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Brain Structure and Mental Health in Typically Developing Youth and Those with Prenatal Alcohol Exposure and Postnatal Adversities

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Brain Structure and Mental Health in Typically Developing Youth and Those with Prenatal Alcohol Exposure and Postnatal Adversities

by

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Abstract

Mental health problems are linked to brain structural changes, primarily in the limbic system and prefrontal cortex, and commonly emerge in adolescence. Although progress has been made in understanding mental health disorders, there are still gaps in mental health research in pediatric typically-developing cohorts. Research clarifying the underlying mental health-related biomarkers aids in recognition and treatment of mental health problems and builds a foundation for studying other populations, such as those with neurodevelopmental disorders.

Prenatal alcohol exposure (PAE) can broadly impact development, including brain structure and mental health. Nearly all individuals with PAE suffer from comorbid mental health disorders, yet little is known about altered brain structure and mental health in youth with PAE.

To assess brain structure, structural magnetic resonance imaging (MRI) was used, specifically T1-weighted and diffusion-weighted imaging to measure anatomical volumes and properties of white matter, respectively. Internalizing and externalizing behaviours, negative behaviours directed either internally or externally, respectively, were used to assess symptoms relevant to mental health.

In a typical-development cohort, lower mean diffusivity (MD) and higher fractional anisotropy (FA) measures in the cingulum and uncinate were the main underlying biomarkers for internalizing and externalizing behaviours.

In the PAE study, youth with PAE showed significantly reduced volumes of the anterior cingulate cortex, superior frontal gyrus, and reduced FA in the cingulum and uncinate compared to controls. Youth with PAE and additional postnatal exposures exhibited similar brain structure to controls (i.e. volumes, FA and MD values), except in MD of the fornix. Both groups with PAE (with or without postnatal exposure) demonstrated higher externalizing behaviours than controls.

Between group differences in mental health-brain structure relationships were found in both limbic gray and white matter.

Together this research informs brain structure and mental health relationships in two important groups. With an understanding of typical development, a better understanding of the altered trajectories in PAE can be evaluated, and by having a more robust characterization of youth with PAE, improved services and interventions can be provided.

Preface

The research described in this thesis received ethics approval from the University of Calgary Conjoint Health Research Ethics Board, Project Name "Brain Development in Childhood and Adolescence", No. REB13-1346, April 24, 2014, and Project Name "Cumulative Risk Project", No. REB17-0663, June 8th, 2017. This thesis and the experimental studies within are original work written and performed by Quinn R. Andre.

Chapter 3 was presented at the 2018 Organization for Human Brain Mapping (OHBM) Annual Meeting and has been submitted for publication to *Brain Structure and Function*. Chapter 4 was presented at the 8th International Research Conference on FASD and the 2019 OHBM Annual Meeting.

Throughout these projects, I was involved in recruitment, data collection, data processing, analysis, and manuscript composition. In Chapter 3, B. Geeraert was responsible for data collection, contributed to manuscript edits, and offered mentorship throughout. In Chapter 4, C. Ritter was responsible for recruitment and behavioural assessment acquisition, P. Kar assisted in recruitment and data collection, and C. McMorris held a supervisory role in the collaboration with an Applied Psychology lab. All authors in Chapter 4, including B. Gibbard and C. Tortorelli, contributed to concept formation and early adversity assessment. C. Lebel was the supervisory author on both projects and played a crucial role in all aspects of this work.

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List of Abbreviations

ADHD – Attention Deficit Hyperactivity Disorder

ASD – Autism Spectrum Disorder

BASC-2, PRS – Behavioural Assessment System for Children, 2nd Edition, Parent-Rating Scale

BD – Bipolar Disorder

BRAVO – Brain Volume Imaging

B_0 – Main Magnetic Field

CBT – Cognitive Behavioural Therapy

CSD – Constrained Spherical Deconvolution

CSF – Cerebrospinal Fluid

DTI – Diffusion Tensor Imaging

EPI – Echo Planar Imaging

f_0 – Larmor Frequency

FA – Fractional Anisotropy

FASD – Fetal Alcohol Spectrum Disorder

FDR – False Discovery Rate

FEG – Frequency Encoding Gradient

FOD – Fiber Orientation Distribution

FSPGR – Fast Spoiled Gradient Echo

GAD – Generalized Anxiety Disorder

GE – General Electric

MANOVA – Multiple Analysis of Variance

MD – Mean Diffusivity

MDD – Major Depressive Disorder

MRI – Magnetic Resonance Imaging

OCD – Obsessive Compulsive Disorder

ODD – Opposition Defiant Disorder

PAE – Prenatal Alcohol Exposure

PAE- - Prenatal Alcohol Exposure Without Postnatal Adversity

PAE+ - Prenatal Alcohol Exposure With Postnatal Adversity

PEG – Phase Encoding Gradient

PFC – Prefrontal Cortex

PTSD – Post Traumatic Stress Disorder

RF – Radiofrequency

ROI – Region of Interest

SES - Socioeconomic Status

SSG – Slice Selection Gradient

TE – Echo Time

TI – Inversion Time

TR – Repetition Time

γ - Gyromagnetic Ratio

λ - Eigenvalue

$\vec{v}$ - Eigenvector

Chapter 1: Thesis Overview

1.1 Thesis Rationale

Adolescence is a time of immense socio-emotional and biological changes. These simultaneous events contribute to the high prevalence of emerging mental health problems in youth (Blakemore, Burnett, & Dahl, 2010; Casey, Getz, & Galvan, 2008). Sadly, over 50% of adolescent mental disorders go untreated (Copeland et al., 2015), even though $51 billion is spent annually in Canada on mental health alone (Mental Health Commission of Canada, 2016). A better understanding of early behavioural indicators and the neurobiology underlying mental health symptoms is instrumental for improving intervention and prevention strategies, which in turn will minimize years of suffering and lower societal burden. Additionally, by understanding the neurological underpinnings of mental health-related symptoms in a typically-developing population, a foundation can be built which may be used for comparison by research in other populations.

Prenatal alcohol exposure (PAE) can cause widespread changes in brain and behaviour, and may result in a diagnosis of fetal alcohol spectrum disorder (FASD), the neurodevelopmental disorder associated with PAE and the number one preventable cause of developmental and intellectual disability in children (Vall, Salat-Batlle, & Garcia-Algar, 2015). The annual societal cost of FASD is approximately $2 billion in Canada alone (Popova, Lange, Burd, & Rehm, 2015), and it has a conservative estimated prevalence of 4% (Flannigan, Unsworth, & Harding, 2018; May et al., 2014). This is higher than autism spectrum disorder (ASD; 1.5%)(Public Health Agency of Canada, 2018), Down Syndrome (0.16%)(Public Health Agency of Canada, 2013), and cerebral palsy (0.1%)(Statistics Canada, 2019). Comorbidity of mental health disorders in FASD

is approximately 90% (Pei, Denys, Hughes, & Rasmussen, 2011), highlighting the need for further understanding of the high susceptibility of this population and possible neurological indicators.

PAE is rarely the sole adverse exposure in this population. One study of 1,400 participants with FASD found 70% were no longer in the care of their biological parents, averaging 3 out-of-home placements, 34% experienced physical abuse, and 24% experienced sexual abuse (Astley, 2010). Another study found that 67% of study participants with PAE had experienced either physical or sexual abuse, or domestic violence (Streissguth et al., 2004). Despite the frequent co-occurrence of these postnatal adversities with PAE, little research has focused on their cumulative effects.

The limbic system and prefrontal cortex (PFC) are key regions of altered development that are associated with a number of mental health disorders (Casey et al., 2008; Price & Drevets, 2010). The limbic system is a network of subcortical gray and white matter regions, and includes the amygdala and hippocampus, along with the cingulum, uncinate fasciculus, and fornix. The PFC is a region of the frontal lobe and includes subregions such as the superior frontal and middle frontal gyri, and the anterior cingulate cortex. During adolescence these brain systems develop extensively and simultaneously and support the development of behavioural functions such as emotion regulation, executive function, and impulsivity control. This is perhaps why mental health problems often arise in adolescence when these abilities and underlying brain systems are developing (Casey et al., 2008). Thus, investigations of the relationships between structure in these regions and mental health behaviors in adolescence are pertinent for various susceptible populations.

Magnetic resonance imaging (MRI) can be used to investigate underlying brain structures related to emergent mental health-related behaviours. MRI is a safe and reliable tool to image the

body by capitalizing on the magnetic properties of atomic nuclei. Different MRI techniques can aid in investigating various structural and functional properties of the brain. For example, T1-weighted imaging is often used for volumetric measurements of gray matter structures. Diffusion tensor imaging (DTI) can be used to probe white matter properties. Using MRI methods, previous research in youth with mental health disorders have shown lowered volumes in the PFC and subcortical structures, and decreased FA and increased MD in the connective white matter tracts (Price & Drevets, 2010; Waller, Dotterer, Murray, Maxwell, & Hyde, 2017). Similarly, altered development including lowered volumes, decreased FA and increased MD have been shown in youth with PAE across the brain (Coles et al., 2011; Lebel, Rasmussen, et al., 2008; Nardelli, Lebel, Rasmussen, Andrew, & Beaulieu, 2011).

1.2 Aims and Hypotheses

The goal of this research was to use T1-weighted and diffusion MRI to elucidate the relationships between internalizing and externalizing behaviours and brain structure in typically developing children and adolescents as well as those who have experienced PAE with or without postnatal adversity. Towards this goal, this project had two aims:

Aim 1: To identify relationships between internalizing and externalizing behaviours and brain structure of the limbic system and prefrontal cortex in typically developing children and adolescents.

Hypothesis 1: Worse internalizing and externalizing behaviours are associated with decreased volumes, decreased fractional anisotropy [FA], and increased mean diffusivity [MD], within limbic and PFC structures.

Aim 2: To identify brain differences in limbic and prefrontal areas, internalizing and externalizing behavioural differences, and the brain-behaviour relationships in children and adolescents with PAE with and without postnatal adversities and unexposed controls.

Hypothesis 2: There is decreased volumes, decreased FA, and increased MD in limbic and prefrontal areas of the brain in children and adolescents who have experienced PAE, as well as more severe mental health behaviours. Those with PAE and postnatal adversity will present with worse outcomes than those with PAE alone. There are different brain-behaviour associations in those with PAE in comparison to those without (e.g. those with PAE show positive relationships, while controls show negative relationships).

1.3 Thesis Overview

Chapter 2 discusses previous literature to build a foundation for the research directions that follow in Chapters 3 and 4. Chapter 3 focusses on a typically-developing child and adolescent population, assessing the relationships between sub-clinical mental health-related behaviours and structural brain measures of white and gray matter using MRI. Chapter 4 investigates brain structure and mental health-related behaviour relationships between a typically developing child and adolescent population, a population with prenatal alcohol exposure (PAE) adopted at birth, and a population with PAE and postnatal adversity. The final chapter, Chapter 5, provides a discussion that integrates all findings, describes the limitations of the studies, and suggests future directions for this research.

Chapter 2: Introduction

2.1 Mental Health and Adversity

2.1.1 Mental Health

Mental health refers to an individual's psychological and/or emotional state. This accounts for both wellness and disorder, the latter meaning a state that causes distress or impairment to an individual. Mental health problems and disorders can develop at any stage of life, yet there tends to be a higher susceptibility during adolescence. Around 50% of people will experience a mental health disorder in their lifetime, as outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), and about half of cases will develop by the age of 14 years, and two thirds by 24 years (Kessler et al., 2005). Mental health disorders that begin before adulthood have a 10-fold increase in societal cost (Lee et al., 2014), likely due to the increased risk of chronic illness, increased suicidality, and hospitalization (Angst, Gamma, Rössler, Ajdacic, & Klein, 2009; Korczak & Goldstein, 2009). In fact, between 15-24 years of age, suicide is one of the leading causes of death (Mental Health Commission of Canada, 2010).

There are numerous developmental processes during adolescence that may help to explain the high rates of mental health problems. On a neurological level, there are substantial changes happening in the brain, both on a whole-brain scale, as well as within individual structures and networks (Blakemore & Choudhury, 2006). Many localized regions of change are involved in emotion and behaviour regulation, risk and reward evaluations, and decision-making and reasoning abilities. Along with the development of specific brain regions, there are changing social relationships and environments, as well as overwhelming biological changes during puberty

(Blakemore et al., 2010). It is, thus, understandable that disruptions in development related to mental health in both brain and behaviour commonly take place during this period. Common mental health disorders that often arise in adolescence include anxiety and depression, substance use disorders, and eating and conduct disorders (Merikangas, Nakamura, & Kessler, 2009; Paus, Keshavan, & Giedd, 2010).

Internalizing disorders, those which are characterized by negative behaviours directed internally, include general anxiety disorder (GAD), major depressive disorder (MDD), and bipolar disorder (BD). Internalizing disorders tend to emerge during adolescence, worsen with age, (Fanti & Henrich, 2010; Gilliom & Shaw, 2004) and are more common in females (Zahn-Waxler, Shirtcliff, & Marceau, 2008). Initial internalizing symptoms include anxiety, depression, and somatization. Externalizing disorders, characterized by negative behaviours directed externally into the environment, include attention deficit hyperactivity disorder (ADHD), conduct disorder, and opposition defiant disorder (ODD). Externalizing disorders tend to arise earlier in childhood, but often fade with age (Fanti & Henrich, 2010; Moffitt, 1993), and are more common in males (Zahn-Waxler et al., 2008). The initial symptoms, termed externalizing behaviours, include hyperactivity, aggression, and conduct problems. To clarify, internalizing and externalizing behaviours are negative behaviours and are not synonymous with introversion and extroversion. Individuals with persistent negative behaviors, internalizing or externalizing, are more susceptible to developing a mental health disorder (Goodwin, Fergusson, & Horwood, 2004; Hofstra, Van Der Ende, & Verhulst, 2002).

One way to evaluate mental health is through behavioural assessments. The Behavioural Assessment System for Children (BASC) (Reynolds, Kamphaus, & Vannest, 2011) uses age-appropriate rated statements to measure the severity of behaviours and can be completed by a

teacher, parent, or by self-report. The BASC provides T-scores and percentiles to allow comparison to a typical population for both positive and negative behaviours. Statements include: "loses temper too easily", "shows fear of strangers", and "volunteers to help with things". Statements are rated on a 4-point Likert scale (never, sometimes, often, or almost always). After scoring, a behavioural profile is given to outline concerning behaviours and/or strengths of the child.

There are a number of options for interventions to help reduce symptoms or treat mental health disorders. Beyond medication, such as antidepressants, there are talk and behavioural therapies, such as cognitive behavioural therapy (CBT). CBT aims to redirect learned negative thoughts, feelings, and behavioural processes by being aware of one's own patterns and triggers, and working to change these thoughts, feelings, and behaviours to more positive or productive ones (James et al., 2015). CBT has been shown to reduce symptoms, increase remission (Gaudiano, 2008; Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012; James et al., 2015), and facilitate neurological improvements (Etkin, 2005; Porto et al., 2009) for many mental health disorders.

2.1.2 Prenatal Alcohol Exposure

Prenatal alcohol exposure (PAE) refers to the consumption of alcohol during any stage of pregnancy. The prevalence rate of alcohol use during pregnancy in Canada is approximately 10%, with about 3% partaking in binge drinking (Popova, Lange, Probst, Parunashvili, & Rehm, 2017). Heavy PAE is defined as ≥6 drinks per week for ≥2 weeks during the pregnancy or ≥2 binge episodes (≥4 drinks per occasion)(Hoyme et al., 2016). PAE can cause widespread adverse changes in brain and behaviour, and can result in a diagnosis of fetal alcohol spectrum disorder (FASD), the number one preventable cause of developmental and intellectual disability in children

(Vall et al., 2015). The annual societal cost of FASD is approximately $2 billion in Canada (Popova et al., 2015), and it has an estimated prevalence of 4% (Flannigan et al., 2018; May et al., 2014). In addition, a study in Canada found that people with FASD and the sentinel facial features have an estimated average life expectancy of 34 years with the leading cause of death being "external causes", including suicide (15%), accidents (14%), and poisoning by illegal drugs and alcohol (7%) (Thanh & Jonsson, 2016).

There are a number of factors that may contribute to alcohol consumption during pregnancy; for example, not knowing about the pregnancy, alcohol or substance use disorders, coping with other physical or mental health diagnoses, a history of ongoing trauma, or misinformation/lack of education around the outcomes (Cooper, Russell, Skinner, & Windle, 1992; Skagerström, Alehagen, Häggström-Nordin, Årestedt, & Nilsen, 2013). Other predictors include maternal age, smoking, lower levels of education, substance use by relatives, urban living, lower social support, and more prominent alcohol habits pre-pregnancy (Mpelo et al., 2018; Skagerström et al., 2013).

Fetal alcohol exposure can affect development through a number of mechanisms. Brain development can be altered by alcohol crossing the placenta to the fetus, which can disrupt neuronal and glial proliferation, migration, synaptogenesis, myelination, and potentially cell death. Other physiological effects of alcohol on the fetus include vasoconstriction, which minimizes blood flow, and disruption of enzyme function which affects metabolism, among other harmful effects (Lebel, Roussotte, & Sowell, 2011; Mattson, Crocker, & Nguyen, 2011; Riley, Infante, & Warren, 2011). In addition, the timing and duration of alcohol exposure during fetal development may alter the impact of exposure (Maier, Chen, Miller, & West, 2006; May et al., 2013), as well as genetic susceptibilities (Streissguth & Dehaene, 1993). Other factors can also play a role, such

as maternal nutrition, maternal age, exposure to other substances prenatally, and maternal stress (May & Gossage, 2011).

Cognitive consequences of PAE have been reported, such as lower IQ, attention, and executive function deficits, as well as motor, visuospatial, and memory difficulties (Mattson et al., 2011). Facial dysmorphology can also occur, which can be used as a diagnostic criterion for FASD. Distinctive facial features used for diagnosis include a smooth philtrum, thin upper lip, and small palpebral fissures (Cook et al., 2016). Other common facial features include a flat nasal bridge and midface, upturned nose, epicanthal folds, and small head circumference (microcephaly). Other birth defects include cardiac, ocular, auditory, renal, and skeletal system problems (Bower & Elliot, 2016), though not all those with PAE will exhibit these physical or neurodevelopmental effects.

Diagnosis of FASD can be difficult, as FASD assessments often cannot be properly completed until age 6, and numerous diagnostic criteria must be met—such as documented exposure and/or sentinel facial features, and delays in multiple neurodevelopmental domains (Cook et al., 2016). This can be a challenge when PAE can have a wide variety of effects. Thus, when I refer to individuals with PAE, I include those who are diagnosed with FASD, but also those who are yet to be diagnosed or may not meet criteria for diagnosis, but were exposed to alcohol during pregnancy. Therefore, in research with a pediatric population, PAE is commonly used rather than FASD due to diagnostic barriers, though some previous literature has been specific to those already diagnosed (Lebel, Mattson, et al., 2012; Treit et al., 2013).

Pre-existing conditions, such as PAE, can often exacerbate the struggle with mental health, especially during adolescence (Einfeld, Ellis, & Emerson, 2011; Simonoff et al., 2008). One study found that 75% of participants with PAE had one or more documented mental health disorders and

similarly for 82% of participants with FASD, which is likely an underestimation due to undiagnosis of disorders (Astley, 2010). Other studies have found rates closer to 90% in those with FASD (Pei et al., 2011). Both higher externalizing and internalizing disorders are reported in people with PAE and FASD (Astley, 2010; Pei et al., 2011). Numerous studies have demonstrated a high rate of comorbid ADHD, which is present in roughly 50% of FASD cases (Astley, 2010; Popova et al., 2016). In addition, the presentation of ADHD in those with FASD differs from people with ADHD alone, suggesting a unique etiology (Pei et al., 2011). Later problems include alcohol dependence in 55% of individuals with FASD (Popova et al., 2016). For internalizing disorders, one study found 68% of adults with FASD had mood disorders and 20% had an anxiety disorder. Half the participants of the same study had attempted suicide (Pei et al., 2011), highlighting the serious implications of untreated mental health disorders in this population. Mothers who drink during pregnancy also have higher prevalence rates of depression, which may predispose their children to mental health problems even before the effects of alcohol exposure (May & Gossage, 2011).

2.1.3 Early Postnatal Adversity

PAE is rarely the sole adversity experienced by this population. Postnatal adversity includes any traumas or exposures after birth that put a person at risk for negative developmental outcomes. Examples of postnatal adversity include abuse (physical/verbal/sexual), witness to abuse, chronic substance use in the home, neglect or insecurity of housing, income, or food, and changes in caregivers.

Insecurity of housing, income, or food is associated with lack of nutrition, unsupportive parenting (which can result from lower education or preoccupation with providing financially),

lower quality education, and higher stress levels (Evans & English, 2002; Yoshikawa, Aber, & Beardslee, 2012). This insecurity of basic needs also increases the risk for mental, physical, learning, and behavioural problems that can last throughout adulthood (Luby et al., 2013; Yoshikawa et al., 2012).

Caregiver transitions are associated with limited attachment and are predictive of negative behavioural outcomes (Bada et al., 2008). Early caregiving environments play a critical role in socio-emotional development, such that early stable placements can act as a protective factor and lead to better socio-emotional and neuropsychological outcomes in children with FASD (Koponen, Kalland, & Autti-Rämö, 2009).

Abuse can result in higher rates of depression and anxiety, increased suicidality, and deficits in numerous cognitive measures (Enlow, Egeland, Blood, Wright, & Wright, 2012; Thompson & Tabone, 2010). Specifically, physical and emotional abuse are related to increased risk of depression and anxiety, with a dose-response relationship seen with emotional abuse and depression, and similarly with physical abuse and anxiety (Norman et al., 2012). With both physical and emotional abuse, there is a 3-fold increased risk of eating disorders and increased rates of alcohol misuse (Norman et al., 2012). Childhood sexual abuse has been associated with sleep disturbances and changes in eating habits, school problems, depression, anxiety, suicidality, and poor self-esteem (Browne, 1986; Maniglio, 2009).

2.1.4 Prenatal Alcohol Exposure and Postnatal Adversity

In the presence of PAE, there is a high frequency of postnatal adversities. For example, infants with PAE are more likely to come from low socioeconomic status (SES) families and/or suffer from neglect postnatally (May & Gossage, 2011). One study of 1,400 patients with FASD found that 70% were no longer in the care of their biological parents, averaging 3 out-of-home

placements, 34% experienced physical abuse, and 24% experienced sexual abuse (Astley, 2010). Another study found 67% of study participants with PAE had experienced either physical or sexual abuse, or domestic violence (Streissguth et al., 2004).

Mental health disorders are present in approximately 90% of FASD cases (Pei et al., 2011), and the combination of teratogenic effects of alcohol on the fetus and postnatal environmental factors likely play a role in this high rate (Streissguth, 1997). A limited number of studies have examined how mental health is affected by postnatal adversities in conjunction with PAE or FASD. Studies have demonstrated that children and adolescents with both FASD and postnatal trauma, as opposed to postnatal trauma alone, exhibit worse externalizing behaviours, most commonly related to ADHD behaviours, as well as other neurocognitive deficits, such as speech, language, memory, intelligence, and other emotional/behavioural challenges (Henry et al., 2007; Hyter, 2012; Price et al., 2017). Similarly, a study comparing children with FASD who were put into care at birth versus children with FASD who lived with their biological parents for the first few years, showed that those who lived with their biological parents demonstrated worse neuropsychological problems, such as hyperactivity and concentration, behavioural and attachment issues, and worse developmental delays (Koponen, Kalland, Autti-Rämö, Laamanen, & Suominen, 2013). Lastly, one study showed that placement outside of the biological family's care early on was a protective factor, while trauma, illness, and disability corresponded with increased socio-emotional problems (Koponen et al., 2009).

2.2 Brain Structure and Development

2.2.1 Trends in Brain Development

The brain plays a critical role in linking adverse experiences and mental health outcomes (Tomalski & Johnson, 2010). To describe atypical development, typical development should first be understood. The brain can be divided into two major tissue types: gray matter and white matter. Gray matter is defined by the cell bodies and dendrites of neurons, while white matter is composed of axons covered by a fatty sheath called myelin. Gray matter is found both in the cortex, the outer layer of the brain, and in subcortical structures, and functions as the centre for information processing. White matter is the connective tissue between these areas and functions as a communication pathway (Stiles & Jernigan, 2010). Another major division of the brain is the cerebrum and cerebellum. The cerebrum, the anterior region encapsulating the majority of the brain, can be further split by hemispheres and lobes. The left and right hemisphere, separated by the interhemispheric fissure, each have 4 lobes: the occipital, temporal, parietal, and frontal lobe. The occipital lobes are the posterior sections of the brain and are largely involved in visual processing. The temporal lobes are the lateral sections of the brain and are involved in memory, hearing, and understanding language. The parietal lobes are located superiorly and are predominantly involved in sensory functions. Lastly, the frontal lobes are found anteriorly and aid in motor processing, speech, and executive functioning, such as decision making and behavioural regulation (Ackerman, 1992). The cerebellum sits inferior to the cerebrum at the posterior end. It is made up of both gray and white matter, and is most commonly known for its role in motor and balance, but has been shown to be involved in a number of other higher order functions (Klein, Ulmer, Quinet, Mathews, & Mark, 2016).

Brain development begins with rapid growth early in pre- and postnatal life and continues into adulthood (Benes, Turtle, Khan, & Farol, 1994; Lebel & Beaulieu, 2011). Maturation tends to follow an inferior to superior, posterior to anterior, and medial to lateral trajectory (Gogtay &

Thompson, 2010; Qiu, Mori, & Miller, 2015; Yakovlev & Lecours, 1967). Generally, brain regions with more fundamental functions—such as the primary visual cortex—mature first, while regions related to higher-order functioning areas—like the prefrontal cortex (PFC)—mature much slower (Chomiak & Hu, 2017).

Early brain development includes over-production of neurons and synapses followed by pruning and myelination to improve efficiency (Stiles & Jernigan, 2010). Pruning is the process by which neural projections that are not used are retracted, while myelination is the wrapping of axons by glial cells to allow more efficient electrical signalling (Bick & Nelson, 2016; Demerens et al., 1996; Monje, 2018). Other mechanisms that characterize early development include axonal changes in diameter and packing (Qiu et al., 2015; Tamnes, Roalf, Goddings, & Lebel, 2018). These processes are influenced by both genetics and the environment.

Experience-expectant (also referred to as sensitive periods) and experience-dependent development have been used to describe the brain's adaptability to one's environment. Experience-expectant development refers to a time period for which expected experiences will allow the development of relevant brain structures and associated skills. These are generally shared across a species (Greenough, Black, & Wallace, 1987). For example, if a person is born blind, the visual cortex will not develop typically, as the expected visual experience does not occur (Burton, 2003). Experience-dependent development refers to the plasticity of the brain in its ability to adapt to each individual's surroundings (Greenough et al., 1987). For example, after brain damage, compensatory mechanisms allow other areas to adapt to repair lost or impaired functions (Giza & Prins, 2006), or those who have learned to play an instrument will have altered motor and auditory brain regions to support this skill (Hyde et al., 2009). Both myelination and pruning support

plasticity and adaptability by establishing functional and effective networks (Bick & Nelson, 2016; Monje, 2018; Stiles & Jernigan, 2010).

