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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.

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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 agonists 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, $1.0 \times 1.0 \times 1.2 \text{ mm}^3$ voxels, field of view (FOV) $256 \times 240 \text{ mm}^2$, 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 auto-calibrating 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 $220 \times 220 \text{ mm}^2$, 39 slices, $2.5 \times 2.5 \times 3.0 \text{ mm}^3$ 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 \pm SD reported for continuous measures).

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

using the ANATICOR method (Jo et al., 2010). Due to recent concern regarding head movement effects on resting-state fMRI (Power et al., 2012), we assessed the degrees of head motion using two criteria that are the frame-wise displacement (FD) and AFNI's Euclidean norms of motion parameters ($\|d\|_{L2}$). There was no significant motion frame at both threshold of $FD > 0.5$ and/or $\|d\|_{L2} > 0.3$ that have been recommended for estimating motion effects and no group difference in the parameters for head motion. The ANATICOR model is known to be less sensitive to the head motion effects than other preprocessing models.

The preprocessed functional images were converted to Talairach space using the N27 template. The correlation coefficient map of whole intracranial brain was calculated with the reference time series of the MRS region of interest (ROI) using AFNI's 3dfim+. The 7 mm radius sphere seed ROI was selected at the approximate center of MRS ROI in the perigenual ACC area projected on the N27 template ($x=0, y=41, z=16$, Brodmann area 32) (Fig. 1-C). Correlation values were normalized with Fisher's Z-transformation and then smoothed with a 7-mm Gaussian filter for group analysis.

To determine the mean resting-state functional connectivity map for each group of the PD patients and control subjects, the Fisher's Z-transformed correlation coefficients were tested to determine whether they were significantly different from zero using a one-sample *t*-test. A two-sample *t*-test was used to identify group differences between the two groups of panic versus control group. All resulting *t*-maps were family-wise error corrected at $p < 0.01$ for whole brain areas via Monte Carlo simulations with 3dClustSim module within AFNI.

2.3.2. MRS for measurement of GABA concentration

GABA detection was performed in each subject from the ROI in the ACC using the MEGA-PRESS J-editing sequence (TR/TE=1500/68 ms, 196 averages with the editing pulse centered at 1.9 ppm

and 196 averages with the pulse centered at 7.5 ppm in an interleaved fashion). Data processing and quantification were performed with LCModel (Provencher, 1993), fitting each spectrum as a weighted linear combination of basis spectra from individual metabolites. Basis sets were generated from density matrix simulations of the sequence using published values for chemical shifts and J-couplings, with an exact treatment of metabolite evolution during the two frequency-selective MEGA inversion pulses. Difference basis spectra were obtained by subtracting the simulated metabolite response to selective inversion at 7.5 ppm from that at 1.9 ppm.

This version of the MEGA-PRESS technique results in difference spectra containing not only a GABA peak, but also a small amount of homocarnosine that exists in all GABA-edited spectra and co-edited macromolecules ("MM30") at 3.0 ppm. Therefore, an extra Gaussian peak at 3.0 ppm was added to the LCModel calculation to explicitly fit MM30 and a soft constraint was applied to the ratio of MM30 and a resonance at 0.9 ppm from macromolecules (MM09) ($MM30/MM09=0.667 \pm 0.1$), in order to eliminate the MM30 contribution to the GABA signal. The ratios of GABA to total creatine (GABA/Cr) and to N-acetyl aspartate (GABA/NAA) are reported, to cancel out variations in signal due to coil loading or partial volume effects.

2.3.3. GABA concentration and functional connectivity

The mean Z-transformed correlation coefficient in the area that showed the group difference of the correlation between ACC and the precuneus was correlated with the parameters representing GABA concentration as measured by GABA/NAA ratio of the ACC. The mean Z-transformed correlation coefficient was also correlated with the scores of the behavioral data including the VAS anxiety, trail making B test, and PDSS scores.

