Decreased Limbic and Increased Fronto-Parietal Connectivity in Unmedicated Patients with Obsessive-Compulsive Disorder

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Abstract: Obsessive-compulsive disorder (OCD) is characterized by recurrent intrusive thoughts and ritualized, repetitive behaviors, or mental acts. Convergent experimental evidence from neuroimaging and neuropsychological studies supports an orbitofronto-striato-thalamo-cortical dysfunction in OCD. Moreover, an over excitability of the amygdala and over monitoring of thoughts and actions involving the anterior cingulate, frontal and parietal cortex has been proposed as aspects of pathophysiology in OCD. We chose a data driven, graph theoretical approach to investigate brain network organization in 17 unmedicated OCD patients and 19 controls using resting-state fMRI. OCD patients showed a decreased connectivity of the limbic network to several other brain networks: the basal ganglia network, the default mode network, and the executive/attention network. The connectivity within the limbic network was also found to be decreased in OCD patients compared to healthy controls. Furthermore, we found a stronger connectivity of brain regions within the executive/attention network in OCD patients. This effect was positively correlated with disease severity. The decreased connectivity of limbic regions (amygdala, hippocampus) may be related to several neurocognitive deficits observed in OCD patients involving implicit learning, emotion processing and expectation, and processing of reward and punishment. Limbic disconnection from fronto-parietal regions relevant for (re)-appraisal may explain why intrusive thoughts become and/or remain threatening to patients but not to healthy subjects. Hyperconnectivity within the executive/attention network might be related to OCD symptoms such as excessive monitoring of thoughts and behavior as a dysfunctional strategy to cope with threat and uncertainty. *Hum Brain Mapp* 35:5617–5632, 2014. © 2014 Wiley Periodicals, Inc.

Key words: obsessive-compulsive disorder; fMRI; functional connectivity; network analysis; graph analysis; network modules; degree

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is characterized by recurrent intrusive thoughts (obsessions) and ritualized, repetitive behaviors or mental acts (compulsions) [Abramowitz et al., 2009; Cooper, 2001]. The compulsions are typically performed to avoid or attenuate intrusive thoughts (obsessions) which are commonly accompanied by distress and anxiety or disgust. Convergent experimental evidence from neuroimaging and neuropsychological studies associated the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), and basal ganglia (BG) with the pathophysiology of OCD. PET studies at rest and PET/fMRI studies during symptom provocation consistently found hypermetabolism in these brain regions [Baxter et al., 1987, 1988, 1990; Rauch et al., 1994; Simon et al., 2010; Swedo et al., 1989]. These findings suggested dysfunctional cortico-striato-thalamo-cortical (CSTC) pathways to be involved in this disorder which led to the formulation of a fronto-striatal model of OCD [Chamberlain et al., 2008; Menzies et al., 2008; Saxena et al., 1999; Saxena et al., 1998; Saxena and Rauch, 2000]. The CSTC model proposes an imbalance between a direct, “affective” circuit (ACC/ventromedial prefrontal cortex—ventral striatum/nucleus accumbens—thalamus) and an indirect, dorsal “cognitive” circuit (dorsolateral prefrontal cortex (DLPFC)—dorsal caudate nucleus—thalamus) in OCD. In this model, the direct loop functions as a self-reinforcing positive feedback loop and contributes to the initiation and continuation of behaviors, whereas the indirect loop provides a mechanism of negative feedback that is important for the inhibition of behaviors and for adaptive switching between behaviors. An imbalance between these pathways is hypothesized to result in a hyperactivated ventral and an inhibited dorsal frontal-striatal system [Saxena and Rauch, 2000]. It should be noted that the current CSTC model of OCD is not specific to this disorder. Historically, it has been in part adopted from models of neurological disorders of the BG like Tourette-Syndrome and Huntington’s disease. Moreover, CSTC dysfunction is discussed for other psychiatric conditions involving deficits in reinforcement learning and action selection including Attention Deficit Hyperactivity Disorder (ADHD) [Mills et al., 2012] and various obsessive-compulsive and anxiety spectrum disorders [Welch et al., 2007].

Findings from structural MRI region of interest analyses indicated gray matter volume alterations within structures involved in the “affective” fronto-striatal loop (BG, ACC, OFC, and thalamus) and limbic structures like the amygdala and hippocampus [Atmaca et al., 2006, 2007; Choi et al., 2004; Kang et al., 2004; Rosenberg et al., 2000; Szeszko et al., 1999, 2004]. Whole-brain voxel-based morphometry (VBM) [Ashburner and Friston, 2000] studies revealed gray matter density abnormalities in the OFC, ACC, insula, superior temporal gyrus, amygdala, parahippocampus, and parietal region including the angular gyrus, supramarginal gyrus, and the inferior parietal lobe

[Kim et al., 2001; Kuhn et al., 2013; Pujol et al., 2004; Valente et al., 2005]. These findings were further consolidated by fMRI studies using symptom provocation paradigms which found increased neural activity in emotion processing areas as well as in the DLPFC and the parietal cortex during symptom provocation [Adler et al., 2000; Breiter et al., 1996; Shapira et al., 2003]. DLPFC and parietal cortex, in particular angular and supramarginal gyri, involvement are also discussed in the context of deficits in set shifting, planning, and response inhibition observed in OCD patients [Chamberlain et al., 2006; Mataix-Cols et al., 2002; Menzies et al., 2008; Veale et al., 1996; Watkins et al., 2005].

So far, only a few fMRI studies investigated changes in intrinsic functional connectivity in OCD. The majority of these studies are based on investigator-dependent definitions of a seed region and focused on frontal and striatal regions [Fitzgerald et al., 2010, 2011; Harrison et al., 2009; Jang et al., 2010; Stern et al., 2012]. Zhang et al. [2011] investigated the functional connectivity between 39 brain regions associated with top-down control [Dosenbach et al., 2006]. The authors found a higher mean clustering coefficient of the brain network [Bullmore and Sporns, 2009] in the OCD group compared to healthy controls.

The CSTC model of OCD does not explicitly integrate the role of the amygdala and hippocampus and their interaction with the frontal cortex in mediating obsession-related fear and anxiety provoking compulsions [Milad and Rauch, 2012]. The model also does not explicitly include parietal regions frequently found to be implicated in the pathophysiology of OCD [Melloni et al., 2012; Menzies et al., 2008]. Given the need to extend the classic CSTC model for OCD [Milad and Rauch, 2012], an approach that is not restricted to particular cognitive tasks and selected anatomical regions appears most promising. Resting-state functional MRI is a powerful method for evaluating interactions between brain regions that occur when a subject is not performing an explicit task. The low-frequency (<0.1 Hz) temporal blood oxygen level dependent (BOLD) fluctuations at rest are elicited by spontaneous neural activity. This view is supported by the fact that known functional brain networks are observed in connectivity analyses, for example, motor network, visual network (VN), or auditory network [Beckmann et al., 2005; Biswal et al., 1997; Fox et al., 2005].

We chose a data driven approach to assess whole-brain connectivity changes in resting-state networks in a group of 17 unmedicated OCD patients compared to 19 healthy controls. The analysis of the complex network data was performed using a graph theoretical approach. A graph can be conceived as a mathematical representation of a network. A network consists of nodes (or vertices), that is, brain regions in our case, and edges connecting nodes [Bullmore and Sporns, 2009]. We investigated the complex data from the perspective of brain network modules. Brain network modules are communities of nodes which are highly interconnected. The network modules correspond

to functional subdivisions of the brain, that is, well-known resting-state networks [Beckmann et al., 2005; Power et al., 2011]. Looking at the data from the perspective of network modules vastly reduces the complexity of the data and helps to clearly identify patterns in altered network organization. The degree centrality of brain regions, defined as the number of its connections, was used as measure of connectivity. We hypothesized that connectivity changes within and between two major circuits implicated in the pathophysiology of OCD are also present during resting state: the CSTC loops (dorsolateral and OFC, striatum, and thalamus) and the emotion processing (fear) circuit (amygdala, ventral striatum, hippocampus, and insula).

MATERIALS AND METHODS

Participants

We recruited patients enrolled in a CBT program at our inpatient unit specialized in OCD. In accordance with the Helsinki convention, all subjects gave informed consent to participate. The study was approved by the Ethics Committee of the University of Lübeck. Twenty unmedicated OCD patients were scanned and clinically evaluated at admission but before the beginning of CBT. Evaluation included diagnosis confirmation, criteria for inclusion and exclusion, assessment of comorbid disorders, and symptom severity. Diagnosis of OCD was confirmed using structured clinical interview for DSM-IV (SCID). SCID was applied by therapists experienced in the treatment of OCD and after completion of certified SCID training. Inclusion criteria were: age 18–65, pretreatment Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) [Goodman et al., 1989] total score ≥ 16 , right-handedness according to the Edinburgh Handedness Inventory [Oldfield, 1971]. Exclusion criteria were: current moderate or severe episode of major depression, history of schizophrenia spectrum disorders, history of drug abuse or dependence (Structured Clinical Interview for DSM-IV), present psychoactive medication (washout ≥ 4 weeks), major medical conditions, history of major head injury or neurological disorders. None of the patients received antidepressants or other psychoactive medication during the study. Six patients did have a history of antiobsessive or antidepressant medication [(S)SRI, SNRI, or Clomipramine], 1 patient had a history of antipsychotic medication, 11 patients were medication-naïve. For assessment of depressive symptoms (secondary outcome variable), the Hamilton Depression Rating Scale (HDRS) [Hamilton, 1960] was used. Comorbid disorders were thoroughly assessed both using SCID for DSM-IV and disorder-specific scales including Wender–Utah Rating Scale and Brown Scale for ADHD and Young Mania Rating Scale for mania. For a detailed description of all measures obtained from the subjects, see Voderholzer et al. [2013]. The following comorbidities were found in the

OCD sample: major depression, mild/moderate episode ($n = 2$), ADHD ($n = 1$), and anorexia nervosa ($n = 1$).

