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Research report

Aberrant limbic and salience network resting-state functional connectivity in panic disorder without comorbidity

Justine Nienke Pannekoek [a,b,*], Ilya M. Veer [b,c,d], Marie-José van Tol [e,f], Steven J.A. van der Werff [a,b], Liliana R. Demenescu [g], André Aleman [e], Dick J. Veltman [h], Frans G. Zitman [a], Serge A.R.B. Rombouts [b,c,d], Nic J.A. van der Wee [a,b]

[a] Department of Psychiatry, Leiden University Medical Centre, Leiden, The Netherlands
[b] Leiden Institute for Brain and Cognition (LIBC), Leiden University Medical Centre, The Netherlands
[c] Institute of Psychology, Leiden University, Leiden, The Netherlands
[d] Department of Radiology, Leiden University Medical Centre, Leiden, The Netherlands
[e] BCN NeuroImaging Centre, University Medical Centre Groningen, The Netherlands
[f] Leibniz Institute for Neurobiology, Otto von Guericke University, Magdeburg, Germany
[g] Department of Psychiatry, Psychotherapy and Psychosomatics, RWTH Aachen, Germany
[h] Department of Psychiatry, VU University Medical Centre, Amsterdam, The Netherlands

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ABSTRACT

Background: Panic disorder (PD) is a prevalent and debilitating disorder but its neurobiology is still poorly understood. We investigated resting-state functional connectivity (RSFC) in PD without comorbidity in three networks that have been linked to PD before. This could provide new insights in how functional integration of brain regions involved in fear and panic might relate to the symptomatology of PD.

Methods: Eleven PD patients without comorbidity and eleven pair-wise matched healthy controls underwent resting-state fMRI. We used seed regions-of-interest in the bilateral amygdala (limbic network), the bilateral dorsal anterior cingulate cortex (dACC) (salience network), and the bilateral posterior cingulate cortex (default mode network). RSFC of these areas was assessed using seed-based correlations. All results were cluster corrected for multiple comparisons ($Z > 2.3$, $p < .05$).

Results: Abnormalities were identified in the limbic network with increased RSFC between the right amygdala and the bilateral precuneus in PD patients. In the salience network the dACC demonstrated altered connectivity with frontal, parietal and occipital areas.

Limitations: The small sample size and hypothesis-driven approach could restrict finding additional group differences that may exist. Other caveats are reflected in the use of medication by two participants and the acquisition of the resting-state scan at the end of a fixed imaging protocol.

Conclusion: We found altered RSFC in PD between areas involved in emotion regulation and emotional and somatosensory stimulus processing, as well as an area engaged in self-referential processing, not implicated in models for PD before. These findings extend existing functional neuroanatomical models of PD, as the altered RSFC may underlie increased sensitivity for bodily symptoms.

1. Introduction

Panic disorder (PD) patients experience recurrent unexpected panic attacks, followed by persistent concerns about having additional attacks, worrying about **their** consequences, and **an associated** change in behaviour (American Psychiatric Association, 1994). An influential neuroanatomical model of PD was proposed by Gorman and colleagues in 1989 (Gorman et al., 2000). Central to their model is that panic derives from an abnormally sensitive fear network consisting of the prefrontal cortex, insula, thalamus, amygdala, and the amygdala's afferent and efferent projections from and to the hippocampus, brainstem, and hypothalamus. Furthermore, a defective prefrontal cortical processing has been suggested to lead to misinterpretation of physiological triggers, ensuing in exaggerated amygdala and fear network activation, resulting in a panic attack (Gorman et al., 2000; Shrestha R. et al., 2009).

Abbreviations: PD, panic disorder; NESDA, Netherlands Study of Depression and Anxiety; RSFC, resting-state functional connectivity; ACC, anterior cingulate cortex; dACC, dorsal anterior cingulate cortex; PCC, posterior cingulate cortex

* Corresponding author at: Leiden University Medical Centre, Department of Psychiatry, B1-P, P.O. Box 9600, 2300 RC Leiden, The Netherlands.
Tel.: +31 71 5261173.
E-mail address: j.pannekoek@lumc.nl (J.N. Pannekoek).

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Although this model has received considerable attention, the number of functional neuroimaging studies in PD is still modest (de Carvalho et al., 2010). PET and SPECT studies of PD revealed decreased glucose use and/or blood flow in temporal and parietal areas, as well as in parts of the prefrontal cortex and (para)-hippocampal areas (Lee et al., 2006; Nordahl et al., 1990; Shin et al., 2010), while fMRI studies using a broad range of task paradigms reported activation and found altered activity in PD in cortical and limbic structures such as the anterior cingulate cortex (ACC), the amygdala, and hippocampus (de Carvalho et al., 2010). The amygdala is perceived as the centre of the fear system with an important function in detecting, signalling, and learning from threat or danger (LeDoux, 1998; Phillips et al., 1992). Aberrant functioning of amygdala circuitry is thought to have a central role in the origin of PD and several other anxiety disorders (de Carvalho et al., 2010; Gorman et al., 2000; LeDoux, 1998; Phillips et al., 1992).

