Prefrontal Cortical Volume in Childhood-Onset Major Depression

Preliminary Findings

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Background: Abnormalities in the prefrontal cortex have been implicated in the pathogenesis of major depressive disorder (MDD). To our knowledge, no prior study has examined prefrontal cortical anatomy in pediatric patients with MDD near the onset of illness before receiving treatment.

Methods: Volumetric magnetic resonance imaging studies were conducted in 22 psychotropic-naive patients with MDD, aged 9 to 17 years (10 males and 12 females), and 22 case-matched healthy comparison control subjects. Twelve of the 22 patients with MDD had at least 1 first-degree relative with MDD (familial MDD), whereas 10 had no clear family history of MDD (nonfamilial MDD).

Results: Patients with nonfamilial MDD had significantly larger left-sided but not right-sided prefrontal cortical volumes than patients with familial MDD (17% larger) and controls (11% larger). Left-sided and right-sided prefrontal cortical volumes did not differ significantly between patients with familial MDD and controls.

Conclusions: These results provide new evidence of prefrontal cortical alterations in pediatric MDD that may differ in familial and nonfamilial subtypes of MDD. Our findings must be considered preliminary, however, in view of the small sample size.

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Major depressive disorder (MDD) is a severe, prevalent, and often chronically disabling illness that is continuous with adult MDD. The lifetime prevalence of pediatric MDD is 15% to 20% consistent with reported rates in adult patients with MDD. Investigations of younger patients with MDD can minimize potentially confounding factors such as illness duration and treatment intervention and may begin to clarify the contribution of neurodevelopmental abnormalities to the pathogenesis of MDD.

The prefrontal cortex plays a critical role in mood regulation (see Byrum et al for review). Abnormalities in the prefrontal cortex have, therefore, been hypothesized to be involved in causing depressive symptoms. The positive correlation between increased severity of depression in patients with strokes and closeness of the lesion to the frontal pole combined with increased rates of MDD in patients with frontal lobe lesions provide indirect support for this hypothesis. More direct evidence comes from functional neuroimaging studies in adult patients with MDD who demonstrate prefrontal cortical (PFC) abnormalities associated with severity of depression and treatment response.

Dolan et al observed increased magnetic resonance imaging (MRI) T1-weighted values in the frontal white matter of patients with MDD but not bipolar disorder. Increased frontal lobe white matter hyperintensities may be especially prominent in elderly patients with late-onset MDD, particularly those with underlying cerebrovascular disease originating from atherosclerotic disease. Krishnan et al noted decreased frontal brain width in elderly patients with MDD vs control subjects. Coffey et al subsequently found a 7% reduction in the total frontal lobe volume in 44 elderly patients with MDD referred for electroconvulsive therapy vs controls. More recently, Kumar et al reported an overall decrease in frontal lobe volume and an increased number of frontal lesions in elderly patients with depression. In contrast, Brenner et al found no significant differences in frontal lobe volumes in younger adult patients with MDD (mean age, 43 years) in remission from antidepressant treatment compared with controls. Steingard et al, however, observed decreased frontal lobe—
20 patients with MDD near-illness onset, before exposure to medication treatment.48-50 The prefrontal cortex, a primary site of metabolic abnormality in MDD, undergoes substantial developmental changes during childhood and adolescence. Therefore, we performed a volumetric MRI study in pediatric patients with MDD, focusing on the prefrontal cortex. We hypothesized reduced left-sided but not right-sided PFC volumes in familial patients with MDD compared with both nonfamilial patients with MDD and healthy comparison subjects.

RESULTS

Intracranial volume and left- and right-sided PFC volumes did not differ significantly between the 22 MDD case-control pairs (Table 1). The ANCOVA with age and intracranial volume as covariates revealed significant intergroup differences in left-sided but not right-sided total PFC volume or prefrontal gray and white matter volumes (Table 2). Post hoc tests revealed that patients with nonfamilial MDD had larger left-sided but not right-sided total PFC volumes and prefrontal white matter volumes than both patients with familial MDD and controls. Left- and right-sided total PFC white matter and gray matter volumes did not differ between patients with cerebral volume ratios in adolescent patients with MDD compared with healthy controls. Postmortem investigation of the prefrontal cortex has identified reduced neuronal and glial densities in the prefrontal cortex of patients with MDD compared with controls. In vivo neuroimaging studies in adult patients with MDD and bipolar disorder have identified reductions in left-sided PFC gray matter volumes associated with reduced cerebral blood flow in this region. These abnormalities were most prominent in patients with MDD and bipolar disorder with at least 1 first-degree relative with MDD or bipolar disorder but were not observed in patients with MDD and bipolar disorder without at least 1 first-degree relative with MDD or bipolar disorder. In a related postmortem histological study, Ongur et al observed a reduction in glial number in the prefrontal cortex in familial but not nonfamilial MDD and bipolar disorder.

