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Gray Matter Structural Alterations in Obsessive-Compulsive Disorder: Relationship to Neuropsychological Functions

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Abstract

Numerous magnetic resonance (MR) studies have examined gray matter structural alterations in patients with obsessive-compulsive disorder (OCD). Few, however, have used automated, highly reliable techniques such as voxel-based morphometry (VBM) to examine the entire brain in contrast to selected regions of interest. Moreover, few studies have examined the functional correlates of gray matter abnormalities in OCD. We used VBM to evaluate regional gray matter differences between 21 OCD patients and 21 age- and sex-matched healthy volunteers. All patients had comprehensive neuropsychological assessments. MR images were normalized to a customized template and segmented using optimized VBM. OCD patients had significantly ($P < 0.001$; uncorrected) more gray matter in the left thalamus compared to healthy volunteers. OCD patients without major depression had significantly more gray matter in the thalamus (bilaterally) and left orbitofrontal cortex as well as an unpredicted region of more right dorsolateral prefrontal gray matter, which remained significant after correction for multiple comparisons, compared to healthy volunteers. In the subgroup of patients without depression greater right hemisphere thalamic and dorsolateral prefrontal gray matter correlated significantly with worse motor functioning and processing speed, respectively. In this subgroup there was also a tendency for more gray matter in the left orbitofrontal cortex and right dorsolateral prefrontal cortex to be associated with greater symptom severity. Our findings provide additional support for involvement of cortical-striatal-thalamic circuits in the pathophysiology of OCD and preliminary evidence that a defect involving the dorsolateral prefrontal cortex may also be implicated. Moreover, our data suggest that gray matter structural alterations in OCD have neuropsychological correlates, which may be useful in further characterizing structure-function relations in this disorder.

Keywords

OCD; MRI; OFC; neuropsychology; thalamus

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1. Introduction

Obsessive-compulsive disorder (OCD) is characterized by distressing, intrusive thoughts and related compulsions that interfere with an individual's daily functioning, with an estimated lifetime prevalence rate of 2–3%. OCD is associated with significant functional disability and concomitant neurocognitive impairment (e.g., Bystritsky et al., 2001). Current models of OCD emphasize dysfunction in cortico-striatal-thalamic-cortical (CSTC) loops that connect specific portions of the frontal lobes with subcortical structures, integrating information throughout the brain to control movement, cognition, motivation, and emotion (Cummings, 1995). Five distinct, parallel CSTC circuits have been identified, three of which are non-motor. The dorsolateral prefrontal circuit is believed to mediate executive behavior. The medial frontal circuit connects the anterior cingulate to subcortical structures and is believed to mediate motivation. The orbitofrontal circuit mediates reward perception and socially acceptable behavior, and is the circuit most consistently linked to OCD by anatomic and functional studies (see Cavedini et al., 2006 for a review). Interestingly, lesions of this latter circuit can also produce obsessive-compulsive disorder in previously healthy individuals (Kim and Lee, 2002).

Early structural neuroimaging studies of OCD used a region of interest (ROI) approach to measure volumes of well-delineated areas of brain for which there existed an apriori hypothesis of involvement in OCD (Szeszko et al., 1999; Gilbert et al., 2000). This technique is time-consuming and is less reliable compared to more automated techniques, however. The development of automated techniques such as voxel based morphometry (VBM) has increased reliability while also allowing investigators to evaluate volume differences between subject groups across the entire brain. Using this technique, Kim and colleagues (2001) found increased gray matter density in the left orbitofrontal cortex (OFC) and thalamus in OCD patients compared to healthy volunteers. Pujol and colleagues (2004) found decreased gray matter volume in the medial frontal gyrus, the orbitofrontal cortex, and left insulo-opercular region and an increase in gray matter in the putamen and anterior cerebellum among patients. Also, Valente and colleagues (2005) reported more gray matter in the orbitofrontal cortex, parahippocampal regions, and right parietal association cortex and decreased gray matter in the left anterior cingulate among patients.

Current neuropsychological models of OCD regard functional deficits in a frontal-subcortical circuit involving the orbitofrontal cortex, anterior cingulate, striatum, and thalamus as a core impairment of the disease (Cavedini et al., 2006). Abnormal neuropsychological findings in OCD include poor performance on the Object Alternating Task (Abbruzzese et al., 1997) and Iowa Gambling Task (Cavedini et al., 2002), impaired spatial working memory (Purcell et al., 1998; Chamberlain et al., 2007), impaired performance on the Rey complex figure test and the Benton visual retention test (reviewed in Kuelz et al., 2004), failures of response inhibition (Rosenberg et al., 1997; Bannon et al., 2002), slowing of motor initiation and execution (Purcell et al., 1998) and heightened attentional bias towards contamination stimuli (Tata et al., 1996), but mixed findings on the Wisconsin Card Sorting Test (Abbruzzese et al., 1995b; Okasha et al., 2000). In contrast, some data suggests patients have relatively preserved verbal memory (reviewed in Kuelz et al., 2004 and Chamberlain et al., 2005). Despite findings of neuropsychological deficits in patients with OCD little research has been directed at understanding the relationship between these deficits and brain structural abnormalities in OCD. In one study, however, Grachev et al. (1998) reported an inverse association between right frontal gray matter and Rey Osterrieth Complex Figure Test performance such that more gray matter was associated with neuropsychological impairment.

