ORIGINAL ARTICLE

Abnormally High Degree Connectivity of the Orbitofrontal Cortex in Obsessive-Compulsive Disorder

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Importance: Neurobiological models of obsessive-compulsive disorder (OCD) predict hyperactivity in brain circuits involving the orbitofrontal cortex and the basal ganglia, but it is unclear whether these areas are also characterized by altered brain network properties.

Objectives: To determine regions of abnormal degree connectivity in patients with OCD and to investigate whether connectivity measures are affected by antidepressant medication in OCD.

Design: Case-control cross-sectional study using resting-state functional magnetic resonance imaging and a data-driven, model-free method to test for alterations in the degree of whole-brain, distant, and local connectivity in unmedicated patients with OCD compared with healthy controls.

Setting: Outpatient clinic for OCD.

Participants: Twenty-three patients with OCD (12 women, 11 men) receiving no medication, 23 patients with OCD (14 women, 9 men) treated with antidepressant medication, and 2 equally sized control samples matched for age, sex, handedness, educational level, and IQ.

Main Outcome Measures: Statistical parametric maps testing the degree of distant and local functional connectivity of each voxel (hub analysis at voxel level) and OCD symptom severity.

Results: Unmedicated patients with OCD showed greater distant connectivity in the orbitofrontal cortex and subthalamic nucleus and greater local connectivity in the orbitofrontal cortex and the putamen. Furthermore, distant connectivity of the orbitofrontal cortex and the putamen positively correlated with global OCD symptom severity. Medicated patients with OCD showed reduced local connectivity of the ventral striatum compared with the unmedicated patients.

Conclusions and Relevance: Consistent with neurobiological models of OCD, the orbitofrontal cortex and the basal ganglia are hyperconnected in unmedicated patients. The finding of distant connectivity alterations of the orbitofrontal cortex and the basal ganglia represents initial evidence of greater connections with distant cortical areas outside of corticostriatal circuitry. Furthermore, these data suggest that antidepressant medication may reduce connectivity within corticobasal ganglia-thalamo-cortical circuits in OCD.

JAMA Psychiatry. 2013;70(6):619-629.
Published online April 17, 2013.
doi:10.1001/jamapsychiatry.2013.173

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THE CEREBRAL CORTEX IS ORganized into functional networks in which a particular set of regions has disproportionately numerous connections, called "cortical hubs" of connectivity.[1-3] Recent methodologic developments allow characterization of cortical hubs in the human brain from structural or functional magnetic resonance imaging (fMRI) data.[2-4] For example, estimation of degree connectivity, a fundamental network measure indexing the number of connections that link one network component to the rest of the network,[3] allows for identification of cortical hubs on the basis of blood oxygen level–dependent (BOLD) signal voxel time-series data.[2] Moreover, assessment of degree connectivity allows testing for alterations in network integrity or hub topography in neuropsychiatric populations.[3] For instance, network alterations and correlation with pathophysiologic mechanisms have been demonstrated in Alzheimer disease and schizophrenia.[2,3,5] More precisely, degree connectivity correlated with amyloid β deposition in Alzheimer disease,[2] and in schizophrenia, network integrity was globally reduced, consistent with dysconnection hypotheses.[5] The present study sought to test for degree connectivity alterations in obsessive-compulsive disorder (OCD) and to

determine whether altered network properties are present in areas predicted by neurobiological models of OCD.[6-8]

In the functional neuroanatomy of OCD, a critical role has been assigned to the orbitofrontal cortex (OFC),[6-8] a brain region crucially involved in reward-guided learning and decision making.[9] Evidence supporting this view comes from neuroimaging studies identifying lower OFC activity during reversal learning[10,11] and from early[12,13] and recent[14,15] findings of OFC hyperactivity during symptom provocation in OCD. In addition to experimental data, initial evidence of abnormal OFC activity has been identified in resting-state positron emission tomography (PET) studies examining patients with OCD.[16-24] In this setting, patients displayed elevated glucose metabolism in the OFC,[16-18,22,23] decreases in OFC metabolism correlated with symptom improvement associated with treatment,[20] and correlations between OFC and thalamic activity before but not after treatment.[19,24] In addition, a consistent observation in resting PET data is that antidepressant medication decreases caudate nucleus metabolism in patients with OCD,[19,24] but more heterogeneous treatment responses have been shown for the putamen.[22] Taken together, these resting-state abnormalities, along with symptom provocation data,[12,13] essentially contribute to the empirical fundament for neurobiological models of OCD, postulating dysfunctional hyperactive corticobasal ganglia-thalamo-cortical (CBGTC) circuits.[6-8] Noteworthy recent theoretical considerations suggest that we revise assumptions involving CBGTC circuitry in OCD, given that consistent functional and structural abnormalities were also identified in dorsal prefrontal,[25] parietal, and occipital areas outside of CBGTC circuitry.[26]

Despite the assumption of dysfunctional loops or circuits in the pathophysiologic characteristics of OCD, fMRI studies have only recently started to assess abnormal interregional connectivity of CBGTC regions in this patient group. Consistent with predictions of abnormal CBGTC connectivity, abnormally high connectivity with the OFC was found for seed regions (ie, the BOLD signal time series in a region of interest, used as a regressor for all other BOLD signal time series) in the ventral striatum in patients with OCD under resting-state conditions.[27,28] However, seed-based approaches exclusively consider connectivity of a single region, thereby limiting potential insights regarding fundamental network alterations. For instance, abnormal connectivity could be present outside of CBGTC circuitry and/or concern not only one but multiple CBGTC areas. This is particularly relevant given anatomic evidence that CBGTC circuits, initially viewed to be functionally segregated,[29] interact in the context of complex behaviors.[30]

To test for fundamental network alterations in OCD and relationships to the pathophysiologic characteristics of the disease, the present study applied a novel approach[2,4] that uses resting-state fMRI data to identify areas displaying a high degree of connectivity, representing cortical hubs.[2] Furthermore, recent developments allow differentiation between the degree of local and distant connectivity of all brain areas.[4] In summary, these methods test for extensive whole-brain, distant, or local connectivity in every brain region and, in contrast to traditional seeding approaches, do not require a priori selection of a particular region.[2,4] Thus, these methods automatically achieve simultaneous testing for hub alterations in OFC and CBGTC areas in an unbiased manner as well as testing for network alterations outside of CBGTC circuitry. The approach further allows observation of whether antidepressant medication affects striatal connectivity as suggested by decreases in striatal activity in response to treatment.[17,19,24]

Aside from exploring cortical hub alterations in OCD using a model-free analysis of brain connectivity, 3 hypotheses were tested in the present study. First, we tested the hypothesis that OFC and basal ganglia display a greater degree of connectivity in unmedicated patients with OCD compared with pair-matched healthy individuals serving as controls. Second, we hypothesized that the degree of connectivity in OFC and basal ganglia regions would correlate with global OCD symptom severity. Third, we predicted that the degree of striatal connectivity would be lower in medicated compared with unmedicated patients with OCD, since antidepressant medication has been shown[19,31] to reduce activity in the striatum.

