Orbitofrontal Cortex Volumes in Medication Naïve Children with Major Depressive Disorder: A Magnetic Resonance Imaging Study

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Abstract

Objectives: Adults with major depressive disorder (MDD) are reported to have reduced orbitofrontal cortex (OFC) volumes, which could be related to decreased neuronal density. We conducted a study on medication naïve children with MDD to determine whether abnormalities of OFC are present early in the illness course.

Methods: Twenty seven medication naïve pediatric *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) MDD patients (mean age $\pm$ SD = 14.4 $\pm$ 2.2 years; 10 males) and 26 healthy controls (mean age $\pm$ SD = 14.4 $\pm$ 2.4 years; 12 males) underwent a 1.5T magnetic resonance imaging (MRI) with 3D spoiled gradient recalled acquisition. The OFC volumes were compared using analysis of covariance with age, gender, and total brain volume as covariates.

Results: There was no significant difference in either total OFC volume or total gray matter OFC volume between MDD patients and healthy controls. Exploratory analysis revealed that patients had unexpectedly larger total right lateral (F = 4.2, df = 1, 48, p = 0.05) and right lateral gray matter (F = 4.6, df = 1, 48, p = 0.04) OFC volumes compared to healthy controls, but this finding was not significant following statistical correction for multiple comparisons. No other OFC subregions showed a significant difference.

Conclusions: The lack of OFC volume abnormalities in pediatric MDD patients suggests the abnormalities previously reported for adults may develop later in life as a result of neural cell loss.

Introduction

THE PREFRONTAL CORTEX IS POSTULATED to participate in the regulation of impulses, emotion and cognition in mood disorders (Soares and Mann 1997). The orbitofrontal cortex (OFC) is the part of the prefrontal cortex that lies on the roof of the orbit and receives input from visual (Barbas et al. 1988), taste (Rolls and Baylis 1994), olfactory (Carmichael et al. 1994), and somatosensory cortices (Fuster 1997; Öngür and Price 2000). The OFC mediates personality, mood, and be-

haviors involved in reward and punishment and decision-making (Damasio 1994). Patients with OFC damage show drastic changes in personality and emotional expression, although they have been reported to retain judgment and logical thinking (Damasio 1994). As these basic components of higher emotional and social behaviors are disturbed in mood disorders patients, there might be corresponding specific abnormalities in the OFC area in those afflicted.

Recent imaging and neuropathological studies suggest that adult mood disorders patients do in fact show various

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OFC abnormalities (Öngür and Price 2000). A postmortem study found smaller neurons and reduced cortical thickness in the medial OFC and dorsolateral prefrontal cortex in patients with major depressive disorder (MDD) (Rajkowska et al. 1999). Structural magnetic resonance imaging (MRI) studies showed smaller medial OFC volumes in 15 patients with remitted MDD compared to 20 healthy controls (Bremner et al. 2002) and smaller total OFC volumes in 20 elderly depressive patients compared to 20 healthy controls (Lai et al. 2000). Lacerda et al. (2004) reported smaller gray matter volumes in the right medial and left lateral OFC in 31 patients with MDD compared to 34 healthy individuals. Left lateral OFC volume correlated negatively with age in patients but not in control subjects. Additionally, a positron emission tomography study revealed lower metabolism in the OFC of patients with depressive relapse compared to healthy controls (Bremner et al. 1997). A functional MRI (fMRI) study revealed a significantly smaller decrease in activation in the medial OFC of MDD patients compared to controls during a working memory task (Rose et al. 2006). This could explain the abnormal frontolimbic activation in clinical depression and might be related to the increased level of state anxiety.

These studies demonstrate that OFC volume loss and functional impairment may be related to the pathophysiology of adult MDD. Although no structural MR studies of the OFC in pediatric MDD patients have been reported, a proton MR spectroscopy (MRS) study found higher levels of choline-containing compounds in the OFC of depressed adolescents compared to healthy control adolescents (Steingard et al. 1998). This suggests that brain choline level may be associated with the depressive symptoms in early-onset depression. The choline-containing compounds are part of the catabolic and anabolic pathways of membrane phospholipid metabolism. The elevation of choline-containing compounds may be the direct evidence of an imbalance in the turnover of membrane phospholipids.

