Effects of Bergen 4-Day Treatment on Resting-State Graph Features in Obsessive-Compulsive Disorder

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Abstract

Background. Exposure and response prevention (ERP) is an effective treatment for obsessive-compulsive disorder (OCD), but it is unclear how symptom reduction is related to changes in the brain. We aimed to determine the effects of a 4-day concentrated ERP program (Bergen 4-Day Treatment, B4DT) on the static and dynamic functional connectome in OCD patients.

Methods. Thirty-four OCD patients (25 unmedicated) underwent resting-state functional magnetic resonance imaging the day before the B4DT, and 28 (21 unmedicated) were rescanned after one week. Twenty-eight healthy controls were also scanned for baseline comparisons and 19 were rescanned after one week. Static and dynamic graph measures were quantified to determine network topology at the global, subnetwork, and regional level (including efficiency, clustering, between-subnetwork connectivity, and node flexibility in module allegiance). The Yale-Brown Obsessive Compulsive Scale was used to measure symptom severity.

Results. Twenty-four (86%) patients responded to treatment. We found significant group × time effects in frontoparietal-limbic connectivity ($\eta p2=0.19$, $p=.03$) and flexibility of the right subgenual anterior cingulate cortex ($\eta p2=0.18$, $p=.03$) where, in both cases, unmedicated patients showed significant decreases while healthy controls showed no significant changes. Healthy controls showed increases in global and subnetwork efficiency and clustering coefficient, particularly in the somatomotor subnetwork.

Conclusions. Concentrated ERP, in unmedicated OCD patients, leads to decreased connectivity between the frontoparietal and limbic subnetworks and less flexibility of the connectivity of the sgACC, suggesting a more independent and stable network topology. This may represent less limbic interference on cognitive control subnetworks after treatment.

Keywords: OCD; B4DT; graph theory; functional connectivity; limbic.

Introduction

Obsessive-compulsive disorder (OCD) is characterized by recurrent and distressing obsessions and repetitive physical or mental compulsions (1). OCD is often highly debilitating (2) and remains chronic if adequate treatment is not provided (3). Exposure and response prevention (ERP) is an effective treatment, but a subset of patients do not benefit from standard ERP (4, 5).

OCD has been related to abnormal function, structure and connectivity of cortico-striato-thalamo-cortical (CSTC), fronto-limbic and fronto-parietal circuits (6-10). Graph theory has increasingly been used to study abnormal brain connectivity and topology in OCD from a network perspective (11-18), and describes the properties of the brain network or "connectome" (19). Previous studies have reported conflicting findings, with some reporting that the connectome of OCD patients showed less small-worldness, indicating that the brain of OCD patients is less well-interconnected (14, 20, 21). Some also found that OCD patients showed less differentiated modules (clusters of highly interconnected nodes) compared with healthy controls, as well as altered connectivity between them (16, 21). Recent technical advances have also made it possible to study time-evolving dynamic connectivity patterns of the functional connectome (22), but has so far not been used in the study of OCD or treatment effects.

Treatment studies measuring changes in static graph measures after ERP in OCD patients have found an increase in global clustering coefficient (23), increased connectivity between frontal, striatal, parietal, and cerebellar regions (24), as well as fewer connections between the dorsolateral prefrontal cortex and the rest of the brain (25). However, previous findings are often limited by high rates of concurrent psychotropic medication (12, 23), where none have investigated dynamic connectivity or used intensive treatment to investigate rapid changes in the connectome. Methodological heterogeneity (e.g. motion correction, global

signal regression, and definition of nodes) has likely also contributed to inconsistencies across studies (26, 27).

The Bergen 4-day treatment (B4DT) is delivered during four consecutive days, where the two middle days are allocated to therapist-assisted ERP, followed by three weeks of self-administered ERP. The B4DT has shown to be highly effective for OCD patients with remission rates of about 75% one week after treatment (28, 29), and stable improvements after four years (30, 31). Given the treatment's rapid effect on OCD symptoms and very high rate of remission, it provides an ideal context to look at brain changes associated with symptom reduction.