For all patients, diagnostic procedures, study enrollment, and fMRI scanning took place during the first week after admission but before start of treatment. The time between Y-BOCS assessment and fMRI was ≤ 7 days with no treatment during this interval.

From the original sample of $n = 20$ patient fMRI datasets, three did not enter further analysis resulting in a final sample of $n = 17$ (12 female; age: 32.6 ± 11.6 years; education: 13.5 ± 1.9 years; Y-BOCS: 25.4 ± 2.7 ; disease duration: 10.5 ± 8.5 years). The reasons of exclusion were as follows: one due to excessive head motion, one due to noncompliance with the fixation task on eye-tracking, and one due to a rapid spontaneous symptom reduction in the time window between assessment and MRI scanning, following a remission and subsequent discharge from ward after 14 days.

Nineteen healthy right-handed control subjects with no history of psychiatric or neurological disorder, dementia, concurrent major medical disorder or major head injury and MRI contraindications were recruited through personal contact and advertisement (15 female; age: 30.4 ± 9.6 years; education: 14.3 ± 2.4 years). Only control subjects were paid for participation.

The patient and the control group did not differ significantly in age (two-tailed two-sample *t*-test; $P = 0.52$), education years (two-tailed two-sample *t*-test; $P = 0.30$) nor gender (chi-square test; $P = 0.56$). All relevant demographic and clinical information are summarized in Table I.

Experimental Design

The functional MRI data were acquired during an 8-min period of rest. Subjects were instructed to neither engage in any particular cognitive nor motor activity and to keep their eyes open fixating a cross in the middle of the screen. Fixation was used to monitor and minimize eye movements and to reduce interindividual variability regarding motor and cognitive processes during rest [Yan et al., 2009]. Eye movements were recorded using an infrared eye-tracking device (Limbus tracker, 500 Hz, Cambridge Research Systems, UK). Eye-tracking allowed us to confirm wakefulness and compliance with fixation, which is of particular value given the significant impact of sleep on resting state connectivity [Tagliazucchi et al., 2013].

Image Acquisition

Structural and functional MRI was performed using a 3-T scanner (Siemens Trio, Erlangen). A total of $N = 240$ functional images per subject were acquired using a single-shot gradient echo echo-planar imaging (EPI) sequence sensitive to BOLD contrast (TR = 2030 ms, TE = 25 ms, flip angle = 90° , in-plane resolution $3 \times 3 \text{ mm}^2$, 3-mm slice thickness, 33% interslice gap, 35 slices, $192 \times 192 \text{ mm}^2$ field of view). Additionally, structural images of the whole brain

using a T1-weighted FLASH three-dimensional sequence (TR = 15 ms, TE = 4.92 ms, flip angle = 25°, 192 slices, 1-mm slice thickness, 20% gap, 256 × 256 mm² field of view, 1 × 1 mm² in-plane resolution) were acquired.

Preprocessing

Preprocessing was performed using the SPM8 software package (<http://www.fil.ion.ucl.ac.uk/spm/>). The first 10 images of each dataset were discarded to allow for magnetization equilibrium and for the subjects to adjust to the environment.

The preprocessing included the following steps: (i) correction for differences in the image acquisition time between slices; (ii) a six parameter rigid body spatial transformation was performed to correct for head motion during data acquisition; (iii) to reduce the influence of motion and unspecific physiological effects, a regression of nuisance variables from the data was performed. Nuisance variables included white matter and ventricular signals and the six motion parameters determined in the realignment procedure. (iv) A spatial normalization of the mean functional image to a standard EPI template (SPM8's MNI EPI template) was conducted and the resulting transformation parameters were applied to the individual functional images. The registered images were resampled to 3 × 3 × 3 mm³; (v) spatial smoothing was performed with a 6-mm full width half maximum Gaussian kernel. (vi) A temporal band-pass filter was applied to all voxel time series (0.01 Hz < f < 0.08 Hz). As several recent studies showed that global signal regression leads to severe biases in connectivity analyses [Murphy et al., 2009; Saad et al., 2012], we did not perform global signal regression in the preprocessing of the fMRI data.

We tested if subjects had to be excluded from the analysis due to strong head motion. The six realignment parameters, that is, three displacements and three elementary rotations with respect to the first image in the series, were used as an estimator for the head motion. The displacements were required to be smaller than 3.0 mm (minimum to maximum) and the individual rotations smaller than 3.0°. One subject had to be excluded from the analysis due to strong head motion using predefined criteria. We conducted a group-wise comparison of head motion and found no significant differences between the two experimental groups (see Supporting Information).

Graph Analysis

A graph consists of a set of nodes which are connected by edges. In this section, we introduce our approach to define the nodes and edges describing the brain network. Nodes represent brain regions, that is, a collection of voxels which are spatially and functionally connected.

Nodes

The brain parcellation approach used in this study was introduced in a previous work [Göttlich et al., 2013]. Here,

we give a short summary. A regional parcellation of each hemisphere of the brain into 45 regions was performed according to the Automatic Anatomical labeling template as described by Tzourio-Mazoyer et al. [2002]. This template is based on an anatomical parcellation according to major sulci and gyri using a spatially normalized single subject high resolution T1 volume provided by the Montreal Neurological Institute (MNI) [Collins et al., 1998]. The AAL regions of interest (ROI) were further parcellated as follows yielding 333 cortical and subcortical nodes in total. For each AAL region and each subject, we obtained a voxel-by-voxel connectivity matrix by correlating the voxel BOLD signal fluctuations (Pearson correlation coefficient). The Pearson correlation coefficients were Fisher z-transformed and the group mean correlation matrix was calculated by averaging all connectivity matrices. The mean connectivity matrix was thresholded keeping 50% of strongest weights (proportional threshold of $S = 0.5$). Structures within the AAL regions were identified using Newman's spectral algorithm [Newman, 2006] applied to the mean correlation matrices. The algorithm maximizes the number of edges falling within modules minus the expected number in an equivalent network with edges placed at random. These modules within the AAL-regions served as nodes for the brain network analysis. In the following, we refer to the new regions as sub-AAL regions. Our main motivation for further parcellating the AAL atlas regions was the observation that these regions are very inhomogeneous in terms of their functional connectivity. Using subdivisions of these AAL atlas regions led to increased homogeneity [Göttlich et al., 2013]. The choice of the sparsity threshold has an influence on the number and size of the AAL subregions. Using this threshold, each AAL atlas region was subdivided into about four sub-ROIs on average. Increasing the number of network nodes improves the ROI homogeneity but on the other hand also increases the complexity of the data. The parcellation of the brain into 333 regions was thus a compromise. Critically, the larger ROI homogeneity revealed the resting-state networks which were not observed with the coarser parcellation. Note that the brain parcellation and the modular structure of the brain network were derived from an independent dataset (20 healthy subjects; 10 male; age: 63 ± 9 years). For more details on this cohort, we refer to [Göttlich et al., 2013].

Edges

The functional connectivity between brain regions was established by correlating the regional mean time courses. As a measure for the temporal correlation, we computed the zero-lag Pearson's linear correlation coefficient. The correlation coefficients were inverse hyperbolic tangent transformed (Fisher z-transformed) and entered into the correlation matrix as basis for the network analysis. Diagonal elements of the correlation matrix were set to zero. The connectivity matrices were standardized by converting

the weights to z-scores: $z_i = (w_i - \bar{w}) / \sigma_w$. Here, $\bar{w}$ denotes the mean degree and σ_w the standard deviation. This transformation ensured that matrices were comparably scaled and could be averaged and compared across subjects. Note that the relative strength of connections is not affected by this transformation.

Network community structure

The aim of our study was to gain a deeper understanding how OCD affects the brain network at the scale of network modules (or network communities). The community structures of a network can be considered an intermediate level of network organization. A graph community structure is a subdivision of a network into groups of nodes in a way that maximizes the number of within-group edges, and minimizes the number of between-group edges. The modular structure of the brain network was derived from the same independent dataset which was used for the data driven brain parcellation (Nodes section). A mean brain network matrix was calculated by averaging the individual network matrices. The mean network matrix was then thresholded keeping 15% of the strongest connections and a community structure was identified applying Newman's spectral algorithm [Newman, 2006] as implemented in the Brain Connectivity Toolbox (<http://www.brain-connectivity-toolbox.net/>). It should be stressed, that we used the same sparsity threshold as in our previous work [Göttlich et al., 2013] and that this threshold was chosen independently from the present analysis. The rationale behind the choice of this threshold was that the community structure did not change running the algorithm multiple times despite the heuristics in the algorithm. This resulted in a stable and reproducible subdivision of the network. The community structure was applied to the network matrices of the control and OCD group.

