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Gray Matter Differences between Pediatric Obsessive-Compulsive Disorder Patients and High-Risk Siblings: A Preliminary Voxel-Based Morphometry Study

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Abstract

Neuroimaging studies have identified alterations in frontostriatal circuitry in OCD. Voxel-based morphometry (VBM) allows for the assessment of differences in gray matter density across the whole brain. VBM has not previously been used to examine regional gray matter density in pediatric OCD patients and the siblings of pediatric OCD patients. Volumetric magnetic resonance imaging (MRI) studies were conducted in 10 psychotropic-naïve pediatric patients with OCD, 10 unaffected siblings of pediatric patients with OCD, and 10 healthy controls. VBM analysis was conducted using SPM2. Statistical comparisons were performed with the general linear model, implementing small volume random field corrections for *a priori* regions of interest (anterior cingulate cortex or ACC, striatum and thalamus). VBM analysis revealed significantly lower gray matter density in OCD patients compared to healthy in the left ACC and bilateral medial superior frontal gyrus (SFG). Furthermore, a small volume correction was used to identify a significantly greater gray matter density in the right putamen in OCD patients as compared to unaffected siblings of OCD patients. These findings in patients, siblings, and healthy controls, although preliminary, suggest the presence of gray matter structural differences between affected subjects and healthy controls as well as between affected subjects and individuals at risk for OCD.

Keywords

Obsessive-compulsive disorder (OCD); pediatric; high-risk; neuroimaging; siblings; voxel-based morphometry (VBM)

Introduction

Obsessive-compulsive disorder (OCD) is a debilitating psychiatric disorder characterized by intrusive thoughts and/or ritualistic behaviors [1]. Genetic epidemiological studies have

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revealed that OCD has a significant familial aggregation [19]. The aggregate risk in first-degree relative of probands with OCD has been estimated at approximately 8–23% [17,19,30]. As relatives of patients are at a significantly higher risk of developing OCD symptoms than the general population, young relatives at risk represent a valuable group to examine potential neurobiological precursors of the disorder.

Structural gray matter abnormalities involving the prefrontal cortex (PFC) and basal ganglia circuits have been described in both adults and children with OCD [34,33,36,41]. However, contradictory reports do exist [5]. This may, in part, be accounted for by the heterogeneity of the illness, differences in illness duration, psychoactive medication exposure and the diversity of neuroimaging methods. New structural imaging analysis methods, such as voxel-based morphometry (VBM), allow for evaluation across the whole brain. This may reduce potential confounds and challenges associated with Region of Interest (ROI) hand-tracing methods, including subjective delineation of landmarks as well as the rigorous training required for rater reliability [3,28,47].

Few studies have used VBM to assess whole brain regional gray matter concentrations in OCD patients [22,31,44,47]. To our knowledge, there have been no VBM studies of pediatric OCD patients and no prior published neuroimaging studies in relatives of patients with OCD. We employed VBM to examine structural brain alterations in pediatric OCD patients, as well as in the high-risk siblings of pediatric OCD patients. Based upon prior investigations [34,33, 12,22,41,44], we predicted regionally specific alterations in frontostriatal-thalamic circuitry in pediatric OCD patients, specifically the anterior cingulate, striatum and thalamus. Given the direction of structural differences involving these regions in prior studies [12,33,34,44], we predicted larger gray matter densities in cingulate and thalamus and smaller gray matter density in striatum in both patients and siblings as compared to healthy controls.