In this study we used optimized voxel based morphometry to examine the neuropsychological correlates of gray matter structural abnormalities identified in patients with OCD compared to

age- and sex-matched healthy volunteers. Based on prior work we hypothesized that gray matter would differ between patients and healthy volunteers in regions comprising cortical-striatal-thalamic-cortical circuits that have most frequently been implicated in the pathophysiology of OCD including the thalamus (Gilbert et al., 2000), anterior cingulate (Rosenberg et al., 1998 and Szeszko et al., 2004a) and orbitofrontal cortex (Szeszko et al., 1999; Kim et al., 2001; Valente et al., 2005). We further predicted that gray matter structural abnormalities would be associated with more severe neurocognitive impairment in OCD patients.

2. Method

2.1 Subjects and Clinical Assessment

Twenty-one adult outpatients with a DSM-IV diagnosis of OCD and 21 healthy volunteers matched for age, sex and handedness participated in this study (see Table 1 for sample characteristics). Patients were recruited from the outpatient department at the Zucker Hillside Hospital in Glen Oaks, NY and surrounding community. All patients were interviewed by a licensed clinical psychologist (PRS) and diagnosed using the Structured Clinical Interview for Axis I DSM-IV Disorders (First et al., 1994). Final diagnoses were established using all available clinical material during a consensus conference involving board-certified adult psychiatrists and a psychologist. All patients had a primary diagnosis of OCD. All but four patients were receiving serotonin reuptake inhibitors (SRIs). Seven patients met DSM-IV criteria for major depression. All subjects were administered the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989). We classified patients according to the 5 clinical dimensions defined by Mataix-Cols and colleagues (Mataix-Cols et al., 1999). Using these criteria we found that patients' predominant obsessions/compulsions were as follows (numbers in parentheses): symmetry/ordering (N=2), hoarding (N=2), contamination/cleaning (N=10), aggressive/checking (N=6), and sexual/religious (N=1).

Exclusion criteria for patients and healthy comparison subjects included: (1) significant medical illness including neurologic (including Gilles de la Tourette's, Huntington's Disease, Parkinson's Disease, encephalitis, strokes, aneurysms, tumors, CNS infections, degenerative brain diseases or trauma) or serious medical disorders; (2) prior psychosurgery; (3) DSM-IV dementia, delirium, schizophrenia, schizoaffective disorder, delusional disorder, brief reactive psychosis or psychotic disorder NOS; (4) DSM-IV mental retardation based upon clinical interview and psychosocial history; (5) pregnancy. There was no history of Axis I psychiatric illness in healthy comparison subjects as determined from the SCID-NP (First et al., 2001) or in any first-degree relative. All procedures were approved by the local IRB and written informed consent was obtained from all participants.

Classification of handedness was based on a modified version of the Edinburgh Inventory consisting of twenty items (Oldfield, 1971). Total number of right and left hand items were scored, and the laterality quotient was computed according to the following formula: $(\text{Total R} - \text{Total L}) / (\text{Total R} + \text{Total L})$. This yielded a total laterality quotient for each subject that ranged from +1.00 (totally dextral) to -1.00 (totally nondextral). Subjects with a laterality quotient greater than or equal to 0.70 were classified as dextral, and the rest as nondextral.

2.2 Neuropsychological Assessment

Details regarding the neuropsychological assessment and statistical analyses used to compute the functional domains are provided elsewhere (Burdick et al., 2008). Briefly, to minimize Type-I error we computed six neuropsychological domains apriori based on what the individual tests purport to measure, a strategy employed by our group previously in first-episode schizophrenia (Bilder et al., 2000), childhood-onset schizophrenia (Rhinewine et al., 2005) and

prodromal schizophrenia (Lencz et al., 2006). Scores were based on a reference group of 38 healthy comparison subjects and computed so that higher values were indicative of better performance. Domains (with coefficient alpha in parentheses) included: (1) Motor (0.70) comprising Finger Tapping (right, left) and Grooved Pegboard (right, left); (2) Verbal Memory (0.78) comprising CVLT total words trials 1–5, CVLT, delayed free recall, WMS-R Logical Memory I and II, WAIS-R Digit Span; (3) Visual Memory (0.79) comprising WMS-R Visual Reproduction I and II; (4) Reasoning and Problem Solving (0.73) comprising WCST Categories and perseverative responses, Ruff Figural Fluency, total unique designs and WAIS-R Block Design; (5) Speed of Processing (0.74) comprising WAIS-R Digit Symbol, Trailmaking Test, Part A and B and Cancellation Test, total time and (6) Language (0.78) comprising Controlled Oral Word Association Test; Animal Naming; WAIS-R Vocabulary and WAIS-R Information.

2.3 Magnetic Resonance (MR) Imaging

MR imaging exams were conducted at the Long Island Jewish Medical Center on a General Electric 1.5 Tesla whole body superconducting system. All scans were reviewed by a neuroradiologist and a member of the research team. Any scan with significant artifacts was repeated. One hundred twenty four contiguous coronal images (slice thickness = 1.5 mm) were acquired through the whole head using a 3D Fast SPGR sequence with IR Prep (TR = 10.1ms, TE = 4.3ms, TI = 600 msec, FOV = 22cm, matrix = 256 × 256 matrix) producing nominal in-plane resolution of 0.86mm × 0.86mm.

