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Preliminary communication

Increased resting-state functional connectivity between the anterior cingulate cortex and the precuneus in panic disorder: Resting-state connectivity in panic disorder

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ABSTRACT

Background: The structural and functional abnormalities of the anterior cingulate cortex (ACC) have been reported in panic disorder (PD). Patients with PD have shown decreased gamma-aminobutyric acid (GABA) concentration in the ACC. The GABA concentration in the ACC was found to be associated with default mode network (DMN) activity in normal human subjects. Therefore, it was hypothesized that the DMN would show abnormal activity in PD.
Methods: We identified and compared the functional connectivity maps with seed region of interest (ROI) located in the perigenual area of ACC between the 11 patients with panic disorder and age- and sex-matched normal control subjects. Combining magnetic resonance spectroscopy (MRS) and resting fMRI, we investigated the correlation between the GABA concentration in the seed ROI and the index of functional connectivity between ACC and the area showing group differences.
Results: The patients with PD showed increased functional connectivity between ACC and precuneus compared to control subjects. The functional connectivity between the ACC and the precuneus negatively correlated with the GABA concentration of the ACC.
Limitations: The relatively small sample size and seed based analysis with the selection of a single ROI limits the generalizability of the result.
Conclusions: Increased functional connectivity in the two medial nodes of the resting-state default mode network, the ACC and the precuneus, might play an important role in the pathophysiology of panic disorder. The treatment aimed to normalize the functional connectivity between ACC and precuneus might have clinical benefits in PD.

1. Introduction

A key feature of panic disorder (PD) is sudden bodily sensations like palpitations or dyspnea, which are experienced by patients as inappropriately dangerous and harmful (Eley et al., 2004). Patients with PD have enhanced cardiac perception (Ehlers and Breuer, 1992) and anxiety sensitivity, a measure of a person's tendency to fear physical symptoms believed to have dangerous consequences (McNally, 2002). Those are consistent with a cognitive-attentional model of PD suggesting that the patients with PD are sensitive to internal autonomic visceral cues, and panic attacks are induced by misinterpretation of the internal visceral cues (Hayward et al., 2000).

The anterior cingulate cortex (ACC) is a major cortical structure to which visceral input is delivered (Weston, 2012), which, in turn, sends modulatory output to the peripheral autonomic centers (Vogt and Derbyshire, 2009). Within the so-called 'central autonomic network' (Benarroch, 1997), the perigenual ACC, corresponding to Brodmann area 32, is involved in monitoring and appraisal of the external environment, reciprocally connecting various brain regions to regulate stressor-related autonomic

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reactions (Gianaros and Sheu, 2009; Ryan et al., 2011). The electrical stimulation of the perigenual ACC evoked panic-like symptoms including increased heart rate accompanied by severe anxiety (Bancaud et al., 1976). Conversely, induced dyspnea elicited ACC activations, localized to Brodmann Areas (BA) 32 and 24 (von Leupoldt et al., 2009). Investigators have also observed increased ACC activity during anxiety provocation or anxiety imagery tasks in PD patients (Boshuisen et al., 2002; Bystritsky et al., 2001).

The involvement of GABA has long been suggested in the pathogenesis of PD, with early observations that panic symptoms were relieved after taking benzodiazepines agonists, while antagonists/inverse agonsists of $GABA_A$/BZD receptors were panicogenic (Freitas et al., 2009). Several groups have reported ACC GABA abnormalities in patients with PD (Ham et al., 2007; Malizia et al., 1998). Using PET, Malizia et al. reported reduced benzodiazepine receptor binding of ACC $GABA_A$ receptors in patients with PD (Malizia et al., 1998). In an MRS study, one group noted abnormally decreased ACC GABA concentrations in patients with PD (Ham et al., 2007).

Combining fMRI and magnetic resonance spectroscopy (MRS) in healthy subjects, Northoff et al. found a significant positive correlation between gamma-aminobutyric acid (GABA) concentration and negative BOLD response in the ACC during an emotional judgment task (Northoff et al., 2007). The negative BOLD response during a cognitive task is the typical response of the default mode network (DMN). The DMN is a set of interconnected brain areas, which are active during rest and deactivated during activities requiring external attention (Raichle et al., 2001). The ACC comprises the anterior portion of the DMN, having functional connectivity with the posterior part of the DMN, the posterior cingulate cortex (PCC) and the precuneus.

