Aberrant functional connectivity density in patients with treatment-refractory obsessive-compulsive disorder: a pilot study

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Abstract

Objective: Functional connectivity (FC) is altered in patients with obsessive-compulsive disorder (OCD). Most previous studies have focused on the strength of FC in patients with OCD; few have examined the number of functional connections in these patients. The number of functional connections is an important index for assessing aberrant FC. In the present study, we used FC density (FCD) mapping to explore alterations in the number of functional connections in patients with treatment-refractory OCD (TROCD) using the FCD index.

Methods: Twenty patients with TROCD and 20 patients with OCD in clinical remission were enrolled in the study. Global FCD (gFCD) was adopted to compare the differences between the two groups of patients.

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Results: The gFCD in the left middle temporal gyrus was lower in the patients with TROCD than in those with remitted OCD, suggesting that decreased information processing ability may play a significant role in TROCD.
Conclusion: The left middle temporal gyrus is a key component of the emotional processing circuit and attentional processing circuit. Decreased information processing ability in this brain region may play a significant role in TROCD; however, further well-designed follow-up studies are needed to support this hypothesis.

Introduction

Obsessive-compulsive disorder (OCD) is associated with disturbed functional connectivity (FC) between many pivotal brain regions, such as the insular, orbital, parietal, and temporal lobes; the posterior cingulate cortex; the thalamus; and the basal ganglia.[1–4] The strength of aberrant FC has been correlated with the severity of some clinical symptoms,[5–8] and specific FC between some brain regions is related to treatment efficacy.[9–12] Furthermore, some specific FCs can be used to predict the effects of therapeutic agents.[10–12] Overall, these findings have provided a basic understanding of the pathological characteristics of OCD.[13] Gürsel et al.[14] recently conducted a meta-analysis that included seed-based FC studies and reported decreased FC within the frontoparietal and salience networks and among the salience, frontoparietal, and default-mode networks. The intrinsic FC in the salience, frontoparietal, and default-mode networks demonstrated a pattern of disturbance. The frontostriatal circuitry also simultaneously demonstrated a pattern of disturbance. This meta-analysis suggests that alterations in the intrinsic connectivity of the frontoparietal regions play a key role in the pathological mechanisms of OCD. This meta-analysis also provides strong evidence for the hypothesis that two distinct pathophysiological models coexist in the brains of patients with OCD: disrupted frontostriatal circuits and impaired large-scale frontoparietal–limbic intrinsic brain networks.[14]

Aberrant FC is correlated with the severity of some clinical symptoms, and the FC between some brain regions is related to treatment efficacy. For example, Gürsel et al.[14] reported that increased FC within the left medial orbitofrontal cortex was positively correlated with Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores in this cortex. Moreover, decreased FC strength (FCS) within the left superior occipital cortex was inversely associated with Y-BOCS total scores. More specifically, the authors also observed that decreased FCS within the cerebellar vermis was negatively correlated with Y-BOCS obsession scores and that decreased FCS within the left superior occipital cortex was negatively correlated

with Y-BOCS compulsion scores and Y-BOCS total scores in the left superior occipital cortex.[14] More notably, aberrant FC was related not only to the severity of OCD symptoms but also to the efficacy of treatment. For example, Dunlop et al.[9] reported that the treatment efficacy of repetitive transcranial magnetic stimulation to the dorsomedial prefrontal cortex in patients with OCD was correlated with FC reductions between the dorsomedial prefrontal cortex and the ventral striatum.

Seed-based FC and data-based FC reflect the FCS between two brain regions. The FCS is an important index that reflects the functional coordinate activities in related brain regions that subsequently influence the functional activity of the entire brain. However, in addition to connectivity strength, the number of functional connections plays a key role in exploring aberrant FC of the brain. Too many or too few connections can also induce brain functional coordinate activities and subsequently influence the functional activity of the entire brain.

Almost all studies on FC in patients with OCD have focused on the FCS,[1–14] which reflects the one-to-one connection relationships and the spontaneous neural activity strength at a given time.[15,16] However, the number of functional connections also plays a key role in FC.[17–20] FC density (FCD) reflects the number of connections that one voxel has to any other voxel or all voxels in the entire brain.[21–22] FCD represents a one-to-many relationship.[23–27] The number of connections of a brain region with other voxels of the entire brain reflects this region's communication with the remainder of the brain.[28–30] In the last five years, FCD has been widely used to investigate connection number alterations in some mental disorders, such as schizophrenia, depression, and alcohol addiction.[17–31] These studies confirmed that FCD could be used to explore FC aberrations from a new perspective.

