Microstructural Abnormality in Left Nucleus Accumbens Predicts Dysfunctional Beliefs in Treatment-Resistant Obsessive-Compulsive Disorder

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Data Collection B
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Background: The aim of this study was to determine whether dysfunctional beliefs might predict treatment-resistance and to examine the relationship between fractional anisotropy (FA) in diffusion tensor imaging (DTI) and cognitive biases for optimal treatment choice.

Material/Methods: We recruited 11 non-resistant obsessive-compulsive disorder (OCD) patients, 11 resistant OCD patients, and 11 healthy subjects.

Results: OCD patients had higher Obsessive Beliefs Questionnaire (OBQ-87) subscale scores than subjects in non-resistant and resistant groups. A significant difference was found between non-resistant and resistant OCD patients in R-Scale and I-Scale. A significant decrease in FA was found in left dorsal frontal gyrus and left inferior parietal lobule in the non-resistant group as compared to the control group. FA also decreased significantly in left anterior cingulate cortex, putamen, and nucleus accumbens in the resistant group as compared to the control group. There was a significant decrease in FA in nucleus accumbens in the resistant group as compared to the non-resistant group. Reduced FA in left nucleus accumbens was negatively associated with OBQ-87 factor R and I and the total Yale-Brown Obsessive-Compulsive Scale (Y-BOCS).

Conclusions: Abnormalities in cortical-striatal white matter networks may contribute to the dysfunctional beliefs in patients with treatment-resistant OCD, and the left nucleus accumbens may be an important and promising target for the treatment of OCD.

MeSH Keywords: Anisotropy • Diffusion Tensor Imaging • Obsessive-Compulsive Disorder

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Background

Obsessive-compulsive disorder (OCD), a chronic psychiatric disorder, affects only 1–3% of the general population. However, it often places an enormous burden on patients and their relatives and has a chronic course with poor long-term prognosis. A study with a mean follow-up period of 5.7 years showed evidence that up to 50% of OCD patients have had OCD since childhood or adolescence. Selective serotonin reuptake inhibitors (SSRI) and/or cognitive-behavioral psychotherapy are first-line treatments for OCD [1], but approximately 40–60% of patients fail to respond [2]. Despite optimal cognitive-behavioral and augmentation pharmacologic therapy, approximately 10% of OCD patients remain treatment-resistant [3]. Treatment-resistant OCD remains a major cause of suffering and disability associated with mental disorders [4]. The second-line treatments include augmentation therapy with antipsychotics, electroconvulsive therapy, transcranial magnetic stimulation, and deep brain stimulation (DBS). DBS has been approved by the U.S. Food and Drug Administration for treatment of OCD and is a promising treatment. However, more studies are required to identify effective treatments with specific reference to risk analysis and to improve understanding of the anatomy and circuitry of OCD [5]. DBS permits the selective and reversible modulation of such networks [6], but obtaining higher efficacy requires the determination of precise anatomical localization.

New functional, structural, and molecular findings have led to a new conceptualization of this disorder as dysfunctions of networks that process motivational, affective, and other cognitive stimuli. Microstructural connectivity using diffusion tensor imaging (DTI) scanning may be a tool for early localization in OCD because MRI is sensitive to the microstructural organization of white matter tracts (WM). It has been shown that the altered WM structure in OCD is proportional to the severity of this disease [7]. Changes in DTI in drug-treated OCD patients may reflect the pathophysiological underpinnings of OCD, or a yet unexplored part of the mechanism of action of drugs. Although personal distress and social dysfunction contribute to the occurrence of OCD, the key, or earliest, factor is the dysfunctional brain function and structure, because grey matter and white matter in OCD patients have changed, as reported by voxel-based morphometry (VBM) studies and DTI studies [8]. Whether the exact anatomical changes may predict the treatment resistance is still unknown.

