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Aberrant functional connectivity of resting state networks associated with trait anxiety

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ABSTRACT

Trait anxiety, a personality dimension, has been characterized by functional consequences such as increased distractibility, attentional bias in favor of threat-related information and hyper-responsive amygdala. However, literature on the association between resting state brain functional connectivity, as studied using resting state functional magnetic resonance imaging (rs-fMRI), and reported anxiety levels in the sub-clinical population is limited. In the present study, we employed rs-fMRI to investigate the possible alterations in the functional integrity of Resting State Networks (RSNs) associated with trait anxiety of the healthy subjects (15 high anxious and 14 low anxious). The rs-fMRI data was analyzed using independent component analysis and a dual regression approach that was applied on 12 RSNs that were identified using FSL. High anxious subjects showed significantly reduced functional connectivity in regions of the default mode network (posterior cingulate gyrus, middle and superior temporal gyrus, planum polare, supramarginal gyrus, temporal pole, angular gyrus and lateral occipital gyrus) which has been suggested to be involved in episodic memory, theory of mind, self-evaluation, and introspection, and perceptual systems including medial visual network, auditory network and another network involving temporal, parieto-occipital and frontal regions. Reduction in resting state connectivity in regions of the perceptual networks might underlie the perceptual, attentional and working memory deficits associated with trait anxiety. To our knowledge, this is the first study to relate trait anxiety to resting state connectivity using independent component analysis.

1. Introduction

Anxiety, a personality dimension in healthy humans, is often characterized by harm avoidance behavior such as worrying, irritability, difficulty to relax and predisposition to interpret ambiguous situations as threatening (Spielberger, 1983; Grachev and Apkarian, 2000; Eysenck et al., 2007). Anxiety has been found to be associated with many functional consequences such as increased distractibility, attentional bias in favor of threat-related information and hyper-responsive amygdala even for unattended threat-related stimuli (Eysenck et al., 2007; Bishop et al., 2004; Bishop, 2008; Berggren and Derakshan, 2012). Similarly, diffusion tensor tractography studies have shown microstructural changes to be associated with anxiety related personality traits (Westlye et al., 2011; Montag et al., 2012; Modi et al., 2013). The high anxiety trait is considered to be a vulnerability factor to develop both depression and anxiety disorders (Pezawas et al., 2005; Sandi and Richter-Levin, 2009; Cremers et al., 2010). Therefore, in order to identify individuals that are at risk for the development of clinical anxiety disorders and depression, identifying hallmarks of anxiety becomes important so that timely preventive interventions (such as exercise training, stress management training, cognitive and behavioral interventions to prevent anxiety and improve self esteem) may be given to them (Roe-Sepowitz et al., 2005). Investigating the alterations in various resting state brain networks associated with the anxiety levels (assessed by measures such as the Spielberger's State-Trait Anxiety Inventory (STAI) (Spielberger, 1983)) of the subjects may provide further insight and understanding of the neurobiology of anxiety.

The discovery of spontaneous and continuous low-frequency fluctuations (*0.01–0.1ce:bold > ce:hsp sp="0.25"/ > Hz) in the baseline blood oxygen level dependent (BOLD) signal that are synchronized across various spatially distributed functional connectivity networks (resting state networks (RSNs)) (Biswal et al., 1995) has opened a new avenue in neuroscience research. Each RSN is characterized by its own specific temporal and spatial signal coherence (Fox and Raichle, 2007). Resting state fMRI has become a valuable tool for the investigation of these RSNs, allowing for a task-free analysis of functional connectivity without a priori

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assumptions about neural activation (Biswal et al., 1995; Fox and Raichle, 2007). The major RSNs that have been shown to be coherent in their spontaneous activity include visual (Cordes et al., 2000; Lowe et al., 1998; Storti et al., 2013), auditory (Cordes et al., 2000; Storti et al., 2013), hippocampus or episodic memory (Rombouts et al., 2003; Vincent et al., 2006), language (Cordes et al., 2000; Hampson et al., 2002), dorsal attention (Laufs et al., 2003; Fox et al., 2006) and ventral attention systems (Fox et al., 2005), executive control network (Storti et al., 2013) and task-negative/default mode networks (DMN) (Fox et al., 2005; Greicius et al., 2003; Fransson, 2005; Storti et al., 2013). RSNs represent functionally-critical neuronal networks that reflect properties of functional brain organization (Filippini et al., 2012). Studying these RSNs has a huge potential to provide insight into the functional topography of the healthy and the diseased brain.

Inter-subject variability in these correlation patterns has been shown to be related to the inter-subject variability in behavior, activation patterns and task performance (Seeley et al., 2007; Hampson et al., 2006; He et al., 2007). Alterations in the correlation structure of resting state activity have been reported for a number of pathological states, including attention deficit hyperactivity disorder (Castellanos et al., 2008), Alzheimer's disease (Greicius et al., 2004), obsessive compulsive disorder (Harrison et al., 2009), depression (Anand et al., 2005), bipolar disorder (Wang et al., 2009), social anxiety disorder (Hahn et al., 2011), post traumatic stress disorder (Rabinak et al., 2011) and schizophrenia (Salvador et al., 2010).