In the present study, we investigated pre-to-post-treatment changes in the static and dynamic functional connectome in OCD patients, and compared patients the day before treatment and one week later (three days after the B4DT) with healthy controls that were also scanned twice. Following a preregistered analysis plan with hypotheses (see https://osf.io/bxmh4/), we investigated graph measures at the global, subnetwork, and regional levels. Based on previous studies of global, subnetwork and regional connectivity in OCD, we hypothesized that before treatment OCD patients would show less efficiency and clustering at the global level (14), within the default mode (DMN), ventral attention (VAN), frontoparietal (FPN) and somatomotor (SMN) subnetworks (32), greater efficiency and clustering in the limbic subnetwork (8), and higher connectivity between subnetworks relative to healthy controls (32). We also expected OCD patients to show higher node strength, clustering, and betweenness centrality in the bilateral subgenual anterior cingulate cortex (sgACC), amygdala, dorsolateral and ventromedial putamen, and caudate nucleus, which have previously been implicated in OCD (11, 13-15, 17). We further hypothesized that the treatment would normalize these abnormalities in OCD patients (see Supplemental Table 2

for all analyses). We used an exploratory approach when investigating the dynamic graph measures, as these have not been previously assessed in OCD.

Methods

Participants

Thirty-five OCD patients were recruited from a specialized outpatient OCD clinic at Haukeland University Hospital, Bergen, Norway. Thirty-one healthy controls were recruited through bulletin boards, social media, and emails to local businesses. Patients were recruited if they were 18 years or older, had a primary diagnosis of OCD, a minimum Y-BOCS score of 16, and were fluent in Norwegian. Exclusion criteria for OCD patients were symptoms primarily associated with hoarding, ongoing substance abuse, lifetime bipolar disorder or psychosis, suicidal ideation, intellectual disability based on previous medical history, unwilling to refrain from anxiety reducing substances such as benzodiazepines) or alcohol during the two days of exposure. No participants could have pacemakers or other contraindications for MRI, epilepsy or pregnancy. After initial data processing the baseline sample consisted of 34 OCD patients (nine used psychotropic medication; seven serotonin re-uptake inhibitors (SRI) only, one SRI plus an antipsychotic drug, one methylphenidate) and 28 healthy controls. Twenty-eight OCD patients (six used SRI only and one used methylphenidate) and 19 healthy controls were included for longitudinal analyses (See Supplemental Figure 1 for flow diagram). The study was approved by the Regional Ethics Committee for South-Eastern Norway and all participants provided informed written consent in accordance with the Declaration of Helsinki.

Treatment

The Bergen 4-Day Treatment (B4DT) is an individually tailored and therapist-assisted exposure-based treatment format delivered during four consecutive days. Effectiveness

studies of both adult and adolescent OCD patients (29, 33) have shown that around 90% of the patients respond and 75% remit one week after treatment. The improvements in symptom severity are durable between three months to four years of follow-up (30, 31), and have been replicated in independent samples of patients and therapists (28, 34), new clinics (35), a randomized controlled trial (36), and is currently being implemented in Sweden, Iceland, and the United States. The B4DT is delivered in a group setting of three to six patients with a 1:1 ratio between patients and therapists. The first day consists of a three-hour group session with psychoeducation and planning of individual exposure tasks. The next two days consist of eight to ten hours of therapist-assisted exposure in a wide range of relevant settings, including in patients' home, work, or local area. Individualized exposures are intermixed with meetings between all patients and therapists. Patients are also instructed to perform exposure as homework between the second and fourth day. The last day consists a three-hour session focused on summarizing the treatment, relapse prevention, and planning self-exposure for the next three weeks. A core principle of B4DT is the "Lean into the anxiety" (LET) technique where patients are taught to actively seek out anxiety-provoking situations without regulating their emotions by performing compulsions, safety behaviors, or subtle avoidance. Instead, patients are instructed to use both planned exposure tasks and spontaneous opportunities to do something that is incompatible with having the disorder, e.g. increase feelings of uncertainty. Therapists act as coaches to support the patient and facilitate relevant exposure tasks while gradually leaving the responsibility to the patient. Therapists work together as a team, and can flexibly reallocate therapists to provide struggling patients with the most experienced therapists (see Kvale, Hansen (35) for more information).

Clinical Assessments

The Structured Clinical Interview for DSM-IV (SCID) (37) was used to diagnose current and lifetime mental health disorders in OCD patients and to rule out any current or lifetime disorders in healthy controls. The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (38) was used as the primary measure of symptom severity in OCD patients. Both the SCID and Y-BOCS were performed by a trained clinical psychologist, and patients were assessed by an external rater that was not part of the treatment. Clinically significant change was calculated based on international consensus criteria for the Y-BOCS (39), where response required a minimum of 35% improvement and remission required a total score under 13. All participants also completed the Obsessive Compulsive Inventory Revised (OCI-R) (40), Patient Health Questionnaire 9 (PHQ-9) (41) and Generalized Anxiety Disorder 7 (GAD-7) (42) for symptoms of OCD, depression and anxiety, respectively.

