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 bivariate voxel-wise Granger Causality (GC) to and from three striatal regions of interest (ROI) using a blind deconvolution procedure. Additionally, we conducted multivariate GC analysis to determine if the effect revealed by the bivariate 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). Multivariate 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...
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. Figue 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 (Figue 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 excess 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-P) (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).
weighted magnetization-prepared rapid gradient echo images were collected using gradient echo Echo Planar Imaging (EPI) sequences. Foam pads were used to generate magnetic resonance images. We used a whole-body 3.0-Tesla MR system (Achieva 3.0 TX, Best, the Netherlands) with an eight-channel phased-array head coil to overcome this issue, Weissenbacher et al. (2009) proposed a method of nuisance covariate regression in the voxel-wise multidimensional manner that is also implemented in the software of DPARSFA. In the pipeline preprocessing steps of DPARSFA, we also conducted this procedure.

2.5. Blind deconvolution procedure

To extract region-specific HRF data and deconvolve the observed BOLD signal into a neural signal, we applied a blind deconvolution procedure. This was obtained from Wu et al. (2013) as a Matlab code.

2.6. Regions of Interest (ROIs) and seed generation

We used spherical seed ROIs (diameter=7 mm), as described by Di Martino et al. (2008). We first distinguished between the VS and the dorsal caudate (DC) then divided the VS into inferior and superior regions (VI and VSs) corresponding to the nucleus accumbens and the ventral caudate, respectively. Next, we generated three seed ROIs in each hemisphere: DC, VSs, and VSI (dorsal to ventral) in which the MNI coordinates were centered at x=(±)13, y=15, z=9; x=(±)10, y=15, z=0; and x=(±)9, y=9, z=−8, respectively. One set of seeds was created for each hemisphere.

2.7. Bivariate voxel-wise Granger Causality Analysis

We performed bivariate voxel-wise GCA using the Resting-State fMRI Data Analysis Toolkit (REST version 1.8, by Song Xiaowei, http://resting-fmri.sourceforge.net) (Zang et al., 2012). We performed bivariate voxel-wise GCA, we used signed-path coefficients considered to be normally distributed and parametric statistical analysis against the residual based F (Palaniyappan et al., 2013) using this model

\[ Y_t = \sum_{i=1}^{p} A_i Y_{t-i} + \sum_{i=1}^{p} B_i X_{t-i} + CZ_t + \varepsilon_t \]

\[ X_t = \sum_{i=1}^{p} A_i Y_{t-i} + \sum_{i=1}^{p} B_i X_{t-i} + CZ_t + \varepsilon_t \]

In this study, we estimated the X-to-Y effects (the Granger causal effects) of the time series of seed regions of interest (ROIs) in the striatum on every other brain region within the fronto-striato-thalamic circuits, and the Y-to-X effects (the Granger causal effects), of the time series of every other brain region within the fronto-striato-thalamic circuits on ROIs in the striatum. We defined the fronto-striato-thalamic circuit using Automated Anatomical Labeling (AAL) and the WFU PickAtlas tool version 3.0. The mask includes the superior frontal gyrus, dorsolateral; middle frontal gyrus; inferior frontal gyrus, opercular part; inferior frontal gyrus, triangular part; superior frontal gyrus, medial; superior frontal gyrus, orbital part; superior frontal gyrus, medial orbital; middle frontal gyrus, orbital part; inferior frontal gyrus, orbital part; anterior cingulate and paracingulate gyri; median cingulate and paracingulate gyri; posterior cingulate gyrus, and the thalamus.