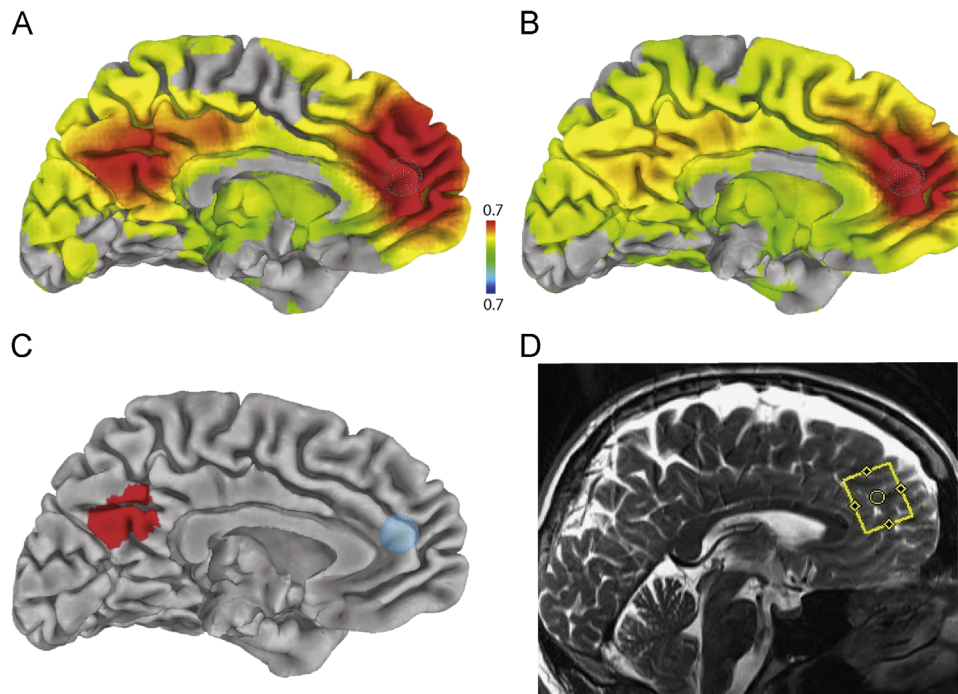


Fig. 1. Functional connectivity maps for the patients with panic disorder (A) and control healthy subjects (B) as measured by Fisher-transformed inter-voxel correlation coefficient projected on brain surface in Talairach space at $p < 0.01$ (family-wise error corrected using Monte Carlo simulation), using seed region at the ACC ($x=0, y=41, z=16, r=7$ mm) represented by a sky-blue-colored sphere in (C). The red color areas in the precuneus represent significant group difference at $p < 0.01$ (family-wise error corrected using Monte Carlo simulation) (C). The region of interest positioned at the ACC (yellow line rectangular box) for the measurement of GABA concentration in a representative subject (D).

3. Results

The resting state functional connectivity maps in each group and *t*-statistics map of the group differences were projected on C. Holmes' pial brain surface in Talairach space (<http://afni.nimh.nih.gov/afni/suma>) (Fig. 1). As shown in Fig. 1, while the functional connectivity in the healthy control subjects is widely distributed, the patient group showed a rather distinct increase of the functional connectivity centered on the precuneus. This increased ACC-precuneus connectivity was significantly different between the patients with PD and control subjects (family-wise error corrected at $p < 0.01$).

Fig. 2 shows significant negative correlations between ACC-precuneus functional connectivity and GABA/NAA concentration ratios of ACC in the complete ($n=22$) sample ($R=-0.43$, $p < 0.05$). There was a trend of correlation between ACC-precuneus functional coupling and GABA/NAA ratio of ACC within the PD patient group ($R=-0.58$, $p=0.06$). In the control group alone, GABA concentration was not correlated with ACC-precuneus functional coupling. No correlations were observed between ACC-precuneus functional coupling and the scores of VAS anxiety, the trail B task, and the PDSS, either in total sample or within each group.

4. Discussion

By combining fMRI and MRS techniques to assess the functional connectivity of the ACC mediated by its GABA concentration during resting state, we found increased functional connectivity between the ACC and the precuneus in the patients with PD compared to control subjects. Since the two structures, the ACC and precuneus, are two core medial components of the DMN (Deco et al., 2011), the increased functional connectivity between those structures can be considered in the context of the function of the DMN. The DMN is known to be involved in the processing of internally-generated thoughts (Buckner et al., 2008). The subjects are isolated from the external stimuli, watching a black screen during resting state. Therefore, they are sensitive to their own internal signals, which might be mediated by the ACC. As mentioned, the ACC is known to be bi-directionally involved in visceromotor and cardiovascular responses (Vogt and Derbyshire, 2009). In the DMN, areas of the perigenual ACC in our ROI were reported to show peak correlations with stress-evoked cardiovascular reactivity ($x=-2$, $y=44$, $z=16$) and reactivity to a conflict situation ($x=-6$, $y=44$, $z=16$) (Ryan et al., 2011).