Twenty percent to 46% of the patients with MDD have a first-degree relative with MDD with an inverse relationship between age of onset of MDD and density of familial loading of MDD.32-47 Although MDD commonly emerges during childhood and adolescence, to our knowledge, no prior brain imaging study has examined patients with MDD near-illness onset, before exposure to psychotropic medication. Studying this population helps minimize potential confounders of illness duration and medication treatment.48-50 The prefrontal cortex, a primary site of metabolic abnormality in MDD, undergoes substantial developmental changes during childhood and adolescence. Therefore, we performed a volumetric MRI study in pediatric patients with MDD, focusing on the prefrontal cortex. We hypothesized reduced left-sided but not right-sided PFC volumes in familial patients with MDD compared with both nonfamilial patients with MDD and healthy comparison subjects.

ASSSESSMENTS

Depression symptom severity was measured by the Childhood Depression Rating Scale-Revised34 (mean±SD score, 57.27±8.64). All patients had a Childhood Depression Rating Scale-Revised score of at least 42, indicative of significant dysfunction. Severity of anxiety was also assessed with the Hamilton Anxiety Rating Scale35 (mean±SD score, 12.41±8.07). A score of 14 or higher is considered clinically significant.56 A screening neuropsychological examination revealed no abnormalities and no significant differences between patients with MDD and controls in general intelligence as measured by the Ammons Quick IQ Test,57 motor coordination assessed with the Grooved Pegboard Test,58 attention measured with the Digit Span scaled score from the Wechsler Intelligence Scale for Children59 or handedness measured by the Annett Behavioral Handedness Index.60 One patient with MDD was unable to complete the neuropsychological screening because of severity of illness.

MRI ACQUISITION AND ANALYSIS

The MRI studies were conducted with a 1.5-T (version 5.7; GE Signa; General Electric, Milwaukee, Wis) magnetic resonance imaging scanner. The high-resolution 1.5-T GE Signa was chosen to optimize the signal-to-noise ratio. Whole-brain T1-weighted and T2*-weighted images were obtained using high spatial and temporal resolution. Intracranial volume and left- and right-sided PFC volumes did not differ significantly between the 22 MDD case-control pairs (Table 1). The ANCOVA with age and intracranial volume as covariates revealed significant intergroup differences in left-sided but not right-sided total PFC volume or prefrontal gray and white matter volumes (Table 2). Post hoc tests revealed that patients with nonfamilial MDD had larger left-sided but not right-sided total PFC volumes and prefrontal white matter volumes than both patients with familial MDD and controls. Left- and right-sided total PFC white matter and gray matter volumes did not differ between patients with cerebral volume ratios in adolescent patients with MDD compared with healthy controls. Postmortem investigation of the prefrontal cortex has identified reduced neuronal and glial densities in the prefrontal cortex of patients with MDD compared with controls. In vivo neuroimaging studies in adult patients with MDD and bipolar disorder have identified reductions in left-sided PFC gray matter volumes associated with reduced cerebral blood flow in this region. These abnormalities were most prominent in patients with MDD and bipolar disorder with at least 1 first-degree relative with MDD or bipolar disorder but were not observed in patients with MDD and bipolar disorder without at least 1 first-degree relative with MDD or bipolar disorder. In a related postmortem histological study, Ongur et al observed a reduction in glial number in the prefrontal cortex in familial but not nonfamilial MDD and bipolar disorder.

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familial MDD and controls. Left-sided PFC gray matter volumes were smaller in patients with familial MDD than in patients with nonfamilial MDD. Intracranial volume did not differ among patients with familial MDD, patients with nonfamilial MDD, and controls. Significant inverse correlations were observed in patients with familial MDD between severity of MDD as measured by the Childhood Depression Rating Scale-Revised and total left-sided PFC volume (r = -0.66, P = .03), left-sided prefrontal gray matter (r = -0.67, P = .023) but not left-sided prefrontal white matter volume. Although not statistically significant, longer illness duration tended to be inversely correlated with reduced total left-sided PFC volume (r = -0.57, P = .07), left-sided prefrontal gray matter (r = -0.58, P = .06) but not left-sided PFC white matter. Illness duration and severity were not associated with PFC volumes in patients with nonfamilial MDD. Comparable ages were observed in male (13.43 ± 2.70 years) and female patients (13.90 ± 2.26 years) with MDD. No sex-related differences were noted in PFC and intracranial volumes between patients with MDD and controls.

