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Research report

Different white matter abnormalities between the first-episode, treatment-naive patients with posttraumatic stress disorder and generalized anxiety disorder without comorbid conditions

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ABSTRACT

Background: This study compared brain white matter integrity in two groups of patients with DSM-IV anxiety disorders.
Method: Seventeen patients with posttraumatic stress disorder (PTSD), 20 with generalized anxiety disorder (GAD), and 28 healthy controls were assessed on diffusion tensor imaging.
Results: As compared to healthy controls, increased fractional anisotropy (FA) in left superior frontal gyrus in PTSD patients, and increased FA in right postcentral gyrus in GAD subjects were exhibited. Furthermore, patients with PTSD showed reduced FA in right anterior cingulate gyrus relative to GAD subjects. However, there was no significant correlation between the FA value of any altered region and the severity of PTSD or GAD.
Limitations: The sample studied can be considered small. Gender and educational level were not well-matched among the groups.
Conclusions: We tentatively speculate that abnormal white matter integrity of right anterior cingulate gyrus is an important neuroimaging marker of PTSD that distinguishes it from other anxiety disorders such as GAD.

1. Introduction

Posttraumatic stress disorder (PTSD) is characterized by reexperiencing symptoms, avoidance of stimuli associated with traumatic event, and hyperarousal that were not present before the traumatic event, whereas generalized anxiety disorder (GAD) is defined as worry that is present most of time for at least six months (Fricchione, 2004; Kim et al., 2005). Estimates of lifetime prevalence of PTSD in the general population vary between 1% and 9.2% (Breslau et al., 1991; Helzer et al., 1987; Kessler et al., 1995), and in GAD vary between 3% and 6% (Peter, 2007). The prevalence in women is twice that of men (Breslau, 2002; Sher, 2010; Wittchen et al., 1994). Both PTSD and GAD have been found to be frequently comorbid with other psychiatric disorders. Among individuals who meet the criteria for lifetime PTSD, 88% of men and

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79% of women have at least one comorbid psychiatric disorder (Sher, 2010), and major depression and GAD were the most common comorbid disorders (Hubbard et al., 1995; Nixon et al., 2004). Population surveys also indicate that comorbidity is approximately 80% in subjects with lifetime GAD (Peter, 2007).

Brain imaging research in PTSD and GAD has become increasingly important and provides evidence to validate the pathophysiology of these two diseases. Magnetic resonance imaging (MRI) studies have reported various brain structural and functional alterations in subjects with PTSD (Fonzo et al., 2010; Landre et al., 2010; Lanius et al., 2006; Lanius et al., 2007). Most consistent findings are enhanced activation in amygdala and activation failure or reduced volumes in hippocampus as well as prefrontal cortex, which has a role in encoding and retrieval of verbal memory (Armony et al., 2005; Bremner, 2005, 2007; Brunetti et al., 2010; De Bellis et al., 2002; Hou et al., 2007; Sachinvala et al., 2000). Recent studies used diffusion tensor imaging (DTI) to report white matter abnormalities in various brain regions in PTSD. DTI is a well-developed MRI technique that can provide information about white matter microstructural integrity in vivo (Ma et al., 2007). Fractional anisotropy (FA) value derived from DTI is measured by magnitude and direction of water diffusion (Basser et al., 1994a). As a quantitative indicator of white matter integrity, FA value is thought to reflect fiber density, axonal diameter, and myelination in white matter (Basser et al., 1994b). Deep white matter hypointensities or hyperintensities at the level of the prefrontal cortex (De Bellis et al., 2002), corpus callosum (De Bellis et al., 2002; Jackowski et al., 2008), and cingulum bundle (Kim et al., 2006) especially anterior cingulate gyrus (Abe et al., 2006; Kim et al., 2005), have been reported in PTSD.

