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Examining Associations Between Severity of Parental Depression and Anxiety Symptoms and Offspring Grey Matter

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Examining Associations Between Severity of Parental Depression and Anxiety Symptoms and Offspring Grey Matter

by

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Abstract

The aim of this thesis was to explore associations between severity of parental depression and anxiety symptoms, and offspring brain structure. Additionally, to see whether certain brain regions in offspring were uniquely associated to parental depression versus anxiety. One hundred and twenty-four adolescents aged 11-18 years (*M= 13.64, SD= 1.51*) were included in the final analysis. Each adolescent had to have at least one parent with a diagnosed mood disorder as per the Mini International Neuropsychiatric Interview (MINI). Adolescents themselves were to be free of any psychopathology at baseline as per the MINI-Kid. Parents filled out the Beck Depression Inventory (BDI-II) and the Generalized Anxiety Disorder Assessment (GAD-7) to assess current symptom severity and youths underwent magnetic resonance imaging on a 3 Tesla magnet to obtain brain structure data. Bivariate correlations revealed that higher parental depression scores were associated with greater cortical thickness in the left middle temporal gyrus, and that higher parental anxiety scores were associated with greater cortical thickness in the right middle temporal gyrus. After controlling for offspring age and intracranial volume (ICV), the left middle temporal gyrus remained significantly associated with parental depression and the right middle temporal gyrus was no longer significantly associated with parental anxiety. Higher parental anxiety scores were significantly associated with cortical thinning in the left inferior parietal region when controlling for offspring age and ICV. Greater cortical thickness in the left middle temporal gyrus was uniquely associated with higher parental depression scores, and reduced cortical thickness in the left inferior parietal region was uniquely associated with higher parental anxiety scores. These findings suggest that even within a group of high-risk adolescents, there may be elevated risk for altered grey matter volume and thickness depending on parent symptom severity.

Preface

This thesis is the independent work of the author J. V. A. Kemp. Portions of the introductory and discussion text are used with permission from Kemp et al (2022) of which I am the author. The experiments covered throughout were covered by the ethics certificate number REB17-2377, issued by the University of Calgary Conjoint Health Research Ethics Board (CHREB) for the study titled “Parenting brain and personality development and early adolescent risk for internalizing psychopathology” on March 21, 2018 – March 20, 2023.

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Dedication

I would like to dedicate this thesis to my Grandma. I started this degree because of a passion for mental health that she instilled into me. From engaging in spirited conversations about mental health and pharmacotherapy, to sharing with me her experiences as a psychiatric nurse in the ‘50s. Although I am finishing this degree without her here, I am so grateful to have had a cheerleader as big as her to get me started. Thank you for the unwavering love, support, and care packages it took to get me here. I aspire to be half the pioneering woman that you were in your day.

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Introduction

Background

Depressive and anxiety disorders are among the most common mental health disorders (Kessler et al., 2005; Liu et al., 2020), with both showing increases in incidence since the 1990s (James et al., 2018). Average age of onset for anxiety is 11 years, and before age 25 for depression (Kessler et al., 2005), but developing depression during adolescence is associated with a 30% increased risk for attempting suicide (Stringaris, 2017). Both disorders are associated with other health related problems such as suicidal ideation (Nguyen et al., 2013), insomnia (Johnson et al., 2006), and substance use (Mohamed et al., 2020). It is thus important to identify what renders individuals more vulnerable or resilient to depression and anxiety.

Extant research indicates differences in subcortical grey matter volume and cortical thickness between individuals with versus without depressive (Nielsen et al., 2020; Schmaal et al.,2016; Shad et al., 2012) and anxiety disorders (Milham et al., 2005; Mueller et al., 2013; Wang et al., 2018). However, it is unclear whether these structural differences are a pre-existing risk factor, or if they are an outcome or concomitant of the disorder (Shapero et al., 2019). One well-established factor that places individuals at risk for developing depression or anxiety is a family history of these disorders (Weissman et al., 2016). As such, researchers have examined brain structure in never clinically depressed or anxious offspring of parents with a history of depression or anxiety, compared to those without a parental history of these disorders. Having a parent with a history of internalizing (i.e., depressive or anxiety) disorders has been linked to altered grey matter volumes in regions involved in cognitive-affective processes broadly, and mood and anxiety disorders specifically (e.g., amygdala, hippocampus, basal ganglia, prefrontal

