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Corticostriatal-limbic correlates of sub-clinical obsessive-compulsive traits

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ABSTRACT

Obsessive-compulsive (OC) traits such as intrusive worrisome ideas or excessive concerns for threats are frequent in general population (5%–13%). However, the structural neural correlates of the sub-clinical OC traits remain largely unknown. Based on the data of obsessive-compulsive disorder (OCD), we hypothesized that the subcortical and cortical structures, constituting the cortico-striatal-thalamo-cortical circuit (CSTC) and the limbic system, could be associated with OC traits. Here we conducted voxel-based morphometry (VBM) in order to investigate fine grained volume changes of these structures in 49 non-clinical subjects. Analysis of structural covariances of these structures was also conducted. We identified volume changes associated with OC traits in the left putamen and the left amygdala. The results of structural covariance analysis revealed increased covariances in relation to the heightened OC traits between the left putamen to bilateral medial prefrontal cortex and to the left cerebellum, and between the left globus pallidus to the bilateral anterior cingulate cortices. The present finding of volume changes of the corticostriatal-limbic structures may reflect neuroplasticity associated with OC traits. Since the abnormality of these structures were also observed in the clinical OCD, the subclinical subjects with OC traits shared "neuronal obsessive traits" that might precondition OCD at the network level.

1. Introduction

Intrusive hostile thoughts or dreadful concerns constitute universal human experience, as exemplified in Greek philosophy (Plato, 1989) and also in the classical conceptualization of obsessional neurosis (Freud, 1907). Patients with obsessive-compulsive disorder (OCD) specifically suffer from such symptoms, including threatening ideas about violence, sex or religions (American Psychiatric Association, 2013). Studies have shown that healthy, non-psychiatric population also shows such symptom dimensions continuous in nature, which is termed obsessive-compulsive (OC) traits. Indeed, thematically diverse symptoms of OCD have been recently conceptualized as dimensional, rather than categorical (Baer, 1994; Leckman et al., 1997; Summerfeldt et al., 1999; Mataix-Cols et al., 2005; McKay et al., 2004; Katerberg et al., 2010). For example, "harm/checking", typically characterized by repeated redoings of actions related to security, orderliness, or accuracy (Reed, 1985), was identified as one of distinct symptom dimensions of OCD, which was also observed as one of the major dimensions of OC traits in a complete cohort study of 1073 subjects (Fullana et al., 2009).

Prevalence of the subclinical OC traits are reported to be relatively high among general populations (approximately 5%–13%) (Blom et al., 2011; de Bruijn et al., 2010; Fullana et al., 2010), which caused significant degree of distress/interference, although less severe than subjects with clinical OCD (Fullana et al., 2009). Notwithstanding these negative sides of personal distress, the OC traits might be "task beneficial" in conflicting or indecisive situations (Riesel et al., 2017; Hauser et al., 2017). For example, 'checking' to ensure whether certain unknown person would not cause harm and whether one should show friendly attitude toward that person constitutes important judgment ensuring social life. Of interest, threat appraisal is one of such socio-affective components related to OC traits, and it has been shown that threat estimation predict checking tendencies in healthy student sample with OC traits (Wheaton et al., 2012). Therefore, control and/or estimation of negative affect such as threat might be primarily implicated as basic mechanism underlying OC traits.

Despite advancements in the clinical knowledge of OC traits, little is known about their neural backgrounds. To our knowledge, only one

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structural magnetic resonance imaging (MRI) study investigated this issue (Kubota et al., 2016). The study assessed 49 healthy subjects using the Maudsley Obsessive Compulsive Inventory (MOCI) and conducted anatomical delineation on MRI to investigate the global volume and local shape of the putamen, the caudate nucleus, and globus pallidus (GP). The volume analysis revealed a positive relationship between the MOCI total score and the bilateral putamen volumes. The shape analysis demonstrated associations between the higher MOCI total score and hypertrophy of the anterior putamen in both hemispheres. However, the study examined only the limited regions of the stratum. Therefore, it is necessary to examine the possibility that the volume changes of other subcortical and cortical structures might be corresponding to the OC traits.