Research using DTI to explore white matter networks in GAD has not revealed specific dysfunctions. However, alteration in other parameters such as brain volume or functional activation have been found in GAD, in particular in the prefrontal cortex (Mohlman et al., 2009), amygdala (Etkin et al., 2009), anterior cingulate cortex (Etkin et al., 2010) and insula (Damsa et al., 2009; Simmons et al., 2008). In addition, some studies indicated new options in the treatment of subjects with GAD (Damsa et al., 2009). One fMRI study revealed significant increase in right ventrolateral prefrontal cortex activation in response to angry faces following treatment with cognitive behavioral therapy or fluoxetine for GAD (Maslowsky et al., 2010). Another fMRI study showed that the pattern of rostral anterior cingulate cortex–amygdala responsivity could prove useful as a predictor of venlafaxine treatment response in GAD (Whalen et al., 2008). Furthermore, fMRI guided repetitive transcranial magnetic stimulation may be associated with clinical improvement in symptom in GAD subjects (Bystritsky et al., 2008).

While previous neuroimaging studies in PTSD or GAD were conducted separately, often on subjects with comorbid psychiatric disorders, no prior study has directly compared changes in white matter integrity of brain regions between PTSD and GAD. Thus, the aim of the present study was to investigate the potentially different changes in white matter integrity between the first-episode and treatment-naive patients with PTSD and GAD without comorbid conditions.

2. Methods

2.1. Participants

Twenty outpatients with GAD (12 males and 8 females) ages 18–41 years (mean = 30.80, SD = 8.58) and 17 participants with PTSD (all males) ages 26–43 years (mean = 34.06, SD = 4.97) were recruited at the Second Xiangya Hospital of Central South University in Changsha, Hunan, PR China. Subjects with PTSD survived from a severe coal mine accident and were studied at 2-months post-trauma. All patients were experiencing their first episode of PTSD or GAD and were treatment naive. All subjects were right-handed and interviewed with the Structured Clinical Interviewed for DSM-IV. Twenty-eight age matched healthy control subjects (14 males and 14 females) ages 23–42 years (mean = 28.96, SD = 6.22; $F = 2.999$; $p > 0.05$) were also recruited. The groups differed with regard to different educational level (GAD group, mean = 12.10 years, SD = 2.05; PTSD group, mean = 7.94 years, SD = 2.30; control group, mean = 13.36 years, SD = 3.61; $F = 19.115$; $p < 0.05$). PTSD patients had scores ranged from 61 to 102 (mean = 76.29, SD = 10.85) on the Clinician-Administered PTSD Scale (CAPS), and GAD patients had scores ranged from 56 to 79 (mean = 67.60, SD = 5.17) on the Penn State Worry Questionnaire (PSWQ) at the time of study.

Exclusion criteria for three groups were (1) any history of loss of consciousness, (2) current or past significant medical or neurological illness. Additional exclusion criteria for PTSD and GAD groups included any current or past psychiatric disorder other than PTSD and GAD respectively. An additional exclusion criterion for healthy control group was any current or past psychiatric illness identified by DSM-IV.

Informed consent was written after the procedures had been fully explained. This study was conducted in accordance with the Helsinki Declaration and approved by the Ethics Committee of the Second Xiangya Hospital of Central South University, China.

2.2. Image acquisition

Diffusion tensor imaging performed MR scans were performed on a 1.5-Tesla General Electric scanner (Twin-speed, Milwaukee, WI, USA) at the Second Xiangya Hospital of Central South University. A standard birdcage head coil was used, along with foam pads to minimize head movement. Single-shot echo planar imaging (EPI) with alignment of the anterior–posterior commissure plane was undertaken. The diffusion sensitizing gradients were applied along 13 non-collinear directions ($b = 1000\ s/mm^2$), together with an acquisition without diffusion weighting (b = 0, b0 images). PTSD and control groups were scanned with the following parameters: repetition time (TR) = 12,000 ms; echo time (TE) = 105 ms; acquisition matrix = 128 × 128; field of view = 24 cm × 24 cm; NEX = 5; slice thickness = 4 mm; no gap, 30 contiguous axial slices. Because the MRI machine upgraded during the research, GAD subjects were scanned with TE time changed to 107 ms.

2.3. MRI data analysis

The methods of imaging processing were similar to those described previously (Hao et al., 2009). Parametric images of FA