Module Connectivity

To gain deeper insights into the nature of the network alterations, we investigated the connectivity between network modules. The connectivity C_{ij} between the modules M_i and M_j was defined as follows:

$$C_{ij} = \sum_{m \in M_i} \sum_{n \in M_j} z_{mn}$$

Here, z_{mn} is the weight of the edge connecting node m in module i to node n in module j . Note that for $i = j$, we obtain the connectivity of nodes within a given module.

The strength of a node is defined as the sum of weights of edges connected to that node [Rubinov and Sporns, 2010]. We extended this definition by introducing the inward and outward node strength (or connectivity). The inward node strength is given by the sum of weights of all connections within a given module. The outward strength is defined as the sum of all weights connecting the given node to nodes in other modules. An advantage of our

Figure 1.

Between-group effects in inward and outward brain network module connectivity. Shown are connections which are significantly different comparing the OCD and the control group (0.05 FDR corrected). Blue lines and sectors indicate outward and inward connections which are significantly stronger in the OCD group, whereas red lines and sectors indicate weaker connections. Also, shown are the brain regions comprising the network modules.

approach is that we do not have to arbitrarily threshold the connectivity matrices and that we use all features in the data to investigate between-group effects.

Statistical Analysis

Statistical tests for significant between-group differences in module and node properties were carried out by nonparametric permutation tests [Nichols and Holmes, 2002]. When testing for group effects in module connectivity, 0.05 FDR-corrected results are presented [Benjamini and Hochberg, 1995]. We tested if the module connectivity was correlated to the Y-BOCS score using Spearman's rank correlation.

RESULTS

Network Module Connectivity

We investigated differences on the intermediate level of brain network organization by comparing properties of ROI communities. The community structure of the brain network was derived from an independent dataset. This analysis yielded seven communities as depicted in Figure 1. The individual modules correspond to well-established resting-

TABLE I. Demographic and clinical information

	Healthy controls N = 19	OCD patients N = 17	Significance (<i>P</i> -value)
Gender female/male	15/4	12/5	0.55
Age in years (s.d.)	30.4 (9.6)	32.6 (11.6)	0.53
Education (years)	14.3 (2.4)	13.5 (1.9)	0.30
Disease duration (years)	n/a	10.5 (8.5)	
Y-BOCS	n/a	25.4 (2.7)	
HDRS-score	n/a	5.9 (5.0)	

Y-BOCS: Yale-Brown Obsessive Compulsive Scale; HDRS: Hamilton Depression Rating Scale; n/a: Not applicable/available. A test for significant between-group difference in age, education years (two-sample *t*-test), and gender (χ^2 -test) was performed. The *P*-values are given.

state networks (default mode, visual, sensorimotor, fronto-parietal attention/executive, subcortical) [Beckmann et al., 2005]. The default mode network (DMN) and VN are clearly identified. We also observed communities corresponding roughly to the sensorimotor network (SMN) and the fronto-parietal attention/executive network (FPN). Whereas SMN module mainly consists of sensorimotor regions, it also contains nodes located in the supramarginal gyrus, insula, and rolandic operculum. The FMN module contains mainly lateral frontal and parietal regions but also nodes in the cingulate cortex, insula, and supramarginal gyrus. The limbic modules comprise temporal pole regions and limbic regions such as the amygdala and the hippocampus. The caudate, putamen, and pallidum comprise the BG module.

For each module, we investigated group differences in the inward and outward module connectivity. Figure 1 depicts between-group effects in inward and outward module connectivity in form of chord diagram. The visualization was done using CIRCOS [Krzywinski et al., 2009]. The individual brain network modules are represented by sectors on a circle. The between-module connections that were significantly stronger in OCD patients are indicated by blue lines. Red lines indicate weaker connectivity in the patients group. Group effects in the inward module connectivity are indicated by blue and red colored sectors. We found 16 connections which showed significant group effects (permutation test; 0.05 FDR corrected). The results are summarized in Table II. OCD patients showed a stronger inward connectivity in the fronto-parietal network (FPN) and the SMN module. The connectivity between the FPN and SMN was increased and the SMN module was also more strongly connected to the VN. The limbic modules essentially showed a weaker connectivity to all other brain network modules. The connectivity between the two limbic modules and the inward degree within the limbic module containing mainly the amygdala and the hippocampus was decreased as well. The DMN module had a weaker connection to the limbic modules and also showed a lower inward connectivity. The BG module showed a

weaker connectivity to both limbic modules and to the VN module.

Correlation Between the Module Connectivity and the Y-BOCS Score

We tested whether the module connectivity was modulated by the disease severity as expressed by the Y-BOCS score. Due to the nonlinearity of the Y-BOCS, we used the Spearman's rank correlation coefficient. We tested all possible connections between network modules for a significant correlation with the Y-BOCS score. We found a significant negative correlation ($r = -0.50$; $P = 0.041$ uncorrected; Spearman's rank correlation) between the inward connectivity in Module 5 (Fig. 1; DMN) and the Y-BOCS score (Fig. 2A). More affected patients showed a decreased inward connectivity in the DMN module. Module 6 (related to the FPN; Fig. 1) showed a significant positive correlation between the inward module connectivity and the Y-BOCS score ($r = 0.72$; $P = 0.0012$ uncorrected; $P = 0.033$ FDR corrected; Fig. 2B). With increased disease severity, OCD patients showed a stronger inward connectivity in the fronto-parietal (FPN) module deviating more strongly from healthy controls.

We tested if the module connectivity was correlated to the HDRS score and found no significant correlation (all $P > 0.05$).

Between-Group Effects in Inward and Outward Node Connectivity

We tested each node for significant between-group effects in the inward and outward connectivity (permutation test;

TABLE II. Between-group effects in module connectivity

Modules		Mean CTR	Mean OCD	<i>P</i> (uncorr.)	<i>P</i> (adjusted)
CTR > OCD					
1	2	62.81	-30.84	0.005	0.021
1	3	-153.56	-244.00	0.009	0.026
1	4	-57.31	-283.31	0.001	0.005
1	5	-52.35	-209.53	0.016	0.035
2	2	325.73	123.07	0.011	0.027
2	3	-118.35	-308.82	0.003	0.014
2	4	-1.02	-404.90	0.000	0.005
2	5	-354.83	-595.28	0.011	0.027
2	6	-725.36	-919.94	0.021	0.041
2	7	-340.46	-680.71	0.006	0.022
3	4	-224.07	-563.03	0.001	0.009
5	5	2769.91	2012.47	0.026	0.046
OCD > CTR					
4	7	1233.85	1698.13	0.023	0.043
6	6	2074.20	2743.97	0.009	0.026
6	7	245.50	1298.11	0.001	0.005
7	7	3001.67	3974.68	0.005	0.021

The first and second columns indicate the modules where significant between-group effects in connectivity are observed. We quote uncorrected and 0.05 FDR-corrected *P*-values.

Figure 2.

Dependence of the module connectivity on the disease severity assessed by the Y-BOCS. **(A)** The inward connectivity in Module 5 (DMN) versus the Y-BOCS score. **(B)** The inward degree in Module 6 (FPN) versus the Y-BOCS score. The red lines indicate the mean ($\pm$ one standard deviation) inward connectivity in the control group.

$P < 0.01$; uncorrected). By this, we gain a deeper understanding of our findings on the level of network modules by identifying the nodes which were mainly contributing to the between group differences in module connectivity. Furthermore, we strengthen our results by showing that our findings are driven by brain regions which are known to play an important role in the context of OCD. The results are depicted in Figure 3 and summarized in Table III.

The weaker connectivity in the limbic modules can be mainly attributed to amygdala, hippocampus, parahippocampus, and olfactory cortex nodes. Interestingly, the ventral striatum was driving the effects in the BG module both for the weaker inward and weaker outward connectivity observed in the OCD group. The weaker inward connectivity in the DMN module was strongest the middle temporal gyrus and the dorsal cingulate cortex. We found a significantly weaker outward connectivity in the ACC and the superior frontal gyrus for the patient group. The strongest between-group effects in the FPN module were found in the middle frontal gyrus (MFG), inferior orbito-frontal cortex (OFC), and the superior parietal cortex. All these regions showed weaker inward/outward connectivity in the patient group compared to healthy controls. In the SMN module, rolandic operculum, precentral, and postcentral nodes showed a significantly stronger inward degree for OCD patients. The outward degree was increased in the same rolandic regions, in the insula and the supramarginal gyrus.

