

ORIGINAL ARTICLE

The neural correlates of obsessive-compulsive disorder: a multimodal perspective

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Obsessive-compulsive disorder (OCD) is one of the most debilitating psychiatric conditions. An extensive body of the literature has described some of the neurobiological mechanisms underlying the core manifestations of the disorder. Nevertheless, most reports have focused on individual modalities of structural/functional brain alterations, mainly through targeted approaches, thus possibly precluding the power of unbiased exploratory approaches. Eighty subjects (40 OCD and 40 healthy controls) participated in a multimodal magnetic resonance imaging (MRI) investigation, integrating structural and functional data. Voxel-based morphometry analysis was conducted to compare between-group volumetric differences. The whole-brain functional connectome, derived from resting-state functional connectivity (FC), was analyzed with the network-based statistic methodology. Results from structural and functional analysis were integrated in mediation models. OCD patients revealed volumetric reductions in the right superior temporal sulcus. Patients had significantly decreased FC in two distinct subnetworks: the first, involving the orbitofrontal cortex, temporal poles and the subgenual anterior cingulate cortex; the second, comprising the lingual and postcentral gyri. On the opposite, a network formed by connections between thalamic and occipital regions had significantly increased FC in patients. Integrative models revealed direct and indirect associations between volumetric alterations and FC networks. This study suggests that OCD patients display alterations in brain structure and FC, involving complex networks of brain regions. Furthermore, we provided evidence for direct and indirect associations between structural and functional alterations representing complex patterns of interactions between separate brain regions, which may be of utmost relevance for explaining the pathophysiology of the disorder.

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is one of the most disabling psychiatric conditions, impacting occupational, academic and social functioning¹ and affecting 2 to 3% of the worldwide population.² OCD is characterized by the occurrence of obsessions (intrusive, persistent and inappropriate thoughts, urges or images) and compulsions (repetitive or ritualistic behaviors or mental acts performed to reduce the anxiety caused by the obsessions).^{3,4} Despite the availability of pharmacological and cognitive-behavioral interventions, these treatments are not effective for a significant number of patients.⁵ This highlights the limited understanding of the neurobiological mechanisms of OCD.⁶

The pathophysiology of OCD has been widely conceptualized within the cortico-striato-thalamo-cortical (CSTC) model.⁷ According to this model, tracts from frontal regions project to the striatum and then, travel through direct and indirect pathways to the thalamus and project back to the frontal regions. This model has been corroborated by several reports of structural and functional alterations observed in magnetic resonance imaging (MRI) studies. In particular, volumetric alterations within the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC) and thalamus have been reported in patients (for example, refs. 8–10). Furthermore, early evidence from functional imaging studies indicated an increased metabolism and hyperactivity in several

brain regions in OCD patients during task performance, including the basal ganglia (BG),^{11,12} OFC¹³ and ACC.¹⁴ On the opposite, a decreased activation in the dorsolateral prefrontal cortex (DLPFC)¹⁵ and parietal cortex^{16–19} has been described. Emerging evidence suggests a broader cortical dysfunction, involving structural and functional alterations of the anterior insula, lateral and medial temporal lobe regions.²⁰ Furthermore, recent multimodal meta-analytic evidence highlights the relevance of the cerebellum and the parietal cortex for the OCD pathophysiology.²¹

Resting-state fMRI (rs-fMRI) studies have also provided important biomarkers of OCD. For instance, alterations in the normal patterns of functional connectivity (FC) in resting-state networks (RSNs) have been reported in children with OCD, including a significantly increased connectivity between the dorsal striatum and ventromedial frontal cortex, and a decreased FC between dorsal striatum and medial dorsal thalamus to rostral and dorsal ACC, respectively.²² In addition, increased FC within the auditory and cingulate networks was also reported in a pediatric sample.²³ Adult OCD individuals exhibited decreased FC of the dorsal striatum and lateral PFC, and of the ventral striatum with ventral tegmental area,²⁴ as well as a decreased dorsal ACC-right anterior operculum FC during rest.²⁵ Altered FC in the default-mode network (DMN) has been reported, particularly its connections with OFC and ACC,^{25,26} and with middle frontal gyrus and

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putamen.²⁶ Moreover, FC alterations between frontoparietal/ventral attention network (VAN) and the structures comprising the DMN, thalamus, lateral frontal cortex and somatosensory/motor regions were observed.²⁰ Using a graph-theory approach, drug-free patients were found to present a diminished FC between the DMN and frontoparietal regions;²⁷ interestingly, these alterations were abolished after SSRI treatment.