and temporoparietal regions), echoing similar findings of altered grey matter in people with versus without depression (e.g., Schmaal et al., 2016; Shad et al., 2012). While affective disorders tend to aggregate within families (Macoveanu et al., 2018; Nickson et al., 2016), many offspring of parents with depression or anxiety disorders do not develop the disorder themselves (Duffy et al., 2012; Hajek et al., 2013), therefore making it imperative to identify premorbid structural biomarkers of risk. Multiple studies have compared brain structure in adults and youth with versus without a parental history of depression (Foland-Ross et al., 2015; Gotlib et al., 2020; Pagliaccio et al., 2020; Peterson et al., 2009), however, no studies to our knowledge have examined whether the severity of parental depressive or anxiety psychopathology within youth with a family history of depression or anxiety is associated with alterations in adolescent brain structure. Understanding whether severity of parental psychopathology is associated with offspring brain structure may further our ability to identify those youth most at risk for depression and anxiety, even within groups of already high-risk adolescents.

Brain Structure Differences in Individuals with versus without Depression

Neuroimaging studies have noted structural differences in adults with versus without major depressive disorder, specifically cortical thinning in the orbitofrontal cortex (OFC) (Grieve et al., 2013; Nielsen et al., 2020; Zhao et al., 2017), the anterior cingulate cortex (ACC) and the posterior cingulate cortex (PCC) (Grieve et al., 2013; Schmaal et al., 2016). The ACC is implicated in goal-directed behaviour, emotional learning, and expressing internal states, and overactivity of this region can alter affective state and expression (Devinsky et al., 1995). The OFC is responsible for stimulus-reinforcement associations, and alterations to this region may impair an individual's ability to gauge when a behavioural response is no longer appropriate (Rolls, 2004). Other studies examining cortical regions in association with depression have

reported thicker grey matter in the fusiform gyrus (Zhao et al., 2017), the medial prefrontal cortex (mPFC) (Schmaal et al., 2017), and the insula (Opel et al., 2019). The fusiform region is implicated in processing of emotionally salient stimuli, specifically processing emotional faces of others (Wang et al., 2018). Alterations to this region may affect one's ability to process the emotions of others, which subsequently affects emotional regulation (Phan et al., 2002). The insula works in concert with the ACC to express internal emotional states (Gasquoine, 2014). The mPFC is responsible for regulating emotional states, and alterations to this region may reflect uncontrollable shifts in mood reflected in depression and anxiety (Waugh et al., 2014).

Studies examining subcortical differences between people with versus without depression have reported reduced grey matter volume in the putamen (Baumann et al., 1999), hippocampus (Bremner et al., 2000; Roddy et al., 2019; Sheline et al., 1999; Zhao et al., 2017) and the amygdala (Hastings et al., 2003; Sheline et al., 1998). The amygdala is a key component of the limbic system, and is responsible for the processing of salient stimuli, regardless of valence, but has been especially implicated in processing and responding to threatening stimuli (Phan et al., 2002). The hippocampus is highly implicated in stress regulation and emotional response, and is vulnerable to environmental stressors during development (Rao et al., 2010). Its key responsibilities in affective processing include processing and responding to positive stimuli, and encoding and retrieving emotional, autobiographical memories (Zhu et al., 2019). Alterations in the amygdala or hippocampus may therefore be linked to altered processing of emotionally salient stimuli in depression.

Adolescents with versus without depression similarly show changes in brain structure. These include reduced global surface area and reduced cortical thickness in the mOFC (Schmaal et al., 2017, Nielson et al., 2020), ACC, and insula (Schmaal et al., 2016), and lower grey matter

volume in the dorsal lateral prefrontal cortex (dlPFC), cerebellum (Shad et al., 2021), and hippocampus (Caetano et al., 2007).

