Distinguishing Between Major Depressive Disorder and Obsessive-Compulsive Disorder in Children by Measuring Regional Cortical Thickness

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Context: Cortical abnormalities have been noted in previous studies of major depressive disorder (MDD).

Objective: To hypothesize differences in regional cortical thickness among children with MDD, children with obsessive-compulsive disorder (OCD), and healthy controls.

Design: Cross-sectional study of groups.

Setting: Children's Hospital of Michigan in Detroit.

Participants: A total of 24 psychotropic drug–naive pediatric patients with MDD (9 boys and 15 girls), 24 psychotropic drug–naive pediatric outpatients with OCD (8 boys and 16 girls), and 30 healthy controls (10 boys and 20 girls).

Intervention: Magnetic resonance imaging.

Main Outcome Measure: Cortical thickness.

Results: In the right hemisphere of the brain, the pericalcarine gyrus was thinner in patients with MDD than in outpatients with OCD ($P = .002$) or healthy controls ($P = .04$), the postcentral gyrus was thinner in patients with MDD than in outpatients with OCD ($P = .002$) or healthy controls ($P = .02$), and the superior parietal gyrus was thinner in patients with MDD than in outpatients with OCD ($P = .008$) or healthy controls ($P = .03$). The outpatients with OCD and the healthy controls did not differ in these regions of the brain. The temporal pole was thicker in patients with MDD than in outpatients with OCD ($P < .001$) or healthy controls ($P = .01$), both of which groups did not differ in temporal pole thickness. The cuneus was thinner in patients with MDD than in outpatients with OCD ($P = .008$), but it did not differ from that in healthy controls. In the left hemisphere, the supramarginal gyrus was thinner in both patients with MDD ($P = .04$) and outpatients with OCD ($P = .01$) than in healthy controls, and the temporal pole was thicker in patients with MDD than in both healthy controls and outpatients with OCD ($P < .001$).

Conclusions: To our knowledge, this is the first study to explore cortical thickness in pediatric patients with MDD. Although differences in some regions of the brain would be expected given neurobiological models of MDD, our study highlights some unexpected regions (ie, supramarginal and superior parietal gyri) that merit further investigation. These results underscore the need to expand exploration beyond the frontal-limbic circuit.

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MAJOR DEPRESSIVE DISORDER (MDD) is a common, debilitating illness with frequent onset in childhood and adolescence. It has a lifetime prevalence of approximately 5% in adolescence and is believed to be continuous with adult MDD.[1,2] Studies of pediatric patients with MDD may minimize potential confounding variables, such as treatment intervention and illness duration.

Abnormalities in frontal,[3,4] limbic,[5-12] and hypothalamic-pituitary-adrenal axis[13-15] structures have been implicated in MDD. In a study of the cytoarchitecture of the left rostral and caudal orbitofrontal and dorsolateral prefrontal cortical regions in subjects with major depression compared with psychiatrically normal controls, Rajkowska et al[16] found decreases in cortical thickness, neuronal size, and neuronal and glial densities in the upper (II-IV) cortical layers of the rostral orbitofrontal region in patients with MDD. In the caudal orbitofrontal cortex in subjects with MDD, prominent reductions in glial densities in the lower (V-VI) cortical layers were accompanied by small but significant decreases in neuronal size. In the dorsolateral prefrontal cortex of subjects with MDD, reductions in the density and size of neurons and glial cells were found in both supra- and infragranular layers. Fam-

Table 1. Demographic and Clinical Characteristics of 78 Children

Characteristic	Healthy Controls (n = 30)	Patients With MDD (n = 24)	Outpatients With OCD (n = 24)
Age, y			
Mean (SD)	14.11 (2.57)	13.96 (2.41)	13.02 (2.92)
Range	9.08-18.82	7.98-17.28	8.24-18.71
Sex, No.			
Male	10	9	8
Female	20	15	16
Duration of illness, mean (SD), mo		24.90 (31.32)	41.17 (39.75)
Mean (SD) score			
HDRS		17.00 (7.65)	7.13 (6.33)
HARS		12.24 (5.07)	7.04 (5.76)
CY-BOCS	2.14 (2.85)		24.21 (7.00)

Abbreviations: CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; MDD, major depressive disorder; OCD, obsessive-compulsive disorder.

ily history may influence the underlying neurobiology of MDD.[3,4,6,17,18] Recently, Peterson et al[19] suggested that cortical thinning in the right hemisphere produces disturbances in arousal, attention, and memory for social stimuli, which in turn may increase the risk of developing depressive illness in those at high risk (via family history) for MDD.