METHODS

STUDY PARTICIPANTS

Forty-six adult outpatients with a *DSM-IV* diagnosis of OCD recruited from the OCD outpatient clinic at the Humboldt-Universität zu Berlin and 46 healthy controls who were matched for demographic variables (age, sex, handedness, and educational level) participated in the study. The total sample was divided into one sample containing 23 unmedicated patients with OCD and 23 matched healthy controls and an additional patient group consisting of 23 patients with OCD treated with antidepressants (20 receiving selective serotonin reuptake inhibitors, 2 receiving selective norepinephrine reuptake inhibitors, and 1 receiving a tricyclic antidepressant) and 23 matched healthy controls. Unmedicated patients did not receive medication related to OCD symptoms for at least 6 weeks before the imaging study. Patients were interviewed by a licensed clinical psychologist and their condition was diagnosed using the German version of the Structured Clinical Interview for *DSM-IV*.[32] Comorbid lifetime diagnoses for the unmedicated sample included major depression (n=12), specific phobia (n=1), hypochondria (n=2), substance abuse (n=2), social phobia (n=6), dysthymia (n=1), bulimia (n=1), anorexia (n=1), generalized anxiety disorder (n=1), panic disorder (n=2), and somatoform disorder (n=1). Comorbid depression was remitted in 4 unmedicated patients at the time of the study. Five unmedicated patients had OCD as their single diagnosis. Comorbid lifetime diagnoses for the medicated sample included major depression (n=12), specific phobia (n=2), hypochondria (n=1), social phobia (n=1), dysthymia (n=1), bulimia (n=1), anorexia (n=1), generalized anxiety disorder (n=4), panic disorder (n=2), agoraphobia (n=1), and adjustment disorder (n=1). Comorbid depression was remitted in 6 medicated patients at the time of the study. Four medicated patients had OCD as their single diagnosis. **Table 1** reports demographic data on the unmedicated patient and control groups; the eTable (http://www.jamapsych.com) reports data on the OCD subgroups.

Exclusion criteria for participants included cardiac pacemakers or other metallic implants or artifacts and pregnancy. Patients could have no significant neurologic illness, prior neurosurgery, dementia, delirium, schizophrenia, delusional dis-

order, or other psychotic disorder. In addition, no patient could have received benzodiazepines within 4 weeks prior to the scanning session. Healthy controls did not fulfill the criteria of any *DSM-IV* diagnosis (lifetime) as indicated by negative results of the Structured Clinical Interview for *DSM-IV* screening questionnaire. All participants gave written informed consent according to the institutional guidelines before enrollment. The local ethics committee approved the study.

CLINICAL SCALES AND QUESTIONNAIRES

Severity of OCD symptoms was evaluated using the German versions of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[33] and the Obsessive-Compulsive Inventory–Revised.[34] In addition, the State-Trait Anxiety Inventory–Revised,[35] the Beck Depression Inventory,[36] and the Montgomery-Åsberg Depression Rating Scale[37] were administered before the imaging study. The Edinburgh Handedness Inventory[38] was used to classify handedness. All participants completed a German vocabulary test[39] as a brief measure of verbal intelligence.

MRI PROCEDURES

A total of 160 volumes (T2*-weighted, single-shot, gradient-echo planar imaging sequence) were acquired on a 1.5-T system equipped with a circular-polarized headcoil (Magnetom Sonata; Siemens) using the following parameters: repetition time, 2000 milliseconds; echo time, 40 milliseconds; 35 consecutive slices; isotropic 3-mm voxel size; flip angle, 90°; field of view,192 mm; 64 × 64 matrix, aligned parallel to the anterior-posterior commissure line; and 176 anatomical slices acquired using the Modified Driven Equilibrium Fourier Transform sequence[40] (spatial resolution 1 × 1 × 1 mm; repetition time, 12.24 milliseconds; echo time, 3.56 milliseconds; flip angle, 23°; and 256 × 224 matrix). Participants were instructed to close their eyes, relax, and not think of anything specific during this 5-minute, 20-second run. Simultaneous electroencephalogram (32 channels, BrainAmp MR; Brain Products) recordings were monitored online by an experimenter trained in sleep stage scoring (C.K.) to ensure that participants did not fall asleep. A vacuum head cushion was used to achieve immobilization. Earplugs were provided to attenuate scanner noise.

IMAGE PROCESSING

The fMRI data were processed using the identical hub analysis stream that has been described in detail.[2,4] In brief, image preprocessing included removal of the first 4 volumes, slice time correction, and spatial normalization to the atlas space of the Montreal Neurological Institute (MNI). Temporal filtering was used to retain frequencies below 0.08 Hz. Spurious or regionally nonspecific variance was removed by regression of nuisance variables, including 6-parameter rigid body head motion, the signal averaged over the whole brain (to account for respiratory effects), the lateral ventricles, and over a region centered in the deep cerebral white matter. The fMRI data were then spatially smoothed using a 4-mm full width at half maximum kernel.

STATISTICAL ANALYSIS

The degree of connectivity in the entire brain was determined through correlation of each voxel's BOLD time series to the BOLD time series of all other voxels and by counting the number of voxels where the correlation with the BOLD time series exceeds a predefined statistical threshold that will be given below.[2] More precisely, preprocessed functional runs were subjected to voxel-based whole-brain correlation analysis, ie, correlation of each voxel's BOLD time series to every other voxel's BOLD time series, resulting in a Pearson correlation coefficient (r) matrix. From this correlation matrix, 3 different kinds of degree connectivity maps were computed: (1) whole-brain total maps, derived by counting for each voxel's BOLD time series the number of voxels where the correlation with the BOLD time series exceeded a predefined optimized threshold[2] ($r > 0.25$) for the entire brain; (2) local maps, derived by the same procedure but exclusively considering voxels inside a 12-mm sphere around each voxel; and (3) distant maps, also derived by the same procedure but exclusively considering voxels outside the 12-mm sphere. Crucially, total maps are the union of local and distant maps, and distant and total maps are highly correlated given that the local degree has a small contribution to the total counts compared with the distant degree.[4] Histograms of all degree connectivity maps were derived on the individual level to check for normal distribution. Statistical parametric mapping (SPM8; Wellcome Department of Cognitive Neurology) was used to smooth connectivity maps with an 8-mm kernel and to analyze degree connectivity maps at the group level. First, group comparisons (2-sample, 2-tailed t tests) involving whole-brain, local, and distant hub connectivity maps between patients with OCD and controls were performed. Here, the main interest was to determine degree connectivity differences in unmedicated patients with OCD (n = 23) compared with matched controls (n = 23). Comparisons between the entire OCD sample (n = 46) vs all controls (n = 46) and between medicated patients with OCD (n = 23) vs controls (n = 23) are reported as supplemental material (Author Tables 2-5; http://www.psychologie.hu-berlin.de/prof/kli/mitarbeiter/AuthorMaterial_JAMA_Psychiatry_2013_173.pdf).

