NEURAL MARKERS OF FAMILIAL RISK FOR DEPRESSION

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Submitted in partial fulfillment of the requirements

for the degree of Master of Science

at

Dalhousie University

Halifax, Nova Scotia

June 2022

DEDICATION

To my three pillars. To my mom, who sparked my curiosity for all things interesting and unknown from a very young age. You taught me that discipline and perfectionism should never come at the expense of my own mental, emotional, and physical health. To Diego, my partner, for your unquivering gentleness and patience during my choir of emotions. You are the best cheerleader that anyone could have ever asked for, without whom this journey would not be possible. To Rosa, for being by my side since the first day of EL CID. Although we are an ocean apart, I am honored to continue our journey of growing into adulthood together.

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ABSTRACT

Depression is associated with structural and functional abnormalities of the brain. It is not known whether these brain abnormalities are precursors or consequences of depression. Study of offspring of parents with depression offers the opportunity to study the risk in the absence of the disorder. I conducted a systematic review to examine whether brain features found in adults with depression exist in asymptomatic offspring who are at high familial risk for depression. My results identified neural markers of familial risk for depression as well as several gaps in knowledge. One of these gaps was that no prior study explored intracortical myelination in high-risk youth. I examined 112 adolescents and found no reduction of intracortical myelin in those at high familial risk for depression compared to those at low risk. These results suggest that a reduction of intracortical myelin is a consequence rather than a precursor of depression.

LIST OF ABBREVIATIONS USED

ACC	Anterior Cingulate Cortex
B	Effect size
BDI	Beck's Depression Inventory
BIOTIC	Biomedical Translational Imaging Center
BL	Bilateral hemisphere
BMI	Body Mass Index
BRAVO	Brain volume imaging
CA-1	Cornu Ammonis region of hippocampus
CCN	Cognitive Control Network
CES-D	Center for Epidemiologic Studies Depression Scale
CI	Confidence Interval
DMN	Default Mode Network
DSM	Diagnostic and Statistical Manual for Mental Disorder
DTI	Diffusion Tensor Imaging
ECN	Executive Control Network
EPDS	Edinburgh Postnatal Depression Scale
ETL	Echo Train Length
FA	Fractional Anisotropy
FHR	Familial High Risk
FHR-MDD	Familial high-risk youth who have a depression diagnosis
FH-RDC	Family History Research Diagnostic Criteria
FIGS	Family Interview for Genetic Studies
FLAIR	Fluid-attenuated inversion recovery
FLR	Familial Low Risk
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
HCP	Human Connectome Pipeline
HPA-axis	Hypothalamic-Pituitary-Adrenal axis
ICC	Intraclass Correlation Coefficient

ICM	Intracortical Myelination
IQ	Intelligence Quotient
KSADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version
L	Left hemisphere
LPFC	Lateral Prefrontal Cortex
M	Mean
MDD	Major Depressive Disorder
MRI	Magnetic Resonance Imaging
N	Sample size
N/A	Not Available
OFC	Orbito-Frontal Cortex
PCC	Posterior Cingulate Cortex
PFC	Prefrontal Cortex
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROMO	Prospective Motion Correction
R	Right hemisphere
SCID	Structured Clinical Interview for DSM-5
SES	Socioeconomic Status
SD	Standard Deviation
SN	Salience Network
T1w	T1-weighted
T2w	T2-weighted
TE	Echo time
TI	Inversion time
TR	Repetition time

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my supervisor, Dr. Rudolf Uher, for providing me the opportunity of pursuing my MSc in Psychiatry Research. Working at your lab has been an incredible learning opportunity through which I have substantially improved my academic, technical, and interpersonal skills. Thank you very much for taking the chance on me as a recent undergraduate that had just moved to Canada. I feel immensely grateful for the stability that working with and being taught by you has provided me over the last several years.

I would like to thank Dr. Drobinin for supporting me every step of the way. Without your help, Vlad, I would still get frightfully anxious whenever I needed to code. A big thanks to Carl, who has been an immeasurable help in teaching me everything that happens behind the scenes in neuroimaging.

Dr. Schmidt and Dr. Cookey, thank you for being part of my thesis committee. Our meetings have been incredibly valuable to me not only because of your feedback and our discussions but also due to your incredibly friendly demeanor. I hope that every student out there has the same sense of positivity and calm about their research that I got after our meetings.

Thank you, Canada Institute of Health Research, Nova Scotia Department of Health and Wellness, and Dalhousie University for funding me. Receiving your

scholarships may have been the extra boost I needed to feel secure and confident in my studies.

A big thank you to Holly, Meg, and Sheri. Your psychological support meant everything to me, especially on days when nothing was quite right. Thank you to the rest of FORBOW, without whom this project would not be possible.

Lastly, I would like to thank the wonderful families that I met during MRI scans. You were one of my most enjoyable highlights every week and I am honored to have had the possibility of working with so many families from all walks of life.

CHAPTER 1: INTRODUCTION

Depression is a mood disorder that affects 5% of the world's population during any 12-month period (Herrman et al., 2022). Structural and functional abnormalities within the brain are associated with depression (Schmaal et al., 2020; Zhang et al., 2018). Whether these changes develop during the illness or precede depression onset and increase vulnerability is under investigation. Offspring of parents with depression have a higher risk of developing this disorder than those without familial risk (van Dijk et al., 2021). Therefore, it is important to investigate neural markers that may signify increased vulnerability to depression prior to disorder onset. I conducted a systematic review to examine whether brain features found in adults with depression exist in asymptomatic offspring who are at high familial risk for depression. My results suggest that neural markers of familial risk for depression do exist. However, several gaps are present in existing literature. One of these gaps was that no one had yet explored intracortical myelination in high-risk youth. Therefore, I decided to conduct a study assessing whether adolescents who are at high familial risk for depression have reduced intracortical myelin, a reduction that is found in depressed adults (Lake et al., 2017; Sacchet & Gotlib, 2017). My results suggest that a reduction of intracortical myelin may be a consequence rather than a precursor of depression.

I present two papers that are part of my thesis by manuscript submission. Paper 1 titled, "Neural Markers of Familial Risk for Depression – A Systematic Review" and paper 2 titled, "Intracortical Myelination and Familial Risk for Depression in Youth".

CHAPTER 2: NEURAL MARKERS OF FAMILIAL RISK FOR DEPRESSION – A SYSTEMATIC REVIEW

Abstract

Structural and functional brain alterations are found in adults with depression. It is not known whether these changes are a result of illness or exist before disorder onset. Asymptomatic offspring of parents with depression offer a unique opportunity to research neural markers of familial risk to depression and clarify the temporal sequence between brain changes and disorder onset. We conducted a systematic review to investigate whether asymptomatic offspring at high familial risk have structural and functional brain changes like those reported in adults with depression. Our literature search resulted in 44 studies on 18,645 offspring ranging from 4 weeks to 25 years old. Cortical thinning, reduced white matter integrity, and altered striatal reward processing were the most consistent findings in high-risk offspring across ages. These alterations are also present in adults with depression, suggesting the existence of neural markers of familial risk for depression. Additional studies reproducing current results, streamlining fMRI data analyses, and investigating underexplored topics (i.e intracortical myelin, gyrification, subcortical shape) may be among the next steps required to improve our understanding of neural markers indexing the vulnerability to depression.

Introduction

Major depressive disorder (MDD), hereafter referred to as 'depression', is a leading cause of disability worldwide (Herrman et al., 2022). It is characterized by episodes of sadness, reduced energy, and lack of interest, that can last weeks, months and in some cases years. The highest risk for depression onset is during adolescence and early adulthood (Duan et al., 2020). Depression affects between 30 and 40 percent of the world's population during their lifetime (James et al., 2018). The contribution of genetic and environmental factors to depression can also be expressed at the level of brain development (Nabeshima & Kim, 2013). Structural and functional differences in the brain of depressed adults have been found in key areas associated with mood, thought regulation, and reward behaviour (Dai et al., 2019). Whether these neural markers precede depression onset and increase vulnerability to the disorder or develop during the illness is an open question. Detecting neural markers that precede and predict MDD would allow for earlier implementation of interventions that could improve the quality of life, prevent, or delay MDD onset and decrease the economic burden on the health care system (de Oliveira et al., 2020).

One way of differentiating between cause and effect is to use high familial risk studies. One of the strongest risk factors for MDD is having a parent with MDD (Uher et al., 2014; van Dijk et al., 2021). One in three high familial risk offspring will go on to develop a mood or psychotic disorder by early adulthood (Rasic et al., 2013). Therefore, examining at-risk offspring allows us to identify possible early neural markers prior to disorder onset.

In this review I will synthesize evidence from high familial risk studies to investigate whether neural markers predate depression and indicate increased vulnerability to this disorder. I first present current findings of neurobiological markers of depression from large-scale neuroimaging studies. I follow by focusing on periods of development to detect when brain differences may first emerge studies. I proceed by focusing on four distinct periods of development to detect when brain differences may first emerge, including infancy, childhood, adolescence, and early adulthood. I conclude by comparing familial risk findings with those present in MDD to identify similarities between the brain of asymptomatic high familial risk offspring and depressed adults. Such similarities of structural and functional abnormalities could indicate early neural markers of depression.

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Methods

I conducted this review using Ovid MEDLINE and EMBASE databases for peer-reviewed studies published up to January 7th, 2022. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were adhered to (Liberati et al., 2009). I created a search strategy with the following search terms: (infan* OR bab* OR child OR youth OR adolescen* OR teen* OR young adult OR offspring* OR son* OR daughter* OR develop*) AND (paren* OR mother* OR maternal OR father* OR paternal OR famil* OR risk) AND (depress* OR MDD OR major depressive disorder OR major mood disorder) AND (neuro* OR brain*) AND (chang* OR alter* OR diff* OR function* OR structur* OR MRI* OR fMRI* OR connect* OR network*).

I screened search results for relevance based on title and abstract, followed by a full-text review to confirm eligibility (Figure 1). References of eligible studies were examined to detect articles that might have been missed by the initial search. Studies were included if their primary aim was to investigate structural and/or functional brain differences between familial high risk (FHR) and familial low risk (FLR) offspring. The FHR group was defined as having at least one parent with either a lifetime (past or present) major depressive disorder or elevated depressive symptoms throughout majority of the offspring lifetime (i.e maternal prenatal and/or postnatal depression). The latter group was included because depressive symptomology is the common paradigm present in literature that assesses younger (i.e infants, pre-school) FHR offspring. FLR group included offspring of parents with no history of major mood and/or psychotic disorders. I excluded studies where the offspring had a current or lifetime history of major mood or psychotic

disorder themselves at the time of brain scanning. To map brain differences across the developmental brain period, I included studies with offspring between the ages of 1 week up to and including 25 years.

Table 1 presents a summary of the 44 eligible articles included in this review.

Results

Neurobiological Markers of Depression

Magnetic Resonance Imaging (MRI) provides a non-invasive method of identifying disorder-related patterns of brain changes associated with MDD (Zhang et al., 2018). Structural scan sequences allow us to investigate brain morphology, such as the volume and structure of cortical and subcortical gray matter regions. Diffusion tensor imaging (DTI) helps examine white matter microstructure by imaging intricate connectivity networks within the brain (Soares et al., 2013). Functional magnetic resonance imaging (fMRI) depicts brain function, showing live activation patterns at rest and/or during tasks (Zhang et al., 2018). We briefly present the most consistent findings from large-scale imaging studies on neurobiological markers of depression below.

Brain Structure

Cortical volume is composed of cortical thickness and cortical surface area, which are genetically and phenotypically distinct (Panizzon et al., 2009; Winkler et al., 2010). Adults with MDD have thinner orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (PFC), anterior cingulate cortex (ACC), insula, and temporal lobes (Bora et al., 2012; Lai, 2013; Zhao et al., 2014). Cortical thinning in these regions is associated with poorer clinical outcomes and may contribute to emotional and cognitive regulation deficits seen in depression (Schmaal et al., 2017). In contrast, the surface area was not significantly altered in MDD adults, suggesting a specific involvement of cortical thickness in depression (Schmaal et al., 2020).

Subcortical gray matter regions, that contribute to memory and emotion, have been extensively studied. The hippocampus, a region implicated in memory and reward, is smaller in adults with MDD (Geerlings & Gerritsen, 2017; Schmaal et al., 2016). Furthermore, the CA-1 region of the hippocampus is indented, resulting in an altered shape of the hippocampus (Grasby & Jahanshad, 2020; Ho et al., 2022). The thalamus, a subcortical structure that helps control and integrates emotion, memory, and arousal, shows significant volume reductions in adults with depression (Lu et al., 2016; Zhang et al., 2016). Findings on the structure and volume of the amygdala, a critical contributor to emotional response, are inconsistent with some evidence suggesting a larger amygdala whilst others report volume reduction (Ho et al., 2018; Schmaal et al., 2016).

Fractional anisotropy (FA) is the most commonly used measure of white matter. Higher FA values are observed when the diffusion of water molecules is directionally constrained, suggesting a greater degree of white matter integrity and compactness of white matter tracts (Soares et al., 2013; van Velzen et al., 2020). Depression is associated with reduced FA in the corpus callosum, corona radiata, internal capsule, external capsule, uncinate fasciculi, and cingulate gyrus (van Velzen et al., 2020). The poorer structural integrity of these white matter tracts may contribute to deficits in mood regulation (Sanjuan et al., 2013; Schmaal et al., 2020).

Brain Function

fMRI is the most common method of measuring brain function by detecting regional blood volume changes that are associated with activation (Chow et al., 2017).

Brain function may be measured at rest, referred to as the resting state, or while performing a task, such as when reacting to emotional stimuli or participating in a reward/loss game. The fMRI method has larger heterogeneity of preprocessing and analytical methods than structural MRI, leading to greater variability of findings (Zhuo et al., 2019). The default-mode network (DMN) is most active when a person is in a state of wakeful rest and plays an important role in executing plans and keeping up with the demands of the external and internal environment (Sormaz et al., 2018). Meta-analyses have associated depression with both stronger connections (hyperconnectivity) and weaker connections (hypoconnectivity) within the DMN (Kaiser et al., 2015; Yan et al., 2019a). Another resting-state network, the cognitive control network (CCN) that is responsible for goal-directed thought processes, appears to be hypoconnected in adults with depression (Kaiser et al., 2015). Reduced activity in the reward network, specifically between the striatum and PFC, between the striatum and ACC, and of the ventral striatum have been found in MDD and related to increased depression severity (Satterthwaite et al., 2015; Segarra et al., 2016; Zhang et al., 2018). There is less agreement among task-based fMRI studies that investigate emotion regulation due to the larger heterogeneity of network region interest, making it difficult to draw conclusions across findings (Schmaal et al., 2020).