The over production of synapses, pruning, and myelination all play a role in morphometric changes in the brain. Whole brain volume dramatically increases in the first two years of life (Knickmeyer et al., 2008). After infancy, gradual volume increases continue until late childhood/early adolescence, around 9 years of age, when brain volume stabilizes (Mills et al., 2016). In typical development, cortical volume increases until about age 9 years, when it begins to decrease, while white matter volume continuously increases across the developmental period (Lebel & Beaulieu, 2011; Raznahan et al., 2011; Tamnes et al., 2017). Decreases in cortical volume are thought to be driven by synaptic pruning and intracortical myelination (Fjell et al., 2015).

White matter tracts develop throughout childhood into adulthood, although the timing of this development differs between tracts. White matter tracts develop non-linearly with age. However, some reach developmental plateaus in childhood, such as the fornix, while others continue to mature into the late twenties and even early thirties, such as the cingulum and uncinate fasciculus (Lebel & Beaulieu, 2011; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Olson, Heide, Alm, & Vyas, 2015). Adolescence may be a time of increased change for some of the slower developing white matter tracts (Asato, Terwilliger, Woo, & Luna, 2010; Genc et al., 2017) and gender differences begin to emerge, such that females tend to develop earlier and males exhibit greater rates of change during adolescence (Asato et al., 2010; Clayden et al., 2012).

2.2.2 Cortico-Limbic Network

Brain structures in the PFC and limbic system play an important role in adolescent development and are involved in emotional and behavioural processing (Casey et al., 2008). In fact, it is theorized that it is the unmatched development of the limbic system and PFC, such that

the limbic system develops earlier than the PFC, that accounts for many of the behaviours commonly associated with adolescence (i.e. risk-taking, lack of behavioural inhibition and self-regulation). The limbic system may play a larger role in emotional situations due to its greater maturity at this time point (Casey et al., 2008). Altered development within the cortico-limbic network is found in many mental health disorders (Paus, Keshavan, & Giedd, 2008).

The limbic system is comprised of subcortical gray matter structures and connecting white matter tracts that are commonly involved in the most basic drives and emotions, such as pain, pleasure, fear, and anger (Ackerman, 1992). More broadly, the limbic system is involved in emotion, memory, learning, stress regulation, and motivation, along with other functions (White, Cullen, et al., 2008). The amygdala and hippocampus are prominent subcortical gray matter structures within the limbic system. The amygdala is located in the anterior region of the temporal lobe near the hippocampus, and functions primarily in involuntary emotional responses (i.e., fear), but is also involved in learning, memory and decision making (Ackerman, 1992; Mincic, 2015). It has a trajectory of volume increase until age 9-11 years, when a volume peak is reached (Uematsu et al., 2012). The hippocampus is adjacent to the amygdala in the medial temporal lobe. It is involved in memory, conflict processing, stress, and emotional reactions (Hanson, Nacewicz, et al., 2015) and follows a similar developmental trajectory to the amygdala, but with ongoing volume increases into adulthood (Uematsu et al., 2012).

The PFC, part of the frontal lobe, (Fig. 2.1) plays a role in a broad array of functions, but is generally involved in higher order executive functions such as decision making, moderating social behaviour, expressing personality, and planning complex cognitive behaviour (Roberts, Robbins, & Weiskrantz, 1998). As mentioned, the cortex increases in volume until late childhood, followed by slight declines until stable volumes are reached in early adulthood. The PFC, however,

is one of the later cortical regions to develop (Gogtay et al., 2004), and only begins to show accelerated thinning during adolescence (Tamnes et al., 2017).

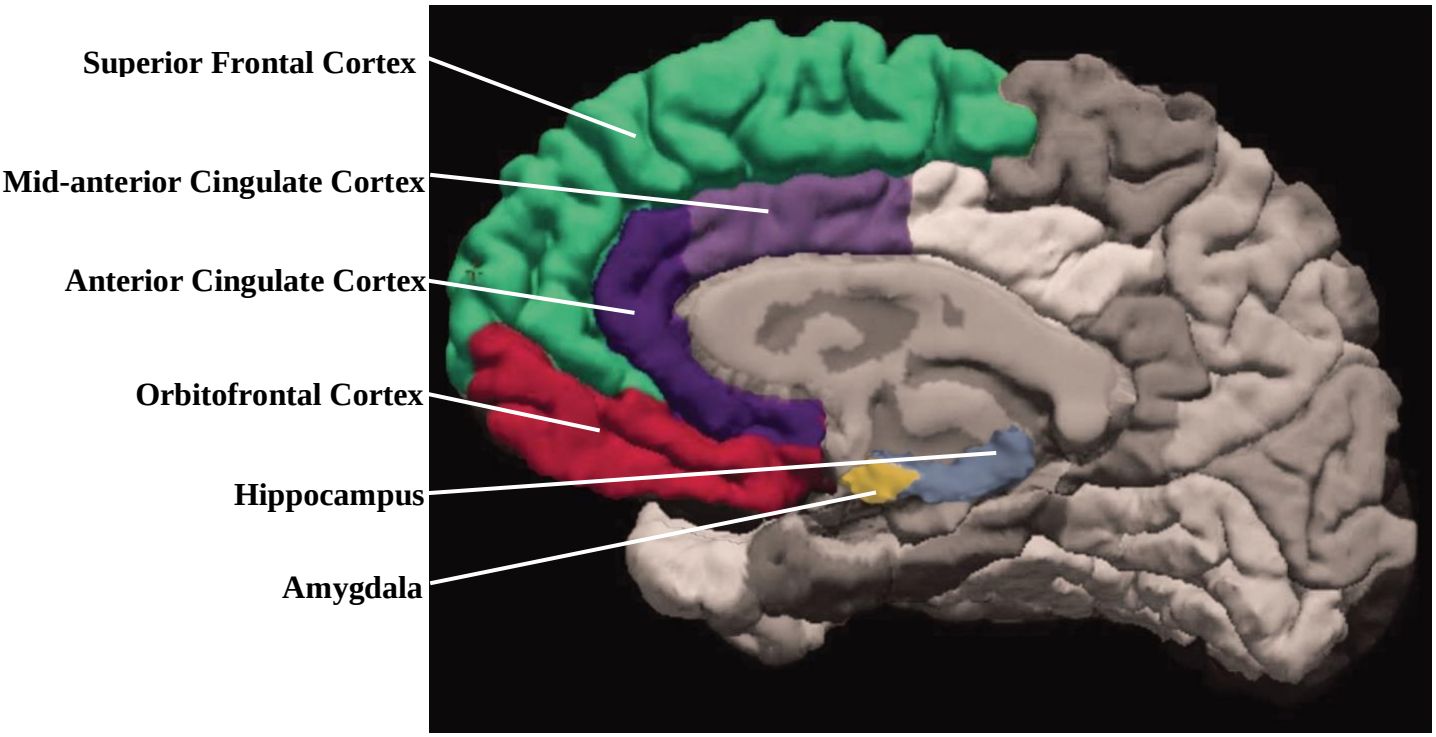

Figure 2.1 Gray matter regions of the prefrontal cortex (PFC) and the limbic system. Structures shown include the superior frontal (green) and orbitofrontal cortex (red), the anterior (purple) and mid-anterior cingulate cortex (violet), the amygdala (yellow) and the hippocampus (steel blue).

The limbic system has many white matter connections to the PFC (Fig. 2.2). For example, the cingulum is a slower developing tract, reaching developmental plateaus around early adulthood (Lebel & Beaulieu, 2011). The cingulum connects the cingulate gyrus to the amygdala, and is important in reinforcement of behaviour, emotion, and memory (Concha, Gross, & Beaulieu, 2005). The uncinate fasciculus also continues to develop into adulthood (Lebel & Beaulieu, 2011), and connects the amygdala to the orbitofrontal cortex and is involved in memory, language, and emotional processing (Olson et al., 2015). Finally, the fornix develops much quicker, reaching

plateaus during childhood (Lebel, Walker, et al., 2008). The fornix connects the mammillary bodies to the hippocampus, and is involved in memory formation and recall (Concha et al., 2005; Waller et al., 2017).

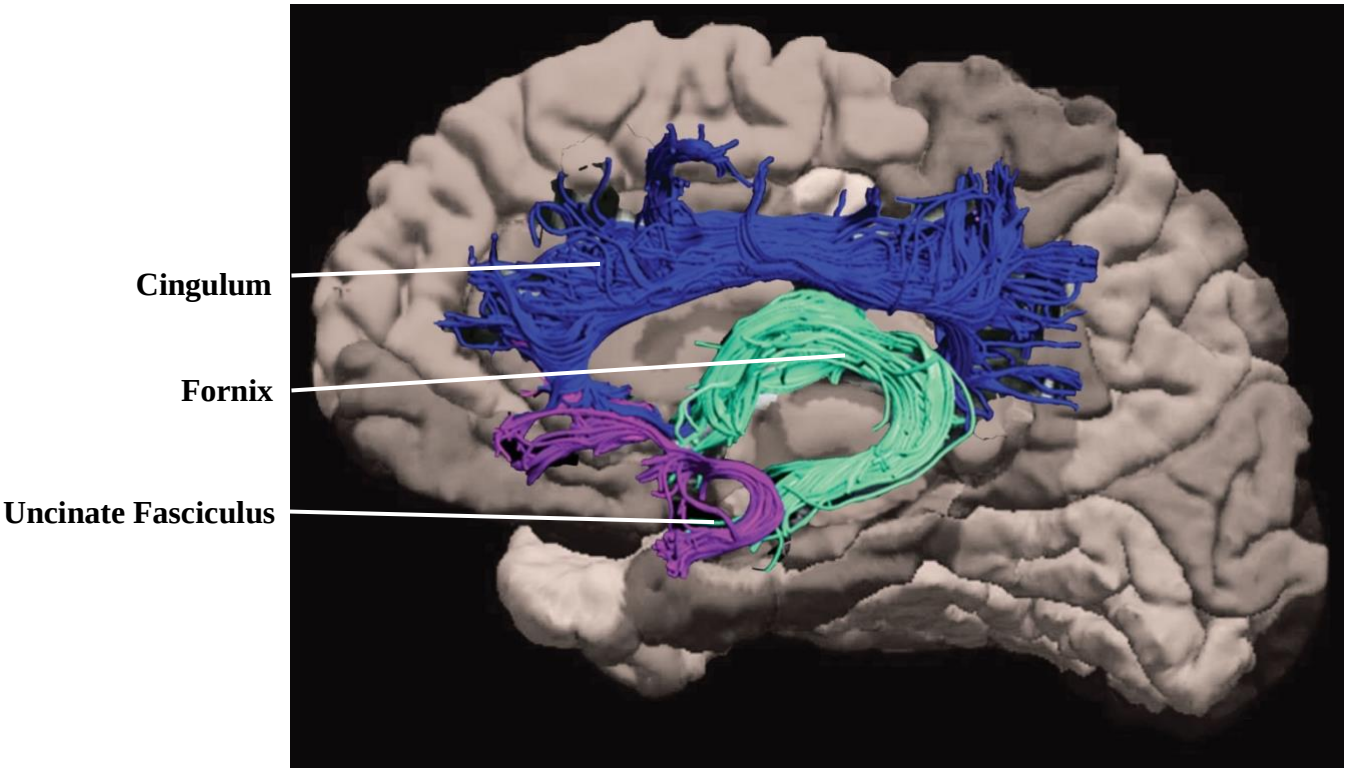

Figure 2.2. White matter tracts connecting the limbic system to the prefrontal cortex (PFC). Tracts shown are the fornix (blue), cingulum (turquoise), and uncinate fasciculus (violet).

2.3 Magnetic Resonance Imaging

2.3.1 Nuclear Magnetic Resonance

The investigations of brain development discussed above were primarily conducted using magnetic resonance imaging (MRI), a non-invasive way to infer about the structure and function of the brain. While MRI is not as precise as *ex vivo* methods, it does enable research within healthy populations and with large sample sizes. Furthermore, MRI allows longitudinal studies with

multiple time points from the same participant. This is a critical requirement for studies of brain development.

Magnetic resonance imaging (MRI) is a safe and reliable way to image the body by capitalizing on the magnetic properties of atomic nuclei. Hydrogen nuclei are the most commonly imaged in MRI, due to their abundance in the human body and their unpaired proton which possesses a magnetic moment and angular momentum. Without an external magnetic field, the magnetic moments of hydrogen nuclei are randomly oriented and cancel each other out. In an MRI scanner, a powerful external magnetic field is applied, and the spinning nuclei have a (near) axis alignment with the applied magnetic field. The alignment is slightly off axis due to quantized angular momentum. A hydrogen nucleus will tend to align in either a parallel or anti-parallel state. Aligned hydrogen nuclei precess about the main magnetic field due to their off-axis orientation. Parallel alignment is a lower energy state and is therefore slightly more abundant. This unequal distribution creates a net magnetization vector ($\vec{M}_0$), the sum of all magnetic dipole moments, in line with the main magnetic field (Fig. 2.3).

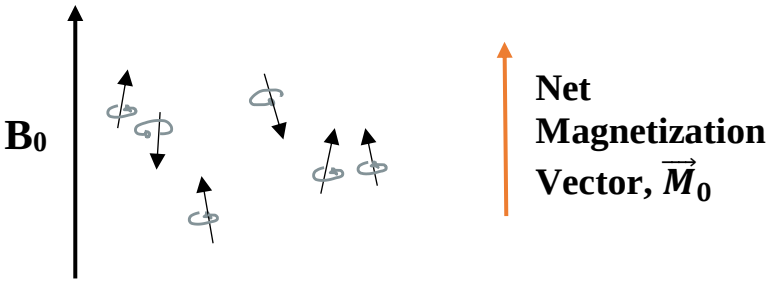

Figure 2.3. A diagram of the magnetic moments of hydrogen nuclei in a main magnetic field ($\vec{B}_0$), and the net magnetization vector ($\vec{M}_0$). The small black arrows are the precessing magnetic moments of individual hydrogen nuclei (note: there are more hydrogen nuclei with parallel alignment than anti-parallel; the magnetic moments of individual nuclei do not have perfect alignment), and the orange arrow is the net magnetization vector ($\vec{M}_0$) of all hydrogen nuclei.

In equilibrium, there is no transverse component of the net magnetization vector since the phases of the spins remain random and cancel each other out. The precession of these spinning nuclei in a magnetic field occurs at the Larmor frequency, ω_o, defined as $\omega_o = \gamma B_o$, where γ is the gyromagnetic ratio (a constant) and B_o is the magnetic field strength. This means the Larmor frequency is proportional to the magnetic field strength. The gyromagnetic ratio (γ) is an inherent property of each type of nucleus.

To create an image, a radiofrequency (RF) pulse must be used to tip magnetization into the transverse plane, since signal can be measured from a net magnetization vector in the transverse plane without interference from the main magnetic field, B_0. These RF pulses are electromagnetic fields applied perpendicular to the main magnetic field. An RF pulse is achieved by a rotating magnetic field produced by an RF coil. The frequency of the pulse matches hydrogen's resonant frequency (Larmor frequency) in order to tip the net magnetization vector into the transverse plane. Once tipped, the net magnetization vector will then precess around the transverse plane. Once the RF pulse is turned off, the net magnetization vector begins to realign with B_0 as the surplus of parallel-alignment hydrogen spins re-establishes and spins dephase (Fig. 2.4). This happens gradually while precession continues in the transverse plane until in-phase coherence is lost. De-phasing occurs by mechanisms such as spin-spin interactions, susceptibility of different tissues, and inhomogeneities in the magnetic field. Regrowth of longitudinal magnetization and dephasing of transverse magnetization occur at different rates in differing tissues (white matter, gray matter, cerebrospinal fluid (CSF) etc.) based on tissue properties, densities, and temperatures.

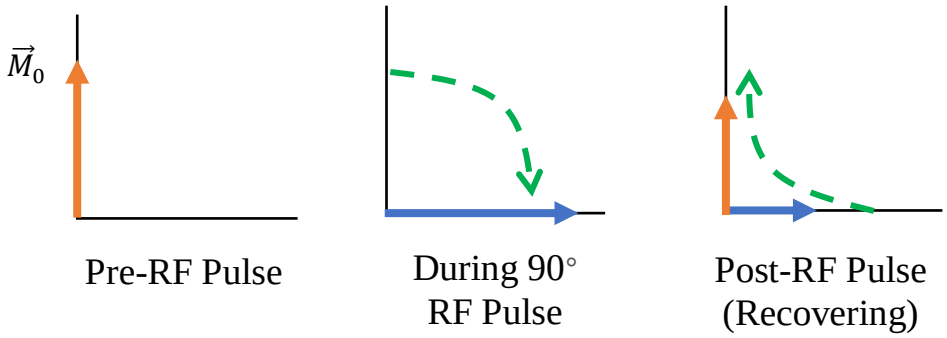

Figure 2.4. A diagram of the longitudinal (y-axis; orange) and transverse (x-axis; blue) components of the net magnetization vector of hydrogen nuclei before, during, and after (recovering) a 90^0 radiofrequency (RF) pulse. Not shown is the continued precession of the net magnetization vector in the transverse plane.

2.3.2 Gradients and K-Space

Signal measurement occurs via the principle that an oscillating magnetic field will induce an electrical current that can be measured within a receiver. However, if we followed the process described above, we would receive signal from all hydrogen nuclei in the brain at once. We must encode spatial information to determine the signal's origin. Gradients can be utilized to localize hydrogen activity and provide spatial information. This is done by superimposing a weak magnetic field that varies with position upon the main magnetic field, thereby modifying the precession frequency of hydrogen nuclei in the body based upon their spatial location (Fig. 2.5). The three planes of gradients are commonly referred to as slice select, phase, and frequency. The slice select gradient is applied perpendicular to the desired slice plane, causing the hydrogen nuclei to experience slightly different magnetic fields based on their positions, and thus precess at slightly different frequencies. Then, when the amplitude modulated RF pulse is applied, a small band (or slice) of hydrogen nuclei will undergo net magnetization vector tipping, because only that band is at the same frequency band as the RF pulse. Slice thickness can be controlled by gradient amplitude

and RF pulse bandwidth (i.e., the range of frequencies included in the pulse). Phase and frequency encoding gradients follow a similar process but are applied at different times of an MRI sequence and in different orientations in order to focus and denote the exact location of a proton population. Phase encoding gradients are momentarily applied after the initial RF pulse and provide phase shifts in the phase encoding direction. Frequency encoding gradients are applied during the signal readout and provide differences in precessional frequencies in the frequency encoding direction. Figure 2.6 provides an example of a commonly used (spin echo) sequence to demonstrate timing of each gradient.

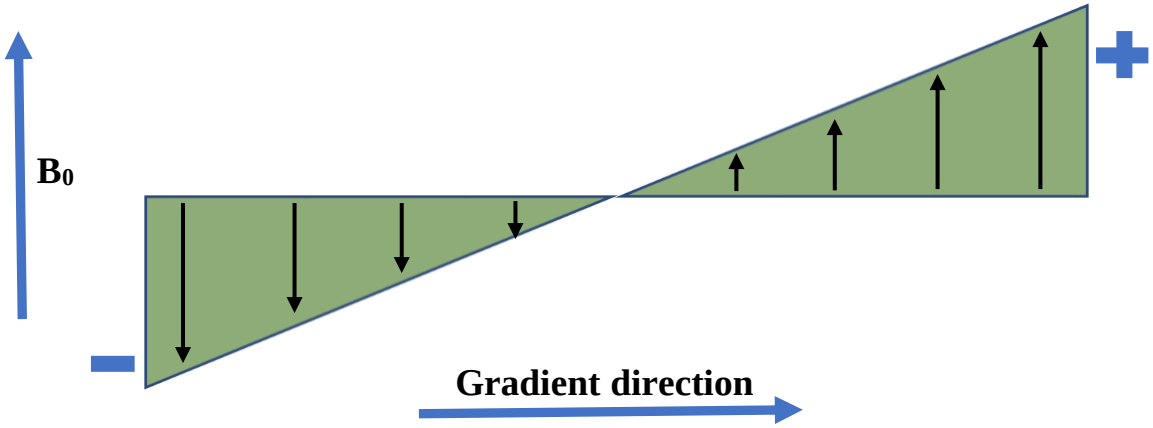

Figure 2.5 A diagram of how a gradient in a given direction acts on the main magnetic field (B_0) to create a linear gradient in the field intensity to designate spatial information.

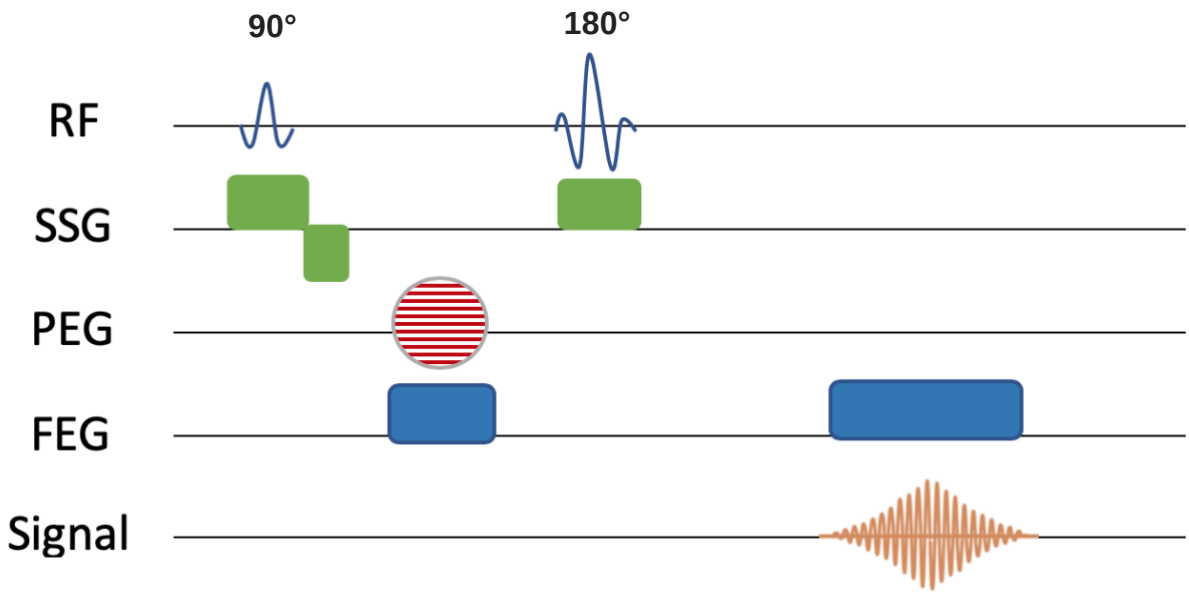

Figure 2.6 An example of a spin echo sequence showing approximate timing, amplitude, and duration of the radiofrequency pulse (RF), the slice selection gradient (SSG), the phase encoding gradient (PEG), the frequency encoding gradient (FEG), and the recorded signal.

As signal is received from a slice with specific spatial information (i.e. phase and frequency encoding), the collected signal can be transferred into k-space, a mapping of spatial frequency of the signal. In a classic spin echo sequence, for each phase encoding step one line of k-space is filled. A Fourier Transform is used to decompose complex wave signals received during readout into its component sine waves, and this information is input into k-space. Each point in k-space corresponds to a specific spatial frequency. Points in the centre of k-space contain low-frequency spatial information and define bulk contrast and general shapes. The periphery of k-space contains high-frequency spatial information, such as edges and details. In order to produce the grey-scale image we are familiar with in MRI, an inverse Fourier Transform must be performed on the entirety of k-space information.

2.3.3 T1 and T2

Various image types, such as T1-weighted and T2-weighted, can be acquired by capitalizing on different properties of hydrogen nuclei behaviour in different tissues based on the timing and composition of sequences. T1 refers to the time it takes for the longitudinal magnetization to return to 63% of its original equilibrium after the termination of an RF pulse. T2 refers to the time for transverse magnetization to decay to 37% of its initial magnitude, due to spin dephasing (Fig. 2.7). T2 most often occurs much faster than T1. T2* is similar to T2 but includes inhomogeneities in the magnetic field, thus T2* occurs faster than T2. Each tissue type (white matter, gray matter, CSF) has different T1, T2, and T2* values. White matter has the shortest T1 and T2, while CSF has the longest.

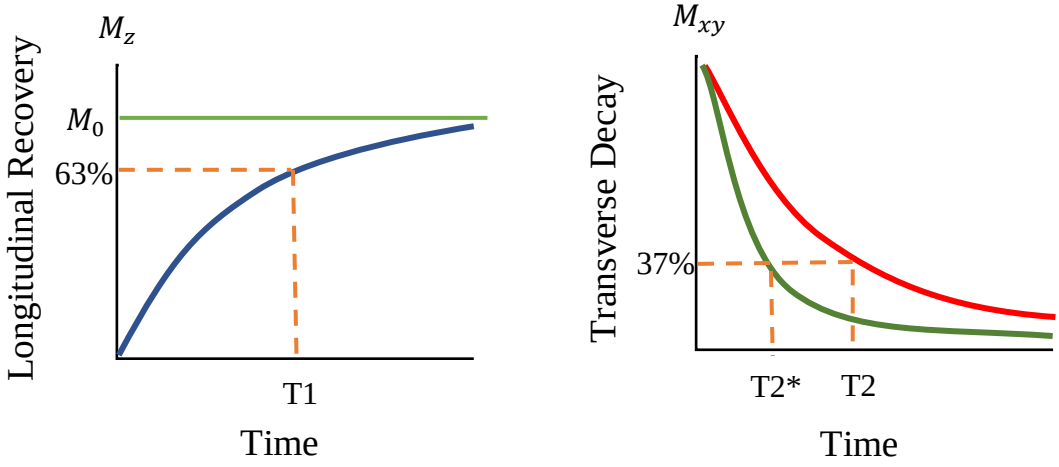

Figure 2.7 An example of longitudinal recovery and a T1 in blue (left), and a diagram of transverse decay with a T2 in red and T2* in green (right) for one tissue type. Longitudinal recovery is driven by the flipping of hydrogen nuclei between antiparallel and parallel states. Transverse decay is driven by the loss of in-phase coherence.

Image acquisition parameters are set to capitalize on these properties. The purposeful timing of RF pulses and signal acquisition can dictate the weighting of an image, such as T1-weighted, T2-weighted etc. This is not to be confused with measuring the actual time constants of relaxation/decay, but instead is a measurement of signal collected, which will be different for each

tissue type as each tissue type relaxes/decays at different rates. Repetition time (TR) and echo time (TE) are acquisition parameters that can be used to generate contrast based upon tissue T1 and T2, or other properties. TR is the amount of time between initial excitation RF pulses, and TE is the amount of time between the excitation RF pulse and middle of MR signal sampling, or readout. A short TR and short TE will produce a T1-weighted image, while a long TR and TE will produce a T2-weighted image.