Second, we tested for correlations between the degrees associated with distant and local connectivity maps and symptom severity by including Y-BOCS total scores as a covariate in a random-effects model containing hub maps of patients with OCD. Again, the emphasis was on the unmedicated patients, but correlations in the entire sample and medicated sample are available as supplemental material (Author Table 7C-F). In accordance with a recent functional connectivity study in OCD,[28]

Table 1. Demographic Data on Unmedicated Patients With OCD and HCs[a]

Characteristic	Mean (SD)		
	Unmedicated OCD Group (n = 23)	HC Group (n = 23)	*t* (*P* Value)
Sex, female/male, No.	12/11	12/11	
Age, y	29.1 (9.1)	28.7 (8.9)	−0.18 (.86)
Educational level, y	12.5 (1.6)	12.1 (1.4)	0.40 (.69)
IQ, verbal	107.5 (8.4)	108.0 (9.1)	−0.19 (.85)
STAI-X1, state	40.3 (8.1)	30.4 (5.0)	5.00 (<.001)
STAI-X2, trait	49.9 (11.2)	29.7 (8.4)	6.78 (<.001)
OCI-R	23.0 (9.8)	3.7 (2.6)	9.16 (<.001)
BDI	14.4 (11.3)	2.5 (2.4)	4.19 (<.001)
Y-BOCS	20.0 (5.7)	. . .	. . .
MADRS	8.0 (7.2)	. . .	. . .
Mean interscan movement	0.07 (0.02)	0.08 (0.03)	−1.18 (.24)

Abbreviations: Ellipses, tests not conducted in the HC group; BDI, Beck Depression Inventory; HC, healthy control; MADRS, Montgomery-Åsberg Depression Scale; OCD, obsessive-compulsive disorder; OCI-R, Obsessive Compulsive Inventory–Revised; STAI, State-Trait Anxiety Inventory (with X1 and X2 subtests); Y-BOCS, Yale-Brown Obsessive Compulsive Scale.
[a] Comparisons based on 2-sample t tests.

only clusters exceeding a threshold of $P < .001$ (uncorrected) and an extent threshold of 8 contiguous voxels were used for further post hoc assessment (ie, correlation between peak voxel values and Y-BOCS scores in SPSS, version 19; SPSS, Inc). All variables used for post hoc assessment were tested for normal distribution using Kolmogorov-Smirnov tests.

Third, we sought to further characterize the networks associated with greater whole-brain connectivity by means of conventional seed-based functional connectivity analyses.[2,41,42] Because hub analyses exclusively determine the number of voxels correlating with a given voxel above the threshold level, seed-based functional connectivity analysis can be used to reveal the regions correlating with a hub area. To use separate samples of unmedicated patients with OCD for seed generation and seed-based connectivity estimation to avoid circularity (double dipping),[43] we split the unmedicated OCD group in 2 subsamples showing no significant differences in demographic variables (Author Table 1) and determined OFC distant connectivity differences (distant maps) between one subsample (n = 12) and pair-matched healthy controls (2-sample *t* test), followed by computation of connectivity maps of the identified OFC peak voxel in the second subsample of unmedicated patients with OCD (n = 11) and their pair-matched healthy controls, and subsequent comparison of the resulting OFC connectivity maps between groups (2-sample *t* test).

Fourth, the effects of antidepressant medication on degree connectivity in patients with OCD were assessed by comparing degree connectivity maps between unmedicated patients (n = 23) and the distinct subgroup of medicated (n = 23) patients (2-sample *t* tests). For all between-group contrasts, a threshold of $P < .05$, corrected for multiple comparisons at the cluster level, was considered significant. In addition, small-volume searches were performed for basal ganglia regions using one combined mask of bilateral caudate, putamen, pallidum, and midbrain masks generated from the Automatic Anatomic Labeling tool[44] of the Wake Forest University WFU PickAtlas (http://fmri.wfubmc.edu/software/PickAtlas)[45] and a family-wise error–corrected threshold of $P < .05$.

Addressing potential confounds involved calculation of each participant's mean interscan movement to exclude head motion as a confounding factor affecting functional connectivity group differences.[46] Mean interscan movement was compared between groups (Table 1 and the eTable) and entered as a covariate in group comparisons of degree connectivity, revealing no effect on the observed group differences. Furthermore, maps of signal to noise ratio were calculated for all participants (eFigure 1 and Author Figure 1), revealing no significant differences between OCD participants and controls. Finally, potential confounding resulting from differences in demographic variables were addressed using *t* tests for independent samples. Values of the *t* tests, means (SDs) of questionnaire data, and demographic comparisons are available in Table 1 and the eTable.

RESULTS

GREATER OFC DISTANT DEGREE CONNECTIVITY IN UNMEDICATED OCD PATIENTS

Patients with OCD and the corresponding healthy control group showed significant within-group (ie, main) effects ($P < .001$, corrected) regarding distant degree connectivity in areas previously identified as cortical hubs (ie, parietal, posterior cingulate, and medial prefrontal areas) (**Table 2** and Author Tables 2 and 4). Furthermore, hub effects were observed in the orbitofrontal cortices in both groups (**Figure 1**A and Author Table 17). Two-sample *t* tests revealed that unmedicated patients with OCD had significantly greater distant connectivity in the OFC (Table 2 and Figure 1C) and the subthalamic nucleus (STN) (Figure 1B) compared with healthy controls. Differences in the entire combined OCD sample and in the medicated patients are reported in Author Table 2 and Author Table 4. No regions were observed indicating a significantly lower degree of connectivity in patients with OCD than in controls. Total and distant degree connectivity maps were highly correlated[4]; therefore, total maps are presented only as supplemental material (Author Table 6).

GREATER OFC LOCAL DEGREE CONNECTIVITY IN UNMEDICATED OCD PATIENTS

Both groups showed high local connectivity in parietal, posterior cingulate, and medial prefrontal areas (**Table 3** and Author Table 3 and Author Table 5) and hub main effects in orbitofrontal areas (**Figure 2**A). Two-sample *t* tests revealed a greater degree of local connectivity in the OFC (Figure 2C) and the right dorsal putamen (Figure 2B and Table 3) in patients with OCD compared with the healthy controls. The reverse contrast (control > OCD, 2-sample *t* test) revealed greater local connectivity in the control group in an area encompassing the inferior frontal gyrus and insula (Table 3). Local connectivity differences in the entire OCD sample and the medicated patients, derived using 2-sample *t* tests, are reported in Author Table 3 and Author Table 5.

