The Relationship Between Individual Differences in Levels of Internalizing Symptomatology and White Matter Tract Integrity in Adolescents

By

Casey Hogan

Department of Psychology and Neuroscience, University of Colorado at Boulder

Defended April 2nd, 2024

Thesis Advisor:

Dr. Marie Banich, Department of Psychology and Neuroscience

Defense Committee:

Dr. Albert Kim, Department of Psychology and Neuroscience

Dr. Deborah Whitehead, Department of Religious Studies

Abstract

Internalizing disorders are those defined by symptoms that focus on internal feelings and thoughts compared to externalizing symptoms which are outward facing. The unique neuroanatomical ambiguities of adolescent brains and how these relate to internalizing disorders, specifically depression and anxiety, are not well understood. Understanding the association between differences amongst youth in their levels of internalizing symptomatology and the integrity of specific neuroanatomical white matter tracts may provide insights into the relationship between brain structure and the development of mental health disorders. Studies have previously shown a relationship between clinical diagnoses of internalizing disorders (i.e., anxiety and depression) and white matter tract integrity, most notably those tracts connecting to the frontal lobes. However, the current study aims to go further by examining the relationships of the integrity of these white matter tracts with specific dimensions underlying symptoms of internalizing disorders involved in adolescent mental health. In the current study, we aimed to identify the white matter tract correlates of four dimensions of internalizing symptoms in adolescents; a common internalizing factor that captures the symptoms that are common to depression and anxiety and then three specific sets of symptoms represented by a low positive affect specific factor, an anxious arousal (panic) specific factor, and an anxious apprehension (worry) specific factor. Our results show a robust relationship between the level of symptoms of internalizing psychopathology with integrity of white matter tracts, specifically with associations between the low positive affect-specific factor and the worry-specific factor with tracts that connect to prefrontal cortex. Results were also influenced by gender, not surprisingly as gender influences the maturation of white matter tracts through adolescents.

INTRODUCTION

The goal of this paper is to understand the relationship between the integrity of particular white matter tracts, specifically those involved in executive functioning, and the levels of symptoms related to internalized psychopathology in adolescents. When looking at the structure of psychiatric disorders, we look to Caspi's model of psychopathology (2014). This model suggests there is a p-factor, which represents general psychopathology or the levels of symptoms one has that lends them to being prone to psychopathology. A higher p-value is associated with the presence of psychiatric symptoms. Once these overall symptoms have been accounted for, symptoms further aggregate into two overarching domains: internalizing and externalizing (See Figure 1).

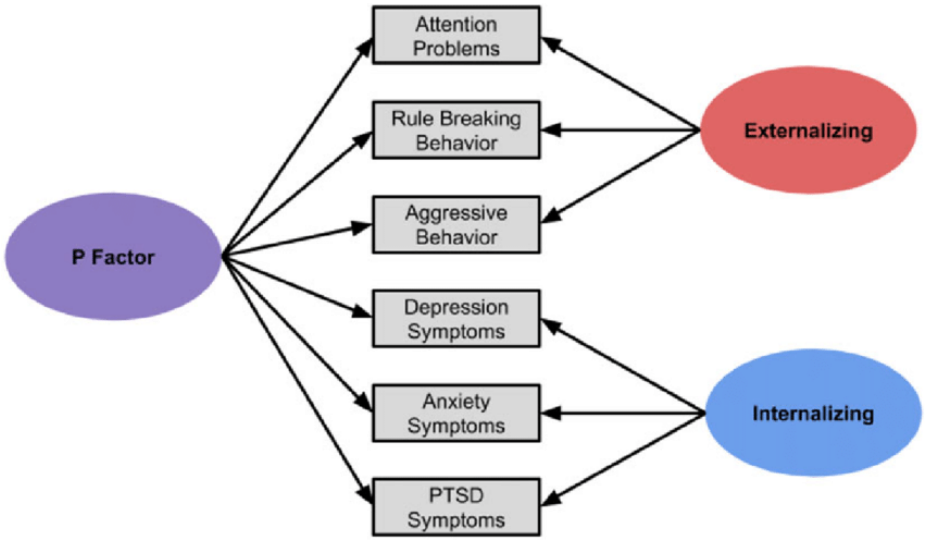


Figure 1: Caspi's Model of the Structure of Psychopathology taken from Weissman et al., 2019 This model shows there is an overarching p factor reflecting symptoms of psychopathology generally, and once those are taken into account, two more specific factors result, one for symptoms related to internalizing disorders and another for symptoms related to externalizing disorders.

Internalizing symptoms focus on internal feelings and thoughts compared to externalizing symptoms which are outward facing. Internalizing disorders, which encompass a wide range of

psychopathology including anxiety and depression, generally include symptoms associated with worry, fear, and rumination (Banich et al, 2020). These disorders frequently begin in youth and often have high comorbidity rates with other psychiatric disorders (Kaczkurkin et al, 2020). Both internalizing and externalizing disorders have negative social, health, and developmental impacts on patients including higher risks of suicide, addiction, and incarceration rates (Askari et al, 2021).

Over the last few decades, studies on adolescent mental health have shown an increase in the level of internalizing symptoms, specifically in female adolescents (Blomqvist et al, 2019). The severity and incidence of internalizing symptoms have increased two-fold within the last decade (Askari et al, 2021; Blomqvist et al, 2019). A 2023 study analyzing the severity and incidence of depression found rates of adolescent depression increased from 8.1% in 2009 to 15.8% in 2019, a larger jump than any previous ten-year comparison (Wilson, 2023). This highlights the relevance of the study, in which we will look at both sexes, as the change in depression incidence was larger for girls (12.0%) than boys (3.7%) (Wilson, 2023). To understand how to treat and prevent these increases it is imperative to understand the integrity of neural substrates and how they are associated with internalizing disorders.

When looking at the 2023 Center for Disease Control (CDC) data (see Figure 2) on children's mental health showed ADHD, anxiety problems, behavior problems, and depression are the most commonly diagnosed mental disorders in children aged 3-17 (Centers for Disease Control and Prevention, 2023). It is imperative to note these diagnoses are happening more often, as seen in Figure 2 the incidence rates of depression and anxiety increase the most when children enter their teen or adolescent years, around 12-17. Diagnoses of ADHD, anxiety, and depression

become more common within this adolescent period (Centers for Disease Control and Prevention, 2023).

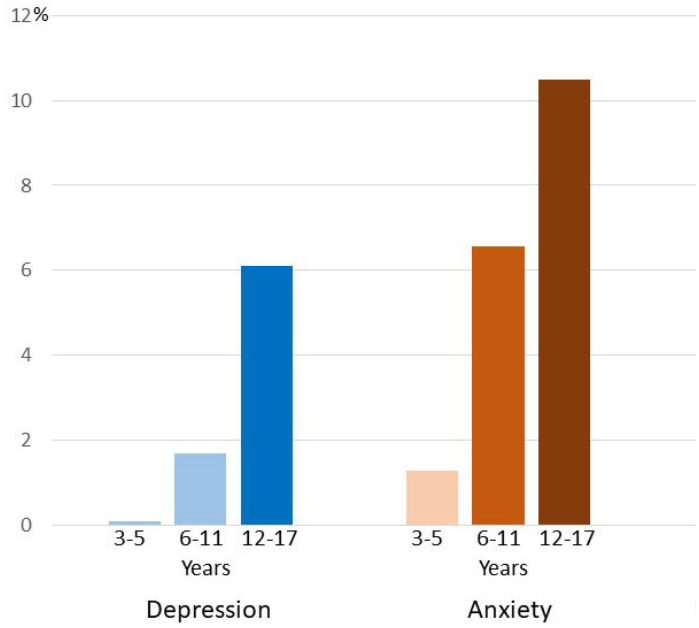


Figure 2: CDC Statistical Report of Adolescent Mental Health by Age

This graph highlights that the prevalence of mental disorders changes with age during adolescence, specifically among internalizing disorders such as depression and anxiety.

