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Research paper

# Abnormal small-world brain functional networks in obsessive-compulsive disorder patients with poor insight



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# ABSTRACT

*Background:* There are limited data on neurobiological correlates of poor insight in obsessive-compulsive disorder (OCD). This study explored whether specific changes occur in small-world network (SWN) properties in the brain functional network of OCD patients with poor insight.

*Method:* Resting-state electroencephalograms (EEGs) were recorded for 12 medication-free OCD patients with poor insight, 50 medication-free OCD patients with good insight, and 36 healthy controls.

*Results*: Both of the OCD groups exhibited topological alterations in the brain functional network characterized by abnormal small-world parameters at the beta band. However, the alterations at the theta band only existed in the OCD patients with poor insight.

*Limitations:* A relatively small sample size. Subjects were naïve to medications and those with Axis I comorbidity were excluded, perhaps limiting generalizability.

*Conclusions:* Disrupted functional integrity at the beta bands of the brain functional network may be related to OCD, while disrupted functional integrity at the theta band may be associated with poor insight in OCD patients, thus this study might provide novel insight into our understanding of the pathophysiology of OCD.

# 1. Introduction

Individuals with obsessive-compulsive disorder (OCD) exhibit obsessions (repetitive intrusive thoughts) and/or compulsions (repetitive ritualistic behaviors) in their actions. Despite being classified as a unitary nosological entity, OCD is a clinically heterogeneous disorder that is characterized by an insight spectrum by the patient that ranges from full recognition of obsessive-compulsive (OC) symptoms as irrational to acceptance of the symptoms as truly realistic and rational (Solyom et al., 1985). The Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) describes a subgroup of OCD patients that are characterized as having "poor insight", and these patients do not recognize their obsessions and compulsions as excessive or unreasonable for the majority of the episodes they experience. Poor insight has been reported to affect 21–36% of all OCD patients (Catapano et al., 2010; Foa et al., 1995; Matsunaga et al., 2002; Ravi et al., 2004), and it has also been associated with greater severity of OCD symptoms (Catapano et al., 2010; Ravi et al., 2004), an earlier age at onset, a longer duration of illness (Catapano et al., 2010; Matsunaga et al., 2002; Ravi et al., 2004), a higher comorbidity rate with depression (Catapano et al., 2010; Ravi et al., 2004), and body dysmorphic disorder (Eisen et al., 2004), and an insufficient response to behavioral therapy (Himle et al., 2006; Mataix-Cols et al., 2010; Erzegovesi et al., 2001; Ravi et al., 2004). Furthermore, different OCD clinical subtypes may be associated with different etiologies, and pathogenic mechanisms.

Neuropsychological studies have reported that OCD patients with

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poor insight exhibit more severe neuropsychological deficits in executive function (Tumkaya et al., 2009) conflict resolution/response inhibition, and verbal memory (Kashyap et al., 2012). A previous neuroimaging study reported that OCD patients with poor insight have a higher frequency of various types of brain structure abnormalities compared with patients with good insight (Aigner et al., 2005). These findings suggest that OCD patients with good insight versus poor insight may possess different neuropsychological and neurobiological characteristics. Nevertheless, very few studies have directly examined the specific neurobiological alterations of OCD patients with poor insight.

Abnormal functional connectivity in the neurocircuitry that comprises the corticostriatal-limbic circuits (Jung et al., 2013) and medial frontal cortex (Fitzgerald et al., 2010) is hypothesized to play an important role in the pathophysiology of OCD. Harrison et al. (2009) found that OCD patients have abnormal and heightened functional connectivity of ventrolimbic corticostriatla regions using resting-state functional magnetic resonance imaging. Furthermore, the abnormalities of functional connectivityis not limited tocortical-striatal-thalamiccortical circuits and involves abnormalities in additional large-scale brain systems, especially the limbic system (Hou et al., 2014). Additionally, evidence of abnormal functional connectivity in subjects with OCD has been found to include alterations in the small-world network (SWN) properties of the brain functional networks of OCD patients compared with nonclinical individuals (Zhang et al., 2011). However, whether poor insight in OCD patients is related to abnormalities in functional brain connectivity remains unclear.

Based on the previous findings of neuropsychological and neurobiological studies (Aigner et al., 2005; Kashyap et al., 2012), it is hypothesized that OCD patients with poor insight have specific abnormalities in their SWN attributes at several electroencephalogram (EEG) bands. The present study was to explore whether specific changes in the properties of the SWN occur within the whole-brain functional networks of OCD patients with poor insight compared with OCD patients with good insight and healthy controls. To evaluate these potential changes, resting-state EEG and graph theoretical analysis were used to investigate the organization of the overall functional brain connectivity of OCD patients with poor insight and good insight at different EEG bands within the SWN.

