Global functional connectivity density increased in treatment of refractory compulsive behaviour

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Abstract: Previous studies have reported widespread aberrant functional connectivity (FC) in patients with obsessive-compulsive disorder (OCD). Global FC density (gFCD) can reflect aberrant FC in terms of connection numbers and can be used as a supplementary index for traditional FC methods, which focus on connectivity strength. However, to the best of our knowledge, few studies have examined the relationship between gFCD and compulsive behaviour or obsessional thoughts, particularly in treatment-refractory OCD patients. The current study aimed to explore gFCD relative to refractory compulsive behaviour (compulsion) in treatment-refractory OCD patients. We adopted FC density mapping (FCDM) to investigate gFCD features in treatment-refractory OCD patients with obsessive compulsive behaviour (TRC) as a primary clinical symptom. Twenty-three TRC and 23 matched treatment-refractory OCD patients with obsessive thought (TRO) were enrolled in the study. gFCD was adopted to examine differences between TRC and TRO patients. The results revealed that TRC patients demonstrated increased gFCD in the right sensorimotor cortex. Moreover, the findings suggested abnormal hyper-information-communication in TRC patients compared with TRO patients. The right sensorimotor cortex is a key component of the sensorimotor network and plays an essential role in the modulation of somatic movements. Abnormal hyper-information-communication in this brain region may be a specific pathological characteristic of TRC. The current results, combined with previous findings, support the hypothesis that TRC has specific clinical symptoms with corresponding neural bases. However, our current study was limited by the absence of a healthy control group, preventing verification of our hypothesis. Nonetheless, our findings provide an experimental approach for clarification of this hypothesis in further studies.

Keywords: Treatment-refractory compulsion, functional connectivity density, right sensorimotor cortex, functional connection numbers

Introduction

In the last two decades, advances in functional magnetic imaging techniques (fMRI) have enabled many investigations of the neural pathological features of obsessive-compulsive disorder (OCD) patients [1-6]. Evidence from previous studies has helped enhance the understanding of the pathophysiological characteristics of OCD [6-10]. Currently, in terms of the brain connectome, the most widely accepted hypothesis of OCD is that dysconnectivity among some brain regions, such as the orbital lobe, frontal lobe, thalamus, and hippocampus, is the pathophysiological basis of OCD [11-14]. Findings from previous studies have provided invaluable information for the further study of the neural basis of the unique symptoms of OCD, particularly in treatment-refractory OCD. However, to the best of our knowledge, most previous studies investigated functional connectivity (FC) differences between OCD patients and healthy controls, while few studies have explored the pathological features of the specific symptoms of OCD, particularly in treatment-refractory OCD patients [1-16].

Previous studies have mainly investigated the strength of FC, which represents the strength of temporal correlations between two brain regions [17, 18] and reflects the relationships among brain regions in a one-to-one fashion. In
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the last 6 years, Tomasi et al. developed a method for measuring FC numbers, which can reflect the number of voxels connected to other voxels in the whole brain and expose aberrant FC from a connection number perspective [19-22]. Contrary to FC strength, FC density (FCD) represents the relationship of one voxel to other voxels [22-25]. FCD was recently adopted to investigate abnormal FC in several mental disorders, including attention deficit hyperactivity disorder (ADHD), depression, alcohol addiction, and schizophrenia, revealing many useful findings [20-29]. All of the studies mentioned above support the notion that FCD can be used as a method for exploring the aberrant brain connectome from a connection number perspective, and can provide useful information.

FCD mapping (FCDM) has been adopted to investigate aberrant FCD. FCDM uses an ultra-fast logic algorithm that is usually adopted to calculate global FCD in samples [24]. Most previous studies have focused on FC strength, while few studies have reported gFCD differences between TRC and TRO patients. In the current study, we used FCDM to investigate functional connection number differences between TRC and TRO patients. We hypothesized that TRC patients would exhibit a different aberrant global FCD pattern compared with TRO patients.

Material and methods

Samples

The present study included 23 treatment-refractory OCD patients with compulsive behaviour as a primary clinical symptom and 23 well-matched patients with obsessive thought as a primary clinical symptom. All patients were enrolled from outpatients and hospitalized patients at the First Affiliated Hospital of Harbin Medical University. Two senior psychiatrists used the Structured Clinical Interview for DSM-IV (SCID) [30] to identify TROCD patients with compulsive behaviour or obsessive thought as a primary clinical symptom according to additional relevant criteria (such as treatment-refractory). The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [31] was adopted to assess the severity of compulsive behaviour and obsessive thought. The Medical Research Ethics Committee of our University approved our study. All patients were fully informed of the risks and benefits of the study, and written informed consent was obtained from each participant.