BRAIN-BEHAVIORAL ASSOCIATION

Voxelwise correlational analyses between degree connectivity and overall OCD symptom severity (Y-BOCS total scores) were conducted. In unmedicated patients with OCD, this revealed significant positive correlations ($P < .001$, uncorrected) between overall OCD symptom severity (Y-BOCS total scores) and the degree of distant connectivity in the OFC (MNI_{XYZ} = 34, 20, and −16, respectively), putamen (MNI_{XYZ} = −18, 4, and 2), and medial prefrontal cortex (MNI_{XYZ} = −10, 44, and 22) (**Figure 3** and Author Table 7A). Negative correlations with Y-BOCS scores were observed for occipital (cuneus, MNI_{XYZ} = −20, −88, and 40), superior temporal (MNI_{XYZ} = −62, −30, and 6), and cerebellar (culmen: MNI_{XYZ} = −32, −38, and 34 and declive: MNI_{XYZ} = −16, −76, and −8) areas in unmedicated patients. Degree connectivity estimates for coordinates of regions showing positive correlations (as hypothesized) were extracted for post hoc assessment. Pearson correlation coefficients (2-tailed in SPSS) revealed significant correlations between OCD overall symptom severity and the degree of distant connectivity in the OFC ($r = 0.74$, $P < .001$), the putamen ($r = 0.69$, $P < .001$), and the medial prefrontal cortex ($r = 0.67$, $P < .001$). Additionally, positive correlations between Y-BOCS scores and local OFC connectivity were observed in unmedicated

Table 2. Degree Connectivity (Distant Maps): Within-Group (Main Effects) and Between-Group Effects for Unmedicated Patients With OCD and HCs[a]

	HC Group						OCD Group						Difference[d,e]						
	Anatomy[a,b]			Statistic[b,c]			Anatomy			Statistic			Anatomy				Statistic		
Distant Map Effect Region	x	y	z	*z* Score	Cluster Size[c,d]	BA	x	y	z	*z* Score	Cluster Size	BA	Direction	x	y	z	*z* Score	Cluster Size	BA
Precuneus	−4	−70	62	6.85		7	**−38**	**−60**	**50**	**5.58**	**3987**	**19**							
							−6	−78	54	4.97		7							
Inferior parietal lobule							−40	−50	60	5.30		40							
							50	−40	50	4.58		40							
Superior parietal lobule	**−40**	**−60**	**56**	**7.37**	**13 164**	**7**	**44**	**−60**	**54**	**5.23**	**1101**	**7**							
Medial frontal gyrus	2	58	−6	6.42		10	0	58	36	5.20		8							
Precentral gyrus							**−28**	**0**	**68**	**4.83**	**233**	**6**							
Superior frontal gyrus	**−4**	**68**	**16**	**6.59**	**7801**	10	−38	16	54	3.60		8							
	−8	24	66	4.25		6													
Middle frontal gyrus	**46**	**38**	**24**	**4.32**	**177**	**9**	**52**	**20**	**40**	**3.75**	**167**	**6**							
	−46	**8**	**46**	**4.30**	**564**	6	52	10	46	3.54		6							
	−38	20	50	4.20		6													
Inferior frontal gyrus							−40	−54	−8	4.89		10							
Orbitofrontal gyrus													OCD > HC	**20**	**40**	**−22**	**4.22**	**274**	**11**
													OCD > HC	20	34	−14	3.66		11
													OCD > HC	4	42	−28	3.16		11
Subgenual prefrontal cortex							**−2**	**6**	**−18**	**5.20**	**6715**	**25**							
Superior temporal gyrus	−52	18	−14	6.03		38													
Middle temporal gyrus	−54	−64	30	7.21		39	**60**	**−42**	**−18**	**4.25**	**455**	**20**							
	−60	**−36**	**−6**	**5.42**	**2397**	21	64	−54	−12	3.94		37							
	−64	−50	0	5.07		21													
Fusiform gyrus							582	−52	−22	4.23		37							
Inferior temporal gyrus							**−58**	**−44**	**−16**	**3.93**	**166**	**37**							
Subthalamic nucleus													OCD > HC	**−6**	**−12**	**−8**	**3.84**[e,f]	**28**	
Pons	0	−50	−60	5.21															
Cerebellum (posterior lobe)							**−48**	**−68**	**−18**	**4.48**	**736**								
							−40	−76	−22	4.11									
							−42	−82	−32	4.11									
							46	**−78**	**−28**	**3.99**	**316**								
							34	−86	−34	3.87									
							38	−82	−40	3.63									

Abbreviations: BA, Brodmann area; HC, healthy control; OCD, obsessive-compulsive disorder.

[a] Empty cells in the first column (Effect Region) indicate that the results in the respective row still refer to the aforementioned region (eg, the first and second rows both report findings for the precuneus, and the third and fourth rows report findings in the inferior parietal lobule). Empty cells in the Anatomy and Statistic columns indicate that a group did not show main effects in a region or that no group differences occurred.

[b] Peaks of total map effect coordinates (x, y, z) are given in Montreal Neurological Institute space.

[c] Magnitude statistics for within-group (ie, main) effects are thresholded at $P < .001$ (cluster-corrected for multiple comparisons).

[d] Cluster sizes correspond to an uncorrected threshold of $P < .001$.

[e] Between-group effects are thresholded at $P < .05$ (cluster-corrected for multiple comparisons).

[f] Significant between-group main effect differences in a priori regions of interest (1 combined mask of bilateral caudate, putamen, pallidum, and midbrain masks generated from the Automatic Anatomic Labeling tool of the Wake Forest University WFU PickAtlas (http://fmri.wfubmc.edu/software/PickAtlas) using a familywise error–corrected threshold of $P < .05$. The peak of significant clusters is indicated in bold, in contrast to subclusters.

patients (Author Table 7B). Correlations between degree connectivity and OCD symptom severity in the entire OCD sample and in medicated patients with OCD are reported in Author Table 7D-I.

EFFECTS OF ANTIDEPRESSANT MEDICATION

A significant reduction in local ventral striatal connectivity was observed in medicated compared with unmedicated patients (2-sample *t* tests; medicated < unmedicated, Author Table 9 and **Figure 4**). There were no significant differences between medicated and unmedicated patients with OCD with respect to demographic variables (eTable, B).

OFC FUNCTIONAL CONNECTIVITY DIFFERENCES

For seed-based functional connectivity analysis, the unmedicated sample of patients with OCD (n = 23) was split in 2 subgroups (hub and seed-based) that did not differ significantly with respect to demographic variables (eTable) to avoid bias in seed-based analyses with findings from hub analyses. First, the degree of distant connectivity (distant maps) was compared between the hub subgroup (n = 12) and their pair-matched controls (n = 12). Two-sample *t* tests revealed a significantly greater degree of connectivity in the OFC (MNI_{XYZ} = 24, 44, and −18) (eFigure 2 and Author Table 10) in patients with OCD compared with healthy controls. Subsequently, this coordinate was used for seed-based functional connec-