Bi-Factor Model of Internalizing Disorders

Previous research shows the high levels of comorbidity of anxiety and depression within internalizing disorders, making the brain bases of these disorders hard to identify. In an attempt to understand this comorbidity, Clark and Watson (1991) focused on the symptoms of each in the Tripartite Model of anxiety and depression. This model characterized symptoms of anxiety and depression as consisting of a common factor, known as negative affect, along with two specific factors, anxious arousal (i.e., panic) and low positive affect (i.e., lack of interest and motivation) (Clark and Watson, 1991). Currently, a prominent model of internalizing disorders has added a fourth subgroup to this model, anxious apprehension (i.e. worry). This bi-factor model highlights

symptom-specific factors of internalizing disorders (Snyder et al., 2023). We will use this model to identify levels of white matter tract integrity associated with the four internalizing dimensions: common internalizing which captures the symptoms shared across depression and anxiety, as well as three specific symptom dimensions, low positive affect (LPA), anxious arousal (i.e. panic), and anxious apprehension (i.e. .,worry) (Snyder et al., 2023).

White Matter Tract Integrity

White matter in the brain is composed of axons covered in fatty myelin. This superhighway of myelin allows distant brain regions to communicate with one another swiftly and efficiently. Myelinated fibers reinforce the speed of conduction, and the connectivity of the white matter tracts allowing the rapid synchronization of information among cortical regions (Ribeiro et al 2024). Previous literature highlights the role these tracts play in motor, language, visuospatial processing, and other cognitive processes (Ribeiro et al 2024). The tracts of interest for this study all connect to the frontal lobe, which is undergoing much development during adolescence (See Figure 3). The frontal lobe is important for higher-order mental function and supports executive functioning (Boutzoukas et al, 2021).

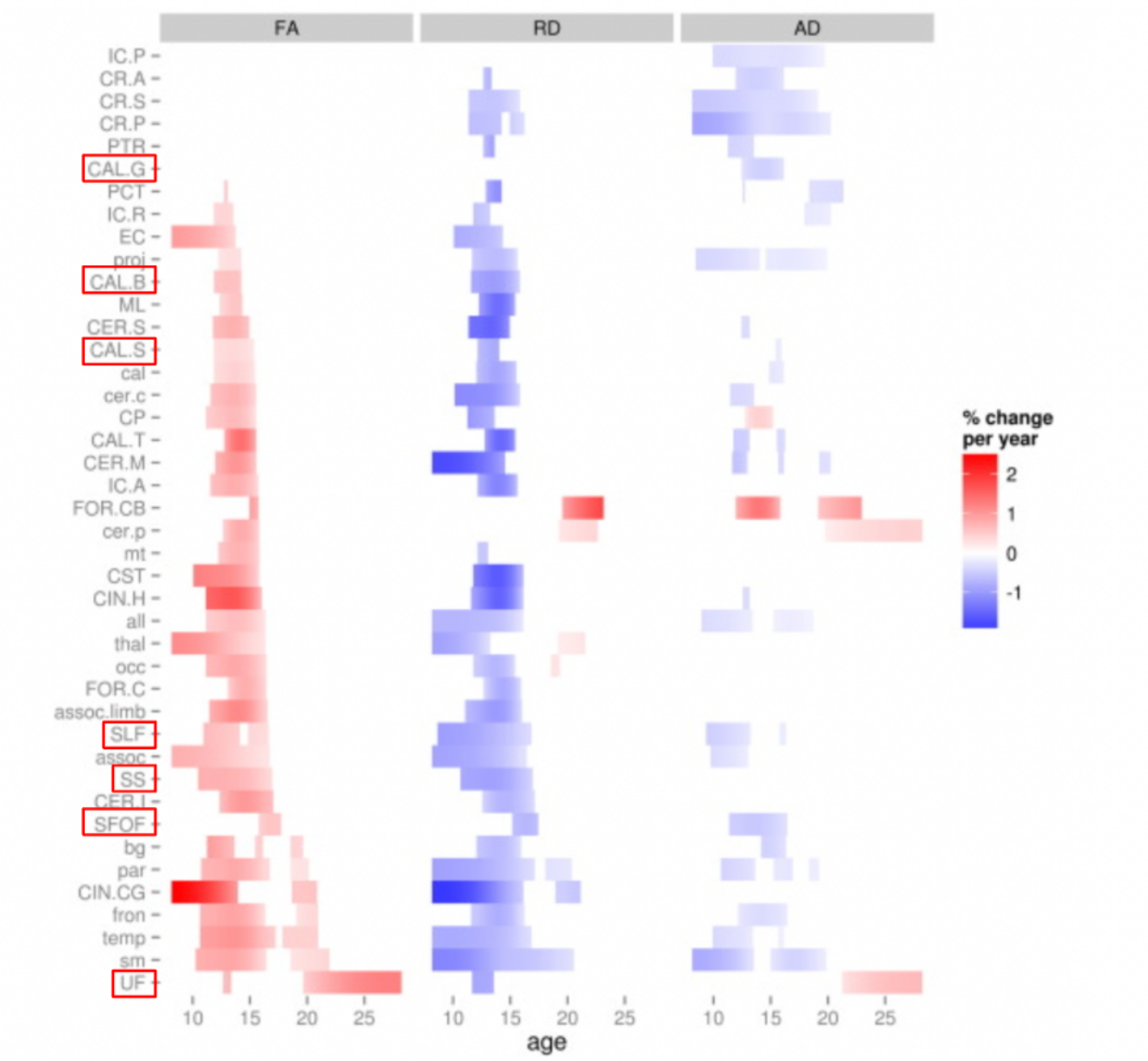


Figure 3: Graph depicting the % change per year in Fractional Anisotropy (FA), Radial Diffusivity (RD) and Axial Diffusivity (AD) taken from Simmons et al, 2014.

This figure highlights the brain maturation and development in tracts connecting to the frontal lobe structures throughout adolescence. These tracts include the genu of the carpus callosum (CAL.G), the body of the corpus callosum (CAL.B), the splenium of the corpus callosum (CAL.S), the superior longitudinal fasciculus (SLF), the sagittal stratum (SS), the superior fronto-occipital fasciculus (SFOF) and the uncinate fasciculus (UF).

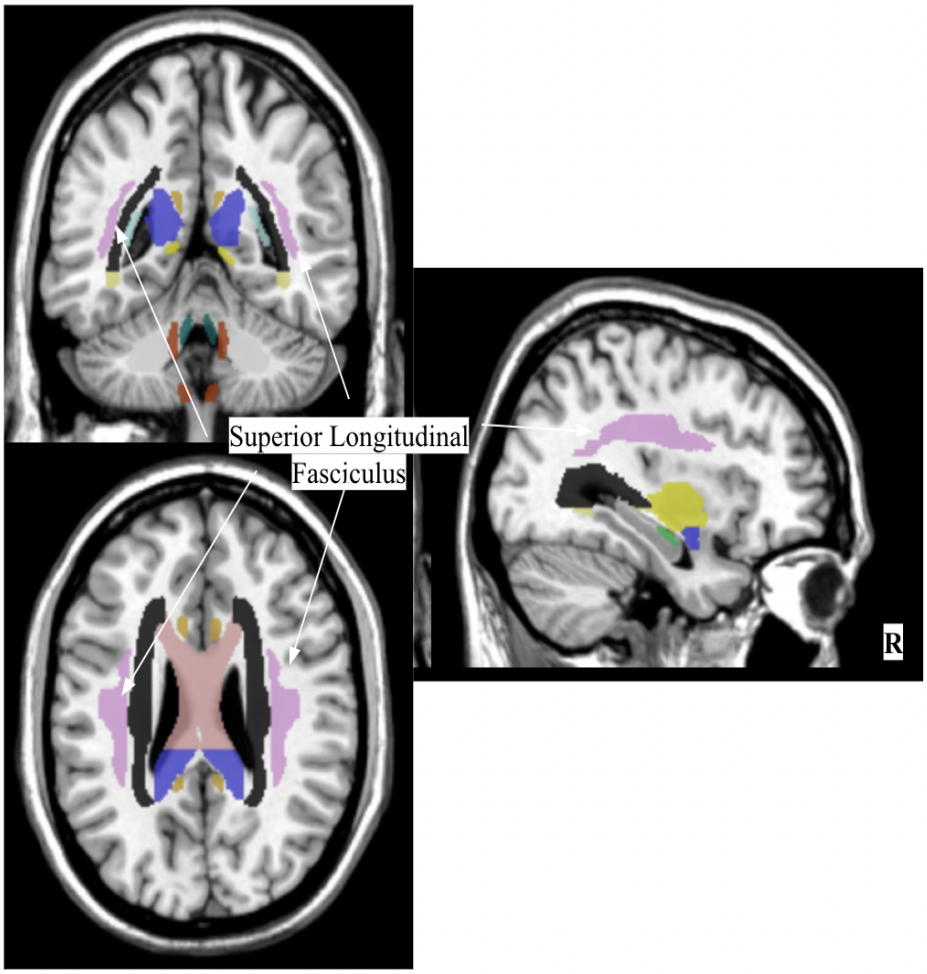
Executive functioning is defined as high-level cognitive processes involving abilities such as working memory/updating, set-shifting and inhibition (Ribeiro et al 2024). These higher-