Strong T1-weighted contrast is useful for measuring volume, thickness and surface area of brain structures like the hippocampus or regions of the cortex (Plewes & Kucharczyk, 2012). T1-weighted images are collected at a time point that minimizes T2 decay effects and the tissue with the shortest T1 value will retain the most measurable signal. For a T1-weighted image of the brain, white matter presents as light grey (short T1), gray matter presents as a darker grey, and CSF as black (long T1) (Fig. 2.6). For a T1-weighted sequence, a short TR and TE are used (typical TR / TE for a T1-weighted spin echo sequence at 1.5T: 250-700ms / 10-25ms)(Bitar et al., 2006). A short TR ensures that insufficient time has passed for longitudinal magnetization in all tissue types to have fully recovered, resulting in more available signal for tissue with shorter T1 times. A short TE ensures that T2 dephasing effects will not heavily affect the signal acquired during readout. While T1-weighted images can be used to assess volume and gray matter morphology, assessments of white matter integrity benefit from techniques such as diffusion-weighted MRI, which can simultaneously infer axon orientation and tract-specific features.

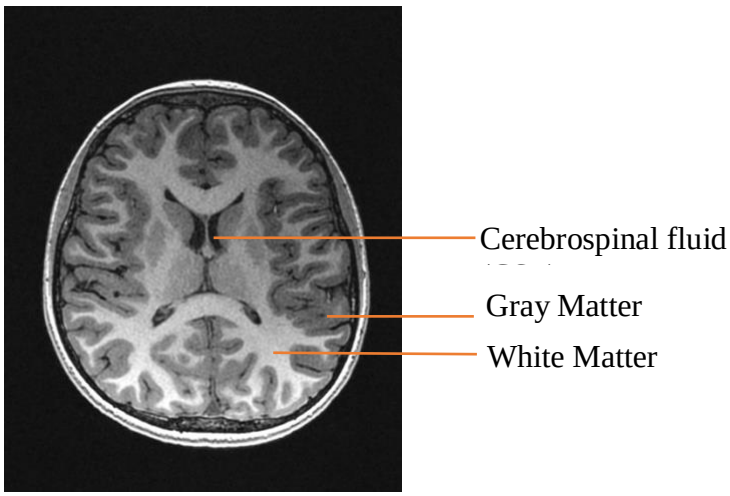

Figure 2.8 T1-weighted MRI image with labelled cerebrospinal fluid (CSF), gray matter, and white matter. White matter appears brightest because it has the shortest T1, meaning that it is more fully recovered between RF pulses than gray matter (darker) or CSF (black).

2.3.4 Diffusion Tensor Imaging

Diffusion-weighted imaging exploits the Brownian (random) motion of water in the brain to capture microstructural information. Diffusion tensor imaging (DTI) methods use gradients to encode diffusion information in various directions. Typically, a spin-echo sequence is used and diffusion-encoding gradients are applied before and after a 180 degree pulse. This is done to dephase then re-phase hydrogen nuclei. If water molecules move in the direction of the diffusion-encoding gradient during this time, they will not rephase properly, resulting in a loss of signal. Sensitivity to diffusion is described by the b-value, which relates the amplitude of diffusion-encoding gradients, the duration of these gradients, and the timing between them. The duration and amplitude of diffusion-encoding gradients will dictate the differences in precession phase exhibited by affected nuclei along the direction of the gradient. Higher gradient power and longer gradient duration will both exaggerate differences in phase between nuclei at different spatial locations. Time between diffusion encoding gradients increases the likelihood of diffusion of a

given hydrogen nucleus. Then, when the second diffusion-encoding gradient is applied to reverse phase differences, if a hydrogen nucleus has moved, its phase will be inappropriately reversed, resulting in a residual phase difference, loss of signal coherence, and thus a decrease in measurable signal. Therefore, with a larger diffusion-encoding gradient amplitude, longer durations, and greater time between gradients, the b-value will increase (Rokem et al., 2017). With that in mind, there is a trade-off between having a high enough b-value to have contrasting signal loss amongst tissues, and not too much signal loss (Alexander, Lee, Lazar, & Field, 2007).

DTI methods measure diffusion in many different directions and generate a three-dimensional tensor within each voxel to quantify diffusion. To construct a tensor, a minimum of 6 non-collinear diffusion-encoding gradients must be applied, and at least one baseline (i.e., b = 0 s/mm^2) measurement must be collected to quantify signal loss (Lebel, Benner, & Beaulieu, 2012). This tensor (a three-dimensional ellipsoid) is characterized by eigenvectors ($\vec{v}$) and eigenvalues (λ). The primary eigenvector describes the principal diffusion direction and is assumed to correspond to the orientation of white matter. Two other eigenvectors, perpendicular to the primary eigenvector, also describe the tensor size and shape. This tensor can then be used to virtually reconstruct white matter fibre tracts using tractography (Alexander et al., 2007; Tamnes et al., 2018)(Fig. 2.9; 2.10a). Typical DTI tractography is very useful to identify streamlines of axons and to segment major fiber bundles, but does not adequately account for the presence of multiple fiber populations or complex fiber architectures. Other tractography methods such as constrained spherical deconvolution (CSD) can be applied to perform tractography in a more sophisticated manner. CSD is similar to DTI tractography except the tensor is replaced by an estimated fiber orientation distribution (FOD) that can account for crossing, kissing, or bridging fibers (Jeurissen,

Leemans, Jones, Tournier, & Sijbers, 2011). The FOD can adequately represent multiple fiber populations within a single voxel, overcoming a major limitation of the tensor model.

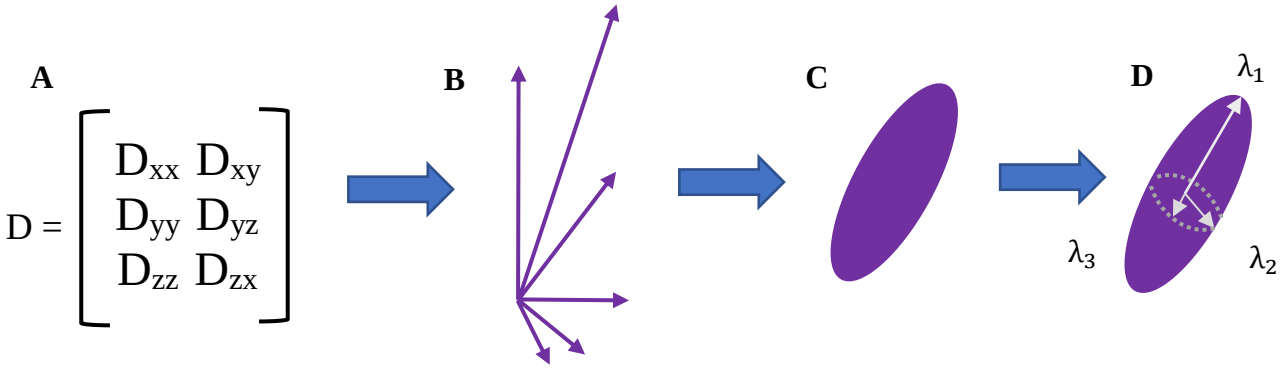

Figure 2.9 A schema demonstrating the construction of a diffusion tensor with eigenvectors. This begins with a minimum of 6 diffusion gradient directions which make up a diffusion matrix (A). This matrix displays rates of diffusion in each given direction (B). This information can be used to construct a tensor (C) with which 3 eigenvectors are used to describe this shape and size (D).

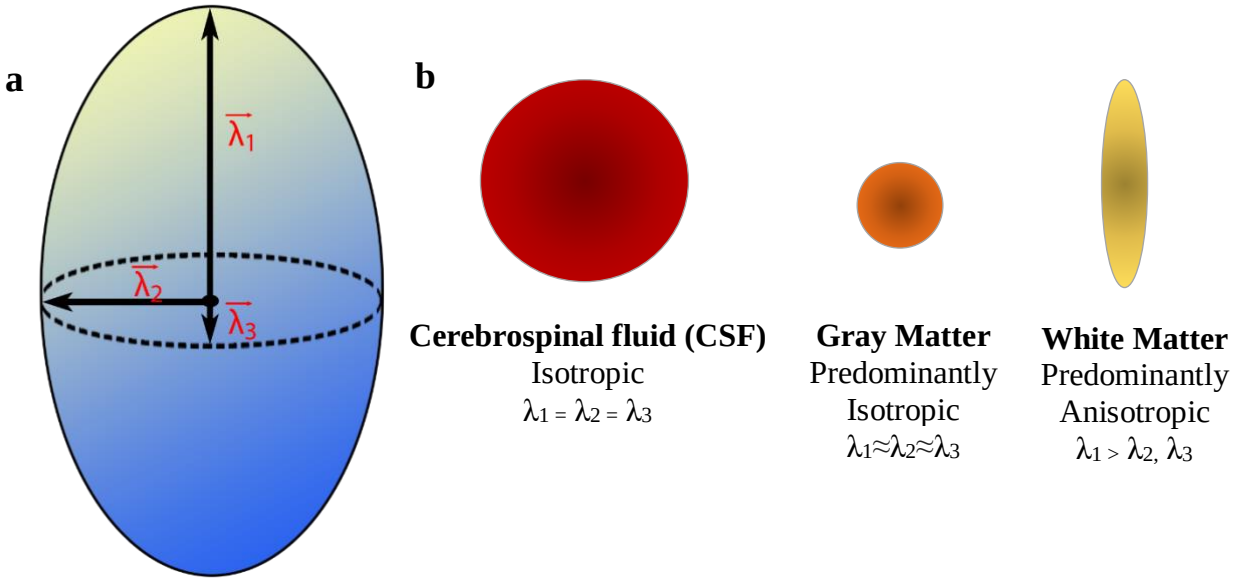

Figure 2.10 [a] A diagram of a tensor with all eigenvectors shown. λ_1 is the primary orientation used to reconstruct fibre tracts. **[b]** Examples of what a tensor might look like in cerebrospinal fluid (CSF; red), gray matter (orange), and white matter (yellow).

Diffusion-weighted imaging can tell us about structures present in a region. If water diffuses equally in all directions, the diffusion is called isotropic. This would be similar to what we might see in cerebrospinal fluid (CSF) within the ventricles, where few barriers are present to inhibit diffusion. If water has ordered and constrained movement, the diffusion is called anisotropic. This is more like the diffusion we would see in white matter (Fig. 2.10b), where many structures (e.g., myelin) are present to restrict diffusion and those structures tend to be ordered. Common measures used in diffusion imaging are mean diffusivity (MD) and fractional anisotropy (FA). MD measures the average diffusivity within each voxel ($MD = (\lambda_1+\lambda_2+\lambda_3)/3$) and is affected by barriers to diffusion in an area, such as the presence of glia and axonal membranes. As white matter develops and more barriers are created, space for the random motion of water is minimized resulting in decreased MD values. FA measures ordered restriction or how unidirectional diffusion is in a voxel ($FA = \sqrt{\frac{3}{2}}\frac{\sqrt{(\lambda_1 - MD)^2+(\lambda_2 - MD)^2+(\lambda_3 - MD)^2}}{\sqrt{\lambda_1^2+\lambda_2^2+\lambda_3^2}}$). FA can be between 0 and 1, 0 being equal diffusion in all directions, and 1 being diffusion only in the primary direction. Factors that affect FA include fiber coherence, axonal density, myelination, and axonal diameter, as these properties restrict diffusion in an ordered manner. As white matter tracts develop and mature, there is an increase in organization and efficiency of fibers, as well as myelination, so an increase in FA is observed (Fig. 2.11). DTI measures are, thus, sensitive to white matter properties, but lack specificity about microstructure (i.e. influence of axon size, fiber density, myelination) (Alexander et al., 2007; Beaulieu, 2002).

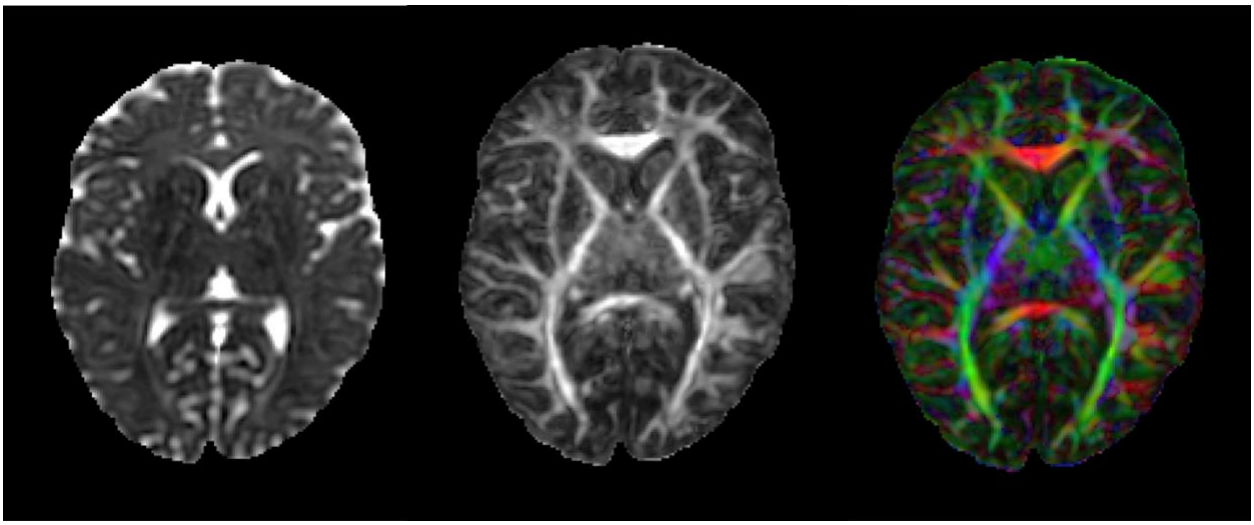

Figure 2.11 Examples of a mean diffusivity (MD) map (left), a fractional anisotropy (FA) map (middle), and an FA map color-coded by primary eigenvector orientation (right). Note: White matter is dark in the MD map, but bright in the FA map, whereas cerebrospinal fluid (CSF) is bright in the MD map, but dark in the FA map. This is because in white matter, ordered barriers are present to restrict diffusion (lowered MD) and bias diffusion to occur along the orientation of axons (increased FA).

2.4 Links Between Mental Health, Adversity and the Brain

2.4.1 Mental Health and Brain Structure

Mental health symptoms and disorders have been linked to structural brain alterations in the cortico-limbic network in children and adolescents. Casey and colleagues suggest many of the distinct behaviours and problems seen in adolescence relate to the unequal maturation of subcortical limbic networks and the PFC, such that subcortical regions develop earlier, while the PFC or "control centre" develops later resulting in adverse impulsive behaviour (Casey et al., 2008).

Previous work has primarily focused on youth and adults with diagnosed mental health disorders. For example, youth diagnosed with anxiety show reductions in amygdala volume (Gold

et al., 2017), and adults diagnosed with internalizing-based disorders (anxiety, depression, bipolar disorder) also exhibit smaller volumes in subcortical gray matter structures (Wijeratne et al., 2013) and the PFC (Drevets, Price, & Furey, 2008). Lower FA measures in the cingulum, uncinate fasciculus, and fornix were also found in a diagnosed (internalizing-based), adult population (Barysheva, Jahanshad, Foland-Ross, Altshuler, & Thompson, 2013; Deng et al., 2018; White, Nelson, & Lim, 2008).

Youth with externalizing-based disorders (conduct disorder, ADHD, antisocial behaviour) demonstrate associations between worse externalizing behaviours and lower amygdala volumes (Fairchild et al., 2011; L. W. Hyde, Shaw, & Hariri, 2013), lower PFC, anterior cingulate cortex (L. W. Hyde et al., 2013), and whole brain volumes (Castellanos et al., 2001), and a later peak in PFC volume (Shaw et al., 2007), as well as mixed diffusivity results in the uncinate fasciculus and cingulum (Sarkar et al., 2013; Waller et al., 2017).

Thus, gray and white matter in the PFC and limbic system are the primary regions of altered development associated with mental health disorders, through adolescence and adulthood. This research has furthered our understanding of the neurological profiles linked to these disorders which helps in developing interventions and treatments. That being said, the brain structures we see in those with disorders likely differs from a typically-developing population, including those who may progress on to develop disorders in the future. Thus, it is critical to also investigate the brain-behaviour relationships in an undiagnosed population to understand the progression of altered brain structure at sub-clinical levels of mental health-related behaviours.

Some research has begun to investigate mental health related behaviours in a typically-developing population of children and adolescents. For example, higher internalizing scores have been associated with smaller amygdala and hippocampal volumes (Koolschijn, van IJzendoorn,

Bakermans-Kranenburg, & Crone, 2013; Muetzel et al., 2018; Snyder, Hankin, Sandman, Head, & Davis, 2017), smaller volumes of the PFC in children (Snyder et al., 2017), and larger PFC volumes in late adolescence (Ducharme et al., 2014) as determined using MRI, suggesting a delay in the growth and thinning processes of the PFC. DTI studies have shown lower FA in the cingulum, uncinate fasciculus, and whole-brain as well as slower age-related increases of FA in the cingulum in a typically-developing youth population with higher internalizing scores (Albaugh et al., 2017; Ali, Vandermeer, Sheikh, Joanisse, & Hayden, 2019; Lichenstein, Verstynen, & Forbes, 2016; Muetzel et al., 2018).

Worse externalizing behaviours, in typically-developing children and adolescents, have been associated with smaller amygdala volumes in males (Caldwell et al., 2015), and lower thickness (Ducharme et al., 2011) and increased asymmetry of the anterior cingulate cortex (Visser et al., 2013). DTI has not yet been used to relate brain structure and externalizing behaviours in typically-developing children and adolescents.

A handful of studies have demonstrated links between cortico-limbic structures and internalizing and externalizing behaviours in previous investigations in a typically-developing population, but no study has conducted a comprehensive investigation of internalizing and externalizing behavioral links with gray matter and white matter structures simultaneously in a healthy population. This type of comprehensive understanding will allow identification of the structures and networks implicated in the presence of mental health behaviors before diagnostic levels are reached. With this foundational knowledge, further research can explore the progression from behaviors to disorder which may help to inform recognition and intervention practices.

2.4.2 Prenatal Alcohol Exposure and Brain Structure

Previous research has linked PAE with widespread altered brain development; this includes reduced whole brain volumes, gray and white matter volumes, and reduced cerebellum volume (Lebel, Roussotte, & Sowell, 2011). Gray matter reductions have been reported in the frontal, parietal, temporal, and occipital regions, as well as limbic subcortical structures. Some of the affected limbic structures include the amygdala, hippocampus, putamen, caudate, thalamus, and basal ganglia (Astley et al., 2009; Lebel et al., 2011; Nardelli, Lebel, Rasmussen, Andrew, & Beaulieu, 2011). One study showed a dose-dependence such that higher exposures to prenatal alcohol were related to greater reductions in the left cingulate gyrus, bilateral middle frontal gyri, right middle temporal gyrus, and right caudate nucleus (Eckstrand et al., 2012). Another study has shown thicker cortex, specifically in the parietal, temporal, and frontal lobes in a youth population, when cortical thinning commonly occurs (Sowell et al., 2008).

Diffusion studies in a PAE population have shown reduced FA and increased MD of white matter in a wide range of tracts. The corpus callosum, an interhemispheric white matter tract, is one of the most consistent findings in PAE literature showing abnormal development, and at times even complete agenesis (Bookstein, Sampson, Streissguth, & Connor, 2001; Bookstein, Streissguth, Sampson, Connor, & Barr, 2002; Wozniak & Muetzel, 2011). Tracts associated with the cortico-limbic network have also displayed lowered FA and increased MD, including the cingulum (Lebel et al., 2008) and uncinate fasciculus (Fryer et al., 2009). Other white matter tracts have also been found to be have abnormal development after PAE, including the inferior and superior longitudinal fasciculus, cortico-spinal tract, and inferior fronto-occipital fasciculus (Lebel et al., 2008).

This previous work shows altered brain development across the brain in the presence of PAE, including regions commonly implicated in mental health disorders (Albaugh et al., 2017; Ali

et al., 2019; Lichenstein et al., 2016; Muetzel et al., 2018). With such high prevalence rates of mental health problems in those with PAE (Pei et al., 2011), there is likely a link between the adverse effects of PAE on the brain and the mental health challenges emerging later in life. With this added adverse mechanism affecting brain development, it can also be hypothesized that these brain-behaviour relationships relevant to mental health may differ in a population with PAE than in a population without PAE. Thus, prevention and treatment may be more effective if we gained a better understanding of these brain-behaviour differences in those with PAE. There is yet to be research that investigates the differences in brain structure, mental health-related behaviours, and the brain-behaviour relationships between a sample of children and adolescents with PAE and those without.

2.4.3 Postnatal Adversity and Brain Structure

Postnatal adversity relates to altered brain structure as well. Maltreated and institutionally-reared children have been shown to have altered amygdala and hippocampal volumes, with both increases and decreases in volume after adversity (Hart & Rubia, 2012; McLaughlin et al., 2016; Tottenham et al., 2010; Whittle et al., 2013). In both child and adult populations, reductions in total brain, PFC, anterior cingulate cortex, cerebellum, and corpus callosum volumes have been reported after maltreatment and sexual abuse, often in combination with PTSD (Andersen et al., 2008; De Bellis et al., 2016; Hart & Rubia, 2012).

Similarly, in both children and adults, increased MD and decreased FA of white matter tracts after maltreatment, early life stress, and institutional rearing has been shown in the corpus callosum, cingulum, uncinate fasciculus, corticospinal tract, inferior fronto-occipital fasciculus, and inferior longitudinal fasciculus (Bick et al., 2015; Hanson et al., 2013; Hanson, Knodt, Brigidi, & Hariri, 2015; Ho et al., 2017). Greater FA has been reported in the cingulum, uncinate fasciculus,

anterior thalamic radiation, and forceps minor after neglect and childhood adversity in adolescents and adults (Hanson et al., 2013; Ugwu, Amico, Carballedo, Fagan, & Frodl, 2015) and lower MD in parts of the corpus callosum and anterior corona radiata in children with mothers with increased postpartum depressive symptoms (Lebel et al., 2016).

As discussed in section 2.1.3, postnatal adversity is associated with mental health and behavioural challenges, and there is a large crossover of associated brain regions in the adversity literature to the mental health literature, specifically in the cortico-limbic network. Adversity and mental health may act on similar brain structures, but perhaps in distinct ways. For example, lower FA in the cingulum has been reported with internalizing-based disorders, but increased FA has been found after childhood adversity (Lichenstein et al., 2016; Ugwu et al., 2015). Therefore, postnatal adversity should not be overlooked in research or clinical practice when in conjunction with other factors effecting development, such as PAE, as it may also contribute to altered brain and behaviour.

2.4.4 Remaining Knowledge Gaps

Brain alterations in mental health disorders are well characterized, there is a need to understand the emerging structural-behavioral links beginning in childhood and throughout adolescence in both gray and white matter. This will allow identification of the structures and networks implicated in the presence of mental health behaviors before diagnostic levels are reached potentially impacting prevention and intervention practices in the future, as well as building a foundation for future research on the progression to mental health disorder.

Mental health problems are experienced by the majority of people with PAE, and research has shown the widespread effects of PAE on the brain, yet no research has assessed how the brain-behaviour links seen in a PAE sample differs from those without PAE in relation to mental health.

By furthering our understanding of the relationships between brain structure and mental health related behaviours in people with PAE, improved and personalized services may be provided to address the unique needs of this population.

Despite the frequent co-occurrence of postnatal adversities with PAE, relatively little research has focused on their cumulative effects on the brain. Research on PAE and adverse exposures, while valuable, does not address overlapping risks, but typically focusses on only one risk (i.e. PAE alone). Several studies have examined combined effects from multiple prenatal exposures on the brain, without incorporating postnatal experiences (De Zeeuw, Zwart, Schrama, Van Engeland, & Durston, 2012; Gautam, Warner, Kan, & Sowell, 2015; Lebel & Sowell, 2011). The PAE and postnatal adversity literature both show the cortico-limbic network as a region of altered development, but perhaps in different ways. For example, PAE literature has shown lowered volumes in the cingulate cortex while larger volumes have been reported after childhood abuse (Eckstrand et al., 2012; Hanson et al., 2010). Therefore, those individuals with PAE and postnatal adversity may have different developmental trajectories of the brain than those with PAE alone. This paucity of literature presents an opportunity for influential imaging studies to connect brain structure and developmental outcomes to inter-related risk factors often present with PAE.

Chapter 3 outlines the white and gray matter links to internalizing and externalizing behaviours in typically-developing children and adolescents. Chapter 4 builds on this knowledge by assessing differences in brain structure, mental health behaviours, and brain-behaviour relationships in children and adolescents with PAE, with or without postnatal adversity, and typically-developing controls.

Chapter 3: Brain Structure and Internalizing and Externalizing Behavior in Typically-Developing Children and Adolescents

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3.1 Introduction

Adolescence is a key period of biological and social change that commonly coincides with the emergence of early mental health problems (Paus et al., 2008). By age 40, 50% of Canadians will have experienced a mental health disorder (RiskAnalytica, 2011). About half of those cases develop by the age of 14 years, and another 25% by 24 years (Kessler et al., 2005); mental health disorders beginning before adulthood have a 10-fold increase in societal cost (Lee et al., 2014).

Mental health can be assessed through internalizing and externalizing behaviors, which are negative behaviors directed internally (e.g., anxiety, depression) or externally (e.g., aggression, hyperactivity) into the environment, respectively. Internalizing behaviors are more common in females (Zahn-Waxler et al., 2008), tend to emerge later in development and worsen with age (Fanti & Henrich, 2010; Gilliom & Shaw, 2004). Externalizing behaviors occur more often in males (Zahn-Waxler et al., 2008), but tend to decrease after the preschool years in most people (Fanti & Henrich, 2010; Moffitt, 1993). Individuals with persistent negative behaviors are more susceptible to developing a mental health disorder (Goodwin et al., 2004; Hofstra et al., 2002).

Adolescence is an important period of development for brain systems related to internalizing and externalizing behaviors, specifically structures in the limbic system and prefrontal cortex (PFC), along with the white matter that connects these regions (Casey et al.,

2008). Limbic structures, including the hippocampus and amygdala, show volume increases through adolescence (Giedd et al., 1996; Uematsu et al., 2012). Fiber tracts connecting limbic structures to the PFC, such as the cingulum and uncinate fasciculus, are among the latest developing white matter, showing continued maturation into young adulthood (Lebel & Beaulieu, 2011). Prolonged maturation in these areas facilitates development of complex functions, such as behavior and emotion regulation, but increases susceptibility to experience-based adaptations and abnormal development (Caldwell et al., 2015; Casey et al., 2008; Roberts et al., 1998).