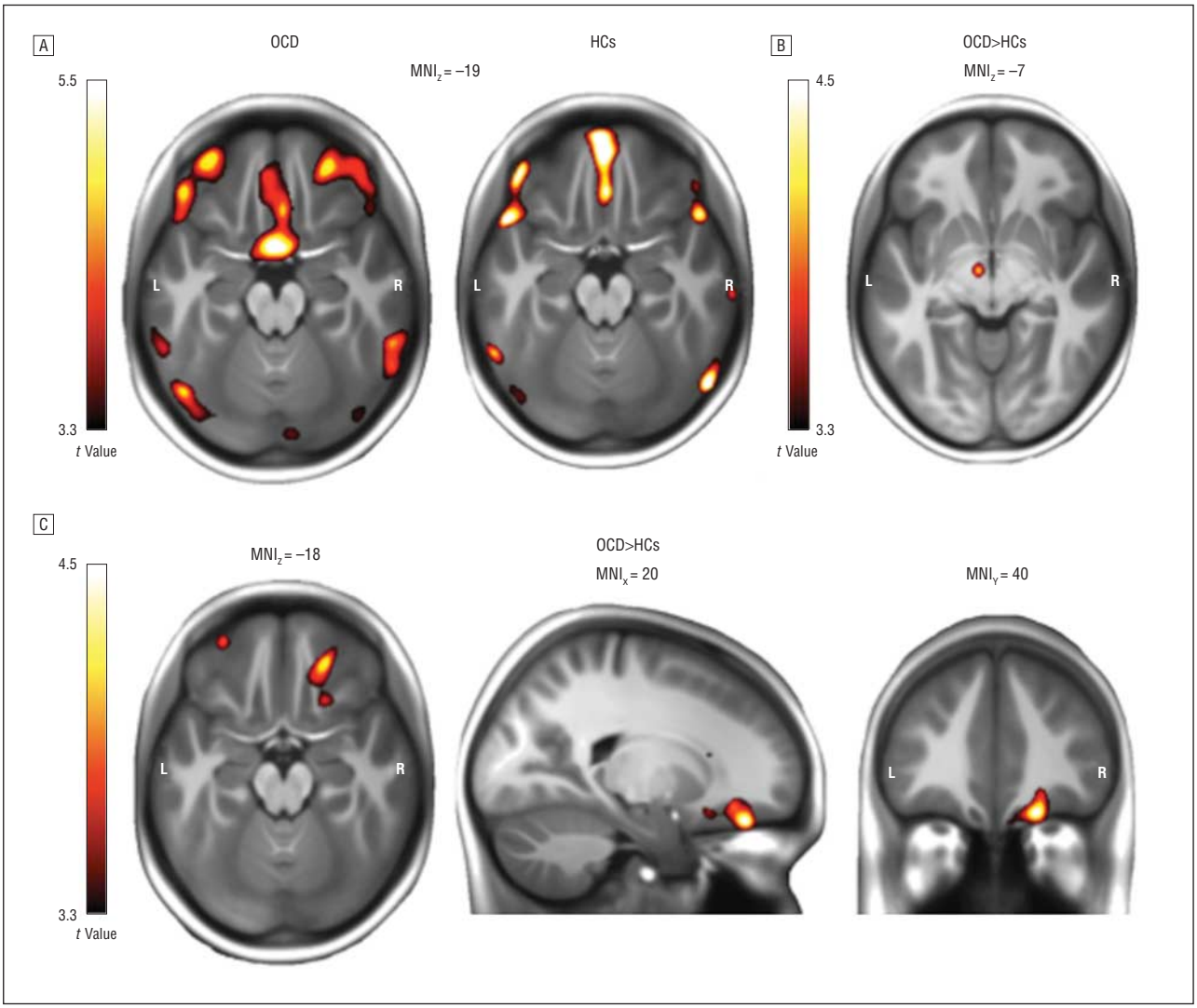

Figure 1. Distant degree connectivity effects. A, Main effects in the orbitofrontal cortex (OFC) displayed for unmedicated patients with obsessive-compulsive disorder (OCD) and matched healthy controls (HCs). B and C, Significantly greater degree of connectivity in the subthalamic nucleus and in the orbitofrontal cortex, respectively, in unmedicated patients compared with HCs. Detailed information regarding signal quality in the OFC is available in eFigure 1 and Author Figure 1. The minimum *t* value threshold of 3.3 used for display of between-group effects is equivalent to a threshold of $P < .001$, uncorrected. MNI indicates Montreal Neurological Institute.

tivity analysis in the remaining 11 unmedicated patients with OCD and pair-matched healthy controls (no significant demographic differences) (Author Table 1). This analysis revealed that patients with OCD were characterized by significantly greater OFC connectivity with precentral and superior temporal cortices (eFigure 3 and Author Table 11).

COMMENT

This study investigated network alterations in patients with OCD under resting-state conditions and aimed to determine whether degree connectivity differences concern areas that are predicted by pathophysiologic models[6-8] of OCD, that is, the OFC and regions of the basal ganglia. In unmedicated patients, the OFC displayed a greater local and distant degree of connectivity. Furthermore, the STN displayed greater distant connectivity and the putamen displayed greater local connectivity. The degree of distant connectivity of the OFC, the putamen, and the medial prefrontal cortex/anterior cingulate cortex correlated with global OCD symptom severity in unmedicated patients, providing a link between CBGTC connectivity and OCD symptom severity. Finally, a reduction in local ventral striatal connectivity was evident in patients receiving antidepressants compared with unmedicated patients. These results, revealing degree connectivity alterations in CBGTC areas using an unbiased, data-driven method, support the assumption of greater orbitofrontal and CBGTC loop function in OCD.[6-8]

The finding of a higher degree of local connectivity of the OFC and putamen under resting-state conditions, indicative of more areas showing correlated activity in the immediate regional neighborhood (≤12 mm), is consistent with the frequent observation of elevated metabolism of these regions in PET studies during the resting state,[16,17,20,31] which is further supported by the correlations between OFC degree connectivity and symptom se-

Table 3. Degree Connectivity (Local Maps): Within-Group (Main Effects) and Between-Group Effects in Unmedicated Patients With OCD and HCs

	HC Group						OCD Group						Difference[d]						
	Anatomy[a]			Statistic[b]			Anatomy			Statistic				Anatomy			Statistic		
Local Map Effect Region	x	y	z	*z* Score	Cluster Size[c]	BA	x	y	z	*z* Score	Cluster Size	BA	Direction	x	y	z	*z* Score	Cluster Size	BA
Cuneus, precuneus	**4**	**−72**	**36**	**>8**	**38 683**	7	4	−72	38	>8		7							
Posterior cingulate cortex	4	−50	28	>8		31	4	−52	28	>8		31							
Precuneus	−36	−66	48	>8		19	**−36**	**−66**	**48**	**>8**	**18 417**	**19**							
Medial prefrontal gyrus	**−2**	**56**	**20**	**7.54**	**6353**	9	0	56	22	6.05		9							
	0	60	10	7.38		9													
Anterior cingulate cortex	0	50	−4	7.21		32	**−4**	**44**	**−14**	**6.43**	**9542**	**32**							
Inferior frontal gyrus							**54**	**16**	**−6**	**5.10**	**411**	**47**							
Orbitofrontal gyrus													OCD>HC	**−8**	**42**	**−22**	**4.25**	**734**	**10**
Inferior frontal gyrus / insula													HC>OCD	**−42**	**18**	**−10**	**4.03**	**94**	**47,13**
Fusiform gyrus	**−58**	**−52**	**−14**	**4.50**	**624**	**37**													
Middle temporal gyrus	−60	−40	−12	4.36		20	66	−48	−2	3.58		21							
Inferior temporal gyrus							62	−52	−12	4.27	**242**	20							
Putamen													OCD>HC	**20**	**12**	**0**	**4.00[e]**	**69**	
Cerebellum (posterior lobe)	−50	−58	−18																
Medulla	2	−46	−62	>8			**2**	**−46**	**−62**	**>8**	**9323**								