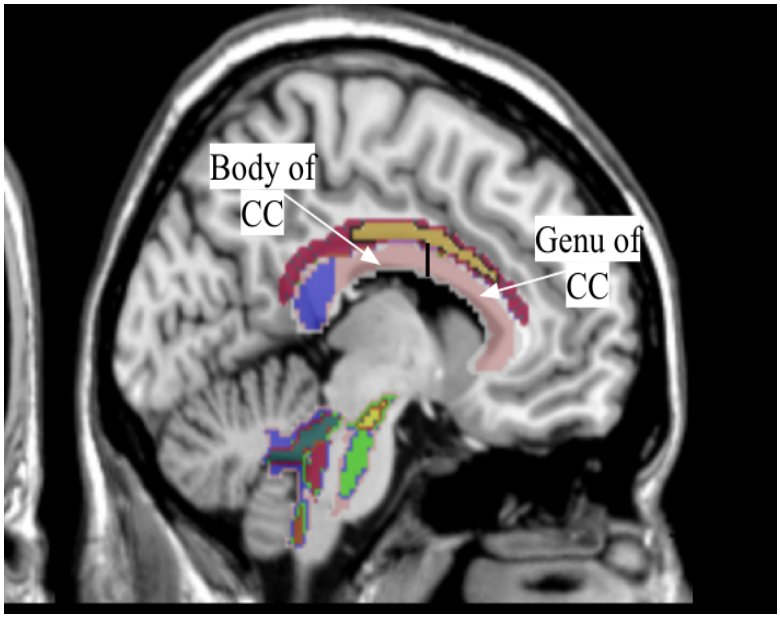
order cognitive functions are reliant on information processing speed, largely supported by white matter tracts. Executive dysfunction is observed in internalizing disorders along with the dysfunction of neural networks being involved in executive function (Ribeiro et al 2024).

White matter tract integrity within the current study was analyzed by looking at Fractional Anisotropy (FA) within nine fiber tracts of interest, based on findings in prior studies of white matter changes in adolescents with clinical diagnoses of anxiety and depression (Adluru et al, 2017; Liao et al, 2014). Fractional Anisotropy is an index of white matter microstructure measured via diffusion tensor imaging (DTI) (Fisher et al;., 2020). Fractional Anisotropy is a measure of the speed and directionality of diffusion of water molecules in white matter tracts. Low FA points to isotropy, meaning diffusion is the same in every direction whereas high FA points to diffusion that varies with direction which occurs in more structured spaces, such as tracts with high integrity. Previous studies have shown that DTI measures and white matter integrity have been linked with internalizing disorders, specifically depression (Khalil, 2023).

Tracts of Interest (TOI):

Our nine white matter tracts of interest, as pictured below, selected for this study are the genu, body and splenium of the corpus callosum (CC), the right and left superior longitudinal fasciculus (SLF), the right and left uncinate fasciculus (UF) and the right and left sagittal stratum which includes the inferior fronto-occipital fasciculus and the inferior longitudinal fasciculus. These regions were picked for their relationship with executive functioning along with their role in emotional regulation, cognition and processing, as detailed below.


Superior Longitudinal
Fasciculus
R


Body of
CC
Genu of
CC

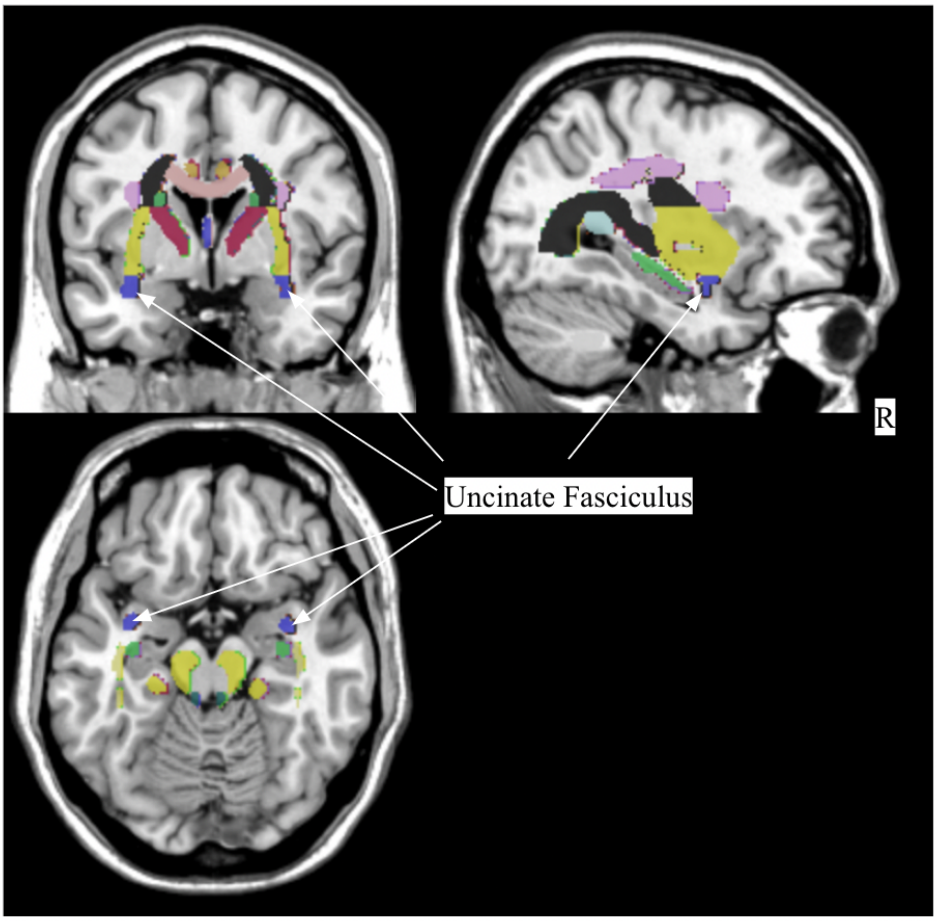


Figure 4: The position of three tracts of interest: the Superior Longitudinal Fasciculus, the body and genu of the corpus callosum, and the uncinate fasciculus. Screen shots taken from MRICron.

Previous studies have noted dysfunctional cortical-subcortical neural circuits are involved in the pathophysiology and psychopathology of depression (Coloigner, 2019). Investigations into white matter tracts have become a rapidly growing area of research in internalizing diseases, specifically depression. Many mood regulation abnormalities underlying internalizing disorders have been correlated with abnormalities in the frontal-limbic network (Coloigner, 2019), decreased activation in the left posterior dorsolateral prefrontal cortex (DLPFC), as well as increased levels of activation in the dorsal anterior cingulate cortex (ACC) (Banich, 2020).

Previous studies also show associations between white matter tract abnormalities and a wide range of cognitive deficits, from basic information processing speed to high-level processes such as executive functions (Ribeiro et al 2024).

The first tract of interest, the uncinate fasciculus connects the frontal lobe with the anterior temporal lobe, a critical structure in emotion and memory. Early internalizing symptoms have previously been linked to lower FA in the cingulum bundle and uncinate fasciculus, with females with increasing symptoms across childhood also showing reduced FA in these tracts (Radoeva et al, 2023).

Another tract, the superior longitudinal fasciculus connects the superior parietal to the superior frontal lobes longitudinally and plays a major role in language, attention, working memory, and emotions (Janelle, 2022). Since this tract connects frontal and parietal regions, it is implicated in executive processes as it connects portions of the fronto-parietal control network. The SLF is likely engaged in executive control because it supports the integration of information within top-down, visual, and goal-oriented attention (Ribeiro et al 2024). When looking at sex differences in these tracts, previous research found males had higher fractional anisotropy (FA) in the left superior longitudinal fasciculus (Kanaan 2012), and hence considering gender in our study will be important.

