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Alteration of Functional Connectivity in OCD by Resting State fMRI

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ABSTRACT

Obsessive-compulsive disorder (OCD) is a mental disorder in which a person repeated a particular thought or feels. The domain of beliefs and guilt predicted OCD symptoms. Although there were some neuroimaging studies investigating OCD symptoms, resting-state functional magnetic resonance imaging (rs-fMRI) study investigating intra-network functional connectivity associated with guilt for OCD is not reported yet. Therefore, in the current study, we assessed the differences between intra-network functional connectivity of healthy control group and OCD group using independent component analysis (ICA) method. In addition, we also aimed to investigate the correlation between changed functional connectivity and guilt score in OCD. Total 86 participants, which consisted of 42 healthy control volunteers and 44 OCD patients, acquired rs-fMRI data using the 3T MRI. After preprocessing the fMRI data, a functional connectivity was used for group independent component analysis. The results showed that OCD patients had higher score in emotion state in beliefs and lower functional connectivity in fronto-parietal network (FPN) than control group. A decrease of functional connectivity in FPN was negatively correlated with feelings of guilt in OCD. Our results suggest excessive increase in guilt negatively affect to process emotional state and behavior or cognitive processing by influencing intrinsic brain activity.

Key words: Obsessive-compulsive Disorder (OCD), Resting-state Functional Magnetic Resonance Imaging (rs-fMRI), Functional Connectivity, Independent Component Analysis.

1. INTRODUCTION

Obsessive-compulsive disorder (OCD) is a mental disorder in which a person repeated a particular thought or feels repeatedly to perform certain routines[1]. These characteristics of OCD have been associated with emotions, such as anxiety and depression, and beliefs, such as responsibility, importance of thought and guilt[2-5]. Anxiety has been reported to cause suffering and burden on extreme cases like patients with psychiatric disorder[6] and depression has been known to be able to occur as a functional consequence associated with OCD[7].

The domain of beliefs and guilt predicted obsessive-compulsive symptoms[8,9]. In particular,

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the guilt, which is defined as dysphoria arising from a moral breach[10], can be problematic when fearful feelings become disproportionate. This guilt feeling was closely linked with anxiety and depression[3,11] as well as relating responsibility[9] and had been associated with OCD symptoms [12-14]. In previous study, trait guilt, which is a tendency to react to experiences with guilt, and state guilt, which is a guilt directly related with a current event, were significantly correlated with psychological disorders such as OCD[15]. Moreover, OCD patients were reported that trait guilt, state guilt, and moral standards were higher responded than control subjects, and trait guilt could predict obsessive compulsive symptom[3]. Trait guilt and state guilt were reported a marker of cognitive dysfunction that are core and enduring deficits of OCD[16,17]. And these were not only interrelated with domains of beliefs but also caused brain neural activity changes[18-20].

Neuroimaging studies have tried to assess alterations of brain activity associated with feeling of guilty[20,21]. Among them, a resting-state functional magnetic resonance imaging (rs-fMRI) study investigated spontaneous neuronal activity changed due to feelings of guilt[21]. In addition, OCD patients were reported that obsessive beliefs, such as inflated responsibility, modulate brain activation on a moral decision task[22].

In this study, we used rs-fMRI technique to investigate the effects of guilt on the alteration of intrinsic neural activity within whole brain network in patients with OCD. Although there were some rs-fMRI studies evaluating association between inter-network functional connectivity of brain and OC symptoms[23-25], rs-fMRI study investigating intra-network functional connectivity associated with guilt for OCD is not reported yet. Therefore, we assessed the differences between intra-network functional connectivity of healthy control (HC) group and OCD patients group using independent component analysis (ICA) method, which can divide independent brain networks by separating blind source in mixture networks of whole brain[26,27]. Furthermore, we aimed to investigate the correlation between changed functional connectivity and guilt score in OCD. We hypothesized that dysfunction of moderation about guilt in OCD is due to alterations of intrinsic activity on brain network.

2. MATERIALS AND METHODS

2.1 Participants

Total 86 participants (42 healthy volunteers and 44 patients with OCD) were included in this study. All participants performed psychiatric interviews for conducting psychotic symptoms, mental retardation or history of brain disease. All healthy volunteers were judged to have no psychiatric symptom and no history of brain disease on psychiatric interviews. All patients were determined the presence of OCD and other comorbidities by performing a Structured Clinical Interview for DSM-5 Disorders, Clinical Version (SCID-5-CV). All interviews were completed by two experienced psychiatrists (S.J.L. and S.W.L.). All participants were provided written informed consent in accordance with the procedures approved by the Institutional Review Board.