The identification of relevant biomarkers in MDD is a major aim of research into the neurobiology of the illness. Previous work found compelling differences between thalamic neurochemistry in patients with obsessive-compulsive disorder (OCD) and patients with MDD[20,21] and areas of similarity, like anterior cingulate neurochemistry.[22] A sensitive and specific biomarker would enhance our understanding of the pathophysiology of MDD and may help us to define the phenotype and reduce heterogeneity in genetic studies and facilitate early detection and intervention. An ideal biomarker for MDD would have high sensitivity and specificity for the disorder in affected patients. The diagnostic specificity of abnormalities in cortical thickness, however, has not been widely studied.

Two-thirds of patients with OCD will develop depression during their lifetime. Prior functional imaging studies in adult and pediatric patients with OCD and MDD have demonstrated comparable findings in some regions and distinct findings in others.[20-23] One important area of research is to determine whether neurobiological findings are specific to a particular psychiatric diagnosis or whether they generalize across diagnoses, so we have also included a group of patients with OCD to serve as a psychiatric control group. In our study, we chose to measure cortical thickness in psychotropic drug–naive children with MDD, psychotropic drug–naive children with OCD, and healthy controls. This method employs a surface-based measurement approach that, unlike voxel-based morphometry, is able to interpret folding across the entire cortex.[24] FreeSurfer's cortical thickness measurement technique has been previously validated using postmortem studies and is able to accurately detect submillimeter variations in gray matter.[24] Based on previous studies of pediatric patients with MDD and pediatric patients with OCD, we hypothesized that significant differences in cortical thickness would exist in the anterior cingulate, orbital frontal cortex, and dorsolateral prefrontal cortex regions. We examined for laterality effects because several of our previously published neuroimaging studies found striking laterality effects for both volumetric and neurochemical measures in pediatric patients with MDD.[3,4] Given prior investigation suggesting distinct alterations in familial vs nonfamilial MDD,[3,4,6,17,18] we also conducted an exploratory analysis of the effect of familial vs nonfamilial MDD on cortical thickness.

METHODS

SUBJECTS

A total of 24 psychotropic drug–naive pediatric patients with MDD (9 boys and 15 girls with a mean [SD] age, unless otherwise stated, of 13.96 [2.41] years) and 24 psychotropic drug–naive pediatric outpatients with OCD (8 boys and 16 girls [as a psychiatric control group] with a mean [SD] age of 13.02 [2.92] years) were included in our study (**Table 1**). In the MDD group, 15 subjects had at least 1 first-degree relative with MDD. A total of 30 healthy controls (10 boys and 20 girls with a mean [SD] age of 13.44 [2.78] years) were used as a comparison group. All patients were recruited through the Wayne State University child psychiatry outpatient clinic. Diagnoses were made using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Versions.[25] A board-certified child and adolescent psychiatrist (D.R.R.) interviewed each subject and their parents to confirm the presence of *DSM-IV* criteria for OCD or MDD.

Fifteen of 24 patients with MDD exhibited comorbid disorders, including attention-deficit disorder without hyperactivity, oppositional defiant disorder, and anxiety disorders (including generalized anxiety disorder and separation anxiety disorder). Three of the patients with MDD who had comorbid attention-deficit disorder without hyperactivity had not been previously treated with stimulant medication or other pharmacotherapy for attention-deficit/hyperactivity disorder. Of the 24 patients with MDD, 9 had MDD as their sole diagnosis. Eleven of the 15 patients with MDD who had at least 1 first-degree relative with MDD and 4 of the 9 patients with MDD who had no obvious family history of MDD had comorbid disorders. Of the 24 outpatients with OCD, 9 exhibited comorbid disorders, in-

cluding dysthymia, anxiety disorders, enuresis, oppositional defiant disorder, and seasonal affective disorder, and 15 had OCD as their sole diagnosis. Exclusion criteria for both patients and healthy controls included a lifetime history of bipolar disorder, psychosis, eating disorders, Sydenham chorea, conduct disorder, substance abuse or dependence, Tourette syndrome, pervasive developmental disorders, mental retardation, learning disorders, or significantly debilitating medical and neurological conditions. Outpatients with OCD did not have a lifetime history of MDD, and patients with MDD did not have a lifetime history of OCD or subthreshold obsessive-compulsive symptoms and behaviors. There was no history of psychiatric illness in the healthy controls or in any of their first-degree relatives. The parents, as well as the children, served as informants for these diagnostic assessments. After a complete description of our study to the subjects, written informed consent was obtained from the legal guardian, and the participants provided written assent. The Wayne State University Human Investigation Committee provided approval to conduct our study.