Cognitive ideas in some cognitive theories predict SSRI resistance, given the possibility that dysfunctional beliefs contribute to the development and maintenance of OCD [9]. A recent study reported that cognitive biases, including responsibility bias, thought-action fusion, thought suppression, and metacognitive beliefs, were associated with more OCD symptoms in adolescents [10]. It has also been found that Obsessive Beliefs Questionnaire-44 scores could effectively predict SSRI resistance [11]. Another study found that obsessive doubt as a real probability was an important dimension to consider when the obsessive and compulsive beliefs were evaluated in patients with treatment-resistant OCD, particularly in those having low perceived ability to resist rituals [12]. In addition to biased beliefs, cognitive deficits may also predict treatment resistance, because most patients with OCD have concomitant cognitive deficits in memory[13] and attentional control disorders [14]. An error-related negativity test has indicated that a cognitive bias in outcome prediction is associated with obsessive-compulsive symptomatology [15]. Recent advances in social cognitive neuroscience suggest that a compelling relationship exists between this cognitive bias and the functional activity of brain regions implicated in OCD, including orbitofrontal cortex, dorsolateral prefrontal cortex [16], and other error detection and control-relevant fronto-cingulate system [17]. These studies highlight the importance of cognitive responses to mistakes in OCD and point out the need for further investigations of network interactions involved in treatment resistance in OCD. The aim of this study was to determine whether dysfunctional beliefs might predict treatment resistance and to examine the relationship between fractional anisotropy (FA) detected by DTI and cognitive biases.

Material and Methods

Subjects

We defined treatment resistance as the failure to respond to at least 2 antidepressants of different types given for longer than 4 weeks at the maximum recommended dose for high percentage (between 40% and 60%) of resistance (without a lowest 25% reduction [18] in the Y-BOCS score within 4 to 6 weeks after treatment in a medium-high dose [19]) to first-line drugs, such as clomipramine or selective serotonin reuptake inhibitors [20]. A total of 33 age-, gender-, and intelligence quotient (IQ)-matched subjects (11 non-resistant OCD, 11 resistant OCD, and 11 healthy controls) were recruited into this study from June 2009 to December 2012. The inclusion criteria were: 1) OCD was diagnosed based on the criteria in the Diagnostic and Statistical Manual of Mental Disorders 4th edition; 2) patients were 18–65 years old; 3) patients were able to smoothly communicate with investigators; 4) clomipramine and an SSRI were independently administered for 4–6 week (total 12 weeks) at sufficient doses; 5) signed informed consent was obtained prior to study; 6) patients had no other current Axis-I psychiatric disorders; 7) the current IQ was greater than 80; 8) patients had no other psychiatric disorders or pharmacotherapy during the year before the study. Patients with structural abnormalities, psychiatric diseases, treatments

Table 1. Demographics and clinical characteristics of participants.

	Healthy Controls	Non-resistant patients	Resistant OCD patients
Age at onset (yr, mean ±SD)	–	20.18±9.90	29.27±9.84
Course of disease (yr, mean ±SD)	–	1.55±0.58	1.95±0.68
Total YBOCS score (mean ±SD)	5.73±2.24**	16.91±4.25	30.09±4.74
HAMA score (mean ±SD)	5.82±2.36**	14.55±2.77	23.81±4.92
HAMD score (mean ±SD)	6.10±1.92**	13.55±2.94	15.36±4.30
IQ score	91.91±7.34	90.45±10.35	85.45±8.89

Student t test, ** $P<0.01$, *vs.* resistant and non-resistant OCD patients.

affecting cognitive function, and other clinically relevant abnormalities shown in laboratory examinations were also excluded. Subjects in the normal control group had no neurologic or psychiatric condition, no cognitive complaints, were taking no psychoactive medication, and the results of neurologic and neurocognitive examinations must be normal. Characteristics of subjects recruited into this study are listed in Table 1. The study protocol, patient characteristics, and consent forms were approved by the Health Research Ethics Committee of our university.

Neuropsychological evaluations

The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) was used to assess the severity of OCD, and the Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAMD) were employed to assess the presence and severity of depressive symptoms. The Wechsler Adult Scale of Intelligence was used to determine the IQ of participants. These questionnaires have long been recommended for use in OCD patients, with great validity and reliability [21]. The Obsessive Beliefs Questionnaire (OBQ-87) measures the strength of belief related to OCD and was recommended by the Obsessive Compulsive Cognitions Working Group. It contains 87 items that are rated on a 7-point Likert-type scale and contains 6 factors: U-Scale: Intolerance of uncertainty; T-Scale: Overestimation of threat; C-Scale: Overcontrol of thoughts; I-Scale: Importance of thoughts; R-Scale: Responsibility; P-Scale: Perfectionism.