2.4 Image Processing

Image analysis was performed on a Linux workstation with MATLAB 6.5.1 (Mathworks, Inc., Natick, MA) and SPM2 software (Wellcome Department of Cognitive Neurology, London) using similar methods described previously (Good et al., 2001; Pujol et al., 2004). In this approach the individual MR images were spatially normalized from native space to the MNI 152-image adult template using a 12-parameter affine transformation with 16 nonlinear iterations and a 25 mm nonlinear basis function cutoff. Normalized images of all subjects were segmented using signal intensity and prior probability information and then smoothed with an 8-mm full-width at half-maximum isotropic Gaussian kernel and averaged to create study-specific gray, white, and CSF templates. The original (untransformed) subject images were segmented in native space. Segmented images for all subjects were spatially normalized to a study-specific template. In addition, intensity modulation was performed on the optimally normalized, segmented gray matter images by increasing or reducing voxel intensity depending on whether the surrounding voxels were compressed or expanded in the normalization process. Modulated gray matter images were smoothed with an 8-mm full-width at half-maximum isotropic Gaussian kernel prior to analysis using voxelwise t-tests.

2.5 Data Analysis

In the SPM analyses alpha was set to 0.001 (using 50 contiguous voxels as the extent threshold), which has been argued to protect against Type-I error when there are apriori hypotheses regarding the neuroanatomical location of findings (Valente et al., 2005). Subsequent analyses excluded OCD patients with major depression, as some research indicates differing neurobiology for patients with comorbid MDD (Saxena et al., 2001; Saxena et al. 2002; Valente et al., 2005). Given that the majority of patients (N=17) were receiving SRIs, however, we could not meaningfully exclude them from ancillary analyses. Group differences in other gray matter regions that survived correction for multiple comparisons are also reported. Post-hoc analyses examined the subgroups of patients with predominant contamination/cleaning (N=10) or aggressive/checking (N=6) symptoms (the only subgroups large enough for analyses) compared to healthy volunteers and each other. Group differences in demographic variables

were examined using independent t tests. Chi-square tests were used to examine differences in joint classifications of discrete variables. Association between continuous variables was examined using Spearman rank-order correlations.

2.6 Neuropsychological Correlations

Individual values of modulated intensity (maximum t -values) were output from SPM2 for investigation of structure-function relations in SPSS (v11.5).

3. Results

Sample characteristics are provided in Table 1. OCD patients did not differ significantly from healthy volunteers in age, sex, education, race and handedness. Results of VBM analyses revealed that OCD patients had significantly more gray matter in the left thalamus ($P < 0.001$, uncorrected; $t = 4.37$, coordinates_{x,y,z} = -19, -21, 9, cluster size = 641) compared to healthy volunteers. There were no areas of less gray matter ($P < 0.001$, uncorrected) among OCD patients compared to healthy volunteers even when the extent threshold was lowered to a single voxel. Exploratory analyses did not reveal any significant differences in left thalamus gray matter in patients with predominant contamination/cleaning symptoms compared to those with predominant aggressive/checking symptoms (the only subgroups large enough for analysis).

Subgroup analyses revealed that OCD patients without major depression had significantly ($P < 0.001$, uncorrected) more gray matter in the left (t value = 4.85, coordinates_{x,y,z} = -18, -22, 9, cluster size = 1609; figure 1) and right (t value = 4.85, coordinates_{x,y,z} = 22, -27, 13, cluster size = 622; figure 1) thalamus and in the left OFC (t value = 4.85, coordinates_{x,y,z} = -15, 48, -23, cluster size = 99; figure 1) compared to healthy volunteers. More gray matter was also observed unexpectedly in this subgroup of patients in the right dorsolateral prefrontal cortex, and this finding survived correction for multiple comparisons using a family-wise error approach ($P < 0.05$; t value = 5.95, coordinates_{x,y,z} = 35, 28, 46, cluster size = 22; figure 1). There were no areas of less gray matter ($P < 0.001$, uncorrected) in the subgroup of OCD patients without major depression compared to healthy volunteers even at the extent threshold of a single voxel. OCD patients without major depression did not differ significantly from healthy volunteers in age, sex, education, race and handedness (all $P > 0.05$).

Subsequent analyses investigated the functional correlates of these abnormalities (table 2). We investigated structure-function relations in the entire group of OCD patients (including those with MDD) but there were no significant correlations. In the subgroup of OCD patients without depression, however, more right thalamic gray matter was significantly correlated with worse motor functioning ($r = -.59$, $df = 14$, $P = 0.027$) and more dorsolateral prefrontal cortex gray matter was associated with slower processing speed ($r = -.54$, $df = 14$, $P = 0.045$). Furthermore, in this subgroup of patients there were trends for more left OFC gray matter ($r = .45$, $df = 14$, $p = .11$) and more right dorsolateral prefrontal grey matter ($r = .44$, $df = 14$, $p = .11$) to be correlated with greater total Y-BOCS scores.

4. Discussion

Although several VBM studies reported structural abnormalities in patients with OCD compared to healthy volunteers, little research has been directed at discerning their functional significance. The main finding of this study was that OCD patients had significantly more gray matter in the left thalamus compared to healthy volunteers. OCD patients without MDD, however, had significantly more gray matter in the thalamus (bilaterally), left OFC and right dorsolateral prefrontal cortex compared to healthy volunteers. Furthermore, among this subgroup of patients more right hemisphere thalamic and dorsolateral prefrontal gray matter correlated significantly with worse motor functioning and processing speed, respectively

suggesting that neuroanatomical structural alterations in OCD have functional correlates. It is noteworthy that study results were enhanced following the exclusion of patients with major depression. This observation converges with structural, functional, and treatment-response neuroimaging data suggesting that OCD with and without major depression may be mediated by different basal ganglia-thalamic circuits (Saxena et al., 2001; Saxena et al., 2002; Valente et al., 2005) and thus, may be an important consideration in future neurobiological studies.

