Published in final edited form as:

Biol Psychiatry. 2014 April 15; 75(8): 595–605. doi:10.1016/j.biopsych.2013.10.021.

Global resting-state fMRI analysis identifies frontal cortex, striatal, and cerebellar dysconnectivity in obsessive-compulsive disorder

Alan Anticevic, Ph.D.^{1,5,6}, Sien Hu, Ph.D.¹, Sheng Zhang, Ph.D.¹, Aleksandar Savic, M.D.^{1,8}, Eileen Billingslea, M.A.¹, Suzanne Wasyluk, R.N.¹, Grega Repovs, Ph.D.⁹, Michael W. Cole, Ph.D.¹⁰, Sarah Bednarski, B.A.¹, John H. Krystal, M.D.^{1,6}, Michael H. Bloch, M.D., M.S.^{1,4}, Chiang-shan R. Li, M.D.^{1,3,7,*}, and Christopher Pittenger, M.D., Ph.D.^{1,2,4,5,7,*}

¹Department of Psychiatry, Yale University

²Department of Psychology, Yale University

³Department of Neurobiology, Yale University

⁴Child Study Center, Yale University

⁵Abraham Ribicoff Research Facilities, Yale University

⁶NIAAA Center for the Translational Neuroscience of Alcoholism, Yale University

⁷Interdepartmental Neuroscience Program, Yale University

⁸University Psychiatric Hospital Vrapce, University of Zagreb, Zagreb 10000, Croatia

⁹Department of Psychology, University of Ljubljana, Ljubljana, Slovenia

¹⁰Washington University in St. Louis, St. Louis, MO, 63130

Abstract

Background—Obsessive-compulsive disorder (OCD) is associated with regional hyperactivity in cortico-striatal circuits. However, the large-scale patterns of abnormal neural connectivity remain uncharacterized. Resting-state functional connectivity (rs-fcMRI) studies have shown altered connectivity within the implicated circuitry, but they have used seed-driven approaches wherein a circuit of interest is defined *a priori*. This limits their ability to identify network abnormalities beyond the prevailing framework. This limitation is particularly problematic within the prefrontal cortex (PFC), which is large and heterogeneous and where *a priori* specification of seeds is therefore difficult. A hypothesis-neutral data-driven approach to the analysis of connectivity is vital.

Method—We analyzed rs-fcMRI data collected at 3T in 27 OCD patients and 66 matched controls using a recently developed data-driven global brain connectivity (GBC) method, both within the PFC and across the whole brain.

© 2013 Society of Biological Psychiatry. Published by Elsevier Inc. All rights reserved.

Correspondence: Christopher Pittenger, MD, Ph.D., 34 Park Street, New Haven, CT 06519, Christopher.pittenger@yale.edu.

*These authors contributed equally to the work.

Financial Disclosures

The remaining authors report no biomedical financial interests or potential conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Results—We found clusters of decreased connectivity in the left lateral PFC in both whole-brain and PFC-restricted analyses. Increased GBC was found in the right putamen and left cerebellar cortex. Within ROIs in the basal ganglia and thalamus, we identified increased GBC in dorsal striatum and anterior thalamus, which was reduced in patients on medication. The ventral striatum/nucleus accumbens exhibited decreased global connectivity, but increased connectivity specifically with the ventral anterior cingulate cortex in subjects with OCD.

Conclusion—These findings identify previously uncharacterized PFC and basal ganglia dysconnectivity in OCD and reveal differentially altered GBC in dorsal and ventral striatum. Results highlight complex disturbances in PFC networks, which could contribute to disrupted cortical-striatal-cerebellar circuits in OCD.

Keywords

obsessive-compulsive disorder; prefrontal cortex; basal ganglia; resting-state fMRI; global connectivity; functional connectivity

Introduction

Obsessive-compulsive disorder (OCD) is characterized by intrusive, anxiety-producing thoughts and repetitive, compulsive behaviors, which cause enormous distress(1,2). OCD affects 2.7% of the population at some point during their lives(3,4). Of these, up to 65% report that their illness produces major functional impairment(4).

OCD was among the first neuropsychiatric conditions in which pathological activity in a defined brain circuit was identified. PET studies of glucose utilization(5–7), PET and SPECT studies of brain perfusion(8, 9), and functional/structural MRI investigations(10–14) suggest increased cerebral metabolism in cortico-striato-thalamo-cortical(CSTC) circuits, particularly in the caudate and putamen, the anterior thalamus, the orbitofrontal cortex(OFC), and (more variably) the anterior cingulate cortex(11,15,16). This circuitry is activated after symptom provocation in patients (17–19); the hyperactivity is reduced in parallel with symptomatic improvement after either pharmacotherapy or psychotherapy(20–22).

The evolutionarily well-preserved CSTC circuitry is involved in diverse computations, including reward processing, action selection, habit formation, and motor control(23–26). To a first approximation, it consists of parallel loops(24,27,28). This parallel organization is complicated by heterogeneity within the striatum itself(29), by afferents from other structures(24), and by recently-appreciated di-synaptic interactions with the cerebellum(30,31). Despite these complexities, the notion of parallel, functionally specialized information-processing loops remains of heuristic value for conceptualizing circuit-level disturbances.

Abnormal activity in a ventral striatum-orbitofrontal cortex loop is well-replicated in the OCD functional neuroimaging literature(11) and has been linked with symptom severity(32,33). Dysregulation in this ‘affective loop’ may be associated with abnormal reward processing(34). Abnormal activity in the more dorsal striatum, especially the head of the right caudate and the putamen, implicates the ‘cognitive loop’, communicating with the dorsolateral prefrontal cortex(35) – although functional imaging analyses of the dorsal prefrontal cortex have been inconsistent(11).

Traditional fMRI studies analyze the blood oxygen level dependent (BOLD) signal after stimulation or during a task. However, BOLD signal fluctuations at rest contain information about functional network architecture(36–39). Resting-state connectivity, defined as

correlations between these spontaneous BOLD fluctuations (rs-fcMRI), has been increasingly used to analyze neural circuit dynamics both in normal populations(28,40,41) and in pathological states(42). In particular, several recent studies have used seed-based analyses of resting-state data to probe functional connectivity within CSTC networks in both adult and pediatric OCD(32,33,43–50). These studies have provided confirmatory evidence of dysconnectivity within the networks previously identified using baseline or provocation-related perfusion measures(11,15,35). Differential patterns of dysconnectivity have been observed in dorsal and ventral striatal networks(32,33).

Most rs-fcMRI analyses in OCD have used seed-based approaches, in which specific regions of interest are identified based on *a priori* anatomical considerations(e.g. 32,33) or on task-based activation(e.g. 46), and the activity of all other brain regions is correlated against those seeds. This approach is useful for testing regionally specific hypotheses of brain function, but it has limited power to detect dysconnectivity not predicted *a priori*. This is particularly problematic when searching for dysconnectivity within large and heterogeneous regions such as basal ganglia or prefrontal cortex (PFC), in which identifying appropriate seeds for connectivity analysis is challenging. Individual differences in anatomy further complicate seed definition. Independent component analyses (ICA) represent an alternative to the *a priori* specification of a seed but have not been extensively applied in OCD(50).