Brain Structure Differences in Individuals with Versus without Anxiety

The literature also shows brain structure differences in individuals with versus without anxiety disorders. Some studies reported that adults with an anxiety disorder show greater grey matter in the dorsal medial prefrontal cortex (dmPFC), the dlPFC (Moon et al., 2014; Schienle et al., 2011), the amygdala (Machado-de-Sousa et al., 2014; Schienle et al., 2011), and the hippocampus (Machado-de-Sousa et al., 2014). The dlPFC is highly connected with the inferior frontal gyrus (iFG) as there exists a negative feedback mechanism between the two regions that regulates appraisals of the salience of emotional stimuli (Morawetz et al., 2016). The dlPFC also contributes to attention and executive functioning, which is often impaired in people with anxiety (Parnham & Buckingham, 2016). Compared to adolescents without generalized anxiety disorder (GAD), adolescents with GAD show greater grey matter in the vmPFC (Gold et al., 2017), superior temporal gyrus (De Bellis et al., 2002), insula (Mueller et al., 2013), and putamen (Liao et al., 2014). Furthermore, adolescents with anxiety disorders show reduced grey matter volume in the amygdala and hippocampus (Gold et al., 2017; Milham et al., 2005; Mueller et al., 2013).

Brain Structure Differences in Individuals with Versus Without a Family History of Depression or Anxiety

Various studies have examined depressive and anxiety symptoms dimensionally in association with the individual's brain structure (Auerbach et al., 2017; Grieve et al., 2013; Nielsen et al., 2020; Schienle et al., 2011). However, no studies, to our knowledge, have examined whether the severity of parental psychopathology within youth with a family history of depression or anxiety is associated with alterations in adolescent brain structure. That is, no

studies to our knowledge have assessed parental symptoms dimensionally, in association with offspring grey matter. It is well documented that anxiety and mood disorders tend to aggregate within families (Macoveanu et al., 2018; Nickson et al., 2016) and that individuals with a first degree relative, more specifically a parent or caregiver suffering from anxiety or depression, are several times more likely to develop an affective disorder themselves (Foland-Ross et al., 2016; Maciejewski et al., 2018; Weissman et al., 1987, 2016). For clarity, we refer to offspring of parents with depression or anxiety as "high-risk." For example, in their seminal work, Weissman et al., (1987) followed 182 offspring aged 6-23 years where at least one parent was depressed, or neither parent was depressed. They found that offspring of parents with depression showed significantly increased incidences of depression, phobias, social anxiety, and alcohol dependence over time. Similarly, Warner et al., (1999) used a multi-generational design to follow offspring of depressed parents until the offspring had their own children. They found that 49% of the third generation offspring who had both a parent and grandparent diagnosed with depression demonstrated elevated anxiety symptoms before pubertal onset (Warner et al., 1999). Additionally, having a parent or caregiver suffer from a mood disorder is associated with a decreased age of onset of affective disorders in offspring (Myrna et al., 1987; Weissman et al., 1997). These youth continued to be at elevated risk for depression up to 30 years later (Weissman et al., 2016).

We recently conducted a scoping review examining associations between parental mood and anxiety disorders and offspring brain structure and found a range of well-replicated structural brain differences in high-risk offspring compared to non-high-risk controls (Kemp et al., 2022). We included studies that used MRI to examine offspring brain structure in association with parental depression, anxiety, and bipolar disorder (BD), and searched for studies that

assessed parental symptoms dimensionally. Furthermore, we examined associations based on sample age ranges; children (age 2-12), adolescents (age 13-24 years), and adults (aged 25 and older).

We found 5 studies that examined the fusiform region in high-risk offspring, and majority of the studies showed that thinning of the fusiform was associated with parental depression (Foland-Ross et al., 2015, 2016; Ozalay et al., 2016; Papmeyer et al., 2015). The fusiform is implicated in perceiving emotional faces (Wang et al., 2018) and processing emotions in general (Zhang et al., 2012). Furthermore, alterations to the right fusiform have been associated with attention biases towards negative stimuli (Leung et al., 2009) and are implicated in the genetic risk for depression (Montag et al., 2009). As majority of the literature examining the fusiform in association with parental psychopathology has reported negative associations with parental psychopathology (Kemp et al., 2022), we therefore expect reduced fusiform thickness to be associated with higher parental depression scores in our sample of high-risk adolescents.

