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EXPLORING BRAIN CHANGES IN SELF-REPORTED ANXIETY: CUTTING-EDGE EXPLORATORY DIFFUSION TENSOR IMAGING STUDY REVEALS DISTINCT ALTERATIONS IN WHITE MATTER TRACT STRUCTURE AMONG NON-CLINICAL INDIVIDUALS

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Abstract

Previous research utilising diffusion tensor imaging (DTI) has reported disruptions in white matter pathways among individuals with anxiety-related disorders. However, there is limited research focusing on healthy or non-clinical groups with self-reported anxiety symptoms. This investigation aims to explore how self-reported anxiety relates to white matter microstructural differences in non-clinical adult brains. A total of twenty-nine participants took part in the study. Each participant completed the Depression Anxiety Stress Scale-21 (DASS-21) and underwent a detailed high-resolution 3T magnetic resonance imaging (MRI). Diffusion MRI connectometry was conducted to generate correlational tractography, identifying links between generalised fractional anisotropy (FA) values of white matter and anxiety scores derived from the DASS-21. The average anxiety score, as measured by the DASS-21, was 10.97 with a standard deviation of 7.002. Notably, a significant inverse association emerged between anxiety levels and FA values in several white matter regions, including the left and right inferior fronto-occipital fasciculi, the left inferior longitudinal fasciculus, the right superior longitudinal fasciculus, and the left parahippocampal cingulum bundle ($p < 0.05$). The local brain connectome associated with anxiety may serve as a biomarker for early diagnosis and prevention of anxiety disorders in non-clinical populations.

Keywords*: Anxiety; Connectometry; Diffusion Tensor Imaging; White Matter; DASS-21*

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INTRODUCTION

Elevated alertness, attentiveness, and reaction to potential threats are some of the characteristics of the emotional state known as anxiety. Among the various types of anxiety-related conditions, social anxiety disorder (SAD) is one of the most prevalent, negatively affects individuals' social functioning and contributes to broader economic burdens (Stein & Stein, 2008). Patients with SAD exhibit intense and persistent fear, worry, and a tendency to avoid social situations (X. Zhang et al., 2022). Individuals with SAD may experience significant functional constraints, particularly in social interactions and relationships (Vidaurre et al., 2023). However, the neurological underpinnings of SAD are not clearly understood. With the emergence and rapidly developing field of psycho-radiology, numerous magnetic resonance imaging (MRI) investigations have yielded important insights into the changes in the brain that are linked to anxiety disorders (F. Li et al., 2021; Lui et al., 2016; X. Zhang et al., 2022).

Numerous studies have attempted to delineate the neurophysiological basis of anxiety, with structural and functional approaches being the most prominent methods applied to address the matter. In fact, both can be achieved by concentrating on specific brain regions or their connections. When considering the brain's structural characteristics, one may take into account the morphological characteristics of its structures, including the volume, which are obtained from high-resolution structural imaging. The alternative technique prioritizes the connections between brain structures rather than individually analysing each structure's anatomical characteristics (Mišić & Sporns, 2016). The quantity and quality of connections influence the brain's capacity to carry out specific functions and transfer information (P. Li et al., 2014). Diffusion tensor imaging (DTI) enables the visualisation of white matter pathways, with its key parameter – fractional anisotropy (FA) – providing insights into the structural characteristics of brain tracts, including aspects like myelination, axonal thickness, and fibre density (Hasan & Narayana, 2006; Zolkefley et al., 2024). The purpose of FA is to quantify the directionality and organization of fibre tracts within the white matter. Whereas anisotropy refers to the preferential orientation of structures, and fractional anisotropy provides a numerical value between 0 and 1 to represent the degree of anisotropy in a given voxel (three-dimensional pixel) of the brain. A higher FA value indicates a more organized and directional diffusion of water molecules, suggesting well-defined and intact fibre tracts (Martinez-Heras et al., 2021). Researchers and clinicians commonly rely on FA to evaluate white matter integrity. Changes in FA values can be linked to shifts in the microstructural organization of white matter pathways, providing valuable insights into conditions affecting the brain, such as neurodevelopmental disorders, neurodegenerative diseases, or psychiatric disorders.

