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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

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and lack of a task-based performance requirement (Lee et al., 2013; Liu et al., 2012; Sheline and Raichle, 2013). In particular, the 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 (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; Freitas-Ferrari et al., 2010; 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 birdcage head coil, which was padded with foam to minimize head movement. Earplugs were used to reduce the influence of scanner noise. All subjects were instructed to relax, keep their eyes closed, and stay awake.

Data preprocessing

The resting-state image data were analyzed using data processing assistant for resting-state (DPARSF) software (http://www.restfmri.net) (Song et al., 2011; Yan and Zang, 2010). This toolbox is based on the SPM8 software package. The first 10 volumes of the functional images were discarded to account for signal equilibrium and the participants' adaptation to their immediate environment. The remaining 232 scans were corrected for slice timing, and then realigned to the middle volume to correct for head motion. Participant with head motion exceeding 3.0 mm in any dimension throughout the course of scans was discarded from further analysis. Subsequently, registered images were spatially normalized to Montreal Neurological Institute (MNI) template (resampling voxel size $= 3 \times 3 \times 3$ mm^3). After the spatial smoothing (full width at half maximum = 6 mm Gaussian kernel) (for ALFF except for ReHo), linear trend of the time series was removed. Next, nuisance signals representing motion parameters, white matter, and cerebrospinal fluid signals were regressed out in order to control the potential impact of physiological artifacts. Here, we used the Friston 24-parameter model (6 motion parameters, 6 temporal derivatives, and their squares) (Friston et al., 1996; Satterthwaite et al., 2013) to regress out head motion effects. This approach is based on recent research demonstrating that higher-order models are more effective at reducing the effects of head movements (Power et al., 2012; Yan et al., 2013).

ALFF analysis

ALFF measures the magnitude of regional activity amplitude, and it reflects the intensity of regional spontaneous brain activity (Zang et al., 2007). The procedure for calculating the ALFF was based on the previous studies (Dai et al., 2012; Song et al., 2011; Yan and Zang, 2010; Wang et al., 2011). The time courses were converted to the frequency domain using a fast Fourier transform. Then the square root of the power spectrum was computed and averaged across 0.01–0.08 Hz at each voxel. This averaged square root was taken as the ALFF (Zang et al., 2007). To reduce the global effects of variability across participants, the ALFF of each voxel was divided by the global mean ALFF value for each subject.

ReHo analysis

First, a 0.01–0.08 Hz band-pass filter was applied to reduce the effects of low-frequency drift and high-frequency noise. Then we used Kendall's coefficient of concordance (KCC) to measure the similarity of the time series within a functional cluster based on regional homogeneity. In this analysis, we defined 27 nearest neighboring voxels as a cluster. Then, the individual ReHo map was divided by each participant's global mean ReHo value within the brain mask for standardization purposes. Finally, the ReHo maps were spatially smoothed (FWHM = 6 mm).

Statistical analysis

Intrinsic brain activity associated with trait anxiety

To assess cross-sectional associations between the trait anxiety scores and intrinsic brain activity, we performed two multiple linear regression analyses to identify regions in which the ALFF and ReHo were associated with individual differences in the level of trait anxiety at the first time point. We used the trait anxiety score as the variable of interest, age, and gender were included as regressors of no interest. Second, to verify the reliability of the results obtained at the first time point, we performed two additional multiple linear regression analyses using the data from the second time point. The significance threshold was set at a corrected $p < 0.05$ at the cluster level (Alphasim correction: uncorrected $p < 0.005$ and cluster size threshold of 27 voxels (729 mm^3). In addition, we used the Dice coefficient to analyze the spatial overlap between the maps that were correlated with trait anxiety at both Time 1 and Time 2 (Barbey et al., 2014; Bennett and Miller, 2010). The Dice coefficient was typically calculated using the following equation: $R_{overlap} = 2^*(V_{overlap}) / (V1 + V2)$, where $V_{overlap}$ was the number of voxels within the ROI that were correlated with trait anxiety at both Time 1 and Time 2, and V1 and V2 were the number of voxels within the ROI that were correlated with trait anxiety at Time 1 and Time 2, respectively. The results obtained using the Dice equation could be interpreted as the number of overlapping voxels divided by the average number of significant voxels over time.