FCD mapping is an ultra-fast calculation method described by Tomasi and Volkow.[21,22] FCD mapping can calculate the global FCD (gFCD), which represents the number of individual voxels connected with other voxels in the entire brain. The gFCD value reflects the importance of this brain region within the entire brain. Aberrant gFCD in a brain region reflects a disturbance in information communication processing in this region, consequently influencing information communication for the entire brain and possibly leading to some mental disorders.[27–31]

In the present study, we investigated alterations in the number of functional connections in patients with treatment-resistant OCD (TROCD) using FCD mapping to compare differences in FCD between patients with TROCD and patients with OCD in clinical remission. We hypothesized that patients with TROCD exhibit specific FCD alterations different from those of patients with remitted OCD and that these differences represent a specific pathological feature of the brain in patients with TROCD.

Materials and methods

Sample

All patients were enrolled following outpatient treatment or hospitalization at the First Affiliated Hospital of Harbin Medical University. Before magnetic resonance imaging (MRI) scans, we tested the patients for drug and alcohol ingestion using urine drug tests and breathalyzer analyses, respectively. Smoking was assessed using the Fagerström Test for Nicotine Dependence; patients with a score of >3 were not enrolled in the study. The demographic and clinical characteristics of all patients are presented in Table 1. All patients fully understood the risks and benefits of the study. No significant group differences in sex, age,

Table 1. Demographic and clinical characteristics of all patients.

Characteristics	TROCD n = 20	R-OCD n = 20	T/X^2	P
Age (years)	33.4 ± 5.8	35.2 ± 5.3	−1.57	0.124
Sex (male/female)	7/13	9/11	0.66	0.275
Education level	11.0 ± 2.1	10.92 ± 2.0	0.191	0.844
Illness duration (years)	4.3 ± 1.2	4.2 ± 1.0	−1.397	0.170
Y-BOCS score	35.2 ± 1.5	4.5 ± 1.0	50.98	0.000

Data are presented as mean ± standard deviation or number of patients.
TROCD: treatment-refractory obsessive-compulsive disorder; R-OCD: remitted obsessive-compulsive disorder; Y-BOCS: Yale-Brown Obsessive Compulsive Scale.

educational level, or illness duration were noted. However, significant group differences in illness severity were observed as indicated by the Y-BOCS score (Table 1). The Medical Research Ethics Committee of Harbin Medical University approved the study. Written informed consent was obtained from each subject.

Methods

Two psychiatrists used the Structured Clinical Interview for DSM-IV[32] to diagnose TROCD. The Y-BOCS[33] was adopted to assess the severity of OCD and identify patients with remitted OCD (according to clinical remission criteria and the Y-BOCS scores). In this pilot study, TROCD was defined as OCD with no or minimal response (Y-BOCS score reduction of <50%) despite treatment with a sufficient dosage of two or more categories of treatment agents and an adequate treatment duration.[10–12] Remitted OCD was defined as an ideal response (Y-BOCS score reduction of >50%) after treatment with a therapeutic agent.[10–12] The exclusion criteria for all patients were a history of drug abuse, pregnancy or breastfeeding participants, neurological diseases, severe physical diseases, a history of consciousness disorder lasting more than 5 minutes, and contraindications to MRI.

MRI data acquisition

Image acquisition. The functional MRI (fMRI) experiments were performed using a GE Signa HDxT 3.0T MRI scanner (GE Healthcare, Chicago, IL, USA). Comfortable and tight foam padding was used to minimize head motion. Earplugs were inserted to minimize scanner noise. Sagittal three-dimensional T1-weighted images were acquired by a brain volume sequence based on the following parameters: repetition time, 8.2 ms; echo time, 3.2 ms; inversion time, 450 ms; flip angle, 12°; field of view, 256 × 256 mm; matrix, 256 × 256; slice thickness, 1 mm, no gap; and 188 sagittal slices. Resting-state fMRI data were acquired using a gradient-echo single-short echo planar imaging sequence with the following parameters: repetition time, 2000 ms; echo time, 45 ms; field of view, 220 × 220 mm; matrix, 64 × 64; flip angle, 90°; slice thickness, 4 mm; gap, 0.5 mm; 32 interleaved transverse slices; and 180 volumes. All patients were asked to keep their eyes closed, relax, move their head as little as possible, think of nothing, and remain awake during the fMRI scans.