#### 2. Methods

#### 2.1. Participants

Sixty-two (63%) OCD patients and 36 (37%) healthy controls participated in this study. The patients with OCD were recruited from the psychology clinic at Second Xiangya Hospital of Central South University. These patients were diagnosed by two certified psychiatrists using the Structured Clinical Interview for DSM-IV (SCID) and fulfilled criteria for OCD. The exclusion criteria included: (i) patients with comorbid DSM-IV axis I disorders; (ii) patients at specific medical or neurological conditions that would interfere with the evaluation of the study results (e.g., Tourette syndrome, hyperactivity, organic mental diseases, mental retardation, history of psychosurgery, history of epilepsy); and (iii) patients taking prescription of psychoactive medication previously or currently. Accordingly, all patients included in this study were naïve to medications. The patients were subsequently dichotomized into those diagnosed with good insight versus poor insight, with the latter including those who generally did not recognize that their obsessions and compulsions were excessive or unrealistic. The quality of insight (poor/good insight) was rated according to SCID for DSM-IV (kappa = 0.90 for the rating of insight). In addition, the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was used to assess disease severity for the patients with OCD (Goodman et al., 1989) while the severity of depressive and anxiety symptoms of each subject were separately rated using the Beck Depression Inventory (BDI-II) (Beck et al., 1996) and the State Trait Anxiety Inventory (STAI) (Spielberger,

1983) Each patient underwent an EEG recording prior to the start of any psychiatric treatment.

Healthy controls were recruited from the community and from Central South University by poster advertisements. All of the controls were screened using the Structured Clinical Interview for the DSM-Non-Patient edition (SCID-NP; First et al., 1995) to confirm a lifetime absence of psychiatric and neurologic illness. No history of psychiatric illness was reported in the controls or in any of their first-degree relatives.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University. All participants provided written informed consent.

## 2.2. EEG recordings

EEGs were recorded using a 32-channel cap (Easy-cap) with 30 Ag/ AgC1 electrodes placed according to the 10/20 system. Electro-oculograms (EOGs) to detect eye movements and blinks were recorded with electrodes placed on the bilateral external canthi and the left infraorbital and supraorbital areas. Both the EEGs and EOGs were sampled at 1000 Hz with a 0.1–200 Hz band pass of a Neuroscan Nuampls digital amplifier system (Neuroscan Inc., USA). The left mastoid was used as a reference for each recording. Electrode impedances were kept below 5 k $\Omega$ . The EEGs were recorded over 180 s when the subjects were sitting in a comfortable fixed chair in a quiet room with their eyes close.

# 2.3. EEG analysis

During preprocessing, the EEG signals were digitally band-pass filtered at 0.5–70 Hz, while a notch filter was used to remove 50 Hz electrical noise. To reduce the non-zero reference effect, the recordings were re-referenced to REST (zero) to avoid systematic effects that may arise from referencing to a particular channel, particularly in the context of synchronization analysis. The software can be found at (http://www.neuro.uestc.edu.cn/REST/) (Qin et al., 2010). A detrend was subtracted based on the entire time range.

Graph analysis was performed in Matlab (The MathWorks, Inc.) using software written by one of the authors (YC). The EEGs were decomposed to the conventional EEG bands, including delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (30-48 Hz) band, using a five-level wavelet filter bank. Functional connectivity was determined by computing the synchronization likelihood (SL) between all pair-wise combinations of channels for the five bands, resulting in a 30  $\times$  30 connectivity matrix. SL is a measure of the dynamic interdependencies between a time series (EEG channel) and one or more other time series. In contrast to some linear technologies, such as coherence, SL is valid for both linear and nonlinear interdependencies as a function of time (Stam and van Dijk, 2002), which means that SL could detect more general interaction between dynamic systems. In general, EEG signals may contain both linear and non-linear components. In this work, we firstly tested the nonlinearity of the EEG data with the measure described in the Appendix A. It showed that 72.54%, 72.71%, and 74.35% of the data were identified to be nonlinear for the data set of the OCD patients with good insight, OCD patients with poor insight, and the controls, respectively. Therefore, the synchronization likelihood was chosen as the measure for our research.

The graph theory analysis was performed to reveal the differences among these three groups. Briefly, the SL connectivity matrices were converted into binary matrices through a set of thresholds with a step of 1%. The set of thresholds save the 10–50% strongest links, with their original values while the other links were set to be zero, which make the matric sparser (Liu et al., 2008). For each threshold, the normalized cluster coefficient  $C_{nml}$ , which represents the probability that the neighbors of a node are also connected, and the normalized character-

istic path length  $L_{nml}$ , which is the average number of edges in the shortest paths between every pair of nodes in the network, were calculated to evaluate the local efficiency and global efficiency of the matric (Milo et al., 2002). We took the optimal threshold as the one which separate the three groups with  $C_{nml}$  or  $L_{nml}$  best. Besides, a small world network typically has the property of  $C_{nml} \geq 1$  and  $L_{nml} \approx 1$ .