Intrinsic brain activity associated with change of state anxiety

To explore the relationships between the changes in the ALFF and ReHo and intra-individual state anxiety variability, we analyzed the association of the maps representing intrinsic brain activity changes in the ALFF and ReHo with intra-individual state anxiety variability, after regressing out age, gender and the changes in trait anxiety. The change in intrinsic brain activity was calculated for each participant by subtracting their ALFF or ReHo map at Time 1 from that at Time 2 ($ALFF_{Time\ 2}$–$ALFF_{Time\ 1}$; $ReHo_{Time\ 2}$–$ReHo_{Time\ 1}$). We determined the intra-individual state and trait anxiety variability in $Change_{state}$ and $Change_{trait}$ for each subject. $Change_{state}$ was calculated as $Change_{state} = State1 - State2$, where State1 was the state anxiety score at Time 1, and State2 was the state anxiety score at Time 2. $Change_{trait}$ was calculated as $Change_{trait} = Trait1 - Trait2$, where Trait1 was the trait anxiety score at Time 1, and Trait 2 was the trait anxiety score at Time 2. The brain regions that were correlated with the change in state anxiety were defined as the ROIs, and the mean values of the ALFF and ReHo were extracted. A change in state anxiety could be caused by changes in somatic and affective symptoms. We used the extracted ROI signals to test whether the intrinsic brain activity in the right insula was correlated with the intra-individual somatic symptom variability or affective symptom variability (the somatic symptom and the affective symptom were measured by the SAS).

Addressing potential confounds

When we did the intrinsic brain activity associated with trait anxiety, the participants' state anxiety scores were found to be significantly correlated with the trait anxiety scores at each time point (Time 1: $r = 0.57$, $p < 0.001$; Time 2: $r = 0.72$, $p < 0.001$). Therefore, to determine whether these results of intrinsic brain activity associated with trait anxiety were influenced by state anxiety, we conducted analyses with inclusion the state anxiety score as a covariate. When we did the intrinsic brain activity associated with change of state anxiety, we also conducted analyses without the change of trait anxiety score as a covariate. Meanwhile, to explore the potential influence of head motion on the correlation results, analyses were conducted both including and not including the mean level of motion for each participant as a covariate. Finally, to explore the potential influence of global signal regression on the correlation results, the data preprocessing were conducted both including regressed out the global signal and not regressed out the global signal.

Table 1
Demographic and psychometric characteristics of the subjects ($n = 114$).

Variable	Time 1, means (SD)	Time 2, means (SD)	Change (Time 2–Time 1)	Time 1 and Time 2 association
Age	19.96 (1.10)	20.71 (1.09)	–	–
Gender	M/F (59/55)	M/F (59/55)	–	–
State anxiety	35.45 (8.44)	36.40 (8.61)	0.96 (9.87)	0.33**
Trait anxiety	40.73 (7.34)	41.19 (8.43)	0.46 (6.17)	0.70**

Time 1 and Time 2 association: the correlation between the score of state anxiety、trait anxiety at Time 1 and Time 2.
** $p < 0.001$.

Table 2
Brain regions exhibiting significant correlations between the ALFF and trait anxiety at each time point, including age and gender as regressors of no interest.

Time point	Brain region	MNI coordinate ($x\ y\ z$)	Peak t-value	Volume (mm^3)
Time 1	*Positive correlation*			
	vACC/vmPFC_R	12,42,−15	3.90	1188
	Negative correlation			
	dACC/aMCC	0,−9,30	−3.66	1026
	Insula_R	45,−21,21	−3.50	1242
Time 2	*Positive correlation*			
	vACC/vmPFC_R	18,48,3	4.99	3672
	Negative correlation			
	dACC/aMCC	0,−15,30	−3.62	1080

Note: ALFF = amplitude of low-frequency fluctuations; vACC/vmPFC = ventral anterior cingulate/medial prefrontal cortex; dACC/aMCC = dorsal anterior cingulate cortex/anterior midcingulate cortex; R = right.