The next region, the sagittal stratum (See Figure 5) is made of the inferior fronto occipital fasciculus and the inferior longitudinal fasciculus. It connects the frontal, temporal and occipital lobes, and is associated with semantic language processing and goal-oriented behavior. Decreases in FA in this region have been shown to be characteristic of adolescents at a high risk for developing a depressive disorder (Hermesdorf, 2017). The last three tracts of interest are all portions of the corpus callosum, the largest white matter tract of the brain, which connects the

two cerebral hemispheres, allowing them to communicate. This tract is broken down into the genu, body, and splenium. A 2024 review found the corpus callosum was consistently associated with all executive processes, notably its anterior segment or the genu (Ribeiro et al 2024). The integrity of the different segments of the corpus callosum has been consistently associated with working memory, specifically, the genu which showed age-related differences in working memory tasks likely due to the myelin differences amongst differing age groups (Ribeiro et al 2024). When looking at gender differences, females had higher FA in the corpus callosum (Kanaan 2012), once again making it important to examine patterns by gender.

Previous literature analyzing the association of tract integrity with internalizing symptoms looked at clinical samples, where participants had already been given a psychiatric diagnosis. These clinical populations showed dysfunctional connectivity and alterations in white matter signaled by lower levels of FA (Radoeva et al, 2023). We therefore hypothesized that less integrity within specified tracts, or lower levels of fractional anisotropy will correlate with higher levels of each the factors of internalizing psychopathology (common internalizing, low positive affect-specific, anxious apprehension-specific, anxious arousal-specific). Less FA is a signal for decreased communication within these tracts, which we predict may be associated with executive dysfunction, including poor emotion regulation, and therefore increase levels of symptoms related to internalizing psychopathology.

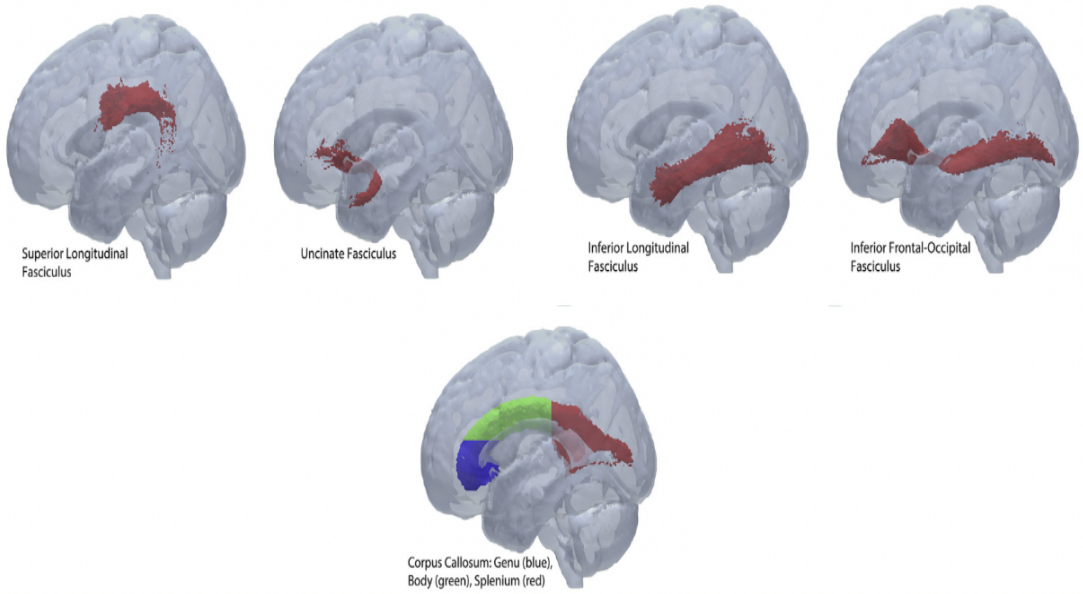


Figure 5: Tracts of interest. The tracts of interest include the Superior Longitudinal Fasciculus (SLF), the Uncinate Fasciculus (UF), the Sagittal Stratum made up of the Interior Fronto Occipital Fasciculus and the Inferior Longitudinal Fasciculus and the Genu, Body and Splenium of the Corpus Callosum. Figure taken from Ivanova et al., 2016.

METHODS

Participants:

The data for this study was collected from a subset of 150 participants in the Colorado Cognitive Neuroimaging Family Emotion Research (CoNiFER) study. These individuals were originally recruited for studies within the Genes and Environment Mood (GEM) lab (for details of these studies, see Hankin et al., 2015). The description of the recruitment and participant methodology is described in more detail in Smolker et al, 2022. Briefly, recruitment of participants was done within public schools and direct mail in the Denver metropolitan area. This recruitment aimed at collecting a community sample, as participants were not screened for psychiatric disorders prior to data collection. Participants were deemed eligible if they were free of a history of neurological insult and MRI contraindications. Of the original, 151 participants, 42 (27.8%) did not return for the second visit of the study, which was the only one in which both DTI and psychopathology data were collected. We then dropped an additional 29 (19.2%) participants as they lacked complete factor scores (derived from questionnaire data), DTI data or demographic data. This yielded a final participant pool consisting of 79 adolescents, 37 males with a mean age of 19.4, *SD* = 1.44, and 42 females, with a mean age of 19.3, *SD* = 1.75. Participants ranged from 16 to 24 years old. The age distribution of the sample is shown in Figure 6, while the demographic characteristics of our sample is shown in Table 1.

Factor scores were derived from questionnaires, completed during a separate session than the MRI. Minor participants assented with signed parental consent prior to participation, and participants 18 and older provided informed consent. Research protocols were approved by the University of Colorado Boulder Institutional Review Board prior to data collection. All participants were paid for their participation in the study.

	Male (N=37)	Female (N=42)	Overall (N=79)
Age			
Mean (SD)	19.4 (1.44)	19.3 (1.75)	19.3 (1.61)
Median [Min, Max]	19.2 [16.3, 23.1]	19.0 [16.3, 24.6]	19.1 [16.3, 24.6]
Ethnicity			
Hispanic/Latino	5 (13.5%)	8 (19.0%)	13 (16.5%)
Non-Hispanic/Latino	32 (86.5%)	34 (81.0%)	66 (83.5%)
Race			
Native American/Alaskan	1 (2.7%)	2 (4.8%)	3 (3.8%)
Asian	1 (2.7%)	2 (4.8%)	3 (3.8%)
Native Hawaiian/Pacific Islander	0 (0%)	0 (0%)	0 (0%)
Black or African American	2 (5.4%)	5 (11.9%)	7 (8.9%)
White	29 (78.4%)	28 (66.7%)	57 (72.2%)
Other	0 (0%)	0 (0%)	0 (0%)
Mulitracial	4 (10.8%)	5 (11.9%)	9 (11.4%)

Table 1: Demographic breakdown of study participants

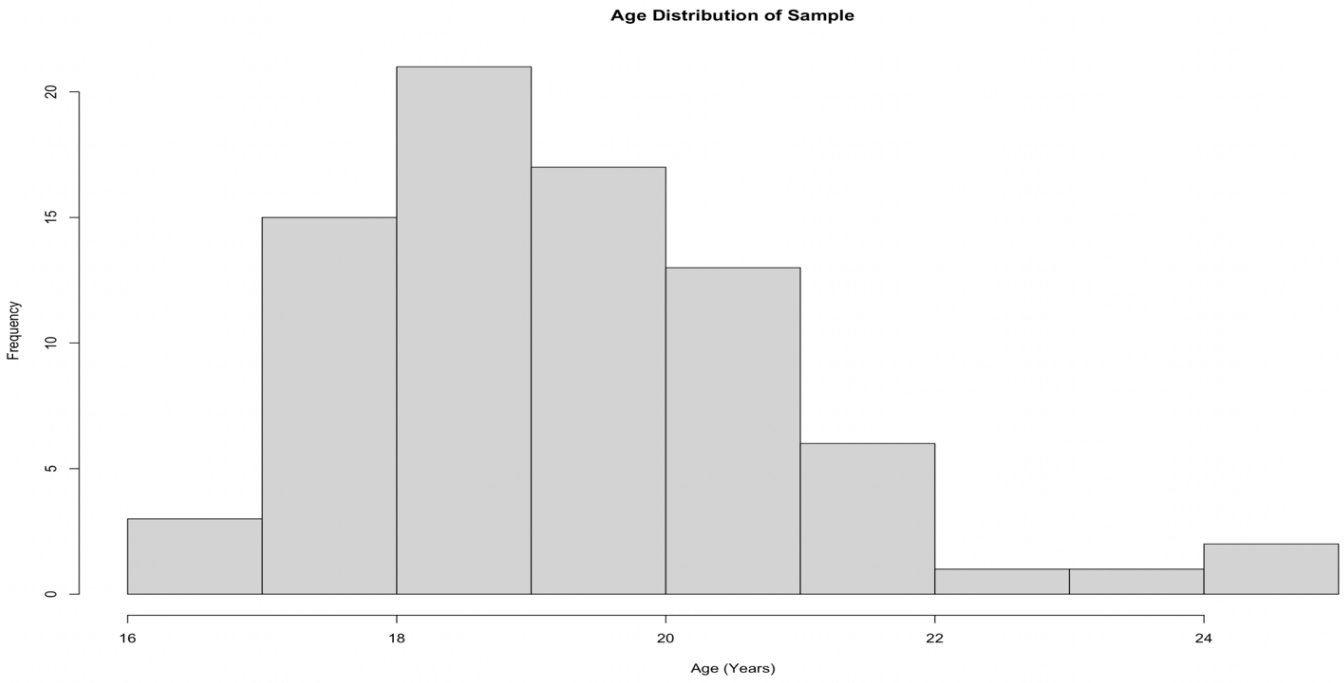


Figure 6: Age Distribution of Study Participants

Internalizing Factor Scores:

