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Greater regional cortical gray matter thickness in obsessive-compulsive disorder

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Abstract

Earlier studies are inconsistent regarding the structural basis of obsessive-compulsive disorder (OCD), and few studies have investigated whether patients with OCD have cortical thickness abnormalities compared with healthy volunteers. Using magnetic resonance imaging we compared regional differences in cortical thickness among 21 patients with OCD and 21 demographically matched healthy volunteers. Our findings indicate that the right inferior frontal cortex and posterior middle temporal gyrus are thicker in patients with OCD compared with healthy controls, which may contribute to response inhibition deficits and other aspects of phenomenology related to the disorder.

Keywords

cortical thickness; MRI; obsessive-compulsive disorder; response inhibition

Introduction

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder that has a lifetime prevalence of 2–3% globally [1]. Patients who suffer from OCD have considerable difficulty suppressing repetitive thoughts and actions. The neurobiology of OCD has been hypothesized to lie within a framework involving the orbitofrontal-striatal circuit [2,3]. A number of voxel-based morphometry (VBM) studies conducted using statistical parametric mapping generally support this model, although findings have been inconsistent [4–7]. Valente and colleagues [7] found that OCD patients had more gray matter in the left posterior orbitofrontal cortex (OFC) and parahippocampal regions and less gray matter in the left anterior cingulate compared with matched controls. Pujol *et al.* [6] reported that OCD patients had reduced gray matter volume in the medial frontal gyrus, the medial OFC, and the left insuloopercular region; and a relative increase in gray matter volume bilaterally in the ventral putamen and anterior cerebellum. Kim and colleagues [5] found increased gray matter density in the left OFC of OCD patients compared with healthy volunteers [5]. In earlier studies by our group, we

identified more gray matter in inferior frontal (orbital) regions in patients compared with healthy volunteers [4,8].

In contrast to VBM studies, little research has been directed at examining cortical thickness in OCD. VBM measures rely on registration to detect gray matter differences between groups and as a result, if registration is not precise, data from corresponding cortical regions cannot always be accurately matched across participants [9]. In contrast, cortical pattern matching methods use manually delineated features in each participant to align surface anatomy, with the aim of controlling for interindividual differences in anatomy more precisely. In addition, whereas VBM compares gray matter concentration per voxel across registered images, cortical pattern matching methods compare gray matter thickness at thousands of homologous cortical coordinates. An earlier study by Shin *et al.* [10] identified cortical thinning in the left inferior frontal, left middle frontal, left precentral, left superior temporal, left parahippocampal, left orbitofrontal, and left lingual cortices in OCD patients compared with healthy volunteers.

The goal of this study was thus to use cortical pattern matching methods to investigate whether cortical thickness abnormalities are present in OCD. We hypothesized that cortical thickness abnormalities would be most robust in inferior frontal and cingulate regions, consistent with neurobiological models of the disorder and our earlier region-of-interest (ROI) work [4,8,11, 12].

Methods

Patients

Twenty-one (15 male and six female) adult outpatients with a Diagnostic and Statistical Manual of Mental Disorder IV diagnosis of OCD and 21 (15 male and six female) healthy volunteers matched for age, sex, and handedness participated in this study. Patients were recruited at the Zucker Hillside Hospital in Glen Oaks, New York. All patients were interviewed by a licensed clinical psychologist and diagnosed using the Structured Clinical Interview for Axis I Diagnostic and Statistical Manual of Mental Disorder IV - Patient Edition. Patients had a mean age of 38.0 years (SD=9.6) and healthy volunteers had a mean age of 38.9 years (SD=9.8). All but four patients were receiving serotonin reuptake inhibitors (SRIs). Seven of the 21 OCD individuals had a comorbid diagnosis of major depression. All participants provided written informed consent and the study was approved by the local Institutional Review Board.

Image acquisition and preprocessing

One hundred and twenty-four contiguous coronal brain MRIs (slice thickness=1.5 mm) were acquired through the whole head using a three-dimensional (3D) fast spoiled gradient sequence with inversion recovery preparation (repetition time=10.1 ms, echo time=4.3 ms, TI=600 ms, field of view=22 cm, matrix=256 × 256 matrix). Image processing included a series of analysis steps performed on the T1-weighted images including: (i) whole-brain extraction to remove nonbrain tissue and the cerebellum; (ii) correction for magnetic field inhomogeneity artifacts; (iii) correction for head tilt and alignment using a three-translation and three-rotation rigid-body transformation; (iv) transformation of structural MR images into common stereotaxic space without scaling; (v) automated tissue classification using a partial volume classifier method in which voxels are labeled as most representative of white matter, gray matter, or cerebral spinal fluid (CSF); and (vi) surface model extraction to produce 3D models representative of the shape of the cortex. For surface rendering, a spherical mesh surface is continuously deformed to fit a cortical surface tissue threshold intensity value (a signal value that differentiates extra cortical CSF and brain tissue) from the brain volume rigidly aligned in ICBM-305 space. Finally, 31 sulcal landmarks were delineated manually in each hemisphere using validated protocols and previously published reliability procedures [13].