Altogether, the abovementioned results suggest that a large variety of brain areas and circuits are involved in the pathophysiology of the disease. In particular, FC abnormalities have been mainly observed in orbitofrontal, cingulate, striatal and default-mode regions. Nevertheless, these results were observed using theoretically driven investigations. To the best of our knowledge, the use of whole-brain exploratory approaches to assess FC patterns in OCD patients is scarce, with few notable exceptions.^{28,29} In these studies, OCD patients were characterized by a reduced FC within the lateral prefrontal cortex and an increased FC within the dorsal striatum and thalamus, as well as with a hyperconnectivity between basal ganglia and cerebellar regions. Nevertheless, none of the abovementioned strategies integrated structural findings in their analyses. Thus, despite the variety of studies investigating structural and functional MRI patterns in OCD patients, a comprehensive integration of distinct modalities is still unclear. The use of this multimodal/integrative approach may be of utmost relevance, as it may provide useful information on how distinct MRI modalities (that is, brain structure and function) are associated with each other.³⁰ Consequently, it will enable a further exploration of our understanding of the pathophysiological core features of OCD. With this purpose, we conducted a multimodal study, using voxel-based morphometry and whole-brain functional connectivity analyses, respectively, in which structural and FC data were integrated in mediation models. We hypothesize that OCD patients will be characterized by disrupted structural and FC patterns of large-scale brain networks, as manifested by alterations at the whole-brain level. Furthermore, in accordance with recent developments on the study of OCD, it is anticipated that FC alterations will be observed in networks comprising regions outside of the CSTC model.

MATERIALS AND METHODS

Participants

A sample of 80 subjects (40 OCD patients, 40 controls) participated in this study. Healthy controls were recruited to match OCD patients for age, sex, educational level and ethnical origin. All the participants were right-handed and had no history of neurological or comorbid disorders. OCD patients were characterized with a comprehensive clinical assessment. The diagnosis of the disorder was established by experienced psychiatrists, using a semi-structured interview based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)-TR. Then, the Mini-International Neuropsychiatric Interview (MINI), a short structured diagnostic interview, was administered to confirm OCD diagnosis and to identify any current psychiatric (non-OCD) comorbidity. Patients that met criteria for additional Axis I psychiatric disorders at the time of the study were not included in this study. The severity of the disease was assessed using the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS³¹). Hamilton Anxiety Rating Scale (HAM-A) and Hamilton Depression Rating Scale (HAM-D) were used to assess anxiety and depression symptoms, respectively. All OCD patients were under medication: the majority of patients (72.2%) was receiving SSRI medication (fluvoxamine, 150–300 mg day⁻¹; fluoxetine, 40–80 mg day⁻¹; sertraline: 100–200 mg day⁻¹), 11.1% of the sample was receiving TCA (clomipramine, 150–300 mg day⁻¹), 16.7% was receiving combined pharmacological intervention. All the patients were receiving stable doses for at least three months prior to the imaging session. The sample characterization is presented on Table 1.

The study was conducted according to the Declaration of Helsinki principles and was approved by the Ethics Committee of Hospital de Braga (Portugal). The study goals were explained, and written informed consent was obtained from each participant.

Table 1. Socio-demographic and clinical characteristics of patients with OCD and HC

Characteristic	OCD (n = 40)	HC (n = 40)	Difference
Age, years	26.28 ± 6.62	26.45 ± 5.39	$t_{(78)} = 0.13$, $P = 0.897$
Education, years	13.53 ± 2.25	14.63 ± 3.20	$t_{(78)} = 1.78$, $P = 0.079$
Sex, n (%) males	13 (32.5%)	13 (32.5%)	—
Y-BOCS, total score	24.93 ± 5.69	—	—
Y-BOCS, obsessions	13.48 ± 3.10	—	—
Y-BOCS, compulsions	11.45 ± 3.36	—	—
Age of onset, years	19.41 ± 6.27	—	—
HAM-A, total score	5.10 ± 4.40	—	—
HAM-D, total score	6.05 ± 4.70	—	—
<i>Medication</i>			
% SSRI	72.20%	—	—
% TCA	11.10%	—	—
% combined	16.70%	—	—
Time with medication, months	23.19 ± 28.75	—	—
Motion spikes	7.35 ± 3.95	6.35 ± 3.32	$t_{(78)} = -1.23$, $P = 0.224$

Abbreviation: HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; HC, healthy controls; OCD, obsessive-compulsive disorder; Y-BOCS, Yale–Brown Obsessive Compulsive. Values are presented as mean ± s.d. Spikes are volumes with high motion, discarded while estimating connectivity patterns.

MRI protocol

The imaging sessions were performed at Hospital de Braga using a clinically approved 1.5 T Siemens Magnetom Avanto MRI scanner (Siemens, Erlangen, Germany) equipped with a standard 12 channel receive-only head coil. Details on the imaging parameters are described in the Supplementary Information.

Volumetric analysis

Before any data processing and analysis, all the acquisitions were visually inspected to confirm that they were not affected by significant artifacts and that participants had no gross anatomical abnormalities. For the volumetric analysis, a Voxel-Based Morphometry (VBM) analysis was performed with FSL-VBM (ref. 32, <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM>), an optimized VBM protocol³³ implemented using tools from the FMRIB Software Library (FSL v5.0.9, www.fmrib.ox.ac.uk/fsl), using the recommended analytical pipeline (Supplementary Information).