Mental health disorders have been linked to abnormal brain structure, including in adolescence. Mood disorders (internalizing-based) are most commonly related to abnormal amygdala and hippocampal volumes (Drevets et al., 2008; Price & Drevets, 2010), reduced PFC volumes, and reduced FA and increased MD of white matter (Lichenstein et al., 2016; Mincic, 2015; Price & Drevets, 2010). Conduct disorder and antisocial traits (externalizing-based) are linked to decreased amygdala and PFC volume (Yang & Raine, 2009), and attention deficit hyperactivity disorder (ADHD; externalizing-based) is associated with decreased PFC volume, total brain, and subcortical limbic structure volumes, and decreased FA and increased MD of frontostriatal white matter (Castellanos et al., 2001; Filipek, Semrud-Clikeman, Steingrad, Kennedy, & Biederman, 1997; Gau, Tseng, Tseng, Wu, & Lo, 2015; Hoogman et al., 2017).

While multiple studies have identified links between brain structure and mental health disorders, it is important to understand whether relationships exist in children and adolescents without disorders. Previous research in a typical population has demonstrated thinner PFC in children and thicker PFC in adolescents with higher anxiety/depression symptoms (Ducharme et al., 2014), thinner PFC in children and adolescents with more externalizing behaviors (Ameis et al., 2014; Ducharme et al., 2011), and reduced thinning (change in thickness over time) in PFC

regions in children with increased internalizing and externalizing behaviours (Whittle, Vijayakumar, Simmons, & Allen, 2019). Decreased dorsolateral PFC volume has also been shown in children with increased internalizing and externalizing behaviors (Snyder et al., 2017), and anterior cingulate volume is related to aggression in male children and adolescents (Boes, Tranel, Anderson, & Nopoulos, 2008; Visser et al., 2013). Relationships between hippocampus and amygdala volume and internalizing behaviors have been inconsistent in previous research (Koolschijn et al., 2013; Snyder et al., 2017; van der Plas, Boes, Wemmie, Tranel, & Nopoulos, 2010; Yap, Whittle, Yücel, & Sheeber, 2008), leaving the role of these structures unclear. The white matter that connects these limbic structures is also critical for proper brain function. The organization and integrity of white matter can be inferred using measures calculated from diffusion tensor imaging (DTI). Reduced fractional anisotropy (FA), which is thought to indicate a decrease in white matter tract integrity, in the cingulum and uncinate fasciculus has been associated with internalizing behaviors in typically-developing young girls (Ali et al., 2019), and slower age-related increases of FA in the right cingulum were reported in children and adolescents with internalizing behaviors (Albaugh et al., 2017). To date, no studies have used DTI to assess relationships between white matter and externalizing behaviors in typically-developing youth. Though brain alterations in mental health disorders are well characterized, there is a need to understand the emerging structural-behavioral links beginning in childhood and throughout adolescence in both gray and white matter. This will allow identification of the structures and networks implicated in the presence of mental health behaviors before diagnostic levels are reached. With this foundational knowledge, further research can explore the progression from behaviors to disorder which may help to inform recognition and intervention practices.

The goal of this study was to examine relationships between internalizing and externalizing behaviors and brain structure in children and adolescents without mental health disorders. Based on previous research (Ahmed, Bittencourt-Hewitt, & Sebastian, 2015; Mincic, 2015; Waller et al., 2017), we examined volume of the anterior cingulate cortex, superior frontal and middle frontal gyri, amygdala, hippocampus, as well as FA and mean diffusivity (MD) in the cingulum, fornix, and uncinate fasciculus. Based on findings in children and adolescents with mental health disorders, we expected to find lower volumes and FA, and higher MD related to more severe internalizing and externalizing behaviors relative to other children in the sample. Gender and age interactions were explored based on differential gender prevalence rates of internalizing and externalizing disorders and the varying average age of disorder onsets (Fanti & Henrich, 2010; Gilliom & Shaw, 2004; Zahn-Waxler et al., 2008).

3.2 Methods

3.2.1 Participants

This study analyzed 67 scans on 48 typically-developing children and adolescents aged 6.0-16.2 years with no prior diagnosis of mental health or neurodevelopmental disorders as reported by guardians, and no MRI contraindications. Gender was determined through parent report. Each participant received an MRI scan and behavioral assessment at baseline (10.3 +/- 2.4 years, 26 males, 22 females). 19 participants returned 2 years later (aged 14.0 +/- 1.9 years, 11 males, 8 females) for a follow-up MRI scan and behavioral assessment. Recruitment was completed through posters, newsletters, and word of mouth. Written informed consent and assent

were obtained from parents/guardians and participants, respectively. The study was approved by the University of Calgary Conjoint Health Research Ethics Board (REB13-1346).

3.2.2 Behavioral Measures

To measure internalizing and externalizing behaviors, and their subcomponents, parents completed the Behavioral Assessment System for Children, Second Edition – Parent Rating Scale (BASC-2-PRS)(Reynolds et al., 2011). The BASC-2 provides T-scores for internalizing behaviors, externalizing behaviors, and the subcomponents of each (internalizing: anxiety, depression, and somatization; externalizing: aggression, conduct problems, and hyperactivity). The BASC-2-PRS is used for both clinical and research purposes, provides high sensitivity to DSM III and IV diagnoses, convergent and discriminant validity, high internal consistency and temporal stability (Baxter & Rattan, 2004; Doyle, Ostrander, Skare, Crosby, & August, 1997; Gladman & Lancaster, 2003; Jarratt, Riccio, & Siekierski, 2005; Vaughn, Riccio, Hynd, & Hall, 2010). It is a continuous scale with higher scores indicating more prominent displays of the emotion or behavior. A T-score of 50 is considered the mean for the general population. In clinical settings cut-offs can be utilized to aid in diagnostic processes. Children with T-scores 60 and above are generally classified as at-risk for developing a disorder, while T-scores of 70 and above indicate clinically significant levels of maladaptive behaviors and suggest that children may meet diagnostic criteria for an emotional or behavioral disorder. However, these T-scores are still continuous, and an increase in score still denotes more negative behaviours even when lower than clinical cut-offs. Table 3.1 provides sample demographics and behavioural means.

Table 3.1 Demographics table of time point 1 and 2 for each gender, and total cohort.

	Time 1		Time 2		
	Females	Males	Females	Males	Total
Number of Datasets	22	26	8	11	67
Age	9.9 ± 2.5 years	10.7 ± 2.2 years	13.9 ± 2.5 years	14.0 ± 1.6 years	11.3 ± 2.7 years
Internalizing T-Score	51.9 ± 8.3	50.0 ± 11.9	57.0 ± 11.8	50.7 ± 12.0	51.6 ± 10.8
Externalizing T-Score	51.4 ± 9.4	53.2 ± 9.8	51.9 ± 11.0	54.4 ± 7.9	52.6 ± 9.4

3.2.3 Brain Imaging

Participants were scanned using a research-dedicated 3T GE MR750w scanner equipped with a 32-channel head coil (GE Healthcare, Waukesha, WI) at the Alberta Children's Hospital. T1-weighted images were acquired using a 3D FSPGR sequence (BRAVO: TI= 600ms, TR= 8.2ms, and TE= 3.2ms, isotropic resolution of 0.8mm, total scan time of 5:38 min). Freesurfer v5.3 (Fischl, 2012) was used for processing, editing, and segmenting structural brain images. The automated recon-all pipeline (Dale, Fischl, & Sereno, 1999) was used to perform brain extraction, image registration, motion and intensity correction, segmentation/parcellation, and calculation of volumes. Each segmentation was manually checked to ensure proper delineation of the outer pial surface and white matter border, and editing steps, using manual placement of control points to denote white matter voxels, were performed to improve segmentations if necessary. After processing, volumes of the amygdala, hippocampus, anterior cingulate cortex, superior frontal and middle frontal gyri were extracted for each hemisphere in each individual (Fig. 3.1). Two

participants had amygdala volumes removed due to poor segmentation results based on manual checks of segmentation and volumes more than 3 standard deviations from the mean, so only 65 datasets were included in the analysis of amygdala volume.

Diffusion MRI was acquired using a spin echo echo planar imaging (EPI) sequence using 30 diffusion encoding gradient directions with a b-value of 900 s/mm^2 and five b=0 s/mm^2 volumes (TE/TR = 88/12000 ms, 2.2-mm isotropic resolution, total scan time 7:12). ExploreDTI (Leemans, Jeurissen, Sijbers, & Jones, 2009) was used to process data including correction for signal drift, Gibb's ringing, subject motion, eddy current distortion, and EPI distortion. One participant's DTI data were removed due to excessive head motion based on manual assessment of raw data and inability to process, therefore only 66 datasets were included in DTI analysis.

Constrained spherical deconvolution (CSD)(Farquharson et al., 2013) was used to compute a whole brain tractogram, then semi-automated tractography (Lebel, Walker, et al., 2008) was performed to extract the uncinate fasciculus, fornix, and cingulum (Fig. 3.1). The ROI placements used to extract these tracts were based on a priori knowledge of tract location (Abdul-Rahman, Qiu, & Sim, 2011; Larroza, Moratal, D'ocon Alcaniz, & Arana, 2014; Plaisier et al., 2014; Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004). FA and MD were extracted for each tract in each hemisphere for analysis.

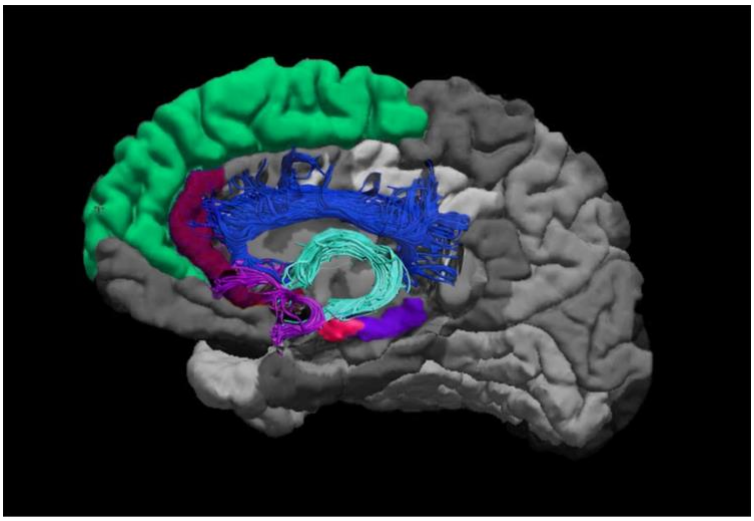


Figure 3.1 Measured brain structures. Volumes from T1-weighted imaging include amygdala (pink), hippocampus (purple), anterior cingulate cortex (burgundy), superior frontal gyrus (green), and middle frontal gyrus (not shown). Tracts from diffusion-weighted imaging include the uncinate fasciculus (purple), fornix (cyan), and cingulum (blue).

3.2.4 Statistical Analysis

IBM SPSS Statistics, Version 24 (IBM Corp., Armonk, NY) was used for all statistical analyses. Linear mixed effects regressions were used to analyze relationships between brain structure and age, gender, internalizing, externalizing behavior, age-gender, age-behavior, and gender-behavior interactions. Age-gender, age-behavior and gender-behavior interactions were removed from the model if not significant. Subject was included as a random effect to account for returning participants. Significant brain-behavior findings were further investigated using separate linear mixed effect regressions with the 3 behavioral subscales of internalizing (anxiety, depression, somatization) or externalizing (aggression, hyperactivity, conduct problems) behavior to elucidate the most relevant behavioral subtype(s). False discovery rate (FDR) was used to account for 24 tests using DTI measures (12 regions*2 behaviors), and then used to account for 20 tests using T1 measures (10 regions*2 behaviors) in the main analysis.

To understand the specificity of results, linear mixed effects models for significant brain-behaviour relationships were re-run including both behaviours in the model (i.e., findings where internalizing behaviour had a significant relationship with brain measures were re-run including externalizing behaviour as a covariate). To ensure participants with high internalizing or externalizing behaviours were not driving any relationships, we re-ran the linear mixed effects models for all significant findings, excluding participants with mental health symptoms at clinically significant levels (T-score >70).

3.2.5 Exploratory Longitudinal Analysis

An exploratory analysis was conducted using linear regressions to test whether time 1 measures of brain structure were associated with time 2 behavioural measures after two years and whether time 1 behaviours were associated with time 2 brain structure. Only brain structures with significant relationships in the primary analysis were tested (5 structural brain measures). Age, gender, and time 1 behavioural measure (internalizing or externalizing) were included as predictors in the model.

3.3 Results

3.3.1 Behavioral Scores

Mean internalizing and externalizing T-scores were 52 ± 11 and 53 ± 9, respectively. No participants were diagnosed with a mental illness, though 6 participants (9%) reached clinical significance in their internalizing scores (T-score ≥70) and 8 were at risk (T-score ≥60); 2 participants (3%) reached clinical significance in their externalizing scores and 12 were at risk. This is similar to rates in the general population of children and adolescents (Merikangas et al.,

2009). It is worth noting there was some crossover of participants being at risk in both behaviors (n=6), but no participants had clinically significant levels of both internalizing and externalizing behavior. The subscales of internalizing and externalizing behaviours exhibited internal reliability (Cronbach's alpha: 0.70 and 0.84, respectively). Figure 3.2 displays internalizing and externalizing behaviour T-scores and their subcomponents for each participant.

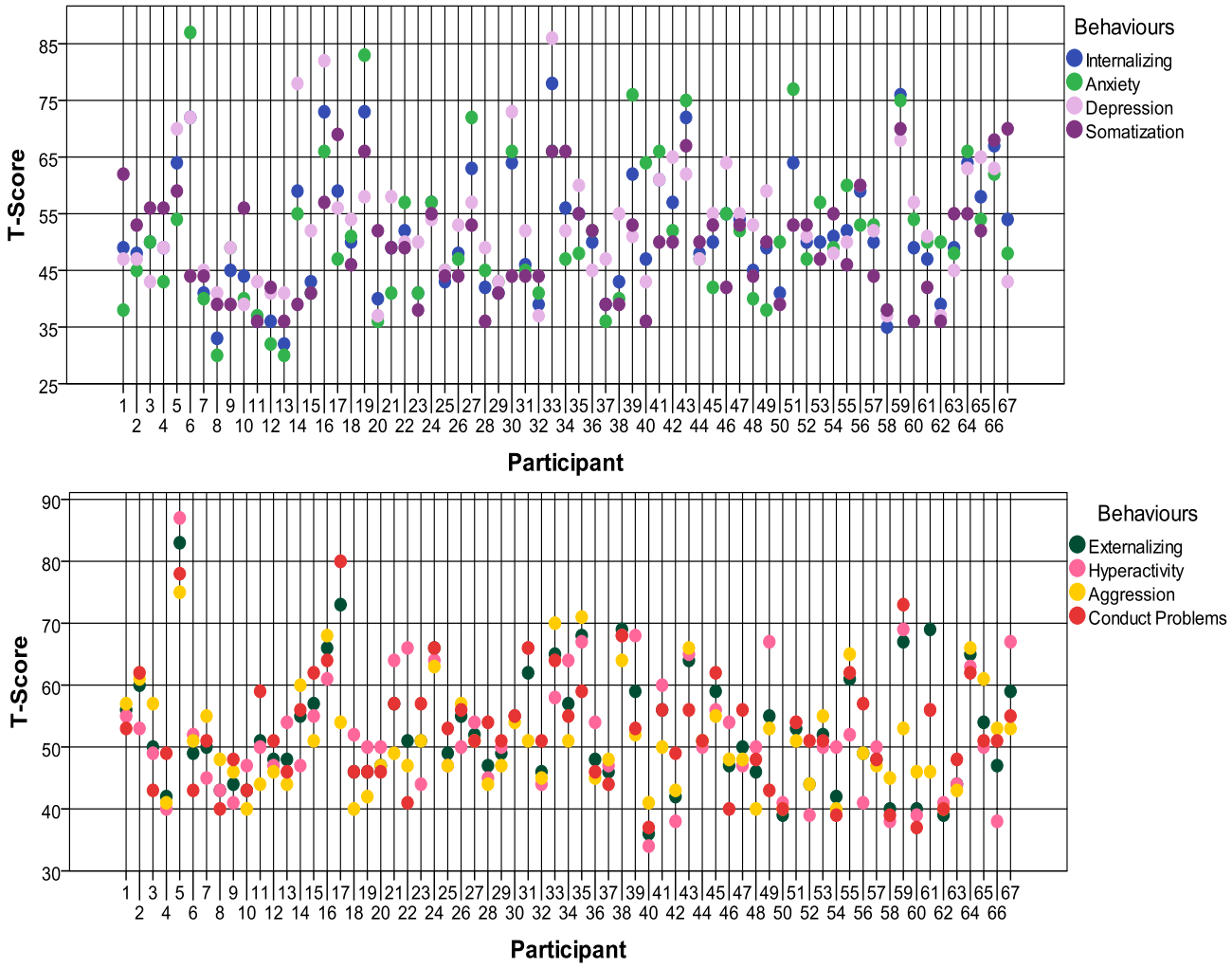


Figure 3.2 Participant T-scores of internalizing and externalizing behaviours and their subcomponents: anxiety, depression, and somatization, and hyperactivity, aggression, and conduct problems, respectively.

3.3.2 Internalizing Behavior and Brain Structure

MD in the bilateral cingulum was positively associated with internalizing behavior with a gender interaction (left: F = 12.458, p = 0.001; right: F = 10.803, p = 0.002). Post hoc analysis showed females had a more positive relationship with internalizing scores than males (Fig. 3.3). All internalizing subtypes were associated with MD of the left cingulum through a similar gender interaction (anxiety*gender: F = 4.640, p = 0.035; depression*gender: F = 10.973, p = 0.002; somatization*gender: F = 10.205, p = 0.003), where females had stronger positive relationships. Depression and somatization, but not anxiety, had similar gender interactions for MD of the right cingulum (depression*gender: F = 4.987, p = 0.03; somatization*gender: F = 6.767, p = 0.013) (Fig. 3.4).

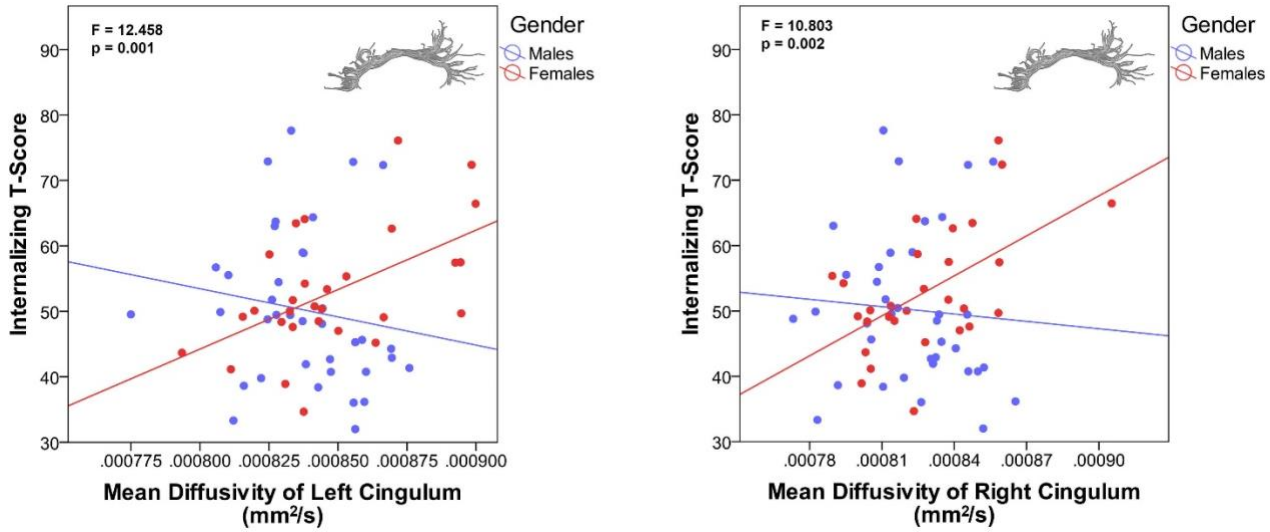
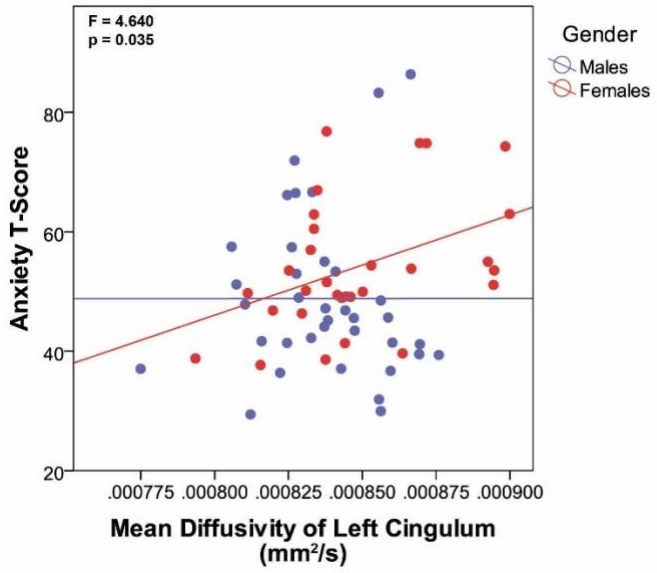
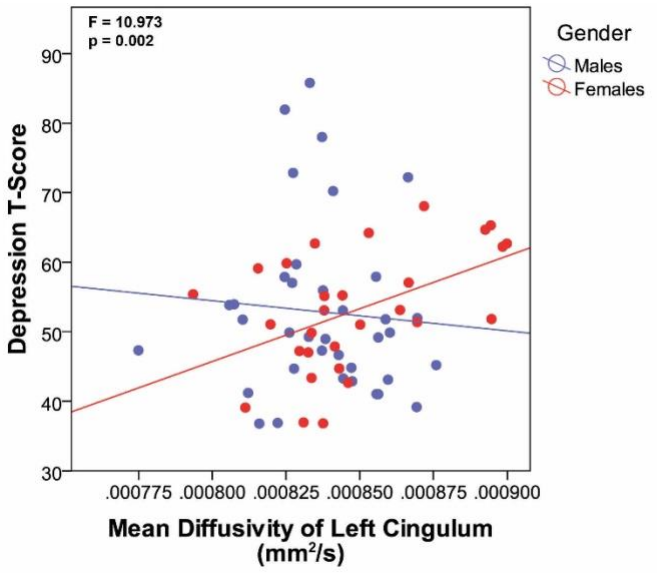


Figure 3.3 Relationships between mean diffusivity (MD) of the bilateral cingulum and internalizing behaviors with a gender interaction. Internalizing T-scores were positively associated with MD of the bilateral cingulum in females (red), but not males (blue).


F = 4.640
p = 0.035
Gender
Males
Females
Anxiety T-Score
80
60
40
20
.000775 .000800 .000825 .000850 .000875 .000900
Mean Diffusivity of Left Cingulum
(mm²/s)


F = 10.973
p = 0.002
Gender
Males
Females
Depression T-Score
90
80
70
60
50
40
30
.000775 .000800 .000825 .000850 .000875 .000900
Mean Diffusivity of Left Cingulum
(mm²/s)

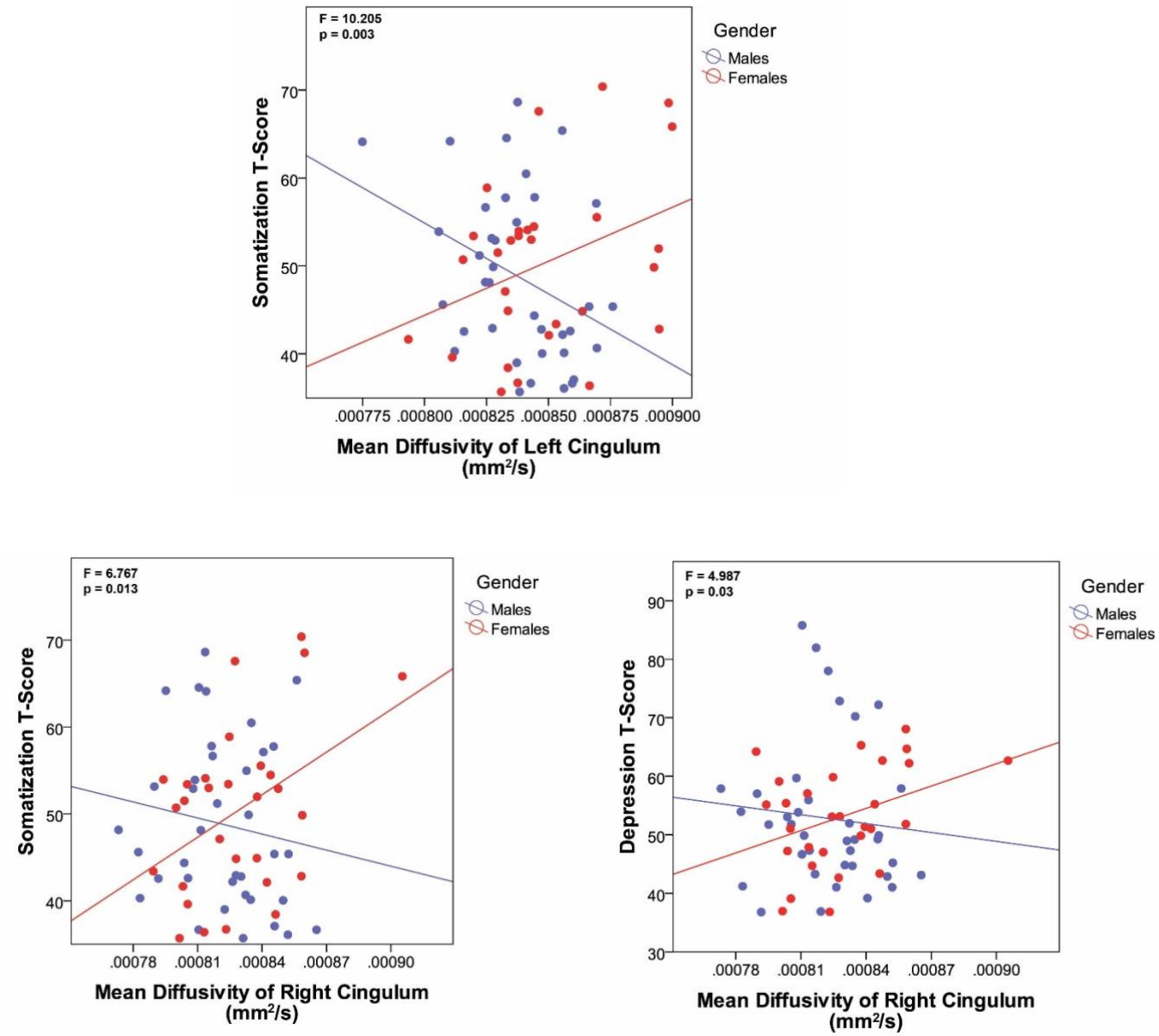


Figure 3.4 Relationships between mean diffusivity (MD) of the bilateral cingulum and the significant subcomponents internalizing behaviors: anxiety, depression, and somatization, with a gender interaction. Behavioural T-scores were positively associated with MD of the bilateral cingulum in females (red), but not males (blue).

