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Common and distinct brain networks underlying panic and social anxiety disorders

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ABSTRACT

Although panic disorder (PD) and phobic disorders are independent anxiety disorders with distinct sets of diagnostic criteria, there is a high level of overlap between them in terms of pathogenesis and neural underpinnings. Functional connectivity research using resting-state functional magnetic resonance imaging (rsfMRI) shows great potential in identifying the similarities and differences between PD and phobias. Understanding common and distinct networks between PD and phobic disorders is critical for identifying both specific and general neural characteristics of these disorders. We review recent rsfMRI studies and explore the clinical relevance of resting-state functional connectivity (rsFC) in PD and phobias. Although findings differ between studies, there are some meaningful, consistent findings. Social anxiety disorder (SAD) and PD share common default mode network alterations. Alterations within the sensorimotor network are observed primarily in PD. Increased connectivity in the salience network is consistently reported in SAD. This review supports hypotheses that PD and phobic disorders share common rsFC abnormalities and that the different clinical phenotypes between the disorders come from distinct brain functional network alterations.

1. Introduction

Phobic disorder or phobia is the most common form of anxiety disorder, and is characterized by persistent, marked, and unreasonable fears of an object or situation. People with a phobia avoid specific situations or objects that induce these types of fears. One of the most famous types of phobia is social anxiety disorder (SAD), also called social phobia, which involves an excessive fear of embarrassment in social situations and avoidance of such situations. Panic disorder (PD) involves repeated and spontaneous panic attacks. A panic attack is an extreme form of fear, and is characterized by physical sensations, such as a racing heart, shortness of breath, and chest pain that lasts for a short period of time. Agoraphobia is characterized by a fear of being alone or a fear of being in public places together with avoidance of such situations. The relationship between PD and agoraphobia is particularly complicated. Traditionally, agoraphobia has been viewed as a complication of panic symptoms and has tended to be co-diagnosed with PD. Currently, agoraphobia is unlinked with PD in the Diagnostic and Statistical Manual of Mental Disorders 5 (2013). However, high comorbidity and the conceptual overlap still pose obstacles to the diagnostic distinction between PD and agoraphobia (Asmundson et al., 2014). While obsessive-compulsive disorder and post-traumatic stress disorder have been split into discrete disorder categories, PD and phobic disorders remain together in the chapter on anxiety disorders. Although PD and phobic disorders are independent anxiety disorders with distinct sets of diagnostic criteria, there is a high level of overlap between them in terms of pathogenesis and neural underpinnings. Epidemiological and translational studies have shown similarities and differences across these disorders. For example, one epidemiological study found high comorbidity among anxiety disorders including PD, SAD, specific phobia (SP), and agoraphobia (Kessler et al., 2005). A twin study reported that PD, agoraphobia, and SP strongly co-aggregated within families, and that common genetic factors explained a moderate to high proportion of variance in these disorders without the

Abbreviations: AI, anterior insular cortex; ACC, anterior cingulate cortex; BOLD, blood-oxygen-level-dependent; CEN, central executive network; dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; DMN, default mode network; dmPFC, dorsomedial prefrontal cortex; DTI, diffusion tensor imaging; EEG, electroencephalography; FC, functional connectivity; fMRI, functional magnetic resonance imaging; ICA, independent component analysis; mOFC, medial orbitofrontal cortex; mPFC, medial prefrontal cortex; MTL, middle temporal lobe; PCC, post cingulate cortex; OFC, orbitofrontal cortex; PD, panic disorder; pgACC, perigenual anterior cingulate cortex; rACC, rostral anterior cingulate cortex; ROI, region of interest; ReHo, regional homogeneity; rsFC, resting-state functional connectivity; rsfMRI, resting-state functional magnetic resonance imaging; SAD, social anxiety disorder; SMN, sensorimotor network; SN, salience network; SP, specific phobia; SPECT, single-photon emission computed tomography; VMHC, Voxel-mirrored homotopic connectivity; vmPFC, ventromedial prefrontal cortex

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influence of a common environment (Mosing et al., 2009). On the other hand, many linkage and candidate gene studies, as well as a PD genome-wide association study and other phobic disorders have produced inconclusive results to date (Shimada-Sugimoto et al., 2015). Understanding similarities and differences between PD and phobic disorders is critical for identifying both specific and general neural characteristics of these disorders.

Resting-state functional MRI (rsfMRI) has been developed for analyzing large-scale connectivity in brain networks. Resting-state functional connectivity (rsFC) measures the temporal correlation of spontaneous blood-oxygen-level-dependent (BOLD) signals between spatially remote brain regions during times without the performance of an explicit task. Several resting-state networks have been identified and investigated. The default mode network (DMN), one of the canonical resting-state brain networks, is the most studied network (Smith et al., 2009). The DMN, a set of temporally correlated brain regions, is most active during rest and is deactivated during the performance of cognitively demanding goal-directed tasks. This network includes the medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC)/precuneus, the ventral/perigenual anterior cingulate cortex (pgACC), and the inferior parietal cortex. In addition to the DMN, many other major canonical resting-state networks are frequently identified in existing literature (Barkhof et al., 2014). These networks include the salience network (SN: dorsal anterior cingulate cortex (dACC) and anterior insular cortex (AI) circuitry), the central executive network (CEN: the dorsolateral prefrontal cortex (dlPFC) and parietal cortex), the dorsal attention network (DAN: intraparietal sulcus, precentral and superior frontal gyrus), the sensorimotor network (SMN: primary sensorimotor cortex, supplementary motor area and secondary somatosensory cortex), the visual network (Striate cortex, occipital pole, and lateral visual areas), and the auditory network (Superior temporal gyrus).