Moreover, the majority of recent studies on anxiety are centred around the examination of white matter tracts, involving uncinate fasciculus and the amygdala-cortical axis. It was suggested that there is a link between anxiety as a clinical disorder, like SAD, or anxiety as a personality feature itself (Lee & Lee, 2020; X. Zhang et al., 2022). Accumulating data indicates that this disorder involves the activation of neurons and functional reorganization of white matter tracts (Gore et al., 2019; Lee & Lee, 2020). Specific white matter activation was also observed in resting state, motor tasks, visual and tactile of function MRI (Gawryluk et al., 2014; Marussich et al., 2017). Additionally, DTI identified large-scale, interacting networks of white matter tracts in anxiety disorder (Huang et al., 2020). Hence, research on the white matter tracts is a novel and powerful method for studying physiology and pathology of numerous psychological disorders such as schizophrenia (Y. S. Fan et al., 2020), major depressive disorder (MDD) as documented by Zhao et al. (2020), as well as benign epilepsy (Thorn et al., 2020) among others.

However, there is a lack of studies that examine a population without clinical conditions but with self-reported early symptoms of anxiety. This is in contrast to the numerous studies that have investigated the changes in brain function and structure in individuals already diagnosed with anxiety-related disorders. This study hypothesized that the microstructural changes in white matter integrity that occur before an anxiety disorder develops may be essential for the early identification and treatment of early anxiety symptoms in the non-clinical group. The present research was conducted to explore the correlation between mild psychopathology of self-reported anxiety state and alterations in microstructural white matter changes in healthy non-clinical adult brains. According to previous reports of network abnormalities in anxiety disorder, this study hypothesized that early signs of self-reported anxiety among the non-clinical populations would demonstrate early disruption within the white matter networks, that would correspond with the clinical diagnosis and prognosis of anxiety disorder.

LITERATURE REVIEW

White Matter Changes in Non-Clinical Anxiety Populations

While much of the existing literature one anxiety has concentrated on individuals within clinical settings, recent attempts have started to investigate neural connections in individuals exhibiting subclinical or self-reported anxiety symptoms (Saviola et al., 2020). These studies have yielded preliminary evidence that anxiety traits, even in the absence of a formal clinical diagnosis, may correlate with specific neural patterns, specifically in reductions in fractional anisotropy (FA) in areas linked to cognitive functioning and emotional regulation (Lu et al., 2018; Yang et al., 2020). The outcomes indicate that initial signs of anxiety may be evident in the brain's structural connectivity, supporting a dimensional perspective of mental health that include subclinical characteristics (Besteher et al., 2020).

Using non-clinical samples in research helps reduce the impact of possible confounders – including factors like medication use or the presence of comorbidities – thereby offering a more precise understanding of the correlation between anxiety symptoms and brain anatomy independently (N. Zhang et al., 2024). White matter alterations have been documented in individuals with high trait anxiety, which includes a decreased integrity in tracts associated with affective processing, such as those that connect the amygdala with the prefrontal cortex (Kolesar et al., 2019; Porta-Casteràs et al., 2020). This change in focus towards healthy individuals with self-reported symptoms is essential for improved understanding of anxiety as a continuum rather than a categorical disorder (Tomczyk et al., 2023), as well as for the identification of early neuroanatomical biomarkers (Abd Razak et al., 2024).

White Matter Tracts and the Significance of DTI in Anxiety Research

One of the most important white matter tracts that has been linked to anxiety is the uncinate fasciculus (Linke, 2019), which is responsible for connecting the amygdala to the orbitofrontal cortex and is essential for linking cognitive processes with emotional responses (Šimić et al., 2021). Decreased FA within this particular tract has been reported among those with elevated anxiety levels, suggesting potential inefficiencies in emotional regulation networks (Hein et al., 2018; Parsaei et al., 2024; Xu et al., 2023). Additional tracts, including the cingulum and superior longitudinal fasciculus, have been associated with altered white matter integrity in both clinical and subclinical anxiety populations (Kartashov et al., 2022; Wang et al., 2016), highlighting the importance of fronto-limbic connectivity in anxiety processing.

