Metabolic and microstructural alterations associated with individual differences in trait anxiety: Preliminary evidence from Magnetic Resonance Spectroscopy and DTI based tractography study

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Target audience – The researchers working in the field of anxiety related disorders.

Purpose – 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[1,2]. The high anxiety trait is considered to be a vulnerability factor to develop both depression and anxiety disorders[3]. 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 to fascilitate timely preventive interventions. In this study we tried to identify potential MR based markers of trait anxiety using invivo ^{1}H MRS and Diffusion Tensor Tractography (DTT)). Alterations in neurometabolites in anterior cingulate cortex (ACC) and strength of major white matter fiber tracts in relation with the trait anxiety levels (assessed by Spielberger's State-Trait Anxiety Inventory (STAI)[1]) of the subjects were assessed.

Methods –Right-handed healthy educated participants drawn from the institute (For MRS: male – 11, female – 13, mean age –23.16 years, SD – 2.20 years; For DTT: male – 11, female – 16, mean age – 23.48 years, SD – 3.24 years) participated in the study. Subjects were median split into two groups based on their trait anxiety scores[1]. Participants were also asked to complete the Beck Depression Inventory (BDI)[4].The study was carried out using 3T whole body MR system (Magnetom Skyra, Siemens, Germany) with a 32 channel head coil for MRS and a 20 channel head and neck coil for DTT. For MRS, 20 x20 x10 mm^3 voxel was positioned in the midline (covering samples from both right and left sides of the brain) on the axial slice in which caudate nucleus was well formed visually. The voxel posteriorly abuts the genu of the corpus callosum. MRS was obtained using PRESS (Point Resolved Spectroscopy) sequence with the following acquisition parameters: TR/TE = 2000ms/33ms; 2048 spectral points; 1200 Hz spectral Bandwidth and 196 averages. The spectra were processed using LCModel software (Provencher, 1993). Only the neurochemicals with Cramer Rao Lower Bounds less than 20% were analysed. Anxiety group (high trait anxiety (STAI-Y2 score above 35) vs lower anxiety (STAI-Y2 score = 20-35)) and Neurochemical ratios were analyzed with Multivariate Analysis of COVAriance (MANCOVA) using general linear model (SPSS (version 15.0, SPSS Inc, Chicago, IL, USA) statistical software). Age, sex, BDI scores, Full Width at Half maxima (FWHM) and Signal to Noise ratio (SNR) of the spectra were taken as covariates of no interest. To determine the predictive value of the anxiety on neurochemical concentration, a partial correlation analysis was also carried out. Diffusion-weighted acquisition parameters were: b-factor= 0 and 1000 s/mm2, 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 X 1.797 mm X 3mm, flip angle 90°, TR = 8800 ms, TE = 95 ms and NEX=2. An in-house-developed JAVA-based software was used to generate and quantify major WM fibre tracts[5]. Partial correlation including age, sex, and BDI scores as covariates of no interest, was computed between trait anxiety scores and Fractional Anisotropy (FA) values of the fiber tracts.

Results – For MRS, subjects with trait anxiety score between 20 and 35 were considered as low trait anxiety group (male – 7, female – 4) and those with trait anxiety score above 35 were considered as high trait anxiety group (median split on the basis of trait anxiety scores) (male – 4, female – 9). The level of Glu/tCr ($p = 0.008$), mI/tCr ($p = 0.046$) and (Glu+Gln)/tCr ($p = 0.003$) were found to be significantly elevated in high trait anxiety group as compared to low trait anxiety group in the ACC. In partial correlation analysis, Glu/tCr ($r = 0.402$, $p = 0.044$) and Glu+Gln/tCr ($r = 0.461$, $p = 0.024$) ratios showed a predictive value for trait anxiety in the ACC (Figure 1a, b). mI/tCr also showed a positive correlation with trait anxiety scores but with marginal significance ($r = 0.380$, $p = 0.054$). In DTT, the partial correlation analysis showed a positive correlation between trait anxiety and FA of left uncinate fasciculus (UF) ($r = 0.416$, $p = 0.030$) and fornix ($r = 0.370$, $p = 0.049$) (Figure 2a, b).

Discussion – ACC has extensive connections with amygdala (region known to be important for emotion processing) and is involved in emotion assessment, emotion-related learning, and autonomic regulation. An increased glutamatergic transmission and/or excessive glutamate release within the limbic system, especially ACC, is associated with fear-related learning and reactivity as has been shown by previous MRS studies on various anxiety disorders. The present findings therefore suggest a role of glutamate in mediating the physiological and behavioral consequences associated with anxiety even at sub-clinical level. Similarly, the inositol pathway has been shown to be critically involved in the anxiety phenotype with several proteins and metabolites that are part of phosphatidylinositol signaling having altered expression levels. UF is a fibre connecting anterior temporal areas including the amygdala with prefrontal-/orbitofrontal cortices including the ACC. Fornix is the main axonal output pathway from the hippocampus to the mammillary bodies. It is a key element of the memory circuitry and has also been identified as a key region in controlling spatial memory functions, episodic memory and executive functions and is also involved in the regulation of emotions by higher order frontal cortical brain regions. Increased activity and volume of amygdala and hippocampus has already been implicated in anxiety related personality traits which might also be associated with better integrity of UF and fornix respectively thereby explaining the positive correlation between FA values of the UF and fornix with trait anxiety as obtained in our study.

Conclusion – These results thus provide preliminary evidence for biological substrates underlying sub-clinical trait anxiety. The altered metabolism in the ACC and the strength of the two major fibers of the limbic system namely, UF and fornix may serve as hallmarks for identification of individuals with high anxiety trait. High anxiety trait being suggested to be a precursor to anxiety disorders and depression, the observed neurochemical and microstructural changes further support the need for preventive interventions in high anxiety individuals.

References –
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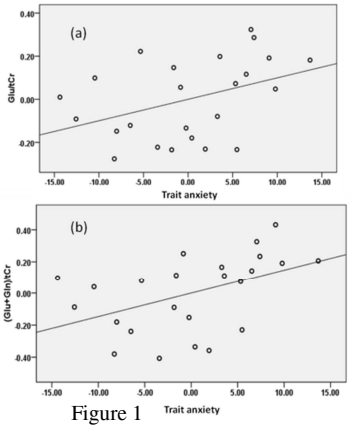

Figure 1

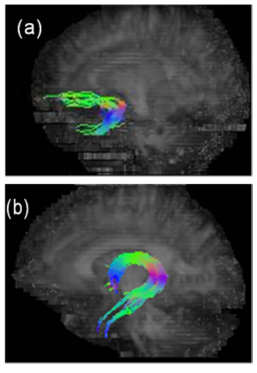

Figure 2