2.2 Psychological Measures

Dysfunctional beliefs were measured by investigating the responsibility, importance of thoughts, and guilt score. The responsibility and importance of thoughts were measured using Obsessive Beliefs Questionnaire-44 (OBQ-44)[4]. The Guilt Inventory (GI), which consisted of 45 items self-reported inventory, was used to evaluate the domains of trait guilt, state guilt, and moral standard[28]. The Beck Depression Inventory (BDI) including 21 items self-reported measure was used to measure the severity of depression[29].

2.3 MRI Data Acquisition and Analyses

The 3.0 Tesla 750W MRI scanner with twenty-four channel head and neck coil (GE Healthcare, Milwaukee, WI) was used to acquire all structural and functional imaging data. Structural brain imaging technique was used a 3D brain volume imaging sequence (BRAVO) with echo time (TE) = 3.2 ms, repetition time (TR) = 8.5 ms, matrix size = 256×256, field of view (FOV) = 25.6 cm^2, and flip angle (FA) = 12°. The resting-state functional imaging technique was used the gradient echo planer T2* weighted imaging (EPI) sequence with TE = 30 ms, TR = 3000 ms, matrix size = 64×64, FOV = 23.0 cm^2, and FA = 90°. All functional image data were preprocessed using a statistical parametric mapping toolbox (SPM12; http://www.fil.ion.ucl.ac.uk/spm). Preprocessing steps consisted of slice timing, realignment, co-registration, normalization to the standard Montreal Neurological Institute (MNI) space, and spatial smoothing with gaussian kernel (FWHM = 8 mm). A functional connectivity toolbox (CONN; https://web.conn-toolbox.org) was used for performing group independent component analysis. The movement and outlier time series components were detected using the artifact detection tools (ART; https://www.nitrc.org/projects/artifact_detect), and these components, white matter and CSF factors were regressed out in the denoising step. The temporal band-pass filtering was applied between 0.008 and 0.09 Hz. In the first level analysis, G1 fastICA[30] for estimation of independent spatial components and GICA3 back-projection[31] for estimation of spatial map were performed for separating spatial components of individual subject. Subject-level dimensionality reduction was performed to 64, and target number of components was set 40. In the group level analysis, independent brain networks were determined by performing correlational spatial matching to CONN toolbox's template. The significant difference in functional connectivity of brain networks between HC and OCD group was determined from two sample t-test. The significant difference of intra-network connectivity between two groups was determined by the false discovery rate (FDR) corrected at the cluster mass $p < 0.05$ and uncorrected $p < 0.01$ at the voxel level based on 6000 permutation analyses[32]. Spheres with 7mm were created at coordinates having maximum connection value to determine regions of interest (ROIs), and final ROIs were selected as common regions between spheres with 7 mm radius and functional connectivity map in two sample t-test. ROIs included anterior cingulate cortex (ACC), mid cingulate cortex (MCC), medial frontal gyrus (MeFG), middle frontal gyrus (MFG), superior frontal gyrus (SFG), precentral gyrus, and post central gyrus. These regions were determined based on standard MNI space using WFU_PickAtlas toolbox (https://www.nitrc.org/projects/wfu_pickatlas). All functional connectivity values were extracted on the ROIs using REX toolbox (https://www.nitrc.org/projects/rex).

2.4 Statistical Analysis

The statistical package for social sciences (SPSS 25; http://www.ibm.com/analytics/spss-statistics-software) was used to perform two sample t-test between HC and OCD for demographic and psychiatric characteristics, as well as a correlation analysis between brain functional connectivity and psychiatric symptoms. The correlation coefficient was calculated by performing partial correlation analysis after controlling for depression effects.

3. RESULTS

3.1 Demographic and Clinical Data

The mean age of OCD patients was 24.9±5.4 years and the mean age of HC were 22.6±2.02 years. This was a statistically significant difference between HC and OCD. As a result of psychiatric score, OCD patients showed higher than HC on domains of responsibility, importance of thoughts, and total OBQ score. In addition, trait guilt, state guilt, and overall total GI score also were greater score on OCD than HC. There was no difference in moral standard subscale between HC and OCD group. OCD patients revealed higher response for depression symptom than HC. Detailed results were summarized in Table 1.