Our review also identified seven studies (Amico et al., 2011; Baaré et al., 2010; Chen et al., 2010; Durmusoglu et al., 2018; MacMaster et al., 2008; Mannie et al., 2014; Papmeyer et al., 2015) that examined the hippocampus in high-risk offspring, and the majority of those studies reported smaller hippocampal volume in association with parental depression. The hippocampus is highly implicated in emotional processing. In particular, the hippocampus is implicated in stress regulation and emotional response, and is vulnerable to environmental stressors during development (Rao et al., 2010). Its key responsibilities in affective processing include processing and responding to positive stimuli, and encoding and retrieving emotional, autobiographical memories (Zhu et al., 2019). As such, we expect to see a negative association between parental depressive and anxiety scores and offspring hippocampus volumes.

Similarly, we identified seven papers in our review that examined the amygdala in high-risk offspring, and majority reported smaller amygdala volumes in association with parental depression and anxiety (Chai et al., 2015; Lupien et al., 2011; Nickson et al., 2016; Saleh et al., 2012; Shapero et al., 2019). The amygdala is a key structure in the processing of emotional stimuli, specifically in evaluating the salience of emotional stimuli and determining whether a stimulus is threatening or not (Phan et al., 2002). As such, it is long known that alterations to the amygdala may lead to diminished emotional responses and behaviours (Bagshaw et al., 1965), which is supported by human and animal studies where parts of the amygdala are damaged or lesioned (Andrewes et al., 2019). We chose the amygdala as one of our regions of interest because its structural associations with depression and anxiety (Hastings et al., 2004), as well as parental depression (Boccardi et al., 2010; Chai et al., 2015; Nickson et al., 2016; Saleh et al., 2012) and anxiety (Donnici et al., 2021; Wen et al., 2017) are well replicated. We expect to see lesser amygdala grey matter volume in association with increased parental depression and anxiety in our sample of high-risk offspring.

Finally, we also identified five studies that examined temporo-parietal regions in high-risk offspring (Foland-Ross et al., 2015, 2016; Hao et al., 2017; Ozalay et al., 2016; Papmeyer et al., 2015; Talati et al., 2013); three of them reported thinning of the inferior parietal region in association with parental depression (Hao et al., 2017; Ozalay et al., 2016; Peterson et al., 2009). The inferior parietal region is a complex region that plays a part in the default mode network and in audiovisual integrational processing of emotions (Müller et al., 2013). Prior studies have suggested that people with depression fail to de-activate the inferior parietal region when processing audiovisual information, which leads to continued inhibition when trying to process positive audiovisual stimuli (Müller et al., 2014). As such, alterations to this region may impair

one's ability to perceive rewarding audiovisual stimuli. Various studies identified in our review also examined the temporal cortex in high-risk offspring (Foland-Ross et al., 2015, 2016; Hao et al., 2017; Ozalay et al., 2016; Papmeyer et al., 2015; Talati et al., 2013). Two studies reported significant associations between parental depression and offspring's middle temporal gyrus (Lebel et al., 2016; Ozalay et al., 2016), however the direction of effect was different in each study. Moreover, a recent study revealed positive associations between the middle temporal gyrus and adolescent anxiety (Wang et al., 2021), warranting examination of this region in association with parental depression and anxiety severity. The middle temporal gyrus is part of the default mode network as well, and connects with the iFG and prefrontal regions in order to aid semantic information retrieval and comprehension of events, relationships, and actions (Davey et al., 2016). As such, we expect to see positive associations between parental depression and anxiety scores and offspring's middle temporal gyrus thickness.