Methods

Subjects consisted of the following three age and sex matched groups: 1) Ten psychotropic naïve pediatric outpatients with OCD (mean ± SD age, 13.26±2.46; range: 8 to 16 years); 2) Ten unaffected siblings of pediatric OCD patients (mean ± SD age, 13.11±2.99; range: 8 to 17 years); and 3) Ten healthy comparison subjects (mean ± SD age, 12.97±2.68; range: 9 to 17 years) (Table 1). All subjects were right handed. This group of subjects did not overlap with the group of subjects used in our previous reports [34,33,12,41]. All subjects were recruited through the child psychiatry outpatient clinic at Wayne State University School of Medicine in Detroit, MI. The patients' diagnoses were made by using DSM-IV criteria [1] using the Kiddie Schedule for Affective Disorders and Schizophrenia of School – Age Children – Present and Lifetime Version (K-SADS-PL) [21]. All subjects and their parents were interviewed by a board certified child and adolescent psychiatrist (DRR). Exclusion criteria for patients and healthy comparison subjects are described in previous reports [12,41]. Briefly, this included lifetime history of unipolar or bipolar disorder, psychosis, eating disorders, substance abuse or dependence, Sydenham's chorea, Tourette's disorder, other tic-related conditions, conduct disorder, significantly debilitating medical or neurological conditions, pervasive developmental disorder, mental retardation, or learning disorder. There was no history of psychiatric illness in the healthy comparison subjects or in any of their first-degree relatives. Siblings of OCD patients had no lifetime history of DSM-IV Axis diagnoses or prior exposure to psychotropic medication. Legal guardians provided written informed consent, and all subjects provided written assent prior to all studies being initiated.

OCD symptom severity was assessed with the Children's Yale Brown Obsessive Compulsive Scale [37]. The 17-item Hamilton Depression Rating Scale [16] was used to measure severity

of depression, and the Hamilton Anxiety Rating Scale [15] was used to measure severity of anxiety.

MRI examinations were conducted at the Children's Hospital of Michigan Imaging Center by using image acquisition methods described previously [19]. Images were acquired in the coronal plane using a three-dimensional spoiled gradient echo pulse sequence with a 40 degree flip angle, 25-msec repetition time, and 5-msec echo time on a 1.5-T whole body superconducting imaging system (Horizon 5.7, General Electric, Milwaukee). This produced 124 contiguous coronal slices (thickness=1.5mm) through the whole head with nominal in-plane resolution of 0.94x0.94 mm in a 256x256 matrix. (TR = 25 ms, TE = 5 ms, rotation angle = 40, FOV = 180 mm in the phase encoding direction and 240 mm in the read direction, slice thickness = 1.5 mm, NEX = 1, matrix = 256x192, and scan time = 7 minutes and 44 seconds). Axial proton density and T2-weighted images were obtained to exclude visually detectable abnormalities on MRI scans.

Images were preprocessed as described in Wilke et al [45,46]. After an initial step wherein images were examined for artifacts and moderate to severe head movement and low quality scans were eliminated, the remaining high quality images were resliced using MEDx imaging software [27] to produce isotropic 1.0x1.0x1.0mm voxels with an axial image orientation. Thereafter, image signal intensity inhomogeneities were corrected using a script in the Freesurfer software package in order to establish standardized signal intensity baselines for all images [38]. Finally, using SPM2 software (http://www.fil.ion.ucl.ac.uk/spm) running in Matlab 7 (MathWorks, Natick, MA), a trained evaluator (PCE), blinded to subject diagnosis, realigned the scan origin along the anterior/posterior commissure line to correct for variations in head positioning during the scanning procedure in order to attain the best alignment with our template.

Image analysis and processing were performed following the optimized voxel based morphometry procedure [14]. T1 -weighted images from subjects were prepared for VBM analyses using a fully automated algorithm script in Matlab. Raw images from scans of all subjects were normalized to the standard SPM MNI T1 template using an affine-only procedure and then averaged to create a study specific whole brain template. Normalized images were then segmented into their gray matter, white matter, and cerebrospinal fluid components with an automated algorithm [3]. Finally, the whole brain template and all segmented tissue templates were smoothed with an 8-mm full-width at half-maximum (FWHM) isotropic Gaussian kernel.

Between-group statistical comparisons of mean gray matter density were performed with the general linear model, based upon Gaussian field theory. Unmodulated gray matter images were analyzed, global brain density measurements of all subjects were generated and compared using independent samples t-tests. Each group comparison generated 2 t-statistic maps (SPM {t}) corresponding to 2 opposite contrasts: density decrease and increase, displayed at a threshold of $p<0.001$, uncorrected. Four small volume corrections were applied: (1) prefrontal (x = 0, y = 52, z = 10, 30 x 50 x 30 mm), (2) thalamus (x = 0, y = −11, z = 6, 30 x 30 x 30 mm), (3) right striatum (x = 17, y = 10, z = 5, 30x50x30 mm) and left striatum (x = −17, y = 10, z = 5, 30 x 50 x 30 mm). Within the small volume correction voxels, we set significance at p (FDR-corrected) < 0.05 and z –score > 3.50. The observed Montreal Neurological Institute (MNI) coordinates were converted to Talairach coordinates to classify the locations of significance [40]. For additional gray matter localization, coordinates were then entered into the Talairach Daemon [24].

