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Anterior insular volume is larger in patients with obsessive–compulsive disorder

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ABSTRACT

There has been increasing evidence indicating gray matter abnormalities in patients with obsessive–compulsive disorder (OCD). Several voxel-based morphometry (VBM) studies have reported volume changes in the insular cortex. Although there are distinct differences in the connectivity and functions in the anterior and posterior insular cortices, these two regions have never been distinguished in previous VBM studies. In this study, we adopted a region of interest (ROI) method to measure insular volume separately. We investigated insular volume in 32 drug-free patients with OCD and in 34 healthy controls using magnetic resonance imaging (MRI). Repeated measures multivariate analysis of covariance (MANCOVA) was conducted to examine the difference between the patients and the controls. Compared with the healthy controls, the patients had a significantly larger gray matter volume in the anterior insular cortex bilaterally (post hoc test, $p = 0.036$; left, $p = 0.047$; right). This is the first volumetric MRI study to separately investigate the anterior and posterior insular cortex volumes in non-medicated patients with OCD. The results suggest that the anterior insular cortex may be related to the pathophysiology of OCD.

1. Introduction

Obsessive–compulsive disorder (OCD) is a common neuropsychiatric disorder with a lifetime prevalence of 2–3% [Carliner et al., 1984; Weissman et al., 1994]. OCD is characterized by persistent intrusive thoughts (obsessions), repetitive actions (compulsions) and excessive anxiety. A major characteristic of obsessions and compulsions is that they are excessive and unreasonable, based on the definitions provided in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [American Psychiatric Association, 1994].

It has been hypothesized that the cortico–striato–thalamic (CSTC) circuits play a key role in the pathophysiology of OCD [Menzies et al., 2008]. Voxel-based morphometry (VBM) studies have reported volume changes in other regions in addition to those of the CSTC circuits, such as the parietal lobe, the cerebellum and the insula [Kim et al., 2001; Pujol et al., 2004; Valente, 2005; Carmona et al., 2007; Yoo et al., 2008; Koprivova et al., 2009; Lazaro et al., 2009; van den Heuvel et al., 2009].

Insular volume changes have been reported in two studies, both indicating a slight difference in size between OCD and normal subjects [Pujol et al., 2004; Yoo et al., 2008]. The insular cortex is located in the center of the cerebral hemisphere and is extensively connected with other brain regions including the primary and secondary somatosensory areas, the anterior cingulate cortex, the amygdaloid body, the prefrontal cortex, the superior temporal gyrus, the temporal pole, the orbitofrontal cortex, the frontal operculum, the parietal operculum, the primary auditory cortex, the auditory association cortex, the visual association cortex, the olfactory bulb, the hippocampus, the entorhinal cortex and the motor cortex. Consequently, the insular cortex is involved in extensive brain processing, including the processing of visceral sensory, vestibular function, attention, pain, emotion, verbal, motor, and musical information in addition to gustatory, olfactory, visual, auditory and tactile data [Augustine, 1996]. Several of these insular functions, especially emotion, may be related to OCD [Mataix-Cols et al., 2004; Schienle et al., 2005; Lawrence et al., 2007].

The anterior and posterior portions of the insular cortex are distinctly different in connectivity and function. These two subregions are diagonally divided by the central insular sulcus [Augustine, 1996; Duvernoy, 1999; Ture et al., 1999]. Although two VBM studies have pointed out insular volume changes [Pujol et al., 2004; Yoo et al., 2008], these two subregions have never been distinguished. Thus, whether the insular cortex volume change in OCD preferentially

Abbreviations: OCD, obsessive–compulsive disorder; VBM, voxel-based morphometry; ROI, region of interest; MRI, magnetic resonance imaging; MANCOVA, multivariate analysis of covariance; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; CSTC, cortico–striato–thalamic; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders; SCID-NP, Structured Clinical Interview for DSM-IV Axis I Disorders Non-patient Edition; Y–BOCS, Yale–Brown Obsessive–Compulsive Scale; 3D-MPRAGE, three-dimensional magnetization-prepared rapid gradient-echo; CSF, cerebrospinal fluid; ICCs, intraclass correlation coefficients.

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involves the anterior insular cortex or the posterior insular cortex has remained unresolved. In this study, we adopt a region of interest (ROI) method to measure the insular volume of the subregions separately.

2. Methods

2.1. Subjects

The subjects were 32 adults patients diagnosed with OCD (based on the DSM-IV criteria) and 34 healthy volunteers matched for age, gender, and handedness, though there was a significant difference in educational years (Table 1). The 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) and had no other Axis I disorders. At the time of the MRI examination, none of the subjects had taken any psychotropic medication for at least eight weeks. In addition, 16 patients were medication-naïve.

The exclusion criteria for patients and healthy volunteers included: 1) significant diseases such as neurological diseases, diseases of the pulmonary, cardiac, renal, hepatic, or endocrine systems and metabolic disorders; 2) current or past DSM-IV Axis I diagnosis of any psychiatric illness other than OCD; and 3) DSM-IV diagnosis of mental retardation or pervasive developmental disorders based on clinical interview and psychosocial history.

