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Neuroimaging Depression Risk in a Sample of Never-Depressed Children

Matthew R. J. Vandermeer, *The University of Western Ontario*

Supervisor: Hayden, Elizabeth P., *The University of Western Ontario*

A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Psychology

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Abstract

Children of mothers with a history of depression are at significantly higher risk for developing depression themselves. Although numerous mechanisms explaining this relationship have been proposed (Goodman & Gotlib, 1999), relatively little is known about the neural substrates of never-depressed children's depression risk. Of the few studies that have used neuroimaging techniques to characterize risk-based differences in children's neural structure, function, and functional connectivity, most have used samples that include participants with a personal history of depression or older samples (i.e., past the typical age of onset for depressive disorders). These approaches limit what can be determined regarding whether findings are true markers of risk (and potential etiological mechanisms) or better reflect resilience to depression or brain-based sequelae of depression. There is a clear need to better characterize children's neuroimaging-based markers of depression risk by focusing on samples with clear statistical risk (i.e., a maternal history of depression or early emerging depression symptoms) *prior* to their own onset of disorder. This dissertation addresses this gap in the literature by characterizing the association between a sample ($Ns = 80-85$) of never-depressed children's risk for depression and magnetic resonance imaging (MRI) markers of children's brain structure (Study 1), functional response to maternal feedback (Study 2), and resting-state functional connectivity (Study 3). Main findings included never-depressed children's self-reported depression symptoms being negatively associated with grey matter volume in regions relevant to reward processing (i.e., orbitofrontal cortex; Study 1), functional activity in salience processing regions (i.e., anterior insula) and reward processing (i.e., putamen) during critical maternal feedback (Study 2), and resting-state functional connectivity within the Central Executive Network and Salience

Network (Study 3). I also demonstrated that children with high maternal risk for depression (i.e., a maternal history of depression) had significantly increased resting-state functional connectivity within the default mode network. Results indicate that brain-based associates of depression risk (i.e., maternal history of depression and children's depression symptoms) pre-exist the development of depression, potentially contributing to the etiology of depression. Future directions for the emerging field of neuroimaging children's risk for depression are discussed.

KEYWORDS: Depression; Voxel-based morphometry; fMRI; resting-state; Maternal history; Pre-adolescence; Risk

Summary for Lay Audience

Depression is among the most common mental health problems and one of the leading causes of disability worldwide. In addition, it is often associated with profoundly negative outcomes at the level of the individual (i.e., relationship and occupational impairment, poor quality of life, early death). Although there are many factors which are associated with an increased risk for depression (e.g., familial history, female sex, certain cognitive styles, etc.), little is known about the mechanisms that cause depression.

Differences in the structure, function (i.e., activity), and connectivity of the brain are thought to contribute to the development of depression. Previous research has found that people with depression have differences in brain structure, function, and connectivity; however, as participants in these studies have already experienced depression, it is unclear whether brain-based associations contributed to the development of depression *or* were a consequence of depression. Using magnetic resonance imaging (MRI) techniques with a sample of never-depressed children, I investigated the associations between depression risk (i.e., a maternal history of depression, and both self- and maternal-reports of children's depression symptoms) and brain structure (Study 1), function during exposure to maternal praise and criticism (Study 2), and connectivity at rest (Study 3). Across all studies I found evidence that early emerging depression symptoms were associated with differences in never-depressed children's brains. Further, I found evidence that a maternal history of depression was associated with differences in brain connectivity at rest. These results have implications for our understanding of the neural mechanisms that contribute to the development of depression.

Co-authorship Statement

In addition to the primary author (Matthew R. J. Vandermeer), several co-authors are listed on the three manuscripts that comprise this doctoral dissertation, including: Dr. Pan Liu, Ola Mohamed Ali, Andrew R. Daoust, Dr. Marc F. Joannis, Dr. Deanna M. Barch, and Dr. Elizabeth P. Hayden.

As primary author of the three manuscripts, Mr. Vandermeer contributed to the design of MRI experiments, formulation of research questions and hypotheses, and collecting data. In addition, Mr. Vandermeer was responsible for analysis and interpretation of research data and preparation of the manuscripts. Dr. Hayden is the principal investigator on the longitudinal research project from which the data for this dissertation is derived. Furthermore, Dr. Hayden has served as my doctoral supervisor and has been essential in helping to formulate hypotheses, interpret results, and conceptualize findings in the context of extant research on depression risk. Dr. Liu, Dr. Joannis, Dr. Barch, and Ms. Mohamed Ali provided support in analyzing neuroimaging data and consultation for conceptualizing results. Ms. Mohamed Ali and Mr. Daoust assisted in data collection and data cleaning. Drs. Joannis and Barch provided early consultation on the design of MRI experiments and data collection. All co-authors supported manuscript development through review and editing.

Dedication

For Mark.

Although no longer with us, you live on in the lives of those who love you.

Thank you for helping to make me who I am.

Acknowledgements

The fact that I'm sitting down to write this continues to boggle my mind. I've heard it said many times that a PhD is a marathon, not a sprint. While there is some truth to this – it takes incredible endurance, you constantly question whether you're capable of finishing while doing it, and you finish the whole thing *very* tired – a marathon is a very solitary endeavour. Truth be told, I think the old adage of “it takes a village” is more applicable. Nobody who undertakes a PhD is able to complete it on their own, I am most certainly not an exception to this rule. That this dissertation bears my name as author does not capture the essential role of many others who made this possible. Although I will never be able to fully articulate the importance of the guidance, support, and love that I have been fortunate to receive over the course of writing my dissertation and completing my PhD, I would like to take the time to briefly acknowledge a few of those who made this possible.

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Chapter 1 – General Overview & Introduction

Depression is among the world's most prevalent mental disorders (James et al., 2018) with major depressive disorder (MDD) having annual and lifetime prevalence rates of approximately 10.4% and 20.6%, respectively (Hasin et al., 2018). Although sometimes referred to as the “common cold” of mental disorders, this analogy understates the oftentimes devastating impact depression has on both individuals and society. Indeed, global epidemiological research has repeatedly found depression to be the leading cause of disability due to mental disorder and among the leading causes of disability overall (James et al., 2018; Vos et al., 2012). Additionally, depression is associated with increased risk for both suicide (Bostwick & Pankratz, 2000; Turecki et al., 2019) and non-suicidal mortality (Cuijpers & Smit, 2002; Cuijpers et al., 2014; Mykletun et al., 2009), as well as a host of other negative outcomes (e.g., academic failure, marital discord and divorce, occupational impairment; Kessler, 2012).

The negative sequelae of depression underscore the value of understanding who is at greatest risk for the purposes of prevention and early intervention. Although multiple factors have been well established as robust markers of depression risk (e.g., female sex/gender, stressful life events, neuroticism; Gotlib & Hammen, 2015; Kendler, Gatz, Gardner, & Pedersen, 2006; Kuehner, 2003; Weissman & Klerman, 1977), these broad risk markers do little to speak to the causal mechanisms and processes through which risk operates. Unfortunately, psychopathology research has been relatively slow to identify robust mechanistic variables, in part due to the field's historical reliance on diagnostic constructs that reflect heterogeneous etiologies (Cuthbert & Insel, 2013; Insel et al., 2010); more specifically, as an outcome, depression is reached through a diverse array of causal environmental and biological pathways, exemplifying the notion of equifinality

(Cicchetti & Rogosch, 1996) and complicating the search for causal influences. In contrast, efforts aimed at identifying relatively parsimonious processes, or *endophenotypes* (i.e., intermediate phenotypes that mediate associations between genetic influence and complex behavioural phenotypes, such as depression and other disorders), through which risk factors eventuate in clinical disorder, are needed to understand the complex etiology of depression (Gottesman & Gould, 2003; Insel et al., 2010).

Neuroimaging research focused on features of the brain and their association with depression and depression risk has emerged as a key approach to identifying endophenotypes for depression (Gottesman & Gould, 2003; Hasler, Drevets, Manji, & Charney, 2004; Hasler & Northoff, 2011). Importantly, although brain structure, function, and functional connectivity are all interconnected and likely influence one another (i.e., neural structure is implicated in neural function and vice-versa; Honey, Thivierge, & Sporns, 2010; Suárez, Markello, Betzel, & Misic, 2020), these vantage points for the study of the brain are not redundant. Similarly, the study and measure of individual differences in neural aspects of depression vulnerability cannot and should not supplant indices of cognitive processes relevant to the etiology of the disorder. It is clear that, in order for research on neural aspects of depression vulnerability to progress, investigators must consider neural vulnerabilities from different levels of analysis (e.g., brain structure, function, and connectivity). In three original research studies, my dissertation characterizes the relationship between never-depressed children's risk for depression and putative neural endophenotypes of depression, including brain structure (Chapter 2; Study 1), functional responses to maternal feedback (Chapter 3; Study 2), and resting-state functional connectivity (Chapter 4; Study 3).

What follows (Chapter 1) is a brief overview of relevant findings from the literature on risk for depression. The primary goal of this overview is to position the relevant neuroimaging literature within a broader framework that accounts for how brain-based depression vulnerability is transmitted to the children of depressed mothers. Specifically, the early emerging neural substrates of depression vulnerability are likely only one component of a multi-level, probabilistic causal process that unfolds in the context of the early environment; therefore, I will briefly review the literature on the family processes and cognitive correlates that may mediate and/or moderate children's neural risk for depression.

Heritable and Environmental Interplay in Neural Vulnerability to Depression

Goodman and Gotlib's seminal developmental model, as described in *Psychological Review* (1999) and their seminal text *Children of Depressed Parents: Mechanisms of Risk and Implications for Treatment* (2002), has played a foundational role in the study of how risk is transmitted from depressed mothers to their children. In this model, Goodman and Gotlib (1999) argue that there are four main mechanisms through which risk to children may be transmitted: (a) heritability of depression; (b) innate dysfunctional neuroregulatory mechanisms; (c) exposure to negative maternal cognitions, behaviour, and affect; (d) environmental stressors related to being raised by a mother with depression.

A family history of depression is among the most widely studied markers of depression risk (Goodman & Gotlib, 1999; Joormann, Eugene, & Gotlib, 2009; Klein, Lewinsohn, Seeley, & Rohde, 2001). Meta-analytic research shows a heritability of approximately 37% for MDD (Sullivan, Neale, & Kendler, 2000). Although this is

relatively low compared to the heritability estimates of other mental health disorders (e.g., bipolar disorder and schizophrenia; Uher, 2009), it nevertheless suggests that a significant proportion of the variability in risk for depression is due to genetic factors. Indeed, studies report a three- to five-time increase in lifetime risk for depression in those with a parent with a history of MDD (Hammen, 2009; Weissman et al., 2006). A maternal history of depression appears to confer a particularly heightened risk for depression (Connell & Goodman, 2002; Goodman et al., 2011), likely due to both heritable factors and aspects of caregiving associated with maternal depression.

Aspects of the brain with relevance to depression, such as brain structure (Blokland, de Zubicaray, McMahon, & Wright, 2012; Jansen, Mous, White, & Posthuma, 2015), function (Blokland, de Zubicaray et al., 2012; Blokland, McMahon et al., 2008; Matthews et al., 2007), and connectivity (Colclough et al., 2017; Miranda-Dominguez et al., 2018) also have an established heritable basis. However, these neural factors operate in a probabilistic, rather than deterministic, manner in predicting depression. Put somewhat differently, it is exceedingly unlikely that heritable neural structure or function plays a direct, strong causal role in depression. Instead, heritable neural risk is most likely moderated and mediated by exposure to various environmental and relational stressors (Joormann et al., 2009) through gene-environment correlation (Jaffee & Price, 2007) and gene-environment interaction (Rutter, Moffitt, & Caspi, 2006). More specifically, with respect to gene-environment correlation, heritable aspects of depression are associated with the increased likelihood of exposure to adverse parenting and negative maternal cognitions, among other environmental hazards. In this way, children may inherit both brain vulnerabilities as well as environmental exposures to influences known to increase depression risk. With respect to gene-environment interaction, children's heritable neural

vulnerabilities may be potentiated through exposure to adverse environments, which may in turn influence how brain-based vulnerability is proximally mediated. For example, children's early emerging neural vulnerability may be exacerbated through exposure to adverse parenting or other stress exposures that increase the likelihood that children develop depressogenic cognitive styles, which serve as relative proximal, later-emerging markers of depression risk with neural underpinnings.

Exposure to negative maternal cognitions, behaviour, and affect. Children of depressed mothers are more regularly exposed to negative maternal cognitions, behaviour, and affect, relative to children without depressed mothers (Goodman, 2007; Lovejoy, Graczyk, O'Hare, & Neuman, 2000). In their meta-analysis of the relationship between maternal depression and parenting behaviour, Lovejoy and colleagues (2000) found that mothers with depression engaged in significantly more negative (e.g., expressions of negative maternal affect, hostility, coerciveness, threatening gestures, anger, intrusiveness) and disengaged (e.g., expressions of neutral affect, ignoring, withdrawal, silence) behaviour when interacting with their children. Further, depressed mothers demonstrated significantly fewer positive (e.g., expressions of pleasant affect, engagement, play, praise, and affectionate contact) behaviours during parent-child interactions (Lovejoy et al., 2000). In this study, although the largest effects on caregiving were found among currently depressed mothers, non-depressed mothers with a lifetime history of depression demonstrated the same overall pattern of maladaptive parenting, suggesting that depression-associated deficits in parenting persist even in the absence of an active depressive episode (Lovejoy et al., 2000).

The manner in which parenting influences children's depression risk is complex and multifaceted. One likely route is through the impact of parenting on children's neural

functioning and subsequent depressogenic cognitive processes. Meta-analysis has demonstrated that maladaptive parenting (e.g., abuse and neglect) increases children's reactivity to negative emotional stimuli in brain structures relevant to salience and emotional processing (Hein & Monk, 2017). Similarly, Pozzi and colleagues (2020) found that even normative aspects of negative parenting (e.g., dysphoric affect and anger toward the child) were positively correlated with children's amygdalar activity during processing of negative emotional stimuli. Finally, both Romund et al. (2016) and Butterfield and colleagues (2020) reported that child-reported maternal warmth was negatively associated with functional activity in similar regions (e.g., amygdala, insula, anterior cingulate) during exposure to negatively valenced emotional stimuli.

Importantly, these same brain regions are implicated in biological theories of depression (Disner, Beevers, Haigh, & Beck, 2011). This literature is consistent not only with the possibility that adverse caregiving shapes children's neural depression vulnerability, but also the possibility that children's heritable neural risk renders them especially sensitive to negative caregiving, even when such caregiving is not especially harsh or prolonged.

Maternal depression is also associated with children's development of cognitive vulnerabilities to depression. For example, previous research has found that children of depressed mothers tend to engage in rumination (i.e., a pattern of repetitive and passive cognitive focus on distress as well as the causes and consequences of distress; Nolen-Hoeksema, Wisco, & Lyubomirsky, 1998) more so than children of non-depressed mothers (Gibb, Grassia, Stone, Uhrlass, & McGeary, 2012; Woody et al., 2016). In addition, negative caregiving styles are associated with rumination in children and adolescents (Douglas, Williams, & Reynolds, 2017; Gaté et al., 2013; Hilt, Armstrong, & Essex, 2012). Importantly, ruminative thinking appears to have functional neural

underpinnings, especially in the DMN (Hamilton, Farmer, Fogelman & Gotlib, 2015; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Mulders, van Eijndhoven, Schene, Beckmann, & Tendolkar, 2015; Sacchet et al., 2016); a familial depression history is associated with increased functional connectivity of the DMN, even in the absence of a personal history of depression (Posner et al., 2016). These findings are consistent with the possibility that a maternal history of depression, and exposure to negative caregiving, may potentiate the maladaptive development of dysfunctional brain activity relevant to depressogenic cognitions (e.g., rumination), subsequently increasing vulnerability to depression. A brief overview of the relevant supporting literature is provided below with the goal of highlighting the need for high-risk studies of the never-depressed offspring of mothers with a depression history.

Neuroimaging Children's Risk for Depression

A vast body of neuroimaging research aimed at characterizing depression and its putative causal mechanisms has accrued, largely focused on adults with current or lifetime history of depression. Although there is a literature investigating depression and depressive risk using other imaging techniques (e.g., electroencephalography [de Aguiar Neto & Rosa, 2019; Proudfit, Bress, Foti, Kujawa, & Klein, 2015], positron emission tomography [Videbech, 2000], functional near-infrared spectroscopy [Yeung & Lin, 2021], diffusion tensor imaging [Bracht, Linden, & Keedwell, 2015; Sexton, Mackay, & Ebmeier, 2009]), in line with the focus of this dissertation, only findings relevant to structural magnetic resonance imaging (MRI), task-based functional MRI (fMRI), and resting-state fMRI (rs-fMRI) methodologies are reviewed.

Meta-analyses have found that depression is associated with structural changes, including (a) decreased volume in PFC regions (e.g., orbitofrontal cortex, frontal gyri); (b) limbic regions (e.g., hippocampus, cingulate cortex [primarily ACC], amygdala, striatum); and (c) with relatively less support, temporal cortical regions (Arnone et al., 2016; Bora, Harrison, Davey, Yücel, & Pantelis, 2012; Du et al., 2012; Koolschijn, van Haren, Lensvelt-Mulders, Hulshoff Pol, & Kahn, 2009; Lai, 2013; Sacher et al., 2012). Meta-analytic review of task-based fMRI studies have similarly found that depression is associated with dysfunctional neural response to emotion processing (Delvecchio et al., 2012; Groenewold, Opmeer, de Jonge, Aleman, & Costafreda, 2013; Hamilton et al., 2012; Lai, 2014; Miller, Hamilton, Sacchet, & Gotlib, 2015; Müller et al., 2017), reward processing (Ng, Alloy, & Smith, 2019; Zhang, Chang, Guo, Zhang, & Wang, 2013), and executive functioning (Miller et al., 2015; Wang et al., 2015). Finally, review of rs-fMRI studies in MDD have found evidence for aberrant functional connectivity among adolescents and adults with depression (Kaiser et al., 2015; Mulders et al., 2015).

While this work is essential to improving understanding of the pathophysiology of depression, given that those who have experienced depression are undoubtedly at risk (Richards, 2011), it is limited in terms of what it can tell us about etiology. Questions regarding etiology and mechanisms of risk are hampered by the fact that differences in brain structure and function among those with a lifetime history of depression may be related to the effects of having experienced or been treated for depression. Given the low prevalence of clinically relevant depression in childhood (Merikangas et al., 2010) relative to adolescence (Avenevoli, Swendsen, He, Burstein, & Merikangas, 2015) and adulthood (Kessler, Chiu, Demler, Merikangas, & Walters, 2005), and the availability of rigorous screening tools that can identify youth without a prior history of depression (e.g.,

the Kiddie Schedule for Affective Disorders and Schizophrenia [KSADS]; Kaufman et al., 1997), children who are at high risk for depression yet without a personal history of the disorder are a useful sample for investigators interested in vulnerability processes (Gotlib, Joormann, & Foland-Ross, 2014). Despite this, relatively little has been published regarding the neuroimaging of never-depressed children with differing levels of maternal depression risk.

Summary

Children of mothers with a history of depression are at significantly higher risk for developing depression themselves. Although numerous mechanisms explaining this relationship have been proposed (Goodman & Gotlib, 1999), relatively little is known about the neural substrates of never-depressed children's depression risk. Of the few studies that have used neuroimaging techniques to characterize risk-based differences in children's neural structure, function, and functional connectivity, the bulk have been conducted in older samples (i.e., past the typical age of onset for depressive disorders) or using samples that include participants with a personal history of depression. As noted above, this limits what can be determined regarding whether findings are true markers of risk (and potential etiological mechanisms) or better reflect resilience to depression or brain-based sequelae of depression. Thus, there is a clear need to better characterize children's neuroimaging-based markers of depression risk by focusing on samples with clear statistical risk (i.e., a maternal history of depression) *prior* to their own onset of disorder.

With this literature in mind, and with the ultimate goals of informing research on early identification and prevention of depression, the following three original research

studies seek to characterize the relationship between never-depressed children's risk for depression and putative neuroimaging-based endophenotypes, including: children's brain structure (Study 1; Chapter 2), functional response to maternal feedback (Study 2; Chapter 3), and resting-state functional connectivity (Study 3; Chapter 4). Finally, the implications of these studies and future directions will be discussed (Chapter 5).

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Chapter 2 – Orbitofrontal cortex grey matter volume is related to children’s depressive symptoms

Introduction

With a worldwide lifetime and annual prevalence of 14.6% and 5.5% (Bromet et al., 2011), respectively, major depression (Major Depressive Disorder; MDD) is sometimes referred to as the “common cold of mental illness.” However, this analogy belies the profound personal and societal consequences of MDD (Lépine & Briley, 2011). Globally, depression is associated with an array of negative psychosocial outcomes (e.g., academic failure, marital discord and divorce, occupational impairment; Kessler, 2012), and is a leading cause of disability (Vos et al., 2012), suicide (Bostwick & Pankratz, 2000), and increased mortality related to other, co-occurring health conditions (Cuijpers & Smit, 2002). Importantly, it is now clearly established that children can and do experience depression; for example, epidemiological research has found a 12-month prevalence of 2.7% for children 8 to 15 years of age (Merikangas, He, Burstein, et al., 2010). This is consistent with a meta-analysis of global epidemiological studies of children and adolescent mental disorder prevalence, which found a pooled prevalence estimate of 2.6% for depressive disorders (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). Finally, even in the absence of frank depressive disorder, subthreshold depressive symptoms are associated with significant functional impairment in both children (Wesselhoeft, Sørensen, Heiervang, & Bilenberg, 2013) and adults (Rodríguez, Nuevo, Chatterji, & Ayuso-Mateos, 2012), and are an established marker of youth risk for future depressive disorders (Klein, Shankman, Lewinsohn, & Seeley, 2009; Shankman et al., 2009).

The pervasive and negative sequelae associated with depression underscore the importance of identifying vulnerabilities early in development and improving our understanding of the mechanisms through which these vulnerabilities lead to disorder. Identification of early vulnerabilities is essential for intervention efforts, which may be especially beneficial during childhood, given that neural plasticity is relatively high (Nelson, 2000) and there is a broader window of opportunity for prevention (Merry et al., 2012; Stice, Shaw, Bohon, Marti, & Rohde, 2009). Research aimed at identifying which children are most vulnerable, and the mechanisms by which depression develops, may hold the key to mitigating its often-devastating impact.

Depression Risk and Vulnerability

Family history of depression marks significantly higher risk for the disorder (Levinson, 2006); indeed, having a first-degree relative (e.g., a parent) with a lifetime history of MDD is associated with approximately three-fold increase in risk (Weissman et al., 2006). Maternal history of MDD is a particularly strong risk factor for depression in offspring (Connell & Goodman, 2002; Klein, Lewinsohn, Rohde, Seeley, & Olino, 2005). Given the high heterotypic continuity and shared etiology between depression and anxiety (Cummings, Caporino, & Kendall, 2014; Kendler, Prescott, Myers, & Neale, 2003), and the preponderance of familial anxiety among those with depression (and vice-versa; Lawrence, Murayama, & Creswell, 2019; Micco et al., 2009), familial anxiety also marks offspring depression risk. Collecting information regarding family history of depression permits “high-risk” designs whereby vulnerable children are identified in advance of the typical age of onset for depression. High-risk designs, focused on youth with a family history but no personal history of disorder, enhance the ability to

distinguish between causal processes versus concomitant features or consequences of the disorder (Talati, Weissman, & Hamilton, 2013); however, the mechanisms and processes through which markers of risk (e.g., family history) eventuate in disorder are unclear, complex, diverse, and probabilistic. Historically, investigators have focused on predicting diagnostic outcomes in high-risk youth (i.e., the presence or absence of MDD); however, like all mental disorders, depression is characterized by *equifinality* or *etiological heterogeneity* (Cicchetti & Rogosch, 1996). Thus, high-risk youth who ultimately develop depression likely do so via a heterogeneous array of mechanisms, such as cognitive, biological, and personality vulnerabilities (Gotlib & Hammen, 2015). These processes are often referred to as *endophenotypes* (i.e., etiologically parsimonious mechanisms thought to mediate the relationship between genotype and complex disorder phenotypes; (Gottesman & Gould, 2003a; Insel et al., 2010); as normally distributed, dimensional phenomena, these hold relatively greater reliability and statistical power than dichotomous diagnoses (Klein, 2008). For these reasons, developmental psychopathologists have focused on quantitative processes that may account for why some high-risk youth ultimately develop clinically significant disorders. With respect to the current study, brain structure may serve as an endophenotype for depression.

Importantly, in order to be useful as an endophenotypic marker of disease risk, measurement of the marker must be reliable. Indices of brain structure (e.g., structural magnetic resonance imaging [MRI]) have very high reliability (Wonderlick et al., 2009), especially in comparison to task-based functional MRI (fMRI; Klein et al., 2013). Despite largely focusing on adults, the literature examining brain structure in those with a history of depression provides hypotheses for particular regions that merit study in high-risk youth.

Brain Structure as an Endophenotype for Depression

Depression is characterized by dysfunction in cognitive, emotional, and behavioural processes related to emotion processing and regulation (Joormann & Gotlib, 2010), responses to reward (Henriques & Davidson, 2000), stress reactivity (Burke, Davis, Otte, & Mohr, 2005; Lopez-Duran, Kovacs, & George, 2009), and executive functioning (Rogers et al., 2004). Thus, development of neurobiologically informed models of depressive etiology focuses on brain regions underlying normative functioning of these processes (Drevets, Price, & Furey, 2008), including examining structural differences in these regions between patients with depression and healthy, never-depressed controls.

This literature implicates a complex network of cortico-limbic and cortico-striatal structures involved in the regulation and processing of emotions (e.g., amygdala, hippocampus, ACC, PFC; Davidson, Pizzagalli, & Nitschke, 2009; Davidson, Pizzagalli, Nitschke, & Putnam, 2002) and reward (e.g., orbitofrontal cortex, medial PFC, and striatum; Drevets, 2007; Drevets et al., 2008; Eshel & Roiser, 2010). This is consistent with prominent neurobiological theories of depression, which posit structural and functional aspects of these regions contribute to maladaptive changes throughout cortico-limbic and cortico-striatal networks, eventuating in depression. Specifically, Mayberg and colleagues developed a cortico-limbic model of depression (e.g., Mayberg, 1997; Mayberg et al., 1999; Seminowicz et al., 2004) where reduced neural top-down regulation of emotion (via fronto-cortical dysregulation) and/or increased bottom-up emotion processing (via limbic dysregulation) result in the cardinal symptoms of depression (i.e., persistent depressed mood and anhedonia; Mayberg, 1997; Mayberg et al., 1999; Seminowicz et al., 2004). Drevets and colleagues (e.g., Drevets, 2007; Drevets

et al., 2008; Price & Drevets, 2010) describe similar neural features as the source of multiple classes of depressive phenotype (e.g., low mood, anhedonia), incorporating additional brain structures relevant to dysregulation of both cortico-limbic *and* cortico-striatal networks.

With respect to empirical studies, meta-analyses indicate that, relative to never-depressed individuals, adults with a history of depression have lower grey matter volume (GMV), concentration (GMC), and structural volume in frontal cortical regions, including prefrontal (PFC; Arnone et al., 2016; Arnone, McIntosh, Ebmeier, Munafò, & Anderson, 2012; Bora, Harrison, et al., 2012; Du et al., 2012; Peng, Chen, Yin, Jia, & Gong, 2016; Sacher et al., 2012) and orbitofrontal cortices (OFC; Arnone et al., 2016; 2012).

Additionally, adults with a history of depression show less GMV and lower structural volume in limbic regions such as the anterior cingulate cortex (ACC; Arnone et al., 2016; Bora, Fornito, Pantelis, & Yücel, 2012; Bora, Harrison, et al., 2012; Du et al., 2012; Lai, 2013), amygdala (Arnone et al., 2016; Bora, Harrison, et al., 2012; Sacher et al., 2012), and hippocampus (Arnone et al., 2016, 2012; Bora, Harrison, et al., 2012; Du et al., 2012), as well as reductions in dorsal striatal (i.e., caudate nucleus and putamen) GMV and structural volumes, relative to never-depressed control subjects (Amico et al., 2011; Arnone et al., 2012). Importantly, these findings are consistent with the aforementioned neurobiological theories of depression (Drevets et al., 2008; Mayberg, 1997; Mayberg et al., 1999; Price & Drevets, 2010; Seminowicz et al., 2004), as do findings that depressive symptoms are negatively associated with GMV in the OFC, PFC, and cingulate (Chen et al., 2007; Vasic, Walter, Höse, & Wolf, 2008).

Brain Structure in Depression Risk

While the structural differences identified in studies of people with depression may be indicative of pre-existing vulnerability, it is also plausible that they are *caused* by the disorder or its treatment (i.e., scar effect). A smaller literature, reviewed below, has explored brain structure in those at risk for the disorder without a personal history of depression.

Familial depression and brain structure. Never-depressed adults with a family history of depression tend to have decreased hippocampal volume (Amico et al., 2011; Baaré et al., 2010; Carballedo et al., 2012; Rao et al., 2010); however, both *increases* (Romanczuk-Seiferth et al., 2014) and *no* differences (Mannie et al., 2014) in hippocampal volume have also been reported. Similarly, the amygdala (Munn et al., 2007; Romanczuk-Seiferth et al., 2014; Saleh et al., 2012), dorsolateral PFC (dlPFC; Amico et al., 2011; Carballedo et al., 2012; Romanczuk-Seiferth et al., 2014), and medial PFC (mPFC; Amico et al., 2011; Carballedo et al., 2012; Ozalay et al., 2016) are also inconsistently related to family history in non-depressed adults.

There is a small literature examining brain structure in never-depressed youth with and without a family history of depression. Youth amygdala volume and familial history of depression are inconsistently related, with some studies finding that a family history of MDD is associated with smaller amygdala volumes (Chai et al., 2015), and others finding no differences (van der Plas, Boes, Wemmie, Tranel, & Nopoulos, 2010). Boys and girls may also differ in brain-risk associations; for example, depressive symptoms predicted boys' ACC volume but not girls' in never-depressed youth with a familial history of depression (Boes, McCormick, Coryell, & Nopoulos, 2008). While intriguing, these studies are limited by examining youth who vary widely in age; for

example, both Boes et al. (2008) and van der Plas et al. (2010) included seven- to seventeen-year-olds in their studies. Wide age ranges are problematic for studies of youth, as it is unclear whether structural associations reported in the aforementioned studies are reflective of risk prior to the typical age of onset for depression or are largely driven by structural changes in the brain that occur in adolescence (e.g., reductions in grey matter [GM] and increases in white matter [WM]; Sowell, Trauner, Gamst, & Jernigan, 2002; Spear, 2013). Even when age is covaried in analyses, including children who vary widely in age may render results more challenging to interpret than recruiting children who fall within a narrow age range.

Maternal depression and brain structure. A maternal history of depression is especially strongly linked to depression risk in children and adults (Connell & Goodman, 2002; Klein et al., 2005); thus, other high-risk studies have focused specifically on the relationship between *maternal* depression history and brain structure in never-depressed children. In 55 never-depressed 9- to 15-year-old girls, those with a recurrent maternal history of depression had lower hippocampal GMC and structural volume relative to low-risk children (Chen, Hamilton, & Gotlib, 2010). Using a region-of-interest approach, maternal history of recurrent depression was associated with thinner cortical GM in bilateral fusiform gyri of never-depressed girls ($N = 14$), compared to girls with no maternal history of mental disorder ($N = 23$; Foland-Ross, Behzadian, LeMoult, & Gotlib, 2016). Ozalay and colleagues (2016) found that never-depressed daughters of mothers with recurrent depression had significant GMV reductions in the right temporoparietal region, bilateral insula, and right dlPFC, relative to never-depressed daughters of never-depressed mothers. Ozalay et al. (2016) also found maternal history of recurrent depression was associated with increased GMV in the left middle temporal

cortex. These studies suggest that a maternal history of depression is correlated with daughters' brain structure, even in the absence of offspring disorder; however, it is unclear whether these findings generalize to boys as well.