All clinical and demographic data were uploaded to SPSS for Windows 11.0 (Chicago, SPSS, 2001) computer statistic package software. For comparison of groups, the One-Way Analysis

of Variance (ANOVA) procedure was used. For significant differences between means, Bonferroni pairwise multiple comparisons were carried out at an alpha level of 0.05.

Results

The patients, siblings, and comparison subjects did not differ significantly in distributions of age, or sex (see table 1). All patients had significant symptom severity as measured by their Children's Yale Brown Obsessive Compulsive Scale (CYBOCS) (total 26.5), Hamilton Anxiety Rating Scale (10.1), and Hamilton Depression Rating Scale (10.0) scores. Using the same instruments, siblings and controls did not have significant symptom severity. There were significant differences in all clinical assessment scores between patients and both siblings and healthy controls.

The significant differences and trends towards significant differences in regional gray matter density between subjects are summarized in Table 2. VBM analysis revealed significantly lower gray matter density in the left ACC and bilateral medial SFG in OCD patients as compared to healthy controls. Furthermore, a small volume correction identified significantly greater gray matter density in the right putamen in OCD patients as compared to unaffected siblings of OCD patients (see figure 1). No differences were noted in the thalamus or left striatum selections.

Discussion

This is the first study, to our knowledge, using VBM to examine brain morphology in pediatric OCD patients as well as in unaffected siblings of OCD patients. Based upon prior neuroimaging studies implicating aberrant frontostriatal circuits in both adult and pediatric OCD patients [34,33,36;12,20,41], we predicted abnormalities in the anterior cingulate, striatum and thalamus. Consistent with one of these predictions, alterations in the left ACC were observed as well as an, unexpected alteration in the bilateral SFG in OCD patients compared to healthy controls. Furthermore, we found increased gray matter density in the right putamen of OCD patients compared to their unaffected siblings.

Our finding of reduced left ACC gray matter density in OCD patients compared to healthy controls is intriguing. Alterations in the ACC may reflect previously described abnormalities of the direct-indirect basal ganglia pathway in the orbitofrontal-subcortical and limbic circuits [32,29,6,36,7]. It has been suggested that abnormal ACC activity may reflect a dysfunctional action-monitoring system in patients with OCD [43]. Developmental studies of the ACC in children have demonstrated correlations between its size and ability to regulate inhibitory processes [8]. Indeed, the presence of alterations in ACC in pediatric OCD patients may support and reflect prior findings of inhibitory control abnormalities present early in the course of illness [35]. In a previous study, we have reported larger total ACC gray matter volumes in pediatric OCD [33]. However, our current study, using VBM, is using a whole brain approach, which may only reveal partial and not total gray matter differences between subjects. Our findings here may differ from our prior study in that we are reporting gray matter density, the probability of finding gray matter in a given voxel, rather than gray matter volume. It is also possible that these conflicting results may relate to differences between subject samples between these studies as well as the heterogeneity of OCD [26]. Concurrent with our findings, a recent VBM study of adults with OCD reported reduced ACC gray matter density [44].

The SFG has also been identified as a potential area of interest in the pathophysiology of obsessive-compulsive disorder. Abnormal functionality of the SFG has been previously implicated in several studies in adults using positron emission tomography (PET) [25] and single photon emission computed tomography (SPECT) [23,9], though the results of these

studies are conflicting. Lacerda et al [23] found significant increases in regional cerebral blood flow (rCBF) in the right SFG in OCD patients versus healthy control subjects, while Lucey et al [25], found significant bilateral decreases in resting rCBF in a population of OCD patients versus healthy controls. Castillo et al [9], found no significant differences in average ratios of rCBF in a population of pediatric OCD patients before and after treatment with clomipramine. Adler et al [2] found significant increases in neural activation of several frontal cortical regions, including the SFG, during symptom provocation using functional magnetic resonance imaging (fMRI). Another study, using electroencephalography (EEG), found reduced activity in the SFG in a sample of OCD patients versus controls during the NoGo portion (i.e. inhibition response) of a Go-NoGo task [18]. Despite evidence indicating functional SFG abnormalities in OCD, there has been only one volumetric analysis of the SFG [42], which reported no significant differences in combined gray and white matter in adult OCD subjects compared to healthy controls.