Results

Behavioral data

Table 1 lists the demographics of the total sample at Time 1 and Time 2. Assessment of the trait anxiety scores at each time point revealed moderately high Time 1–Time 2 correlations ($r = 0.70$), indicating that trait anxiety was a relatively stable individual personality. The correlation coefficient of state anxiety at each time point was 0.33, which was lower than that of trait anxiety. We used the one-sample t test to compare whether the change of trait anxiety was greater than zero, we found there was no significant differences between the change of trait anxiety and zero ($p = 0.423$). That means the variance of trait anxiety was not significant. Changes in the scores for trait and state anxiety were positively correlated, with $r = 0.47$ (see Table 1). There were no significant differences between the males and females in trait anxiety (Time 1 (112) = 0.58, $p = 0.56$; Time 2 (112) = 1.38, $p = 0.17$) or state anxiety (Time 1 (112) = 0.81, $p = 0.42$; Time 2 (112) = 1.20, $p = 0.23$) at each time point, and there were also no differences in the changes in trait anxiety (t (112) = 1.17, $p = 0.24$).

Intrinsic brain activity associated with trait anxiety

To assess cross-sectional associations between the trait anxiety scores and intrinsic brain activity, we performed two multiple linear regression analyses to identify regions for which the ALFF and ReHo were associated with individual differences in the level of trait anxiety. The results indicated that the ALFF and ReHo were significantly positively correlated with trait anxiety in the vmPFC at the first time point, and we also found a negative correlation between the ALFF in the dACC/aMCC and the trait anxiety score after including age and gender as regressors of no interest. Importantly, these results were verified at the second time point (Fig. 1, Table 2; Fig. 2, Table 3). The overlapping clusters for the two time points in the vmPFC and dACC/aMCC also showed significant correlations with trait anxiety at Time 1 and Time 2. These results indicated that the differences in intrinsic brain activity in the vmPFC and dACC/aMCC were predictive of the individual differences in trait anxiety.

