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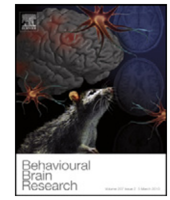

Research report

Individual differences in trait anxiety are associated with white matter tract integrity in fornix and uncinate fasciculus: Preliminary evidence from a DTI based tractography study

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HIGHLIGHTS

- ▶ We assessed relation between trait anxiety and white matter microstructure of brain.
- ▶ Positive correlation obtained with mean FA in fornix and left uncinate fasciculus.
- ▶ Study provides interesting insights into the biological foundation of trait anxiety.

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ABSTRACT

Trait anxiety, a personality dimension that measures an individual's higher disposition to anxiety, has been found to be associated with many functional consequences viz. increased distractibility, attentional bias in favor of threat-related information etc. Similarly, volumetric studies have reported morphological changes viz. a decrease in the volume of left uncinate fasciculus (fiber connecting anterior temporal areas including the amygdala with prefrontal-/orbitofrontal cortices) and an increase in the volume of the left amygdala and right hippocampus, to be associated with trait anxiety. The functional and morphological changes associated with trait anxiety might also be associated with the changes in the integrity of WM tracts in relation with the trait anxiety levels of the subjects. Therefore, in the present diffusion tensor tractography (DTT) study, we investigated the possible relationship between the diffusion tensor imaging (DTI) derived indices of a wide array of fiber tracts and the trait anxiety scores in our subject group. A positive correlation between trait anxiety scores and the mean fractional anisotropy (FA) value was obtained in fornix and left uncinate fasciculus. The study provides first account of a positive relation between sub-clinical anxiety levels of subjects and the FA of fornix thereby providing interesting insights into the biological foundation of sub-clinical anxiety.

1. Introduction

Anxiety is an aversive emotional and motivational state that results in many behavioral and cognitive consequences [1]. These effects are seen not only in clinical anxiety but also within the normal population as a personality dimension which is generally assessed by measures of trait anxiety such as the Spielberger's State-Trait Anxiety Inventory (STAI) [1,2]. Anxiety impairs the inhibition function and, as a result, increased distractibility is found in anxious individuals when compared with non-anxious individuals [1,3]. People high on trait anxiety also have an attentional bias in favor of threat-related information and are easily distracted by it. Amygdala being the key structure in the processing of threat-related stimuli is proposed to be involved in the rapid preattentive detection of threat-related stimuli as well as processing of emotional stimuli [4]. In their functional magnetic resonance imaging (fMRI) study, Bishop et al. [4] showed that regardless of attentional focus, high-anxious participants showed an increased amygdala response to fearful versus neutral faces. Moreover, in the absence of threat-related stimuli, trait anxiety is linked to impoverished recruitment of prefrontal attentional control mechanisms to inhibit distractor processing [5].

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Previous structural MR imaging studies have demonstrated alterations in the morphology of attention and emotion processing networks of the brain in individuals with high anxiety-related personality traits. Yamasue et al. [6], using voxel based morphometry (VBM) showed that higher scores on Harm Avoidance (HA) were associated with smaller regional gray matter volume in the right hippocampus in both males and females. However, females also showed a negative correlation between higher anxiety-related personality traits and regional brain volume in the left anterior prefrontal cortex. Similarly, using surface analysis Pujol et al. [7] showed that a large right anterior cingulate is related to a temperamental disposition to fear and anticipatory worry. Another volumetric study reported a negative correlation between the volume of left uncinate fasciculus (UF), fiber connecting anterior temporal areas including the amygdala with prefrontal-/orbitofrontal cortices), and trait anxiety [8]. However, in the same study a positive correlation was obtained between the volume of the left amygdale and right hippocampus and trait anxiety [8].

The above functional and morphological changes associated with trait anxiety in healthy population warrants the importance of analyzing the integrity of white matter (WM) tracts in relation with the trait anxiety levels of the subjects. Examination of WM tracts in a wide array of cerebral circuits may elucidate the abnormal mechanisms that underlie the functional deficits associated with anxiety. Diffusion tensor imaging (DTI) is a MRI technique that measures the strength and direction of water diffusivity (i.e., anisotropy) in brain tissue to estimate the axonal organization of the brain. Water moves more easily along the axonal bundles rather than perpendicular to these bundles because there are fewer obstacles to prevent movement along the fibers [9]. A popular scale that measures the degree of anisotropy is fractional anisotropy (FA), which is thought to be modulated by the degree of myelination, axonal membrane thickness and diameter, and/or amount of parallel organization of axons, is interpreted as an indicator of WM pathway strength, or integrity [10].