3.2 Intra-network Functional Connectivity of HC and OCD in Group ICA Analysis

As a result of group ICA, independent components were matched with eight neural networks including default mode (r=0.325), fronto-parietal (r=0.176), sensorimotor (r=0.430), visual (r=0.500), salience (r=0.327), dorsal-attention (r=0.469), language (r=0.372), and cerebellar (r= 0.507). There was a significant difference on fronto-parietal network (FPN) between HC and OCD. FPN of HC group included ACC, MCC and insula regions. In addition, medial, middle, superior and lateral frontal gyrus were also included in FPN as well as inferior and superior parietal gyrus. Additionally, precuneus, cuneus, putamen and lingual gyrus were functionally connected. Detailed results are provided in Fig. 1. In the group comparison, HC showed higher functional connectivity than OCD within FPN (FDR corrected $p < 0.05$ in cluster level, and uncorrected $p < 0.01$ in voxel level). The regions within FPN included left ACC, bilateral MCC, MeFG, MFG, SFG, left precentral gyrus, and left postcentral gyrus (Fig. 2 and Table 2).

Table 1. Demographic and psychiatric characteristics of participants.

Participants	HC (N=42)	OCD (N=44)	Two-sample t-test (t)	P-value
Age, mean±SD (years)	22.6±2.02	24.9±5.4	-2.252	0.013
BDI	4.78±4.21	19.77±12.06	-7.618	0.000
Dysfunctional beliefs				
Total OBQ-44	88.3±20.74	117.70±35.43	-4.662	0.000
Responsibility	54.57±12.61	65.77±20.86	-2.995	0.004
Importance of thoughts	33.76±11.43	51.93±17.08	-5.769	0.000
Total GI	120.90±14.88	144.15±18.70	-6.393	0.000
Trait guilt	55.92±8.83	68.68±11.62	-5.707	0.000
State guilt	25.11±6.25	33.36±6.73	-5.885	0.000
Moral standard	39.85±5.33	42.11±6.66	-1.737	0.086

BDI, Beck Depression Inventory; OBQ-44, Obsesseive Beliefs Questionnaire-44; GI, Guilt Inventory

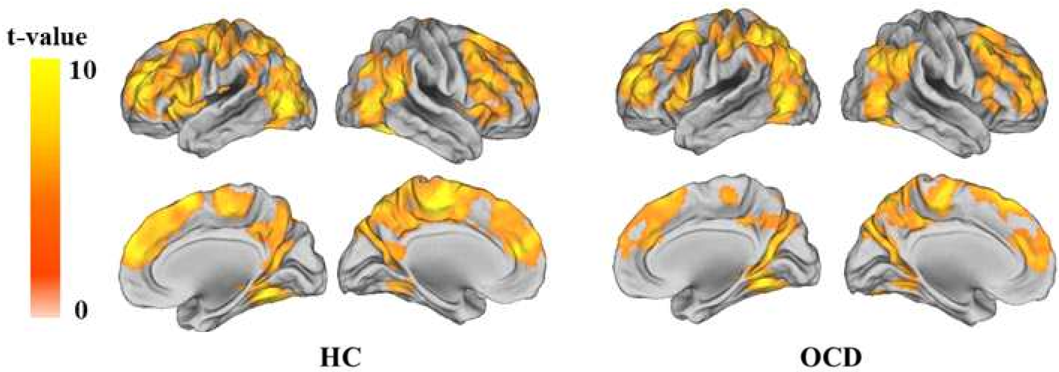

Fig. 1. Results of within group ICA in fronto-parietal network component.