Data preprocessing of functional data

Data preprocessing was performed using FSL tools. Images were corrected for slice timing using the first slice as reference and then motion corrected by aligning every volume with the mean volume using a rigid-body (six degrees of freedom) spatial transformation. As a means to further reduce the possible contamination of motion on functional connectivity, motion scrubbing was performed, to identify and exclude time points in which head motion could have a critical impact. Following the recommendations from Van Dijk *et al.*³⁴ only participants with < 20 outlier time points were included in the analysis, ensuring that more than 5 min of motion-free data was obtained for each subject. None of the participants exceeded head motion higher than 2 mm in translation or 1° in rotation. Images were non-linearly normalized to the MNI standard space using an indirect procedure (Supplementary Information). Linear regression of motion parameters, mean white-matter (WM) and cerebrospinal fluid (CSF) signal and motion outliers was performed to reduce motion related variance in fMRI signals and the residuals of the regression were used for the subsequent analysis.^{35,36} Finally, images were spatially smoothed with a Gaussian kernel of 8 mm full-width at half-maximum (FWHM) and band-pass filtered (0.01–0.08 Hz).

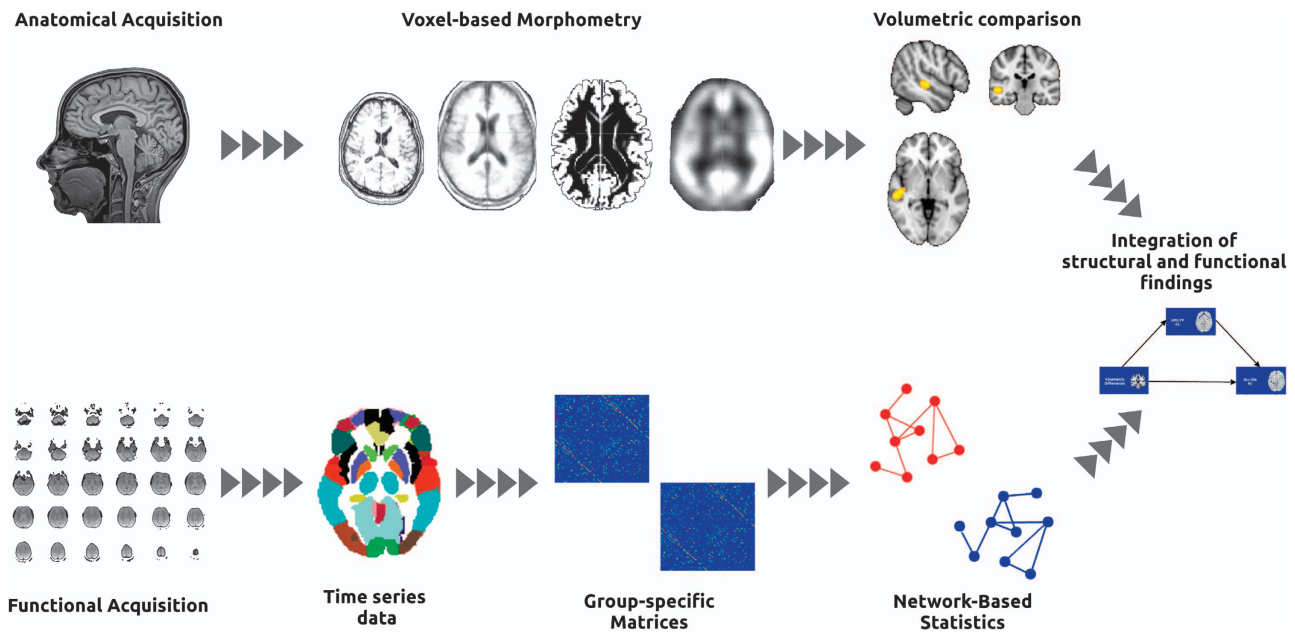


Figure 1. Overview of the methodological approach. Structural and functional magnetic resonance imaging (MRI) sequences were acquired. For the structural acquisitions, a voxel-based morphometry analysis was conducted to detect clusters with significantly between-group differences. For the functional acquisitions, the time-series of Anatomical Automatic Labelling (AAL) cortical and subcortical brain regions was extracted to create group-specific matrices, corresponding to the correlation between regions. Afterwards, a network-based statistic approach was implemented to detect networks with significantly different functional connectivity between groups. As the final step, the structural and functional results were analyzed in integrative models, using mediation analyses.