CLINICAL ASSESSMENTS

Measures of depression and anxiety were obtained using the 17-item Hamilton Depression Rating Scale[26] (mean [SD] score of 17.00 [7.65] for patients with MDD and 7.13 [6.33] for outpatients with OCD) and the 17-item Hamilton Anxiety Rating Scale[27] (mean [SD] score of 12.24 [5.07] for patients with MDD patients and 7.04 [5.76] for outpatients with OCD), respectively. These scales were used to ascertain depression and anxiety for consistency of measurement across diagnoses. The Children's Yale-Brown Obsessive Compulsive Scale[28] was used to assess the OCD symptom severity in outpatients with OCD (mean [SD] score, 24.21 [7.00]). Mean (SD) duration of illness was 24.90 (31.32) months for the patients with MDD and 41.17 (39.75) months for the outpatients with OCD.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging examinations were conducted at the Children's Hospital of Michigan Imaging Center in Detroit. The imaging acquisition methods have been described previously in detail.[29,30] All images were acquired in the coronal plane after performing a sagittal scout series to verify patient position, patient cooperation, and image quality. The sequence was produced using a 3-dimensional spoiled gradient echo pulse sequence with a 40° flip angle, 25-millisecond repetition time, and a 5-millisecond echo time on a 1.5-T whole-body superconducting imaging system (General Electric, Milwaukee, Wisconsin). A total of 124 contiguous coronal slices (slice thickness, 1.5 mm, no gap) were produced through the whole brain using this sequence. The in-plane resolution produced was 0.94×0.94 mm in a 256×256 matrix. Axial proton density and T2-weighted images were obtained to exclude structural abnormalities. A pediatric neuroradiologist reviewed all scans to rule out clinically significant abnormalities.

IMAGE ANALYSIS

Cortical reconstruction and volumetric segmentation were performed with the automated FreeSurfer image analysis suite, which is documented and freely available for download (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures have been described in detail previously.[24] FreeSurfer uses a cortical surface model based on probabilistic information estimated from a manually labeled training set to create cortical sulci and gyri parcellations. This procedure (which incorporates geometric information derived from the cortical

model) and neuroanatomical convention (as defined by the training set) have been described previously.[31,32] Briefly, after the application of intensity variations to correct magnetic field inhomogeneities, nonbrain voxels from each subject's T1-weighted magnetic resonance imaging scan were removed, and then these images were segmented using an estimation of the gray-white interface.[33] Each scan was inflated to create a smooth spherical surface, in order to reduce interference created by folds in the cortical mantle,[33,34] and was registered to a spherical surface representation reference template that was created from an averaged pattern of a group of representative subjects and is the default template provided by FreeSurfer. Alignment of the spherical surface of the reconstructed brains to the reference template was achieved through a 2-dimensional warp of the subject's sphere surface that aligned the sulcal and gyral features of each subject to the curvature data pattern of the template, ensuring optimal alignment across subjects.[33,34] Next, a circularly symmetric Gaussian kernel was used to smooth the maps, and averaging across subjects was performed to align cortical folding patterns.[34] Average measures of cortical thickness were produced at each point on the reconstructed surface. The spherical transform was used to map the thickness measurements at each vertex on each subject's cortical surface into a common spherical coordinate system.[33,34] The data were smoothed on the surface tessellation using an iterative nearest-neighbor averaging procedure (50 iterations were applied, equivalent to applying a 2-dimensional Gaussian smoothing kernel along the cortical surface with a full-width half-maximum of 13 mm), and a deformable surface algorithm was used to define the pial surface with submillimeter accuracy.[24] Data were then resampled for participants into a common spherical coordinate system.[34] Manual corrections to the segmentation were then made to each cortex. These procedures were performed by an investigator who was blinded to subject group assignment. Thickness across the cortex was measured by averaging each point between the gray-white boundary surface and the estimated pial surface.[24] Validation of this technique has been confirmed by direct comparisons with manual measures on postmortem brains as well as by direct comparisons with manual measures on magnetic resonance imaging data.[24]

STATISTICAL ANALYSIS

All statistical analyses were conducted using the Statistical Package for Social Sciences, version 18.0.[35] An analysis of covariance was used to compare the 3 groups using age as a covariate. Post hoc analysis used least significant differences tests. There were 31 comparisons ($.05/31 = .002$), and α was set at $P < .002$. Age was selected as a covariate given the wide age range and likelihood of regions of interest correlating with age. Sex was also used as a covariate to accommodate possible sex effects. Pearson correlations were used to examine the relationship between significant differences in cortical thickness and clinical variables. In an exploratory manner, a subanalysis comparing patients with familial MDD, patients with nonfamilial MDD, outpatients with OCD, and healthy controls was also performed, and because this is an exploratory subanalysis, α was set at .05.