Our finding of greater gray matter density in the right putamen of OCD patients as compared to their unaffected siblings is especially interesting. The putamen has been implicated in the pathophysiology of OCD; indeed, a recent VBM analysis of adult OCD patients reported increased gray matter volumes bilaterally in the ventral putamen [31]. Previously, we found smaller putamen volumes in OCD patients as compared to healthy controls [34]. In our current study, no difference was noted between siblings and healthy controls nor OCD patients and healthy controls with regard to putamen gray matter density.

These neuroimaging findings may reflect potential brain maturational deviations in both affected and unaffected populations, although due to the cross-sectional approach of these analyses, we are unable to draw any conclusions regarding age-related changes in our subjects. Prior neuroimaging studies have reported significant age-related changes in gray matter during childhood and adolescence [11,39]. It has been postulated that smaller gray matter density may reflect increased synaptic pruning during adolescence and early adulthood [13]. Prior studies of pediatric OCD patients suggest that a developmentally mediated network dysplasia, secondary to abnormal peri-adolescent pruning mechanisms may contribute to the development of OCD in childhood [33]. Different gray matter patterns in affected patients and unaffected at-risk subjects may reflect a failure of normal pruning or defective neural proliferation. Finally, low GM density in subjects with OCD may reflect white matter hypertrophy expanding into the cortex and lowering the probability of finding GM in a particular cortical or nuclear voxel.

The absence of predicted alterations [12] in the thalamus may be a result of the small sample size. Furthermore, as OCD is a clinically heterogenous disorder, and studies have reported specific neural correlates of OCD symptom dimensions, structural and functional abnormalities may be missed in studies that do not examine groups of patients differentiated by specific symptom dimensions [26].

There are several limitations to the preliminary findings, especially regarding the exploratory analysis of this novel high-risk sibling population. The sample size is small and, despite small volume corrections for multiple comparisons, future assessment of a larger cohort of patients and siblings will be important to reduce the potential for both Type I and Type II errors. Comorbid disorders in OCD patients are another limitation. Furthermore, although the sibling subjects are at greater risk for the development of OCD than healthy controls, we are unable to verify that they will indeed develop the disorder. Therefore, it is premature to conclude that differences between unaffected high-risk subjects and affected siblings represent markers for risk of developing OCD. Nonetheless, we believe that the uniqueness of our sample, e.g., psychotropic naïve pediatric OCD patients and unaffected siblings, may contribute to a broader

understanding of neurodevelopmental factors involved in the etiopathogenesis of OCD. Clearly, future reports of longitudinal analyses of these populations will be informative.