Our findings are consistent with neurobiological models implicating dysfunction of cortical-striatal-thalamic-cortical circuits in the pathophysiology of OCD and converge with prior voxel based morphometry studies reporting more thalamic (Kim et al., 2001) and OFC gray matter (Kim et al., 2001; Valente et al., 2005) in patients compared to healthy volunteers. More gray matter among patients in these regions could reflect neuronal hypertrophy or a neurodevelopmental defect in cortical and/or subcortical pruning. Alternatively, we could not rule out the possibility that more gray matter is an epiphenomenon of illness duration, a compensatory mechanism to the illness or a byproduct of prior SRI usage. It should be acknowledged that our results are inconsistent with two volumetric investigations reporting less orbitofrontal volume in patients compared to healthy volunteers (Szeszko et al., 1999; Kang et al., 2004). It is conceivable that methodologic differences between VBM and regional volumetry could account for discrepant findings. For example, Kim et al. (2001) reported increased OFC gray matter density in OCD patients using VBM, but this group also reported smaller OFC volume among patients using a region-of-interest approach (Kang et al., 2004).

We observed a tendency for more left OFC gray matter to be associated with greater OCD symptom severity among patients. Functional imaging studies during symptom provocation have demonstrated increased regional cerebral blood flow (rCBF) in the OFC of OCD patients (Rauch et al., 1994; Chen et al., 2004), while another study found pretreatment orbitofrontal rCBF of patients with OCD to be inversely correlated with response to fluvoxamine (Rauch et al., 2002). PET studies of pre- and post-treatment OCD have similarly demonstrated a decrease in orbitofrontal metabolism with response to treatment with paroxetine (Saxena et al., 2002). Neuropsychological investigations also implicate the OFC, as OCD patients perform poorly on tests that purportedly assess the functional integrity of this region such as the Object Alternation Test (Abbruzzese et al., 1995a; Cavedini et al., 1998). Also, OCD patients perform similarly to patients with ventromedial lesions on tests of decision making such as the Iowa Gambling Task (reviewed in Cavedini et al., 2006).

Recent studies have identified two separate systems within the OFC that have different connectivity patterns, cytoarchitecture, and functional correlates, which may have relevance for our findings of more lateral OFC volume in patients compared to healthy volunteers. In particular, Elliott and colleagues (Elliott et al., 2000) have proposed a distinction between medial and lateral orbital frontal regions. Whereas the medial orbital frontal region plays a role in monitoring the relationship among stimuli under changing environmental exigencies, the lateral orbital region plays a role in the interruption of behaviors based on prior reward values of stimulus-response associations. Our findings are thus consistent with the possibility that the lateral OFC may play a role in patients' inability to suppress compulsions, especially given how rewarding they are in reducing anxiety. The finding that more orbital frontal cortex volume was associated with greater symptom severity among patients supports this possibility.

We also identified a nonpredicted region of more dorsolateral prefrontal gray matter in patients compared to healthy volunteers, a finding that survived correction for multiple comparisons. The dorsolateral prefrontal region has been less well-investigated compared to other brain structures in OCD and thus, it is difficult to compare our findings with the results from prior studies. Our data are consistent, however, with fMRI results indicating significant activation in this region among patients following presentation of provocative stimuli (Adler et al.,

2000) and an increase in left dorsolateral prefrontal N-acetyl-aspartate in pediatric OCD patients (Russell et al., 2003). Furthermore, van den Heuvel et al., (2005) reported that poor planning in OCD was associated with decreased dorsal prefrontal-striatal responsiveness during performance of the Tower of London task. This region may also be particularly important to the phenomenology of OCD given its role in implementing behavioral changes depending on reinforcement contingencies (Remijnse et al., 2006).

Supporting the possibility that the dorsolateral prefrontal cortex may be implicated in the pathophysiology of OCD we found that gray matter structural alterations in this region were associated with worse neuropsychological functioning. Specifically, more dorsolateral prefrontal gray matter correlated significantly with slower processing speed among patients. Interestingly, processing speed tasks have been linked to the integrity of the dorsal lateral prefrontal cortex through lesion analysis (Stuss et al., 2001) and fMRI (Moll et al., 2002; Sweet et al., 2005) studies, which may be a function of the “inter-related” components of processing speed and working memory (Hillary et al., 2006). It may also be of relevance that some prior work suggests that OCD may be characterized by “obsessional slowness” in everyday tasks (Rachman 1974), and that increased metabolism in the dorsolateral prefrontal cortex is observed among patients with “obsessional slowness” while in a resting state (Sawle et al., 1991).

Our study also revealed more thalamic gray matter among OCD patients compared to healthy volunteers, which is consistent with the results from several prior structural neuroimaging studies. Specifically, one study reported more thalamic volume among patients using a region of interest approach (Atmaca et al., 2007), while a pediatric study found more thalamic volume in psychotropic drug naïve patients compared to healthy volunteers, which declined to volumes comparable to healthy volunteers following psychotropic drug administration (Gilbert et al., 2000). Similarly, Kim and colleagues (2001) reported more gray matter density in the thalamus among patients with OCD compared to healthy volunteers. Our findings also converge with prior functional neuroimaging studies reporting hypermetabolism in the thalamus in OCD (Perani et al., 1995; Alptekin et al., 2001; Lacerda et al., 2003) and increased right thalamic blood flow during symptom provocation (Chen et al., 2004).

