International Journal of Psychophysiology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

Altered resting-state functional connectivity in patients with obsessive–compulsive disorder: A magnetoencephalography study

Min Jung Koh[a], Jaeho Seol[b,1], Jee In Kang[c], Bong Soo Kim[d], Kee Namkoong[c], Jin Woo Chang[e,*], Se Joo Kim[c,**]

[a] Medical Affairs, Janssen Korea, Seoul, Republic of Korea
[b] Department of Neuroscience and Biomedical Engineering, and Aalto NeuroImaging, Aalto University, Espoo, Finland
[c] Department of Psychiatry & Institute of Behavioral Science in Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
[d] EIT/LOFUS Center, International St. Mary's Hospital, Catholic Kwandong University, Incheon, Republic of Korea
[e] Department of Neurosurgery, Brain Research Institute, Yonsei University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Keywords:
Functional hub
Magnetoencephalography
Obsessive-compulsive disorder (OCD)
Phase-locking value
Resting-state functional connectivity
Synchronization

ABSTRACT

Aberrant cortical–striatal–thalamic–cortical circuits have been implicated in the pathophysiology of obsessive − compulsive disorder (OCD). However, the neurobiological basis of OCD remains unclear. We compared patterns of functional connectivity in patients with OCD and in healthy controls using resting-state magnetoencephalography (MEG). Participants comprised 24 patients with OCD (21 men, 3 women) and 22 age- and sex-matched healthy controls (19 men, 3 women). Resting-state measurements were obtained over a 6-min period using a 152-channel whole-head MEG system. We examined group differences in oscillatory activity and distribution of functional cortical hubs based on the nodal centrality of phase-locking value (PLV) maps. Differences in resting-state functional connectivity were examined through PLV analysis in selected regions of interest based on these two findings. Patients with OCD demonstrated significantly lower delta band activity in the cortical regions of the limbic lobe, insula, orbitofrontal, and temporal regions, and theta band activity in the parietal lobe regions than healthy controls. Patients with OCD exhibited fewer functional hubs in the insula and orbitofrontal cortex and additional hubs in the cingulate and temporo-parietal regions. The OCD group exhibited significantly lower phase synchronization among the insula, orbitofrontal cortex, and cortical regions of the limbic lobe in all band frequencies, except in the delta band. Altered functional networks in the resting state may be associated with the pathophysiology of OCD. These MEG findings indicate that OCD is associated with decreased functional connectivity in terms of phase synchrony, particularly in the insula, orbitofrontal cortex, and cortical regions of the limbic lobe.

1. Introduction

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder associated with recurrent intrusive, disturbing thoughts (obsessions) and/or stereotyped behaviors (compulsions) (American Psychiatric Association, 2013). The condition is a severe, often debilitating mental illness with a lifetime prevalence of 2% to 3% in the general population (Abramowitz et al., 2009; Horwath and Weissman, 2000). Despite its high morbidity, the underlying pathophysiology of OCD remains unclear.

The concept of executive function might reasonably explain this recurrent intrusive thought and behavior of OCD, and there is abundant evidence for the existence of executive functioning deficits in OCD (Del Casale et al., 2016). Different aspects of executive function that are

Abbreviations: CSTC, cortico-striato-thalamo-cortical circuitry; D_{nodal}, nodal degree; EC, eyes-closed; EEG, electroencephalography; EO, eyes-open; fMRI, functional magnetic resonance imaging; FSIQ, full-scale IQ; GAI, general ability index; HPI, head-position-indicator; K-WAIS, Korean Wechsler adult intelligence scale; MADRS, Montgomery–Åsberg depression rating scale; MEG, magnetoencephalography; MNE, minimum norm estimation; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; PCA, principal components analysis; PLV, phase-locking value; PRI, perceptual reasoning index; PSI, processing speed index; ROIs, regions of interest; SD, standard deviation; VCI, verbal comprehension index; WMI, working memory index; Y-BOCS, Yale–Brown obsessive compulsive scale

* Correspondence to: J.W. Chang, Department of Neurosurgery, Brain Research Institute, Yonsei University College of Medicine, 50-1 Yonsei-Ro, Seodaemun-Gu, Seoul 03722, Republic of Korea.
** Correspondence to: S.J. Kim, Department of Psychiatry & Institute of Behavioral Science in Medicine, Yonsei University College of Medicine, 50-1 Yonsei-Ro, Seodaemun-Gu, Seoul, 03722, Republic of Korea.
E-mail addresses: jchang@yuhs.ac (J.W. Chang), kimsejoo@yuhs.ac (S.J. Kim).
[1] The author currently works as a principal scientist at MoneyBrain, Inc. in South Korea.

http://dx.doi.org/10.1016/j.ijpsycho.2017.10.012
Received 26 June 2017; Received in revised form 10 October 2017; Accepted 26 October 2017
0167-8760/

relevant to OCD include inhibitory control and working memory (Pauls et al., 2014). According to recent studies, patients with OCD have specific functional abnormalities in the insula, anterior cingulate cortex (ACC), and medial prefrontal regions during inhibitory control (Norman et al., 2016; Peng et al., 2012; Radua et al., 2010). A meta-analysis showed that, at different developmental stages, the regions exhibiting functional abnormalities may differ (Hu et al., 2017).

