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Short communication

Cortical thickness reductions in the middle frontal cortex in patients with panic disorder

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ABSTRACT

Background: Panic disorder (PD), an anxiety disorder characterized by the recurrence of panic attacks, has been reported to be associated with volumetric changes in several brain regions. There are, however, very few studies investigating abnormalities in cortical thickness, and little is known about the relationship between cortical thickness and social dysfunction in PD.

Methods: Thirty-eight patients with PD and 38 healthy control participants (HC) were recruited for this study. A whole-brain analysis was performed to evaluate groupwise differences in cortical thickness using the FreeSurfer software. Symptom severity and social functioning were evaluated with the Panic Disorder Severity Scale (PDSS) and the Global Assessment of Functioning (GAF) scale.

Results: The patients with PD demonstrated a significant reduction in cortical thickness in the left rostral middle frontal cortex (MFC), compared with the HC. Correlational analyses revealed that cortical thickness in the left rostral MFC showed a significant negative relationship with PDSS score and a significant positive relationship with GAF scores in the PD patients.

Limitations: All the patients received medication.

Conclusion: PD patients showed reduced cortical thickness in the left rostral MFC compared with HC. Furthermore, cortical thickness in this region was associated with patients' symptom severity and degree of social dysfunction.

1. Introduction

Panic disorder (PD) is an anxiety disorder which is characterized by the recurrence of cued and uncued panic attacks. Its typical course is chronic. Previous epidemiological studies have revealed that PD can lead to social dysfunction and lower quality of life, both of which have been shown to track with symptom severity (Kim et al., 2017; Ormel et al., 1994). PD has also been found to be associated with increased mortality and higher rate of suicide. It is, thus, important to elucidate neurobiological basis of social dysfunction in patients with PD.

With regards to the neural mechanisms underlying PD, certain brain regions have been particularly strongly implicated, including the amygdala (a region principally associated with fear and anxiety), and the medial prefrontal cortex (PFC), which (among many other functions) regulates amygdala activity (Gorman et al., 2000; Grambal et al., 2015). In support of this hypothesis, previous structural magnetic resonance imaging (MRI) studies have reported gray matter volume reductions in the amygdala and medial PFC, including anterior cingulate gyrus (Asami et al.,2008, 2009), in patients with PD compared with healthy control subjects (HC). Other volumetric MRI studies have also detected gray matter volume reductions in other brain regions such as inferior frontal gyrus and orbitofrontal gyrus (Lai and Wu, 2012).

More recent structural MRI studies have investigated for regional abnormalities in cortical thickness in patients with various psychiatric disorders. While gray matter volume is the product of cortical thickness and surface area, it has been suggested that these three metrics may be differentially associated with patients' symptom profile and level of social dysfunction (Gerrits et al., 2016). It is, therefore, important to further investigate how cortical thickness abnormalities could relate to the neurobiological bases of PD. However, there is, to the best of our knowledge, only one previous study which has reported cortical thickness abnormalities in patients with PD compared with HC

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(Kang et al., 2017). This study reported cortical thickness reductions in the right temporal pole, left insula, and bilateral pars triangularis in the patient group. However, this study only evaluated cortical thickness changes in six predefined regions of interest (bilateral temporal pole, insula, and pars triangularis); they did not evaluate cortical thickness across the whole brain. We, thus, decided to conduct a whole brain analysis to investigate abnormalities of cortical thickness in patients with PD compared with HC.

In terms of the relationship between structural abnormalities in regional cortical gray matter and symptom severity and social functioning, the previous study of Kang et al. (2017) identified associations between cortical thickness in the left pars triangularis and scores of the Panic Disorder Severity Scale (PDSS) and Beck Anxiety Inventory. However, there is, as far as we know, no previous volumetric study showing such association in patients with PD, and thus the neurobiological basis of symptom severity and social dysfunction is still unclear in PD.

In this study, we conducted a whole brain analysis to uncover group differences in cortical thickness between patients with PD and HC. We also performed correlational analyses to uncover the neurobiological basis of PD symptoms and social dysfunction in patients with PD.

2. Methods

2.1. Subjects

Thirty-eight patients with PD (25 female and 13 male) and 38 HC (25 female and 13 male) participated in this study (Table 1). Patients were recruited from inpatient and outpatient units of Yokohama City University Hospital. HC were recruited from the community and hospital staff. All the participants in this study were thought to be representative sample of urban areas in Japan. All subjects had participated in our previous study (Konishi et al., 2014). This study included six patients with a past history of major depressive disorder, which is often associated with PD. Patients had been receiving selective serotonin reuptake inhibitors (SSRIs) alone ($n = 3$); benzodiazepines alone ($n = 7$); SSRIs and benzodiazepines ($n = 22$); serotonin-norepinephrine reuptake inhibitors (SNRIs) and benzodiazepines ($n = 2$); SSRIs, SNRIs, and benzodiazepines ($n = 1$); tricyclic antidepressants and benzodiazepines ($n = 2$); and tetracyclic antidepressants, SSRIs, and benzodiazepines ($n = 1$). The socio-economic status (SES) of all subjects and their parents was assessed with the Hollingshead Two-Factor Index. Severity of illness and general level of functioning was evaluated with the PDSS and Global Assessment of Functioning (GAF). This study was approved by the Medical Research Ethics Committee of Yokohama City University. After providing a complete description of the study, we obtained written informed consent from all participants.