Investigation of the neuropsychological correlates of abnormal thalamus volume in OCD patients revealed that greater right thalamus volume was associated with worse motor functioning. Given that the thalamus is the final common subcortical target of the direct and indirect motor pathways in the basal ganglia (Alexander et al., 1986), it serves as an important region for motor control. For example, functional neuroimaging studies have linked thalamic activation to high frequency finger movements (Lehericy et al., 2006) and to increased rhythmic complexity in tapping tasks (Dhamala et al., 2003; Chan et al., 2006). Our neuroimaging data suggest that abnormalities in OCD may be most robust in the lateral thalamus, an interesting finding in light of the ventral lateral nucleus’ well-established connections to the motor cortex (Sim et al., 2006). Thus, given evidence for motor deficits among patients with OCD (Hollander et al., 1990; Bolton et al., 1998) our data suggest that such abnormalities may be mediated, at least in part, by the lateral thalamus.

A potential limitation of our study is that most patients were taking SRIs and that these medications may be associated with changes in brain structure (e.g., Szeszko et al., 2004b; Gilbert et al 2000). Thus, future studies could include a group of depressed patients without OCD who are receiving SRIs to exclude this potential medication bias problem. It may be noteworthy, however, that gray matter reductions (Gilbert et al., 2000) and decreased functional brain activity (Swedo et al., 1992) in OCD have been linked with reductions in symptom severity following pharmacotherapy. Given that patients in the present study were moderately ill (as reflected by their Y-BOCS scores) and that most were receiving treatment the finding

of more brain gray matter among patients could conceivably reflect nonresponse to SRIs, although longitudinal MR imaging studies linked to controlled clinical trials could best address this possibility. It should also be acknowledged that given the number of correlations performed our significant structure-function relations would not survive strict Bonferroni correction. Given the paucity of studies investigating the functional correlates of abnormal brain structure in OCD we believed it important to report these relationships to guide future research in this area. Future studies with larger sample sizes will thus be helpful in clarifying these preliminary structure-function relationships.

In sum, our findings provide evidence for gray matter structural alterations in brain regions comprising cortical-striatal-thalamic-cortical circuits in the pathogenesis of OCD and that these abnormalities have neuropsychological correlates. Our data also suggest that further evaluation of the dorsolateral prefrontal cortex in the pathophysiology of OCD may be warranted.

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References

- Abbruzzese M, Bellodi L, Ferri S, Scarone S. Frontal lobe dysfunction in schizophrenia and obsessive-compulsive disorder: a neuropsychological study. *Brain and Cognition* 1995a;27:202–212. [PubMed: 7772333]
- Abbruzzese M, Ferri S, Scarone S. Wisconsin Card Sorting Test performance in obsessive-compulsive disorder: no evidence for involvement of dorsolateral prefrontal cortex. *Psychiatry Research* 1995b; 58:37–43. [PubMed: 8539310]
- Abbruzzese M, Ferri S, Scarone S. The selective breakdown of frontal functions in patients with obsessive-compulsive disorder and in patients with schizophrenia: a double dissociation experimental finding. *Neuropsychologia* 1997;35:907–912. [PubMed: 9204494]
- Adler CM, McDonough-Ryan P, Sax KW, Holland SK, Arndt S, Strakowski SM. fMRI of neuronal activation with symptom provocation in unmedicated patients with obsessive compulsive disorder. *Journal of Psychiatric Research* 2000;34:317–324. [PubMed: 11104844]
- Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience* 1986;9:357–381.
- Alptekin K, Degirmenci B, Kivircik B, Durak H, Yemez B, Derebek E, Tunca Z. Tc-99m HMPAO brain perfusion SPECT in drug-free obsessive-compulsive patients without depression. *Psychiatry Research* 2001;107:51–56. [PubMed: 11472864]
- Atmaca M, Yildirim H, Ozdemir H, Tezcan E, Kursad Poyraz A. Volumetric MRI study of key brain regions implicated in obsessive-compulsive disorder. *Progress in Neuropsychopharmacology & Biological Psychiatry* 2007;31:46–52.
- Bannon S, Gonsalvez CJ, Croft RJ, Boyce PM. Response inhibition deficits in obsessive-compulsive disorder. *Psychiatry Research* 2002;110:165–174. [PubMed: 12057828]
- Bilder RM, Goldman RS, Robinson D, Reiter G, Bell L, Bates JA, Pappadopulos E, Willson DF, Alvir JM, Woerner MG, Geisler S, Kane JM, Lieberman JA. Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *American Journal of Psychiatry* 2000;157:549–559. [PubMed: 10739413]
- Bolton D, Gibb W, Lees A, Raven P, Gray JA, Chen E, Shafran R. Neurological soft signs in obsessive compulsive disorder: standardized assessment and comparison with schizophrenia. *Behavioural Neurology* 1998;11:197–204. [PubMed: 11568420]
- Burdick KE, Robinson DG, Malhotra AK, Szeszko PR. Neurocognitive profile analysis in obsessive-compulsive disorder. *J Int Neuropsychol Soc* 2008 Jul;14(4):640–645. [PubMed: 18577293]