For illustrative purposes, we discuss some key studies examining associations between parental depression and offspring brain structure. Peterson et al. (2009) compared 54 adults and 12 children aged 6-54 with a family history of depression to 34 adults and 31 children with no such family history; the group with family history showed cortical thinning of the inferior and middle frontal gyri, the posterior temporal cortex, and the superior frontal gyrus. Their results were similar for both the children and adults. Baaré et al. (2010) compared 59 sets of twins in their mid 30s to late 40s with a family history of depression to 53 sets of age matched twins without any first degree relatives having history of any clinically significant psychopathology and compared their grey matter volume. Baaré et al. (2010) reported lesser hippocampal grey matter volume in the adults at high familial risk for depression compared to the low-risk group. Similarly, Amico et al. (2011) reported lesser right hippocampal and dlPFC grey matter when

comparing 30 high risk adults (30-32 years) to 64 adults without a family history of depression. Recently, Burhanoglu et al. (2021) compared a group of high-risk, never-depressed 22 year old's to an age matched, high-risk group with depression. The never-depressed high-risk group had significantly larger left amygdala volumes than the high-risk group with depression; the authors suggested that greater amygdala volume may serve as a resilience factor against depression in high-risk youth. Most of these studies recruited both high and low risk youth, but in some studies, a number of the adolescent participants had already experienced clinically significant symptoms of depression or anxiety (Chai et al., 2015; Pagliaccio et al., 2020). To our knowledge, Foland-Ross et al., (2015, 2016) and Burhanoglu et al. (2021) are the only studies to date whose high-risk adolescent sample had no history of clinically significant psychopathology, which points to a gap in the literature in establishing premorbid markers of risk for depression and anxiety. Our scoping review identified no studies that examined adult or adolescent offspring of parents with versus without only an anxiety disorder (Kemp et al., 2022), possibly due to the high comorbidity of anxiety and depressive symptoms (Aina & Susman, 2006).

Seven perinatal studies in parents with non-clinical levels of depressive and anxiety symptoms suggest links between severity of maternal depressive or anxiety symptoms assessed dimensionally and offspring brain structure. All seven of the studies used longitudinal designs, measuring maternal anxiety or depressive symptoms in the second or third trimester or the postnatal period. Of the four studies that examined the amygdala, two found that higher prenatal depressive symptoms (Wen et al., 2017) and postnatal anxiety symptoms (Donnici et al., 2021) were associated with larger amygdala volumes in offspring, whereas one study found no association between maternal depressive symptoms and offspring (age 10 years) amygdala volume (Zou et al., 2019). Another study found that higher prenatal depressive scores were

associated with smaller amygdala volumes in offspring (age 4 years) (Acosta et al., 2020). Three other studies examined associations between perinatal maternal depressive symptoms and offspring cortical thickness; two reported that higher depressive scores across various perinatal time points were associated with cortical thinning in the frontal and temporal lobe (Zou et al., 2019), as well as the right iFG (pars triangularis, pars opercularis, precentral and rostral middle frontal regions) and the middle and superior temporal region (inferior temporal and supramarginal regions) (Lebel et al., 2016). The third study reported that second trimester anxiety scores were significantly associated with reduced grey matter in the anterior, dorsolateral, ventrolateral and orbitofrontal prefrontal cortex, medial and lateral temporal lobe, post central gyrus, and middle occipital and fusiform gyri (Buss et al., 2010).

For the present study, we used an ROI-based approach rather than a whole brain analysis. Our recent review (Kemp et al., 2022) included 39 neuroimaging studies exploring associations between parental psychopathology and offspring brain structure, 30 of which were ROI-based. As such, Kemp et al. (2022) revealed that most studies report significant negative associations between parental psychopathology and offspring amygdala, hippocampus, fusiform, and inferior parietal region grey matter; and two studies found alterations in the middle temporal gyrus were associated with parental psychopathology, though the direction of effect differed. Additionally, whole brain analyses may have an increased likelihood of type I errors, and smaller sample sizes may be underpowered to correct for multiple comparisons.

Developmental Trajectories

It is important to consider the typical developmental trajectory of brain structure when examining its associations with parental mental health. Cortical thinning begins in early or mid-childhood and continues steadily through adulthood (Walhovd et al., 2017;Mills et al.,

2016), with a slight acceleration during adolescence (Tamnes et al., 2017). Peak grey matter density occurs first in the primary sensorimotor cortex and later in higher order areas (dlPFC, inferior parietal and superior temporal gyrus) (Giedd et al., 2010). Additionally, subcortical structures such as the caudate follow a similar trajectory as frontal lobes and reach peak grey matter density later on in adolescence (Giedd et al., 2010). Higher order regions mature temporally after the lower-order sensori-motor regions because the high order regions functionally integrate the lower order regions (Gogtay et al., 2004). Typically, thinning of grey matter begins in the dorsal parietal cortex, spreads rostrally over the frontal cortex and caudally and laterally over the parietal and occipital cortex, ending with the temporal cortex (Gogtay et al., 2004).