Following a hypothesis driven approach and to allow for comparisons with previous studies on resting-state functional connectivity in OCD [Anticevic et al., 2014; Beucke et al., 2013], we also investigated significant between-group effects in the OFC using a P -threshold of $P = 0.05$ (uncorrected; tested 40 nodes in the OFC). The results are depicted in Supporting Information Figure S1 and summar-

ized in Supporting Information Table S2. Medial OFC nodes were part of the DMN module, whereas nodes in the lateral OFC were assigned to the FPN module. OCD patients showed a significantly lower inward connectivity in medial OFC nodes. In the lateral OFC, the inward connectivity was increased in patients. We found no significant between-group effects for the outward connectivity.

DISCUSSION

We used a data-driven approach to investigate altered whole-brain intrinsic functional connectivity in 17 unmedicated OCD patients compared to 19 healthy control subjects. A graph theoretical approach was used for the analysis of the complex network data.

We observed decreased connectivity between modules comprising limbic regions (amygdala and hippocampus) and BG in OCD patients compared to healthy controls. Our data also indicated a lower connectivity between limbic and cortical regions for OCD patients. Furthermore, OCD patients showed a stronger connectivity between brain regions within the fronto-parietal executive/attention network. This effect was positively correlated with disease severity as measured by the Y-BOCS. OCD patients also showed a stronger connectivity between the FPN and the somatosensory network compared to healthy controls.

Decreased Connectivity of Limbic and Striatal Brain Regions in OCD

We found evidence for lower connectedness of emotion processing (limbic) structures (amygdala and hippocampus) to BG in OCD patients compared to healthy control

Figure 3.

Between-group effects in inward (left column) and outward (right column) connectivity at the level of network nodes. Brain regions showing a lower inward/outward connectivity in the OCD group are highlighted in red while blue indicates a higher connectivity in OCD patients ($P < 0.01$ uncorrected). The

subjects (Fig. 1). We also found decreased inward connectivity of the hippocampus and the amygdala and decreased connectivity between limbic modules (Fig. 1).

results are presented for each module separately (rows). Abbreviations: MFG, middle frontal gyrus; MTG, middle temporal gyrus; PHC, parahippocampus; RO, rolandic operculum; SMG, supramarginal gyrus.

Within the limbic modules, we identified nodes in the amygdala, parahippocampus, the hippocampus, and the olfactory cortex to show a decreased outward connectivity.

TABLE III. Group differences in inward and outward node connectivity

Module	Node	Center of mass			P-value
		x (mm)	y (mm)	z (mm)	
Inward					
Limbic 1	ParaHippocampal_R_1	23	-1	-28	0.0036
Limbic 2	Amygdala_L_1	-19	-1	-16	0.0048
Limbic 2	Frontal_Inf_Orb_L_1	-22	18	-22	0.0055
Limbic 2	Hippocampus_L_1	-29	-12	-20	0.0071
Limbic 2	Hippocampus_L_2	-23	-35	-2	0.0097
Limbic 2	Hippocampus_L_3	-28	-25	-12	0.0060
Limbic 2	Hippocampus_L_4	-19	-12	-17	0.0083
Limbic 2	Hippocampus_R_2	26	-34	-2	0.0041
Limbic 2	Hippocampus_R_3	30	-23	-12	0.0099
Limbic 2	Olfactory_L_1	-18	7	-16	0.0004
BG	Caudate_L_4	-9	15	-7	0.0091
DMN	Cingulate_Cortex_Mid_L_3	-5	-37	39	0.0084
DMN	Temporal_Mid_L_3	-60	-31	-5	0.0081
FPN	Frontal_Inf_Orb_L_3	-46	34	-9	0.0064
FPN	Frontal_Inf_Orb_R_4	34	34	-15	0.0045
FPN	Frontal_Mid_L_1	-41	17	44	0.0071
FPN	Frontal_Mid_Orb_L_2	-38	52	-6	0.0097
FPN	Frontal_Mid_R_4	36	25	43	0.0011
SMN	Insula_L_1	-36	-12	8	0.0091
SMN	Postcentral_L_1	-36	-31	57	0.0050
SMN	Postcentral_L_2	-55	-12	31	0.0057
SMN	Postcentral_R_3	27	-38	64	0.0058
SMN	Precentral_L_2	-31	-16	60	0.0041
SMN	Rolandic_Oper_L_5	-42	-26	18	0.0004
SMN	Rolandic_Oper_R_3	50	-22	18	0.0082
SMN	Thalamus_L_2	-9	-19	4	0.0053
Outward					
Limbic 1	Amygdala_R_1	29	0	-20	0.0007
Limbic 1	Amygdala_R_3	31	0	-25	0.0070
Limbic 1	ParaHippocampal_R_1	23	-1	-28	0.0005
Limbic 2	Amygdala_L_1	-19	-1	-16	0.0001
Limbic 2	Amygdala_R_2	25	-1	-15	0.0094
Limbic 2	Olfactory_L_1	-18	7	-16	0.0003
Limbic 2	Olfactory_R_2	24	10	-17	0.0001
Limbic 2	ParaHippocampal_L_3	-17	2	-26	0.0013
Limbic 2	ParaHippocampal_L_4	-23	-23	-22	0.0038
LB 2	Temporal_Pole_Sup_R_4	35	13	-27	0.0008
BG	Caudate_R_2	16	14	11	0.0098
BG	Caudate_R_4	12	15	-5	0.0060
BG	Olfactory_R_3	13	11	-17	0.0079
DMN	Cingulate_Cortex_Ant_L_3	-3	37	19	0.0092
DMN	Frontal_Sup_R_1	20	35	47	0.0070
FPN	Frontal_Mid_R_2	42	45	16	0.0074
FPN	Insula_R_4	37	16	3	0.0098
FPN	Parietal_Sup_R_2	24	-67	54	0.0091
SMN	Insula_R_3	39	-12	6	0.0024
SMN	Rolandic_Oper_L_5	-42	-26	18	0.0012
SMN	Rolandic_Oper_R_3	50	-22	18	0.0063
SMN	SupraMarginal_L_3	-59	-28	35	0.0014

Regions with significant differences in inward/outward node connectivity between controls and OCD patients (permutation test, $P < 0.01$; uncorrected). Listed are the node names, the center of mass coordinates (MNI) and the P -values.

The strongest effects in the BG module were found in the ventral striatum and the caudate (rostral part). These structures are known to be involved in several neural networks repeatedly found to be deficient in OCD: fear circuit (acquisition/conditioning, extinction learning, extinction recall) [Milad et al., 2013; Milad and Rauch, 2012], implicit learning [Deckersbach et al., 2002; Kathmann et al., 2005; Valerius et al., 2008] and the reward/punishment system [Figeo et al., 2011]. Our observation of a lower functional connectivity between limbic regions and BG in OCD patients may thus be related to deficiencies in these neural networks as will be discussed in the following.

The amygdala is most commonly viewed as a region mediating fear and anxiety but also responds to novelty, salience, and to other emotional stimuli [Balderston et al., 2011; Ball et al., 2009; Blackford et al., 2010; Davis and Whalen, 2001; Etkin and Wager, 2007; Hariri et al., 2002; Phan et al., 2004; Santos et al., 2011]. The amygdala receives modulatory input from several subcortical (e.g., ventral striatum and hippocampus) and cortical structures (e.g., medial prefrontal cortex and ventromedial prefrontal cortex). During fear extinction recall, the amygdala receives contextual input from the ventromedial prefrontal cortex and the hippocampus [Kalisch et al., 2006; Maren and Hobin, 2007; Milad et al., 2007; Orsini et al., 2011]. Milad et al. [2013] reported impaired fear extinction recall in OCD patients, as derived from skin conductance measurements, and found reduced activations in the caudate and hippocampus during fear conditioning and in the posterior cingulate cortex and putamen during extinction recall. The role of the ventral striatum in extinction of conditioned fear was addressed by Rodriguez-Romaguera et al. [2012] using deep brain stimulation (DBS) in rats. DBS of the ventral striatum during the extinction training reduced fear expression and strengthened extinction memory. DBS targeting the NAC (part of the ventral striatum) has been successfully used to treat severely ill, therapy-refractory OCD patients [Denys et al., 2010; Sturm et al., 2003]. The ventral striatum can be regarded as a region which integrates signals with emotional content (amygdala), contextual information (hippocampus), motivational significance (dopaminergic inputs), information about the state of arousal (midline thalamus), and executive/cognitive information (prefrontal cortex) [Alexander et al., 1990; Groenewegen and Trimble, 2007]. It is thus an important component of many neural networks known to be affected in OCD. Our finding of a decreased connectivity in the nucleus accumbens/ventral striatum (Fig. 3) is well in agreement with findings from Anticevic et al. [2014] who found a decreased whole-brain functional connectivity in these brain areas. The authors also discuss their findings in context of DBS applied in this area for treating severe, refractory OCD.

OCD patients show deficits in implicit learning [Deckersbach et al., 2002; Kathmann et al., 2005; Valerius et al., 2008]. Several neuroimaging studies found aberrant activations in the ventral striatum, hippocampus, and OFC dur-

ing implicit learning tasks comparing healthy controls and OCD patients [Rauch et al., 1997, 2007]. A disturbed connectivity between limbic (in particular the hippocampus) and striatal structures may thus be related to implicit learning deficits observed in OCD.

