Functional connectivity in obsessive-compulsive disorder : a magnetoencephalographic study

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Functional connectivity in obsessive-compulsive disorder : a magnetoencephalographic study

Directed by Professor Kee Namkoong

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Koh, Min Jung

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ABSTRACT

Functional connectivity in obsessive-compulsive disorder : a magnetoencephalographic study

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Researchers have associated obsessive-compulsive disorder (OCD) with aberrant functional connectivity among a number of brain regions. Analysis of functional connectivity in the resting state may provide important evidence in elucidating the pathophysiology of OCD. The aim of the present study is to evaluate whether patients with OCD exhibit differences in resting-state functional connectivity when compared to healthy controls using MEG.

We recruited 24 patients with OCD (21 males, 3 females), in addition to 22 healthy controls (19 males, 3 females). Prior to our analysis of functional connectivity, we examined group differences in brain activity and oscillatory activity and the association between overall OCD symptom severity and regional oscillatory activity. We utilized the phase locking value (PLV) to

examine group differences in functional connectivity between regions of interest and to determine the distribution of functional hubs based on weighted-graph theory.

Patients with OCD exhibited significantly reduced phase synchronization in all band frequencies, with the exception of the delta band, when compared with healthy controls. In addition, the OCD group exhibited significantly lower phase synchronization in theta and gamma band frequencies between the left insula and right limbic regions, as well as among left orbitofrontal areas. A similar tendency was observed with respect to alpha and beta band frequencies, though patients with OCD exhibited greater connectivity with lower phase synchrony than healthy controls. We further observed differences in the distribution of the upper functional hubs for each group in all band frequencies. Healthy controls exhibited a greater number of central hubs in the orbitofrontal and left insular regions, whereas patients in the OCD group exhibited additional functional hubs in the temporo-parietal and cingulate regions.

The results of the present study indicate that, during the resting state, patients with OCD exhibit lower phase synchronization and fewer functional hubs in ventral areas, including the orbitofrontal, limbic, and insular regions when compared with healthy controls. These findings suggest that reduced functional connectivity in areas of the limbic loop and functionally connected neighboring regions reflect an underlying pathophysiology associated with dysfunction of inhibitory control in patients with OCD.

Key Words: obsessive-compulsive disorder, resting state, functional connectivity, magnetoencephalography, phase-locking value, synchronization, hub, pathophysiology

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I. INTRODUCTION

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder associated with recurrent and disturbing thoughts (obsessions) and/or repetitive, stereotyped behaviors (compulsions) that the individual feels driven to perform though recognizes as irrational or excessive[1]. OCD is a severe, often debilitating mental illness with a lifetime prevalence of 2% to 3% in the general population[2,3]. Despite its high morbidity, the underlying pathophysiology of OCD remains unclear.

The most widely accepted neurobiological models of OCD have suggested the involvement of dysfunctional cortico-striato-thalamo-cortical

(CSTC) circuitry, including the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and striatum[4]. The dysregulation of connectivity within CSTC circuits is thought to be associated with impaired executive function, inability to inhibit cognition and behavior, and enhanced error monitoring in patients with OCD[5,6]. However, some researchers have suggested that the brains of patients with OCD exhibit more complex and extensive aberrant functional connectivity among such regions as the prefrontal cortex, parietal cortex, and insula[7,8]. Therefore, an investigation of the functional interactions among different brain regions in patients with OCD is important in developing an understanding of the pathophysiology of OCD.

Analysis of resting-state functional interactions among brain regions enables researchers to analyze intrinsic, unprompted brain activity. Electrophysiological approaches have gained attention in this respect due to their high temporal resolution. Since magnetic fields are less distorted than electric fields by the skull and scalp, magnetoencephalography (MEG) allows for better spatial resolution/localization and improves oscillatory detectability when compared to electroencephalography (EEG)[9,10]. Previous researchers have used MEG to investigate resting-state functional connectivity in a number of psychiatric disorders, including schizophrenia and autism spectrum disorder.[11-16]. In addition, several studies have proven the efficacy of using phase relationships as a measure of functional connectivity[7,17-19]. Phase-locking value (PLV) has been applied to MEG studies of resting state connectivity and is used to measure the phase synchrony of narrowband signals at a given frequency, independent of their signal amplitude [18,20].

From a network perspective, important brain regions often interact with many other regions to facilitate functional integration. Such regions are considered functional "hubs", which can be detected using weighted graph measures. The simplest of these measures is the node degree, also called degree centrality, which is equal to the number of edges that are maintained by each node[21,22] Nodes with a high degree are considered to exhibit structural or functional interaction with many other nodes in the network. Therefore, identifying the distribution of functional hubs may significantly enhance our understanding of functional connectivity.

To date, no study has examined resting-state functional connectivity in patients with OCD at the source level using MEG. In the present study, we investigated resting-state functional connectivity among brain regions in patients with OCD compared with that observed for healthy controls by analyzing the PLV between regions of interest. In addition, we used weighted-graph theory to determine functional hubs in each group. We hypothesized that patients with OCD would exhibit different patterns of resting-state functional connectivity when compared with healthy controls and that this difference may be involved in the pathophysiology of OCD.

II. MATERIALS AND METHODS

1. Participants

Twenty-four patients with OCD (mean age=27.5 years, SD=6.21 years, 87.5% males) were recruited from Severance Hospital in Seoul, South Korea. Diagnoses were confirmed by a psychiatrist trained in the use of the Structured Clinical Interview for DSM-IV[23]. Patients with psychotic disorders, substance-related disorders, mental retardation, or neurological/medical illnesses were excluded. We recruited the healthy controls aged 19 and over by advertisement from September 2014 to January 2015. The same exclusion criteria were applied to twenty-two healthy controls (mean age=24.6 years, SD=5.27 years, 86.4% males). Each participant completed self-reported assessments and clinician rating scales prior to MEG recording. The protocol for the present study was approved by the Institutional Review Board of Severance Hospital. All patients and healthy controls provided written informed consent prior to their participation in the study.

2. Measures

A. Korean Wechsler Adult Intelligence Scale-IV

We utilized the Korean version of the Wechsler Adult Intelligence Scale to assess cognitive ability in both participant groups. The WAIS is the most widely used intelligence test for adults and older adolescents around the

world. The current version (WAIS-IV) was released in 2008 and is composed of 10 core subtests comprising the Full-Scale IQ, in addition to five supplemental subtests[24]. The major components of intelligence are represented by four index scores: Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), Processing Speed Index (PSI). The Full-Scale IQ (FSIQ) is derived from all four index scores, while the General Ability Index (GAI) is based only upon the VCI and PRI.

B. Yale–Brown Obsessive Compulsive Scale (Y-BOCS)

The severity and dimensions of OCD symptoms were evaluated using the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) and the accompanying Y-BOCS symptom checklist[25]. The Y-BOCS is a highly valid and reliable clinician-administered 10-item scale used to assess the severity of obsessions and compulsions. Patients are asked to complete a checklist that contains a comprehensive list of more than 50 examples of obsessions and compulsions grouped into 13 major categories. Responses are scored from 0 to 4 for each of the seven obsession and six compulsion categories, with higher scores indicating more severe symptoms.

C. Montgomery–Åsberg Depression Rating Scale (MADRS)

We used the MADRS to assess levels of depressive symptoms[26]. The MADRS is a 10-item diagnostic questionnaire and includes items related to apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic

thoughts, and suicidal ideation. Responses are scored from 0 to 6, with higher scores indicating more severe depressive symptoms.