Previous structural MRI studies in the clinical population can provide clues about this issue given the continuous nature of OC symptoms across clinical and sub-clinical populations. These studies reported structural abnormalities in several subcortical and cortical brain regions other than the striatum. For example, some studies showed that volume alterations in the amygdala were associated with negative affect control related to OC traits (Mataix-Cols et al., 2003; Simon et al., 2010) or aggressive/checking symptoms (Pujol et al., 2004; van den Heuvel et al., 2009). Indeed, the amygdala and its connection with the frontal cortex seems to play an important role in processing reward, negative affect, and specifically fear and anxiety in OCD patients (Milad and Rauch, 2012). These findings were to be integrated into a recent model of OCD, which extends prevailing views focusing on the cortico-striatal-thalamo-cortical circuit (CSTC) (Saxena et al., 1998) and encompasses wide spreading brain regions such as the amygdala, hippocampus, anterior cingulate, prefrontal cortex (PFC) and parietal cortex (for review, see (Milad and Rauch, 2012; Menzies et al., 2008)). The cerebellum is also implicated for its integration with cortico-striatal circuitries (Menzies et al., 2007). Thus, we hypothesized that, in addition to the striatum structures centered on the putamen, several other structures described above might be critically involved in the expression of the OC traits.

To investigate these issues, we applied voxel-based morphometry (VBM) to the MRI data we analyzed in the previous study (Kubota et al., 2016) in order to investigated volume changes in the entire brain corresponding to OC traits of non-clinical subjects. We also conducted analysis of structural covariances of these structures so as to investigate synchronized maturational changes in network level that might be critically involved in the manifestation of OC traits.

2. Materials and methods

2.1. Participants

The study included 49 volunteers (23 females; mean ± *SD* age, 22.4 ± 4.4 years). The participants were administered the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998), a short structured diagnostic interview, by a psychiatrist or psychologist. The interview revealed no neuropsychiatric conditions among participants. All participants were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). After a detailed explanation of the experimental procedure, all participants provided informed consent. Our study was approved by the ethics committee of the Primate Research Institute, Kyoto University. The study was conducted in accordance with the Declaration of Helsinki.

2.2. Psychological questionnaires

The Japanese version of MOCI was used to measure the OC trait (Hodgson and Rachman, 1977; Hosoba et al., 1992). The MOCI is a self-report questionnaire of 30 items (Hodgson and Rachman, 1977). In the Japanese version of MOCI (Hosoba et al., 1992), all items are rated on a three-point scale: 0 (disagree), 0.5 (undecided), or 1 (agree). The total score for a subject will range between 0 (absence of symptoms) and 30 (maximum presence of symptoms).

The State-Trait Anxiety Inventory (STAI) was also used to assess state- and trait-anxiety. The STAI is a 40-item self-report scale, with 20 items assessing state anxiety (e.g., I am presently worrying over possible misfortunes) and 20 assessing trait anxiety (e.g., I am a steady person) (Spielberger et al., 1970). All items are rated on a four-point scale: 0 (almost never) to 3 (almost always). The Japanese version of the STAI was developed and validated (Hidano et al., 2000).

2.3. MRI acquisition

Each participant underwent MRI and then completed a set of questionnaires. Image scanning was performed using a 3-Tesla scanning system (MAGNETOM Trio, A Tim System; Siemens) using a 12-channel head coil. A forehead pad was used to stabilize the head position. A T1-weighted high-resolution anatomical image was obtained using magnetization-prepared rapid-acquisition gradient-echo sequence (repetition time = 2250 ms; echo time = 3.06 ms; inversion time = 1000 ms; flip angle = 9°; field of view = 256 × 256 mm; voxel size = 1 × 1 × 1 mm).

2.4. Image analysis

Image analyses were performed using the SPM8 statistical parametric mapping package (http://www.fil.ion.ucl.ac.uk/spm) and the VBM8 toolbox (http://dbm.neuro.uni-jena.de) implemented in MATLAB R2012b (Mathworks).

First, image preprocessing was performed using the VBM8 toolbox using the default settings. All structural T1 images were segmented into gray matter, white matter, and cerebrospinal fluid using an adaptive maximum a posteriori approach (Rajapakse et al., 1997). Intensity inhomogeneity in the MRI was modeled as slowly varying spatial functions, and thus corrected in the estimation. The segmented images were then used for a partial volume estimation using a simple model with mixed tissue types to improve segmentation (Tohka et al., 2004). Furthermore, a spatially adaptive non-local means denoising filter was applied to deal with spatially varying noise levels (Manjón et al., 2010). A Markov Random Field cleanup was used to improve the image quality. The gray and white matter images in native space were subsequently normalized into standard stereotactic space defined by the Montreal Neurological Institute using the diffeomorphic anatomical registration using the exponentiated Lie algebra algorithm approach (Ashburner, 2007). We used the predefined templates provided with the VBM8 toolbox, derived from 550 healthy brains from the IXI-database (http://www.brain-development.org). The resulting normalized gray matter images were modulated using Jacobian determinants with non-linear warping only (i.e., m0 image in VBM8 outputs) to exclude the effect of total intracranial volume. Finally, the normalized modulated gray matter images were resampled to a resolution of 1.5 × 1.5 × 1.5 mm and smoothed using an isotropic Gaussian kernel 12-mm full width at half-maximum to compensate for anatomical variability among participants.