While promising, findings regarding brain structure in high-risk children and adults are mixed, possibly due to several factors. First, rather than directly interviewing family members, investigators oftentimes use participants' reports of their family members' psychopathology history, a methodologically limited approach subject to an array of biases (Kendler et al., 1991; Milne et al., 2009). Further, given that recurrent depression is more heritable than single episodes (Fernandez-Pujals et al., 2015), using recurrent depression history as an index of children's risk may be a more powerful marker of vulnerability. Finally, given that the limited studies available on the relationship between children's brain structure and maternal depression history have focused exclusively on girls, work including both boys and girls is needed.

Sex differences in depression and brain structure. Depression is approximately twice as prevalent in women compared to men (Nolen-Hoeksema & Hilt, 2009), and being female is a significant prospective predictor of depression (Klein et al., 2013). The reasons for this well-established pattern are complex and heterogeneous, likely involving both biological and psychosocial mechanisms. Sex differences in prevalence suggest the possibility that women and men differ on average in the degree to which vulnerability processes are present; however, it is also possible that women are more impacted by these vulnerabilities, even in the absence of mean differences (i.e., a sex-by-vulnerability interaction). For example, studies of cognitive risk (e.g., Mezulis, Funasaki, Charbonneau, & Hyde, 2010) show that the longitudinal relationship between stress and depression is stronger for girls than boys, and work from our group (Daoust et al., 2018;

Kryski, Smith, Sheikh, Singh, & Hayden, 2013) indicates that stress reactivity is more strongly associated with internalizing symptoms in girls than boys.

Few studies have examined sex differences in the relationship between brain structure and depression; however, brain structure in regions related to emotion/reward processing may be more strongly related to depression risk in girls. For example, Kong et al. (2013) found that reductions in limbic (e.g., bilateral amygdala and hippocampus) GMC were associated with depression in women, while men with depression had reduced GMC among striatal regions (bilateral caudate, left ventral striatum). Similarly, Vulser et al. (2015) reported that decreased medial PFC GMV mediated the relationship between subclinical depressive symptoms at 14-years-old and major depressive episodes at age 16 for girls but not boys. These few studies suggest that the relationship between depression risk and brain structure may differ by sex.

In addition to sex-based differences in depression risk and vulnerability, it is important to acknowledge that neurodevelopment is also characterized by sexual dimorphisms. Specifically, females consistently show smaller GM and WM volumes across the brain and developmental stages (Lenroot et al., 2007); however, after controlling for differences in total brain size, females have *proportionately* greater volumes in some anatomical regions (i.e., greater GMV in frontal lobes and greater corpus callosum area; Lenroot et al., 2007). In addition, while both sexes follow an inverted U curve with respect to development of GMV, girls tend to reach peak frontal GMV approximately 1 to 2 years earlier than boys (Lenroot et al., 2007), suggesting that the rate of some aspects of brain development is sexually dimorphic.

The Current Study

Overall, decreased volume and GMC in a number of frontal cortical (e.g., dorsolateral PFC [dlPFC] and OFC), limbic (e.g., ACC, amygdala, hippocampus), and striatal structures (e.g., caudate nuclei and putamen) appear to be related to a history of MDD and, with less consistency, to risk for depression among never-depressed individuals, including youth. Importantly, these are regions consistent with prominent cortico-limbic and cortico-striatal theories of depression (e.g., Drevets et al., 2008; Mayberg, 1997; Mayberg et al., 1999; Price & Drevets, 2010; Seminowicz et al., 2004); however, much of this work comes from adults with a history of MDD. Similarly, the less-developed literature investigating the relationship between brain structure and depression risk in never-depressed individuals is also largely based on adults. While important, this work is limited in terms of what it can tell us about brain structure in risk for depression.

In this study, we addressed the limitations of the extant literature in several ways. First, we tested the relationship between depression risk and brain structure in never-depressed children. Additionally, we operationalized risk relatively stringently by only including children of mothers with recurrent depression. Further, we analyzed the relationship between brain structure and both self- and maternally reported children's depressive symptoms, treating symptoms in the absence of depressive disorder as a marker of risk. A small literature indicates that associations between brain structure and depression differ by sex, although little is known about whether such patterns are related to pre-existing risk versus current depression, and many of the high-risk studies have used all-female samples. We therefore examined whether the relationship between depressive symptoms and brain structure was moderated by sex.

Material and Methods

Participants

Children ($n = 87$) and their mothers were recruited from a larger longitudinal study of children's depression risk ($N = 409$) that began when children were 3-year-olds. At baseline, children with major medical or psychological problems were excluded, and typical cognitive development was verified using the Peabody Picture Vocabulary Test-Fourth Edition (Dunn & Dunn, 2007). For the current study, children were recruited from the larger longitudinal sample based on maternal history of depression (MH+) drawn from data collected at a previous round of data collection for this study (Liu, Kryski, Smith, Joannisse, & Hayden, 2019). Children were considered high-risk based on a maternal history of recurrent major depression ($n = 26$), or a maternal lifetime history of a single major depressive episode *and* a serious anxiety disorder (i.e., any anxiety disorder except a specific phobia; $n = 3$)¹. Low-risk children had no maternal history of major depression or anxiety disorder (see Procedures and Measures for details). From this sample, 237 families were contacted (58 MH+). Children with any contraindications to the MRI scan (e.g., braces, metallic objects implanted in the body, claustrophobic) were deemed ineligible, leaving a pool of 231 families, from which 110 families agreed to participate (36 MH+). Children from these families were screened as described in the following section to ensure the absence of current or lifetime depressive disorder². Eighty-seven children (29 MH+; 49 boys) participated in the MRI session with 85

¹ We excluded specific phobia and social anxiety limited to public speaking given that these are less heritable, less impairing, and potentially weaker markers of children's internalizing risk (Kendler, Neale, Kessler, Heath, & Eaves, 1992).

² no child was excluded based on current or lifetime depressive disorder

contributing usable structural MRI scans (29 MH+; 48 boys).³ See Table 1 for demographic statistics of this final sample of 85 children and mothers. These 85 children did not differ from the 25 children who either did not participate in the MRI session or did not contribute useable structural MRI scans, on age, Children's Depression Inventory, Child Behaviour Checklist-Withdrawn Depressed subscale, Youth Self-Report-Withdrawn Depressed subscale, or Peabody Picture Vocabulary Test (collected at age 3) scores, or frequency distributions of children's sex or maternal risk status (all $p > .05$).

Procedures and Measures

Data were collected during four separate assessments of children and their mothers. The first assessment, a phone interview, was conducted with mothers over the telephone and consisted of the parent portion of the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) administered by trained graduate students in clinical psychology.

At the second assessment ($M = 17.86$ days, $SD = 14.51$ days after the first assessment), conducted in the participants' homes, children were administered the K-SADS-PL and completed self-reported symptom and severity measures, including the Children's Depression Inventory 2nd Edition (CDI⁴; Kovacs, 2011); $\alpha = .83$) and the Youth Self-Report (Achenbach & Rescorla, 2001) with the help of trained graduate

³ One child had orthodontic braces installed between the laboratory visit and the MRI scan; another child had low-quality T1 images despite several attempts at scanning.

⁴ Despite not meeting criteria for MDD based on the K-SADS-PL, three child participants ($N_{MH+} = 2$) had CDI scores greater than 19, which is above the cut-off suggestive of clinically significant symptoms in a community sample (Kovacs, 2011). Excluding these participants from subsequent analyses did not change the pattern of results found using the full sample, although findings were no longer significant after correcting for multiple comparisons and given the reduced sample size.

students in clinical psychology. The K-SADS-PL demonstrated 100% interrater agreement ($N = 11$) for all diagnoses in the current study, including depression⁵. In addition, mothers completed the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001); we used the withdrawn-depressed subscale from both the CBCL (CBCL-WD; $\alpha = .72$) and the YSR (YSR-WD; $\alpha = .72$) as indices of maternally and self-reported child depressive symptoms, respectively.

During the third assessment ($M = 17.04$ days, $SD = 20.03$ days after the second assessment), children participated in a laboratory social stressor task; these data are not used in the current analyses. Mothers were also interviewed during this visit by trained graduate students in clinical psychology to assess lifetime history of psychopathology using the Structured Clinical Interview for the DSM-IV-TR Axis I Disorder Non-Patient Edition (SCID; First, Spitzer, Gibbon, & Williams, 2002). As all mothers had completed a SCID several years prior as part of the larger longitudinal study, we focused solely on the interval since participants' last SCID. The SCID demonstrated good inter-rater reliability for specific diagnoses and for lifetime history of any depressive episodes (Kappa = 1.00, $N = 10$). Finally, in keeping with best practices for scanning children (de Bie et al., 2010), children completed a "mock scan" session during this visit in a replica MRI system in order to prepare them for the fourth and final visit (MRI visit). During the mock scan, the upcoming MRI session procedures were explained and children were given the opportunity to ask questions. Finally, structural and functional MRI scans were acquired from children during an MRI visit held approximately one week after the

⁵ For some K-SADS and SCID diagnoses (e.g., K-SADS depression), no participant met criteria for the disorder. While interviewer agreement on the absence of the diagnosis was 100%, given no variability, we could not compute Cohen's Kappa in these cases.

laboratory visit ($M = 8.78$ days; $SD = 7.38$ days); only the structural data are reported in the current analyses.

MRI Data Acquisition

Magnetic resonance images were obtained using a Siemens 3T Tim Trio MRI scanner with a 32-channel head RF coil at Western University's Centre for Functional and Metabolic Mapping. Children's heads were immobilized during scanning using foam padding in the RF coil. All children wore foam ear buds to dampen scanner noise. Structural images were acquired with a T_1 -weighted 3D magnetization prepared rapid gradient echo (MPRAGE) sequence (1×1×1 mm voxel size, repetition time (TR) = 2300 ms, echo time (TE) = 2.98 ms, field of view (FOV) = 256 mm), 192 slices.

VBM Preprocessing

Initially, all raw DICOM scans were reviewed and converted into NIFTI format, using MRICRON software (Rorden, Karnath, & Bonilha, 2007). VBM preprocessing was conducted using default settings for Computational Anatomy Toolbox (CAT12, <https://dbm.neuro.uni-jena.de/cat/>), an extension of SPM12 (Wellcome Trust Center for Neuroimaging, London, UK), and MATLAB 9.5 (Mathworks, Inc., Natick, MA). T_1 -weighted images were bias, noise, and global intensity corrected prior to spatial normalization to the MNI152 template using the DARTEL algorithm (Ashburner, 2007). Next, normalized images were segmented into GM, WM, and cerebrospinal fluid (CSF; Ashburner & Friston, 2005) and written as modulated normalized volumes, allowing for interpretation of localized grey matter volume (GMV). Intracranial volumes (ICV) were calculated during segmentation for use as a nuisance variable during statistical analyses. Quality assurance was conducted via visual inspection and an automated quality check

protocol embedded in CAT12, leading to the exclusion of one participant. All scans were then spatially smoothed using a 6 mm (FWHM) Gaussian smoothing kernel and resampled into 1.5×1.5×1.5 mm voxel size.

Data Analyses

SPM12 was used to analyze VBM data. All VBM analyses included age, sex, and intracranial volume (ICV) as covariates. Analysis of covariance (ANCOVA) was conducted to test differences in GMV between high- and low-risk children in both *a priori* regions of interest (ROI) and whole-brain analyses. We also used multiple regression to examine associations between children's depressive symptoms (i.e., CBCL-WD, CDI, and YSR-WD) and GMV in both *a priori* ROI and whole-brain analyses. In addition, we tested statistical interactions between children's depressive symptoms and child sex, given evidence of sex-based differences in structural brain correlates of depression and depression risk (e.g., Carlson, Depetro, Maxwell, Harmon-Jones, & Hajcak, 2015; Kong et al., 2013; Vulser et al., 2015). Specifically, we hypothesized that structure-symptoms associations would be stronger among girls than boys. Therefore, interaction terms were created by taking the product of standardized values of children's depressive symptoms (i.e., CBCL-WD, CDI, or YSR-WD) and sex. Moderation analyses included the main effects of sex, depressive symptoms, and MH+/MH- status as covariates in the regression model. Average GMV values were extracted from voxel clusters that were significantly associated with an interaction term using MarsBaR, Version 0.44 (Brett, Anton, Valabregue, Poline, & Others, 2002) and plotted using R 3.6.1 (R Core Team, 2019) and the *interactions* (Long, 2019a), *jtools* (Long, 2019b),

ggplot2 (Wickham, 2016), and *emmeans* (Lenth, 2019) packages to interpret the interaction.

A priori ROIs, selected based on previous work on the relationship between depression risk and brain structure (e.g., Arnone et al., 2016, 2012; Bora, Fornito, et al., 2012; Bora, Harrison, et al., 2012; Du et al., 2012; Lai, 2013; Sacher et al., 2012) were the anterior cingulate cortex (ACC), bilateral amygdala, bilateral hippocampus, orbitofrontal cortex (OFC), and the dorsal striatum (caudate and putamen). All ROI analyses were conducted using a single ROI mask combining the aforementioned anatomical ROI defined using the Wake Forest University PickAtlas Toolbox, Version 3.0.5 (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003; Tzourio-Mazoyer et al., 2002). Exploratory whole-brain analyses were also conducted using the same statistical models described above. Both ROI and whole-brain analyses were considered significant at $p_{FWE} < .05$ (random-field theory family-wise error corrected, as implemented in SPM12).

Results

Associations Among Major Study Variables

See Table 2 for bivariate associations between all major study variables. CBCL-WD, CDI, and YSR-WD scores were all positively correlated with one another and with child risk based on maternal history (dummy coded such that 0 = MH- and 1 = MH+). MH+ children had higher CBCL-WD ($t(81) = -3.10, p = .003$) and CDI ($t(82) = -2.24, p = .027$) scores compared to MH- children; there were no significant differences for YSR-WD scores. Girls tended to have smaller ICV (Table 2) with *t*-tests also showing that

boys had significantly larger ICV than girls ($t(83) = 7.485, p < .001$). Neither maternal nor self-reported depressive symptoms were associated with child biological sex.

VBM Analyses

Main effects of risk group and depressive symptoms. There were no significant differences in GMV between high- and low-risk children in ROIs ($p_{FWE} > .05$) or whole-brain analyses ($p_{FWE} > .05$) using ANCOVA. Additionally, maternally reported children's depressive symptoms (i.e., CBCL-WD scores) were not significantly related to GMV in any of the ROI-based or whole-brain analyses.

Based on ROI regression analyses of the OFC (Table 3; Figure 1), children's self-reported depressive symptoms on the CDI were significantly negatively associated with GMV in a single cluster of voxels in the medial OFC. Similarly, GMV of two independent voxel clusters, the medial and right lateral OFC, was negatively associated with children's self-reported depressive symptoms on the YSR-WD (Table 4; Figure 2). The medial clusters identified in regressions using both the CDI and YSR-WD largely overlapped with one another. Depressive symptoms were not significantly related to GMV in any of the other ROI analyses. Exploratory whole-brain voxel-wise analyses identified similarly located clusters of voxels in the OFC where higher CDI (Table 3; Figure 1) and YSR-WD (Table 4; Figure 2) were both related to lower GMV ($p_{FWE} < .05$).

Interactions between child sex and subthreshold depressive symptoms. The relationship between CDI and GMV during *a priori* ROI analysis of the OFC was significantly moderated by the sex of child participants (Table 3; Table 5; Figure 3). A similar effect was found whereby the relationship between CBCL-WD and GMV in the

OFC ROI were also moderated by sex (Table 6; Table 7; Figure 4). In both cases, simple slopes analyses using the mean GMV of respective significant voxel clusters indicated a significant relationship between GMV and both boys' and girls' depressive symptoms (indexed via the CDI and CBCL-WD), although the association was negative for girls and positive for boys (Figures 5 & 6). Sex did not significantly moderate the relationship between YSR-WD and GMV. Additionally, no significant interactions were identified in any of the other ROI analyses.

Exploratory whole-brain analysis identified a cluster in the left inferior frontal gyrus where the relationship between GMV and depressive symptoms (indexed via maternal-reported CBCL-WD) was significantly moderated by children's sex (Table 6; Table 8). Simple slopes analysis indicated that boys' GMV and maternally reported symptoms (i.e., CBCL-WD) were significantly positively related, while the relationship was non-significant among girls (Figure 7).

Discussion

We investigated the relationship between brain structure and an established marker of children's depression risk, namely a maternal history of recurrent depression (or depression and serious anxiety disorder). Contrary to our expectations, children at high- and low-risk for depression, according to maternal history, did not differ in GMV. This was especially surprising given that children's maternal risk was relatively stringently defined relative to other studies, and our comparison group of children was drawn from mothers without any history of depression or anxiety. However, while children of mothers with a history of recurrent depression are at relatively higher risk for developing the disorder themselves (Connell & Goodman, 2002; Klein et al., 2005), not all offspring of depressed mothers become depressed, and some develop other forms of

psychopathology. Thus, not all children with a maternal history of depression inherit risk, including what may be relatively specific risk marked by brain structure. It is also possible that our high-risk children have risk mechanisms other than those captured by brain structure. Finally, aspects of brain structure that distinguish children with and without a maternal depression history may emerge later in development, a possibility worth exploring in other studies as well as in follow-up assessments of this sample.

In analyses of brain structure-symptom associations, we found that GMV in the medial OFC was significantly negatively associated with children's self-reported subthreshold depressive symptoms (i.e., CDI and YSR-WD) using both *a priori* ROI and exploratory whole-brain analyses. Furthermore, children's self-reported depressive symptoms (i.e., YSR-WD) were also negatively associated with GMV in the right lateral OFC, exclusively at the ROI level of analysis. These associations were found solely with children's self-reported symptoms based on the YSR-WD, and not the CDI nor the CBCL-WD scale (maternal report), perhaps capturing some aspect specific to social withdrawal being more specifically measured using the self-reported YSR-WD. Given the known homotypic continuity of early depressive symptoms with later depressive disorder (Cuijpers & Smit, 2004; Klein et al., 2013; Shankman et al., 2009), these findings highlight structural brain markers of youth at risk for depression.

Contrary to our expectations, maternal history of depression was unrelated to children's brain structure in the current study, with all associations with brain structure limited to children's depressive symptoms. Early subthreshold depression symptoms portend later clinically significant disorder (Cuijpers & Smit, 2004; Klein et al., 2013; Shankman et al., 2009) and can therefore be conceptualized as an index of children's risk for later disorder; however, we acknowledge that it is more complicated to differentiate

between subthreshold symptoms and the disorder itself in terms of understanding causal processes. Having said that, many other indices of putative depression risk (e.g., cognitive styles; Alloy et al., 2000) show conceptual overlap with depression, so this conceptual issue is not limited to the current findings. Given that brain structure and symptoms were related in children rigorously screened for a personal history of depression, our findings speak to brain structure-risk associations that cannot be attributed to a depression history or treatment.

Despite the lack of associations between maternal depression history and children's brain structure, children's self- and mother-reported depressive symptoms were significantly associated with *both* brain structure and maternal history of depression (i.e., MH+ and MH- groups significantly differed in CDI and CBCL-WD scores). While children with a maternal depression history are unquestionably at greater risk than children of mothers without depression, this risk is probabilistic rather than deterministic. More specifically, depression is etiologically complex with multiple contributing factors that interact with each other and with the environment. In our sample, elevated symptoms in youth with a maternal history of depression stem from an array of risks that are somewhat distinct from the risk marked by a maternal depression history. Similarly, even though we anticipated group differences in brain structure related to maternal depression, we did not expect to find strong associations. This is consistent with relatively modest estimates of the heritability of depression (Fernandez-Pujals et al., 2015). Integrating other etiologically relevant variables (e.g., cognitive style, environmental stressors, other biological factors) with brain data is an important future direction in mapping youth risk more comprehensively.

Our finding that OFC GMV was negatively related to depressive symptoms in never-depressed children is consistent with the literature on adults with a lifetime history of depression (Arnone et al., 2016, 2012). The OFC is consistently associated with depression, with meta-analysis showing that a lifetime history of MDD is correlated with a significant decrease in both OFC volume and GMV (Arnone et al., 2016; 2012). Additionally, lesions in the OFC are associated with depression in adults (MacFall, Payne, Provenzale, & Krishnan, 2001). That said, the bulk of the aforementioned work has been conducted in adults with either current or lifetime history of MDD. Of studies focusing on children at high risk for depression, Chen and colleagues' (2010) study of brain structure in 12-year-old girls also found no significant risk-GMV association during whole-brain analysis; however, they did report significantly lower GMV in bilateral hippocampi during ROI analyses. That said, Chen et al. (2010) used an uncorrected p value during ROI analyses, increasing the chance of false-positive findings. While the current data do not allow for determination of causality, our more stringent analyses indicate morphological features of the OFC (i.e., lower GMV in youth without a history of depression) are related to early vulnerability to depression.

Many depressive symptoms reflect behavior guided by neurofunctional circuits involving the OFC (Drevets, 2007). Perhaps most importantly, the OFC is, both individually and as part of a larger network of structures, involved in the processing of reward and reward-based learning (Delgado, Miller, Inati, & Phelps, 2005; Fettes, Schulze, & Downar, 2017; Liu, Hairston, Schrier, & Fan, 2011; Rolls, 2017). The OFC is thought to be involved in the cognitive encoding of representations of reward outcomes (Klein-Flügge, Barron, Brodersen, Dolan, & Behrens, 2013) and tracking the relative value of rewarding stimuli (O'Doherty, 2004). Relatedly, signal detection theory shows

that depressive symptoms, especially anhedonia (i.e., deficits in motivation, anticipatory and consummatory pleasure, and reward learning), are associated with reduced reward learning (Kunisato et al., 2012; Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008; Pizzagalli, Jahn, & O'Shea, 2005; Vrieze et al., 2013) that persists even after remission of MDD (Pechtel, Dutra, Goetz, & Pizzagalli, 2013). Given that anhedonia is a core symptom of depression, characterizing neural structures related to reward processing and reward-based learning in depression risk is an important aspect of understanding the disorder. Our findings that children's depressive symptoms are related to OFC GMV are consistent with findings of reduced functional activity in the OFC of both adults (e.g., Macoveanu et al., 2014; McCabe, Cowen, & Harmer, 2009; Osuch et al., 2009; Redlich et al., 2015) and children (e.g., McCabe, Woffindale, Harmer, & Cowen, 2012) at risk for, or with a history of, depression, during reward-based tasks.

While the OFC in general is thought to be important for reward processing and reward-based learning, medial and lateral OFC are thought to serve slightly different roles regarding these processes (Elliott, Dolan, & Frith, 2000; Fettes et al., 2017). Regarding reward-based learning, the medial OFC is putatively responsible for encoding the subjective value of rewarding stimuli and for learning based on probability-based behavioural feedback (Fettes et al., 2017; Kringelbach, 2005; Kringelbach & Rolls, 2004), while the lateral OFC is thought to be involved with reversal learning (e.g., suppressing previously rewarded behavior in favor of new behaviors that were previously unrewarded; Clark, Cools, & Robbins, 2004; Fellows, 2007; Fettes et al., 2017). Thus, our findings of associations between medial and lateral OFC morphology (regions involved with reward processing; Fettes et al., 2017) with depressive symptoms in never-depressed children are consistent with theories of depression that emphasize maladaptive

reward responding as an etiological factor in the disorder (Davidson et al., 2002; Treadway & Zald, 2011). However, we did not investigate functional brain activity during reward processing activities in the current study. Although we have identified structural associations with depressive symptoms in anatomical regions of the brain thought to be associated with reward processes, functional brain studies of non-depressed youth in the context of reward processing are necessary to specifically elucidate this relationship.

In addition to the aforementioned main effects relating brain structure and children's symptoms, we also tested whether boys and girls differed in the relationship between structure and depressive symptoms, in light of evidence that girls may be impacted more strongly than boys by other putative depression vulnerabilities (Hankin & Abramson, 2001; Mackrell, Johnson, Dozois, & Hayden, 2013). Depressive symptoms and child sex interacted such that depressive symptoms and OFC GMV were significantly positively related in boys, but negatively related in girls. Our sample size was relatively small for testing interactions, and these effects require replication in other samples; however, the fact that sex similarly moderated both maternally and self-reported depressive symptoms and their relationship to OFC GMV, despite the low intercorrelation between the two measures, suggests that this finding may be robust. The negative association between OFC GMV and depressive symptoms among girls is consistent with previous work focusing on adults with a depression history (Arnone et al., 2016; 2012); however, the positive association between depressive symptoms and GMV in boys was unexpected. This positive slope may reflect differences in the way that depression presents across sex. For example, epidemiological study has shown that females are significantly more likely than males to experience anhedonic symptoms

during depressive episodes (Romans, Tyas, Cohen, & Silverstone, 2007). Further, the positive relationship between OFC GMV and depressive symptoms among boys may be related to the typical pattern of externalizing and reward-focused comorbidities seen among males with depression (i.e., higher rates of comorbid substance use disorders in males, relative to females; Marcus et al., 2005). Of course, these explanations are largely speculative at this point, and further research is needed to adequately explain this pattern of results. Nevertheless, biological abnormalities in the GMV of structures responsible for reward processing and rewarding learning may contribute to an increased vulnerability for depression among girls, but not boys. Similarly, it is also possible that GMV in OFC regions may have opposite relationships with depression risk (i.e., depressive symptoms) among boys and girls, such that greater GMV is a risk factor for boys, whereas decreased GMV is relevant to girls' risk.

As with other VBM-based studies, the relationship between individual differences in GMV and individual differences in brain *function* remains unclear. To the best of our knowledge, there is no research available directly relating GMV to brain function. Instead, studies linking anatomical and functional differences in the brain typically focus on relating functional connectivity in the brain with structural connectivity (i.e., using white matter tractography; de Kwaasteniet et al., 2013; Nixon et al., 2014). While we have characterized statistical relationships between GMV and depression risk (i.e., subthreshold depressive symptoms) in our sample according to the typical functional role of the identified structural regions, it is possible that these associations do not confer differences in brain function. Future studies are needed to explicitly test the relationship between VBM-based study of brain structure and related differences in brain function in structural regions.

Strengths

Our study has a number of important strengths. We studied children without a personal history of depression, based on rigorous screening procedures, prior to the typical age of onset for depression. This indicates that the structural associations with depressive symptoms that we found are not a consequence of clinically significant depression or its treatment. Our sample was relatively large for neuroimaging studies of high-risk youth. Further, using a community-based sample of mothers and their children, rather than a clinical sample, may increase the generalizability of our findings.

Limitations & Future Directions

Despite the strengths of our study, results should be considered alongside a number of limitations. First, although up to 50% of all adults will meet criteria for a mental disorder during their lives (Kessler et al., 2007; Kessler, Berglund, et al., 2005), we used strict selection criteria for our “low-risk” group, only recruiting children whose mothers had no history of *any* disorder to this group. This may have limited low-risk children to offspring of especially resilient or healthy mothers, potentially limiting the generalisability of our results. Second, symptom/diagnostic data collection occurred an average of one month prior to MRI acquisition. Given the high stability of depressive symptoms in children and adolescents (Focke et al., 2011) and brain structure (Focke et al., 2011) over similar durations, it is unlikely this lag influenced our results. Indeed, treating time between assessments as a covariate did not significantly change our results.

Additionally, although the data used in this study were gathered as part of an ongoing longitudinal study of childhood development, the structural MRI data collected here is the first assessment of brain structure we have for these children. With these

cross-sectional data we cannot claim causal relationships between brain structure and depression; however, we plan to continue assessing brain development and psychopathology at subsequent follow-ups, thereby permitting testing of stronger claims about causal mechanisms in the brain-depression relationship. Finally, while we aimed to characterize structural features of the brain as they relate to depression risk *before* onset of depressive disorder or the typical age of onset, the brains of our participants have already undergone considerable maturation from a neurodevelopmental perspective. Future investigations should consider applying similar methodology to samples of even younger children to better characterize the brain-depression risk relationship across early development.

Another limitation concerns other relevant variables not included in the current study. While age was included as a covariate in all analyses of imaging data, participants' pubertal development was not assessed as part of the current study. Given the age of our sample and the established relationship between pubertal development and the development of depression (Angold, Costello, & Worthman, 1998; Adrian Angold & Costello, 2006), covarying for pubertal development in future studies is an important next step in better understanding these relationships. Finally, human development (including development of the brain and mental disorders) does not exist in a vacuum; the relationship between brain structure and depression risk is most likely influenced by gene-environment interactions and epigenetic changes (Meaney, 2010). Future research should collect more data regarding potentially relevant environmental factors (e.g., adverse childhood events, early parenting behaviour, children's chronic life stress, etc.) and investigate both the direct effect of environmental variables, beyond maternal

depression, as well as their interaction with biology (i.e., genotype, brain-based endophenotypes, sex, stress reactivity, etc.).

Conclusion

Our results demonstrate that depressive symptoms are associated with brain structure among never-depressed children, specifically in the medial and right lateral OFC. These regions are largely associated with functional roles involving reward processing and reward learning, both functions which are highly relevant to core symptoms of depression (i.e., anhedonia). Reduced GMV in these regions may reflect a pre-existing biomarker for depression, potentially contributing to risk for developing depressive disorders.

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Tables

Table 1
Descriptive statistics.

Variable	<u>Full Sample</u>			<u>Low Risk</u>			<u>High Risk</u>			<u>Comparison</u>	
	<i>M</i>	<i>SD</i>	Frequency	<i>M</i>	<i>SD</i>	Frequency	<i>M</i>	<i>SD</i>	Frequency	statistic	<i>p</i>
Child Age at MRI Visit	11.12	0.63	-	11.19	0.51	-	11.00	0.81	-	$t = 1.11$.27
PPVT	112.87	14.16	-	114.22	14.70	-	110.31	12.94	-	$t = 1.21$.23
CDI	6.61	5.07	-	5.73	4.29	-	8.28	6.02	-	$t = -2.03$.049
CBCL Withdrawn/Depressed	1.31	1.79	-	0.89	1.30	-	2.10	2.27	-	$t = -3.10$.0026
YSR Withdrawn/Depressed	3.32	2.71	-	3.11	2.61	-	3.75	2.89	-	$t = -1.03$.31
ICV	1616.92	137.46	-	1613.01	133.80	-	1624.48	146.39	-	$t = -0.36$.72
Sex (Male/Female)	-	-	48/37	-	-	31/25	-	-	17/12	$\chi = .08$.77

Note. PPVT = standardized scores from age 3 Peabody Picture Vocabulary Test; CDI = Children's Depression Inventory; CBCL = Child Behavior Checklist; YSR = Youth Self-Report; ICV = intracranial volume (cm³).

Table 2
Bivariate correlations

	1	2	3	4	5	6	7	8
1. Child Age at MRI Visit	–							
2. CBCL Withdrawn/Depressed	-.17	–						
3. CDI	-.18	.50***	–					
4. YSR Withdrawn/Depressed	-.20	.47***	.65***	–				
5. ICV	-.11	-.12	-.01	-.01	–			
6. Sex	.12	.16	.06	-.06	-.64***	–		
7. Risk Group	-.14	.33**	.24*	.11	.04	-.03	–	
8. PPVT	-.02	-.06	-.12	-.09	-.05	-.06	-.13	–

Note. * = $p < .05$; ** = $p < .01$; *** = $p < .001$; CBCL = Child Behavior Checklist; CDI = Children's Depression Inventory; YSR = Youth Self-Report; ICV = Intracranial Volume (cm^3); PPVT = standardized scores from age 3 Peabody Picture Vocabulary Test; Dummy coding was used for sex (0 = male, 1 = female) and Risk Group (0 = Low maternal risk group, 1 = High maternal risk group).

Table 3
Regression analyses of grey matter volume for CDI.

Regressor	Cluster Size (mm ³)	MNI Coordinates (peak voxel)			<i>p</i> -value (FWE corrected)	<i>Z</i> (peak voxel)
		x	y	z		
ROI Analyses						
CDI x Sex	25.5	-9	62	-8	.012	4.67
CDI	90	14	45	-21	.002	4.97
Whole Brain Analyses						
CDI	22.5	14	45	-21	.009	4.97

Note. All analyses covaried for the main effects of age, sex, maternal risk group, and total intracranial volume. All *p* values were FWE corrected and refer to cluster level significance. All regression analyses were two-tailed. CDI = Children's Depression Inventory.