3. MEG acquisition

A 152-channel MEG system (Korea Institute of Standards and Science; KRISS, Daejeon, Korea) was used to measure brain magnetic fields during a six-minute resting period, during which participants were seated comfortably and instructed to remain awaken in a magnetically shielded room. Resting state recordings were conducted with other experimental paradigms, though these recordings always preceded the other experiments. Resting state recording consisted of a 3-minute eyes-closed (EC) condition followed by a 3-minute eyes-open (EO) condition for all participants. During the EO period, participants were instructed to look at a small cross-hair on the screen in front of them. For all participants, the psychiatric assessments were conducted prior to obtaining MEG measurements. Magnetic fields were recorded at a sampling rate of 1000Hz with an analog filter between 0.1 and 100Hz. Four head-position-indicator (HPI) coils were attached to the participant's scalp in order to align head position relative to the sensor array using a 3D-head digitization system (Polhemus Fastrak).

4. MEG data preprocessing

EO conditions were recorded to check the reliability of data in EC

conditions but not utilized in further analysis. A 60-Hz notch filter was applied in the preprocessing of the raw data. Channels with poor signal were visually inspected and excluded for each individual. In addition to the visual inspection, the Brainstorm [27] (http://neuroimage.usc.edu/brainstorm) detection functionality was used to detect movement (1-7 Hz) and muscle/sensor related (40-240 Hz) contamination. Following exclusion of compromised data, artifact-free segments of 1024 ms in duration were collected for each individual. In order to make a balanced comparison, data from 19 EC segments (19.456 ms) were used in the analysis.

5. MEG source imaging

In order to perform source modeling, we utilized an overlapping sphere model, which derives the strength of a set of electric dipoles (15000 vertices) located at the cortical surface, to perform source modeling in Brainstorm. With this method, homogenous spheres are refined by fitting one local sphere to each sensor [reference in Brainstorm]. Given that individual magnetic resonance imaging (MRI) data were unavailable to determine precise anatomy for each participant, the forward model and subsequent analysis were based on the template brain (ICBM152). An identical noise covariance matrix was used to estimate the distribution of source activity. Minimum Norm Estimation (MNE) using a standardized level of activation relative to the noise level (Statistical Parametric Mapping: dSPM) was performed. Normal source orientations with respect to the cortical surface were favored by weighting the transverse currents

by a factor of 0.2. Depth-weighting was used to reduce the bias towards superficial sources [28]. The noise covariance level was regularized with a factor of 0.1 at a signal-to-noise ratio of 3.0. After reconstructing the cortical surface using distributed source modeling, the 148 atlas-based cortical parcellation (Destrieux cortical atlas)[29] was applied in Brainstorm in order to obtain representative source responses for regions of interest (ROIs). Principal component analysis (PCA) was applied to the set of sources (vertex) for each ROI, and the first component of PCA was determined as the response of the source scouts, which represent the regions of interest in Brainstorm jargon. **(Figure 1, Table 1)**. PCA is a mathematical algorithm that reduces the dimensionality of the data while retaining most of the variation in the data set. It creates successive components all of whose pair-wise correlation coefficients are zero and can be used to separate multichannel MEG data into temporally and spatially independent components that can often be associated with particular neural generators [30,31].

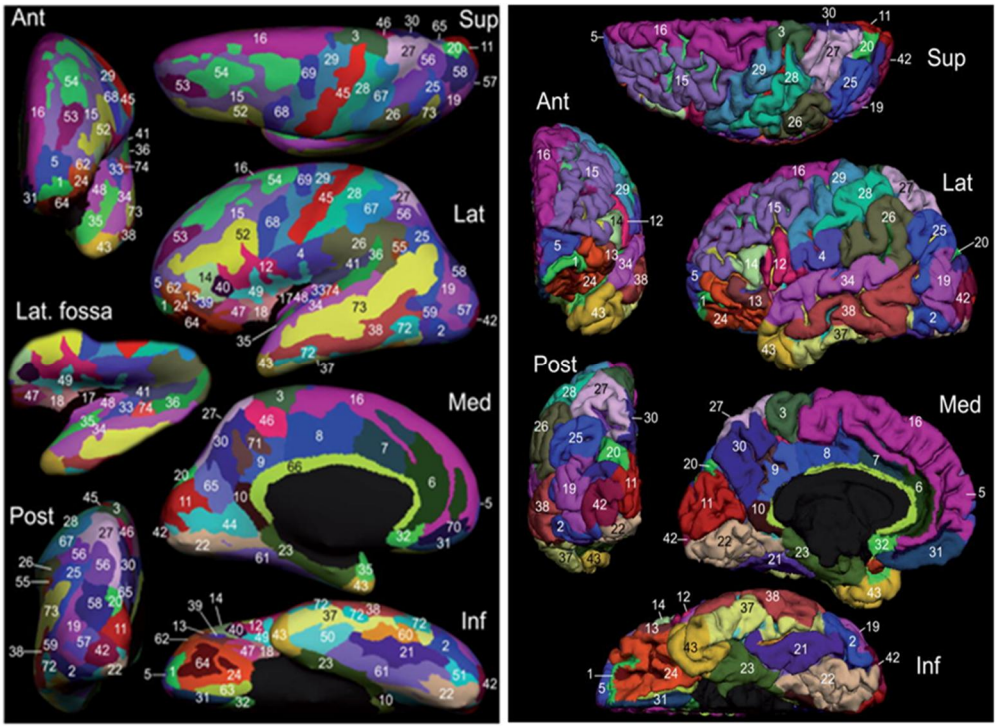

Figure 1. Destrieux cortical atlas[29]. Inflated and pial view of the 148 atlas-based cortical parcellation are shown. Superior (Sup), anterior (Ant), lateral (Lat), posterior (Post), medial (Med) and inferior (Inf) views are provided. This atlas was developed by Christophe Destrieux in 2010.

Table 1. The 148 sources in the Destrieux cortical atlas[29]

index	Short Name	Long name
1	G_and_S_frontomargin	Fronto-marginal gyrus (of Wernicke) and sulcus
2	G_and_S_occipital_inf	Inferior occipital gyrus and sulcus
3	G_and_S_paracentral	Paracentral lobule and sulcus
4	G_and_S_subcentral	Subcentral gyrus (central operculum) and sulci
5	G_and_S_transv_frontopol	Transverse frontopolar gyri and sulci
6	G_and_S_cingul-Ant	Anterior part of the cingulate gyrus and sulcus (ACC)
7	G_and_S_cingul-Mid-Ant	Middle-anterior part of the cingulate gyrus and sulcus (aMCC)
8	G_and_S_cingul-Mid-Post	Middle-posterior part of the cingulate gyrus and sulcus (pMCC)
9	G_cingul-Post-dorsal	Posterior-dorsal part of the cingulate gyrus (dPCC)
10	G_cingul-Post-ventral	Posterior-ventral part of the cingulate gyrus (vPCC)
11	G_cuneus	Cuneus
12	G_front_inf-Opercular	Opercular part of the inferior frontal gyrus
13	G_front_inf-Orbital	Orbital part of the inferior frontal gyrus
14	G_front_inf-Triangul	Triangular part of the inferior frontal gyrus
15	G_front_middle	Middle frontal gyrus
16	G_front_sup	Superior frontal gyrus
17	G_Ins_lg_and_S_cent_ins	Long insular gyrus and central sulcus of the insula
18	G_insular_short	Short insular gyri
19	G_occipital_middle	Middle occipital gyrus
20	G_occipital_sup	Superior occipital gyrus
21	G_oc-temp_lat-fusifor	Lateral occipito-temporal gyrus (fusiform gyrus)
22	G_oc-temp_med-Lingual	Lingual gyrus, ligual part of the medial occipito-temporal gyrus
23	G_oc-temp_med-Parahip	Parahippocampal gyrus, parahippocampal part of the medial occipito-temporal gyrus
24	G_orbital	Orbital gyri
25	G_pariet_inf-Angular	Angular gyrus
26	G_pariet_inf-Supramar	Supramarginal gyrus
27	G_parietal_sup	Superior parietal lobule
28	G_postcentral	Postcentral gyrus
29	G_precentral	Precentral gyrus
30	G_precuneus	Precuneus
31	G_rectus	Straight gyrus, Gyrus rectus
32	G_subcallosal	Subcallosal area, subcallosal gyrus
33	G_temp_sup-G_T_transv	Anterior transverse temporal gyrus (of Heschl)
34	G_temp_sup-Lateral	Lateral aspect of the superior temporal gyrus
35	G_temp_sup-Plan_polar	Planum polare of the superior temporal gyrus
36	G_temp_sup-Plan_tempo	Planum temporale or temporal plane of the superior temporal gyrus
37	G_temporal_inf	Inferior temporal gyrus
38	G_temporal_middle	Middle temporal gyrus
39	Lat_Fis-ant-Horizont	Horizontal ramus of the anterior segment of the lateral sulcus
40	Lat_Fis-ant-Vertical	Vertical ramus of the anterior segment of the lateral sulcus (or fissure)
41	Lat_Fis-post	Posterior ramus (or segment) of the lateral sulcus (or fissure)