Image acquisition

A GE Signa HDxT 3.0 T MRI scanner (GE Company, USA) was used to acquire the MRI data. Foam pads were used to minimize head motion. Earplugs were used to reduce scanner noise. Sagittal 3D T1-weighted images were acquired with a brain volume sequence with the following parameters: repetition time (TR) = 8.2 ms; echo time (TE) = 3.2 ms; inversion time (TI) = 450 ms; fractional anisotropy (FA) = 12; field of view (FOV) = 256 mm²; matrix = 256 × 256; slice thickness = 1 mm, no gap. A total of 188 sagittal slices were acquired. Resting-state fMRI data were acquired by a gradient-echo single-shot echo planar imaging sequence with the following parameters: TR = 2000 ms, TE = 45 ms; FOV = 220 mm²; matrix = 64 × 64; FA = 90°; slice thickness = 4 mm; gap = 0.5 mm. A total of 32 slices and 180 volumes were acquired. All subjects were asked to keep their eyes closed, keep their heads still, relax, think of nothing, and not fall asleep during fMRI scanning.

fMRI data preprocessing

The resting-state fMRI data were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). First, 10 volumes for each patient were discarded to allow the signal to equilibrate and the patients to adapt to the scanning noise. The remaining volumes were then corrected for the acquisition time delay between slices. Realignment was used to correct head motion between different time points. Subjects whose heads moved more than 2 mm or 2° were excluded. In addition, we compared frame-wise displacement (FD), which reflects volume-to-volume changes in head position. No significant differences were observed in FD (t = 0.61, P = 0.57) between the two patient groups (TRC: 0.110 ± 0.007, TRO: 0.116 ± 0.002). Some covariates, such as first-time derivations and average blood-oxygen-level dependent (BOLD) signals of the ventricular and white matter were regressed out. Signal spikes induced by head motion significantly contaminated the final resting-state fMRI results even after regressing out the linear motion parameters.
Therefore, spike volumes were regressed out when the FD of a specific volume was greater than 0.5. The datasets were then bandpass filtered using a frequency range of 0.01-0.08 Hz. In the normalization step, subjects' structural images were linearly co-registered with the mean functional image and the structural images were linearly co-registered to Montreal Neurological Institute (MNI) space. Ultimately, each filtered functional volume was spatially normalized to MNI space by co-registration parameters and resampled into 3-mm³ voxels.

**Grey matter volume calculation**

We used the voxel-based morphometry (VBM) method to calculate the grey matter volume (GMV) of each voxel using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html). Structural images were divided into GM, cerebrospinal fluid (CSF) and white matter (WM) using a standard segmentation template. After initial affine registration of the GM concentration map into MNI space, GM concentration images were non-linearly warped through diffeomorphic anatomical registration using the exponentiated Lie algebra (DARTEL) method. The results were then resampled to a voxel size of 3 mm³. The relative GMV of each voxel was obtained by multiplying the GM concentration map by the non-linear determinants that were derived from the spatial normalization step. Next, the GMV images were smoothed with a Gaussian kernel of 6 × 6 × 6 mm full-width at half maximum (FWHM). Spatial preprocessing was performed and the smoothed GMV maps were used for statistical analyses.

**gFCD calculation**

An in-house script that was written in the Linux platform was used to calculate each voxel's gFCD according to the method described by Tomasi and Volkow [22-27]. Therefore, the gFCD calculation was restricted to the cerebral GM mask. The gFCD 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. Grand mean scaling of gFCD was performed by dividing by the mean value of all brain voxels to increase the normality of the distribution. Finally, the gFCD maps were spatially smoothed using a 6 × 6 × 6 mm FWHM Gaussian kernel.

**Statistical analysis**

gFCD differences between the groups were calculated using a voxel-wise method with a general linear model with age and gender as nuisance variables. The permutation-based inference tool for non-parametric statistics in FMRIB's diffusion toolbox (FSL 4.0, http://www.fmrib.ox.ac.uk/fsl) was used to complete this analysis. The number of permutations was set to 5000 and the significance threshold was set at P < 0.05. After family-wise error (FWE) correction, we used the threshold-free cluster enhancement (TFCE) option in FSL. To exclude the possible effects of GMV on aberrant gFCD, we repeated the group comparisons with GMV as an additional covariate of no interest. The average gFCD of each cluster with significant group differences was extracted for each subject. The partial correlation method was used to calculate the correlations between gFCD and clinical symptoms, illness duration and Y-BCOX scores. Age and gender effects were also controlled and multiple comparisons were corrected using the Bonferroni method (P < 0.05). Correlation analyses between gFCD and obsessive-compulsive symptoms were completed in a voxel-wise manner in

<table>
<thead>
<tr>
<th>Demographic and clinical Features</th>
<th>TROD-CB N = 23</th>
<th>TROD-OT N = 23</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35.3 ± 4.8</td>
<td>33.2 ± 4.7</td>
<td>1.47</td>
<td>0.125</td>
</tr>
<tr>
<td>Education level</td>
<td>11.2 ± 2.4</td>
<td>11.2 ± 2.3</td>
<td>0.94</td>
<td>0.926</td>
</tr>
<tr>
<td>Illness duration (years)</td>
<td>4.9 ± 1.2</td>
<td>4.3 ± 1.3</td>
<td>1.60</td>
<td>0.116</td>
</tr>
<tr>
<td>Total Y-BCOX scores</td>
<td>35.2 ± 2.5</td>
<td>35.3 ± 2.6</td>
<td>-0.06</td>
<td>0.955</td>
</tr>
<tr>
<td>Compulsive behaviour scores</td>
<td>25.04 ± 2.9</td>
<td>9.26 ± 3.5</td>
<td>16.38</td>
<td>0.000</td>
</tr>
<tr>
<td>Obsessive thought scores</td>
<td>10.7 ± 3.5</td>
<td>26.5 ± 10.7</td>
<td>-13.75</td>
<td>0.000</td>
</tr>
</tbody>
</table>