An alternative, data-driven approach, successfully used in complex neuropsychiatric illness(51–53), has the potential to identify novel patterns of brain dysconnectivity independent of *a priori* seeds. This permits both independent support of established hypotheses and the discovery of new patterns of connectivity alterations that may be missed by seed-driven approaches. Such a ‘bottom-up’ approach is particularly well suited to characterization of abnormalities in PFC connectivity. Here we have applied an approach, derived from graph theory, in which the global connectivity of all voxels in the brain is determined, relative to all other voxels, and then compared between diagnostic groups(54–56). This global connectivity (GBC) analysis has proven powerful for detecting ‘hubs’ of connectivity in healthy populations(57) and has also been successfully applied to studies of PFC dysconnectivity in schizophrenia and bipolar disorder(51–53), as well as following pharmacological challenge(58). A single recent study has examined global connectivity in OCD and identified predicted abnormalities in the OFC and the ventral striatum(59).

GBC addresses qualitatively different questions about brain connectivity than seed-based analyses. Areas of high GBC are maximally functionally connected with other areas and may play a role in coordinating large-scale patterns of brain activity(54,55). A significant between-group difference in GBC thus indicates areas and networks in which the large-scale coordination of information processing may be altered in a disease state. Decreased GBC in a disease state may suggest decreased participation of a particular brain region in broader networks, while increased GBC may suggest a pathological broadening or synchronization of functional networks. Importantly, such alterations in connectivity need not parallel the metabolic activity of the implicated brain areas. We examined alterations in network connectivity in 27 OCD patients, compared to 66 matched healthy comparison subjects (HCS), within the PFC and across the whole brain (to provide a fully unbiased, data-driven and partially independent search). We predicted alterations both in prefrontal network connectivity and in the basal ganglia.

Materials and Methods

Participants

All procedures were approved by the Yale Human Investigations Committee. Adult OCD patients, aged 18–65, were recruited through the Yale OCD Research Clinic through

referrals and advertising. Diagnoses were confirmed by clinical interview by a psychiatrist and the Structured Clinical Interview for DSM-IV (60). All patients met DSM-IV criteria for OCD. Comorbid DSM-IV depression and other anxiety disorders were permitted, to capture a representative sample. Patients with any psychotic illness, autism, history of substance abuse, major head trauma or neurological disease, unstable medical illness, or pregnancy were excluded. High-quality neuroimaging data that passed quality control criteria (see Supplementary Methods) were acquired from 27/32 patients (84.6%) and are included in analysis (Table 1 & Supplement). 13 of these patients were medication-free for at least 8 weeks at the time of fMRI scanning; 14 were treated with an SSRI antidepressant at a stable dose for • 8 weeks at the time of scanning (Table 1). We examined the effect of medication and of comorbid depression in secondary analyses. Healthy control subjects (HCS), matched as a group for age and gender, were recruited through advertising; high-quality data were acquired from 66/80 subjects (83.5%) and included in analysis. OCD symptom severity was evaluated using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; (61,62)); comorbid symptomatology was evaluated using the Hamilton Depression Rating Scale (HAM-D, 17-item version)(63) and the Hamilton Anxiety Rating Scale (HAM-A)(64). Ratings were performed on the same day as the scan in most cases, and always within 3 days of the day of scanning.

Data Acquisition

Imaging data were acquired on a Siemens Trio 3T scanner. A standard 12-channel head coil was used, with foam padding to minimize head motion. Participants were instructed to rest with their eyes closed during scanning, but were monitored to ensure they stayed awake. Images sensitive to BOLD signal were acquired using a T2*-weighted gradient-echo planar imaging (EPI) sequence sensitive to BOLD contrast (TR/TE=2000/25ms, flip angle=85°, field of view (FOV)=220x220mm, acquisition matrix=64x64). Thirty-two axial slices (4mm) were collected without gap; acquisition lasted 10 minutes and produced 300 volumetric images per subject with 3.4375x3.4375mm voxels. For spatial normalization and structural segmentation, high-resolution images were acquired using a T1-weighted, 3D fast spoiled gradient-echo (FSPGR) sequence (TR/TE=2530/3.66ms, flip angle=7°, FOV=256x256mm, matrix=256x256, 176 slices without gap, voxel size=1mm³).

Global brain connectivity

All analyses followed our prior published approaches (51); see Supplemental Information for details. Briefly, GBC(55) was computed(51) as the average of each voxel's BOLD signal time series correlation with every other gray matter voxel in the prefrontal lobes, as identified by Freesurfer automated segmentation (Figure 1)(65), or in the whole brain (Figure 2, 4). For specific examination of striatal and thalamic ROIs (Figure 4), a probabilistic ROI mask for each region was derived on the basis of Freesurfer segmentation for each subject; average GBC across all voxels in this ROI was extracted for each subject. Seed-based connectivity analysis (Figure 5,S1) was performed as previously(51).

Results

OCD is Associated with Reduced Prefrontal Connectivity

To test for alterations in intrinsic PFC networks in OCD, we performed a GBC analysis restricted to PFC gray matter voxels, anatomically defined for each subject (restricted GBC or rGBC; see Supplement for details). This analysis is based on the hypothesis that there is dysconnectivity intrinsic to the PFC in OCD but is otherwise data-driven. It revealed several clusters of reduced PFC rGBC in OCD relative to HCS (Figure 1 & Table 2). We did not find any clusters of increased PFC rGBC in OCD patients. Reduced GBC was seen

bilaterally in the lateral OFC; we did not find any evidence of reduced functional connectivity in ACC.

OCD is Associated with Reduced Prefrontal and Increased Striatal and Cerebellar Whole-brain GBC

We next extended this approach to the entire brain, in a wholly data-driven analysis. Between-group t-tests revealed five clusters that differed significantly between OCD patients and controls (Table 2): three clusters of decreased GBC centered within the prefrontal cortex, and clusters of increased GBC in the right putamen and the left cerebellum (Figure 2). All of these findings remained significant when we explicitly co-varied for effects of age and gender; within the OCD group, there were no differences in GBC between subjects with and without a history of comorbid depression. Effect sizes were robust across PFC regions of reduced GBC (Cohen's $d=1.32$) and across the putamen/cerebellar regions of increased GBC (Cohen's $d=0.96$).

Overlapping Loci of Reduced Prefrontal rGBC Identified by Whole-Brain GBC and Prefrontal Restricted rGBC

To examine the convergence of whole-brain and PFC-restricted analyses, we computed a formal conjunction of all PFC voxels passing type I error correction in each analysis. Two clusters of overlap between the analyses (left inferior and superior frontal gyri) emerged (Figure 3A & Table 2). OCD subjects showed reduced GBC across the two clusters (Figure 3B; Cohen's $d=1.22$). Collectively, the PFC-focused analyses and the conjunction with whole-brain effects support the hypothesis that OCD is associated with alterations in PFC network connectivity.