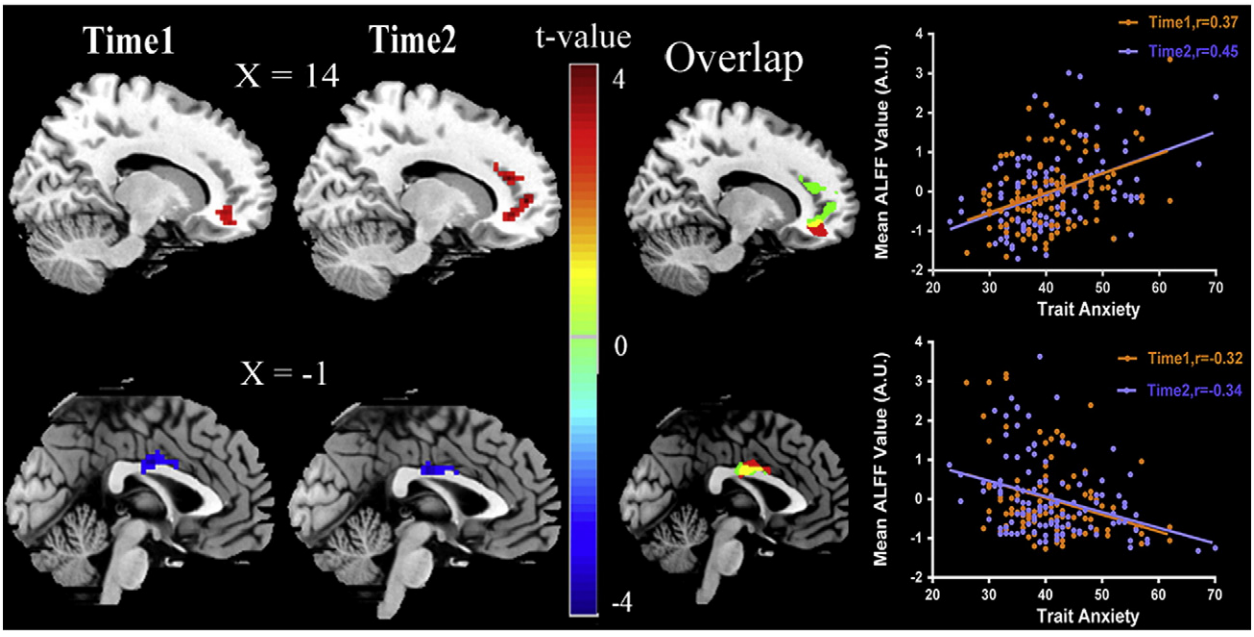

Fig. 1. Regions showing significant partial correlation between the ALFF and trait anxiety for the Time 1 and Time 2 data. The maps show that the intrinsic brain activities of significant regions of the ventral medial prefrontal cortex (vmPFC) and the dorsal anterior cingulate cortex/anterior midcingulate cortex (dACC/aMCC) are correlated with individual differences in trait anxiety at each time point. For the maps of Overlap, the red patches indicate significant regions identified from the Time 1 data, and the green patches indicate those determined from the Time 2 data. Overlapping regions, which indicate consistency over time, are colored in yellow. The scatterplots of the relationship between the mean ALFF within the significant cluster and the trait anxiety scores, adjusted for age, and gender, are shown for illustrative purposes only. The color bar represents the range of t-value. The threshold was set at $p < 0.05$ (corrected).

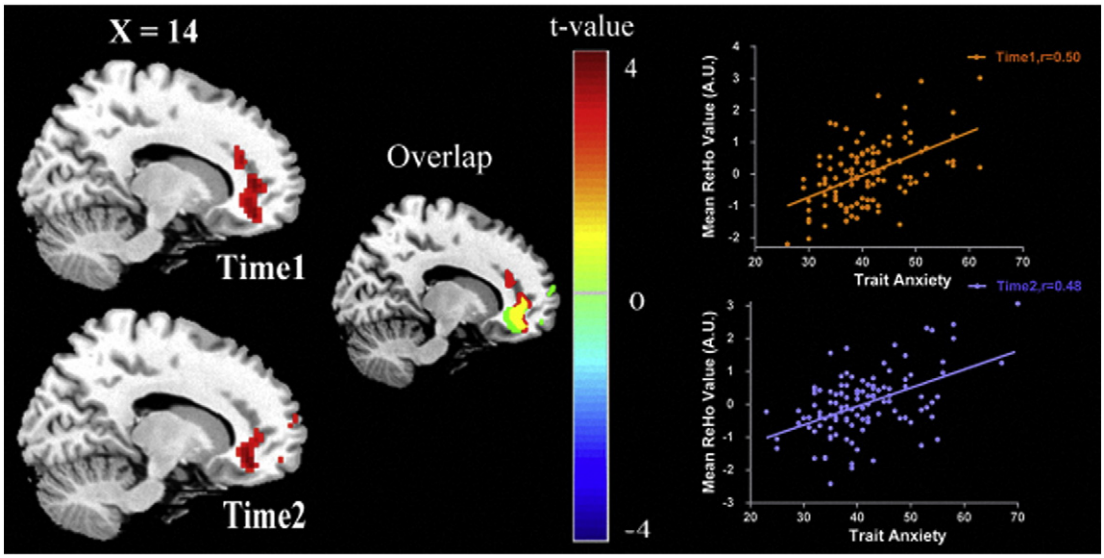

Fig. 2. Regions showing remarkable partial correlations between the ReHo and trait anxiety for Time 1 data and Time 2 data. The maps show that the intrinsic brain activities of the significant regions of the ventral medial prefrontal cortex (vmPFC) are correlated with the individual differences in trait anxiety at each time point. For the maps of Overlap, the red patches indicate the significant regions identified from the Time 1 data, and the green patches indicate those determined from the Time 2 data. Overlapping regions, indicating consistency over time, are colored in yellow. The scatter plots of the relationship between the mean ReHo within the significant cluster and the trait anxiety scores, adjusted for age and gender, are shown for illustrative purposes only. The color bar represents the range of *t*-value. The threshold was set at $p < 0.05$ (corrected).

In addition, a significant insula cluster showed negative correlations between the ALFF and the ReHo and trait anxiety at Time 1 but not at Time 2 (Fig. 3). Finally, we used the Dice coefficient to compute the overlap rate between the maps that were correlated with trait anxiety at both Time 1 and Time 2 after correction (Table 4). We also had checked the Dice coefficient for ROI's separately. The Dice coefficient represents the proportion of voxels that remain significant across repetitions relative to the proportion that are significant in only a subset of the results. The overlap rate of the ALFF was 0.22, and the overlap rate of ReHo was 0.20.