MRI acquisition, preprocessing and construction of connectivity matrices

Scanning was performed on a 3T General Electric Discovery MR750 (GE Healthcare, Milwaukee, Wisconsin, USA) using an eight-channel head coil. A T1-weighted image was acquired using a 256x256 matrix, 192 slices, voxel size= 1x1x1mm, TE=3ms, TR=7s, flip angle=12°, FoV=256mm. Resting state functional magnetic resonance imaging (fMRI; not including most of the cerebellum) was acquired using 160 echo-planar images (EPI; 64x64 matrix, 34 slices, slice thickness=3mm (gap=0.3mm), TE=30ms, TR=1.8s, FoV=220mm, flip angle=80°, voxel size=3.44x3.44x3.3mm, interleaved slice acquisition). Four dummy volumes were acquired and automatically discarded to reach steady-state magnetization. Participants were instructed to lie still with closed eyes and not fall asleep.

Participants were excluded if they showed movement exceeding a mean relative root mean square (RMS) displacement of 0.2mm or more than 20 volumes with RMS above 0.25mm (26). FMRIB's Software Library version 5.0.10 (FSL) (43) was used to preprocess

the fMRI data. Briefly, EPI volumes were motion corrected (using 6 regressors and ICA-AROMA) (44), smoothed (5mm kernel), nuisance signals in white matter and cerebrospinal fluid were removed using linear regression, and the volumes were then high-pass filtered (100s cut-off). Global signal regression was not used due to its controversial effects on the connectivity between nodes (27). EPIs were registered to the T1-weighted image and subsequently parcellated into 226 nodes. Two–hundred-and-ten cortical, as well as four bilateral dorsolateral and ventromedial putamen nodes, were defined based on the Brainnetome Atlas (45). The bilateral thalamus, caudate nucleus, pallidum, hippocampus, amygdala, and nucleus accumbens were individually segmented using FSL FIRST (46). FSL was also used to calculate voxels with signal intensities in the lowest quartile and nodes with less than four voxels with adequate signal, where then discarded to ensure the robustness of nodal connections. This resulted in 200 nodes with adequate signal across all participants (see Supplemental Table 2 for a complete list). Time-series were then extracted from each node, and we used Morlet wavelet coherence (47) to calculate the coherence between each pair of nodes to construct a weighted connectivity matrix per subject and time point. We chose the frequency range between 0.06 to 0.125Hz as connections in this range has been suggested as most reliable, robust to artifacts, and sensitive to neuropsychiatric disorders (20, 48). The resulting fully weighted connectivity matrices were not thresholded in order to maximize the contained information and to avoid arbitrary sparsity levels (49, 50), and were used to calculate static network measures using in-house scripts and the Brain Connectivity Toolbox (version 2017-15-01)(19). For dynamic measures we used 136 sliding windows to assess variation during scanning (window size=25 TRs, each window was shifted 1 TR) (51), and dynamic measures were then calculated (22). Analyses were performed in MATLAB R2017a (MathWorks, Inc, Natick, MA, USA). We assigned all nodes to the visual, dorsal attention (DAN), limbic, SMN, VAN, FPN, or DMN subnetworks (See Supplemental Table 2) based

on the atlas by Yeo and colleagues (52-54). Between-subnetwork connectivity was tested by averaging the connectivity between the nodes of each subnetwork pair.

Graph measures

Based on previous studies of OCD we calculated efficiency, clustering coefficient, modularity, strength, and betweenness centrality as static graph measures. For dynamic measures we used flexibility (switches in module allegiance), promiscuity (switches in allegiance between multiple modules), temporal correlation coefficient (stability of connections between neighboring nodes, similar to clustering coefficient) (22), and temporal variation in efficiency and clustering coefficient (55). We also calculated total functional connectivity, as it may affect group comparisons of other graph measures (56). See Figure 1 for examples and Supplemental Methods for definitions.

Statistical analysis

Changes in clinical measures were analyzed using ANOVAs and t-tests, and Cohen's d effect size was calculated (57). Group differences in graph measures were analyzed using permutated Wilcoxon-Mann–Whitney tests in the coin package in R (version 3.5.0), while main effects of time, group and group × time interactions were performed using the nparLD package (58). NparLD applies a non-parametric rank-based model (58), and p-values were calculated using a modified F-statistic that is well suited to small sample sizes (59). Within-group changes over time were analyzed using Wilcoxon signed-rank tests. P-values for Wilcoxon-Mann–Whitney and Wilcoxon signed-rank tests were calculated based on 10,000 Monte Carlo resamples. Kendall's tau was used to correlate Y-BOCS, graph measures, and changes in these variables over time. We used the false discovery rate (FDR; $q<.05$) (60) to correct for multiple comparisons, and report corrected results except when otherwise