RESULTS

RIGHT HEMISPHERE

In the right hemisphere of the brain, the pericalcarine gyrus was thinner in patients with MDD than in outpatients with OCD ($P = .002$) or healthy controls ($P = .04$),
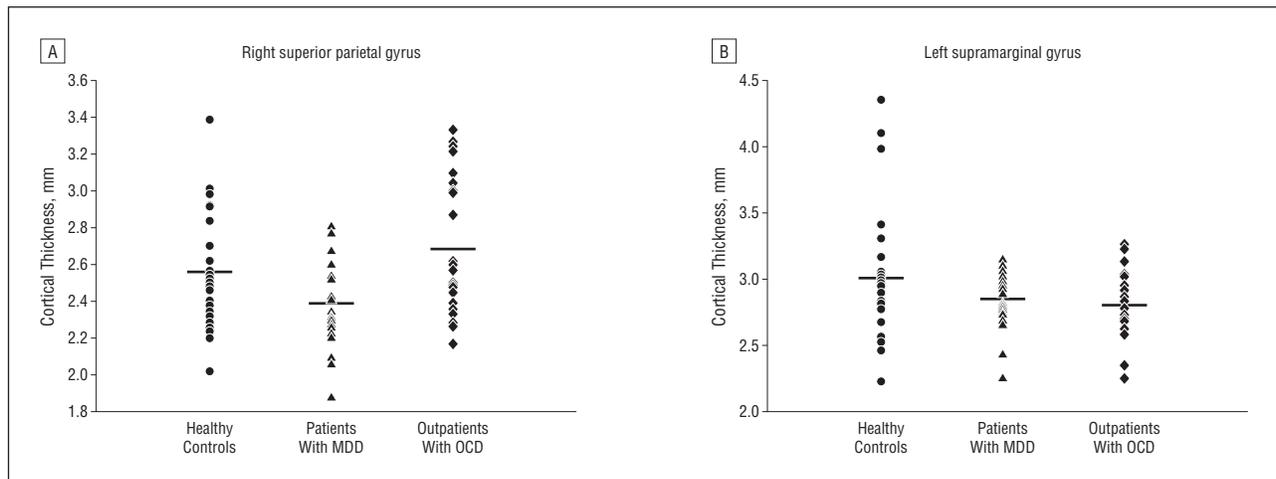
Figure. Cortical thickness results for the right superior parietal gyrus (A) and the left supramarginal gyrus (B). Horizontal lines indicate mean values. MDD indicates major depressive disorder; OCD, obsessive-compulsive disorder.

Table 2. Cortical Thickness Results of 3-Group Comparison

| | Cortical Thickness, Mean (SD), mm | | | | | P Value Determined From Post Hoc Analyses | | |
Region of Interest	HCs (n = 30)	Patients With MDD (n = 24)	Outpatients With OCD (n = 24)	F Value	P Value	HCs vs Patients With MDD	HCs vs Outpatients With OCD	Patients With MDD vs Outpatients With OCD
Right pericalcarine gyrus	1.847 (0.205)	1.722 (0.132)	1.926 (0.329)	8.09	<.001	.04	.18	.002
Right postcentral gyrus	2.408 (0.391)	2.184 (0.171)	2.495 (0.417)	6.94	.002	.02	.33	.002
Right superior parietal gyrus	2.560 (0.318)	2.387 (0.224)	2.676 (0.380)	7.33	.001	.03	.14	.008
Right temporal pole	3.655 (0.773)	4.092 (0.316)	3.446 (0.676)	8.06	<.001	.01	.22	<.001
Right cuneus	2.306 (0.448)	2.083 (0.187)	2.511 (0.585)	8.35	<.001	.06	.06	<.001
Left supramarginal gyrus	3.009 (0.457)	2.843 (0.201)	2.800 (0.281)	6.41	.003	.04	.01	.61
Left temporal pole	3.586 (0.657)	4.012 (0.319)	3.322 (0.663)	7.73	<.001	.005	.08	<.001

