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Research report

The alterations in inter-hemispheric functional coordination of patients with panic disorder: The findings in the posterior sub-network of default mode network

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ABSTRACT

Objective: Voxel-mirrored homotopic connectivity (VMHC) has been studied in several neuropsychiatric illnesses. The inter-hemispheric interactions probably could explain the important aspects for the pathophysiology of panic disorder (PD). Therefore, we initiated this study to estimate the differences in VMHC values between the PD patients and controls.

Methods: Thirty first-episode medication-naïve patients with PD and 21 controls were enrolled with age and gender controlled. All the participants received the scanning of resting-state functional magnetic resonance imaging (R-FMRI). The R-FMRI images were preprocessed and analyzed to obtain the VMHC values. The two-sample t test of VMHC data between PD patients and controls was performed. We also explored the relationship between the VMHC values and clinical characteristics.

Results: The controls had significantly higher VMHC values than patients in the posterior cingulate cortex and precuneus (false discovery rate corrected $p < 0.005$). The one-sided results by the unilateral hemisphere mask also confirmed that the results were indeed found in the right hemisphere. The VMHC value in the posterior cingulate cortex was also negatively correlated with panic severity.

Conclusion: The alterations of inter-hemispheric coordination in cingulate-precuneus may play a role in the pathophysiology of PD.

1. Introduction

Panic disorder (PD) is manifested with multiple kinds of autonomic dysregulations, such as chest tightness, palpitations, dizziness, numbness, shortness of breathing, which happens within 10 min and causes significant anticipatory anxiety. The limbic structures will connect with other regions of brain to process the responses to fear. An inadequate control of fear responses will provoke panic attacks (Gorman et al., 2000). The cortico-subcortical functional connections are responsible for subliminal fear processing, which play a role in the pathophysiology of PD (Pantazatos et al., 2012). PD might be associated with certain types of functional abnormalities in the default mode network (DMN) (Katon, 1986; Lai and Wu, 2012, 2013b). Pannekoek et al. (2013a) found that patients with PD would have altered activities in the DMN for emotion, somatosensory and self-referential processing functions. Increased functional connectivity between the anterior cingulate and precuneus has also been reported to play a role in the pathophysiology of PD (Shin et al., 2013). The abnormalities in regional stability of the occipital lobe might influence the fear processing, sensory and inhibitory function of patients with PD (Lai and Wu, 2013b). In addition, the alterations in amplitude of low frequency fluctuations in the occipito-striato-thalamic circuit have been reported in PD and the alterations might correlate with fear processing, sensory and cognitive dysfunction in PD (Lai and Wu, 2012). Several of our reports studying DMN found that alterations in regional homogeneity and fractional amplitude of low frequency fluctuations of PD patients (Lai and Wu, 2012, 2013b). In addition, the widespread alterations in function connectivity of DMN, fear network, cognitive-sensory network have been reported in PD or anxiety (Kircher et al., 2013; Sylvester et al., 2012). The differences in functional connectivity between fronto-cingulate and fear network of PD patients can also predict the treatment responses for cognitive behavioral therapy (Kircher et al., 2013; Lueken et al., 2013). The results suggested that PD patients might have certain dysregulations

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between fear, sensory, autonomic and cognitive related regions. The resting brain activities in PD could also explain the connection between behavioral symptoms and brain function.

However, the inter-hemispheric functional connectivity in PD is still an unexplored field for the study. Hoptman and Davidson (1994) suggested that the brain commissural system, such as the corpus callosum or commissures, can mediate the inter-hemispheric interaction. In the past, several studies showed that split brain patients had deficits in sensory processing (Nebes, 1972), deficits in selective, sustained attention and poor vigilance towards external stimulus (Dimond, 1979a), lack of ability to switch the sensory signal from one hemisphere to another and considerable depletion of cognitive attention (Dimond, 1979b). Moreover, bi-hemispheric actions can also give the ability of having the competence for task demand for each hemisphere and inter-hemispheric functional connectivity could maintain our ability of strategic deployment for attentional resources (Belger and Banich, 1992; Levy and Trevarthen, 1976). The previous studies have shown the importance of inter-hemispheric interaction for the cognitive and sensory processing ability. As we know, PD is associated with cognitive and sensory dysfunctions, which suggests that inter-hemispheric dysfunction might play a role in the pathophysiology of PD.

The relationship between the DMN and inter-hemispheric connectivity seems interesting. The DMN activities can be identified as reduced overall inter-hemispheric connectivity coherence (Berkovich-Ohana et al., in press). Lee et al. (2013) found that maturation of brain is associated with enhancements of inter-hemispheric connectivity to preliminary DMN . The regions of inter-hemispheric homotopic resting-state functional connectivity by the seed-based analysis also include the DMN components (Sforazzini et al., 2014). The activities of DMN can be measured by the method of resting-state functional magnetic resonance imaging (R-FMRI). The R-FMRI is a technique which can be used to measure the intra-hemispheric and inter-hemispheric functional connectivity (Hoptman et al., 2012). In the recent years, a new concept, "voxel-mirrored homotopic connectivity" (VMHC), has been proposed to represent the functional architecture for the synchrony of spontaneous brain activities between geometrically corresponding regions in each hemisphere (Salvador et al., 2005). Stark et al. (2008) found that different strengths of VMHC between different symmetric regions might represent different characteristics of hemispheric specialization in the information processing, sensory integration and motor coordination. The VMHC characteristic can also be used to investigate the diversity of disease process.

