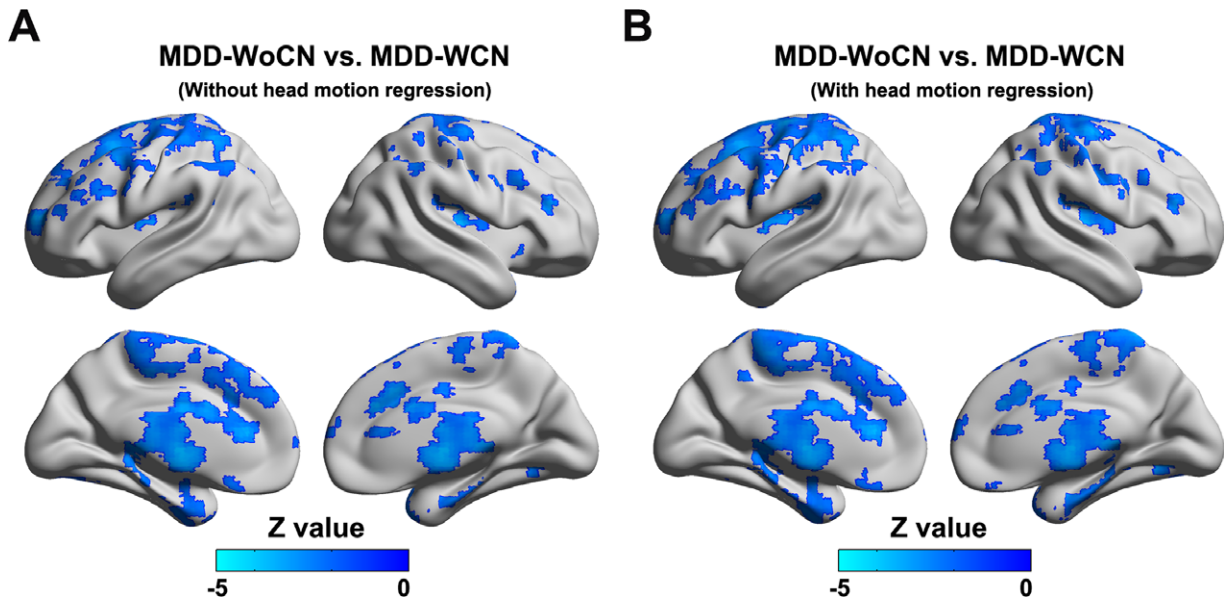

Figure 4.

Difference of functional connectivity strength maps between major depressive disorder patients with and without childhood neglect after taking disease duration and medication classes as additional covariates with and without head motion regression. **A**: *Z*-statistical difference maps between MDD-WoCN and MDD-WCN groups after removing the effects of disease duration and medication classes. **B**: *Z*-statistical difference maps between MDD-WoCN and MDD-WCN groups after removing the effects of disease duration, medication classes and head motion. The statistical significance threshold was set at $|z| > 1.96$ ($P < 0.05$), and cluster size $> 1{,}728$ mm^3, which corresponded to a corrected $P < 0.05$. Of note, the results with between-group comparisons were obtained within a mask showing significant group differences in the ANCOVA analysis (Fig. 1D). HC, healthy controls; MDD-WoCN, major depressive disorder patients without childhood neglect; MDD-WCN, major depressive disorder patients with childhood neglect; R, right; L, left. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

2005]. The vlPFC has been implicated in a wide range of cognitive control mechanisms involving response inhibition and inhibitory control [Aron et al., 2003, 2004]. Evidence also exists for vlPFC involvement in emotional control together with the dlPFC [Ray and Zald, 2012]. The dmPFC is suggested to play a central role in aspects of cognitive control and emotional regulation as well [Phillips et al., 2003b; Venkatraman et al., 2009]. The reductions of FCS in these PFC regions, identified by us in the study, suggest that MDD-WCN patients are associated with disruption in a neural system that subserves cognitive and emotional control functions, and which may be related to cognitive bias. This is in accordance with the evidence that for depressed patients with childhood trauma, psychotherapy was more effective than pharmacotherapy [Nemeroff et al., 2003].