The amygdala is generally linked to negative emotions and fear conditioning but it is just as important for processing positive reward and reinforcement as it is for negative [Baxter and Murray, 2002; Murray, 2007]. Figeo et al. [2011] used a monetary incentive delay task and functional magnetic resonance imaging to investigate dysfunctional reward processing in OCD patients. OCD patients showed attenuated activity in the NAC in anticipation of reward compared with healthy control subjects.

In a seed-based approach, Posner et al. (2014) investigated the resting-state functional connectivity within the limbic CSCT loop (seeds in the ventral striatum) and found decreased connectivity to the ACC and the medial OFC in unmedicated OCD patients compared to healthy controls. Our observation of a lower connectivity between limbic and striatal brain regions is in line with these findings pointing to a hypoconnectivity of limbic regions in unmedicated patients.

Decreased Connectivity Between Limbic and FPN

Figure 1 suggests a lower functional connectivity between emotion processing (limbic) regions and cortical networks in OCD patients compared to healthy controls. We hypothesize that the lower connectivity of limbic structures to the executive/attention network in patients may be related to a lower cognitive control over fear signals which drive compulsive behavior. The functional consequence of the latter finding could be an insufficient regulation of over-excitable emotion processing regions by FPNs providing reappraisal of inner (thoughts, images), and outer events [Campbell-Sills et al., 2011; Drabant et al., 2009]. Notably, instructed reappraisal of fear-provoking stimuli has been shown to result in a reduced activity of the amygdala, together with a reduced subjective discomfort [Drabant et al., 2009; Hariri et al., 2003]. Consistently, cognitive-behavioral therapy of OCD strongly relies on implementing reappraisal strategies and repeated exposure to provoking stimuli strongly supports reappraisal in the course of therapy [Salkovskis, 1985].

Hyperconnectivity Within the FPN in OCD

OCD patients showed a stronger inward connectivity in the FPN and a stronger connectivity between the executive/attention network and the SMN (Fig. 1). Regarding the FPN network, the MFG and the superior parietal cortex showed the strongest between-group effect in outward connectivity, that is, stronger outward connectivity in OCD patients (Fig. 3). Nodes in the SMN showing the

strongest between-group effects in outward connectivity were located in the supramarginal gyrus (SMG) and the rolandic operculum (RO). Note that nodes in the SMG and RO are partly assigned to the fronto-parietal and SMN by Newman's spectral algorithm used to define the community structure. The higher connectivity between the SMG/RO and the MFG is the reason for both the higher connectivity within the executive/attention network and between the executive/attention and the SMN (Fig. 1). The stronger connectivity within brain regions involved in executive function and attention can be related to excessive monitoring of thoughts and behavior observed in OCD patients. Maltby et al. [2005] provided support that action-monitoring processes are hyperactive in OCD. Using a speeded reaction time task and fMRI they showed that correctly rejected, high conflict trials produced excessive activation in both action-monitoring (ACC and lateral prefrontal cortex), frontal and striatal regions (lateral OFC, caudate) in OCD patients.

A multitude of studies associated the parietal cortex, in particular the supramarginal and angular gyrus, with OCD. Whole-brain VBM [Ashburner and Friston, 2000] studies revealed gray matter density abnormalities in parietal regions including the angular gyrus, supramarginal gyrus, and the inferior parietal lobe [Kim et al., 2001; Pujol et al., 2004; Rotge et al., 2010; Valente et al., 2005]. These findings were further consolidated by fMRI studies using symptom provocation paradigms which found increased recruitment of the DLPFC and the parietal cortex during symptom provocation [Adler et al., 2000; Breiter et al., 1996; Shapira et al., 2003]. The DLPFC and parietal cortex, in particular angular and supramarginal gyri, are discussed in the context of cognitive deficits in attention, planning, and response inhibition observed in OCD patients [Chamberlain et al., 2006; Mataix-Cols et al., 2002; Menzies et al., 2008; Veale et al., 1996; Watkins et al., 2005]. Our network analysis provided evidence for a higher connectedness of the supramarginal gyrus in OCD patients at rest (Fig. 3) which well complements the current research as we were able to directly relate this observation to an over-connected FPN (Fig. 1). We were also able to show that our findings are related to disease severity. The mean degree of nodes in the executive/attention network was positively correlated to the Y-BOCS score. With increasing disease severity patients showed increasing deviations from the mean degree observed in the control group (Fig. 2B). A clear dependence on the Y-BOCS score but not on depression scores (HDRS) indicates that our findings are specific to OCD.

As depicted in Figure 3, a node in the ACC showed a significantly higher connectedness in OCD patients compared to healthy controls. The ACC is implicated in conflict detection, error monitoring, and error detection and contributes to executive processes [Botvinick et al., 1999; Carter et al., 1998, 1999; van Veen and Carter, 2002]. Several studies show a hyperactivation of the dACC during error monitoring in OCD patients [Fitzgerald et al., 2005,

2010; Maltby et al., 2005]. Moreover, OCD patients showed an enhanced connectivity between the dACC and the DLPFC during a Stroop task [Schlosser et al., 2010]. Our observation of a higher degree in the dACC suggests that the task-related abnormalities within networks supporting action execution and monitoring are also present during rest.

Decreased Inward Connectivity in the DMN Depends on Disease Severity

In this section, we discuss our findings concerning the DMN (Figs. 1 and 2A). The inward connectivity of the DMN was negatively correlated to the disease severity as expressed by the Y-BOCS score (Fig. 2A). With increasing disease severity patients showed a decrease in inward connectedness. Less affected patients show a connectedness which was comparable to the control group. Furthermore, we found a lower connectivity between the limbic and the DMN (Fig. 1). Similarly, Posner and colleagues recently reported a negative correlation between symptom strength and connectivity within limbic CSTC loops in unmedicated patients with OCD [Posner et al., 2014].

We observed a weaker connectivity between the limbic and the DMN (Fig. 1). Amygdala activity is modulated by individual stimulus/event value and expected probability of a negative event and different portions of the PFC have been shown to exert this modulatory influence [Kalisch et al., 2006; Maren and Hobin, 2007; Milad et al., 2007; Orsini et al., 2011; Pessoa, 2008]. We hypothesize that a weaker connectivity between limbic structures and the DMN in OCD patients may be related to a deficient (contextual) modulation of the amygdala, suggesting a neural correlate of patient's bias toward processing and expectation of negative events and outcomes of behavior [Fullana et al., 2004a, 2004b].

OCD Patients Showed Reduced Connectivity of the VN

Figure 2B indicates a weaker connectivity of the VN to limbic regions and BG (Fig. 1). Interestingly, Szeszko et al. [2005] found evidence for a decreased fractional anisotropy within the white matter of the lingual gyrus (left) in OCD patients, compared to healthy controls. Szeszko et al. [2005] discussed this finding in the context of neuroimaging studies pointing to the role of lingual gyrus for processing emotionally charged visual stimuli [Lane et al., 1997, 1999; Lang et al., 1998] and to a study associating the lingual gyrus to somatic arousal [Critchley et al., 2000]. In light of these functional insights into the role of the lingual gyrus, we hypothesize that our observation relates to the phenomenology of OCD or anxiety disorders in general where an actual visual stimulus, for example, dirt, or an intrusive thought or image of dirt provokes a strong emotional reaction in patients with contamination obsessions.

Consistently, the same is true for other subtypes of OCD as shown by symptom provocation studies using individually adapted stimuli [Schiepek et al., 2007]. Still, the interpretation of this finding remains suggestive and hypothetical and needs to be addressed in dedicated studies which combine fMRI both, during resting-state and during symptom provocation in patients with OCD.

Altered OFC Connectivity

OCD patients showed a lower inward connectivity of nodes within the medial OFC (Supporting Information Fig. S1 and Table S2). These nodes were part of the DMN module. A lower inward connectivity thus points to lower connectivity of these nodes to other nodes within the DMN. This is in agreement with work from Fitzgerald et al., [2010] who found a lower connectivity between the mOFC and the posterior cingulate cortex. Fitzgerald et al., [2010] discuss this finding as a consequence of intrusive and distressing thoughts which may interrupt self-related, episodic memories during stimulus-independent thought.

Interestingly, patients showed a stronger inward connectivity for nodes in the later OFC which were assigned to the FPN module (Supporting Information Fig. S1 and Table S2). Our data suggest a lower inward connectivity in the medial OFC and a higher connectivity for more lateral OFC regions. Beucke et al., [2013] found a higher whole-brain connectivity in the OFC in unmedicated OCD patients. The location of the cluster maximum is indicated in Supporting Information Figure S1 (green dot). Note that the cluster maximum is in close proximity to a network node where we found a significantly higher inward degree. Our data extend the finding from Beucke et al., [2013] and suggests that the increased degree is due to stronger connectivity within the FPN.