2.8. Statistical analysis

The bivariate voxel-wise GCA maps of each seed ROI from each individual subject were analyzed using one-sample t-test for each group at a threshold of cluster-level p<.05, uncorrected. In this analysis, we employed a liberal threshold to detect the topographic distribution of effects to and from each seed ROI. Then, we combined the depicted

**Table 2** Subjects’ characteristicsb.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients with OCD (n=37)</th>
<th>Controls (n=38)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F, No.</td>
<td>15/22</td>
<td>18/20</td>
<td>0.550</td>
</tr>
<tr>
<td>Handedness, Left/Right, No.</td>
<td>2/32</td>
<td>1/36</td>
<td>0.500</td>
</tr>
<tr>
<td>Age, y</td>
<td>30.4±7.5</td>
<td>32.7±9.7</td>
<td>0.250</td>
</tr>
<tr>
<td>Psychotropic Medication naive/free patients, No.</td>
<td>14/23</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Total Y-BOCS score</td>
<td>21.8±6.8</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>HDRS score</td>
<td>3.9±3.4</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>HARS score</td>
<td>5.3±4.3</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

HARS: Hamilton Anxiety Rating Scale; HDRS: Hamilton Depression Rating Scale; NA: not applicable; OCD: obsessive-compulsive disorder; and Y-BOCS: Yale-Brown Obsessive-Compulsive Scale.

bValues represent the mean±SD score unless otherwise specified. For all scales, high scores denote greater severity.

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regions of HC and that of OCD to create masks. We were interested only in brain regions with positive influences to and from each seed ROI and employed these as a mask. We conducted the between-group analysis using a two-sample t-test (p < .05, corrected). However, when using the same data set for selection and selective analysis, there is an issue of “double dipping” that may cause false positive results (Kriegeskorte et al., 2009). To avoid this problem, we conducted the two sample t-test again (p < .05, corrected) with an anatomically defined mask containing the brain regions we were interested in. The mask includes; the superior frontal gyrus, orbital part; superior frontal gyrus, medial orbital; middle frontal gyrus, orbital part; and the inferior frontal gyrus, orbital part.

To detect the difference in distribution of the effects to and from the seed ROIs, we performed paired-sample t-tests in a voxel-wise manner, selecting every two of three ROIs (DC versus VSi, DC versus VSs, and VSs versus VSi). Only HC data were used in this analysis.

2.9. Multivariative, ROI-wise Granger Causality Analysis

Assuming that \((Y_1, Y_2, ..., Y_n)\) are time series of selected brain regions (n regions), the signed path coefficient multivariative GCA is:

\[
\begin{align*}
Y_t &= \sum_{i=1}^{n} A_{yi} Y_i(t) + \sum_{i=1}^{n} A_{yi} Y_i(t) + C_i Z_i + \epsilon_t \\
Y_{it} &= \sum_{i=1}^{n} A_{yi} Y_i(t) + \sum_{i=1}^{n} A_{yi} Y_i(t) + C_i Z_i + \epsilon_t
\end{align*}
\]

Fronto-striato-thalamic circuits are linked to each other through striato-nigro-striatal projections and one region of the prefrontal cortex connects the striatum not only focally but also diffusely (Haber and Knutson, 2010). To consider whether the effect we detected through the bivariative voxel-wise GCA is mediated by another seed ROI or not, we performed multivariative ROI-wise GCA by using the REST toolkit, adding to the bivariative voxel-wise GCA. In this analysis, ROIs were the set of the seeds used in the bivariative voxel-wise GCA and the region detected in the between group analysis. This test was Bonferroni corrected for a total of 49 comparisons.

3. Results

3.1. Subjects’ characteristics

The demographic and clinical characteristics of the subjects are shown in Table 1. Patients with OCD did not differ from the healthy controls in terms of age (p = .55), sex (\(\chi^2\) p = .50), and handedness (\(\chi^2\) p = .25) while the data of handedness was not acquired in three patients with OCD and one of HC. In regards to psychiatric medication, 14 patients were drug-naïve and the others were drug-free for at least 8 weeks prior to the study.

3.2. Bivariative voxel-wise Granger Causality Analysis

The maps of Granger causal influence to and from each seed ROI (cluster-level p < .05, uncorrected) are shown in Fig. 1.