Infancy

This literature review identified 5 studies on the brain of 246 infants aged 5 to 40 weeks (Table 1A). This includes 3 studies assessing brain structure, 1 study assessing brain function and 1 study assessing both.

Brain Structure

Maternal depression may have significant implications on offspring brain development from an early age (Duan et al., 2020). Literature on FHR infants and young children largely focus on the effects of maternal depression during pregnancy and the postnatal period. FHR infants as young as 4 weeks show structural brain differences compared to FLR. The most consistently identified difference is the reduced white matter connectivity in areas involved in emotion processing, such as in the uncinate fasciculus, amygdala-ventral PFC pathway and within amygdala microstructure (Dennis et al., 2019; Posner et al., 2016; Rifkin-Graboi et al., 2013). Alterations of subcortical grey matter volumes have also been reported. FHR infants show smaller midbrains and larger caudate, putamen, globus pallidus and thalamus volumes (Rifkin-Graboi et al., 2013; Sethna et al., 2017).

Brain Function

Resting state studies in FHR infants reported altered connectivity between key emotion processing regions, such as between the amygdala and PFC. However, contradicting results make the directionality unclear, with both hyperconnectivity or hypoconnectivity suggested (Posner, 2016; Qiu et al., 2015). The relatively small size of the literature and heterogeneous methods leave the possibility that no association is present, with contradicting results representing noise rather than true signal.

Childhood

This literature review identified 12 studies on the brain of 11 205 children aged 3 to 10 years (Table 1B). This includes 7 studies assessing brain structure and 5 studies assessing brain function.

Brain Structure

Increased maternal depressive symptoms during the second trimester and 2 months postnatally were associated with cortical thinning in pre-school and elementary school-aged children (El Marroun et al., 2016; Lebel et al., 2016; Sandman et al., 2015). Although cortical thinning, not thickening, has been detected across studies, there is less agreement on which specific cortical regions are affected. The largest study (N = 654) in this age group reported cortical thinning in the left superior frontal gyrus only (El Marroun et al., 2016), whilst others suggest other fronto-temporal regions are affected, including the right superior and medial orbital PFC, right inferior frontal region, and middle and superior temporal regions (Lebel et al., 2016; Sandman et al., 2015). An increase in surface area of the caudal middle frontal region was also observed in FHR youth (El Marroun et al., 2016).

A reduction of the putamen and right nucleus accumbens, both structures part of the basal nuclei that aid in movement coordination, have been detected in FHR children (Pagliaccio et al., 2014). FHR children also show reduced hippocampal volume as well as contraction of the CA-1 region (Hubachek et al., 2021). The directionality of amygdala volume remains unclear. There are reports of smaller right amygdala volumes, increased

amygdala volumes in FHR girls only, and no significant differences between FHR and FLR children (Acosta et al., 2020; Pagliaccio et al., 2020; Wen et al., 2017). When examining the microstructure of white matter fibers within the amygdala, postnatal depression in mothers was associated with increased FA in the offspring's right amygdala (Wen et al., 2017).

Brain Function

FHR 5-year-old youth have reduced resting state functional connectivity between the right amygdala and left OFC and temporal pole (Soe et al., 2018). In addition, the same study reported a sex-specific effect, with FHR girls showing reduced connectivity between the left amygdala and right insula, right putamen, bilateral ACC, and bilateral caudate. Reward-task functional connectivity studies in this population have focused on the neural response elicited by gaining a reward. Overall, hypoactivation of the striatum, dorsolateral PFC, parahippocampal gyri, and insula was observed in young offspring of depressed mothers (Luking et al., 2016; Morgan et al., 2019; Wiggins et al., 2017). Furthermore, hypoactivation of the striatum was also associated with reduced reward-seeking behaviour in FHR youth (Morgan et al., 2019). As a result of region analysis, hyperactivation of FHR youth's amygdala in response to negative emotional stimuli has been reported in a task-based fMRI study on emotion regulation (van der Knaap et al., 2018).

Adolescents

This literature review identified 23 studies on the brain of 7,028 adolescents aged 11 to 18 (Table 1C). This includes 6 studies assessing brain structure, 16 studies assessing brain function and 1 study assessing both.

Brain Structure

Several findings suggest that FHR daughters exhibit cortical thinning, some of which is concordant with gray matter reductions seen in MDD. Adolescent females showed significant cortical thinning in the fusiform gyri, which was also found in their depressed mothers (Foland-Ross et al., 2015, 2016). These reports of cortical thinning in FHR youth support the findings in younger age groups. However, there is less agreement across studies on which exact regions demonstrate cortical thinning.

Some reports of the hippocampus in FHR adolescents and young adults suggest volume reductions, whereas others find no significant differences (Chen et al., 2010; Mannie et al., 2014). Amygdala volumes appear to be reduced in the only study that investigated it (Chai et al., 2015). These results show lack of agreement and/or repeated findings across studies on the directionality of subcortical gray matter volumes, an issue which persists from reports of younger age groups. However, assessment of hippocampal shape has yielded interesting results. A reduction of the hippocampal head and contraction of the CA-1 region have been observed in FHR adolescents, a finding which has been previously reported in depressed adults (Hubachek et al., 2021).

A reduction of white matter integrity has been detected in FHR adolescents. This includes the cingulum, corpus callosum, superior longitudinal fasciculus, inferior fronto-temporal fasciculus and uncinate fasciculus (Huang et al., 2011; Hung et al., 2016). Furthermore, lower FA of the cingulum, particularly within the ACC region, was associated with elevated depression scores in FHR youth (Hung et al., 2016). Concordant with findings in infants, FHR adolescents appear to have regional reductions of white matter integrity.

Brain Function

Abnormalities in resting-state connectivity networks have been reported in FHR adolescents and young adults. In FHR compared to FLR adolescents, the DMN appears to be less strongly connected with the ACC, posterior insular cortex and postcentral gyrus (Chai et al., 2016). Another study identified diminished connectivity between the DMN and the ventral striatum (Frost Bellgowan et al., 2015). Hypoconnectivity is also observed in the CCN, particularly between the dorsolateral PFC, ACC and inferior frontal gyri (Chai et al., 2016; Clasen et al., 2014). Aberrant connectivity between regions implicated in mood processing and emotional regulation have also been reported. FHR adolescents had stronger connections between the ACC and inferior parietal lobule and weaker connections between the amygdala, orbitofrontal PFC and precuneus (Hirshfeld-Becker et al., 2019; Singh et al., 2018). Furthermore, they also demonstrated hyperconnectivity at rest between the posterior cingulate cortex and subcortical structures such as the amygdala and hippocampus (Singh et al., 2018). Hyperconnectivity between the amygdala and

dorsolateral PFC has been detected in FHR adolescents (Fischer et al., 2018). Overall, the large heterogeneity between studies and the small number of reproduced findings makes it difficult to conclude the directionality of activity and exact regions affected within these resting state networks.

FHR offspring had altered activation patterns during reward processing. Blunted activity in the striatum was reported during reward anticipation and reward receiving in FHR adolescents (Fischer et al., 2019; Olino et al., 2014, 2015; Sharp et al., 2014). Additionally, this group showed increased activation within the putamen and insula during reward anticipation and hypoactivation in the striatum, insula and parahippocampal region during reward loss (Colich et al., 2017; Luking et al., 2016). Similarly, during reward anticipation, the middle frontal gyrus was more active in older FHR adolescents compared to healthy controls and those with a depression diagnosis (Fischer et al., 2019). This finding on older FHR adolescents who were past the age of typical MDD onset suggest the possibility of a neurobiological marker of resilience.

Several studies have showed that high-risk adolescents demonstrate altered neural activation in amygdala and PFC areas during emotion response. When viewing negatively valenced emotional stimuli, FHR adolescents showed more activity in ACC and dorsolateral PFC, and less activity in the amygdala than FLR youth (Chai et al., 2015; Mannie et al., 2011; Pilhatsch et al., 2014). Blunted activation in the dorsolateral PFC was also observed during mood regulation (Joormann et al., 2012). These results suggest altered emotion processing in FHR adolescents.

Young Adults

This literature review identified 4 studies on the brain of 166 young adults aged 19 to 25 (Table 1D). This included 2 papers on brain structure and 2 papers on brain function.

Brain Structure

Cortical thinning of the temporal-parietal region and dorsomedial PFC has been detected in a sample of FHR young adult daughters (Ozalay et al., 2016). No change in hippocampal volume had been observed (Durmusoglu et al., 2018). However, similar to the results of FHR adolescents and adults with depression, a contraction of the CA-1 region of the hippocampus was found in FHR young adults (Durmusoglu et al., 2018).

Brain Function

Two fMRI studies assessing emotion processing found no differences in the amygdala, ACC, and PFC activity during the presentation of negative, positive, or neutral stimuli (Mannie et al., 2008; Simsek et al., 2017). The contrast in findings between altered emotion processing detected in FHR adolescents and no change in FHR young adults suggests a possible marker of resilience in brain activation when dealing with emotional stimuli. However, further research is required to confirm whether such a neurobiological protective factor exists.

Discussion

In this review I examined neural markers of familial risk for depression. I focused on a wide age range, infancy to early adulthood, to encompass the time during which brain development is most rapid and the risk of depression onset increases (Herrman et al., 2022; Levman et al., 2017). Although large heterogeneity between studies creates difficulty in making conclusions, I have found some consistencies across brain structure and function between FHR youth and adults with depression. This presents the possibility for the existence of familial neural risk factors for depression and underlies the importance of additional research.

Brain Structure

The most consistent finding across age groups is the presence of cortical thinning in FHR youth (Figure 2). Cortical thinning has been detected in FHR offspring as young as at age 4 and as old as 25 (Lebel et al., 2016; Ozalay et al., 2016). Studies on adults with MDD also report smaller cortical volume that is most likely attributed to reduced cortical thickness (Bora et al., 2012; Lai, 2013; Schmaal et al., 2020). This similarity between FHR offspring and adults with MDD suggests that cortical thinning may be a familial neural risk factor for depression.

Cortical thinning in FHR offspring is most frequently reported in frontal and temporal regions (El Marroun et al., 2016; Foland-Ross et al., 2015; Ozalay et al., 2016). These regions are typically implicated in emotion regulation, goal-directed behaviour and

behavioural inhibition, faculties which are often impaired in depression (Zhang et al., 2018). However, there is less agreement between studies about the specific location(s) that are most affected, making functional claims uncertain. What is apparent is that cortical thinning, not cortical thickening, occurs FHR youth. Cortical grey matter reduction is a normal process of brain maturation, occurring as the child ages (Levman et al., 2017). This is done by increased pruning, the removal of inefficient dendrites and synapses, as well as by increased myelination, the addition of myelin sheaths, improving the efficiency of neural signals (Natu et al., 2019; Parker et al., 2020). However, what process governs earlier brain maturation in FHR youth is not yet known. Early brain maturation can occur as a response to exposure to early adversity, such as maternal depression during gestation or postnatal period. Indeed, FHR young children whose mothers experienced prenatal or postnatal depression exhibit significant cortical thinning (El Marroun et al., 2016; Lebel et al., 2016; Sandman et al., 2015). The link between maternal depression and offspring brain structure is also found in FHR adolescents and young adults. Daughters exhibit similar patterns of cortical thinning as their mothers who have a history of MDD (Foland-Ross et al., 2015, 2016). Whether this effect occurs due to familial transmission of a neural phenotype, early adversity or exposure to similar environmental stressors is uncertain and warrants further investigations.

Loss of white matter tract integrity in FHR offspring is the second relatively consistent finding. Studies report lower FA values in FHR infants and adolescents, but there is little agreement over the specific tracts affected (Dennis et al., 2019; Huang et al., 2011; Hung et al., 2016). Reduced integrity of white matter tracts is found in depressed

adults, particularly within the genu of the corpus callosum, corona radiata and cingulum (Schmaal et al., 2020). Axonal disruption that is associated with lower FA values in adults with MDD has been linked to executive, cognitive and behavioural deficits that are seen in depression (Coloigner et al., 2019). White matter development begins in utero, increases through childhood to early adulthood until it peaks in middle age (Lebel & Deoni, 2018). Therefore, poorer integrity of white matter in FHR offspring suggests deviations from normal development. It is possible that reduced white matter integrity found in FHR offspring may be a familial risk factor for depression. However, gaps in literature persist, with no studies examining white matter content in FHR young children and young adults. Longitudinal studies may provide further insight on developmental differences of white matter in familial risk youth compared to those of lower risk.

The association between high familial risk and subcortical gray matter structures is unclear. Comparable to findings in adults with MDD, there is little consensus among studies on volumetric differences of the amygdala in FHR offspring (Acosta et al., 2020; Chai et al., 2015; Ho et al., 2022; Pagliaccio et al., 2014; Wen et al., 2017). Reports on subcortical structures such as the thalamus, caudate, pallidum and midbrain are too few to make any conclusions. Although decreased hippocampal volumes are associated with depression, results are inconsistent in FHR offspring (Geerlings & Gerritsen, 2017; Schmaal et al., 2016). Therefore, it is still unclear whether hippocampal abnormalities precede MDD or are a consequence of the illness. It has been suggested that MDD is associated with reduced hippocampal volume due to the role that the hippocampus plays in the HPA-axis stress response (Czéh & Lucassen, 2007). A possible explanation may be

that a dysfunction in the stress response that is often seen in patients with MDD creates a neurotoxic effect in the brain due to excessive production of glucocorticoids, resulting in an abnormalities in the structure of the hippocampus (Sapolsky, 2000). This would suggest that reduced hippocampal volumes are a consequence of MDD. On the other hand, the vulnerability hypothesis suggests that hippocampal abnormalities could be a result of excessive childhood stress, trauma and family risk factors that disrupt neurodevelopmental processes of the hippocampus, resulting in increased vulnerability to MDD onset (Frodl et al., 2010). My review leaves this debate open, with hippocampal volume reductions observed in FHR adolescents but not in young adults (Chen et al., 2010; Durmusoglu et al., 2018; Hubachek et al., 2021; Mannie et al., 2014). Further research is required to get a clear picture on whether hippocampal reductions may be a familial risk factor for MDD and if there is any age-related trend.