Prefrontal and parietal regions reach peak grey matter density much later compared to regions in the primary sensorimotor cortex, with typical peaks occuring around 10-11 years of age (Giedd et al., 2010) and they do not reach full maturity until the early to mid twenties (Geidd, 2004). This is beacause these regions follow cubic trajectories in which they initially increase in grey matter during childhood, followed by decreases in adolescence and then stabilization during adulthood (Shaw et al., 2008). As such, the cubic development of these cortical regions (Shaw et al., 2008) indicate that higher cortical grey matter denisty during childhood, lower cortical grey matter density during adolescence, and higher cortical grey matter density during adulthood in these regions may reflect risk for psychiatric disorders. Conversely, larger subcortical structures (amygdala and hippocampus) during the adolescent developmental window may represent abberant development (Lupien et al., 2011; Pechtel et al., 2014), whereas smaller subcortical structures earlier on in childhood may represent abberant development (Acosta et al., 2020). Both the amygdala and hippocampus are rich in glucocorticoid receptors,

rendering them vulnerable to the effects of stress during critical developmental periods (Dahmen et al., 2018). Stress may be most damaging to subcortical regions first between ages 3-5, then again around age 11-13, and to cortical regions around age 14-16 (Andersen et al., 2008a; Hanson et al., 2015). As such, the effects of stress exposure on brain maturation at during specific developmental periods may increase susceptibility to developing psychopathology in adolescence (Andersen et al., 2008b).

Cortical expansion occurs via neurogenesis and cortical column generation during the perinatal developmental period (Bhardwaj et al., 2006; Borrell et al., 2019), though less is known about these changes that occur throughout the lifespan. The brain remains plastic throughout the lifespan, and studies suggest that adult neurogenesis can take place in the hippocampus (Kempermann et al., 2018). Given that brain regions develop at different rates and have potentially different sensitive windows, parental psychopathology may have varying effects throughout childhood, adolescence, and early adulthood, and may have effects in opposite directions. As such, we controlled for offspring age and sex when examining associations between parental psychopathology and offspring brain structure.

Aims and Hypotheses

While there are well-established brain structure differences in offspring with versus without a parental history of depression, and associations of parental perinatal anxiety and depressive symptoms with offspring brain structure (Kemp et al., 2022), it remains unclear whether adolescent offspring cortical thickness and subcortical volume is associated with severity of parental psychopathology within a sample of youth whose parents have a history of depressive or anxiety disorders. The current study examined brain regions whose volume or thickness differentiate those with versus without depression or anxiety and that differentiate

individuals with versus without a family history of these disorders. As such, the current study examined the inferior parietal region, the middle temporal gyrus, the fusiform, hippocampus, and amygdala. We hypothesize that higher parental depression and anxiety symptoms will be associated with smaller subcortical volumes and reduced grey matter in the inferior parietal region and greater grey matter in the middle temporal gyrus. Furthermore, we hypothesize that depressive and anxiety symptom scores will show unique associations with offspring brain structure.

Methods

Participants and procedure

Participants were recruited from the general population through online and paper advertisements posted around the community that targeted parents with a current or lifetime history of depression or anxiety. The final analyses contained 124 parent/child dyad participants. Youth were 11-18 years of age (*M= 13.64, SD= 1.51*) and 62% female, (*n = 84*) (Table 1.). Parents were 92% female (*n=124*) and 76% of the sample were of Caucasian decent (*n=103*)(Table 1.). The median household income was $75,000-$100,000 and 68% of parents in the study had completed some university or college training (Table 1). Youth had no history of clinically significant mood or anxiety disorders at baseline, and the parent met diagnostic criteria for either current or lifetime history of a mood or anxiety disorder (Table 2). Parental depression severity ranged from minimal (48%) and mild (25.2%), to moderate (14%) and severe (12.8%), as per the cut-off scores outlined in the Beck Depression Inventory-II Manual (Beck et al., 1996). Power analysis with an alpha of .05 indicated that a study sample size of 124 had 80% power to detect medium effect size in correlations (*r= 0.24*) between parent depression and anxiety symptoms and offspring brain structure.