# 2.4. Statistical analysis

Statistical comparisons of the demographic (age, years of education) and clinical variables among three groups (OCD with good insight, OCD with poor insight, and controls) were performed by using a One-way analysis of variance (ANOVA). A statistical comparison of the gender ratio was performed with a Chi-squared test. Statistical differences in  $C_{nml}$  and  $L_{nml}$  for different frequency bands among three groups were analyzed by the ANOVAs with a Levene's test for equality of variance. Given that the significant difference between the patients with OCD and controls in the total scores of the BDI, SAI, and TAI, these scores were entered as a covariate into the ANOVA analysis. To account for the increased probability of type I error, a false discovery rates (FDR) with p-value adjustment was used for the ANOVAs and the post hoc tests. All statistical tests were two-tailed and had a significance level of  $\alpha = 0.05$ .

#### 3. Results

#### 3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of the subjects were shown in Table 1. Of the 62 patients with OCD, 12 (19%) were OCD with poor insight. Total of six OCD patients had family history for psychiatric disorder (two of them in the group of OCD patients with poor insight). There was no significant difference between the three groups in terms of age, years of education, and gender ratio. Compared with the healthy controls, both OCD groups had significantly higher scores on the BDI-II, SAI, and TAI (p < 0.001), whereas no significant differences were observed between two OCD groups (p = 0.76; 0.50; 0.30 separately). Furthermore, no significant difference between the two OCD groups was observed regarding disease duration, age of disease onset, and the Y-BOCS scores (p = 0.92; 0.06; 0.66 separately).

#### 3.2. Graph theoretical analysis

The homogeneity assumptions were not violated based on the

Table 1

Demographic and clinical characteristics of the three groups.

results obtained on the Levene's test (p values ranging from 0.076 to 0.926). The differences among three groups in the normalized clustering coefficients  $(C_{nml})$  and path lengths  $(L_{nml})$  that were assessed at a threshold of 18% were shown in the Fig. 1. There were no significant differences in the  $C_{nml}$  values among the three groups for the five EEG frequency bands [delta: F(2,92) = 0.11, p = 0.90; theta: F(2,92) =0.48, p = 0.62; alpha: F(2,92) = 0.39, p = 0.68; beta: F(2,92) = 0.20, p = 0.82; gamma: F(2,92) = 1.51, p = 0.23] (Fig. 1a). However, the findings showed a main effect of group in the  $L_{nml}$  values [theta: F(2,92) = 5.04, corrected p < 0.05,  $\eta_p^2 = 0.10$ ; beta: F(2,92) = 8.13, corrected p < 0.05,  $\eta_n^2 = 0.15$ ]. For the theta band,  $L_{nml}$  exhibited a significant decrease in the OCD with poor insight group compared with the healthy group (corrected p < 0.05) (Fig. 1b); however, no significant difference was observed between the OCD with good insight group and the healthy group (p = 0.26). For the beta band,  $L_{nml}$  significantly decreased for both of the OCD groups compared with the healthy group (corrected p < 0.05); but no significant difference between the two OCD groups was observed. No significant differences were observed in the *L*<sub>nml</sub> values for the delta, alpha, and gamma bands among the three groups [delta: F(2,92) = 1.59, p = 0.21; alpha: F(2,92) =0.71, p = 0.49; gamma: F(2,92) = 0.11, p = 0.89].

Fig. 2 shows the mean normalized clustering coefficient ( $C_{nml}$ ) and characteristic path length ( $L_{nml}$ ) values for the three groups plotted against thresholds of 10–50% of strongest edges. The left panels in Fig. 2 show a comparison of the  $C_{nml}$  values between the three groups at thresholds of 10–50% for the five EEG frequency bands. No significant differences in  $C_{nml}$  values in any band were observed between groups at the thresholds of 10–50%. The right panels in Fig. 2 show a comparison of the  $L_{nml}$  values for the five EEG frequency bands between the three groups at the thresholds of 10–50%. The right panels in Fig. 2 show a comparison of the  $L_{nml}$  values for the five EEG frequency bands between the three groups at thresholds of 10–50%. The  $L_{nml}$  values in the delta, theta, and beta bands were differed between the three groups at the thresholds roughly ranged from 10% to 20%.

Notably, the networks in the OCD patients with good insight or poor insight manifested small-world properties, similar to those of the healthy controls. Specifically, in all of the examined frequency bands, the clustering coefficients were considerably larger than in the corresponding random graphs ( $C_{nml} > 1$ ), and simultaneously, the path length stayed reasonably close to the random graph path length ( $L_{nml} \approx 1$ ) at all of the thresholds (Fig. 2).