Another major finding in this study was reduced FCS in the limbic system in MDD-WCN individuals relative to that in MDD-WoCN patients. The limbic system is the central part of the "emotional brain" circuitry, dedicated to the processing and regulation of emotion [Phillips et al., 2003a; Roxo et al., 2011]. Moreover, through its role in memory and in the integration of memory with physiological sensations and affective states, the limbic system functions to make emotion-based decisions adapted to the current environment based on previous experience [McDonald and White, 1993]. Top-down and bottom-up disruptions to limbic circuits have been implicated in the pathogenesis of MDD [Fitzgerald et al., 2008; Mayberg et al., 1999; Phillips et al., 2003b]. Meanwhile, structural and functional alterations in this system are also found in adults reporting childhood maltreatment. For example, many structural imaging studies have consistently demonstrated reduced hippocampal volume in adults with childhood maltreatment [Bremner et al., 2003; Driessen et al., 2000; Frodl et al., 2010b; Vythilingam et al., 2002]. Moreover, a previous study has shown that the depressive patients had smaller hippocampal volumes if they experienced an emotional neglect [Frodl et al., 2010b]. There was also evidence that a small hippocampal volume was associated with the early life trauma and the onset of depression [Rao et al., 2010]. Volume decreases in ACC, caudate, amygdala and insula have also been shown in studies of adults reporting childhood maltreatment with and without psychiatric diagnosis [Cohen et al., 2006; Dannlowski et al., 2012; Driessen et al., 2000; Edmiston et al., 2011]. Furthermore, studies in rodents and non-human primates suggest maternal separation or low maternal care—which are often used as models of human neglect—induces

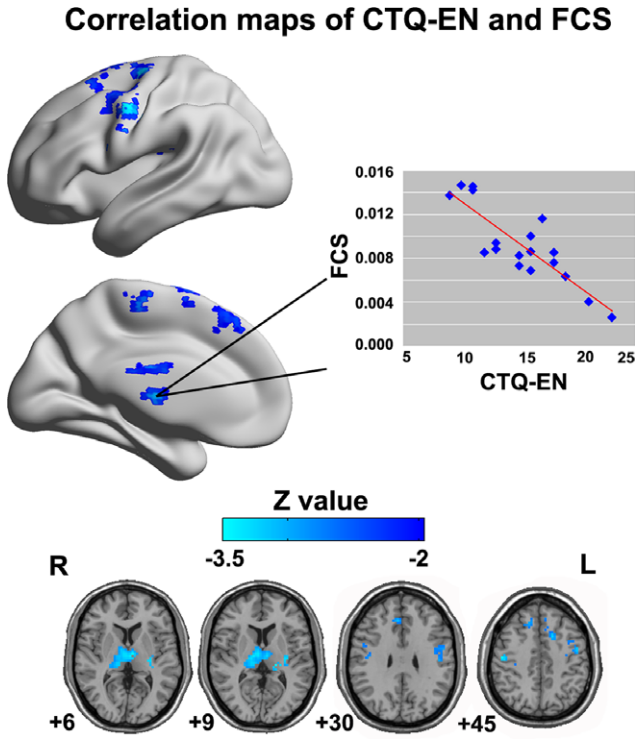

Figure 5.

Relationship of childhood emotional neglect and functional connectivity strength. Correlation maps of CTQ-EN score and FCS values in patients with MDD-WCN patients. The statistical significance threshold was set at $|z| > 1.96$ ($P < 0.05$), and cluster size $>$ 1,620 mm^3, which corresponded to a corrected $P < 0.05$. Of note, the correlation results were obtained within a mask showing significant group FCS differences between the MDD-WCN and the HC group (Fig. 2B). The representative scatter plots between FCS values of the peaks of the left thalamus and CTQ-EN score are presented in the top right panel. FCS, functional connectivity strength; CTQ-EN, emotional subscale of childhood trauma questionnaire; MDD-WCN, major depressive disorder patients with childhood neglect; R, right; L, left. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

persistent structural and functional changes in this neural circuit [Sanchez et al., 2001; Spinelli et al., 2009]. Particularly, previous brain imaging studies have demonstrated structural and functional distinctions in the limbic areas between the depressed patients with and without childhood trauma. For instance, Vythilingam et al. [2002] found a smaller hippocampal volume in MDD adults who had a history of childhood trauma than those without such a history. Using selected Ekman faces as stimuli, Grant et al. [2011] observed that depressed patients with a history of early life trauma had enhanced amygdale response to negative stimuli but not those without such a history. These studies provide further supports for our findings of disrupted functional connectivity in the limbic system.