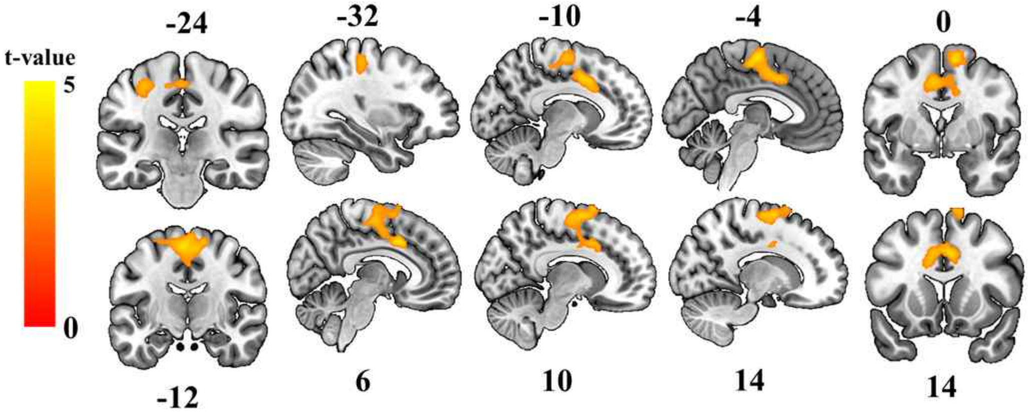

Fig. 2. Differences of functional connectivity in fronto-parietal network in HC-OCD.

Table 2. Difference of functional connectivity between HC and OCD in fronto-parietal network.

Comparison	ROIs Fronto-parietal network	L / R	Coordinates (mm)			Two-sample t-test (t)
			x	y	z	
HC > OCD	Anterior cingulate cortex	L	-10	16	30	3.35
	Mid cingulate cortex	L	-8	6	40	4.34
		R	6	10	38	4.51
	Medial frontal gyrus	L	-4	-14	60	4.44
		R	12	0	64	4.29
	Middle frontal gyrus	L	-12	-14	62	3.35
		R	14	-12	66	3.76
	Superior frontal gyrus	L	-2	-10	68	3.56
		R	10	4	64	4.09
	Precentral gyrus	L	-32	-26	52	3.62
	Postcentral gyrus	L	-2	-20	56	4.30

minimum cluster >10, FDR<0.05 corrected in cluster level, and uncorrected<0.01 in voxel level

3.3 The Correlation between Functional Connectivity within FPN and Guilt Score in OCD

All subscales of OBQ-44 had no significant relationships with functional connectivity within FPN. Overall guilt subscale was associated with four regions of left side including ACC, MCC, MeFG, and SFG within FPN (Fig. 3). The score of total GI, included trait guilt, state guilt and moral standard score was negatively correlated with left ACC ($r = -0.313$, $p = 0.038$), left MCC ($r = -0.399$, $p = 0.007$), left MeFG ($r = 0.305$, $p = 0.044$) and left SFG ($r = -0.472$, $p = 0.001$), respectively. Trait guilt showed negative correlation with left ACC ($r = -0.310$, $p = 0.041$), left MCC ($r = -0.325$, $p = 0.031$), left MeFG ($r = 0.299$, $p = 0.049$), and left SFG ($r = -0.343$, $p = 0.023$), respectively. State guilt was negatively correlated with ACC ($r = -0.309$, $p = 0.041$), left MCC ($r = -0.303$, $p = 0.046$), and left SFG ($r = -0.369$, $p = 0.014$).

4. DISCUSSION

The current study showed a decrease in resting state intra-network functional connectivity in obsessive-compulsive symptoms. In particular, the altered functional connectivity within FPN, con-