We conducted an MRI study to examine the OFC volumes in medication naïve children with MDD, matched by age and gender to healthy controls, to determine whether OFC volume abnormalities are present early in the illness course. We predicted that children and adolescents with MDD would have smaller total OFC volumes compared to healthy individuals, as previously reported for adults with MDD (Lai et al. 2000; Bremner et al. 2002; Lacerda et al. 2004). On an exploratory basis we also examined the subregional OFC volumes.

Methods

Subjects

The sample included 27 pediatric MDD patients (mean age $\pm$ standard deviation [SD] = 14.4 ± 2.2 years; 17 female/10 male) and 26 healthy controls (mean age $\pm$ SD = 14.4 ± 2.4 years; 14 female/12 male). Legal guardians provided written, informed consent, and children and adolescents gave written assent before initiating all studies, in compliance with the regulations of the Wayne State University Human Investigation Committee. Subjects were evaluated using the Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Lifetime Version (K-SADS-PL) interview (Kaufman et al. 1997), which provides a diagnosis according to *Diagnostic and Statistical Man-*

ual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association 1994) criteria. All subjects were treatment naïve at the time of the scan. Exclusion criteria were history of psychosis, bipolar disorder, anorexia or bulimia nervosa, substance-dependence disorder, Tourette syndrome or other tic-related conditions, autism, and mental retardation. None of the healthy control subjects had current or past Axis I DSM-IV psychiatric disorders. A medical history was taken, and any participant with current endocrinological disease, history of head trauma with loss of consciousness, current or previous neurological disease, family history of hereditary neurological disorder, or a current medical condition such as active liver disease, kidney problems, or respiratory problems was excluded; female subjects who were postpuberty received a pregnancy test, and we recorded weight, height, supine pulse rate, and blood pressure.

The MDD patients were evaluated for depressive mood severity with the 21-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1967), and the Children's Depression Rating Scale, Revised (CDRS-R) (Poznanski et al. 1985). Families were characterized in terms of single-versus two-parent households, the Hollingshead Four-Factor Index (Hollingshead et al. 1975), and the Socioeconomic Composite Index (SCI) (Yeates et al. 1997). The Grooved Pegboard Test (Trites 1977; Knights and Norwood 1980) was used to assess complex visual-motor coordination. No participant showed abnormal motor coordination.

Magnetic resonance imaging

MR data were acquired in a 1.5T GE Signa MR scanner (General Electric Medical Systems, Milwaukee, WI). First, T₁-weighted sagittal images were acquired as a localizer to confirm subject's head position. Then, 124 coronal slices through the entire brain were acquired with a three-dimensional gradient echo-pulse sequence (time to echo (TE) = 5 msec; time of repetition (TR) = 25 msec; acquisition matrix = 256×256 pixels; field of view = 24 cm; and flip angle = 10° ; thickness = 1.5 mm). All of the slices were perpendicular to the anterior commissure-posterior commissure line (AC-PC line).

Definition of the total OFC and lateral and medial OFC

The OFC was manually traced in the coronal view. The OFC tracing consisted of two sections. Tracing of the first part began at the tip of the genu of the corpus callosum, which was located in sagittal images and continued to be traced in coronal images (moving in the anterior direction) until the last slice where the corpus callosum was visible. The superior limit for this section was represented by a point 5 mm below the intersection of the AC-PC line and the interhemispheric fissure. The second section began on the first slice anterior to the corpus callosum and continued in the anterior direction and included the most anterior portion of the brain tissue. Here, the intersection of the AC-PC line and the interhemispheric fissure provided the superior border (Fig. 1). To trace the OFC volume, one horizontal and two vertical lines were placed at the inferior and lateral surface of the frontal lobes to serve as the right and left boundaries. The brain tissue within the area of the superior, right, and left limit is defined as the total OFC volume. Details of this tracing method were reported in a previous study (Lacerda et al. 2003). Medial and lateral OFC were

FIG. 1. The tracing for the total volume of OFC in MR image. All the tracing was done in coronal images (a). First, the landmark of the posterior boundary, the tip of the genu of the corpus callosum (indicated by the arrow in a and b), was located in the middle slice of the sagittal images (b). Then, we traced the coronal slices anteriorly. For tracing of the OFC volume, one horizontal and two vertical lines were placed at the inferior and lateral surfaces of the frontal lobes, respectively, to mark the right and left boundaries (dotted lines). The brain tissue within the area within the superior, right and left limits is defined as the OFC volume (thicker line). Details of this tracing method were reported in a previous study (Lacerda et al. 2003).

divided by the olfactory sulcus and traced from the tip of the genu of the corpus callosum to the slice where the olfactory sulcus disappeared.