Table 1
Demographic and clinical characteristics of the study groups.

Variable	PD group ($n = 38$)		HC group ($n = 38$)		t[b]	P
	Mean	SD	Mean	SD		
Age (years)	38.8	10.1	37.8	10.3	0.39	.69
Sex, No. M/F	13/25		13/25			
Participant's Socioeconomic Status[a]	2.5	1.0	2.1	0.9	1.73	.09
Parental Socioeconomic Status[a]	2.6	0.8	2.4	0.9	0.96	.34
Duration of illness (years)	5.2	6.5				
PDSS Score	10.6	5.9				
GAF Score	64.4	11.6				

Abbreviations: PD, panic disorder; HC, healthy control subject; PDSS, panic disorder severity scale; GAF, Global Assessment of Functioning; M/F, male/female.

[a] Higher scores mean lower socioeconomic status.

[b] Independent *t*-tests were performed to evaluate group differences in age, and self and parental Socioeconomic Status.

2.2. MRI data acquisition and cortical thickness analysis

MR images were acquired with a 1.5-T Magnetom Symphony system (Siemens Medical System, Erlangen, Germany) at Yokohama City University Hospital. A series of 128 contiguous, sagittal T1-weighted slices were acquired (Konishi et al., 2014).

Image analysis was carried out with the FreeSurfer software (v.5.3.0). The technical details of the procedures have been described elsewhere (Fischl and Dale, 2000). In short, the image procedure included motion correction, intensity normalization, skull stripping, segmentation of white matter, tessellation of the grey/white matter boundary, automated topology correction, and surface deformation. Cortical maps were then smoothed using a Gaussian kernel with full-width at half-maximum of 10 mm.

To assess group differences in cortical thickness, a vertex-wise analysis was conducted using FreeSurfer's statistical program QDEC 1.4. We used a general linear model (controlling for the effect of age and sex) to estimate differences in cortical thickness between the groups at each vertex of the surface. Monte Carlo simulations with 10,000 iterations were performed to identify contiguous clusters of significant group differences (family-wise error corrected, $P < .05$). The right and left hemispheres were tested separately.

Once a significant group difference was observed, mean cortical thickness in the significant region were calculated for each subject using the *mris_anatomical_stats* command in FreeSurfer. To assess the relationship between cortical thickness and patients' scores of the PDSS, as well as the GAF, Spearman correlations were conducted. A critical *P*-value of $P < .05$ was used for the correlation analyses.

3. Results

There were no significant group differences in age, gender, or parental SES. In the cortical thickness analysis, the patients with PD showed significantly reduced cortical thickness in the left rostral middle frontal cortex (MFC) compared with the HC (Fig. 1). Mean cortical thickness of the left rostral MFC was (mean ± SD) 2.49 ± 0.16 mm in the patients with PD and 2.68 ± 0.15 mm in the HC. There were no significant group differences in cortical thickness in the right hemisphere.

In the correlation analyses for the patients with PD, cortical thickness in the left rostral MFC showed a significant negative association with scores of the PDSS ($n = 38$, rho = −0.37, $P = .02$), in other words, the reduced cortical thickness was related with more severe panic disorder symptoms. Cortical thickness in the left rostral MFC also demonstrated a significant positive relationship with scores of the GAF ($n = 38$, rho = 0.34, $P = .04$). This result indicated that reduced cortical thickness was associated with lower levels of functioning in the PD patients.

4. Discussion

To the best of our knowledge, the present study is the first to compare cortical thickness between patients with PD and HC across the whole brain. The results revealed a significant reduction in cortical thickness in the left rostral MFC in the PD patients. Furthermore, cortical thickness in the left MFC was found to be significantly negatively associated with patients' scores on the PDSS, and positively associated with their scores on the GAF.

Several previous functional neuroimaging studies have demonstrated significant relationships between emotion regulation and neural activity in the PFC in HC participants, particularly in the medial, but not lateral, PFC (Simpson et al., 2001). This finding accords with evidence that the medial PFC is both anatomically and functionally connected with the amygdala (Gold et al., 2015). It has, however, been