The middle frontal gyrus area of reduced GBC emerged only in the whole-brain analysis, not in the PFC-restricted analysis. This suggests that its connectivity, and its dysregulation in OCD, may differ qualitatively from that of the other two PFC regions. To assess this, we performed follow-up exploratory seed-based connectivity analyses on the three PFC clusters identified by the whole-brain GBC analysis (Figure 2). The middle frontal gyrus cluster showed reduced connectivity to lateral PFC but stronger connectivity with the medial frontal cortex in OCD patients than in controls. This pattern was qualitatively distinct from the other PFC clusters (Figure S1), indicating a complex pattern of PFC alterations in OCD.

Correlation with Symptoms and Medication

We examined the relationship between GBC and symptom severity within the OCD group. Clinical measures of obsessions (YBOCS-O), compulsions (YBOCS-C), depression (HAM-D), and anxiety (HAM-A) were inter-correlated in our sample (Figure S3), as is generally the case in OCD (e.g. (66)). To avoid a statistically unmanageable number of comparisons, we performed one correlation analysis across all clusters showing decreased GBC in OCD and a second across all clusters showing increased GBC. Across the clusters showing reduced PFC rGBC (Figure 1), there was a negative relationship between rGBC and all symptom measures ($r(\text{HAM-D})=-0.42$, $p<.013$; $r(\text{HAM-A})=-0.46$, $p<.016$; $r(\text{YBOCS-O})=-0.28$, $p=.15$ and $r(\text{YBOCS-C})=-0.32$, $p=.1$; all p-values 2-tailed) (Figure S2a-d): that is, lower prefrontal rGBC predicted more severe symptomatology in OCD patients. The internal consistency of this relationship across all four clinical measures is notable. Correlations were less impressive, and not statistically significant, for prefrontal GBC clusters identified in the whole-brain analysis.

We observed a positive correlation between all symptom measurements and the increased GBC identified in the putamen and cerebellum in the whole-brain analysis (Figure 2). While none of the individual correlations reached statistical significance in isolation, the internal

consistency of these correlations is again striking: no region showing increased GBC in OCD was negatively correlated with symptoms, and no region showing decreased GBC was positively correlated with symptomatology. We computed a difference score for each subject between their putamen/cerebellar increased GBC and their reduced PFC rGBC. All symptom measures correlated with this difference score (Figure S2B). These analyses support the conclusion that the altered PFC and striatal network functional integrity revealed by the GBC analysis contributes to symptom severity in OCD patients.

The elevated GBC observed in the basal ganglia and cerebellum (Figure 2) was significantly reduced in medicated OCD patients ($n=14$), compared to unmedicated patients ($n=13$; Figure S4). There were no regions of greater GBC in medicated than unmedicated patients; there were no statistically significant effects of medication in the PFC clusters of hypoconnectivity (Figure 1, 2).

Differential Dysconnectivity in Dorsal and Ventral Striatum

In a more hypothesis-guided approach, we next examined global connectivity within anatomically-defined ROIs for the accumbens, putamen, caudate and thalamus. Although it is restricted to *a priori* defined ROIs, this analysis is conceptually and computationally distinct from previously reported seed-based analyses(32,33) in that it quantitatively captures an ROI's connectivity with the entire rest of the brain, rather than identifying specific voxels correlated with a defined seed. Figure 4A shows the between-group GBC contrast (OCD vs. HCS) across the anatomically defined mask, at a relaxed statistical threshold to facilitate visual inspection. The ROI-specific analyses revealed a striking dissociation: the accumbens was associated with decreased whole-brain GBC in OCD, relative to HCS (Figure 4B), but all other ROIs were associated with increased whole-brain GBC for OCD patients relative to HCS (Figure 4C–E). A 2-way ANOVA with a between-group factor of diagnosis (OCD vs. HCS) and a within-subject factor of region confirmed a significant *Diagnosis $\times$ Region* interaction ($F(3,273)=3.55$, $p<.02$). This dissociation reveals a qualitatively different pattern of network dysfunction in ventral versus dorsal striatal loops.

Previous seed-based connectivity analyses (32,33) reported increased functional connectivity between a voxel in the ventral striatum and the ventromedial and orbitofrontal PFC in subjects with OCD; this contrasts with our finding of reduced GBC in the accumbens. We performed a similar seed-based analysis to identify specific regions of dysconnectivity to the accumbens between OCD patients and HCS, although here we explicitly used the entire anatomically-defined accumbens region as the seed, rather than arbitrarily chosen voxels within it. This analysis revealed a cluster in the ventral anterior cingulate cortex (ACC) in which connectivity to the accumbens was increased (Figure 5A). This increased connectivity (Figure 5B; Cohen's $d=.7$) positively correlated with symptom severity (HAM-D=.31; HAM-A=.55; YBOCS-O=.17; YBOCS-C=.24); the correlation was most impressive with HAM-A ($p<.0035$, surviving Bonferroni correction across four comparisons) (Figure 5C).

Discussion

Cortico-striatal circuits are central to reward processing, action selection, habit formation, and motor control(23–26). Dysregulation of this circuitry contributes to numerous forms of psychopathology. In particular, metabolic hyperactivity of dorsal and ventral striatum and regions of the PFC has been implicated in OCD pathophysiology(11,15,16), a view supported by recent seed-based fMRI analyses(32,33). Intrinsic PFC functional connectivity has been less examined in OCD. We identify specific patterns of cortical and subcortical dysconnectivity in OCD, using a recently developed global connectivity metric. Results revealed dysregulated connectivity in unexpected regions of lateral PFC, differential

abnormalities in dorsal and ventral striatal circuits, and new evidence for cerebellar abnormalities.

Abnormalities in CSTC Connectivity Identified Using a Data-driven Approach

The functional heterogeneity and anatomical complexity of the CSTC and PFC make circuitry analysis challenging, especially in the context of psychopathology. Traditional rs-fMRI provides tools for testing functional network abnormalities, but require *a priori* specification of seed regions of interest. The specification of multiple seeds allows broader exploration but increases the risk of false positives due to multiple comparisons. Therefore, we used a data-driven GBC approach to identify disrupted connectivity in OCD in a hypothesis-independent way(59), circumventing the need for *a priori* seed specification(54–56). We provide both independent support for existing models of CSTC dysregulation in OCD and important new findings, especially within the PFC.

Prefrontal Hypo-connectivity in OCD

Abnormalities in PFC function are implicated in many neuropsychiatric conditions. The PFC is large and heterogeneous. Data-driven approaches have been particularly useful in this context(51–53). We analyzed connectivity by computing GBC in two ways: restricted to the PFC (Figure 1) and across the entire brain (Figure 2). These analyses converged on two nodes of dysconnectivity in the left lateral PFC, centered on the supplementary motor area (SMA) and on the ventrolateral PFC (VLPFC). Convergence across analyses provides added confidence in the observed connectivity alterations. Connectivity in these regions correlated negatively with symptom severity (Figure S2).