Image processing

Gray matter volume calculation. Voxel-based morphometry was used to calculate the gray matter volume (GMV) of each voxel as implemented in the VBM8 toolbox

(http://dbm.neuro.uni-jena.de/vbm.html). Structural images were segmented into gray matter, white matter, and cerebrospinal fluid using the standard segmentation template. After an initial affine registration of the gray matter concentration map onto the Montreal Neurological Institute (MNI) template, gray matter concentration images were nonlinearly warped using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra method. The results were then resampled to a voxel size of $3\,mm^3$. The relative GMV of each voxel was acquired by multiplying the gray matter concentration map by the nonlinear determinants that were extracted from the spatial normalization step. Next, the GMV images were smoothed by a Gaussian kernel of 6- × 6- × 6-mm full-width at half maximum. After completion of spatial preprocessing, the smoothed GMV maps were adopted for statistical analyses.

fMRI data preprocessing. SPM8 (http://www.fil.ion.ucl.ac.uk/spm) was used to preprocess the resting-state fMRI data. We discarded the first 10 volumes of each patient to allow the signal to reach equilibrium and the patients to adapt to the scanning noise. The remaining volumes were corrected for the acquisition time delay between slices. Volumes were realigned to correct for the motion between different time points. The data of patients whose heads rotated >2 mm or >2° were also discarded. We also compared frame-wise displacement, which indexes volume-to-volume changes in head position. No significant group differences in frame-wise displacement were noted between the two patient groups (TROCD, 0.115 ± 0.004; remitted OCD, 0.110 ± 0.009). Some nuisance covariates, such as their first-time derivations and the average blood oxygen level-dependent signals of the ventricular and white matter, were regressed from the data. A recent study showed that the signal spike induced by head motion significantly contaminates the final resting-state fMRI results even after regression of the linear motion parameters.[34] We regressed spike volumes when the frame-wise displacement of the specific volume exceeded 0.5. The datasets were then bandpass filtered by a frequency range of 0.01 to 0.08 Hz. In the normalization step, individual structural images were linearly co-registered with the mean functional image; the structural images were also linearly co-registered to the MNI template. Finally, each filtered functional volume was spatially normalized to the MNI template by co-registration parameters and resampled into a 3-mm^3 voxel.[21–23]

Resting-state FCD calculation. Each voxel's resting-state FCD (rsFCD) was calculated using an in-house script that was written in the Linux platform according to the method described by Tomasi and Volkow.[21,22] We adopted Pearson's linear correlation method to evaluate the strength of the FC between voxels. Two voxels with a correlation coefficient of $R > 0.6$ were defined as significantly connected. This threshold was suggested to be the optimal threshold for calculating rsFCD in a previous study.[23] The rsFCD calculation was restricted to the cerebral gray matter mask. The rsFCD at a given voxel x0 was calculated as the total number of functional connections k(x0) between x0 and all other voxels in the entire brain. This calculation was repeated for all x0 voxels in the entire brain. The grand mean scaling of rsFCD was acquired by dividing by the mean value of all brain voxels to increase the normality of the distribution. Ultimately, the rsFCD maps were spatially smoothed using a 6- × 6- × 6-mm full-width at half maximum Gaussian kernel.

Statistical analysis

Group differences in rsFCD were calculated in a voxel-wise manner using a general linear model with age and sex as nuisance variables. A permutation-based inference tool for non-parametric statistics in FMRIB's diffusion toolbox (FSL 4.0, http://www.fmrib.ox.ac.uk/fsl) was adopted to conduct this analysis. The number of permutations was set to 5000, and the significance threshold was set at $P < 0.05$ after family-wise error correction, adopting the threshold-free cluster enhancement option in FSL 4.0. To exclude the possible effects of GMV on globally aberrant FCD, we repeated the group comparisons using GMV as an additional covariate of no interest at the voxel-wise level. Thus, the gFCD of each cluster with significant group differences was drawn for each patient. The partial correlation coefficient was adopted to test the correlation between gFCD and the patients' clinical characteristics, illness duration, and Y-BOCS scores. Age and sex effects were controlled, and multiple comparisons were corrected using the Bonferroni method ($P < 0.05$).

Moreover, correlation analyses between gFCD and obsessive-compulsive symptoms were completed in a voxel-wise manner for the entire brain. A linear regression model was adopted to calculate correlation analyses with age and sex as covariates of no interest. Multiple comparisons were corrected using a family-wise error method ($P < 0.05$). Two-sample t-tests were used to detect differences in age, education level, illness duration, and other factors. The chi-square test was used to compare the sex ratio. A P value of <0.05 was considered statistically significant.