42	Pole_occipital	Occipital pole
43	Pole_temporal	Temporal pole
44	S_calcarine	Calcarine sulcus
45	S_central	Central sulcus (Rolando's fissure)
46	S_cingul-Marginalis	Marginal branch (or part) of the cingulate sulcus
47	S_circular_insula_ant	Anterior segment of the circular sulcus of the insula
48	S_circular_insula_inf	Inferior segment of the circular sulcus of the insula
49	S_circular_insula_sup	Superior segment of the circular sulcus of the insula
50	S_collat_transv_ant	Anterior transverse collateral sulcus
51	S_collat_transv_post	Posterior transverse collateral sulcus
52	S_front_inf	Inferior frontal sulcus
53	S_front_middle	Middle frontal sulcus
54	S_front_sup	Superior frontal sulcus
55	S_interm_prim-Jensen	Sulcus intermedius primus (of Jensen)
56	S_intrapariet_and_P_trans	Intraparietal sulcus (interparietal sulcus) and transverse parietal sulci
57	S_oc_middle_and_Lunatus	Middle occipital sulcus and lunatus sulcus
58	S_oc_sup_and_transversal	Superior occipital sulcus and transverse occipital sulcus
59	S_occipital_ant	Anterior occipital sulcus and preoccipital notch (temporo-occipital incisure)
60	S_oc-temp_lat	Lateral occipito-temporal sulcus
61	S_oc-temp_med_and_Lingual	Medial occipito-temporal sulcus (collateral sulcus) and lingual sulcus
62	S_orbital_lateral	Lateral orbital sulcus
63	S_orbital_med-olfact	Medial orbital sulcus (olfactory sulcus)
64	S_orbital-H_Shaped	Orbital sulci (H-shaped sulci)
65	S_parieto_occipital	Parieto-occipital sulcus (or fissure)
66	S_pericallosal	Pericallosal sulcus (S of corpus callosum)
67	S_postcentral	Postcentral sulcus
68	S_precentral-inf-part	Inferior part of the precentral sulcus
69	S_precentral-sup-part	Superior part of the precentral sulcus
70	S_suborbital	Suborbital sulcus (sulcus rostrales, supraorbital sulcus)
71	S_subparietal	Subparietal sulcus
72	S_temporal_inf	Inferior temporal sulcus
73	S_temporal_sup	Superior temporal sulcus (parallel sulcus)
74	S_temporal_transverse	Transverse temporal sulcus

6. Analysis of functional connectivity

The following frequency bands were used in the time-frequency analysis: delta (2-4 Hz), theta (5-7 Hz), alpha (8-12 Hz), beta (13-29 Hz), gamma (low: 30-59 Hz; high: 61-90 Hz). For each band, the frequency band

power for an individual participant was calculated by averaging over time and across segments.

We then utilized phase locking value (PLV) as a measure of functional connectivity. PLV allows researchers to detect phase differences between two signals or sources. PLV does not require a stationary signal, whereas coherence can be applied only to stationary signals[18]. Furthermore, PLV is sufficient to conclude that two brain regions interact, while coherence does not specifically quantify phase relationships[18] Therefore, we calculated PLV for each frequency between ROI pairs.

In order to compare the distribution of functional hubs between the OCD group and the control group, we assumed that the strength of connectivity was represented as a value in the adjacency matrix of the weighted graph. To characterize the network centrality, we calculated the total weight connected to a node and defined this value as the nodal degree (D_{nodal})[32]. All nodes except those with D_{nodal} values ranked in the top 5 percent of nodes were excluded and the included nodes were sorted according to participant. The top 10 percent of D_{nodal} nodes were considered individual hubs in each participant and each hub was analyzed in the 148 source locations in each frequency band.

7. Statistical analysis and Software

Group differences in brain and oscillatory activity for each of the 148 source regions were respectively analyzed using two-tailed independent *t*-tests in Brainstorm software (significance level $p<0.01$). Associations between

overall OCD symptom severity and regional oscillatory activity of the sources were assessed using Spearman's bivariate correlation test (significance level $p<0.05$).

Comparisons of PLV between groups in each band frequency were conducted using the permutation test (bootstrapping) with replacements for each ROI-ROI connection. The permutation test is widely used in nonparametric statistics where a parametric form of the underlying distribution is not specified. Under the null hypothesis in which there is no difference in PLV between the control and OCD groups, 10000 permutations were performed at an α-level of 0.01 to provide surrogate data distributions.

Data analysis was conducted using the following open-access toolboxes: Brainstorm (http://neuroimage.usc.edu/brainstorm) and R Statistics 3.2.2 (http://r-project.org).

