Journal of Affective Disorders 225 (2018) 676–683

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Selective functional dysconnectivity of the dorsal-anterior subregion of the precuneus in drug-naive major depressive disorder

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ARTICLE INFO

Keywords:
Major depressive disorder
Functional magnetic resonance imaging
Resting-state functional connectivity
Precuneus
Subregion

ABSTRACT

Background: Patients with major depressive disorder (MDD) have shown altered resting-state functional connectivity (rsFC) of the precuneus; however, it is unknown whether rsFC of the precuneus subregions is differentially affected in this disorder.

Methods: In this study, we aimed to clarify this issue by comparing rsFC of each precuneus subregion between patients with MDD and healthy controls. Forty-seven drug-naive patients with MDD and 47 sex-, age- and education-matched healthy controls underwent resting-state functional magnetic resonance imaging (fMRI). The precuneus was divided into PCun-1 (dorsal-central portion; medial area 7), PCun-2 (dorsal-anterior portion; medial area 5), PCun-3 (dorsal-posterior portion; dorsomedial parietooccipital sulcus) and PCun-4 (ventral portion; area 31). The rsFC of each precuneus subregion was compared between the two groups.

Results: Compared with healthy controls, patients with MDD exhibited increased rsFC between the left PCun-2 and the right fusiform gyrus, lateral prefrontal cortex, sensorimotor cortex and supramarginal gyrus. No significant inter-group difference was observed in the rsFC of other precuneus subregions. In addition, there was no difference in gray matter volume of all the precuneus subregions between patients with MDD and healthy controls.

Limitations: Some of the patients had chronic MDD and relevant neuropsychological data were not collected.

Conclusions: These findings suggest a selective functional dysconnectivity of the precuneus subregions in drug-naive MDD, characterized by the hyperconnnectivity between the dorsal-anterior subregion and regions involved in visual, executive control, sensorimotor and bottom-up attention functions.

1. Introduction

Major depressive disorder (MDD) is a serious psychiatric disease characterized by affective, cognitive, and vegetative symptoms. Given its high prevalence, MDD has been ranked as the second leading cause of disability across the world (Ferrari et al., 2013). Despite several decades of intensive research, its pathophysiology is yet to be fully understood. Earlier neuroimaging studies have documented that MDD is related to local functional and structural abnormalities in many brain regions (Drevets et al., 2008; Price and Drevets, 2012). However, the human brain is organized into a complex network (referred to as the human connectome) that facilitates the effective segregation and integration of information processing (Sporns et al., 2005), and thus MDD is increasingly understood as a disorder of brain connectivity (Gong and He, 2015; Hamilton et al., 2013; Mulders et al., 2015; Zhang et al., 2016). Resting-state functional magnetic resonance imaging (fMRI) has emerged as a non-invasive imaging technique to measure spontaneous brain activity based on the blood-oxygen-level-dependent signal (Biswal et al., 1995). This approach has been extensively applied to investigate resting-state functional connectivity (rsFC) changes in MDD, including abnormal rsFC between specific region pairs, aberrant rsFC within or between functional networks, and topological disruption of the whole brain (Gong and He, 2015; Mulders et al., 2015; Wang et al., 2012; Zhang et al., 2016). Notably, there is consistent evidence for rsFC impairment of the default mode network (DMN) in MDD (Alexopoulos et al., 2012; Berman et al., 2011; Guo et al., 2014b; Li et al., 2013; Zhu et al., 2012). For example, Alexopoulos et al. have found high rsFC within the DMN in late-life depression by using a seed-based connectivity approach (a seed placed in the posterior cingulate) (Alexopoulos et al., 2012). Increased rsFC between the posterior-

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http://dx.doi.org/10.1016/j.jad.2017.08.084
Received 6 May 2017; Received in revised form 13 July 2017; Accepted 27 August 2017
Available online 30 August 2017

cingulate cortex and the subgenual-cingulate cortex has been found to correlate with rumination in MDD patients (Berman et al., 2011). Guo et al. have reported that network homogeneity of DMN could be applied as candidate markers to distinguish MDD patients from healthy controls (Guo et al., 2014b). In a longitudinal study of MDD, increased rsFC in the posterior subnetwork of DMN was normalized after antidepressant treatment, while increased rsFC persisted within the anterior subnetwork (Li et al., 2013). Zhu et al. have observed increased rsFC in the anterior medial cortex regions and decreased rsFC in the posterior medial cortex regions in first-episode, treatment-naïve MDD patients by using independent component analysis (Zhu et al., 2012).