Recent studies have detected subcortical shape alterations in adults with depression, such as of the basolateral amygdala and CA-1 region of the hippocampus (Ho et al., 2020). Contraction of the CA-1 region has similarly been reported in a couple of studies of FHR children and young adults, appearing as one of the more consistent findings in this review (Durmusoglu et al., 2018; Hubachek et al., 2021). Caution due to the small number of studies on this topic prevents from making any definite conclusions. However, it does raise questions on whether studying subcortical gray matter shape, in addition to volume, may be beneficial in providing additional information on gray matter structures in FHR youth.

Brain Function

Assessing similarities across functional brain findings has proven to be more challenging than brain structure. The field of fMRI is newer than that of structural neuroimaging, with greater heterogeneity in analysis methods, templates and choice of brain regions to investigate (Schmaal et al., 2020). Particularly, the choice between region-focused and whole brain analysis creates difficulty in comparing resting state data. I found 10 studies in total (2 in infants, 1 in children and 7 in adolescents and young adults) investigating resting state in FHR offspring. Although a few similarities across findings did emerge, such as amygdala – PFC connectivity, the DMN and CNN, the directionality of them was less consistent (Figure 3). The lack of consistent findings is not exclusive to FHR youth, as functional literature on adults with MDD similarly shows great heterogeneity in findings (Kaiser et al., 2015; Yan et al., 2019). This stresses the importance of establishing harmonized processing methods, standard seed networks and templates to allow greater comparability of functional data between research groups.

Task-based fMRI on reward and emotion processing possess the same heterogeneity as discussed above in addition to the choice of task selection. Although task paradigms attempt to illicit similar responses (i.e perceptional discrimination task for emotion processing) slight differences and/or adaptations across studies add to the heterogeneity of findings (Bishop et al., 2004; Hariri et al., 2005). This is particularly evident across studies on emotion processing, with most studies using the different tasks which may contribute to the patchwork of results. However, there is some agreement across studies on functional reward processing. Consistent reports of reduced striatal activation

during reward anticipation appears in FHR children and adolescents (Gotlib et al., 2010; Morgan et al., 2019; Olino et al., 2015; Sharp et al., 2014; Wiggins et al., 2017). This is concordant to the reduced striatal activation associated with increased depression severity and the altered activation that is common in adults with depression (Arrondo et al., 2015; Segarra et al., 2016; Zhang et al., 2018). This suggests that altered reward processing may be a neural risk factor for depression. However, additional research is warranted particularly on younger FHR offspring to elaborate when this marker may first emerge.

Future Directions

I have identified several similarities as well as discrepancies of brain alterations between FHR offspring and adults with MDD. In doing so, I have noted a few shortcomings of current literature on neural markers in FHR youth. The first, is the small number of reproduced findings due to only a few studies examining a given modality or region of interest in FHR offspring. Even across studies that investigate the same topic and make similar conclusions (i.e. loss of white matter integrity), only a handful of studies with relatively small sample sizes exist. An addition of rigorous studies with larger sample sizes would enrich our understanding on neural markers of familial risk to depression and provide more certainty on the emerging findings. The second shortcoming discussed was the heterogeneity of fMRI results. Development of streamlined analysis techniques would allow for improved comparison across studies, allowing further insight into the functional alterations that may exist in FHR offspring (Schmaal et al., 2020).

Throughout this review several additional gaps in literature have become apparent. Figures 2 and 3 show the various structural and functional brain alterations present in FHR youth. One of the striking visual findings is the lack of data investigating numerous neural measures across different age groups. Filling these gaps could provide us with a better developmental perspective on when brain alterations may first emerge and how they progress as the offspring ages. Furthermore, many topics have not yet been investigated. Altered gyrification and reduced intracortical myelin have been observed in depression but not yet explored in FHR offspring (Lake et al., 2017; Long et al., 2020; Sacchet & Gotlib, 2017). Research on these topics could further enrich our perspective on brain alterations present in FHR offspring as well as provide neurobiological explanations for their occurrence.

Another shortcoming in current literature is the frequent overlap of adolescents and young adults in studies. The average age of MDD onset is between 14 to 16 (Herrman et al., 2022). Therefore, it is possible that asymptomatic FHR offspring older than 16 may be a phenotypically distinct group compared to those who are younger. This argument is supported by a few studies, which suggest that their brain alterations present in older asymptomatic FHR offspring differ to those observed in FHR offspring who became depressed (FHR-MDD) as well as low risk controls (Fischer et al., 2021; Nimarko et al., 2019; Toenders et al., 2019). For example, older FHR adolescents showed greater activation in the middle frontal gyrus during reward anticipation, a trend not seen in FHR-MDD and FLR groups, despite having blunted striatal activation during reward tasks (Fischer et al., 2016). This suggests a possible compensatory mechanism that might allow

for adaptive cognitive reappraisal of stimuli and may be a marker of resilience (Bermpohl et al., 2009; Erk et al., 2010). Multiple studies presented in this review have a large overlap in age range, particularly in the adolescent and young adult category. This makes it difficult to discern whether a result is representative of FHR offspring prior to typical age of onset versus those who are older and may have forms of compensatory brain alterations. Stricter separation of youth prior to age of onset and those past the age of onset would not only increase our understanding of whether certain brain alterations are adaptive in FHR youth but also potentially remove some inconsistency of results found in these age groups.

Depression is more common in females compared to males (Herrman et al., 2022). Multiple studies have focused on the effect of maternal depression on the offspring brain, with 29 out of 44 studies included in this review categorizing youths familial risk status based solely on the presence or absence of maternal depression. However, there are reports of paternal depression at different stages of offspring life (i.e. during gestation, postnatally, in childhood) being associated with varying psychological and behavioural outcomes in boys and girls (Gutierrez-Galve et al., 2019; Lewis et al., 2017; Thiel et al., 2020). Future studies need to compare the effects of maternal and paternal depression on offspring brain development and whether any sex-specific associations are present. Furthermore, 13 out of 27 studies on adolescents and young adults included in this review have exclusively female samples. Sex differences in structural brain alterations have been reported in younger samples of FHR youth (Acosta et al., 2020; Soe et al., 2018; Wen et al., 2017). Additional research on brain alterations detected in older male and female FHR youth could provide

insight on the presence of possible sex-specific neural markers, which could elaborate on the varying phenotypic presentation of depression in males and females.

Conclusion

Structural and functional brain abnormalities that are associated with depression appear in youth at high familial risk for depression. This suggests the presence of neural markers of depression prior to disorder onset. However, streamlined fMRI analyses and increased number of studies whose findings reproduce current results would increase my confidence of the emerging conclusions presented in this review. Furthermore, future studies are necessary to gain further perspective on when various neural markers first emerge and whether there are any sex-specific trends present. Improved detection and understanding of the course of neural markers that precede MDD could allow for earlier implementation of interventions that can help reduce the burden of depression on individuals.

CHAPTER 3: FROM SYSTEMATIC REVIEW TO INDEPENDENT RESEARCH

Writing the systematic review brought my attention to several gaps present in the literature on neural markers of familial risk to depression. One of these gaps, intracortical myelination, particularly intrigued me for several reasons. First, no studies appeared to have investigated this topic in familial high-risk youth although reduction of intracortical myelination is found in adults with MDD. Second, I had the pleasure of working as a research assistant on another project assessing intracortical myelin and cognition in adults with mood disorders. This involvement heightened my curiosity about the behavioural, cognitive, and emotional implications associated with a disruption of intracortical myelin in individuals. Therefore, I wanted to start my project that investigated whether reduced intracortical myelin may be a neural marker of familial risk of depression in high-risk youth.

CHAPTER 4: INTRACORTICAL MYELINATION AND FAMILIAL RISK FOR DEPRESSION IN YOUTH

Abstract

Major depressive disorder (MDD), characterized by persistent sadness and loss of interest, is a leading cause of disability. To understand why depression develops, it is important to distinguish between early neural markers of vulnerability that precede the onset of MDD and features that develop later as a consequence of MDD. Recent neuroimaging findings suggest that reduced intracortical myelination (ICM) may be associated with depression, but it is unknown whether it is a precursor or a consequence of MDD. The study of offspring of affected parents offers the opportunity to distinguish between precursors and consequences by examining individuals who carry high risk at a time when they have not experienced depression. My objective was to investigate whether ICM abnormalities occur in youth offspring who are at high familial risk of developing depression. I examined ICM globally, across the entire cortex, as well as in the lateral prefrontal cortex, a region that has been linked to depression. Participants were 53 offspring of parents with major depressive disorder and 59 youth without a family history of depression, aged between 9 and 16 at the time of assessment. I acquired T1-weighted and T2-weighted magnetic resonance imaging (MRI) whole brain scans. I used the ratio of T1-weighted and T2-weighted images to calculate cortical myelin maps for 68 cortical regions based on the Desikan-Killiany atlas. I found that ICM did not differ between high and low familial risk youth in my global and regional analyses. Combined with prior evidence, this finding suggests that reduced ICM may be a consequence rather than a precursor of MDD.

Introduction

Major depressive disorder (MDD) is characterised by persistent sadness, loss of interest, fatigue, and an increased risk of suicide (Haroz et al., 2017). The onset of MDD typically occurs in late-adolescence or early adulthood (Malhi & Mann, 2018). Depression is the most prevalent mood disorder, affecting 1 in 5 people worldwide (Lim et al., 2018). The negative impact on daily functioning and associated cost of healthcare demand advancement of treatment and earlier detection to improve prognosis (Herrman et al., 2022).

Early detection of risk can be informed by knowledge of factors involved in the development of depression. MDD is influenced by genetic and environmental factors, both of which affect brain development (Tozzi et al., 2020; Wray et al., 2018). Cortical thinning, abnormalities in subcortical structure volumes, white matter, and aberrant functional connectivity networks characterize patients with depression (Schmaal et al., 2020). It is not known whether these brain abnormalities precede or develop during the illness. It has been suggested that abnormal structure and function of several key brain regions may lead to the development of symptoms seen in depression (Dai et al., 2019).

Brain abnormalities may manifest globally, across the entire brain as well as regionally, in specific cortical areas. For example, depression is associated with global cortical thinning across both hemispheres (Pink et al., 2017). A cortical region of particular interest is the lateral prefrontal cortex (LPFC). The LPFC is involved in executive control

functions such as working memory, attention, response inhibition, emotion regulation and behavioural planning through extensive connections to other cortical and subcortical areas (Tanji & Hoshi, 2008), which are often impaired and associated with poorer prognosis among individuals with depression (Semkovska et al., 2019) Functional and structural abnormalities of the LPFC have been found in adults with depression, suggesting a neural link between depression and difficulties in executive control as well as emotional regulation (Friedman & Robbins, 2021; Lake et al., 2017; Lapate et al., 2017; Martin et al., 2017; Sampath et al., 2017).

Abnormalities at the cellular level have been observed in depressed patients. Decreased cell number, size and density of oligodendrocyte lineage cells have been found in MDD (Boda, 2021). Oligodendrocytes compose the myelin sheaths, a fatty covering of axons that increase action potential speed and consequently improves processing capacity of the brain. Abnormalities of the white matter myelin sheathes and slower processing capacity are associated with depression (Zhou et al., 2021). Many myelinated axons are in the cerebral cortex and create intricate myeloarchitecture of the brain (Rowley et al., 2015). Abnormalities in intracortical myelination (ICM) may underlie changes in cognitive and behavioural abilities. Studies examining neonatal separation of rat pups from their mother have linked reduced ICM in the LPFC with increased anxiety and deficit in working memory (Yang et al., 2016). Reduced ICM has been associated with psychotic and mood disorders, including depression, in adults (Lake et al., 2017; Regenold et al., 2007; Toschi & Passamonti, 2019). Furthermore, oligodendrogenesis of the prefrontal cortex is sensitive to stressful environmental and physical conditions that have been shown to affect myelin

development (Liu et al., 2012; Makinodan et al., 2012). During human development, intracortical myelination follows an inverted U-trajectory with a rapid increase in teenage and early adult years, peak in mid-30s and a decline in later adult years (Haroutunian et al., 2014). However, the development of ICM within the frontal, parietal and temporal regions, is altered in adults with mood disorders (Sehmbi et al., 2019). The LPFC appears to be one of the regions most affected, with MRI and histological studies detecting decreased ICM in LPFC in depressed adults (Lake et al., 2017; Regenold et al., 2007; Sampath et al., 2017).

The cellular vulnerability to environmental, psychological, and physiological conditions increases the risk of ICM disruptions, especially in the adolescent years during which myelination is most rapid. The rapid development of intracortical myelination in adolescence and early adulthood coincides with the greatest risk for mood and psychotic disorders (van Haren et al., 2020). However, it is unknown whether early disruptions of ICM development may increase the risk of depression onset (Toenders et al., 2019). Familial high-risk studies have been used to investigate whether neural abnormalities predate the onset of MDD or are a consequence of the disorder. Youth at high familial risk have similar patterns of neural abnormalities compared to adults with MDD, specifically in cortical volume and functional connectivity networks (Nickson et al., 2016; Toenders et al., 2019). Compared to general population, high risk youth have increased probability of mood disorder onset due to their genetic relation with family member(s) who have a severe mental disorder (Rasic et al., 2013; Rudaz et al., 2021). Familial risk is known from birth or an early age, allowing to study development in individuals who are at risk at a time when they have not experienced depression. Furthermore, adolescents at high familial risk are

typically naïve to psychiatric medications, removing the possibility of psychopharmacological influences on clinical and neural measures (Boccia et al., 2016).

One key challenge in answering this type of question is measuring ICM in living humans. Histological studies provide accurate information on myelin content in post-mortem brains (Eickhoff et al., 2005). Magnetic resonance imaging (MRI) studies allow insight in the myelination in the living brain, however the accuracy of these methods especially within the developmental range, has not yet been established (Patel et al., 2020). I plan to look for the expected age-related increase of ICM and establish the intraclass correlation coefficient of ICM to gain more certainty of myelin measures used in this development sample.

The current study addresses the gap by examining whether intracortical myelination abnormalities may be a neural risk factor that predates depression onset. I implement a familial high risk study design to investigate whether global and regional levels of intracortical myelination differ between familial high-risk (FHR) and familial low-risk (FLR) adolescents. I focus on an age range younger than the typical onset of depression to examine brain development in youth who are at high risk before depression develops. First, I hypothesize that there will be a reduction in global ICM in FHR youth. Second, I hypothesize a reduction of ICM in the LPFC in FHR youth. I anticipate FHR youth to have a reduction of ICM, similar to adults with MDD, reproducing a similar trend found in family high risk studies investigating other brain modalities (Heinze et al., 2020; Toenders et al., 2019).