Fig. 1 Granger Causal influence to and from left striatum. The figures show the Granger Causal effects to and from (A) left inferior striatum, (B) left superior striatum, and (C) left dorsal caudate that are the result of one sample t-test of GCA maps on all subjects at a threshold of cluster-level p < .05, uncorrected. In this analysis, we employed a liberal threshold to detect the topographic distribution of effects to and from each seed ROI. Blue color indicates the distribution of the X-to-Y effects, which is the influence from each region of interest to the rest of brain regions within the fronto-striato-thalamic circuits and red color indicates the Y-to-X effects. Numbers at the top of each row indicate the section number in MNI space. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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The left VSi had a GC influence on the bilateral dorsolateral prefrontal cortex (DLPFC) and the ventromedial prefrontal cortex (vmPFC) had a GC influence on left VSi. The OFC exerted a GC influence on the left VSs and the dorsal anterior cingulate cortex (dACC) exerted a GC influence on the left DC. The difference in distribution of GC influences was also detected in paired t-tests (Fig. 2). The DC was influenced more from the dACC compared with VSs and VSi (p < .05, corrected) while the VSi was influenced greatly from the vmPFC compared with the DC (p < .05, corrected).

The results of the two sample t-tests revealed a significantly greater influence (p < .05, corrected) of the OFC on the left VSs in patients with OCD (Fig. 3 and Table 2). The results of the additional between group analyses, with the anatomically defined mask, showed similar clusters (see Table 3).

### 3.3. Multivariate ROI-wise Granger Causality Analysis

We performed multivariate ROI-wise GCA using the six ROIs also used in the bivariate, voxel-wise GCA. An additional ROI, the OFC described as the result in the two-sample t-test, was also analyzed. In the 49 comparisons, only the influence of the OFC on the left VSs was significantly greater in OCD patients (p < .05, corrected) than in HC. This connection was shown not to be mediated by other seed ROIs in the striatum (Fig. 4).

### 4. Discussion

We investigated the abnormality of the frontostriatal circuit in patients with OCD using a deconvolved GCA and detected the hyper-influence of the OFC to the VSs. First, we conducted bivariate voxel-wise GCA. The distribution of the influences to and from each seed ROI differ from each other. The vmPFC, the OFC and the dACC have GC influences on the VSi, VSs and DC, respectively. Thus, our analysis revealed three different circuits that have been detected

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anatomically in previous studies of primates (Haber and Knutson, 2010). This was confirmed by the paired t-test (p < .05, corrected) and these results ensure the validity of the subsequent analyses. Although the threshold of the one sample t-test was liberal, if we set the more strict one, we would analyze in the smaller search volumes in the two sample t-test and the severity of correction for multiple comparisons would decrease. Thus, the results of the one sample t-test were displayed to show the regions in which the following analysis conducted. In the result of our between group analysis, the OFC had a significantly greater effect on VSs activity in patients with OCD. Even when using an anatomically defined mask to avoid the issue of double dipping, we acquired very similar results. In the multi-variate ROI-wise GCA, taking into account the influences of the other seed ROIs, only the direct effect of the OFC on the VSs was significant (p < .05, corrected) and there was no mediation of this by other brain regions within the striatum.

Previous studies have shown that hyperactivity of the fronto-striato-thalamic circuit routing through the OFC plays the main role in the pathophysiology of OCD (Menzies et al., 2008) and the increased FC between the OFC and the VS has been reported repeatedly (Harrison et al., 2009; Sakai et al., 2011). However, while FC provided only non-directed information and the directed influence was unclear. In mice (Ahmari et al., 2013), repeated stimulation of the OFC-VMS projections increases firing of the postsynaptic VMS cells and the frequency of over grooming behavior, which represents OCD symptoms in mice. In the present study, we hypothesized that an excessive influence on the VSs occurs in patients with OCD. This was indeed observed by employing the deconvolved GCA technique. The circuit routing the OFC and the VS is integrated with the limbic system. Kopell and Greenberg (2008) reviewed that this loop is involved in the weighing up of stimuli in the reward vs punishment continuum and that the OFC is crucial in integrating information about of the internal state (hypothalamus) and the external state (striatum). Dysregulation of this function may cause behavioral alterations due to the inhibition of previously learned behavioral responses. Deficient responses of patients with OCD in decision-making tasks such as the Iowa gambling tasks or the monetary incentive delayed tasks have been reported (Pauls et al., 2014) and these abnormalities may cause the pathological repetitive behaviors of OCD. In summary, the excessive influence of the OFC on the VSs may trigger the dysregulation of the limbic circuit that causes behavioral alterations and OCD in humans.