Measurements

All of the OFC regional volumes were traced manually by a well-trained evaluator (H.H.C.) who was blind to the subjects' diagnoses using the BRAINS2 software (Andreassen et al. 1992). High interrater reliability (intraclass correlation [ICC] > 0.97) was demonstrated by correlating the ratings of the present rater with independent ratings of another highly trained rater on a sample of 10 images. Total brain volumes were also traced, with high interrater reliability (ICC > 0.99). Gray matter volumes were calculated from the segmentation images using BRAINS2.

Statistical analysis

Statistical analyses were conducted using SPSS version 14.0 (SPSS, Inc, Chicago, IL). The total and gray matter regional OFC volumes were compared using analysis of covariance (ANCOVA) with age, gender, and total brain volume as covariates. Effect size was estimated with the partial eta-squared statistic. Spearman correlations were performed to test the relationship between the OFC volumes and some clinical variables, including age, age of illness onset, and illness duration. Differences with $p < 0.05$ were considered statistically significant. The primary hypothesis was that total OFC volumes are smaller in pediatric MDD patients compared to healthy comparison children. We also performed exploratory analyses of total and gray matter volumes of several OFC subregions. Given the lack of prior volumetric MRI studies in pediatric depression, we report the results of these exploratory analyses both with and without Bonferroni adjustment.

Results

There were no significant differences between patients and controls regarding age, gender, or intelligence quotient (IQ) (Table 1). Ten MDD patients had co-morbid anxiety disorder (1 obsessive compulsive disorder, 1 agoraphobia with-

out panic disorder, 2 specific phobias, 3 generalized anxiety disorders, and 3 posttraumatic stress disorders) and 1 had co-morbid dysthymia. In the evaluation of the depressive mood severity, MDD subjects had a mean score of 20.1 ± 7.5 (range, 8–33) on the HAM-D, and they had a mean score of 57.4 ± 9.4 (range, 38–76) on the CDRS-R.

There was no statistically significant difference between the total OFC volumes of MDD patients compared with the healthy controls ($F = 0.1$, $df = 1$, 48, $p = 0.7$, effect size = 0.00) (Table 2). Total OFC gray matter volumes also were not significantly different ($F = 0.3$, $df = 1$, 48, $p = 0.6$, effect size = 0.01).

Contrary to our predictions, the exploratory analysis revealed that right lateral OFC volumes were significantly larger in the patients compared to the controls (Table 2). This was found for the total volume of the right lateral OFC ($F = 4.2$, $df = 1$, 48, uncorrected $p = 0.05$, effect size = 0.08) and also for the gray matter volume of right lateral OFC ($F = 4.6$, $df = 1$, 48, uncorrected $p = 0.04$, effect size = 0.09). When we applied the Bonferroni correction, the finding of larger right lateral OFC volumes in MDD patients was not statistically significant ($p = 0.8$ for total and $p = 0.6$ for gray matter of right lateral OFC). No other OFC subregions showed a statistically significant difference.

Moreover, we did not find any significant relationship between total volume or gray matter volume of total OFC with respect to age (Pearson correlation = 0.074, $df = 51$, $p = 0.6$ for total and Pearson correlation = 0.052, $df = 51$, $p = 0.71$ for gray matter of OFC) within all the subjects, nor was there any significant relationship with family history of MDD, co-morbid anxiety disorders, age at illness onset, illness duration, HAM-D, or CDRS-R scores within patients. However, the males had larger total and gray matter OFC volumes compared to females ($t = 2.51$, $df = 51$, $p = 0.02$ for total, and $t = 2.52$, $df = 51$, $p = 0.02$ for gray matter) within all the subjects.

Discussion

The total OFC volumes of medication naïve MDD children and adolescents were not significantly different from those of matched healthy comparison subjects. These results are

TABLE 1. DEMOGRAPHIC AND CLINIC CHARACTERISTICS OF THE SAMPLE

	Healthy (n = 26)	MDD (n = 27)	p
Age (mean $\pm$ SD), years	14.4 $\pm$ 2.4	14.4 $\pm$ 2.2	1.0
Age range (years)	9.2–18.0	9.0–17.7	
Gender			0.4
Male	12	10	
Female	14	17	
Age of onset (months)	—	141 $\pm$ 36.3	
Duration of illness (months)	—	28.8 $\pm$ 34.3	
Co-morbid anxiety disorder			
Yes	—	10	
No	—	17	
Family history of MDD			
Yes	—	14	
No	—	12	
Handedness			0.2
Right	16	12	
Left	1	0	
Mixed	9	15	
Adjusted IQ (mean $\pm$ SD)	121 $\pm$ 22	112 $\pm$ 15	0.1