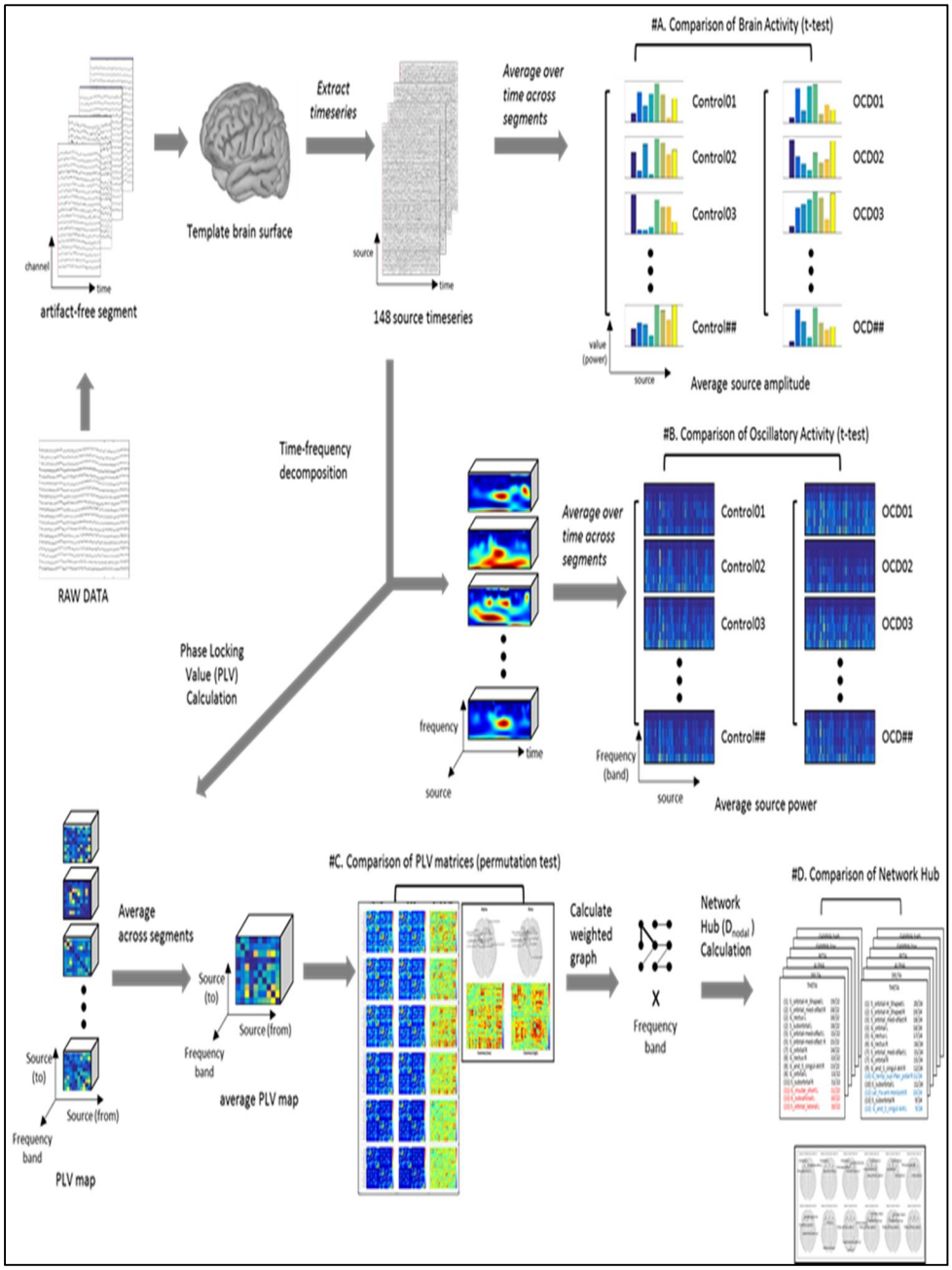

Figure 2. Data analysis pipeline. The procedure for analysis of resting state MEG data is depicted from start to finish.

III. RESULTS

1. Characteristics of participants

A total of 24 patients with OCD and 22 healthy controls were recruited to participate in this study. Six of the patients were drug-naïve, while 18 patients had been prescribed selective serotonin reuptake inhibitors. **Table 2** summarizes the demographic and clinical characteristics of both the OCD and control groups. There were no significant differences in the distributions of age (t = 1.655, p = 0.105), gender (x^2 = 0.013, p=0.909), years of education (t = -0.759, p = 0.452), Full Scale IQ (t = -1.707, p = 0.096), or handedness between the groups. Only the MADRS total score for patients in the OCD group was significantly higher than that of the control group (t = 5.342, p <0.001). The mean Y-BOCS total score for the OCD group indicated that symptom severity was in the moderate range.

Table 2. Demographic and clinical characteristics of participants

Variable	**OCD** **N=24**	**Control** **N=22**	***t*/x^2 (*p* value)**
	Mean (SD) or N (%)	**Mean (SD) or N (%)**	
Age (Years)	27.5 (6.21)	24.6 (5.27)	1.655 (0.105)
Gender, Male : Female	21 : 3	19 : 3	0.013 (0.909)
Education (Years)	13.5 (2.15)	14.0 (1.89)	-0.759 (0.452)
Full scale IQ	106.0 (15.50)	112.6 (10.39)	-1.707 (0.096)
MADRS total score	16.0 (9.22)	4.2 (5.31)	5.342 (<.001)
Y-BOCS total score	20.2 (9.89)	-	
Rt. Handedness	24 (100)	22 (100)	
Medication at Time of study			
Medication free	6 (25.0)	-	
SSRI	11 (45.8)	-	
SSRI with Clomipramine	3 (12.5)	-	
SSRI combination	4 (16.7)	-	
Antipsychotic augmentations	5 (20.8)	-	
With Benzodiazepines	11 (45.8)	-	

OCD, obsessive-compulsive disorder; SD, standard deviation; MADRS, Montgomery–Åsberg Depression Rating Scale; Y-BOCS, Yale–Brown Obsessive Compulsive Scale; SSRI, selective serotonin reuptake inhibitor.

2. Group differences in brain activity

Prior to our analysis of functional connectivity, we compared brain activity in 148 source regions between the OCD and control groups. Statistical significance was calculated based on the subtraction of control amplitude from OCD amplitude in sources. Significantly lower brain activation was observed only in the left superior parietal lobule in OCD patients when compared to healthy controls (t-score = -2.940, df = 42.577, p = 0.005) (**Figure 3**).

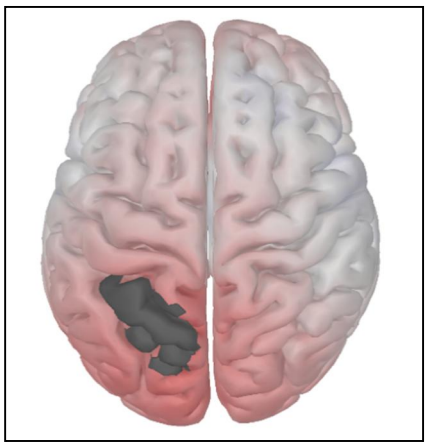

Figure 3. Differences in resting state brain activity between patients with OCD (n=24) and healthy controls (n=22). Red areas represent those regions in which lower levels of brain activity were observed in the OCD group. The dark gray region indicates the region of statistically significant difference between the two groups**.** This region corresponds to the left superior parietal lobule.

3. Group differences in oscillatory activity

We investigated group differences in oscillatory activity using time-frequency analysis. Statistical significance was calculated based on the subtraction of OCD group values from those of the control group. Significantly lower delta activity was observed in patients with OCD across seven source regions (limbic and insular regions), while significantly lower theta activity was observed across two sources (parieto-occipital area) when compared to that for healthy controls (**Table 3, Figure 4).** The following frequency bands were used in the time-frequency analysis: delta (2-4 Hz), theta (5-7 Hz), alpha (8-12 Hz), beta (13-29 Hz), gamma (low: 30-59 Hz; high: 61-90 Hz). For each band, the frequency band power for an individual participant was calculated by averaging over time and across segments.