Next, to identify the association between regional gray matter volume and MOCI score, we conducted multiple regression analyses using the MOCI score as the effect-of-interest factor and sex, age, full-scale Intelligence Quotient (IQ), and state- and trait-anxiety score as effect-of-no-interest covariates. The association between gray matter volume and MOCI score was tested using *t*-statistics. For the regions of interest (ROIs) described in the Introduction, a small volume correction (Worsley et al., 1996) was performed for the union of anatomical masks. The anatomical masks were centered for the BG (the putamen, caudate nucleus, and GP) and the amygdala in both hemispheres using WFU PickAtlas 2.4 (Maldjian et al., 2003). Voxels were deemed to be statistically significant if they reached the extent threshold of $p < 0.05$, with family-wise error (FWE) correction for multiple comparisons, with

a cluster-forming threshold of $p < 0.005$ (uncorrected). Other areas were corrected for the entire brain volume. The brain structures were labeled anatomically using Talairach Client (http://www.talairach.org/) (Lancaster et al., 2007) and Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002) included in the MRIcron software (http://www.mccauslandcenter.sc.edu/mricro/mricron/). Amygdala subregions were identified according to the cytoarchitectonic map derived from human postmortem brain data using Anatomy Toolbox ver. 2.0 (Amunts et al., 2005; Eickhoff et al., 2005).

Furthermore, we analyzed the whole-brain structural covariance patterns of our seed regions of interest. Based on our predictions described in the Introduction, we selected the BG (the putamen, caudate nucleus, and GP) and the amygdala as the seed regions and calculated the mean voxel-volume-values in the regions using WFU PickAtlas 2.4 (Maldjian et al., 2003). Then, we calculated multiple regression equations with the interaction between MOCI score (mean centered) and seed volume value as the effect-of-interest factor, and MOCI score, seed volume value, age, sex, full-scale IQ, and state- and trait-anxiety score as effect-of-no-interest covariates. Voxels were deemed to be statistically significant if they reached the extent threshold of $p < 0.05$, with FWE-corrected for the entire brain volume, with a cluster-forming threshold of $p < 0.005$ (uncorrected).

To illustrate the associations between regional gray matter volumes and MOCI scores, the gray matter values extracted at the peak voxels were plotted against the MOCI scores after adjusting for the effect-of-no-interest covariates. To illustrate the structural covariance patterns, the gray matter values extracted at the peak voxels were plotted against the seed voxel values adjusted for the effect-of-no-interest covariates after median splitting the groups into low- and high-MOCI score groups.

3. Results

3.1. Psychological rating

The mean ± *SD* of total MOCI scores were 12.9 ± 4.3 (range: 3–21.5).

3.2. Regional gray matter volume associated with MOCI score

The association between MOCI score and regional gray matter volume was analyzed using VBM. First, based on our interest, we conducted ROI analyses for the BG and amygdala. The results revealed significant ($p < 0.05$, FWE-corrected extent threshold) positive associations between the MOCI score and gray matter volume in the left putamen ($x-18$, $y8$, $z-12$; $T(42) = 3.21$) and the left amygdala ($x-17$, $y-4$, $z-17$; $T(42) = 3.84$) (Fig. 1). According to the highest assignment probability of the cytoarchitectonic map (Amunts et al., 2005; Eickhoff et al., 2005), the peak in the amygdala was located at the superficial (SF) subregion. The left and right GP also showed the non-significant trends ($p < 0.10$, FWE- corrected extent threshold) of associations with MOCIS score (left: $x-15$, $y5$, $z-6$; $T(42) = 2.88$; right: $x17$, $y5$, $z-5$; $T(4) = 2.82$). The ROI analyses for other regions and the whole brain analysis showed that MOCI score was not significantly associated with any other brain regions.