Parameters examined	OCD with good insight (n = $50$ )	OCD with poor insight (n = $12$ )	Healthy controls $(n = 36)$	Test statistics	<i>p</i> -value	$\eta_p^2$	Post hoc comparison
	Mean (SD)	Mean (SD)	Mean (SD)				
Demographic variables							
Age (years)	21.74 (5.30)	21.33 (4.10)	22.58 (3.05)	0.53 <sup>a</sup>	0.591		
Education (years)	13.54 (2.57)	13 (3.25)	13.72 (2.46)	0.34 <sup>a</sup>	0.71		
Gender ratio (M/F)	28 / 22	7 / 5	22 / 14	0.23 <sup>b</sup>	0.894		
Clinical Assessments							
BDI-II	21.44 (9.76)	22.08 (8.86)	6.56 (6.82)	34.07 <sup>a</sup>	< 0.001	0.42	OCD-GI, OCD-PI > HC
SAI	52.64 (12.83)	50.42 (11.83)	35.33 (10.24)	23.38 <sup>a</sup>	< 0.001	0.33	OCD-GI, OCD-PI > HC
TAI	57.05 (9.17)	54.22 (7.58)	39.45 (7.50)	47.35 <sup>a</sup>	< 0.001	0.50	OCD-GI, OCD-PI > HC
Age of onset	16.84 (4.80)	14.92 (5.96)	-	1.42 <sup>c</sup>	0.239		
Illness duration (years)	4.28 (3.76)	4.52 (4.28)	-	0.04 <sup>c</sup>	0.847		
Y-BOCS	29.32 (5.70)	28.83 (7.23)	-	0.06 <sup>c</sup>	0.802		
Obsessive	13.96 (3.92)	13.92 (4.32)	-	$0.22^{c}$	0.644		
Compulsive	15.36 (2.77)	14.92 (3.75)	-	0.01 <sup>c</sup>	0.973		

OCD-GI: obsessive-compulsive disorder (OCD) with good insight; OCD-PI: OCD with poor insight; HC: healthy controls.

BDI-II: Beck Depression Inventory; SAI: State Anxiety Inventory; TAI: Trait Anxiety Inventory; Y-BOCS: Yale-Brown Obsessive Compulsive Scale.

<sup>a</sup> F value of ANOVA

<sup>b</sup>  $\chi^2$ value of Chi square test.

c t value of t-test.



**Fig. 1.** The significantly different mean normalized clustering coefficients ( $C_{nml}$ ) and path length ( $L_{nml}$ ) at a threshold of 18% between the three groups (OCD-GI: OCD patients with good insight, OCD-PI: OCD patients with poor insight, and HC: healthy controls). The black asterisks denote statistically significant between-group differences (p < 0.05, *t*-test with FDR correction).

#### 4. Discussion

This study investigated the framework of small-world network (SWN) among OCD patients with good insight, OCD patients with poor insight, and healthy controls at five EEG frequency bands. OCD patients exhibited topological alterations at the beta bands compared with the healthy controls. However, the topological alterations at the theta band existed only in the OCD patients with poor insight not in the OCD patients with good insight. These findings suggest that poor insight OCD may be associated with disruptive functional integrity in the brain functional network at the theta band. To our knowledge, this is the first study to demonstrate that the poor insight subtype of OCD may be related to alterations in functional brain connectivity patterns in the framework of small-world network (SWN) that can be detected using resting-state EEG. This insight into the pathophysiology of OCD could be particularly valuable for characterizing the poor insight subgroup.

Healthy controls that were examined in the present study exhibited small world functional connectivity in five frequency bands, which provides further support for the presence of small-world features in functional networks in the brain. These results are consistent with previous findings with resting state MEG, EEG, and fMRI (Stam, 2004; Stam et al., 2007; Zhang et al., 2011). The SWN is characterized by combinations of highly clustered connections and short path lengths which lead to dense local clustering and a small number of connections among network units (Watts and Strogatz, 1998). These small-world topology characteristics ensure the coexistence of functional segregation and integration capacities, and these facilitate the effective integration of multiple segregated sources of information during cognitive processing (Sporns and Zwi, 2004).

The OCD patients with poor insight had a significantly shorter path length  $(L_{nml})$  at the theta band compared to the healthy controls. The SWN is defined as a network that maintains an optimum balance between local specialization and global integration. The observed decrease in path length may disrupt this balance (Bartolomei et al., 2013), thereby resulting in a less optimal organization of topological brain networks in OCD patients with poor insight.

The different frequency bands of EEGs have different synchronization functions (Stam, 2004). For example, theta oscillations have a role in working memory (Lisman, 2010). It is hypothesized that disrupted integrity of the theta band in OCD patients with poor insight affects their working memory. A previous neuropsychological study of subjects with poor insight OCD observed greater deficits in working memory (Kashyap et al., 2012). Thus, according to the neuropsychological model of insight that was used, individuals with poor insight may have difficulty in updating their memory with corrective information from the environment, and this could cause them to maintain their irrational beliefs, i.e., that their OC symptoms are reasonable and are not excessive. In addition, dynamics in EEG theta band are particularly sensitive to the processing of emotional stimuli (Bekkedal et al., 2011; Knyazev, 2007). For example, the presentation of unpleasant and pleasant pictures of faces of human or primate babies produced the event-related synchronization of hippocampal theta activity (Nishitani, 2003). Consistent evidence suggests that poor insight is associated with higher perceived expressed emotion (De Berardis et al., 2008; Ozkiris et al., 2015). However, we cannot conclude whether or not the disrupted integrity of the theta band in OCD patients with poor insight affects their perception of expressed emotion. Thus, the exact functional significance of the disrupted integrity of the theta band has to be addressed in future work.