Table 3. Areas of significantly lower power in oscillatory activity patients with OCD

frequency	area	t-score	df	*p* value
Delta	left subcallosal gyrus	3.994	42.456	0.0003
	right subcallosal gyrus	3.916	40.142	0.0003
	left posterior-dorsal part of the cingulate gyrus	3.456	42.531	0.0013
	right medial orbital sulcus	3.530	30.866	0.0013
	right short insular gyrus	3.524	28.250	0.0015
	right medial occipito-temporal sulcus and lingual sulcus	3.382	42.879	0.0015
	right anterior segment of the circular sulcus of the insula	3.444	33.436	0.0016
Theta	left superior parietal lobule	3.888	42.202	0.0004
	left parieto-occipital sulcus	3.376	43.935	0.0015

Statistical significance was calculated based on the subtraction of OCD group values from those of the control group. T-scores were calculated based on the subtraction of OCD patients from controls. Frequency bands are defined as delta for 2-4 Hz, theta for 5-7 Hz, alpha for 8-12 Hz, beta for 15-29 Hz, gamma (low) for 30-59 Hz, and gamma (high) for 61-90 Hz

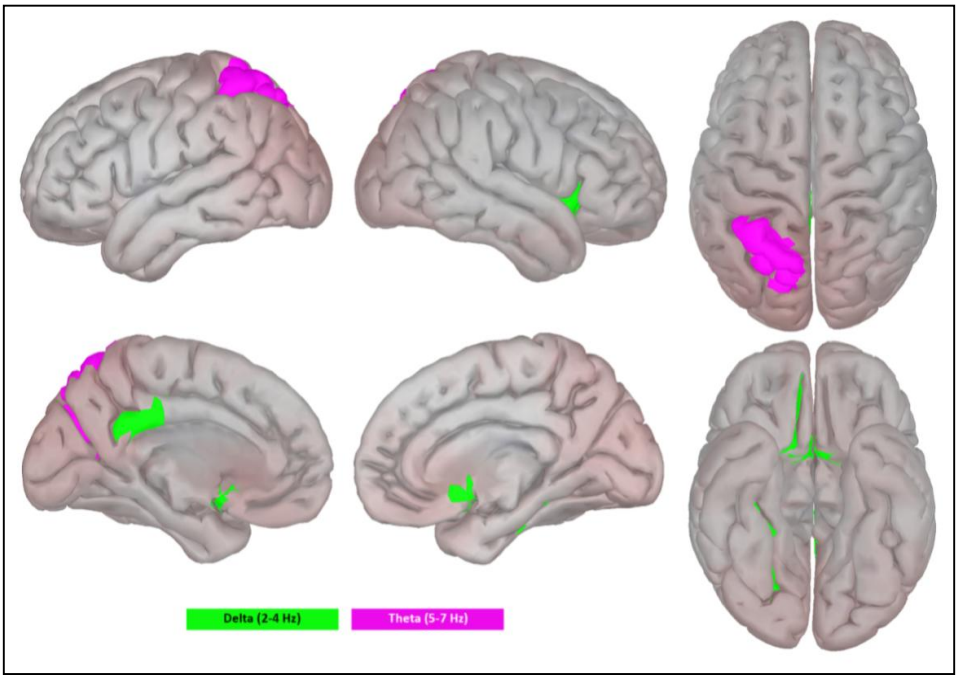

Figure 4. The following frequency bands were used in the time-frequency analysis: delta (2-4 Hz), theta (5-7 Hz), alpha (8-12 Hz), beta (13-29 Hz), gamma (low: 30-59 Hz; high: 61-90 Hz). For each band, the frequency band power for an individual participant was calculated by averaging over time and across segments. Green areas indicate regions of lower delta activity in patients with OCD, while pink areas indicate regions of lower theta activity when compared to that observed for healthy controls.

4. Association between neurophysiology and clinical symptoms

Associations between overall OCD symptom severity (Y-BOCS total scores) and regional oscillatory activities of the nine source regions listed in **Table 3** were assessed using Spearman's bivariate correlation test. No significant correlation between overall OCD symptom severity (Y-BOCS total scores) and oscillatory activity was observed across the seven regions in which differences in delta activity were observed (left subcallosal gyrus, right subcallosal gyrus, left posterior-dorsal part of the cingulate gyrus, right medial orbital sulcus, right short insular gyrus, right medial occipito-temporal sulcus and lingual sulcus, right anterior segment of the circular sulcus of the insula). However, significant negative correlation was observed between OCD symptom severity and theta activity in the left superior parietal lobule (Spearman's rho= -0.434, p = 0.034) and left parieto-occipital sulcus (Spearman's rho= -0.409, p = 0.047), though explanatory power was relatively low (**Figure 5)**.

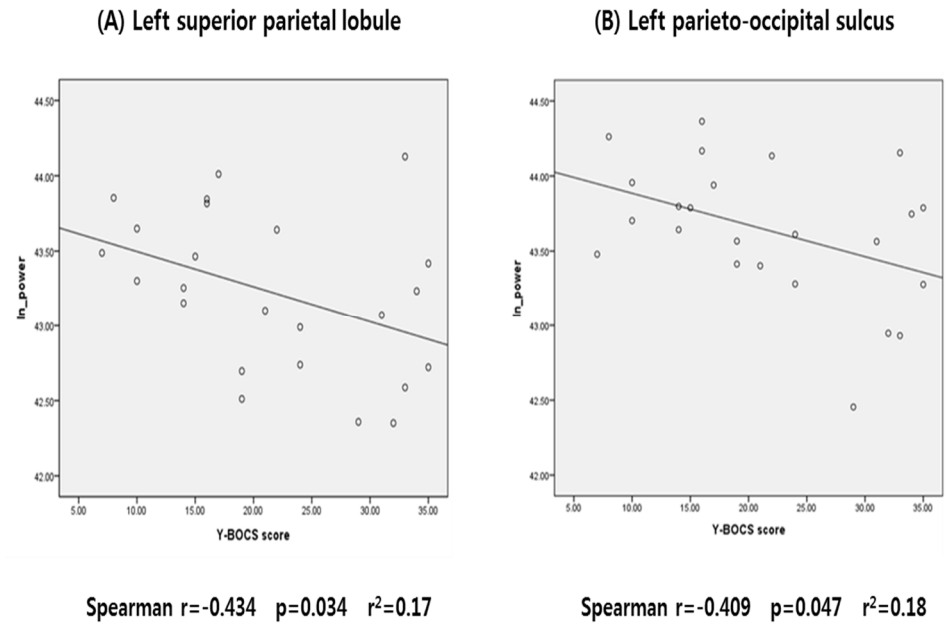

Figure 5. Correlation between overall OCD symptom severity and regional oscillatory activity. Statistically significant negative correlations between symptom severity and theta activity were observed in both the left superior parietal lobule (A) and left parieto-occipital sulcus (B) using Spearman's bivariate correlation test. Y-BOCS: Yale-Brown Obsessive Compulsive Scale.

5. Group differences in functional connectivity

A. Phase-locking value between selected regions of interest (ROIs)

We selected 52 ROIs that have been considered important in the pathophysiology of OCD. The selected ROIs included the dorsolateral prefrontal cortex, orbitofrontal cortex, insula, limbic regions, and regions exhibiting significant between-group differences in oscillatory activity in previous analyses[33-37]. A 52-by-52 connectivity matrix was computed for each participant for each frequency band to analyze functional networks. Group averages and group differences for each band frequency are presented in **Figure 6**. We examined in detail the statistically significant differences in PLV between the OCD and control groups (**Figure 7-1, Figure 7-2**). No significant differences in phase synchrony were observed between groups with respect to delta bands, though patients in the OCD group exhibited significantly lower phase synchrony between the left insular and right limbic (callosum) regions as well as between left orbitofrontal regions with respect to theta and gamma band frequencies (significance level $p<0.01$). Similar tendencies were observed for the alpha and beta band frequencies, though a greater number of connections having lower phase synchrony were observed for the OCD group when compared to the control group.