We also explored MOCI subscales in the same manner as the MOCI total score. Both the ROI and whole brain analyses did not detect any significant clusters. The ROI analyses only showed the non-significant trends ($p < 0.10$, FWE- corrected extent threshold) of positive associations between the MOCI checking subscale and left amygdala volume ($x-18$, $y2$, $z-20$; $T(42) = 3.72$) and the MOCI doubting subscale and the volume of the left putamen ($x-14$, $y12$, $z-9$; $T(42) = 2.89$) and left amygdala ($x-20$, $y-3$, $z-14$; $T(42) = 2.83$). Because the analyses for subscales did not show clear-cut effects, following structural covariance analyses were conducted only for the total score.

3.3. Structural covariance associated with MOCI score

Based on our interest, we used the BG and amygdala as the seed regions and searched for the structural covariance patterns depending on MOCI scores in the entire brain. When the left putamen was analyzed as the seed region, significantly increased correlations depending on MOCI scales were found in the bilateral dorsomedial prefrontal regions and left cerebellum (Fig. 2). The analysis with the left GP seed also showed a significantly heightened correlation depending on MOCI scales in bilateral anterior cingulate cortices (ACC) (Fig. 2). Our search with these and other seed regions interactions revealed no significant clusters in other regions of the brain.

4. Discussion

We found volume change reflecting OC traits in the non-clinical population in the left putamen, and also non-significant tendency for volume changes as related to OC traits in the bilateral GP. These striatal structures are known to comprise the CSTC along with the ACC and medial-orbitofrontal cortex (Alexander et al., 1986; Haber, 2003; Haber and Knutson, 2010). Recent VBM meta-analysis of studies on OCD showed increases of the volume of these structures (Rotge et al., 2010; Radua et al., 2010; Norman et al., 2016). Furthermore, we previously reported the positive correlation between the putamen structure and the MOCI score using a different surface analysis (Kubota et al., 2016). Together with these findings, the present results suggested that the CSTC involving these striatal structures were neural backgrounds not only for clinical OCD but also for non-clinical OC traits.

We additionally identified volume changes localized in the left amygdala associated OC traits. As far as we know, this is the first study that depicted structural abnormality of the amygdala reflecting the subclinical OC traits. A small number of studies have reported amygdala volume changes in subjects with OCD and the results were inconsistent (Rosenberg and Keshavan, 1998; Szeszko et al., 1999; Kwon et al., 2003; Pujol et al., 2004; van den Heuvel et al., 2009). The discrepancy might be partly attributable to heterogeneity of studied subjects, divergent symptomatology, and also comorbidity such as anxiety, depression and/or tic-related disorders (Nestadt et al., 2009), all of which were possibly related to different structural abnormalities. Thus, the present study focusing on pure form of intrusive thoughts or concerns in the non-clinical subjects might shed some insight in uncovering a pathogenetic involvement of limbic circuitries involving the amygdala in the OCD.

We found increased structural covariances in relation to OC traits (1) between the left putamen to bilateral medial PFC, and also to the left cerebellum, and (2) between the left GP to the bilateral ACC increasing with the MOCI score (Fig. 2). A previous study on clinical OCD reported increased structural covariance between the left putamen and the left PFC, though only the lateral regions were included such as the inferior frontal gyrus and frontal operculum (Subirà et al., 2016). The medial PFC and the ACC are known to be highly interconnected with the ventral striatum and the limbic structures, which complies the reward system subserving negative emotional processing or threat appraisal (Haber and Knutson, 2010). Therefore, it is highly plausible that these regions were involved in pathophysiology of OCD (Fettes et al., 2017). Decreases in gray matter volume in the medial PFC and the ACC, along with increases in the striatal regions, were reported in recent meta-analysis of VBM studies on OCD (Radua et al., 2010; Norman et al., 2016). Although the relationships of the volume changes between these structures were in opposite to our findings, these reports at least support their pathophysiological role in OCD. Furthermore a recent study invested structural network alterations in OCD using/adopting a network-based statistic (NBS) approach observed a single network of decreased structural connectivity in OCD as compared with healthy controls. The network comprised of seven nodes in the left hemisphere: medial orbitofrontal cortex, putamen, pallidum, amygdala, entorhinal