MDD, major depressive disorder; SD, standard deviation; IQ, intelligence quotient.

inconsistent with previous reports in elderly depressive patients of smaller total OFC volumes compared to healthy controls (Lai et al. 2000; Bremner et al. 2002). There also were no significant differences in the volumes of OFC subregions

in pediatric MDD patients compared to healthy controls. Effect size statistics suggest that our results are not due to the small sample size, but rather to the similarity of patients and controls on their OFC volumes.

TABLE 2. TOTAL AND GRAY MATTER ORBITOFRONTAL CORTEX VOLUMES (CM³) IN MAJOR DEPRESSIVE DISORDER PATIENTS AND HEALTHY CONTROLS

Dependent variable	Healthy (n = 26) mean $\pm$ SD	MDD (n = 27) mean $\pm$ SD	F (df = 1, 48)	p	Effect size
Total OFC					
Total volume	26.7 $\pm$ 6.0	28.0 $\pm$ 7.1	0.1	0.7	0.00
Gray matter volume	15.6 $\pm$ 3.3	16.5 $\pm$ 4.2	0.3	0.6	0.01
Right OFC					
Total volume	13.7 $\pm$ 3.0	14.5 $\pm$ 3.6	0.3	0.6	0.01
Gray matter volume	8.0 $\pm$ 1.7	8.6 $\pm$ 2.1	0.8	0.4	0.02
Left OFC					
Total volume	13.0 $\pm$ 3.1	13.5 $\pm$ 3.7	0.1	0.9	0.00
Gray matter volume	7.6 $\pm$ 1.7	7.9 $\pm$ 2.2	0.1	0.8	0.00
Total medial OFC					
Total volume	10.1 $\pm$ 2.4	10.9 $\pm$ 2.4	0.7	0.4	0.01
Gray matter volume	6.4 $\pm$ 1.5	6.9 $\pm$ 1.4	1.3	0.3	0.03
Right medial OFC					
Total volume	5.2 $\pm$ 1.3	5.7 $\pm$ 1.2	0.9	0.3	0.02
Gray matter volume	3.3 $\pm$ 0.8	3.6 $\pm$ 0.7	1.3	0.3	0.03
Left medial OFC					
Total volume	4.9 $\pm$ 1.1	5.2 $\pm$ 1.2	0.4	0.5	0.01
Gray matter volume	3.1 $\pm$ 0.7	3.4 $\pm$ 0.8	1.2	0.3	0.02
Right lateral OFC					
Total volume	5.1 $\pm$ 0.9	5.8 $\pm$ 1.2	4.2	0.05	0.08
Gray matter volume	2.8 $\pm$ 0.6	3.2 $\pm$ 0.8	4.6	0.04	0.09
Left lateral OFC					
Total volume	5.1 $\pm$ 1.2	5.5 $\pm$ 1.3	1.2	0.3	0.02
Gray matter volume	2.8 $\pm$ 0.7	3.0 $\pm$ 0.9	0.8	0.4	0.02
Total brain volume ^a	1183.5 $\pm$ 120.2	1205.9 $\pm$ 139.4	2.2	0.1	0.04

^aAnalysis of covariance (ANCOVA) adjusting for sex and age, df = 1, 49. Uncorrected *p* values are shown. OFC, orbitofrontal cortex; MDD, major depressive disorder; SD, standard deviation.

Prior anatomical studies showed that MDD adults have smaller total OFC (Lai et al. 2000) and medial OFC volumes (Bremner et al. 2002) compared to healthy individuals. The findings of smaller OFC volumes in MDD adults are corroborated by *postmortem* studies of subjects with depression showing decreased neuronal and glial cell density and size of medial OFC in patients with MDD (Rajkowska et al. 1999). It is possible that the neurotoxic effects of glucocorticoids, which are secreted over the course of illness, are responsible for the neuronal loss/shrinkage seen in adults with MDD. Alternatively, smaller total OFC volumes could correspond to a primary neurodevelopmental abnormality, in which case it would be present early in illness course. Our present findings of normal OFC volumes in juvenile MDD subjects do not support the neurodevelopmental hypothesis.