Both PFC regions have interesting implications for OCD pathophysiology. Increased somatosensory evoked potentials and reduced sensory gating of ERPs were reported in the precentral gyrus in OCD(67); repetitive low-frequency SMA stimulation has been reported to improve symptoms in treatment-resistant patients(68). The anterior VLPFC has been implicated in cognitive control. Damage to the left VLPFC has been associated with impairments in task switching, possibly reflecting a deficiency in top-down regulation of established procedures(69); a related deficiency might contribute to the perseverative behaviors seen in OCD and to difficulty in controlling habitual behavior(70). The homologous region on the right, in which we do not see a corresponding disruption of GBC, has been associated with response inhibition(69,71).

A third PFC region, centered on the left middle prefrontal gyrus, was found to be hypo-connected only in the whole-brain analysis (Figure 3). This implies that connectivity abnormalities in this PFC region differ qualitatively from the other two. An exploratory between-group analysis, using each of these three regions as a seed, confirmed this (Figure S1). The middle prefrontal region exhibited decreased connectivity with the lateral cortical surface but increased connectivity with the medial PFC. The qualitative distinction between the connectivity patterns of the three PFC clusters emphasizes the heterogeneous ways in which psychopathology can influence connectivity and the importance of well-powered data-driven efforts to identify key nodes of dysregulation.

Pathology of the orbitofrontal cortex has frequently been associated with OCD(11). We find decreased GBC in the lateral OFC in OCD patients, only in the PFC-restricted analysis (Figure 1). This contrasts with the findings of a recent connectivity analysis (59). That study applied a threshold to the connectivity measure and therefore counts only the strongest connections, whereas our metric incorporates information from both strong and weak connections. Imaging in this area is particularly challenging, because artifactual signal

dropout can compromise analysis. Analysis of larger samples will be critical to clarify these OFC connectivity abnormalities.

Interestingly, dysconnectivity in these prefrontal regions correlated most significantly with anxiety symptoms (Figure S1), rather than with Y-BOCS. Prefrontal pathology is well established in anxiety disorders more generally (e.g. 72); it may be that lateral prefrontal hypoconnectivity contributes to anxiety symptoms in these OCD patients, rather than to OCD symptoms *per se*. Anxiety is prominent in many cases of OCD. Comparison to an anxious control group in a future replication study would clarify whether the pattern of dysconnectivity we describe is specific to OCD or is a more general signature of anxiety symptoms. This is an important area for future study.

Striatal and Cerebellar Hyper-connectivity in OCD

Our whole-brain GBC analysis also revealed increased functional connectivity in the right putamen and the left cerebellum (Figure 2). The right caudate and putamen have emerged as loci of pathology in many previous studies, using a variety of functional and structural imaging methods(11,13,15,73). The emergence of this striatal GBC abnormality increases confidence that reported alterations are consistent with previous studies using other methods.

The cerebellum has not received major attention in studies of OCD. A recently reported morphological analysis in a pediatric cohort described reduced gray matter that correlated with tic severity and relative enlargement that correlated with OCD severity, suggesting a potentially important role(74). Abnormalities in cerebellar perfusion have also been reported(11). There is increasing appreciation that the interconnectivity between association neocortex, limbic cortex and the cerebellar hemispheres may play a key role in the processing of multimodal information. In turn, disruption of this circuitry may play an important and underappreciated role in neuropsychiatric disease(75).

Cerebellar and striatal hyperconnectivity was modulated by medication status. Within the OCD subjects, hyperconnectivity was reduced in caudate, putamen, and cerebellum in the subset who were on stable SSRI medication, relative to those who were unmedicated (Figure S4). The two subgroups were indistinguishable in terms of age, sex, and symptom severity. A medication effect on striatal connectivity was also reported in a recent study of connectivity in OCD, although the effect was reported in the ventral striatum rather than the caudate and putamen(59). These observations indicate that pharmacotherapy can modulate the circuitry that is altered in OCD. It remains possible that medicated and unmedicated patients differ in some aspect of their underlying disease; comparison of connectivity before and after treatment in a longitudinal study would be required to definitively clarify this question.

Global Connectivity Dissociation Within the Striatum

Analysis focused on striatal and thalamic ROIs revealed a striking dissociation between the nucleus accumbens and the dorsal striatum for OCD patients: GBC was increased in the caudate and putamen, as initially revealed by whole-brain analysis (Figure 2) but was decreased in the anatomically-defined nucleus accumbens (Figure 4). Our results emphasize that striatal network pathology in OCD is not unitary, but rather differs across anatomically discrete information processing loops(32,33,76).

The finding of reduced GBC in the ventral striatum contrasts with the reports of increased seed-based functional connectivity with OFC and ventromedial PFC(32,33). However, when we performed a similar seed-based analysis, we also found increased connectivity between

the accumbens, anatomically defined in each subject, and a region of the ventral anterior cingulate cortex in OCD patients (Figure 5)(32,33). This co-occurrence of reduced GBC but increased focal accumbens-cingulate functional connectivity suggests that nucleus accumbens may be integrated into a narrowed functional circuitry, with greater connectivity with ventromedial PFC but decreased interactions with other brain regions.

The nucleus accumbens(77) and adjacent white matter(78) have been targeted by deep brain stimulation (DBS). A recent report found that accumbens DBS normalized connectivity with the medial frontal cortex(79), further supporting the functional importance of the network dysregulation characterized here.

Limitations

The GBC measure appears to be quite robust in samples of this size (e.g. 54); nevertheless, our single sample is a limitation, especially given the exploratory nature of our analysis, and replication will be critical. We have been rigorous in the elimination of images potentially compromised by movement artifact; replication in larger samples with state-of-the-art movement correction will help solidify and refine the results. We did not distinguish between dimensions of OCD symptomatology(80), which may influence network dysregulation(33). Larger cohorts will be required to adequately account for the symptomatic heterogeneity among OCD patients. Half of our patients were medicated, which may have increased heterogeneity within the OCD cohort. Connectivity abnormalities were associated with disease severity and correlated with all symptom measures but most robustly with measures of anxiety, rather than of OCD specifically. Identification of abnormalities in the basal ganglia circuitry, which have not generally been implicated in other anxiety disorders, suggests that these abnormalities are indeed characteristic of OCD. Nonetheless, comparison to an anxious control group would be valuable to establish the specificity of this effect. Lastly, these connectivity analyses are correlational and therefore cannot establish whether observed abnormalities are causes or consequences of OCD symptomatology.

