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Girls' Internalizing Symptoms and White Matter Tracts in Cortico-Limbic Circuitry

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Graduate Program in Psychology
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Abstract

Dysfunction in cortico-limbic circuitry is implicated in internalizing disorders, but less is known about whether structural abnormalities precede disorder, thus potentially marking risk. I therefore examined associations between white matter tract integrity in cortico-limbic circuitry at age 7, obtained using Diffusion Tensor Imaging, and concurrent and longitudinal patterns of internalizing symptoms, collected over a 5-year period, in 42 typically developing girls. Using Automated Fiber Quantification, diffusion properties were examined at multiple points along tract length (cf., an average diffusion measure of the entire tract). Concurrent internalizing symptoms were associated with reduced fractional anisotropy in segments of the cingulum bundle and uncinate fasciculus, bilaterally. Moreover, latent profile analysis showed that girls with increasing internalizing symptoms in early and middle childhood had reduced fractional anisotropy in these segments compared to girls with stably low internalizing symptoms. These results point to a putative neural mechanism underlying the course of internalizing symptoms in early childhood.

Keywords

Internalizing symptoms, white matter microstructure, Diffusion Tensor Imaging (DTI), latent profile analysis

Co-Authorship Statement

This thesis contains material from a manuscript bearing the same title that was submitted for publication. The manuscript was coauthored by Ola Mohamed Ali, Matthew Vandermeer, Dr. Haroon Sheikh, Dr. Marc Joannis, and Dr. Elizabeth Hayden. Ola Mohamed Ali analyzed the data and wrote the manuscript. Dr. Joannis provided guidance in the application of Automated Fiber Quantification to analyze DTI data. Matthew Vandermeer, Dr. Sheikh, Dr. Joannis and Dr. Hayden provided manuscript editing and feedback. Dr. Hayden provided supervision and was the principal investigator of the larger project.

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Table of Contents

Abstract	i
Keywords	i
Co-Authorship Statement	ii
Acknowledgments	iii
Table of Contents	iv
List of Tables	vi
List of Figures	vii
1. Introduction	1
1.1. Childhood Internalizing Symptoms	1
1.2. Neural Mechanisms	2
1.3. Functional Connectivity	5
1.4. Structural Connectivity	6
1.4.1. Diffusion Tensor Imaging	7
1.4.2. Quantitative analysis of DTI data	8
1.4.3. Automated Fiber Quantification	10
1.5. WM Microstructure in Internalizing Disorders	11
1.6. WM Microstructure in Subclinical Internalizing Problems	12
1.7. WM Structure and Internalizing Symptoms across Development	13
1.8. Current Study	14
2. Methods	15
2.1. Participants	15
2.2. Study procedure	15
2.3. Longitudinal Symptom Analysis	17

2.4. Diffusion Tensor Image Acquisition	18
2.5. Data Preprocessing and Analysis	19
2.6. Analytic plan	20
3. Results	22
3.1. Cross-sectional associations	22
3.2. Longitudinal Symptom Profiles.....	25
3.3. Risk group comparisons.....	27
4. Discussion.....	29
References.....	35
Ethics Approval.....	53
Curriculum Vitae.....	54

List of Tables

Table 1 Bivariate correlations between symptoms and mean FA of segments of interest of the bilateral CB and UF	23
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List of Figures

Figure 1 Examples of shapes of diffusion tensors	8
Figure 2 Tract profiles of a) left CB, b) right CB, c) left UF, and d) right UF, with red color indicating the segment where FA was significantly negatively correlated with internalizing symptoms. The range of p-values is shown on the color bar.....	25
Figure 3 Latent Profile Analysis plot for CBCL Anxiety/Depression symptom profiles (2-class model).	26
Figure 4 Tract FA profiles for the a) left CB, b) right CB, c) left UF, and d) right UF showing regions where mean FA differed significantly between risk groups.....	28

Girls' Internalizing Symptoms and White Matter Tracts in Cortico-Limbic Circuitry

1. Introduction

1.1. Childhood Internalizing Symptoms

Internalizing symptoms are a broad class of emotional and behavioral problems that are internally experienced, and are differentiated from externalizing problems, which are those that manifest outwardly as disruptive or aggressive behavior (Tandon, Cardeli, & Luby, 2009). In particular, internalizing problems are characterized by a propensity to experience negative emotions, increased perceptions of threat, and an elevated fear response. While the covert nature of these symptoms makes them difficult to detect and identify as problematic in young children, they are not uncommon early in development, and are fairly stable across the life span (Tandon et al., 2009; Zahn-Waxler, Klimes-Dougan, & Slattery, 2016). Moreover, early emerging subthreshold symptoms mark increased risk for depressive and anxiety disorders in later life (Clark, Rodgers, Caldwell, Power, & Stansfeld, 2007; Copeland, Shanahan, Costello, & Angold, 2009; Reinke & Ostrander, 2008; Toumbourou, Williams, Letcher, Sanson, & Smart, 2011), particularly when relatively elevated and stable.

The impact of early internalizing symptoms, even when subthreshold, is significant. For example, children with these symptoms have poor academic performance, low emotional competence, and problematic peer and family relationships (Ialongo, Edelsohn, Werthamer-Larsson, Crockett, & Kellam, 1994; Masten & Cicchetti, 2010; Masten et al., 2005; Mathews, Koehn, Abtahi, & Kerns, 2016). Moreover, as noted previously, they are at especially high risk for persistent and severe mental health outcomes (Kaplow et al.,

2002; Luby, 2010; Luby, Si, Belden, Tandon, & Spitznagel, 2009) which exact a substantial economic burden. Indeed, annual estimates of the burden due to depression alone are as high as \$53 billion USD (Greenberg et al., 2003), with more recent studies reporting indirect costs as high as USD \$210.5 billion USD (Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015). Given this steep toll, research that speaks to the early origins of risk is vital for informing early identification, prevention, and intervention efforts.

1.2. Neural Mechanisms

Deficits in affect processing and regulation characterize an array of internalizing problems (Pagliaccio, Luby, Luking, Belden, & Barch, 2014; Zahn-Waxler et al., 2016), implicating brain structures that govern these functions as mediators of risk for disorder. Indeed, extant literature on adult internalizing psychopathology points to structural and functional abnormalities in cortico-limbic circuitry, a primary neural network governing affective processing (Leppänen, 2006a; Phillips, Drevets, Rauch, & Lane, 2003b). This circuitry is composed of key structures in the limbic system and frontal lobe, each with a specialized function in the processing of emotional information (Phillips, Drevets, Rauch, & Lane, 2003a). In particular, activation of the amygdala occurs in response to emotionally evocative stimuli, including facial expressions, pictures, videos, and words (Okon-Singer, Lichtenstein-Vidne, & Cohen, 2013). Accordingly, the amygdala plays a crucial role in the detection of emotional valence, integrating information about the personal relevance of a stimulus through afferent projections from neocortical structures (Lindquist, Wager, Kober, Bliss-Moreau, & Feldman Barrett, 2012; Tsuchiya, Moradi, Felsen, & Yamazaki, 2009). In addition, amygdalar connections to the hippocampus

modulate the formation of emotional memories, while hippocampal influence on the amygdala affects the amygdala's response to emotional stimuli (Phelps, 2004; Richardson, Strange, & Dolan, 2004). Conscious experience of emotion is thought to be governed by frontal regions, including the prefrontal cortex (PFC), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC; Quirin & Lane, 2012). For instance, functioning of the OFC is associated with integration of internal and external sensory cues, while that of the PFC and ACC is associated with selective attention and inhibitory control (Lindquist et al., 2012).

Magnetic resonance imaging (MRI) studies demonstrate volumetric reductions in the PFC, OFC, ACC, amygdala, and the hippocampus, in both adults with current and remitted depression (Bremner et al., 2002; Hastings, Parsey, Oquendo, Arango, & Mann, 2004; MacQueen et al., 2003). The precise causal mechanisms that account for these brain-disorder associations are unclear; however, work on healthy adults at risk for depression, indexed by family history, suggests that these structural factors may be a precursor to illness, rather than a consequence (Amico et al., 2011). It is also possible that these structural characteristics interact with environmental factors that serve as more proximal triggers of disorder; for example, reduced hippocampal volume has been found in depressed women with a history of childhood sexual abuse (Vythilingam et al., 2002). Volumetric reductions in the amygdala and PFC have also been reported in anxiety disorders (van Tol et al., 2010), although findings have been less consistent (Shin & Liberzon, 2010).