specified. P-values of Wilcoxon signed-ranks were not corrected but were only performed when time or group × time effects were significant. Partial eta squared (ηp2) was calculated for time, group and group × time effects using the modified F-statistic (61), and we calculated the r effect size for Wilcoxon-Mann–Whitney and Wilcoxon signed-rank tests (62) (small r≥0.10, medium r≥0.30, large r≥0.50) (63). A positive r for Wilcoxon-Mann–Whitney tests indicates that the value was greater in OCD patients than healthy controls. For Wilcoxon signed-rank tests a positive r indicates an increase over time. As previous studies have shown effects of SRIs on limbic, frontal and striatal activation and connectivity (10, 12, 23, 64), we investigated graph measures in both the entire OCD sample and in unmedicated patients only. We also explored whether comorbid mood and anxiety disorders and age of onset were related to changes in graph measures in OCD patients.

Results

Clinical and demographic characteristics

Patients and healthy controls were matched on sex, age, handedness and educational achievement both before and after treatment (p>.58) (Table 1 and Supplemental Table 3). OCD patients scored significantly higher on OCI-R, PHQ-9, and GAD-7 (Table 1).

Treatment effectiveness

One week after B4DT, OCD patients showed significantly lower severity scores on the Y-BOCS (t(27)=11.77, d=2.93, p<.01), OCI-R (t(24)=6.66, d=1.28, p<.01), GAD-7 (t(24)=3.74, d=0.73, p<.01), but not PHQ-9 (t(24)=1.93, d=0.40, p=.07) compared with baseline. Seventeen (61%) OCD patients were in remission, 7 (25%) responded, while only 4 (14%) showed no clinically significant change. There were no significant group × time effects between unmedicated and medicated OCD patients on any clinical measure. Healthy controls

showed no significant changes in OCI-R (t(17)=0.34, p=.74), PHQ-9 (t(18)=0.28, p=.78), or GAD-7 (t(18)=0.42, p=.68) scores after one week.

Group differences at baseline

Movement parameters (relative RMS displacement) were not significantly different between OCD patients and healthy controls at baseline (t(60)=-1.52, p=.13) or after one week (t(45)=.22, p=.83). There were no significant differences after FDR-correction between the groups in static or dynamic measures at baseline. At an uncorrected threshold, OCD patients showed less variation in connectivity between the FPN and DMN subnetworks compared to healthy controls before treatment (r=-0.26, p=.04), which was no longer significant after treatment (r<0.01, p=.99). In addition, unmedicated OCD patients showed more connectivity between the FPN and limbic subnetwork compared to healthy controls (r=0.30, p=.03), which was no longer significant after treatment (r=-0.15, p=.36).

Longitudinal effects

At the global level

Static In the entire sample of OCD patients and healthy controls we found significant effects of time for increased global efficiency and average clustering coefficient (ηp2=0.17, p<.01 for both). There were no between-group differences in total functional connectivity at baseline (r=0.05, p=.69) or after one week (r=-0.08, p=.60), but there was a significant effect of time for increased total functional connectivity (ηp2=0.14, p<.01)(See Table 2 for detailed information). When medicated OCD patients were excluded from the analyses significant group × time effects were found for efficiency, clustering coefficient, and total functional connectivity (Table 3). There were no significant effects for modularity.

Dynamic In the entire sample of OCD patients and healthy controls we found a significant effect of time for the mean temporal correlation coefficient (ηp2=0.19, p<.01), driven by an increase in healthy controls (r=0.53, p=.02), while OCD patients showed no significant change over time (r=0.1, p=.62). When medicated OCD patients were excluded from the analyses significant group × time effects were found for the temporal correlation coefficient. There were no significant effects for flexibility or promiscuity.

At the subnetwork level

Static In the entire sample of OCD patients and healthy controls we found a significant effect of time for increased connectivity between the SMN and VAN (ηp2=0.20, p=.01), which was not observed when medicated OCD patients were excluded from the analysis. We also found a significant group × time effect for connectivity between the FPN and limbic subnetwork (ηp2=0.16, p=.03). However, neither OCD patients (r=-0.22, p=.24) nor healthy controls (r=0.29, p=.23) showed no significant changes over time in within-group analyses. When comparing unmedicated OCD patients to healthy controls we also found the significant group × time effect for connectivity between the FPN and limbic subnetwork (ηp2=0.19, p=.03, see Figure 2 and Table 3), where unmedicated OCD patients showed significantly reduced FPN-limbic connectivity over time (r=-0.44, p=.04) while healthy controls showed no significant change (r=0.29, p=.23).

