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Hyper-influence of the orbitofrontal cortex over the ventral striatum in obsessive-compulsive disorder

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Abstract
Dysfunction of the fronto-striato-thalamic circuit routing through the orbitofrontal cortex (OFC) is thought to play the main role in the pathophysiology of obsessive-compulsive disorder (OCD). Repetitious stimulation of the OFC–ventral striatum (VS) projections in mice has been shown to increase the firing of the postsynaptic VS cells and the frequency of OCD-like symptoms. Moreover, increased functional connectivity (FC) between the OFC and the VS has been reported in patients with OCD. While FC is a synchronous, non-directed correlation, the directed influence between these brain regions remains unclear in patients with OCD. We obtained resting state functional magnetic resonance imaging scans from 37 non-medicated patients with OCD and 38 matched healthy volunteers, and calculated bivariative voxel-wise Granger Causality (GC) to and from three striatal regions of interest (ROI) using a blind deconvolution procedure. Additionally, we conducted multivariative GC analysis to determine if the effect revealed by the bivariative voxel-wise GCA is mediated by another seed ROI. We found a significant hyper-influence of the OFC over the VS of subjects with OCD ($p<.05$, corrected). Multivariative GC analysis confirmed this effect ($p<.05$, corrected) and that it was not mediated by another brain area within the striatum. This is the first study investigating the directed influence of the fronto-striato-thalamic loop in non-medicated patients with OCD. We confirmed the hyperactive connection from the OFC to the VS that is consistent with

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previous animal studies. These findings provide evidence for the more detailed pathophysiology of OCD.

1. Introduction

Obsessive-compulsive disorder (OCD) is a common neuropsychiatric disorder affecting many behaviors in daily life such as washing, checking and the like, with a population risk of 2–3% (Menzies et al., 2008). Patients with OCD suffer from recurrent thoughts, urges, or impulses that cause anxiety or distress and repetitive time-consuming behaviors or mental acts aimed at reducing the unwanted obsessions. Figee et al. (2013b) reviewed 71 cases whose OCD symptoms appeared or disappeared following brain lesions such as hemorrhages, infarctions, or the removal of brain tumors. In that study, many of the lesions involved were in the fronto-striato-thalamic circuit routing through the orbitofrontal cortex (OFC). Numerous neuroimaging studies have also converged to suggest that the fronto-striato-thalamic circuit plays the main role in the pathophysiology of OCD (Menzies et al., 2008). This hypothesis is supported by the fact that deep brain stimulation (DBS) targeting the ventral striatum is effective for refractory OCD (de Koning et al., 2011). Additionally, Ahmari et al. (2013) reported that repeated stimulation of the OFC–ventromedial striatum (VMS) projections in mice using optogenetics increased the firing of postsynaptic VMS cells and the frequency of overgrooming behavior, which represents OCD symptoms in mice. Thus, we hypothesized that hyperactivity of the OFC projections to the ventral striatum (VS) exists in patients with OCD.

To investigate the default state of neural networks, connectivity analysis using resting-state functional magnetic resonance imaging (fMRI) data has been used. Friston defined functional connectivity (FC) as *the temporal correlation between spatially remote neurophysiological events* and effective connectivity (EC) as *the influence one neural system exerts over another* (Friston, 2011). Brain regions forming neural circuits are connected not only in zero time-lagged synchronous correlations, but also in time-lagged correlations. The increased resting-state FC between the OFC and the VS in patients with OCD has been reported (Harrison et al., 2009; Sakai et al., 2011) and DBS normalizes this excessive connectivity (Figee et al., 2013a). In contrast to what is known about FC, the directed influences between these brain regions in OCD remains unclear, so to test our hypothesis we investigated this. EC, as well as FC, has been derived from resting-state fMRI data (Deshpande et al., 2011; Liao et al., 2011). While most FC studies employ correlation coefficient or independent component analyses, there are several methods for determining EC; dynamic causal modeling (DCM) (Friston et al., 2003), sequential equation modeling (SEM) (Zhuang et al., 2005), and Granger Causality Analysis (GCA) (Deshpande and Hu, 2012). GCA has been successfully applied to other neuropsychiatric disorders such as schizophrenia (Palaniyappan et al., 2013), major depressive disorder (Hamilton et al., 2011), and Alzheimer's disease (Miao et al., 2011).

GCA is a powerful technique although it may be subject to the confounding effects of hemodynamic response function (HRF) when applied to blood-oxygen-level-dependent (BOLD) fMRI data. In the case of task-related fMRI data, the stimulation paradigm requires a preceding hypothesis about neural activity and a generative model whose inversion corresponds to deconvolution. Nonetheless, resting-state fMRI is considered 'spontaneous event-related', and the absence of explicit inputs makes this task more difficult. In order to overcome these issues, Wu et al. (2013) developed a blind deconvolution technique for BOLD-fMRI signals. This tool allows us to extract a region-specific HRF and deconvolve the observed BOLD signal into a neural signal.

In the present study, our goal is to test the hypothesis that excessive activity of projections from the OFC to the VS exist in non-medicated patients with OCD. To do this, we used GCA of resting-state fMRI with a blind deconvolution procedure.

2. Experimental procedures

2.1. Subjects

Thirty-eight patients diagnosed with OCD (based on DSM-IV criteria) and 40 healthy controls matched for age and sex participated in this study (see Table 1 for subject characteristics). Three subjects were excluded at a preprocessing step. Trained and experienced clinical psychiatrists and psychologists assessed all patients and healthy controls. Patients were recruited at the Kyoto Prefectural University of Medicine Hospital, Kyoto, Japan. All patients were primarily diagnosed using the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID) (First MB et al., 1994).

The exclusion criteria for patients and healthy controls were: (1) cardiac pacemakers or other metallic implants or artifacts; (2) significant disease, including neurological diseases, disorders of the pulmonary, cardiac, renal, hepatic, or endocrine systems, or metabolic disorders; (3) prior psychosurgery; (4) current or past DSM-IV axis I diagnosis of psychiatric diseases except OCD; (5) DSM-IV diagnosis of mental retardation and pervasive developmental disorders based on a clinical interview and psychosocial history; (6) pregnancy; and (7) the use of any kind of psychotropic medication. None of the subjects had been taking any kind of psychotropic medication for at least 8 weeks.

There was no history of psychiatric illness in the healthy controls as determined by the Structured Clinical Interview for DSM-IV Axis I Disorders, Non-patient Edition (SCID-NP) (First MB et al., 2001). Additionally, we confirmed that there was no psychiatric treatment history in any of their first-degree relatives. The Medical Committee on Human Studies at the Kyoto Prefectural University of Medicine approved all the procedures in this study. All participants gave written, informed consent after receiving a complete description of the study.

2.2. Clinical assessments

All patients were surveyed for obsessive-compulsive symptoms, depression, and anxiety using the Japanese version of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) symptom checklist (Nakajima et al., 1995), the 17-item Hamilton Depression Rating Scale (Hamilton, 1967), and the Hamilton Anxiety Rating Scale (Hamilton, 1959).

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