This rsfMRI analysis-based method has several specific features for investigating functional alterations of brain networks in psychiatric disorders (Woodward and Cascio, 2015). First, reliable and reproducible results can be obtained through this relatively standard method. Second, because this method does not depend on explicit task performance, it can be evaluated in populations incapable of performing task-based functional MR imaging, such as pediatric subjects and patients with reduced consciousness. Moreover, in comparison to the modular representations of traditional fMRI, functional connectivity provides a broader network representation of the functional architecture of the brain. Proper connection and harmonious interaction between brain areas are crucial for optimal brain functioning. Therefore, this technique may offer a new understanding of the functional integration of brain regions involved in the symptomatology of anxiety and other psychiatric disorders (Peterson et al., 2014).

Several different approaches can be used in rsfMRI analysis. There are two widely used rsFC analysis methods, namely, seed-based approaches and independent component analysis (ICA) (Fox and Raichle, 2007; van den Heuvel and Hulshoff Pol, 2010). In seed-based approaches, according to an a priori hypothesis, individual seed voxels are extracted from a predefined brain region and are correlated with the time courses of other voxels in selected seeds of the brain. In contrast, ICA is a multivariate, data-driven method that decomposes fMRI time-series data throughout the brain into linear mixtures of spatially independent and temporally coherent components.

Our comprehensive literature review focuses on PD and SAD because there are, to our knowledge, no resting-state studies in patient samples with SP as a primary diagnosis. Based on a literature review, we elaborate on the common and distinct network alterations between the disorders, explore the clinical relevance of rsFC alterations, and discuss future considerations regarding the usefulness of rsfMRI for biomarkers of psychiatric disorders.

2. Panic disorder

Until recently, the majority of work on brain function in PD has focused on cognitive task-related or conditioned stimuli-related brain activity. There is growing evidence, however, for resting-state networks in PD.

Two studies on PD have demonstrated alterations of DMN. The work of Shin et al. (2013) reported that rsFC between the pgACC and the precuneus was increased in patients with PD compared to control subjects. The research also observed that GABA concentration of the pgACC was correlated with functional connectivity between the pgACC and the precuneus. Using voxel-mirrored homotopic connectivity (VMHC) analysis, another rsfMRI study also reported an aberrant rsFC within the DMN (Lai and Wu, 2014). Therein, investigators found decreased inter-hemispheric connectivity of bilateral PCC and the precuneus in PD. The mPFC (including the pgACC) has been associated with cognitive processes, such as mental representation, theory-of-mind, and/or narrative processing (Frith and Frith, 2007; Hartwright et al., 2014; Mano et al., 2009). The pgACC plays a role in monitoring and appraising the external environment and mutually interacting with various regions of the brain to regulate stressor-related autonomic reactions. (Gianaros and Sheu, 2009; Ryan et al., 2011). Though the PCC/precuneus is not directly connected to the visceral autonomic system, it is involved in a wide spectrum of attentional processes including self-monitoring, remembering the past, thinking about the future, and assessing the environment (Wagner et al., 2005). The PCC is also implicated in somatosensory processing, evaluation of sensory events, spatial orientation, and memory and memory retrieval (Olson and Musil, 1992).

Several studies examining resting-state connectivity in PD reported consistent changes in the SMN. The work of Pannekoek et al. (2013a) examined rsFC using seed regions of interest (ROI) in bilateral amygdala, bilateral dACC, and bilateral PCC. The research found increased rsFC between the right amygdala and bilateral precuneus in patients with PD compared to healthy control subjects. Altered dACC rsFC with frontal, parietal, and occipital areas was also found. Notably, the left dACC demonstrated increased positive connectivity with the postcentral gyrus, known as the somatosensory cortex, with the function of integrating and interpreting most of the sensory information from the body (Northoff et al., 2006). A whole-brain analysis study using a novel functional connectivity metric revealed increased FC between the thalamus and postcentral gyrus in PD patients (Cui et al., 2016). Altered connectivity between the post/precentral gyrus and the thalamus was found to be positively related to the scores on the Spielberger State-Trait Anxiety Inventory and the Body Perception Questionnaire. The postcentral and precentral gyrus are known to be engaged in interoception processing (Critchley et al., 2004; Inoue et al., 2013). Recently, a whole-brain functional connectome study using the new method of network-based statistics revealed limbic-motor-sensory region connectivity alteration in certain subjects (Lai and Wu, 2016). In that study, the precentral gyrus was one of the central hubs for altered functional connectivity network in PD. The findings of that study seemed to make the original “fear network model” more comprehensive in terms of our understanding of the sensory-related symptoms of PD. These sensorimotor region-centered results are quite distinct from the findings of functional connectome alterations in other anxiety disorders, such as posttraumatic stress disorder.

To summarize, although contemporary rsfMRI studies on PD are still scarce, emerging evidence consistently suggests that abnormalities of the DMN in PD appear prominent within emotion regulatory networks. Functional connectivity in the DMN has been linked to core processes of human cognition, such as the integration of cognitive and emotional processing, mentalizing, autobiographical memory retrieval, and envisioning the future (Buckner et al., 2008; Greicius et al., 2003). Hyperconnectivity has also been suggested in SMN. This hyperconnectivity of SMN may cause abnormally high interoceptive