Significant time effects were also found for increased efficiency in the SMN (ηp2=0.11, p=.04) and VA (ηp2=0.12, p=.04) and for increased clustering coefficient in the SMN (ηp2=0.18, p=.01), VAN (ηp2=0.16, p=.01), DMN (ηp2=0.12, p=.02) and limbic subnetwork (ηp2=0.09, p=.04). When medicated OCD patients were excluded from the analyses significant group × time effects were found for SMN, VAN, FPN, limbic and DMN clustering as well as limbic efficiency.

Dynamic In the entire sample of OCD patients and healthy controls we found a significant effect of time for the SMN with increased variation in efficiency (ηp2=0.21, p<.01). When medicated OCD patients were excluded from the analyses significant group × time effects were found for variation in SMN efficiency and clustering (Table 3).

At the regional level

Static No significant time or group × time effects were found in the entire sample of OCD patients and healthy controls, nor when medicated OCD patients were excluded from the analyses.

Dynamic No significant time or group × time effects were found in the entire sample of OCD patients and healthy controls. The analysis in unmedicated OCD patients versus healthy controls showed a significant group × time effect for flexibility of the right sgACC (ηp2 = 0.18, p = .03, see Figure 2 and Table 3), driven by a reduction in OCD patients (r=-.52, p=.02) while healthy controls showed no significant change (r=0.37, p=.11). There was also a significant effect of time with reduced flexibility in the right dorsolateral putamen (ηp2=0.21). There were no significant effects for variation in clustering coefficient, strength, flexibility or promiscuity in other regions.

Relation between graph measures and clinical characteristics in OCD patients

We found no significant correlations between pre-treatment Y-BOCS, and graph measures nor between changes in symptom severity and graph measures. Secondary analyses showed that the presence of comorbid anxiety disorders and the age at onset of OCD were not significantly related to change in FPN-limbic connectivity or sgACC flexibility. Changes in right sgACC flexibility in depressed versus non-depressed OCD (measured using the SCID) patients showed a significant group × time effect (F(1,19)=6.11, ηp2=0.26, p=.01), which was

driven by a larger decrease in depressed (r=-0.89, p=.02) than non-depressed (r=-0.23, p=.41) patients.

Discussion

This is the first study to investigate treatment-induced changes of the functional connectome of OCD patients after concentrated ERP, and the first to utilize dynamic graph measures in OCD patients. The concentrated treatment format allowed for investigating rapid changes after only one week. Analyses of the whole sample, including both medicated and unmedicated patients, showed few significant results. After excluding medicated patients, however, we found significant reductions in FPN-limbic connectivity and sgACC flexibility after treatment in OCD patients. The connectivity between the FPN and limbic subnetwork was also higher in unmedicated OCD patients than healthy controls before treatment but only at an uncorrected threshold. Our findings suggest that concentrated ERP leads to a direct reduction and normalization of frontoparietal-limbic topology and a more stable network state in the sgACC after only one week of concentrated ERP.

Connectivity and flexibility of the FPN has been linked to cognitive control in healthy controls (50, 65, 66). OCD patients show altered connectivity within the FPN, between the FPN and other subnetwork, and altered FPN activation and fronto-limbic connectivity during executive and emotion regulation tasks (16, 32, 67-70). Decreased FPN-limbic connectivity after treatment could result from a reduced demand for top-down cognitive control, less bottom-up limbic interference, or a combination of both (71, 72). This is consistent with current models of CSTC, fronto-limbic and fronto-parietal circuits in OCD (6, 7) and the focus on emotion regulation in B4DT. Changes in FPN-limbic functional connectivity may also overlap with less effective structural connections between limbic regions (such as the amygdala and temporal pole) than healthy controls (73), which deserves further investigation. In line with our results, previous studies have also shown that medication use may obscure abnormal connectivity and activation in OCD, especially in limbic areas (10, 12, 23).

The sgACC is involved in many mental processes, including emotional and interoceptive processing through its striatal and thalamic projections and is a major node within the affective CSTC circuit (6, 72). OCD patients show greater sgACC activation and connectivity with striatal and limbic regions than healthy controls (8-10). The reduction in flexibility of sgACC after treatment could therefore represent a shift to a more stable network and less effort towards bridging communication between regions involved in obsessive thoughts, emotion regulation, and compulsive behaviors. The sgACC has been implicated in altered network communication with limbic and DMN subnetworks in depression (74). Patients who were depressed before treatment showed larger decreases in sgACC flexibility compared to non-depressed patients, which suggests that a more stable network state in this region is particularly relevant in OCD patients with depression.