Cortical thickness analysis

Cortical pattern matching methods were used to spatially relate homologous regions of cortex between participants, allowing cortical thickness to be measured and compared at homologous hemispheric locations in each individual. The sulcal landmarks are used as anchors to drive the surrounding cortical surface anatomy of each individual into correspondence. Cortical thickness measurements were made at 65 536 spatially matched cortical surface points. Using an implementation of the 3D Eikonal equation, cortical thickness was defined as the shortest 3D distance, without crossing voxels classified as CSF, from the cortical white-gray matter boundary to the hemispheric surface (gray-CSF boundary). Further details regarding the methodology are provided elsewhere [13].

Statistical analyses

Main effects of OCD were examined with and without covarying for comorbidity of depression and total brain volume using the General Linear Model (GLM). We included diagnosis of depression as a covariate in our statistical model, given prior work suggesting that the neurobiology of OCD may be different with and without a comorbid diagnosis of depression [7,14]. The same model was used to examine effects of OCD on total gray matter volume and other tissue compartments (white matter and CSF) and subsequently, for examining regional cortical thickness differences between groups. To examine regional thickness differences, statistical comparisons were made at each of the hemispheric surface locations in 3D using the statistical program R (www.r-project.org). The results of these tests were mapped onto the 3D group-averaged hemispheric surface models, whereas statistically significant results were indexed in color (Fig. 1). An uncorrected two-tailed α level of $P < 0.05$ was determined as the threshold for statistical significance and for interpreting results. As comparisons were, however, made at thousands of spatially correlated surface locations, permutation testing was used to confirm the overall significance of regional results. On the basis of our *a priori* hypotheses, permutation testing was performed within an atlas-based ROI for the right inferior frontal cortex (rIFC) and across the entire cortex [15]. The number of surface points showing significant group effects were compared with the number of surface points showing significant effects by chance in 10 000 permutations when participants were randomized to groups.

Results

Table 1 shows the means and standard deviations for the volumes of each intracranial tissue compartment (total brain volume, whole brain gray matter, white matter, and CSF volumes) for each study group. After covarying for comorbidity of depression and total brain volume, no significant differences in whole brain gray matter, white matter, or CSF were observed between groups.

Significant regional effects of OCD were observed for cortical thickness. These results are illustrated in Fig. 1: significant differences in cortical thickness are shown by the color bar where positive and negative effects are represented by different color scales. Statistical maps show that the main effect of OCD (Fig. 1) is associated with greater thickness in the rIFC [Brodmann's area (BA) 47, 45] ($P < 0.05$). The OCD group also showed greater thickness in the right posterior middle temporal gyrus (between BAs 22 and 37) compared with the healthy control group ($P < 0.05$). OCD diagnosis was also associated with subtle cortical thinning in the left supramarginal gyrus (BA 40) ($P < 0.1$). Regional results were confirmed by permutations performed within the rIFC ROI (corrected one-tailed $P = 0.04$), although were not significant for permutations performed across the entire cortex ($P > 0.05$).

We also compared the number of points with greater and less cortical thickness in patients compared with healthy volunteers. These analyses revealed that when controlling for the effects

of depression and total brain volume there were 4085 and 2338 points, respectively, in the left and right hemispheres that had significantly ($P<0.05$; uncorrected) greater cortical thickness in patients compared with healthy volunteers. In contrast, we identified only 215 and 425 points, respectively, in the left and right hemispheres that had significantly ($P<0.05$; uncorrected) less cortical thickness in patients compared with healthy volunteers. Chi-square analysis indicated there was a significantly greater number of points across the cortex where OCD patients have greater thickness compared with matched controls ($P<0.001$).

Discussion

In this study, we examined regionally specific differences in cortical thickness in patients with OCD compared with healthy volunteers. Consistent with our *a priori* hypothesis we found that patients with OCD have greater cortical thickness in the rIFC compared with healthy volunteers. Cortical thickness may be related to regional neuronal density in the cortical mantle and may also depend on unknown vascular factors, glial cell numbers, and the extent and integrity of cortical myelination [16]. Developmental studies suggest that greater cortical thickness may be due to unmyelinated neuronal fibers that are categorized as gray matter [17]. Greater cortical thickness may thus implicate poor neuronal connectivity that may affect the speed of information processing locally.