Table 4*Regression analyses of grey matter volume for YSR-WD.*

Regressor	Cluster Size (mm ³)	MNI Coordinates (peak voxel)			<i>p</i> -value (FWE corrected)	<i>Z</i> (peak voxel)
		x	y	z		
ROI Analyses						
YSR-WD	183	12	48	-21	< .001	5.46
	72	38	42	-11	.002	4.78
Whole Brain Analyses						
YSR-WD	288	11	50	-18	< .001	5.63
	1.5	39	42	-11	.037	4.82

Note. All analyses covaried for the main effects of age, sex, maternal risk group, and total intracranial volume. All *p* values were FWE corrected and refer to cluster level significance. All regression analyses were two-tailed. YSR-WD = Youth Self-Report Withdrawn/Depressed subscale.

Table 5

Moderated regression analysis of grey matter volume for 25.5 mm³ cluster with peak voxel at (-9, 62, -8) based on ROI analysis.

Predictor	<i>b</i>	<i>sr</i> ²	<i>R</i> ²
(Intercept)	.33	–	
ICV	.00**	.13	
Sex	.07*	.04	
Age	-.03*	.03	.564**
Risk	.00	.00	
CDI	.01*	.02	
CDIxSex	-.02**	.15	

Note. A significant regression coefficient indicates the semi-partial correlation is also significant. *b* = unstandardized regression weights. *sr*² = semi-partial correlation squared. * = *p* < .05; ** *p* < .01; ICV = intracranial volume (mm³); CDI = Children's Depression Inventory.

Table 6*Regression analyses of grey matter volume for CBCL-WD.*

Regressor	Cluster Size (mm ³)	MNI Coordinates (peak voxel)			<i>p</i> -value (FWE corrected)	<i>Z</i> (peak voxel)
		x	y	z		
ROI Analyses						
CBCL-WD x Sex	6	-3	68	-3	.029	4.38
Whole Brain Analyses						
CBCL-WD x Sex	27	-41	38	6	.007	5.34

Note. All analyses covaried for the main effects of age, sex, maternal risk group, and total intracranial volume. All *p* values were FWE corrected and refer to cluster level significance. All regression analyses were two-tailed. CBCL-WD = Child Behavior Checklist Withdrawn/Depressed subscale.

Table 7

Moderated regression analysis of grey matter volume for 6 mm³ cluster with peak voxel at (-3, 68, -3) based on ROI analysis.

Predictor	<i>b</i>	<i>sr</i> ²	<i>R</i> ²
(Intercept)	.08	–	
ICV	.00**	.26	
Sex	.02*	.03	
Age	-.01	.01	.594**
Risk	-.01	.02	
CBCL-WD	.02**	.10	
CBCL-WDxSex	-.02**	.13	

Note. A significant regression coefficient indicates the semi-partial correlation is also significant. *b* = unstandardized regression weights. *sr*² = semi-partial correlation squared. * = *p* < .05; ** *p* < .01; ICV = intracranial volume (mm³); CBCL-WD = Child Behavior Checklist Withdrawn-Depressed scale.

Table 8

Moderated regression analysis of grey matter volume for 27 mm³ cluster with peak voxel at (-41, 38, 3) based on whole brain analysis.

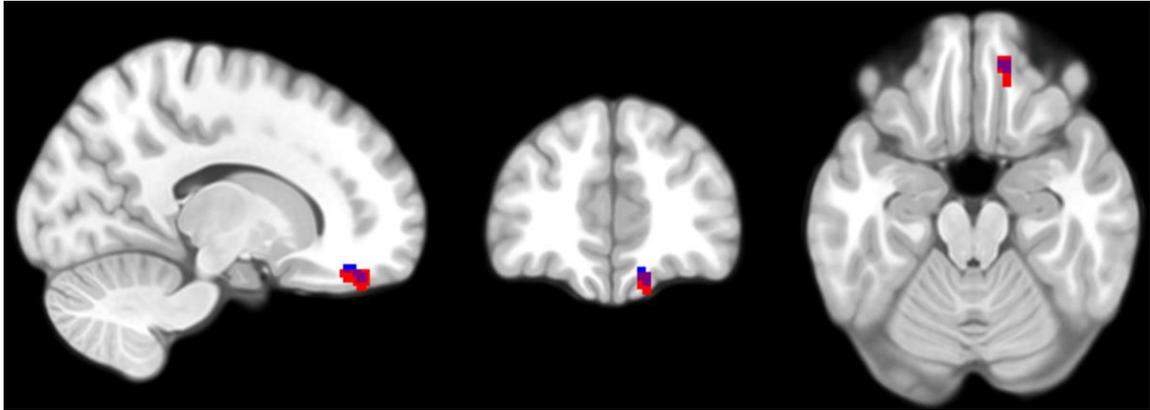
Predictor	<i>b</i>	<i>sr</i> ²	<i>R</i> ²
(Intercept)	-.91**	–	
ICV	.00**	.34	
Sex	.14**	.11	
Age	.02	.01	.593**
Risk	-.02	.00	
CBCL-WD	.08**	.21	
CBCL-WDxSex	-.08**	.20	

Note. A significant regression coefficient indicates the semi-partial correlation is also significant. *b* = unstandardized regression weights. *sr*² = semi-partial correlation squared. * = $p < .05$; ** $p < .01$; ICV = intracranial volume (mm³); CBCL-WD = Child Behavior Checklist Withdrawn-Depressed scale.

Figures

Figure 1

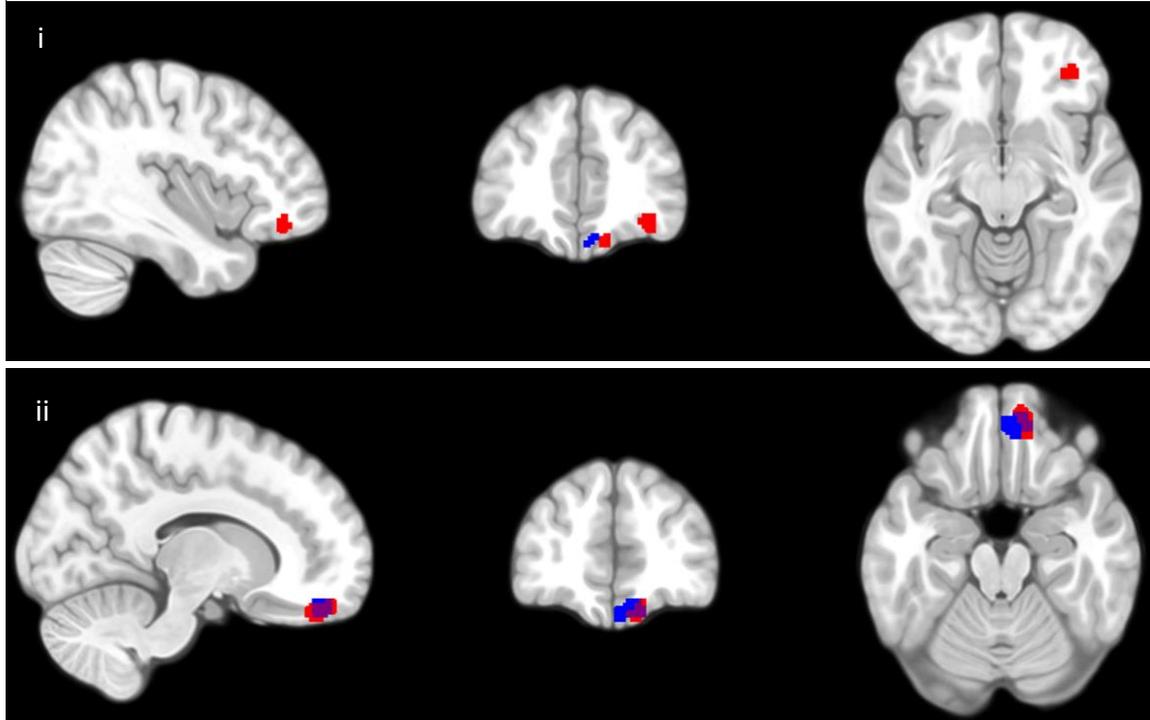
Subthreshold Depressive Symptoms Are Negatively Associated with Grey Matter Volume



Note. Children's self-reported subthreshold depressive symptoms (as measured by the CDI) are negatively associated with GMV during both ROI regression analysis (clusters highlighted in red for voxels where $p_{FWE} < .05$) and whole-brain regression analysis (highlighted in blue for voxels where $p_{FWE} < .05$) regression analyses. CDI = Children's Depression Inventory.

Figure 2

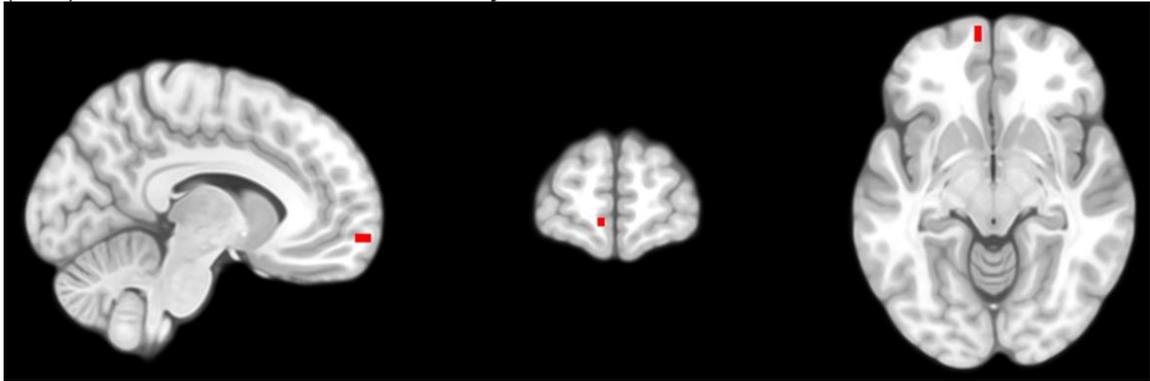
Subthreshold Depressive Symptoms (YSR-WD) Are Negatively Associated with Grey Matter Volume



Note. Children's self-reported subthreshold depressive symptoms (as measured by the YSR-WD) are negatively associated with GMV during both ROI regression analysis (clusters highlighted in red for voxels where $p_{FWE} < .05$) and whole-brain regression analysis (clusters highlighted in blue for voxels where $p_{FWE} < .05$); i = view of lateral OFC cluster; ii = view of medial OFC cluster; YSR-WD = Youth Self-Report Withdrawn-Depressed subscale.

Figure 3

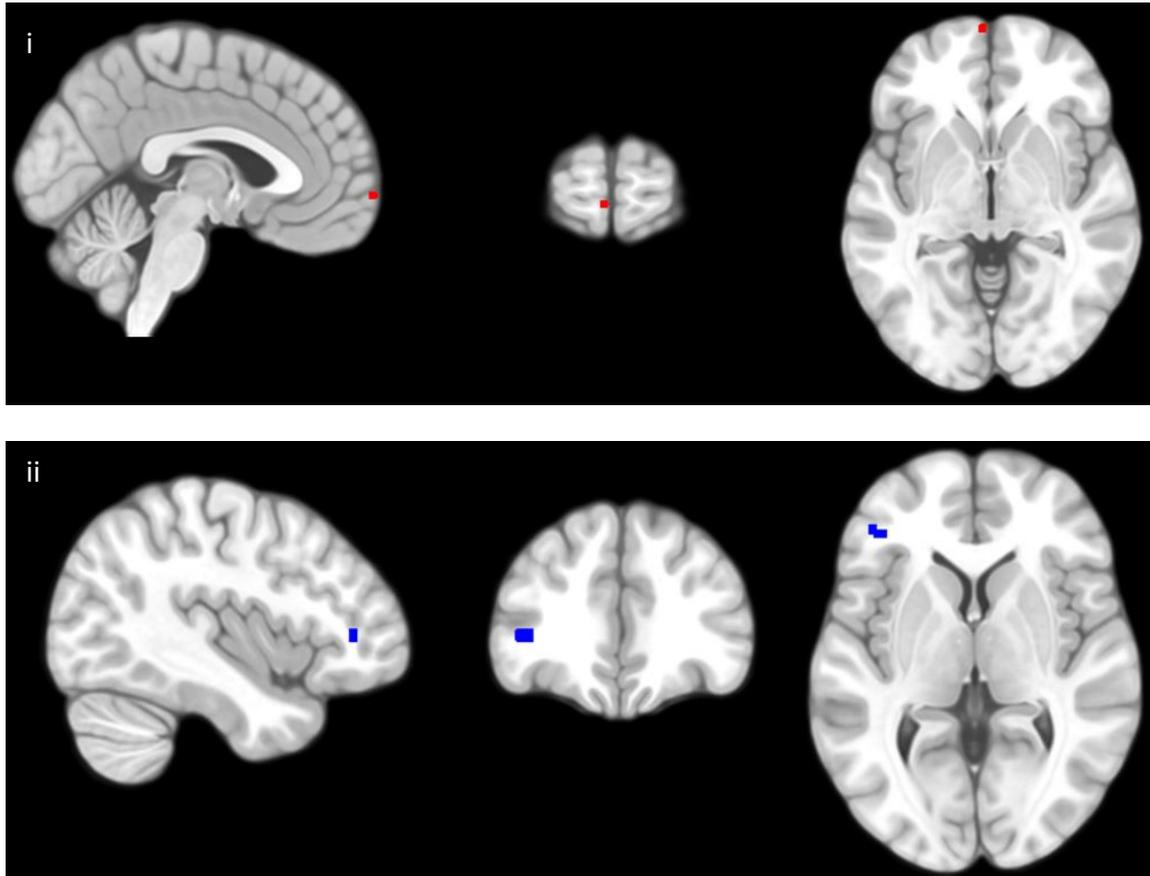
Sex Moderates the Relationship Between Subthreshold Depressive Symptoms (CDI) and Orbitofrontal Cortex Grey Matter Volume



Note. The association between children's subthreshold depressive symptoms (CDI) and OFC GMV is moderated by sex during ROI analysis (clusters highlighted in red for voxels where $p_{FWE} < .05$). CDI = Children's Depression Inventory

Figure 4

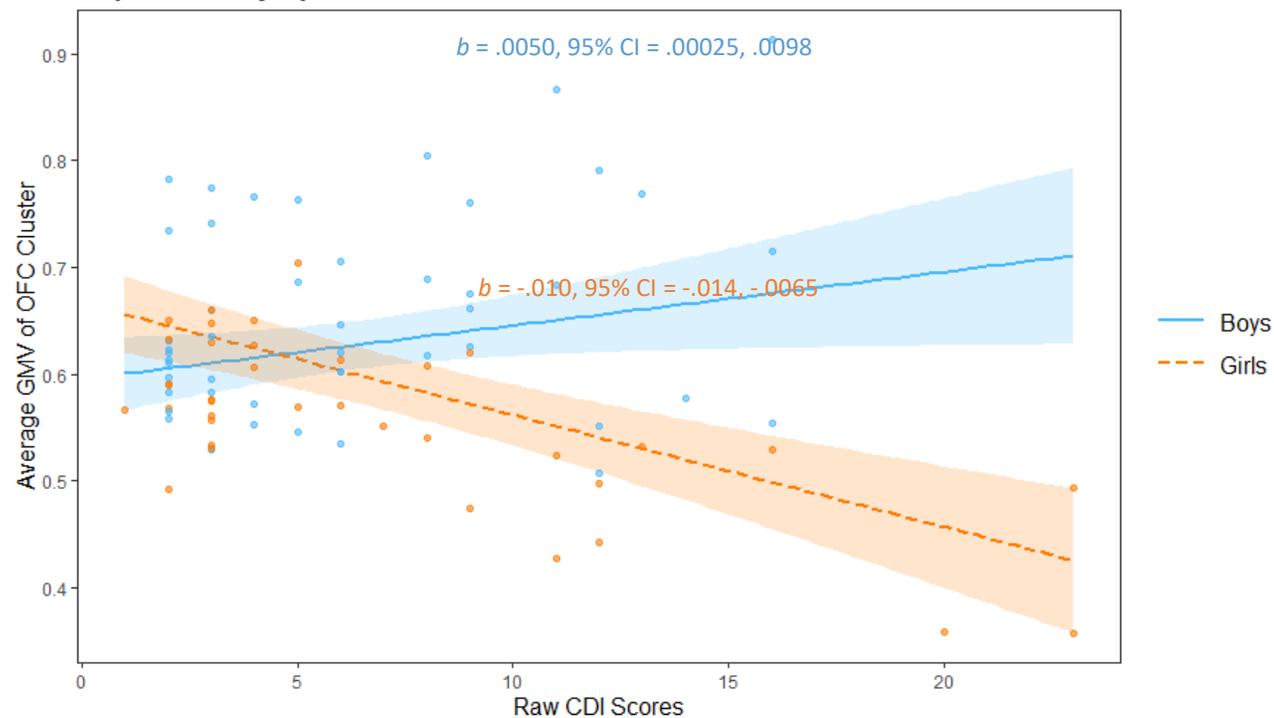
Sex Moderates the Relationship Between Maternal-reports of Children's Subthreshold Depressive Symptoms (CBCL-WD) and Grey Matter Volume



Note. The association between maternal-report of children's subthreshold depressive symptoms (CBCL-WD) and GMV is moderated by sex both during ROI regression analysis (clusters highlighted in red for voxels where $p_{FWE} < .05$) and whole-brain regression analysis (clusters highlighted in blue for voxels where $p_{FWE} < .05$); i = view of medial OFC cluster; ii = view of inferior frontal gyrus cluster; CBCL-WD = Child Behavior Checklist Withdrawn-Depressed subscale.

Figure 5

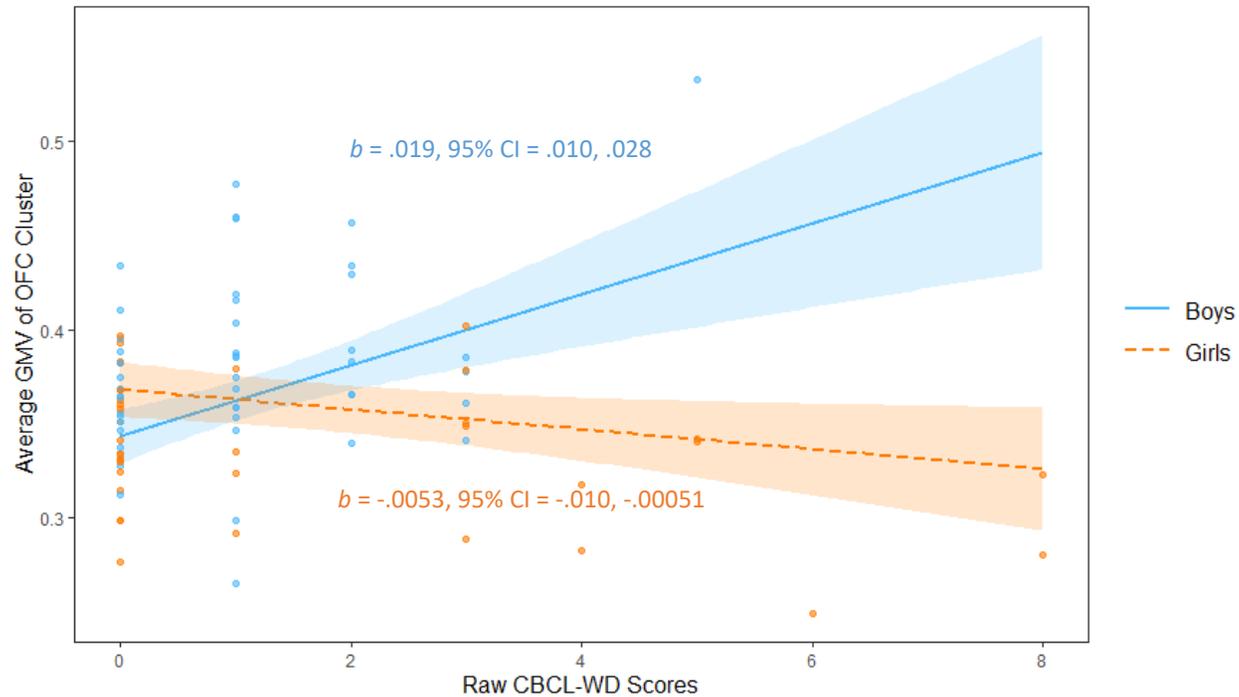
Sex Moderates the Relationship Between Children's Self-Reported Depressive Symptoms and GMV in the OFC



Note. Children's sex moderates the relationship between self-reported depressive symptoms (according to the CDI) and GMV in an OFC cluster (peak voxel -9, 62, -8), during ROI analysis of the OFC. Highlighted regions indicate 95% confidence intervals.

Figure 6

Sex Moderates the Relationship Between Maternal-Reported Depressive Symptoms and GMV in the OFC



Note. Children's sex moderates the relationship between maternal report of children's depressive symptoms (according to the CBCL-WD) and GMV in an OFC cluster (peak voxel -3, 68, -3), during ROI analysis of the OFC. Highlighted regions indicate 95% confidence intervals.

Figure 7

Sex Moderates the Relationship Between Maternal Reported Depressive Symptoms and GMV in the left inferior frontal gyrus

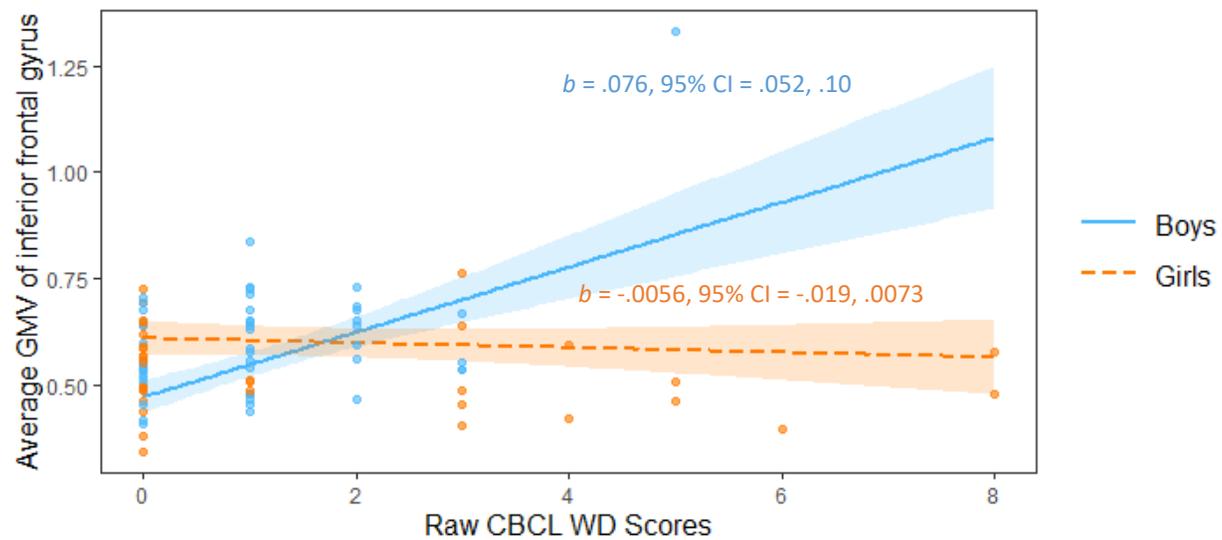


Figure 7. Children's sex moderates the relationship between maternal report of children's depressive symptoms (according to the CBCL-WD) and GMV in a cluster (peak voxel -41, 38, 3) in the left inferior frontal gyrus, during whole brain analysis. Highlighted regions indicate 95% confidence intervals.

Chapter 3 – Children’s Neural Reactivity to Maternal Praise and Criticism: Associations with Early Depressive Symptoms and Maternal Depression

Introduction

Major depression is among the most common mental disorders with annual and lifetime prevalence rates of 10.4% and 20.6% (Hasin et al., 2018), respectively. Depression is also a global leading cause of disability (Vos et al., 2012), suicide (Bostwick & Pankratz, 2000), increased mortality due to co-occurring health conditions (Cuijpers & Smit, 2002), and a host of other negative psychosocial outcomes (Kessler, 2012). Identifying early emerging vulnerabilities and mechanisms that lead to depression may ultimately reduce its considerable impact by informing prevention and early intervention efforts. Although relatively few young children meet criteria for a depressive disorder (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003), the transition from late childhood to adolescence is characterized by a substantial increase in depressive symptoms and disorders (Merikangas, He, Brody, et al., 2010; Merikangas, He, Burstein, et al., 2010). Research examining vulnerability in youth at risk for depression is therefore well suited to identifying associations between putative early vulnerability mechanisms and increased rates of depression. With this in mind, the goal of our study was to investigate the relationship between never-depressed children’s neural responses to valanced maternal feedback, and their depressive symptoms (Bertha & Balázs, 2013; Cuijpers & Smit, 2004; Fergusson, Horwood, Ridder, & Beautrais, 2005; Wesselhoeft et al., 2013) and maternal depression history (Brennan, Hammen, Katz, & Le Brocque, 2002; Goodman et al., 2011; Klein et al., 2005), used as markers of depression risk.

Although depression is etiologically complex, at least some variance in risk appears to stem from early experience, particular early caregiving. Meta-analytic findings

from cross-sectional, retrospective, and longitudinal studies show moderate associations between negative parenting styles and subsequent depression (McLeod, Weisz, & Wood, 2007; Yap & Jorm, 2015; Yap, Pilkington, Ryan, & Jorm, 2014). Specifically, parental withdrawal (i.e., lack of involvement with, or interest in, the child), hostility/criticism, inconsistent discipline, over-involvement (i.e., parental interference with age appropriate autonomy and independence), and both authoritarian and permissive (i.e., demanding, directive, and punitive caregiving) parenting are associated with childhood and adolescent depression symptoms and diagnoses (McLeod et al., 2007; Yap & Jorm, 2015; Yap et al., 2014). In contrast, parental warmth, monitoring (i.e., parental knowledge of their child's activities and relationships), and autonomy granting (i.e., encouragement, acknowledgement, and solicitation of child's opinions and choices) are associated with lower depressive symptoms and depression diagnoses in youth (McLeod et al., 2007; Yap & Jorm, 2015; Yap et al., 2014).

As with other etiological factors, the processes by which parenting influences youth depression are complex and likely involve interactions with a variety of endogenous and exogenous influences (e.g., genetics, exposure to negative parental cognitions, behaviour, or affect, and exposure to environmental stress; Goodman & Gotlib, 2002). However, an extant literature supports the notion that parenting behaviour may confer depression risk at least in part by contributing to the development of maladaptive neural functioning in childhood. For example, meta-analysis has found that extreme forms of maladaptive parenting (e.g., abuse and neglect) are positively associated with children's amygdala and insula reactivity during processing of negative emotional stimuli (Hein & Monk, 2017). However, studies of how more typical caregiving styles (i.e., parental over-involvement, criticism, etc.) relate to children's

neural development are rare, which is problematic given ample evidence that more common, relatively mild negative environmental exposures also influence development across the lifespan (e.g., Rutter, 2005).

The small extant literature on this topic indicates that, among healthy youth, normative variation in parenting behaviour is associated with youths' neural response to affectively valenced stimuli. Specifically, Romund and colleagues (2016) found that maternal warmth, assessed via child-reported maternal caregiving behaviour, was associated with lower amygdala activity when processing fearful face stimuli. Similarly, observational ratings of negative parenting behaviour (i.e., aggressive and dysphoric affect, and anger toward the child) during a lab-based parent-child interaction task were correlated with children's amygdala activity when processing angry and fearful face stimuli (Pozzi et al., 2020). Child-reported maternal warmth predicted lower functional activity in children's amygdala, insula, subgenual ACC (sgACC), vIPFC, and ACC during exposure to audio recordings of maternal criticism (Butterfield et al., 2020). Thus, while the extant literature is limited, it appears that, among youth, positive parenting behaviour is associated with lower functional activity in brain regions relevant to processing and regulating emotional stimuli, while negative parenting is associated with increased activity in similar regions. These same brain regions are central to prominent theories of the role of the brain in depression and depression risk (Disner, Beevers, Haigh, & Beck, 2011), supporting the notion that early caregiving may shape depression risk through its impact on children's early neural development.

Research examining neural function in the context of tests of interpersonal models of depression (Starr & Davila, 2008) may also be relevant to understanding associations between parenting and children's brain development and depression risk. For example,

research on attachment has found that early parent-child care experiences are not only foundations upon which individuals base future interpersonal relationships (Sroufe, 2005), but are also related to the brain's functional response to social interactions (DeWall et al., 2012); these early experiences also mark vulnerability to depression (Morley & Moran, 2011). Disruptions to interpersonal relationships are associated with the onset of depressive episodes (Eberhart & Hammen, 2006; Monroe, Rohde, Seeley, & Lewinsohn, 1999; Slavich, O'Donovan, Epel, & Kemeny, 2010). With respect to research on the role of the brain in processing interpersonal feedback, most studies have used "pseudoparticipant" stimuli (i.e., standardized interpersonal feedback stimuli presented to research participants as though it came from another study participant) to elicit neural responses to social exclusion versus inclusion (e.g., Davey, Allen, Harrison, & Yücel, 2011; Silk et al., 2012; Williams & Jarvis, 2006). Studies using these paradigms in healthy populations generally show that negative interpersonal feedback is typically associated with activation in the anterior insula (AIC), ACC, and the inferior orbitofrontal cortex (Cacioppo et al., 2013).

In studies examining neural responses to interpersonal feedback in depression, Davey and colleagues (2011) found that young adults with depression had significantly greater amygdala activity in response to peer acceptance (i.e., being rated as "likeable" by a pseudoparticipant peer) compared to healthy controls. While Silk and colleagues (2014) found no differences in neural activity between depressed and healthy adolescents during peer acceptance trials, negative interpersonal feedback (i.e., peer rejection) elicited increased amygdala, subgenual ACC, and striatal activity among depressed adolescents. Yttredahl et al. (2018) found that women with depression had greater activity in the right AIC and dorsal ACC during rejection trials (vs. neutral stimuli) compared to non-

depressed controls. Other studies indicate that depressed individuals show increased activity in the insula during negative interpersonal feedback, indexed using a Cyberball task (i.e., social exclusion; Jankowski et al., 2018; Kumar et al., 2017; Mellick, 2017). Mellick (2017) reported that negative interpersonal feedback is associated with increased activity in the ventral striatum, and Kumar and colleagues (2017) found increased activity in the amygdala and vIPFC among depressed participants. Similarly, single studies have reported that positive interpersonal feedback (i.e., social inclusion) among depressed participants is associated with *decreased* activity in the middle temporal gyrus (Jankowski et al., 2018), precuneus, and middle cingulate (Mellick, 2017). Overall, while this literature is somewhat inconsistent, it appears that depression is associated with greater insula, ACC, and striatal activity during negative interpersonal feedback; additionally, increased amygdalar activity is associated with both positive and negative feedback during interpersonal feedback tasks among people with depression.

While this literature provides initial clues concerning brain regions that are potentially important in shaping early caregiving-depression associations, much less is known about neural reactivity to maternal feedback in never-depressed youth at *risk* for depression. High-risk studies may help establish whether differences in neurofunctional processes emerge prior to depression, thereby potentially contributing to its onset. With respect to the small extant literature on this topic, Aupperle et al. (2016) reported that adolescents' internalizing symptoms were positively associated with right amygdala activity during maternal criticism and negatively related to activity during maternal praise; left amygdala activity was also negatively related to both types of maternal feedback. In studies of high-risk children using non-maternal stimuli, children with a family history of depression showed diminished activity in reward processing regions

(e.g., ACC and ventral striatum) during positive interpersonal feedback (i.e., peer acceptance; Olino, Silk, Osterritter, & Forbes, 2015); however, relative to low-risk children, high-risk children showed increased BOLD activity in regions important for self-referential thought (e.g., superior and middle temporal gyri, middle frontal gyri, and precuneus) during positive feedback trials. Olino and colleagues (2015) did not report the relationship between negative social feedback trials (i.e., social rejection) and neural function. Masten and colleagues (2011) found that thirteen-year-olds' sgACC, dorsomedial PFC (dmPFC), and middle temporal gyrus response to peer rejection during the Cyberball Task prospectively predicted increases in depressive symptoms one year later, although activation was unrelated to concurrent depressive symptoms. While these findings are compelling, the small size of this literature precludes conclusions regarding specific aspects of brain activity in response to maternal feedback that may contribute to depression risk.

