A common brain network among state, trait, and pathological anxiety from whole-brain functional connectivity

Yu Takagi a,b,*, Yuki Sakai a,c, Yoshinari Abe c, Seiji Nishida c, Ben J. Harrison d, Ignacio Martinez-Zalacaín e, Carles Soriano-Mas f,g, Jin Narumoto c, Saori C. Tanaka a,*

a ATR Brain Information Communication Research Laboratory Group, Kyoto, Japan
b Graduate School of Information Science, Nara Institute of Science and Technology, Nara, Japan
c Department of Psychiatry, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan
d Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne and Melbourne Health, Melbourne, Australia
e Department of Psychiatry, Bellvitge Biomedical Research Institute-IDIBELL, Barcelona, Spain
f Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Spain
g Department of Psychobiology and Methodology of Health Sciences, Universitat Autònoma de Barcelona, Barcelona, Spain

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ABSTRACT

Anxiety is one of the most common mental states of humans. Although it drives us to avoid frightening situations and to achieve our goals, it may also impose significant suffering and burden if it becomes extreme. Because we experience anxiety in a variety of forms, previous studies investigated neural substrates of anxiety in a variety of ways. These studies revealed that individuals with high state, trait, or pathological anxiety showed altered neural substrates. However, no studies have directly investigated whether the different dimensions of anxiety share a common neural substrate, despite its theoretical and practical importance. Here, we investigated a brain network of anxiety shared by different dimensions of anxiety in a unified analytical framework using functional magnetic resonance imaging (fMRI). We analyzed different datasets in a single scale, which was defined by an anxiety-related brain network derived from whole brain. We first conducted the anxiety provocation task with healthy participants who tended to feel anxiety related to obsessive-compulsive disorder (OCD) in their daily life. We found a common state anxiety brain network across participants (1585 trials obtained from 10 participants). Then, using the resting-state fMRI in combination with the participants’ behavioral trait anxiety scale scores (879 participants from the Human Connectome Project), we demonstrated that trait anxiety shared the same brain network as state anxiety. Furthermore, the brain network between common to state and trait anxiety could detect patients with OCD, which is characterized by pathological anxiety-driven behaviors (174 participants from multisite datasets). Our findings provide direct evidence that different dimensions of anxiety have a substantial biological inter-relationship. Our results also provide a biologically defined dimension of anxiety, which may promote further investigation of various human characteristics, including psychiatric disorders, from the perspective of anxiety.

Introduction

Anxiety is a future-oriented mental state activated by distant and potential threats rather than specific and predictable ones (Calhoon and Tye, 2015). On the one hand, anxiety drives us to avoid frightening situations and to achieve our goals. On the other hand, excessive anxiety may cause distress and impairment in daily life. Although anxiety is a common mental state in humans, we experience anxiety in a variety of forms. For example, public speaking or leaving one’s home can induce anxiety related to a fear of negative evaluation by others and risk of theft, respectively. Such anxieties may drive us to do something to overcome our anxiety, such as practicing a speech or repeatedly checking that the house door is locked.

One conventional way to study anxiety is to investigate the state associated with the feeling of anxiety, namely, state anxiety. Other studies focus on the frequency of anxiousness, namely, trait anxiety, which is measured using self-report questionnaires. Another major research field concerns the anxiety of patients with psychiatric...
disorder. This type of anxiety includes social anxiety disorder, obsessive-compulsive disorder (OCD), and generalized anxiety disorder. Such “pathological anxiety”, which is defined by clinically significant levels of anxiety (i.e., excessive, uncontrollable anxiety), incurs tremendous socioeconomic costs (Greenberg et al., 1999) and roughly 30% of people experience an anxiety-related disorder at some point in their lifetime (Kessler et al., 2005).

In the neuroscience field, a large number of studies have investigated the neural substrates of anxiety using functional magnetic resonance imaging (fMRI). For each dimension of anxiety, these studies have used different experimental approaches to investigate neural substrates. To investigate the brain activity underlying state anxiety, researchers have experimentally induced participant’s anxiety inside of the MRI scanner (Mataix-Cols et al., 2003; Satpute et al., 2012). Other studies focused on the relationship between trait anxiety and brain activity (Baur et al., 2013; Kim et al., 2011; Modi et al., 2015; Tian et al., 2016; Yin et al., 2016). These latter studies have recently focused on changes in brain activity, measured by resting-state fMRI (rs-fMRI). Finally, other studies have focused on the difference between populations with pathological anxiety and healthy controls. Some studies have found altered brain activation during anxiety provocation tasks, and others have found altered brain networks during rest state or anxiety provocation tasks (Banca et al., 2015; Beucke et al., 2013; Cha et al., 2014; Etkin et al., 2010; Giménez et al., 2012; Hahn et al., 2011; Harrison et al., 2009; Liu et al., 2015; Sakai et al., 2011; Wang et al., 2016).

