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Research report

Altered spontaneous neuronal activity in chronic posttraumatic stress disorder patients before and after a 12-week paroxetine treatment

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ABSTRACT

Background: Abnormal functional brain activity has been revealed in patients with Posttraumatic Stress Disorder (PTSD) in recent years, while the recovery neuromechanism of PTSD has not yet been elucidated. The aim of this study was to investigate the altered spontaneous brain activity in treatment-naïve chronic PTSD patients before and after 12 weeks' treatment with paroxetine.
Methods: Twenty-one earthquake-related PTSD patients and seventeen traumatized controls underwent a resting functional magnetic resonance imaging (Rs-fMRI) scan at baseline. Amplitude of low-frequency fluctuation (ALFF) was calculated and compared between PTSD patients and controls. Then, the PTSD group completed 12 weeks of treatment with paroxetine, and Rs-fMRI was repeated to compare with the baseline. Lastly, correlation analyses of ALFF values within altered brain areas were conducted.
Results: Hyperactive function of visual cortex was observed in PTSD patients before and after treatment. After treatment, significantly increased ALFF values were observed in the left orbitofrontal cortex (OFC), while decreased ALFF values were found in the precuneus. Interestingly, a negative correlation between the mean ALFF values of OFC and those of precuneus and visual cortex was only observed in controls, but not in PTSD patients pre- or post-treatment.
Limitations: A corresponding control condition was absent in this study.
Conclusion: The findings showed that manipulating regional spontaneous activity of precuneus and OFC could be a potential prognostic indicator of PTSD. However, hyperactive function of visual cortex and disrupted connections between OFC, precuneus and visual cortex did not reverse after treatment, which could be a potential target for further treatment.

1. Introduction

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder, and the symptoms persist for a long time after the trauma (McFarlane, 1986; Kulka, 1990). Previous functional neuroimaging studies have revealed abnormal increased or decreased regional function in PTSD patients, including amygdala (Hendler et al., 2003; Armony et al., 2005; Williams et al., 2006), prefrontal cortex (Lindauer et al., 2004; Shin et al., 2004a; Britton et al., 2005), hippocampus (Bremner et al., 2003a; Kitayama et al., 2005; Geuze et al., 2008; Osuch et al., 2008; Werner et al., 2009), insular (Bremner et al., 2004; Hopper et al., 2007; Chen et al., 2009; Fonzo et al., 2010) and visual cortex (Rauch et al., 1996; Zhu et al., 2014), it is still unclear whether these imaging deficits could change associated with clinical improvement. The recovery neuralmechanisms underlying the treatment efficacy in PTSD are not yet elucidated. Studying the brain changes before and after treatment in PTSD patients would not only improving our understanding of the pathogenesis and recovery of PTSD, but also help in understanding the neuromechanism of treatment effect from molecular chemistry to neurocircuit level. The previous study has shown that fluoxetine normalized increased activity in the cerebellum,

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precuneus and supplementary motor cortex in PTSD (Fernandez et al., 2001). Besides, Vermetten et al. found an increase in hippocampal volume, and significant improvements in verbal declarative memory after 9–12 months of treatment with paroxetine (Vermetten et al., 2003). Fani et al. showed increased rCBF of anterior cingulate cortex (ACC) function in PTSD during trauma versus neutral script presentations, and increased orbitofrontal cortex (OFC) function was specifically associated with paroxetine treatment as compared to placebo in PTSD (Fani et al., 2011). Moreover, similar functional changes were found after different psychotherapy treatments were applied, such as cognitive behavior therapy (Felmingham et al., 2007), eye movement desensitization and reprocessing (Lansing et al., 2005), and exposure therapy (Roy et al., 2010).

However, findings from previous studies could have been confounded by the lack of trauma-exposed control groups. Thus, it is not clear whether the changes found in the brain areas in PTSD after treatment are abnormal areas, which differ from the trauma-exposed controls. Additionally, different trauma sources and traumatic times result in heterogeneous patient population, which makes it hard to explain the findings (Deering et al., 1996). Furthermore, previous functional neuroimaging studies related to treatment have shown abnormalities in the PTSD patients using symptom provocation and cognitive activation task. However, group or individual differences in motivation or cognitive abilities during these tasks can result in difficulties in interpretation. Besides, differences in tasks can create difficulties in comparisons across different studies. Resting-state MRI analysis was used to explore spontaneous brain activity at baseline without any task or stimulus, which avoids any instability due to the task, and similar to the reality of daily life situations. The changes in spontaneous brain activity in PTSD before and after treatment during resting-state have not yet been investigated so far. Paroxetine, as a first-line drug for the treatment of PTSD, was shown to be effective through randomized controlled trials (Marshall et al., 2001; Tucker et al., 2001). Further, it inhibits the reuptake of norepinephrine more than the other SSRIs (Gilmor et al., 2002). It was the most frequently used drug for PTSD patients in trials related to before and after fMRI studies as previously mentioned.