Conclusion

Data-driven connectivity analyses hold great promise for the identification of dysregulated network patterns beyond those predicted by current theories. Our analyses reveal new patterns of disruption in OCD. We find reduced connectivity across three lateral PFC areas. While disruption in PFC was expected and motivated our analysis, these specific areas were not defined *a priori* and may not have emerged from seed-driven analyses. We also observe a fascinating bidirectional dysregulation of connectivity within the striatum; GBC is increased for dorsal striatum and thalamus, while the accumbens exhibits increased connectivity with a region of the ventral anterior cingulate cortex but decreased connectivity overall, suggesting a potential narrowing of the information processing networks in which it participates. Finally, our analysis identified increased GBC in the cerebellar cortex, which has not been a major focus of interest in OCD but merits further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by DP5OD012109 (AA), 2P50AA012879 (PI: JHK; AA), The Yale Center for Clinical Investigation (UL1RR024139), The Brain and Behavior Research Foundation (C-SRL, AA), The Fullbright Foundation (AS), K99MH0968010 (MWC), K08MH081190 (CP), R01MH095790 (CP), The Doris Duke Charitable Foundation (CP), The Allison Family Foundation (CP), and The Nancy Taylor Foundation for Chronic

Disease (CP), and the State of Connecticut through in support of the Abraham Ribicoff Research Facilities at the Connecticut Mental Health Center. John Krystal consults for several pharmaceutical and biotechnology companies, with compensation less than \$10 000 per year. These companies include AbbVie, Inc.; Amgen; AstraZeneca Pharmaceuticals; Bristol-Myers Squibb; Eli Lilly and Co.; Janssen Research & Development; Lundbeck Research USA; Otsuka Pharmaceutical, Development & Commercialization, Inc.; Sage Therapeutics, Inc.; Shire Pharmaceuticals; Sunovion Pharmaceuticals, Inc.; Takeda Industries; and Teva Pharmaceutical Industries, Ltd. Dr Krystal is a member of the following scientific advisory boards: CHDI Foundation, Inc.; Lohocla Research Corporation, Mnemosyne Pharmaceuticals, Inc.; Naurex, Inc.; and Pfizer Pharmaceuticals. In addition, Dr Krystal is a board member of the Coalition for Translational Research in Alcohol and Substance Use Disorders, past president of the American College of Neuropsychopharmacology, editor of *Biological Psychiatry*; and an employee of the Yale University School of Medicine and the VA CT Health System. He is an originator on the following patent: Seibyl JP, Krystal JH, and Charney DS; Dopamine and noradrenergic reuptake inhibitors in treatment of schizophrenia; Patent #:5 447 948; 5 September 1995. In addition, he is an originator of the following relevant pending patents: (1) Vladimir, Coric; Krystal, John H, Sanacora, Gerard—Glutamate Agents in the Treatment of Mental Disorders No 11/399 188; 5 April 2006 (Pending). (2) Intranasal Administration of Ketamine to Treat Depression (Pending). S. Bednarski is currently an employee of Bristol Myers-Squibb, Ltd., though she was not at the time of her participation in this work.

References

1. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder. Arlington, VA: American Psychiatric Association; 2007.
2. Jenike MA. Clinical practice. Obsessive-compulsive disorder. *N Engl J Med*. 2004; 350:259–265. [PubMed: 14724305]
3. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *International journal of methods in psychiatric research*. 2012; 21:169–184. [PubMed: 22865617]
4. Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol Psychiatry*. 2010; 15:53–63. [PubMed: 18725912]
5. Baxter LR Jr, Schwartz JM, Mazziotta JC, Phelps ME, Pahl JJ, Guze BH, et al. Cerebral glucose metabolic rates in nondepressed patients with obsessive-compulsive disorder. *The American journal of psychiatry*. 1988; 145:1560–1563. [PubMed: 3264118]
6. Baxter LR Jr, Phelps ME, Mazziotta JC, Guze BH, Schwartz JM, Selin CE. Local cerebral glucose metabolic rates in obsessive-compulsive disorder. A comparison with rates in unipolar depression and in normal controls. *Archives of general psychiatry*. 1987; 44:211–218. [PubMed: 3493749]
7. Swedo SE, Schapiro MB, Grady CL, Cheslow DL, Leonard HL, Kumar A, et al. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. *Archives of general psychiatry*. 1989; 46:518–523. [PubMed: 2786402]
8. Machlin SR, Harris GJ, Pearlson GD, Hoehn-Saric R, Jeffery P, Camargo EE. Elevated medial-frontal cerebral blood flow in obsessive-compulsive patients: a SPECT study. *The American journal of psychiatry*. 1991; 148:1240–1242. [PubMed: 1883006]
9. Rauch SL, Jenike MA, Alpert NM, Baer L, Breiter HC, Savage CR, et al. 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]
10. Whiteside SP, Port JD, Abramowitz JS. A meta-analysis of functional neuroimaging in obsessive-compulsive disorder. *Psychiatry research*. 2004; 132:69–79. [PubMed: 15546704]
11. Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. *Neurosci Biobehav Rev*. 2008; 32:525–549. [PubMed: 18061263]
12. Rotge JY, Guehl D, Dilharreguy B, Tignol J, Bioulac B, Allard M, et al. Meta-analysis of brain volume changes in obsessive-compulsive disorder. *Biological psychiatry*. 2009; 65:75–83. [PubMed: 18718575]