Methods

Participants

FHR participants were those who have at least one biological parent with a lifetime diagnosis of MDD according to the Diagnostic and Statistical manual fifth edition (DSM-5). FLR participants included offspring of parents without any history of mental illnesses. FHR participants were recruited by clinical referral by physicians treating the parent. FLR participants were recruited from schools and communities matched by similar socioeconomic background as FHR participants.

Inclusion criteria were age between 9 and 16, who had no current or previous diagnosis of a major mood, psychotic, substance abuse or autism spectrum disorder according to the DSM-5. This age range was selected to allow measurement in representative samples of individuals at high and low familial risk, who are at a developmental stage before the typical age of the first major mood episode onset (Lieb et al., 2002; Moffitt et al., 2010). Exclusion criteria were neurological disorders, history of head trauma with loss of consciousness and contraindications to the MRI.

This study was approved by the Nova Scotia Health Authority Research Ethics Board. All participants and their parents or legal guardians signed informed consent.

Procedure

The participants and their parents completed semi-structure diagnostic interviews and provided their demographic information during their assessment Separate groups of assessors collected information about the parents and the offspring.

Participants were scheduled for an MRI within a two-week period of their assessment. A poster about the MRI procedure was shared with the participants prior to them coming to their appointment[1]. The scans took place at the Biomedical Translational Imaging Centre (BIOTIC) at the Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia. All participants were safety screened by an MRI technician before the scan. The MRI session lasted approximately 35 minutes. Participants received reimbursement after the MRI scan was complete.

To capture the development of ICM over time I invited all participants to repeat scans in one-year intervals based on their own availability and interest. In addition, to establish test-retest reliability I invited a proportion (25%) of participants to repeat scans within two weeks of their initial scan date.

[1] The poster can be found in Appendix A.

Measures

Semi-Structured Interviews

Parent Assessment. To assess familial high risk, adult assessors completed a Structured Clinical Interview for DSM-5 (SCID-5) with each parent (First et al., 2014). If a parent was incapable of attending the interview, their health records were reviewed, and informant information assessed through the Family Interview for Genetic Studies to identify their history of mental illness.

Offspring Assessment. Youth assessors completed a Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL) for DSM-5 with each youth participant (Kaufman et al., 1997).

All interviews were performed by trained youth and adult assessors. Assessors that completed youth interviews were blind to the parental diagnosis and those that completed parent assessments were blind to the offspring diagnoses. The SCID-5 and K-SADS-PL are validated instruments that establish a diagnoses of mood disorders with high interrater reliability (Kaufman et al., 1997; Osório et al., 2019). DSM-5 diagnoses for youth and parents were confirmed in consensus meetings with licensed psychiatrists who were blind to diagnoses in other family members.

Demographic Information

Demographic data, including participant sex, age, ethnicity, measured height (cm) and weight (kg), was gathered during the annual assessment. I indexed socio-economic status (SES) as a composite of maternal and paternal levels of education, family household annual income, ownership of primary residence, and ratio of bedrooms to residents in household (Zwicker et al., 2020). I measured the full-scale intelligence quotient (IQ) with the Wechsler Abbreviated Scale of Intelligence. I computed the Body Mass Index (BMI) using participant height and weight.

Imaging Methods

Image Acquisition

I acquired MRI images with a 3T General Electric Discovery MR750 scanner equipped with a 32-channel RF head coil. I collected *a T1-weighted* (T1w) Brain Volume imaging (BRAVO) sequence with whole-brain coverage, 1 mm^3 isotropic resolution, matrix = 224 x 224, field of view (FOV) = 224 mm, 168 sagittal slices at 1 mm thickness, repetition time (TR) = 5.9 ms, echo time (TE) = 2.2 ms, inversion time (TI) = 450 ms, flip angle = 12°, scan duration = 5 minutes. I also collected a *T2-weighted* (T2w) fluid-attenuated inversion recovery (FLAIR) sequence using a T2 prep contrast option (T2PREP) with identical coverage, resolution, and acquisition orientation to the T1w sequence, TR = 5100 ms, TE = 98 ms, TI = 1427 ms, echo train length (ETL) = 250 echoes, flip angle = 90°, with prospective-motion correction (PROMO) enabled, scan duration = 5 minutes. The 35-minute scanning protocol also included diffusion tensor imaging (DTI) and

functional magnetic resonance imaging (fMRI) sequences, which will be used in future research projects.

Image Pre-processing

I processed the T1-w and T2-w scans using the Human Connectome Project (HCP) Minimal Preprocessing Pipeline (Glasser et al., 2013). The HCP pipeline is a well-documented set of scripts that uses open-source MRI processing software including FreeSurfer 6 and the FMRIB Library (Fischl, 2012). This pipeline was optimized for the present data by replacing the MNI template with an age-appropriate pediatric template for registration (Fonov et al., 2011). The modified pipeline is available and freely accessible online https://github.com/GitDro/YouthReliability/ tree/master/HCP_custom_ pipeline. I implemented quality control to minimize artifacts, especially motion, that may affect results (Marcus et al., 2013). Quality control was carried out manually, using trained raters to assess the quality of T1w and T2w scans, and with Qoala-T, an automated supervised-learning tool (Klapwijk et al., 2019). I excluded 11 out of 227 scans due to large motion artifacts, leaving 216 for analyses.

T1w/T2w Ratio Myelin Maps

I acquired cortical myelin maps following a method developed by Glasser and Van Essen (2011). T1w image registers the hyper-intensity of white matter that is associated with the spatial distribution of myelin-bound cholesterol (Ganzetti et al., 2014). In contrast, a T2w image registers hypo-intensity of myelin as a result of the hydrophobic properties

of the lipidic bilayer in myelin (Barkovich, 2000). The ratio of T1w to T2w images creates myelin maps that quantify regional differences in myelin content in the cortex (Glasser & Van Essen, 2011) that correspond to myelin content in post-mortem histology (Grydeland et al., 2013; Patel et al., 2020). A FreeSurfer automated tool segmented the cortex into 68 regions based on the Desikan-Killiany atlas (Desikan et al., 2006), providing a total of 68 cortical myelin measurements, 34 per hemisphere.

Data analysis

To test my first hypothesis, I computed global intracortical myelination by averaging the ICM values across all 68 cortical regions. I followed this global analysis up by testing the right and left hemispheres separately. To test my second hypothesis, I first computed the total ICM of bilateral LPFC, by averaging 12 cortical regions (6 from each hemisphere) that anatomically compose the LPFC, including; the caudal middle frontal, rostral middle frontal, pars opercularis, pars triangularis, pars orbitalis and orbital frontal regions (Desikan et al., 2006; Petrides, 2005). I followed this regional analysis up by testing the right and left LPFC separately.

I indexed test-retest reliability as the intraclass correlation coefficient between the short repeat scans for each of the 68 cortical regions and mean reliability for my global (total, left, and right hemisphere) and regional (right and left LPFC) analysis. I used the following criteria to classify reliability: poor (<.40), fair (.41 - .59), good (.60 - .74), excellent (>.74) (Cicchetti, 1994).

I tested the global and regional hypotheses in mixed effects linear regression models, as the fixed-effects of the familial risk status variable on ICM. I accounted for the non-independence of multiple scans (i.e. short- and long-term repeats) from the same participant and related participants through nested random effects of individual and family. I included sex and age as covariates in all models to account for sex differences and developmental changes in brain structure (Damoiseaux, 2017; Kaczkurkin et al., 2019; Wierenga et al., 2019). I applied Bonferroni correction for multiple testing across the global (adjusted p-value across 3 tests, p = .0125) and regional (adjusted p-value across 3 tests, p = .0125) hypotheses. In the sensitivity analyses, I included SES, IQ, and BMI as additional fixed covariates to control for other factors that may affect brain measures. (Bathelt et al., 2019; Colom et al., 2010; Dekkers et al., 2019; Hackman & Farah, 2009; McDermott et al., 2019). I completed all statistical tests in RStudio (R Version 4.0.3; RStudio version 1.2.5033).

Results

Demographic Characteristics

After quality control, I retained 216 scans (112 baselines, 66 long-term follow-ups, 38 short-term follow-ups) from 112 youth (53 FHR, 59 FLR) for analysis (Table 2). Participants ranged between 9 and 16 years of age (M = 11.89, SD = 1.99). The participants were predominantly white (90%). The groups had an equal distribution of males and females (X^2 (1, N = 112) = 2.46, p = .11) and similar SES and IQ.

Test-retest Reliability

I calculated excellent ICM test-retest reliability across the entire brain (ICC = 0.79, 95% CI [0.58, 0.89]) and across the left (ICC = 0.79, 95% CI [0.58, 0.88]) and right (ICC = 0.80, 95% CI [0.60, 0.89]) hemisphere separately (Figure 4). I also calculated good to excellent test-retest reliability in the total (ICC = 0.75, 95% CI [0.49, 0.86]), left (ICC = 0.74, 95% CI [0.47, 0.85]) and right (ICC = 0.75, 95% CI [0.51, 0.87) LPFC.

Global Intracortical Myelination

I confirmed the expected developmental trend for the total ICM to increase with age (B = .03, SE = .007, p < .001), regardless of familial risk status (Figure 5). I tested my first hypothesis by examining the effect of familial risk group on ICM across the entire brain, as well as separately across the left and right hemispheres. I found a slight trend of increased total, right, and left hemisphere ICM in the FHR group (Table 3, Figure 6). The linear mixed-effects regression model showed that global ICM did not significantly differ between FHR and FLR youth (B = .06, SE = .03, p = .08) (Table 4). Similarly, there was no significant group difference in ICM of the right (B = .06, SE = .03, p = .08) or the left (B = .06, SE = .03, p = .06) hemispheres (Table 4). The result remained unchanged across a range of sensitivity analyses controlling for SES, IQ, and BMI, with all estimates within 1 SE of the primary analysis estimates (Table 5).

Intracortical Myelination of the Lateral Prefrontal Cortex

I tested my second hypothesis by examining the effect of familial risk group on ICM in my region of interest, the LPFC. A slight trend towards increased LPFC ICM in the FHR group was apparent (Table 3, Figure 6). However, like the global analysis, there was no significant group difference in ICM of the total, (B = .05, SE = .03, p = .10), right (B = .06, SE = .03, *p* = .08) or left (B = .05, SE = .03, *p* = .15) LPFC (Table 6). The result remained unchanged across a range of sensitivity analyses controlling for SES, IQ, and BMI (Tables 7).

Stratified analysis

To help understand the unexpected trend toward increased ICM in FHR youth, I conducted a stratified analysis to detect any differences in ICM that may be restricted to males or females. I found that FHR boys had significantly increased ICM globally, (B = .1, SE = .04, p = .023), in the right (B = .11, SE = .05, p = .02) and left (B = .09, SE = .04, p = .03) hemisphere as well as in the total (B = .08, SE = .04, p = .04) and right (B = .1, SE = .04, p = .03) LPFC. These were unplanned analyses, and the differences were not statistically significant after controlling for the total number of tests completed. Furthermore, the effect remained within 1SE of the original but was slightly attenuated when controlling for BMI, SES, and IQ in sensitivity analyses. There was no relationship between ICM and high familial high risk in girls. Detailed results of the stratified analyses can be found in tables 8 through 15.

Discussion

This study was the first to examine whether intracortical myelination abnormalities exist in youth at high familial risk for depression. My results found no association between familial risk status and global intracortical myelination. Lack of association was also seen between familial risk status and ICM in the lateral prefrontal cortex. However, I did detect an unexpected trend towards increased ICM across all my hypotheses, which has an opposite directionality compared to previous findings in adults with MDD. These results suggest that decreased intracortical myelination found in depression may develop during or after illness onset. Unplanned stratified analyses suggest a possible sex dimorphic manifestation of familial risk of depression as increased intracortical myelination in males at high familial risk.

A reduction of intracortical myelination has been linked with MDD in adults (Lake et al., 2017; Regenold et al., 2007; Sacchet & Gotlib, 2017). Furthermore, findings from post-mortem studies suggest that abnormal ICM may play a crucial role in the development of depression due to reduced number of oligodendrocytes in MDD (Hayashi et al., 2011; Uranova et al., 2004). I implemented a family risk design to detect whether this reduction of ICM exists prior to illness onset and thus, increases vulnerability to it. While I did not discover a significant effect of familial risk group on ICM, I was surprised by the directionality of my non-significant result. Contrary to my expectation, I detected a trend towards increased ICM in FHR offspring. Furthermore, my stratified analysis showed a significant increase of ICM in boys. These trends suggest that intracortical myelination

reduction is not a sign of increased vulnerability, but rather, may develop during the onset or the course of the illness.

Cortical myelination continues development into middle age. Research suggests that ICM development throughout life allows for fine-tuning of synchronization between cognitive and behavioural networks of the brain (Chorghay et al., 2018). Evidence that myelination and white matter structure changes may be a key mechanism for brain plasticity that can explain how personal and environmental experiences shape the brain (Kaller et al., 2017). However, this also makes ICM highly vulnerable to disturbances and may contribute to the development of psychopathology (Haroutunian et al., 2014). The rate at which cortical areas myelinate differs, with the prefrontal cortex ICM continuing development until adulthood (Nickel & Gu, 2018). Cortical areas are at increased vulnerability at different times, with later developing areas at greater risk of exposure to adverse events that may negatively affect ICM development. Thus, it is possible that ICM reduction arises after the onset and during psychopathology. This could explain why depression is associated with reduced regional and global ICM in patients, whereas high-risk youth in this study have not been affected or showed an increased ICM relative to their low-risk peers (Lake et al., 2017; Regenold et al., 2007).

There is also a possibility that ICM abnormalities found in depression may present differently across the developmental trajectory of ICM and therefore, should be examined longitudinally. Age-related increases in oligodendrocytes, the cells composing myelin, are often disrupted in psychiatric patients (Vostrikov & Uranova, 2011). As a result, mood

disorder patients may lack the normal ICM inverse U-trajectory (Sehmbi et al., 2019). Young adults with bipolar disorder have increased myelin compared to controls at the start of illness. However, with age, the development of ICM slows down, creating an overall flatter trajectory. The trend of my results suggests that youth who are at greater risk for developing a mood disorder may have greater ICM than low-risk controls. Future studies should examine how ICM changes longitudinally from adolescence into adulthood, starting at youth. This could establish whether the developmental trajectory of ICM itself may be a neural marker of depression.