Notably, we found that OCD patients exhibit shorter path lengths at the beta band in the sparse graph (at a threshold of 18%). In addition, alterations of path lengths at the delta band were observed in OCD patients with good insight or poor insight compared with healthy controls at other thresholds. These alterations in the observed smallworld attributes may manifest as a less optimal organization of the topological brain network in patients with OCD. Correspondingly, a few EEG studies have previously provided preliminary evidence of altered functional connectivity in the frontal and subcortical brain areas in OCD patients. For example, Velikova et al. (2010) observed an increased delta density in the insula and beta density in the frontal, parietal, and limbic lobes. A decrease in inter-hemispheric coherence and reduced coupling between delta and beta frequencies were also detected using power and coherence analyses. Similarly, Olbrich et al. (2013) reported that lagged non-linear coherence significantly decreased for the beta 2 (20.5-30 Hz) frequency band between the frontal brain areas. The results of the present study further identified and characterized the possible abnormal functional connectivity that may exist in OCD subjects as they relate to the global organization of the functional networks.

Many investigators have suggested that delta oscillations may occur in relation to attention processes (Schroeder and Lakatos, 2009). Specifically, Lakatos et al. (2008) has proposed that the entrainment of cortical delta oscillations may represent a key mechanism of selective attention to the rhythmic auditory of a visual stimulus streams. It seems reasonable to postulate that the alterations observed in the present study regarding the small-world attributes at the delta band may affect selective attention processing. Interestingly, several previous studies consistently reported that OCD patients display selective attention bias and selectively attend to threatening information, particularly information related to their particular concerns (e.g., contamination-related words) (Fan et al., 2014; Moritz et al., 2009; Sizino et al., 2012). It is possible that such biases in selective attention contribute to the development and maintenance of intrusive obsessive thoughts in OCD (Muller and Roberts, 2005).



**Fig. 2.** Mean normalized clustering coefficients (left panels) and path length (right panels) at thresholds of 10–50% among the three groups (OCD-GI, red lines; OCD-PI, green lines; HC, blue lines). The green asterisks denote statistically significant differences (p < 0.05, *t*-test with FDR correction) between the OCD-PI and HC, the blue asterisks denote statistically significant differences between the OCD-GI and OCD-PI. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The decrease of beta power (desynchronization) relative to a baseline level is viewed as a reliable indicator of the onset of movement preparation, movement execution, and even motor imagery (Kuhn et al., 2004). Correspondingly, Zhang et al. (2008) provided empirical evidence that beta recurrence signifies a termination of movement preparation. They found that beta activity rebounded significantly only under the NO-GO condition when subjects were asked to inhibit inappropriate responses. Thus, it appears that beta oscillations play an important functional role in response inhibition. Several previous studies have also provided consistent findings that patients with OCD display deficits in response inhibition, which is considered a major contributing factor to the pathophysiology of OCD (Chamberlain et al., 2007: Lei et al., 2013: Penades et al., 2007). In addition, impaired response inhibition has been found to be independent of OC symptom dimensions (Lei et al., 2015). Based on these findings, we hypothesize that the alterations in the small-world attributes at the beta band that were observed for both of the OCD groups in the present study account for the deficits in the inhibition response that characterize these subjects with OCD.

In addition, it has been suggested that another functional role of beta band oscillations is to highlight a stimulus as novel or salient that warrants further attention (Kisley and Cornwell, 2006). Previous studies demonstrated that set-shifting deficit is a feature of the neurocognitive profile of OCD (Chamberlain et al., 2007). It is hypothesized that the alterations in the small-world attributes at the beta band that we found in the OCD patients might be associated with their set-shifting impairments.

It is worth noting that synchronization likelihood is a measure for the dynamic interdependencies between pairs of time series. As discussed in Ernesto Pereda's paper (Pereda et al., 2005), nonlinear measures should be adopted if we have good reasons to think that the data had any nonlinear structure. In our study, with the measure of surrogate data which have been suggested for the testing of nonlinearity in time series (Theiler et al., 1992), the data were found to be nonlinear. Therefore, synchronization likelihood was chose as the measure for our research. In addition, a different choice of the threshold might alter the results. In this work, we keep the first 10-50% stronger links while the other links are set to zero. The best threshold is taken as the one that makes the largest differences among these three groups. However, we must point out that different methods for threshold choices including the best threshold definition may alter the results and generate different conclusion, and it's a valuable problem for the future.

The present study had several limitations. First, our findings are based on resting-state EEGs and our results remain to be verified by other techniques that assess human brain function, such as magnetoencephalogram (MEG) and functional magnetic resonance imaging (fMRI). Second, the sample size was small, especially for the group of OCD patients with poor insight. Therefore, future studies should be conducted with a larger sample of OCD patients with poor insight and the cross-validation or resampling analysis should be used to evaluate the robustness of this conclusion if it is used for out-of sample prediction or classification. Third, the recruited patients were naïve to medications, and therefore, the effects of pharmacotherapy on topological alterations in the brain functional network were not examined. Forth, patients with any Axis I comorbidity were excluded from this study, and it was not possible to examine OCD patients with one Axis I comorbidity, such as with major depression disorder. Further studies should take into account the effect of comorbidity on topological property of brain functional networks in patients with OCD. Lastly, the information about patients' main symptom phenotype was not gained and reported in the study. The profile of phenotype may affect the results of the study, and should be considered in future studies.