13. Radua J, van den Heuvel OA, Surguladze S, Mataix-Cols D. Meta-analytical comparison of voxel-based morphometry studies in obsessive-compulsive disorder vs other anxiety disorders. *Archives of general psychiatry*. 2010; 67:701–711. [PubMed: 20603451]
14. Radua J, Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *The British journal of psychiatry : the journal of mental science*. 2009; 195:393–402. [PubMed: 19880927]
15. Maia TV, Cooney RE, Peterson BS. The neural bases of obsessive-compulsive disorder in children and adults. *Dev Psychopathol*. 2008; 20:1251–1283. [PubMed: 18838041]
16. Saxena S, Bota RG, Brody AL. Brain-behavior relationships in obsessive-compulsive disorder. *Seminars in clinical neuropsychiatry*. 2001; 6:82–101. [PubMed: 11296309]
17. Breiter HC, Rauch SL, Kwong KK, Baker JR, Weisskoff RM, Kennedy DN, et al. Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder. *Archives of general psychiatry*. 1996; 53:595–606. [PubMed: 8660126]
18. 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]
19. Rotge JY, Langbour N, Jaafari N, Guehl D, Bioulac B, Aouizerate B, et al. Anatomical alterations and symptom-related functional activity in obsessive-compulsive disorder are correlated in the lateral orbitofrontal cortex. *Biological psychiatry*. 2010; 67:e37–38. [PubMed: 20015485]
20. Baxter LR Jr, Schwartz JM, Bergman KS, Szuba MP, Guze BH, Mazziotta JC, et al. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. *Archives of general psychiatry*. 1992; 49:681–689. [PubMed: 1514872]
21. Swedo SE, Pietrini P, Leonard HL, Schapiro MB, Rettew DC, Goldberger EL, et al. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. Revisualization during pharmacotherapy. *Archives of general psychiatry*. 1992; 49:690–694. [PubMed: 1514873]
22. Saxena S, Brody AL, Ho ML, Alborzian S, Maidment KM, Zohrabi N, et al. Differential cerebral metabolic changes with paroxetine treatment of obsessive-compulsive disorder vs major depression. *Archives of general psychiatry*. 2002; 59:250–261. [PubMed: 11879163]
23. Graybiel AM. Habits, rituals, and the evaluative brain. *Annual review of neuroscience*. 2008; 31:359–387.
24. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2010; 35:4–26. [PubMed: 19812543]
25. Grillner S, Robertson B, Stephenson-Jones M. The evolutionary origin of the vertebrate basal ganglia and its role in action-selection. *The Journal of physiology*. 2013
26. Pennartz CM, Berke JD, Graybiel AM, Ito R, Lansink CS, van der Meer M, et al. Corticostriatal Interactions during Learning, Memory Processing, and Decision Making. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2009; 29:12831–12838. [PubMed: 19828796]
27. 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.
28. Choi EY, Yeo BT, Buckner RL. The organization of the human striatum estimated by intrinsic functional connectivity. *Journal of neurophysiology*. 2012; 108:2242–2263. [PubMed: 22832566]
29. Crittenden JR, Graybiel AM. Basal Ganglia disorders associated with imbalances in the striatal striosome and matrix compartments. *Frontiers in neuroanatomy*. 2011; 5:59. [PubMed: 21941467]
30. Bostan AC, Dum RP, Strick PL. The basal ganglia communicate with the cerebellum. *Proceedings of the National Academy of Sciences of the United States of America*. 2010; 107:8452–8456. [PubMed: 20404184]
31. Hoshi E, Tremblay L, Feger J, Carras PL, Strick PL. The cerebellum communicates with the basal ganglia. *Nature neuroscience*. 2005; 8:1491–1493.
32. Harrison BJ, Soriano-Mas C, Pujol J, Ortiz H, Lopez-Sola M, Hernandez-Ribas R, et al. Altered corticostriatal functional connectivity in obsessive-compulsive disorder. *Archives of general psychiatry*. 2009; 66:1189–1200. [PubMed: 19884607]

33. Harrison BJ, Pujol J, Cardoner N, Deus J, Alonso P, Lopez-Sola M, et al. Brain corticostriatal systems and the major clinical symptom dimensions of obsessive-compulsive disorder. *Biological psychiatry*. 2013; 73:321–328. [PubMed: 23200527]
34. Figeo M, Vink M, de Geus F, Vulink N, Veltman DJ, Westenberg H, et al. Dysfunctional reward circuitry in obsessive-compulsive disorder. *Biological psychiatry*. 2011; 69:867–874. [PubMed: 21272861]
35. Rotge JY, Guehl D, Dilharreguy B, Cuny E, Tignol J, Bioulac B, et al. Provocation of obsessive-compulsive symptoms: a quantitative voxel-based meta-analysis of functional neuroimaging studies. *Journal of psychiatry & neuroscience : JPN*. 2008; 33:405–412. [PubMed: 18787662]
36. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature reviews Neuroscience*. 2007; 8:700–711.
37. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*. 2005; 102:9673–9678. [PubMed: 15976020]
38. Biswal BB. Resting state fMRI: a personal history. *NeuroImage*. 2012; 62:938–944. [PubMed: 22326802]
39. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine*. 1995; 34:537–541. [PubMed: 8524021]
40. Biswal BB, Mennes M, Zuo X-N, Gohel S, Kelly C, Smith SM, et al. Toward discovery science of human brain function. *Proc Natl Acad Sci USA*. 2010; 107:4734–4739. [PubMed: 20176931]
41. Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of neurophysiology*. 2011; 106:1125–1165. [PubMed: 21653723]
42. Fox MD, Greicius M. Clinical applications of resting state functional connectivity. *Frontiers in systems neuroscience*. 2010; 4:19. [PubMed: 20592951]
43. Fitzgerald KD, Stern ER, Angstadt M, Nicholson-Muth KC, Maynor MR, Welsh RC, et al. Altered function and connectivity of the medial frontal cortex in pediatric obsessive-compulsive disorder. *Biological psychiatry*. 2010; 68:1039–1047. [PubMed: 20947065]
44. Fitzgerald KD, Welsh RC, Stern ER, Angstadt M, Hanna GL, Abelson JL, et al. Developmental alterations of frontal-striatal-thalamic connectivity in obsessive-compulsive disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2011; 50:938–948 e933. [PubMed: 21871375]
45. Jang JH, Kim JH, Jung WH, Choi JS, Jung MH, Lee JM, et al. Functional connectivity in fronto-subcortical circuitry during the resting state in obsessive-compulsive disorder. *Neuroscience letters*. 2010; 474:158–162. [PubMed: 20302914]
46. Kang DH, Jang JH, Han JY, Kim JH, Jung WH, Choi JS, et al. Neural correlates of altered response inhibition and dysfunctional connectivity at rest in obsessive-compulsive disorder. *Progress in neuropsychopharmacology & biological psychiatry*. 2013; 40:340–346.
47. Li P, Li S, Dong Z, Luo J, Han H, Xiong H, et al. Altered resting state functional connectivity patterns of the anterior prefrontal cortex in obsessive-compulsive disorder. *Neuroreport*. 2012; 23:681–686. [PubMed: 22692554]
48. Sakai Y, Narumoto J, Nishida S, Nakamae T, Yamada K, Nishimura T, et al. Corticostriatal functional connectivity in non-medicated patients with obsessive-compulsive disorder. *European psychiatry : the journal of the Association of European Psychiatrists*. 2011; 26:463–469. [PubMed: 21067900]
49. Stern ER, Fitzgerald KD, Welsh RC, Abelson JL, Taylor SF. Resting-state functional connectivity between fronto-parietal and default mode networks in obsessive-compulsive disorder. *PloS one*. 2012; 7:e36356. [PubMed: 22570705]
50. Zhang T, Wang J, Yang Y, Wu Q, Li B, Chen L, et al. Abnormal small-world architecture of top-down control networks in obsessive-compulsive disorder. *Journal of psychiatry & neuroscience : JPN*. 2011; 36:23–31. [PubMed: 20964957]