One challenge to developmental investigation of ICM is that it is unknown how accurately ICM can be measured across the developmental age range. To examine the quality of myelin measurement in my pediatric sample, I investigated the reliability of the T1w/T2w myelin map method. Reliability classifies the ability of a measurement to provide the same results under similar circumstances (Drobinin et al., 2020). Notably, image artifacts such as head motion can greatly increase measurement error, especially in a pediatric sample that may be more sensitive to scanner noise and therefore experience more movement (Ducharme et al., 2016). Overall, I found excellent to good reliability across my global and local hypothesis, which increases my confidence over the quality of this imaging data.

The result of the present study should be interpreted in the context of several limitations. Although I attempted to track progressive changes of ICM across development, not all my participants had multiple long and short-term repeats limiting my main

hypotheses results to cross-sectional. Second, as more accurate MRI measurements of myelin become available, future studies may be able to determine myelin content in a pediatric sample with greater accuracy (Grydeland et al., 2013; Patel et al., 2020). Third, although I controlled for confounds such as IQ and SES in my sensitivity analysis, some youth may have been exposed to medications and recreational substances that have not been reported and controlled for in my analyses.

Conclusion

In summary, I did not find a reduction of intracortical myelination in youth at high familial risk to depression. However, the trend towards increased myelination observed in my main and secondary analyses, suggests that the developmental trajectory of intracortical myelination in depression should be more closely examined.

CHAPTER 5: CONCLUSION

I began this journey with the desire to improve my understanding of depression. Specifically, I wanted to learn whether offspring of parents who have depression may have neural markers that suggest increased vulnerability for depression. Through my systematic literature review, I found that there are several markers of familial risk in offspring ranging from a couple of weeks to several decades old. However, several limitations in the field also became apparent, such as little focus on sex-specific effects, fMRI analysis heterogeneity, and an overall small number of studies investigating various neural markers throughout different age groups. Additionally, I found that intracortical myelination has not yet been assessed in high familial risk offspring. I decided to be one of the first to examine whether FHR youth have global and regional ICM reductions like adults with depression. Through my research I have identified that reduced intracortical myelination is not present in youth offspring, suggesting that it may be a consequence rather than a precursor of depression. This adds to our understanding of neural markers in depression, particularly by highlighting that whereas some structural and functional brain differences seen in depression may exist before disorder onset, others may emerge during the course of the illness. Further exploration of these topics can provide insight into neurobiological mechanisms of depression onset and the relationship between neural markers and phenotypic presentations of depression, which could allow us to predict onset and implement early interventions catered to individuals in hope of reducing the burden of depression.

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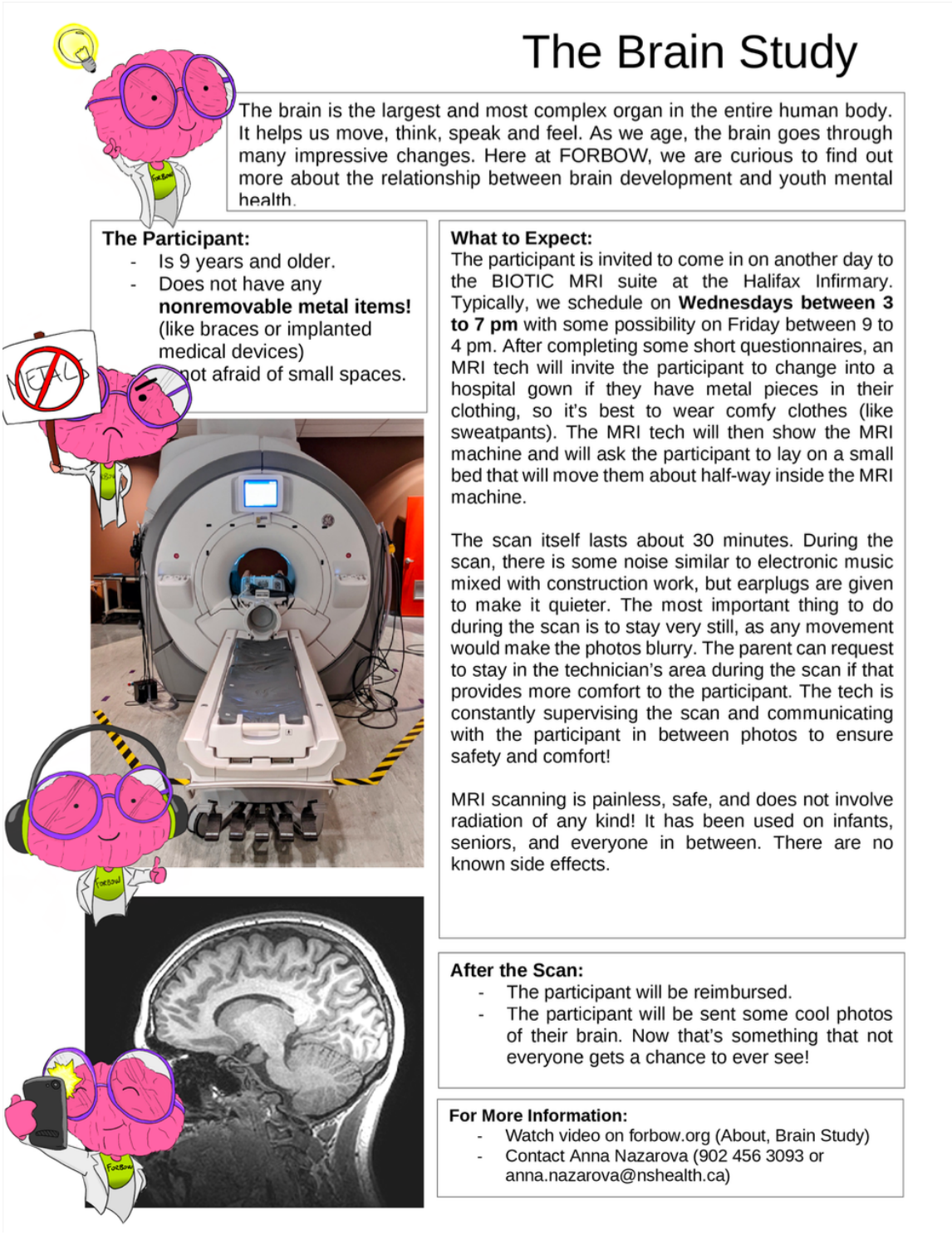
APPENDIX A: MRI STUDY INFORMATION POSTER



APPENDIX B: SYSTEMATIC REVIEW SUMMARY TABLE

Table 1.

Systematic Review Article Summary Table

A. Infants (> 2 years)

Author	Year	N (Female)	Age years (SD)	Familial Risk Classification	Neuroimaging Measure	Region(s) of Interest	Main Finding
Sethna et al.	2021	FHR = 31 (11) FLR = 33 (27)	FHR = .4 (.12) FLR = .4 (.1)	Maternal depression: Structured clinical interview for DSM-IV	Subcortical grey matter structure	Whole brain, midbrain.	↑ Caudate, putamen, globus pallidus and thalamus volume ↓ Midbrain volume
Dennis et al.	2019	Total = 24 (13)	Total = .55 (.03)	Maternal depressive symptomatology: EPDS	White matter structure	Fronto-limbic regions, uncinate fasciculus	↓ FA of right uncinate fasciculus
Posner et al.	2016	FHR = 20 (14) FLR = 44 (23)	FHR = .1 (.03) FLR = .1 (.03)	Maternal depressive symptomatology: CES-D	Resting state fMRI; White matter structure	Amygdala, PFC	↓ Connectivity between amygdala and dorsal PFC ↓ Connectivity between R amygdala and R ventral PFC
Qiu al.	2015	Total = 24 (12)	Total = .74 (.02)	Maternal depressive symptomatology: EPDS	Resting state fMRI	Amygdala	↑ Connectivity between L amygdala and BL medial prefrontal cortex, ACC, insula, and temporal cortex
Rifkin-Graboi et al.	2013	FHR = 28 (13) FLR = 42 (19)	FHR = .77 (.01) FLR = .77 (.01)	Maternal depressive symptomatology: EPDS	White matter microstructure; Subcortical grey matter structure	Amygdala	↓ FA of amygdala = Amygdala volume

B. Childhood (2 – 9 years)

El Marroun et al.	2016	Total = 654 (327)	Total = 7.9 (.95)	Maternal depressive symptomatology: BDI	Cortical structure	Whole brain	↓ Thickness of L superior frontal gyrus ↑ Surface area of caudal middle frontal
Lebel et al.	2016	Total = 52 (20)	Total = 3.6 (.5)	Maternal depressive symptomatology: EPDS	Cortical structure	Whole brain	↓ Thickness in R inferior frontal and medial and superior temporal areas
Sandman et al.	2015	Total = 82 (40)	N/A (6 – 9 range)	Maternal depressive symptomatology: CES-D	Cortical structure	Whole brain	↓ Thickness in R superior and medial orbital PFC
Hubachek et al.	2021	Total = 74 (31)	Total = 10.74 (.84)	Maternal depression: Structured clinical interview for DSM-IV	Subcortical gray matter structure	Hippocampus	↓ Hippocampal volume ↓ CA-1 region
Pagliaccio et al.	2020	FHR = 2,938 (1407) FLR = 6780 (3217)	FHR = 9.8(.6) FLR = 9.9 (.6)	Questionnaire battery of familial mental health history	Subcortical gray matter structure	Amygdala, hippocampus, striatum, pallidum, thalamus	↓ R putamen and nucleus accumbens volume
Acosta et al.	2020	Total = 28 (14)	Total = 4.2 (.15)	Maternal depressive symptomatology: EPDS	Subcortical gray matter structure	Amygdala	↓ R amygdala volumes
Wen et al.	2017	Total = 235 (122)	Total = 4.58 (0.08)	Maternal depressive symptomatology: EPDS	White matter microstructure; Subcortical grey matter structure	Amygdala	↑ FA in R amygdala ↑ Amygdala volume in girls only
Soe et al.	2018	Total = 128 (71)	Total = 4.58 (.08)	Maternal depressive symptomatology: EPDS, BDI	Resting State fMRI	Amygdala	↓ Connectivity between L amygdala and R insula, R putamen, BL ACC, BL caudate in girls only.

							↓ Connectivity between R amygdala and L OFC, temporal pole.
Morgan et al.	2019	FHR = 25 (15) FLR = 31 (16)	FHR = 6.72 (N/A) FLR = 6.87 (N/A)	Maternal depression: Structured clinical interview for DSM-IV	Reward processing fMRI	Striatum, OFC, PFC	↓ Activity of dorsal striatum to reward
Wiggins et al.	2017	FHR = 27 (14) FLR = 19 (14)	FHR = 7.44 (.73) FLR = 7.64 (.84)	Maternal depression: Structured clinical interview for DSM-IV	Reward processing fMRI	Striatum, PFC, limbic regions	↓ Activation of R DLPFC and parahippocampal gyrus to reward ↑ Activation of R DLPFC and parahippocampal gyrus to loss
Luking et al.	2016	FHR = 16 (8) FLR = 32 (17)	FHR = 9.05 (1.14) FLR = 9.28 (1)	Maternal depression: Structured clinical interview for DSM-IV	Reward processing fMRI	Striatum, insula, ACC, amygdala	↓ Activation of striatum and anterior insula to reward ↓ Activation of striatum, anterior insula and parahippocampal regions to loss
van der Knaap et al.	2018	FHR = 47 (28) FLR = 37 (14)	FHR = 7.75 (.76) FLR = 7.77 (.95)	Maternal depressive symptomatology: BDI	Emotion regulation fMRI	Amygdala	↑ Activation of BL amygdala to negative emotional faces
C. Adolescents (11 – 18)							
Foland-Ross et al.	2016	FHR = 14 (14) FLR = 23 (23)	FHR = 14.11 (2.33) FLR = 13.29 (2.41)	Maternal depression: Structured clinical interview for DSM-IV	Cortical structure	Whole brain	↓ Thickness of fusiform, inferior, temporal, and lateral occipital gyri
Foland-Ross et al.	2015	FHR = 28 (28) FLR = 35 (35)	FHR = 13.2 (1.5) FLR = 13.9 (1.7)	Maternal depression: Structured clinical interview for DSM-IV	Cortical structure	Whole brain	↓ Thickness of R fusiform gyrus

Chai et al.	2015	FHR = 36 (18) FLR = 14 (6)	FHR = 11.1 (1.35) FLR = 11.6 (2.14)	Parental depression: Structured clinical interview for DSM-IV	Emotion regulation fMRI; Subcortical gray matter structure	Amygdala	↑ Activation of amygdala to fearful faces ↓ Activation of ACC and supramarginal gyrus to happy faces ↓ Amygdala volume
Mannie et al.	2014	FHR = 62 (39) FLR = 59 (35)	FHR = 18.8 (1) FLR = 19 (.8)	Parental depression reported by participant	Subcortical gray matter structure	Hippocampus	= Hippocampal volume
Chen et al.	2010	FHR = 23 (23) FLR = 32 (32)	FHR = 12.76 (1.6) FLR = 12.9 (1.55)	Maternal depression: Structured clinical interview for DSM-IV	Subcortical gray matter structure	Hippocampus	↓ Hippocampal volume
Hung et al.	2016	FHR = 20 (10) FLR = 20 (10)	FHR = 11.1 (1.57) FLR = 10.65 (2.12)	Parental depression: Structured clinical interview for DSM-IV	White matter structure	Whole brain	↓ FA in anterior cingulum, genu of corpus callosum.
Huang et al.	2011	FHR = 18 (10) FLR = 13 (7)	FHR = 15.7 (2.3) FLR = 15.5 (3)	Parental current and lifetime mood disorder diagnoses: FH-RDS	White matter structure	Whole brain	↓ FA in the L cingulum, splenium of corpus callosum, superior longitudinal fasciculi, uncinate fasciculi, inferior fronto-occipital fasciculi
Hirshfeld-Becker et al.	2019	FHR = 15 (N/A) FLR = 8 (N/A)	FHR = 10.9 (1.51) FLR = 11.3 (1.84)	depression: Structured clinical interview for DSM-IV	Resting State fMRI	ACC	↑ Connectivity between subgenual ACC and inferior parietal lobule
Fischer et al.	2018	FHR = 20 (20) FLR = 25 (25)	FHR = 18.94 (2.62) FLR = 18.99 (2.61)	Maternal depression: Structured clinical interview for DSM-IV	Resting State fMRI	Limbic regions, ECN, SN	↑ Connectivity between amygdala and PFC ↑ Connectivity within SN ↑ Connectivity within CCN