Whole-brain connectome

Whole-brain functional connectomes were built by extracting the mean time-series of 116 cortical, subcortical and cerebellar regions from the Anatomical Automatic Labelling (AAL) atlas.³⁷ A symmetric adjacency matrix R was then produced, where each cell r_{ij} corresponded to the correlation coefficient (r) between the time-series of regions i and j . This matrix was then transformed with Fisher's r -to- Z transformation to convert Pearson coefficients r to normally distributed Z -values. Individual matrices were then aggregated for further statistical analysis.

Statistical analysis

Statistical group comparisons on volumetric and functional MRI data were conducted using two-samples t -tests, adjusted for confounding effects. For the different analysis, sex and age were used as between-subjects' covariates.

VBM analysis was performed voxel-wise with a General Linear Model (GLM) using a non-parametric permutation procedure as implemented in the randomise tool from FSL.³⁸ Threshold-free cluster enhancement (TFCE) was used to detect widespread significant differences, whereas controlling the family-wise error rate (FWE-R) at $\alpha=0.05$. Each contrast underwent 5.000 permutations.

The identification of significantly different FC subnetworks between groups at the whole-brain connectome was performed through the network-based statistic (NBS) procedure, implemented with NBS.³⁹ The differences between the adjacency matrices of each group were estimated with 5.000 random permutations, based on two different thresholds for significance: $\alpha=0.001$ and $\alpha=0.0001$. Networks were considered significant at $\alpha=0.05$ family-wise error (FWE) corrected. BrainNet Viewer (<http://www.nitrc.org/projects/bnv>) was used to display significant networks.⁴⁰

Associations between symptoms' severity and structural/functional findings were evaluated computing Pearson correlations between total Y-BOCS score and findings significantly different between groups.

With the goal of integrating structural and functional findings, mediation models were established. For these models, direct (that is, the impact of the independent on the dependent variable) and indirect effects (that is, the impact of one proposed mediator variable on the key relationship) were evaluated. For both approaches, bootstrap sampling was implemented to generate bias-corrected 95% confidence intervals to estimate indirect and interactive effects.

An overview of the methodological pipeline is summarized on Figure 1.

RESULTS

Sample characteristics

As shown in Table 1, the groups are similar with respect to sex, age and education level. As represented, all the participants were taking medication. The Y-BOCS total score ranged from 11 to 35 ($M=24.93$, $s.d.=5.69$). The groups did not differ on the number of motion outliers ($t_{(78)}=-1.23$, $P=0.224$).

Volumetric analysis

Results from the VBM analysis revealed that OCD patients had significantly reduced volumes in one cluster comprising 394 voxels with peak on the right temporal middle gyrus, extending to the superior temporal gyrus (Figure 2). We will refer to this region as the superior temporal sulcus (STS). No results of volumetric increases in OCD patients were found.

Whole-brain functional connectivity

Using the most restrict threshold ($P < 0.0001$), it was noted that OCD patients displayed significantly reduced FC in two subnetworks with short-range configurations: the first subnetwork (orbitofrontal-temporal pole subnetwork, OFC-TM) comprised anterior regions, including the bilateral medial orbitofrontal cortex (mOFC), bilateral temporal poles and the subgenual anterior cingulate cortex (sgACC) (Figure 3a; $P=0.010$); the second subnetwork (occipital-sensorimotor, Occ-SM) was formed by the connection between left postcentral and bilateral lingual gyri (Figure 3a; $P=0.045$). Using the less restrict threshold ($P < 0.001$), it was observed that these subnetworks were aggregated in a main single network with wide-range properties, which was also constituted by edges connecting occipital and sensorimotor brain regions and also involving edges connecting the temporal middle gyrus to the mOFC (Figure 3b; $P=0.039$). In contrast, even though no networks with significantly different FC patterns were identified with the more restrict threshold, using the less restrict threshold, a network (thalamic-occipital, Thal-Occ) with marginally

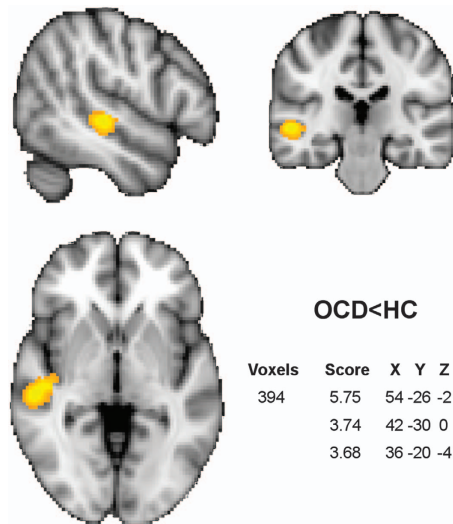


Figure 2. Volumetric differences obtained using a voxel-based morphometry (VBM) analysis. Obsessive compulsive disorder (OCD) patients display significantly reduced volumes in one cluster (with 394 voxels), with peak on the middle temporal gyrus (MTG, $t_{(78)} = 5.75$).

significant increased FC ($P = 0.057$) in OCD patients was identified, encompassing edges connecting the thalamus to occipital inferior, lingual and fusiform gyri (Figure 3d).