Magnetic resonance imaging acquisition

The MRI scans used in the present study were performed between June 2009 and December 2012. All subjects underwent MRI scanning with a Philips 3T Achieva Quasar Dual MRI scanner (Philips Medical System, Best, The Netherlands) at the First Affiliated Hospital of Zhejiang University. For each participant, the MRI scanning was performed within 2 weeks after neuropsychological testing. Foam pads were used to minimize head motion, and earplugs were used to diminish noise

during scanning. High-resolution T1-weighted structural images were acquired for a whole-brain 3-D MRI with a magnetization-prepared rapid-acquisition gradient echo sequence using the following parameters: 144 sagittal slices; thickness, 1.0 mm; 256×256 matrix; field of view, 256×256 mm; TE, 3.7 ms; and TR, 2000 ms. A diffusion-weighted data set was also collected with an echo planar image sequence using the following parameters: 45 transversal slices; 30 gradient directions; thickness, 3.0 mm; no gap; 192×192 matrix; field of view, 240×240 mm; TE, 93 ms; TR, 6046 ms; b1, 0; and b2, 1000 s/mm^2.

Diffusion tensor imaging preprocessing

DTI data were preprocessed and analyzed with the voxel-based analysis using a traditional method [22]. The diffusion dataset was pre-aligned to correct for head motion, and the effects of gradient coil eddy currents were corrected using tools from the FMRIB software library (*http://www.fmrib.ox.ac.uk/fsl*). Then, a diffusion tensor model was fitted to each imaging voxel of the preprocessed DTI data in the native diffusion space to derive FA. The resulting FA images were transformed into Montreal Neurological Institute (MNI) standard space using Statistical Parametric Mapping (SPM8, *http://www.fil.ion.ucl.ac.uk/spm/*). For each subject, the b=0 images were co-registered with the structural T1 image; the same co-registration parameters were applied to the FA maps (in the same space as the b=0 images). The T1 image of each individual was then normalized to the SPM T1 template (in MNI standard space), and the same normalization parameters were then applied to the co-registered FA images. All images were re-sampled with a voxel size of 2×2×2 mm^3. The normalized FA images were smoothed with an 8-mm full-width at half-maximum Gaussian kernel to decrease the spatial noise, and a mean image (FA template) was created.

Statistical analysis

A 2-sample t-test was performed on diffusion tensor images of FA using xjview (*http://www.alivelearn.net/xjview8*) to compare

Table 2. Regions with significantly reduced FA in the left brain.

Compared group	Region	Cluster Level		MNI Coordinates			T
		Cluster size	Pcorrected	x	y	z	
Non-resistant OCD *vs.* control	Dorsal frontal gyrus	152	<0.001	−10	42	32	4.31
	Inferior parietal lobule	125	<0.002	−8	56	48	3.07
Treat-resistant OCD *vs.* control	Anterior cingulate	113	<0.001	−16	34	14	4.18
	Putamen	93	<0.001	−10	19	4	4.46
	Nucleus accumbens	68	<0.001	−9	20	6	4.51
Treat-resistant OCD *vs.* non-resistant OCD	Nucleus accumbens	52	<0.001	−8	17	2	3.93

between either 2 groups of subjects. An initial threshold of 50 voxels or greater, surviving a false discovery rate (FDR) threshold of $P<0.05$ was considered statistically significant between 2 groups. The mean FA of regions that previously showed significant difference in FA were calculated for controls, patients with best efficacy, and patients with treatment-resistance, using the normalized and smoothed FA maps. Data were analyzed using SPSS version 15.0. A multiple-regression analysis was performed to estimate the correlation of average FA with OBQ-87 scores and other disease-related variables. A value of 2-tailed $P<0.05$ was considered statistically significant.

Results

Clinical and demographic characteristics of subjects

There were no significant differences in the age at onset, course of disease, HAMD score, or IQ score between non-resistant patients and resistant patients ($P>0.05$) (Table 1).