The application of DTI in anxiety disorders is generally confined to DSM IV anxiety disorders and has been very limited in panic disorder, social anxiety disorder, and generalized anxiety disorder, and relatively more extensive in post-traumatic stress disorder and obsessive-compulsive disorder [11]. DTI in non-clinical population having trait anxiety as a personality dimension are again very few. Kim and Whalen [10] found that individual differences in the structural integrity of amygdala–prefrontal pathway were inversely correlated with trait anxiety levels of the subjects (i.e., higher pathway strength predicted lower anxiety). Similarly, Baur et al. [12] found a negative correlation between FA and trait anxiety in the same area as reported by Kim and Whalen [10] when examining a pooled sample consisting of both patients with social anxiety disorder and healthy controls. However in the same study, no such correlation between FA and trait anxiety was obtained in healthy subjects. Moreover, focusing on the UF in an independent healthy sample, Baur et al. [8] identified a trend towards negative correlation between left UF FA and trait anxiety. Westlye et al. [13] found that increased harm avoidance as assessed by Temperament and Character Inventory [14] was associated with decreased FA and increased mean and radial diffusivity in major WM tracts, including corticolimbic pathways, the anterior thalamic radiations and in large association fibers (inferior fronto occipital and right superior longitudinal fasciculus). However, a negative correlation between negative personality traits and FA of the tracts under investigation is not a norm. A recent study by Montag et al. [15] showed that especially in men the FA values of several WM tracts in the temporal lobe of the left hemisphere positively correlate substantially with individual differences in negative emotionality. Similarly, Blood et al. [16] demonstrated that FA values in the ventral tegmental area of depressed patients were higher as compared to healthy controls. Another DTI study on patients with obsessive compulsive disorder (OCD) found an association between increased FA in the anterior limb of the internal capsule and depression and anxiety scores of the patients [17].

Therefore, given a limited literature available on the relationship between trait anxiety in healthy population and the microstructure of brain parenchyma and inconsistencies of these findings, we performed the diffusion tensor tractography (DTT) of a wide array of fiber tracts to analyze the association between fiber tract integrity and trait anxiety levels in these subjects, if any. However, considering the growing body of literature pointing towards the hyper-responsivity of amygdale in individuals high in trait anxiety and a negative correlation between anxiety related personality traits and FA and volume of the left UF, one of our objectives was also to replicate the findings observed in UF in relation with trait anxiety.

2. Materials and methods

2.1. Subjects

27 right-handed healthy participants (male – 11, female – 16, mean age – 23.48 years, SD – 3.24 years) were screened for current or past illness using the Hindi version of the diagnostic interview for genetic studies [18]. None of the subjects chosen for the study had any clinical evidence of stroke, head injury, cardiovascular diseases, or history of alcohol or drug dependence, hypertension, neurological, psychiatric disorder or sensori-cognitive impairment, nor did they have any cortical infarctions on the T2-weighted MR images. The procedure followed in the current study was in accordance with the Declaration of Helsinki and also in accordance with the guidelines set by the ethical committee of the Institute. Further, all subjects gave their consent to participate in the study and the study procedure was thoroughly explained to them. Participants' trait anxiety levels were assessed using STAI self-report questionnaires for adults [2]. Participants also completed the Beck Depression Inventory (BDI) [19].

2.2. Diffusion weighted image acquisition

All images were acquired in the axial plane using 3-T MRI scanner (Megnetom, Skyra, Siemens) with a 24 channel head and neck coil and 25 mT/m actively shielded gradient system. The head was supported and immobilized within the head coil to minimize head movement and gradient noise. The conventional MR imaging was done prior to DTI to rule out any structural abnormality using routine T2-weighted turbo spin-echo sequence. DTI data were acquired using a single-shot echo-planar dual SE sequence in 30 directions with ramp sampling. Diffusion-weighted acquisition parameters were: b-factor = 0 and 1000 s/mm^2, slice thickness = 3 mm with no interslice space, number of slices = 45, FOV = 230 mm × 230 mm, matrix size = 128 × 128, spatial resolution = 1.797 mm × 1.797 mm × 3 mm, flip angle 90°, TR = 8800 ms, TE = 95 ms and NEX = 2.

2.3. DTT and data quantitation

An in-house-developed JAVA-based software was used to generate and quantify major WM fiber tracts such as, corpus callosum (CC), superior longitudinal fasciculus (SLF), cortico-spinal tracts (CST), cingulum (CNG), superior (SCP), middle (MCP) and inferior (ICP) cerebeller peduncle, fornix, arcuate fasciculus (AF), uncinate fasciculus (UF), thalamic radiations [anterior (ATR), superior (STR), and posterior (PTR) thalamic radiation], inferior fronto-occipital fasciculus (IFO). Details of the generation of the white matter fiber tracts are described in detail elsewhere [20]. In brief, diffusion tensor imaging (DTI)-derived fractional anisotropy (FA) and the principal eigenvector field were used to create the stable fiber mass (SFM) consisting of a collection of linear voxel structures which were grouped together by color-coding them into seven natural classes to provide principal eigenvector field segmentation (PEVFS) signature segments. These segments greatly facilitate the selection of regions of interest (ROIs) for fiber tractography using just a single mouse click. Different fiber bundles are easily reconstructed by the segmented components using fiber assignment by continuous tracking (FACT) algorithm [9]. The method is better than the classical Region of Interest (ROI) approach where investigators draw polygons using a mouse over one of the many potential 2D MR images. In SFM mapping, however, mouse click once on any pixel of the colored segment of interest is required. The PEVFS method is user independent and has been found to be robust, automatic, and efficient and compares favorably with the classical ROI methods for diffusion tensor tractography (DTT). DTI measures were calculated for the entire fiber and reported. FA threshold of 0.15 was used for fiber tracking.