The DMN is often divided into an anterior sub-network that centers on the medial prefrontal cortex and a posterior sub-network that centers on the medial posteromedial cortex (Andrews-Hanna et al., 2010; Buckner et al., 2008). As a central node of the posteromedial cortex, the precuneus is engaged in a variety of functions (Cavanna, 2007; Cavanna and Trimble, 2006), such as self-related processing (Kjaer et al., 2002; Lou et al., 2004), consciousness (Vogt and Laureys, 2005), episodic memory (Dorfel et al., 2009; Lundstrom et al., 2005, 2003), and visuospatial imagery (Kawashima et al., 1995; Wenderoth et al., 2005). However, Yang et al. have demonstrated that precuneus shows functional characteristics and lifespan dynamics that differ from those of the DMN (Yang et al., 2014). Furthermore, Utevsky et al. found that rest-state increased connectivity between the precuneus and the DMN, whereas task-state increased connectivity between the precuneus and the frontoparietal network, indicating that the precuneus plays a core role not only in DMN, but also more broadly through its engagement in various processing states (Utevsky et al., 2014). In addition, a recent study has provide evidence that a longitudinal expansion of the precuneus is a key feature of modern human evolution, a major source of human cognitive specializations, and a main difference between humans and chimpanzees (Bruner et al., 2016). Given these findings, the precuneus is a region with high heterogeneity, strongly suggesting the existence of subregions. Indeed, using modern neuroimaging techniques, several previous studies have parcellated the human precuneus into subregions based on their specific functional and anatomical connectivity patterns (Cauda et al., 2010; Margulies et al., 2009; Zhang and Li, 2012; Zhang et al., 2014). To our knowledge, only one prior study used the precuneus as a single seed region to explore its rsFC alterations in MDD (Peng et al., 2015). In that study, MDD patients were found to exhibit a more negative rsFC between the precuneus and the sensory processing and secondary motor regions. Investigating the rsFC changes of the precuneus at the subregional level may further improve our understanding on the role of the precuneus in MDD.

In this study, we aimed to systematically test the rsFC differences of each precuneus subregion between drug-naive patients with MDD and healthy controls using resting-state fMRI data. We hypothesize that the rsFC of the precuneus subregions is not uniformly impaired in drug-naive MDD.

2. Methods

2.1. Participants

A total of ninety-four right-handed individuals were enrolled in the present study, including 47 drug-naive patients with MDD recruited consecutively from the psychiatric outpatient or inpatient department of the local hospital and 47 healthy controls recruited from the local community via advertisements. The patients and controls were well-matched in terms of age, sex and education (Table 1). The diagnosis of MDD was made according to the Structural Clinical Interview of the DSM-IV(SCID) (First MB et al., 1997), patient edition. The severity of depression was assessed using the 24-item Hamilton Rating Scale for Depression (HRSD-24) (Williams, 1988). Only those patients with a HRSD-24 score ≥ 20 were eligible for this study. The detailed clinical characteristics of the patients are shown in Table 1, including the HDRS score, illness duration, onset age, episode number, and current episode duration. Healthy controls were carefully screened for a current or lifetime diagnosis of any Axis I and II disorder using the SCID, non-patient edition. Exclusion criteria for all participants were 1) the presence of other Axis I psychiatric disorders such as schizophrenia, bipolar disorder, substance-induced mood disorder, anxiety disorders, substance abuse or dependence; 2) a history of neurological diseases or other physical illness; 3) a history of head injury resulting in loss of consciousness; 4) the inability to undergo an MRI. In addition, all healthy controls reported no psychiatric disorders among their first-degree relatives. This study was approved by the local ethics committee, and written informed consent was obtained from all participants after they had been given a detailed description of the study.

Table 1
Demographic and clinical characteristics of the sample.

Characteristics	MDD	HC	Statistics	*P* value
Number of subjects	47	47		
Age (years)	46.4 ± 13.5	47.0 ± 17.9	t = 0.182	0.856[b]
Sex (female/male)	27/20	23/24	χ^2 = 0.684	0.408[c]
Education (years)	11.2 ± 3.8	11.7 ± 4.1	t = 0.657	0.513[b]
FD	0.141 ± 0.066	0.149 ± 0.073	t = 0.601	0.549[b]
HDRS score	30.3 ± 7.1	–		
Illness duration (months)[a]	23.7 ± 36.1	–		
Onset age (years)[a]	43.4 ± 12.4	–		
Episode number[a]	1.3 ± 0.7	–		
Current episode duration (months)	5.0 ± 6.3	–		

The data are presented as the mean ± SD. Abbreviations: FD, frame-wise displacement; HC, healthy controls; HDRS, Hamilton Depression Rating Scale; MDD, major depressive disorder.
[a] The data are available for 39 of 47 patients.
[b] The *P* values were obtained by two-sample *t*-tests.
[c] The *P* value was obtained by chi-square test.

2.2. Data acquisition

MRI data were acquired using a 3.0-Tesla scanner (Magnetom Verio, Siemens, Erlangen, Germany). Tight but comfortable foam padding was used to minimize head motion, and earplugs were used to reduce scanner noise. High resolution structural images were acquired sagittally using a 3D T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence with the following parameters: repetition time (TR) = 1900 ms; echo time (TE) = 2.48 ms; inversion time (TI) = 900 ms; flip angle (FA) = 9°; field of view (FOV) = 250 mm × 250 mm; matrix = 256 × 256; slice thickness = 1 mm, no gap; slice number = 176; and acquisition time = 258 s. Resting-state functional blood-oxygen-level-dependent (BOLD) images were acquired axially using a gradient-echo planar imaging (GRE-EPI) sequence with the following parameters: TR/TE = 2000/25 ms; FA = 90°; FOV = 240 mm × 240 mm; matrix = 64 × 64; slice thickness = 4 mm; no gap; slice number = 36; 240 volumes; and acquisition time = 480 s. Before the scanning, all subjects were instructed to keep their eyes closed, relax, move as little as possible, think of nothing in particular, and not fall asleep during the scans. During and after the scanning, we asked subjects whether they had fallen asleep to confirm that none of them had done so. All MR images were visually inspected to ensure that only images without visible artifacts were included in subsequent analyses.

2.3. fMRI data preprocessing

BOLD MRI data were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The first 10 volumes for each participant were discarded to allow the signal to reach equilibrium and the participants to adapt to the scanning noise. The remaining volumes were corrected for