The most widely accepted neurobiological models of OCD have suggested the involvement of dysfunctional cortico–striato–thalamo–cortical (CSTC) circuit, which is supported by the observation of neuropsychological impairments, mainly that of the executive function of OCD patients (Pauls et al., 2014). Harrison et al. showed that these impairments of executive function might result from the connectivity imbalance between two CSTC loops: a ventral loop related to inhibitory control and a dorsal loop associated with working memory and cognitive flexibility (Harrison et al., 2009). However, several studies have suggested that multiple brain regions outside of the CSTC loops play a role in the pathophysiology of OCD, such as the insula (Menzies et al., 2008; Remijnse et al., 2006).

To date, researchers have most frequently utilized functional magnetic resonance imaging (fMRI) to investigate dysfunctional interactions among different brain regions during the resting-state in patients with OCD (Abe et al., 2015; Chen et al., 2016; Gottlich et al., 2014; Harrison et al., 2013; Posner et al., 2014; Sakai et al., 2011; Zhang et al., 2011). Several studies have reported significantly increased functional connectivity in the limbic loop of the CSTC circuit, while others have demonstrated reduced functional connectivity within this loop (Fitzgerald et al., 2010; Harrison et al., 2009; Posner et al., 2014; Sakai et al., 2011). These inconsistent findings are most likely due to the use of different seed regions or different analytical methods. Oscillatory analysis has also been utilized to analyze functional connectivity in the resting brain. Several electroencephalography (EEG) studies have reported decreased interhemispheric coherence and lagged non-linear coherence between frontal brain areas, including the anterior cingulate cortex, during the resting state in patients with OCD (Olbrich et al., 2013; Velikova et al., 2010). In contrast, Desarkar et al. (2007) observed increased phase coherence between frontal and occipital regions in patients with OCD. However, despite their excellent temporal resolution, conventional EEG methods are limited by low spatial resolution (Desarkar et al., 2007).

Magnetoencephalography (MEG) has higher spatial resolution than EEG and can be used to characterize resting-state networks based on interacting sources of oscillatory activity, due to volume reduction and field spread. The phase-locking value (PLV), which represents the phase synchrony of narrowband signals at a given frequency, has been applied in MEG studies of resting state connectivity (Casimo et al., 2016; Garces et al., 2016). Regions that exhibit greater interactions with other brain areas in order to facilitate functional integration are regarded as functional hubs (Jin et al., 2013). By applying graph theory and its mathematical notations, a hub can be determined and detected using a weighted graph. Therefore, identifying the distribution of functional hubs in patients with a particular homogenous disease may significantly enhance our understanding of functional connectivity as well as the electrophysiological aspects of the disease.

In this exploratory study, we examined differences in oscillatory activity and hub distribution between patients with OCD and healthy controls, using whole MEG sources, and then explored the whole brain cortical activity in patients with OCD, with the aim of providing a basic guideline for further clinical application. Based on the results of this approach, we investigated the characteristics of patterns of resting-state functional connectivity among OCD-related regions of interest (ROIs).

2. Materials and methods

2.1. Participants

The study was in accordance with the ethical standards of the Declaration of Helsinki and 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. Twenty-four patients with OCD (mean age = 27.5 years, SD = 6.21 years; 21 men, 3 women) were recruited from Yonsei University Health System in Seoul, South Korea. Diagnoses of OCD were confirmed by a psychiatrist trained in the use of the Structured Clinical Interview for DSM-IV (First et al., 1996). Patients with psychotic disorders, substance-related disorders, mental retardation, or other neurological/medical illnesses were excluded. We recruited healthy controls over 19 years of age via advertisements between September 2014 and January 2015. The same exclusion criteria were applied to the 22 healthy controls (mean age = 24.6 years, SD = 5.27 years, 19 male participants). Each participant completed self-reported assessments and clinician rating scales prior to MEG recording.

2.2. Clinical assessment

2.2.1. Korean Wechsler adult intelligence scale (K-WAIS)-IV

We utilized the Korean version of the Wechsler Adult Intelligence Scale (WAIS)-IV to assess cognitive ability in both participant groups (Kim et al., 2015). The WAIS is the most widely used intelligence test for adults and older adolescents worldwide. The current version (WAIS-IV) was released in 2008 and is composed of 10 core subtests, which comprise the Full-Scale IQ, in addition to five supplemental subtests. The major components of intelligence are represented by four index scores: the Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), and 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.

2.2.2. 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 (Goodman et al., 1991). The Y-BOCS is a validated and reliable clinician-administered 10-item scale that is 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 indicative of more severe symptoms.

2.2.3. Montgomery–Åsberg depression rating scale (MADRS)

We used the MADRS to assess the severity of symptoms of depression (Montgomery and Asberg, 1979). 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 symptoms of depression.

2.3. MEG procedures and data analyses

2.3.1. MEG acquisition

For all participants, the psychiatric assessments were conducted prior to the MEG measurements. A 152-channel whole-head MEG system (Korea Institute of Standards and Science; KRISS, Daejeon, Korea) was used to measure the magnetic fields induced by the brain activity during a 6-min resting period, during which participants were