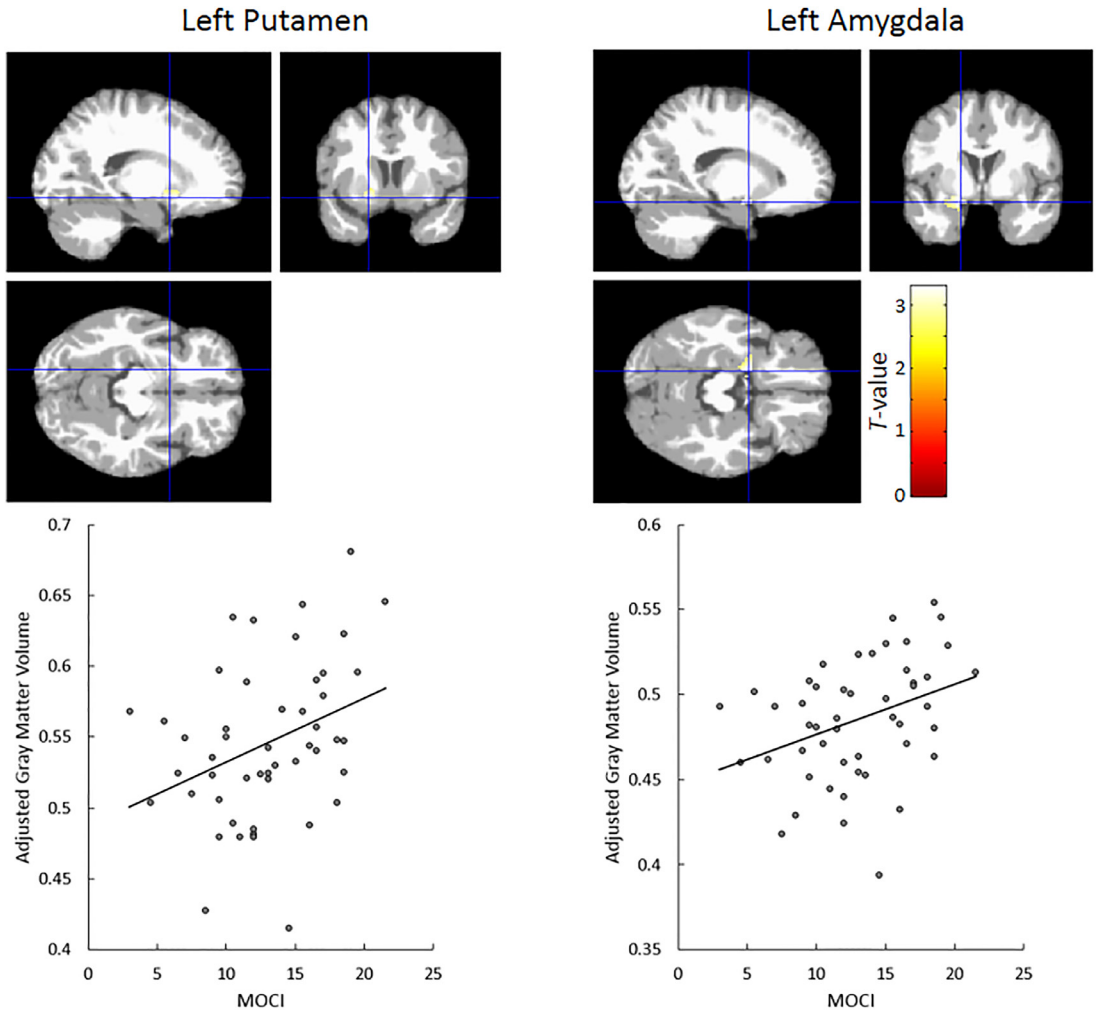

Fig. 1. Brain regions significantly associated with the Maudsley Obsessive Compulsive Inventory (MOCI) score. (Upper) A statistical parametric map ($p < 0.005$, peak-level uncorrected). The areas are overlaid on the spatially normalized gray matter tissue probability map of a representative participant. The blue crosses indicate the locations of the peak voxels. The red-white color scale indicates the *T*-value. The left putamen and the left amygdala are indicated. (Lower) Scatter plots and regression lines of the adjusted gray matter volume as functions of the MOCI scores at the peak voxels. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

cortex, insula and temporal pole (Reess et al., 2016). These findings were largely in line with the view that limbic circuitries were implicated in the neural background of OCD. The putamen to cerebellum connectivity was not previously reported in OCD. However, a recent surface morphometry study found the local volume of the cerebellum was positively correlated with the comorbidity of OCD in the patients with Tourette syndrome (Tobe et al., 2010). Another study conducted multimodal network analysis using multivariate analysis(Kim et al., 2015) and reported alterations of connection in the large area of cerebella, in which the multi-site VBM study reported higher regional volume of the gray matter (de Wit et al., 2014). Together with these findings, the present findings of structural covariances suggest involvement of widely distributed circuitries including limbic structures and cerebellum as neural underlying of the subclinical OC traits, which complements the classical model of clinical OCD as CSTC impairments.