And Pittenger et al. (2011) reviewed the glutamatergic projections from the prefrontal cortex to the striatum and the therapeutic benefits of glutamate-modulating medications. The effects we confirmed in the present study might reflect the increase in releasing glutamate in the OFC and this mechanism will be a candidate for future pharmacological targets.

As the diagnosis of OCD is simply based on two major aspects of invoked obsessions and acted-upon compulsions, probably reflecting abnormalities in the fronto-striato-thalamic circuits, it provides a good platform for examining the validity of network research in psychiatry (Hendler et al., 2014). In the present study, the distribution of influences to and from each seed ROI revealed networks detected anatomically in prior studies. Additionally, we detected a novel abnormality of the fronto-striato-thalamic circuit. Therefore, deconvolved GCA has potential for being applied to network research for other neuropsychiatric diseases.

This study has three major limitations. First, Smith et al. (2011) compared different connectivity approaches using their simulated fMRI data in which hemodynamic delay varied randomly between subjects and concluded that Granger Causality and related lag-based measures had performed very poorly in detecting a network connection. However, Schippers et al. (2011) simulated GCA using the data of 20 participants with known directions of influences and demonstrated GCA has good sensitivity and specificity. Additionally, to overcome the confounding effects of hemodynamic response functions, we used the blind deconvolution procedure (22).

Second, Webb et al. (2013) reported that GCA using fMRI data has possible reproducible vascular confounds independent of the hemodynamic response functions. It is quite natural that BOLD GCA reflects vascular anatomy because the BOLD signal is caused by neurovascular coupling and this problem is common to all techniques using BOLD signals. In the present study, the differences between groups were barely influenced by this issue.
Analysis. The values of table (A) are the result of multivariate, ROI-wise Granger Causality Analysis. The values of table (A) are the p values comparing the group mean path coefficients of patients with OCD and healthy controls with prediction going from row to column. Region of interests are the orbitofrontal cortex (OFC) described as the result in the two-sample t-test, bilateral inferior ventral striatum (VSI), superior ventral striatum (VSS), and dorsal caudate (DC). Graph (B) shows the distribution of path coefficients of the Granger Causal effect from OFC to left VSS. The distribution of path coefficients of the other effects is shown in Supplemental Tables S1 and S2.

At last, increasing temporal resolution improves the accuracy of GCA (Deshpande and Hu, 2012) and the repetition time of fMRI in our study was 2000 ms, while that of the existing studies (Deshpande et al., 2011; Kujala et al., 2014; Miao et al., 2011; Palaniyappan et al., 2013) was 2000 ms or more. In order to detect the hidden neural signals and improve the accuracy of the analysis, we employed the blind-deconvolution procedure. Wu et al. (2013) proposed this technique and tested the validity of it in several settings of the repetition time in their study. However, the present analysis still maybe did not detect networks with short time scales.

In conclusion, this is the first study investigating the directed influence in the frontostriatal loop in non-medicated patients with OCD and demonstrated the hyper-influence of the OFC over the VSS in these subjects. This is consistent with existing animal studies and these findings provide evidence for the more detailed pathophysiology of OCD.

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Contributors

Abe Y., Sakai Y., Nishida S., Nakamae T., Yamada K., Fukui K., and Narumoto J. designed the study and wrote the protocol. Abe Y., Sakai Y., Nishida S. and Nakamae T. collected the data. Abe Y. managed the literature searches and analysis, undertook the statistical analysis, and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

None of the authors has an actual or perceived conflict of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.euroneuro.2015.08.017.

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