Diffusion tensor imaging (DTI) enables the assessment of water diffusion patterns in brain tissue, offering a valuable means to identify subtle alterations in white matter microstructure by quantifying directional flow and coherence (Jeurissen et al., 2019). Studies utilising DTI have consistently identified diminished FA in individuals with elevated anxiety, specifically within circuits facilitating top-down emotional regulation (Ayling et al., 2012; Vandekerckhove, 2020). By concentrating on a non-clinical sample, this study enhances the existing research utilising DTI to identify early neuroanatomical biomarkers of anxiety, thereby broadening the understanding of how mild and subtle symptoms manifest in white matter microstructure.

METHODOLOGY

Participants and Procedure

Given the exploratory nature of this study, thirty healthy participants without any mental or neurological disorders were initially included. The sample size was determined based on a previously published article (Y. T. Fan et al., 2015), which used a mean difference (MD) of 0.25 and a standard deviation (SD) of 0.20 to estimate the necessary sample size. The PS Software (Dupont & Plummer, 1990) was utilised to calculate the sample size, setting a two-tailed significance threshold of $p < 0.05$ and statistical power set at 80%. Consequently, the sample size was calculated to be 15 participants for each group.

Two experienced psychologists administered the Depression Anxiety Stress Scale-21 (DASS-21) questionnaire to the participants, adhering to established guidelines for the experimental procedure. Participants were excluded if they were pregnant or nursing, had neurological conditions, significant psychological disorders, head injuries, or were unable to remain still while undergoing the scan. The presence of MRI artifacts led to the exclusion of one participant's data, yielding a total of 29 participants in the final analysis.

Instruments

The DASS-21 is a shortened version of the original DASS-42, developed to measure an individual's experience of depression, anxiety, and stress through self-report. It provides a concise assessment of these emotional states using fewer items while maintaining the core structure of the full scale. The Depression Anxiety Stress Scale-21 has Cronbach alpha values of 0.88, 0.82, and 0.90, respectively, which indicates strong internal reliabilities (Henry & Crawford, 2005). There are seven sub-items that measure anxiety in the DASS-21, and these sub-items were used for this study to gauge the participant's levels of anxiety. To guarantee consistent interpretation with the version of DASS-42, scores were obtained by adding up the scores for each sub-item and multiplying by two.

Ethical Statement

The study protocol has received approval from the International Islamic University Malaysia Research Ethics Committee (IREC) (IREC ID – 2022-047). Each participant completed and signed a written informed consent form, and a consent form pertaining to the processing of their personal information prior to the start of the DTI acquisition.

Data Acquisition

The MRI brain scan was conducted using a Siemens 3-Tesla MR scanner at the Department of Radiology, Sultan Ahmad Shah Medical Centre, International Islamic University Malaysia (SASMEC, IIUM) in Kuantan, Pahang, Malaysia. Diffusion tensor imaging (DTI) acquisition was conducted using the following settings: a field of view

(FOV) of 240 mm, a 96 x 96 imaging matrix, slice thickness of 2.5 mm with no inter-slice gap, a single excitation (NEX = 1.0), and a flip angle of 90°. The repetition time (TR) was set at 7649 ms, and the echo time (TE) at 72 ms. The entire scan was completed within approximately 4 minutes and 28 seconds. To capture diffusion properties, gradients were applied using the electrostatic repulsion strategy. The protocol involved two non-diffusion-weighted baseline scans (b = 0), and a series of diffusion-weighted scans (b = 1000 s/mm^2) captured along 32 distinct, non-collinear orientations.

Each participant underwent high-resolution structural MRI, which included T1-weighted, T2-weighted, and FLAIR (fluid-attenuated inversion recovery) sequences. The acquisition details for each sequence are as follows:

a) T1-weighted axial images were performed with a repetition time (TR) of 678 milliseconds and an echo time (TE) of 10 milliseconds. Images were reconstructed using a matrix of 512 x 512 x 40, covering a field of view of 230 mm. The resolution was set at 0.45 x 0.45 mm per voxel, with 2.5 mm slices, 1.0 mm spacing between slices, and a flip angle of 70 degrees.
b) T2-weighted axial images utilized TR and TE values of 3000 ms and 80 ms, respectively. The reconstruction matrix measured 512 by 512 by 24, with a consistent FOV of 230 mm. Voxel dimensions were kept at 0.45 mm x 0.45 mm, with a 2.5 mm slice thickness, 1.0 mm spacing, and a flip angle of 90 degrees.
c) FLAIR axial images were acquired using a TR of 11000 ms, TE of 125 ms, and an inversion time (TI) of 2800 ms, reconstructed with a 512 x 512 matrix.