Singh et al.	2018	FHR = 39 (21) FLR = 39 (24)	FHR = 13.93 (2.38) FLR = 13.85 (2.45)	Parental depression: Structured clinical interview for DSM-IV, FIGS	Resting State fMRI	Amygdala, ACC, PFC	↓ Connectivity between amygdala and R PFC ↓ Connectivity between amygdala and precuneus
Singh et al.	2018	FHR = 49 (22) FLR = 31 (26)	FHR = 12.98 (2.62) FLR = 12.55 (3.04)	Parental depression: Structured clinical interview for DSM-IV	Resting State fMRI	PCC	↓ Connectivity between PCC and BL amygdala, hippocampus
Chai et al.	2016	FHR = 27 (13) FLR = 16 (8)	FHR = 11.2 (1.67) FLR = 11.3 (2.14)	Parental depression: Structured clinical interview for DSM-IV	Resting State fMRI	Limbic regions, DMN, CCN	↑ Connectivity between DMN and subgenual ACC ↑ Connectivity between amygdala and R inferior frontal gyrus ↓ Connectivity between L DPLFC and subgenual ACC ↓ Connectivity within CCN
Frost Bellgowan et al	2015	FHR = 16 (8) FLR = 18 (9)	FHR = 13.2 (.7) FLR = 12.6 (.7)	Maternal depression: Structured clinical interview for DSM-IV	Resting State fMRI	DMN, SN	↓ Connectivity between DMN and R ventral striatum, BL postcentral gyri and R posterior insular cortex
Clasen et al.	2014	FHR = 11 (11) FLR = 13 (13)	FHR = 13.82 (.75) FLR = 13.54 (.88)	Parental depression: Structured clinical interview for DSM-IV	Resting State fMRI	CCN	↓ Connectivity between R inferior frontal gyrus and R dorsolateral PFC, BL medial PFC
Fischer et al.	2019	FHR = 17 (17) FLR = 18 (18)	FHR = 18.74 (2.47) FLR = 19.09 (2.93)	Maternal depression: Unspecified	Reward processing fMRI	Striatum	↓ Activation of striatum during reward anticipation ↑ Activation of middle frontal gyrus during reward anticipation ↓ Activation of superior frontal gyrus and cuneus during reward

Colich et al.	2017	FHR = 15 (15) FLR = 23 (23)	FHR = 12.83 (1.57) FLR = 13.07 (1.36)	Maternal depression: Structured clinical interview for DSM-IV	Reward processing fMRI	Whole brain	↓ Activation of putamen to loss
Olino et al.	2015	Total = 33 (19)	Total = 12.98 (2.14)	Parental depression: Structured clinical interview for DSM-IV	Reward processing fMRI	Whole brain, striatum	↓ Activation of ventral striatum and ACC to reward
Olino et al.	2014	FHR = 14 (11) FLR = 12 (8)	FHR = 15.85 (3.09) FLR = 15.58 (2.59)	Parental depression: Structured clinical interview for DSM-IV	Reward processing fMRI	Whole brain	↓ Activation of striatum during reward anticipation
Sharp et al.	2014	FHR = 19 (19) FLR = 19 (19)	FHR = 13 (1.92) FLR = 13.71 (1.85)	Maternal depression: Structured clinical interview for DSM-IV	Reward processing fMRI	Striatum	↓ Activation of R ventral striatum to reward
Gotlib et al.	2010	FHR = 13 (13) FLR = 13 (13)	FHR = 12.2 (1.7) FLR = 12.7 (1.4)	Maternal depression: Structured clinical interview for DSM-IV	Reward processing fMRI	Striatum, insula, ACC	↓ Activation of putamen and L insula during reward anticipation ↑ Activation of R insula during reward anticipation ↑ Activation of dorsal ACC to loss
Pilhatsch et al.	2014	FHR = 28 (15) FLR = 136 (68)	FHR = 14.54 (.33) FLR = 14.56 (.33)	Parental depression: Unspecified	Emotion regulation fMRI	Amygdala	↑ Activation of amygdala to negative stimuli
Joormann et al.	2012	FHR = 20 (N/A) FLR = 27 (N/A)	FHR = 11.9 (1.21) FLR = 11.74 (1.29)	Maternal depression: Structured clinical interview for DSM-IV	Emotion regulation fMRI	Limbic regions, PFC, ACC	↑ Activation of L ventrolateral PFC during sad mood induction ↓ Activation of dorsolateral PFC and ACC during mood regulation

Mannie et al.	2011	FHR = 28 (16) FLR = 28 (13)	FHR = 18.79 (1.4) FLR = 19.68 (1.44)	Parental depression: Reported by participant	Emotion regulation fMRI	Whole brain	↓ Activation in L dorsolateral PFC to fearful faces
D. Young Adulthood (19 – 25)							
Ozalay et al.	2016	FHR = 24 (24) FHR = 24 (24)	FHR = 22.3 (2.1) FLR = 22.1 (2.1)	Maternal depression: Structured clinical interview for DSM-IV	Cortical structure	Fronto-limbic regions	↓ Volume and thickness of temporoparietal and dorsomedial PFC
Durmusoglu et al.	2018	FHR = 27 (27) FLR = 26 (26)	FHR = 22.3 (2.1) FLR = 22.1 (2.1)	Maternal depression: Structured clinical interview for DSM-IV	Subcortical gray matter structure	Hippocampus	= Hippocampal volume ↓ CA-1 region
Simsek et al.	2017	FHR = 16 (16) FLR = 15 (15)	FHR = 21.94 (2.32) FLR = 22.53 (1.8)	Maternal depression: specified	Emotion regulation fMRI	Amygdala, PFC	= No significant differences
Mannie et al.	2008	FHR = 18 (9) FLR = 16 (10)	FHR = 19.8 (.9) FLR = 19.9 (.7)	Parental depression: Reported by participant	Emotion regulation fMRI	ACC	= Activation in ACC to negative, neutral and positive stimuli

Note: ↑ Represents an increase. ↓ Represents a decrease. = Represents no significant difference.

APPENDIX C: PARTICIPANT DESCRIPTIVE STATISTICS

Table 2

Descriptive Statistics of Participants, including Age, Sex, IQ, SES and Scan Time Frequency.

Variable	Group	
	High Risk (*n* = 53)	Low Risk (*n* = 59)
Age (in years) *M* (SD)	11.69 (2)	12.07 (1.98)
Sex (%) Female	23 (43.4)	34 (57.6)
IQ *M* (SD)	105.22 (12.74)	108.77 (12.53)
SES *M* (SD)	3.11 (1.38)	3.78 (1.02)
BMI *M* (SD)	20.73 (4.42)	19.68 (3.97)
Scan Times *n* (%)	High Risk (*n* = 111)	Low Risk (*n* = 105)
Baseline	53 (47.7)	59 (55.1)
Long-term	34 (30.6)	32 (30.4)
Short-term	24 (21.6)	14 (13.3)

Note: Due to 6 missing IQ values, the mean is averaged across 51 high-risk and 55 low-risk participants. Due to 18 missing BMI values, the mean is averaged across 46 high-risk and 48 low-risk participants.

APPENDIX D: INTRACORTICAL MYELIN DESCRIPTIVE STATISTICS

Table 3

Descriptive Statistics of Intracortical Myelination by Family History Group for all Scan Times (N=216).

Variable	Group	
	High Risk (*N* = 111)	Low Risk (*N* = 105)
Global ICM *M* (SD)	1.28 (0.21)	1.23 (0.22)
Hemisphere *M* (SD)		
Right Hemisphere	1.27 (0.21)	1.22 (0.23)
Left Hemisphere	1.28 (0.2)	1.24 (0.22)
LPFC ICM *M* (SD)	1.17 (0.2)	1.13 (0.21)
Hemisphere *M* (SD)		
Right Hemisphere	1.14 (0.21)	1.1 (0.21)
Left Hemisphere	1.2 (0.2)	1.16 (0.22)

APPENDIX E: HYPOTHESIS 1 LINEAR MIXED MODELS

Table 4

Linear Mixed Model Results for Family History Group Predicting Intracortical Myelin, Controlled for Fixed Effects of Age and Sex and Nested Random Effects of Family (fid) and Individual (pscan_id).

	Total Intracortical Myelin			Right Hemisphere			Left Hemisphere		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	0.86	0.67 – 1.05	**<0.001**	0.83	0.63 – 1.03	**<0.001**	0.89	0.70 – 1.08	**<0.001**
Group	0.06	-0.01 – 0.13	0.071	0.06	-0.01 – 0.13	0.081	0.06	-0.00 – 0.13	0.064
Age	0.03	0.01 – 0.04	**<0.001**	0.03	0.02 – 0.05	**<0.001**	0.03	0.01 – 0.04	**<0.001**
Sex	0.01	-0.05 – 0.07	0.683	0.01	-0.05 – 0.08	0.663	0.01	-0.05 – 0.07	0.710
Random Effects									
σ^2	0.03			0.04			0.03		
$\tau_{00\ fid}$	0.00			0.00			0.00		
$\tau_{00\ pscan\_id}$	0.01			0.01			0.01		
N_{pscan_id}	112			112			112		
N_{fid}	77			77			77		

Note: 216 observations each for total intracortical myelin, right hemisphere, and left hemisphere analyses. Marginal R^2 is .103 for total intracortical myelin. Marginal R^2 is .106 for right hemisphere. Marginal R^2 is .099 for left hemisphere.

APPENDIX F: SENSITIVITY ANALYSIS FOR HYPOTHESIS 1

Table 5

Sensitivity Analysis for Family History Group Predicting Intracortical Myelin, Controlled for Fixed Effects of Age, Sex, IQ, SES and BMI, and Nested Random Effects of Family (fid) and Individual (pscan_id).

	Total Intracortical Myelin			Right Hemisphere			Left Hemisphere		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	0.65	0.31 – 0.99	**<0.001**	0.61	0.26 – 0.96	**0.001**	0.69	0.35 – 1.03	**<0.001**
Group	0.04	-0.03 – 0.11	0.251	0.04	-0.03 – 0.11	0.253	0.04	-0.03 – 0.11	0.253
Age	0.01	-0.01 – 0.03	0.230	0.01	-0.01 – 0.03	0.182	0.01	-0.01 – 0.03	0.293
Sex	0.01	-0.06 – 0.07	0.868	0.01	-0.06 – 0.07	0.862	0.00	-0.06 – 0.07	0.877
IQ	0.00	-0.00 – 0.00	0.217	0.00	-0.00 – 0.00	0.199	0.00	-0.00 – 0.00	0.244
SES	-0.01	-0.04 – 0.01	0.290	-0.01	-0.04 – 0.01	0.279	-0.01	-0.04 – 0.01	0.308
BMI	0.01	0.01 – 0.02	**<0.001**	0.01	0.01 – 0.02	**<0.001**	0.01	0.01 – 0.02	**<0.001**
Random Effects									
σ^2	0.03			0.04			0.03		
$\tau_{00\ fid}$	0.00			0.00			0.00		
$\tau_{00\ scan\_time}$	0.00			0.00			0.00		
N_{scan_time}	97			97			97		
N_{fid}	68			68			68		

Note: 186 observations each for total intracortical myelin, right hemisphere, and left hemisphere analyses. Marginal R^2 is .185 for total intracortical myelin. Marginal R^2 is .183 for right hemisphere. Marginal R^2 is .186 for left hemisphere.

APPENDIX G: HYPOTHESIS 2 LINEAR MIXED MODELS

Table 6

Linear Mixed Model Results for Family History Group Predicting Lateral Prefrontal Cortex Intracortical Myelin, Controlled for Fixed Effects of Age and Sex and Nested Random Effects of Family (fid) and Individual (pscan_id).

	Total LPFC Myelin			Right LPFC			Left LPFC		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	0.82	0.63 – 1.01	**<0.001**	0.76	0.57 – 0.95	**<0.001**	0.88	0.69 – 1.07	**<0.001**
Group	0.05	-0.01 – 0.11	0.109	0.06	-0.01 – 0.12	0.085	0.05	-0.02 – 0.11	0.150
Age	0.02	0.01 – 0.04	**0.001**	0.03	0.01 – 0.04	**<0.001**	0.02	0.01 – 0.04	**0.003**
Sex	0.01	-0.04 – 0.07	0.630	0.02	-0.04 – 0.08	0.459	0.01	-0.05 – 0.07	0.832
Random Effects									
σ^2	0.04			0.04			0.04		
$\tau_{00\ fid}$	0.00			0.00			0.00		
$\tau_{00\ scan\_time}$	0.01			0.01			0.01		
N_{scan_time}	112			112			112		
N_{fid}	77			77			77		

Note: 214 observations each for total LPFC, right LPFC, and left LPFC analyses. Marginal R^2 is .071 for total LPFC. Marginal R^2 is .08 for right LPFC. Marginal R^2 is .06 for left LPFC.

APPENDIX H: SENSITIVITY ANALYSIS FOR HYPOTHESIS 2

Table 7

Sensitivity Analysis for Family History Group Predicting LPFC Intracortical Myelin, Controlled for Fixed Effects of Age, Sex, IQ, SES and BMI, and Nested Random Effects of Family (fid) and Individual (pscan_id).

	Total LPFC Myelin			Right LPFC			Left LPFC		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	0.65	0.31 – 0.98	**<0.001**	0.57	0.24 – 0.91	**0.001**	0.72	0.37 – 1.06	**<0.001**
Group	0.04	-0.03 – 0.10	0.235	0.04	-0.02 – 0.11	0.181	0.04	-0.03 – 0.10	0.314
Age	0.01	-0.01 – 0.02	0.443	0.01	-0.01 – 0.03	0.280	0.00	-0.01 – 0.02	0.650
Sex	0.01	-0.05 – 0.07	0.781	0.02	-0.04 – 0.07	0.619	0.00	-0.06 – 0.06	0.941
IQ	0.00	-0.00 – 0.00	0.304	0.00	-0.00 – 0.00	0.271	0.00	-0.00 – 0.00	0.358
SES	-0.01	-0.03 – 0.02	0.547	-0.01	-0.03 – 0.02	0.533	-0.01	-0.03 – 0.02	0.578
BMI	0.01	0.01 – 0.02	**<0.001**	0.01	0.01 – 0.02	**<0.001**	0.01	0.01 – 0.02	**<0.001**
Random Effects									
σ^2	0.04			0.04			0.04		
$\tau_{00\ fid}$	0.00			0.00			0.00		
$\tau_{00\ scan\_time}$	0.00			0.00			0.00		
N_{scan_time}	97			97			97		
N_{fid}	68			68			68		

Note: 186 observations each for total LPFC, right LPFC, and left LPFC analyses. Marginal R^2 is .13 for total LPFC. Marginal R^2 is .136 for right LPFC. Marginal R^2 is .121 for left LPFC.