51. Anticevic A, Brumbaugh MS, Winkler AM, Lombardo LE, Barrett J, Corlett PR, et al. Global prefrontal and fronto-amygdala dysconnectivity in bipolar I disorder with psychosis history. *Biological psychiatry*. 2013; 73:565–573. [PubMed: 22980587]
52. Anticevic A, Repovs G, Krystal JH, Barch DM. A broken filter: prefrontal functional connectivity abnormalities in schizophrenia during working memory interference. *Schizophrenia research*. 2012; 141:8–14. [PubMed: 22863548]
53. Cole MW, Anticevic A, Repovs G, Barch D. Variable global dysconnectivity and individual differences in schizophrenia. *Biological psychiatry*. 2011; 70:43–50. [PubMed: 21496789]
54. Buckner RL, Sepulcre J, Talukdar T, Krienen FM, Liu H, Hedden T, et al. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2009; 29:1860–1873. [PubMed: 19211893]
55. Cole MW, Pathak S, Schneider W. Identifying the brain's most globally connected regions. *NeuroImage*. 2010; 49:3132–3148. [PubMed: 19909818]
56. Martuzzi R, Ramani R, Qiu M, Shen X, Papademetris X, Constable RT. A whole-brain voxel based measure of intrinsic connectivity contrast reveals local changes in tissue connectivity with anesthetic without a priori assumptions on thresholds or regions of interest. *NeuroImage*. 2011; 58:1044–1050. [PubMed: 21763437]
57. Cole MW, Yarkoni T, Repovs G, Anticevic A, Braver TS. Global connectivity of prefrontal cortex predicts cognitive control and intelligence. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2012; 32:8988–8999. [PubMed: 22745498]
58. Driesen NR, McCarthy G, Bhagwagar Z, Bloch M, Calhoun V, D'Souza DC, et al. Relationship of resting brain hyperconnectivity and schizophrenia-like symptoms produced by the NMDA receptor antagonist ketamine in humans. *Mol Psychiatry*. 2013
59. Beucke JC, Sepulcre J, Talukdar T, Linnman C, Zschenderlein K, Endrass T, et al. Abnormally high degree connectivity of the orbitofrontal cortex in obsessive-compulsive disorder. *JAMA psychiatry*. 2013; 70:619–629. [PubMed: 23740050]
60. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured clinical interview for the DSM-IV-TR Axis I disorders. Washington, D. C: American Psychiatric Press; 2001.
61. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Archives of general psychiatry*. 1989; 46:1006–1011. [PubMed: 2684084]
62. Goodman WK, Price LH, Rasmussen SA, Mazure C, Delgado P, Heninger GR, et al. The Yale-Brown Obsessive Compulsive Scale. II. Validity. *Archives of general psychiatry*. 1989; 46:1012–1016. [PubMed: 2510699]
63. Hamilton M. A rating scale for depression. *Journal of neurology, neurosurgery, and psychiatry*. 1960; 23:56–62.
64. Hamilton M. The assessment of anxiety states by rating. *The British journal of medical psychology*. 1959; 32:50–55. [PubMed: 13638508]
65. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002; 33:341–355. [PubMed: 11832223]
66. Pittenger C, Kelmendi B, Wasylink S, Bloch MH, Coric V. Riluzole augmentation in treatment-refractory obsessive-compulsive disorder: a series of 13 cases, with long-term follow-up. *Journal of clinical psychopharmacology*. 2008; 28:363–367. [PubMed: 18480706]
67. Rossi S, Bartalini S, Olivelli M, Mantovani A, Di Muro A, Goracci A, et al. Hypofunctioning of sensory gating mechanisms in patients with obsessive-compulsive disorder. *Biological psychiatry*. 2005; 57:16–20. [PubMed: 15607295]
68. Mantovani A, Simpson HB, Fallon BA, Rossi S, Lisanby SH. Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive-compulsive disorder. *Int J Neuropsychopharmacol*. 2010; 13:217–227. [PubMed: 19691873]
69. Aron AR, Monsell S, Sahakian BJ, Robbins TW. A componential analysis of task-switching deficits associated with lesions of left and right frontal cortex. *Brain : a journal of neurology*. 2004; 127:1561–1573. [PubMed: 15090477]

70. Gillan CM, Pappmeyer M, Morein-Zamir S, Sahakian BJ, Fineberg NA, Robbins TW, et al. Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder. *The American journal of psychiatry*. 2011; 168:718–726. [PubMed: 21572165]
71. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. *Trends in cognitive sciences*. 2004; 8:170–177. [PubMed: 15050513]
72. Ochsner KN, Ray RR, Hughes B, McRae K, Cooper JC, Weber J, et al. Bottom-up and top-down processes in emotion generation: common and distinct neural mechanisms. *Psychological science*. 2009; 20:1322–1331. [PubMed: 19883494]
73. Rotge JY, Langbour N, Guehl D, Bioulac B, Jaafari N, Allard M, et al. Gray matter alterations in obsessive-compulsive disorder: an anatomic likelihood estimation meta-analysis. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2010; 35:686–691. [PubMed: 19890260]
74. Tobe RH, Bansal R, Xu D, Hao X, Liu J, Sanchez J, et al. Cerebellar morphology in Tourette syndrome and obsessive-compulsive disorder. *Annals of neurology*. 2010; 67:479–487. [PubMed: 20437583]
75. Buckner RL, Krienen FM, Castellanos A, Diaz JC, Yeo BT. The organization of the human cerebellum estimated by intrinsic functional connectivity. *Journal of neurophysiology*. 2011; 106:2322–2345. [PubMed: 21795627]
76. Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, “prefrontal” and “limbic” functions. *Progress in brain research*. 1990; 85:119–146. [PubMed: 2094891]
77. Denys D, Mantione M, Figee M, van den Munckhof P, Koerselman F, Westenberg H, et al. Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. *Archives of general psychiatry*. 2010; 67:1061–1068. [PubMed: 20921122]
78. Goodman WK, Foote KD, Greenberg BD, Ricciuti N, Bauer R, Ward H, et al. Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design. *Biological psychiatry*. 2010; 67:535–542. [PubMed: 20116047]
79. Figee M, Luigjes J, Smolders R, Valencia-Alfonso CE, van Wingen G, de Kwaasteniet B, et al. Deep brain stimulation restores frontostriatal network activity in obsessive-compulsive disorder. *Nature neuroscience*. 2013
80. Bloch MH, Landeros-Weisenberger A, Rosario MC, Pittenger C, Leckman JF. Meta-analysis of the symptom structure of obsessive-compulsive disorder. *The American journal of psychiatry*. 2008; 165:1532–1542. [PubMed: 18923068]
81. Cohen J. A power primer. *Psychological Bulletin*. 1992; 112:155–159. [PubMed: 19565683]

Figure 1. Reduced PFC rGBC in Obsessive-compulsive Disorder (OCD)

(A) Clusters where OCD patients showed significantly decreased PFC-restricted rGBC connectivity relative to HCS (see Table 2 for all cluster coordinates). The black border marks the approximate PFC boundary. (B) PFC rGBC reductions for OCD patients (red distribution) relative to HCS (blue distribution), across all voxels in identified clusters of dysconnectivity (see Table 2 for individual cluster statistics). Reported effect sizes are computed across subjects; histograms of voxel distribution within regions of between-group difference are provided for illustrative purposes.