Our primary finding is in contrast to the prior studies of adults. This inconsistency may indicate that some methodological differences should be considered. The brain images were traced in a different orientation in our pediatric study compared with the prior studies (Lai et al. 2000; Bremner et al. 2002), and they did not indicate which type of brain map was used. The determination of the exact borders of the OFC varies according to which brain map is used. Using Brodmann's maps, the OFC borders are less detailed, being restricted to area 11 (prefrontal cortex) and area 12 (rostral portion of the frontal lobe). Walker (1940) tried to resolve the inconsistencies present in Brodmann's maps and proposed that the OFC includes areas 11, 12, 13, and 14. Areas 12 and 13 occupy the lateral and medial orbital surface. The OFC volume is a difficult area to define and trace, and this complicates the comparisons between studies of children and adults.

In prior studies, Lai et al. (2000) traced axial images of OFC. Bremner et al. (2002) defined medial OFC as comprising the cortex from the most anterior extension of the internal capsule to the most anterior extension of the corpus callosum visualized in the coronal plane. Those methods are different from ours, where tracing terminated at the slice where the olfactory sulcus disappears. Our study used a new geometrical method for measuring the OFC, which takes into account individual brain variability proposed by Lacerda et al. (2003). This method appears to be valid for measuring the OFC with excellent reliability and also indicates the OFC medial and lateral subdivisions measurements.

We did not find any significant relationship between total OFC volume and age, age of illness onset, or duration of illness within patients. However, this may be related to particularities of our patient sample with late age of onset. We could speculate that glucocorticoid exposure was not long enough to have neurotoxic effects on OFC volume. These findings do not rule out the possibility that OFC atrophy would occur in children with more prolonged illness duration.

The exploratory analysis revealed unexpectedly larger right lateral OFC volumes in MDD patients compared to healthy controls. Because this result was not predicted and was not significant after Bonferroni adjustment it may represent only a Type I error. However, Lacerda et al. (2004) reported the left lateral OFC volume correlated negatively with age in patients but not in control subjects. A meta-analysis about the differentiation of function in the lateral and medial OFC in humans indicated that the medial area correlates

with reward and the lateral area correlates with loss/punishment (O'Doherty et al. 2001). Thus, there is evidence for a functional difference between medial and lateral OFC to enact different behaviors and brain activation patterns. The medial OFC monitors the reward value of reinforcing stimuli, and the lateral OFC is involved in regulating current behavior change due to the detection of punishers (Kringelbach and Rolls 2004). Therefore, a larger lateral right OFC might underlie changes in sensitivity to punishments rather than to rewards in children with MDD, which should be examined in future studies.

One MRS study reported higher levels of choline-containing compounds in the OFC of depressed adolescents (Steingard et al. 1998), which supports findings that overactivity of the cholinergic system could lead to depressive symptoms in depressed adolescents. Functional studies in adult MDD patients suggest that the metabolic pattern or blood flow (regional cerebral blood flow [rCBF]) differs across the specific subregions of the OFC in patients with depression (Mayberg et al. 1990; Mayberg et al. 1992; Ring et al. 1994), unmedicated depressive subjects (Baxter et al. 1989; Ebert et al. 1991; Drevets et al. 1992), and in MDD patients (Buchsbaum et al. 1986; Drevets and Raichle 1992; Biver et al. 1994). We can only speculate about whether the observed larger lateral OFC volume in MDD children corresponds to hyperfunction of the neural activity, overactivity of cholinergic system depression symptoms, and local metabolic rates. Correspondingly, an enlarged lateral OFC volume could have increased rCBF, and high choline levels might reflect altered endocrine status that can accompany mood disorders.

If Bonferroni correction is applied, the exploratory finding of larger right lateral OFC volumes in MDD patients would not be statistically significant. Therefore, this finding may represent a Type I error and should be viewed with caution until it is independently replicated. Future studies are required to examine a larger number of subjects with untreated MDD to investigate the correlation between the OFC volume, rCBF, and choline level.

Conclusion

We found no volumetric differences in the total OFC volumes of medication naïve pediatric MDD patients and age- and sex-matched healthy comparison subjects. This suggests that anatomical abnormalities in the total OFC volumes probably develop later in the course of illness, possibly due to neurotoxicity-neural cell loss. The tentative finding of larger right lateral OFC volumes in patients, which could potentially underlie phenomenological features of MDD, such as pervasive feelings of punishment and guilt, should be examined in the future studies. Those will be important directions for future studies in this area.

Disclosures

The authors have not financial ties or conflicts of interest to report.

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