Intrinsic brain activity associated with change of state anxiety

To explore the relationships between changes in the ALFF and ReHo and intra-individual state anxiety variability, we analyzed the associations of the maps representing intrinsic brain activity changes in the ALFF and ReHo with intra-individual state anxiety variability, after regressing out age, gender, and the changes in trait anxiety. The resting-state data demonstrated a significant positive correlation between changes in the ALFF and ReHo in the insula and intra-individual state anxiety variability over time, after including age, gender and change of trait anxiety as regressors of no interest. Specifically, the change in the ALFF in this region predicted 18.5% of the variance in intra-individual state anxiety ($r = 0.43$, $p < 0.001$). Further, the change in ReHo in the insula predicted 20.3% of the variance in intra-individual state anxiety ($r = 0.45$, $p < 0.001$) (Fig. 4, Table 5). In addition, we found that the changes in the ALFF and ReHo in the insula were positively correlated with the changes in the somatic symptom scores (measured by the SAS) (ALFF: $r = 0.20$, $p = 0.041$; ReHo: $r = 0.20$, $p = 0.032$), but not with the affective symptom scores (measured by the SAS).

Table 3
Brain regions exhibiting significant correlations between the ReHo and trait anxiety at each time point, including age and gender as regressors of no interest.

Time point	Brain region	MNI coordinate (*x y z*)	Peak *t*-value	Volume (mm^3)
Time 1	*Positive correlation*			
	vACC/vmPFC_R	18,42,−15	4.20	4536
	Negative correlation			
	Insula_R	42,−18,21	−4.37	945
Time 2	*Positive correlation*			
	vACC/vmPFC_R	9,42,−9	3.76	2025

Note: ReHo, regional homogeneity; vACC/vmPFC = ventral anterior cingulate/medial prefrontal cortex; R = right.

Addressing potential confounds

When did the intrinsic brain activity associated with trait anxiety, these results of correlation analyses with the state anxiety score as a covariate were largely similar when the state anxiety score was not included as a covariate (see Supplementary Tables 4 and 5). However, including state anxiety as a covariate resulted in the loss of significance of the negative correlation between the ALFF in the dACC/aMCC and the trait anxiety score (the dACC/aMCC cluster failed to reach the minimum cluster threshold).

When did the intrinsic brain activity associated with change of state anxiety, the changes in trait anxiety scores were not included as covariates, these results of correlation analyses were predominantly similar, except that the correlation between the change in the ALFF of the insula and the change of state anxiety score was no longer significant (the insula cluster failed to reach the minimum cluster threshold) (see Supplementary Table 6).

Finally, the global signal regressed out or not, these results of correlation analyses were predominantly similar, except that the correlation between ALFF and trait anxiety score was no longer significant in the dACC/aMCC (see Table 2 and Supplementary Table 7). Meanwhile, the relationship between the ReHo and trait anxiety score in the precentral cortex, the changes of ReHo in inferior frontal gyrus and the changes of state anxiety were significantly correlated only the global signal not removed (see Table 3 and Supplementary Table 8), (see Table 5 and Supplementary Table 9). When mean level of motion were conducted both including and not including as a covariate, the results of the correlation analyses did not change (see Supplementary Tables 10 and 11).