Given the stimuli used, much of this literature may also be limited in its ecological validity for understanding neural processes involved in social or interpersonal feedback. While rigorously controlled experimental paradigms (e.g., the Cyberball task) that allow for relatively easy manipulation of positive and negative interpersonal feedback maximize internal validity, the relatively simple stimuli used in these paradigms may lack external validity in terms of tapping brain activity during “real-world” interactions, including those with parents. In contrast, a number of studies have used an ecologically valid Maternal Feedback Challenge (MFC; Hooley, Gruber, Scott, Hiller, & Yurgelun-Todd, 2005) task to study interpersonal feedback/caregiving processes in the context of depression and depression risk. During the MFC task, participants listen to audio recordings of their own mother providing neutral, critical, and positive feedback

with content directed specifically toward them and drawn from actual topics of discussion between the dyads (Hooley et al., 2005). By using maternal stimuli individualized to the participant, tasks such as the MFC may have increased ecological validity, potentially capturing how the affective tone of early, naturalistic, day-to-day interactions with mothers, one of children's most important early relationships, is related to brain function and depression risk. Although the MFC does not measure the characteristic patterns of parenting per se (i.e., it does not speak to the *extent* to which mothers provide positive and negative feedback to their children), presumably all children are exposed to both positively and negatively valenced feedback from their mothers with regularity. Hence, the MFC can be viewed as an index of children's individual differences in brain activity in response to valenced feedback from their mothers.

In the earliest use of the MFC (Hooley et al., 2005), women with a history of depression had decreased dlPFC activity while listening to maternal criticism stimuli, while never-depressed women had substantial increases in dlPFC activity. In a replication and extension of this study, Hooley and colleagues (2009) reported the same pattern of significantly lower dlPFC activity, as well as diminished anterior cingulate cortex (ACC) activity, in response to maternal criticism among formerly depressed women. Additional analyses found that maternal criticism was associated with greater amygdalar activity in formerly depressed women, relative to never-depressed controls (Hooley et al., 2009). In a follow-up study (Hooley, Siegle, & Gruber, 2012), currently depressed women were added to the sample from Hooley and colleagues' (2009) paper. Both current depression and a history of depression were unrelated to BOLD response to maternal criticism or praise in either the dlPFC or amygdala; however, participants' self-reported *perceptions* of maternal criticism were associated with diminished dlPFC and enhanced amygdala

response to maternal criticism. That distinct patterns of activity in the ACC, dlPFC, and amygdala are found even once depression has remitted suggests that activation in these regions may be associated with a trait vulnerability to depression, rather than simply being associated with current depression (Hooley et al., 2009; 2012); however, “scar” effects are also possible. Similarly, Silk and colleagues (2017) found that adolescents with depression showed greater activity in limbic regions (i.e., parahippocampal gyrus) when listening to maternal criticism (versus neutral feedback), as well as diminished activity in the thalamus, caudate, vmPFC, and precuneus during maternal praise (versus neutral feedback), relative to healthy controls.

Current Study

In summary, maladaptive responses to both early caregiving and interpersonal relationships are implicated in depression; however, the neural underpinnings of responsivity to positive and negative feedback from close others in never-depressed children is poorly understood. More specifically, our understanding of the directionality of the relationship between brain function and depression is limited by the fact that most relevant studies have been done with adults and adolescents with either a personal history of, *or* current, depression. In the current study, we therefore focused on 81 never-depressed 9- to 12-year-olds ($M_{\text{age}} = 11.12$, $SD_{\text{age}} = .63$), contrasting the functional brain response to ecologically valid positive and negative maternal feedback (i.e., the MFC) among those with and without a maternal history of depression; (Connell & Goodman, 2002; Klein et al., 2005). In addition, given the predictive validity of subthreshold symptoms for later disorder (Cuijpers & Smit, 2004; Shankman et al., 2009), we also examined associations between never-depressed children’s early emerging depressive

symptoms and their brain activity during both positive and negative maternal feedback in the MFC. By focusing analyses on children with no personal history of depression, we aimed to characterize the brain-based correlates of depression risk in youth. Notably, to our knowledge this is the first study to examine the relationship between children's depression risk and brain response to maternal feedback using the MFC in a sample of never-depressed children.

The novelty of the current study design precludes strong hypotheses; however, based on previous reports that depression (Kumar et al., 2017; Silk et al., 2017, 2014; Yttredahl et al., 2018), depression history (Hooley et al., 2009), and depression risk (Aupperle et al., 2016; Masten et al., 2011) are associated with increased BOLD reactivity to negative interpersonal feedback in brain regions responsible for affective salience (e.g., insula, amygdala, sgACC) and reward/punishment processing (e.g., striatal regions including caudate, putamen, and nucleus accumbens), we hypothesized that depression risk indexed by maternal history of depression would be associated with functional responses to negative maternal feedback in these same regions. Specifically, we predicted that children with a maternal history of depression would have significantly greater BOLD response in affective salience and striatal regions during maternal criticism, relative to children with no maternal history of depression. Furthermore, we predicted that children's sub-clinical depressive symptoms (self- and maternal-reported) would be positively associated with BOLD response in these same brain regions during negative maternal feedback. Consistent with literature suggesting that depression is associated with diminished functional activity in regions relevant to emotion regulation (e.g., dlPFC, vlPFC, ACC) during exposure to criticism (e.g., Hooley et al., 2009; 2005), we further predicted that a maternal history of depression and children's own depressive

symptoms would be associated with diminished BOLD response in these same brain regions.

The relationship between children's depression risk and brain response to maternal feedback was first examined using small volume corrections within three *a priori* regions of interest (ROI). Our ROI were based on previous research on interpersonal feedback (Butterfield et al., 2020; Lee, Siegle, Dahl, Hooley, & Silk, 2014) and included an affective-salience ROI (bilateral amygdala, bilateral insula, and the subgenual anterior cingulate [sgACC]), emotion-regulation ROI (bilateral dlPFC, bilateral vlPFC, and bilateral ACC), and (c) a reward-processing ROI (bilateral caudate, putamen, and nucleus accumbens). Exploratory whole-brain analyses were conducted following small volume corrected ROI analyses.

Materials and Methods

Participants

Children and their mothers were recruited from a larger longitudinal study of children's depression risk and temperament development ($N = 409$) that began when children were 3-year-olds. Children with major medical or psychological problems were excluded from participation and all child participants were of typical cognitive development based on the Peabody Picture Vocabulary Test-Fourth Edition ($M = 113.21$, $SD = 14.31$; Dunn & Dunn, 2007). An average of 7.52 years later ($SD = 0.58$) a subset of children was recruited for the current study based on maternal depression history (MH+), according to previously collected diagnostic data using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Non-patient Edition (SCID-I/NP; First et al., 2002). Children were considered high- or low-risk for depression based on whether their

mothers had a history of recurrent major depression ($n = 26$) *or* a single major depressive episode *and* an anxiety disorder ($n = 3$)⁶.

Two hundred and thirty-seven families were contacted (58 MH+) for participation in the current study. Six children were excluded due to contraindications to the MRI environment (e.g., metallic orthodontic work, metallic objects implanted in the body, or self-reported claustrophobia). Of the remaining 231 families, 102 agreed to participate, of which 82 participated in the MFC task in the scanner. Of the 28 families who agreed to participate but did not contribute MFC data, four participants were unable to finish the MRI visit due to discomfort in the scanner, nine families declined to participate in the MRI portion of the study, and seven families discontinued participation in the current study before the MRI visit. Ultimately, 81 children contributed MRI data of sufficient quality to be analyzed. All children were screened for a personal history of mood disorder (see Procedures and Measures for details)⁷. The majority of child participants identified their race as White (96%), with one participant each identifying as Black, Hispanic/Latino, and Mixed Race. Modal family income was $> \$100,000$ CAD (5.1% $< \$20,000$ CAD; 10.1% $\$20,000 - \$40,000$ CAD; 20.3% $\$40,001 - \$70,000$ CAD; 27.8% $\$70,000 - \$100,000$ CAD; 36.7% $> \$100,000$ CAD). The demographic data for this sample closely resembles the census data of the community from which it was drawn (i.e., London, Ontario; Statistics Canada, 2006). See Table 1 for an overview of additional demographic statistics of the final sample of 81 participants.

⁶ We excluded specific phobia and social anxiety limited to public speaking in our definition given that these are less heritable, generally less impairing, and are likely weaker markers of children's risk for internalizing disorder (Kendler, Neale, Kessler, Heath, & Eaves, 1992).

⁷ No children were excluded based on current or lifetime history of mood disorder.

Procedures and Measures

Data for this study were collected from children and their mothers across four separate assessment visits (for more details see Vandermeer et al., 2020). Briefly, this included: 1) a phone interview to complete the parent-report portion of the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997); 2) a home visit to complete the child self-report portion of the K-SADS-PL, gather MFC audio stimuli, and complete questionnaire measures; 3) a lab visit to complete the SCID-I/NP with moms and the Trier Social Stress Task for Children (Buske-Kirschbaum et al., 1997) with child participants (not discussed in this paper); 4) a MRI visit.

Structured Diagnostic Interviews. All children and their mothers were administered structured clinical interviews by graduate students in clinical psychology trained by the senior author (EPH). To assess children's lifetime history of mental disorder, children and their mothers were interviewed using the K-SADS-PL (Kaufman et al., 1997). All child diagnoses⁸ had 100% interrater agreement ($N = 11$), including major depression⁹.

Mothers' lifetime history of mental disorder was assessed using the SCID-I/NP (First et al., 2002). All participating mothers had completed the same version of the SCID-I/NP several years prior in a previous wave of data collection; thus, the current

⁸ In total, seven children had a lifetime history of a DSM-IV-TR diagnosis (primarily one of the anxiety disorders; $n = 7$; $n_{\text{ADHD}} = 3$; $n_{\text{oppositional defiant disorder}} = 2$). Only four children currently met criteria for a diagnosis.

⁹ In the case of some K-SADS and SCID-I/NP diagnoses (e.g., K-SADS depression), no participant had a history of the disorder, precluding the calculation of Cohen's Kappa; however, interviewer agreement on the absence of the diagnosis was 100%.

SCID-I/NP interviews focused solely on the period of time since participants' previous SCID-I/NP. We had excellent inter-rater reliability for all specific diagnoses covered by the SCID-I/NP⁴, including lifetime history of depressive episodes ($Kappa = 1.00$, $N = 10$).

Questionnaire Measures. Children completed self-reported symptom measures, including the Children's Depression Inventory 2nd Edition (CDI; Kovacs, 2011); $\alpha = .83$) and the Youth Self-Report (YSR; Achenbach & Rescorla, 2001). Mothers were also asked to report on their child's symptoms by completing the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001). The withdrawn-depressed subscales of the YSR (YSR-WD; $\alpha = .72$) and the CBCL (CBCL-WD; $\alpha = .72$) were used as indices of child self- and mother-reported children's depressive symptoms, respectively.

Maternal Feedback Challenge. Maternal Feedback Challenge Stimuli. During fMRI scanning, all children participated in a MFC task adapted from procedures outlined in Hooley et al. (2005). All MFC stimuli were created and collected during the home visit with the family in a quiet room in each participant's home, separate from the child participant. Mothers wrote two feedback stimuli for each of three affective valences for a total of six stimuli (i.e., two neutral, two critical, and two praising comments) for subsequent audio recording. Each of the three affective valence conditions started with a standardized sentence stem specific to that condition (Table 2). To enhance the validity of the task, mothers were told that they could give feedback on any topic they chose as long as it was an issue frequently discussed with the child. The researcher collecting these stimuli ensured that there was sufficient material in each written statement for a 30s audio recording.

Mothers were then audio recorded using a NESSIE adaptive USB condenser microphone (Blue Microphones, Westlake Village, CA, USA) and Audacity (Version 2.1.2) while reading their valanced feedback statements. Raw audio tracks were then edited by trained graduate students to ensure all audio stimuli were exactly 30s in length (i.e., by cropping extended periods of silence from audio clips), had a maximum amplitude of -1.0 dB (using Audacity's "Amplify" effect), and a consistent dynamic range (using Audacity's "Compressor" effect with default settings). All audio stimuli were reviewed during the editing process to ensure that no essential content was lost and no audio artifacts were introduced during editing.

To ensure that the affective intensity of MFC stimuli was not systematically related to maternal history of disorder, two undergraduate research assistants blind to other study data rated all MFC audio stimuli for their "positivity" and "negativity" on a 10-point scale (1 = "Not at all" and 10 = "Very" positive or negative). Mothers with and without a depression history did not differ in the intensity of the feedback stimuli they provided based on independent *t*-test analysis (all $p > .05$).

Maternal Feedback Challenge Administration. Children were presented with their individualized MFC audio stimuli over MRI-safe in-ear headphones using E-prime 2.0 (Version 2.0.10.242) during whole-brain fMRI scanning. MFC stimuli were presented in a blocked design such that each of the three scanner runs consisted of two blocks of MFC stimuli of the same valence (i.e., one run each of: two Neutral, two Criticism, two Praise) interspersed with periods of rest (Figure 1). Children were instructed to listen to MFC stimuli while fixating their gaze on a black cross against a white background. Following each run, children were presented with a Likert-type rating scale of emotionally valanced cartoon faces and asked to rate their emotional response to the previous run of MFC

stimuli. Neutral MFC stimuli were always presented first, followed by praise and criticism trials, with the order of praise/criticism presentation counterbalanced across participants.

MRI Acquisition. Consistent with best practices for scanning children (de Bie et al., 2010), children completed a “mock scan” session in a replica MRI system prior to participating in the MRI portion of the study. During the mock scan, the upcoming MRI session procedures were explained and children were given the opportunity to ask questions.

Children’s MRIs were obtained using a 3T Siemens Magnetom Prisma scanner with a 32-channel head RF coil (Siemens, Erlangen, Germany). Each of the three runs of the MFC task (i.e., one neutral run with two blocks of feedback, one praise run with two blocks of feedback, and one critical feedback run with two blocks of feedback) consisted of 89 T_2^* -weighted volumes collected using an echo-planar imaging (EPI) sequence (3×3×3 mm voxel size, repetition time [TR] = 1000 ms, echo time [TE] = 30 ms, field of view [FOV] = 210 mm) yielding 48 axial slices. T_1 -weighted anatomical scans were also acquired, for co-registration with the EPI series, using a 3D magnetization prepared rapid gradient echo sequence (1×1×1 mm voxel size, TR = 2300 ms, TE = 2.98 ms, FOV = 256 mm) yielding 192 sagittal slices per participant.

fMRI Quality Assurance and Preprocessing. All raw DICOM scans were reviewed and converted into NIFTI format using MRICRON software (Rorden et al., 2007). Quality assurance and preprocessing were conducted using SPM12 (Version 7487; <http://www.fil.ion.ucl.ac.uk/spm>) and MATLAB 9.7 (Version 9.7.0.1247435; Mathworks, Inc., Natick, MA, USA). All quality assurance and preprocessing steps were performed separately according to functional run condition (i.e., neutral, critical, and

praising feedback runs were preprocessed separately from one another). T_1 -weighted anatomical scans were manually reoriented to set the anterior commissure as the point of origin for all participants. The ArtRepair toolbox (Mazaika, Hoefft, Glover, Reiss, & Others, 2009; Mazaika, Whitfield, & Cooper, 2005; Mazaika, Whitfield-Gabrieli, Reiss, & Glover, 2007) was used as a quality assurance protocol. Specifically, ArtRepair was used to flag and interpolate (linear interpolation using the nearest unrepaired scans before and after a flagged scan) individual scans with frame-wise displacement threshold of > 0.9 mm (calculated using Power, Barnes, Snyder, Schlaggar, and Petersen's [2012] formula for frame-wise displacement) or frame-wise global signal intensity threshold $> 1.3\%$ deviation from the mean. Scanner runs with excessive repair (i.e., $\geq 20\%$ [18 scans]) or where mean frame-wise displacement was > 0.9 mm were dropped from further analyses¹⁰. Preprocessing included realignment to a mean image, co-registering functional data to T_1 -weighted anatomical scans in a standardized MNI space with $2 \times 2 \times 2$ mm voxels, and spatial smoothing using a 3-dimensional 6 mm full width at half maximum (FWHM) Gaussian smoothing kernel.

Data Analyses

fMRI Data Analyses. SPM12 was used to analyze all fMRI data. All fMRI analyses included children's age and sex as covariates. All analyses of the MFC fMRI data were modelled using mixed effects models in which individual children's data were first modelled using a fixed effects model (i.e., Level One) before modelling group differences and regressions using a random effects model (i.e., Level Two).

¹⁰ Across all participants, only two scan runs were dropped. One participant's neutral stimuli scans were dropped due to excessive repair and another participant's praise scans were dropped due to high mean frame-wise displacement.

Level One: Intra-Individual Analyses. A first-level, fixed effects multiple regression was used to model functional responses of individuals. Neutral, Praise, and Critical MFC conditions were modelled separately at this stage using a canonical hemodynamic response function (Poldrack, Mumford, & Nichols, 2011). Motion parameters (three translational and three rotational, per scanner run) were treated as covariates in these analyses (Jahn, 2019; Poldrack et al., 2011). Main effects of each of the three MFC conditions were modelled by contrasting activity during MFC stimuli presentation with functional activity during the resting portion of the MFC task (e.g., Neutral vs. Rest, Praise vs. Rest, and Criticism vs. Rest).

Level Two: Group and Regression Analyses. At Level Two, a 2x3 factorial ANOVA was conducted to examine differences in functional response to the MFC (as modelled at Level One) according to maternal depression history, modelled as a between-subjects factor; MFC stimuli condition was modelled as a within-subjects factor. Similarly, random effects regression analyses were modelled to test associations between children's self- (i.e., CDI and YSR-WD) and mother-reported (i.e., CBCL-WD) depressive symptoms (Jahn, 2019). Children's sex and age were included as covariates in all level two analyses. Participant counterbalancing of MFC stimuli presentation order were also entered as covariates; however, given that counterbalancing did not meaningfully alter results, this variable was dropped in final analyses to retain statistical power.

Results of Level Two analyses were first interpreted using small volume correction to constrain analyses within three *a priori* regions of interest (ROI), chosen based on previous research on interpersonal feedback (Butterfield et al., 2020; Lee et al., 2014). These included: (a) an Affective-Salience ROI (bilateral amygdala, bilateral

insula, and the subgenual anterior cingulate [sgAC]); (b) an Emotion-Regulation ROI (bilateral dlPFC, bilateral vlPFC, and bilateral ACC); and (c) a Reward-Processing ROI (bilateral caudate, putamen, and nucleus accumbens). All ROIs were defined using the WFU PickAtlas (Maldjian et al., 2004, 2003), and the Automated Anatomical Labeling atlas 3 (AAL; Rolls, Huang, Lin, Feng, & Joliot, 2020) and Talairach Daemon (TD; Lancaster, Summerlin, Rainey, Freitas, & Fox, 1997; Lancaster et al., 2000) atlases (see Table 3 for ROI). Finally, exploratory whole-brain analyses were conducted. Based on recommendations by Woo, Krishnan, & Wager (2014) all analyses were conducted using cluster-extend thresholding with a voxel-wise threshold of $p < .0001$ and a cluster-level significance threshold of $p < .05$ (family-wise error corrected) at both the ROI and whole-brain level of analysis.

Results¹¹

Correlations Among Major Study Variables

See Table 4 for bivariate correlations among all major study variables. All continuous measures of depressive symptoms (i.e., CDI, CBCL-WD, and YSR-WD) were positively associated with one another. Children with a maternal history of depression had higher CDI and CBCL-WD scores than children without a maternal depression history, although they did not differ in YSR-WD scores. CDI and CBCL-WD scales were negatively associated with children's self-reported emotional response to MFC praise stimuli (i.e., as children's self- and parent-reported depressive symptoms

¹¹ Although no child participant had a lifetime depression history based on the K-SADS-PL (lifetime or current), three ($N_{MH+} = 2$) had CDI scores above the suggested cut-off (> 19) for clinically significant symptoms in a community sample (Kovacs, 2011); excluding these participants from analyses did not change the pattern of results.

increased, maternal praise stimuli were rated less positively); however, children's self-reported emotional responses to MFC neutral and critical stimuli were unrelated to either measure of children's depressive symptoms. Children's self-reported emotional responses to MFC stimuli did not differ based on maternal depression history for any of the three conditions (all $p > .05$). Movement in the scanner (operationalized as mean frame-wise displacement, in mm) was strongly associated within individuals across MFC trials and was negatively correlated with age. Importantly, neither a maternal history of depression nor any of the symptom measures (i.e., CDI, CBCL-WD, or YSR-WD) were associated with scanner movement.

Manipulation Checks

There was a significant effect of MFC condition on children's self-reported emotional response for the three conditions, $F(1.77, 138.23) = 120.18, p < .001$. Post-hoc analyses by pairwise t -tests found that children experienced neutral stimuli ($M = 3.65, SD = .78$) as more positive than critical stimuli ($M = 2.69, SD = 1.01; t(78) = 7.73, p < .001$), praise stimuli were experienced as more positive than neutral stimuli ($M = 4.56, SD = .76; t(78) = -9.29, p < .001$), and praise stimuli as more positive than critical stimuli ($t(80) = 13.19, p < .001$), indicating that children responded to the MFC stimuli as intended.

MFC fMRI Results

Region of Interest Analyses. Factorial ANOVA found no main effects of maternal depression history, MFC stimuli condition, nor interactive effects between the two factors in our *a priori* ROI.

A priori ROI analyses identified a number of voxel clusters that were significantly related to children's self-reported depressive symptoms (CDI scores). Specifically, during

maternal criticism trials (i.e., negative interpersonal feedback), children's self-reported CDI scores were negatively related to BOLD activity in the left Affective Salience Network ROI (i.e., left AIC; Table 5; Figure 2A) and the right Reward Network ROI (i.e., right putamen; Table 5; Figure 2B); both the AIC and putamen have been previously linked to depressogenic processes (e.g., Dedovic et al., 2014; Gotlib et al., 2010; He, Zhang, Muhlert, & Elliott, 2019; Thomas et al., 2011). No other voxel clusters were related to any of the other independent variables (i.e., CBCL-WD, or YSR-WD) based on ROI analyses.

Whole-brain Analyses. Similar to results at the ROI level of analyses, ANOVA showed no main effect of maternal depression history during whole-brain analysis. Although there was a significant within-subjects effect¹² (i.e., MFC stimuli condition), we found no evidence of an interaction between the two factors (i.e., maternal depression history and MFC stimuli condition).

Exploratory whole-brain analyses showed that BOLD activity in a cluster of voxels largely comprised of the left inferior frontal gyrus (Table 5; Figure 2C) was related to children's CDI scores during the maternal praise condition. Specifically, while listening to maternal praise, children with higher self-reported depressive symptoms had greater BOLD activity within a portion of the left inferior frontal gyrus, a region previously implicated in language comprehension (Liakakis, Nickel, & Seitz, 2011) and inner dialogue (Morin & Hamper, 2012; Morin & Michaud, 2007). No other significant voxel clusters were identified using whole-brain analyses.

¹² As the main effect of the within-subjects factor was not relevant to our study aims, it is not discussed further here.

Discussion

Past work has explored the relationship between depression and neural responses to parental and other interpersonal feedback in adults and adolescents with a history of, or current, depression, limiting the understanding of children's neural reactivity to maternal feedback in the development of depression. We therefore examined never-depressed children's functional brain response during exposure to positive (i.e., praise) and negative (i.e., criticism) feedback from their mothers. To our knowledge, this is the first study to investigate indices of children's risk for depression using an ecologically valid maternal feedback task in youth with no personal history of depression. Children with and without a maternal depression history did not differ in BOLD response to maternal feedback stimuli, regardless of valence, using either ROI or whole-brain analyses. However, children's depressive symptoms were related to neural responses to maternal criticism in *a priori* ROIs in the brain involved in emotional and reward/punishment processing; specifically, exploratory whole-brain analyses identified a relationship between children's depressive symptoms and functional activity in the left inferior frontal gyrus during maternal praise stimuli.

Contrary to our hypotheses, children's functional activity did not differ during either the maternal praise or criticism trials based on whether children had a maternal history of depression. The lack of associations with maternal depression history contrasts with findings implicating reactivity of limbic and prefrontal regions to maternal feedback in adults and adolescents with personal histories of depression (Hooley et al., 2009; 2005; Silk et al., 2017). More specifically, Hooley and colleagues (2009; 2005) found that adults who had recovered from depression demonstrated increased BOLD response in the amygdala and diminished BOLD activity in the dlPFC and ACC in response to maternal

criticism. As these patterns were not found in our sample of never-depressed children at risk for depression (based on maternal history), maladaptive brain activity during maternal criticism that persists after recovery from depression (Hooley et al., 2009; 2005; Silk et al., 2017) may be a lasting consequence of depression itself (i.e., a scarring effect). That said, in addition to having a much larger sample size, our sample was notably younger than those in the aforementioned studies that examined adolescent and adult participants; thus, it is also possible that the pattern of brain activity reported by Hooley and colleagues (2009; 2005) and Silk and colleagues (2017) does not emerge until later in development.

Children's self-reported depressive symptoms were negatively associated with brain activity in the left AIC and right dorsal striatum (i.e., right putamen) during maternal criticism, suggesting that diminished activity in the insula (namely, the AIC) and dorsal striatum during negative maternal feedback (i.e., criticism) mark risk for depression. The insula has an array of functional roles, including (but not limited to) attention, decision-making, music and time perception, and awareness of bodily movement and sensations (Chang, Yarkoni, Khaw, & Sanfey, 2013; Craig, 2009; Gasquoine, 2014); however, a convergence of contemporary research suggests that the AIC has a primary role in the cognitive representation and processing of subjective feelings and emotions (Chang et al., 2013; Craig, 2009). This is consistent with fMRI literature on interpersonal feedback showing that the AIC tends to be more active during processing of negative interpersonal feedback (e.g., social rejection) in healthy participants (Cacioppo et al., 2013) and has greater activity in groups with depression during negative interpersonal feedback (Jankowski et al., 2018; Kumar et al., 2017; Mellick, 2017; Yttredahl et al., 2018). However, other studies have found that subclinical

depressive symptoms are associated with *diminished* AIC activity in response to social rejection and social-evaluative threat (Dedovic et al., 2014; He et al., 2019). Taken together, these studies suggest that negative social information is associated with an increased BOLD response in the AIC among individuals with depression; however, similar to our sample, healthy individuals at *risk* for depression (i.e., never-disorder individuals with subclinical depressive symptoms) demonstrate a diminished AIC BOLD response to negative social information (maternal feedback in the case of our sample).

Our results are consistent with previous findings that, even in the absence of frank disorder, depressive symptoms are associated with neural processing of negative social information by a hub region of the salience network – the AIC (Dedovic et al., 2014; He et al., 2019). This could reflect the early emergence of a developmental pathway to depression characterized by maladaptive processing of interpersonal feedback that ultimately contributes to dysfunction in interpersonal relations. It is well established that relationship dysfunction and social skills deficits both predict, and are predicted by, depression (e.g., Eberhart & Hammen, 2006; Monroe et al., 1999; Segrin, 2000). However, it is important to note that, in contrast to our young sample, the vast majority of studies reporting on AIC activity during social feedback (e.g., Dedovic et al., 2014; He et al., 2019; Jankowski et al., 2018; Kumar et al., 2017; Mellick, 2017; Yttredahl et al., 2018) have studied adults or older adolescents. To the best of our knowledge, ours is the first study to examine this relationship in never-depressed children prior to the typical age of onset for depression (Kessler et al., 2007). Our findings suggest that neural mechanisms for depressive risk may be present in the years preceding onset of depression.

In addition to the negative relationship between depression risk and AIC BOLD activity during maternal criticism, we also found a negative association between children's subclinical depressive symptoms and BOLD activity in the right striatum. The striatum is a set of subcortical structures with a central role in the processing of affective stimuli (including rewarding and punishing stimuli; Delgado, 2007) and motor activity (Grillner, Hellgren, Ménard, Saitoh, & Wikström, 2005). Although not entirely distinct, these functional roles are typically thought to be separated along structural subdivisions, with the ventral striatum (VS) more heavily involved in processing affective stimuli (e.g., rewarding and punishing stimuli) and the dorsal striatum (DS) responsible for motor activity (O'Doherty et al., 2004). The bulk of extant literature has focused on the relationship between reward-related striatal activity, mainly in the VS, finding that depression is associated with diminished striatal response to reward (e.g., Keren et al., 2018); however, our analyses identified a cluster of voxels in the right DS (i.e., the putamen) where the BOLD response was negatively associated with children's subclinical depressive symptoms during critical maternal feedback. Although not specific to critical maternal feedback, a number of studies have identified depression and depression-risk associated decreases in putamen activity in response to negative stimuli (including negative social information). Thomas and colleagues (2011) found that remitted depression was associated with diminished putamen activity during exposure to negative social cues (e.g., sad faces). Similarly, Gotlib et al. (2010) found that loss of monetary reward was associated with a diminished putamen response among those at high familial risk for depression. Finally, during negative social interactions, trait neuroticism (a well-established risk factor for depression; Goldstein & Klein, 2014) was negatively associated with putamen response (Servaas et al., 2015). These studies suggest

that negative and aversive stimuli are associated with diminished putamen activity among those at risk for depression, in the context of depressive disorder, and even following recovery from depression. These findings, combined with our own, suggest that diminished putamen response to negative stimuli (including social information) may mark depression risk.

As described above, the DS (including the putamen) is implicated in numerous cognitive functions; however, previous research and theory has focused on its role in goal-directed behaviour, decision-making processes (including selection and initiation of behavioural actions), and stimulus-response learning (Balleine, Delgado, & Hikosaka, 2007; Haruno & Kawato, 2006). Whereas a healthy response to critical social feedback may include engaging in constructive behaviours with an aim of reducing future criticism (e.g., changing behavior that is viewed negatively by others), our findings show that, as depressive symptoms increase, functional activity in brain regions responsible for recruiting such behaviors (i.e., the DS/putamen) *decreases* during exposure to negative social stimuli. Our results may reflect a diminished ability to respond adaptively to negative feedback that ultimately increases children's depression risk. Morgan, Silk, Woods, & Forbes' (2019) study of never-depressed 6- to 8-year-olds at high familial risk for depression found lower DS activity during rewarding social stimuli was associated with decreased reward-seeking activity. While we did not measure reward processing in the current study, our findings complement this work showing that diminished DS activity in the context of depression risk is related to decreases in goal-directed behaviour.

In addition to the aforementioned ROI-based results, exploratory whole-brain analysis found CDI scores were positively associated with BOLD activity in a cluster of

voxels largely comprised of the opercular and triangular portions of the left inferior frontal gyrus during maternal praise trials. There is little research on the role of the left inferior frontal gyrus during interpersonal feedback; however, the importance of the left inferior frontal gyrus in speech production and comprehension (the left inferior frontal gyrus contains Broca's area) is well established. In addition to its primary role in speech, and like many other regions in the brain, numerous other functional roles have been suggested for the left inferior frontal gyrus (e.g., language processing, working memory, fine motor control, empathy; Liakakis et al., 2011). Some researchers have argued (Morin & Hamper, 2012; Morin & Michaud, 2007) that the left inferior frontal gyrus is activated during self-reflection tasks due to the private, internal dialogue that occurs when processing abstract information related to the self (e.g., emotions, personality, etc.). The valenced MFC stimuli children heard while in the scanner (i.e., personalized maternal praise and criticism directed toward children) may account for the activation of the left inferior frontal gyrus; however, why this activity was related to children's depressive symptoms is unclear based on past work. It may be that children with higher self-reported depressive symptoms find it more challenging to process the relevance of positive self-relevant information, if it is inconsistent with their self-views. Processing what is perceived as incongruent information in turn leads to cognitive interference, generating activation in the left inferior frontal gyrus. Indeed, we previously found that children at high risk for depression had greater activation in similar regions when processing positive self-referential adjectives, in this same sample (Liu et al., 2020).