Abbreviations: HCs, healthy controls; MDD, major depressive disorder; OCD, obsessive-compulsive disorder.

the postcentral gyrus was thinner in patients with MDD than in outpatients with OCD ($P=.002$) or healthy controls ($P=.02$), and the superior parietal gyrus was thinner in patients with MDD than in outpatients with OCD ($P=.008$) or healthy controls ($P=.03$). The outpatients with OCD and the healthy controls did not differ in these regions of the brain (**Figure**). The temporal pole was thicker in patients with MDD than in outpatients with OCD ($P<.001$) or healthy controls ($P=.01$), both of which groups did not differ in temporal pole thickness. The cuneus was thinner in patients with MDD than in outpatients with OCD ($P=.008$), but it did not differ from that in healthy controls (**Table 2**).

LEFT HEMISPHERE

In the left hemisphere of the brain, the supramarginal gyrus was thinner in both patients with MDD ($P=.04$) and outpatients with OCD ($P=.01$) than in healthy controls (Figure), and the temporal pole was thicker in patients with MDD than in both healthy controls and outpatients with OCD ($P<.001$) (Table 2).

DEMOGRAPHIC AND CLINICAL CORRELATIONS

In patients with MDD, an association with age at onset of illness was seen ($r=-0.516$; $P=.01$) with the left supramarginal gyrus. The right temporal pole correlated negatively with the Hamilton Depression Rating Scale[26] in patients with MDD ($r=-0.450$; $P=.03$). No other correlations with clinical variables were significant.

EXPLORATORY ANALYSIS

The effect of variations of cortical thickness observed in patients with MDD was driven by patients with a familial history of MDD. The right postcentral gyrus was thinner in patients with familial MDD than in healthy controls ($P=.01$) or outpatients with OCD ($P=.002$), and the right superior parietal gyrus was thinner in patients with familial MDD than in healthy controls ($P=.03$) or outpatients with OCD ($P=.001$). The outpatients with OCD and the healthy controls did not differ in these regions of the brain. Similarly, the left supramarginal gyrus was also thinner in patients with famil-

ial MDD than in healthy controls ($P=.04$); it was also thinner in outpatients with OCD than in healthy controls ($P=.01$). The right temporal pole was also thicker in patients with familial MDD than in health controls ($P=.02$) or outpatients with OCD subjects ($P=.002$), and the left temporal pole was also thicker in patients with familial MDD than in health controls ($P=.009$) or outpatients with OCD subjects ($P<.001$). The outpatients with OCD and the healthy controls did not differ in these regions of the brain (eTable, http://www.archgenpsychiatry.com).

COMMENT

To our knowledge, ours is the first study to use the automated FreeSurfer technique to explore cortical thickness in pediatric patients with MDD and pediatric outpatients with OCD. In patients with MDD, decreased cortical thickness was observed in the left supramarginal gyrus, the right pericalcarine gyrus, the postcentral gyrus, the superior parietal lobule, and the cuneus. Greater thickness in the bilateral temporal pole was noted. In outpatients with OCD, the only significantly different region from healthy controls was a thinner left supramarginal gyrus. Our findings of cortical thickness were unexpected because no significant differences were found in the anterior cingulate, the dorsolateral prefrontal cortex, or the orbital frontal cortex in patients with MDD or outpatients with OCD. This lack of patient group differences in hypothesized regions (anterior cingulate, orbital frontal cortex, and dorsal prefrontal cortex) could possibly be due to type II error. However, it should be noted that the types of errors introduced are not limited only to type II based on significance level choices but also to limitations in specific cortical regions, proximity to subcortical gray matter structures, and cortical folding patterns.[36-38] Additionally, the process of subdividing our sample into 4 comparison groups (ie, healthy controls, patients with familial MDD, patients with nonfamilial MDD, and outpatients with OCD) will have weakened the statistical power and the ability to detect differences. It is also possible that this may be due to the relatively small sample size or to limitations in method, such as our use of the standard template provided by FreeSurfer rather than a pediatric template that would have been more closely representative of our sample. Although use of an adult template was not expected to have had much of an effect for the age range examined in our study, the choice of template for segmentation could have resulted in possible bias related to adult vs an age-appropriate atlas.[39,40] The sample was, however, unique in that all patients with MDD and all outpatients with OCD were naive to psychotropic drugs. These findings also underscore the need to look beyond standard frontal-limbic (MDD) and frontal striatal (OCD) models in these disorders.