- Bystritsky A, Liberman RP, Hwang S, Wallace CJ, Vapnik T, Maindment K, Saxena S. Social functioning and quality of life comparisons between obsessive-compulsive and schizophrenic disorders. *Depression and Anxiety* 2001;14:214–218. [PubMed: 11754128]
- Cavedini P, Ferri S, Scarone S, Bellodi L. Frontal lobe dysfunction in obsessive-compulsive disorder and major depression: a clinical-neuropsychological study. *Psychiatry Research* 1998;78:21–28. [PubMed: 9579699]
- Cavedini P, Riboldi G, D'Annunzi A, Belotti P, Cisima M, Bellodi L. Decision-making heterogeneity in obsessive-compulsive disorder: ventromedial prefrontal cortex function predicts different treatment outcomes. *Neuropsychologia* 2002;40:205–211. [PubMed: 11640942]
- Cavedini P, Gorini A, Bellodi L. Understanding obsessive-compulsive disorder: focus on decision making. *Neuropsychology Review* 2006;16:3–15. [PubMed: 16708289]
- Chamberlain SR, Blackwell AD, Fineberg NA, Robbins TW, Sahakian BJ. The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. *Neuroscience and Biobehavioral Reviews* 2005;29:399–419. [PubMed: 15820546]
- Chamberlain SR, Fineberg NA, Blackwell AD, Clark L, Robbins TW, Sahakian BJ. A neuropsychological comparison of obsessive-compulsive disorder and trichotillomania. *Neuropsychologia* 2007;45:654–662. [PubMed: 17005210]
- Chan RC, Rao H, Chen EE, Ye B, Zhang C. The neural basis of motor sequencing: an fMRI study of healthy subjects. *Neuroscience Letters* 2006;398:189–194. [PubMed: 16469446]
- Chen XL, Xie JX, Han HB, Cui YH, Zhang BQ. MR perfusion-weighted imaging and quantitative analysis of cerebral hemodynamics with symptom provocation in unmedicated patients with obsessive-compulsive disorder. *Neuroscience Letters* 2004;370:206–211. [PubMed: 15488324]
- Cummings JL. Anatomic and Behavioral Aspects of Frontal-Subcortical Circuits. *Annals of the New York Academy of Sciences* 1995;769:1–13. [PubMed: 8595019]
- Dhamala M, Pagnoni G, Wiesenfeld K, Zink CF, Martin M, Berns GS. Neural correlates of the complexity of rhythmic finger tapping. *Neuroimage* 2003;20:918–926. [PubMed: 14568462]
- Elliott R, Dolan RJ, Frith CD. Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. *Cerebral Cortex* 2000;10:308–317. [PubMed: 10731225]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for Axis I DSM-IV Disorders-Patient Edition (CID-I/P). New York: New York State Psychiatric Institute, Biometrics Research Department; 1994.
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM IV-TR Axis I Disorders - Non-patient Edition (SCID-I/NP). New York: New York State Psychiatric Institute, Biometrics Research Department; 2001.
- Gilbert AR, Moore GJ, Keshavan MS, Paulson LA, Narula V, MacMaster FP, Stewart CM, Rosenberg DR. Decrease in thalamic volumes of pediatric patients with obsessive-compulsive disorder who are taking paroxetine. *Archives of General Psychiatry* 2000;57:449–456. [PubMed: 10807485]
- Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 2001;14:21–36. [PubMed: 11525331]
- Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Archives of General Psychiatry* 1989;46:1006–1011. [PubMed: 2684084]
- Grachev ID, Breiter HC, Rauch SL, Savage CR, Baer L, Shera DM, Kennedy D, Makris N, Caviness VS, Jenike MA. Structural abnormalities of frontal neocortex in obsessive-compulsive disorder. *Archives of General Psychiatry* 1998;55:181–182. [PubMed: 9477933]
- Hillary FG, Genova HM, Chiaravalloti ND, Rypma B, DeLuca J. Prefrontal modulation of working memory performance in brain injury and disease. *Human Brain Mapping* 2006;27:837–847. [PubMed: 16447183]
- Hollander E, Schiffman E, Cohen B, Rivera-Stein MA, Rosen W, Gorman JM, Fyer AJ, Papp L, Liebowitz MR. Signs of central nervous system dysfunction in obsessive-compulsive disorder. *Archives General Psychiatry* 1990;47:27–32.