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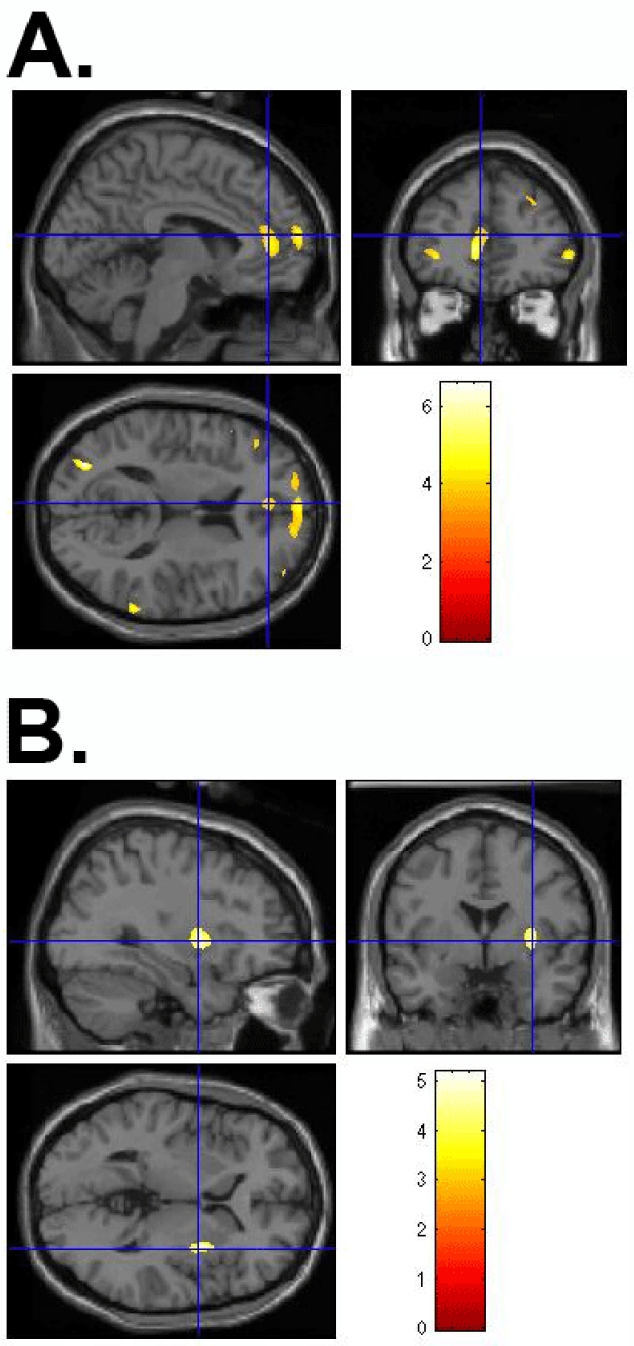

Figure 1.
(A) VBM-measured significantly lower gray matter density in the left ACC and bilateral medial SFG in pediatric OCD patients compared to healthy controls and (B) VBM-measured significantly greater gray matter density in the right putamen in pediatric OCD patients compared to unaffected siblings. (Non-radiologic convention: Right=Right/Left=Left; color map reflects z-score)

Table 1

Subject Characteristics

Clinical and Demographic characteristics	OCD Patients (N=10; 6 male, 4 female)	Siblings (N=10; 6 male, 4 female)	Healthy Comparison (N=10; 6 male, 4 female)	ANOVA	
	Mean/SD	Mean/SD	Mean/SD	F	p
Age (years)	12.9/2.7	13.1/3.0	13.4/2.6	0.084	ns
Children's Yale-Brown Obsessive-Compulsive Scale Score	26.5/5.4	1.9/3.1	2.1/2.6	123.26	<0.001, [ab]
Obsessive Subscale Score	13.7/2.9	0.3/0.7	1.3/2.2	123.01	<0.001, [ab]
Compulsive Subscale Score	12.7/3.1	0.7/0.9	0.8/1.3	122.17	<0.001, [ab]
Hamilton Anxiety Rating Scale Score	10.1/7.3	3.2/3.8	3.3/3.1	7.73	0.007, 0.006 [ab]
Hamilton Depression Rating Scale Score	10.0/7.3	1.0/1.6	2.3/2.6	11.41	0.002 [a], >0.001 [b]

[a] Patients vs. Controls and

[b] Patients vs. Siblings

Table 2

Regional Changes in Gray Matter Density Between OCD Patients and Healthy Control Subjects*

	Coordinates			Statistic	
OCD > Siblings	**X**	**Y**	**Z**	**Z Score**	**p (FDR-corr)[1]**
Right Putamen	31	4	0	3.99	0.04
Right Putamen	32	0	3	3.85	0.04
OCD < Control	**X**	**Y**	**Z**	**Z Score**	**p (FDR-corr)[2]**
Left Anterior Cingulate Gyrus	−8	46	3	4.43	0.01
Right Medial Superior Frontal Gyrus	12	50	15	3.51	0.01
Left Medial Superior Frontal Gyrus	−4	63	12	3.91	0.01

*OCD > Controls and OCD < Siblings did not demonstrate any significant differences.

[1]Based on small volume correction and

[2]main comparison.