Abbreviations: BA, Brodmann area; HC, healthy controls; OCD, obsessive-compulsive disorder.
[a] Peaks of local map effect coordinates (x, y, z) are given in Montreal Neurological Institute space.
[b] Magnitude statistics for within-group (ie, main) effects correspond to a minimum cluster-corrected threshold of $P < .001$.
[c] Cluster sizes correspond to an uncorrected threshold of $P < .001$.
[d] Between-group effects are thresholded at $P < .05$ (cluster-corrected for multiple comparisons).
[e] Significant between-group main effect differences in a priori regions of interest (1 combined mask of bilateral caudate, putamen, pallidum, and midbrain masks generated from the Automatic Anatomic Labeling tool of the Wake Forest University WFU PickAtlas (http://fmri.wfubmc.edu/software/PickAtlas) using a familywise error–corrected threshold of $P < .05$. The peak of significant clusters is indicated in bold, in contrast to subclusters.

verity given that similar associations are known for metabolic activity of the OFC.[12] Degree connectivity in the posterior/lateral OFC correlated with symptom severity, whereas group differences were found in the medial OFC, which might be interesting given that dissociable roles for these 2 OFC regions are subject to research on reward-guided decision making.[9,47] In summary, the present functional connectivity data extend previous PET findings in OCD by adding the observation that the OFC and putamen show greater connectivity with locally adjacent regions to findings of local hyperactivity during rest.[15,16,19,44]

In addition to consistencies with previous resting metabolism studies in OCD, the present findings converge with structural local alterations identified in this patient group.[48,49] More precisely, recent meta-analyses[49] revealed greater bilateral striatal volume in patients with OCD, which is consistent with a greater local degree connectivity of the putamen and correlations between OCD symptom severity and distant connectivity of the putamen identified in the present study. Furthermore, the correlation between medial prefrontal cortex/anterior cingulate cortex distant degree connectivity and symptom severity converges with the finding of reduced gray matter volume in this area.[48,49] Thus, positive relationships between symptom severity and degree connectivity in areas known to exhibit structural abnormalities in OCD were evident in this study. At the same time, correlational findings should be interpreted with caution given that the initial correlations were derived with uncorrected statistics and that the reported correlation coefficients observed might be inflated because of the voxelwise regression approach.[50]

Similar to local connectivity effects, distant degree connectivity differences occurred in regions of the OFC and the basal ganglia. The STN, the region revealing greater distant connectivity in addition to the OFC, is known to receive multiple cortical inputs, thereby representing the only entry point into the basal ganglia other than the striatum.[8] Despite its pivotal role in Parkinson disease,[51,52] the STN is not simply a motor area but instead shares connections with associative dorsolateral prefrontal CBGTC loops in addition to connections with the OFC.[8] Considering these connections, greater distant connectivity of the STN found in this study may suggest that CBGTC loops in patients with OCD receive greater cortical input via the STN. Furthermore, greater STN connectivity might affect communication within the basal ganglia in the sense that greater cortical input into the STN alters processing in the indirect pathway within the basal ganglia,[6,8] which is particularly interesting in the light of theoretical considerations suggesting an imbalance between direct and indirect basal ganglia pathways in the neurobiological models of OCD.[6]

Although local degree connectivity abnormalities converge with findings of altered local metabolism and volume, the present distant degree connectivity results offer new insights into the functional neuroanatomy of OCD because they indicate that OFC and basal ganglia are more connected with distant areas outside of CBGTC circuitry. Accordingly, the OFC showed greater functional connectivity with precentral and superior temporal regions rather than CBGTC areas in unmedicated patients relative to healthy controls (eFigure 3 and Author Table 11). Both results contradict the initial conception of specific segregated CBGTC circuits,[29] which has been refined on the basis of neuroanatomic evidence suggesting that these loops interact to allow information transfer among CBGTC circuits.[30,53-55] In fact, the present find-