Image Processing

Diffusion MRI connectometry analysis was performed using DSI Studio software (Yeh et al., 2016) to assess the relationships between generalized FA and anxiety scores. The analysis employed the "correlation tracking" paradigm, which identifies white matter pathways linked to the variable of interest. Correlations were assessed using the nonparametric Spearman correlation coefficient. Following this, deterministic fibre tracking was conducted as described by Yeh et al. (2013) to perform correlational tractography. The quantitative anisotropy (QA) metrics underwent normalisation prior to further processing. Subsequently, the generated fibre pathways were refined through topology-informed pruning, performed in 16 iterative steps as described in (Yeh et al., 2019). Statistical significance was assessed by applying a false discovery rate (FDR) correction, with the threshold set at 0.05, along with adjustments for multiple evaluations. Through FDR-adjusted p-value estimation, 4000 random permutations were conducted at the group level to derive the track length of the null distribution.

RESULT AND DISCUSSION

Clinical Variables

The study included 29 participants (21 male participants and 8 female participants) with an average age of 40.97 ± 8.424 years, ranging from 27 to 57 years (see Figure 1). The average anxiety score, as measured by the DASS-21, was 10.97 ± 7.002. There was no meaningful association observed between participants' age and anxiety levels, nor were there significant differences between genders.

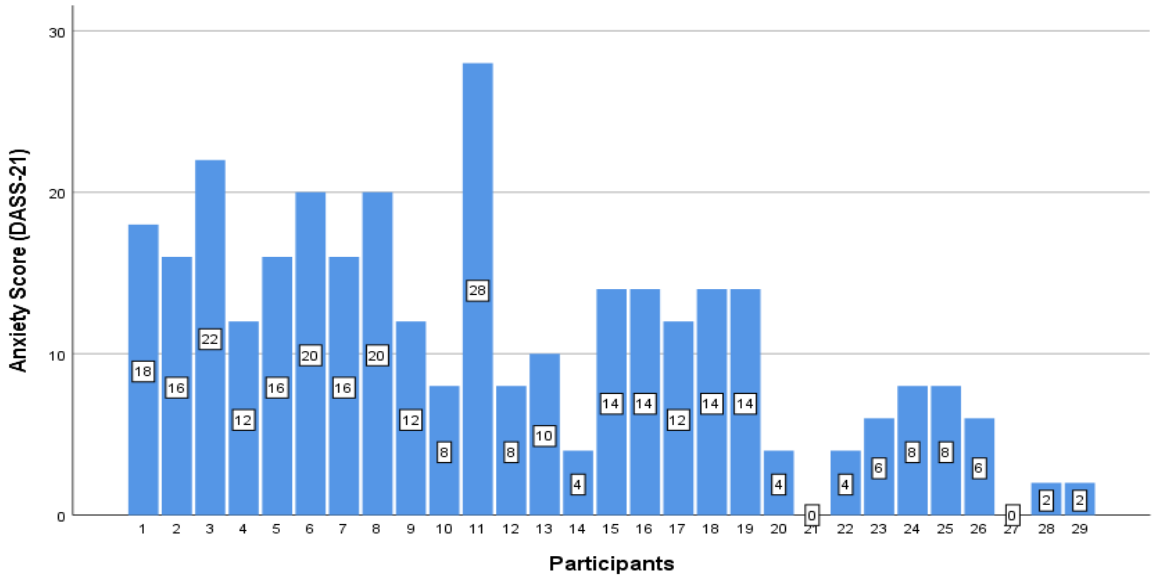

Figure 1: The distribution of the Anxiety Score (DASS-21) in non-clinical participants

Based on Table 1, majority (n = 9) of the participants fell into the "normal" category of the anxiety trait score, with the second highest number of participants (n = 8) that were categorized as falling into the "moderate" level of anxiety severity. The remaining participants had evenly scored either mild, severe, or extremely severe levels of anxiety (n = 4 for each category).