Results

Demographics and clinical characteristics

This study included 20 patients with TROCD and 20 patients with remitted OCD whose MRI data could be analyzed by FCD mapping. All patients' demographic and clinical characteristics are summarized in Table 1. No significant group differences were noted in sex ($X^2 = -0.806$), age (t = -0.497), educational level (t = 0.539), or illness duration (t = -0.331). Several categories of anti-compulsive agents were administered to the patients with TROCD. Most patients were taking two or three agents. Most patients with remitted OCD were taking one medication.

Comparison of gFCD between the two groups

The gFCD in the left middle temporal gyrus was lower in patients with TROCD than in patients with remitted OCD (Figure 1). This lower gFCD in the left middle temporal gyrus indicated that the number of functional connections in this region was lower than that in other voxels in the whole brain.

Relationship between aberrant gFCD and Y-BOCS scores

In this study, we adopted partial correlation analysis to investigate the relationship between decreased gFCD in the left middle temporal gyrus and the Y-BOCS score. We found no significant correlations between them. Moreover, we did not identify any Y-BOCS item scores that correlated with the reduced gFCD in the left middle temporal gyrus.

Discussion

In the present study, the gFCD in the left middle temporal gyrus was lower in patients with TROCD than remitted OCD. This finding reflects reduced numbers of connections in this region, suggesting deficient neural connectivity in the left temporal gyrus. This lower number of functional
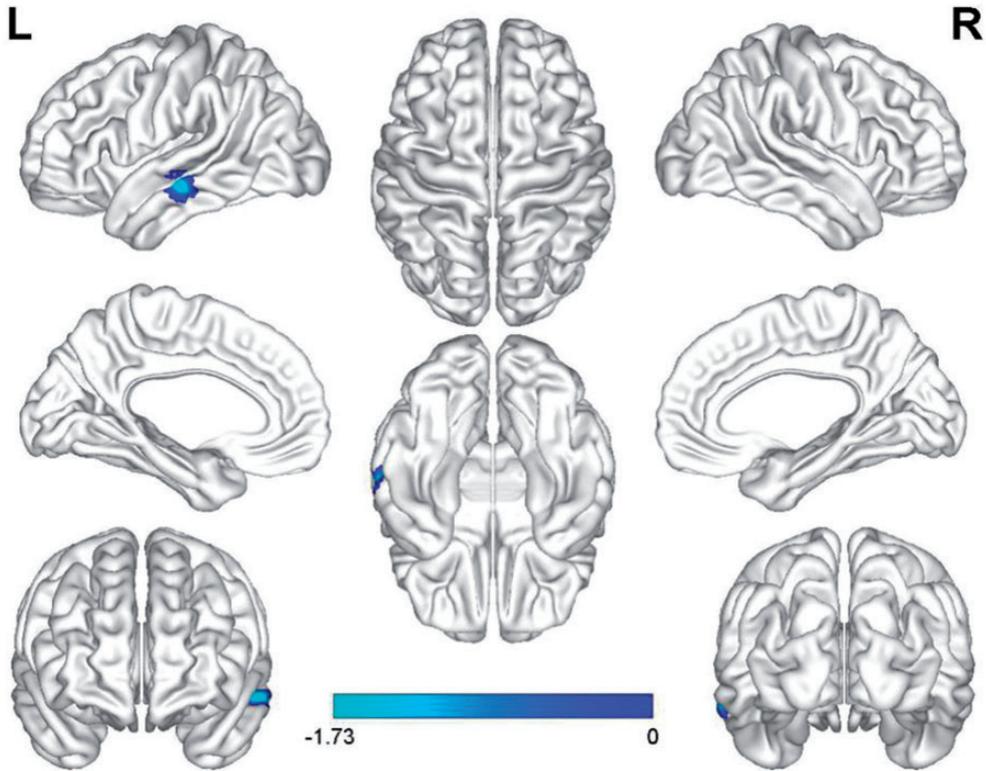
Figure 1. Differences in global functional connectivity density between patients with treatment-refractory obsessive-compulsive disorder and remitted obsessive-compulsive disorder. L, left; R, right.

connections also indicated that the information communication processing ability was reduced. Decreased information communication processing ability may play a significant role in TROCD. Several previous studies that focused on FCS reported decreased FC in patients with OCD and even in their close relatives.[35,36] The left middle temporal gyrus is a key component of the emotional, cognitive, and memory processing circuits and plays a key role in the limbic system.[37–45] The reduced connections in this pivotal region impair information communication ability, thereby impairing the modulation of emotion, cognitive, and memory processing and leading to more complex and more serious obsessive-compulsive symptoms.[9,33,35,46–54]

Overall, our findings suggest that decreased gFCD may be a specific brain-pathological characteristic of TROCD. The impaired information communication processing caused by decreased gFCD in the left middle temporal gyrus may cause OCD to become refractory to treatment.