It is important to note, all of our reported findings that reached statistical significance were centered on depression risk operationalized as children's self-reported subclinical symptoms of depression. Although all child participants in our study were

rigorously assessed to ensure none had a personal history of depressive disorder, it is possible that their subclinical symptoms are capturing depressive disorder (albeit on the lower end of a spectrum of the disorder). That said, treating subclinical depressive symptoms among healthy, never-depressed participants as a marker of depression risk is consistent with widespread evidence that are longitudinal predictors of depressive disorder (e.g., Bertha & Balázs, 2013; Brennan et al., 2002; Cuijpers & Smit, 2004; Fergusson et al., 2005; Goodman et al., 2011; Klein et al., 2005; Wesselhoeft et al., 2013).

Although no relationship was found between children's depressive symptoms and their self-reported emotional response to either MFC neutral or critical stimuli, both CDI and CBCL-WD were negatively associated with children's self-reported emotional response to MFC praise stimuli. Specifically, as self- and maternal-reported depressive symptoms increased, children's self-reported emotional response to MFC praise stimuli became less positive. While behavioural responses to the maternal stimuli were not a focus of the current study, these findings are consistent with previous research findings suggest that depression is associated with attenuated emotional response to affectively positive stimuli (Bylsma, Morris, & Rottenberg, 2008). Further, at least some of this diminished emotional positivity may be related to the aforementioned pattern of increased functional response to praise in the left inferior frontal gyrus (and potential increased self-talk). Examining how behavioural and neural responses to maternal feedback are related to one another and to depression over time is an important next step for this line of research.

Our study is novel given its focus on the relationship between depression and brain function during maternal feedback in youth without depression, as the vast majority

of this work has been conducted in adults or older adolescents with a personal history of depression. By relating functional activity to established markers of risk in rigorously screened, healthy, never-depressed children, prior to the typical age of onset for depression, we were able to better identify those functional differences that pre-empt disorder, potentially acting as biological markers of depression risk. Our results suggest that functional activity in the AIC, putamen, and left inferior frontal gyrus while listening to personally relevant maternal feedback is associated with depression risk *prior* to the onset of clinically significant depression or its treatment. Relative to most fMRI studies (Szucs & Ioannidis, 2020), our study had a relatively large sample size. Additionally, use of a community-based sample of families, rather than recruiting solely from clinical sources, may increase generalizability of our findings to typically developing youth. Instead of relying on artificial feedback from pseudoparticipants, as in the majority of interpersonal feedback investigations, the MFC task (Hooley et al., 2005) allowed us to understand risk-associated differences in brain function using a far more ecologically valid operationalization of interpersonal feedback and mother-child interactions. To the best of our knowledge this is the first study to use such stimuli to understand depression risk processes in never-depressed children. Finally, we used standardized semi-structured clinical interviews (SCID-I/NP and K-SADS-PL) to assess for personal history of mental disorder among mother and child participants, respectively. This allowed us to ensure that children's risk for depression was not confounded by personal history of depressive disorders, and that risk due to maternal depression history was based on the gold-standard assessment of mental disorder.

In addition to the aforementioned strengths, our study also had some important limitations. First, the cross-sectional nature of our data precludes conclusions regarding

causal relationships between neural reactivity and depressive symptoms. Continued longitudinal study of this sample is needed to more clearly determine whether these putative brain-based markers of risk are associated with later onset of depression and related disorders. Additionally, despite thorough investigation of both children and mothers' mental health history, we did not collect data on other family members' (e.g., siblings, fathers, grandparents, etc.) history of depression. We chose to focus on maternal history of depression as it is especially relevant to children's depression risk (Connell & Goodman, 2002; Klein et al., 2005); however, more extensive characterization of family history should be explored in future study. Finally, we did not collect data on children's pubertal development. While we attempted to control for this by including age as a covariate in all imaging analyses, given both the age of our sample and relationships between pubertal status and depression onset (Adrian Angold & Costello, 2006), future studies should include measures of puberty when assessing the relationship between depressive risk and fMRI response to maternal feedback.

Conclusion

To the best of our knowledge, this is the first fMRI study of depression risk in never-depressed children to use the MFC to explore depression-associated differences in processing maternal praise and criticism. We found that children's risk for depression, characterized by subclinical depressive symptoms, was related to brain activity during processing of personally relevant interpersonal feedback from an important caregiver (e.g., mothers). In particular, depression risk is associated with diminished functional activity in regions responsible for salience detection (i.e., the AIC) and goal-directed behavioural responding (i.e., putamen) during negative social feedback (i.e., maternal

criticism). Reduced responding in the regions during processing of negative social information may contribute to depression vulnerability by reducing one's ability to effectively attend to and respond to information.

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Tables

Table 1*Descriptive statistics.*

Variable	Full Sample			MH-			MH+			Comparison	
	<i>M</i>	<i>SD</i>	Frequency	<i>M</i>	<i>SD</i>	Frequency	<i>M</i>	<i>SD</i>	Frequency	statistic	<i>p</i>
Child Age at MRI Visit	11.12	0.63	-	11.16	0.51	-	11.02	0.84	-	$t = 0.80$.43
PPVT	113.21	14.31	-	114.11	14.84	-	111.35	13.24	-	$t = 0.81$.42
CDI	6.59	5.22	-	5.74	4.40	-	83.5	6.35	-	$t = -1.89$.07
CBCL Withdrawn/Depressed	1.32	1.82	-	0.89	1.31	-	2.19	2.35	-	$t = -2.64$.01
YSR Withdrawn/Depressed	3.32	2.76	-	3.11	2.61	-	3.76	3.06	-	$t = -0.99$.33
Mean FD - Neutral MFC	0.19	0.08	-	0.20	0.08	-	0.19	0.07	-	$t = 0.57$.57
Mean FD - Critical MFC	0.21	0.08	-	0.21	0.09	-	0.21	0.07	-	$t = 0.32$.75
Mean FD - Praise MFC	0.22	0.14	-	0.22	0.09	-	0.23	0.21	-	$t = -0.34$.73
SR Response - Neutral MFC	3.65	0.79	-	3.59	0.74	-	3.76	0.88	-	$t = -0.88$.38
SR Response - Critical MFC	2.69	1.01	-	2.64	1.01	-	2.81	1.02	-	$t = -.71$.48
SR Response - Praise MFC	4.56	0.76	-	4.62	0.71	-	4.42	0.86	-	$t = 1.08$.28
Sex (Male/Female)	-	-	45/36	-	-	31/24	-	-	14/12	$\chi = .05$.83

Note. MH- = No maternal history of depression; MH+ = Maternal history of depression; PPVT = Peabody Picture Vocabulary Test; CBCL-WD = Child Behavior Checklist withdrawn-depressed subscale; YSR-WD = Youth Self Report withdrawn-depressed subscale; CDI = Children's Depression Inventory 2nd Edition; SR Response = children's self-reported emotional response to MFC stimuli; FD = children's frame-wise displacement (mm).

Table 2*Maternal feedback challenge stimuli.*

Stimuli Valence	Sentence Stem
Neutral	"(Child's name), one thing I want to talk about is ..."
Praising	"(Child's name), one thing I really like about you is ..."
Critical	"(Child's name), one thing that really bothers me about you is ..."

Note. Sentence stems for each stimuli valence were standardized and mothers were instructed that they were to choose how to complete the sentences, drawing upon topics frequently discussed with their child. Recorded clips were edited to be exactly 30s in length.

Table 3*Definition of regions of interest.*

ROI	Volume (cm ³)	Anatomical Structure	Definition by Atlas Label
Affective Salience	35.17	bilateral amygdala bilateral insula bilateral subgenual ACC	Amygdala_R [†] , Amygdala_L [†] Insula_R [†] , Insula_L [†] ACC_sub_R [†] , ACC_sub_L [†]
Emotion Regulation	73.06	bilateral dlPFC bilateral vlPFC ACC	BA 9 [‡] , BA 46 [‡] BA 44 [‡] , BA 45 [‡] , BA 47 [‡] ACC_sup_R [†] , ACC_sup_L [†] , ACC_pre_R [†] , ACC_pre_L [†]
Reward Processing	32.26	bilateral caudate bilateral putamen bilateral nucleus accumbens	Caudate_R [†] , Caudate_L [†] Putamen_R [†] , Putamen_L [†] N_Acc_R [†] , N_Acc_L [†]

Note. ROI = Region of interest; ACC = anterior cingulate cortex; BA = Brodmann area † = defined by the automated anatomical labelling atlas 3 (AAL3; Rolls et al., 2020); ‡ = defined by the Talairach Daemon database atlas (Lancaster et al., 1997; Lancaster et al., 2000).

Table 4
Correlations among study variables

Variable	1	2	3	4	5	6	7	8	9	10
1. Maternal Depression History	–									
2. Sex	.02	–								
3. Age	-.11	.13	–							
4. CDI	.24*	.04	-.20	–						
5. CBCL-WD	.34**	.17	-.17	.49**	–					
6. YSR-WD	.11	-.09	-.21	.66**	.47**	–				
7. SR Response – Neutral MFC	.10	.06	.07	-.05	-.06	-.08	–			
8. SR Response – Critical MFC	.08	.00	-.29**	-.01	-.10	-.03	.24*	–		
9. SR Response – Praise MFC	-.12	.07	.05	-.27*	-.28*	-.14	.28*	-.02	–	
10. Mean FD	-.01	-.06	-.36**	.03	-.04	.06	-.01	.01	.02	–

Note. * = $p < .05$. ** = $p < .01$. Maternal Depression History was dummy coded such that 0 = no and 1 = yes; CDI = Children's Depression Inventory, 2nd Edition; CBCL-WD = Child Behavior Checklist withdrawn-depressed subscale; YSR-WD = Youth Self-Report withdrawn-depressed subscale; SR Response = children's self-reported emotional response to MFC stimuli; mean FD = children's mean frame-wise displacement across all three runs (mm).

Table 5
fMRI regression analysis results based on relationship to CDI scores.

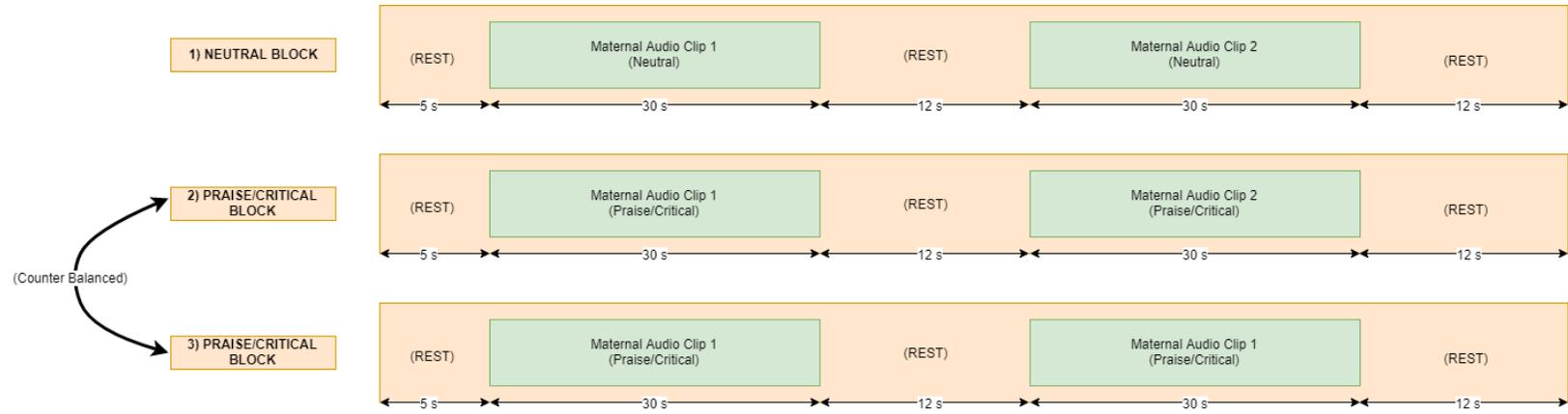
Contrasts		ROI	<i>F</i>	<i>Z</i>	Peak Voxel MNI Coordinates			Anatomical Region	<i>k</i>	<i>p_{FWE}</i>
Level 1	Level 2				<i>x</i>	<i>y</i>	<i>z</i>			
Main Effect of Praise	CDI +	Whole-Brain	21.65	4.19	-34	12	26	left inferior frontal gyrus	38	0.046
Main Effect of Criticism	CDI -	ASN	24.86	4.48	-36	10	4	left AIC	21	0.008
		RN	22.69	4.29	32	2	-8	right putamen	6	0.029

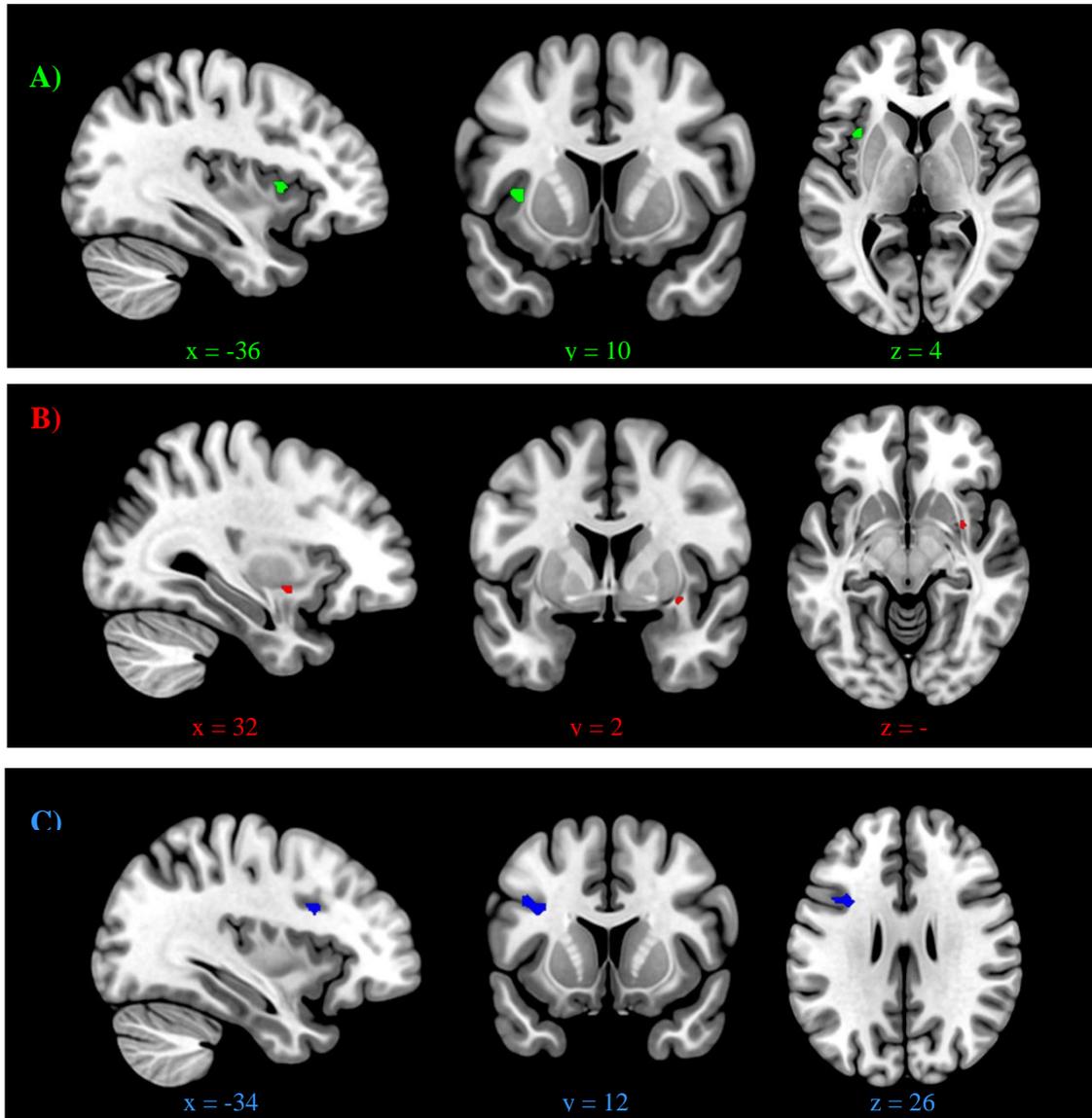
Note. All values refer to two-tailed regression analyses. All analyses included six motion parameter time courses (three translational and three rotational, per scanner run), children's age, and children's sex as covariates. CDI = Children's Depression Inventory; + = positive relationship; - = negative relationship; ASN = affective salience network ROI; RN = reward network ROI; *p_{FWE}* = family-wise error corrected *p* value.

Figures

Figure 1

Maternal Feedback Challenge fMRI Design



fMRI Activation Maps During Maternal Feedback Challenge

Note. A) a priori ROI analysis (affective salience ROI) shows that children's subclinical depressive symptoms (Children's Depression Inventory scores) are negatively associated with BOLD activity in the left anterior insula during maternal criticism. Significant cluster ($k = 21$, $p_{FWE} = .008$) highlighted in green. B) a priori ROI analysis (reward network ROI) shows that children's subclinical depressive symptoms (Children's Depression Inventory scores) are negatively associated with BOLD activity in the right putamen during maternal criticism. Significant cluster ($k = 6$, $p_{FWE} = .029$) highlighted in red. C) Exploratory whole-brain analysis shows that children's subclinical depressive symptoms (Children's Depression Inventory scores) are positively associated with BOLD activity in the left inferior frontal gyrus during maternal praise. Significant cluster ($k = 38$, $p_{FWE} = .046$) highlighted in blue.

Chapter 4 – Resting State Functional Connectivity and Risk for Depression Among Never-Depressed Youth

Introduction

Depression, which is among the most prevalent of the mental disorders (Hasin et al., 2018), is associated with multiple negative outcomes including disability (Vos et al., 2012), suicide (Bostwick & Pankratz, 2000), mortality (Cuijpers & Smit, 2002), and a host of other negative psychosocial sequelae (Kessler, 2012). Identification of early emerging vulnerabilities and the mechanisms that lead to depression may ultimately reduce its considerable impact by informing preventative and early intervention efforts.

Toward the goal of elucidating the neural mechanisms relevant to depression's etiology, the current study examined patterns of functional connectivity associated with a maternal history of depression, a known marker of risk in never-depressed children (Brennan, Hammen, Katz, & Le Brocque, 2002; Goodman et al., 2011; Klein, Lewinsohn, Rohde, Seeley, & Olino, 2005) given that children of depressed mothers evince greater rates of depression themselves relative to children of non-depressed mothers (Brennan et al., 2002; Goodman et al., 2011; Klein et al., 2005). In their seminal text focused on the mechanisms that mediate associations between maternal depression history and offspring depression, Goodman & Gotlib (1999; 2002) emphasized the role of heritable influences, psychosocial factors, and neurobiology in accounting for the increased depression risk found in children of depressed mothers. With respect to the latter domain, resting state networks (RSN), which are groups of spatially distinct brain regions that exhibit distinct patterns of functional connectivity at rest (Shen, 2015), are clearly implicated in the etiology of depression. In addition to its heritable basis (Barber, Hegarty, Lindquist, & Karlsgodt, 2021), resting state functional connectivity (rsFC) has

emerged as a prominent biological mechanism for depressive vulnerability (Mulders, van Eijndhoven, Schene, Beckmann, & Tendolkar, 2015), potentially partially mediating depression risk in children of depressed mothers. In the sections that follow, the research literature on rsFC in depression is reviewed with the goal of highlighting specific networks of importance to depression and methodological limitations of the current body of research, thereby laying the foundation for the current study.

Resting state fMRI

Traditionally, functional neuroimaging studies of psychopathology, including depression, have focused on the relationship between disorder and task-induced changes in BOLD activity within localized brain regions (i.e., task-based activation studies). For example, neuroimaging researchers studying depression have used tasks designed to elicit neurofunctional processes known to be disrupted in depression, including reward processing (Zhang et al., 2016; Zhang, Chang, Guo, Zhang, & Wang, 2013), emotion processing (Groenewold, Opmeer, de Jonge, Aleman, & Costafreda, 2013; Müller et al., 2017), and working memory (Müller et al., 2017; Wang et al., 2015).

Although task-based activation studies have made significant contributions to the field, the focus of these studies on localized functional brain activity is likely overly narrow. Indeed, modern neuroimaging research shows that neural function is most accurately characterized as a complex of interconnected structural and functional networks in near-constant communication (van den Heuvel & Hulshoff Pol, 2010). Consistent with this conceptualization of an interconnected brain, modern psychopathologists argue that depression is, in part, a disorder of dysfunctional brain networks (Anand et al., 2005). Subsequently, research on associations between

depressive disorder and functional connectivity has emerged in recent years. In contrast to older studies of activation, functional connectivity studies analyze the relationship between disorder and the covariance of BOLD time-series in remote regions across the brain (e.g., between individual voxels, regions of interest, or a mixture of both; Fox & Greicius, 2010; Smitha et al., 2017). Larger absolute correlation values between brain regions are thought to reflect increased functional connectivity between those regions.

Although task-based experiments can be used to investigate functional connectivity (Fox & Greicius, 2010), resting-state fMRI (rs-fMRI) paradigms are more widely used (Li, Guo, Nie, Li, & Liu, 2009). In rs-fMRI studies, fluctuations in spontaneous fMRI signals at rest (i.e., in the absence of an explicit task; Fox & Greicius, 2010; van den Heuvel & Hulshoff Pol, 2010) are examined to study functional connectivity and ongoing cognitive processing during rest (Biswal, Kylen, & Hyde, 1997; Biswal, Yetkin, Haughton, & Hyde, 1995). This method has been widely used to map and analyze functional RSNs in healthy (Mueller et al., 2013; Yeo et al., 2011) and clinical populations, including individuals with bipolar disorder (Vargas, López-Jaramillo, & Vieta, 2013), schizophrenia (Dong, Wang, Chang, Luo, & Yao, 2018; Karbasforoushan & Woodward, 2012), autism spectrum disorder (Cherkassky, Kana, Keller, & Just, 2006; Hull et al., 2016), and depression (Dutta, McKie, & Deakin, 2014).

Strong correspondence in network organization has been found across resting-state and task-based studies (Cole, Bassett, Power, Braver, & Petersen, 2014; Cole, Ito, Bassett, & Schultz, 2016; Nickerson, 2018; Smith et al., 2009), suggesting the same functional networks engaged during active cognitive processing (i.e., tasks) are also present and measurable during rest; thus, the patterns of functional connectivity and integrity of networks relevant to specific cognitive processes can be investigated without

the use of tasks in the scanner. This is useful given that rs-fMRI paradigms offer numerous advantages over task-based studies of functional connectivity. Removing the behavioural component from the fMRI paradigm may reduce the methodological heterogeneity typically found in task-based fMRI, negating the requirement of controlling for and interpreting individual or group-based differences in task performance (Shen, 2015). Additionally, the simplified methodology of rs-MRI reduces demands on participants, making rs-fMRI especially suitable for use with populations from whom obtaining fMRI data of sufficient quality is often challenging (e.g., clinical populations and children; Lee, Smyser, & Shimony, 2013; Shen, 2015).

Resting-state Functional Connectivity in Depression

In recent years, a rich literature has developed using rs-fMRI methods to characterize relationships between functional connectivity and depression. Several RSNs appear especially relevant to risk for psychopathology and depression in particular (Chahal, Gotlib, & Guyer, 2020; Mulders et al., 2015), including those described in Menon's (2011) triple network model (i.e., the default mode network [DMN], central executive network [CEN], and the salience network [SN]). Below is an overview of the most commonly cited anatomical nodes of these networks¹³, a brief summary of their putative functional roles, and relevant findings from the depression literature.

Default Mode Network. The DMN was among the first RSNs to be identified and is the most widely investigated in depression (Broyd et al., 2009; Raichle et al., 2001). This is likely due to both widespread interest in the DMN in cognitive

¹³ Definitions of each of these networks vary slightly across the literature (Uddin, Yeo, & Spreng, 2019); here, the most widely used definitions are emphasized.

neuroscience research since its initial discovery (Broyd et al., 2009; Mak et al., 2017) as well as similarities between the DMN's proposed functional role (i.e., introspective and self-referential thought) and the self-referential rumination and self-criticism that characterize depression (Hamilton, Farmer, Fogelman, & Gotlib, 2015). Anatomically, the DMN is typically defined by four core anatomical nodes, including the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC)/precuneus, and bilateral lateral parietal lobes (Raichle, 2015). The DMN is characterized by increased activity and functional connectivity during waking rest in the absence of demanding tasks (hence the name "default mode"), as well as attenuated activity during externally oriented, goal-directed tasks (Raichle, 2015). This pattern of increased activity during rest, along with functional roles for DMN nodes during spontaneous and internally directed thought, indicate that the DMN is important to spontaneous, introspective, self-referential thought (Broyd et al., 2009; Buckner, Andrews-Hanna, & Schacter, 2008; Mulders et al., 2015).

Meta-analytic and review studies show that currently depressed adults (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Mulders et al., 2015) and adolescents (Sacchet et al., 2016) tend to have increased positive rsFC within the DMN, relative to healthy controls. However, DMN hyperconnectivity is not consistently found when comparing those with *remitted* depression to never-depressed controls (Stange et al., 2017; Vega et al., 2020), consistent with the possibility that DMN hyperconnectivity characterizes current depression rather than trait-like activity that marks depressive risk. Additionally, results from a recent large consortium study (Yan et al., 2019) showed that depressed participants had *decreased* functional connectivity within the DMN; however, Yan and colleagues (2019) examined mean functional connectivity between DMN nodes, rather than comparing functional connectivity between regions of the DMN. Averaging

across all functional connectivity parameters may obscure relevant DMN activity in depression, given that functional connectivity may vary between specific DMN nodes (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010).

Central Executive Network. Most consider the CEN (also referred to as the fronto-parietal network or the cognitive control network; Uddin et al., 2019) to be comprised of four core anatomical nodes: bilateral dorsolateral prefrontal cortices (dlPFC) and bilateral posterior parietal cortices (PPC). The CEN and its component nodes are important to maintaining executive functioning, including working memory, decision making, and response inhibition (Menon, 2011; Seeley et al., 2007). In contrast to the DMN, which exhibits the most functional activity during wakeful rest, the CEN demonstrates increased functional activity during cognitively demanding tasks (Menon, 2011). Patterns of functional connectivity within the CEN have been associated with depression; however, in contrast to the DMN, the CEN of depressed individuals is characterized by *reduced* within-network functional connectivity relative to healthy controls (Kaiser et al., 2015). Kaiser and colleagues (2015), in a meta-analysis of CEN functional connectivity in adults, found reduced positive functional connectivity between CEN nodes, with depressed participants showing attenuated, albeit positive, functional connectivity within the CEN relative to control participants.

Reduced functional connectivity within the CEN has also been found in both depressed adolescents (Sacchet et al., 2016) and older adults (Alexopoulos et al., 2012). Additionally, diminished rsFC within the CEN of individuals with remitted depression, relative to never-depressed controls, is also reported (Dong et al., 2019; Jiao et al., 2020; Stange et al., 2017). Using longitudinal methods, Stange and colleagues (2017) reported reduced CEN rsFC in remitted depression was reliably found in the same participants

across repeated rs-fMRI sessions (separated by roughly two months). In addition, Stange et al. (2017) found that CEN rsFC mediated the relationship between remitted MDD status and cognitive factors associated with depressive relapse (e.g., ruminative brooding, negative automatic thoughts), suggesting that attenuated functional connectivity within the CEN is a trait-marker of depression. Taken together, these findings suggest that depression and depressive vulnerability are associated with decreased functional connectivity within the CEN, consistent with the executive dysfunction that characterizes depression (Snyder, 2013).

Salience Network. The third network of Menon's (2011) triple network model, the SN, is comprised of core nodes including the anterior cingulate cortex (ACC), bilateral anterior insula (AI), and bilateral amygdala (Dai, Zhou, Xu, & Zuo, 2019; Menon, 2011, 2015; Uddin et al., 2019). The SN is relevant to the identification of important (i.e., “salient”) stimuli (Menon, 2011; 2015; Uddin et al., 2019). Within this network, the AI receives and integrates information from sensory inputs as well as affective/reward related information from limbic regions (e.g., the amygdala), information which is then processed in the ACC as part of response selection and monitoring (Menon, 2015). Part of this process involves the SN directing cognitive resources to those stimuli that are determined to be most salient (Menon, 2011; 2015; Uddin et al., 2019). Related to this function, the SN appears to play an important role in switching between networks responsible for internally (e.g., the DMN) and externally oriented processing (e.g., the CEN), depending on the relative salience of competing stimuli (Goulden et al., 2014; Menon, 2015; Menon & Uddin, 2010; Sridharan, Levitin, & Menon, 2008).

In contrast to the DMN and CEN, rsFC of the SN in depression is relatively understudied (Mulders et al., 2015). Mulders and colleagues (2015) noted that, relative to the DMN and CEN, the SN is inconsistently defined in the literature and depression-related changes in SN rsFC tend to vary depending on the selection of network nodes in studies. In general, available research suggests that depression is associated with diminished rsFC within the SN (Dong et al., 2019) although a small number of studies contrasting rsFC in groups with remitted depression and never-depressed healthy controls (Stange et al., 2017; Vega et al., 2020) did not find group-based differences in SN connectivity. Taken together, these findings suggest that reduced SN rsFC may be a marker of the depressive *state*, rather than a stable marker of depression risk; however, more research is necessary to better develop an understanding of the role of the SN in depression, given the less well-developed literature.

Summary. Although the considerable heterogeneity in the methodology used in this field may have contributed to inconsistent findings, depression is associated with widespread aberrance in functional connectivity, with distinct patterns of rsFC in the DMN, CEN, and SN reported in depressed individuals, relative to healthy controls. More specifically, depression appears to be associated with increased functional connectivity within the DMN. Additionally, diminished functional connectivity within the CEN has been demonstrated in both currently depressed and remitted groups, suggesting this may be a trait-based feature of depression. More tentative support has been reported for reduced intranetwork SN functional connectivity among depressed samples, although this literature is less well-developed than those relevant to the DMN and CEN.

Resting-state Functional Connectivity and Familial Risk for Depression

Although investigations of depression-associated differences in functional connectivity suggest network disruption is relevant to understanding depression, it is oftentimes unclear whether different patterns of functional connectivity are caused by depression (i.e., a concomitant or scarring effect; Klein, Kotov, & Bufferd, 2011) or represent a pre-existing vulnerability or neurobiological risk factor for depression. Studies focusing on populations *at risk* for depression, prior to onset of disorder, are essential toward developing a better understanding of the etiological role of network functional connectivity in MDD. Only a few studies have investigated the relationship between family history of depression and rsFC in individuals with no personal history of depression, with the majority of these comparing patterns of rsFC between never-depressed participants with a family history of depression (i.e., high-risk participants) to low-risk (i.e., no family history) controls. Similar to the literature focused on currently depressed individuals, there is some variability in the networks examined and the methodologies applied; however, the majority of studies have investigated rsFC within networks of the triple-network model (i.e., DMN, CEN, and SN).