Associations between symptom's severity and structural/functional findings

The Y-BOCS total score revealed a significant negative association with the fronto-temporal subnetwork with decreased FC in OCD patients ($r = -0.325$, $P = 0.040$). No associations between symptoms' severity and the other functional and volumetric findings were found.

Mediation effects between structural and functional findings

Bivariate correlations revealed that the volumetric and FC findings were significantly associated (Supplementary Table 1), enabling the test for mediation effects. Different models were conducted, using the volumetric differences as either independent or dependent variables. It was observed that, controlling for confounding effects (sex and age), the mean FC of the OFC-TP subnetwork significantly mediated the association between volumetric differences and the mean FC of the Occ-SM subnetwork (Figure 4a), as observed by a significant indirect between these variables. On the other hand, we could also observe that there was a significant indirect effect of the mean FC of the Thal-Occ subnetwork on volumetric differences within the STS, which was mediated by two mediator variables, corresponding to the mean FC of the Occ-SM and OFC-TP subnetworks (Figure 4b).

DISCUSSION

In this work, we conducted an exploratory multimodal MRI investigation to study volumetric and FC patterns in OCD patients. We observed that OCD patients display volumetric reductions of one cluster comprising the right medial and superior temporal gyri and significantly altered FC in distinct subnetworks, particularly a reduced FC in networks connecting the medial OFC, temporal poles, lingual and postcentral gyri; and on the opposite, patients had increased FC in a network composed of connections involving the thalamus and occipital regions. Mediation analyses

revealed that the association between structural findings and specific FC networks were mediated by other FC networks.

Volumetric alterations in OCD patients

We observed that OCD patients display volumetric reductions of one cluster with peak on the right STS, extending to both the medial and superior temporal gyri. This result is corroborated by previous reports, which implicated the superior temporal cortex on the pathophysiology of the disease.⁴¹ Furthermore, in a meta-analytic investigation, it was demonstrated that OCD patients display a reduction of the middle temporal gyrus during the aging process.⁴²

Decreased functional connectivity in OCD patients

In our study, a FC network comprising connections between bilateral mOFC and bilateral temporal pole, as well as between the left temporal pole and the sgACC, revealed decreased FC in OCD patients. The mOFC is functionally connected with default-mode network, autonomic and subcortical regions, including the ventral striatum, amygdala and the hippocampus,^{43,44} being relevant for multiple psychological processes, including episodic memory, reward, decision-making and fear.^{43,45} Previous studies demonstrated bilateral volume reductions⁴⁶ and hypo-functioning of the mOFC during extinction recall in OCD.⁷ Furthermore, the temporal pole, is directly linked to prefrontal brain regions, through a large white-matter tract, the uncinate fasciculus. Owing to its dense connections with the amygdala and the OFC, the temporal pole is considered an important hub of the affective brain circuit.⁴⁷ The temporal pole, together with the sgACC, were implicated in the mental effort to overcome fear.⁴⁸ With respect to OCD pathophysiology, these nodes have been previously associated with the severity of harm/checking symptoms⁴⁹ and dysfunctional beliefs.⁵⁰ A recent report also revealed a decrease in the structural connectivity among these regions in OCD, highlighting the role of emotional processing on the clinical manifestations of the disorder.⁵¹ Altogether, and due to the fact that this subnetwork was significantly associated with the severity of OCD symptoms, it seems reasonable to hypothesize that the reduced link between OFC and these 'affective' hubs may contribute to a deficient emotional processing and a consequent impaired regulation of the anxiety following obsessive thoughts.

Another subnetwork with decreased FC in OCD patients was composed of edges involving bilateral lingual gyrus and the left postcentral. Previous studies reported alterations in functional⁵² and structural⁵³ connectivity patterns of this region in OCD patients. The lingual gyrus was proposed to be involved in the processing of emotionally charged visual stimuli⁵⁴ and with the generation of somatic arousal,⁵⁵ which is typically dysregulated in disorders of the obsessive-compulsive spectrum.⁵³ It has been recently hypothesized that its activity is tightly linked to the phenomenology of OCD, where, for instance, intrusive thoughts or images of dirt, provoke strong emotional responses in patients with contamination obsessions.⁵⁶ In addition, the activity of the lingual gyrus, together with the amygdala and orbital regions, was reported to be elicited by emotional, unpleasant, stimuli,⁵⁷ being also activated during the visualization of fearful faces.⁵⁸ Providing further evidence for this hypothesis, it has been demonstrated that the activity of this brain region is altered in psychiatric conditions characterized by anxious⁵⁹ and depressive symptoms.⁶⁰ Altogether, it is reasonable to hypothesize that this network of reduced FC may underlie an altered emotional processing, particularly related with fear content. Following this hypothesis, the decreased FC between visual and sensorimotor networks herein observed may be contextualized in line with a previous hypothesis suggesting that an exaggerated FC between distinct sensory regions may contribute to a heightened encoding of fear-related stimuli during task performance.⁶¹ Despite the fact