Thus, we aimed to examine the altered spontaneous brain activity in treatment-naïve PTSD patients before and after 12 weeks' treatment with paroxetine. Amplitude of low-frequency fluctuation (ALFF) (Zang et al., 2007) in Rs-fMRI was analyzed to characterize regional spontaneous neuronal activity (Kiviniemi et al., 2000). We hypothesized that PTSD patients would show aberrant ALFF at baseline, mainly in frontolimbic, default mode network (DMN) and visual brain circuitry, and would recover after 12 weeks' treatment, along with clinical improvement.

2. Materials and methods

2.1. Participants

We recruited thirty treatment-naïve chronic PTSD subjects aged 18 to 60 years, who survived the Wenchuan 8.0-magnitude earthquake which caused tremendous damage in 2008 (Stone, 2009). All participants were recruited from the disaster areas of the earthquake, approximately four years after the earthquake (2012–2013). Twenty-three patients completed the entire treatment and two MRI scans. Data of two male patients were discarded because of head movement during the MRI scan. Therefore, imaging data from twenty-one patients were included for statistical analysis (four males and seventeen females, with a mean age of 46.76 ± 5.81 years). We recruited seventeen survivors (five males and twelve females, with a mean age of 43.24 ± 10.62 years) of the earthquake who never were diagnosed with PTSD or any other psychiatric disorders as controls (earthquake-exposed group). All controls were recruited from the same disaster areas of the earthquake.

Of participants in the PTSD group, six patients had been hospitalized due to injury in the earthquake. Ten patients had lost family members. Eight patients had family members who were severely injured in the earthquake. In the controls group, two patients had been hospitalized due to injury in the earthquake. Seven patients had lost family members. Four patients had family members who were severely injured in the earthquake. There was no significant difference between these two groups in self-injury, death and injury in the family (Chi-squared test, $p > 0.05$). All of subjects witnessed people buried and suffered heavy losses of property in the disaster.

2.2. Inclusion/exclusion criteria:

All individuals were recruited from the disaster areas, and met the DSM-IV criteria for PTSD (First et al., 1995). Left-handed subjects were excluded, and none of the patients had received any regular medication or psychological therapy.

Exclusion criteria included any history of neurological disease, bipolar disorder; alcohol and/or other substance abuse/dependence; history of major head injury involving loss of consciousness for more than 10 min; and mental retardation. Subjects with metal implants (e.g., surgical clips or pacemaker) and pregnancy were excluded from MRI. A total of 23 individuals completed all procedures for this study. According to the Structured Clinical Interview for DSM-IV (First et al., 1995), participants in the PTSD group met criteria for current comorbid diagnoses: major depression ($N=5$), dysthymia ($N=1$), and general anxiety disorder ($N=2$).

All participants were assessed using the Clinician Administered Posttraumatic Stress Disorder Scale (CAPS; Blake et al., 1995), Hamilton Rating Scale for Depression (HAMD-24), Hamilton Rating Scale for Anxiety (HAMA-14), and Clinical Global Impression (CGI; Guy, 1976) scales at baseline.

This study was approved by the Medical Ethics Committee of West China Hospital, Sichuan University, and all subjects gave written informed consent.

2.3. Treatment phase

Participants with PTSD received paroxetine (Seroxat) treatment for 12 weeks. The dosage at the beginning of treatment was 10 mg/day, which was increased to 20 mg/day after four days. The paroxetine dosage was adjusted based on the judgment of the investigating psychiatrist every four weeks by 10 mg/day up to 40 mg/day. The CGI, CAPS, HAMD, HAMA, and Asberg's antidepressant side-effect rating scales (SERS) were assessed every four weeks to evaluate the patient's condition and adverse drug reactions. The 24/7 emergency telephone number of a psychiatrist was given to all subjects in case of any emergency during treatment. No other drugs were permitted during treatment, unless required for the patients' safety.

After finishing 12 weeks of treatment, the PTSD patients were divided into three secondary outcome groups based on the CAPS scores: response (decrease from baseline ≥ 10 points but still met the diagnosis of PTSD); loss of diagnosis (no longer meeting symptom criteria and $20 <$ CAPS score < 45); and total remission (CAPS score < 20) (Schnurr et al., 2007).

2.4. fMRI procedures

We used a 3.0 T magnetic resonance scanner (Siemens 3.0 T Trio Tim, Germany) with 8-channel phase array head coil. The fMRI blood-oxygen-level-dependent (BOLD) images were acquired by a gradient-echo-planar imaging (EPI) sequence (TR/TE$==$2000/30 ms; flip