Limitations and Conclusions

A potential disadvantage of investigating brain networks at the level of network modules is the lower sensitivity to small, localized network changes. The module related to the default mode resting-state network, for instance, contains a large number of brain regions and is quite heterogeneous. The danger here is that effects may cancel each other out. We circumvented this problem by investigating connectivity changes at the node level. This also allowed us to identify the brain regions which were accountable for the observed effects on module level to guide our interpretation of the results.

The reported between-group differences in module connectivity are ultimately related to altered connectivity between individual nodes (edges). We performed a two-sample two-tailed *t*-test and tested for between-group effects in network edges based on *z*-transformed network matrices. In Supporting Information Figure S2, we plotted the distribution of *P*-values and *t*-scores. As expected, the

P-value distribution is flat for larger *P*-values but peaks toward small *P*-values. We see this as strong evidence that our analytical approach is valid.

The sample of OCD patients was too small (17 subjects) to study the dependency of our findings on major clinical symptom dimensions (sexual/religious, aggression, hoarding, contamination fear). Harrison et al. [2013] showed that ventral striatum connectivity may be modulated by symptom dimension. However, the major pattern of orbitofronto-striatal abnormalities was present across symptom dimensions, suggesting a subsyndrome-independent core deficit in OCD.

We have no behavioral data concerning fear conditioning, fear extinction, fear extinction recall, implicit learning, reward processing, or reappraisal. Future studies may be targeted to specifically test if changes in resting-state networks are related to any of these parameters. However, we did find a modulation of the mean module degree in the default mode and executive/attention network by the disease severity as indicated by the Y-BOCS score. Furthermore, aberrant connectedness of network nodes was observed in regions well known to be related to OCD. In agreement with our hypotheses, we found both altered connectivity between striatal and cortical brain regions as well as between emotion processing (limbic) brain regions and the striatum.

Our approach does not depend on an a priori hypothesis about OCD-related network changes. Investigating the brain network data from the perspective of modules allowed us to reduce the complexity of the data and at the same time preserve the sensitivity to OCD specific changes in network organization.

REFERENCES

- Abramowitz JS, Taylor S, McKay D (2009): Obsessive-compulsive disorder. *Lancet* 374:491–499.
- Adler CM, McDonough-Ryan P, Sax KW, Holland SK, Arndt S, Strakowski SM (2000): fMRI of neuronal activation with symptom provocation in unmedicated patients with obsessive compulsive disorder. *J Psychiatr Res* 34:317–324.
- Alexander GE, Crutcher MD, DeLong MR (1990): Basal ganglia-thalamocortical circuits: Parallel substrates for motor, oculomotor, “prefrontal” and “limbic” functions. *Prog Brain Res* 85:119–146.
- Anticevic A, Hu S, Zhang S, Savic A, Billingslea E, Wasylink S, Repovs G, Cole MW, Bednarski S, Krystal JH, Bloch MH, Li CS, Pittenger C. (2014): Global resting-state functional magnetic resonance imaging analysis identifies frontal cortex, striatal, and cerebellar dysconnectivity in obsessive-compulsive disorder. *Biological psychiatry* 75:595–605.
- Ashburner J, Friston KJ (2000): Voxel-based morphometry—the methods. *NeuroImage* 11(Pt 1):805–821.
- Atmaca M, Yildirim BH, Ozdemir BH, Aydin BA, Tezcan AE, Ozler AS. (2006): Volumetric MRI assessment of brain regions in patients with refractory obsessive-compulsive disorder. *Prog Neuro Psychopharmacol Biol Psychiatry* 30:1051–1057.
- Atmaca M, Yildirim H, Ozdemir H, Tezcan E, Poyraz AK (2007): Volumetric MRI study of key brain regions implicated in obsessive-compulsive disorder. *Prog Neuro Psychopharmacol Biol Psychiatry* 31:46–52.

- Balderston NL, Schultz DH, Helmstetter FJ (2011): The human amygdala plays a stimulus specific role in the detection of novelty. *NeuroImage* 55:1889–1898.
- Ball T, Derix J, Wentlandt J, Wieckhorst B, Speck O, Schulze-Bonhage A, Mutschler I (2009): Anatomical specificity of functional amygdala imaging of responses to stimuli with positive and negative emotional valence. *J Neurosci Methods* 180:57–70.
- Baxter MG, Murray EA (2002): The amygdala and reward. *Nat Rev Neurosci* 3:563–573.
- Baxter LR Jr, Phelps ME, Mazziotta JC, Guze BH, Schwartz JM, Selin CE (1987): Local cerebral glucose metabolic rates in obsessive-compulsive disorder. A comparison with rates in unipolar depression and in normal controls. *Arch Gen Psychiatry* 44:211–218.
- Baxter LR Jr, Schwartz JM, Mazziotta JC, Phelps ME, Pahl JJ, Guze BH, Fairbanks L (1988): Cerebral glucose metabolic rates in nondepressed patients with obsessive-compulsive disorder. *Am J Psychiatry* 145:1560–1563.
- Baxter LR Jr, Schwartz JM, Guze BH, Bergman K, Szuba MP (1990): PET imaging in obsessive compulsive disorder with and without depression. *J Clin Psychiatry* 51(Suppl 61-9); discussion 70.
- Beckmann CF, DeLuca M, Devlin JT, Smith SM (2005): Investigations into resting-state connectivity using independent component analysis. *Philos Trans R Soc London Ser B Biol Sci* 360: 1001–1013.
- Benjamini Y, Hochberg Y (1995): Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Stat Soc Ser B (Methodol)* 57:289–300.
- Beucke JC, Sepulcre J, Talukdar T, Linnman C, Zschenderlein K, Endrass T, Kaufmann C, Kathmann N (2013): Abnormally high degree connectivity of the orbitofrontal cortex in obsessive-compulsive disorder. *JAMA Psychiatry* 70:619–629.
- Biswal BB, Van Kynen J, Hyde JS (1997): Simultaneous assessment of flow and BOLD signals in resting-state functional connectivity maps. *NMR Biomed* 10:165–170.
- Blackford JU, Buckholtz JW, Avery SN, Zald DH (2010): A unique role for the human amygdala in novelty detection. *NeuroImage* 50:1188–1193.
- Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD (1999): Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature* 402:179–181.
- Breiter HC, Rauch SL, Kwong KK, Baker JR, Weisskoff RM, Kennedy DN, Kendrick AD, Davis TL, Jiang A, Cohen MS, et al. (1996): Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder. *Arch Gen Psychiatry* 53:595–606.
- Bullmore E, Sporns O (2009): Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci* 10:186–198.
- Campbell-Sills L, Simmons AN, Lovero KL, Rochlin AA, Paulus MP, Stein MB (2011): Functioning of neural systems supporting emotion regulation in anxiety-prone individuals. *NeuroImage* 54:689–696.
- Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD (1998): Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 280:747–749.
- Carter CS, Botvinick MM, Cohen JD (1999): The contribution of the anterior cingulate cortex to executive processes in cognition. *Rev Neurosci* 10:49–57.
- Chamberlain SR, Fineberg NA, Blackwell AD, Robbins TW, Sahakian BJ (2006): Motor inhibition and cognitive flexibility in obsessive-compulsive disorder and trichotillomania. *Am J Psychiatry* 163:1282–1284.
- Chamberlain SR, Menzies L, Hampshire A, Suckling J, Fineberg NA, del Campo N, Aitken M, Craig K, Owen AM, Bullmore ET, et al. (2008): Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives. *Science* 321:421–422.
- Choi JS, Kang DH, Kim JJ, Ha TH, Lee JM, Youn T, Kim IY, Kim SI, Kwon JS (2004): Left anterior subregion of orbitofrontal cortex volume reduction and impaired organizational strategies in obsessive-compulsive disorder. *J Psychiatr Res* 38:193–199.
- Collins DL, Zijdenbos AP, Kollokian V, Sled JG, Kabani NJ, Holmes CJ, Evans AC (1998): Design and construction of a realistic digital brain phantom. *IEEE Trans Med Imaging* 17: 463–468.
- Cooper J (2001): Diagnostic and statistical manual of mental disorders (4th ed, text revision) (DsM-IV-TR). *Br J Psychiatry* 179:85.
- Critchley HD, Elliott R, Mathias CJ, Dolan RJ (2000): Neural activity relating to generation and representation of galvanic skin conductance responses: A functional magnetic resonance imaging study. *J Neurosci* 20:3033–3040.
- Davis M, Whalen PJ (2001): The amygdala: Vigilance and emotion. *Mol Psychiatry* 6:13–34.
- Deckersbach T, Savage CR, Curran T, Bohné A, Wilhelm S, Baer L, Jenike MA, Rauch SL (2002): A study of parallel implicit and explicit information processing in patients with obsessive-compulsive disorder. *Am J Psychiatry* 159:1780–1782.
- Denys D, Mantione M, Figeé M, van den Munckhof P, Koerselman F, Westenberg H, Bosch A, Schuurman R (2010): Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. *Arch Gen Psychiatry* 67:1061–1068.
- Dosenbach NU, Visscher KM, Palmer ED, Miezin FM, Wenger KK, Kang HC, Burgund ED, Grimes AL, Schlaggar BL, Petersen SE (2006): A core system for the implementation of task sets. *Neuron* 50:799–812.
- Drabant EM, McRae K, Manuck SB, Hariri AR, Gross JJ (2009): Individual differences in typical reappraisal use predict amygdala and prefrontal responses. *Biol Psychiatry* 65:367–373.
- Etkin A, Wager TD (2007): Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psychiatry* 164:1476–1488.
- Figeé M, Vink M, de Geus F, Vulink N, Veltman DJ, Westenberg H, Denys D (2011): Dysfunctional reward circuitry in obsessive-compulsive disorder. *Biol Psychiatry* 69:867–874.
- Fitzgerald KD, Welsh RC, Gehring WJ, Abelson JL, Himle JA, Liberzon I, Taylor SF (2005): Error-related hyperactivity of the anterior cingulate cortex in obsessive-compulsive disorder. *Biol Psychiatry* 57:287–294.
- Fitzgerald KD, Stern ER, Angstadt M, Nicholson-Muth KC, Maynor MR, Welsh RC, Hanna GL, Taylor SF (2010): Altered function and connectivity of the medial frontal cortex in pediatric obsessive-compulsive disorder. *Biol Psychiatry* 68:1039–1047.
- Fitzgerald KD, Welsh RC, Stern ER, Angstadt M, Hanna GL, Abelson JL, Taylor SF (2011): Developmental alterations of frontal-striatal-thalamic connectivity in obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry* 50:938–948.e3.
- Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005): The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci USA* 102:9673–9678.
- Fullana MA, Mataix-Cols D, Caseras X, Alonso P, Manuel Menchon J, Vallejo J, Torrubia R (2004a): High sensitivity to