Previous findings have suggested an interaction among state, trait, and pathological anxiety (e.g., Mathews, 1990; Williams et al., 1996). If there is a common biological substrate, it has the potential to be used for risk assessment and early detection of pathological anxiety, which would enable its evaluation for treatment. From a theoretical perspective, it would also be helpful to understand the dynamics of the development of pathological anxiety. In addition, given that the hypothesis of a psychiatric disorder spectrum is gaining attention (Adam, 2013), such a biologically defined index would provide an objective, reliable biological dimension of anxiety for the spectrum, which may be valuable for understanding various human characteristics, including psychiatric disorders. However, no studies have directly investigated whether there is a common biological substrate among state, trait, and pathological anxiety.

To determine whether there is a common biological substrate among state, trait, and pathological anxiety, we adopted a single neuronal index defined by anxiety-related functional connectivity (FC), a measure of temporally correlated fluctuations in blood oxygen level-dependent (BOLD) signal among different regions. FC has been successfully used to elucidate neural mechanisms of various individual characteristics (Cole et al., 2012; Finn et al., 2015; Liem et al., 2016; Rosenberg et al., 2016). Indeed, FCs have been correlated with individual differences in state or trait anxiety (Baur et al., 2013; Modi et al., 2015; Satpute et al., 2012; Tian et al., 2016) and are different between healthy people and individuals with pathological anxiety (Banca et al., 2015; Beucke et al., 2013; Cha et al., 2014; Etkin et al., 2010; Giménez et al., 2012; Hahn et al., 2011; Harrison et al., 2009; Liao et al., 2010; Liu et al., 2015; Sakai et al., 2011; Wang et al., 2016).

Here, in a data-driven manner, we directly tested the hypothesis that there is a common brain network among state, trait, and pathological anxiety. We first investigated whether state and trait anxiety shared a common brain network in healthy people. Then, to investigate how state and trait anxiety are involved in pathological anxiety, we tested which sets of FCs were generalized to patients with OCD, a disorder characterized by pathological anxiety-driven behavior, among the brain networks related to state and/or trait anxiety.

Materials and methods

Anxiety provocation task

Participant recruitment

To effectively extract anxiety-related brain networks, we recruited 10 healthy participants (9 men, ages 20–24 years, mean age 22.2 years) who tended to be anxious in their daily life from 432 volunteers who completed a questionnaire prior to the fMRI experiments. Specifically, we recruited participants who had a score of greater than or equal to 80 on the Padua Inventory (BURNS, 1996) or 13 on the Maudsley Obsessional Compulsive Inventory (Hodson and Rachman, 1977). All participants were primarily evaluated using the Structured Clinical Interview for DSM-IV Axis I Disorders-Non-Patient Edition (SCID-NP) (First et al., 2002). No participant had a current DSM-IV Axis I diagnosis of any significant psychiatric disorder. Participant consent was obtained in accordance with a protocol reviewed and approved by the Ethics Committee of the Advanced Telecommunications Research Institute International. At the time of the experiments, the mean ± standard deviation of the Padua Inventory and Maudsley Obsessional Compulsive Inventory were 71.5 ± 23.6 and 13.2 ± 2.3, respectively.

Stimuli selection

Previous studies demonstrated that neural activity related to anxiety can be extracted using fMRI by presenting two sets of stimuli to participants (Blair et al., 2008; Giménez et al., 2012; Lorberbaum et al., 2004; Mataix-Cols et al., 2003; Rotge et al., 2008; Tillfors et al., 2001) One set of stimuli is for provoking anxiety (anxiety stimuli), for example, the image of a key hole, which may induce anxiety about theft. The other set of stimuli is a relatively neutral stimulus, for example, the image of a nature scene. Here, we conducted a similar task, by iteratively presenting two sets of stimuli to the participants while controlling the semantics (categories of the objects) and basic features (color and luminance) of the two sets of stimuli (Fig. 1a; see Supplementary Notes). Before the fMRI experiments, all participants rated their subjective anxiety in response to approximately 200 images in a Likert scale between 1 and 9 (rate 1 for lowest anxiety and 9 highest anxiety among all images). Then, for each participant, anxiety images, those with the top 50 rating scales, and neutral images, those with the bottom 50 rating scales, were selected as stimuli for the fMRI.

Experimental paradigm

Seven participants attended 6 MRI scanner sessions and 3 participants attended 12 sessions. Each session consisted of 4 blocks, an anxiety block or a neutral block, and each block consisted of 6 trials. The block type order was randomized for all participants. In the first trial of each block, a cue was presented on the screen for 1 s (“anxiety” in the anxiety block, “neutral” in the neutral block). Twenty stimuli were then presented at a rate of 200 ms per stimulus, to minimize the effects of the basic feature and semantic content of a particular stimulus, and was followed by a 14-s imagination period, during which participants were instructed to be anxious if they were in the anxiety block or to relax if they were in the neutral block. After the imagination period, participants were asked to rate their level of anxiety on a 4-point Likert scale (rate 1 for “no anxiety” and 4 for “very anxious”). A fixation cross was superimposed on each stimulus, and participants were instructed to maintain fixation on this cross throughout the scanning session. For each session, in two randomly selected trials, participants were instructed to push the button in response to the change in fixation color on the display to guarantee that participants maintained fixation. These trials were excluded from the subsequent analysis.

fMRI procedure

A 3-T Siemens Trio scanner (Erlangen, Germany) with a 12-channel head coil was used to perform T2*-weighted echo planar imaging (EPI). We acquired 275 scans for each session with a gradient echo EPI
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