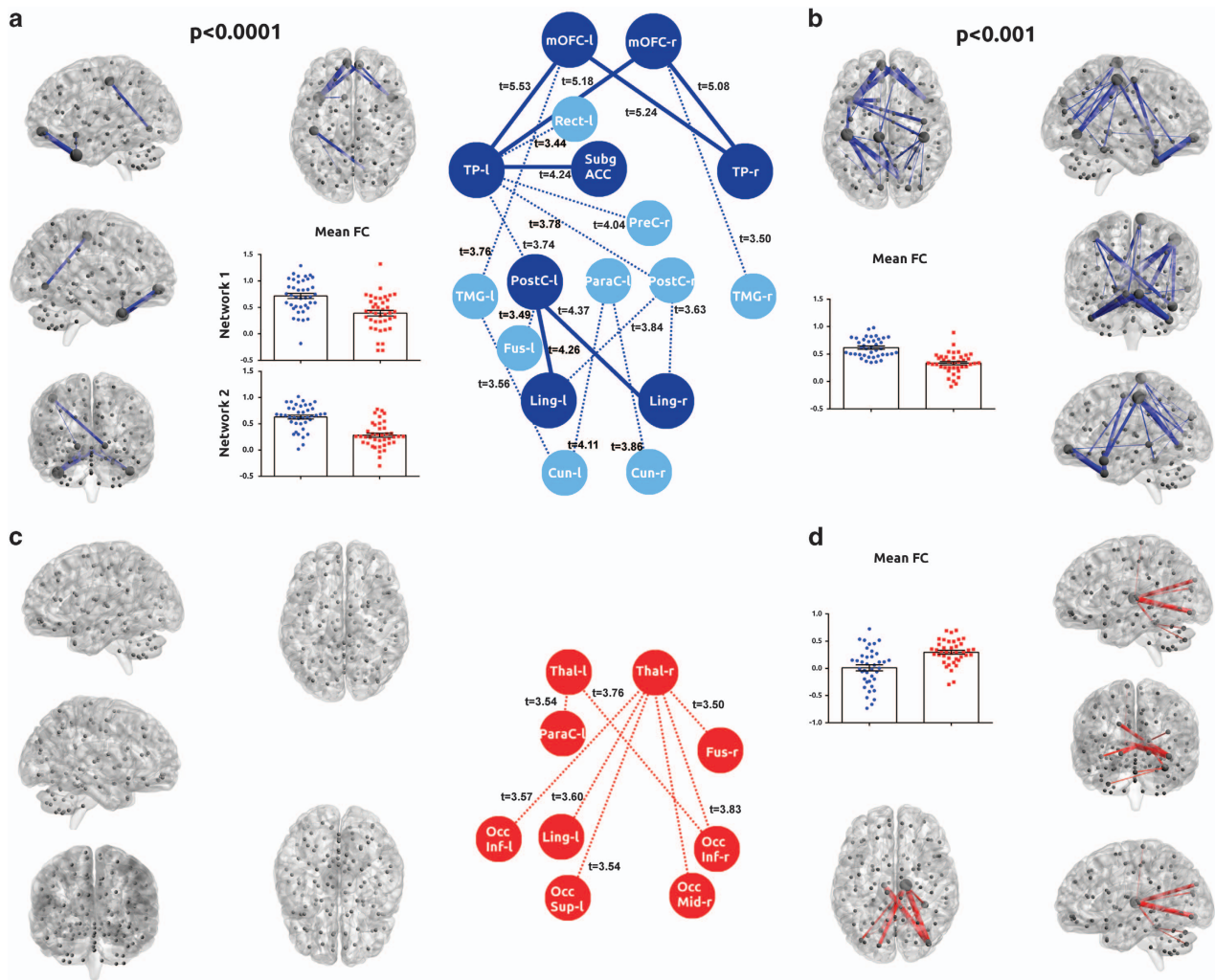


Figure 3. Whole-brain networks with altered functional connectivity (FC) in obsessive-compulsive disorder (OCD) patients, using two primary thresholds: networks with significantly decreased FC (blue) in OCD patients at $P < 0.0001$ (a) and $P < 0.001$ (b) levels are presented on the top; (c) no networks with significantly increased FC was found at the $P < 0.0001$ level; (d) a network with significantly increased FC (red) was found in OCD patients at $P < 0.001$ level. Bar graphs correspond to individual levels of mean FC in each group. On the middle, the t-statistic corresponding to each individual edge is represented for networks with increased and decreased FC levels.

that our findings are in apparent contradiction with the above-mentioned report, it is important to note that whereas Wiemer's findings were obtained while subjects were viewing emotional, fear-related stimuli, our results were obtained with the absence of stimuli, that is, during rest. As such, it is reasonable to hypothesize that the abnormal FC between these regions may be context-dependent, being highly connected during the processing of emotional information, and hypoconnected in default brain processing.