Assessment of group by side (left-right) interactions for PFC volume revealed a significant group effect (F(2,87) = 4.33, P = .02) and a significant interaction with side (F(1,87) = 11.06, P = .001). Although there was a significant hemisphere difference in mean PFC volume, the magnitude of difference varied across group so that the interaction, while present, was a weak interaction given no crossover of the mean PFC values (F(2,87) = 0.84, P = .44).

Alterations in left-sided PFC volume were most prominent in patients with nonfamilial MDD who had larger left-sided PFC volumes than both patients with familial MDD (17%) and controls (11%). This hypothesis-driven, preliminary investigation failed to replicate in vivo neuroimaging and postmortem investigation in adult patients with MDD and bipolar disorder that found reductions in left-sided prefrontal gray matter volumes, cerebral blood flow, and glial number in patients with at least 1 first-degree relative with MDD compared with both controls and patients without at least 1 first-degree relative with MDD or bipolar disorder. Our study provides new data about distinct differences in PFC anatomy in patients with familial and nonfamilial MDD without the confounders of central nervous system–active medications and with less potential influence of disease progression. Specifically, abnormalities in PFC anatomy may be associated with the clinical presentation of MDD, and this pathological involvement may be an early and central neurobiological deficit in the illness.
The association of reduced left-sided PFC volume with increased depressive symptom severity in patients with familial MDD but not nonfamilial MDD may reflect a continuum of illness in which reduction of left-sided PFC volume increases with increased severity of illness and duration of illness. The results of this study, as well as studies in adult patients with MDD demonstrating that PFC abnormalities are most prominent in patients with a clear family history of MDD or bipolar disorder, suggest that prefrontal volume reduction in patients with familial MDD may reflect left-sided PFC degeneration. Increased left-sided PFC volume in treatment-naive pediatric patients with nonfamilial MDD may, in contrast, reflect abnormal PFC maturation. These arguments must be considered speculative, however. Our division of patients with MDD into familial and nonfamilial MDD was arbitrary and does not consider patients with several relatives (e.g., grandparents) who have MDD. Future studies with more precise delineation of familial and nonfamilial subtypes of MDD are clearly warranted.

It is possible that comorbid disorders associated with familial and nonfamilial patients with MDD might have a differential influence on brain anatomy and potentially confound results in this study. Seven of the 12 patients with familial MDD had comorbid DSM-IV Axis 1 psychiatric disorders, while 7 of the 10 patients with nonfamilial MDD had comorbid disorders. Comorbid anxiety disorders were also comparable in both groups (5 patients with familial MDD and 3 patients with nonfamilial MDD). However, all 3 patients with oppositional defiant disorder were patients with nonfamilial MDD. Patients with nonfamilial MDD had significantly larger left-sided PFC volumes compared with both patients with familial MDD and controls. Major depressive disorder with comorbid oppositional defiant disorder could, therefore, represent a discrete subtype of MDD with a differential influence on brain anatomy. The small sample size in the present study precludes more definitive conclusions but merits further investigation since MDD is commonly associated with comorbid psychiatric conditions.

Consistent with neuroimaging studies in adult patients with MDD, we observed greater alterations in left-than right-sided PFC volumes in treatment-naive pediatric patients with MDD. Although definitive conclusions regarding laterality and depression cannot be made at this time, a recent review of the literature found that left hemisphere lesions were more frequently associated with depression, while right hemisphere lesions were more commonly associated with mania.

To our knowledge, our study is the first to report increased left-sided PFC white matter volumes in patients with nonfamilial MDD compared with both patients with familial MDD and controls. Drevets et al did not report PFC white matter volumes in their sample of adult patients with MDD and bipolar disorder. This may have important implications in the pathogenesis of MDD since white matter plays a critical role in signal conduction and neurotransmission. Prefrontal cortical white matter lesions and abnormalities have been reported in adult patients with MDD and bipolar disorder. The prefrontal cortex distributes terminal fibers through white matter to the hippocampus, a component of the limbic system.
system that plays a particularly critical role in emotion.73-75 Alterations in hippocampal volumes have been reported in adults with MDD.76-78