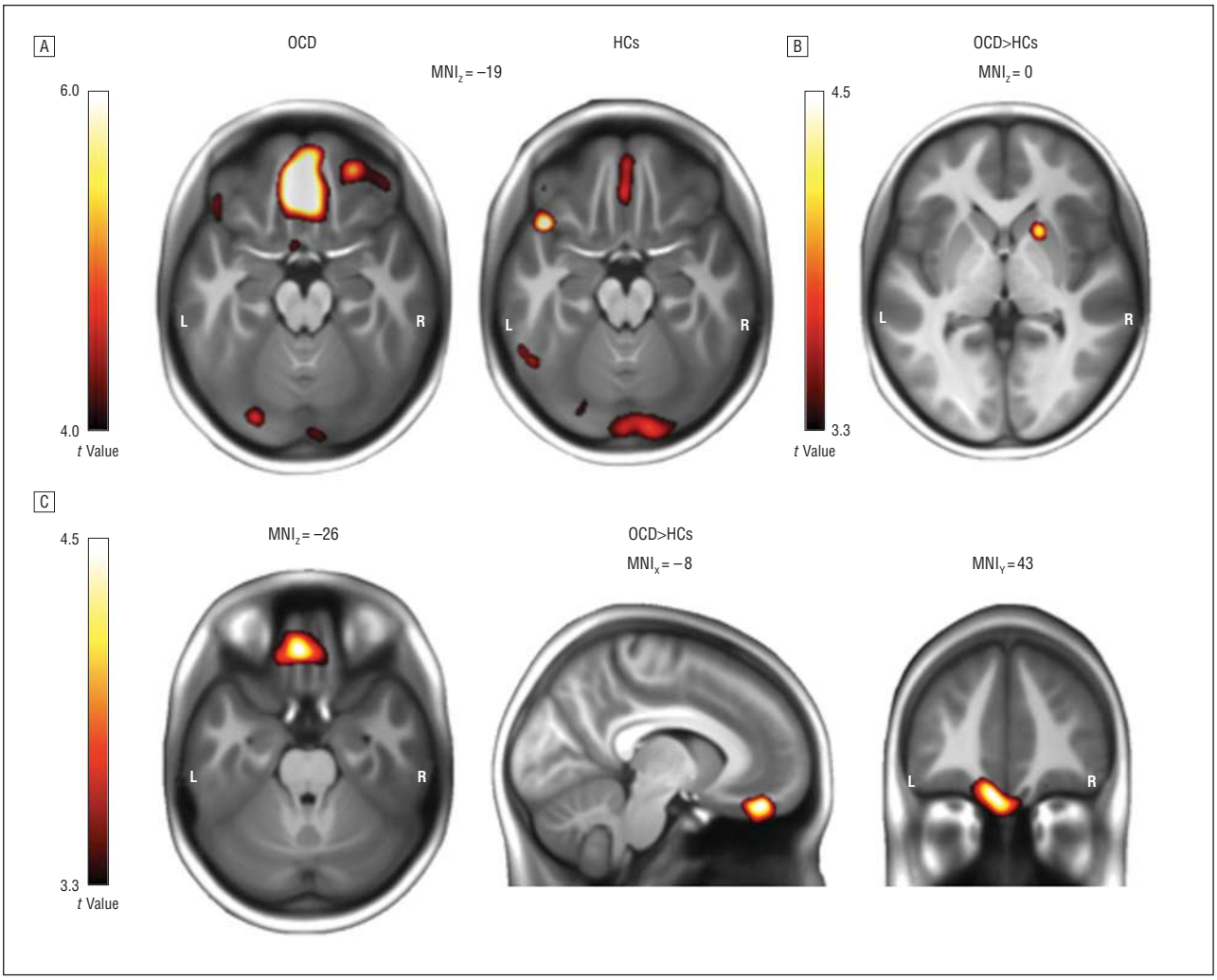

Figure 2. Local degree connectivity effects, considering exclusively a 12-mm sphere around each voxel for computation of degree connectivity. A, Main effects in the orbitofrontal cortex (OFC) displayed for unmedicated patients with obsessive-compulsive disorder (OCD) and matched healthy controls (HCs). B and C, Significantly greater local degree of connectivity in the right dorsal putamen and in the orbitofrontal cortex, respectively, in unmedicated patients compared with HCs. The minimum *t* value threshold of 3.3 used for display of between-group effects is equivalent to a threshold of $P < .001$, uncorrected. MNI indicates Montreal Neurological Institute.

ings might provide an integrative perspective on alternating theoretical positions with respect to the functional neuroanatomy of OCD. In agreement with traditional CBGTC models of OCD,[6-8] the unbiased search for regions of abnormal connectivity revealed OFC and basal ganglia. At the same time, greater distant connectivity of OFC and basal ganglia with areas outside of CBGTC circuitry was evident, which may relate to more recent models emphasizing consistent abnormalities outside orbitofrontal-striatal circuitry in OCD.[26]

Serotonin was originally suggested to be involved in OCD on the basis of therapeutic effects of selective serotonin reuptake inhibitors[56] and also on the basis of PET studies consistently showing that antidepressant medication leads to reduced metabolism in CBGTC areas (ie, the OFC and the caudate head).[19,20,31] Testing for the effect of antidepressant treatment (mostly selective serotonin reuptake inhibitors) on the connectivity of the striatum in this study revealed that medicated patients with OCD exhibited reduced local striatal connectivity in comparison with the unmedicated patients (Figure 4). Although stronger connectivity in unmedicated compared with medicated patients is generally consistent with studies finding that antidepressants reduce functional connectivity,[57,58] the evidence provided for medication effects on degree connectivity is preliminary, and longitudinal assessments of degree connectivity in patients with OCD undergoing treatment are required to directly address the effects of antidepressants on corticostriatal connectivity.

Limitations of the present study concern sample sizes and the fact that measures of functional connectivity do not inform about causal interactions among brain regions.[59] A central issue that arises from these findings is how resting-state connectivity abnormalities translate into OCD behavior. The correlations between the degree of connectivity in the OFC and putamen and OCD symptom severity in unmedicated patients suggest effects of resting abnormalities on OCD behavior. This question could be addressed directly by a collection of resting and experimental data in the same OCD population and controls. Indi-

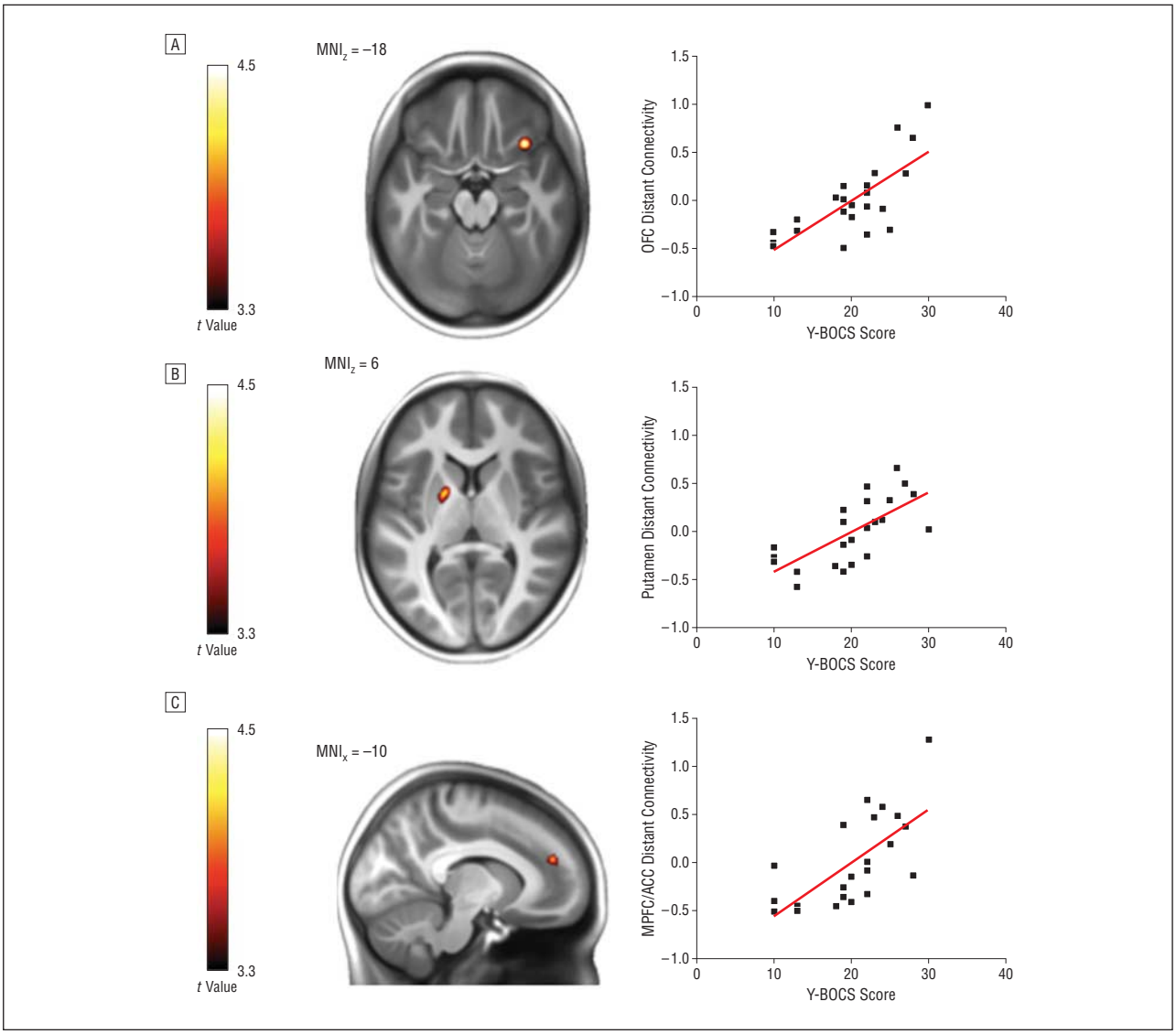

Figure 3. Positive correlation between overall obsessive-compulsive disorder (OCD) symptom severity (Yale-Brown Obsessive Compulsive Scale [Y-BOCS] total scores) and degree connectivity (peak voxels derived from correlational analyses between Y-BOCS scores and distant maps). A, The posterior/lateral orbitofrontal cortex (Montreal Neurological Institute [MNI]$_{XYZ}$ = –34, 20, –16; z = 4.07, r = 0.74, R^2 = 0.55, $P < .001$). B, The left dorsal putamen/pallidum (MNI$_{XYZ}$ = –18, 2, 4; z = 3.65, r = 0.69, R^2 = 0.48, $P < .001$). C, Medial prefrontal cortex/anterior cingulate cortex (MPFC/ACC) (MNI$_{XYZ}$ = –10, 44, 22; z = 3.52, r = 0.67, R^2 = 0.45, $P < .001$) in unmedicated patients. The minimum t value threshold of 3.3 used for display of correlational effects is equivalent to a threshold of $P < .001$, uncorrected.