Evidence is mixed for increased intranetwork rsFC of the DMN among those with a family history of depression. Using a much larger sample than earlier studies ($N = 104$), Posner et al. (2016) used a longitudinal multigenerational sample to examine rsFC, finding that second- and third-generation participants with a family history of depression had significantly higher rsFC within the DMN than those without a family history of depression. While Posner and colleagues' (2016) full sample included 44 participants with a personal history of depression ($n = 60$ with no personal depression history), dropping these participants from analyses did not meaningfully change the results. In

contrast, others have reported that participants with a family history of depression do not differ from those without a family history in terms of DMN rsFC (Cai, Elsayed, & Barch, 2021; Chai et al., 2016; Frost Bellgowan et al., 2015). Cai and colleagues (2021) used data from the Adolescent Brain Cognitive Development project and thus had a substantially larger sample size than most other neuroimaging studies (i.e., $N = 9403$), likely yielding more robust findings. However, similar to Yan and colleagues' (2019) study of depressed adults, Cai et al. (2021) only examined mean functional connectivity between DMN nodes. Thus, study findings did not inform whether functional connectivity between specific DMN nodes varied between adolescents at high and low depression risk. Although Cai and colleagues (2021) did not find differences in mean rsFC of the DMN based on family history of depression, stronger negative DMN rsFC was associated with participants' personal history of major depression among those who also had a familial depression history, but not among formerly depressed adolescents with no familial depression history. Additionally, rather than using a structured clinical interview designed to assess family history of disorder (e.g., Nurnberger et al., 1994; Weissman et al., 2000), Cai et al.'s (2021) study used a single item measure of family depression history (i.e., written response to whether any family members have ever "felt so low for a period of at least two weeks that they hardly ate or slept or couldn't work" [p. 231]); such approaches are known to underestimate familial history of psychopathology (Andreasen, Rice, Endicott, Reich, & Coryell, 1986) potentially leading to inaccuracies in determining risk.

Regarding rsFC within the CEN and its association with familial history of depression, Clasen, Beevers, Mumford, and Schnyer (2014) found that never-depressed adolescent girls with a parental history of depression had significantly reduced rsFC

between regions of the CEN at both the whole-brain level of analysis and between *a priori* CEN ROI (Clasen et al., 2014). Similarly, Chai et al. (2016) found reduced rsFC of the CEN (i.e., diminished dlPFC-IPL connectivity, in both hemispheres) in high-risk (i.e., children with a parental history of depression), never-depressed pre-adolescent youth. Chai and colleagues (2016) results were significant even after controlling for children's subclinical depressive symptoms, suggesting that diminished CEN rsFC may be a marker of intergenerational transmission of depression risk. More recently, Shapero et al. (2019) found that the aforementioned patterns of diminished CEN rsFC that were associated with a parental history of depression at age 11 (Chai et al., 2016) prospectively predicted onset of depressive episodes by age 14, above and beyond a parental history of depression (Shapero et al., 2019).

In a sample that partially overlapped with Shapero and colleagues (2019), high-risk youth (i.e., those with a parental history of depression) who subsequently had an onset of depression had significantly lower rsFC within the CEN, relative to high-risk youth who remained depression-free (Hirshfeld-Becker et al., 2019). Although CEN rsFC at age 11 was not associated with self- or parent-report of youth depressive symptoms (Shapero et al., 2019), this may be because the majority of participants' depressive episodes had resolved prior to the follow-up interviews when symptom scales were administered (Shapero et al., 2019). A different group (Fischer, Camacho, Ho, Whitfield-Gabrieli, & Gotlib, 2018) found that rsFC within the CEN was significantly higher in high-risk (i.e., those with a family history of depression) late-adolescent girls who did not develop depression, relative to both high-risk depressed girls and low-risk controls. This suggests that, in addition to diminished CEN being a potential marker of depression risk,

increased CEN functional connectivity may serve as a biomarker of resilience to depression among high-risk individuals (Fischer et al., 2018).

In contrast to high-risk studies investigating rsFC of the CEN and DMN, relatively little work has been published on SN functional connectivity. Fischer and colleagues' (2018) study of older adolescent girls found that girls with high familial risk for depression had increased rsFC within the SN, relative to never-depressed low-risk controls. This finding remained significant regardless of whether the high-risk girls had a personal history of depression (Fischer et al., 2018).

Current Study

Extant literature has demonstrated that depression is associated with changes in rsFC (Duran, 2021; Kaiser et al., 2015; Mulders et al., 2015). The bulk of this work has focused on rsFC within and between networks of the so-called “triple-network” theory of psychopathology (i.e., the DMN, CEN, and SN; Duran, 2021; Menon, 2011). A number of studies investigating rsFC of these same networks in never-depressed people at high risk for depression have begun to emerge. To date, the majority of these studies have relied on relatively small sample sizes and tend to take a brain-wide semi-exploratory approach to data analysis (i.e., seed-based correlation analyses to examine the functional connectivity between a single region and the rest of the brain). Although these studies show that depression risk appears to be associated with alterations of functional connectivity within and between the three networks of Menon's (2011) triple-network model, to the best of our knowledge, no study has taken a strictly *a priori* approach to investigating the rsFC within and between the core nodes of these networks. Further, studies with larger sample sizes (i.e., Cai et al., 2021) have relied on limited and

potentially inaccurate operationalizations of family risk. Approaches that use best-practice approaches for determining family history (e.g., structured clinical interview) are needed to complement studies of larger samples.

We sought to better identify the relationship between depression risk and patterns of rsFC in the triple-network model of psychopathology. Rather than using brain-wide analyses, we quantified rsFC between *a priori* regions of interest (ROI) previously identified as core nodes of the DMN, CEN, and SN. Specifically, we investigated the relationship between never-depressed children's depressive risk (i.e., maternal history of recurrent depression) and rsFC between core hubs of the DMN, CEN, and SN. We also examined associations between rsFC and never-depressed children's early emerging depressive symptoms, given that subclinical symptoms are both an established marker of depressive risk (Bertha & Balázs, 2013; Cuijpers & Smit, 2004; Fergusson, Horwood, Ridder, & Beautrais, 2005; Horwath, Johnson, Klerman, & Weissman, 1992; Shankman et al., 2009) and emerging evidence suggests they are associated with changes in rsFC of the DMN, CEN, and SN (Felder et al., 2012; Hwang et al., 2016; Kaiser et al., 2019; Provenzano, Fossati, Dejonckheere, Verduyn, & Kuppens, 2021).

We hypothesized that, consistent with the depression literature, never-depressed children's depression risk (and early emerging depressive symptoms) will be associated with increased intranetwork rsFC for the DMN and diminished intranetwork rsFC for both the CEN and SN. We tested these hypotheses in a community-dwelling sample of never-depressed children, who were prior to the typical age of onset for depressive disorders (Kessler et al., 2007), assessing for maternal and child history of psychopathology using gold-standard clinical interview techniques.

Methods

Participants

Children and their mothers were recruited as part of a larger ongoing longitudinal study of community-based children's depression risk and temperament development ($N = 409$) beginning when children were 3 years old. Children were excluded from participation if they had major medical or psychological problems. Approximately 7.5 years after the baseline study, a subset of children were recruited for the current study. As we were interested in brain-based risk for depression, recruitment for the current study sought to oversample for depression risk from within our larger sample; therefore, children were recruited for the current study based on their mother's history of depression, according to diagnostic data previously acquired using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Non-Patient Edition (SCID-I/NP; First, Spitzer, Gibbon, & Williams, 2002). Children were considered to be at high risk for depression if their mother had a lifetime history of either recurrent major depression *or* a single major depressive episode *and* a significant anxiety disorder (MH+)¹⁴. Low-risk children had a mother with no lifetime history of any mental disorders according to the SCID-I/NP (MH-).

Two hundred and thirty-seven families were contacted (58 MH+) for recruitment in the current study. Six children of the 237 contacted were ineligible due to contraindications to the MRI environment (e.g., metallic orthodontic work, metallic objects implanted in the body, or self-reported claustrophobia). Of the remaining 231

¹⁴ We excluded specific phobia and social anxiety limited to public speaking given that these are less heritable, generally less impairing, and potentially weaker markers of children's risk for internalizing disorder (Kendler, Neale, Kessler, Heath, & Eaves, 1992).

families, 102 agreed to participate, of which 86 contributed rs-fMRI data. Of the 24 families who agreed to participate but did not contribute MRI data, four children were unable to finish the MRI visit due to discomfort in the scanner, nine families declined to have their child participate in the MRI portion of the study, and seven families dropped out of the current study before the MRI visit (citing they were too busy). After preprocessing MRI data, an additional six participants were dropped from further analyses due to excessive scanner movement (e.g., mean framewise displacement [FD]); ultimately, 80 children contributed MRI data of sufficient quality to be analyzed (34 girls; 54 MH+). Compared to children who contributed usable data, the six excluded outliers did not differ in symptom measures (e.g., CDI, YSR-WD, CBCL-WD), age, or distribution of sex or maternal risk status (all $p > .21$). All children were screened for a personal history of mood disorder (see “Procedures and Measures” for details)¹⁵. See Table 1 for an overview of demographic statistics of the final sample of the 80 participants.

Procedures and Measures

Data for this study were collected from children and their mothers across four separate visits (see Vandermeer et al., 2020; Appendix).

Structured Diagnostic Interviews. Participants’ lifetime history of mental disorder was assessed by structured clinical interviews conducted by graduate students in clinical psychology trained by the senior author (EPH). Children’s lifetime history of mental disorder was assessed by the K-SADS-PL, conducted with both children and their

¹⁵ No children were excluded based on current or lifetime history of mood disorder.

mothers. All child diagnoses¹⁶ had 100% interrater agreement ($N = 11$), including major depression¹⁷. Mothers' lifetime history of mental disorder was assessed using the SCID-I/NP. We had excellent inter-rater reliability for all specific diagnoses covered by the SCID-I/NP⁴, including lifetime history of depressive episodes ($Kappa = 1.00$, $N = 10$).

Questionnaire Measures. Children completed self-reported symptom measures, including the Children's Depression Inventory 2nd Edition (CDI; Kovacs, 2011; $\alpha = .83$) and the Youth Self-Report (YSR; Achenbach & Rescorla, 2001). Mothers were also asked to report on their child's symptoms by completing the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001). The withdrawn-depressed subscales of the YSR (YSR-WD; $\alpha = .72$) and the CBCL (CBCL-WD; $\alpha = .72$) were used as indices of current child self- and mother-reported children's depressive symptoms, respectively¹⁸. To reduce the number of analyses, and given the conceptual similarity and high correlation between measures of children's self-reported depressive symptoms in our sample (i.e., CDI and YSR-WD scores, $r = .57$, $p < .001$), a composite variable (referred to as *SR symptom composite*) was created by summing the standardized values of participants' CDI and YSR-WD scores and was used in all analyses.

¹⁶ In total, seven children had a lifetime history of a DSM-IV-TR diagnosis (primarily an anxiety disorder [$n = 4$] or an externalizing disorder [$n = 4$]). Only four children currently met criteria for a diagnosis.

¹⁷ In the case of some K-SADS and SCID-I/NP diagnoses (e.g., K-SADS depression), no participant had a history of the disorder, precluding the calculation of Cohen's Kappa; however, interviewer agreement on the absence of the diagnosis was 100%.

¹⁸ Only three children had symptom scores in clinical ranges and excluding these participants from analyses did not meaningfully change the pattern of results based on the full sample.

MRI Acquisition

In keeping with best practices for scanning children (de Bie et al., 2010), children completed a “mock scan” session in a replica MRI system prior to MRI data acquisition ($M = 8.1$, $SD = 7.8$ days prior to MRI scan), during which the upcoming MRI session procedures were explained and children were given the opportunity to ask questions. At the MRI session, anatomical and functional magnetic resonance images were obtained using a 3T Tim Trio MRI scanner with a 32-channel head RF coil (Siemens). Participants’ heads were immobilized during scanning using foam padding in the RF coil. A capsule of vitamin E was placed in the foam padding next to the participant’s right temple to ensure correct identification of the right side in image data. Although multiple fMRI experiments were conducted with each child participant, the current study focuses solely on rs-fMRI data.

T_1 -weighted anatomical scans were acquired for co-registration with participants’ rs-fMRI data using a 3D magnetization prepared rapid gradient echo (MPRAGE) sequence ($1 \times 1 \times 1 \text{ mm}^3$ voxel size, repetition time [TR] = 2300 ms, echo time [TE] = 2.98 ms, field of view [FOV] = 256 mm) yielding 192 sagittal slices per participant. A 6-minute T_2^* -weighted resting state scan of 360 volumes was collected using an echoplanar imaging (EPI) sequence ($3 \times 3 \times 3 \text{ mm}$ voxel size, TR = 1000 ms, TE = 30 ms, FOV = 210 mm) yielding 48 axial slices. During the resting state scan participants were instructed to open their eyes and fixate on a black cross against a white background. Importantly, rs-fMRI data was collected immediately following acquisition of anatomical scans and prior to collection of any task-based fMRI data.

MRI Processing

All resting-state fMRI data were preprocessed and denoised using CONN functional connectivity toolbox (CONN v20.b; Whitfield-Gabrieli & Nieto-Castanon, 2012); <https://www.nitrc.org/projects/conn>), alongside SPM12 (Wellcome Department of Cognitive Neurology, London, UK; <https://www.fil.ion.ucl.ac.uk/spm>), using CONN's default preprocessing pipeline. Specifically, raw functional images were realigned (motion corrected) and unwrapped, centered, slice-time corrected, and segmented and normalized to Montreal Neurological Institute (MNI) coordinate space. Raw anatomical images were then centered, segmented, and normalized to MNI coordinate space. Finally, functional volumes were smoothed using a 6 mm (full-width at half maximum) Gaussian kernel, and resampled to 2×2×2 mm voxels.

Translational and rotational motion in the x, y, and z axes were assessed during preprocessing as part of the realign and unwarp procedure. Excessive head motion and fluctuations in magnetic field intensity for individual time points (i.e., > 0.9 mm motion from previous volume, global mean intensity > 5 SD from mean intensity across functional scans) were assessed using the Artifact Detection Tool (ART; https://www.nitrc.org/projects/artifact_detect/). Volumes with excessive head motion or fluctuations in magnetic field intensity were modelled as outlier “scrubbing” parameters applied during denoising. Finally, the first three volumes of each participant's rs-fMRI run were entered as scrubbing parameters in order to allow for stabilization of the scanner signal.

Following preprocessing, a denoising step was applied in CONN. This included estimation of and regressing out physiological noise using the aCompCor method (Behzadi, Restom, Liao, & Liu, 2007; Chai, Castañón, Ongür, & Whitfield-Gabrieli,

2012; Whitfield-Gabrieli & Nieto-Castanon, 2012), movement artifacts (24 motion covariates consisting of 3 rotational and 3 translational motion parameters, their first-order temporal derivatives, and quadratic effects), and the aforementioned scrubbing parameters. Simultaneous to the denoising regression (Hallquist, Hwang, & Luna, 2013) a temporal band-pass filter of 0.009 – 0.08 Hz was applied to the resting state time series.

Functional Connectivity Analyses

Analyses of functional connectivity within and between *a priori* identified networks (e.g., the default mode network [DMN], salience network [SN], and central executive network [CEN]) were conducted using CONN's "ROI-to-ROI" function. ROI included four nodes of the DMN (e.g., medial prefrontal cortex [MPFC], left and right lateral parietal cortices [LPC (L) and LPC (R)], and the posterior cingulate cortex [PCC]), five nodes of the SN (e.g., anterior cingulate cortex [ACC], left and right anterior insula [AI (L) and AI (R)], and left and right amygdala [Amg (L) and Amg (R)], and four nodes of the CEN (e.g., left and right lateral prefrontal cortex [IPFC (L) and IPFC (R)], and the left and right posterior parietal cortex [PPC (L) and PPC (R)]). All ROI, except for the bilateral Amg, were taken from the Networks atlas included in CONN (Whitfield-Gabrieli & Nieto-Castanon, 2012), which is based on an independent component analysis (ICA) of 497 individuals from the Human Connectome Project (HCP) as described in CONN changelogs (Nieto-Castanon, 2020). The Amg ROI were derived from the FSL Harvard-Oxford Atlas maximum likelihood subcortical atlas (Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006). ROI central coordinates and sizes are detailed in Table 2.

First-level analyses were conducted using an unweighted general linear model. Correlation maps were computed for every participant based on bivariate Pearson correlation coefficients between the mean time-course of voxels within each ROI. In order to improve normality for second-level analyses, all correlation coefficients from first-level analyses were converted to z scores using the Fisher z -transformation (Alfonso Nieto-Castanon, 2020). For second-level analyses, ANCOVA was used to test differences in rsFC between children at high and low risk for depression due to maternal history. ANCOVA analyses included children's age and sex as covariates; additionally, for these analyses, children's self-reported depressive symptoms (i.e., SR Symptom Composite) were statistically controlled for in order to determine the effect of maternal depression history above and beyond children's concurrent depressive symptoms. Regression analyses were conducted to analyze the relationship between continuous measures of depressive risk and rsFC, using maternal- (i.e., CBCL-WD) and self-reported (i.e., SR symptom composite) measures of subthreshold depressive symptoms as independent variables. All regression analyses controlled for the effect of children's age, sex, and maternal risk status. Results were corrected for multiple comparisons (i.e., $p_{FDR} < .05$) following Threshold Free Cluster Enhancement (TFCE; Smith & Nichols, 2009). Within network functional connectivity was tested by restricting analyses to correlations of ROI within each respective network.

In addition to the aforementioned group-based differences, because early depressive symptoms are associated with later disorder (Kessler et al., 2007), we also examined the relationship between children's early emerging depressive symptoms (as measured by the SR symptom composite and CBCL-WD, respectively) and rsFC within the three *a priori* networks (i.e., DMN, SN, and CEN) to guide future research on the

neural correlates of depression. Similar to the group-based analyses, symptom associations with rsFC for each specific network were conducted by including only the ROI of a respective network. All regression analyses included child age, sex, and mothers' history of depression as covariates.

Results

Correlations between Major Study Variables

See Table 1 for bivariate correlations among major study variables. Continuous measures of depressive symptoms (i.e., CBCL-WD, SR symptom composite) were positively associated with one another. Participants' mean motion during rs-fMRI scanning was negatively associated with age and positively associated with children's self-reported depressive symptoms. There was no association between maternal report of children's depressive symptoms (i.e., CBCL-WD) and movement in the scanner. *T*-tests showed that children with a maternal history of depression had significantly higher CBCL-WD scores, relative to children without a maternal depression history (Table 3); however, there were no other significant differences based on maternal depression history. Additionally, boys and girls did not differ in age, depressive symptoms (i.e., CBCL-WD, SR symptom composite), or movement in the scanner (all $p > .12$).

Functional Connectivity

Differences between low- and high-risk children in rsFC. A significant cluster of group-level differences were identified within the DMN (TFCE = 8.63, $p_{FDR} = .026$). Specifically, relative to their low-risk peers, children with a maternal history of depression had greater functional connectivity between the mPFC and bilateral LPC ROI (Table 4; Figure 1). Similarly, high-risk children demonstrated greater rsFC between the

mPFC-PPC relative to low-risk peers; however, this finding only trended toward significance after correcting for multiple comparisons (Table 4). There was no evidence of diminished rsFC within the DMN in high-risk children. Additionally, there were no significant differences in intranetwork functional connectivity for either the SN or the CEN when comparing high- and low-risk children.

Associations with subthreshold depressive symptoms. Children's self-reported depressive symptoms were significantly associated with a cluster of ROI pairs within the CEN (TFCE = 21.42, $p_{FDR} = .007$; Table 5) as well as within the SN (TFCE = 12.79, $p_{FDR} = .020$; Table 6). Of the six possible connections between the four ROI making up the CEN, five were significant and negatively related to children's self-reported depressive symptoms (Table 5; Figure 2). Regarding the ten possible connections between the five SN ROI, two were significantly related to self-reported depressive symptoms (in the negative direction; Table 6; Figure 3). Neither intranetwork rsFC of the CEN nor the SN had positive relationships with children's self-reported depressive symptoms. Additionally, rsFC within the DMN was not associated with children's self-reported depressive symptoms. Finally, there was no relationship between maternal report of children's depressive symptoms (e.g., CBCL-WD) and rsFC for any of the *a priori* networks.

Discussion

Contemporary models of neural function conceptualize the brain as a complex set of interconnected networks (van den Heuvel & Hulshoff Pol, 2010). Consistent with this notion, modern psychopathologists argue that depression is, in part, a disorder of dysfunctional neural networks (Anand et al., 2005). Building on this idea, a substantial body of work on the relationship between depression and network connectivity has

emerged over the previous 10-15 years (Duran, 2021; Kaiser et al., 2015; Mulders et al., 2015); however, the vast majority of this work has focused on adults and adolescents with a personal history of, or current, depression (Duran, 2021; Kaiser et al., 2015; Mulders et al., 2015). We built upon this past work by examining never-depressed children's functional connectivity within three RSN's (i.e., the DMN, CEN, and SN). To the best of our knowledge, ours is among the first studies to examine associations between children's depressive risk and rsFC within RSNs based on *a priori* ROI. Additionally, ours is among the first studies of this size ($N = 80$) to examine these relationships in youth without a personal history of depression, prior to typical age of onset for depression (Kessler et al., 2007).

Consistent with our hypotheses, we found that high-risk, never-depressed children had significantly increased functional connectivity within the DMN. In contrast, we did not find differences in functional connectivity based on mothers' depression history for either the CEN or SN; however, regression analyses showed that functional connectivity within both the CEN and SN was negatively associated with children's self-reported depressive symptoms, which show homotypic continuity with later depressive disorder (Bertha & Balázs, 2013; Cuijpers & Smit, 2004; Fergusson et al., 2005; Horwath et al., 1992; Shankman et al., 2009). In contrast, children's self-reported depressive symptoms were unrelated to functional connectivity within the DMN. Finally, maternal-report of children's symptoms (i.e., CBCL-WD) was unrelated to functional connectivity for any of the three RSN analyzed.

Maternal Depression Risk and DMN Hyperconnectivity

To the best of our knowledge, ours is the first study to report hyperconnectivity within the DMN of never-depressed children at high familial risk for depression, prior to the typical age of depression onset. Although hyperconnectivity within the DMN has been widely reported among adults and adolescents with depression (Duran, 2021; Kaiser et al., 2015), findings have been equivocal in the high-risk literature. While Posner et al. (2016) found that familial history of depression was associated with increased functional connectivity within the DMN, their sample included individuals with a personal history of depression, was much older than ours ($M = 32.4$ -years-old), and largely composed of individuals well past the typical age of onset for depression (Kessler et al., 2007). For this reason, it is possible that DMN hyperconnectivity in these participants reflected resilience to depression, given that they were at high familial risk for depression. In contrast, the few other relevant studies have not found an association between familial history and DMN rsFC (Cai et al., 2021; Chai et al., 2016; Frost Bellgowan et al., 2015). However, both Chai et al. (2016) and Frost Bellgowan et al. (2015) examined smaller samples ($n = 43$ and $n = 34$, respectively) than the current study and focused on functional connectivity between seed regions of the DMN and every voxel across the whole brain, potentially overlooking associations between family history of depression and DMN rsFC. Although Cai and colleagues' (2021) study of never-depressed children involved an impressive sample size ($n = 9403$), their use of a single-item measure of family depression history and an average index of functional connectivity between ROI composing the DMN may have obscured relationships between depression risk and rsFC.

Increased DMN rsFC among never-depressed children at high familial risk for depression suggests that DMN hyperconnectivity may be a biological marker of

depressive risk. Group differences remained significant after statistically controlling for children's self-reported depressive symptoms and in the absence of any personal history of depression. This, alongside other evidence, suggests that DMN hyperconnectivity meets many of (Hasler & Northoff, 2011) criteria for psychiatric endophenotypes (i.e., an intermediate phenotype laying between genes and complex behavioural phenotypes, such as depression; Gottesman & Gould, 2003). Specifically, DMN hyperconnectivity is associated with depression in the general population (Duran, 2021; Kaiser et al., 2015; Mulders et al., 2015), RSN patterns are heritable (Barber et al., 2021), and our study suggests that the never-depressed offspring of affected family members show DMN hyperconnectivity (Hasler & Northoff, 2011). Although additional research is needed to explore DMN hyperconnectivity as a depression endophenotype, the associations we found support the idea that DMN hyperconnectivity may be a mechanism that mediates the relationship between maternal depression and increased risk in their children. Given that we were unable to test such mediation models with our cross-sectional data, future longitudinal studies are needed to determine whether increased DMN functional connectivity among children with a maternal history of depression is associated with the emergence of depressive disorder.

The DMN is generally thought to be involved in spontaneous, introspective, self-referential thought and autobiographical memory (Broyd et al., 2009; Buckner et al., 2008; Mulders et al., 2015). Similarly, characteristic symptoms of self-referential rumination and self-criticism in depression have led to the idea that DMN dysfunction is relevant to depression and depressive risk (Hamilton et al., 2015). A number of studies have reported a robust role for rumination in predicting future depressive episodes (Gibb, Grassia, Stone, Uhrlass, & McGeary, 2012) and in mediating the relationship between

depressive risk and later onset of depressive episodes (Kuyken, Watkins, Holden, & Cook, 2006; Spasojević & Alloy, 2001). Although we did not examine ruminative or self-referential behavior in the current study, previous work from our group using the same sample (Liu et al., 2020) showed that children with a maternal history of depression had increased functional activity in one of the DMN central hubs (the mPFC) while engaging in self-referential processing task. Further, in addition to increased DMN connectivity among those with depression (Kaiser et al., 2015), meta-analytic research has found that DMN regions are specifically recruited during lab-based rumination tasks (Zhou et al., 2020). Together, these findings suggest that alterations in DMN functioning may be associated with patterns of rumination and related increases in depression risk.

Our analyses of connectivity between core nodes of the DMN shed further light on the potential relevance of rumination to DMN and depression. Specifically, we found that children with a maternal history of recurrent depression had greater rsFC within the DMN that was largely driven by increased functional connectivity with the mPFC. The mPFC, as a core hub of the DMN, is thought to be central to self-referential processing, while the bilateral LPC are thought to be involved in autobiographical/episodic memory and related processes (Andrews-Hanna, Smallwood, & Spreng, 2014). Previous work by (Andrews-Hanna et al., 2010) suggests that the bilateral LPC, as part of medial temporal lobe subsystem of the DMN, is especially active in both recall of autobiographical memory but also “mnemonic scene construction” (i.e., using autobiographical/episodic memories to imagine and project into future scenarios). This is consistent with prominent conceptualizations of rumination (for a review, see Smith and Alloy, 2009), which argue that rumination involves repetitive thinking about the causes, consequences, and symptoms of negative affect and experiences. Indeed, while rumination is traditionally

thought of being focused on the past, a number of studies suggest that lab-induced rumination involves a progression from past- to future-oriented thought (Lavender & Watkins, 2004; McLaughlin, Borkovec, & Sibrava, 2007). Thus, we propose that the observed hyperconnectivity between DMN regions central to self-oriented thinking (i.e., the mPFC) and regions involved with autobiographical memory and mnemonic scene construction (i.e., bilateral LPC) may increase the likelihood of ruminative cognition among never-depressed youth at risk for depression. While speculative, this could explain the neural processes that underlie the transmission of depression from mothers to children. Future work is necessary to determine whether high-risk children go on to develop depression at higher rates and whether this is in fact associated with increased ruminative cognitions; however, the latter has some support from a recent study conducted by Provenzano and colleagues (2021), who found that rumination partially mediated the relationship between DMN connectivity (especially between the mPFC and other DMN nodes) and depression risk.

Depressive Symptoms and CEN Hypoconnectivity

In our sample of youth screened for a personal history of depressive disorder, children's current self-reported depressive symptoms were negatively related to functional connectivity within the CEN, even after accounting for the effect of maternal depression history. The CEN is most active during engagement in cognitively demanding tasks, and is thought to be responsible for executive functioning processes, including working memory, decision making, and response inhibition (Menon, 2011; Seeley et al., 2007). Given widespread deficits in executive function seen in depression (Bredemeier, Warren, Berenbaum, Miller, & Heller, 2016; DeBattista, 2005; Snyder, 2013), disorder-

and risk-associated differences in functional connectivity of the network central to these cognitive functions has been proposed (Menon, 2011; Snyder, 2013).

Our findings of negative associations between CEN functional connectivity and depressive risk in never-depressed children is consistent with previous investigations of the CEN. Namely, extant research has found CEN hypoconnectivity in adolescents (Sacchet et al., 2016), adults (Kaiser et al., 2015), and seniors (Alexopoulos et al., 2012) with depression. Further, CEN hypoconnectivity has been found in never-depressed youth with familial depression (Chai et al., 2016; Clasen et al., 2014). Finally, previous reports that CEN hypoconnectivity of never-depressed 11-year-olds prospectively predicted onset of depression among a sample of 14-year-olds (Hirshfeld-Becker et al., 2019; Shapero et al., 2019). Although we did not find differences based on mothers' history of depression in the current study, an association with children's depressive symptoms is consistent with the notion of CEN hypoconnectivity as a risk factor for depression. That said, the discrepancy between our findings and those previously reported in the literature warrants further investigation.

In contrast to our other findings, the negative association between CEN functional connectivity and children's depressive symptoms was not driven by functional connections between specific nodes in our sample. Instead, this association was characterized by widespread reductions in functional connectivity between almost all CEN ROI tested. Broad hypoconnectivity between the core nodes of the CEN is suggestive that depressive-risk is characterized by widespread disruption of the CEN, eventually manifesting as the aforementioned executive dysfunction seen in depression. Previous research has found that CEN hypoconnectivity mediated the relationship between cognitive dysfunction and depression status (Stange et al., 2017), and executive

dysfunction has been demonstrated to prospectively predict depression onset in high-risk twins (Vinberg, Miskowiak, & Kessing, 2013). Given that the current study did not include measures of cognitive or executive functioning, further research is necessary to determine whether CEN hypoconnectivity is associated with executive functioning, which could, in turn, mediate associations between the CEN and depression.

Depressive Symptoms and SN Hypoconnectivity

Similar to our findings for the CEN, children's self-reported depressive symptoms were negatively related to functional connectivity within the SN. The SN is thought to be important to the integration of sensory and affective stimuli, the determination of stimuli importance (i.e., salience), and the deployment of the cognitive resources needed to respond appropriately (Menon, 2011, 2015; Seeley et al., 2007; Uddin et al., 2019). The SN is not as widely studied or understood as either the DMN or the CEN (Mulders et al., 2015), and the current literature on its role in depression is equivocal, with one meta-analysis finding that depression is associated with diminished SN functional connectivity (Dong et al., 2019) and individual studies reporting no difference in SN rsFC between depressed and non-depressed samples (Stange et al., 2017; Vega et al., 2020).

Additionally, Fischer et al. (2018) found that girls in late adolescence with a high familial risk for depression had *increased* SN rsFC.

Associations between depressive symptoms and SN hypoconnectivity in our sample may reflect deficits in salience detection and inefficient integration of disparate sources of information. Given the putative role of the SN in context-dependent network switching between the DMN and the CEN (Goulden et al., 2014; Menon, 2015; Menon & Uddin, 2010; Sridharan et al., 2008), it is possible that the SN hypoconnectivity seen in our

sample reflects early emerging dysfunction in network switching that could lead to increases in maladaptive DMN activity and connectivity. Future studies of inter-network functional connectivity (i.e., patterns of rsFC between the DMN, CEN, and SN) as well as dynamic causal modelling (DCM; Friston, Harrison, & Penny, 2003) are needed to determine the nature of RSN interactions among children at risk for depression.

The current study has several important strengths, including the nature of our sample. Previous research on rsFC in depression has largely focused on older adolescents and adults with a personal history of disorder, with few studies of the relationship between rsFC and *risk* for depression. Using rigorous screening of pre-adolescent children's mental health, we recruited youth with no personal history of depression, prior to the typical age of onset for depression, increasing the likelihood that the patterns of rsFC we found in high-risk youth reflect biological markers of depression risk rather than consequences of depression or its treatment. Our sample was large relative to the average functional neuroimaging study (Szucs & Ioannidis, 2020) and used community-dwelling families, which may increase the generalizability of our findings to typically developing youth.