As described in Smolker et al., (2022), the four internalizing dimensions of interest were derived from responses to specific items on two questionnaires: the Mood and Anxiety Symptom Questionnaire (MASQ) (Watson et al., 1995) and the Penn State Worry Questionnaire (PSWQ) (Meyer et al., 1990). This study used the 39 items capturing the anxious arousal (AA, e.g., "Hands were shaky), low positive affect (LPA, e.g., "Felt like I was having a lot of fun" – reverse coded), and loss of interest (LI, e.g., "felt really bored") subscales within the MASQ (Nitchke et al., 2001; Watson et al., 1995). The PSWQ is a 16-item questionnaire assessing a tendency to worry (e.g., "My worries overwhelm me"). The MASQ and PSWQ have both previously been shown to have good internal consistency and test-rest reliability (Nitchke et al., 2001; Watson et al.,1995; Brown et al., 1992; Molina & Borkovec, 1994).

Bi-Factor Model:

As previous mentioned we used bifactor model to measure symptom levels of internalized psychopathology. It accounts for co-occurring symptoms (e.g., common internalizing), and distinct, independent, factors capturing what is specific to each symptom (e.g., depression- and anxiety-specific factors) (Banich et al, 2020). This is important as we are trying to understand the neural correlates of common and specific factors of internalizing symptomatology (See Figure 8) focusing on symptoms rather than diagnoses.

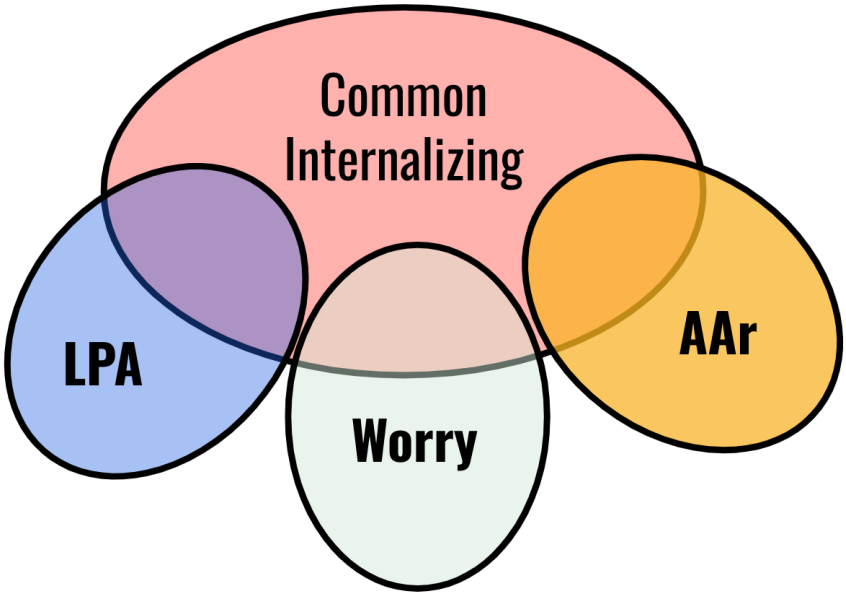


Figure 7: Venn Diagram of the association of all four factor scores

This Venn Diagram shows the common variance explained by Common Internalizing along with the other specific factors; Anxious Arousal (AAr), Low Positive Affect (LPA) and Worry or Anxious Apprehension. Our analyses focus on the common component and then the aspects that are unique to each of LPA, Anxious Arousal, and Worry (Anxious Apprehension.

As stated in Smolker et al (2022), we utilized parcels instead of individual questions as indicators because of the relatively small sample size and large number of items, with four parcels per factor (PSWQ: 4 item parcels; MASQ AA: 4-5 item parcels; MASQ LPA: 3-4 item parcels; MASQ LI: 2 item parcels). This model was designed so that all factors would load onto the common internalizing factor as this is meant to capture the covariance across all measures. The specific factors could then represent their unique, individual variance as the commonality between all three had already been captured by common internalizing. Each factor score could then be used as their own specific factor, analyzing what unique parts of internalizing disorders correlate to certain neural substrates.

Neuroimaging:

Diffusion Tensor Imaging (DTI), a type of structural Magnetic Resonance Imaging (MRI) technique was used to scan each adolescent's brain as this method evaluates microstructural changes in the brain by measuring the motility of water molecules in tissue (Tae et al, 2018). Structural MRI data were acquired at the Intermountain Neuroimaging Consortium located at the University of Colorado Boulder (Smolker, 2022). Testing for associations between individual differences in internalizing dimension factor scores and white-matter integrity was carried out employing the FSL analysis suite (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki). Brain matter was further broken down into tissue types differentiating, gray matter, white matter, and cerebral spinal fluid. We focused only on the white matter, our dependent variable whose integrity was measured in levels of FA, or the directionality and speed of water molecules along these tracts.

White Matter Analysis:

Analyses were carried out in a tract of-interest fashion. Tracts of interest included the genu, body, and splenium of the corpus callosum, the superior longitudinal fasciculus, the uncinate fasciculus, and the sagittal stratum. For all tracts besides the corpus callosum, we looked bilaterally at both hemispheres, obtaining measures for each tract in each hemisphere separately instead of averaging. To test for associations between tract white matter tract morphometry and the internalizing dimension factor scores, we carried out mixed-effects models, predicting white matter volume for each tract by factor scores for all four dimensions simultaneously, while controlling for sex, age, and mean fractional anisotropy of the entire brain. Gender has been shown previously to be a confounding factor influencing fractional anisotropy and resulting in sexual dimorphism in brain structure (Kanaan et al, 2012). This sexual dimorphism in myelination led us to include gender as a nuisance variable. We also wanted to control for individual differences in fractional anisotropy and therefore created a variable

controlling for mean diffusivity, the average mobility of water molecules along all 48 white matter tracts within the dataset. We ran analyses with and without this variable. The first model looked at how much variance was accounted for by each factor variable, along with the nuisance variables gender and age. The second model was identical but included a variable controlling for mean fractional anisotropy, allowing us to determine if associations were tract-specific.

When running these regressions, we used a Cook's D approach, which removed outliers that had undue influence on the results. Since we were running models with multiple tracts, we corrected our results with False Discovery Rates (FDR). This is a correction for p-values when running multiple comparisons and corrects for random events that falsely appear significant across tracts. We reported only findings that were significant once removing outliers with the Cook's D approach, which also had FDR-corrected p-values < 0.05.

RESULTS:

In order to understand how my independent variables of interest, the Common Internalizing factor score, the Low Positive Affect (LPA)-specific factor score, the Anxious Arousal-specific factor score, the Anxious Apprehension-specific factor score (i.e. worry), and Age and Gender are associated with the FA of the nine specific white matter tracts, I ran multiple regressions, one for each fiber tract.

A. Examinations Across the Entire Group (both Females and Males)

We only observed relationships between FA and factor scores for two aspects of internalizing psychopathology: Low Positive Affect and Worry (See Table 1). No relationships were observed for the Common Internalizing Factor or Anxious Apprehension.