OBQ-87 factors

There was a significant difference (t test, $P<0.01$) in OBQ-87 factors between healthy controls and non-resistant OCD patients, and between healthy controls and resistant OCD patients. All the OCD patients showed higher factor scores than controls (Table 2). When compared with non-resistant OCD patients, treatment-resistant OCD patients had higher scores in R-Scale (4.84 ± 0.29 *vs.* 5.31 ± 0.39) and I-Scale (4.87 ± 0.37 *vs.* 5.29 ± 0.39) ($t=3.15$, $P=0.005$ and $t=2.59$, $P=0.02$, respectively) (Figure 1).

Diffusion tensor imaging

Voxel-wise analysis revealed the reduced FA in 2 regions in the non-resistant group as compared to the control group ($P<0.001$,

corrected, cluster size >50). One area was located at the left dorsal frontal gyrus [x, y, z: −10 42 32], and the second at the left inferior parietal lobule [x, y, z: −8 56 48]. When compared with controls, the treatment-resistant OCD patients showed lower FA in 3 areas: the left anterior cingulate [x, y, z: −16 34 14], left putamen near the head of the caudate [x, y, z: −10 19 4], and left accumbens nucleus [x, y, z: −9 20 6]. The FA of the nucleus accumbens [x, y, z: −9 11−5] significantly decreased in the treatment-resistant patients as compared to non-resistant patients. There were no other regions with significantly reduced or increased FA between resistant and non-resistant patients (Figure 2).

Multi-regression analysis

Regression analysis revealed that the reduced FA of the left nucleus accumbens was negatively associated with the OBQ-87 factor R ($R^2=0.41$, Beta=−0.57, $P<0.05$), factor I ($R^2=0.37$, Beta=−0.55, $P<0.05$), and Total YBOCS score ($R^2=0.53$, Beta=−0.64, $P<0.01$), which were strongly correlated with the severity of OCD symptoms (Figure 3). Moderate correlations were observed between FA of different regions of the brain and severity of OCD symptoms. The disease variables (duration of illness, anxiety score, and other OBQ-87 factors) are shown in Table 3. The FA of the left inferior parietal lobule had a moderate negative correlation (Beta=−0.47, $P=0.05$). The correlation of putamen FA with YBOCS score (Beta=−0.46, $P=0.04$), HAMA score (Beta=−0.43, $P=0.05$) and OBQ-87 R-Scale (Beta=−0.45, $P=0.05$) was also found.