The assumption that the reward network implementing the CSTC and the limbic structures such as the amygdala is a key structure across OCD symptom dimensions were supported by fMRI studies using symptom provocation paradigm that confronted patients with symptom related picture(Breiter et al., 1996; Olatunji et al., 2014; Simon et al., 2014; Simon et al., 2010; Via et al., 2014). Furthermore, recent functional imaging studies on OCD directly investigating activity of circuitries subserving affective tasks reported abnormal activity of the amygdala (Admon et al., 2012; Jung et al., 2013). For example, a study using interactive game encompassing distinct intervals of threat (Admon et al., 2012) found that, compared to healthy controls, OCD patients reluctant to make risky choices showed higher amygdala activation to threat. Based on these findings, we speculate that the observed structural abnormality of the amygdala, along with the CSTC impairments, might be underlying relatively excessive style of fear/threat estimation in our subjects with OC traits.

In this line, the result of the left SF amygdala volume increment in correlation with higher OC traits scores might be interpreted as reflecting the general tendency to over-estimate threat. Previous studies reported that the SF subregions, along with the centromedial subregions play a central role in the context of more general negative affect control or threat estimation (Prévost et al., 2012). As to the issue of the laterality, involvement of the left amygdala was reported in a functional (Simon et al., 2014) and a connectivity study on the OCD (Rus et al. 2017). The left amygdala is known to be a critical structure for processing cognitively-learned, elaborated and/or subjectively interpreted negative emotional information (Phelps et al., 2001). Taken together, it can be postulated that abnormality of the general affect control system involving the left SF might indicate a potential/precursor form of OCD.

The view is generally consistent with clinical observation. OC traits can be primarily regarded as dysfunction of general control system for

