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Assessment of trait anxiety and prediction of changes in state anxiety using functional brain imaging: A test–retest study

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ABSTRACT

Anxiety is a multidimensional construct that includes stable trait anxiety and momentary state anxiety, which have a combined effect on our mental and physical well-being. However, the relationship between intrinsic brain activity and the feeling of anxiety, particularly trait and state anxiety, remain unclear. In this study, we used resting-state functional magnetic resonance imaging (fMRI) (amplitude of low-frequency fluctuations (ALFF) and regional homogeneity (ReHo)) to determine the effects of intrinsic brain activity on stable inter-individual trait anxiety and intra-individual state anxiety variability in a cross-sectional and test–retest study. We found that at both time points, the trait anxiety score was significantly associated with intrinsic brain activity (both the ALFF and ReHo) in the right ventral medial prefrontal cortex (vmPFC) and ALFF of the dorsal anterior cingulate cortex/anterior midcingulate cortex (dACC/aMCC). More importantly, the change in intrinsic brain activity in the right insula was predictive of intra-individual state anxiety variability over a 9-month interval. The test–retest nature of this study's design could provide an opportunity to distinguish between the intrinsic brain activity associated with state and trait anxiety. These results could deepen our understanding of anxiety from a neuroscientific perspective.

Introduction

Anxiety refers to feelings of fear, worry, and unease caused by external or internal potential threats (Grupe and Nitschke, 2013; Calvo and Dolores Castillo, 2001). The responses to the potential threats have been shown to exhibit stable individual characteristics (Andrews and Thomson, 2009; Etkin et al., 2004). To some extent, higher sensitivity to anxiety places individuals at greater risk of developing psychopathology and physical illness (Bower et al., 2010; Hoge et al., 2011; McNally, 2002). Interestingly, anxiety is a multifaceted construct that includes stable trait anxiety and momentary state anxiety (Spielberger 1983, 2010). Trait and state anxiety are related but separate psychological measures that have fairly distinct influences on individual cognitive processes, such as attention and cognitive control (Bishop, 2007; Bishop et al., 2007; Bishop, 2009; Crocker et al., 2012; Hur et al., 2015; Pacheco-Unguetti et al., 2010). However, previous studies on this subject have mainly employed task fMRI, and the relationship of intrinsic brain activity with the feeling of anxiety, particularly with trait and state anxiety, remain unclear. Previous studies have mainly explored the brain mechanisms of state and trait anxiety using cross-sectional designs. Few studies have directly explored the differences in intrinsic brain activity related to trait and state anxiety. Therefore, in this study, we used resting-state fMRI (the amplitude of low-frequency fluctuations (ALFF) and regional homogeneity (ReHo)) to explore the role of intrinsic brain activity in trait and state anxiety variability.

A previous test–retest study has proposed that trait and state anxiety variability is based on both stable intra-individual variability and inter-individual variability (MacDonald et al., 2006; Wang et al., 2012; Zuo and Xing, 2014). Trait anxiety is relatively stable and may reflect inter-individual variability among personalities. An individual's trait anxiety level may be correlated with the differences in several brain regions (Barnes et al., 2002; Bieling et al., 1998). On the other hand, state anxiety exhibits changes that partially reflect intra-individual variability (Bechara and Naqvi, 2004; Birtchnell, 2002). Therefore, a test–retest study could provide an opportunity to distinguish between the intrinsic brain activity associated with state and trait anxiety. In addition, resting-state fMRI has become a potentially useful tool for understanding the functions of the human brain due to its low cost and lack of a task-based performance requirement (Lee et al., 2013; Liu et al., 2012; Sheline and Raichle, 2013). In particular, the

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relationships of regional activity amplitude and local functional connectivity with the feeling of anxiety remain unclear. Therefore, this study focused on the ALFF and ReHo, which are two important indicators of resting-state fMRI (Yuan et al., 2013; Zang et al., 2007; Zou et al., 2009). Specifically, the ALFF measures the magnitude of regional activity amplitude, and it reflects the intensity of regional spontaneous brain activity (Zang et al., 2007). ReHo measures the similarity in the time series of a given voxel to its nearest neighbors, which reflects the coherence of spontaneous neuronal activity (Zang et al., 2004). It has been shown that both ALFF and ReHo have high test–retest reliability (Küblböck et al., 2014; Zuo et al., 2010, 2013), and they are widely used in studies of both healthy and clinical populations (Zhang et al., 2015; Han et al., 2011; Kong et al., 2015; Liu et al., 2014).

Neuroimaging studies of anxiety have primarily focused on the limbic regions (e.g., amygdala and insula), prefrontal cortex, and anterior cingulate cortex (ACC) (Blackmon et al., 2011; Baur, 2012; Shang et al., 2014; Sladky et al., 2013; Spampinato et al., 2009). Meta-analysis of voxel-based morphometry (VBM) studies of anxiety disorders has revealed evidence that the gray matter volumes in the anterior cingulate gyrus and prefrontal cortex are abnormal in patients with anxiety disorders (Shang et al., 2014). In addition, the structures of distributed neural networks, including those of the amygdala, posterior cingulate cortex, and medial and dorsolateral PFC, have been found to be correlated with the anxiety level in healthy volunteers (Blackmon et al., 2011; Spampinato et al., 2009). Further, functional neuroimaging studies have examined the functions of limbic regions, the prefrontal cortex and the cingulate gyrus in social anxiety disorder (SAD) (Zhang et al., 2015) and in association with healthy individuals' anxiety-related traits (Sehlmeyer et al., 2011; Zald et al., 2002). Notably, changes in state anxiety to some extent reflect emotional changes caused by the awareness of feelings in the body (Bechara and Naqvi, 2004; Birtchnell, 2002). Studies of the awareness of internal body states have consistently indicated that the insula plays a central role in sensing information about the body state and then integrating it to generate a subjective affective experience (Craig, 2003, 2009, 2011; Ernst et al., 2013; Khalsa et al., 2009; Terasawa et al., 2013a).