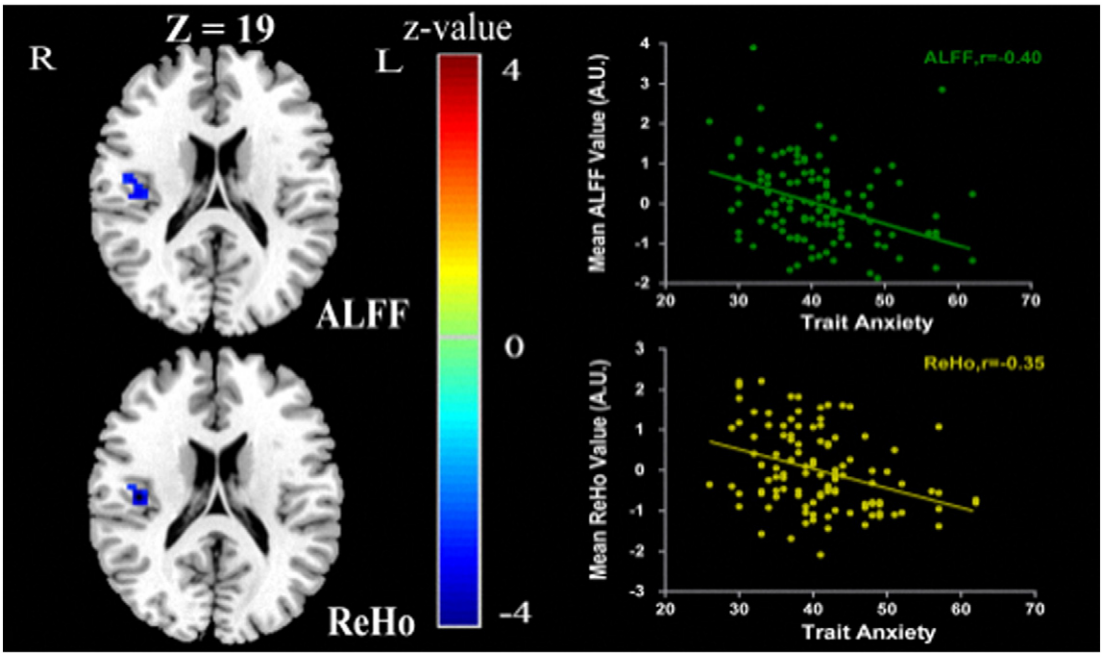

Fig. 3. The maps show that the intrinsic brain activity in the insula is correlated with individual differences in trait anxiety at Time 1. The scatter plots shown above depict the negative partial correlations between the participants' trait anxiety and the average ALFF value of the right insula region determined from the Time 1 data. The lower panel shows a scatter plot of the relationship between the trait anxiety scores and the average ReHo value of the right insula region determined from the Time 1 data. The contributions of participants' age and gender were removed, and the scatter plots are shown for illustrative purposes only. The color bar represents the range of *t*-value. The threshold was set at $p < 0.05$ (corrected).

Discussion

The aim of the current study was to investigate the association of intrinsic brain activity with the feeling of anxiety, particularly trait and state anxiety. We performed resting-state fMRI to investigate the roles of intrinsic brain activity in trait and state anxiety using a cross-sectional and test–retest design. We found that the intrinsic brain activities of the right vmPFC and dACC/aMCC were significantly associated with inter-individual trait anxiety differences. Furthermore, changes in the ALFF and ReHo in the right insula were significantly correlated with intra-individual state anxiety variability over a 9-month interval.

We used the test–retest method to identify the stable regions in which intrinsic brain activity associated with trait anxiety. To our knowledge, few studies have evaluated the test–retest reliability of intrinsic brain activity in association with the emotional state over the long-term. Using this method, it is possible to search for the stable regions for which intrinsic brain activity is associated with trait anxiety. In addition, the test–retest nature could permit the discernment between intrinsic brain activity associated with state and trait anxiety.

Table 4
Spatial overlap between the maps correlated with trait anxiety at both Time 1 and Time 2. This analysis includes age, gender, and the mean level of motion as regressors of no interest.

		Dice coefficient
Trait anxiety	ALFF	0.22
	ALFF of vmPFC	0.16
	ALFF of dACC/aMCC	0.49
	ReHo	0.26
	ReHo of vmPFC	0.29

Note: ALFF = amplitude of low-frequency fluctuations; ReHo, regional homogeneity; vACC/vmPFC = ventral anterior cingulate/medial prefrontal cortex; dACC/aMCC = dorsal anterior cingulate cortex/anterior midcingulate cortex. The maximum value of 1 indicated perfect similarity whereas the minimum value of 0 indicated no similarity.

First, we found overlapping regions associated with trait anxiety in the vmPFC and dACC/aMCC between the scans performed at the two time points, indicating that the intrinsic brain activity associated with trait anxiety was quite stable in some regions. The associations between trait anxiety and the ALFF and ReHo in the right vmPFC were consistent with previous studies describing a role of the right vmPFC in the negative affect of individuals (Kross et al., 2009; Lemogne et al., 2012; Zald et al., 2002) and this associations were also observed in anxiety disorder (Shang et al., 2014). For example, Evans found the therapeutic effects in generalized social anxiety disorder (gSAD) may be effected on the vmPFC (Evans et al., 2009) and Etkin identified blunted vmPFC activity as a common finding in studies of posttraumatic stress disorder (PTSD) (Etkin and Wager, 2007). Generally, the vmPFC acted as a hub that integrated external and internal stimuli to determine the affective value of the stimuli and to influence behavioral reactions (Bickart et al., 2012; Dunn et al., 2006; Lindquist et al., 2012), and it was largely associated with affective regulation (e.g., cognitive reappraisal) (Motzkin et al., 2015; Ochsner and Gross, 2005; Ochsner et al., 2012). Further, meta-analysis had shown that regulation of negative affect engages the vmPFC (Diekhof et al., 2011).