Sex differences in the prevalence of internalizing disorders are robust, such that they are more common in women than men (McLean, Asnaani, Litz, & Hofmann, 2011;

Nolen-Hoeksema, 2001). As such, extant work on normative sex differences in neural functioning related to emotion processing may also inform our understanding of risk pathways. Functional MRI (fMRI) studies show that women exhibit stronger brain activation to emotional stimuli, especially those with negative valence, compared to men (Stevens & Hamann, 2012). In particular, relative to men, women display greater activation of regions within the cortico-limbic circuitry to such stimuli, namely the amygdala and medial PFC, and this activation is accompanied by subjective report of elevated emotional and physiological arousal (Bradley, Codispoti, Sabatinelli, & Lang, 2001; Stevens & Hamann, 2012). fMRI studies of clinical populations are fairly consistent with this literature, showing abnormalities in activity of the cortico-limbic circuitry in depression and anxiety (Etkin & Wager, 2007; Leppänen, 2006b; Price & Drevets, 2012). For instance, depressed patients show greater amygdalar activation to sad stimuli and reduced activity in response to positively-valenced stimuli (Price & Drevets, 2012). In addition, regions of the ACC and the PFC that are associated with reward and positive emotions show reduced activity in response to reward in depression, which is further associated with subjective ratings of anhedonia (Price & Drevets, 2012). Hyperactivation of the amygdala and dorsal ACC has been implicated in the threat hypersensitivity and elevated fear response that characterize anxiety disorders (Duval, Javanbakht, & Liberzon, 2015; Shin & Liberzon, 2010). Increased and reduced activation of the PFC have both been reported, and appear to vary depending on the anxiety disorder in question (Duval et al., 2015). Thus, investigating structure and function of the cortico-limbic circuitry in at-risk and clinical populations can shed light on the mechanisms implicated in the development of internalizing psychopathology.

1.3. Functional Connectivity

While work on abnormalities in grey matter volume and neural activation has vastly improved our understanding of the neural bases of internalizing disorders, a focus on individual grey matter structures fails to capture the dynamic nature of brain functioning. Contemporary models of brain function emphasize the highly connected and interactive organization of the brain, whereby distinct regions communicate with and influence each other (Sporns, Chialvo, Kaiser, & Hilgetag, 2004). Indeed, bidirectional axonal connections exist between elements of the cortico-limbic circuitry, such that the limbic system relays information to cortical regions which in turn regulate limbic activation, influencing emotional reactivity (Banks, Eddy, Angstadt, Nathan, & Luan Phan, 2007; Ghashghaei, Hilgetag, & Barbas, 2007). Consistent with this notion, a recent meta-analysis of the literature on resting-state functional connectivity in major depressive disorder showed reduced connectivity within networks involved in the cognitive control of attention, emotion processing, and emotion regulation (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015). In addition, increased connectivity within networks involved in self-referential thought, a key cognitive process that goes awry in depression, has been reported (Kaiser et al., 2015; Nejad, Fossati, & Lemogne, 2013). Similarly, decreased connectivity between emotion processing centers (e.g., amygdala) and frontal regulation regions (e.g., PFC) has been reported in patients with social anxiety disorder, generalized anxiety disorder, and panic disorder, suggesting a brain correlate of the dysregulated fear responding that characterizes these disorders (Etkin, 2010a, 2010b; Etkin, Prater, Schatzberg, Menon, & Greicius, 2009; Etkin & Wager, 2007). However, studies of functional connectivity have tended to show low within-subject test-retest reliability,

perhaps due to the rapid reconfiguration of neuronal activity (Honey et al., 2009). In contrast, methods that speak to structural connectivity provide a practical, potentially more robust approach to studying brain networks (Van Den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009), especially in children whose brains are undergoing especially rapid change.

1.4. Structural Connectivity

Structural connectivity describes the anatomical structures that mediate communication between grey matter structures; past work has shown this method yields anatomical indices that are relatively stable over time and highly predictive of functional connectivity (Honey et al., 2009). These anatomical structures are primarily composed of myelinated axons that are organized into fiber bundles known as white matter (WM) tracts. The cingulum bundle (CB) and the uncinate fasciculus (UF) are two major WM tracts that govern communication within the cortico-limbic circuitry, and connect grey matter structures within the same hemisphere. As they mediate communication between regions that subservise different functions, these tracts are integral to the organization of complex behaviors (Schmahmann, Smith, Eichler, & Filley, 2008). The CB runs from the anterior to the posterior of the brain, and is thought to mediate communication between components of the limbic system and the cingulate gyrus, as well as between regions of the cingulate gyrus (Catani & Thiebaut de Schotten, 2008). The UF is a hook-shaped bundle that connects the limbic system to regions of the PFC (Catani & Thiebaut de Schotten, 2008), and is implicated in relaying information about emotional valence to the PFC, as well as top-down regulatory information from cortical regions to the limbic

system. Given their anatomical projections, structural integrity of these tracts is crucial to emotion processing and regulation (Schmahmann et al., 2008).

1.4.1. Diffusion Tensor Imaging

In-vivo investigation of the structural integrity of WM tracts is made possible by Diffusion Tensor Imaging (DTI), an MRI technique that relies on the diffusion of water molecules within brain tissue to create the MR contrast (Soares, Marques, Alves, & Sousa, 2013). Patterns of diffusion of water molecules vary depending on the properties of the medium which they are in; for instance, water diffusion in cerebrospinal fluid is random and equal in all directions but is directionally-restricted in axonal tracts. In particular, water diffusivity in the highly organized WM bundles is greatest along the tract axis rather than perpendicular to it (Jellison et al., 2004). Moreover, the rate and directionality of water diffusion is influenced by WM microstructure, such as the degree of myelination of a fiber bundle, axonal packing, and composition of intra-cellular fluid (Alexander et al., 2011).

Several indices of tract integrity can be obtained from DTI: Fractional Anisotropy (FA) reflects the degree of overall diffusion, with lower values indicating reduced WM integrity, axial diffusivity (AD) reflects motion of water molecules parallel to the axis of an axon or fiber bundle, and radial diffusivity (RD) reflects motion of water molecules perpendicular to the tract axis. Accordingly, AD and RD provide more specific information about the axonal factors driving FA (Alexander et al., 2011). For example, reduced myelination and diffuse packing of axons within a bundle result in greater perpendicular diffusion, indexed by increased RD values, while degeneration of axons

leads to cellular infiltration that results in lower AD values, due to change in the composition of intracellular fluids (Aung, Mar, & Benzinger, 2013).

1.4.2. Quantitative analysis of DTI data

DTI images WM microstructure by modeling diffusion of water molecules as a tensor in a voxel, the basic unit of 3D space in MRI. A tensor is a 3D representation of the magnitude (described in eigenvalues) and direction (described as eigenvectors) of diffusion of water molecules in a voxel. A diffusion tensor where water molecules are diffusing equally in all directions, and as such having equal eigenvalues, is said to be isotropic (Figure 1a), whereas an anisotropic tensor represents a voxel where diffusion is greatest along one direction (Figure 1b).



Figure 1 Examples of shapes of diffusion tensors
(From: Tromp, 2016)

Indices of WM integrity are a scalar quantification of a tensor's eigenvalues, such that λ_1 corresponds to AD, and the average of λ_2 and λ_3 corresponds to RD. FA quantifies the fraction of diffusion that is anisotropic by providing a measure of the difference between the largest eigenvalue relative to the others (Aung et al., 2013; Tromp, 2016). After tensors at each voxel are estimated, fiber tracts are generated by tractography algorithms that trace a path of greatest likelihood between neighboring voxels, according

to the orientation of the previous tensor. Tractography occurs in three steps: seeding, propagation, and termination. Seeding describes defining the points from which fiber tracts will be drawn. Seeding can be user-defined such that the user selects region(s) of interest (ROIs) and manually places the seeds in them. Alternatively, it can be conducted on the whole brain so that it is initiated from each WM-containing voxel that has FA greater than a predetermined threshold. While whole-brain seeding is aptly used for exploratory research, user-defined seeding is best suited when ROIs are decided upon *a priori*. During propagation, the direction of greatest diffusivity is tracked from voxel to voxel to generate fiber tracts. Deterministic fiber tracking assumes that the largest eigenvector reflects the dominant orientation of the fiber tract, generating one path from each voxel (Descoteaux, Deriche, & Anwander, 2007; Soares et al., 2013). In contrast, probabilistic algorithms take into account a degree of uncertainty and calculate a distribution of fiber tract orientations from each voxel (Descoteaux et al., 2007; Feldman, Yeatman, Lee, Barde, & Gaman-Bean, 2010). As a voxel may contain multiple fiber tracts, each with a different orientation, probabilistic algorithms produce more accurate results, especially for tracts whose trajectories are unknown (Feldman et al., 2010). However, probabilistic tractography can be computationally burdensome and time-consuming, and deterministic algorithms are sufficiently reliable for producing WM tracts whose trajectories are well-established (Feldman et al., 2010; Mukherjee, Chung, Berman, Hess, & Henry, 2008). Finally, fiber tracking is terminated when FA drops below a predetermined threshold, or a projected pathway exceeds a specified turning angle (Soares et al., 2013).