Variables								
ROI	VOI	model	outliers removed	r^2	stand. beta	t-value	uncorr. p-value	FDR P
Left Superior Longitudinal Fasciculus	Low Positive Affect	Without Mean FA	4	0.29	0.464	4.197	0	0.001
Left Superior Longitudinal Fasciculus	Low Positive Affect	With Mean FA	4	0.342	0.401	3.563	0.001	0.006
Right Sagittal Stratum	Worry	Without Mean FA	5	0.171	-0.458	-3.397	0.001	0.01
Right Sagittal Stratum	Worry	With Mean FA	2	0.326	-0.305	-2.627	0.011	0.096

Table 2: Results table from the initial model with and without mean FA.

This table shows the statistically significant results found with the initial model, looking at the entire sample with and without mean fractional anisotropy.

i. Associations with the level of the Low Positive Affect-Specific Factor

After using a Cook's distance approach to remove outliers from the model (N= 4) the Left Superior Longitudinal Fasciculus and LPA-specific factors score had a positive and significant association (b = 0.46, $t(6,65)$ = 4.197, FDR-p = 0.001). This means the higher integrity within the left LPA was associated with participants experiencing higher levels of LPA (see Figure 8).

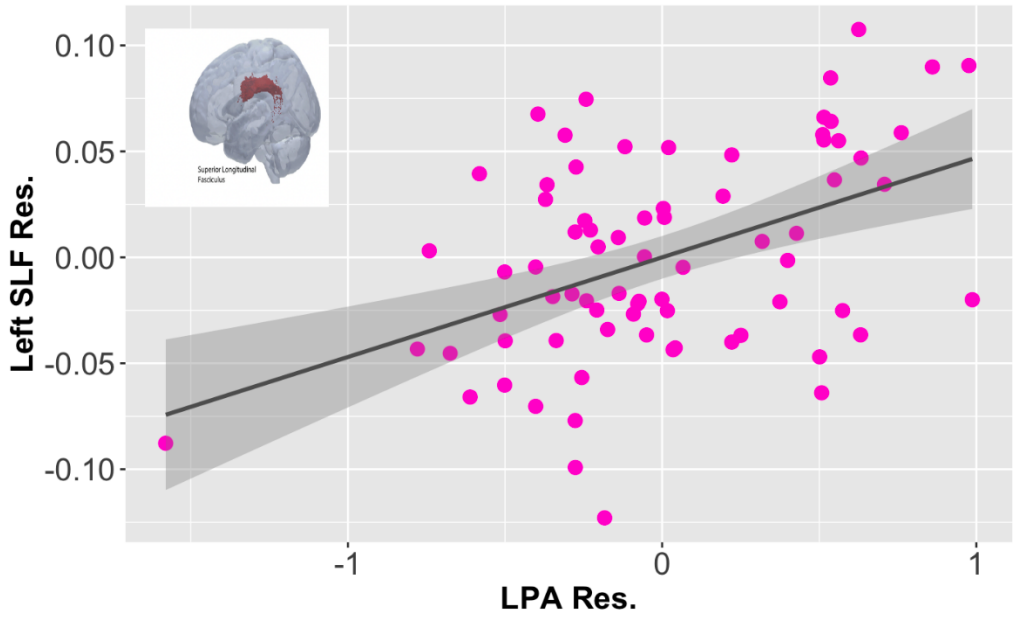


Figure 8: The relationship between residuals of the Low Positive Affect-specific factor and FA in the left superior longitudinal fasciculus accounting for age and gender

When we ran this regression also including mean average FA, after removing outliers (N=4), the FA of the left superior longitudinal fasciculus also had a significant and positive relationship with the LPA-specific factor (b= 0.401, t(7,67) = 3.563, FDR-p = 0.006). Results show the previous relationship holds strong even when accounting for individual FA differences (see Figure 9).

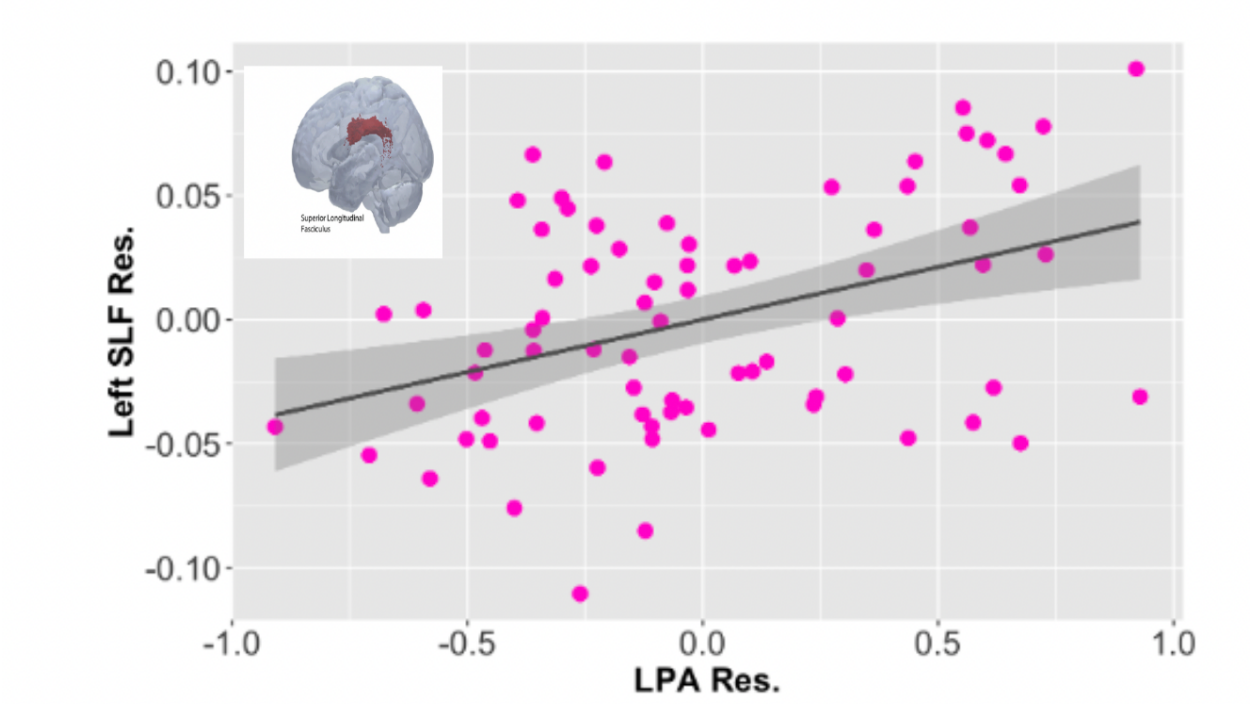


Figure 9: The relationship between the residuals of the Low Positive Affect-specific factor and FA in the left superior longitudinal fasciculus accounting for age, gender and mean brain FA

ii. Associations with the Anxious Apprehension-Specific (i.e., Worry) Factor

After using a Cook's distance approach to remove outliers from the model (N=5), FA of the Right Sagittal Stratum and levels of the Anxious Apprehension- specific factor score had a significant negative association (b = -0.46, t(6,67) = -3.397, FDR-p = 0.01). When mean brain FA was included (N=2) as a covariate in the analysis, this association only approached significance (b = -0.31, t(7,69) = -2.267, FDR-p = 0.096). This association means that participants with greater levels of worry showed lower levels of FA, or less integrity along the right sagittal stratum.