Our analyses also revealed an association between trait anxiety and ReHo in the dACC/aMCC. A meta-analysis of studies examining the processing of negative affect had implicated the dACC/aMCC in negative affect (Mechias et al., 2010), and two studies had found that dACC responses were predictive of the response to treatment in generalized anxiety disorder (Nitschke et al., 2009; Whalen et al., 2008). Convergent evidence obtained using functional neuroimaging indicates that the dACC/aMCC was involved in the brain circuitry underlying the detection and allocation of attentional resources to threat stimuli (Blair et al., 2012; Cavanagh and Shackman, 2014; Etkin et al., 2011; Kohn et al., 2014; Shackman et al., 2011). In addition, studies of anxiety disorder had reported reduced dACC/aMCC activity during top-down attentional control (Blair et al., 2012; Klumpp et al., 2012). In contrast, functional neuroimaging about the individuals with higher levels of anxiety shown enhanced dACC/aMCC signals when performing emotional cognitive control tasks (Cavanagh and Shackman, 2014; Moser et al.,

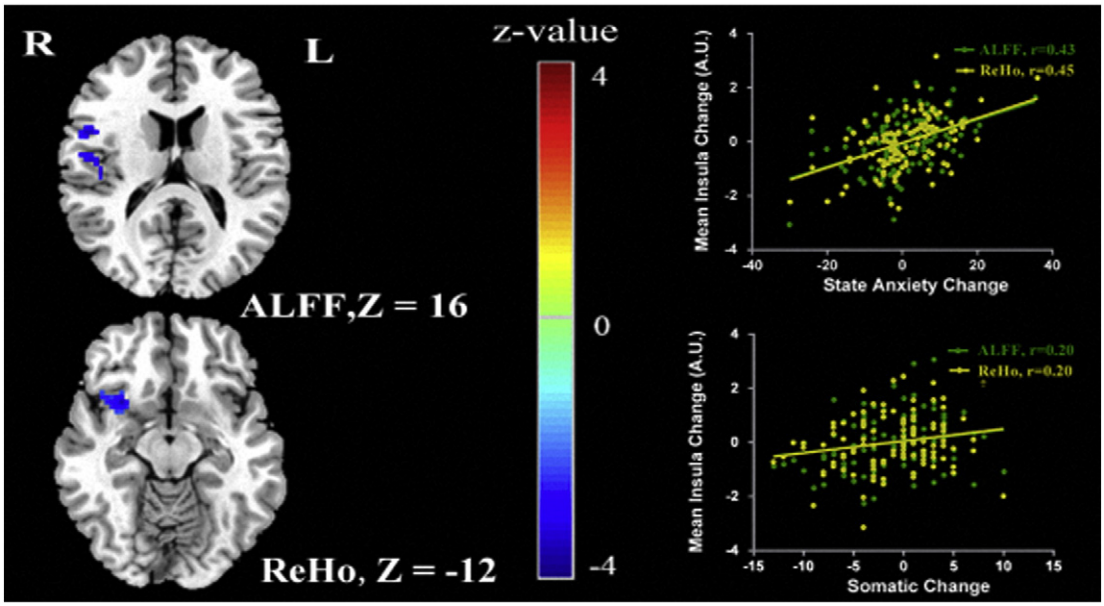

Fig. 4. The effects of changes in intrinsic brain activity in the insula on changes in state anxiety and somatic symptoms. The maps shown above indicate that the average change in the ALFF value in the right insula was significantly correlated with the changes in state anxiety and somatic symptoms (measured by the self-rating anxiety scale (SAS)). The lower map shows that the change in the average ReHo value of the right insula was significantly correlated with the changes in state anxiety and somatic symptoms. The scatterplots shown on the right illustrate the relationships between the changes in the average ALFF and ReHo values in the right insula with the changes in state anxiety and somatic symptoms. Analysis was adjusted for age and gender, and the scatterplots are shown for illustrative purposes only. The color bar represents the range of *t*-value. The threshold was set at $p < 0.05$ (corrected).