FA in the left uncinate fasciculus was negatively associated with internalizing behaviors ($F = 4.439$, $p = 0.039$). Volume of the right hippocampus was negatively associated with internalizing behavior, both the main effect ($F = 4.867$, $p = 0.031$), and the interaction with age (F

= 6.297, p = 0.015). Post hoc analysis demonstrated a relationship which was stronger in older adolescents, though these results did not survive FDR correction for multiple comparisons.

3.3.3 Externalizing Behavior and Brain Structure

FA of the bilateral cingulum (L: F = 9.174, p = 0.004, R: F = 7.010, p = 0.01) was negatively associated with externalizing behaviors (Fig. 3.5). FA in the left uncinate fasciculus had an externalizing–age interaction (F = 7.666, p = 0.008). Post-hoc analysis showed a positive relationship between FA and age in participants with low externalizing scores, but was not present in those with high externalizing scores (Fig. 3.7). Of the externalizing subtypes, conduct problems (F = 5.054, p = 0.028) and aggression (F = 9.489, p = 0.003) were both associated with FA in the left cingulum; only conduct problems (F = 9.726, p = 0.003) were associated with FA in the right cingulum (Fig. 3.6). Age-aggression (F = 6.292, p = 0.015) and age-hyperactivity (F = 5.564, p = 0.022) interactions were associated with FA of the left uncinate fasciculus, with stronger age-FA relationships in participants with lower externalizing scores (Fig. 3.8).

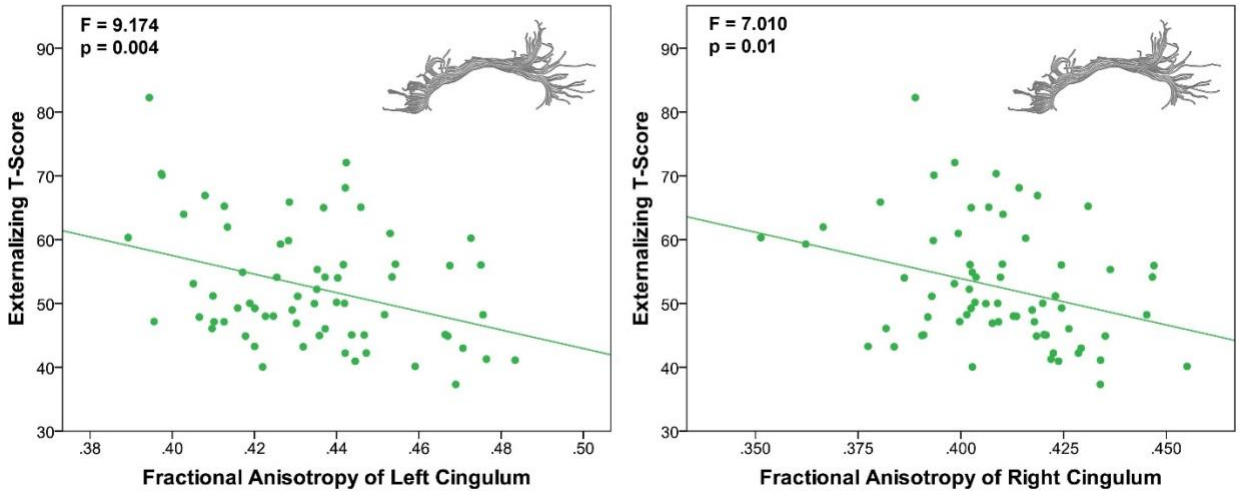
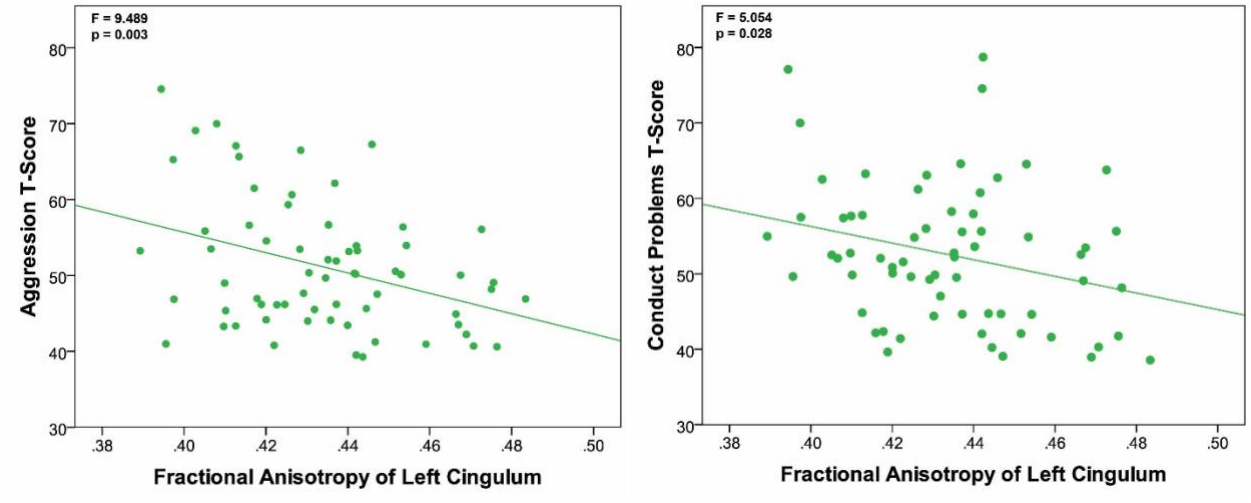


Figure 3.5 Relationships between fractional anisotropy (FA) of the bilateral cingulum and externalizing behaviors, such that higher externalizing T-scores were associated with lower FA of the bilateral cingulum.



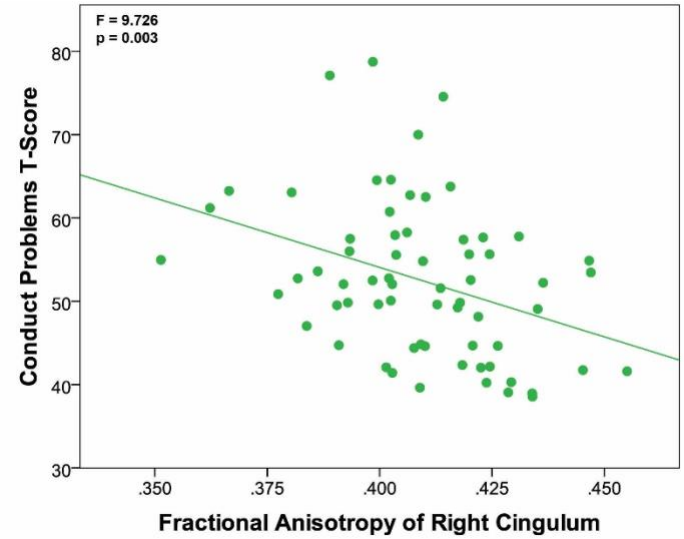


Figure 3.6 Relationships between fractional anisotropy (FA) of the bilateral cingulum and the significant subcomponents of externalizing behavior: aggression and conduct problems, such that higher behavioural T-scores were associated with lower FA of the bilateral cingulum.

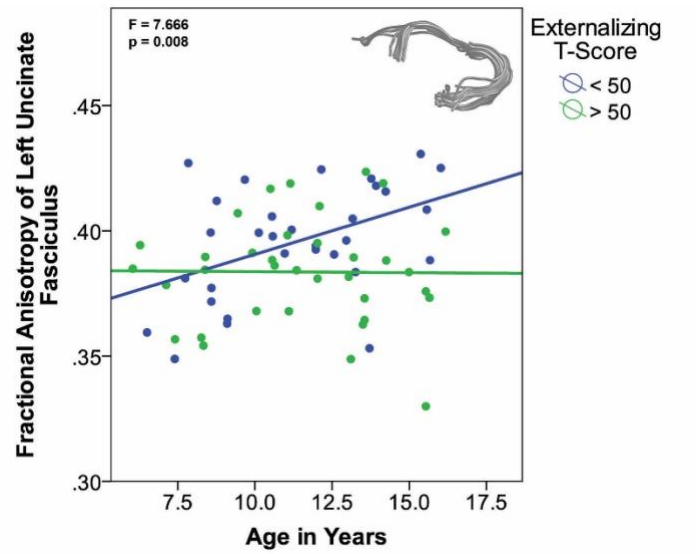


Figure 3.7 The relationship between fractional anisotropy (FA) of the left uncinate fasciculus and an age-externalizing behavior interaction, such that the age-FA relationship was stronger in participants with lower externalizing scores (blue) compared to those with higher externalizing scores (green). A T-score of 50 was used here to define groups as this is the mean score in the general population.

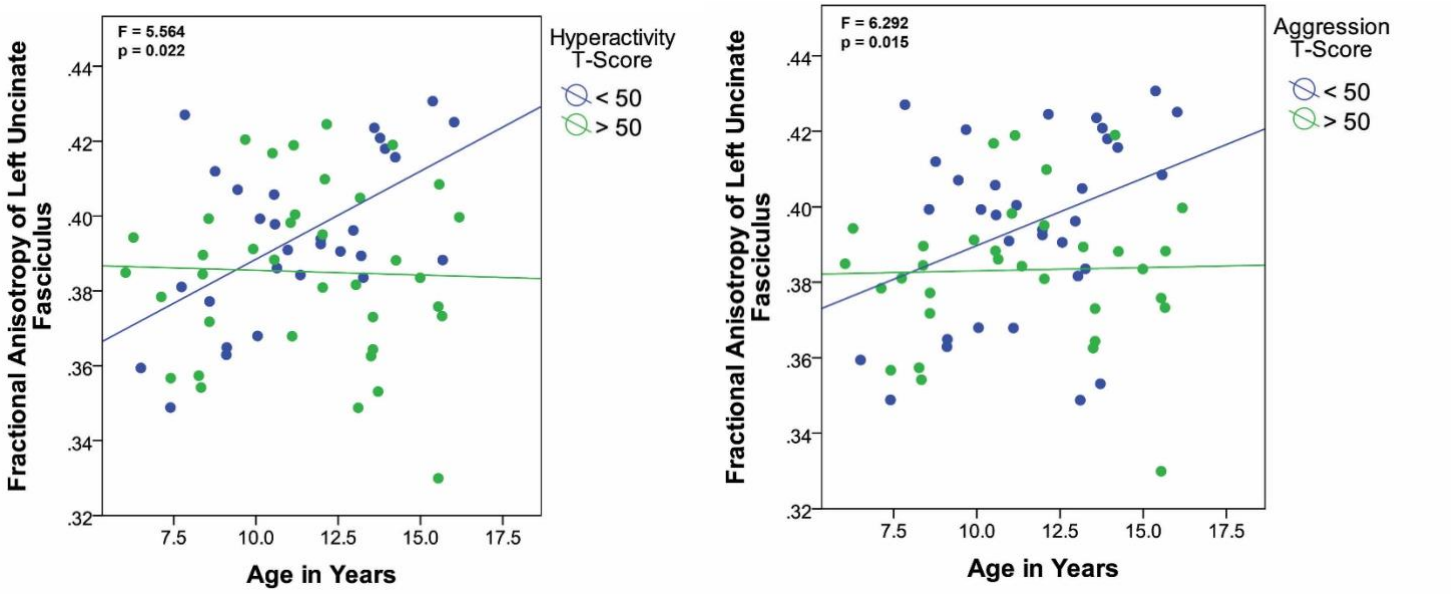


Figure 3.8 The relationship between fractional anisotropy (FA) of the left uncinate fasciculus and the significant subcomponents of externalizing behavior with an age interaction, such that the age-FA relationship was stronger in participants with lower externalizing scores (blue) compared to those with higher externalizing scores (green). A T-score of 50 was used here to define groups as this is the mean score in the general population.

Bilateral anterior cingulate cortex volumes (L: F = 6.847, p = 0.011, R: F = 6.818, p = 0.012) and the right middle frontal gyrus volume (F = 5.607, p = 0.022) were negatively associated with externalizing behavior. None of the volume-behavior relationships survived FDR correction for multiple comparisons. Table 3.2 details the main analysis findings.

All linear mixed effects regression analyses of significant internalizing or externalizing relationships excluding participants with clinically significant levels (T-score >70) of internalizing and externalizing behaviours remained significant (all $p<0.05$) (Fig. 3.9). All analyses of significant internalizing or externalizing relationships including both behaviours in the model remained significant (all $p<0.05$).

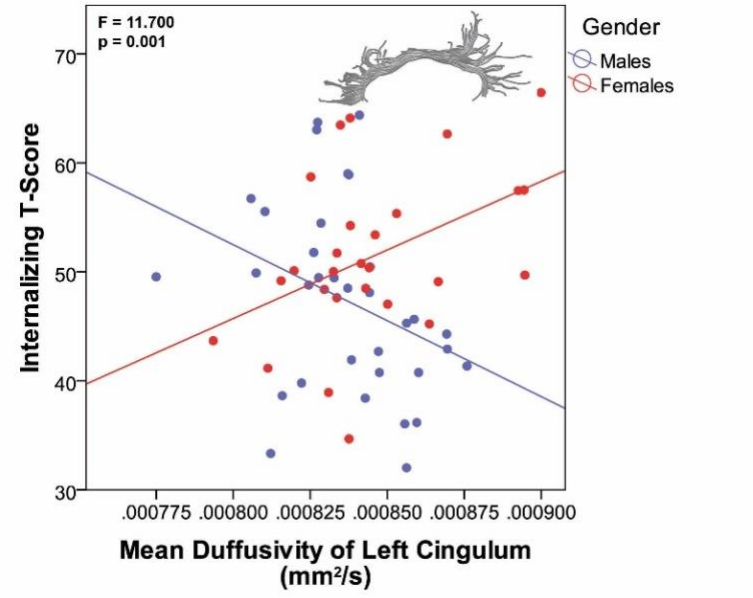
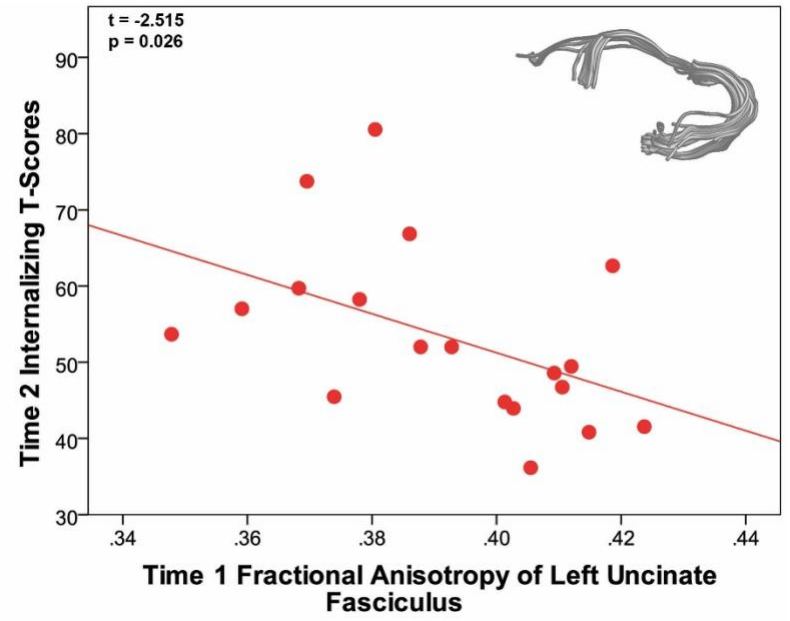


Figure 3.9 Relationships between mean diffusivity (MD) of the left cingulum and internalizing behaviors below clinically significant levels (T scores < 70) with a gender interaction. The same positive relationship in females and negative relationship in males remains.

3.3.4 Exploratory Longitudinal Analysis

FA of the left uncinate fasciculus at time 1 was associated with internalizing behaviours at time 2 (t = -2.515, p = 0.026), such that lower FA at time 1 predicted higher internalizing scores at time 2. Time 1 internalizing behaviours also predicted time 2 FA of the left uncinate (t = 2.738, p = 0.017), such that higher internalizing scores at time 1 predicted higher FA at time 2 (Fig. 3.10). No other significant longitudinal relationships were found.



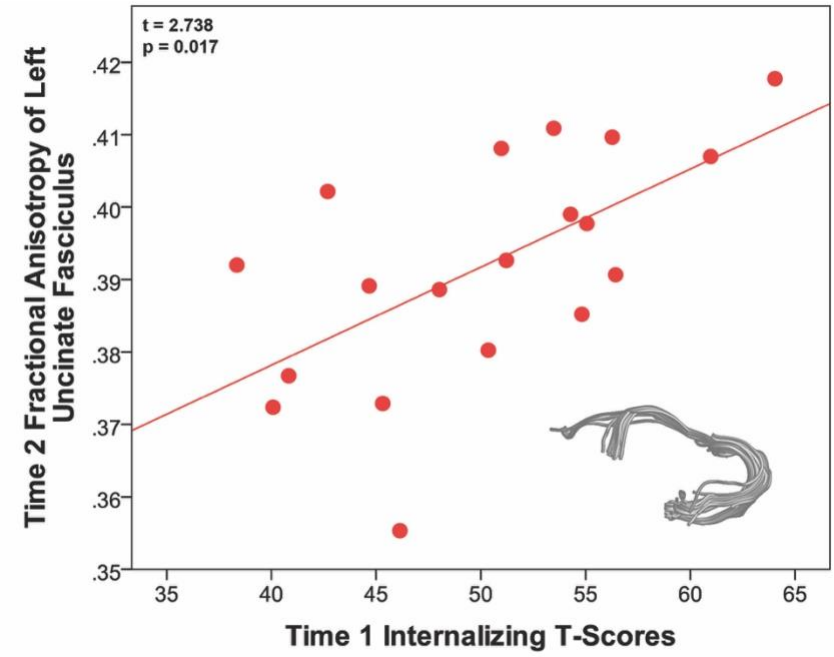


Figure 3.10 The relationship between Time 1 fractional anisotropy (FA) of the left uncinate fasciculus and Time 2 internalizing T-scores with a two year time gap. Lower FA in the left uncinate fasciculus at Time 1 was associated with higher internalizing scores at Time 2. The opposite relationship, Time 1 internalizing T-scores and Time 2 FA of the left uncinate is also shown. Higher internalizing scores at Time 1 were associated with higher FA at time 2.

Table 3.2 Relationships Between Brain Structure and Mental Health Behaviors. Overview of significant findings between brain and behavioral measures. All relationships between behavior and volume or behavior and fractional anisotropy (FA) relationships were negative, such that lower volume or FA was associated with more severe behavior than other children. All relationships between behavior and mean diffusivity (MD) were positive, such that higher MD was associated with more severe behavior than other children.

	Brain Region	Main Effect		Interaction Type	Interaction	
		F	p		F	p
Internalizing Behavior	Right Hippocampus	4.867	0.031	Internalizing x Age	6.297	0.015
	FA Left Uncinate Fasciculus	2.515	0.118	Internalizing x Age	4.402	0.04
	MD Left Cingulum	5.396	0.025	Internalizing x Gender	12.458	0.001*
	MD Right Cingulum	8.172	0.006	Internalizing x Gender	10.803	0.002*
Externalizing Behavior	Left Anterior Cingulate Cortex	6.847	0.011			
	Right Anterior Cingulate Cortex	6.818	0.012			
	Right Middle Frontal Gyrus	5.607	0.022			

FA Left Cingulum	9.174	0.004*			
FA Right Cingulum	7.01	0.010*			
FA Left Uncinate Fasciculus	4.053	0.049	Externalizing x Age	7.666	0.008*

*Indicates findings that survive false discovery rate (FDR) correction for multiple comparisons.

3.4 Discussion

Here we show that decreased FA and increased MD are associated with more internalizing and externalizing behaviors in cortico-limbic white matter tracts in a population of typical children and adolescents. Our study is the first to identify relationships between diffusion measures of white matter and externalizing behaviors in typically-developing children and adolescents and builds on previous research of diffusion measures of white matter and internalizing behaviour relationships. Some significant interactions were present, such that females had stronger relationships between MD of cortico-limbic white matter and internalizing behaviors than males, and those with lower externalizing scores showed positive associations of FA of cortico-limbic white matter and age, while those with higher scores did not. Overall, these relationships highlight the importance of even sub-threshold mental health-related behaviors as they are associated with white matter alterations often seen in mental health disorders. Structural integrity of the uncinate and cingulum may be early indicators of susceptibility to mental health disorders.

Diffusion parameters (lower FA and/or higher MD) in the cingulum and uncinate fasciculus were associated with more problem behaviors. The cingulum was bilaterally related to both internalizing and externalizing behavior, while FA in the left uncinate fasciculus was

associated with externalizing behaviors. The cingulum connects prefrontal cortical and limbic regions and is involved with behavioral monitoring and emotional processing (Bubb, Metzler-Baddeley, & Aggleton, 2018), while the uncinate connects the temporal pole with important prefrontal regions related to emotional regulation and impulsivity (Olson et al., 2015). The cingulum and uncinate fasciculus are limbic system pathways frequently implicated in studies of depression, conduct disorder, post-traumatic stress disorder, and obsessive compulsive disorder (Bubb et al., 2018; Lichenstein et al., 2016; Mincic, 2015; Olson et al., 2015; Sarkar et al., 2013). Few DTI studies have investigated whether these tracts are associated with behaviors in a typical sample, though decreased FA in the bilateral cingulum and uncinate fasciculus in females (Ali et al., 2019), and slower age-related changes of FA in the right cingulum, have been associated with more internalizing behaviors (Albaugh et al., 2017). Our findings suggest that similar relationships are present in children and adolescents with sub-threshold symptoms. In this regard, alterations in the uncinate and cingulum may be early indicators of susceptibility to mental health disorders.

Interactions between internalizing behaviour and gender were found for MD of the bilateral cingulum, such that females held a strong positive relationship and males held a slight negative relationship between MD and behaviour. The cingulum and uncinate fasciculus exhibit prolonged developmental periods, with FA increases and MD decreases continuing into adulthood (Lebel & Beaulieu, 2011; Lebel, Walker, et al., 2008; Tamnes et al., 2010), as well as sexual dimorphism where females appear to develop earlier than males (Asato et al., 2010; Seunarine et al., 2016). The gender interactions observed here may arise from earlier white matter development in females, resulting in the relationship with internalizing behaviors forming earlier. Thus, it may be that males will display a similar relationship between the cingulum and internalizing behaviors later in development. On the other hand, this relationship may be unique to females. Females tend to

exhibit more internalizing symptoms across the lifespan than males (Eaton et al., 2012; Zahn-Waxler et al., 2008), and women at familial risk for depression showed reductions in FA bilaterally in the cingulum (Keedwell et al., 2012). With further research, it may become clear whether this gender interaction is a product of the earlier development of white matter in females or whether females hold a distinct relationship between the cingulum and internalizing behaviors that males do not.

FA of the left uncinate fasciculus showed an externalizing-age interaction such that participants with lower levels of externalizing behaviours had stronger positive relationships between FA and age than those with higher externalizing behaviours. For many individuals, externalizing behaviors diminish after early childhood (Fanti & Henrich, 2010; Moffitt, 1993). However, individuals whose behavioural symptoms are persistent are more susceptible to developing a mental health disorder (Hofstra et al., 2002) and may have reduced or delayed co-development of the uncinate and behavior such as socio-emotional processing. In other words, participants with higher externalizing behaviours may not be experiencing the same developmental increases in FA of the uncinate with age, which results in a more pronounced delay in the associated socio-emotional processing. A negative association has been shown between FA of the uncinate fasciculus and antisocial behavior in adults (Waller et al., 2017) suggesting this relationship persists into adulthood.

Our exploratory longitudinal analysis showed FA of the uncinate fasciculus at baseline was associated with internalizing behaviours at time 2. Internalizing behaviours at baseline were also significantly associated with FA of the uncinate at time 2. It may be that altered microstructure reflects reduced capacity to process socio-emotional demands, leading to higher internalizing symptoms later or it may be that change in behaviour impacts white matter microstructure

development. This does, however, show changing relationships over time. Worse internalizing behaviours early predict higher FA later on, and in contrast, low FA of the uncinate early on predicts worse behaviours later. With a small longitudinal sample and a 2 year gap, more studies are needed to clarify these relationships.

Our secondary analysis of behavioral subtypes suggests the brain-behavior relationships are broad, rather that attributable to specific domains of symptoms. For both internalizing and externalizing behaviour, multiple subtypes were associated with white matter microstructure. In support of these representing broad, rather than specific relationships, previous research has suggested altered structural integrity, shown through diffusion metrics, of the uncinate fasciculus in conduct disorder, bipolar disorder, and depression (Decety, Yoder, & Lahey, 2015; Heng, Song, & Sim, 2010; Sexton, Mackay, & Ebmeier, 2009; White, Nelson, et al., 2008), as well as altered structural connectivity of the cingulum in bipolar disorder, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and panic disorder (Sexton et al., 2009; White, Nelson, et al., 2008).

Here, we found MD was related to internalizing behaviors while FA was associated with externalizing behaviors, though baseline FA was associated with time 2 internalizing behaviour. FA and MD are inherently related but are differentially sensitive to white matter tissue (Basser & Pierpoali, 1996). Distinct findings between FA and MD suggest that the structure of the cingulum may be linked to behavioral outcomes in unique ways. FA tends to be more sensitive to diffusion restriction along a primary axis, which is driven by factors such as myelin and tract coherence, while MD reflects gross water movement, and is strongly influenced by white matter density (Beaulieu, 2002). Future studies using techniques more sensitive to particular aspects of white matter, for example myelin water imaging or advanced diffusion models, will provide better

insight into the biological processes driving these relationships (Geeraert et al., 2018; Zhang, Schneider, Wheeler-Kingshott, & Alexander, 2012).

Findings relating behavior to brain volumes were not significant in our study. Previous studies of typically-developing children and adolescents have found mixed results, with some reporting that externalizing behaviors are related to reduced volume of PFC regions (Boes et al., 2008; Montigny et al., 2013; Snyder et al., 2017) and internalizing behaviors were related to reduced hippocampus volume (Koolschijn et al., 2013; Snyder et al., 2017), and another finding of no significant relationships between hippocampal volume and depressive behaviors in a community sample (Yap et al., 2008). These significant findings, together with our lack of significant results, may suggest only very subtle changes to gray matter at subclinical levels of mental health behaviours.