In conclusion, the small-world topological properties at the theta frequency band are altered in OCD patients with poor insight, and are not altered in OCD patients with good insight. However, alterations at the beta bands were detected in both OCD groups. It is suggested that poor insight may be associated with disrupted functional integrity in the brain functional network at the theta band, whereas disrupted functional integrity at the beta bands may be related to OCD. Taken together, our findings might provide valuable insights in understandings the pathophysiology of this disease.

# Contributors

X. Zhu designed research and revised the article; H. Lei and Y. Cui drafted the article and analyzed data; J. Fan, X. Zhang, M. Zhong, J. Yi, and L. Cai collected data and interpreted the data; D. Yao interpreted data and revised the draft. All authors reviewed the paper and approved it to submit.

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# **Conflict of interest**

The authors declare no conflict of interest.

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# Appendix A. Non-linear test

A common way to investigate non-linear properties of time series is the use of phase-randomized surrogate data for the reason that the nonlinearity of surrogated data was removed (Theiler et al., 1992). In this study, we applied the Kolmogorov-Smirnov test (the KS test) for the non-linearity test. Based on the theory that empirical distribution is the distribution principle of consistent estimator, the KS test is usually used to describe the similarity between two independent statistics samples. Totally we generated 1000 surrogate data for each time series which have the same power spectrum and cross-spectra as the original data and the KS test was estimated between each surrogate data and the original data. With the significance level of p = 0.05, if more than 950 surrogated data significantly differed from the original data, then we regard the original data as a non-linear data and if less than 950 surrogated data significantly differed from the original data, then we regard the original data as a linear data (Stam and van Dijk, 2002).

#### References

- Aigner, M., Zitterl, W., Prayer, D., Demal, U., Bach, M., Prayer, L., Stompe, T., Lenz, G., 2005. Magnetic resonance imaging in patients with obsessive-compulsive disorder with good versus poor insight. Psychiatry Res. 140, 173–179.
- Bartolomei, F., Bettus, G., Stam, C.J., Guye, M., 2013. Interictal network properties in mesial temporal lobe epilepsy: a graph theoretical study from intracerebral recordings. Clin. Neurophysiol. 124, 2345–2353.
- Beck, A.T., Steer, R.A., Brown, G.K., 1996. Manual for the Beck Depression Inventory-II. Psychological Corporation, San Antonio.
- Bekkedal, M.Y.V., Rossi, J., Panksepp, J., 2011. Human brain EEG indices of emotions: delineating responses to affective vocalizations by measuring frontal theta eventrelated synchronization. Neurosci. Biobehav. Rev. 35, 1959–1970.
- Catapano, F., Perris, F., Fabrazzo, M., Cioffi, V., Giacco, D., De Santis, V., Maj, M., 2010. Obsessive-compulsive disorder with poor insight: a three-year prospective study. Prog. Neuropsychopharmacol. Biol. Psychiatry 34, 323–330.
- Chamberlain, S.R., Fineberg, N.A., Menzies, L.A., Blackwell, A.D., Bullmore, E.T., Robbins, T.W., Sahakian, B.J., 2007. Impaired cognitive flexibility and motor inhibition in unaffected first-degree relatives of patients with obsessive-compulsive disorder. Am. J. Psychiatry 164, 335–338.
- De Berardis, D., Campanella, D., Serront, N., Gambi, F., Carano, A., La Rovere, R.,

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Nardella, E., Pizzorno, A.M., Cotellassa, C., Salerno, R.M., Ferro, F.M., 2008. Insight and perceived expressed emotion among adult outpatients with obsessive-compulsive disorder. J. Psychiatr. Pract. 14, 154–159.

Eisen, J.L., Phillips, K.A., Coles, M.E., Rasmussen, S.A., 2004. Insight in obsessive compulsive disorder and body dysmorphic disorder. Compr. Psychiatry 45, 10–15.