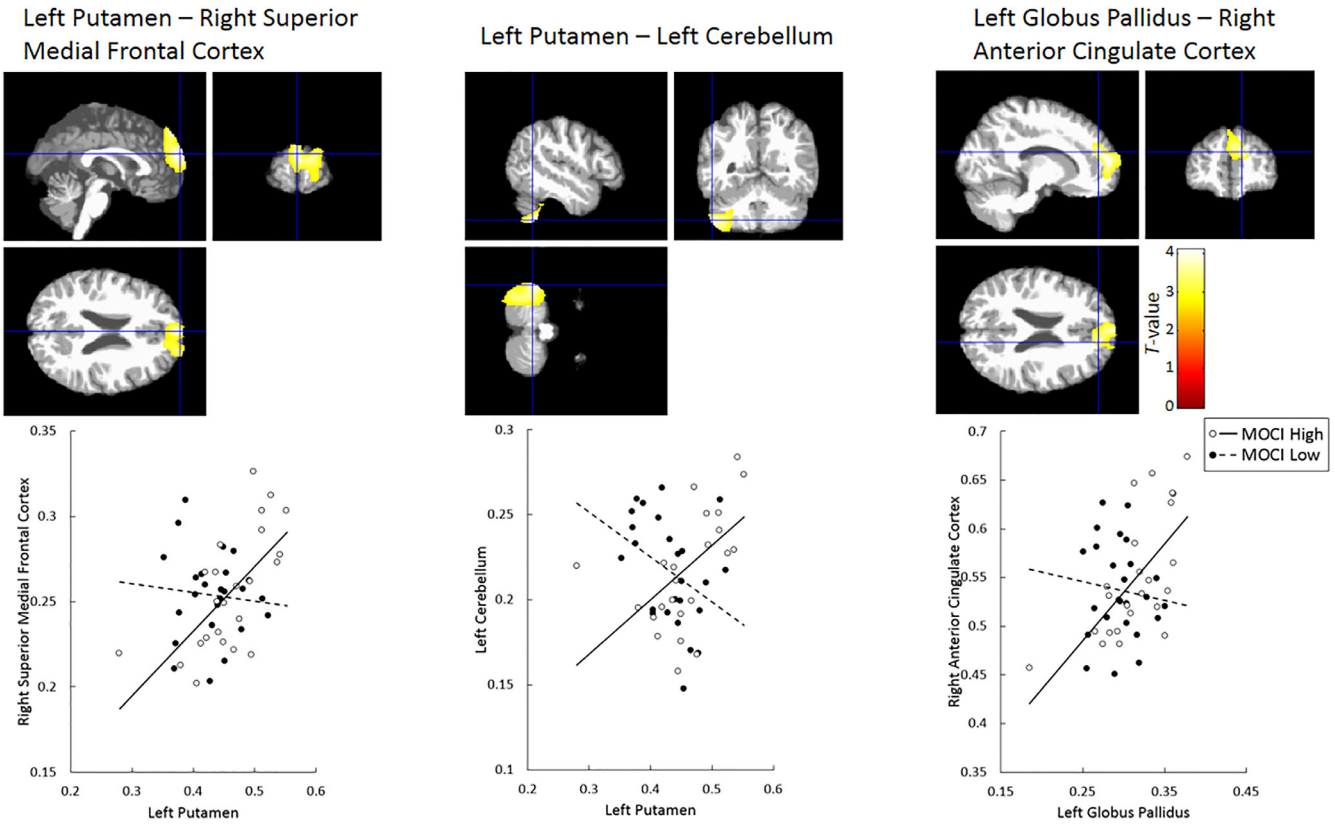

Fig. 2. Structural covariance patterns associated with the Maudsley Obsessive Compulsive Inventory (MOCI) score. (Upper) A statistical parametric map ($p < 0.005$, peak-level uncorrected). The areas are rendered on the spatially normalized gray matter tissue probability map of a representative participant. The blue crosses indicate the locations of the peak voxels. The red-white color scale indicates the *T*-value. (Lower) Scatter plots and regression lines of adjusted gray matter volume as functions of seed region volume values at the peak voxels. To illustrate the different structural covariance patterns across participants depending on the MOCI scores, the participants were divided into low- and high-MOCI score groups using a median split procedure. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

potential threats. Classical psychoanalytical literatures on OCD (obsessive neurosis) highlighted a pathological defense mechanism against threatening thoughts, which is also observed in normal religious attitude (Freud, 1907). Cognitive theory for OCD also focused on intrusive, threatening thoughts whose content is similar to obsessions (van Oppen and Arntz, 1994; Freeston et al., 1996; Rachman, 1978; Rachman, 1997; Salkovskis et al., 1998). Studies on clinical outcome implicated this dysfunctional system for appraisal of fear/anxiety as key component for controlling OCs. Finally, a recent study found that the activity in the temporal pole and amygdala during symptom provocation were associated with better outcome (Olatunji et al., 2014).

Together, based on these findings, it can be postulated that the observed volume changes of the structures involved in the CSTC and the limbic structures may reflect neuroplastic modulation corresponding OC traits. Excessive recruitment of this widely distributed system for motor/cognitive/affective information was mostly commonly observed in clinical OCD as well as the present subclinical population. Thus this might represent "neuronal obsessive traits," or preconditions for OCD at the network level. Further studies are needed to elucidate whether these neuronal changes might be a real precursor for more severe, clinical form of the OCD.

5. Limitations

The present study investigated only healthy population and it remains to be elucidated whether the present findings can be directly applied for clinical OCD. Given the current shift to a dimensional view of OCD symptoms, we believe that our findings had certain importance in order to elucidate neurobiology of OCD. It should be noted, however, that the effect size was relatively small and much larger sample size might be needed to fully elucidate the significance of the present findings. The present study using the MOCI did not examine overall subset of OC symptoms, and further study using more detailed OC symptoms check list are warranted. However, the present Japanese version of MOCI seemed effectively capture the heterogeneity of OC characteristics in the non-clinical subjects. Given relatively infrequent occurrence of distinct OCD symptomatology in this population, we believe that the present use of the MOCI was justifiable. In our previous study on healthy subjects with OC traits, we observed positive correlation of the putamen, but failed to detect volumes changes of the amygdala. This can be explained from technical problems of automated delineation methodology for subcortical structures we used. It should be noted that the present structural brain scans do not enable the differentiation of individual subregions of the human amygdala. The exact location of the amygdala subregions was known to vary between individuals. Therefore, the present analysis using the standard atlas system had limitation in not providing information about the inter-individual anatomical variability.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.01.012.

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