Discussion

OCD is defined as unwanted recurrent and persistent obsessions and/or compulsions characterized by unnecessary ideas, thoughts, impulses, and images always causing marked anxiety and distress. Although the exact pathogenesis of OCD is not fully understood, a theory that has been universally accepted
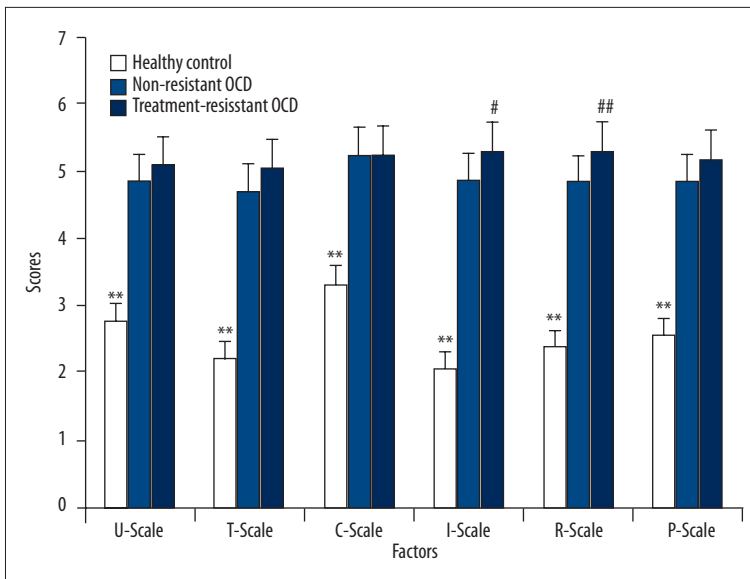
Figure 1. OBQ-87 factors in three groups. Student *t* test, ** $P<0.01$, *vs.* resistant and non-resistant OCD patients; # $P<0.05$, ## $P<0.01$, *vs.* non-resistant OCD patients.
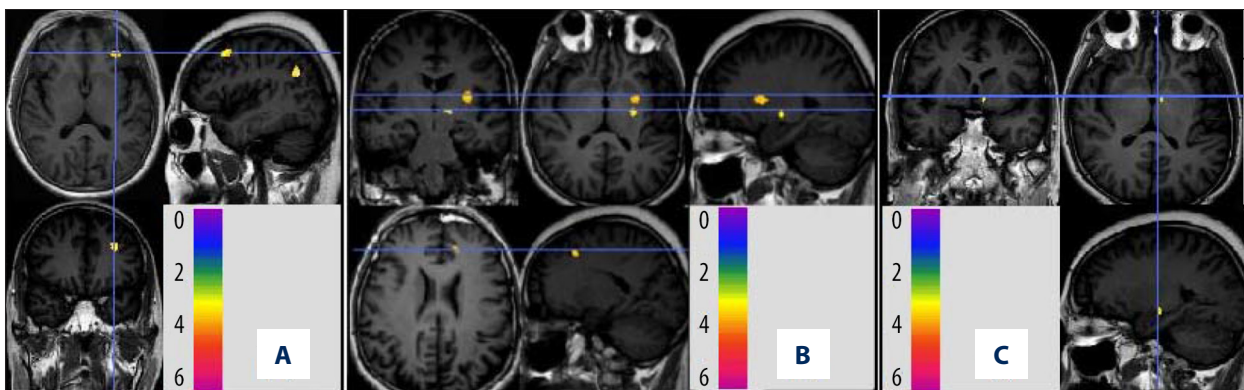

Figure 2. Regions with decreased FA (left dorsal frontal gyrus and left Inferior parietal lobule) in non-resistant OCD patients when compared with healthy controls (**A**) and in treatment-resistant OCD patients (left anterior cingulate, left putamen and left nucleus accumbens) when compared with healthy controls (**B**). Regions with marked difference in FA (left nucleus accumbens) between non-resistant OCD group and resistant OCD group (**C**).
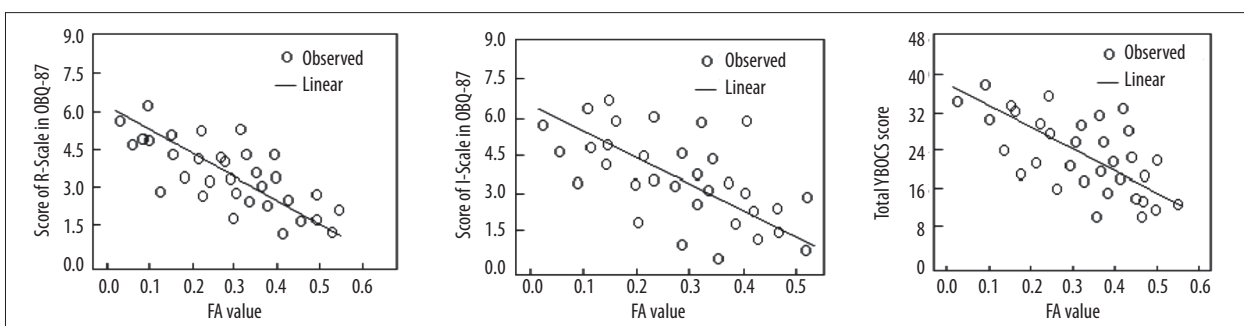

Figure 3. Significantly negative correlation of reduced FA of left nucleus accumbens with factor R and I in OBQ-87 and total YBOCS score. FA, fractional anisotropy; OBQ-87, Obsessive Beliefs Questionnaire; YBOCS, Yale-Brown Obsessive-Compulsive Scale.

is that the combined effect of genetic and environmental factors is related to the occurrence of this disease. Among many risk factors, the dysfunctional cognitive beliefs have long been studied. Cognitive-behavioral models, which are currently the most prominent psychological theories of OCD, emphasize the role of dysfunctional beliefs in this disorder. Some inappropriate beliefs, such as inflated responsibility, perfectionism, intolerance of insecurity, and overestimation of threat, were proven

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Table 3. Correlations of FA of different regions of left brain with disease variables (Beta/*P*).