Our data are consistent with a number of VBM studies reporting increased gray matter in ventral prefrontal regions in patients with OCD compared with healthy volunteers [4,5,7,8]. Moreover, these findings converge with our earlier work in this same cohort of participants demonstrating more gray matter among patients in a similar region [5]. Our findings are consistent with functional neuroimaging studies identifying greater metabolic activity in ventral prefrontal regions while patients are in a resting state [2]. Moreover, hyperactivity in ventral prefrontal regions has been shown to attenuate with the administration of SRIs, further implicating this region in the pathophysiology of OCD [18]. Hyperactivity in orbitofrontostriatal circuits may be mediated by elevated activity of the direct pathway between the OFC and basal ganglia [2] and it is conceivable that greater cortical thickness could underlie such metabolic changes. As our methods include the use of cortical pattern matching, they result in regionally specific cortical thickness measurements. Our findings of increased cortical thickness in the rIFC thus suggest a more precise location for the focus of hyperactivity in the prefrontal cortex than what has been described previously in the literature.

Several models of OCD have focused on hyperactivity within the orbitofrontostriatal circuit [19], which may be mediated by elevated activity of the direct pathway between the OFC and basal ganglia [2]. The direct and indirect frontal-basal ganglia-thalamocortical pathways are positive and negative feedback loops that result in excitation or inhibition of the frontal cortex, respectively. Among healthy individuals, concerns and behavioral responses to stimuli that are perceived as dangerous may be mediated by these frontosubcortical pathways, with appropriate inhibition of certain behaviors mediated specifically by the indirect pathway. However, in OCD, it is believed that the direct pathway is hyperactive relative to the indirect pathway resulting in overstimulation or activation of the frontal cortex leading to the inappropriate disinhibition of ritualistic behavior. Overstimulation of the PFC may cause OCD patients to continually allocate attention to stimuli that they may perceive as harmful (concerns about danger, violence, hygiene, order, etc.), making it difficult for them to switch to other behaviors/thoughts or inhibiting habitual responses [2]. It is conceivable that greater cortical thickness in the rIFC either facilitates or is the result of an increase in tone of the direct pathway relative to the indirect pathway and may be related to the repetitive behavior observed in OCD.

Our findings further converge with evidence implicating dysfunction of right hemisphere brain regions in frontalsubcortical circuits in the pathophysiology of OCD [20]. Using methods for

neocortical parcellation, Grachev *et al.* reported that larger neocortical volumes were observed more robustly in the right hemisphere among OCD patients compared with healthy volunteers. Furthermore, larger right inferior frontal cortical volume was correlated with worse memory performance in patients [21]. In addition, topographic analysis of lesions following right hemisphere anterior capsulotomy were associated with good postoperative outcome in patients with OCD [22]. It is also noteworthy that functional MRI studies have shown that the rIFC and the subthalamic nucleus are involved in inhibition of prepotent or already initiated motor responses [23] and that patients with OCD have less activation compared with healthy volunteers in right hemisphere brain regions, including the inferior frontal gyrus, while performing such tasks [24]. Furthermore, patients with severe OCD showed the least activation in the right orbital frontal cortex while performing a response inhibition task [24]. It is plausible that cortical thickening accompanied by hyperactivity in the rIFC disrupts the proper functioning of the frontostriatal circuit, forcing the system to recruit other brain regions to perform a response inhibition task equally as well as healthy individuals.

The finding of greater rIFC cortical thickening survived permutation testing within an atlas-generated ROI in line with our *a priori* predictions and consistent with earlier findings from our group using VBM [4]. The failure of these regional observations to withstand correction for statistical comparisons made at thousands of cortical surface locations when permutations were performed across the entire cortex may be attributable to a lack of statistical power in this study. We did demonstrate, however, that patients had a greater number of points across the cortex where they exhibited greater as opposed to less cortical thickness compared with matched controls ($P < 0.001$).

Possible limitations of our study include the use of SRIs, which have been demonstrated to alter brain structure [25]. Furthermore, additional studies using larger sample sizes that address the relationship between response inhibition and cortical thickness variability may confirm its role as a structural correlate of impulse control in OCD.

Conclusion

Our data show that OCD patients have greater cortical thickness in a region believed to play a role in successful inhibition, the rIFC. Our findings may have relevance for neurobiological models that have implicated this region in response inhibition deficits in OCD.

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Fig. 1.

Uncorrected statistical mapping results of cortical thickness effects between groups defined by diagnosis of obsessive–compulsive disorder (OCD). The color bar encodes the P value associated with comparisons using the General Linear Model (GLM) performed at each cortical surface point. All rows indicate the cortical thickness differences between OCD patients compared with healthy controls. Each row is defined by the covariates included in the analyses. Red colors indicate regions where OCD patients have significantly thinner cortex than healthy participants, whereas blue regions indicate areas of greater cortical thickness in patients with OCD compared with healthy participants.

Table 1

Means and standard deviations (SDs) for intracranial tissue compartments in healthy control participants and obsessive-compulsive disorder patients

Volume (cm ³)	Total gray matter (SD)	Total white matter (SD)	Total CSF (SD)
Healthy control participants (<i>N</i> =21)	592.4 (69.1)	456.1 (47.5)	158.5 (19.7)
Obsessive-compulsive disorder patients (<i>N</i> =21)	608.9 (77.4)	478.0 (80.4)	167.0 (41.3)

CSF, cerebral spinal fluid.