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White-matter density abnormalities in depressive patients with and without childhood neglect: A voxel-based morphometry (VBM) analysis

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HIGHLIGHTS

- White-matter density abnormalities in IPL in depression with childhood neglect.
- Abnormal white-matter densities in sub-lobar extra-nuclear in those without childhood neglect.
- Dysfunctional attitudes are related to abnormal white-matter densities in IPL.

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ABSTRACT

Childhood maltreatment (abuse or neglect) can result in changes to the brain structures and functions that underlie adult depression. Few studies have explored the impact of childhood maltreatment on white-matter microstructure, especially for childhood neglect. Nineteen depressive patients who experienced childhood neglect, 21 depressive patients who did not experience childhood neglect, and 20 healthy control subjects were compared in this study. The Childhood Trauma Questionnaire (CTQ), Hamilton Depressive Rating Scale (HAMD), Self-Rating Depression Scale (SDS), and Dysfunctional Attitude Scale (DAS) were used to evaluate each subject. High-resolution T1-weighted 3 T magnetic resonance imaging scans and a whole-brain optimized voxel-based morphometry (VBM) approach were also used. Compared with healthy controls, the depressive group of subjects with childhood neglect showed significantly lower white-matter densities in the bilateral inferior parietal lobe (IPL) [43 −32 24] [−42 −42 25], whereas the depressive group without childhood neglect showed significantly lower densities in bilateral sub-lobar extra-nuclear white matter [27 −15 16] [−27 32 4]. White-matter densities in the bilateral sub-lobar extra-nuclear [−25 −17 18] [27 −13 20] and right brainstem midbrain [9 −34 −13] regions were higher in the depressive patients with childhood neglect than in the depressive patients without childhood neglect. White-matter densities in the bilateral inferior parietal lobe were negatively correlated with neglect total scores on the CTQ and with HAMD and DAS scores. White-matter densities in the bilateral sub-lobar extra-nuclear region were only negatively correlated with HAMD scores. Subjects that have depression with or without childhood neglect show different white-matter microstructural abnormalities.

1. Introduction

Many studies have examined the pathogenesis of depression [3]. One of the most consistent viewpoints is that interactions between genetic predispositions and the environment contribute to depression [22]. Child maltreatment is an external environmental factor can lead to internal biological changes involving endocrine and neurobiological systems [13]. One hypothesis of biological vulnerability suggests that childhood adversities lead to changes to the

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brain structures and functions that underlie adult depression [13]. An alternative hypothesis of cognitive vulnerability suggests early adverse experiences may distort normal views of the self and the world [15]. Both theories support the belief that childhood maltreatment is closely related to adult depression.

Childhood maltreatment includes child abuse, neglect, and other forms of early adverse experiences [9]. Some studies have suggested that the combination of depression and childhood maltreatment may be a functional subtype of depression, as it includes distinct changes in brain structure and function and in the endocrine system [19]. To date, few studies have explored the impact of childhood maltreatment, especially childhood neglect, on white-matter microstructure in depressive patients. Childhood neglect is the most common form of childhood maltreatment in the United States [9]. It is defined by a lack of provision of medical care, education, supervision, protection from unsafe environments, physical needs (e.g., food, shelter, and clothing), and emotional support [28]. The absence of a child's basic needs can result in neuropsychological changes [9]. One prospective investigation showed that both childhood physical abuse and neglect were associated with an increased risk for depression in young adulthood [35]. Another study found emotional neglect was associated with significant reductions in predominantly left dorsal medial PFC gray matter volumes [31]. Teicher et al. reported that childhood neglect was associated with reduced regional corpus callosum areas, which suggested that early experience may affect the development of this region [29]. Frodl et al. reported that left hippocampal white matter is smaller in patients who experienced emotional childhood neglect than in those who did not experience neglect, and there are significant interactions between emotional neglect and prefrontal volumes and hippocampal white matter [10]. In addition, some researchers have suggested that childhood neglect may cause insufficient stimulation of specific brain areas related to sensation, cognition, and affective regulation, and changes in these areas may underlie adult depression [12]. Therefore, in this study, we hypothesized that childhood neglect affects the structure and function of specific brain areas related to sensation, perception, cognition, and affective modulation.