- punishment and low impulsivity in obsessive-compulsive patients with hoarding symptoms. *Psychiatry Res* 129:21–27.
- Fullana MA, Mataix-Cols D, Trujillo JL, Caseras X, Serrano F, Alonso P, Menchon JM, Vallejo J, Torrubia R (2004b): Personality characteristics in obsessive-compulsive disorder and individuals with subclinical obsessive-compulsive problems. *Br J Clin Psychol* 43(Pt 4):387–398.
- Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS (1989): The Yale-Brown obsessive compulsive scale. I. Development, use, and reliability. *Arch Gen Psychiatry* 46:1006–1011.
- Göttlich M, Münte TF, Heldmann M, Kasten M, Hagenah J, Krämer UM (2013): Altered resting state brain networks in Parkinson's disease. *PloS one* 8:e77336.
- Groenewegen HJ, Trimble M (2007): The ventral striatum as an interface between the limbic and motor systems. *CNS Spectr* 12:887–892.
- Hamilton M (1960): A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56–62.
- Hariri AR, Tessitore A, Mattay VS, Fera F, Weinberger DR (2002): The amygdala response to emotional stimuli: A comparison of faces and scenes. *NeuroImage* 17:317–323.
- Hariri AR, Mattay VS, Tessitore A, Fera F, Weinberger DR (2003): Neocortical modulation of the amygdala response to fearful stimuli. *Biol Psychiatry* 53:494–501.
- Harrison BJ, Soriano-Mas C, Pujol J, Ortiz H, Lopez-Sola M, Hernandez-Ribas R, Deus J, Alonso P, Yucel M, Pantelis C, et al. (2009): Altered corticostriatal functional connectivity in obsessive-compulsive disorder. *Arch Gen Psychiatry* 66:1189–1200.
- Harrison BJ, Pujol J, Cardoner N, Deus J, Alonso P, Lopez-Sola M, Contreras-Rodriguez O, Real E, Segalas C, Blanco-Hinojo L, et al. (2013): Brain corticostriatal systems and the major clinical symptom dimensions of obsessive-compulsive disorder. *Biol Psychiatry* 73:321–328.
- Jang JH, Kim JH, Jung WH, Choi JS, Jung MH, Lee JM, Choi CH, Kang DH, Kwon JS (2010): Functional connectivity in fronto-subcortical circuitry during the resting state in obsessive-compulsive disorder. *Neurosci Lett* 474:158–162.
- Kalisch R, Korenfeld E, Stephan KE, Weiskopf N, Seymour B, Dolan RJ (2006): Context-dependent human extinction memory is mediated by a ventromedial prefrontal and hippocampal network. *J Neurosci* 26:9503–9511.
- Kang DH, Kim JJ, Choi JS, Kim YI, Kim CW, Youn T, Han MH, Chang KH, Kwon JS (2004): Volumetric investigation of the frontal-subcortical circuitry in patients with obsessive-compulsive disorder. *J Neuropsychiatry Clin Neurosci* 16:342–349.
- Kathmann N, Rupertseder C, Hauke W, Zaudig M (2005): Implicit sequence learning in obsessive-compulsive disorder: Further support for the fronto-striatal dysfunction model. *Biol Psychiatry* 58:239–244.
- Kim JJ, Lee MC, Kim J, Kim IY, Kim SI, Han MH, Chang KH, Kwon JS (2001): Grey matter abnormalities in obsessive-compulsive disorder: Statistical parametric mapping of segmented magnetic resonance images. *Br J Psychiatry* 179:330–334.
- Krzywinski M, Schein J, Birol I, Connors J, Gascoyne R, Horsman D, Jones SJ, Marra MA (2009): Circos: an information aesthetic for comparative genomics. *Genome Res* 19:1639–1645.
- Kuhn S, Kaufmann C, Simon D, Endrass T, Gallinat J, Kathmann N (2013): Reduced thickness of anterior cingulate cortex in obsessive-compulsive disorder. *Cortex* 49:2178–2185.
- Lane RD, Reiman EM, Bradley MM, Lang PJ, Ahern GL, Davidson RJ, Schwartz GE (1997): Neuroanatomical correlates of pleasant and unpleasant emotion. *Neuropsychologia* 35:1437–1444.
- Lane RD, Chua PM, Dolan RJ (1999): Common effects of emotional valence, arousal and attention on neural activation during visual processing of pictures. *Neuropsychologia* 37:989–997.
- Lang PJ, Bradley MM, Fitzsimmons JR, Cuthbert BN, Scott JD, Moulder B, Nangia V (1998): Emotional arousal and activation of the visual cortex: An fMRI analysis. *Psychophysiology* 35:199–210.
- Maltby N, Tolin DF, Worhunsky P, O'Keefe TM, Kiehl KA (2005): Dysfunctional action monitoring hyperactivates frontal-striatal circuits in obsessive-compulsive disorder: an event-related fMRI study. *NeuroImage* 24:495–503.
- Maren S, Hobin JA (2007): Hippocampal regulation of context-dependent neuronal activity in the lateral amygdala. *Learn Mem* 14:318–324.
- Mataix-Cols D, Alonso P, Pifarre J, Menchon JM, Vallejo J (2002): Neuropsychological performance in medicated vs. unmedicated patients with obsessive-compulsive disorder. *Psychiatry Res* 109:255–264.
- Melloni M, Urbistondo C, Sedeno L, Gelormini C, Kichic R, Ibanez A (2012): The extended fronto-striatal model of obsessive compulsive disorder: Convergence from event-related potentials, neuropsychology and neuroimaging. *Front Hum Neurosci* 6:259.
- Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET (2008): Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: The orbitofronto-striatal model revisited. *Neurosci Biobehav Rev* 32:525–549.
- Milad MR, Rauch SL (2012): Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways. *Trends Cogn Sci* 16:43–51.
- Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ, Rauch SL (2007): Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. *Biol Psychiatry* 62:446–454.
- Milad MR, Furtak SC, Greenberg JL, Keshaviah A, Im JJ, Falkenstein MJ, Jenike M, Rauch SL, Wilhelm S (2013): Deficits in conditioned fear extinction in obsessive-compulsive disorder and neurobiological changes in the fear circuit. *JAMA Psychiatry* 70:608–618; quiz 554.
- Mills KL, Bathula D, Dias TG, Iyer SP, Fenesy MC, Musser ED, Stevens CA, Thurlow BL, Carpenter SD, Nagel BJ, et al. (2012): Altered cortico-striatal-thalamic connectivity in relation to spatial working memory capacity in children with ADHD. *Front Psychiatry* 3:2.
- Murphy K, Birn RM, Handwerker DA, Jones TB, Bandettini PA (2009): The impact of global signal regression on resting state correlations: Are anti-correlated networks introduced? *NeuroImage* 44:893–905.
- Murray EA (2007): The amygdala, reward and emotion. *Trends Cogn Sci* 11:489–497.
- Newman ME (2006): Modularity and community structure in networks. *Proc Natl Acad Sci USA* 103:8577–8582.
- Nichols TE, Holmes AP (2002): Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Hum Brain Mapp* 15:1–25.
- Oldfield RC (1971): The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia* 9:97–113.

