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Abnormal functional connectivity density in psychogenic non-epileptic seizures

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Summary
Purpose: Psychogenic non-epileptic seizures (PNES) are paroxysmal behaviors that resemble epileptic seizures but lack abnormal electrical activity. Some neuroimaging studies have reported that PNES exhibits aberrant functional connectivity in specific brain networks. Thus, advanced neuroimaging technologies may aid clinical diagnosis and treatment of PNES.
Methods: We investigated changes in brain functional connectivity in 18 patients with PNES and 20 healthy controls. Functional connectivity density mapping (FCDM), a voxelwise data-driven technique, was employed to compute local and global FCD maps. Then, short-range and long-range FCD values were calculated and group analyses performed between patents with PNES and healthy controls. A correlation analysis with clinical variables was also performed.
Results: We found that patients with PNES showed abnormal FCD regions mainly in the frontal cortex, sensorimotor cortex, cingulate gyrus, insula and occipital cortex. Seed-voxel correlation analyses also showed disrupted functional connectivity between these regions. In addition, the occipital cortex FCD correlated with duration of disease.
Conclusion: The present results support the hypothesis that patients with PNES are associated with altered attention, sensorimotor and emotion systems. Furthermore, correlations between

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altered regions in the occipital cortex and duration of disease may reflect an adaptation in these patients for long-term hypervigilance and increased response to external stimuli. This study adds new knowledge to our understanding of the pathophysiological mechanisms underlying PNES.

Introduction

Psychogenic non-epileptic seizures (PNES) are paroxysmal behaviors with altered movement, sensation, or experience, which resemble epileptic seizures, but are not accompanied by ictal epileptiform brain discharges (Baslet, 2011; Devinsky et al., 2011). PNES can be interpreted as an experiential or behavioral response to emotional, psychological, or social distress (Reuber, 2008). Patients with PNES are often misdiagnosed and treated for epilepsy, which is detrimental because of the side effects of antiepileptic drugs and the delay in proper treatment (Leis et al., 1992; Reuber et al., 2004). It has been observed that the diagnosis of PNES is usually delayed for an average of 7 years (Reuber et al., 2002), significantly impacting patients' quality of life (Szaflarski et al., 2003a,b).

Etiologically, PNES is related to the dysfunction in processing of psychological or social distress (Baslet, 2011; Uliaszek et al., 2012), manifesting as an altered cognitive-emotional attention system (Baslet, 2011). During episodes of PNES, sensorimotor and cognitive processes are affected and not properly integrated, resulting in a range of involuntary behavioral patterns (Baslet, 2011). Findings from recent neuroimaging studies have provided evidence to support this notion. Using resting-state functional magnetic resonance imaging (rs-fMRI) technology, van der Kruijs et al. found dysfunctional connectivity between emotional, executive control, and sensorimotor networks in PNES (van der Kruijs et al., 2012). In addition, an EEG synchronization study revealed decreased prefrontal and parietal synchronization in PNES, reflecting dysfunction of fronto-parietal networks (Knyazeva et al., 2011). Overall, these studies suggest aberrant functional connectivity in specific brain networks, contributing to understanding the pathophysiological mechanism of PNES. Therefore, advanced neuroimaging technologies may aid the clinical diagnosis and treatment of PNES.

In the present study, we compared brain functional connectivity density (FCD) between patients with PNES and healthy controls. Functional connectivity density mapping (FCDM) is a voxelwise data-driven technique, recently proposed by Tomasi and Volkow (2010). Simple voxelwise functional connectivity analyses only depict brain functional connectivity. In contrast, FCDM can locate highly connected brain regions (functional hubs), and is broadly equivalent to the combination of simple voxelwise functional connectivity analyses and graph theory analysis. In addition, simple voxelwise functional connectivity analyses are computationally demanding. However, FCDM is an ultrafast method and can compute local and global FCD maps with high spatial resolution (3-mm isotropic), allowing identification of functional hubs (regions that are densely connected) with high sensitivity and discrimination among short-range FCD hubs and long-range FCD hubs (Tomasi and Volkow, 2012a,b). Thus, the present study used FCDM analysis to investigate abnormal connectivity in PNES. We aimed to find regions exhibiting altered FCD in patients with PNES, and further investigate whether altered brain regions were related to the duration of disease. On the basis of previous findings and clinical symptoms of PNES, we hypothesized that regions with altered FCD in patients with PNES might be associated with attention, emotion, and sensorimotor systems.

Materials and methods

Participants

The participants were the same as in our previous study (Ding et al., 2013). A total of 20 patients with PNES (7 males, mean age: 19.65 ± 7.56 years) and 20 healthy volunteers (8 males, mean age: 21.85 ± 1.70 years) from the Department of Neurology, West China Hospital, Chengdu, China were recruited. Patients with PNES were given definitive diagnoses by experienced neurologists using clinical descriptions of symptoms and long-term video/EEG monitoring, consistent with recent recommendations (Benbadis et al., 2004; Devinsky et al., 2011). The inclusion criteria were: (1) at least one single typical episode recorded by video EEG, and EEG did not show any epileptiform discharge or ictal slowing; (2) patients had no history of neurological disease; (3) patients had no obvious abnormality in routine structural MRI examinations. The exclusion criteria were: (1) patients with neurological comorbidity (e.g. epilepsy); (2) patients with malingering, or any psychiatric disorders (e.g. mood and anxiety disorders, schizophrenia, and psychosis). Here, the diagnosis of malingering or psychiatric disorders was determined by two attending psychiatrists using the Structured Clinical Interview for DSM-IV (SCID)-Patients Version and their scores on the Hamilton Anxiety Rating Scale and Hamilton Depression Rating Scale. Only patients with a diagnosis of definite PNES were included in the study. Four out of 20 patients were taking antiepileptic drugs before the diagnosis of PNES. All drugs were discontinued at least 2 weeks prior to MRI examination. Demographic and Clinical Characteristics of the patients with PNES are shown in Table 1. To increase the homogeneity of the patient group, two patients with very long duration of disease (approximately 18 years) were excluded from the study, resulting in a final analysis of 18 patients with PNES and 20 healthy controls. The control subjects had no neurologic/psychiatric disorders, evaluated using the SCID-Non-Patient Version, and had not taken any psychotropic medication within the past 6 months. This study was approved by the Local