This study has several limitations. Parent rating questionnaires, as used in this study, may not accurately reflect a child's behaviors. Parent reports offer sensitivity to diagnoses as has been demonstrated (Doyle et al., 1997; Vaughn et al., 2010) , though they provide different information than child self-reports (Barnhill et al., 2000; Kolko & Kazdin, 1993). Additionally, longitudinal data were not available for all participants, so the longitudinal analysis is purely exploratory and must be confirmed by larger studies. Lastly, pubertal stage was not measured, though there is evidence that it may influence white matter (Genc et al., 2017). Future studies with larger, longitudinal cohorts, and incorporating self-reports and assessments of puberty, will help further elucidate the role of brain structure in internalizing and externalizing behaviours in typical children and youth.

In conclusion, this study demonstrates that reduced FA and increased MD in the bilateral cingulum and left uncinate fasciculus is associated with mental health-related behaviors in

typically-developing children and adolescents. These results suggest that children with more severe behaviors, even sub-clinically, exhibit altered trajectories of development in white matter tracts important for their mental health. Improved understanding of mental health may better inform diagnosis, treatment, and reduce societal burden overall. This includes earlier interventions and prevention methods, such as cognitive behavioral therapy, shown to lower the risk of developing mental health disorders, remission of diagnosis (Gaudiano, 2008; Hofmann et al., 2012; James et al., 2015), and neurological improvements (Etkin, 2005; Porto et al., 2009), which translates to fewer childhood years compromised by mental illness.

Chapter 4: Brain Structure and Behaviour in Children and Adolescents with Prenatal Alcohol Exposure and Early Adverse Exposures

Presented at the 2019 Organization for Human Brain Mapping (OHBM) Annual Meeting and the 8th International Conference on Fetal Alcohol Spectrum Disorder

4.1 Introduction

Alcohol can cross the placenta and blood-brain barrier, and directly affect fetal development and cause long-term changes in brain and behaviour (Uban et al., 2010). Heavy prenatal alcohol exposure (PAE) has been linked with widespread brain abnormalities including reduced brain volume, altered cortical thickness, reduced fractional anisotropy (FA), and increased mean diffusivity (MD) (Lebel et al., 2011; Wozniak & Muetzel, 2011), FA and MD being white matter diffusion measures thought to indicate white matter integrity (Beaulieu, 2002). PAE can lead to a diagnosis of fetal alcohol spectrum disorder (FASD), the most common cause of preventable developmental disabilities in children (Cook et al., 2016). Heavy PAE is also strongly linked with mental health problems; the vast majority of individuals with FASD have at least one mental health disorder (Astley, 2010; Pei et al., 2011). For example, attention deficit hyperactivity disorder (ADHD) occurs in approximately 50% of people with FASD, 10 times the prevalence in the general population (Weyrauch, Schwartz, Hart, Klug, & Burd, 2017). Similarly, anxiety and depression occur in individuals with FASD at a rate of 11x and 4x the prevalence in the general population, respectively (Weyrauch et al., 2017). Externalizing and internalizing behaviours, defined as negative behaviours directed externally (aggression, hyperactivity, conduct problems),

or internally (anxiety, depression, somatization), respectively, offer one way to understand the symptoms of mental-health disorders.

Children with heavy PAE are more likely than the general population to experience postnatal adversity such as neglect, impoverishment, caregiver transitions, abuse (i.e. verbal, physical, sexual), and being a witness to violence or chronic substance use (Astley, 2010; Lebel et al., 2019). These types of postnatal experiences can negatively affect brain development (Bick et al., 2015; Hart & Rubia, 2012) and have been associated with increased internalizing and externalizing disorders (Enlow, Egeland, Blood, Wright, & Wright, 2012; Felitti, Anda, Nordenberg, Williamson, Spitz, Edwards, 1998; Flaherty et al., 2013; Henry, Sloane, & Black-Pond, 2007; Kerker et al., 2015). The vast majority of previous studies of PAE do not address co-occurring postnatal exposures (Fryer et al., 2009; Nardelli et al., 2011), though a few studies have demonstrated that children and adolescents with FASD and postnatal trauma had more severe externalizing behaviours than children and adolescents with postnatal trauma and no PAE (Henry et al., 2007; Hyter, 2012; Price et al., 2017). Similarly, another study showed that children with FASD who lived with their biological parents had worse behaviour problems and worse developmental delays than children with FASD who were adopted at birth (Koponen et al., 2009, 2013).

Heavy PAE has been linked with brain abnormalities throughout the brain. This contains volume reductions in the frontal lobe (Astley, Aylward, Carmichael Olson, et al., 2009), including subregions such as the middle frontal gyri in the prefrontal cortex (PFC) (Eckstrand et al., 2012). Midline structures, such as the corpus callosum, hippocampus, and amygdala, are consistently affected (Astley, Aylward, Carmichael Olson, et al., 2009; Bookstein, Sampson, Connor, & Streissguth, 2002; Nardelli et al., 2011; Sowell, Elizabeth et al., 2001; Wozniak et al., 2013). White

matter also shows widespread effects, including in limbic tracts, such as the uncinate fasciculus and cingulum (Fryer et al., 2009; Lebel et al., 2008). Postnatal adversity is also associated with brain changes, specifically smaller prefrontal cortex (PFC) and hippocampal volumes, increased amygdala volume (Andersen et al., 2008; Hanson et al., 2010; Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014), and decreased FA and increased MD in the cingulum and fornix (Bick et al., 2015; Choi, Jeong, Rohan, Polcari, & Teicher, 2009; Dufford & Kim, 2017). However, none of the previous neuroimaging studies of PAE have also considered postnatal exposures, so it remains unclear whether postnatal effects moderate the association between PAE and brain structure.

The goal of this study was to understand how PAE in the presence or absence of postnatal exposures affects brain structure brain alterations in children and adolescents, and how it is associated with mental health. Based on their role in mental health symptoms (Ahmed et al., 2015; Mincic, 2015) and alterations in individuals with PAE (Coles et al., 2011; Lebel, Rasmussen, et al., 2008; Nardelli et al., 2011), we examined prefrontal (anterior cingulate cortex, superior frontal and middle frontal gyri) and limbic (amygdala, hippocampus) structures and their corresponding white matter connections (cingulum, fornix, uncinate fasciculus). We hypothesized that children and adolescents with PAE and postnatal adversities would have lower volumes, and FA, and higher MD in the brain, increased mental health symptoms, and altered relationships of brain structure and mental health symptoms in comparison to controls and those with PAE and no postnatal adversity.

4.2 Methods

4.2.1 Participants

31 children and adolescents with PAE aged 7-16 years and 31 age- and gender-matched unexposed controls were recruited through posters, social media, newsletters, word of mouth, and (for participants with PAE) through the Cumulative Risk Diagnostic Clinic located in Calgary. Gender was determined through parent report. Controls had no prior diagnoses of mental health problems or neurodevelopmental disorders. 94% of the participants with PAE had prior diagnoses of ADHD, anxiety, depression, learning disability, oppositional defiant disorder, Tourette syndrome, attachment disorder and/or obsessive-compulsive disorder. All participants had no MRI contraindications. This study was approved by the University of Calgary Conjoint Health Research Ethics Board (REB 17-0663).

4.2.2 Behavioural Measures

Internalizing and externalizing behaviours were measured using the Behavioural Assessment System for Children, Second Edition – Parent Rating Scale (BASC-2-PRS)(Reynolds et al., 2011). The BASC-2 computes T-scores for internalizing behaviours and externalizing behaviours. It is used for both clinical and research purposes, provides high sensitivity to DSM III and IV diagnoses, convergent and discriminant validity, high internal consistency and temporal stability (Baxter & Rattan, 2004; Doyle et al., 1997; Gladman & Lancaster, 2003; Jarratt et al., 2005; Vaughn et al., 2010). It is a continuous scale with higher scores indicating more prominent displays of the emotion or behavior. A T-score of 50 is considered the mean for the general population. In clinical settings, cut-offs can be utilized to aid in diagnostic processes. A T-score ≥60 is considered at-risk, while a score ≥70 is considered clinically significant and indicates the participant may meet diagnostic criteria for an emotional or behavioural disorder. However, these T-scores are still continuous, and an increase in score denotes more negative behaviours even when

lower than clinical cut-offs. Two PAE participants were missing BASC-2 scores due to incomplete forms.

4.2.3 Assessment of Exposures

All non-control participants had PAE, confirmed by maternal report, direct observation by close friends of family of the mother drinking alcohol while pregnant, and/or positive blood or urine test. Postnatal adversity was defined as traumatic exposures that put a child at risk for altered developmental outcomes and included abuse or witnessing abuse; neglect; insecurity of food, housing, or income; and caregiver changes. Information about PAE and postnatal exposures were obtained through assessments and interviews from biological and foster/adoptive families, and documentation from child welfare records, physicians, police reports, and social workers. Due to relatively small sample size, we assessed presence or absence of postnatal adversity in the children and youth with PAE rather than subdividing postnatal adversity into categories of exposure (Lebel et al., 2019). 11 participants with PAE did not have postnatal adversity (PAE-), and 20 participants with PAE had some form postnatal adversity (PAE+), as defined above and confirmed via medical, child welfare, and/or legal records. The age at which children were placed in a stable home environment (i.e. when they entered their current, permanent home, typically via adoption) was obtained from child welfare records and interviews with caregivers for use in a follow-up analysis.

4.2.4 Brain Imaging

Participants were scanned on a 3T GE MR750w system using a 32-channel head coil at the Alberta Children's Hospital. T1-weighted anatomical imaging was acquired using a 3D FSPGR sequence with TI = 600ms, TR=8.2 ms, and TE = 3.2ms, 0.8mm isotropic resolution, and a total scan time of 5:38 min. Freesurfer v5.3 was used for processing, editing, and segmenting the T1-weighted anatomical images (Fischl, 2012). An automated pipeline was applied to register the

individual brains to a template brain and complete brain extraction, image registration, intensity correction, segmentation/parcellation, and volume calculation. All segmentations were manually checked to ensure proper delineation of the outer pial and white matter border, and manual editing, which consists of adding control points to denote white matter voxels, was performed when necessary. Volumes of the amygdala, hippocampus, anterior cingulate cortex, superior frontal gyrus, and middle frontal gyrus were extracted. Two participants' PFC volumes were removed (bilateral anterior cingulate, middle frontal, and superior frontal gyri) due to poor segmentation.

Diffusion tensor imaging (DTI) was acquired with a spin echo echo planar imaging (EPI) sequence using 30 gradient-encoding diffusion directions at b=900s/mm^2 and 5 images at b=0 s/mm^2, TR=12s, TE = 88ms, 2.2mm isotropic resolution, and a total scan time of 7:12min. ExploreDTI (Leemans et al., 2009) was used for diffusion-weighted image processing, including correction for signal drift, Gibb's ringing, subject motion, eddy current distortion, and EPI distortion. Constrained spherical deconvolution (CSD)(Farquharson et al., 2013) was used to compute a whole brain tractogram. Semi-automated tractography (Lebel et al., 2008) was performed to extract the cingulum, fornix, and uncinate fasciculus using regions of interest based on a priori knowledge of tract location (Abdul-Rahman, Qiu, & Sim, 2011; Larroza, Moratal, D'ocon Alcaniz, & Arana, 2014; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Plaisier et al., 2014; Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004). Manual checks of each tract were done to ensure quality of the segmentations and edits were performed when necessary. Average fractional anisotropy (FA) and mean diffusivity (MD) were calculated for each tract for

each participant, separately for the left and right hemispheres. Figure 4.1 outlines the volumes and tracts assessed.

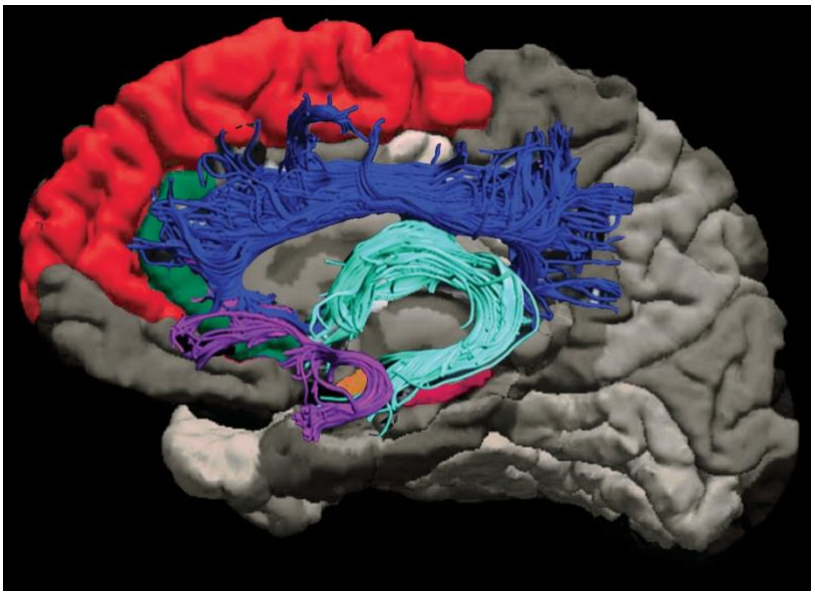


Figure 4.1 Diagram of measured brain structures. For anatomical volumes, the amygdala (orange), hippocampus (pink), anterior cingulate cortex (green), superior frontal gyrus (red), and the middle frontal gyrus (not shown), were assessed. For DTI tractography, the uncinate fasciculus (magenta), fornix (cyan), and the cingulum (blue), were assessed.

4.2.5 Statistical Analysis

IBM SPSS Statistics, Version 24 (IBM Corp., Armonk, NY) was used for all statistical analyses. Mental health symptoms, T1-weighted volumes, and DTI measures (FA and MD) were tested with three separate MANOVAs, with group and gender as factors and age as a covariate. Interaction terms were included but removed from the model if not significant. When the overall MANOVA indicated group differences, Scheffe post hoc tests were used to determine significant between-group differences. MANOVAs were used to test relationships between brain structure and mental health symptoms with group interactions (4 models; volume*2 behaviours, DTI*2

behaviours). Age and the behavioural measure (internalizing or externalizing) were included as covariates, and gender was included as a factor.

Follow-up analysis used three separate MANOVAs (mental health symptoms, T1-weighted volumes, DTI measures) to test relationships between mental health and brain measures and age at stable placement (for all PAE participants) with age as covariates, and gender as a factor.

4.3 Results

4.3.1 Postnatal Exposures

Of the children and adolescents with PAE, 65% had postnatal adversities, of which 45% experienced abuse, 50% experienced neglect (30% experienced both), 35% were witness to domestic violence, 20% were witness to substance misuse and all but one child had caregiver changes.

4.3.2 Internalizing and Externalizing Symptoms

The MANOVA for internalizing and externalizing symptoms was significant for both group differences ($p = 0.001$) and the group-by-gender interaction ($p = 0.046$). Internalizing behaviours had between subject effects for the group ($F = 3.813$, $p = 0.028$) and the group*gender interaction ($F = 5.456$, $p = 0.007$). Post-hoc tests revealed that males in the PAE+ group had higher internalizing scores than males in the PAE- group ($p = 0.038$) (Fig. 4.2). Externalizing behaviours had between subject effects for group ($F = 12.155$, $p < 0.001$), with the PAE alone (PAE-) and PAE with postnatal adversity (PAE+) groups having higher externalizing scores than controls ($p=0.031$, $p<0.001$, respectively; Fig. 4.2). Table 4.1 outlines behavioural means, and prevalence of at-risk and clinically significant scores for each group.

Table 4.1 Mean T-scores and prevalence of at risk and clinically significant levels of internalizing and externalizing scores for the prenatal alcohol exposed group without postnatal exposure (PAE-), the prenatal alcohol exposed group with postnatal exposure (PAE+), and unexposed controls. The PAE- and PAE+ groups each had one incomplete behavioural assessment. * Indicates mean scores significantly higher than controls. ^ Indicates mean scores with a gender interaction significantly higher than PAE-.

		PAE- (n=10)	**PAE+** (n=19)	**Controls** (n=31)	**MANOVA**
Internalizing Scores	**Mean Score**	55.6 ± 20.5	59.3 ± 16.5^	49.8 ± 10.2	F = 3.813 p = 0.028
	At Risk (≥60)	0% (0/10)	11% (2/19)	6% (2/31)	
	Clinically Significant (≥70)	30% (3/10)	26% (5/19)	6% (2/31)	
	Total	30%	37%	12%	
Externalizing Scores	**Mean Score**	63.5 ± 11.8*	67.9 ± 15.2*	51.6 ± 9.7	F = 12.155 p < 0.001
	At Risk (≥60)	40% (4/10)	42% (8/19)	10% (3/31)	
	Clinically Significant (≥70)	30% (3/10)	32% (6/19)	6% (2/31)	
	Total	70%	74%	16%	

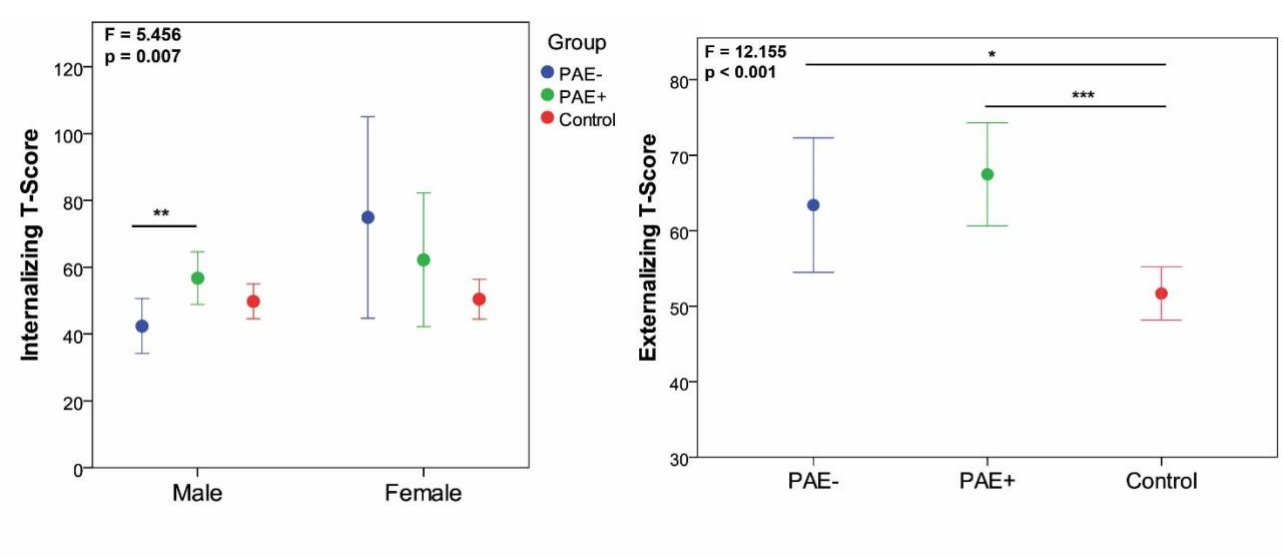


Figure 4.2 Plots show group differences in internalizing behaviours with a gender interaction, and externalizing behaviours between children and adolescents with prenatal alcohol exposure (PAE) and no postnatal adversities (PAE-) (blue), those with PAE and postnatal adversities (PAE+) (green), and unexposed controls (red). * Indicates significant between group differences p<0.05,

** indicates between group differences p<0.01, *** indicates between group differences p<0.001. F and p-values indicate overall group differences.

4.3.3 Brain Volumes

The MANOVA for brain volumes revealed significant group differences (overall p = 0.038), with significant between subject effects for the bilateral anterior cingulate cortex (Left: F = 6.487, p = 0.003; Right: F = 6.268, p = 0.004), bilateral superior frontal volume (Left: F = 3.352, p = 0.042; Right: F = 7.195, p = 0.002), and right hippocampus volume (F = 2.607, p = 0.048). Post hoc tests revealed that the PAE- group had smaller volumes than controls in the bilateral anterior cingulate cortex (Left: p = 0.005; Right: p = 0.009) and right superior frontal gyrus (p = 0.005). The PAE- group had smaller volumes than PAE+ in the left anterior cingulate (p = 0.028) (Fig. 4.3).

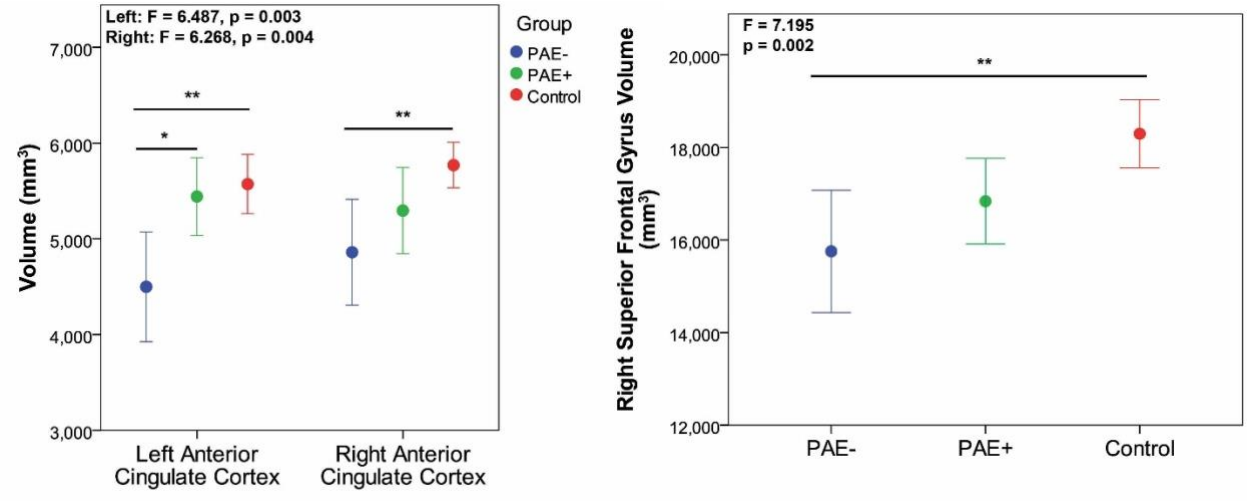


Figure 4.3 Plots show group differences in volume of the anterior cingulate cortex, and right superior frontal gyrus between children and adolescents with prenatal alcohol exposure (PAE) and no postnatal adversities (PAE-) (blue), those with PAE and postnatal adversities (PAE+) (green),

and unexposed controls (red). * Indicates significant between group differences $p<0.05$, and ** indicates between group differences $P<0.01$. F and p-values indicate overall group differences.

4.3.4 White Matter

The MANOVA for white matter measures revealed significant effects of group ($p < 0.001$) and age ($p = 0.001$). Between subject effects for group were significant for FA of the bilateral cingulum (Left: $F = 16.316$, $p < 0.001$; Right: $F = 3.923$, $p = 0.025$) and uncinate fasciculus ($F = 8.777$, $p < 0.001$), and MD of the left cingulum ($F = 3.784$, $p = 0.029$), left uncinate fasciculus ($F = 4.129$, $p = 0.021$), and right fornix ($F = 4.359$, $p = 0.017$). A significant effect of age was present for FA of the right cingulum ($F = 15.518$, $p < 0.001$) and the left uncinate ($F = 5.682$, $p = 0.020$), and MD of the bilateral cingulum (Left: $F = 19.191$, $p < 0.001$; Right: $F = 24.924$, $p < 0.001$) and bilateral uncinate (L: $F = 5.065$, $p = 0.028$; R: $F = 11.602$, $p = 0.001$). Post hoc tests revealed that the group with PAE- had lower FA than controls and PAE+ in the left cingulum (both $p < 0.001$) and left uncinate fasciculus (both $p = 0.001$; Fig. 4.4). The PAE- group also had lower FA than controls in the right cingulum ($p = 0.027$) and higher MD than the PAE+ group in the left uncinate ($p = 0.021$). The PAE+ group had higher MD than controls in the right fornix ($p = 0.020$; Fig. 4.4).

Group differences were not significant for volumes of the middle frontal gyrus, and amygdala, FA of the fornix, or MD of the cingulum. Table 4.2 outlines all group differences of brain measures.

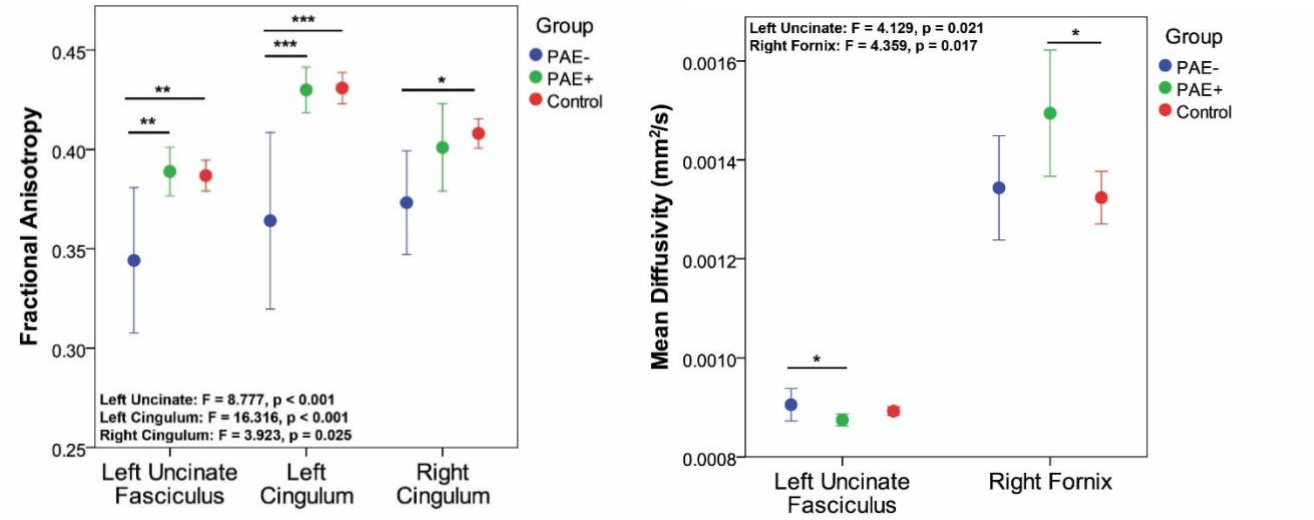


Figure 4.4 Plots show group differences in fractional anisotropy (FA) of the left uncinate fasciculus and bilateral cingulum, and mean diffusivity (MD) of the left uncinate fasciculus and right fornix between children and adolescents with prenatal alcohol exposure (PAE) and no postnatal adversities (PAE-) (blue), those with PAE and postnatal adversities (PAE+) (green), and unexposed controls (red). * Indicates significant between group differences $p<0.05$, ** indicates between group differences $p<0.01$, and *** indicates between group differences $p<0.001$. F and p-values indicate overall group differences.