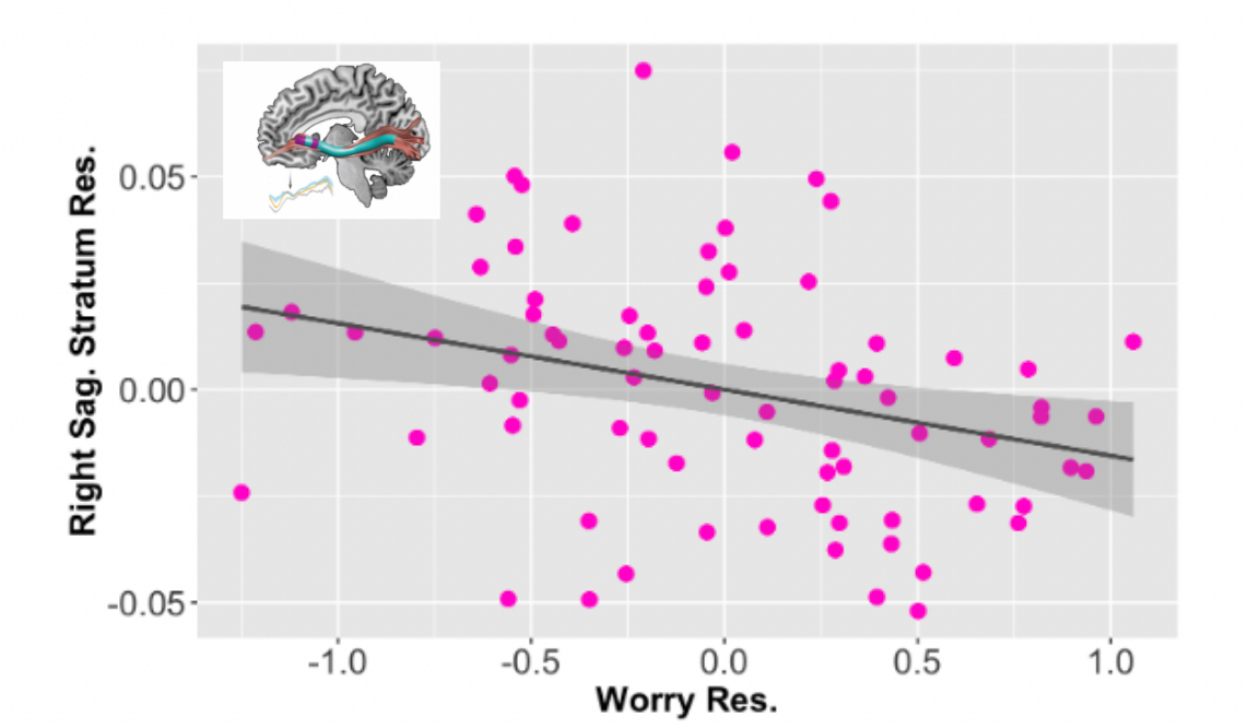


Figure 10: The relationship between the residuals of Apprehension-specific factor and FA of the right Sagittal Stratum accounting for age and gender.

B. Analyses of each Gender Separately

Because of sexual dimorphism in brain development and psychopathology among females and males in adolescence (Kanaan, 2012), we ran exploratory models with each respective gender separately. Because of the small group sizes, these results should be interpreted cautiously. Regressions run with only female participants resulted in no significant associations outside nuisance variables. Regressions run with only male participants resulted in four significant relationships.

Just as found for the group as a whole, after removing outliers (N= 2), the Left Superior Longitudinal Fasciculus had a positive association with LPA, (b = 0.60, $t(5,39)$ = 4.375, FDR-p = 0.001) in the model without brain mean anisotropy. Also as found for the group as a whole,

after removing outliers (N=1) the Left Superior Longitudinal Fasciculus had a positive association with LPA, (b = 0.483, $t(5,40)$ = 3.135, FDR-p = 0.035) when mean brain FA was included in the model. **A**n effect observed only in males was that the Body of the Corpus Callosum and anxious arousal had a positive association (N= 3, b = 0.53, $t(5,38)$ = 3.14, FDR-p = 0.035) when mean brain FA was not in the model, and also when it was, (N=2, b = 0.47, $t(5,39)$ = 3.245, FDR-p = 0.027). Neither of these findings reached significance in females, as seen in Table 3 below.

ROI	VOI	Model	r^2	stand. beta	t-value	uncorr. p-value	FDR P
Left Superior Longitudinal Fasciculus	Low Positive Affect	Without Mean FA	0.506	0.598	4.375	0	0.001
Left Superior Longitudinal Fasciculus	Low Positive Affect	With Mean FA	0.47	0.483	3.135	0.004	0.035
Body of the Corpus Callosum	Anxious Arousal	With Mean FA	0.506	0.467	3.245	0.003	0.027
Body of the Corpus Callosum	Anxious Arousal	Without Mean FA	0.493	0.53	3.142	0.004	0.035

Table 3: Results of regressions in males only, controlling for age. Results are shown for models in which mean brain FA was not controlled and separately when it was.

ROI	VOI	Model	r^2	stand. beta	t-value	uncorr. p-value	FDR P
Left Superior Longitudinal Fasciculus	Low Positive Affect	With Mean FA	0.284	0.067	0.405	0.688	0.857
Left Superior Longitudinal Fasciculus	Low Positive Affect	Without Mean FA	0.225	0.097	0.574	0.569	0.845
Body of the Corpus Callosum	Anxious Arousal	With Mean FA	0.469	0.015	0.113	0.911	0.911
Body of the Corpus Callosum	Anxious Arousal	With Mean FA	0.051	-0.005	-0.029	0.977	0.977

Table 4: Comparative regression findings for females. Results of regressions in females only, controlling for age. Results are shown for models in which mean brain FA was not controlled and separately when it was.

DISCUSSION:

By using a bifactor model of internalizing psychopathology in an adolescent sample, we found evidence that the integrity of specified white matter tracts in the brain is associated with symptom-specific dimensions of internalizing disorders. These results show that symptoms specific to low positive affect are associated with differences in fractional anisotropy across the left superior longitudinal fasciculus. This remained when accounting for mean fractional anisotropy, meaning this finding is tract-specific. Worry was also shown to be associated with the FA of the right sagittal stratum when not accounting for mean fractional anisotropy. However, results with mean FA included were trending leading us to believe the findings could still be tract linked.

Low Positive Affect associated with Left Superior Longitudinal Fasciculus

The superior longitudinal fasciculus is known to be one of the largest associative fiber bundle systems in the brain, connecting the frontal, parietal, and temporal lobes or the anterior to posterior regions of the brain (Janelle et al, 2022). Our findings suggest that the specific factor of low positive affect symptomatology is related to the speed and ease of communication from the anterior to posterior regions of the brain along this white matter tract. Higher integrity of this tact correlates to higher levels of reported LPA, meaning those individuals whose FA in this region is higher tend to have symptoms characterized by sadness, lethargy, and loss of pleasure. This finding is unusual, as we would expect higher integrity of these tracts to associate with higher cognition and therefore lead to reduced symptoms of internalizing disorders. The majority of prior research links higher FA with lower levels of psychopathology. To understand why our findings do not align with this we can consider a 2020 study that analyzed patterns of

neurobiological heterogeneity within youths with internalizing symptoms in two clinical subgroups (Kaczkurkin et al), 2020). The first subgroup showed greater overall psychopathology symptoms when compared to the second subgroup, however, both groups included participants who met the diagnostic criteria for an internalizing disorder subgroup. The results of this study found that the second subgroup showed relatively similar fractional anisotropy to typically developing youths, but with increased FA in both the right and left thalamic radiation. Hence, there is at least some precedent for increased FA in a group of individuals with higher levels of internalizing symptoms. Participants in our study were not screened for internalizing diagnoses and therefore our findings could potentially represent the subjects within our sample whose symptoms approached clinical levels.

A second hypothesis points to the function of the superior longitudinal fasciculus. The left lateralization of this tract is said to be implicated in verbal memory (Ribiero et al; 2024). Higher tract integrity, especially in males who tend to reach brain maturation slower than females might allow for more verbalization of thoughts and feelings. Low positive affect represents one loss of interest in pleasurable activities, sadness, and lethargy. If someone can verbalize these feelings quite well, it may allow them to ruminate or stew over them.

Due to the robust findings that remained after controlling for mean FA, we can state these findings are tract-specific and do not only account for differences in one's individual FA. Further research is needed to understand the exact correlation between this longitudinal tract and the impact of its integrity on one's levels of pleasure and engagement. One might explore these findings in clinical samples, or again within longitudinal data would be very telling as to what is tract-specific, population, and individual specific about these findings.

Right Sagittal Stratum and Worry

The sagittal stratum is composed of the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus, and posterior thalamic radiation. Due to the complexity of this tract, there is much unknown about its function and morphology. However, it has previously been characterized by involvement in language, visual information processing, and cognitive functioning (Di Carlo et al, 2019). The observed relationship is negative, meaning as participants showed less integrity within this tract or lower levels of FA they also experienced more symptoms of worry. This wasn't present when controlling for mean fractional anisotropy (although it approached significance), meaning this relationship may in part be explained by the individual differences in FA across participants and can not be characterized as tract-specific. We know this tract has previously been implicated in goal-oriented behavior which links to higher executive functioning (Hermesdorf, 2017). If participants had less integrity in these tracts, they may be experiencing executive dysfunction, explaining the association with high levels of worry. Abnormalities within this tract, which connects inferior frontal regions, have been implicated in expected value calculation (Grupe et al, 2013). This means that abnormalities in this tract inflate one's threat perception, increasing threat attention and heightening reactivity and maladaptive behaviors, all of which have resulted in higher levels of anxiety and worry (Grupe et al, 2013). However, more studies would need to repeat this study's findings to be able to say this concretely as this region is largely unstudied in adolescents, especially when looking at differences in FA.