Therefore, in this study, we sought to identify the intrinsic brain activity associated with state and trait anxiety by determining the ALFF and ReHo in a cross-sectional and test–retest study based on a large healthy sample ($n = 114$). For this purpose, we first analyzed the cross-sectional relationships of maps of the ALFF and ReHo with trait anxiety at the first time point in the sample of 114 subjects. Second, we compared the correlation maps of the ALFF and ReHo and trait anxiety at the second time point to verify the reliability of the results obtained from the first time point using the same group. Finally, the test–retest design allowed us to examine whether changes in the ALFF and ReHo in specific brain regions over time predict intra-individual state anxiety variability. Based on the above mentioned study results (Baur, 2012; Shang et al., 2014; Blackmon et al., 2011; Sladky et al., 2013; Talati et al., 2013; Zhang et al., 2015), we hypothesized that individual differences in trait anxiety would be stably correlated with the ALFF and ReHo variability in brain regions such as the limbic regions, prefrontal cortex, and ACC and that the intrinsic brain activity in the insula might effectively predict intra-individual state anxiety variability.

Methods

Participants

The participants were healthy college students attending Southwest University (China) who were involved in this study as part of a larger longitudinal study assessing brain imaging, creativity and mental health. Particularly, our resting-state fMRI data sets are part of the Consortium for Reliability and Reproducibility (CoRR) (Zuo et al., 2014). First, they provided written informed consent prior to the study, which was approved by the Institutional Human Participants Review Board of the Southwest University Imaging Center for Brain Research. Then, all participants were screened using a Structured Clinical Interview for DSM-IV by two well-trained and experienced graduate students at the Department of Psychology. Thus, participants who met the DSM-IV criteria for any psychiatric disorder or neurological disease or condition who were not suitable for scanning, were on medication that can alter brain function, or had a history of loss of consciousness, head trauma, pregnancy, or breast-feeding, were excluded. At the first time point (Time 1), 561 participants consented to participate in this study and underwent fMRI. At approximately 9 months after the first examination, the participants were invited for follow-up examination (Time 2). However, only 114 participants completed the scans both at the Time 1 and Time 2, related questionnaires and screening. Therefore, we included 114 participants in this study.

Behavioral assessments

Each participant was evaluated based on his or her level of anxiety using the State Trait Anxiety Inventory (STAI) and the self-rating anxiety scale (SAS). The STAI is a self-report questionnaire that consists of 40 items for measuring two dimensions of anxiety: state anxiety (A-State) and trait anxiety (A-Trait) (Spielberger, 1983, 2010). The A-Trait scale consists of 20 statements that describe how people generally feel that are rated on a 4-point intensity scale, and it captures the dimensions of personality linked to anxiety. This A-State scale assesses the feelings of people at a particular moment, and it is affected by temporary conditions. The STAI is valued for its high reliability based on its internal consistency and test reliability scores ranging from 0.73 to 0.86 across multiple samples (Spielberger, 1983). For the STAI, Cronbach's alpha coefficient for internal consistency in our sample is acceptable (A-State: $\alpha_{\text{Time 1}} = 0.88$, $\alpha_{\text{Time 2}} = 0.89$; A-Trait: $\alpha_{\text{Time 1}} = 0.83$, $\alpha_{\text{Time 2}} = 0.88$). The Chinese version of the STAI could be regarded as an objective tool for measuring anxiety in the Chinese population, and the factor analytic data tended to support Spielberger's conception of the multidimensional natures of the A-State and A-Trait scales (Li and Lopez, 2004; Shek, 1988). The self-rating anxiety scale (SAS) is a 20-item scale used to measure the frequency of anxiety symptoms. It addresses 15 somatic and 5 affective symptoms that are linked to anxiety (Zung, 1971). It is a 4-point scale, with each response ranging from 'none of the time' to 'most of the time'. Examples of SAS items are as follows: 'My arms and legs shake and tremble' (somatic symptoms) and 'I feel more nervous and anxious than usual' (affective symptoms). The SAS is considered to be a sensitive and ecologically valid measure, and it has shown adequate internal consistency in normal college students ($a = 0.81$) (Olatunji et al., 2006) and good test–retest reliability in a clinical sample of agoraphobics over a period ranging from 1 to 16 weeks (r values $= 0.81$–0.84) (Michelson and Mavissakalian, 1983). For the SAS, Cronbach's alpha coefficient for internal consistency in our sample is acceptable ($\alpha_{\text{Time 1}} = 0.76$, $\alpha_{\text{Time 2}} = 0.79$), and the Chinese version of this scale has been validated and has been shown to have acceptable construct validity for measuring anxiety in the Chinese population (Tao and Gao, 1994; Wei et al., 2014).

Resting-state fMRI data acquisition

Resting-state fMRI images were acquired using a 3.0-T Siemens Trio MRI scanner (Siemens Medical, Erlangen, Germany) at the Brain Imaging Research Center of Southwest University, Chongqing, China. Whole-brain resting-state functional images were acquired using a gradient-echo echo-planar imaging (EPI) sequence, with the following parameters: slices = 32; TR/TE = 2000/30 ms; flip angle = 90°; field of view = 220 mm × 220 mm; thickness/slice gap = 3/1 mm; and matrix = 64 × 64, resulting in a voxel with 3.4 × 3.4 × 3 mm^3. As a result, 242 functional volumes were acquired for each participant. During resting-state fMRI scanning, the participants laid in the supine position with their heads comfortably positioned within a 1-channel