The thalamus and the cerebellum also exhibited decreased functional connectivity in the MDD-WCN group compared with the MDD-WoCN group. Through extensive connectivity to cortical and subcortical circuits, the thalamus is a vital region in the establishment of oscillatory dynamics that integrate brain function [Jones, 2001; McCormick, 1992; Steriade, 2006], and it is believed to play a key role in the experience and expression of emotion and in stress responses [Price and Drevets, 2010]. The observation of FCS reduction is consistent with the findings of a meta-analysis which reported gray matter decrease in the thalamus in MDD [Du et al., 2012]. This result is also in accordance with resting-state fMRI studies showing decreased functional connectivity in the thalamus in depressed subjects relative to healthy controls [Anand et al., 2005; Lui et al., 2011]. The cerebellum is anatomically connected with the frontal cortex and the limbic regions, and there is ample evidence that the cerebellum not only subserves motor function, but also has roles in emotional and cognitive processes [Schmahmann and Caplan, 2006]. The involvement of the cerebellum in the neuropathology of MDD has recently been reported in neuroimaging studies [Guo et al., 2011; Liu et al., 2010]. Moreover, studies have also shown that cerebellar volume reductions are associated with childhood neglect [Bauer et al., 2009; Edmiston et al., 2011].

There are some possibilities for the widely impaired functional connectivity in frontal-limbic-thalamic-cerebellar regions in MDD subjects having suffered childhood neglect. Neglect basically involves a lack of appropriate stimulation or interaction needed by the brain during maturation [De Bellis, 2005]. Deprivation of developmentally appropriate experience may reduce neuronal activity, resulting in a generalized decrease in neurotrophin production, synaptic connectivity, neuronal survival, and ultimately resulting in profound abnormalities in brain organization and connectivity of brain networks [Anda et al., 2006]. Additionally, neglect may be experienced by a child, a member of social species, as traumatic, and leading to disruption of typical neurodevelopmental processes and long-term negative consequences [De Bellis, 2005]. The neurodevelopmental anomalies linked to chronic exposure to childhood neglect, inhibit the successful developmental of cognitive, emotional, and behavioral functions, which in turn increases the risk for the development of depression.

Several issues need to be addressed further. First, childhood trauma evaluation was done retrospectively, which may involve some degree of inaccurate information. The CTQ has been shown to have very good sensitivity and specificity, however, future studies would benefit from a prospective analysis of the relationship between childhood neglect and subsequent changes in functional connectivity based on an interview-based measure of childhood trauma. Second, the MDD participants were using antidepressants. The effect of antidepressants medications on the resting-state functional networks in depression is still

unclear, although recent studies suggested that antidepressants seemed to normalize brain function [Anand et al., 2005; Fu et al., 2007]. After removing the effect of medication classes in our study, the comparative results of two MDD groups remained little changed. The future studies would analyze the data from drug-naive MDD patients, but that would face substantial practical and ethical difficulties. Third, there are currently many graph metrics that can be used to describe the topological properties of brain networks. In this study, we focused mainly on the nodal functional connectivity strength (i.e., weighted degree centrality) as it is very hard to compute other graph attributes (e.g., small-world and modularity) in a huge network with 67,632 nodes due to a highly computational load. In the future, it would be interesting to compute these graph metrics of voxel-based brain networks with the help of high-performance computing systems. Fourth, there is currently no consensus whether whole-brain signal should be removed in the imaging preprocessing stage. In this study, we regressed out the global signal to reduce the effects of the respiration [Birn et al., 2006; Chang and Glover, 2009]. While reanalyzing the data without regressing out global signal, our main findings were still observed. However, we also noticed that there were widespread differences in the results between two processes (Supporting Information Fig. S4 vs. Figs. 1–3). It indicates that the global signal might be biologically meaningful, which needs to be careful to deal with in the future study. Finally, a combined analysis of multimodal imaging data would provide integrated information on the underlying neurophysiological mechanisms of MDD with and without child neglect.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Robert Wohlhueter for English-language editing of this article.

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