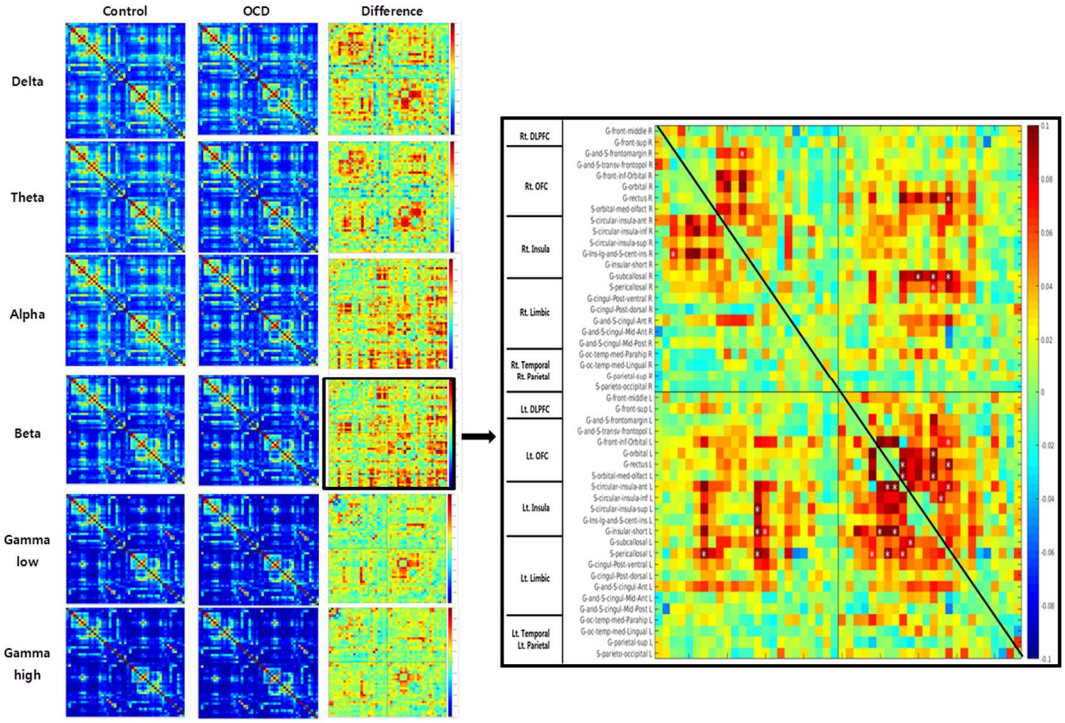

Figure 6. Phase-locking value (PLV) matrices between selected regions of interest (ROIs). Full connectivity matrices comprising 52 sources are depicted for each of the six frequency bands according to group (columns labeled Control and OCD). Differences between the group averages are depicted in the Difference column (Control minus OCD). Color bar values depict the PLV.

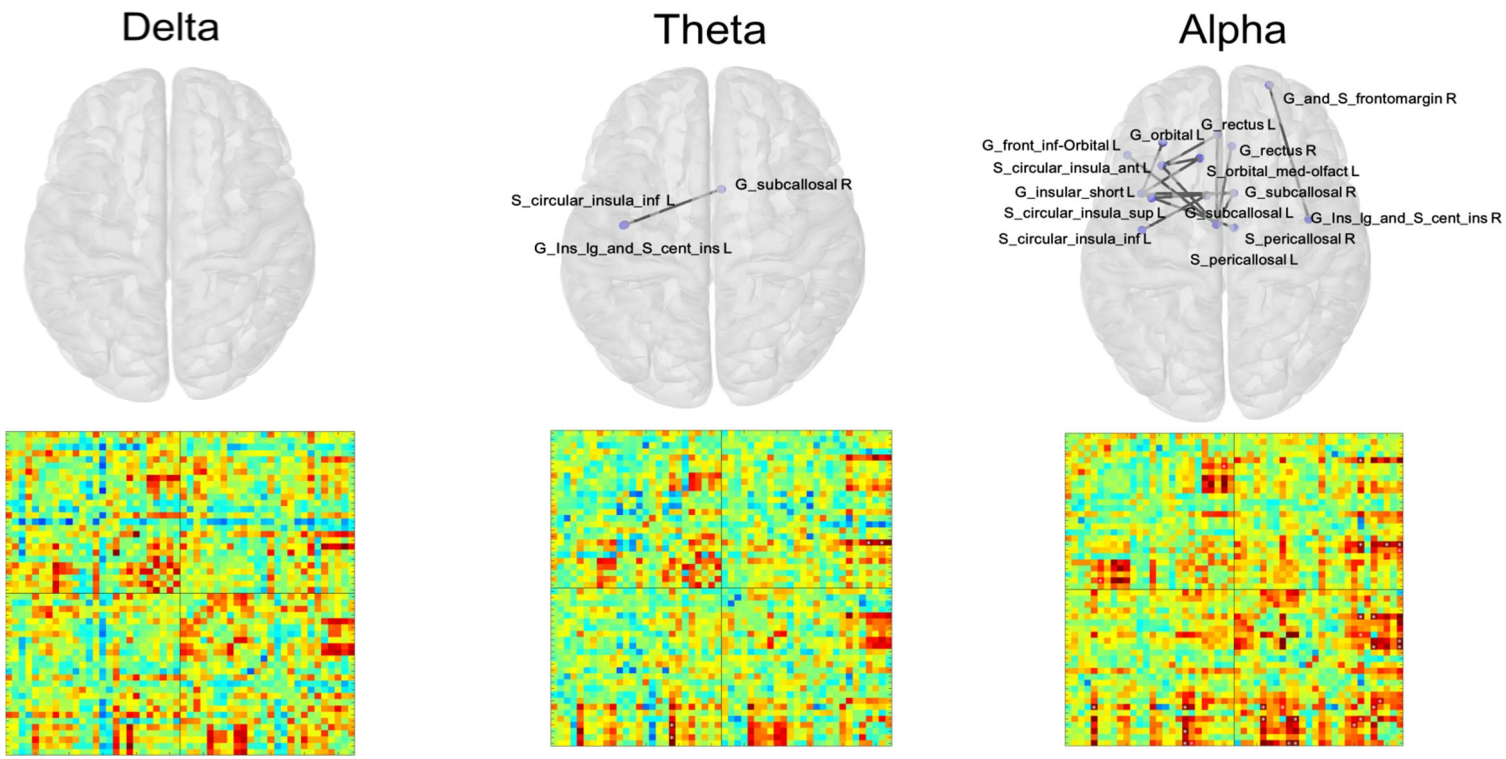

Figure 7-1. Group differences in phase-locking value (PLV) between selected regions of interest (ROIs). ROIs exhibiting statistically significant associations are indicated by white stars in the PLV matrices (p<0.01). The permutation test was used to analyze differences between the OCD and control groups.