There are several reports of VMHC in the field of neuropsychiatric illnesses, such as schizophrenia (Hoptman et al., 2012), depression (Guo et al., 2013; Wang et al., 2013), cocaine abusers (Kelly et al., 2011) and migraine (Yuan et al., 2012). However, there are still no studies of VMHC in PD till now. Yang et al. (2013) ever found that anxiety might be related to decreases in the functional connectivity of the DMN regions, such as the precuneus, medial prefrontal cortex and posterior cingulate cortex (PCC), and inferior parietal cortex. Our previous studies of PD also suggested that R-FMRI abnormalities in cuneus, lingual gyrus, occipital lobe, striatum and thalamus (Lai and Wu, 2012, 2013b). From the above results in combination of the previous section about functional connectivity in PD, we hypothesized that PD patients might have alterations of VMHC in DMN regions when they were compared to controls. In addition, the values of VMHC might be correlated with the severity of PD symptoms. The greater symptom severity will be associated with lower VMHC values. The study of VMHC might help us to explore the pathophysiology of fear processing deficits, hypervigilance, sensory and cognitive deficits, salience network and executive dysfunctions in PD.

2. Methods

2.1. Participants

This study was approved by Institute of Review Board, Buddhist Tzu-Chi Hospital Taipei Branch. The criteria of selection for patients were as follows: (1) first-onset PD diagnosis and psychiatric diagnoses were made on the basis of DSM-IV criteria and the Structured Clinical Interview for DSM-IV. (2) No other psychiatric illnesses or medical illnesses. (3) The severity of PD was at least more severe than moderate: Clinician Global Impression of Severity >4, Quick Inventory for Depressive Symptoms-Self Rating 16-item version (QIDS-SR16) <9, Hamilton Rating Scales for Depression (HDRS) score <7, Hamilton Rating Scales for Anxiety (HARS) score >22, Panic Disorder Symptom Severity Scale (PDSS) >15, panic attacks of full blown symptom >4 times within previous 4 weeks before the baseline visit. (4) No cognitive behavioral therapy or other psychotherapies. (5) Psychotropic medication-naïve. (6) No alcohol and substance abuse or dependence (verified by the Structured Clinical Interview for DSM-IV). (7) No past history of claustrophobia or discomforts while receiving MR scanning. The healthy controls had no psychiatric illnesses or significant medical illnesses (verified by the Structured Clinical Interview for DSM-IV). The participating subjects were enrolled at Buddhist Tzu-Chi Hospital Taipei Branch. 30 first-episode drug-naïve patients with PD (13 subjects with agoraphobia; 19 females, 11 males, age: 47.03 ± 10.63 years old) and 21 healthy controls (11 females, 10 males, age: 41.40 ± 13.94 years old) were recruited from the Department of Psychiatry, Buddhist Tzu-Chi General Hospital Taipei Branch, Taiwan. At the time of MR imaging, all these participating subjects did not receive the treatment of any psychotropic medications. Handedness was determined by using the Edinburgh Inventory of handedness (Oldfield, 1971). The population sample was overlapping with our previous reports (Lai and Wu, 2012, 2013a, 2013b).

2.2. Structural MRI data acquisition

The structural MR imaging scans of brain were obtained with 3 T Siemens version scanner housed at MR Center, National Yang Ming University. Scans with three-dimensional fast spoiled gradient-echo recovery (3D-FSPGR) T1W1 (TR 25.30 ms; TE 3.03 ms; slice thickness $=1$ mm (no gap); 192 slices; matrix $=224 \times 256$; field of view: 256 mm; number of excitation $=1$) were performed. We obtained the T1 image data to exclude structural bias and establish study-specific template for our VMHC analysis.

2.3. R-FMRI data acquisition and pulse sequence

Echo planar imaging (EPI) sequence were acquired in 20 axial slices (TR $=2000$ ms, TE $=40$ ms, flip angle $=90^{\circ}$, field of view $=24$ cm; 5 mm thickness and 1 mm gap; the sequence duration was 400 s for each subject, 150 time points were acquired, voxel dimension: $64 \times 64 \times 20\ mm^3$) at baseline visit (3T Siemens scanner housed at MR Center of National Yang Ming University) in patients and controls. All the patients and controls were requested to close their eyes and not fall sleepy while scanning. The participating subjects were instructed to move as little as possible and stay fully awake while scanning. All these patients and controls reported that they could be fully awake while MRI scanning.

2.4. VMHC analysis by REST toolbox

We performed a whole-brain approach to detect the group-related differences in VMHC values. The EPI data was first pre-processed by DPARSF (Data Processing Assistant and Resting-State