Tensor estimation and tractography parameters differ depending on the processing method used, and the purposes of the study. For example, ROI analysis entails manual delineation of *a priori* regions of interest for each subject, which requires extensive anatomical knowledge, is time-consuming, and prone to error due to intra-subject variability in brain structure (Snook, Plewes, & Beaulieu, 2007; Soares et al., 2013). In Voxel-Based Analysis (VBA), subjects' brains are automatically registered to a common stereotaxic space, and whole brain, voxel-by-voxel comparisons are done between subjects, which increases the chance of false positives due to multiple comparisons (Snook et al., 2007). Tract-based Spatial Statistics (TBSS) overcomes some of these issues by conducting whole brain seeding, then creating tract representations based only on voxels assumed to be at the center of well-established tracts (Feldman et al., 2010; Smith et al., 2007). One limitation common to these methods is that they average diffusion properties along an entire tract once its constructed, disregarding normative variations in WM microstructure that occur along its trajectory (Johnson et al., 2014; Yeatman, Dougherty, Myall, Wandell, & Feldman, 2012).

1.4.3. Automated Fiber Quantification

Automated Fiber Quantification (AFQ) is a novel quantitative analysis method that overcomes some of the shortcomings of traditional DTI analysis methods by automating identification of ROIs across subjects, and allowing quantification of diffusion properties at individual points along a tract (Yeatman et al., 2012). Briefly, diffusion maps are registered onto standard space so that ROIs are consistent across subjects. Seeding is performed on the whole brain, and deterministic tractography is used to generate fiber tracts that are later segmented based on standard ROI coordinates (Yeatman et al., 2012).

AFQ allows the user to select the number of equidistant nodes along a tract for which diffusion properties (e.g., FA) can be quantified, which can then be averaged to produce segments of interest within a tract (Yeatman et al., 2012). AFQ is described in more detail in Methods.

Due to its novelty, few studies have used AFQ to examine brain-behavior associations, especially in the context of internalizing psychopathology. However, those that have indicate that fine-grained analyses of WM microstructure are more sensitive to disorder progression (Hall, Dougherty, & Reiss, 2016; Sarica et al., 2017), making it well-suited to the study of the neural correlates of early emerging internalizing symptoms.

1.5. WM Microstructure in Internalizing Disorders

Consistent with the functional connectivity literature, past work using DTI, irrespective of the quantitative analysis method used, implicates abnormalities in the WM microstructure of major tracts within cortico-limbic circuitry in adult depressive and anxiety disorders (Ayling, Aghajani, & Fouche, 2012; Sexton, Mackay, & Ebmeier, 2009). These studies have focused largely on geriatric depression, given that aging is associated with WM decline. However, differences in WM can and do appear earlier in development; specifically, the limited work on depressed adolescents and young adults using DTI shows reduced FA of WM in prefrontal areas, cingulum, limbic system and thalamic projection tracts, as well as lower FA in the superior longitudinal fasciculus (SLF) which connects the frontal and parietal lobes and plays a role in attention and memory (Bessette, Nave, Caprihan, & Stevens, 2014; Cullen et al., 2010; Kamali,

Flanders, Brody, Hunter, & Hasan, 2014; Klarborg et al., 2013; Murphy & Frodl, 2011) Conversely, AFQ of DTI data indicated increased FA in segments of the corticospinal tract (CST) in depressed women compared to controls, a finding which otherwise may have been obscured if comparisons based on mean FA of this tract were used (Sacchet et al., 2014). Given its connectivity to cortical motor centers, structural abnormalities of the CST may be related to the psychomotor symptoms of depression (Sacchet et al., 2014).

1.6. WM Microstructure in Subclinical Internalizing Problems

WM abnormalities may also mark vulnerability to early onset depression. For instance, healthy young women with parental history of depression and subclinical anhedonia have lower FA of both left and right CBs (Keedwell et al., 2012). Similarly, Huang and colleagues (2011a) report reduced WM integrity of the left CB, corpus callosum, bilateral SLF, UF, and fronto-occipital fasciculi in at-risk adolescents with parental history of depression. Young adults with social anxiety and generalized anxiety disorder exhibit reduced volume and FA of the UF compared to controls (Baur et al., 2013; Baur, Hänggi, & Jäncke, 2012; Hilbert, Lueken, & Beesdo-baum, 2014; Phan et al., 2009). However, Han and colleagues (2008) reported increased FA of the anterior and posterior regions of the cingulate gyrus in adults with panic disorder, which may account for the increased attention to interoceptive cues seen in this disorder, given that the cingulate is involved in associative learning and selective attention (Hayden & Platt, 2009). Using AFQ, Ho and colleagues (2017) reported that reduced FA in a frontal segment of the right UF predicted sensitivity to early life stress and subsequent anxiety symptoms in a community sample of adolescents. Thus, more fine-grained identification of specific loci in WM tracts may elucidate how microstructure variations within a tract

drive observed behavioral differences, compared to averaging diffusion properties along an entire tract's length. As a whole, these findings support cross-sectional associations between WM abnormalities and both subthreshold and clinical manifestations of internalizing psychopathology in adolescents and adults.

1.7. WM Structure and Internalizing Symptoms across Development

Despite evidence that structural and functional abnormalities in cortico-limbic circuitry mediate risk for internalizing psychopathology, it is unclear whether such abnormalities appear early in life, and whether they are associated with markers of risk in childhood. Early emerging internalizing symptoms, even when subthreshold in severity, are clearly related to increased risk for later disorder (Copeland et al., 2009; Roza, Hofstra, Van Der Ende, & Verhulst, 2003; Toumbourou et al., 2011), particularly when such symptoms are persistently elevated across childhood. Typically developing children show variation in symptom manifestations such that some have consistently low symptoms while others show stably elevated symptoms over time, and are hence at greater risk for later disorder (Fernandez Castelao & Kröner-Herwig, 2013; Sterba, Printein, & Cox, 2007). Consistent with increased prevalence of depression and anxiety in women, longitudinal studies of internalizing symptoms in preschoolers further reveal higher initial levels of general anxiety in girls than boys, as well as greater increases in symptoms over a 2-year period (Carter et al., 2010). Similarly, steeper increases in internalizing symptoms towards late childhood have been observed in girls compared to boys (Shanahan, Calkins, Keane, Kelleher, & Suffness, 2014). However, longitudinal research examining factors that contribute to persistence of internalizing symptoms over time, particularly in girls, is lacking. If specific patterns of structural connectivity in

cortico-limbic circuitry are associated with girls' elevated early symptoms, this would provide additional support for the notion that these structural patterns serve as a mechanism of risk for internalizing symptoms.

1.8.Current Study

We used DTI to examine the integrity of the WM of the CB and UF in a community sample of 42 seven-year-old girls, looking at cross-sectional associations with internalizing symptoms. In addition to its aforementioned value as a tool for investigating structural connectivity, DTI also has the key benefit of facilitating the study of neural structures in children as acquisition time is considerably shorter compared to other neuroimaging methods. Moreover, to see whether any cross-sectional associations between FA and symptoms were found when considering more long-term symptom presentations, I capitalized on the availability of multiple waves of symptom scores, collected over a 5-year period, to examine whether WM integrity was associated with stably elevated symptoms during early childhood. We anticipated that elevated internalizing symptoms concurrent to DTI data collection would be associated with reduced FA in the CB and UF, and that girls with stably elevated symptoms would also show reduced FA in these tracts compared to girls with other symptom patterns.