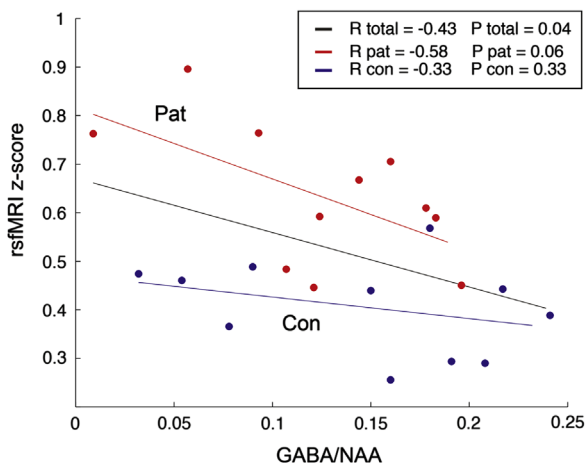


Fig. 2. The Fisher-transformed correlation coefficient between the ACC and the precuneus had a negative correlation with the GABA/NAA ratio in the ACC in the patients with PD ($R=-0.43$, $p=0.04$).

Unlike the ACC, the precuneus is not directly connected to visceral autonomic functions (Vogt and Derbyshire, 2009). Instead, the precuneus functions as a hub to organize attention where information from various areas of the brain is integrated (Lin et al., 2011). While the ACC was involved specifically in self-referential processing (Qin and Northoff, 2011), the posterior part of the DMN including the precuneus/PCC is involved in a wide spectrum of attentional processes like monitoring the environment, and assessing the context of stimuli (Vogt and Derbyshire, 2009; Wagner et al., 2005). Considering the function of the precuneus to modulate and integrate attention (Lin et al., 2011), we tentatively suggest that the increased functional connectivity of the ACC with the precuneus could be a functional combination of each structure, which might be translated into a subject's tendency to have too much attention directed to internal visceral signals, one of the key clinical features of PD. The treatment aimed to normalize the functional connectivity between ACC and precuneus using transcranial magnetic stimulation (TMS), a promising method to manipulate cortico-cortical connectivity (Fox et al., 2012), might have clinical benefits in PD.

Despite the rise in the number of resting-state fMRI studies, studies of the underlying neurochemical mechanisms of the DMN are scarce. In healthy subjects, Northoff et al. found a positive correlation between the GABA concentration in the ACC and the negative BOLD response in the same area during emotional stimulation (Northoff et al., 2007). Although they implicated GABA in decreasing neuronal activity of the DMN while observing the negative BOLD response of the ACC during an emotional task, they did not directly measure the resting-state brain activity. Muthukumaraswamy et al. measured resting state BOLD response and GABA concentration of the visual cortex simultaneously; however they did not explore the functional connectivity between brain areas (Muthukumaraswamy et al., 2009). Previously, it has been unclear whether GABA could modulate the functional connectivity of DMN of human brain. The negative correlations of GABA concentration of the ACC with the functional connectivity between the ACC and the precuneus found in the total subject sample and the PD patient group in the present study is, thus, the first direct evidence that the functional connectivity of the DMN is modulated by GABA concentrations.

4.1. Limitations

There are several limitations in the study including the small sample size and seed-based analysis with the selection of single ROI. A recent study, recruiting 11 patients with PD selected seed ROI in the posterior cingulate cortex, reported no difference of DMN activity in comparison to control subjects (Pannekoek et al., 2012). The different location of the seed point, data acquisition at the end of task-related scans, and the pooling of the data from different centers might have contributed to the negative group difference of DMN in that study (Pannekoek et al., 2012). The small sample size of our study might also have accounted for the lack of correlations between clinical symptoms and the functional connectivity in the PD patients. In a hypothesis-driven approach, we explored resting-state functional connectivity associated with only the ACC, which could ignore other brain areas having group differences. In a previous study recruiting 10 patients with anxiety disorder among which 3 patients had PD, the functional connectivity of the amygdala with the posterior cingulate cortex and the precuneus was decreased (Hahn et al., 2011). Further studies with larger sample size and different methods of analysis are needed to confirm our current findings.

5. Conclusion

This is the first study to report a DMN abnormality in the patients with PD. We found increased functional connectivity

between the ACC and the precuneus in the patients with PD. Although it remains hypothetical, the increased functional connectivity might be associated with the patients' catastrophic misinterpretations of the internal autonomic visceral cues. We also found that the GABA concentration of the ACC was associated with the functional connectivity between ACC and precuneus, suggesting a role of GABA in the pathophysiology of panic disorder via abnormal functional connectivity of the ACC with the precuneus.

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Conflict of interest

Dr. Goddard discloses financial support by a Naurex industry trial and a Janssen-independent study grant. All other authors report no biomedical financial interests or potential conflicts of interest.

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