We expected OCD patients to show less global and subnetwork efficiency and clustering coefficient before treatment than healthy controls (and more in the limbic subnetwork), normalizing after treatment. However, we found no difference between the groups at any time-point while only healthy controls showed a significant increase over time, particularly in the SMN. Previous studies have also found increased connection strength between visual, frontal, parietal, and posterior cingulate cortices and the rest of the brain in healthy controls after 12-14 weeks (21, 25). Similar increases and variation have also been found in other studies of healthy controls (75). These may be explained by 1) OCD patients showing less normal increases in network integration and clustering over time, 2) controls reacting differently to being in the scanner for the second time, or 3) controls showing a greater increase in total functional connectivity. Unexpectedly, several of our hypothesized baseline differences between OCD patients and healthy controls were not found in the present study, which may result from methodological differences between studies and differences in clinical characteristics of the included participants. Several unexpected group × time effects

were also found for some measures where there was no significant difference between OCD patients and healthy controls before or after treatment. These indicate subtle but opposing changes in the groups over time. Future comparisons over longer time periods are needed to determine the role and stability of these network characteristics over time.

The present study has some limitations. First, the limited sample size required balancing power and controlling sample heterogeneity (such as medication status). Having few non-responding patients also limited the correlations between treatment outcome and graph measures, and the lack of a comparison condition leaves a small possibility that the changes are not specific to psychological treatment. A longer fMRI session may have improved the reliability of the static measures and allowed for more windows in the dynamic measures (76), but the duration was similar to other relevant studies of OCD (12, 77). We were also unable to rule out intermittent sleeping during scanning. Graph measures can be influenced by movement during scanning, graph thresholding, preprocessing, and scanning duration (26, 27). We therefore applied strict exclusion criteria for movement and applied independent component and regression analyses to further correct for movement and physiological noise. However, there is currently no consensus on how to process and analyze rs-fMRI data, and it is likely that some of the variation in imaging studies are due to differences in preprocessing and analyses. More research is also needed to determine the role of different clinical characteristics (e.g. medication use, comorbidity, severity) in connectome abnormality and plasticity.

Our results show that concentrated ERP for OCD leads to rapid decreases in FPN-limbic connectivity and flexibility in the right sgACC in unmedicated OCD patients after only a week, suggesting a more independent topology and stable network state after effective treatment. In line with previous studies, we found that SRI use was not related to treatment outcome but may obscure limbic abnormalities and treatment-related changes over time in

limbic regions. Future studies should compare the short-term effects of symptom reduction and long-term effects of normalized behavior, in addition accounting for the effects of medication use, on the connectome.

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Disclosures

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Figure legends

Figure 1 *Levels of network analyses and model of selected graph measures*

Topological model of hypothetical nodes of a brain. Panel A: Illustration of included nodes at the global, subnetwork, and regional levels. The rostral PFC was chosen as it is part of the DMN and is easily visible on the same axial slice. Panel B: Shows how nodes can be divided into functional modules. Global efficiency measures how easily information can cross from one side of the network to the other. Clustering coefficient measures if a node's neighbors are also neighbors of each other and indicates functional segregation. Betweenness centrality indicates a nodes importance for efficient network communication. Panel C: Flexibility is how often a node switches which module it belongs to. Panel D: Promiscuity is how often a node switches between multiple different modules. Panel E: Temporal correlation coefficient is how stable the connections of a node's neighbors are over time.

Figure 2 *Frontoparietal-limbic connectivity and subgenual ACC flexibility over time*

Panel A: Mean (± standard error) connectivity between the frontoparietal and limbic subnetworks over time where unmedicated OCD patients showed more connectivity before treatment relative to healthy controls, which normalised after treatment. Healthy controls did not show any significant change over time. Frontal regions of the FPN (blue) and frontal and temporal regions of the limbic subnetwork (red) are overlaid on MNI template. Panel B: Mean (± standard error) flexibility of the right sgACC over time, where unmedicated OCD patients showed a decrease after treatment relative to healthy controls. Healthy controls did not show any significant change over time. SgACC (red) is overlaid on MNI template.