Many brain regions have been implicated in the neuroanatomy of MDD.6-8 Our findings suggest that the relevant brain circuits underlying the pathophysiology of pediatric MDD likely include the prefrontal cortex with distinct patterns in pediatric patients with familial vs nonfamilial MDD. However, it is likely that several other regions and abnormalities in regional interaction are involved in the pathogenesis of this heterogeneous and complex disorder. Our findings are preliminary in view of the small sample size and require replication in a separate, larger cohort before more definitive conclusions can be drawn. In vivo neuroimaging14,64 and postmortem investigations31 in adult patients with MDD have focused on specific subdivisions of the prefrontal cortex (eg, subgenual region) where volumetric reductions as high as 40% have been observed.13-15 Such an approach may identify subtle localized region-specific alterations in PFC volume. Thus, future neuropathological as well as in vivo neuroimaging studies are critical to examine subdivisions of the prefrontal cortex as well as other brain regions including the amygdala, hippocampus, and basal ganglia that may also be involved in the pathogenesis of pediatric MDD.5-8 Recent studies also suggest the feasibility of investigating PFC function and chemistry in vivo using functional19,80 and spectroscopic imaging techniques.79,80 These studies must control for potential neuroanatomical differences and subtypes of illness (eg, familial vs nonfamilial) for appropriate data interpretation. Given the evidence that PFC function continues to develop throughout adolescence into early adulthood,81-83 studies of prefrontal cortex in MDD may help to identify critical windows for treatment intervention. Studies in children at high risk for developing MDD may also be helpful given recent neuroendocrine studies demonstrating abnormalities in this population.84

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Table 1. Volumetric Results for Treatment-Naive Patients With MDD and Healthy Control Subjects*

<table>
<thead>
<tr>
<th>Region</th>
<th>Treatment-Naive Patients With MDD (n = 22)</th>
<th>Healthy Control Subjects (n = 22)</th>
<th>95% Confidence Interval of Difference Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial volume</td>
<td>1224.87 (198.06)</td>
<td>1158.62 (116.19)</td>
<td>66.25 (165.05-32.54)</td>
</tr>
<tr>
<td>Left PFC, total</td>
<td>70.02 (11.15)</td>
<td>68.64 (9.78)</td>
<td>1.38 (7.76-5.01)</td>
</tr>
<tr>
<td>Right PFC, total</td>
<td>78.30 (11.52)</td>
<td>76.68 (11.79)</td>
<td>1.62 (8.72-5.47)</td>
</tr>
<tr>
<td>Left PFC, gray matter</td>
<td>50.40 (6.95)</td>
<td>50.35 (7.28)</td>
<td>0.05 (4.38-4.28)</td>
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<tr>
<td>Right PFC, gray matter</td>
<td>52.36 (6.38)</td>
<td>51.66 (8.06)</td>
<td>0.70 (5.12-3.72)</td>
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<tr>
<td>Left PFC, white matter</td>
<td>19.61 (4.97)</td>
<td>18.29 (3.01)</td>
<td>1.33 (8.33-1.17)</td>
</tr>
<tr>
<td>Right PFC, white matter</td>
<td>25.94 (7.66)</td>
<td>25.02 (4.47)</td>
<td>0.92 (4.74-2.89)</td>
</tr>
</tbody>
</table>

*Data are given as mean (SD). MDD indicates major depressive disorder; PFC, prefrontal cortex.

Table 2. Volumetric Results for Patients With Familial and Nonfamilial MDD and Healthy Comparison Subjects*

<table>
<thead>
<tr>
<th>Region</th>
<th>Patients With Familial MDD (n = 12)</th>
<th>Patients With Nonfamilial MDD (n = 10)</th>
<th>Healthy Comparison Subjects (n = 22)</th>
<th>Analysis†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial volume</td>
<td>1181.93 (172.80)</td>
<td>1276.39 (222.78)</td>
<td>1158.62 (116.19)</td>
<td>F2,38</td>
</tr>
<tr>
<td>Left PFC, total</td>
<td>63.93 (6.80)</td>
<td>77.32 (11.18)</td>
<td>68.64 (9.78)</td>
<td>1.83</td>
</tr>
<tr>
<td>Right PFC, total</td>
<td>75.99 (11.21)</td>
<td>81.07 (11.87)</td>
<td>76.68 (11.79)</td>
<td>4.12</td>
</tr>
<tr>
<td>Left PFC, gray matter</td>
<td>46.66 (5.23)</td>
<td>54.88 (6.18)</td>
<td>50.35 (7.28)</td>
<td>0.00</td>
</tr>
<tr>
<td>Right PFC, gray matter</td>
<td>50.87 (6.28)</td>
<td>54.14 (6.34)</td>
<td>51.66 (8.06)</td>
<td>2.91</td>
</tr>
<tr>
<td>Left PFC, white matter</td>
<td>17.27 (2.80)</td>
<td>22.43 (5.65)</td>
<td>18.29 (3.01)</td>
<td>4.39</td>
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<tr>
<td>Right PFC, white matter</td>
<td>25.12 (8.57)</td>
<td>26.93 (6.73)</td>
<td>25.02 (4.47)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Data are given as mean (SD). MDD indicates major depressive disorder; PFC, prefrontal cortex.
†Analysis of covariance using age, sex, and intracranial volume as covariates.