- Erzegovesi, S., Cavallini, M.C., Cavedini, P., Diaferia, G., Locatelli, M., Bellodi, L., 2001. Clinical predictors of drug response in obsessive-compulsive disorder. J. Clin. Psychopharmacol. 21, 488–492.
- Fan, J., Zhong, M., Zhu, X., Lei, H., Dong, J., Zhou, C., Liu, W., 2014. An attentional inhibitory deficit for irrelevant information in obsessive-compulsive disorder: evidence from ERPs. Int. J. Psychophysiol. 94, 420–426.
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1995. Structured Clinical Interview for DSM-IV Axis I disorders. NewYork State PsychiatricInstitute, New York.
- Fitzgerald, K.D., Stern, E.R., Angstadt, M., Nicholson-Muth, K.C., Maynor, M.R., Welsh, R.C., Hanna, G.L., Taylor, S.F., 2010. Altered function and connectivity of the medial frontal cortex in pediatric obsessive-compulsive disorder. Biol. Psychiatry 68, 1039–1047.
- Foa, E.B., Kozak, M.J., Goodman, W.K., Hollander, E., Jenike, M.A., Rasmussen, S.A., 1995. DSM-IV field trial: obsessive-compulsive disorder. Am. J. Psychiatry 152, 90–96.
- Goodman, W.K., Price, L.H., Rasmussen, S.A., Mazure, C., Fleischmann, R.L., Hill, C.L., Heninger, G.R., Charney, D.S., 1989. The Yale-Brown obsessive compulsive scale. I. Development, use, and reliability. Arch. Gen. Psychiatry 46, 1006–1011.
- Harrison, B., Soriano-Mas, C., Ortiz, H., López-Solà, M., Hernández-Ribas, R., Deus, J., Alonso, P., Yücel, M., Pantelis, C., Menchon, J.M., Cardoner, N., 2009. Altered corticostriatal functional connectivity in obsessive-compulsive disorder. Arch. Gen. Psychiatry 66, 1189–1200.
- Himle, J.A., Van Etten, M.L., Janeck, A.S., Fischer, D.J., 2006. Insight as a predictor of treatment outcome in behavioral group treatment for obsessive-compulsive disorder. Cogn. Ther. Res. 30, 661–666.
- Hou, J., Zhao, M., Zhang, W., Song, L., Wu, W., Wang, J., Zhou, D., Xie, B., He, M., Guo, J., Qu, W., Li, H., 2014. Resting-state functional connectivity abnormalities in patients with obsessive-compulsive disorder and their healthy first-degree relatives. J. Psychiatry Neurosci. 39, 304–311.
- Jung, W.H., Kang, D.H., Kim, E., Shin, K.S., Jang, J.H., Kwon, J.S., 2013. Abnormal corticostriatal-limbic functional connectivity in obsessive-compulsive disorder during reward processing and resting-state. NeuroImage: Clin. 3, 27–38.
- Kashyap, H., Kumar, J.K., Kandavel, T., Reddy, Y.C., 2012. Neuropsychological correlates of insight in obsessive-compulsive disorder. Acta Psychiatr. Scand. 126, 106–114.

Kisley, M.A., Cornwell, Z.M., 2006. Gamma and beta neural activity evoked during a sensory gating paradigm: effects of auditory, somatosensory and cross-modal stimulation. Clin. Neurophysiol. 117, 2549–2563.

Knyazev, G.G., 2007. Motivation, emotion, and their inhibitory control mirrored in brain oscillations. Neurosci. Biobehav. Rev. 31, 377–395.

- Kuhn, A.A., Williams, D., Kupsch, A., Limousin, P., Hariz, M., Schneider, G., Yarrow, K., Brown, P., 2004. Event-related beta desynchronization in human subthalamic nucleus correlates with motor performance. Brain 127, 735–746.
- Lakatos, P., Karmos, G., Mehta, A.D., Ulbert, I., Schroeder, C.E., 2008. Entrainment of neuronal oscillations as a mechanism of attentional selection. Science 320, 110–113.
- Lei, H., Yi, J., Wang, H., Zhang, X., Dong, J., Zhou, C., Fan, J., Zhong, M., Zhu, X., 2013. Inhibitory deficit in semantic conflict in obsessive-compulsive disorder: an eventrelated potential study. Neurosci. Lett. 552, 162–167.
- Lei, H., Zhu, X., Fan, J., Dong, J., Zhou, C., Zhang, X., Zhong, M., 2015. Is impaired response inhibition independent of symptom dimensions in obsessive-compulsive disorder? Evidence from ERPs. Sci. Rep. 5, 10413.
- Lisman, J., 2010. Working memory: the importance of theta and gamma oscillations. Curr. Biol. 20, R490–R492.
- Liu, Y., Liang, M., Zhou, Y., He, Y., Hao, Y., Song, M., Yu, C., Liu, H., Liu, Z., Jiang, T., 2008. Disrupted small-world networks in schizophrenia. Brain 131, 945–961.
- Mataix-Cols, D., Marks, I.M., Greist, J.H., Kobak, K.A., Baer, L., 2002. Obsessivecompulsive symptom dimensions as predictors of compliance with and response to behaviour therapy: results from a controlled trial. Psychother. Psychosom. 71, 255–262.