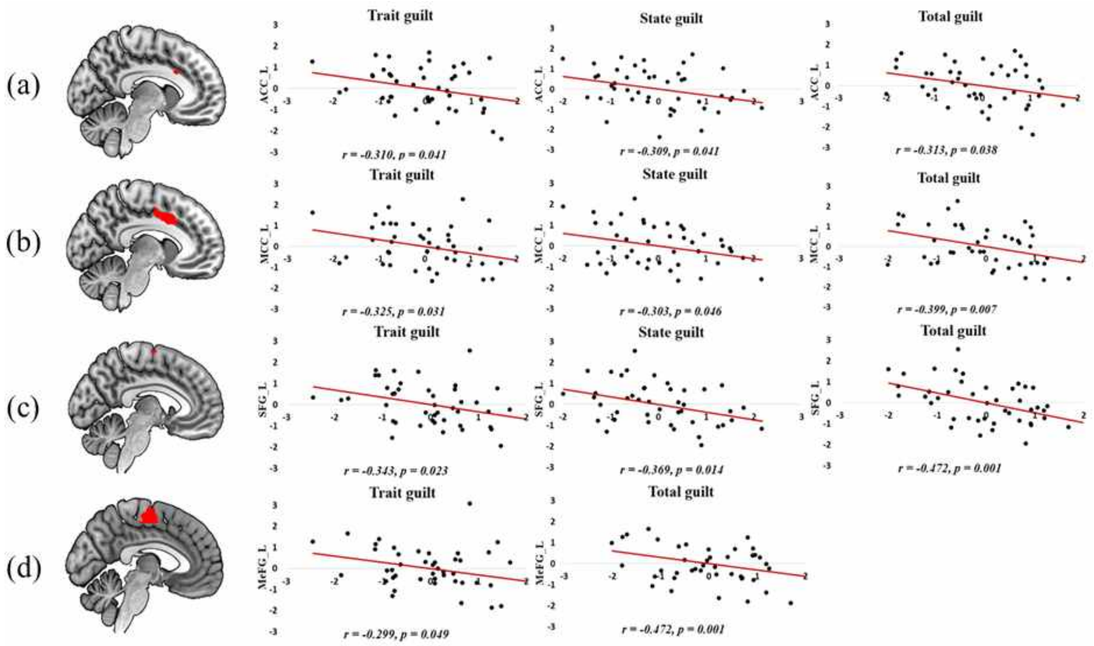

Fig. 3. The correlation between feelings of guilt and functional connectivity of fronto-parietal network in OCD (a) left side anterior cingulate cortex (ACC_L), (b) left side mid cingulate cortex (MCC_L), (c) left side superior frontal gyrus (SFG_L), and (d) left side medial frontal gyrus (MeFG_L).

cerned to emotional and cognitive processing, was closely associated with feelings of guilty in OCD patients. Up to our knowledge, the current study is the first rs-fMRI study investigating intra-network functional connectivity associated with guilt for OCD.

In the current study, we evaluated emotion state in beliefs by measuring responsibility, importance of thought and feelings of guilty for HC and OCD. OCD patients had significantly higher score than HC suggesting that OCD have dysfunction in emotional control about beliefs. Particularly, feelings of guilty was correlated with brain functional connectivity in OCD. Increased guilt factors including trait, state and total guilt score were negatively correlated with decreased functional connectivity within FPN (Fig. 3), which is known as networks for salience processing and executive control[33]. In previous studies, OCD patients have shown dysfunction in emotional control which was interacted with cognitive processing such as decision making and solving subgoal conflicts[34-36]. OCD patients impaired coupling within brain core networks including default mode, salience and executive network[37].

Our results showed that OCD patients had lower functional connectivity than HC within FPN (Fig. 2). Decreased functional connectivity of OCD in ACC and MCC was negatively correlated with trait guilt, state guilt and total guilt score, respectively. ACC and MCC were known to mediate negative emotional state as key nodes of the salience processing[38]. In addition, MeFG, which modulate emotional behavior[39], had negative correlation with trait guilt and total guilt score. These results are in line with previous studies that OCD patients had shown difficulties in task switching and emotional control functions associated with salience network[40] and decreased intrinsic functional connectivity in salience network[41]. Decreased functional connectivity in SFG showed negative correlation with trait guilt, state guilt and total guilt score. Because SFG is known to contribute to higher cognitive functions and working memory[42], This result is good agreement with previous study showing a decrease intrinsic brain activity in SFG in OCD[43]. In addition, the decrease of functional connectivity in SFG suggested that OCD shows deficits in cognitive and behavior element for executive processing[44].

This study has some limitations. First, although we used enough component factor as 40 in ICA to separate independent component network, component optimization is needed to assess a more accurate network. Second, the association between feeling of guilt and functional connectivity was estimated by performing a correlation analysis. Therefore, more detailed analyses are required to investigate causality. Third, we could not investigate direct relationship between resting state functional connectivity and cognitive ability because there was no behavior measure for cognitive ability.

5. CONCLUSION

We showed that state of emotion, particularly guilt, affect to change of intrinsic brain activity by measuring the correlation between increased feelings of guilty and decreased functional connectivity in OCD. Our findings suggest excessive increase in guilt negatively affect to process emotional state and behavior or cognitive processing by influencing intrinsic brain activity. Moreover, decreased functional connectivity of FPN may be a major cause of dysfunction in emotional and cognitive control in OCD patients.

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