2. Methods

2.1. Participants

Participants were 46 seven-year-old girls drawn from a larger study of 409 community-dwelling children, recruited to this study based on their responses to a stress task designed to elicit cortisol reactivity (described further below). At the larger study baseline, eligible three-year-old children were living with at least one biological parent and had no significant medical or psychological problems (e.g., Kryski, Smith, Sheikh, Singh, & Hayden, 2011; Kryski et al., 2013). As a further screen at baseline, children were administered the Peabody Picture Vocabulary Test (PPVT; Dunn & Dunn, 1997), and were of average cognitive ability ($M = 112.0$, $SD = 14.05$). The larger sample was predominantly White (93.2%) and over half of families were middle-class, reporting a family income between CAD \$40,000 and CAD \$100,000. These characteristics are comparable to that of the population of London, ON. area from which the children were recruited (Statistics Canada, 2017). In addition to the baseline assessment at age three, children and families in the larger study participated in additional waves of data collection when children were six and eight years old, with girls in the current study participating in a DTI session at age 7 ($M = 6.7$, $SD = .68$). This study was approved by the University of Western Ontario Health Sciences Research Ethics Board.

2.2. Study procedure

Of the 409 children comprising the longitudinal sample, only right-handed girls ($N = 210$) were eligible to participate in this follow-up, given that the aim of this study is to investigate early neural risk factors in girls, and to control for sex differences in neural

development. The eligible participant pool was refined further based on girls' cortisol reactivity to a stress task conducted at baseline (Kryski et al., 2011), such that only girls at the extreme ends of cortisol reactivity (i.e., using quartile scores based on mean cortisol level over time and cortisol change from baseline in response to the stress task) were eligible (N = 117). The effect of cortisol reactivity on neural factors was part of a different planned analysis from the one examined in the present study, and for the present purposes all children were considered in a single group irrespective of cortisol reactivity data ¹. Parents gave consent for 58 girls, who were then invited to participate in a 1-hour mock scanning session to determine whether girls were likely to be compliant with imaging data collection procedures. Forty-six girls completed both the mock-scanner training and the DTI session. To further increase compliance at the DTI session, the assessment was described as a "space mission" and girls were given an astronaut suit to wear during the visit. Girls also watched a developmentally appropriate film during image acquisition. The primary caregiver completed the Child Behavior Check List (CBCL; Achenbach, 1991) during either the mock scanner or DTI visit.

¹ While cortisol reactivity was not a variable of interest in the current study, I conducted further analyses to ensure that high- vs. low-cortisol reactivity did not influence any current findings. A chi-square test showed that latent profile membership was not associated with cortisol reactivity group $\chi(1) = 0.120, p = .729$. Moreover, cortisol reactivity groups did not differ on demographics, symptom scores, or white matter microstructure measures reported below (all $ps > .05$).

2.3. Longitudinal Symptom Analysis

The CBCL was also completed by the child's primary caregiver when girls were three ($M = 3.5$, $SD = .30$), six ($M = 6.0$, $SD = .31$), and eight ($M = 8.7$, $SD = .71$) years old. The CBCL asks the parent to rate the frequency and intensity of their child's emotional and behavioral problems over the past 6 months. As I was interested in internalizing symptoms common in middle childhood, scores from the anxious/depressed subscale were used in this study (12 items; range of Cronbach's α s = .68 - .80).

Early internalizing symptoms show homotypic continuity with later clinically significant manifestations of anxiety and depression (Toumbourou et al., 2011; Zahn-Waxler et al., 2016), particularly when stably elevated over time. To support our analyses using cross-sectional measures of symptoms, and to better capture symptom presentation over time, I used longitudinal Latent Profile Analysis (LPA; Mplus v.8, Muthén & Muthén, 2017) to characterize our participants in terms of internalizing symptom patterns across early childhood (obtained concurrent to the DTI session as well as at ages 3, 6, and 8). LPA allows one to examine individuals based on shared patterns of observations that can then be related to other variables of interest (Berlin, Parra, & Williams, 2014). As a data reduction method, LPA identifies the smallest number of homogenous groups that account for maximum variation in the indicator variables (Lazarsfeld & Henry, 1968; Oberski, 2016), symptom scores at each time point in this case. The optimal number of profile groups is determined by estimating a series of *a priori* models that can then be compared against each other using relative goodness-of-fit indices. Each individual is assigned probability scores that reflect the likelihood that they

belong to each of the profile groups in each model based on their similarity to others in the group.

Past work on childhood internalizing symptom patterns suggests some youth exhibit low-stable symptoms, others show high variability, and other youth show stably elevated symptoms (Sterba et al., 2007). Accordingly, and given our relatively small sample, I tested 3- and 2-profile group models. To determine the best fitting model, the Vuong-Lo-Mendell-Rubin and Lo-Mendell-Rubin adjusted LRT goodness-of-fit indices were used, which test whether an additional profile group significantly improves the model's ability to explain variation in the indicator variables. The resulting groups were used for further analyses, described subsequently.

2.4. Diffusion Tensor Image Acquisition

MRI scans were conducted at Western's Centre for Functional and Metabolic Mapping (CFMM), on a 3T Siemens TIM Trio scanner equipped with a 32-channel head coil. Using echo planar imaging, a non-diffusion weighted b0 scan was first acquired in the axial plane, followed by diffusion-weighted scans in 30 directions ($b_1 = 700 \text{ s/mm}^2$; iPAT GRAPPA acceleration factor = 2; TR = 9100 ms; TE = 91 ms; voxel size = 2 x 2 x 2 mm; 62 slices; in-plane FOV = 192 mm²). Additionally, a T1-weighted anatomical MRI scan was collected using a T1 MPRAGE sequence (iPAT GRAPPA acceleration factor = 2; TR = 2300 ms; TE = 3.01 ms; voxel size = 1 x 1 x 1 mm; 192 slices; in-plane FOV = 256 mm²).

2.5. Data Preprocessing and Analysis

Diffusion MRI data were preprocessed using the mrDiffusion package available as part of the open-source VISTA Lab MATLAB toolbox (<http://web.stanford.edu/group/vista/cgi-bin/wiki/index.php/MrDiffusion>). The raw diffusion weighted images were first corrected for eddy current distortions and movement by co-registration to the non-diffusion weighted (b0) image, using a rigid body transformation algorithm. Raw images were then resampled, combining the eddy current-correction, motion-correction and anatomical alignment parameters using the 7th-order b-spline algorithm available in the SPM8 toolbox. Due to excessive motion, 4 girls were excluded yielding a final sample of 42 participants. Diffusion tensors were fit using a least-squares algorithm, which also removed outliers from the tensor estimation. The eigenvalue decomposition of the diffusion tensor at each voxel was then computed, and used to calculate AD, RD and FA at each voxel.

2.5.1. Automated Fiber Quantification Pipeline

Analysis of the processed DTI data and identification of major fiber tracts was done individually for each participant using the Automated Fiber Quantification pipeline (Yeatman et al., 2012). This pipeline consists of 3 main steps: (1) whole-brain tractography, (2) region-of-interest (ROI)-based tract segmentation and cleaning, and (3) fiber tract quantification. First, a deterministic streamline tracking algorithm (STT) is applied to estimate fiber tracts, and tracking is initiated from voxels with FA values greater than 0.3. Streamlines are traced in both directions along the principal diffusion axes, and propagation is terminated if the FA estimated at the current position is below

0.2 in addition to the angle between the last path segment and next step direction being greater than 30° (Yeatman et al., 2012).

In the second step, the resulting tracts are segmented into anatomically defined fascicles using the waypoint ROI procedure (Wakana et al., 2007). Briefly, this procedure categorizes tracts as belonging to the same fascicle if they pass through two waypoint ROIs, pre-defined based on anatomical locations derived from group-averaged DTI data in the Montreal Neurological Institute ((MNI) space for each of the twenty major white matter fascicles. Each resulting fiber is then compared to a standard fiber tract probability map (Hua et al., 2008) and tracts with high scores, reflecting higher probability of belonging to a fascicle, are retained. Using a 3-dimensional Gaussian distribution of fiber spread at each node, outlier fibers (i.e., those with a mean length more than 4 standard deviations above the mean or more than 5 standard deviations from the fiber tract core) are removed. This results in coherently bundled fibers at the center of the tract's trajectory. The third step, quantification, is limited to the tract's core which spans the portion bounded by the ROIs. This limits variability between subjects due to anatomical differences between brains. The relative contribution of a fiber to the fascicle is weighted based on its distance from the core.