Increased functional connectivity in OCD patients: extension of the typical CTSC model

A network with marginally significant increases of FC between thalamic and occipital brain regions was observed in OCD patients. The most widely accepted neurobiological models of OCD rely on an increased cerebral metabolism in circuits involving the thalamus, OFC and the striatum—the CTSC model—which is thought to underlie behavioral alterations in multiple domains, including reward processing, action selection or habit-based functioning. This hypothesis is partially corroborated by our

results in which edges with (marginally) significant increases in resting-state FC, connecting the thalamus to cortical regions were found in OCD patients. Furthermore, the involvement of other regions not included in the CTSC model also corroborates more recent models, in which parietal, occipital and cerebellar regions have been identified as relevant for the pathophysiology of the disease.²¹

Integration of structural and functional findings

We observed that the structural and functional findings herein obtained were significantly associated. Nevertheless, it was noted that the associations between structural and specific functional results were significantly mediated by specific FC patterns that altered the relationship between structure and function: the mean FC of OFC-TP subnetwork significantly mediated the association between volumetric differences within the STS and Occ-SM subnetwork (model 1); the mean FC of Occ-SM and OFC-TP subnetworks significantly mediated the association between the mean FC of the Thal-Occ subnetwork and volumetric differences

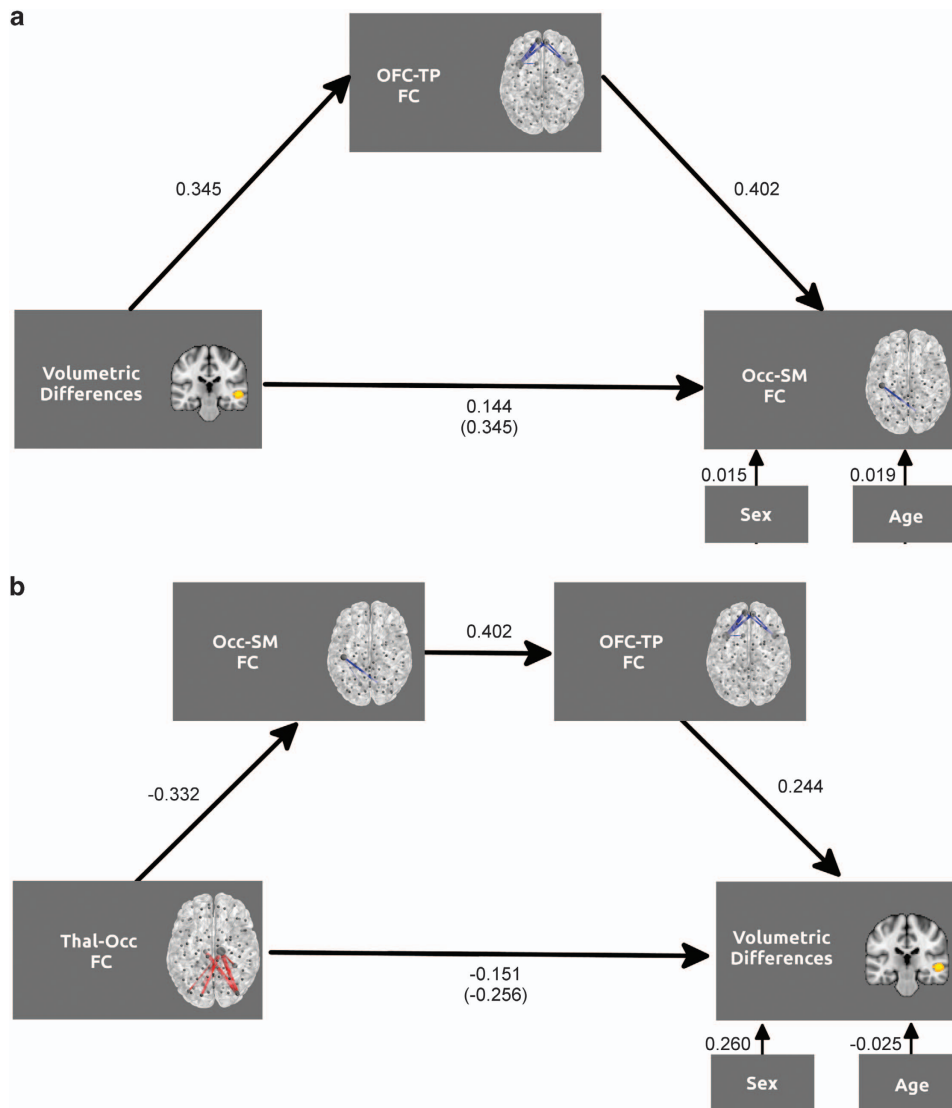


Figure 4. Mediation models. (a) Mediator effects of the orbitofrontal-temporal pole subnetwork (OFC-TP) on the association between volumetric differences within the superior temporal sulcus (STS) and the mean functional connectivity (FC) of the occipito-sensorimotor subnetwork (Occ-SM); (b) mediator effects of the occipito-sensorimotor (Occ-SM) and orbitofrontal-temporal pole (OFC-TP) subnetworks on the association between the mean FC of the thalamic-occipital subnetwork (Thal-Occ) and volumetric differences. Both models revealed significant indirect effects between independent and dependent variables, controlling for confounding factors (sex and age). Values next to each arrow represent standardized coefficients. Values in parenthesis correspond to standardized coefficients when the effects of mediator variables are removed.