APPENDIX I: GLOBAL INTRACORTICAL MYELIN IN BOYS

Table 8

Linear Mixed Model Results for Family History Group Predicting Intracortical Myelin, Controlled for Fixed Effects of Age and Nested Random Effects of Family (fid) and Individual (pscan_id) in Boys

	Total Intracortical Myelin			Right Hemisphere			Left Hemisphere		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	0.81	0.56 – 1.07	**<0.001**	0.77	0.51 – 1.03	**<0.001**	0.86	0.60 – 1.11	**<0.001**
Group	0.10	0.01 – 0.19	**0.023**	0.11	0.02 – 0.19	**0.020**	0.10	0.01 – 0.18	**0.030**
Age	0.03	0.01 – 0.05	**0.002**	0.03	0.01 – 0.05	**0.001**	0.03	0.01 – 0.05	**0.005**
Random Effects									
σ^2	0.03			0.03			0.03		
$\tau_{00\ fid}$	0.00			0.00			0.00		
$\tau_{00\ scan\_time}$	0.01			0.01			0.01		
N_{scan_time}	55			55			55		
N_{fid}	49			49			49		

Note: 104 observations each for total intracortical myelin, right hemisphere, and left hemisphere analyses. Marginal R^2 is .171 for total intracortical myelin. Marginal R^2 is .186 for right hemisphere. Marginal R^2 is .154 for left hemisphere.

APPENDIX J: SENSITIVITY ANALYSIS OF GLOBAL INTRACORTICAL MYELIN IN BOYS

Table 9

Sensitivity Analysis for Family History Group Predicting Intracortical Myelin, Controlled for Fixed Effects of Age, IQ, SES and BMI, and Nested Random Effects of Family (fid) and Individual (pscan_id) in Boys.

	Total Intracortical Myelin			Right Hemisphere			Left Hemisphere		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	0.83	0.38 – 1.27	**<0.001**	0.77	0.33 – 1.22	**0.001**	0.88	0.43 – 1.33	**<0.001**
Group	0.08	-0.01 – 0.17	0.080	0.09	-0.00 – 0.18	0.054	0.07	-0.02 – 0.16	0.120
Age	0.02	-0.00 – 0.04	0.052	0.02	0.00 – 0.05	**0.030**	0.02	-0.00 – 0.04	0.091
IQ	-0.00	-0.00 – 0.00	0.581	-0.00	-0.00 – 0.00	0.620	-0.00	-0.00 – 0.00	0.547
SES	-0.01	-0.04 – 0.02	0.473	-0.01	-0.04 – 0.02	0.451	-0.01	-0.04 – 0.02	0.506
BMI	0.01	0.00 – 0.02	**0.041**	0.01	0.00 – 0.02	**0.044**	0.01	0.00 – 0.02	**0.039**
Random Effects									
σ^2	0.03			0.03			0.03		
$\tau_{00\ fid}$	0.00			0.00			0.00		
$\tau_{00\ scan\_time}$	0.00			0.00			0.00		
N_{scan_time}	48			48			48		
N_{fid}	44			44			44		

Note: 90 observations each for total LPFC, right LPFC, and left LPFC analyses. Marginal R^2 is .22 for total LPFC. Marginal R^2 is .24 for right LPFC. Marginal R^2 is .21 for left LPFC.

APPENDIX K: GLOBAL INTRACORTICAL MYELIN IN GIRLS

Table 10

Linear Mixed Model Results for Family History Group Predicting Intracortical Myelin, Controlled for Fixed Effects of Age and Nested Random Effects of Family (fid) and Individual (pscan_id) in Girls

	Total Intracortical Myelin			Right Hemisphere			Left Hemisphere		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	0.93	0.65 – 1.21	**<0.001**	0.92	0.63 – 1.21	**<0.001**	0.94	0.67 – 1.21	**<0.001**
Group	0.01	-0.08 – 0.11	0.788	0.01	-0.09 – 0.10	0.916	0.02	-0.07 – 0.11	0.662
Age	0.03	0.00 – 0.05	**0.020**	0.03	0.00 – 0.05	**0.021**	0.03	0.00 – 0.05	**0.019**
Random Effects									
σ^2	0.04			0.04			0.04		
$\tau_{00\ fid}$	0.00			0.00			0.00		
$\tau_{00\ scan\_time}$	0.01			0.01			0.01		
N_{scan_time}	57			57			57		
N_{fid}	45			45			45		

Note: 112 observations each for total intracortical myelin, right hemisphere, and left hemisphere analyses. Marginal R^2 is .05 for total intracortical myelin. Marginal R^2 is .049 for right hemisphere. Marginal R^2 is .05 for left hemisphere.

APPENDIX L: SENSITIVITY ANALYSIS OF GLOBAL INTRACORTICAL MYELIN IN GIRLS

Table 11

Sensitivity Analysis for Family History Group Predicting Intracortical Myelin, Controlled for Fixed Effects of Age, IQ, SES and BMI, and Nested Random Effects of Family (fid) and Individual (pscan_id) in Girls.

	Total Intracortical Myelin			Right Hemisphere			Left Hemisphere		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	0.37	-0.14 – 0.88	0.158	0.35	-0.17 – 0.87	0.186	0.39	-0.12 – 0.89	0.133
Group	-0.04	-0.13 – 0.06	0.467	-0.04	-0.14 – 0.05	0.365	-0.03	-0.12 – 0.07	0.585
Age	-0.01	-0.04 – 0.02	0.502	-0.01	-0.04 – 0.02	0.467	-0.01	-0.03 – 0.02	0.543
IQ	0.01	0.00 – 0.01	**0.003**	0.01	0.00 – 0.01	**0.003**	0.01	0.00 – 0.01	**0.004**
SES	-0.02	-0.06 – 0.02	0.299	-0.02	-0.06 – 0.02	0.288	-0.02	-0.06 – 0.02	0.311
BMI	0.02	0.01 – 0.03	**<0.001**	0.02	0.01 – 0.03	**<0.001**	0.02	0.01 – 0.03	**<0.001**
Random Effects									
σ^2	0.04			0.04			0.03		
$\tau_{00\ fid}$	0.00			0.00			0.00		
$\tau_{00\ scan\_time}$	0.00			0.00			0.00		
N_{scan_time}	49			49			49		
N_{fid}	38			38			38		

Note: 96 observations each for total LPFC, right LPFC, and left LPFC analyses. Marginal R^2 is .23 for total LPFC. Marginal R^2 is .23 for right LPFC. Marginal R^2 is .23 for left LPFC.

APPENDIX M: LPFC INTRACORTICAL MYELIN IN BOYS

Table 12

Linear Mixed Model Results for Family History Group Predicting Lateral Prefrontal Cortex Intracortical Myelin, Controlled for Fixed Effects of Age and Nested Random Effects of Family (fid) and Individual (pscan_id) in Boys.

	Total LPFC Myelin			Right LPFC			Left LPFC		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	0.79	0.54 – 1.04	**<0.001**	0.73	0.47 – 0.99	**<0.001**	0.86	0.60 – 1.11	**<0.001**
Group	0.09	0.00 – 0.17	**0.041**	0.10	0.01 – 0.19	**0.030**	0.08	-0.01 – 0.16	0.072
Age	0.03	0.01 – 0.05	**0.012**	0.03	0.01 – 0.05	**0.008**	0.02	0.00 – 0.04	**0.027**
Random Effects									
σ^2	0.03			0.03			0.04		
$\tau_{00\ fid}$	0.00			0.00			0.00		
$\tau_{00\ scan\_time}$	0.01			0.01			0.00		
N_{scan_time}	55			55			55		
N_{fid}	49			49			49		

Note: 104 observations each for total LPFC, right LPFC, and left LPFC analyses. Marginal R^2 is .125 for total LPFC. Marginal R^2 is .153 for right LPFC. Marginal R^2 is .094 for left LPFC.

APPENDIX N: SENSITIVITY ANALYSIS OF LPFC INTRACORTICAL MYELIN IN BOYS

Table 13

Sensitivity Analysis for Family History Group Predicting LPFC Intracortical Myelin, Controlled for Fixed Effects of Age, IQ, SES and BMI, and Nested Random Effects of Family (fid) and Individual (pscan_id) in Boys.

	Total LPFC Myelin			Right LPFC			Left LPFC		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	0.83	0.39 – 1.28	**<0.001**	0.73	0.30 – 1.17	**0.001**	0.93	0.46 – 1.40	**<0.001**
Group	0.08	-0.01 – 0.17	0.098	0.09	-0.00 – 0.17	0.056	0.07	-0.03 – 0.16	0.179
Age	0.02	-0.00 – 0.04	0.100	0.02	0.00 – 0.04	**0.043**	0.01	-0.01 – 0.04	0.219
IQ	-0.00	-0.00 – 0.00	0.519	-0.00	-0.00 – 0.00	0.593	-0.00	-0.00 – 0.00	0.470
SES	-0.00	-0.03 – 0.03	0.879	-0.00	-0.03 – 0.03	0.875	-0.00	-0.04 – 0.03	0.902
BMI	0.01	-0.00 – 0.02	0.190	0.01	-0.00 – 0.02	0.203	0.01	-0.00 – 0.02	0.195
Random Effects									
σ^2	0.03			0.03			0.03		
$\tau_{00\ fid}$	0.00			0.00			0.00		
$\tau_{00\ scan\_time}$	0.00			0.00			0.00		
N_{scan_time}	48			48			48		
N_{fid}	44			44			44		

Note: 90 observations each for total LPFC, right LPFC, and left LPFC analyses. Marginal R^2 is .157 for total LPFC. Marginal R^2 is .188 for right LPFC. Marginal R^2 is .124 for left LPFC.

APPENDIX O: LPFC INTRACORTICAL MYELIN IN GIRLS

Table 14

Linear Mixed Model Results for Family History Group Predicting Lateral Prefrontal Cortex Intracortical Myelin, Controlled for Fixed Effects of Age and Nested Random Effects of Family (fid) and Individual (pscan_id) in Girls

	Total LPFC Myelin			Right LPFC			Left LPFC		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	0.88	0.61 – 1.16	**<0.001**	0.85	0.57 – 1.13	**<0.001**	0.91	0.63 – 1.19	**<0.001**
Group	0.01	-0.08 – 0.10	0.850	0.00	-0.09 – 0.09	0.931	0.01	-0.08 – 0.10	0.773
Age	0.02	0.00 – 0.04	**0.049**	0.02	0.00 – 0.04	**0.046**	0.02	-0.00 – 0.04	0.055
Random Effects									
σ^2	0.04			0.04			0.04		
$\tau_{00\ fid}$	0.00			0.00			0.00		
$\tau_{00\ scan\_time}$	0.01			0.00			0.01		
N_{scan_time}	57			57			57		
N_{fid}	45			45			45		

Note: 112 observations each for total LPFC, right LPFC, and left LPFC analyses. Marginal R^2 is .04 for total LPFC. Marginal R^2 is .04 for right LPFC. Marginal R^2 is .038 for left LPFC.

APPENDIX P: SENSITIVITY ANALYSIS OF LPFC INTRACORTICAL MYELIN IN GIRLS

Table 15

Sensitivity Analysis for Family History Group Predicting LPFC Intracortical Myelin, Controlled for Fixed Effects of Age, IQ, SES and BMI, and Nested Random Effects of Family (fid) and Individual (pscan_id) in Girls.

	Total LPFC Myelin			Right LPFC			Left LPFC		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	0.41	-0.08 – 0.90	0.102	0.37	-0.12 – 0.87	0.140	0.44	-0.06 – 0.94	0.088
Group	-0.03	-0.12 – 0.06	0.491	-0.03	-0.12 – 0.06	0.483	-0.03	-0.12 – 0.06	0.521
Age	-0.01	-0.04 – 0.01	0.281	-0.01	-0.04 – 0.01	0.296	-0.01	-0.04 – 0.01	0.282
IQ	0.01	0.00 – 0.01	**0.007**	0.01	0.00 – 0.01	**0.007**	0.01	0.00 – 0.01	**0.008**
SES	-0.02	-0.05 – 0.02	0.387	-0.02	-0.05 – 0.02	0.389	-0.02	-0.05 – 0.02	0.405
BMI	0.02	0.01 – 0.03	**<0.001**	0.02	0.01 – 0.03	**<0.001**	0.02	0.01 – 0.03	**<0.001**
Random Effects									
σ^2	0.04			0.04			0.04		
$\tau_{00\ fid}$	0.00			0.00			0.00		
$\tau_{00\ scan\_time}$	0.00			0.00			0.00		
N_{scan_time}	49			49			49		
N_{fid}	38			38			38		

Note: 96 observations each for total LPFC, right LPFC, and left LPFC analyses. Marginal R^2 is .187 for total LPFC. Marginal R^2 is .185 for right LPFC. Marginal R^2 is .186 for left LPFC.