2013; Shackman et al., 2011). Individuals with higher levels of anxiety may have lower intrinsic brain activity of dACC/aMCC at rest, when conducted the emotional cognitive control tasks, healthy subjects managed their emotions through enhanced dACC/aMCC signals, while the anxiety disorder could not effectively activate the dACC/aMCC. Thus, the stable intrinsic brain activity observed in association with trait anxiety in the vmPFC and dACC/aMCC was agreement with the findings of previous studies.

Importantly, the finding of the association of the changes in the ALFF and ReHo in the right insula with intra-individual state anxiety variability and, in particular, variability in the somatic symptoms of anxiety, was of interest considering that the insula had important roles in emotional and homeostatic processes, including the processing of subjective emotional experiences (Critchley et al., 2004; Ernst et al., 2013; Paulus and Stein, 2006; Singer et al., 2009), anticipation of emotionally negative stimuli (Lutz et al., 2013; Simmons et al., 2011), and attention to and awareness of internal body states (Craig, 2003, 2011; Khalsa et al., 2009). To some extent, a change in state anxiety reflected an emotional change caused by the awareness of feelings in the body. An earlier study performed by Craig (2002) had proposed that the insula may be an essential neural region responsible for the awareness of feelings in the body, as well as the engendering of subjective emotions from body signals (Craig, 2002, 2009, 2011). Paulus and Stein (Paulus and Stein, 2006) proposed a general hypothesis that anxious individuals were prone to augmented the difference between the observed and expected body state. In addition, Critchley and colleagues had performed a heartbeat detection task and found that interoceptive awareness was accompanied by increased neural activity in the insula and that this increase was correlated with the anxiety score (Critchley et al., 2004). A similar result had been described by Terasawa et al., who had reported that the insula was activated when people evaluated their own emotional and body states and that this activation was positively correlated with individual levels of anxiety (Terasawa et al., 2013a, 2013b). All of these studies had demonstrated strong links between the insula, awareness of the body state, and the experience of anxiety.

Notably, although our results indicated the presence of strong links between the ALFF and ReHo in the vmPFC and dACC/aMCC and trait anxiety, as well as those in the insula and change of state anxiety, we could not prove their causal relationships in this study. There are many unknown related or confounding factors that could influenced these findings. However, we have demonstrated the link between intrinsic brain activity and trait anxiety in cross-sectional and test–retest analyses, and our results are largely consistent with the studies findings about the individuals with high anxiety and anxiety disorder (Baur, 2012; Shang et al., 2014; Blackmon et al., 2011; Sladky et al., 2013; Talati et al., 2013; Zhang et al., 2015). Therefore, despite the short time interval between the two imaging assessments, the unclear relationship between the ALFF and ReHo and the existence of other approaches used for measuring the association of intrinsic brain activity with anxiety, we have provided a reliable and valid model of the effects of anxiety on the brain.

In conclusion, we used a test–retest study design to distinguish between the intrinsic brain activity associated with state and trait anxiety. The present results explicitly indicate that the intrinsic brain activities of the vmPFC and dACC/aMCC might be of strong importance for trait anxiety-related processes, whereas a change in intrinsic brain activity in the insula might be predictive of mental state anxiety changes in the healthy population. Finally, our results support the view that state and trait anxiety are specifically subserved by the intrinsic brain activities of different regions. Further studies must be performed to establish the causal relationships between intrinsic brain activity and

Table 5
Brain regions for which the change in spontaneous neuronal activity was significantly correlated with a change in state anxiety, including age and gender as regressors of no interest.

	Brain region	MNI coordinate (*x y z*)	Peak *t*-value	Volume (mm^3)
ALFF	Insula_R	39,12,9	3.49	891
Reho	Insula_R	30,12,-15	4.59	1836
	Insula_R	51,6,12	3.56	1836

Note: ALFF = amplitude of low-frequency fluctuations; ReHo, regional homogeneity; R = right.

state/trait anxiety, as well as the different influences of trait and state anxiety on individuals' mental and physical well-being.

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Appendix A. Supplementary data

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