2.6. Analytic plan

Diffusion properties (FA, AD, and RD) were quantified at 100 equidistant nodes along the core of the CB and UF bilaterally, yielding a tract profile for each tract. Cross-sectional associations between concurrent CBCL score on the Anxious/Depressed subscale and FA were examined using bivariate correlations, which were used to

determine whether region-wise brain-behavior associations were localized to specific segments within each tract. We corrected for multiple comparisons using permutation-based suprathreshold cluster tests outlined by Nichols and Holmes (2002); this approach employs a Monte Carlo method to assess a false positive rate for each tract, which can then be used to determine the number of spatially contiguous nodes that must meet an alpha of .05 in order to be considered significant. Cluster threshold was set at $p = .01$, corrected, and yielded the following cluster sizes for each tract: left CB = 7; right CB = 7; left UF = 8; right UF = 9. FA was averaged across the contiguous nodes, and the mean FA of each segment was used in further analyses. As FA is a global index of WM microstructure, I was interested in investigating which axonal properties influenced FA in these regions. To this end, I computed correlations between concurrent symptoms and mean RD, and mean AD, for each segment. Next, I used to t-tests to compare mean FA of the resulting segments between the risk groups derived from LPA.

3. Results

3.1. Cross-sectional associations

Table 1 presents bivariate correlations between all major study variables. FA at each node along the tracts of interest were used as our primary DVs. No significant associations of FA and internalizing symptoms with demographic variables were noted. Bivariate correlations between FA and CBCL Anxious/Depressed subscale scores revealed that FA in two distinct segments of the left CB was significantly associated with concurrent internalizing symptoms: a posterior segment and a medial segment (shown in Figure 2a). Similarly, a significant negative correlation between concurrent symptoms and FA of a medial segment of the right CB was found, shown in Figure 2b. Further analyses with other diffusion measures revealed that only mean RD of the posterior segment of the left CB was positively correlated with concurrent symptoms ($r(38) = .351$, $p = .031$), suggesting that reduced integrity of that segment may be due to increased diffusion in the direction perpendicular to the fascicle axis.

In the UF, bivariate correlations revealed significant negative associations between concurrent symptoms and medial segments in the left UF (Figure 2c), and right UF (Figure 2d). AD in the medial segment of the left UF was found to be negatively correlated with concurrent symptom scores; $r(39) = -.338$, $p = .035$, suggesting that reduced FA in this region can be explained by impeded diffusion along the long axis of the fascicle. In the right UF, RD in the medial segment was found to be positively associated with concurrent symptoms; $r(39) = .400$, $p = .012$, indicating that reductions in mean FA can be accounted for by impeded diffusion in the direction perpendicular to the fascicle axis.

Table 1 Bivariate correlations between symptoms and mean FA of segments of interest of the bilateral CB and UF

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. T1 CBCL Anxious/Depressed Symptoms	-													
2. T2 CBCL Anxious/Depressed Symptoms	-0.01													
3. T3 CBCL Anxious/Depressed Symptoms	0.11	.72**												
4. T4 CBCL Anxious/Depressed Symptoms	0.09	.45**	.42*											
5. FA of the posterior segment of the left CB	0.21	-.55**	-.51**	-.34*										
6. FA of the medial segment of the left CB	0.14	-.33*	-.45**	-0.17	.36*									
7. FA of the medial segment of the right CB	.38*	-.39*	-.43*	-0.33	.47**	.62**								
8. FA of the medial segment of the left UF	-0.27	-0.29	-.38*	-0.09	0.31	0.19	0.09							
9. FA of the medial segment of the right UF	0.10	-.42**	-.45**	-0.09	.54**	.42**	0.20	.40**						
10. Age at DTI (years)	0.04	-0.19	-0.12	-0.18	-0.04	-0.05	0.09	0.18	0.03					
11. Risk group	0.19	.68**	.85**	.51**	-.44**	-.39*	-0.32	-.36*	-.38*	-0.23				
12. PPVT	-0.18	-0.01	-0.01	0.14	-0.03	-0.28	-0.24	0.20	0.09	.33*	-0.09			
13. Family Income	-0.27	-0.10	-0.25	0.09	-0.10	0.26	-0.14	0.01	0.21	-0.17	-0.24	0.22		
14. Ethnicity	0.04	0.01	-0.24	-0.06	0.14	0.05	0.09	0.25	0.15	0.28	-0.23	0.20	-0.23	-
Mean	1.60	2.53	2.26	3.16	0.40	0.51	0.49	0.44	0.39	6.72	0.24	112.00	3.85	1.14

SD	1.78	2.12	2.26	3.01	0.06	0.07	0.08	0.06	0.05	0.68	0.43	14.43	1.09	0.35
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Note. * $p < 0.05$; ** $p < 0.01$; CBCL = Child Behavior Checklist; FA = Fractional Anisotropy; CB = Cingulum Bundle; UF = Uncinate Fasciculus; PPVT Peabody Picture Vocabulary Test; DTI = Diffusion Tensor Imaging; Risk group: Low = 0; High = 1; Family income: 1 <\$20,000, 2 = \$20,000—\$40,000, \$40,001—\$70,000 = 3, \$70,001—\$100,000 = 4, and >\$100,001 = 5; Ethnicity: 1 = Caucasian, 2 = Other.

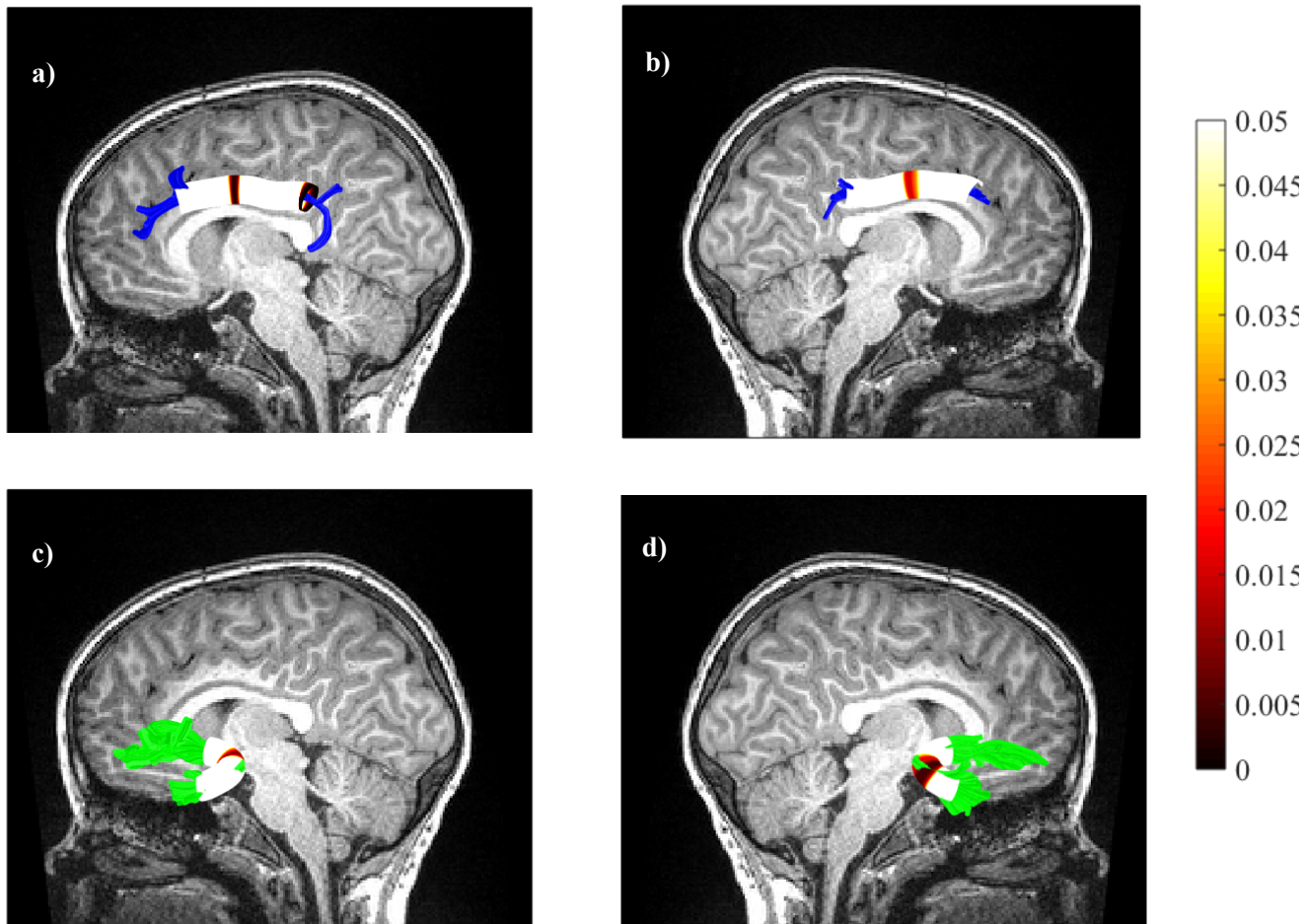


Figure 2 Tract profiles of a) left CB, b) right CB, c) left UF, and d) right UF, with red color indicating the segment where FA was significantly negatively correlated with internalizing symptoms. The range of p-values is shown on the color bar.

