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Preliminary communication

Lack of gender effects on gray matter volumes in adolescent generalized anxiety disorder

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ABSTRACT

Background: Previous epidemiological and clinical studies have reported gender differences in prevalence and clinical features of generalized anxiety disorder (GAD). Such gender differences in clinical phenomenology suggest that the underlying neural circuitry of GAD could also be different in males and females. This study aimed to explore the possible gender effect on gray matter volumes in adolescents with GAD.

Methods: Twenty-six adolescent GAD patients and 25 healthy controls participated and underwent high-resolution structural magnetic resonance scans. Voxel-based morphometry (VBM) was used to investigate gray matter alterations.

Results: Our study revealed a significant diagnosis main effect in the right putamen, with larger gray matter volumes in GAD patients compared to healthy controls, and a significant gender main effect in the left precuneus/posterior cingulate cortex, with larger gray matter volumes in males compared to females. No gender-by-diagnosis interaction effect was found in this study.

Limitations: The relatively small sample size in this study might result in a lack of power to demonstrate gender effects on brain structure in GAD.

Conclusions: The results suggested that there are differences in gray matter volumes between males and females, but gray matter volumes in GAD are not influenced by gender.

1. Introduction

Generalized anxiety disorder (GAD) is a common anxiety disorder with an estimated lifetime prevalence of 5.7% in the general population (Kessler et al., 2005) and characterized by uncontrollable and excessive worry about everyday things. GAD often co-occurs with other psychiatric disorders and causes significant personal, societal, and economical burden (Grant et al., 2005). Gender differences in prevalence and clinical features of GAD have been reported in a series of epidemiological and clinical studies (Rodriguez et al., 2006; Steiner et al., 2005; Vesga-Lopez et al., 2008). The lifetime or 12-month prevalence of GAD in female is about two times higher than that in male (Vesga-Lopez et al., 2008). Women with GAD have an earlier age of onset (Steiner et al., 2005), more somatic symptoms (Steiner et al., 2005), and lower rates of remission and relapse (Rodriguez et al., 2006). Women with GAD have significantly higher rates of comorbid mood disorders and anxiety disorders, while men with GAD have significantly higher rates of comorbid substance abuse or dependence and antisocial personality (Vesga-Lopez et al., 2008).

Such gender differences in clinical phenomenology suggest that the underlying neural circuitry of GAD could also be different in males and females. There have been a large number of studies investigating gender differences of brain structure in healthy participants (Chen et al., 2007; Cosgrove et al., 2007; Goldstein et al., 2001; Lenroot and Giedd, 2010; Luders et al., 2009; Raz et al., 2004). The most consistent result is that men have greater brain volumes than women (Chen et al., 2007; Cosgrove et al., 2007; Goldstein et al., 2001; Lenroot and Giedd, 2010; Luders et al., 2009; Raz et al., 2004). Yet, when controlling for total intracranial volumes, women have a higher percentage of gray matter, and men a higher percentage of white matter (Chen et al., 2007; Cosgrove et al., 2007; Goldstein et al., 2001). Regional brain volumes differences are inconsistent (Chen et al., 2007; Cosgrove et al., 2007; Goldstein et al., 2001; Lenroot and Giedd, 2010; Luders et al., 2009; Raz et al., 2004). Some studies have suggested that men have more gray matter volumes in the amygdala (Cosgrove et al., 2007; Goldstein et al., 2001; Lenroot and Giedd, 2010), occipital lingual gyrus (Chen et al., 2007), temporal lobe (Chen et al., 2007; Raz et al., 2004), and hypothalamus (Cosgrove

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et al., 2007; Goldstein et al., 2001) while women have larger gray matter volumes in the basal ganglia (Cosgrove et al., 2007; Lenroot and Giedd, 2010; Luders et al., 2009), cingulate gyrus (Chen et al., 2007), orbitofrontal cortex (Lenroot and Giedd, 2010; Luders et al., 2009), and hippocampus (Cosgrove et al., 2007; Lenroot and Giedd, 2010). Other studies have shown different findings, including larger gray matter volumes in the frontomedial cortex (Goldstein et al., 2001; Raz et al., 2004), cingulate cortex (Raz et al., 2004), and hippocampus (Raz et al., 2004) in men and larger gray matter volumes in the temporal gyrus (Luders et al., 2009) in women or no gender differences in the basal ganglia (Chen et al., 2007), amygdala (Gur et al., 2002) and hippocampus (Gur et al., 2002). One study (Yamasue et al., 2008) investigated the gender-related neuroanatomical basis of human anxiety-related personality traits and found a correlation between smaller regional brain volume in the left anterior prefrontal cortex and higher anxiety-related personality traits only in female group. The brain regions with gender differences, such as the amygdala, hippocampus, cingulate gyrus and prefrontal cortex, have been suggested to be involved in anxiety circuitry (Shin and Liberzon, 2010). The question arises as to whether gender might interact with the development of GAD.