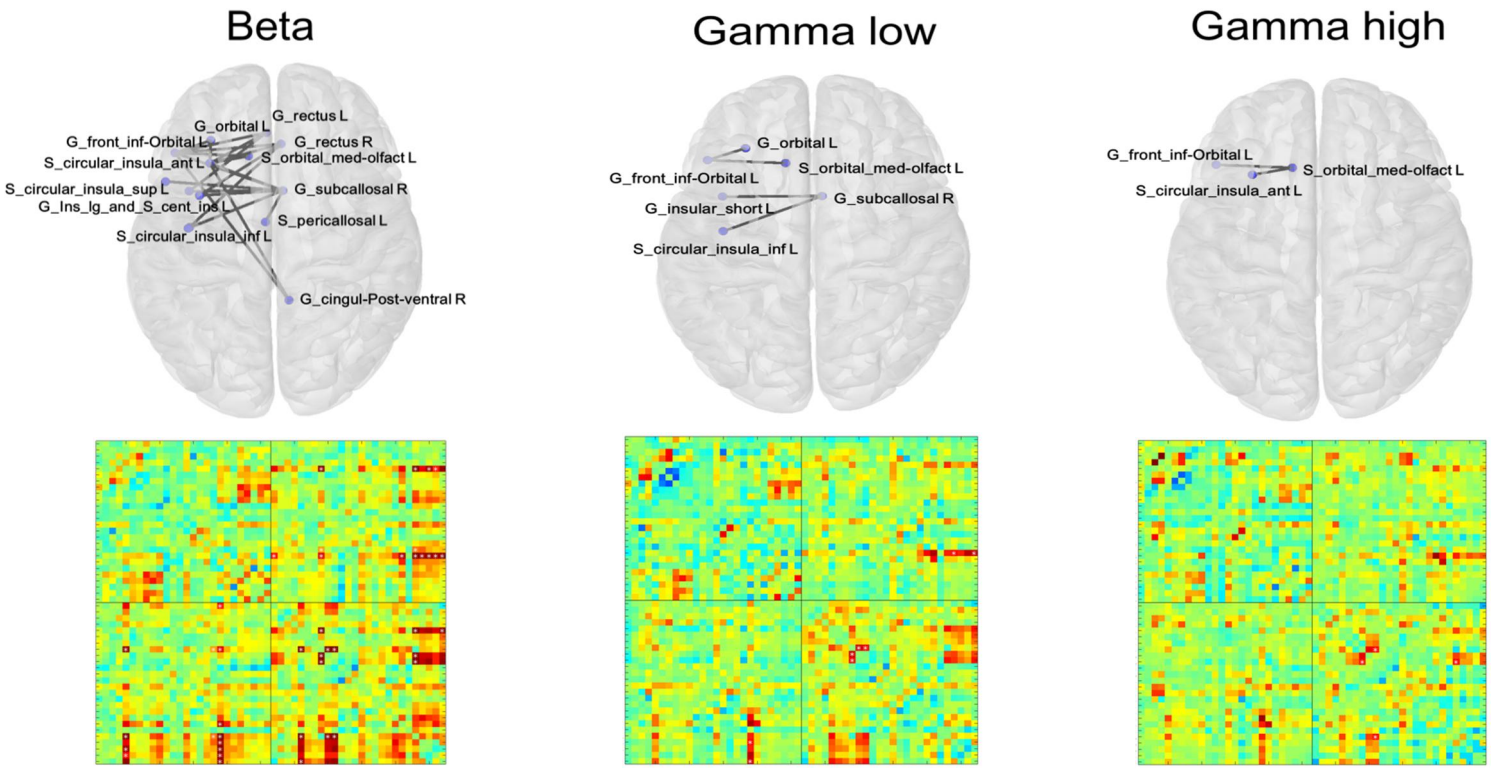

Figure 7-2. Group differences in phase-locking value (PLV) between selected regions of interest (ROIs). ROIs exhibiting statistically significant associations are indicated by white stars in the PLV matrices (p<0.01). The permutation test was used to analyze differences between the OCD and control groups.

B. Functional hubs with high degree (D_{nodal}) extracted from phase-locking value (PLV)

In order to compare the distribution of functional hubs between groups, we assumed that the strength of connectivity was represented as a value in the adjacency matrix of the weighted graph. The top 10 percent of D_{nodal} nodes were considered individual hubs in each participant and compared between the OCD and control groups (**Figure 8**). Differential hub distributions were observed in all band frequencies. Patients with OCD exhibited fewer functional hubs in the insula and orbitofrontal cortex when compared to healthy controls.

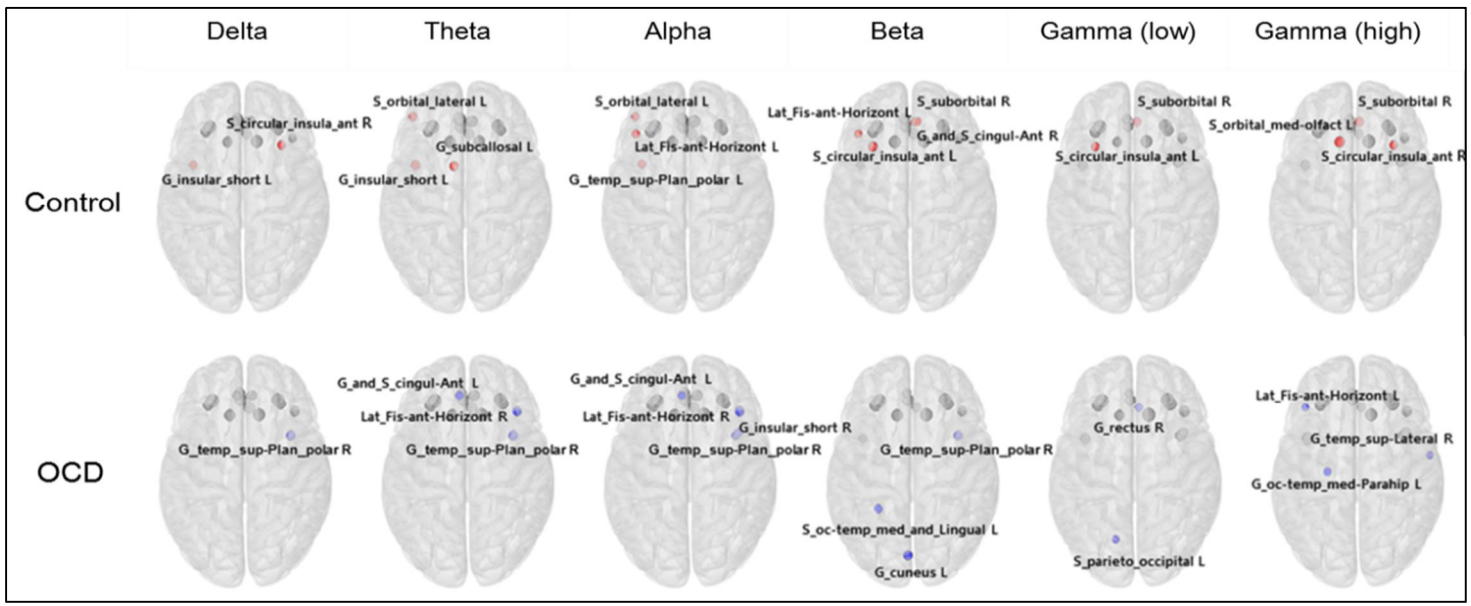

Figure 8. Group differences in functional hubs with high degree (D_{nodal}). Topological projections of the delta, theta, alpha, beta, gamma (low), and gamma (high) bands obtained from D_{nodal} estimation are presented above. Gray colored areas represent functional hubs shared between the OCD and control groups. Blue colored hubs represent functional hubs of the OCD group alone, while red colored hubs represent functional hubs of the control group lone.

IV. DISCUSSION

The aim of present study was to evaluate whether patients with OCD exhibit differences in resting-state functional connectivity when compared to healthy controls by analyzing phase locking value and examining the presence of differential functional hubs. We observed that patients with OCD exhibited reduced phase synchronization and differential distribution of functional hubs when compared to healthy controls. In addition, patients with OCD exhibited reduced functional connectivity in all band frequencies with the exception of the delta band. These results were particularly prominent in the insula, limbic regions, and orbitofrontal cortex.

Prior to our analysis of functional connectivity, we examined differences in brain activity between patients with OCD and healthy controls. Patients with OCD exhibited significantly lower brain activity in the posterior cortex when compared to healthy controls. Since alpha waves are generated from the occipital lobe in an eyes-closed resting state, this result suggests that patients with OCD may exhibit relatively lower alpha power than healthy controls[38]. This finding also aligns with the results of previous studies that have reported lower levels of resting-state alpha power for anterior and posterior brain regions in patients with OCD[39,40].