Whole-brain GBC Differences in Obsessive-Compulsive Disorder

Figure 2. Reduced Prefrontal and Increased Striatal-Cerebellar Whole-brain GBC in Obsessive-compulsive Disorder (OCD)

(A) Clusters where OCD patients showed significantly *decreased* whole-brain GBC connectivity relative to HCS. This pattern was centered on the left middle frontal gyrus, inferior frontal gyrus, and precentral gyrus (see Table 2 for cluster coordinates). (B) GBC reductions for OCD patients (red histogram) relative to HCS (blue histogram), averaged across all identified clusters (see Table 2 for individual cluster statistics). (C) Clusters where OCD patients showed significantly *increased* whole-brain GBC connectivity relative to HCS. This pattern was centered on the right putamen and left cerebellum (see Table 2 for cluster coordinates and statistics). (D) GBC *increases* for OCD patients (red histogram) relative to HCS (blue histogram) across both clusters (see Table 2 for individual cluster statistics). Blue vertical dashed line marks the mean for the HCS group.

Conjunction of PFC and Whole-brain GBC Effects

Figure 3. Conjunction of PFC and Whole-brain GBC Effects in Obsessive-compulsive Disorder (OCD)

(A) Red clusters mark regions where OCD patients showed significantly decreased whole-brain GBC connectivity relative to HCS (Figure 2). Yellow clusters show regions where OCD patients significantly decreased PFC rGBC connectivity relative to HCS (Figure 1). Blue foci mark the conjunction. The PFC and whole-brain effects are partially independent (as the whole-brain analysis involves many more voxels). (B) Reductions for OCD patients (red histogram) relative to HCS (blue histogram) averaged across the two clusters surviving the conjunction (see Table 2 for individual cluster statistics)

Striatum & Thalamus GBC Differences in Obsessive-Compulsive Disorder

OCD vs. HCS - Threshold-free Contrast for Subcortical Regions

Anatomically-defined Region of Interest (ROI) Analyses

Figure 4. Region-of-interest (ROI)-focused Analyses of Accumbens, Caudate, Putamen and Thalamic GBC

(A) Differences between OCD and HCS within striatum and thalamus, defined on the basis of subjects' individual anatomy. Red-yellow foci mark regions where OCD patients showed increased GBC relative to HCS, while blue foci show regions where OCD patients showed reduced GBC relative to HCS. Note the dissociation between the accumbens and the rest of the striatum and thalamus: OCD was associated with reduced GBC in the accumbens, but increased GBC elsewhere, as illustrated in the bar graph on the right. (B–E) GBC across all voxels in *a priori* anatomically-defined ROIs for the accumbens, caudate, putamen and thalamus (insets highlight each region). As noted in the main text, there was a significant dissociation between accumbens and other ROIs across the groups ($F(3,273)=3.55$, $p<.02$).

Figure 5. Seed-based Anatomically-defined Nucleus Accumbens Group Difference in Connectivity

Prior seed-based connectivity analyses of striatal structures in OCD have reported an increase in coupling between the nucleus accumbens and ventral anterior cingulate cortex (ACC)(32, 33). We performed a similar analysis to see whether such increased seed-based connectivity coexisted with the reduced GBC seen in the accumbens (Figure 4). (A) Increased connectivity with the anatomically-defined accumbens seed was seen in the ventral ACC (Talairach coordinates: $x = -16$, $y = 27$, $z = 14$, 864mm^3 in size, Mean t -statistic=3.19). (B) Increased accumbens-ACC connectivity, across all voxels in the area of significant between-group difference. Given *a priori* evidence for increased connectivity between ACC and accumbens in OCD(32), to increase power, we employed a small-volume type I error correction for PFC voxels identical to that used in our restricted GBC approach reported in the main text. (C) The positive relationship between accumbens-MPFC over-connectivity positively correlated with symptom severity across all four measures reported in the main text (HAM-D=.31; HAM-A=.55; YBOCS-O=.17; YBOCS-C=.24), particularly prominent for HAM-A ($r=.55$, $p<.0035$, surviving Bonferroni correction across four comparisons, **panel C**).

Table 1

Clinical and Demographic Characteristics

Characteristic	Controls (N=66)			Patients (N=27)			Significance	
	M	S.D.		M	S.D.		T Value/Chi-Square	P Value (two-tailed)
Age (in years)	33.00	10.36		36.37	13.59		0.58	0.562
Gender (% male)	62			56			1.30	0.198
Participants' Education (in years)	15.85	3.08		15.41	2.21		0.67	0.504
Fam Hx OCD	-	-		56				
Age of Onset of Minor Symptoms	-	-		10.52	6.23			
Age of Onset of Major OCD Symptoms	-	-		19.00	13.46			
Age at Dx	-	-		25.22	12.82			
Comorbid Depression (lifetime) (%)	-	-		70				
Receiving Psychotherapy (%)	-	-		15				
Receiving Stable SSRI Pharmacotherapy (%)	-	-		52				
Ham-D 17	-	-		12.65	6.31			
Ham-A	-	-		13.60	7.85			
YBOC-Total	-	-		27.15	5.74			
YBOC-O	-	-		13.93	2.84			
YBOC-C	-	-		13.22	3.19			
Signal-to-noise (SNR) Ratio	231.61	75.94		237.77	84.60		0.34	0.73
% of Frames Removed with Scrubbing	10.37	10.99		11.39	14.86		0.37	0.71

Table 2

Between-group Differences - Region Coordinates & Effect Sizes

X	Y	Z	Hemisphere	Anatomical Landmark	Effect Sizes (Cohen's d) - OCD vs. HCS	Mean T Value	Cluster size (mm ³)	P Value
+Whole-brain GBC Findings								
-34	-61	-32	left	cerebellum	1.06	4.64	2268	0.00001
-44	41	-3	left	inferior frontal gyrus (BA 47)	-1.41	5.15	5535	0.00000
14	-1	8	right	putamen	0.71	3.06	1269	0.00288
-46	23	19	left	middle frontal gyrus (BA 46)	-1.18	4.54	4536	0.00002
-36	1	37	left	precentral gyrus (BA 6)	-0.95	3.68	1674	0.00040
Prefrontal rGBC Findings								
-28	15	-18	left	inferior frontal gyrus (BA 47)	-1.01	4.25	729	0.00005
30	12	-19	right	inferior frontal gyrus (BA 47)	-0.90	3.96	729	0.00015
-45	39	-1	left	inferior frontal gyrus (BA 47)	-1.08	4.49	3267	0.00002
-16	61	10	left	medial frontal gyrus (BA 10)	-1.10	4.87	2565	0.00000
-36	4	37	left	precentral gyrus (BA 6)	-0.99	4.00	2430	0.00013
10	22	63	right	superior frontal gyrus (BA 6)	-0.94	4.10	729	0.00009
Conjunction (Whole-brain and Prefrontal Findings)								
-46	40	-1	left	inferior frontal gyrus (BA 47)	-1.23	4.66	2187	0.00001
-37	2	38	left	precentral gyrus (BA 6)	-0.91	3.44	1026	0.00089

* negative Cohen's d value denotes a reduction for OCD vs. HCS