3.2. Longitudinal Symptom Profiles

As a supplement to the cross-sectional symptom measures, I used LPA to examine whether similar associations with structural connectivity would be found with any high-risk groups that emerged based on symptom manifestations over time. The Vuong-Lo-Mendell-Rubin and Lo-Mendell-Rubin adjusted LRT tests comparing a 2- vs. a 3-profile

group model were non-significant ($p = .28$ and $p = .29$, respectively), indicating that a more parsimonious, 2-profile group model was sufficient to represent the symptom patterns during childhood in this sample (Figure 3).

The first profile group consisted of girls whose symptoms remained consistently low over time (referred to as the low-risk group; $N = 32$, 76.2%), while girls in the second profile group had symptoms that increased over time and then stabilized (referred to as the high-risk group; $N = 10$, 23.8%). The groups did not differ on age at each data collection time point, family income, or ethnicity (all $ps > .05$). While T1 symptoms did not differ significantly between the groups ($p > .05$), not surprisingly, the high-risk group exhibited significantly higher symptoms than the low-risk group at T2 ($t(38) = -5.74$, $p < .001$), T3 ($t(37) = -9.98$, $p < .001$), and T4 ($t(36) = -3.54$, $p = .001$).

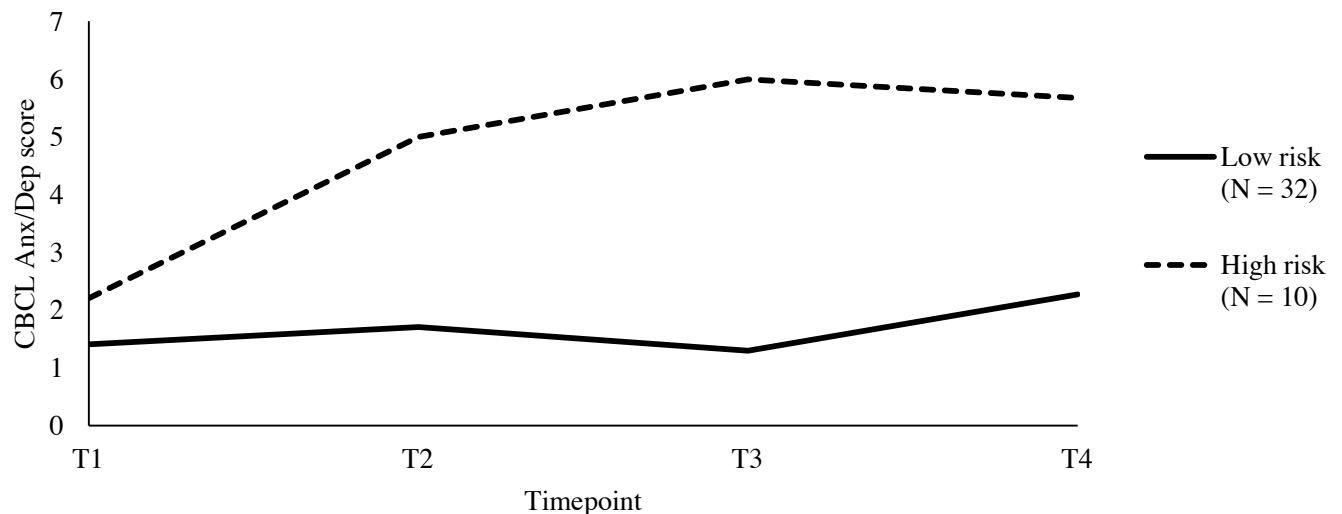


Figure 3 Latent Profile Analysis plot for CBCL Anxiety/Depression symptom profiles (2-class model).

3.3. Risk group comparisons

Next, I used independent group t-tests to compare the high- and low-risk groups on mean FA of segments previously identified; i.e., the medial and posterior segment of the left CB, medial segment of the right CB, medial segment of the left UF, and medial segment of the right UF. The high-risk group had significantly lower FA of the left medial and posterior CB segments ($t(39) = 3.07, p = .004$; $t(39) = 2.60, p = .013$, respectively) as compared to the low-risk group. This difference was marginal for the right CB segment ($t(39) = 1.99, p = .055$). The high-risk group also had lower FA in medial segments of the left ($t(39) = 2.41, p = .020$), and right UF ($t(39) = 2.63, p = .012$), compared to the low-risk group. Regions of significance along each tract profile are shown in Figure 4. These findings are consistent with cross-sectional associations with symptoms reported here, implicating reduced FA in segments of the left and right CB, and left and right UF in girls at high-risk for internalizing disorders, suggesting that these brain patterns mark the presence of persistent behavioral manifestations of internalizing disorders risk, rather than just concurrent symptoms.