APPENDIX Q: PRISMA FLOW DIAGRAM

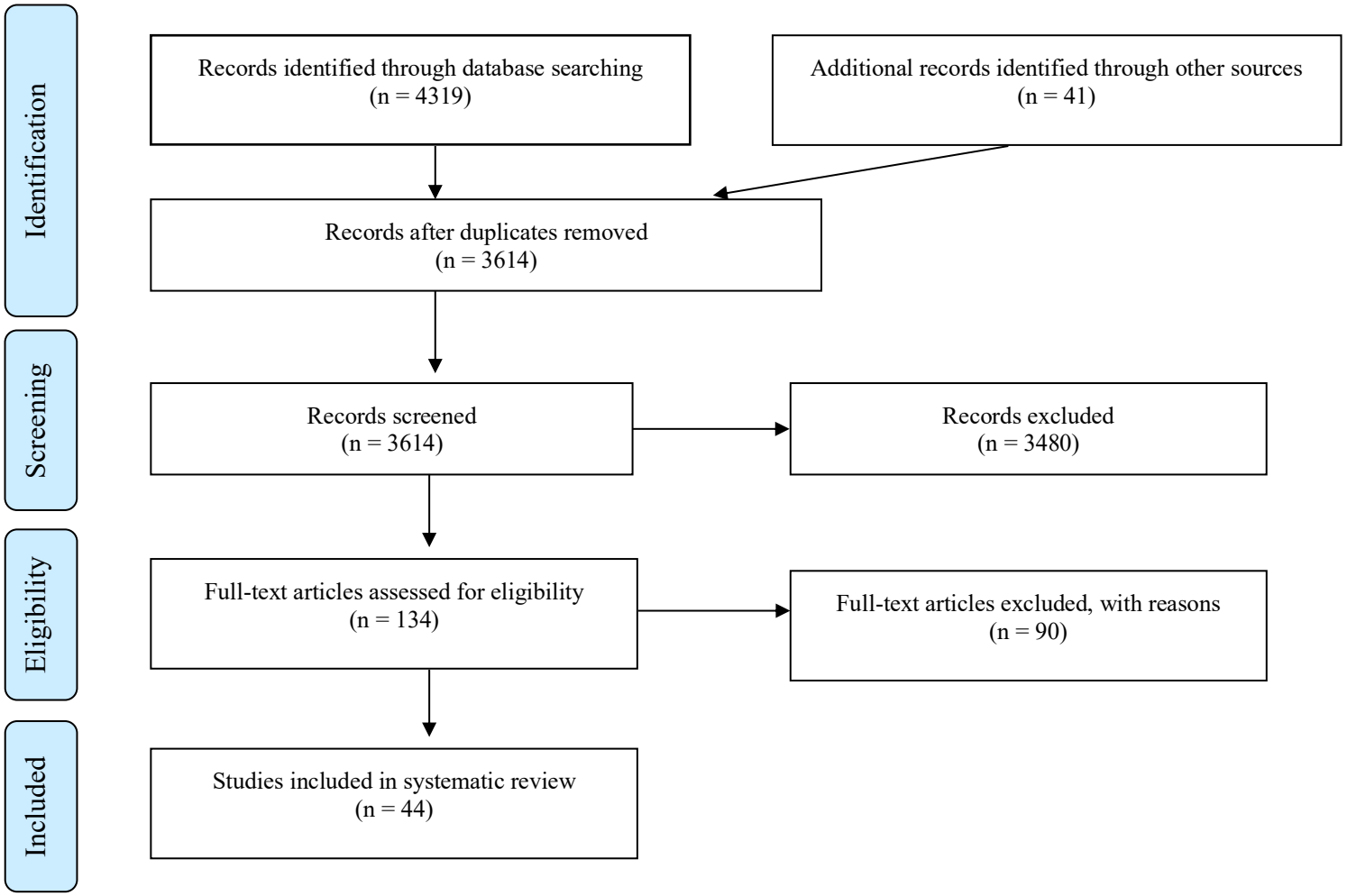


Figure 1. Systematic review PRISMA flow diagram for study selection

APPENDIX R: BRAIN STRUCTURE IN FAMILIAL HIGH-RISK YOUTH

	Familial High Risk				Depression
Brain Structure	**Infancy**	**Childhood**	**Adolescence**	**Early Adulthood**	**Adults**
Cortical Thickness	No data	Reduced	Reduced	Reduced	Reduced
Cortical Surface Area	No data	Increased	No data	No change	No change
Amygdala Volume	No change	Inconsistent	Increased	No data	Inconsistent
Hippocampal Volume	No data	Reduced	Reduced	No change	Reduced
CA1 of Hippocampus	No data	Reduced	No data	Reduced	Reduced
Thalamic Volume	Increased	No data	No change	No data	Reduced
White Matter FA	Reduced	No data	Reduced	No data	Reduced

Figure 2. Structural brain changes in high familial risk offspring across age compared to MDD adults.

	Familial High Risk				Depression
Brain Function	**Infancy**	**Childhood**	**Adolescence**	**Early Adulthood**	**Adults**
Resting State					
Amygdala - PFC	Inconsistent	Reduced	Inconsistent	No data	Inconsistent
DMN	No data	No data	Inconsistent	No data	Inconsistent
CCN	No data	No data	Reduced	No data	Reduced
Reward Processing					
Striatum - Reward Anticipation	No data	No data	Reduced	No data	Reduced
Striatum - Reward	No data	Inconsistent	Reduced	No data	Reduced
Emotion Processing					
Amygdala - Negative Stimuli	No data	Increased	Inconsistent	No change	Inconsistent

Figure 3. Functional brain changes in high familial risk offspring across age compared to MDD adults.

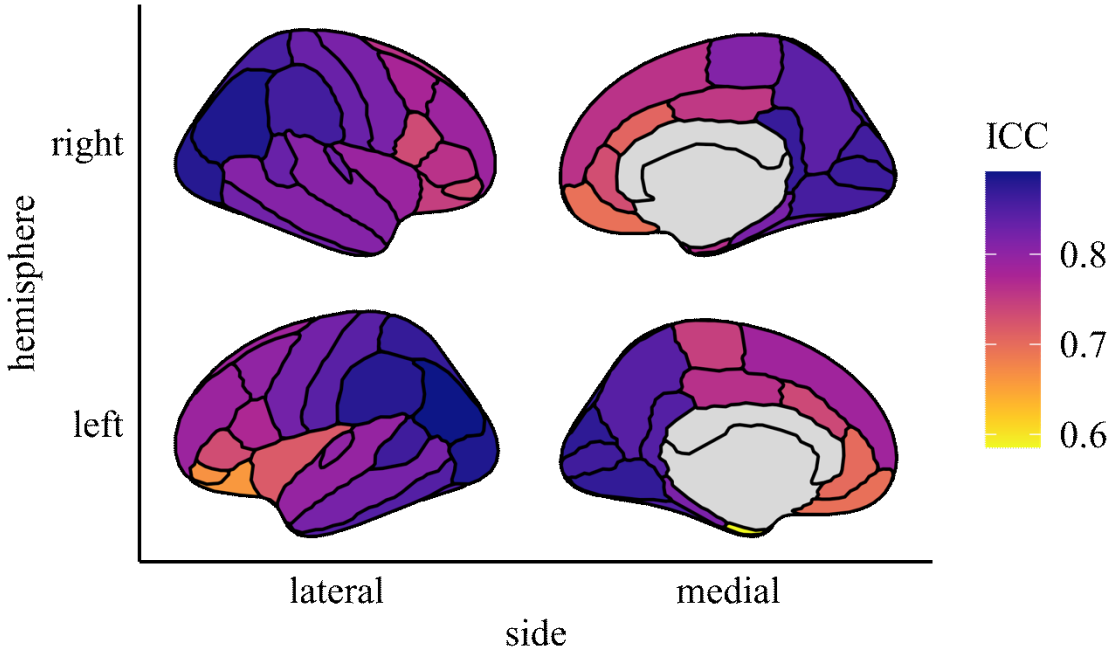


Figure 4. Intracortical myelination test-retest reliability

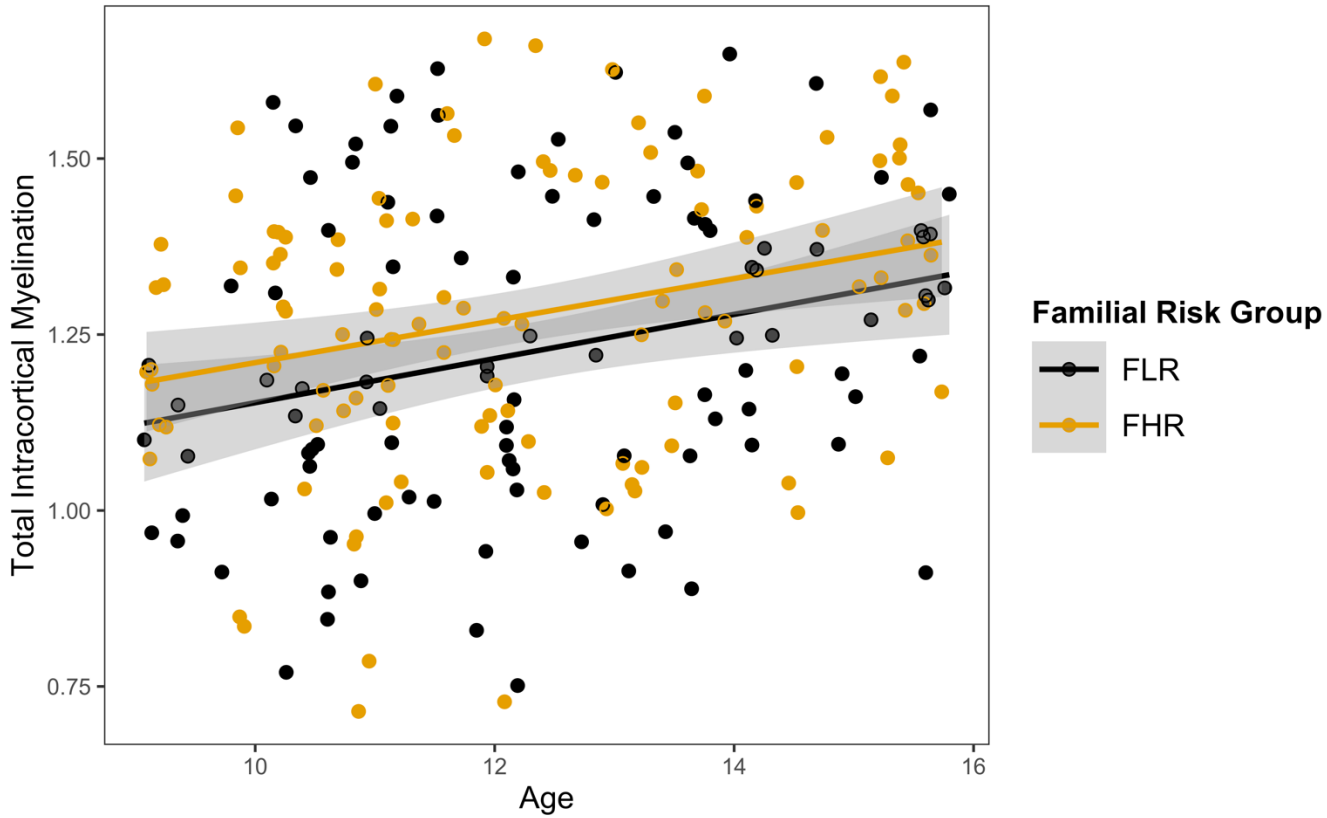


Figure 5. Total intracortical myelin across age with 95% CI.

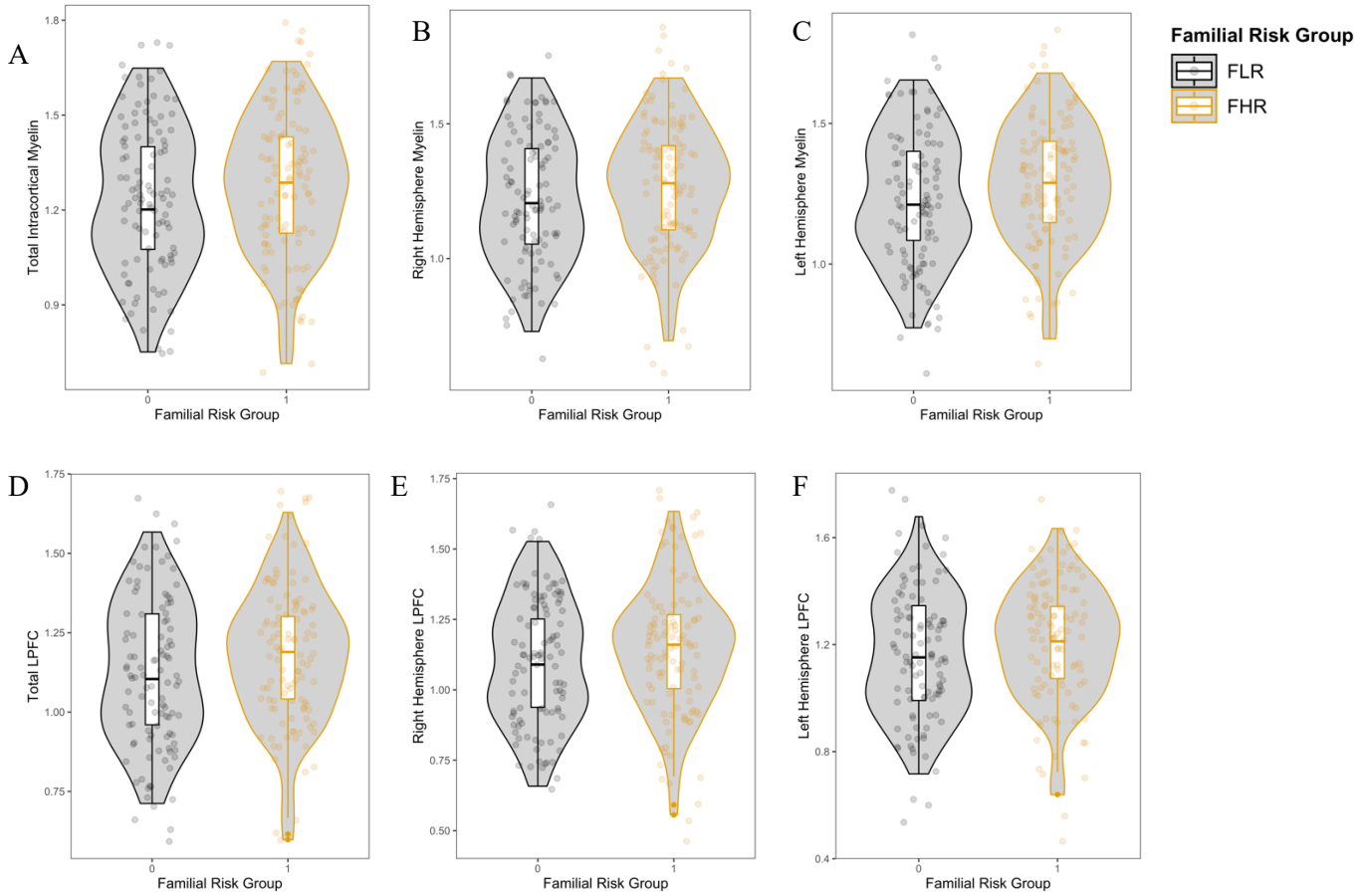


Figure 6. Intracortical myelin in FHR and FLR youth across the entire cortex (A), right (B) and left (C) hemispheres and across the total (D) right (E) and left (F) lateral prefrontal cortex.