In patients with OCD, the left middle temporal gyrus plays a key role in the development of pathology and its trajectory and is also related to the treatment efficacy of OCD. For example, previous studies have reported that FC alterations in the left middle temporal gyrus may reflect neuroimaging endophenotypes for OCD.[35] Fan et al.[55] reported that reduced spontaneous neural activity in the left middle temporal gyrus is associated with a level of insight

into OCD. Moreover, a recent study showed that the GMVs of the cerebellar anterior lobe, left orbital frontal gyrus, right middle frontal gyrus, left middle temporal gyrus, precentral gyrus, and postcentral gyrus were increased after 12 weeks of treatment with sertraline.[45] The above-mentioned studies suggest that structural and functional impairments (including decreased FCS or reduced numbers of connections) in the left middle temporal gyrus in patients with OCD are associated with the pathological development and trajectory and the treatment effect. Hence, to improve the treatment efficacy of OCD, further well-designed studies are needed to precisely explore the effect of modulating the functional activity of the left middle temporal gyrus by multiple techniques, such as deep brain stimulation, transcranial direct current stimulation, and repetitive transcranial magnetic stimulation.

The orbital lobe is a key brain region influencing the treatment effect of OCD.[33,35,54] In the present study, however, we did not identify aberrant FCD in the orbital lobe; this outcome is inconsistent with previous studies. Previous studies have compared patients with OCD versus healthy controls, whereas we compared patients with TROCD versus those with remitted OCD. This difference may explain why we did not identify alterations in the orbital lobe and other brain regions that are reported to influence OCD symptoms and treatment effects. In future studies, we will enroll matched healthy controls for comparison with both patients with TROCD and patients with non-TROCD.

This pilot study has several limitations. First, we only compared patients with TROCD versus those with remitted OCD, and all of these patients exhibited extreme symptoms of OCD. Hence, our findings and our postulations may not be generalizable to all patients with OCD. Further long-term follow-up studies that enroll sufficient

numbers of subjects, especially those experiencing their first episode, are needed to observe the treatment efficacy and brain-dynamic character alterations induced by the treatment and to explore the special treatment targets for TROCD. Through a follow-up study, we will also dynamically characterize the trajectory of brain features as the illness progresses. Such a follow-up study will allow us to explore the exclusive pathological features specific to the brains of patients with TROCD and explore the reason why these patients do not respond ideally to treatments. Such a study will be worth the time and expense that are required because it will provide vital information for the precise treatment of different subtypes of OCD. Second, we also should consider more specific measurements of the number of functional connections as a surrogate marker of overall function instead of determining the strength of each connection in future studies. Third, the present study lacked a group of healthy controls. By investigating the aberrations in FCD among controls, we can explore the mechanisms of TROCD from the perspective of connectivity numbers. This information can enhance our understanding of the mechanisms of TROCD and may be useful to explore new treatment targets. Fourth, we also lacked a group of patients with treatment-responsive OCD. By investigating the aberrations in gFCD in this group of patients, we can explore the mechanisms of treatment-responsive OCD based on the perspective of connectivity numbers. This information can enhance our understanding of the different mechanisms between treatment-responsive OCD and TROCD and may aid us in the identification of new treatment targets. Fifth, structural and functional alterations in the striatum play a key role in the pathological mechanisms of OCD. Previous studies have shown that aberrant striatum structure and functional activity is related to the severity of

the symptoms of OCD and efficacy of treatment. This finding indicates that we must conduct a well-designed study to research the trajectory of dynamic aberrations in the structure and functional activity of the striatum in patients with OCD to explore new treatment targets of OCD, especially TROCD.

Conclusions

In this pilot study, decreased gFCD in the left middle temporal gyrus was observed in patients with TROCD when compared with patients with remitted OCD, suggesting that decreased information communication processing ability may play a significant role in TROCD. The left middle temporal gyrus is a key component of the emotional and attentional processing circuits. The reduction in information processing ability in this brain region may play a significant role in TROCD. Further well-designed follow-up studies are needed to support this hypothesis.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

W.L. conceived and designed the experiments and wrote the manuscript. Y.H., L.W., F.L., and Q.C. conducted the experiments and collected, analyzed, and interpreted the data. All authors reviewed the manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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