vidual resting connectivity parameters could be included in modeling of experimental data to determine how variance in neural responses to symptom provocation could be explained by resting-state abnormalities. This could lead to an improved understanding of how the greater degree of connectivity of the OFC and CBGTC components contributes to the established abnormalities in response to confrontation with OCD-related stimuli[12-15] and reversal learning demands.[10,11] In a similar vein, associations between lower distant degree connectivity in the inferior frontal gyrus identified in the present study and inhibitory deficits in patients with OCD[60-62] could be examined. In addition, testing the potential specificity of the identified degree connectivity alterations to OCD is an important subject for future research. Although there is evidence that abnormalities in OFC metabolism[16,56] and striatal volume[49] are specific to OCD, investigation of OFC degree connectivity in a clinical control group of patients with mood or anxiety disorders is required to elucidate this issue. Similarly, given the clinical heterogeneity of OCD and its influence on regional resting-state brain abnormalities, including the OFC,[63-65] the degree connectivity abnormalities associated with the major OCD symptom dimensions require investigation.

In conclusion, this study applied a data-driven, unbiased search for brain regions displaying a high degree of local and whole-brain connectivity. The findings demonstrate network alterations in patients with OCD that are highly consistent with neurobiological models of OCD. Areas of greater connectivity identified in this analysis involved the OFC and the basal ganglia, consistent with the assumption of pathophysiologic changes in orbito-

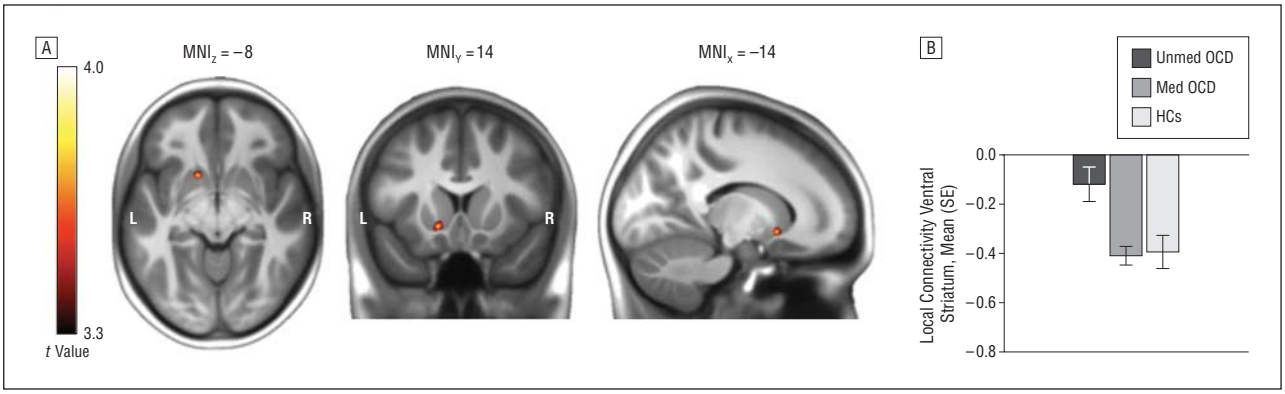

Figure 4. Reduced local connectivity of the ventral striatum in patients with obsessive-compulsive disorder (OCD) treated with antidepressants (Med) (n = 23) in comparison with unmedicated (Unmed) patients with OCD (n = 23). A, Sagittal, coronal, and axial slices displaying the peak of group differences at Montreal Neurological Institute $(MNI)_{XYZ}$ = −14, 14, and −8. B, Simple bar graph shows effects in both OCD groups and healthy controls (HC). Effects are displayed relative to the mean of the respective groups, revealing high similarity between local connectivity of the ventral striatum in medicated patients and HCs. β Values are negative in all 3 groups because the ventral striatum does not represent an extensively locally connected hub in comparison with previously described local hubs, which are, for example, found in motor, somatosensory, and auditory areas.[4] The minimum *t* value threshold of 3.3 used for display of between-group effects is equivalent to a threshold of $P < .001$, uncorrected.

frontal CBGTC circuits and numerous findings of greater metabolism in orbitofrontal and striatal brain regions. At the same time, these data open novel perspectives on certain aspects of CBGTC models in OCD. Preliminary evidence is provided that antidepressant medication affects local CBGTC connectivity, and hyperconnectivity was not only identified locally (ie, within CBGTC circuits) but also for the distant connections outside of CBGTC circuitry.

Submitted for Publication: February 10, 2012; final revision received July 27, 2012; accepted August 21, 2012.
Published Online: April 17, 2013. doi:10.1001/jamapsychiatry.2013.173. Corrected April 22, 2013.
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Author Contributions: Mr Beucke had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Conflict of Interest Disclosures: None reported.
Funding/Support: This work was supported by grant BMBF-01GW0724 from the Federal Ministry of Education and Research of Germany. Mr Beucke is supported by a PhD scholarship from Evangelisches Studienwerk e.V. Villigst and is a European Recovery Program scholar of the German National Academic Foundation. Dr Linnman was supported by the Swedish Society for Medical Research.
Online-Only Material: The 3 eFigures and the eTable are available at http://www.jamapsych.com. The Author Tables and Author Figures are available at http://www.psychologie.hu-berlin.de/prof/kli/mitarbeiter/AuthorMaterial_JAMA_Psychiatry_2013_173.pdf.
Additional Contributions: David Borsook, MD, PhD, Lino Becerra, PhD, and the P.A.I.N. group at McLean Hospital provided insightful comments and discussion. The Cognitive Neuroscience Lab at Harvard University and the Athinoula A. Martinos Center for Biomedical Imaging provided space and tools for fMRI analyses, and Koene Van Dijk, PhD, assisted with head motion analyses. Eva Kischkel, PhD, and Rüdiger Spielberg, PhD, performed clinical assessments; Susanne Schwab, MS, recruited patients; Rosa Grützmann, MS, and Miriam Sebold, MS, assisted in data acquisition; Rainer Kniesche provided technical assistance; and scanning facility access was provided by Charité Universitätsmedizin Berlin.

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