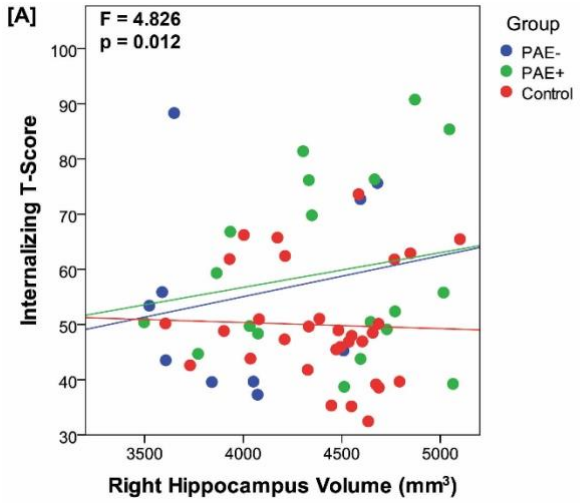
Table 4.2 Group differences in brain structure as revealed by post-hoc Scheffe tests. Groups are prenatal alcohol exposure without postnatal adversity (PAE-), PAE with postnatal adversity (PAE+), and unexposed controls.

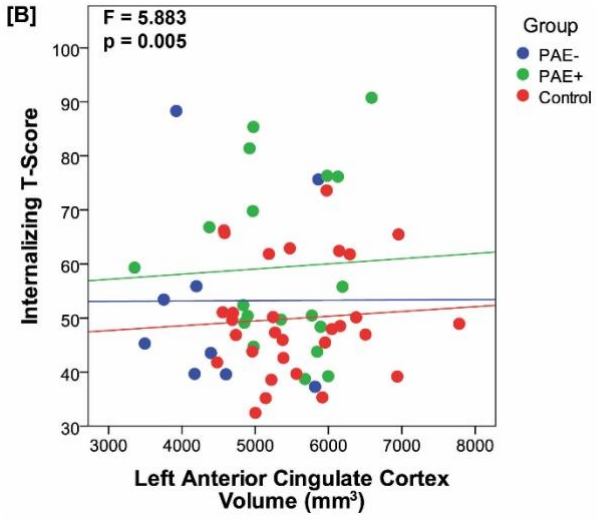
Group Relationship	Brain Region	p
PAE- < Controls	Left Anterior Cingulate Cortex Volume	0.005

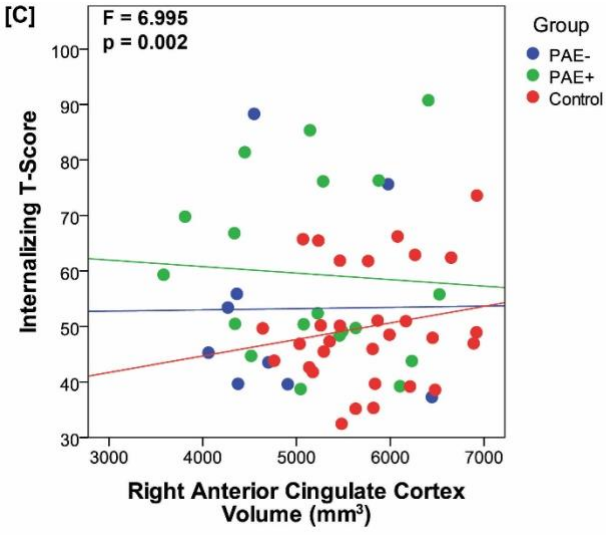
	Right Anterior Cingulate Cortex Volume	0.009
	Right Superior Frontal Gyrus Volume	0.005
	FA Left Cingulum	<0.001
	FA Right Cingulum	0.027
	FA Left Uncinate Fasciculus	0.001
PAE- < PAE+	Left Anterior Cingulate Cortex Volume	0.028
	FA Left Cingulum	<0.001
	FA Left Uncinate Fasciculus	0.001
PAE+ < PAE-	MD Left Uncinate Fasciculus	0.021
Controls < PAE+	MD Right Fornix	0.020

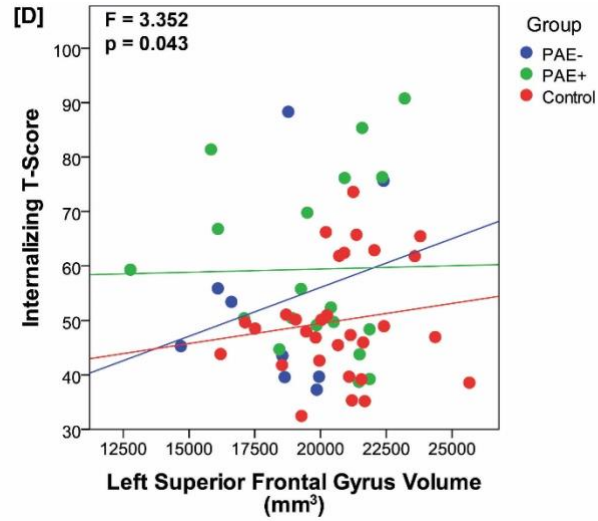
4.3.5 Relationships between Brain and Mental Health Measures

The MANOVA for brain volumes and internalizing behaviours revealed a significant group-behaviour interaction ($p = 0.041$). Between subject effects for the group*internalizing interaction were significant for right hippocampus ($F = 4.826$, $p = 0.012$)(Fig. 4.5A), anterior cingulate cortex (Left: $F = 5.883$, $p = 0.005$; Right: $F = 6.995$, $p = 0.002$)(Fig 4.5B and C), and superior frontal gyrus volume (Left: $F = 3.352$, $p = 0.043$; Right: $F = 4.470$, $p = 0.016$)(Fig. 4.5 D and E). For the right hippocampus and right superior frontal gyrus, controls had a negative relationship with internalizing symptoms, while both PAE groups had a positive association. The right anterior cingulate showed a negative relationship with internalizing behaviour in the PAE+ group, with a positive relationship seen in controls and the PAE- group, and the left anterior cingulate and superior frontal gyrus showed positive relationship in all groups.


[A]
F = 4.826
p = 0.012
Group
PAE-
PAE+
Control
Internalizing T-Score
Right Hippocampus Volume (mm³)


[B]
F = 5.883
p = 0.005
Group
PAE-
PAE+
Control
Internalizing T-Score
Left Anterior Cingulate Cortex Volume (mm³)


[C]
F = 6.995
p = 0.002
Group
PAE-
PAE+
Control
Internalizing T-Score
Right Anterior Cingulate Cortex Volume (mm³)


[D]
F = 3.352
p = 0.043
Group
PAE-
PAE+
Control
Internalizing T-Score
Left Superior Frontal Gyrus Volume (mm³)

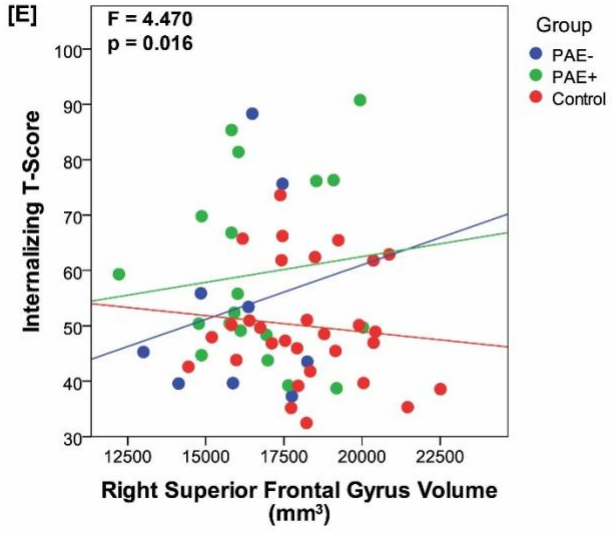
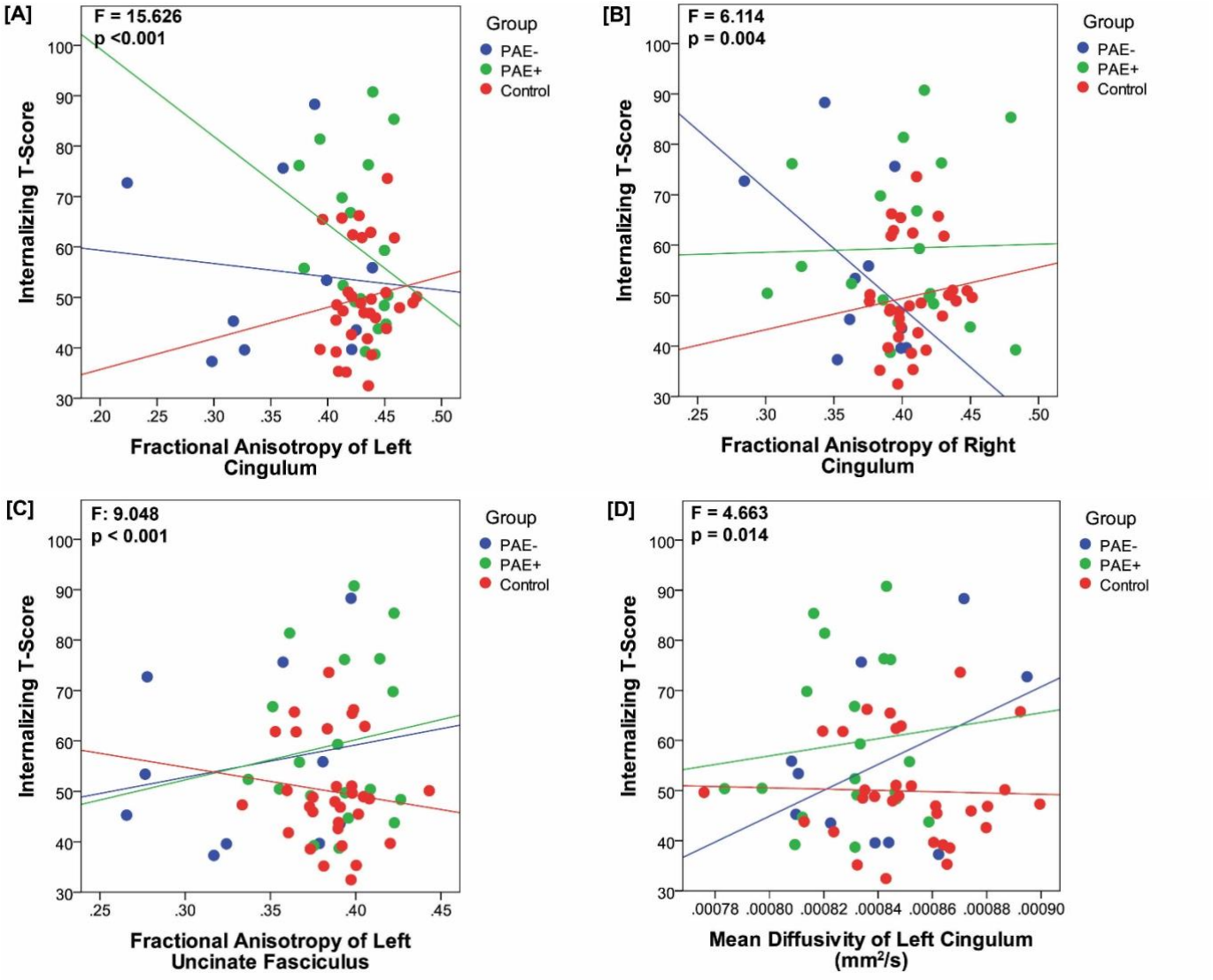

[E]
F = 4.470
p = 0.016
Group
PAE-
PAE+
Control
Internalizing T-Score
Right Superior Frontal Gyrus Volume (mm³)

Figure 4.5 Plots show group*internalizing interaction differences in volume of the **[A]** right hippocampus, **[B]** left anterior cingulate cortex, **[C]** right anterior cingulate cortex, **[D]** left superior frontal gyrus, **[E]** and right superior frontal gyrus between children and adolescents with prenatal alcohol exposure (PAE) and no postnatal adversities (PAE-) (blue), those with PAE and postnatal adversities (PAE+) (green), and unexposed controls (red). F and p-values indicate overall group differences.

The white matter measures and internalizing MANOVA revealed a significant group interaction ($p < 0.001$). Between subject effects for the group*internalizing interaction were significant for FA of the cingulum (Left: $F = 15.626$, $p < 0.001$; Right: $F = 6.114$, $p = 0.004$)(Fig. 4.6A and B), left uncinate (F: 9.048, $p < 0.001$)(Fig. 4.6C), MD of the left cingulum ($F = 4.663$, $p = 0.014$)(Fig. 4.6D) and uncinate ($F = 4.421$, $p = 0.017$)(Fig. 4.6E) and right fornix ($F = 4.251$, $p = 0.019$)(Fig. 4.6F). For FA of the left cingulum, both PAE groups had a negative relationship with internalizing behaviours, while controls had a positive relationship. In FA of the right cingulum, PAE- participants demonstrated negative relationships with internalizing behaviours, while controls and PAE+ demonstrated positive associations. For FA and MD of the left

uncinate, MD of the left cingulum, and MD of the right fornix, both PAE groups showed positive associations with internalizing behaviours, while controls showed a negative relationship.



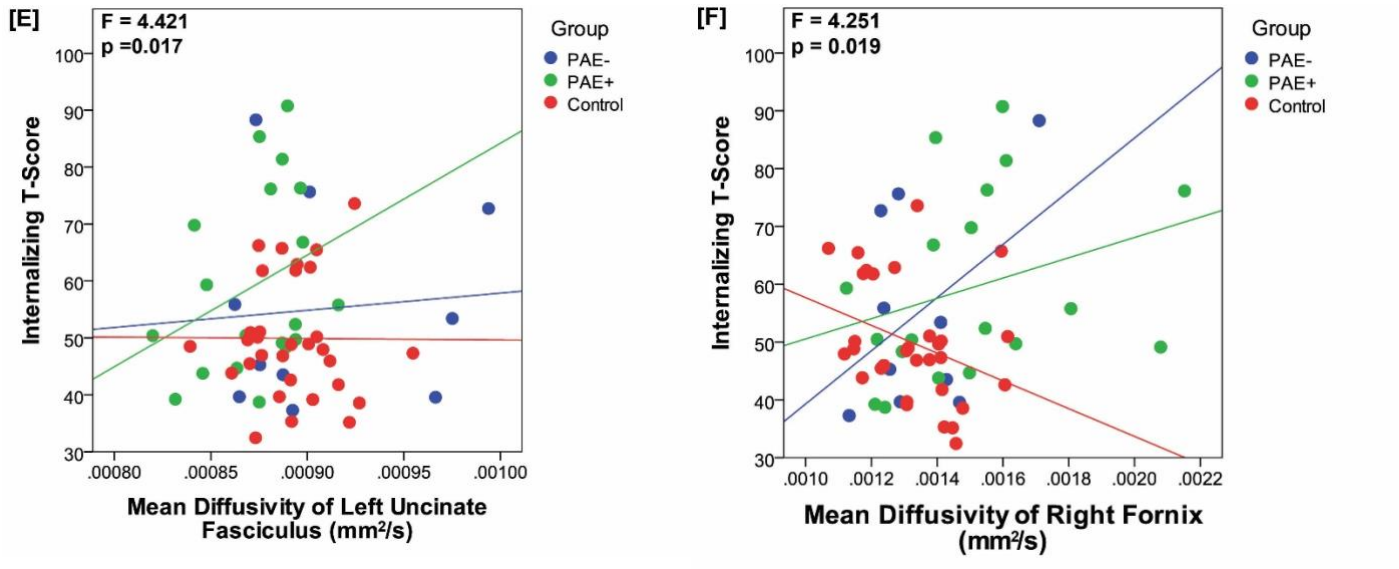
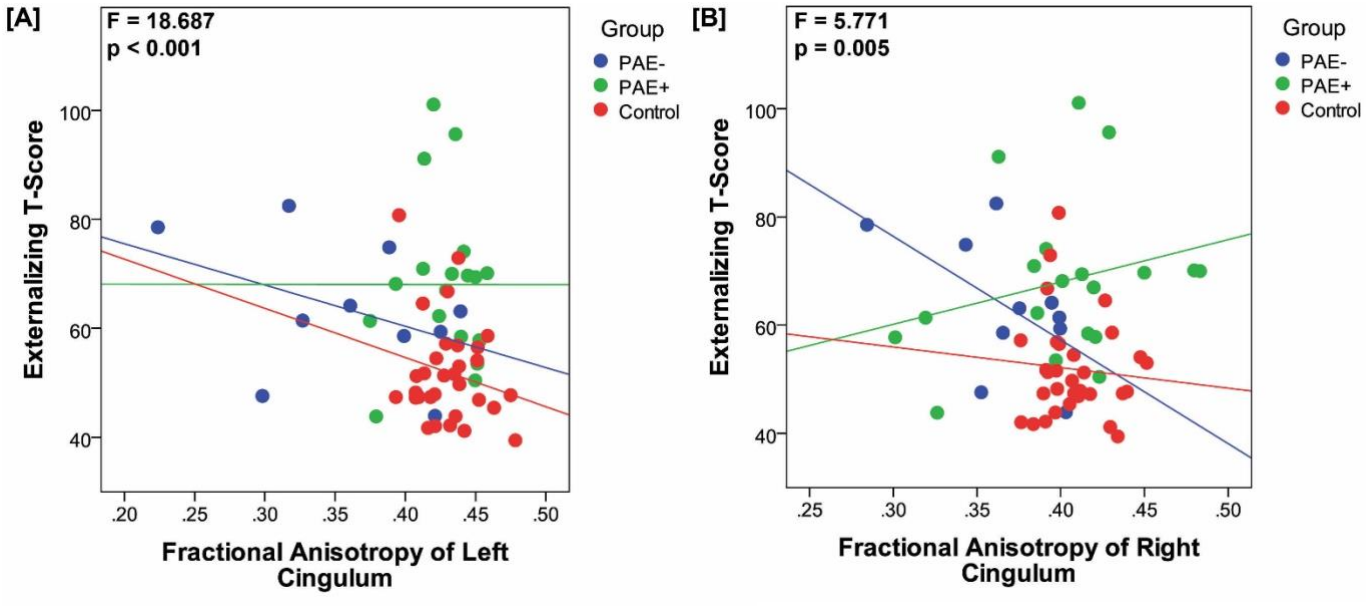


Figure 4.6 Plots show group*internalizing interaction differences in fractional anisotropy (FA) of the **[A]** left cingulum, **[B]** right cingulum, **[C]** and left uncinate fasciculus, and mean diffusivity (MD) of the **[D]** left cingulum, **[E]** left uncinate fasciculus, **[F]** and the right fornix between children and adolescents with prenatal alcohol exposure (PAE) and no postnatal adversities (PAE-) (blue), those with PAE and postnatal adversities (PAE+) (green), and unexposed controls (red). F and p-values indicate overall group differences.

The MANOVA for white matter measures and externalizing behaviours revealed a significant group interaction ($p < 0.001$). Between subject effects for the group*externalizing interaction were significant for FA of the cingulum (Left: $F = 18.687$, $p < 0.001$; Right: $F = 5.771$, $p = 0.005$)(Fig. 4.7A and B), and left uncinate ($F = 13.394$, $p < 0.001$)(Fig. 4.7C), MD of the left uncinate ($F = 4.775$, $p = 0.012$)(Fig. 4.7D), and right fornix ($F = 4.445$, $p = 0.016$)(Fig. 4.7E). In FA of the left cingulum and left uncinate, all groups showed negative relationships with externalizing behaviours. FA of the right cingulum showed negative relationships with externalizing behaviours in the PAE- group and controls, while the PAE+ group showed a positive association. MD of the left uncinate demonstrated positive associations with externalizing behaviours in both PAE groups, with controls being negatively associated. Lastly MD of the right

fornix showed negative relationships with externalizing behaviours in the PAE+ group and controls, while the PAE- group should a positive relationship. See Supplementary Table 4.1 for an outline of post hoc correlations of within group brain structure and mental health behaviour relationships.



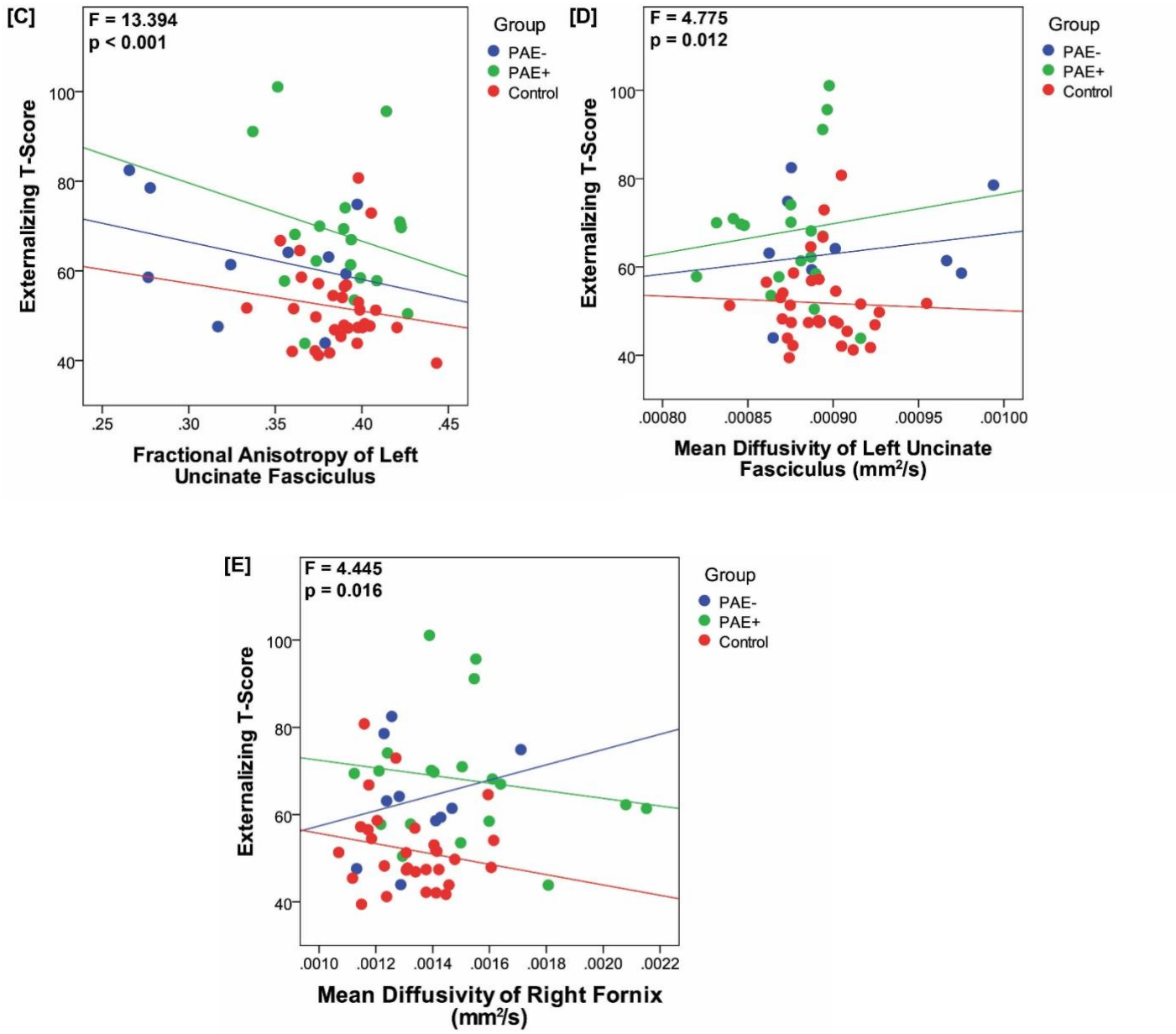


Figure 4.7 Plots show group*externalizing interaction differences in fractional anisotropy (FA) of the **[A]** left cingulum, **[B]** right cingulum, **[C]** and left uncinate fasciculus, and mean diffusivity (MD) of the **[D]** left uncinate fasciculus, **[E]** and right fornix between children and adolescents with prenatal alcohol exposure (PAE) and no postnatal adversities (PAE-) (blue), those with PAE and postnatal adversities (PAE+) (green), and unexposed controls (red). F and p-values indicate overall group differences.

4.3.6 Age at Stable Placement

MANOVAs for age at stable placement revealed no significant effects on mental health symptoms, white matter measures, or brain volumes.

4.4 Discussion

Here, we show for the first time that children and youth with PAE have different brain structure depending on the presence or absence of postnatal adversity. Children and adolescents with PAE, regardless of postnatal adversity, showed more mental health symptoms than unexposed controls. However, the group with PAE and no postnatal adversity (PAE-) showed more widespread structural brain differences from controls than the group with PAE and postnatal adversity (PAE+), suggesting that prenatal and postnatal exposures may interact to influence brain development in different ways.

Both PAE groups had more externalizing symptoms than controls. 70% and 74% of the PAE- and PAE+ groups, respectively, had at risk or clinical levels of externalizing symptoms, compared to only 16% of unexposed controls. Symptoms were not significantly different between the PAE groups with and without postnatal exposure. Previous research shows elevated risk of mental health disorders in children with PAE (Pei et al., 2011), or with postnatal trauma (Norman et al., 2012), though the majority of previous work did not consider other exposures (i.e., postnatal studies do not ask about PAE and PAE studies do not report postnatal adversities). One study did show that children with FASD and postnatal trauma had worse externalizing symptoms than children with postnatal trauma alone (Henry et al., 2007a). Thus, although postnatal trauma increases risk for mental health disorders, PAE itself appears to be of critical importance in the mental health difficulties of children and youth.

Structural brain differences were prevalent in the PAE- group, and consistent with previous findings. Gray matter volume was significantly smaller in the anterior cingulate cortex and superior frontal gyrus volumes compared to controls, in good agreement with previous reports of widespread smaller gray matter volumes in children and youth with PAE (Fryer et al., 2009; Lebel et al., 2008, 2011). The PAE- group also had lower FA in the cingulum and uncinate fasciculus compared to controls, consistent with earlier studies showing reductions of FA in the cingulum and uncinate fasciculus in children and youth with FASD (Fryer et al., 2009; Lebel et al., 2008). A previous study showed altered developmental trajectories of cortical volume in children and youth with PAE, suggesting earlier peaks and reduced brain plasticity (Lebel et al., 2012). Here, the smaller volumes in the PAE- group may reflect these earlier volume peaks. A different study showed steeper decreases of MD with age in the uncinate fasciculus in children and adolescents with PAE; children with PAE had higher MD than controls until age ~10 years, and then lower MD (Treit et al., 2013), suggesting delayed white matter development.