	Dorsal frontal gyrus	Inferior parietal lobule	Anterior cingulate	Putamen	Nucleus accumbens
Age at onset	−0.12/0.51	−0.19/0.21	−0.08/0.62	−0.20/0.46	−0.23/0.17
Illness duration	−0.09/0.74	−0.15/0.33	−0.11/0.77	−0.16/0.55	−0.07/0.89
YBOCS score	−0.35/0.25	−0.47/0.05	−0.37/0.20	−0.46/0.04	−0.64/0.01
HAMA score	−0.37/0.07	−0.35/0.09	−0.35/0.11	−0.43/0.05	−0.49/0.04
HAMD score	−0.16/0.42	−0.06/0.71	−0.20/0.32	−0.17/0.48	−0.12/0.51
IQ score	−0.04/0.95	−0.08/0.62	−0.13/0.62	−0.15/0.60	−0.19/0.37
OBQ-87-U	−0.11/0.54	−0.17/0.26	−0.17/0.38	−0.25/0.29	−0.29/0.08
OBQ-87-T	−0.13/0.46	−0.11/0.59	−0.03/0.97	−0.31/0.16	−0.26/0.10
OBQ-87-C	−0.06/0.86	−0.13/0.46	−0.08/0.69	−0.27/0.21	−0.24/0.13
OBQ-87-I	−0.12/0.50	−0.33/0.15	−0.06/0.81	−0.39/0.07	−0.55/0.04
OBQ-87-R	−0.17/0.39	−0.26/0.19	−0.14/0.50	−0.45/0.04	−0.57/0.03
OBQ-87-P	−0.08/0.77	−0.16/0.30	−0.16/0.41	−0.22/0.33	−0.35/0.06

to be positively and significantly correlated with OCD symptoms. The aim of this study was to test whether the cognitive biases cause the treatment resistance in OCD and to explore the relationship between dysfunctional beliefs and the reduced structural integrity in clusters within the limbic-frontal connectivity pathways.

Age-, sex- and IQ-matched participants were recruited, aiming to ensure the balance of demographics. Our results showed higher Y-BOCS and HAMA scores in the treatment-resistant OCD patients as compared to non-resistant patients, indicating that drug resistance in OCD patients makes the symptoms refractory and induces concomitant anxiety symptoms, which is clinically reasonable and understandable.

Modern cognitive approaches have postulated that obsessions and compulsions are caused and/or maintained by misinterpretations about their meaning, and confirmed that some core beliefs are crucial for the development, maintenance, and treatment of OCD. There are a number of obsessive beliefs that are considered fundamental to OCD, including personal responsibility, threat estimation, perfectionism, need for certainty, importance of thoughts, and thought control. The OBQ-87 scale and its simplified edition Obsessive Beliefs Questionnaire-44 were developed based these characteristics by the Obsessive Compulsive Cognitions Working Group and are used to measure beliefs considered important in the development and maintenance of OCD. Using OBQ-87 and OBQ-44, investigators have made great progresses, such as the prediction of OCD symptom dimension [23], OCD-related anatomical basis [9,24], and

genetic background [25] with specific cognitive beliefs. In this study, 6 inflated cognitive beliefs – intolerance of uncertainty, overestimation of threat, over-control of thoughts, importance of thoughts, responsibility and perfectionism – were found to be obvious in Chinese OCD patients. Further regression analysis showed that importance of thoughts and responsibility were related to drug-resistance in OCD. Importance of thoughts has been reported to be strongly correlated with the OCD severity, and a moderate relationship was reported between other biased beliefs and OCD severity [26], which means that this dysfunctional belief is more specific in OCD prediction. Recently, the importance of thoughts has been found to be a unique predictor [27] of poor cognitive therapeutic efficacy [26] and resistance to selective serotonin reuptake inhibitors [11]. Inflated responsibility is proposed to be a main feature of cognitive-behavioral models of OCD [28] and may specifically mediate the attitudes of family members of OCD patients, leading to the development of this illness [29] and less reduction in overall OCD symptom after cognitive behavioral therapy [30]. Our study similarly found that importance of thoughts and responsibility were better predictors of resistance to OCD treatment.