The rs-fMRI studies in the non-clinical population having trait anxiety as a personality dimension are very few. A study by Dennis et al. (2011) studied the relation between naturally occurring mood and resting state connectivity in a healthy population. In their study, with increased anxiety levels the left insular cortex showed increased connectivity to the DMN. In another study on psychiatrically healthy subjects it was observed that the typical positive correlation between amygdala—ventral medial Prefrontal Cortex functional connectivity at rest is compromised in high anxious subjects (Kim et al., 2011). Similarly, resting-state functional connectivity between the anterior insula and the basolateral amygdala was shown to be strongly related to state anxiety (Baur et al., 2013). In another study, the prescan anxiety ratings correlated with intrinsic functional connectivity of the dorsal anterior cingulate cortex and dorsolateral prefrontal cortex nodes of the salience network (Seeley et al., 2007). However, these earlier studies had either restricted their functional connectivity analysis to limited brain regions of interest (Seeley et al., 2007; Kim et al., 2011; Baur et al., 2013) or did not directly study the effects of trait anxiety on functional connectivity (Seeley et al., 2007; Dennis et al., 2011). The seed based analysis of resting state fMRI data is also limited by the fact it relies on the time-course at the seed-voxel location being a ‘good’ representative for the set of correlated voxels under rest (Beckmann et al., 2005). Therefore, the seed-voxel-based approach is restricted to cases where seed areas can be inferred accurately and robustly from activation studies. Furthermore, the choice of the seed voxel is rather arbitrary (as, indeed, is the exact location of a peak Z-stat) and can be biased by different types of fMRI noise (Beckmann et al., 2005). An important advantage of independent component analyses over hypothesis-based region of interest techniques is the ability to identify various types of signal fluctuations by virtue of their spatial and/or temporal characteristics without the need to specify an explicit temporal model. It further becomes essential in cases where the effects of interest are not very well understood and cannot be predicted accurately (Beckmann et al., 2005). The present study was therefore aimed to study the functional brain connectivity changes associated with individual self reported trait anxiety levels in all the resting state networks as identified using independent component analysis approach within the limits of our data.

2. Methods

2.1. Subjects

Twenty nine right-handed (based on Edinburgh Handedness Inventory (Oldfield 1971)), healthy and educated (graduates/post graduates) participants (male – 16, female – 13, mean age – 24.10 years, SD – 2.79 years) drawn from the authors' home institute were screened for current or past medical and psychiatric illness using the Hindi version of the Diagnostic Interview for Genetic Studies (version 2) (Deshpande et al., 1998). None of the subjects recruited for the study had any clinical evidence of stroke, head injury, cardiovascular diseases, history of alcohol or drug dependence, hypertension, neurological, psychiatric disorder or sensory-cognitive impairment, nor did they have any cortical infarctions on the T2-weighted MR images. None of the subject was on psychotropic medications. In case of females care was taken that while undergoing imaging session they were not in the premenstrual or menstrual period to avoid the hormonal changes that can cause physical and emotional effects that may contribute to anxiety (Sigmon and Schartel, 2008). The study complied with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and was also in accordance with the guidelines set by the ethical committee of the Institute. Further, informed consent was taken from all subjects to participate in the study ones the procedure was thoroughly explained to them. After the rs-fMRI session, participants' state anxiety (as felt inside the scanner) and trait anxiety (disposition to anxiety) levels were assessed using STAI self-report questionnaires for adults (Spielberger, 1983). Following some of the earlier studies, subjects were median split into two groups based on their trait anxiety scores (Grachev and Apkarian, 2000; Modi et al., 2014), such that the subjects with their trait anxiety scores above and below the median constituted the high anxiety and low anxiety groups respectively. Participants were also asked to complete the Beck Depression Inventory (BDI) (Beck et al., 1996).

2.2. Image acquisition

The study was carried out using 3 T whole body MR system (Magnetom Skyra, Siemens, Germany) with a circularly polarized 20 channel matrix head and neck coil and 45 mT/m actively shielded gradient system. Subjects lay in the supine position with their heads supported and immobilized within the head coil using foam-pads (vendor provided), to minimize head movement and gradient noise. For anatomical reference, a T1-weighted 3D gradient echo sequence (MPRAGE: Magnetization Prepared Rapid Acquisition Gradient Echo, 160 sagittal slices, slice thickness = 1 mm, field of view = 256 mm, TR = 1900 ms, TE = 2.07 ms) image data set was acquired. Functional brain volumes were acquired using echo-planar T2*-weighted imaging sequence. Each volume consisted of 30 interleaved 5-mm thick slices without interslice gap (TE = 30 ms, TR = 2000 ms, FOV = 240 mm, flip angle = 90°, and voxel size = $3.75 \times 3.75 \times 5\ mm^3$). Total scanning time was 410 s (205 brain volumes), during which the subjects were asked to keep their eyes closed without thinking of anything in particular and not falling asleep.

2.3. Data analysis

The resting state functional data were first pre-processed using the FMRI Expert Analysis Tool (FEAT), which is a part of FSL