Our analyses of rsFC may also shed new light on neural networks relevant to depression. Prior studies of rsFC in risk for depression have largely relied on seed-based analyses (i.e., functional connectivity between an ROI or the average of several ROI and the rest of the voxels of the brain) or by focusing on the average functional connectivity between nodes of a RSN. While methodologically sound, seed-based analyses tend to be relatively exploratory and are not necessarily specific to *a priori* identified networks. In contrast, while the latter approach (as seen in Cai et al., 2021) focuses on functional connectivity within *a priori* networks, averaging all connectivity values potentially

obscures interesting patterns of functional connectivity between specific nodes or ROI composing the RSN. Analyzing rsFC patterns using an ROI-to-ROI approach allowed us to investigate the specific connections within broader networks that were driving associations between networks, depression risk, and symptoms. This approach potentially provides a more detailed understanding of which aspects of RSNs are especially important contributors to biological risk for depression.

Despite the aforementioned strengths, our study also has a number of limitations that must be noted. First, although the data used in this study were gathered as part of an ongoing longitudinal study of temperament and developmental psychopathology, this was the first wave of fMRI data collected for these children. Given the cross-sectional nature of our data, we are unable to make causal claims regarding the relationship between rsFC and risk for depression. Further longitudinal study of this sample is needed to determine whether putative rsFC-based markers of risk predict later development of depression and related disorders.

Other limitations relate to variables we were unable to include in the current study. While up to 50% of all adults will meet criteria for a mental disorder during their lives (Kessler et al., 2007, 2005), we limited our “low-risk” group to children whose mothers had no history of *any* disorder. This may have limited low-risk children to individuals with especially resilient or healthy mothers, potentially limiting the generalizability of our results. We did not collect data on other family members’ (e.g., siblings, fathers, grandparents, etc.) history of depression. While we chose to focus on maternal history of depression as it is especially relevant to children’s depression risk (Connell & Goodman, 2002; Klein et al., 2005), a richer characterization of familial risk involving multiple generations of families might better capture children’s own risk for

depression. In addition, although age was included as a covariate in all analyses of imaging data, we did not assess children's pubertal development as part of the current study. Given the age of our sample and the established relationship between puberty and depression (Angold, Costello, & Worthman, 1998; Angold & Costello, 2006), covarying for pubertal development is an important future direction in better understanding the relationship between rsFC and risk for depression. Finally, future research should collect data on relevant environmental factors (e.g., adverse childhood events, early parenting behaviour, children's chronic life stress, etc.) and investigate both their direct and interactive effects on children's rsFC.

Conclusions

To the best of our knowledge, this is among the first studies of the association between depression risk and rsFC in never-depressed children. Children at high risk for depression due to a maternal history of depression had significantly higher rsFC within the DMN, even after controlling for the effects of children's self-reported depressive symptoms. Additionally, children's depressive symptoms (a continuous marker of depression risk) were negatively associated with rsFC within both the CEN and SN. These patterns of rsFC may represent early mechanisms by which risk eventuates in disorder, potentially contributing to increased self-referential thoughts and rumination (in the case of DMN hyperconnectivity), depressive executive dysfunction (in the case of CEN hypoconnectivity), and saliency detection (in the case of SN hypoconnectivity).

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Tables

Table 3

Descriptive statistics and correlations of major study variables

Variable	MH-			MH+			Comparison		Correlations				
	<i>M</i>	<i>SD</i>	Freq.	<i>M</i>	<i>SD</i>	Freq.	<i>t</i>	<i>p</i>	1	2	3	4	
1. Age	11.2	0.52	-	11.03	0.79	-	1.25	.22	11.15 (0.62)				
2. CBCL-WD	1.02	1.36	-	2.00	2.19	-	-1.88	.07	-0.05	1.35 (1.74)			
3. SR Symptom Comp.	-0.39	1.40	-	0.35	1.86	-	-1.78	.08	-0.15	.56 [‡]	-0.14 (1.60)		
4. Mean FD	0.18	0.03	-	0.18	0.04	-	0.54	.59	-.28*	-0.05	.23*	0.18 (0.04)	

Note. MH- = No maternal history of depression; MH+ = Maternal history of depression; Freq. = Frequency; CBCL-WD = Child Behavior Checklist Withdrawn/Depressed scale; SR Symptom Composite = Children's self-reported depressive symptoms composite scale; FD = framewise displacement (mm); bolded values in the correlation table are *M (SD)* for the full sample; * = $p < .05$; † = $p < .01$; ‡ = $p < .001$.

Table 2
Definitions of regions-of-interest.

Network	Region	Center of Mass (x, y, z)	Volume (mm³)
Default Mode Network	Medial Prefrontal Cortex	1, 55, -3	10768
	Posterior Cingulate Cortex	1, -61, 38	38664
	Lateral Parietal (L)	-39, -77, 33	8328
	Lateral Parietal (R)	47, -67, 29	10608
Salience Network	Anterior Cingulate Cortex	0, 22, 35	8504
	Anterior Insula (L)	-44, 13, 1	3568
	Anterior Insula (R)	47, 14, 0	3104
	Amygdala (L)	-24, 0, -16	2709
	Amygdala (R)	26, 0, -16	2606
Central Executive Network	Lateral Prefrontal Cortex (L)	-43, 33, 28	13624
	Lateral Prefrontal Cortex (R)	41, 38, 30	14064
	Posterior Parietal Cortex (L)	-46, -58, 49	6656
	Posterior Parietal Cortex (R)	52, -52, 45	6696

Note. (L) = left; (R) = right; Center of mass coordinates provided in MNI space.

Table 3*T-test comparisons of children at low- and high-risk for depression.*

	Low Risk (<i>n</i> = 26)		High Risk (<i>n</i> = 54)		<i>t</i> -test
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
Age	11.20	0.52	11.03	0.79	1.01
CBCL-WD	1.02	1.36	2.00	2.19	-2.09*
SR Symptom Composite	-0.39	1.4	0.35	1.86	-1.78
Mean FD	0.18	0.03	0.18	0.04	0.15

Note. CBCL-WD = Child Behavior Checklist Withdrawn/Depressed scale; SR = self-report; FD = framewise displacement (mm). * = $p < .05$; † = $p < .01$; ‡ = $p < .001$.

Table 4

Differences in default mode network resting-state functional connectivity by maternal risk.

Analysis	TFCE	<i>F</i>	<i>df</i>	<i>p</i> FDR
<u>HR > LR</u>				
DMN Cluster	8.63	-	-	.026
mPFC - LPC (R)		6.95	1, 74	.047
mPFC - LPC (L)		6.14	1, 74	.047
mPFC - PCC		4.48	1, 74	.076
<u>HR < LR</u>				
N/A	-	-	-	NS

Note. DMN = default mode network; TFCE = threshold free cluster enhancement; mPFC = medial prefrontal cortex; LPC = lateral parietal cortex; PCC = posterior cingulate cortex; (L) = left; (R) = right.

Table 5

Functional connectivity within the CEN regressed on children's self-reported depressive symptoms.

Analysis	TFCE	<i>F</i>	<i>df</i>	<i>p</i> FDR
<u>Positive Association with Depressive Symptoms</u>				
N/A	-	-	-	NS
<u>Negative Association with Depressive Symptoms</u>				
CEN Cluster	21.42			.007
PPC (L) – PPC (R)		10.84	1, 74	.007
IPFC (R) – PPC (R)		9.25	1, 74	.007
IPFC (R) – IPFC (L)		9.00	1, 74	.007
PPC (L) – IPFC (R)		7.75	1, 74	.010
IPFC (R) – PPC (L)		7.16	1, 74	.011
IPFC (L) – PPC (R)		7.16	1, 74	.011
PPC (L) – IPFC (L)		1.87	1, 74	.176

Note. CEN = central executive network; TFCE = threshold free cluster enhancement; IPFC = lateral prefrontal cortex; PPC = posterior parietal cortex; (L) = left; (R) = right.

Table 6

Functional connectivity within the SN regressed on children's self-reported depressive symptoms.

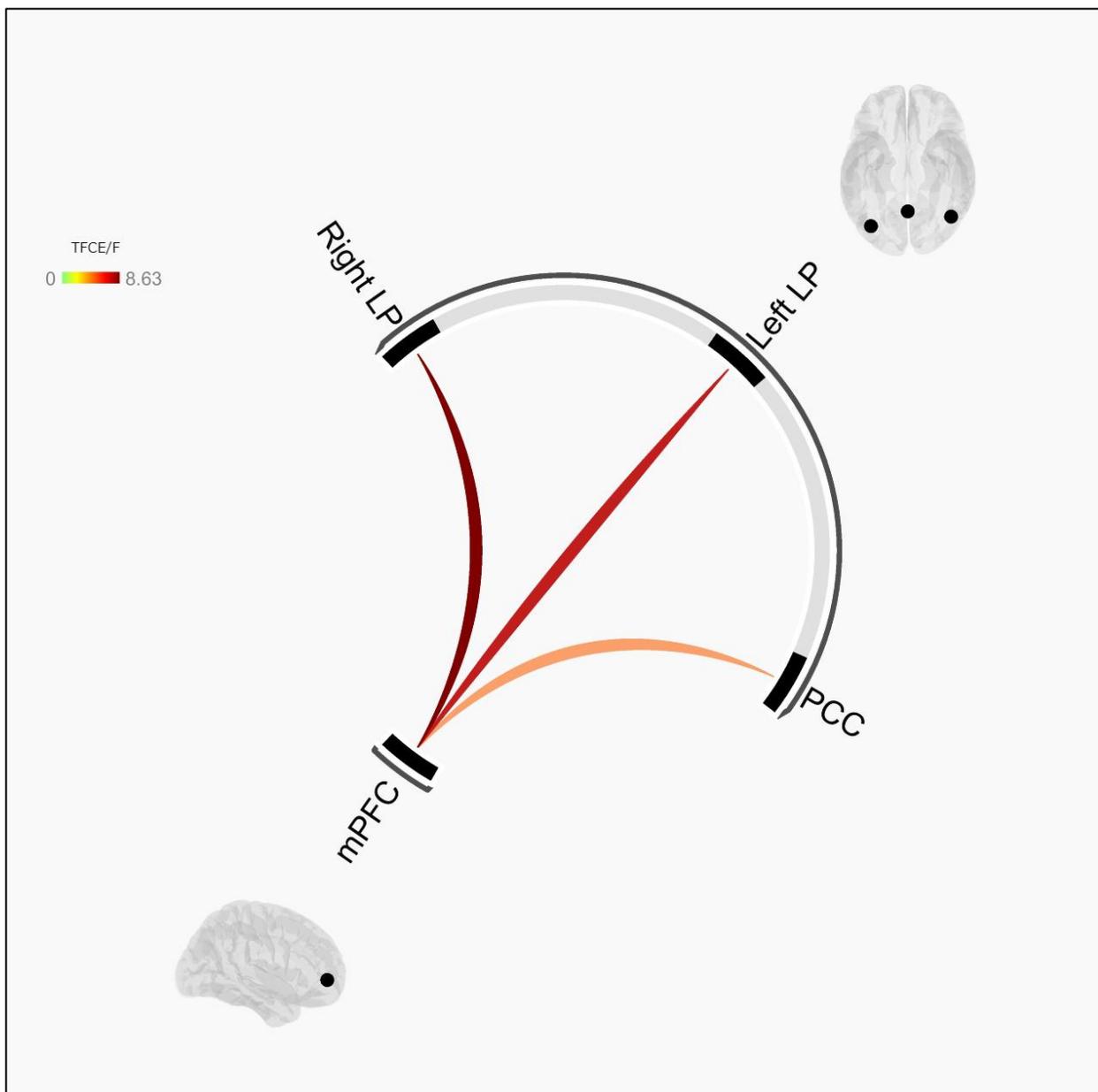
Analysis	TFCE	<i>F</i>	<i>df</i>	<i>p</i> FDR
<u>Positive Association with Depressive Symptoms</u>				
N/A	-	-	-	NS
<u>Negative Association with Depressive Symptoms</u>				
SN Cluster	12.79			.020
AI (L) - AI (R)		9.21	1, 74	.003
AI (L) - ACC		7.63	1, 74	.036
AI (R) - ACC		4.06	1, 74	.159
AI (L) - Amygdala (R)		2.20	1, 74	.356
AI (R) - Amygdala (L)		1.62	1, 74	.415

Note. CEN = central executive network; TFCE = threshold free cluster enhancement; IPFC = lateral prefrontal cortex; PPC = posterior parietal cortex; (L) = left; (R) = right.

Figures

Figure 1

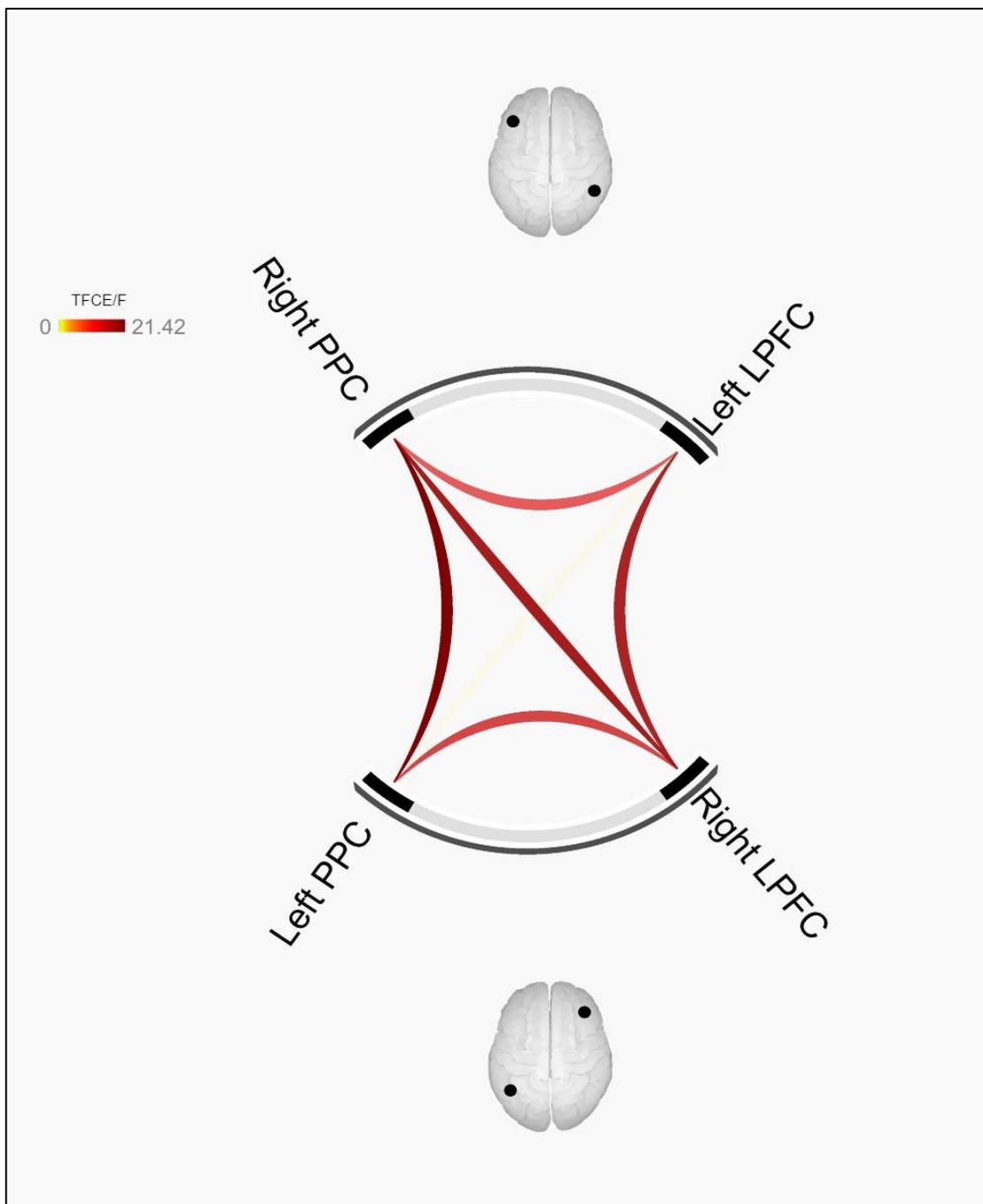
Differences in resting-state functional connectivity of the default mode network according to maternal history of depression.



Note. Never-depressed children's risk for depression (i.e., a maternal history of depression) is associated with significantly increased resting state functional connectivity in the default mode network. *F* scores representing the difference in connectivity by risk group are depicted in colour.

Figure 2

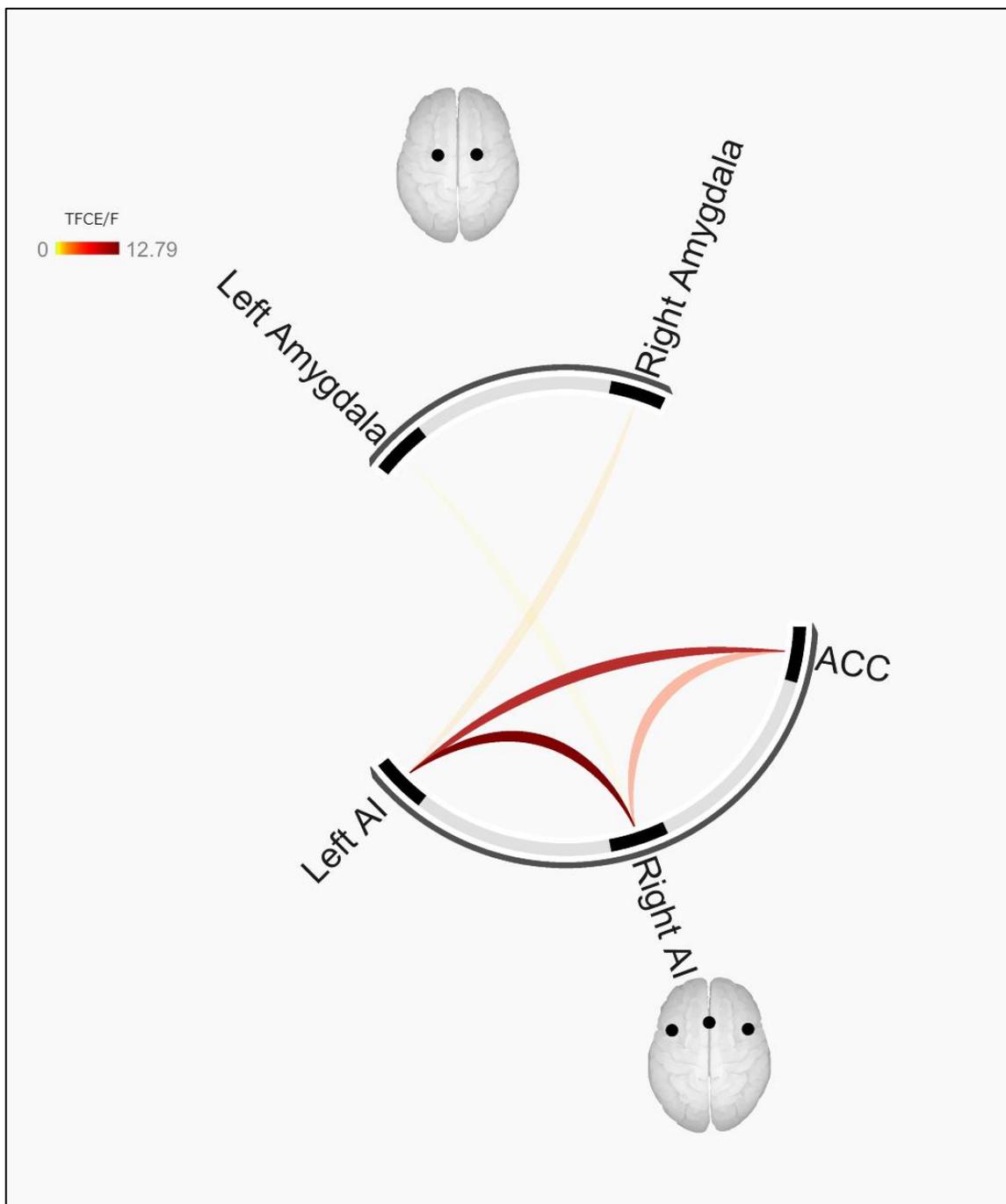
Associations between resting-state functional connectivity of the central executive network and children's self-reported depressive symptoms



Note. Children's self-reported symptoms of depression are negatively associated with resting state functional connectivity in the central executive network. *F* scores representing the strength of association are depicted in colour.

Figure 3

Associations between resting-state functional connectivity of the salience network and children's self-reported depressive symptoms



Note. Children's self-reported depressive symptoms are negatively associated with resting state functional connectivity in the salience network. *F* scores representing the strength of association are depicted in colour.

Chapter 5 – General Summary & Discussion

As a leading global cause of disability (James et al., 2018; Vos et al., 2012), depression has a profound impact on both the individual and wider society. Its high prevalence (Hasin et al., 2018) and association with a variety of negative outcomes (e.g., early death by suicide [Bostwick & Pankratz, 2000; Turecki et al., 2019] and co-occurring health problems [Cuijpers & Smit, 2002; Cuijpers et al., 2014; Mykletun et al., 2009], occupational impairment, academic failure, and marital discord and divorce [Kessler, 2012]) combine to make depression a particularly problematic disorder (Lépine & Briley, 2011). The negative sequelae associated with depression underscore the importance of identifying early vulnerabilities which lead to an increased risk for disorder.

A familial history of depression is among the most widely recognized markers of depression risk (Levinson, 2006; Weissman et al., 2006), with maternal depression appearing to confer a particularly higher degree of depression risk in offspring (Brennan, Hammen, Katz, & Le Brocque, 2002; Goodman et al., 2011; Klein, Lewinsohn, Rohde, Seeley, & Olino, 2005). Foundational models have proposed several mechanisms through which risk is transmitted from mothers to their children (Goodman & Gotlib, 1999, 2002a), including neurobiological vulnerabilities. While there is a substantial literature on neural mechanisms of depression (Disner, Beevers, Haigh, & Beck, 2011; Krishnan & Nestler, 2010; Wohleb, Franklin, Iwata, & Duman, 2016), including a large magnetic resonance imaging (MRI) literature (Bora, Fornito, Pantelis, & Yücel, 2012; Dai, Zhou, Xu, & Zuo, 2019; Wang, Hermens, Hickie, & Lagopoulos, 2012), most past work has studied individuals with personal history of depression. While important, this work is

relatively limited in what it can tell us about the role of neural mechanisms as a mechanistic vulnerability to depression, given that it is unclear whether neural characteristics reflect pre-existing vulnerabilities in depressed individuals or are a consequence of depression itself.

Summary & Review of Studies

In this dissertation, I examined putative neural vulnerabilities for depression, as measured by MRI, in three novel studies using a relatively large sample (Szucs & Ioannidis, 2020) of never-depressed high- and low-risk children. Specifically, I investigated associations between depression risk and children's brain structure (Chapter 2), functional response to maternal feedback (Chapter 3), and resting-state functional connectivity (Chapter 4). In all three studies, I found associations between children's depression risk and the brain, thereby identifying potential early emerging biomarkers of depression risk.

Study 1

In Study 1, I found that never-depressed children's symptoms were negatively associated with grey matter volume (GMV) in the orbitofrontal cortex (OFC; See Chapter 2 and Vandermeer et al., 2020). Further, this association differed for boys and girls, such that girls' depressive symptoms were negatively associated with OFC GMV, while boys' symptoms were positively associated with OFC GMV. Many of the symptoms used to diagnose depression are maladaptive expressions of behaviour for which the OFC plays a crucial role (Drevets, 2007), including the processing of reward and reward-based learning (Delgado, Miller, Inati, & Phelps, 2005; Fettes, Schulze, & Downar, 2017; X. Liu, Hairston, Schrier, & Fan, 2011; Rolls, 2017). Indeed, one of the core symptoms of

depression, anhedonia, is characterized by deficits in motivation, anticipatory and consummatory pleasure, and reward learning. Negative associations between children's depression risk and GMV in the OFC may reflect a pathway to depression involving early emerging pathology in neural reward circuits, consistent with well-established findings of aberrant reward functioning in depressive disorders (Davidson, Pizzagalli, Nitschke, & Putnam, 2002; Treadway & Zald, 2011; Vrieze et al., 2013). In this study, I speculated that the moderation effect of children's sex may be related to sex differences in psychopathology risk. Epidemiological research consistently shows that women are more likely than men to experience anhedonic symptoms during depressive episodes (Romans, Tyas, Cohen, & Silverstone, 2007); my findings highlight a potential neural mechanism for this pattern of symptomatology. Conversely, the positive relationship between OFC GMV and depression risk among boys may be related to externalizing comorbidities often seen among depressed males (Marcus et al., 2005); more specifically, OFC GMV may mark a sex-specific pathway to depression in boys that is more likely to be accompanied by externalizing symptoms driven by maladaptive reward processing (e.g., impulsivity; overvaluation of short- versus long-term rewards; Marcus et al., 2008).

Study 2

In Study 2 (see Chapter 3 and Vandermeer et al., 2021), I used task-based functional magnetic resonance imaging (fMRI) to examine the relationship between never-depressed children's depression risk and neural responses to personally relevant maternal praise and criticism using a maternal feedback challenge protocol (MFC; Hooley, Gruber, Scott, Hiller, & Yurgelun-Todd, 2005). As in Study 1, I found no relationship between maternal depression history and children's functional brain response

to maternal praise or criticism; however, children's self-reported depressive symptoms were negatively associated with functional activity in response to maternal criticism in the left anterior insula (a region associated with salience detection; Uddin, 2015) and right putamen (part of the dorsal striatum involved with selection and initiation of goal-directed behaviour; Balleine, Delgado, & Hikosaka, 2007; Haruno & Kawato, 2006). Further, children's self-reported depressive symptoms were positively associated with activity in the left inferior frontal gyrus during maternal praise. It is possible that altered neural activity in the aforementioned regions during processing of social information may reflect early emerging deficits in adaptive attention and responses to salient social information. Overall, findings indicate that maladaptive neural processing of maternal feedback may contribute to children's early emerging depressive symptoms and subsequent risk for later depression.

Study 3

My final paper, Study 3 (see Chapter 4), built on an emerging literature suggesting that altered resting-state functional connectivity (rsFC) of three networks (i.e., the default mode network [DMN], central executive network [CEN], and salience network [SN]) is relevant to the development of depression (Chahal, Gotlib, & Guyer, 2020; Menon, 2011; Mulders, van Eijndhoven, Schene, Beckmann, & Tendolkar, 2015). While rsFC within these networks has previously been investigated in adolescents and adults with either current or a previous history of depression, to the best of my knowledge, my study is the first to investigate rsFC within these networks in never-depressed children. I found that never-depressed children at high risk for depression (i.e., due to a maternal history of depression) had significantly increased functional

connectivity within the DMN, even after covarying children's self-reported depressive symptoms contemporaneous to the imaging data collection. This finding was discussed in light of the DMN's putative role in spontaneous, introspective, self-referential thought and autobiographical memory (Broyd et al., 2009; Buckner, Andrews-Hanna, & Schacter, 2008; Mulders et al., 2015). Although speculative, given that I did not measure rumination in this study, DMN hyperconnectivity in never-depressed children at high risk for depression may reflect a neural tendency to engage in ruminative thinking (a known cognitive vulnerability to depression; Aldao, Nolen-Hoeksema, & Schweizer, 2010).

Further, children's self-reported depressive symptoms were negatively associated with rsFC within both the CEN and SN, even after controlling for maternal depression history. CEN hypoconnectivity may be indicative of early emerging executive dysfunction, a known prospective predictor of depression onset in high-risk samples (Vinberg, Miskowiak, & Kessing, 2013). SN hypoconnectivity was posited to reflect early deficits in salience detection and dysfunctional context-dependent network switching between the DMN and the CEN previously reported in studies of people with depression (Goulden et al., 2014; Menon, 2015; Sridharan, Levitin, & Menon, 2008). Overall, findings were generally consistent with extant research on resting-state functional connectivity in people with depression (Alexopoulos et al., 2012; Dong et al., 2019; Jiao et al., 2020; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Mulders et al., 2015; Sacchet et al., 2016; Stange et al., 2017).

Integration

This dissertation used multiple modalities of magnetic resonance imaging to study the neural correlates of depression risk in a single sample of never-depressed children.

Across all studies, children's self-reported depressive symptoms were significantly associated with relatively distinct neural structures and processes (e.g., brain structure, function, and connectivity). Although the three studies investigated different aspects of neural risk for depression, there was some commonality in terms of the neural regions implicated, including regions of the prefrontal cortex (PFC). This is in line with the broader literature demonstrating that the PFC is the region most consistently impaired in depression across different imaging modalities and studies (Pizzagalli & Roberts, 2021). Given the wide range of PFC-supported cognitive functions that also show aberrations in depression (e.g., reward processing, emotion regulation, executive functioning, etc.; Pizzagalli & Roberts, 2021), it is unsurprising that the PFC was repeatedly associated with children's depression risk across my studies. As a group, these studies suggest that early depression risk is associated with relatively widespread abnormalities in the PFC, consistent with the etiological heterogeneity of depression that characterizes even the relatively narrow domain of neural depression risk.

The anterior insula (AI) was also associated with depression risk (namely children's early emerging self-reported depression symptoms) in two of the current studies; specifically, I found associations between children's depressive symptoms and functional activity during the processing of maternal criticism (Study 2) and resting-state functional connectivity (Study 3). Like most brain structures, the AI has multiple functions (Chang, Yarkoni, Khaw, & Sanfey, 2013; Craig, 2009; Gasquoin, 2014) including serving as a hub region of the SN, which is important for the integration of sensory and cognitive information when determining appropriate and adaptive responding to internal and external stimuli (Menon, 2015; Uddin, 2015). Based on my results, it

appears that early emerging risk for depression may be, in part, driven by neural aberrations in salience processing. Dysfunction in the ability to appropriately identify important stimuli in external and internal environments may impair appropriate cognitive and behavioural responses typically disrupted in depression, including reward processing (Rolls, 2016) and social skills (Odriozola et al., 2016). However, I note that, although two of my studies showed involvement of AI in depression risk, these studies investigated the AI in distinct contexts (i.e., during a maternal feedback task and during a resting-state protocol) using distinct MRI-based measures (i.e., BOLD response to a task-based fMRI protocol and functional connectivity). While direct comparison of these results is difficult, they are consistent with the possibility that AI activity is associated with depression risk, as well as depression itself (Avery et al., 2014; Mulders et al., 2015).

Although I was most interested in understanding the relationship between a maternal history of depression and children's neural risk for depression, most of my findings involved neural associations with children's self-reported symptoms, rather than a maternal depression history; the sole exception to this was that, relative to children with no maternal history of depression, children with a maternal history of depression had significantly greater functional connectivity within the DMN (Study 3). This pattern of findings likely reflects the high etiological heterogeneity for depression (Hasler, 2010), such that inconsistent associations between risk (i.e., maternal history and children's depressive symptoms) and neural structure and function are indicative of distinct etiological pathways.

Moderators and Mediators for Future Study of Children's Depression Risk

Future research on this topic should integrate other factors not investigated in the aforementioned studies that may mediate or moderate pathways between children's neural function and structure and later depression. Complex models such as these are needed to better capture the etiological complexity of depression. In this section, I highlight a few key directions worthy of prioritizing in future research.

Although I focused on the role of maternal history in my analyses, the availability, behaviour, and mental health of fathers are all likely to contribute to and interact with neural risk (among other etiological factors) in shaping children's risk for depression. Meta-analytic research has demonstrated that, similar to maternal depression, paternal depression is associated with significant increases in negative and decreases in positive parenting (Wilson & Durbin, 2010), and that paternal depression is associated with increased internalizing symptoms in children and father-child conflict (Kane & Garber, 2004). In a large, longitudinal study, Reeb, Conger, and Wu (2010) showed that fathers' depression symptoms were positively associated with prospective increases in children's depression symptoms, even after controlling for the effect of maternal depression and children's baseline depression symptoms. In addition to paternal depression directly and indirectly increasing risk for depression, several studies have demonstrated that the presence of a warm and supportive fathers can mitigate the impact of a depressed mother (Collishaw et al., 2016; Mahedy et al., 2018).