There was no history of psychiatric illness in the healthy volunteers as determined by the Structured Clinical Interview for DSM-IV Axis I Disorders Non-patient Edition (SCID-NP). In addition, we confirmed that there was no psychiatric treatment history in any of the healthy volunteers' first-degree relatives. Classification of handedness was based on a modified 25-item version of the Edinburgh Inventory [Oldfield, 1971]. All of the patients were surveyed for obsessive–compulsive symptoms 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], respectively.

Frequencies of the major symptom categories of the Y-BOCS were as follows: twenty two (68.7%) aggressive obsessions, twenty one (65.6%) contamination obsessions, four (12.5%) sexual obsessions, five (15.6%) hoarding/saving obsessions, fourteen (43.7%) religious obsessions, fourteen (43.7%) symmetry obsessions, nine (28.1%) somatic obsessions, twenty four (75.0%) washing compulsions, twenty seven (84.3%) checking compulsions, nineteen (59.3%) repeating compulsions, four (12.5%) counting compulsions, six (18.7%) ordering compulsions and four (12.5%) hoarding compulsions respectively.

The Medical Committee on Human Studies of the Kyoto Prefectural University of Medicine approved all of the procedures. All participants provided written, informed consent after receiving a complete description of the study.

2.2. Magnetic resonance imaging acquisition

MR images were obtained at the Kyoto Prefectural University Hospital on a whole-body 1.5-Tesla MR system (Gyroscan Intera; Philips Medical Systems, Best, The Netherlands) with a six-channel phased-array head coil. The scanning parameters of the three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequences were as follows: TE = 5.8 ms; TR = 9.9 ms; FOV = 250; slice plane = sagittal; slice thickness = 1.5 mm; and resolution = 1 × 1 × 1.5 mm.

2.3. Image processing

Brain images were realigned in three dimensions and reconstructed into contiguous sagittal images with a 1-mm thickness by MRIcro software (Chris Rorden, University of Nottingham, Great Britain). The signal intensity histogram distributions from T1-weighted images across the whole brain for each subject were used to segment the voxels semi-automatically into the gray matter, white matter, and cerebrospinal fluid (CSF). The histogram of gray levels was computed and used to select the minimal intensity points between the gray matter and the CSF peaks (representing the lower intensity threshold) and between the gray and white matter peaks (representing the upper intensity threshold) [Takahashi et al., 2005; Takahashi et al., 2010]. First, the CSF and tissues were separated by the lower intensity threshold; then, based on the resulting tissue compartment, the insular cortex was traced on 1-mm consecutive coronal slices using the following procedures. First, the most rostral coronal slice containing the insular cortex and the coronal plane containing the fusion of the superior and inferior circular insular sulci were chosen as the anterior and posterior boundaries, respectively. On each coronal slice, the insular cortex was bounded superiorly by the superior circular insular sulcus and inferiorly by the inferior circular insular sulcus or the orbitoinsular sulcus [Crespo-Facorro et al., 2000; Pujol et al., 2004; Takahashi et al., 2005; Takahashi et al., 2010]. Next, the insular cortex was divided into the anterior and posterior insular cortices by the central insular sulcus, which was readily identified using both coronal and sagittal views. These ROIs were segmented into gray matter regions and white matter regions by the intensity threshold (Fig. 1), and we measured the insular cortex volume with the segmented ROIs. We also measured the whole brain volume of each subject with SPM5 (Wellcome Department of Imaging Neuroscience, London, United Kingdom).

Magnetic field inhomogeneities in our scanner were monitored with daily phantom scanning and basic quality control, and had been stable over the MR acquisition time for this study. Although the images were not corrected for the magnetic field inhomogeneities, no visible effect on the quality of the segmentation was detected for any case.

All measurements were performed by one rater (S.N.), without any knowledge of the subjects' identity. The intra-rater reliability was established by rating seven subjects randomly sampled from the

Table 1
Clinical characteristics of patients with OCD and of healthy volunteers.

	Patients with OCD (n = 32)	Healthy comparison subjects (n = 34)	Statistics	*p*-value
	Mean ± SD	Mean ± SD		
Sex, M/F	15/17	17/17	$\chi^2 = .064$	0.800
Handedness, R/L	31/1	32/2	$\chi^2 = .29$	0.59
Age, years	31.5 ± 9.3	28.9 ± 6.9	$t = 1.29$	0.202
Total Y-BOCS score	24.0 ± 6.1	NA	NA	NA
HDRS score	5.8 ± 4.3	NA	NA	NA
HARS score	8.1 ± 5.4	NA	NA	NA
Duration of illness, month	81.6 ± 79.2	NA	NA	NA
Educational years, year	13.6 ± 2.4	15.2 ± 1.0	$t = 3.51$	<0.001

F, female; L, left; M, male; OCD, obsessive–compulsive disorder; R, right; Y-BOCS, Yale–Brown Obsessive–Compulsive Scale; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; NA, not applicable.