In contrast to task-evoked activity, resting-state fMRI enables examination of the brain's intrinsic functional connections in the absence of externally controlled stimuli or tasks (Biswal et al., 1995; Fox et al., 2007). Functional interactions between brain areas are crucial for proper functioning of the brain. This technique may therefore provide new insights in how functional integration of brain regions involved in fear and panic might relate to the symptomatology of PD (Fox et al., 2007). Consistently reported resting-state networks of potential relevance to PD include the default mode network (precuneus/posterior cingulate cortex (PCC), medial prefrontal cortex, and lateral parietal cortex), networks involving the amygdala, and the salience network (Damoiseaux et al., 2006; Seeley et al., 2007; Veer et al., 2011). The salience network, comprising the dACC and bilateral anterior insula, is important in assessing the relevance of internal and external stimuli in order to guide behavior (Seeley et al., 2007).

Resting-state functional connectivity (RSFC) in PD has not been investigated before, in contrast to many other (neuro)psychiatric disorders (Broyd et al., 2009; Greicius, 2008). In the present study we examined RSFC in patients with PD without comorbidity, using a seed-based correlation approach. Given the postulated model and the anatomical and functional abnormalities found in previous neuroimaging studies in PD, such as the frequently reported involvement of the amygdala circuitry and the ACC (Damsa et al., 2009; de Carvalho et al., 2010; Gorman et al., 2000; Shin et al., 2010), we hypothesized that the amygdala-centred network would show altered connectivity of the amygdala with hypersensitivity of the fear circuitry and less top-down control. For instance, PD patients are known to be more aware of and to attribute a greater significance to signals coming from their own body than healthy controls. Specifically, we expected to find altered RSFC in networks involved in fear and emotion, and in distinguishing relevant from less relevant stimuli. For the salience network we expected a heightened awareness of bodily signals, i.e. increased connectivity of areas involved in somatosensory processing. As the default mode network shows altered connectivity in depression and other anxiety disorders (Broyd et al., 2009; Fox et al., 2007; Greicius, 2008), we also expected abnormalities in the connectivity of this network in PD.

2. Methods

2.1. Participants

All subjects were recruited from the MRI study from the large-scale longitudinal multi-centre cohort Netherlands Study of Depression and Anxiety (NESDA). NESDA is designed to investigate the long-term course and consequences of depression and anxiety disorders. NESDA participants were recruited from the community, through primary care and specialized mental health institutions. The rationales, methods and recruitment for NESDA have been described in detail elsewhere; for an overview of diagnostics, inclusion and exclusion criteria see: (Penninx et al., 2008; van Tol et al., 2010).

After receiving written information, all subjects provided written informed consent. Participants underwent MRI in one of the three participating centres (Academic Medical Centre Amsterdam, Leiden University Medical Centre, and University Medical Centre Groningen) (van Tol et al., 2010). The study was approved by the Medical Ethics Committees of all three centres.

For the present study on PD without comorbidity, resting-state fMRI data were available from 11 right-handed PD patients, and from 11 healthy controls pair-wise matched for age, gender, education, and scan-location (Table 1). All participants were new to lying in an MRI scanner. Patients were diagnosed with PD and no other psychopathology using the DSM-IV-based CIDI, lifetime version 2.1 (American Psychiatric Association, 1994). Participants were scanned within 8 weeks after the CIDI assessment. Severity of anxiety symptoms at baseline and at the time of scanning was measured with the Dutch version of the Beck Anxiety Inventory (BAI) (Beck et al., 1988). Patients were excluded if they scored lower than seven on the Beck Anxiety Inventory, since they were then considered to have a 'minimal' level of anxiety and considered in remission (Beck et al., 1988). Depressive symptoms on the day of scanning were rated with the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery et al., 1979), as well as with the Inventory of Depressive Symptomatology (IDS) at baseline and at the time of scanning (Rush et al., 1986).

Table 1
Demographic and clinical characteristics of patients with panic disorder and healthy controls.

			Panic disorder patients ($N=11$)	Healthy controls ($N=11$)		
Gender			1 male / 10 female	1 male / 10 female		
Scan location			3 AMC; 2 LUMC; 6 UMCG	3 AMC; 4 LUMC 4 UMCG		
	Mean	SD	Mean	SD	F / Z	p
Age (years)	34.5	10.6	35.0	9.7	0.258[a]	0.974
Education (years)	12.8	3.5	14.1	2.1	−1.127[b]	0.260
BAI[†] score at scanning	14.5	5.6	1.9	2.5	−3.993[b]	0.001**
MADRS[‡] score at scanning	12.6	8.4	1.0	1.7	−3.776[b]	0.001**

Ams = Academic Medical Center Amsterdam; Lei = Leiden University Medical Center; Gro = University Medical Center Groningen.

[a] F-value.
[b] Z-value.
** Mann-Whitney U Test.
[†] BAI = Beck Anxiety Inventory.
[‡] MADRS = Montgomery-Åsberg Depression Rating Scale.