Table 1: DASS-21 Score Interpretation (Anxiety Trait)

Severity	Anxiety Trait Score	Participants (*n=29*)
Normal	0 – 7	9
Mild	8 – 9	4
Moderate	10 – 14	8
Severe	15 – 19	4
Extremely Severe	20+	4

Correlation Analysis between FA Values of White Matter Tracts and Anxiety Scores

Figures 2 and 3, along with Table 2, illustrate the correlations between anxiety scores and generalized FA of various white matter tracts identified through connectometry analysis. These tracts include the left inferior fronto-occipital fasciculus (L-IFOF), right inferior fronto-occipital fasciculus (R-IFOF), left inferior longitudinal fasciculus (L-ILF), right superior longitudinal fasciculus (R-SLF), and left parahippocampal cingulum bundle (L-PHCB).

Table 2: Generalised FA of white matter tracts which have correlation with anxiety score

White matter tract	Mean FA value	R-value	p-value
L-IFOF	0.298 ± 0.33	-0.399	0.032*
R-IFOF	0.238 ± 0.31	-0.404	0.030*
L-ILF	0.168 ± 0.04	-0.381	0.042*
R-SLF	0.284 ± 0.35	-0.442	0.016*
L-PHCB	0.291 ± 0.37	-0.424	0.022*

*FA, fractional anisotropy, *p < 0.05*

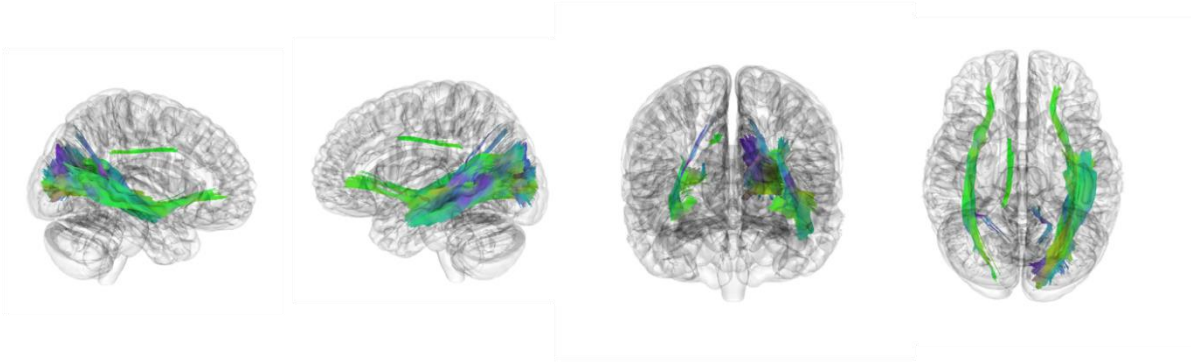

Figure 2: Correlational tractography, presented from a three-dimensional (3D) perspective, displays the generalised FA of white matter tracts associated with anxiety trait scores.