In the present investigation, we hypothesized that the perigenual ACC has an abnormal functional connectivity in the DMN of the patients with PD, and this abnormality is associated by decreased concentrations of GABA in the ACC. Therefore, we evaluated the resting state BOLD activity in PD patients and healthy comparison subjects to explore the functional connectivity of the ACC with a seed point located at the perigenual ACC, and also measured the GABA concentration of the ACC, allowing us to investigate its modulating effects on the functional connectivity of the ACC.

2. Materials and methods

2.1. Subjects

Eleven patients with PD and 11 age- and sex-matched, healthy control subjects participated in the study. The patients met DSM-IV criteria for the diagnosis of panic disorder, with or without agoraphobia. At screening, 5 patients were taking SSRI medications including paroxetine, escitalopram, venlafaxine and sertraline. Four patients were taking benzodiazepines on an as needed basis, while two patients were drug-naïve. Patients were medication free for at least 2 weeks prior to imaging. Patients with any lifetime history of major depression, psychotic disorder, bipolar disorder, eating disorder, personality disorder and other anxiety disorders including obsessive-compulsive disorder or post-traumatic stress disorder were excluded. To rule out comorbid depression, the patients were required not to have a lifetime episode of major depressive disorder, and had to have a screening visit Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) total score <12 Subjects were also excluded if they had a substance or alcohol abuse disorder within 6 months of the diagnostic interview. Patients were also excluded from the study if they presented with any serious or unstable medical or neurologic illness. Patients and controls were recruited at the Indiana University (IU) Anxiety Disorders Clinic, located within the Adult Psychiatry Clinic at IU Hospital in Indianapolis. Patients were diagnosed using the Structured Clinical Interview for Psychiatric Disorders (SCID)(DSM-IV edition)(First, 1997). The healthy comparison group consisted of individuals with no anxiety problems or other major psychiatric diagnoses, who were screened by the non-patient edition of the SCID.

In addition, we administered, the panic disorder severity scale (PDSS) (Shear et al., 2001) to the patient group. We assessed resting anxiety, by means of a subject-rated visual analog scale (VAS) (scoring range 0 to 100 mm (most severe)) score, as well as cognitive performance on the trail making B test, immediately before each imaging session. All participants gave their written informed consent in accordance with Institutional Review Board of Indiana University School of Medicine. The demographic and clinical information of the study population is summarized in Table 1.

2.2. Imaging acquisition

Imaging was performed with a 32-channel head coil array on a 3 T Siemens scanner (Siemens Healthcare, Erlangen, Germany) located at the IU Center for Neuroimaging. All participants underwent a resting-state scan prior to the MRS. During resting state scan, subjects were instructed to keep their eyes closed and rest without any specific thoughts. A high resolution anatomic image was acquired using a 3D magnetization prepared rapid gradient echo (MPRAGE) MRI sequence; 160 sagittal slices, $1.0 \times 1.0 \times 1.2\ mm^3$ voxels, field of view (FOV) $256 \times 240\ mm^2$, repetition time (TR) 2300 ms, echo time (TE) 2.91 ms, flip angle 9°. The scan duration of 5:03 min was achieved by applying generalized autocalibrating partially parallel acquisition (GRAPPA) mode, with the acceleration factor of 2.

Whole-brain blood oxygenation level dependent (BOLD) functional imaging was acquired during 333 s, using an echo-planar gradient echo pulse sequence; TR 2250 ms, TE 29 ms, FA 79°, FOV $220 \times 220\ mm^2$, 39 slices, $2.5 \times 2.5 \times 3.0\ mm^3$ voxels, GRAPPA acceleration factor of 2.

2.3. Image analysis

2.3.1. Preprocessing and functional connectivity analysis

Analysis of Functional NeuroImages (AFNI) (Cox, 1996) was used to perform the initial preprocessing steps of despiking, slice timing correction for interleaved acquisition, and head motion correction by rigid-body aligning each volume to the first scan image. The noise and nuisance physiological signals associated with white matter and ventricles, cardiac and respiratory signals, as well as possible head coil/hardware artifacts were regressed out

Table 1
Clinical characteristics of the study participants (mean ± SD reported for continuous measures).

	Panic disorder ($N=11$)	Control ($N=11$)
Age (yrs)	38.18 ± 12.76	38.18 ± 12.40
Sex		
Male	6	6
Female	7	7
Duration of illness (yrs)	7.92 ± 11.49	n/a
PDSS total score	9.36 ± 2.50	n/a
Baseline VAS anxiety score	45.82 ± 28.79	4.09 ± 8.01
Trails B task score	10.27 ± 2.57	12.27 ± 3.66
GABA/Cr	0.14 ± 0.08	0.19 ± 0.13
GABA/NAA	0.12 ± 0.06	0.15 ± 0.07