- Kang DH, Kim JJ, Choi JS, Kim YI, Kim CW, Youn T, Han MH, Chang KH, Kwon JS. Volumetric investigation of the frontal-subcortical circuitry in patients with obsessive-compulsive disorder. *Journal of Neuropsychiatry and Clinical Neurosciences* 2004;16:342–349. [PubMed: 15377742]
- Kim JJ, Lee MC, Kim J, Kim IY, Kim SI, Han MH, Chang KH, Kwon JS. Gray matter abnormalities in obsessive-compulsive disorder: statistical parametric mapping of segmented magnetic resonance images. *British Journal of Psychiatry* 2001;179:330–334. [PubMed: 11581113]
- Kim KW, Lee DY. Obsessive-compulsive disorder associated with a left orbitofrontal infarct. *Journal of Neuropsychiatry and Clinical Neurosciences* 2002;14:88–89. [PubMed: 11884667]
- Kuelz AK, Hohagen F, Voderholzer U. Neuropsychological performance in obsessive-compulsive disorder: a critical review. *Biological Psychology* 2004;65:185–236. [PubMed: 14757309]
- Lacerda AL, Dalgalarondo P, Caetano D, Camargo EE, Etchebehere EC, Soares JC. Elevated thalamic and prefrontal regional cerebral blood flow in obsessive-compulsive disorder: a SPECT study. *Psychiatry Research* 2003;123:125–134. [PubMed: 12850251]
- Lehericy S, Bardinet E, Tremblay L, Van de Moortele PF, Pochon JB, Dormont D, Kim DS, Yelnik J, Ugurbil K. Motor control in basal ganglia circuits using fMRI and brain atlas approaches. *Cerebral Cortex* 2006;16:149–161. [PubMed: 15858164]
- Lencz T, Smith CW, McLaughlin D, Auther A, Nakayama E, Hovey L, Cornblatt BA. Generalized and specific neurocognitive deficits in prodromal schizophrenia. *Biological Psychiatry* 2006;59:863–871. [PubMed: 16325151]
- Mataix-Cols D, Rauch SL, Manzo PA, Jenike MA, Baer L. Use of factor-analyzed symptom dimensions to predict outcome with serotonin reuptake inhibitors and placebo in the treatment of obsessive-compulsive disorder. *American Journal of Psychiatry* 1999;156:1409–1416. [PubMed: 10484953]
- Mathworks, Incorporated. MATLAB 6.5.1. Massachusetts: Natick;
- Moll J, de Oliveira-Souza R, Moll FT, Bramati IE, Andreiuolo PA. The cerebral correlates of set-shifting: an fMRI study of the trail making test. *Arquivos de neuro-psiquiatria* 2002;60:900–905. [PubMed: 12563376]
- Okasha A, Rafaat M, Mahallawy N, El Nahas G, El Dawla AS, Sayed M, El Kholi S. Cognitive dysfunction in obsessive-compulsive disorder. *Acta Psychiatrica Scandinavica* 2000;101:281–285. [PubMed: 10782547]
- Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971;9:97–113. [PubMed: 5146491]
- Perani D, Colombo C, Bressi S, Bonfanti A, Grassi F, Scarone S, Bellodi L, Smeraldi E, Fazio F. [18F] FDG PET study in obsessive-compulsive disorder. A clinical/metabolic correlation study after treatment. *British Journal of Psychiatry* 1995;166:244–250. [PubMed: 7728370]
- Pujol J, Soriano-Mas C, Alonso P, Cardoner N, Menchon JM, Deus J, Vallejo J. Mapping structural brain alterations in obsessive-compulsive disorder. *Archives of General Psychiatry* 2004;61:720–730. [PubMed: 15237084]
- Purcell R, Maruff P, Kyrios M, Pantelis C. Neuropsychological deficits in obsessive-compulsive disorder: a comparison with unipolar depression, panic disorder, and normal controls. *Archives of General Psychiatry* 1998;55:415–423. [PubMed: 9596044]
- Rachman S. Primary obsessional slowness. *Behaviour Research and Therapy* 1974;12:9–18. [PubMed: 4816233]
- Rauch SL, Jenike MA, Alpert NM, Baer L, Breiter HC, Savage CR, Fischman AJ. Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. *Archives of General Psychiatry* 1994;51:62–70. [PubMed: 8279930]
- Rauch SL, Shin LM, Dougherty DD, Alpert NM, Fischman AJ, Jenike MA. Predictors of fluvoxamine response in contamination-related obsessive compulsive disorder: a PET symptom provocation study. *Neuropsychopharmacology* 2002;27:782–791. [PubMed: 12431852]
- Remijnse PL, Nielen MM, van Balkom AJ, Cath DC, van Oppen P, Uylings HB, Veltman DJ. Reduced orbitofrontal-striatal activity on a reversal learning task in obsessive-compulsive disorder. *Archives of General Psychiatry* 2006;63:1225–1236. [PubMed: 17088503]
- Rhinewine JP, Lencz T, Thaden EP, Cervellione KL, Burdick KE, Henderson I, Bhaskar S, Keehlisen L, Kane J, Kohn N, Fisch GS, Bilder RM, Kumra S. Neurocognitive profile in adolescents with early-