- Matsunaga, H., Kiriike, N., Matsui, T., Oya, K., Iwasaki, Y., Koshimune, K., Miyata, A., Stein, D.J., 2002. Obsessive-compulsive disorder with poor insight. Compr. Psychiatry 43, 150–157.
- Milo, R., Shen-Orr, S., Itzkovitz, S., Kashtan, N., Chklovskii, D., Alon, U., 2002. Network motifs: simple building blocks of complex networks. Science 298, 824–827.
- Moritz, S., Von Muhlenen, A., Randjbar, S., Fricke, S., Jelinek, L., 2009. Evidence for an attentional bias for washing- and checking-relevant stimuli in obsessive-compulsive disorder. J. Int. Neuropsychol. Soc. 15, 365–371.
- Muller, J., Roberts, J.E., 2005. Memory and attention in Obsessive-Compulsive Disorder: a review. J. Anxiety Disord. 19, 1–28.
- Nishitani, N., 2003. Dynamics of cognitive processing in the human hippocampus by neuromagnetic and neurochemical assessments. NeuroImage 20, 561–571.
- Olbrich, S., Olbrich, H., Adamaszek, M., Jahn, I., Hegerl, U., Stengler, K., 2013. Altered EEG lagged coherence during rest in obsessive-compulsive disorder. Clin. Neurophysiol. 124, 2421–2430.
- Ozkiris, A., Essizoglu, A., Gulec, G., Aksaray, G., 2015. The relationship between insight and the level of expressed emotion in patients with obsessive-compulsive disorder. Nord. J. Psychiatry 69, 204–209.
- Penades, R., Catalan, R., Rubia, K., Andres, S., Salamero, M., Gasto, C., 2007. Impaired response inhibition in obsessive compulsive disorder. Eur. Psychiatry 22, 404–410.
- Pereda, E., Quiroga, R.,Q., Bhattacharya, J., 2005. Nonlinear multivariate analysis of neurophysiological signals. Prog. Neurobiol. 77, 1–37.
- Qin, Y., Xu, P., Yao, D., 2010. A comparative study of different references for EEG default mode network: the use of the infinity reference. Clin. Neurophysiol. 121, 1981–1991.
- Ravi, K.V., Samar, R., Janardhan, R.Y., Chandrasekhar, C.R., Thennarasu, K., 2004. Clinical characteristics and treatment response in poor and good insight obsessivecompulsive disorder. Eur. Psychiatry 19, 202–208.
- Schroeder, C.E., Lakatos, P., 2009. Low-frequency neuronal oscillations as instruments of sensory selection. Trends Neurosci. 32, 9–18.
- Sizino, D.V.M., Nascimento, A.L., Fontenelle, L.F., 2012. Symptom-specific attentional bias to threatening stimuli in obsessive-compulsive disorder. Compr. Psychiatry 53, 783–788.
- Solyom, L., DiNicola, V.F., Phil, M., Sookman, D., Luchins, D., 1985. Is there an obsessive psychosis? Aetiological and prognostic factors of an atypical form of obsessivecompulsive neurosis. Can. J. Psychiatry 30, 372–380.
- Spielberger, C.D., 1983. Manual for the State-Trait Anxiety Inventory (Form Y). Consulting Psychologists Press, Inc., Palo Alto, CA.
- Sporns, O., Zwi, J.D., 2004. The small world of the cerebral cortex. Neuroinformatics 2, 145–162.

Stam, C.J., Jones, B.F., Nolte, G., Breakspear, M., Scheltens, Ph, 2007. Small-world networks and functional connectivity in Alzheimer's disease. Cereb. Cortex 17, 92–99.

- Stam, C.,J., van Dijk, B.W., 2002. Synchronization likelihood: an unbiased measure of generalized synchronization in multivariate data sets. Physica D 163, 236–251.
- Stam, C.J., 2004. Functional connectivity patterns of human magnetoencephalographic recordings: a 'small-world' network? Neurosci. Lett. 355, 25–28.
- Theiler, J., Eubank, S., Longtin, A., Galdrikian, B., Farmer, J.D., 1992. Testing for nonlinearity in time series: the method of surrogate data. Physica D 58, 77–94.
- Tumkaya, S., Karadag, F., Oguzhanoglu, N.K., Tekkanat, C., Varma, G., Ozdel, O., Atesci, F., 2009. Schizophrenia with obsessive-compulsive disorder and obsessivecompulsive disorder with poor insight: a neuropsychological comparison. Psychiatry Res. 165, 38–46.
- Velikova, S., Locatelli, M., Insacco, C., Smeraldi, E., Comi, G., Leocani, L., 2010. Dysfunctional brain circuitry in obsessive-compulsive disorder: source and coherence analysis of EEG rhythms. NeuroImage 49, 977–983.
- Watts, D.J., Strogatz, S.H., 1998. Collective dynamics of 'small-world' networks. Nature 393, 440–442.

Zhang, T., Wang, J., Yang, Y., Wu, Q., Li, B., Chen, L., Yue, Q., Tang, H., Yan, C., Lui, S., Huang, X., Chan, R.C., Zang, Y., He, Y., Gong, Q., 2011. Abnormal small-world architecture of top-down control networks in obsessive-compulsive disorder. J. Psychiatry Neurosci. 36, 23–31.

Zhang, Y., Chen, Y., Bressler, S.L., Ding, M., 2008. Response preparation and inhibition: the role of the cortical sensorimotor beta rhythm. Neuroscience 156, 238–246.