Although these studies suggest that father influence children's depression risk and moderate the relationship between maternal depression and child risk, very few studies have investigated the main or moderating effects of fathers' depression on children's

neural risk for depression. In what appears to be only two studies on the subject, El Marroun et al. (2016; 2018) found no relationship between fathers' depressive symptoms and children's brain morphology or white matter structure, respectively. Nevertheless, given the biological and environmental influences that fathers have on their children (Kane & Garber, 2004), as well as potential moderating effects of paternal depression on other aspects of children's risk, future research should test for the direct and interactive effects of paternal depression history on children's neural risk for depression.

Unfortunately, I was unable to consider the influence of timing of maternal depression in the current study. Previous research has found that the timing of maternal depression has a significant impact on risk, with highest risk seen in children who were first exposed from age 2- to 5-years-old (Naicker, Wickham, & Colman, 2012). This suggests that, in addition to direct inheritance, the effect of parental depression child risk is especially pronounced during specific sensitive periods for children. To the best of my knowledge, no study has specifically investigated the impact of timing of parental depression on children's neural risk for depression; however, given past work (Naicker et al., 2012), maternal depression may be particularly potent during specific developmental stages such that children's neurodevelopment is more sensitive to the depressogenic influences of familial stress, negative parenting behaviour, and modeling of poor emotion regulation strategies associated with having an actively depressed parent. The sample size, although large in the context of most neuroimaging research (Szucs & Ioannidis, 2020), may have been too small to detect associations between maternal depression and children's neural developmental, possibly contributing to the lack of differences between high- and low-risk children in GMV (Study 1) and functional response to maternal praise

and criticism (Study 2). Future efforts at understanding children's neural risk for depression will need to draw upon large samples of mothers who vary in depression history and timing of episodes to investigate the potential impact of timing of maternal depression exposure on children's neurodevelopment.

I also did not examine the potential role of pubertal development in the current studies. It has been firmly established that pubertal development is a critical period of time for depression and is associated with both spikes in prevalence and the emergence of sex-based differences in depressive disorders (Angold, Costello, & Worthman, 1998). Unfortunately, pubertal status was not assessed in the course of my studies. While all analyses covaried for child age as a proxy of pubertal development, future studies will benefit from the collection of more fine-grained indices of pubertal development in order to determine its influence on the neural mechanisms of depression. Given that such pathways may differ for boys versus girls (Angold et al., 1998; Marcus et al., 2005), investigations of larger samples with greater variability in age than the current sample is needed.

Additionally, although findings from the current studies highlight the impact of neural development in brain regions that may influence depressogenic cognition (Stange et al., 2017; Zhou et al., 2020), I did not measure cognitive styles directly in these studies, an important direction for future research. Finally, given the key role of stressful life events in depression (Kendler & Gardner, 2010; Kendler et al., 2010) and the potential for stress to moderate brain function relevant to depression (Pizzagalli, 2014), measures of such events should be included in future research on the neural substrates of developmental psychopathology of depression.

Strengths, Limitations, and Future Directions

All three studies that comprise this dissertation have important strengths that support their individual and collective contributions to the literature. As the strengths of the individual studies have already been discussed in their respective chapters, the following is a brief discussion of the strengths common to the three studies.

A number of the core strengths of my studies derive from the qualities and demographics of the sample. For example, one of the most important strengths of the current studies is their use of a sample of never-depressed children. As has been mentioned throughout this manuscript, most extant work on the neural mechanisms and neuroimaging of depression has been conducted on adult and adolescent samples with a personal history of depression (i.e., either current depressive disorder or recovered from a previous episode, or episodes, of depression; Bora et al., 2012; Dai et al., 2019; Wang et al., 2012). Similarly, many previous studies of depression risk have used samples of high-risk *adults* who have never experienced a depressive episode (e.g., Amico et al., 2011; Miskowiak et al., 2018, 2017). Although both approaches have led to meaningful contributions to the field, they are inherently confounded. In the case of the former, it remains difficult to disentangle whether distinct patterns of brain structure or function are representative of an etiologically important vulnerability to depression (i.e., it pre-exists the onset of depression) or are a consequence of depression (i.e., either a state marker of depressive disorder or a stable ‘scarring-effect’). This is further complicated by the relatively unknown effect of participants’ clinical treatment on neural structure or function (e.g., psychotherapy, psychopharmacology, brain stimulation, etc.). Similarly, risk-based studies that use samples of high-risk, never-depressed adults may be more

relevant to depression resilience, rather than risk. In contrast, my focus on never-depressed children, prior to the typical age of onset for depression, permits more confidence that findings are indeed related to *risk* for depression. Finally, characterizing neural risk for depression in children during a relatively understudied developmental stage is an important contribution to the literature and understanding of developmental psychopathology for depression.

Additionally, the sample used in this dissertation was derived from an ongoing community-based longitudinal study of temperament and developmental psychopathology (Kryski, Smith, Sheikh, Singh, & Hayden, 2011; Liu, Kryski, Smith, Joannisse, & Hayden, 2019; Sheikh, Kryski, Smith, Hayden, & Singh, 2013). Recruiting participants from a community-based sample increases confidence that findings are representative of the broader community from which participants were drawn and increases the generalizability of my findings.

Other strengths come from methodological choices employed in the three studies. All participants in the aforementioned three studies underwent extensive diagnostic assessment using gold-standard approaches for clinical assessment, namely semi-structured clinical interviews in the form of the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) and the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Non-patient Edition (SCID-I/NP; First, Spitzer, Gibbon, & Williams, 2002) in children and mothers, respectively. Use of standardized semi-structured clinical interviews to assess for personal history of mental disorder allowed me to ensure that children's risk for depression was not confounded by a personal history of depressive disorder, and that risk

due to maternal history was based on best-practices in assessment of depression (Stuart et al., 2014).

In addition to the aforementioned strengths of this dissertation (and the studies contained therein), it is important to discuss their inherent weaknesses as well as future directions to address them. Consistent with the above discussion of study strengths, given that weaknesses of individual studies were previously discussed in their respective chapters, the following provides a brief review of weaknesses that are shared across the three studies.

Perhaps the most important limitation of the three studies is their cross-sectional nature. Despite the sample being derived from a larger (and ongoing) longitudinal study of temperament and developmental psychopathology, the data reported represents the first application of neuroimaging methods. Future work with this sample is necessary to examine whether the neural markers that characterize high-risk children and depressive symptoms in childhood predict the onset of clinically significant depression. Specifically, ongoing longitudinal study of this sample will allow us to determine whether reported differences in neurodevelopment are *causally* implicated in the developmental psychopathology of depression.

The studies making up this dissertation all used maternal history of depression as the main marker of depression risk in child participants. This was done as a maternal history of depression appears to have an especially strong link to offspring depression risk (Connell & Goodman, 2002; Klein et al., 2005) and mothers typically act as the primary parent; however, a history of depression in other family members is also known to increase risk for depression (Gotlib, Joormann, & Folland-Ross, 2014). Given that I did

not assess depression history in other family members, it is probable that I have underestimated the number of children at risk for depression in this sample. Future studies should extend risk to include a broader spectrum of family members. It is especially important that future research investigate the role of paternal depression history, as previously noted.

Similarly, Goodman & Gotlib's (1999) highlighted other, potentially important moderating factors on intergenerational transmission of depression. In particular, they proposed that individual differences in children (e.g., temperament, intellectual abilities, social-cognitive skills, etc.) interact with neurobiology, among other vulnerabilities, to confer children's risk for depression. Research with larger samples and multimethod approaches is necessary to better understand the role of neural depression vulnerabilities within the broader context of children's depression risk.

Finally, although the sample was representative of the community from which it was drawn, it was fairly homogenous both in terms of ethnicity and socioeconomic status (SES). Namely, the majority of the sample identified as White (96%) and had relatively high SES (64.5% had household income > \$70,000 CAD). It is unclear whether my findings on MRI-based markers of depression risk generalize to more diverse samples. Future research efforts should prioritize sampling from traditionally understudied populations (e.g., ethnically diverse families, children of same-sex parents, broader range of socioeconomic statuses).

Conclusions

Across three studies, my results demonstrate that never-depressed children's risk for depression (e.g., maternal history of depression and early emerging symptoms of

depression) is associated with significant differences in brain morphology, function, and connectivity. Such differences in brains of never-depressed children may reflect biological mechanisms that contribute to the etiology of depression; however, further research, especially multi-wave, longitudinal studies, is necessary to properly test the potential mediating role of these brain-based differences in the transition from risk to disorder. Despite this, the three studies that comprise this dissertation are, to the best of my knowledge, the first to characterize neural aspects of depression risk in a relatively large sample of never-depressed children. As such, this represents an important contribution to the literature and a key step toward improving understanding of the neural mechanisms of depression risk.

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Appendix

Visit Number	Location	Data Collected	
		Child	Mother
1	Phone	N/A	Parent-report portion of the K-SADS-PL
2	Home	Child-report portion of the K-SADS-PL YSR CDI	MFC Audio Stimuli CBCL
3	Laboratory	N/A	SCID-I/NP
4	MRI Scanner	Anatomical Scan Resting state* MFC*	N/A

Appendix. Data collection schedule. Only data used as part of the studies that make up this dissertation are depicted. K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (Kaufman et al., 1997); YSR = Youth Self-Report (Achenbach & Rescorla, 2001); CDI = Child Depression Inventory (Kovacs, 2011); MFC = Maternal Feedback Challenge (Hooley, Gruber, Scott, Hiller, & Yurgelun-Todd, 2005); CBCL = Child Behavior Checklist (Achenbach & Rescorla, 2001); SCID-I/NP = Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Non-Patient Edition (First, Spitzer, Gibbon, & Williams, 2002); * = functional MRI experiments.

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MATTHEW R. J. VANDERMEER

Curriculum Vitae

Personal Information

Address Department of Psychology & the Brain and Mind Institute
Western Interdisciplinary Research Building
University of Western Ontario
London, Ontario, Canada
N6A 3K7

E-Mail XXXXXXXXXX

Telephone XXXXXXXXXX

Education

Postdoctoral Fellow 2021 – Present
Queen's University – Kingston, Ontario

Ph.D., Clinical Psychology 2022
University of Western Ontario – London, Ontario
Dissertation: Neuroimaging Endophenotypes in Major Depressive Disorder
Supervisor: Dr. Elizabeth Hayden, Ph.D.

Psychology Resident, Clinical Psychology 2021
London Clinical Psychology Residency Consortium – London Ontario

Master of Arts, Counselling Psychology 2014
University of Western Ontario – London, Ontario
Thesis: Secondary Traumatic Stress and Alexithymia in High-Risk Professionals
Supervisor: Dr. Susan Rodger, Ph.D. C. Psych.

Honours Bachelor of Science, Mental Health Studies & Biology 2012
University of Toronto – Toronto, Ontario
Senior Study: Assessing the Utility of a Virtual Reality Test of Executive Dysfunction on
Traumatic Brain Injury Patients
Supervisor: Dr. Konstantine Zakzanis, Ph.D. C. Psych.

Academic Awards & Research Grants

Smadar Levin Award for Outstanding Poster Presentation (Finalist) 2019
The Society for Research in Psychopathology

Graduate Student Teaching Assistant Award (Nominated) 2017
UWO Society of Graduate Students

Frederick Banting & Charles Best CGS Doctoral Award 2016 – 2019
Canadian Institutes of Health Research \$105,000

MATTHEW R. J. VANDERMEER

Curriculum Vitae

Doctoral Excellence Research Award University of Western Ontario \$30,000	2016 – 2019
Research Studentship Ontario Mental Health Foundation	2016 – 2020 (declined) \$75,000
Ontario Graduate Scholarship (declined) Ministry of Education and Training	2016 – 2017 \$15,000
Quality of Life Initiative Children’s Health Research Institute	2015 – 2017 \$16,000
Graduate Student Grant Canadian Counselling & Psychotherapy Association (CCPA)	2014 \$500
Ontario Graduate Scholarship (OGS) University of Western Ontario	2013 – 2014 \$15,000
Western Graduate Research Scholarship (WGRS) University of Western Ontario	2012 – 2013 \$12,000
University of Toronto Scarborough Campus Entrance Scholarship University of Toronto	2007 \$1000

Memberships in Professional Societies

Flux: The Society for Developmental Cognitive Neuroscience	2018 – 2019
Society for Research in Psychopathology	2016 – Present
Association for Psychological Science	2016 – Present
Canadian Psychological Association	2014 – Present
Canadian Counselling and Psychotherapy Association	2013 – 2014

Teaching Experience

Child Abnormal Psychology (PSYCHOL-2320, Instructor) Department of Psychology, University of Western Ontario	2020
Psychological Assessment Practicum (PSYCHOL-9900, Teaching Assistant) Clinical Science & Psychopathology, University of Western Ontario	2018-2019
Child Abnormal Psychology (PSYCHOL-2320, Teaching Assistant) Department of Psychology, University of Western Ontario	2017; 2018
Counselling Interventions (GRADEDUC-9547, Teaching Assistant) Faculty of Education, University of Western Ontario	2014

MATTHEW R. J. VANDERMEER

Curriculum Vitae

Practicum in Counselling (GRADEDUC-9545, Teaching Assistant) 2013
Faculty of Education, University of Western Ontario

Invited Lectures

Temperament, Personality, & Psychopathology 2017
Introduction to Personality Theory and Research (PSYCH-2550)
Huron at Western

Clinical Versus Counselling Psychology 2017; 2019; 2020; 2021
Introduction to Clinical Psychology (PSYCH-2301)
Brescia University College

Professional Service & Advocacy

Advocacy Through Action – Letter Writing Campaign & Public Lecturer 2017; 2019
Department of Psychology, University of Western Ontario

Clinical Adjunct Advisory Committee 2018
Department of Psychology, University of Western Ontario

Reviewer, Canadian Psychological Association Annual Convention 2018
Canadian Psychological Association Section on Brain and Cognitive Science

Clinical Students Advisory Committee 2017 – 2019
Department of Psychology, University of Western Ontario

Society of Graduate Students Representative 2015 – 2016
University of Western Ontario

Society of Graduate Students - Academic Committee 2015 – 2016
University of Western Ontario

Student Representative for University of Western Ontario 2013 – 2014
Canadian Counselling and Psychotherapy Association

Peer Review Activity

Developmental Cognitive Neuroscience 2020
Psychiatry Research 2020
Journal of Family Psychology 2020
Biological Psychiatry 2019
Development and Psychopathology 2015

MATTHEW R. J. VANDERMEER

Curriculum Vitae

Manuscripts in Preparation

1. **Vandermeer, M. R. J.**, Liu, P., Mohamed Ali, O., Daoust, A. R., Joanisse, M. F., Barch, D. A., & Hayden, E. P. (In preparation). *Resting state functional connectivity as a putative marker of depression vulnerability in never-depressed youth.*
2. Mohamed Ali, O., **Vandermeer, M. R. J.**, Daoust, A. R., Liu, P., Joanisse, M. F., Barch, D. M. & Hayden, E. P. (In preparation). *The association between perceived parent-child relationship quality and adolescent reactivity to maternal feedback is moderated by early irritability.*
3. Daoust, A. R., Green, H., **Vandermeer, M. R. J.**, Liu, P., Stanton, K., ... & Hayden, E. P. (In preparation). *Associations between adolescents' and parents' depressive symptoms during the COVID-19 pandemic.*
4. Daoust, A. R., Green, H., **Vandermeer, M. R. J.**, Liu, P., Stanton, K., ... & Hayden, E. P. (In preparation). *Pre-pandemic cortisol reactivity predicts youths' trajectories of internalizing symptoms during the COVID-19 pandemic.*

Manuscripts Under Review

1. Daoust, A. R., Stanton, K., **Vandermeer, M. R. J.**, Liu, P., Harkness, K. L., & Hayden, E. P. (2021). Development and primary validation of the Pandemic Avoidance and Concern Scales (PACS). *Manuscript submitted for publication.*
2. **Vandermeer, M. R. J.**, Liu, P., Mohamed Ali, O., Daoust, A. R., Joanisse, M., Barch, D., & Hayden, E. P. (2021). Children's neural reactivity to maternal praise and criticism: Associations with early depressive symptoms and maternal depression. *Manuscript submitted for publication.* <https://doi.org/10.31234/osf.io/5m7nd>

Peer-reviewed Publications

1. Liu, P., **Vandermeer, M. R. J.**, Mohamed Ali, O., Daoust, A. R., Joanisse, M. F., Barch, D. M., & Hayden, E. P. (2021). Maternal depression, child temperament, and early-life stress predict never-depressed preadolescents' functional connectivity during a negative-mood induction. *Clinical Psychological Science*, 216770262110164. <https://doi.org/10.1177/21677026211016419>
2. Cross, A. M., Ramdajal, R., Peters, L., **Vandermeer, M. R. J.**, Hayden, E. P., Frijters, J. C., Steinbach, K. A., Lovett, M. W., Archibald, L. M. D., & Joanisse, M. F. (In Press). Resting-state functional connectivity and reading subskills in children. *NeuroImage*. <https://doi.org/10.1016/j.neuroimage.2021.118529>
3. **Vandermeer, M. R. J.**, Liu, P., Ali, O. M., Daoust, A. R., Joanisse, M. F., Barch, D. M., & Hayden, E. P. (2020). Orbitofrontal cortex grey matter volume is related to children's depressive symptoms. *NeuroImage: Clinical*, 102395. <https://doi.org/10.1016/j.nicl.2020.102395>

MATTHEW R. J. VANDERMEER

Curriculum Vitae

4. Liu, P., **Vandermeer, M. R. J.**, Joanisse, M. F., Barch, D. M., Dozois, D. J., & Hayden, E. P. (2020). Depressogenic self-schemas are associated with smaller regional grey matter volume in never-depressed preadolescents. *NeuroImage: Clinical*, 28, 102422. <https://doi.org/10.1016/j.nicl.2020.102422>
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MATTHEW R. J. VANDERMEER

Curriculum Vitae

13. Rodger, S., Hibbert, K., Leschied, A., Pickel, L., Magdalena, S., Atkins, M-A., Koenig, A., Woods, J., & **Vandermeer, M.** (2014). Shaping a mental health curriculum for Canada's teacher education programs: Rationale and brief overview. *Physical & Health Education Journal*, 80(3), 28-29.
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3. Szaszi, K., **Vandermeer, M.**, & Amoozadeh, Y. (2012). Epithelial wound healing and the effects of cytokines investigated by ECIS. In W. G. Jiang (Ed.), *Electric Cell-Substrate Impedance Sensing in Cancer and Cancer Metastasis Research* (pp. 131-176). London: Springer Verlag.

Other Publications

1. Rodger, S., Hibbert, K., Leschied, A., Pickel, L., Magdalena, S., Atkins, M-A., Koenig, A., Woods, J., & **Vandermeer, M.** (2014). *Mental health education in Canada: An analysis of teacher education and provincial/territorial curricula*. Ottawa, ON: Physical & Health Education Canada.
2. **Vandermeer, M. R. J.** (2014). Be kind to yourself: Practicing basic self-care. *Canadian Counselling and Psychotherapy Association's Newsletter*, 7(1), 12-13.

Presentations

1. Daoust, A. R., Green, H., **Vandermeer, M. R. J.**, Liu, P., Stanton, K., Olino, T. M., Harkness, K., & Hayden, E. P. (2021). *Associations between adolescents' and parents' depressive symptoms during the COVID-19 pandemic*. 2021 Association for Psychological Science Virtual Convention.

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2. Green, H., Daoust, A., **Vandermeer, M.**, Liu, P., Stanton, K., Harkness, K., & Hayden, E. (2021). *Self-referential processing at age 11 predicts internalizing symptoms during the COVID-19 pandemic*. 2021 Association for Psychological Sciences Virtual Convention.
3. Green, H., Daoust, A., **Vandermeer, M.**, Liu, P., Stanton, K., Harkness, K., & Hayden, E. (2021). *Stable early behavioral inhibition predicts within-person variability in adolescents' internalizing symptoms during the COVID-19 pandemic*. Canadian Stress Research Summit, Toronto, ON.
4. Daoust, A. R., Green, H., **Vandermeer, M. R. J.**, Stanton, K., Harkness, K., & Hayden, E. P. (2021). *Pre-pandemic cortisol reactivity predicts youths' trajectories of internalizing symptoms during the COVID-19 pandemic*. Canadian Stress Research Summit, Toronto, ON.
5. Daoust, A. R., Stanton, K., **Vandermeer, M. R. J.** Liu, P., Harkness, K., & Hayden, E. P. (2021). *Measuring parents' and childrens' responses to the COVID-19 pandemic*. Society for Research in Child Development Virtual Biennial Meeting.
6. Liu, P., Daoust, A., **Vandermeer, M.**, Stanton, K., Harkness, K., & Hayden, E. (2021). *Default mode network resting-state functional connectivity predicts COVID-19-related concerns in youth*. Society for Research in Child Development Virtual Biennial Meeting.
7. **Vandermeer, M. R. J.**, Liu, P., Mohamed Ali, O., Daoust, A. R., Joanisse, M. F., ... & Hayden, E. P. (2019). *A neuroimaging study of high-risk children's reactivity to maternal expressed emotion*. 33rd Annual Meeting of Society for Research in Psychopathology, Buffalo, NY, USA.
8. Mohamed Ali, O., **Vandermeer, M. R. J.**, Daoust, A. R., Liu, P., Kryski, K. R., ... & Hayden, E. P. (2019). *Associations between early parenting and children's neural development*. 33rd Annual Meeting of Society for Research in Psychopathology, Buffalo, NY, USA.
9. Daoust, A. R., **Vandermeer, M. R. J.**, Mohamed Ali, O., Kryski, K., Singh, S., & Hayden, E. P. (2019). *Investigating the stability of cortisol stress reactivity across development: Potential moderating factors*. 33rd Annual Meeting of Society for Research in Psychopathology, Buffalo, NY, USA.

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10. **Vandermeer, M. R. J.**, Daoust, A. R., Mohamed Ali, O., Joannis, M. F., Barch, D. M., & Hayden, E. P. (2018). *Associations between children's resting state functional connectivity and maternal history of depression*. 32nd annual meeting of Society for Research in Psychopathology, Indianapolis, IN, USA.
11. Liu, P., **Vandermeer, M. R. J.**, Joannis, M. F., Barch, D. M., Dozois, D. J. A., Hayden, E. P. (2018). *Associations between brain structure and depressogenic self-schematic processing in childhood*. 32nd annual meeting of Society for Research in Psychopathology, Indianapolis, IN, USA.
12. **Vandermeer, M. R. J.**, Vandermeer, M. R. J., Daoust, A. R., Mohamed Ali, O., Joannis, M. F., Barch, D. M., & Hayden, E. P., (2018). *Gray matter concentrations in never-depressed children at risk for depression*. 6th Annual Flux Congress, Berlin, Germany.
13. Mohamed Ali, O., **Vandermeer, M. R. J.**, Sheikh, H. I., Mackrell, S. V. M., Joannis, M. F., & Hayden, E. P. (2018). *Associations between elevated internalizing symptoms during early childhood and integrity of white matter tracts in cortico-limbic circuitry*. 6th Annual Flux Congress, Berlin, Germany.
14. **Vandermeer, M. R. J.**, Joannis, M. F., Daoust, A., Mohamed Ali, O., Salisbury, M., Barch, D. M., & Hayden, E. P. (2017). *Resting state functional connectivity in children at high risk for depression*. Thirty First Annual Meeting of the Society for Research in Psychopathology, Denver, CO, USA.
15. **Vandermeer, M.**, Kotelnikova, Y., Kryski, K., & Hayden, E. (2016). *Implications of self- and informant-reported personality for relationship discord and psychopathology*. Thirtieth Annual Meeting of the Society for Research in Psychopathology, Baltimore, MD, USA.
16. **Vandermeer, M. R. J.**, Kotelnikova, Y., Kryski, K. R., & Hayden, E.P. (2016). *Relationship quality moderates mother-father personality agreement*. Association for Psychological Science 28th Annual Convention, Chicago, IL, USA.
17. Kotelnikova, Y., Sheikh, H. I., **Vandermeer, M.R.J.**, Kryski, K. R., Singh, S. M., Olino, T. M., & Hayden, E. P. (2016). *Predictors of latent cortisol trajectory classes in the context of stress*. Association for Psychological Science 28th Annual Convention, Chicago, IL, USA.

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18. MacDougall, A., Norman, R., Anderson, K., Carr, J., Koffler, T., **Vandermeer, M.**, ... Shanmugalingam, A. (2016). *Group mindfulness-based intervention improves affective symptoms in individuals with early psychosis: A pilot randomized controlled trial*. Association for Psychological Science 28th Annual Convention, Chicago, IL.
19. MacDougall, A., Krupa, T., Lysaght, R., Mutiso, V. Ndetei, D., Kidd, S., ... **Vandermeer, M. R. J.** (2015). *Promoting recovery from serious mental illness in low-income contexts: The CREATE model*. Schulich School of Medicine Department of Psychiatry Academic Research Day. London, ON.
20. MacDougall, A., Carr, J., & **Vandermeer, M. R. J.** (2015). *Mindfulness group intervention for early psychosis: A pilot study of the Mindfulness Ambassador Council*. Schulich School of Medicine Department of Psychiatry Academic Research Day. London, ON.
21. MacDougall, A., **Vandermeer, M. R. J.**, & Norman, R. (2015). *Possible-self as a mediator of the insight-depression relationship in schizophrenia spectrum disorders*. 76th Canadian Psychological Association Convention. Ottawa, ON.
22. **Vandermeer, M. R. J.**, & Rodger, S. (2014). *The Relationship Between Alexithymia and Secondary Traumatic Stress in Novice Psychotherapists*. 75th Canadian Psychological Association Convention. Vancouver, BC.
23. **Vandermeer, M.**, & Rodger, S. (2014). *Secondary Traumatic Stress and Alexithymia in Counselling Students*. Canadian Counselling and Psychotherapy Association 2014 Annual Conference. Victoria, BC.
24. **Vandermeer, M.** (2014). *The Relationship Between Secondary Traumatic Stress and Alexithymia in Students Working with Vulnerable Clients*. International Association for Counselling 2014 Conference. Victoria, BC.
25. **Vandermeer, M.**, & Rodger, S. (2014). *Secondary traumatic stress and alexithymia in novice counsellors*. Canadian Counselling and Psychotherapy Association 2014 Research Conference. Moncton, NB.
26. Hanna, S., Klas, P., Jeffay, E., Zanjani, A., **Vandermeer, M.**, & Zakzanis, K. (2013). *Pre-injury income and return to work after mild traumatic brain injury*. 41st Annual Meeting of the International Neuropsychological Society. Waikoloa, HI.
27. Klas, P., Hanna, S., Jeffay, E., Zanjani, A., **Vandermeer, M.**, & Zakzanis, K. (2013). *Predicting disability using neuropsychological testing in patients with mild traumatic brain injury*. 41st Annual Meeting of the International Neuropsychological Society. Waikoloa, HI.

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28. **Vandermeer, M.**, Zanjani, A., Jeffay, E., Klas, P., Hanna, S., & Zakzanis, K. (2013). *A Novel, Ecologically Valid, Measure of Executive Functioning: A Pilot Study*. 41st Annual Meeting of the International Neuropsychological Society. Waikoloa, HI.
29. Zanjani, A., Jeffay, E., Klas, P., Hanna, S., **Vandermeer, M.**, & Zakzanis, K. (2013). *Component analysis of memory function schizophrenia: A quantitative review*. 41st Annual Meeting of the International Neuropsychological Society. Waikoloa, HI.
30. Zanjani, A., **Vandermeer, M.**, Jeffay, E., Hanna, S., Klas, P., & Zakzanis, K. (2013). *A novel virtual environment test and selective, sustained and divided attention in an mTBI population: A pilot study*. 41st Annual Meeting of the International Neuropsychological Society. Waikoloa, HI.
31. **Vandermeer, M.**, Jeffay, E., & Zakzanis, K. (2012). *Examining the differential sensitivity of a virtual reality test measure of executive functioning in traumatic brain injury*. National Academy of Neuropsychology 32nd Annual Conference. Nashville, TN.
32. **Vandermeer, M.**, Dan, Q., Zhang, J., Waheed, F., Kakiashvili, E., & Szaszi, K. (2011). *Tumor necrosis factor- α enhances proliferation and wound healing in the tubular epithelium: Role of the epidermal growth factor receptor*. Keystone Symposium on Epithelial Plasticity. Vancouver, BC.
33. Kakiashvili, E., Dan, Q., **Vandermeer, M.**, Zhang, J., Waheed, F., & Szaszi, K. (2010). *The epidermal growth factor receptor mediates tumor necrosis factor- α -induced GEF-H1 and Rho activation in tubular epithelial cells*. 50th Annual Meeting of the American Society for Cell Biology. Philadelphia, PA.
34. Kakiashvili, E., Dan, Q., **Vandermeer, M.**, Zhang, J., Waheed, F., & Szaszi, K. (2010). *The epidermal growth factor receptor mediates tumor necrosis factor- α -induced Rho activation in the tubular epithelium*. 6th International Congress of Pathophysiology. Montreal, QC.
35. **Vandermeer, M.**, Zhang, J., Dan, Q., & Szaszi, K. (2010). *Tumor necrosis factor- α enhances wound healing and proliferation in tubular epithelium via the transactivation of the epidermal growth factor receptor*. ECIS User's Meeting 2010. Rensselaerville, NY.

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Curriculum Vitae

Undergraduate Thesis Supervision

Charlotte Hammill 2018 – 2019
Title: Parenting Behaviour and Child Brain Morphology

Mika Ohtsuka 2017 – 2018
Title: Objectively Measured Similarities between Parent Personality and Child Temperament

Rayyan Khalif 2017 – 2018
Title: Relationship Satisfaction and Depression: Moderating Effects of Self- and Informant-Reported Neuroticism

Stephanie Castello 2016 – 2017
Title: Child Temperament as a Predictor of Anxiety Disorder

Additional Research Experience

Clinical Psychology Residency Research Minor 2021
Dr. Marnin Heisel, University of Western Ontario

Research Assistant 2017 – 2019
Dr. David Dozois, University of Western Ontario

Research Assistant 2014 – 2016
Dr. Arlene MacDougall, London Health Sciences Centre

Senior Research Associate 2014
Dr. Susan Rodger, University of Western Ontario

Research Assistant/e-Learning Developer 2013 – 2014
Dr. Susan Rodger, University of Western Ontario

Research Assistant 2011 – 2012
Dr. Konstantine Zakzanis, University of Toronto

Research Assistant 2010 – 2011
Dr. Katalin Szaszi, Keenan Research Centre of St. Michael's Hospital Toronto

Clinical Experience

Adult Ambulatory Care CBT Program 2021
London Health Sciences Centre: Victoria Hospital

Adult Inpatient Psychiatry 2020 – 2021
St. Joseph's Health Care London: Parkwood Institute

Psychometrist 2019 – 2020
McKenzie Psychology

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Prodromal Symptoms of Psychosis – Early Clinical Identification and Treatment (PROSPECT) Clinic <i>Prevention and Early Intervention Program for Psychoses (PEPP)</i>	2019
Early Psychosis Intervention Practicum <i>PEPP</i>	2018 – 2019
Clinical Assessment Practicum <i>Dr. Forbes & Associates</i>	2018
Private Practice Practicum <i>Dr. Biederman and Associates</i>	2017 – 2018
Health Rehabilitation Practicum <i>Cardiac Rehabilitation & Secondary Prevention Program, St. Joseph's Healthcare</i>	2017
Adult Intervention Practicum <i>Psychological Services, University of Western Ontario</i>	2016 – 2017
Forensic Intervention Practicum <i>Southwest Centre for Forensic Mental Health Care, St. Joseph's Healthcare</i>	2016
Adult Assessment Practicum <i>Adult Neuropsychology, London Health Sciences Centre</i>	2016
Child & Adolescent Assessment Practicum <i>ASD Screening Clinic, Child and Parent Resource Institute</i>	2016
Clinical Counsellor <i>Graham Guidance</i>	2015
Counselling Psychology Practicum <i>Psychological Services, University of Western Ontario</i>	2013 – 2014
Group Therapy Facilitator <i>Journey Through Loss Grief Group</i>	2013
Student Counsellor <i>Waitlist Clinic, CMHA London</i>	2012