Tables

Table 1 *Demographics and clinical information of sample*

	OCD (n = 34) n (%)	HC (n = 28) n (%)	χ^2	p-value*
Sex			5.37	.60
Male	14 (41)	9 (32)		
Female	20 (59)	19 (68)		
Handedness			5.89	.58
Right	33 (97)	26 (93)		
Left	1 (3)	2 (7)		
OCD onset				
Childhood	15 (44)	NA		
Adult	19 (56)	NA		
Comorbid disorders				
MDD	10 (29)	NA		
GAD	11 (32)	NA		
SAD	8 (24)	NA		
SP	4 (12)	NA		
PD±AG	5 (15)	NA		
Hypochondriasis	3 (9)	NA		
Dysthymia	2 (6)	NA		
PTSD	1 (3)	NA		
ADHD	1 (3)	NA		
Somatization disorder	1 (3)	NA		
Pain disorder	1 (3)	NA		
	M (SD)	M (SD)	t	p-value
Age	30.12 (8.84)	30.96 (10.75)	0.34	.74
Education (years)	14.68 (2.40)	14.43 (2.30)	0.41	.68
Before treatment				
Y-BOCS	26.68 (3.97)	NA		
OCI-R	25.21 (9.72)	6.56 (7.87)	6.45	< .01
PHQ-9	11.55 (6.30)	2.41 (1.55)	8.39	< .01
GAD-7	12.79 (5.06)	2.30 (1.90)	10.46	< .01
Mean RMS	.07 (.03)	.06 (.02)	1.61	.13
After one week for 28 OCD and 19 HC				
Y-BOCS	10.96 (6.39)	NA		
OCI-R	13.20 (9.33)	5.78 (7.77)	2.75	< .01
PHQ-9	9.24 (6.55)	2.17 (1.95)	5.10	< .01
GAD-7	9.16 (5.06)	1.83 (2.09)	6.50	< .01
Mean RMS	.07 (.03)	.07 (.02)	-.22	.83

* P-values are not corrected for multiple comparisons. ADHD, Attention-deficit/hyperactivity disorder; AG, Agoraphobia; GAD-7, Generalized Anxiety Disorder-7; HC, Healthy controls; MDD, Major depressive disorder; NA, Not applicable; OCD, Obsessive-Compulsive Disorder; PHQ-9, Patient Health Questionnaire-9; PD, Panic

disorder; PTSD, Post-traumatic stress disorder; RMS, root mean square; SAD, Social anxiety disorder; SP, specific phobia; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

Table 2 *Significant changes in graph measures over time in entire sample of OCD patients (n=28) and healthy controls (n=19)*

	Non-parametric ANOVA*									Within-group comparisons			
	Group			Time			Interaction			OCD		HC	
	F	ηp2	p	F	ηp2	p	F	ηp2	p	p	r	p	r
Global													
Efficiency	0.05	0	.82	9.40	0.17	< .01	2.93	0.06	.09	.76	0.06	.03	0.51
Clustering coefficient	0.06	0	.81	9.27	0.17	< .01	2.97	0.06	.09	.81	0.05	.03	0.52
Temporal correlation coefficient	0.06	0	.75	9.27	0.17	.01	2.97	0.06	.32	.62	0.1	.02	0.53
Total functional connectivity	0.12	0	.73	7.12	0.14	< .01	2.37	0.05	.12	.69	0.08	.06	0.42
Subnetwork													
FPN-limbic connectivity	1.14	0.03	.99	0.18	0.01	.90	8.67	0.19	.03	0.04	-0.44	0.22	0.29
SMN-VAN connectivity	0.07	0	.90	9.83	0.18	.02	1.36	0.03	.32	0.33	0.19	0.02	0.53
SMN-VAN connectivity	0.16	0	.98	11.44	0.2	.01	2.08	0.04	.35	.34	0.19	.01	0.58
SMN efficiency	0.05	0	.99	5.50	0.11	.05	2.34	0.05	.32	0.42	0.16	0.05	0.44
SMN efficiency	0.03	0	.94	5.8	0.11	.04	2.88	0.06	.22	.47	0.14	.05	0.44
VAN efficiency	0.01	0	.99	6.96	0.13	.04	0.54	0.01	.47	0.28	0.21	0.08	0.41
VAN efficiency	0.01	0	.94	5.96	0.12	.04	0.54	0.01	.46	.36	0.18	.12	0.37
SMN clustering	0.02	0	.90	9.94	0.18	.01	3.85	0.08	.15	0.64	0.09	0.02	0.55
SMN clustering	0.02	0	.93	10.01	0.18	.01	4.33	0.09	.15	.58	0.11	.02	0.55
VAN clustering	0.02	0	.90	9.11	0.17	.01	2.06	0.04	.15	0.66	0.09	0.09	0.40
VAN clustering	0.01	0	.93	8.71	0.16	.01	2.03	0.04	.15	.59	0.1	.10	0.39

DMN clustering	0.04	0	.90	5.32	0.11	.04	2.15	0.05	.15	0.85	0.04	0.03	0.49
DMN clustering	0.05	0	.93	6.07	0.12	.02	2.19	0.05	.15	.80	0.05	.04	0.46
Limbic clustering	0.02	0	.90	4.59	0.09	.04	3.47	0.07	.15	0.79	-0.05	0.04	0.46
Limbic clustering	0.01	0	.93	4.56	0.09	.04	2.49	0.05	.15	.90	-0.03	.05	0.45
Variation in SMN efficiency	3.16	0.07	.38	13.43	0.23	< .01	1.00	0.02	.67	0.09	0.33	0.02	0.55
Variation in SMN efficiency	2.36	0.05	.29	11.69	0.21	< .01	1.46	0.03	.59	.14	0.28	.01	0.55
Regional													
None after FDR correction													

*P-values are corrected for multiple comparisons. DMN, Default mode network; FDR, False discovery rate; FPN, Frontoparietal network; HC, Healthy controls; OCD, Obsessive-compulsive disorder; SMN, Somatomotor network; VAN, Ventral attention network.