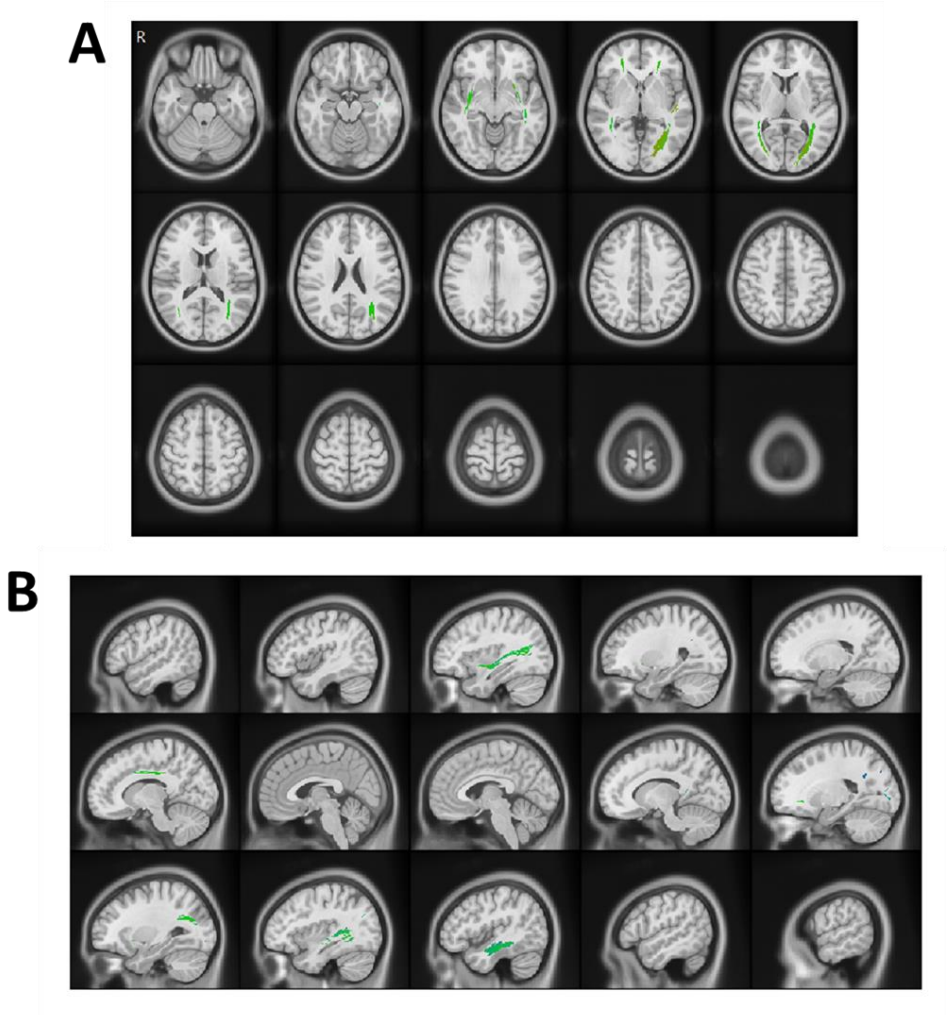

Figure 3: Correlational tractography showing generalised FA of white matter tracts (green colour) that are associated with anxiety score; which can be seem from A) axial and B) sagittal section view.

This study investigated the relationship between generalized FA in cerebral white matter tracts in relation to self-reported anxiety among individuals without clinical diagnoses. The findings revealed significant associations involving anxiety scores and FA in several white matter pathways: the right inferior fronto-occipital fasciculus (R-IFOF), left inferior fronto-occipital fasciculus (L-IFOF), right inferior longitudinal fasciculus (R-ILF), left superior longitudinal fasciculus (L-SLF), and left parahippocampal cingulum bundle (L-PHCB).

Reproducible associations were observed in these tracts, which aligns with previous research indicating that anxiety-related conditions are often associated with decreased FA in these regions. The cingulum bundle, in particular, has been well-studied in relation to anxiety disorders, with evidence suggesting disrupted microstructural integrity in this pathway (Lochner et al., 2012; Westlye et al., 2011). Serving a central role in the limbic network, the cingulum is involved in emotional regulation and is connected to areas including the anterior thalamic nuclei, cingulate gyrus, and parahippocampal region (Dalgleish, 2004). Higher activation in the left hemisphere, specifically the anterior cingulate cortex, has been associated with effective control of negative emotions (S. H. Kim et al., 2012), suggesting that the white matter tracts in the left cingulum may be more efficient in this process. Additionally, the left hemisphere's role in episodic memory may relate to the observed negative correlation involving the structural integrity of the left parahippocampal cingulum bundle along with anxiety trait (Tulving et al., 1994). Long-term fear conditioning studies have also highlighted left-lateralized limbic system functional connectivity patterns (Martynova et al., 2020).

Furthermore, the limbic network, which encompasses the cingulum tracts, ILF, and IFOF, is critically involved in the processing of emotional cues associated with anxiety and social fear (Y. K. Kim & Yoon, 2018). Prefrontal areas are involved in modulating attention to threat-related distractions and the perception of potential threats (Bishop, 2007). The interaction linking the limbic system with the prefrontal cortex constitutes the "fear circuitry," essential for anxiety disorder development. Altered fibre connections between these networks, particularly involving prefrontal-amygdala regions, are well-documented as a consistent finding in anxiety (Mizzi et al., 2022). This disturbance in the limbic-dorsal prefrontal network may account for the reduced FA in related white matter tracts.