within the STS (model 2). According to these results, two distinct hypotheses are proposed.

Hypothesis 1: Direct and indirect contributions of volumetric alterations to a decreased connectivity between the STS and the OFC, and between the OFC and posterior regions, respectively.

The results from the mediation model revealed that the association between structural findings and the mean FC of the Occ-SM subnetwork was significantly mediated by the mean FC of the OFC-TP subnetwork. One possible explanation of this mediation effect relies on the hypothesis that the structural reductions of the STS may contribute to a diminished number of tracts of the arcuate fasciculus (one subcomponent of the superior longitudinal fasciculus (SLF), connecting regions from the temporal lobe to frontal areas) in OCD patients. Consequently, this may contribute to a diminishment of the projections between the OFC and limbic areas (for example, the temporal pole, through

the uncinate fasciculus), contributing to an impaired behavioral and emotional regulation. In turn, projections from the OFC to occipital brain regions (for example, the lingual gyri), and to posterior brain regions (through another subcomponent of the SLF) may in turn be diminished.

Hypothesis 2: Hyperconnectivity between thalamic-cortical projections has an impact on volumetric reductions on the superior temporal sulcus mediated by abnormal FC involving posterior and anterior regions.

Another alternative hypothesis, which follows an inverse path of the one proposed in the first hypothesis, suggests that volumetric alterations are a consequence rather than a cause of FC alterations. We have previously discussed that the Thal-Occ network may represent the aberrant CSTC loops typically described in OCD patients. This network is significantly associated with the remaining observed structural and functional between-

group differences. Nevertheless, it was found that the association between this network and volumetric differences was significantly mediated by both subnetworks with decreased FC in OCD patients. In this context, one may hypothesize that the hyperconnectivity of the loops projecting from the thalamus to parietal and occipital cortical regions may have an impact on the occipito-sensorimotor connectivity. Projections from these regions to orbitofrontal regions, through the SLF, may disturb the functioning of the OFC and its synchrony with limbic regions and the temporal pole (linked via the uncinate fasciculus). An impaired feedback between these regions may, in turn, result in an impaired structural connectivity between the OFC and the STS (throughout the arcuate fasciculus), which may ultimately cause volumetric reductions in this area.

Strengths and limitations

It is worth to acknowledge some strengths and limitations associated with this work. The first strength is associated with the multimodal approach here implemented. With this, we could provide complementary evidence for abnormal structural and functional brain patterns in OCD patients and how they can be integrated to understand the neural mechanisms associated with the disorder. In addition, the group differences were identified using very conservative approaches, with restrict thresholds for assessing both volumetric (with non-parametric permutation testing) and whole-brain ($P < 0.001$ and $P < 0.0001$) differences. Thus, considering the recent debate associated with the problem of false-positive findings in neuroimaging experiments, this conservative strategy enables an additional level of confidence in the reported findings.

On the other hand, it is relevant to highlight that the network with increases in FC (the Thal-Occ network) was identified with marginally significant results. Thus, these results need to be interpreted with additional caution. Other limitations pertain to the characteristics of the sample. One aspect relies on the fact that our sample was under medication. Recent reports have demonstrated that specific FC alterations stabilize after pharmacological intervention in OCD patients.²⁷ Consequently, it is reasonable to speculate that the pharmacological treatment could ameliorate the differences herein obtained. Nevertheless, it is important to mention that the duration of medication was not associated with the magnitude of the differences between OCD and HC groups, considering either the structural and functional alterations here described (data not shown). Another important issue pertains to the high heterogeneity observed among OCD patients. It is also important to highlight that the hypotheses raised with this work strongly rely on structural connections between particular brain regions. Thus, our theoretical model could be better sustained with the complementary characterization with diffusion tractography approaches.

CONCLUSIONS

In sum, we could detect a variety of functional and structural brain alterations in OCD patients. Using this multimodal approach, we could integrate these results in an integrated, theoretical model that may provide useful insights associated with the pathophysiology of the disorder. In addition, our results reinforce the importance of extending the CSTC model to fully understand the pathophysiology of the disease.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DISCLAIMER

The paper has not been published previously, or is under consideration for publication elsewhere, in English or in any other language.

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