Table 3 *Significant changes in graph measures over time in unmedicated OCD patients (n=21) and healthy controls (n=19)*

	Non-parametric ANOVA*									Within-group comparisons			
	Group			Time			Interaction			OCD		HC	
	F	ηp2	p	F	ηp2	p	F	ηp2	p	p	r	p	r
Global													
Efficiency	0.30	0.01	.58	5.37	0.12	.02	5.37	0.12	0.02	.54	-0.14	.02	0.51
Clustering coefficient	0.32	0.01	.57	5.29	0.12	.02	5.29	0.12	0.02	.55	-0.14	.02	0.52
Temporal correlation coefficient	0	0	.96	4.99	0.12	.07	7.19	0.16	0.04	.52	-0.15	.02	0.53
Total functional connectivity	0.32	0.01	.57	3.94	0.09	.05	4.52	0.11	0.03	.68	-0.09	.06	0.42
Subnetwork													
FPN-limbic connectivity	1.14	0.03	.99	0.18	0.01	.90	8.67	0.19	0.03	.04	-0.44	.22	0.29
FPN-limbic connectivity	1.14	0.03	.99	0.18	0	.90	8.67	0.19	0.03	.04	-0.44	.23	0.29
SMN clustering	0.20	0.01	.67	6.53	0.15	.05	5.72	0.13	0.04	.76	-0.07	.02	0.55
SMN clustering	0.20	0.01	.66	6.61	0.15	.05	6.33	0.14	0.03	.92	-0.03	.01	0.55
VAN clustering	0.23	0.01	.67	4.96	0.12	.07	5.16	0.12	0.04	.73	-0.08	.09	0.40
VAN clustering	0.20	0.01	.66	4.66	0.11	.08	5.33	0.12	0.03	.78	-0.06	.10	0.39
FPN clustering	0.37	0.01	.67	1.57	0.04	.21	4.70	0.11	0.04	.43	-0.18	.03	0.49
FPN clustering	0.44	0.01	.66	1.20	0.03	.27	4.67	0.11	0.03	.49	-0.16	.04	0.46
DMN clustering	0.18	0.01	.67	2.82	0.07	.16	4.30	0.10	0.04	.48	-0.16	.03	0.49
DMN clustering	0.19	0	.66	3.38	0.08	.11	4.51	0.11	0.03	.50	-0.16	.05	0.46
Limbic clustering	0.30	0.01	.67	1.80	0.05	.21	6.33	0.14	0.04	.19	-0.30	.04	0.46

Limbic clustering	0.23	0.01	.66	1.76	0.04	.23	4.72	0.11	0.03	.26	-0.25	.05	0.45
Limbic efficiency	0.13	0	.72	0.14	0.00	.89	6.85	0.15	.04	.07	-0.39	.09	0.40
Variation in SMN efficiency	2.78	0.07	.48	12.21	0.24	< .01	0.68	0.02	0.51	.10	0.37	.02	0.55
Variation in SMN efficiency	2.36	0.05	.43	11.69	0.21	< .01	1.46	0.03	0.47	.11	0.35	.01	0.55
Variation in SMN clustering	1.97	0.05	.57	7.28	0.16	.04	0.22	0.01	.88	.24	0.27	.10	0.38
Variation in SMN clustering	1.27	0.03	.64	6.48	0.13	.04	0.53	0.01	0.82	.21	0.28	.10	0.38
					Regional								
Flexibility in R sgACC	1.13	0.03	.70	0.14	0	.79	8.53	0.18	0.03	.02	-0.52	.11	0.37
Flexibility in R dorsolateral putamen	0.00	0	.96	10.08	0.21	.01	0.3	0.01	0.77	.09	-0.37	.04	-0.48

*P-values are corrected for multiple comparisons. DMN, Default mode network; FPN, Frontoparietal network; HC, Healthy controls; OCD, Obsessive-compulsive disorder; R, Right; SgACC, Subgenual anterior cingulate cortex; SMN, Somatomotor network; VAN, Ventral attention network