Cognitive theories suggest that distortions in how information is processed might influence the persistence of anxiety disorders (Mellings and Alden, 2000). Prior studies found that those diagnosed with social anxiety exhibit biases in interpreting the negative valence of faces and show hypervigilance-avoidance towards unfavourable expressions (Claudino et al., 2019). The temporal lobe, which responds to facial images and aids in visual processing and object recognition (Rolls, 2000), interacts with the limbic network to evaluate emotional significance and influence social behaviour (Baron-Cohen et al., 1994). Negative expression processing involves both the limbic and temporal networks (Iidaka et al., 2002). Furthermore, past resting-state fMRI studies have documented reduced fibre connections between the temporal gyrus and amygdala in groups of samples with anxiety disorders (Hahn et al., 2011; Jung et al., 2018). The inferior longitudinal fasciculus (ILF), known for linking to limbic areas, is one such tract observed with reduced FA in anxiety disorders (Latini, 2015; Tükel et al., 2017).

Additionally, the ILF is involved in proprioception and motor movements (Ramos-Fresnedo et al., 2019). Pathological anxiety may result from disrupted connections in either the limbic or perceptual networks, which are crucial for anxiety (Cannistraro and Rauch, 2003). The motor responses to affective material may involve the motor gyrus. Transcranial magnetic stimulation has shown that activating the somatosensory cortex can influence emotion

detection in social face recognition tasks (Pourtois et al., 2004). Disruptions in fibre connections between sensorimotor processing regions and the limbic network might relate to sensitivity to emotional signals (Sandman et al., 2020). The negative correlation between limbic network structural integrity and anxiety scores provides additional insights into emotional disturbances in anxiety.

While the study offers valuable insights, it also has certain limitations. First and foremost, the small sample size restricted the ability to stratify participants based on anxiety levels, suggesting a need for larger studies with more participants and varying severity levels of anxiety traits. The broad age range of participants may also include age-related brain changes, so future studies should involve a larger, more age-specific sample. Moreover, this study did not assess the prolonged implications of anxiety on the neural structure, and future longitudinal studies would be beneficial for exploring alterations in neuroimaging and anxiety scores over time. Finally, the lack of reproducibility in FA correlations with repeated anxiety scores may also reflect as a limitation in correlation analysis.

CONCLUSION

Through the use of connectometry analysis combined with generalised FA (GFA), this study has been able to successfully identify critical white matter pathways associated with self-reported anxiety. The outcomes of this study emphasise the crucial role that big associative fibres play in the susceptibility to anxiety; these fibres include the SLF, ILF, IFOF, and the cingulum bundle.

The tracts are known for facilitating attention, emotional regulation, and integration of cognitive-affective processes, and their participation corresponds with previous studies indicating disrupted fronto-limbic connectivity in individuals exhibiting elevated anxiety symptoms (Liu et al., 2021; Shan et al., 2023). This indicates that abnormalities in white matter integrity may occur even in the absence of a clinical diagnosis, emphasising the necessity of examining anxiety as a dimensional construct among individuals with and without clinical diagnoses (Kotov et al., 2017; Osma et al., 2021).

Due to constraints in sample size and statistical power, the correlation analysis warrants a measured interpretation; yet the results offer significant insights into the structural foundations of self-reported anxiety. This study contributes to the existing literature by identifying tract-specific alterations through connectometry, thereby highlighting the potential applicability of diffusion-based markers in psychological research. We propose that the local connectome of anxiety-related associations may function as a biomarker as a tool to detect and address anxiety disorders at an early stage; these biomarkers may ultimately complement conventional screening methods, facilitating more proactive mental health interventions (Etkin & Mathalon, 2024).

Future research involving larger and more heterogeneous cohorts is essential to corroborate these findings, investigate longitudinal outcomes, and evaluate the potential of white matter alterations in predicting symptom progression or treatment response. The integration of multimodal imaging techniques and behavioural data may further enhance our understanding of the neurophysiological pathways of underlying anxiety and facilitate the formulation of personalised preventative strategies.

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Declaration of Conflicting Interests
The authors declare that there are no known conflicts of interest concerning the writing or dissemination of this manuscript.

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