the entire brain. A linear regression model was used to conduct the correlation analyses, with age and gender as covariates of no interest. Correction for multiple comparisons was conducted using the FWE method (P < 0.05). Two-sample t-tests were used to detect differences in age, education level, and illness duration. The chi-square test was used to compare the gender ratio. P < 0.05 was set as the significance threshold.

Results

Demographic and clinical features

The demographic and clinical features of the patients are shown in Table 1. No significant differences were found in gender, age, education, illness duration, or illness severity. Because anti-obsessive-compulsive therapeutic agents are very complex, we did not list them in the table. Ten types of agents were used in these patients, and most patients were taking two or three therapeutic agents.

Comparison of global FCD between the two groups

In the current study, we found that the TRC group demonstrated increased global FCD in the right sensorimotor cortex compared with the TRO group (Figure 1). We did not find a significant correlation between increased global FCD and the severity of TRC symptoms.

Discussion

In the present study, we used the FCDM method to compare gFCD differences between TRC and TRO patients. Importantly, the results revealed increased global FCD in the right sensorimotor cortex. Increased global FCD indicates that the number of connections of this region with other voxels in the whole brain is abnormally increased compared with the normal state. Increased voxel connections can cause hyper-information-communication processing in patients. This hyper-information-communication subsequently induces disturbed neural spontaneous activity in the brain, thereby generating abnormal thoughts or behaviours of patients [33, 34]. This possibility was proposed in several previous studies reporting abnormal global FCD in patients with mental disorders [22-29, 33]. The current findings also support this proposal.

Although we did not find a relationship between increased global FCD and the severity of TRC symptoms, our findings provide information that may be useful for facilitating understanding of the neural pathological features of specific symptoms in treatment-refractory OCD. TRC patients demonstrated increased global FCD in the sensorimotor cortex, reflecting increased functional connection numbers and an increased number of brain neuron connections in this region. The neurons that constitute the sensorimotor cortex are thought to participate in the information processing circuit [34-37]. Increased global FCD in the sensorimotor cortex plays a key role in the modulation of somatic movement [38-41]. Therefore, we postulated that hyper-information-communication in the sensorimotor cortex and other brain regions in the whole brain may cause compulsive behaviour in TRC patients. Similarly, some previous studies reported that the sensorimotor cortex also participates in the regulation of emotional and executive processing [42-44]. The reciprocal actions of these regions may represent the neural basis underlying the sym-
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Pinpoints of patients who become treatment-refractory.

Previous studies reported that some brain FC alterations were correlated with some symptoms of OCD [45-47]. However, the current results revealed no correlation between increased global FCD and compulsion symptom scores in TRC patients. Several factors may explain this phenomenon. First, in previous studies, researchers mainly focused on functional differences between OCD patients and healthy controls. Second, compared with OCD studies, fewer studies have investigated treatment-refractory OCD. Third, even fewer studies have examined the specific symptoms of OCD or treatment-refractory OCD. The specific symptoms of OCD examined in the current study were defined according to clinical symptom expression patterns rather than formal diagnostic classification.

Because the current study was limited by the absence of a healthy control group, we did not use a multiple comparison analysis method to further investigate functional alterations in the groups. This limitation should be addressed in future studies.

Three important limitations of the current study should be considered. First, as mentioned above, we did not include a healthy control group for conducting multiple comparison analyses, reducing the strength of our conclusions. Second, we only compared TRC and TRO patients in this study, and did not enrol OCD patients who responded well to treatment. This also limits the strength of our conclusions. Third, we did not control for the influence of therapeutic agents on the results. This is a widespread problem because these kinds of agents are complex and methods for normalization are not available. These limitations should be addressed in future studies to clarify the current results.

Ideally, future research will involve long-term follow-up studies with a large sample of first-episode drug-naive OCD patients and a multiple-mode MRI method to dynamically characterize the trajectory of brain features with illness progression, observe treatment efficacy and brain alterations induced by the treatment, describe the specific dynamic trajectories of brain features related to clinical symptoms, and explore specific treatment targets and the pathological mechanisms involved in failed responses to treatment. Although these research methods are time-consuming, such studies would be valuable for accelerating the progress of understanding the pathological basis of OCD and providing an objective index for psychiatrists to develop precise treatments in future, particularly for treatment-refractory patients.

TRC patients exhibited increased global FCD in the right sensorimotor cortex, indicating that hyper-information-communication among the sensorimotor cortex and other brain regions may be a feature of TRC. Because the current study contained several limitations, the strength of our conclusions was restricted. Nonetheless, our preliminary findings can provide useful background information for future studies.

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Disclosure of conflict of interest

None.

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