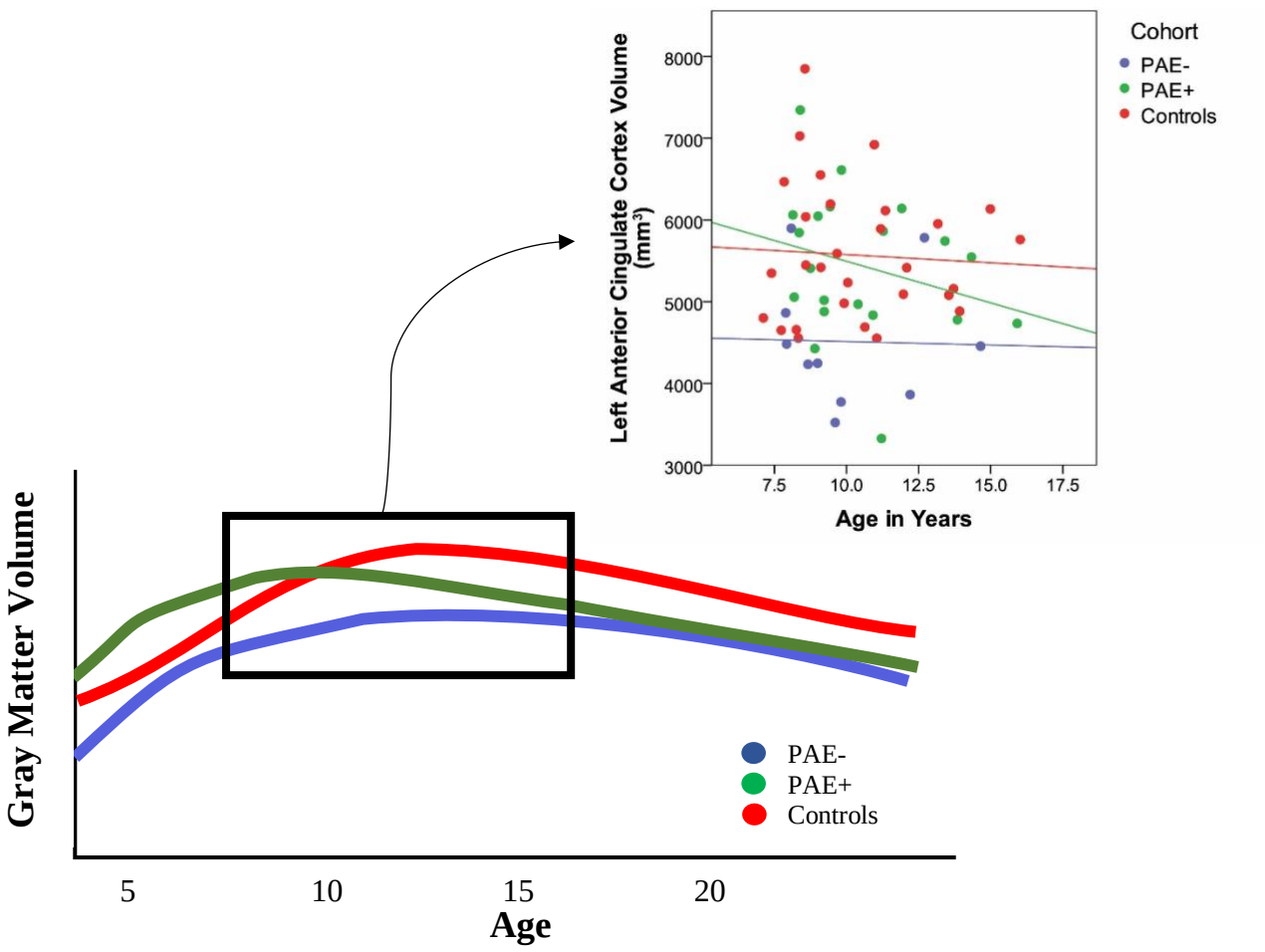
The group with PAE+ showed similar brain structure to controls, unlike PAE-, suggesting the combined effects of both PAE and postnatal adversity result in different developmental outcomes than PAE alone. The PAE+ group had a larger left anterior cingulate cortex volume than the PAE- group, as well as higher FA in the cingulum and uncinate fasciculus, and lower MD in the left uncinate. The only significant difference between the PAE+ group and controls was higher MD in the right fornix. Previous studies have observed structural differences related to postnatal adversity without reporting information on PAE. Previously reported alterations include smaller superior frontal and dorsolateral PFC volumes (Hanson et al., 2010), but larger cingulate volumes in children who had been abused (Hanson et al., 2010), as well as larger amygdala volumes in both humans and rodents after maternal absence (Callaghan, Sullivan, Howell, & Tottenham, 2014).

Diffusion imaging studies report mixed findings. Some have shown higher MD after institutional neglect (Bick et al., 2015), and lower FA associated with low family income (Dufford & Kim, 2017), and verbal abuse (Choi et al., 2009). Other studies have shown higher FA in the cingulum, uncinate fasciculus, anterior thalamic radiation, and forceps minor in adolescents and adults after neglect and childhood adversity (Hanson et al., 2013; Ugwu, Amico, Carballedo, Fagan, & Frodl, 2015) and lower MD in parts of the corpus callosum and anterior corona radiata in children with mothers with increased postpartum depressive symptoms (Lebel et al., 2016). These mixed results suggest that various types of adversity may impact the brain differently.

Given previous findings of higher FA and larger volumes in children with early life neglect and abuse, it may be that PAE drives lower FA and smaller volumes, but some postnatal adversities accelerate brain development, resulting in little-to-no measurable difference during late childhood and early adolescence. In addition, it may be that accelerated early development is accompanied by an earlier developmental plateau. In fact, premature brain development often results in underdevelopment later on, such that plateaus are reached earlier and less developed (Courchesne et al., 2007; Deoni et al., 2016; Shaw et al., 2006). In our sample, the trajectory of PAE+ appears to be similar to controls in gray matter volumes and slower developing white matter tracts (cingulum and uncinate) in adolescence. In contrast, the fornix (an earlier developing tract) showed higher MD in the PAE+ group compared to controls. This supports that once a developmental plateau is reached there may be lower FA and higher MD in those with PAE+.

Cortical brain volume and white matter structure are dynamic, particularly across childhood (Raznahan et al., 2011; Tamnes et al., 2010), and thus it may be that the results observed here will not be the same as those in a younger or older group. It could be hypothesized that a younger age range of children with PAE and postnatal adversity may present more developed PFC

and limbic regions than controls and by adolescence the developmental trajectories may be at a cross-over point before reaching a premature plateau. Figure 4.8 demonstrates these interpretations. This does not mean postnatal adversity is advantageous for development. As demonstrated, externalizing symptoms in those with PAE and postnatal adversity (PAE+) are significantly more severe than controls. With both PAE and postnatal adversity, although sometimes similar in structure to controls, brain development remains maladaptive. Longitudinal studies from early childhood to adulthood will help to clarify these trajectories in the future.


Left Anterior Cingulate Cortex Volume (mm³)
8000
7000
6000
5000
4000
3000
7.5
10.0
12.5
15.0
17.5
Age in Years
Cohort
PAE-
PAE+
Controls
Gray Matter Volume
PAE-
PAE+
Controls
5
10
15
20
Age

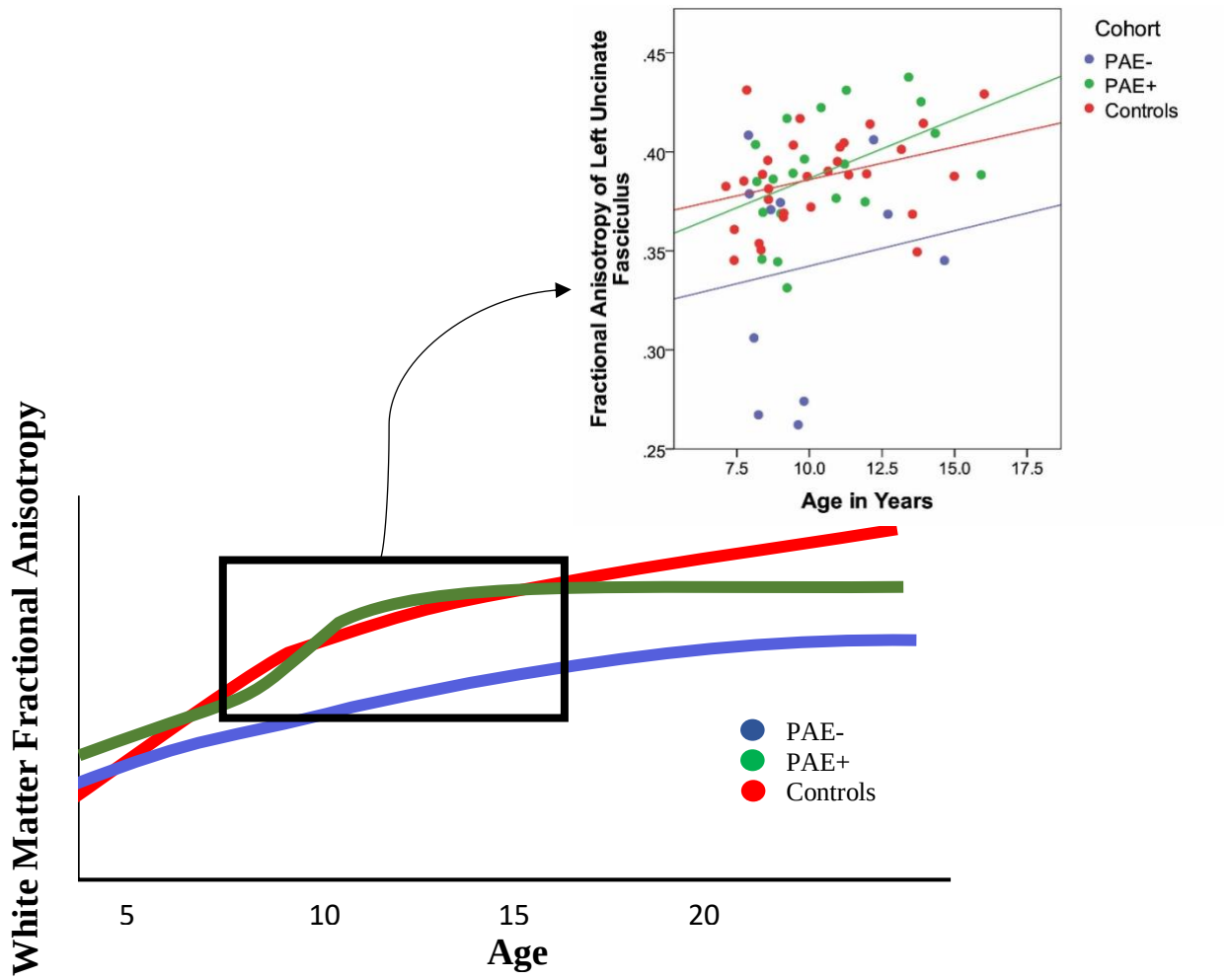


Figure 4.8 Visual depiction of altered structural brain trajectories hypothesis for grey matter volume and white matter fractional anisotropy (FA) in those with PAE with (PAE+) or without (PAE-) postnatal adversity compared to controls based on the left anterior cingulate cortex volume and age relationship, and the FA of the uncinate and age relationship.

We found group differences in brain structure and mental health behaviour relationships. This shows group differences, not only in brain development discussed previously, but how brain development relates to mental health symptoms. The PAE groups followed similar trends for brain-behaviour relationships in many, but not all, regions. Controls primarily had relationships that differed from either PAE group. Previous work has shown structural brain relationships with mental health symptoms in typically-developing children and adolescents (Ameis et al., 2014;

Boes, Tranel, Anderson, & Nopoulos, 2008; Ducharme et al., 2011, 2014; Koolschijn, van IJzendoorn, Bakermans-Kranenburg, & Crone, 2013; Ali, Vandermeer, Sheikh, Joanisse, & Hayden, 2019; Snyder, Hankin, Sandman, Head, & Davis, 2017; van der Plas, Boes, Wemmie, Tranel, & Nopoulos, 2010; Yap, Whittle, Yücel, & Sheeber, 2008) but our study is the first to address the neural correlates of mental health symptoms in a PAE population. Differing structural brain relationships with mental health symptoms in those with PAE has implications for future treatment protocols. The development of mental health disorders may not be related to the same structural brain relationships as those who have not experienced PAE and may be altered further in the presence of postnatal adversities. Therefore, individuals with PAE likely require unique treatments and/or services to address their specific needs while acknowledging the potential impact of their postnatal environments.

One limitation of this study is the use of parent-rating questionnaires for mental health symptoms, which can differ from child self-reports and do not necessarily provide a full assessment of a child's behaviours (Barnhill et al., 2000; Kolko & Kazdin, 1993). Future research including child self-reports will further expand our knowledge of brain-behaviour relationships. We used extensive documentation and interviews to characterize prenatal and postnatal exposure, although some unknowns still remain. For example, the amount, frequency, and duration of alcohol consumption during pregnancy was not always available. There is evidence that postnatal threat and deprivation impact the brain in different ways (McLaughlin & Sheridan, 2016), however, our sample was too small to separate different types of postnatal adversity. Future research with larger samples will be necessary to further tease apart these relationships.

In conclusion, children and youth with PAE had more externalizing symptoms than controls regardless of postnatal exposures, while cortical and white matter brain differences were

found only in the PAE- group. These findings suggest that prenatal exposures and postnatal experiences interact with brain development differently. The effects of adverse exposures on mental health and the divergent brain developmental trajectories based on the timing of exposure highlights the need for recognition of multiple exposures in PAE research.

Supplementary Table 4.1 Post-hoc correlations (r-values) between brain structure and mental health behaviours within groups: prenatal alcohol exposure alone (PAE-), prenatal alcohol exposure with postnatal adversities (PAE+), and controls. Only brain structures significantly associated with group*behaviour interactions in the MANOVA analysis were included. No significant within group relationships were found.

	Internalizing Behaviour			**Externalizing Behaviour**		
	PAE-	*PAE+*	*Control*	*PAE-*	*PAE+*	*Control*
Left Anterior Cingulate Cortex	0.003	0.046	0.069			
Right Anterior Cingulate Cortex	0.010	-0.062	0.179			
Left Superior Frontal Gyrus	0.234	0.019	0.145			
Right Superior Frontal Gyrus	0.193	0.115	-0.106			
Right Hippocampus	0.185	0.180	-0.037			
FA Left Cingulum	-0.101	-0.269	0.127	-0.415	-0.001	-0.207
FA Right Cingulum	-0.479	0.024	0.120	-0.558	0.256	-0.082
FA Left Uncinate	0.184	0.132	-0.114	-0.343	-0.235	-0.141
MD Left Cingulum	0.422	0.104	-0.032			
MD Left Uncinate	0.084	0.312	-0.006	0.184	0.117	-0.041
MD Right Fornix	0.425	0.300	-0.336	0.232	-0.164	-0.184

Chapter 5: Conclusion

5.1 Discussion

This project expands our knowledge of brain structure and mental health in two populations: typically-developing, and children and adolescents with prenatal alcohol exposure. To date, previous literature has found associations of brain structure to specific mental health disorders (Drevets et al., 2008; Yang & Raine, 2009), but limited research has explored the associations of sub-clinical mental health problems in a typically-developing population. Similarly, previous work has assessed sole adverse exposures such as prenatal alcohol exposure (PAE)(Astley, Aylward, Olson, et al., 2009; Eckstrand et al., 2012; Nardelli et al., 2011), but studies have not adequately addressed the cumulative adversities often occurring in conjunction with PAE. To our knowledge, this is the first work to investigate white matter and externalizing behaviours in a typically-developing population, and the first to use neuroimaging to investigate the combined effects of PAE and postnatal adversity on the brain. With this research, we have shown that typically-developing children and adolescents present associations between limbic white matter measures and mental health-related behaviours, suggesting these tracts are early indicators of susceptibility to mental health disorders. In the PAE cohort, we have shown more severe mental health behaviours than typically-developing, unexposed controls, and distinct structural brain alterations and brain-behaviour relationships dependent on PAE and postnatal environments.

Understanding which underlying brain structures relate to emerging mental health symptoms gives insight as to how and why mental health symptoms may arise in the first place. For example, the study in Chapter 3 demonstrated the cingulum and uncinate fasciculus are

significant structures related to sub-clinical internalizing and externalizing behaviour severity, with exploratory longitudinal results associating uncinate fasciculus structure with internalizing behaviour. We know these white matter tracts aid in communication between the limbic system and prefrontal cortex (PFC)(Casey et al., 2008; Lebel & Beaulieu, 2011; Roberts et al., 1998). The limbic system is involved in basic drives and emotions, such as appetite, fear, reward and pleasure, as well as social cognition and memory (Ackerman, 1992; Casey et al., 2008; Mincic, 2015), while the PFC aids in higher-level processing such as emotional and behavioural regulation (Roberts et al., 1998; White, Cullen, et al., 2008). Thus, with weaker structural connectivity between the limbic system and the PFC there may be less control over emotional and behavioural reactions to stimuli, which may be expressed as internalizing or externalizing behaviours. An age interaction in our data suggests there is a strengthening of these relationships with time. It may be the inability of relevant regions to adapt or "catch up" in brain development that contributes to further progression of mental health problems. Identification of potential biomarkers for development of internalizing or externalizing behavioral problems, even at subclinical levels, in a typical population provides future investigations with a baseline for comparison to other populations.

If we do not understand early signs of mental health problems in a typically-developing population, it is impossible to compare the manifestation of early warning signs in other populations. Previous work has shown the vast physical and neurodevelopmental impact PAE can have, including widespread brain alterations, facial dysmorphology and physical health problems, as well various cognitive and mental health challenges (Cook et al., 2016; Lebel et al., 2011; Pei et al., 2011). Individuals with PAE are at a high risk for comorbid mental health problems (Pei et al., 2011), significantly more so than those without PAE as demonstrated in Chapter 4. Chapter 4 also outlines the differences in brain structure related to mental health-related behaviours found in

gray and white matter in the cortico-limbic network in the presence of PAE. Understanding differences in brain structure and mental health in those with PAE in comparison to a typically-developing population offers insight as to how treatment of mental health problems should differ between populations. Between typical and PAE populations, there may be different neurological mechanisms at play with similar behavioural expressions. Thus, new methods uniquely catered to the specific challenges of those with PAE may improve the mental health outcomes of these individuals compared to a uniform protocol for treatment.

Beyond prenatal alcohol exposure, Chapter 4 highlights the critical influence of both prenatal and postnatal environments on development. Previous research has focussed on the sole influence of PAE (Fryer et al., 2009; Nardelli et al., 2011) or postnatal adversities on brain development (Pechtel et al., 2014), but we have provided evidence that cumulative effects, a common reality in this population (Astley, 2010), may differ from PAE alone. Our findings reinforce prior research showing lower volumes, reduced FA, and increased MD after PAE (Astley, Aylward, Olson, et al., 2009; Eckstrand et al., 2012; Fryer et al., 2009), but we also show that cumulative effects from postnatal exposures may interact in unexpected ways and result in differing outcomes. In our PAE with postnatal adversity cohort, we found a similar structural brain profile to controls in adolescence. We propose this may be a cross-over point in development (See Fig. 4.8), such that those with PAE and postnatal adversity exhibit premature development in the cortico-limbic network, but also plateau early. Therefore, in adolescence the control group may be still gradually developing, but the PAE with postnatal adversity group may be reaching their developmental plateau.

Proposed hypotheses about early development may help in our understanding of the complexities of brain development after PAE and/or postnatal adversities, such as fetal

programming. This theory states that prenatal development of organ systems and functions includes programming effects that may cause permanent changes that persist throughout life. Thus, adverse experiences during prenatal development can cause physical, physiological, and metabolic alterations which may predispose an individual to additional negative outcomes later on (Kwon & Kim, 2017). For example, PAE has lasting developmental alterations leading to increased susceptibility to other comorbidities, such as mental health challenges. For those who experience continued adversity, postnatally, the experience-dependent model of development may also help to understand outcomes (Greenough et al., 1987), which refers to the adaptability to one's unique environmental demands. It may be that children exposed to adversity prenatally and postnatally adapt through experience-dependent development in a way that shortens the sensitive growth periods in order to minimize vulnerability to an adverse environment. Thus, development may be premature and underdeveloped. Lastly, the multiple-hit hypothesis (Barnett et al., 2018; Miller & O'Callaghan, 2008), may explain some of the cognitive and behavioural outcomes seen in those with additional postnatal exposures on top of PAE. Chapter 4 in conjunction with previous work has shown worse outcomes with PAE and postnatal exposure compared to either adversity alone (Henry, Sloane, & Black-Pond, 2007b), suggesting the multiple "hits" or exposures contribute to a cumulative effect.

Longitudinal studies are needed to provide further evidence for these interpretations, as are studies in broader age ranges in order to more comprehensively describe developmental trajectories. This research will impact future work by showing there are unique structural brain effects dependent on postnatal environments in a PAE population, which provides rationale for addressing cumulative exposures in the literature. Additionally, the unique brain development

trajectories suggested by this work further support personalized prevention and treatment methods, as they may be more effective for complex cases in children and adolescents with PAE.

Subcortical limbic structures have been linked to mental health in previous work, but strong relationships were not found here. This may be due to more subtle effects that we do not have the power to detect, such that altered developmental trajectories may be in their infancy in adolescence therefore limiting variation between subjects. It may also be that subcortical structures are not as vulnerable in the early manifestations of mental health problems but develop as mental health problems progress.

5.2 Limitations

The research presented in this thesis has certain limitations. Although our sample achieved 80% power to detect medium effect sizes (f^2: 0.13 - 0.19), a larger sample size would be ideal for detecting the more subtle effects that may be present in a subclinical population. For example, subcortical volumes (amygdala and hippocampus) were not significant in either study presented here, but have been noted in previous work as having altered development in a typically-developing population with subclinical mental health behaviours (Koolschijn et al., 2013; van der Plas et al., 2010).

To process and analyze T1-weighted data we used Freesurfer v5.3 (Fischl, 2012). Freesurfer v5.3 does not manage scans with motion as well as other programs and is no longer the most current version. This was the original program used in the beginning of this research, therefore was used throughout for consistency. We were able to use manual editing through placement of control points to improve the delineation of brain structures in those participants with motion artifacts. This took more time but allowed inclusion of most participant data. Future work should be analyzed on Freesurfer v6.0 or on a new program, such as MaCRUISE (Huo, Bao,

Landman, & Parvathaneni, 2018), that can manage motion artifacts with less manual editing required.

The BASC-2 Parent-Rating System (Reynolds et al., 2011) is a useful tool to evaluate mental health behavioural symptoms, but may be more effective in conjunction with the self-report. Studies have shown parent and self-reports can have divergent results (Barnhill et al., 2000; Kolko & Kazdin, 1993). Thus, collecting both report styles may offer a more accurate evaluation of an individual's behaviour.

Additionally, our analysis controlled for age and gender. Although all participants in our research were likely cis-gendered, further research should distinguish between sex and gender to better capture different influences from environmental and biological factors (Clayton & Tannenbaum, 2016). Thus, without measuring these as separate constructs, the gender effects we report likely encompass many sex effects. Age should also be combined with a pubertal stage measurement. Puberty could have an influence separate from that of age, as previous studies have shown puberty influences white matter and the emergence of mental health problems (Genc et al., 2017; Paus et al., 2008).

Lastly, although only a subset of the characterization of early adversity (absence or presence of postnatal adversity) was used in this project, there were multiple instances where unknown information limited our ability to make clear distinctions. The absence or presence of postnatal adversity was arguably the clearest distinction to make, as those without postnatal adversity were adopted at birth. Other exposure distinctions were sometimes less clear, such as amount or frequency of PAE or types of postnatal exposures in the home. This limited our ability to measure more specific properties of PAE and early adversity. The homogeneity of our sample also limited our ability to form sizeable groups with exposure to differing risks. For example,

nearly all participants had prenatal exposures to other substances along with exposure to alcohol. This meant comparisons could not be made on the basis of presence versus absence of other prenatal exposures.

5.3 Future Work

This research creates a foundation to build upon both in the typically-developing population and the PAE population. Suggestions for replication and extension of this research includes use of more specific white matter brain measures, advanced image processing procedures, a larger longitudinal sample, and expanded early adversity characterization in a PAE sample.

Future work should extend our understanding of the role of white matter in mental health within these populations. This work used diffusion tensor imaging (DTI) and analyzed fractional anisotropy (FA) and mean diffusivity (MD) measures. Although valuable for sensitivity to white matter, conclusions cannot be made about specificity of mechanisms or specific contributions of numerous microstructural factors to these measures. For example, FA is affected by numerous factors such as axonal size and packing, myelination, and crossing fibers (Beaulieu, 2002). Other MRI techniques are available which can provide measures with greater specificity to particular aspects of white matter microstructure than DTI measures. For example, both inhomogeneous magnetization transfer (IhMT) and multicomponent driven equilibrium single-pulse observation of T1/T2 (mcDESPOT) can provide more specific white matter measures of myelin (Geeraert et al., 2018). Including these measures in work to come will be an important step in understanding the microstructural mechanisms underlying the white matter-mental health symptom relationships in both a typically-developing and PAE cohort.

A large longitudinal sample will help to further uncover valuable structural brain alterations present before behavioural symptoms emerge, as explored in Chapter 3. Uncovering

developmental trajectories in the PAE population with or without postnatal adversities will be a critical next step and should begin early in development to see when deviations from typical-development begin and continue into adulthood at which point developmental plateaus can be assessed. Our cross-sectional data seems to suggest different trajectories in all three groups, but within participant development over a broader age range will offer more insight. A larger sample may enable analysis of more specific adverse exposures (i.e. prenatal other substance exposures, neglect, abuse etc.) as the current sample had many exposures present in nearly all participants which limited our ability to compare between groups (i.e. almost all had other prenatal substance exposures).

Following studies should assess additional regions of the brain and other developmental outcomes in the PAE cohort as well. Additional brain structures should be examined to ensure the cortico-limbic network is the main relationship with mental health in the PAE cohort. For example, it may be that there is less "high-level" processing after emotional stimuli, but instead quicker reactions stemming from primary sensory and associated regions. Assessing other brain regions will also help to identify whether the structural brain differences between PAE groups is unique to mental health-related regions or is similar across the brain. More diverse developmental outcomes beyond mental health should be assessed in relation to brain structure, as mental health is only one neurodevelopmental domain of many that is often affected with PAE and/or postnatal adversity (Cook et al., 2016; Martel et al., 2007; Oh et al., 2018). This may include assessments of cognitive abilities, physical health measures, and resiliency.

5.4 Conclusions

The research presented here is instrumental in creating a foundation to understand structural brain alterations associated with mental health indicators in typically developing children. We have

also begun to uncover the cumulative effects of PAE and early adversity on brain structure and mental health. It is critical to understand links between brain structure and mental health symptoms, and the differences in these relationships in various populations. With this knowledge, caregivers and medical professionals will be able to recognize and understand the implications of early mental health indicators, which will help to enable early interventions catered to the specific needs of a given population. This gain in knowledge will be a key step in prevention of emerging mental health disorders in the future and improved health services provided sooner to those at-risk.

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Appendix

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Dr. Catherine Lebel 2019/08/08

2019/08/08

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