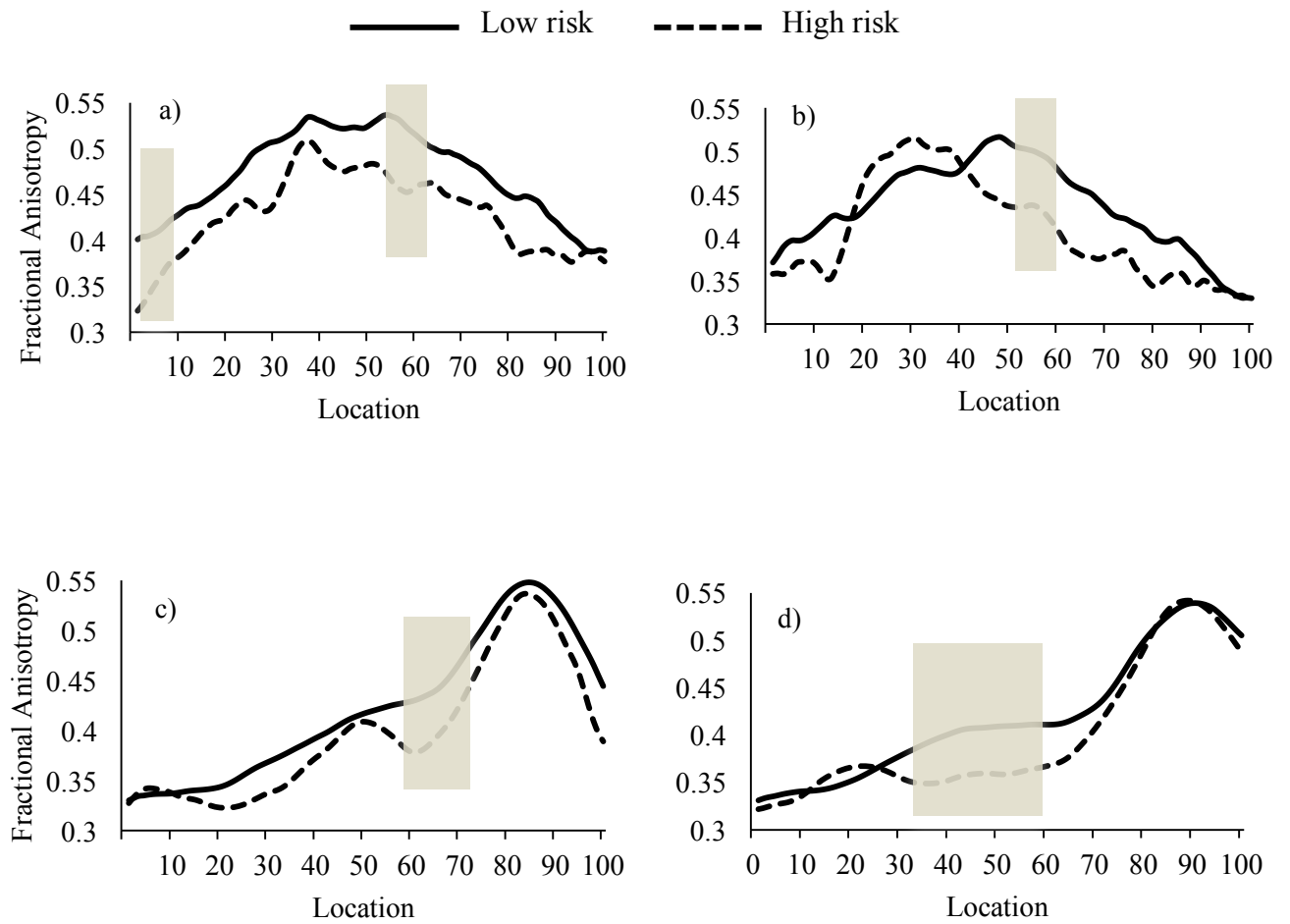


Figure 4 Tract FA profiles for the a) left CB, b) right CB, c) left UF, and d) right UF showing regions where mean FA differed significantly between risk groups. Location of cingulum bundle nodes are shown posterior to anterior, and those of the uncinate fasciculus are shown temporal to prefrontal.

4. Discussion

I investigated associations between early emerging internalizing symptoms and microstructure of WM tracts involved in emotion processing and regulation in a community sample of girls. Consistent with previous literature on at-risk adolescents and adults (Huang, Fan, Williamson, & Rao, 2011b; Keedwell et al., 2012; Whalley et al., 2013), concurrent internalizing symptoms were associated with reduced integrity of two major WM tracts within cortico-limbic circuitry, the cingulum bundle and uncinate fasciculus. Further, girls with elevated internalizing symptoms across childhood exhibited reduced integrity of WM in segments of these tracts. In line with past work with clinical populations demonstrating abnormalities in structural connectivity within affective processing networks (Kaiser et al., 2015), reduced integrity within the CB and UF appearing in childhood may underlie aberrant emotion processing patterns that manifest as early emerging anxious and depressed symptoms. Overall, abnormal structural connectivity of the cortico-limbic circuitry may be a mechanism by which early emerging symptoms confer elevated risk for later internalizing psychopathology.

My finding that reduced integrity of WM in the CB and UF is associated with internalizing symptoms in childhood sheds light on specific brain-behavior relationships that may put children at risk for anxious and depressive symptoms specifically. Internalizing disorders are characterized by maladaptive emotion processing, which is governed by cortico-limbic circuitry (Drevets, Price, & Furey, 2008; Phillips et al., 2003a; Price & Drevets, 2012). Phillips and colleagues (2003) proposed that emotion perception occurs through processes that are determined by activity of specific neural structures within this circuitry. In particular, the amygdala is involved in modulating

attention and immediate response to emotionally evocative stimuli, suggesting that its activity governs identification of the emotional significance of a stimulus, information that is relayed to frontal regions such as the cingulate gyrus and PFC (Phillips et al., 2003a; Stein et al., 2007). Activity of the cingulate and PFC is associated with affective and behavioral responding, as well as reward anticipation and modulation of autonomic nervous system functioning, which, in turn, underlies neurovegetative processes, such as arousal, sleep and appetite known to go awry in internalizing psychopathology (Koenigs & Grafman, 2009; Phillips et al., 2003a). Finally, appraisal and production of affective state processes are regulated by activity in the dorsal regions of the PFC and anterior cingulate gyrus, and the hippocampus (Phillips et al., 2003a). In particular, activity of these regions is correlated with inhibition of the stress response, effortful control, and active allocation of attentional resources (Ahmed, Bittencourt-Hewitt, & Sebastian, 2015). Taken together, this model highlights the significance of bidirectional pathways between frontal regions and the limbic system in determining both adaptive and maladaptive emotion expression and regulation (Stein et al., 2007). Accordingly, the reduced WM integrity in the UF and CB found here in young girls may mark impairments in the capacity to effectively regulate responses to stress, potentially laying the groundwork for internalizing vulnerability in the context of negative life events. Indeed, previous work from our lab revealed reduced FA in tracts adjacent to the thalamus, right ACC and superior frontal gyrus in girls with elevated cortisol reactivity, that was moderated by early parenting (Sheikh et al., 2014). Furthermore, Dufford and Kim (2017) recently demonstrated lower FA in portions of the UF and CB in children from lower-income families who had greater exposure to cumulative stress. Longitudinal

studies are needed to more clearly understand interactions between stressors and brain structure as they relate to the development of risk for internalizing disorders.

I identified reduced FA in localized segments of the CB and UF using an automatic fiber alignment, identification and quantification procedure that also permitted me to identify behavioral associations with specific points along each tract (Yeatman et al., 2012). Specifically, reduction in WM integrity was limited to medial and posterior segments of the left CB, medial segment of the right CB, and medial segments of the left and right UF. I focused on the core region of the CB, which runs within the WM of the cingulate gyrus, a key structure implicated in controlling arousal and visceral states associated with emotion and social behavior (Hadland, Rushworth, Gaffan, & Passingham, 2003). In particular, the CB mediates communication between distal portions of the cingulate gyrus, and links the prefrontal regions with the temporal cortex by way of the cingulate gyrus (Catani & Thiebaut de Schotten, 2008; Jellison et al., 2004; Kier, Staib, Davis, & Bronen, 2004; Schmahmann et al., 2008). Accordingly, the CB is hypothesized to play an integral role in organizing perception of emotional valence associated with memory, motivation and somatic sensations (Schmahmann et al., 2008). It is likely that the segments with reduced WM integrity identified in the current sample are those where the CB receives input from the medial cingulate gyrus and projects to the rostral cingulate gyrus, reflecting dysfunction in communication within this structure. This may in turn contribute to the deficits in emotional arousal and social withdrawal associated with internalizing symptoms.

The UF is a local association fiber that links the PFC with structures within the temporal lobe, specifically the amygdala (Catani & Thiebaut de Schotten, 2008; Kier et

al., 2004). Given the top-down regulatory influence of the PFC on the temporal lobe (Banks et al., 2007; Ghashghaei et al., 2007), the UF is implicated in regulating emotional responsivity to auditory and visual stimuli, as well as cognitive processes underlying emotion (Schmahmann et al., 2008). My findings tie elevated symptom profiles in girls with reduced WM integrity abnormalities in the medial segments of the left and right UF, which may correspond to the region that marks the tract's entry into the temporal lobe (Catani, Howard, Pajevic, & Jones, 2002; Kier et al., 2004). Reduced WM integrity of this segment may indicate disruptions in regulatory control by the PFC on the amygdala, accounting for elevated negative emotional responsivity seen in girls with elevated internalizing symptom profiles. Essentially, reduced WM integrity localized to specific segments, rather than the entire tract, may be related to the subthreshold nature of the internalizing symptoms in this sample. It is possible that reductions in WM integrity becomes increasingly prominent as symptoms become more pronounced and impairing.

By examining specific diffusion indices, I found that elevated symptoms were associated with higher RD in the left posterior CB and right medial UF, and reduced AD in the left medial UF. Directionality and degree of water diffusion is a passive process that is determined by the boundaries that restrict motion. Generally, radial diffusivity is restricted by myelin that occupies intra-axonal space within a bundle, whereas diffusivity along the axis of the tract is influenced by changes in the extracellular water due to inflammation and degree of axonal maturation that impedes motion of water molecules, and is higher in healthy axonal bundles (Alexander et al., 2011; Alexander, Lee, Lazar, & Field, 2007; Aung et al., 2013). Thus, reduced AD may indicate delayed maturation in that region of the tract, or potential degeneration of the axonal bundle, whereas higher

RD indicates less restricted diffusivity of water molecules perpendicular to the tract axis and may be suggestive of demyelination. Future studies should examine RD and AD in clinical populations to determine which axonal properties account for WM abnormalities in internalizing disorders toward the goal of replicating and extending current findings.