Our time-frequency analysis results for oscillatory activity indicate that significantly lower delta activity was observed in the insular and limbic regions for patients with OCD. Furthermore, these regions aligned with those

exhibiting lower phase synchronization and differential distribution of functional hubs in the OCD group. With regard to the alpha and beta band frequencies, patients with OCD exhibited coarser connections among the insular and limbic regions as well as the orbitofrontal cortex when compared to healthy controls. Patients with OCD also exhibited fewer functional hubs in these regions in all band frequencies when compared to healthy controls.

Researches have suggested that OCD symptoms may be due to dysfunctional activity in CSTC loops[4,41]. Each of the CSTC loops is thought to be related to a different neurocognitive domain. Although the precise number of loops remains controversial, CSTC has been commonly subdivided into three main loops: sensorimotor, associative (cognitive), and limbic (inhibition)[42]. While some researchers have reported corticostriatal hypoconnectivity in both children and adults with OCD[43,44], others have reported hyperconnectivity in the limbic CSTC loop[33,45-47]. Yet other studies have reported reduced connectivity within the limbic CSTC loop in unmedicated patients with OCD[48] as well as lower neighboring efficiency in orbitofrontal areas[49]. Such discrepancies among study results may be due to variation in tools of data acquisition, methods of analysis, ROIs selected, medication status of the participants, and OCD symptom severity.

The results of the present study align with previous research that has suggested that OCD involves functional abnormalities in the limbic CSTC loop, including the orbitofrontal cortex, cingulate cortex, and ventral striatum[50]. Furthermore, the insula, as part of the salience network, is involved

in motivation as well as emotional processing and is functionally connected with the orbitofrontal cortex and the dorsal anterior cingulate cortex of the limbic area[46,51,52]. Previous resting state fMRI studies of patients with OCD have reported that the insula exhibits decreased connectivity with the limbic areas[37,53]. The reduced functional connectivity between insular and limbic areas observed in the present study may suggest a deterioration of normally consistent activity between the insular and limbic loops in OCD[49].

OCD is characterized by deficits in inhibitory control[54.] Inhibitory control refers to the ability to inhibit goal-irrelevant behaviors and cognition. Indeed, altered inhibition-related brain activation has been observed in the insular cortex of patients with OCD[55]. Therefore, the findings of the present study may provide valuable evidence that reduced functional connectivity in areas of the limbic loop and functionally connected neighboring regions reflect an underlying pathophysiology associated with dysfunction of inhibitory control in patients with OCD. Furthermore, the altered functional connectivity observed in the present study may be utilized as a biomarker for OCD, though further studies are required to more fully describe this pattern.

Unlike healthy controls, patients with OCD exhibited a greater number of functional hubs in the posterior cortex, suggesting that patients with OCD may exhibit an imbalance of integration in functional brain networks due to greater connectivity among other regions during the resting state. These findings align with the results of previous studies that have reported increased fast MEG activity in the temporal regions as well as higher

efficiency in the neighboring parietal regions of patients with OCD[56,57].

The present study possesses several limitations. One of the main confounding factors when interpreting the results of our study is the effect of psychoactive drug treatment on MEG data. Most of the patients with OCD (18 of 24) had been receiving pharmacological treatment. Thus, we cannot completely rule out the possibility that our results were influenced by the effects of medication. However, one study reported no differences in mean absolute current density at delta and theta band frequencies between patients receiving and not receiving medication, and both groups displayed the same pattern of differential connectivity when compared to controls[58]. Furthermore, our analysis of differences in oscillatory activity between patients with OCD taking medication and drug-naïve patients indicated no significant difference in delta and theta band frequencies. Further investigations using large, drug-naïve patient samples are warranted to confirm whether OCD is associated with intrinsic or spontaneous changes in brain function. Second, since individual MRIs were not obtained, the accuracy of the source localization from MEG data may be questionable. However, no previous studies have utilized MEG to analyze functional connectivity in terms of PLV, and our preliminary results suggest that patients with OCD have abnormal resting-state functional connectivity that involves abnormalities in additional large-scale brain systems, with particularly significant effects on the insula, limbic regions, and orbitofrontal cortex.

V. CONCLUSION

The results of the present study indicate that, during the resting state, patients with OCD exhibit lower phase synchronization and fewer functional hubs in the orbitofrontal cortex, limbic, and insular regions when compared with healthy controls. These findings suggest that reduced functional connectivity in areas of the limbic loop and functionally connected neighboring regions may reflect an underlying pathophysiology associated with dysfunction of inhibitory control in patients with OCD. Although the sample size is too small to draw any firm conclusions regarding this issue, the results of the present study provide the first evidence of frequency- and region-specific alterations of resting-state neurophysiological interactions in OCD. Further investigation utilizing a larger sample of drug-naïve patients with OCD and individual MRI analysis is required to confirm these findings.

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ABSTRACT (IN KOREAN)

강박장애의 뇌 기능적 연결성: 뇌자도 연구

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고 민 정

강박장애는 뇌의 영역들간의 기능적 연결성에 이상이 있다고 알려져 왔다. 따라서 휴지기 동안의 기능적 연결성을 분석해보는 것은, 강박장애의 병태생리를 규명하는데 중요한 근거를 제공할 수 있을 것이다. 본 연구의 목적은, 휴지기 동안의 기능적 연결성에서, 강박장애 환자군이 정상군과 차이가 있는지를, 뇌자도를 사용하여 살펴보았다.

우리는 24명의 강박장애 환자 (남 21, 여 3)와 22명의 정상군 (남 19, 여 3)을 연구의 대상자로 모집하였다. 기능적 연결성 분석을 하기 전에, 우리는 뇌 영역에서의 활동성 및 뇌파의 활동성에서 강박장애군과 정상군 간의 그룹간 차이를 살펴보았고, 강박장애 증상의 정도와 뇌파 활동성과의 관련성을 살펴보았다.

기능적 연결성 분석에서는, 관심 영역간 위상 동기화 지수를 구하고, 이 위상동기화지수를 가중치그래프 이론에 적용시켜 도출한 기능적 허브의 분포를 통해 그룹간 차이를 검증하고자 하였다.

분석 결과, 강박장애 환자군이 델타파를 제외한 모든 주파수(쎄타, 알파, 베타, 감마) 영역에서 정상군에 비해 통계적으로 유의미한 동기화 패턴의 차이를 보였다. 쎄타 및 감마 주파수에서, 강박장애 환자군은 좌측 섬엽과 우측 변연계 영역 사이의 위상 동기화와 좌측 안와전두엽 영역간에서의 위상 동기화가, 정상군에 비해 저하된 양상을 보였다. 알파와 베타 주파수에서는 낮은 위상 동기화를 보인 영역간의 연결이 더 많이 관찰되었으나, 그 연결의 경향성은 비슷하였다. 또한 정상군이 안와전두엽과 좌측 섬엽 영역에서 중앙 허브가 더 많이 관찰되었던 반면, 강박장애 환자군에서는 측두-두정엽 영역과 대상회 영역에서 부가적인 허브가 관찰되었다.

본 연구에서 휴지기 동안, 강박장애 환자군이 정상군에 비해, 안와전두엽, 변연계, 섬엽의 영역에서 낮은 동기화를 보이고, 기능적 허브가 적다는 것을 확인할 수 있었다. 변연계 회로 및 이와 기능적으로 연결된 인접 영역 간에 기능적 연결성의 저하를 보이는 본 연구의 결과는, 억제 조절의 기능장애를 보이는 강박장애의 병태생리를 반영하는 것이라 제안할 수 있겠다.

핵심되는 말: 강박장애, 휴지기, 기능적 연결성, 뇌자도, 위상동기화지수, 동기화, 허브 병태생리