The neuroanatomical findings in the right postcentral gyrus, the superior parietal lobule, the left supramarginal gyrus, and the bilateral temporal pole appear to be driven by patients with familial MDD. The neuroanatomical findings in the right hemisphere are consistent with Peterson et al,[19] who found cortical thinning in the right hemisphere in subjects with no personal history of MDD who were at increased risk for developing MDD. Our investigation extends these results by finding differences in affected pediatric patients with MDD compared with a psychiatric comparison group of pediatric outpatients with OCD. Although speculative, cortical thinning effects may be stronger for familial than nonfamilial depression owing to environmental and genetic factors. There may be a protective factor in pediatric patients with nonfamilial MDD who may be in an environment in which they can better cope with their illness.

Possibly consistent with our finding of a thinner postcentral gyrus in patients with MDD, lower regional cerebral blood flow has also been noted in the postcentral gyrus in these patients.[41] In a group at high risk for depression, abnormal activation of the superior parietal lobule was noted compared with low-risk controls.[42] Cognitive changes with MDD, like impaired sustained attention, may be associated with parietal dysfunction.[43] Abnormal glucose metabolism was also noted in the cunei of patients with MDD compared with controls.[44] Although we found the temporal pole to be thicker in patients with MDD than in healthy controls, no volumetric differences have been noted previously.[45] Greater activation in the temporal pole has been noted in patients with MDD trying to voluntarily downregulate sad feelings.[46] In 12 severely depressed subjects, Keedwell et al[47] found that depression severity correlated positively with responses to sad stimuli in the temporal pole. Lower gray matter density has also been noted with voxel-based morphometry studies of the temporal pole in first-episode MDD,[48] although negative findings do exist.[45] The temporal pole has connections to orbital and medial prefrontal regions,[49] areas commonly implicated in MDD. The supramarginal gyri have not been previously implicated in the pathogenesis of MDD. The effects noted in the right superior parietal lobule, the postcentral gyrus, the supramarginal gyrus, and the bilateral temporal poles were also driven by familial MDD primarily, akin to previous findings in the hippocampus in pediatric MDD.[6]

The cortical thinning found in the left supramarginal gyrus was the only significant difference noted between outpatients with OCD and healthy controls. It has been hypothesized that the repetitive behaviors of OCD reflect problems in set shifting[50] and that the supramarginal gyrus plays a role in set shifting.[51] Interestingly, the supramarginal gyrus and the parietal lobe, in general, have been implicated in OCD previously, but their role in the disorder remains little explored.[52-58]

More critically, cortical thickness distinguished psychotropic drug–naive pediatric patients with MDD from both psychotropic drug–naive pediatric outpatients with OCD and healthy controls in several regions. This builds on prior work in pediatric OCD and MDD, which has demonstrated distinct functional and neurochemical alterations in some, but not all, regions of interest.[23-26] These results also suggest that alterations in cortical thickness may be more prominent in patients with familial MDD than in patients with nonfamilial MDD. Some of the identified regions have also been identified as being thinner in children who were born prematurely. According to his-

tory reports obtained during our assessments, all subjects were of normal gestational age and had no in utero exposure. However, more sophisticated interviews and personal histories are likely necessary for the best assessment of this. Comorbidity also differed between patients with MDD and outpatients with OCD. The cortical thinning found in patients with MDD but not in outpatients with OCD or healthy controls could be confounded by comorbid disorders (eg, attention-deficit/hyperactivity disorder in patients with MDD but not in outpatients with OCD). We also performed ancillary analyses in which we excluded patients with MDD who had comorbid anxiety disorders and nondepressed outpatients with OCD patients who had dysthymia and high levels of depressive symptoms on the Hamilton Depression Rating Scale[26] because it is possible that overlap in depression-anxiety diagnoses might preclude our ability to see MDD vs OCD group differences in the frontal region and in other regions. However, comparable results were observed with these ancillary analyses, underscoring the need for further study in larger samples.

Our study did not produce the expected results in this sample of pediatric patients with MDD and pediatric outpatients with OCD. No significant abnormalities were found in the frontal lobe structures. However, changes in the parietal cortex and the temporal cortex were observed. This highlights the need to expand our exploration of brain regions from the typical standard regions of interest. Further exploration to determine whether these findings are reproducible in larger, independent samples of patients with MDD and patients with OCD is needed.

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