Integration of neurobiological and cognitive models of OCD is a key approach to clarify the complex etiology of drug-resistant OCD. DTI scanning was used to detect the FA, and the relationship between dysfunctional beliefs and FA was evaluated. Results showed that decreased FA of left dorsal frontal gyrus, left inferior parietal lobule, left anterior cingulate cortex, nucleus accumbens, and left putamen was related to OCD. This is consistent with findings that the abnormalities

in frontal-striatal neural connectivity were involved in the advancement and maintenance of OCD [31]. The anterior cingulate, a key element of the neuroanatomical brain system for error detection [32] and emotional modulation in the striatal-cortical network, is thickened [33] and is less active during cognitive tasks [34], and the NAA and Cho ratios in magnetic resonance spectroscopy also are reduced [35] in OCD patients. Recently, a study [8] reported that the smaller anterior cingulate cortex in OCD patients with lower FA underlay the etiology of OCD. The structural and functional changes in the anterior cingulate also provide evidence for deeper understanding of the pathogenesis of OCD. Our study further confirmed that several microstructural damages, including anterior cingulate, were involved in the pathogenesis of OCD. The FA was compared between non-resistant group and treatment-resistance group and results showed FA of the left nucleus accumbens was decreased significantly in the treatment-resistance group, and could strongly predict the biased ideas (importance of thoughts and responsibility). The nucleus accumbens (NAcc) is a key structure in the reward pathway, and reward-processing deficits related to ventral striatal abnormalities have been proposed to be involved in the pathogenesis of OCD [36]. Studies have shown that: 1) OCD patients display stronger activation in the nucleus accumbens under standardized symptom provocation [37]; 2) Compulsive aversion learning process in OCD is mediated by abnormal limbic responses to threatening and rewarding stimuli, as well as by deficient functional and structural limbic-frontal connectivity [38]; 3) the nucleus accumbens connects the orbitofrontal cortex, anterior cingulate cortex, ventral striatum, and mediodorsal thalamus, and constitutes a cortico-striato-thalamo-cortical circuit implicated in OCD [39]. On the basis of the above findings, it is clear that the nucleus accumbens plays an important role in the pathogenesis and treatment of OCD. Injury to the left nucleus accumbens may induce activation of axonal fibers spanning the nucleus accumbens, alter its oscillatory activity within its projecting network, and/or promote neurotransmission in its interior. DBS has emerged as a treatment for severe, therapy-refractory OCD, and promising results have been reported. To date, the mechanism of its action is still largely unknown and therapeutic experience is limited [40]. Considering that the different targets for therapy in OCD are somewhat unclear, the nucleus accumbens as a new target [41] may provide a good choice for precise localization, and aid in effective treatment of drug-resistant OCD.

There were limitations in this study. First, the sample size was small, which can increase the risk of Type II errors. Considering that OCD is a highly multidimensional and heterogeneous disorder [42], small sample size prevents this report from fully analyzing the relation between different symptom phenotypes and bias beliefs, as well as damaged brain micro-connection. Second, this study had a cross-sectional design, which means that causative conclusions cannot be drawn. Prospective studies with larger sample sizes are needed to test this relationship. Finally, the weak definition of "treatment-resistant" means our results must be interpreted cautiously, because the pathology is a gradual process, affected by drug selection, dosage, treatment duration, and response criteria. The reasons for treatment resistance are very complicated, involving drug metabolism *in vivo*, neuro-circuit disturbance, comorbid disorders such as major depression, tic disorders, and alcohol use [43].

Conclusions

Abnormalities in cortical-striatal white matter networks may contribute to the dysfunctional beliefs in treatment-resistant OCD, and the left nucleus accumbens may be a substantial and promising target for treatment of OCD.

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