In the limited studies exploring the alterations of gray matter volumes in GAD patients, three studies (Etkin et al., 2009; Milham et al., 2005; Mohlman et al., 2009) did not examine the gender effect on the gray matter volumes, two studies (Hettema et al., 2012; Schienle et al., 2011) only investigated female population, one study (Terlevic et al., 2013) considered gender as a covariant to control, and only one study (De Bellis et al., 2000) examined the gender effect but found no gender-by-diagnosis interaction effects on gray matter volumes. In this study, we employed high-resolution structural magnetic resonance imaging techniques and a voxel-based morphometry (VMB) analysis approach to assess the gender-by-diagnosis interaction effects in gray matter volumes. Given the existence of gender-related differences in brain structure and gender differences of clinical phenomenology in GAD, we hypothesized that the gender-related brain structural differences might be associated with GAD. For lack of evidence on gender related differences in brain structure in GAD, we conducted a whole brain analysis to explore the possible brain regions that might mediate gender effect and the development of GAD.

2. Materials and methods

2.1. Subjects

Twenty-six adolescents with GAD (13 female and 13 male) and 25 healthy controls (12 female and 13 male) were recruited in the present study. All subjects were recruited from local high schools in Hunan Province via advertisements and school notice, as described in our previous study (Liao et al., 2013). First, 1885 subjects finished the 41-item self-report questionnaire, the Screen for Child Anxiety Related Emotional Disorders (SCARED) (Birmaher et al., 1999; Su et al., 2008). The SCARED is a reliable and valid screening tool for childhood anxiety disorder, with an optimal total cutoff point score of 25 to separate children with anxiety disorders from those without (Birmaher et al., 1999; Su et al., 2008). Among 1885 subjects, 508 subjects' SCARED scores were greater than 25, and the scores of the rest were lower than 25. Then, 673 subjects (508 SCARED scores ≥ 25; 165 SCARED scores < 25) were investigated by the same trained clinician and diagnosed using DSM-IV criteria and the Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime (K-SADS-PL) version (Kaufman et al., 1997). In this study the age range of subjects was 16–18, so we only interviewed the adolescent. All patients fulfilled the criteria for current first-episode, generalized anxiety disorder without co-morbidity disorders. Healthy controls without mental disorders and physical disease were selected to match patients in age, and gender. Exclusion criteria for all subjects included any neurological abnormalities, history of seizures, head trauma or unconsciousness, any physical disease, and use of psychoactive substances. All subjects enrolled in this study were non-medicated, right-handed, and volunteered to participate in this study. The Penn State Worry Questionnaire (PSWQ) (Meyer et al., 1990) and the Beck Depression Inventory (BDI) (Beck and Beamesderfer, 1974) were introduced to assess anxiety and depression levels in adolescent GAD patients, respectively. The Ethics Committee of the Second Xiangya Hospital of Central South University in China approved this study. After a complete explanation of this study, written informed consents were obtained from each adolescent and one of his or her legal guardians.

2.2. Structural magnetic resonance imaging (MRI) acquisition

MRI scans were acquired at the Second Xiangya Hospital of Central South University in China and performed with a Philips 3.0 T Scanner, equipped with a SENSE-8 channel head coil. For each participant, T1-weighted high-resolution anatomical images were obtained using a 3-dimensional (3D) rapid acquisition gradient echo sequence, with the following parameters: repetition time (TR)=7.5 ms, echo time (TE)=3.7 ms, flip angle=8°, field of view=256 mm × 256 mm, slice=180, voxel size=1 mm × 1 mm × 1 mm.

2.3. Image analysis

Image analysis was conducted using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) and the VBM8 toolbox (VBM8, version 435; http://dbm.neuro.uni-jena.de/vbm8/), as described in our previous study (Liao et al., 2013). Individual structural images were preprocessed with the VBM8 toolbox following the default parameter. T1-weighted images were bias-corrected, tissue classified, normalized to the Montreal Neurological Institute standard template space, and segmented into gray matter, white matter and cerebrospinal fluid, within a unified model (Ashburner and Friston, 2005) including high-dimensional DARTEL normalization. The segmented gray matter was modulated with the option of non-linear only, which allows comparing the absolute amount of tissue corrected for individual brain sizes. The voxel resolution after normalization was 1.5 mm × 1.5 mm × 1.5 mm. The check data quality function was adopted to check homogeneity of gray matter images. Finally, the segmented, modulated gray matter images were smoothed by a Gaussian kernel of 8 mm FWHM.

2.4. Statistical methods

Demographic and clinical measures were tested by means of a general linear model with a 2 (diagnosis: GAD vs CON) × 2 (gender: female vs male) comparison or chi-square test or *t*-test, as needed, in SPSS16. The whole brain image analysis was conducted with second-level models in SPM8. The smoothed gray matter images were entered into a voxel-by-voxel general linear model with a 2 (diagnosis: GAD vs CON) × 2 (gender: female vs male) comparison, controlling for age, to assess the diagnosis main effect (GAD > or < CON), the gender main effect (female > or < or male) and the gender-by-diagnosis interaction effects, with extent threshold of 100 contiguous voxels per cluster and an alpha level of $p < 0.001$, uncorrected. *P*-values < 0.05 corrected for family-wise error (FWE) were considered significant. According to the aim of this study, the gender-by-diagnosis interaction effect was of particular interest.