The present study has several strengths: I capitalized on multiple waves of data collection across childhood in girls not yet experiencing clinically significant symptoms, providing novel information regarding structural connectivity patterns that may be important in driving vulnerability to disorder. However, DTI data were obtained at one time point only, precluding my ability to make conclusions about the temporal association between symptoms and abnormalities in brain structure. Relatedly, given that DTI data were collected midway through this longitudinal study, data were unsuitable for tests of DTI as a predictor of growth/trajectories of symptoms over time. I focused on subthreshold symptoms, a known marker of risk for later disorder (Clark et al., 2007; Copeland et al., 2009; Toumbourou et al., 2011); thus, further longitudinal work that follows participants well into the age of risk for frank disorder is needed to provide more conclusive information on brain-disorder associations over time. The current investigation was limited to girls, which is a reasonable first step toward uncovering mechanisms that contribute to the increased risk of internalizing psychopathology in women. However, further research is needed to determine if similar patterns are observable in young boys. Moreover, the use of a primarily Caucasian, low-risk sample limits the generalizability of our findings, and extending this work to more heterogeneous and higher-risk samples is needed.

My findings dovetail with past work on the neural correlates of adolescent and adult internalizing disorders by demonstrating similar patterns in childhood, highlighting aspects of structural connectivity of the cortico-limbic circuitry in girls that may put them at risk for later internalizing psychopathology. Findings suggest that WM alterations constitute a putative mechanism that underlies the maintenance of internalizing symptoms across childhood, potentially laying the groundwork for the onset of depressive and anxiety disorders later in development.

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Ethics Approval



Use of Human Participants - Ethics Approval Notice

Principal Investigator: Prof. Elizabeth Hayden
File Number: 100725
Review Level: Delegated
Approved Local Adult Participants: 0
Approved Local Minor Participants: 44
Protocol Title: Neural correlates of early adversity and stress-sensitivity in young children (REB #18093)
Department & Institution: Social Science/Psychology, Western University
Sponsor: University of Western Ontario

Ethics Approval Date: June 19, 2012 **Expiry Date:** September 30, 2012
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Revised Study End Date		

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.


 Signature

Ethics Officer to Contact for Further Information

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Curriculum Vitae

Name:	Ola Mohamed Ali
Post-secondary Education and Degrees:	<p>McMaster University Hamilton, Ontario, Canada 2008-2012 H. B.Sc.</p> <p>McGill University Montreal, Quebec, Canada 2013-2015 M.Sc.</p>
Honours and Awards:	<p>Western University Ralph S. Devereux Award in Psychology (\$1,600) 2017-2018</p> <p>Western University Graduate Research Award (\$200) 2018</p> <p>Children's Health Research Institute (CHRI) (\$10,000) Graduate Research Fellowship 2018-2019, 2017-2018, 2016-2017</p> <p>McGill University – Faculty of Medicine (\$1,900) International Travel Award 2014</p> <p>McGill University (\$2,025) Graduate Excellence Award 2013</p> <p>McMaster University Dean's Honor List 2011-2012, 2010-2011</p> <p>McMaster University (\$6,000) President's Entrance Award 2008</p>
Related Work Experience	<p>Clinical Research Coordinator American Center for Psychiatry and Neurology</p>

2015-2016

Graduate Teaching Assistant
Western University
2017, 2016

Publications and Conference Presentations:

Mohamed Ali, O., Vandermeer, M., R., J., Sheikh, H., I., V., M., Joanisse, M., F. & Hayden, E. P., (under review). *Girls' Internalizing Symptoms and White Matter Tracts in Cortico-Limbic Circuitry*. Submitted.

Mohamed Ali, O., Vandermeer, M., R., J., Sheikh, H., I., Mackrell, S., V., M., Joanisse, M., F. & Hayden, E. P., (2018). *Associations between elevated internalizing symptoms during early childhood and integrity of white matter tracts in cortico-limbic circuitry*. Abstract accepted to the annual meeting of the Flux Society, Berlin, Germany.

Mohamed Ali, O., Kryski, K. R., Durbin, C. E. & Hayden, E. P., (2018). *Caregiver personality and child temperament interact to predict change in hostile parenting*. Abstract accepted to the annual meeting of the Society for Research in Psychopathology, Indianapolis, IN.

Vandermeer, M. R. J., Daoust, A. R., **Mohamed Ali, O.**, Joanisse, M. F., Barch, D. M. & Hayden, E. P., (2018). Gray matter concentrations in never-depressed children at risk for depression. Abstract accepted to the annual meeting of the Flux Society, Berlin, Germany.

Alsaadi T., Kassie S., **Mohamed Ali O.**, Mozahem K., Al Fardan S. & Ahmed A. M., (2018). Psychiatric comorbidity in neurological disorders: Towards a multidisciplinary approach to illness management in the United Arab Emirates. *Front. Hum. Neurosci. Conference Abstract: 3rd International Conference on Educational Neuroscience*. doi: 10.3389/conf.fnhum.2018.225.00010

Ali, O. M. (in press). Behavioral inhibition/activation, personality correlates of. In B. J. Carducci (Editor-in-Chief) & A. Di Fabio, D. H. Saklofske, & C. Stough (Vol. Eds.), *The Wiley-Blackwell encyclopedia of personality and individual differences: Vol. III. Personality processes and individual differences*. Hoboken, NJ: John Wiley & Sons.

Mohamed Ali, O., Sheikh, H. I., Mackrell, S. M. V., Kryski, K. R., Joanisse, M. F. & Hayden, E. P., (2017, September). *Investigating the association between white matter microstructure of the uncinate fasciculus and vulnerability markers of anxiety: A Diffusion Tensor Imaging study*. Poster presented at the Thirty First Annual Meeting of the Society for Research in Psychopathology, Denver, CO, USA.

Vandermeer, M. R. J., Joanisse, M. F., Daoust, A., **Mohamed Ali, O.**, Salisbury, M., Barch, D. M., & Hayden, E. P. (2017). *Resting state functional connectivity in children at high risk for depression*. Poster presented at the Thirty First Annual Meeting of the Society for Research in Psychopathology, Denver, CO, USA.

Fernandez Cruz, A.L., **Ali, O. M.**, Asare, G., Whyte, M. S., Walpola, I., Segal, J. & Debruille, J.B., (2016), Embrained drives to play extraordinary roles predict schizotypal traits in the general population. *Npj Schizophrenia* (2), doi:10.1038/npjschz.2016.35

Gu, V., **Mohamed Ali, O.**, L'Abbée Lacas, K. & Debruille, J. B. (2014). Investigating the effects of antipsychotics and schizotypy on the N400 using event-related potentials and semantic categorization. *J. Vis. Exp.* (93), e52082, doi:10.3791/52082

Mohamed Ali, O., Walker, A., Laporte, J. & Debruille, J.B., (2014, July). The effect of atypical antipsychotics on an index of semantic processing in highly schizotypal participants. Poster presented at the IMPRS Neurocom Summer School, London, U.K.

Mohamed Ali, O., Walker, A., Laporte, J. & Debruille, J.B., (2014, April). The effect of atypical antipsychotics on an index of semantic processing in highly schizotypal participants. Poster presented at the annual meeting of the Cognitive Neuroscience Society, Boston, MA.

Mohamed Ali, O., Slikhanian, A., Fernandez Cruz, A.L., Walpola, I. & Debruille, J.B., (2013, November). The effect of atypical antipsychotics on event-related potentials according to schizotypal personality traits. Poster presented at the annual meeting of the Society for Neuroscience, San Diego, CA.

Mohamed Ali, O., Berman, A., Slikhanian, A., Fernandez Cruz, A.L., Walpola, I. & Debruille, J.B., (2013, November). The effect of antipsychotics and schizotypy on slow positive waves evoked by social information. Poster presented at the annual pre-meeting of the Society for Social Neuroscience, San Diego, CA.

Fernandez Cruz, A.L., Walpola, I., **Mohamed Ali, O.** & Debruille, J.B., (2013, April). Deciding whether or not a social role fits us: An electrophysiological study of the timing of role processing. Poster presented at the annual meeting of the Cognitive Neuroscience Society, San Francisco, CA.

Mohamed Ali, O. & Hapidou, E., (2012, May). Coping with chronic pain: A retrospective data analysis of the Chronic Pain Coping Inventory. Poster presented at the annual Day in Psychiatry conference, Hamilton, ON.

Mohamed Ali, O. & Hapidou, E., (2012, April). Coping with Chronic Pain. Oral presentation at the annual Ontario Undergraduate Research conference, York, ON.