- onset schizophrenia: clinical correlates. *Biological Psychiatry* 2005;58:705–712. [PubMed: 16023084]
- Rosenberg DR, Dick EL, O'Hearn KM, Sweeney JA. Response-inhibition deficits in obsessive-compulsive disorder: an indicator of dysfunction in frontostriatal circuits. *Journal of Psychiatry & Neuroscience* 1997;22:29–38. [PubMed: 9002390]
- Rosenberg DR, Keshavan MS. Toward a neurodevelopmental model of obsessive—compulsive disorder. *Biological Psychiatry* 1998;43:623–640. [PubMed: 9582996]
- Russell A, Cortese B, Lorch E, Ivey J, Banerjee SP, Moore GJ, Rosenberg DR. Localized functional neurochemical marker abnormalities in dorsolateral prefrontal cortex in pediatric obsessive-compulsive disorder. *Journal of Child and Adolescent Psychopharmacology* 2003;13:S31–S38. [PubMed: 12880498]
- Sawle GV, Hymas NF, Lees AJ, Frackowiak RS. Obsessional slowness. Functional studies with positron emission tomography. *Brain* 1991;114:2191–2202. [PubMed: 1933241]
- Saxena S, Brody AL, Ho ML, Alborzian S, Ho MK, Maidment KM, Huang SC, Wu HM, Au SC, Baxter LR Jr. Cerebral metabolism in major depression and obsessive-compulsive disorder occurring separately and concurrently. *Biological Psychiatry* 2001;50:159–170. [PubMed: 11513814]
- Saxena S, Brody AL, Ho ML, Alborzian S, Maidment KM, Zohrabi N, Ho MK, Huang SC, Wu HM, Baxter LR Jr. Differential cerebral metabolic changes with paroxetine treatment of obsessive-compulsive disorder vs major depression. *Archives of General Psychiatry* 2002;59:250–261. [PubMed: 11879163]
- Sim K, Cullen T, Ongur D, Heckers S. Testing models of thalamic dysfunction in schizophrenia using neuroimaging. *Journal of Neural Transmission* 2006;113:907–928. [PubMed: 16252070]
- Stuss DT, Bisschop SM, Alexander MP, Levine B, Katz D, Izukawa D. The Trail Making Test: a study in focal lesion patients. *Psychological Assessment* 2001;13:230–239. [PubMed: 11433797]
- Swedo SE, Pietrini P, Leonard HL, Schapiro MB, Rettew DC, Goldberger EL, Rapoport SI, Rapoport JL, Grady CL. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. Revisualization during pharmacotherapy. *Archives of General Psychiatry* 1992;49:690–694. [PubMed: 1514873]
- Sweet LH, Paskavitz JF, O'Connor MJ, Browndyke JN, Wellen JW, Cohen RA. FMRI correlates of the WAIS-III symbol search subtest. *Journal of the International Neuropsychological Society* 2005;11:471–476. [PubMed: 16209427]
- Szeszko PR, Robinson D, Alvir JM, Bilder RM, Lencz T, Ashtari M, Wu H, Bogerts B. Orbital frontal and amygdala volume reductions in obsessive-compulsive disorder. *Archives of General Psychiatry* 1999;56:913–919. [PubMed: 10530633]
- Szeszko PR, MacMillan S, McMeniman M, Chen S, Baribault K, Lim KO, Ivey J, Rose M, Banerjee SP, Bhandari R, Moore GJ, Rosenberg DR. Brain structural abnormalities in psychotropic drug-naïve pediatric patients with obsessive-compulsive disorder. *American Journal of Psychiatry* 2004a; 161:1049–1056. [PubMed: 15169693]
- Szeszko PR, MacMillan S, McMeniman M, Lorch E, Madden R, Ivey J, Banerjee SP, Moore GJ, Rosenberg DR. Amygdala volume reductions in pediatric patients with obsessive-compulsive disorder treated with paroxetine: preliminary findings. *Neuropsychopharmacology* 2004b;29:826–832. [PubMed: 14970831]
- Tata PR, Leibowitz JA, Prunty MJ, Cameron M, Pickering AD. Attentional bias in obsessional compulsive disorder. *Acta Psychiatrica Scandinavica* 1996;101:281–285.
- Valente AA Jr, Miguel EC, Castro CC, Amaro E Jr, Duran FL, Buchpiguel CA, Chitnis X, McGuire PK, Busatto GF. Regional gray matter abnormalities in obsessive-compulsive disorder: a voxel-based morphometry study. *Biological Psychiatry* 2005;58:479–487. [PubMed: 15978549]
- van den Heuvel OA, Veltman DJ, Groenewegen HJ, Cath DC, van Balkom AJ, van Hartkamp J, Barkhof F, van Dyck R. Frontal-striatal dysfunction during planning in obsessive-compulsive disorder. *Archives of General Psychiatry* 2005;62:301–309. [PubMed: 15753243]

Figure 1.

Brain regions where more gray matter was observed in OCD patients without major depression compared to healthy volunteers. Regions predicted to differ between groups apriori include the bilateral thalamus (panel A; arrows) and left orbitofrontal cortex (panel B), which were significant at $P < 0.001$, uncorrected for multiple comparisons. In addition, an unpredicted site of more gray matter was observed in patients in the right dorsolateral prefrontal region (panel C), which remained significant following correction for multiple comparisons ($P < 0.05$). See text for MNI coordinates corresponding to these regions. R=right, L=left, A=anterior, P=posterior.

Table 1

Sample and Clinical Characteristics

Sample Characteristic	OCD Patients (N=21)	Healthy Comparison Subjects (N=21)	Statistic	df	P
Age, years	38.0 (9.6)	38.9 (9.8)	$t = -0.30$	40	NS
Education, years ¹	14.6 (1.7)	14.9 (1.9)	$t = -0.47$	38	NS
Sex	15M/6F	15M/6F	$\chi^2 = 0$	1	NS
Race (C, AA, H, A, O) ²	19,1,1,0,0	16,2,1,1,1	$\chi^2 = 1.54$	1	NS
Handedness (R, L) ³	14/7	16/5	$\chi^2 = 0.47$	1	NS
Clinical Assessment Data					
Total Y-BOCS ⁴	27.0 ± 5.2				
Obsessive subscale	13.1 ± 2.9				
Compulsive subscale	13.9 ± 2.9				

Data are presented as mean ± SD, unless otherwise indicated.

¹ Education was missing for 2 patients

² Due to the low number of expected frequencies we combined the latter 3 groups for analysis

³ Handedness data for 1 control was based on hand preference for writing

⁴ Yale-Brown Obsessive-Compulsive Scale

Table 2
Structure-function Relations in OCD patients without MDD

	Left Thalamus	Right Thalamus	Left OFC	Right DLPFC
Language	−0.01	0.35	−0.15	−0.04
Motor	0.16	−0.59 [*]	0.01	−0.03
Verbal Memory	0.18	−0.16	−0.13	−0.04
Visual Memory	0.14	−0.13	−0.16	0.11
Reasoning and Problem Solving	0.20	−0.12	−0.06	0.35
Processing Speed	−0.48	−0.47	0.18	−0.54 [*]

^{*}
 $P < 0.05$