- Orsini CA, Kim JH, Knapska E, Maren S (2011): Hippocampal and prefrontal projections to the basal amygdala mediate contextual regulation of fear after extinction. *J Neurosci* 31:17269–17277.
- Pessoa L (2008): On the relationship between emotion and cognition. *Nature Rev Neurosci* 9:148–158.
- Phan KL, Wager TD, Taylor SF, Liberzon I (2004): Functional neuroimaging studies of human emotions. *CNS Spectr* 9:258–266.
- Posner J, Marsh R, Maia TV, Peterson BS, Gruber A, Simpson HB (2014): Reduced functional connectivity within the limbic cortico-striato-thalamo-cortical loop in unmedicated adults with obsessive-compulsive disorder. *Human brain mapping* 35:2852–2890.
- Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, Vogel AC, Laumann TO, Miezin FM, Schlaggar BL, et al. (2011): Functional network organization of the human brain. *Neuron* 72:665–678.
- Pujol J, Soriano-Mas C, Alonso P, Cardoner N, Menchon JM, Deus J, Vallejo J (2004): Mapping structural brain alterations in obsessive-compulsive disorder. *Arch Gen Psychiatry* 61:720–730.
- Rauch SL, Jenike MA, Alpert NM, Baer L, Breiter HC, Savage CR, Fischman AJ (1994): Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. *Arch Gen Psychiatry* 51:62–70.
- Rauch SL, Savage CR, Alpert NM, Dougherty D, Kendrick A, Curran T, Brown HD, Manzo P, Fischman AJ, Jenike MA (1997): Probing striatal function in obsessive-compulsive disorder: A PET study of implicit sequence learning. *J Neuropsychiatry Clin Neurosci* 9:568–573.
- Rauch SL, Wedig MM, Wright CI, Martis B, McMullin KG, Shin LM, Cannistraro PA, Wilhelm S (2007): Functional magnetic resonance imaging study of regional brain activation during implicit sequence learning in obsessive-compulsive disorder. *Biol Psychiatry* 61:330–336.
- Rodriguez-Romaguera J, Do Monte FH, Quirk GJ (2012): Deep brain stimulation of the ventral striatum enhances extinction of conditioned fear. *Proc Natl Acad Sci USA* 109:8764–8769.
- Rosenberg DR, Benazon NR, Gilbert A, Sullivan A, Moore GJ (2000): Thalamic volume in pediatric obsessive-compulsive disorder patients before and after cognitive behavioral therapy. *Biol Psychiatry* 48:294–300.
- Rotge JY, Langbour N, Guehl D, Bioulac B, Jaafari N, Allard M, Aouizerate B, Burbaud P (2010): Gray matter alterations in obsessive-compulsive disorder: An anatomic likelihood estimation meta-analysis. *Neuropsychopharmacology* 35:686–691.
- Rubinov M, Sporns O (2010): Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage* 52:1059–1069.
- Saad ZS, Gotts SJ, Murphy K, Chen G, Jo HJ, Martin A, Cox RW (2012): Trouble at rest: How correlation patterns and group differences become distorted after global signal regression. *Brain Connect* 2:25–32.
- Salkovskis PM (1985): Obsessional-compulsive problems: A cognitive-behavioural analysis. *Behav Res Ther* 23:571–583.
- Santos A, Mier D, Kirsch P, Meyer-Lindenberg A (2011): Evidence for a general face salience signal in human amygdala. *NeuroImage* 54:3111–3116.
- Saxena S, Rauch SL (2000): Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. *Psychiatr Clin North Am* 23:563–586.
- Saxena S, Brody AL, Schwartz JM, Baxter LR (1998): Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. *Br J Psychiatry Suppl* 26–37.
- Saxena S, Brody AL, Maidment KM, Dunkin JJ, Colgan M, Alborzian S, Phelps ME, Baxter LR Jr (1999): Localized orbitofrontal and subcortical metabolic changes and predictors of response to paroxetine treatment in obsessive-compulsive disorder. *Neuropsychopharmacology* 21:683–693.
- Schiepek G, Tominschek I, Karch S, Mulert C, Pogarell O (2007): [Neuroimaging and the neurobiology of obsessive-compulsive disorder]. *Psychother Psychosom Med Psychol* 57:379–394.
- Schlosser RG, Wagner G, Schachtzabel C, Peikert G, Koch K, Reichenbach JR, Sauer H (2010): Fronto-cingulate effective connectivity in obsessive compulsive disorder: A study with fMRI and dynamic causal modeling. *Hum Brain Mapp* 31:1834–1850.
- Shapira NA, Liu Y, He AG, Bradley MM, Lessig MC, James GA, Stein DJ, Lang PJ, Goodman WK (2003): Brain activation by disgust-inducing pictures in obsessive-compulsive disorder. *Biol Psychiatry* 54:751–756.
- Simon D, Kaufmann C, Musch K, Kischkel E, Kathmann N (2010): Fronto-striato-limbic hyperactivation in obsessive-compulsive disorder during individually tailored symptom provocation. *Psychophysiology* 47:728–738.
- Stern ER, Fitzgerald KD, Welsh RC, Abelson JL, Taylor SF (2012): Resting-state functional connectivity between fronto-parietal and default mode networks in obsessive-compulsive disorder. *PLoS one* 7:e36356.
- Sturm V, Lenartz D, Koulousakis A, Treuer H, Herholz K, Klein JC, Klosterkötter J (2003): The nucleus accumbens: a target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. *J Chem Neuroanat* 26:293–299.
- Swedo SE, Schapiro MB, Grady CL, Cheslow DL, Leonard HL, Kumar A, Friedland R, Rapoport SI, Rapoport JL (1989): Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. *Arch Gen Psychiatry* 46:518–523.
- Szeszko PR, Robinson D, Alvir JM, Bilder RM, Lencz T, Ashtari M, Wu H, Bogerts B (1999): Orbital frontal and amygdala volume reductions in obsessive-compulsive disorder. *Arch Gen Psychiatry* 56:913–919.
- Szeszko PR, MacMillan S, McMeniman M, Lorch E, Madden R, Ivey J, Banerjee SP, Moore GJ, Rosenberg DR (2004): Amygdala volume reductions in pediatric patients with obsessive-compulsive disorder treated with paroxetine: Preliminary findings. *Neuropsychopharmacology* 29:826–832.
- Szeszko PR, Ardekani BA, Ashtari M, Malhotra AK, Robinson DG, Bilder RM, Lim KO (2005): White matter abnormalities in obsessive-compulsive disorder: A diffusion tensor imaging study. *Arch Gen Psychiatry* 62:782–790.
- Tagliazucchi E, von Wegner F, Morzelewski A, Brodbeck V, Jahnke K, Laufs H (2013): Breakdown of long-range temporal dependence in default mode and attention networks during deep sleep. *Proc Natl Acad Sci USA* 110:15419–15424.
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M (2002): Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage* 15:273–289.
- Valente AA Jr, Miguel EC, Castro CC, Amaro E Jr, Duran FL, Buchpiguel CA, Chitnis X, McGuire PK, Busatto GF (2005): Regional gray matter abnormalities in obsessive-compulsive disorder: A voxel-based morphometry study. *Biol Psychiatry* 58:479–487.

-
- Valerius G, Lumpp A, Kuelz AK, Freyer T, Voderholzer U (2008): Reversal learning as a neuropsychological indicator for the neuropathology of obsessive compulsive disorder? A behavioral study. *J Neuropsychiatry Clin Neurosci* 20: 210–218.
- van Veen V, Carter CS (2002): The anterior cingulate as a conflict monitor: fMRI and ERP studies. *Physiol Behav* 77:477–482.
- Veale DM, Sahakian BJ, Owen AM, Marks IM. (1996): Specific cognitive deficits in tests sensitive to frontal lobe dysfunction in obsessive-compulsive disorder. *Psychol Med* 26: 1261–1269.
- Voderholzer U, Schwartz C, Freyer T, Zurowski B, Thiel N, Herbst N, Wahl K, Kordon A, Hohagen F, Kuelz AK (2013): Cognitive functioning in medication-free obsessive-compulsive patients treated with cognitive-behavioural therapy. *Journal of Obsessive-Compulsive and Related Disorders* 2:241–248.
- Watkins LH, Sahakian BJ, Robertson MM, Veale DM, Rogers RD, Pickard KM, Aitken MR, Robbins TW (2005): Executive function in Tourette's syndrome and obsessive-compulsive disorder. *Psychol Med* 35:571–582.
- Welch JM, Lu J, Rodriguiz RM, Trotta NC, Peca J, Ding JD, Feliciano C, Chen M, Adams JP, Luo J, et al. (2007): Corticostriatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice. *Nature* 448:894–900.
- Yan C, Liu D, He Y, Zou Q, Zhu C, Zuo X, Long X, Zang Y (2009): Spontaneous brain activity in the default mode network is sensitive to different resting-state conditions with limited cognitive load. *PloS one* 4:e5743.
- Zhang T, Wang J, Yang Y, Wu Q, Li B, Chen L, Yue Q, Tang H, Yan C, Lui S, et al. (2011): Abnormal small-world architecture of top-down control networks in obsessive-compulsive disorder. *J Psychiatry Neurosci* 36:23–31.