Gender effects on neural correlates of internalized psychopathology

We ran all regressions for each gender population to see if there were separate findings when splitting up the two genders. However, the small sample size and inequivalent samples of each sex, suggest these findings be understood with caution as there were no specific *a priori*

hypotheses of sex differences. These differences were particularly notable in the left superior longitudinal fasciculus with LPA for males. This association remained for males in this region when also controlling for mean fractional anisotropy. We found a similar finding within the whole group but found no association with females, leading us to believe males were the driving force for this effect in the entire group. The developmental differences between males and females for white matter maturation have been previously looked at in populations slightly younger than the one in the current study. These studies have shown females tend to reach white matter maturation much earlier (Wang et al, 2012). This preliminary data could explain these differences as sexual brain dimorphism is more evident in adolescence.

We also found a significant association between decreased integrity of the body of the corpus callosum and anxious arousal in males. This means males who had lower levels of FA in this tract were more likely to experience somatic symptoms of anxiety. This finding may be related to the morphometry of the body of the corpus callosum, which connects the somatosensory areas of the brain.

These results provide more insight into the possible timeline of white matter maturation in adolescents, highlighting individual differences such as gender, age and mean FA that influence individual psychopathology. As stated previously, we expected gendered differences as previous studies have shown sexual dimorphism in white matter maturation. Our findings within the Corpus Callosum, align with previous findings which showed females had higher FA in this region as compared to males (Kanaan, 2012). Understanding the mechanisms that drive these gender differences helps explain our findings as differences in spatial and temporal patterns of myelination in males and females may be due to changes in sex steroid hormone levels during adolescent development (Ducharme et al, 1976).

Previous Literature

Previous studies looking at the neural substrates implicated in internalizing psychopathology have focused largely on FA in white matter tracts of clinically depressed adults and adolescents. The consensus of the majority of these studies reported reduced FA in adolescents with MDD (Radoeva, 2023) This supports the notion that dysconnectivity across brain regions may be a feature of adolescent depression, especially when those tracts reach the frontal lobe as executive functioning is a key aspect of mental health. A previous meta-analysis in adults with MDD reported lower FA in a widespread set of white matter regions: cingulum, corpus callosum, corona radiata, inferior fronto-occipital fasciculus, internal capsule, fornix, superior fronto-occipital fasciculus, and sagittal stratum (Zhou et al; 2022). However, the same meta-analysis did not find differences in white matter tracts in adolescents with MDD (Zhou et al; 2022) as the brain morphology of adolescents is much different from adults as adolescence is a time of brain development. One major difference between these age groups, which aligns with our findings is the importance of corpus callosum dysconnectivity in adolescents with internalizing disorders, as information is less efficiently relayed across the hemispheres in adolescents with MDD (Radoeva et al, 2023).

Studying adolescents is problematic as a seemingly small age range (16-24) encompasses a huge variation in brain development and it is possible that using this wider age range may be a contributing factor to the lack of statistically significant differences between adolescent FA and differences in levels of internalizing symptomology. Using age as a nuisance variable helped absorb some of this noise, but chronological age during adolescence may not be the best measure of actual development. Said differently, the maturity of any given 16-year-old varies greatly.

Limitations and Future Directions

The first limitation outlined in this study is the lack of causal relations. The correlational nature of these results limits our ability to make inferences regarding the etiology of internalizing psychopathology. However, our results provide a foundation, providing insight into the possible neural systems that may drive both comorbidity and heterogeneity in internalizing diagnoses. Another limitation is the lack of clinical screening. This study aimed at using participants that would reflect the general Denver adolescent population as a whole, a community sample. Yet, there is much unknown about the correlation between the general population and the clinical population. Understanding the psychological history of our participants may have helped us understand the individual differences in each participant's internalizing factor scores. Mental health diagnoses were not screened for before this study and replicating this study within a clinical group could clarify how individual differences in pre-study psychopathology influenced our findings. However, as previous studies have focused on these clinical diagnoses, the aim of our study was to rather focus on the symptom-specific dimensions of internalized psychopathology. This sample is also somewhat small, had a broad age range, and lacks equal gender representation which could have impacted our findings. Ongoing studies should be targeted to understand longitudinal approaches, looking at the maturation of adolescent brain matter over multiple time points.

Looking at the limitations of our DTI variables, we used FA which is not the best tool for understanding white matter integrity. Tools have advanced from the initial time of data collection for our participants and more myelin-specific instruments should be used in further studies. We also only analyzed nine tracts of interest due to previous research with implicated executive dysfunction in the presence of internalized disorders. However, we lacked a specific variable to control for one’s executive function. This additional variable could be added to highlight the

regions that are specific to each factor score dimension while separating how executive function outside of these dimensions is associated with psychopathology. This study should be replicated in a larger study to understand the true implications of neural substrates in associations with internalized psychopathology.

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Appendix A

ROI	VOI	model	outliers removed	stand. beta	t-value	uncorr. p-value	FDR P
Left Superior Longitudinal Fasciculus	Low Positive Affect	With Mean FA	4	0.401	3.563	0.001	0.006
Left Superior Longitudinal Fasciculus	Worry	With Mean FA	4	-0.014	-0.114	0.909	0.909
Left Superior Longitudinal Fasciculus	Anxious Arousal	With Mean FA	4	0.013	0.122	0.903	0.959
Left Superior Longitudinal Fasciculus	Common Intenalzing	With Mean FA	4	-0.266	-2.464	0.016	0.073
Left Superior Longitudinal Fasciculus	Age	With Mean FA	4	0.203	1.894	0.063	0.211

Table A: Overall output in the entire sample between left superior longitudinal fasciculus and all variables of interest when controlling for mean FA

ROI	VOI	model	outliers removed	stand. beta	t-value	uncorr. p-value	FDR P
Left Superior Longitudinal Fasciculus	Anxious Arousal	Without Mean FA	4	-0.002	-0.022	0.982	0.982
Left Superior Longitudinal Fasciculus	Age	Without Mean FA	4	0.195	1.799	0.076	0.689
Left Superior Longitudinal Fasciculus	Common Intenalzing	Without Mean FA	4	-0.223	-2.099	0.04	0.094
Left Superior Longitudinal Fasciculus	Low Positive Affect	Without Mean FA	4	0.464	4.197	0	0.001
Left Superior Longitudinal Fasciculus	Worry	Without Mean FA	4	-0.055	-0.443	0.659	0.933

Table B: Overall output in the entire sample between left superior longitudinal fasciculus and all variables of interest when not controlling for mean FA

ROI	VOI	model	outliers removed	stand. beta	t-value	uncorr. p-value	FDR P
Body of the Corpus Callosum	Worry	With Mean FA	2	0.142	0.935	0.358	0.46
Body of the Corpus Callosum	LPA	With Mean FA	2	0.014	0.082	0.935	0.967
Body of the Corpus Callosum	Anxious Arousal	With Mean FA	2	0.467	3.245	0.003	0.027
Body of the Corpus Callosum	Common Internalzing	With Mean FA	2	0.083	0.559	0.581	0.581
Body of the Corpus Callosum	Age	With Mean FA	2	0.015	0.101	0.92	0.92
Body of the Corpus Callosum	Mean Fractional Anisitropy	With Mean FA	2	0.494	2.833	0.009	0.015

Table C: Overall output in the entire sample between the body of the corpus callosum and variables of interest when controlling for mean FA

ROI	VOI	model	outliers removed	stand. beta	t-value	uncorr. p-value	FDR P
Left Superior Longitudinal Fasciculus	Low Positive Affect	With Mean FA	2	0.483	3.135	0.004	0.035
Left Superior Longitudinal Fasciculus	Anxious Arousal	With Mean FA	2	-0.179	-1.185	0.246	0.56
Left Superior Longitudinal Fasciculus	Common Internalzing	With Mean FA	2	-0.239	-1.62	0.116	0.576
Left Superior Longitudinal Fasciculus	Worry	With Mean FA	2	-0.099	-0.643	0.525	0.525
Left Superior Longitudinal Fasciculus	Age	With Mean FA	2	0.059	0.373	0.712	0.916

Table D: Overall output in the entire sample between the body of the corpus callosum and variables of interest when not controlling for mean FA