2. Materials and methods

2.1. Subjects

One hundred and fifteen depressive patients between the ages of 18 and 45 years were recruited from the inpatient and outpatient units at the Institute of Mental Health at the second Xiangya Hospital of Central South University. The structured clinical interview (SCID) for DSM-IV diagnostic criteria was used to assess the presence or absence of major depressive disorder (MDD). Any patient with other psychiatric axis-I or axis-II disorders, any other neurological disorder, any substance use within the past 6 months, electroconvulsive therapy, any kind of contraindication for magnetic resonance imaging (MRI), and any other clinically relevant abnormalities in their medical history or laboratory examinations was excluded. The Childhood Trauma Questionnaire (CTQ) was used to evaluate childhood maltreatment. A 17-item Hamilton Depressive Rating Scale (HAMD) and Zung's Self-Rating Depression Scale (SDS) were used to evaluate depression severity [38]. The Dysfunctional Attitude Scale (DAS) was used to evaluate the dysfunctional attitude of the subject. In this study, childhood emotional and physical neglect were assessed using the Childhood Trauma Questionnaire (CTQ), and the cutoff score for moderate-severe exposure was set at $\geq$15 for emotional neglect, $\geq$10 for physical neglect, or $\geq$20 for comorbid emotional and physical neglect, excluding any other form of childhood trauma through subscale scores on the CTQ of less than 8 [32]. A lack of childhood neglect in our study was defined by a determination of a value of less than 8 on all CTQ subscale scores. Of the 115 depressive patients we examined, 31 met the criteria for childhood neglect, and 19 of these subjects underwent MRI. Moreover, 21 patients without childhood neglect were also scanned. There were no significant differences in age, gender, illness course, severity of depression, or treatments received (no patient had been treated by systemic psychotherapy, and the patients were primarily treated using selective serotonin reuptake inhibitors) between the two depressive groups. In addition, 20 sex- and age-matched healthy controls were recruited from the local community. Before enrollment, all subjects were fully informed of the details of the study and written informed consent was obtained. These studies were performed according to the Declaration of Helsinki and approved by the Central South University Ethics Committee.

2.2. MRI

2.2.1. Image acquisition

Imaging data were acquired using a Philips 3 T MR system (Philips, Best, The Netherlands) located at the second Xiangya hospital of Central South University. For each subject, an anatomical image was obtained using a sagittal three-dimensional gradient-echo T1-weighted sequence (TR = 7.6 ms, TED = 3.7 ms, TI = 795 ms, flip angle = 8°, 180 slices, slice thickness = 1 mm, gap = 0 mm, matrix = 256 × 256, inversion time = 0).

2.2.2. Image processing

An optimized VBM approach was conducted using DARTEL [1] implemented in SPM5 (Statistical Parametric Mapping software; http://www.fil.ion.ucl.ac.uk/spm). The images were first reoriented to the anterior commissure, and then, a standard segmentation option was used to segment the anatomical images. The images then underwent registration, normalization, and modulation, leaving the images in DARTEL space by applying the DARTEL approach. Finally, we smoothed the WM images using an 8-mm, full-width-at-half-maximum Gaussian kernel.

2.2.3. VBM and statistical analysis

Absolute total white-matter volumes were calculated using white-matter segments in native space. Using age and total absolute white matter as covariates to correct for total brain volume, smoothed white-matter density images were entered into a voxel-by-voxel analysis of variance for between-group comparisons. Voxel-wise comparisons were masked using a comparison-specific explicit optimal threshold white-matter mask created using a Masking toolbox (http://www.cs.ucl.ac.uk/staff/g.ridgway/masking).

Analyses of variance (ANOVA) were used to compare differences in white-matter densities among the depressive patients with and without childhood neglect and normal control subjects. Post hoc testing was used to compare differences in white-matter densities between any two groups. We retrieved white-matter densities from identified clusters (the bilateral inferior parietal lobe and sublobar extra-nuclear region) with a custom-developed program as previously described [18], and we analyzed these clusters using SPSS17.0 software. We performed a multiple-correlation analysis to estimate the relationship between average white-matter density values and CTQ, HAMD, and DAS scores. A statistical threshold of $P < 0.05$ (two-tailed) was used to accept statistical significance.