Table 1.

Participant Demographic Information

Sex	Parents (%)	Youths (%)
Male	8.1	38
Female	91.9	62
Ethnicity	Parents (%)	Youths (%)
Aboriginal/Metis	3.7	3.0
Arabic	2.2	2.2
Asian	3.7	5.2
East Indian	0.7	n/a
Filipino	1.5	0.7
Hispanic	5.2	2.2
Indian	0.7	n/a
Melado	0.7	n/a
Mixed Heritage	1.4	17.8
Nepali	.7	n/a
Sikh	.7	n/a
South Asian	.7	n/a
White/Caucasian	76.3	66.7
Household Income	%	
Under $25,000	4.4	
$25,000-$49,000	17.0	
$50,000-$74,999	10.4	
$75,000-$99,000	18.5	
$100,000-$124,999	15.6	
$125,000-$149,999	8.1	
$150,000-$174,999	7.4	
Over $175,000	14.8	
Not disclosed	3.7	
Parent Education Level	%	
Some High School	4.5	
High School Diploma	4.4	
Trades	17.0	
College/University	54.9	
Postgraduate	18.6	
Other	0.7	

Table 2.

Parental Depressive Diagnostic Status

Parent Diagnostic Status		
	Current (%)	Past (%)
Major Depressive Disorder	26.7	73.3
Generalized Anxiety Disorder	17.0	11.9

*Parental anxiety diagnostic status does not add up to 100 because not every parent met diagnostic criteria for anxiety

Participants from this study were a part of a broader study to assess adolescent premorbid risk and resiliency factors for the development of clinical depressive and anxiety episodes. A parental history of major depression, persistent depressive disorder, bipolar disorder, or generalized or social anxiety disorder was assessed via the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), and the absence of a history of these disorders in youth was confirmed via the MINI-KID (Sheehan et al., 2010). The breakdown of parent mental disorders was 76% major depressive disorder (n= 103), 20% PDD (n=27), 15.5% bipolar disorder (n=21), 27.4% social anxiety (n=37), and 26.6% generalized anxiety disorder (GAD) (n=36) (Percentages do not add to 100 given many parents had multiple diagnoses). Inclusion criteria required that the child did not have braces or other contradictions to MRI scans.

Youth completed MRI scans and parents completed the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996) and the Generalized Anxiety Disorder-7 (Spitzer et al., 2006) as respective measures of depressive and anxiety symptom severity only, not diagnostic status. The MINI alone, was used to assess both parent and youth diagnostic status.

Measures

Psychopathology

Parent diagnostic status, not severity, for current and lifetime history of psychopathology was assessed using the MINI. The MINI is a short, semi-structured interview that was designed for clinical trials and epidemiology studies to facilitate accurate data collection (Sheehan et al., 1998). The MINI consists of 17 modules in which different disorders are assessed, and answers from each module are coded on a dichotomous scale by the interviewer. The MINI is a well-validated and widely-used diagnostic measure for DSM-V illnesses and converges well with the Structural Clinical Interview for the DSM (SCID) (Sheehan et al., 1998). Adolescents' current and lifetime history of diagnostic status was assessed via the MINI-Kid. The MINI-Kid follows the same format as the MINI, but with 24 modules rather than 17. Diagnoses on the MINI-Kid converge with the well-validated Kiddie Schedule for Affective Disorders (KSADS) (Sheehan et al., 2010).

Depression Severity

Parents completed the BDI-II to assess current depressive symptom severity rather than diagnostic status. The BDI-II is a 21 item self-report measure used to assess depression symptom severity (A.T. Beck et al., 1996) and each item is rated by the participant on a scale of 0-3. The BDI-II is a well validated measure (Richter et al., 1998) and showed high internal consistency in the current sample (alpha = .90).

Anxiety Severity

Parents completed the GAD-7 to assess current anxiety symptom severity rather than diagnostic status. The GAD is a 7-item self-report measure used to assess anxiety symptom severity and each item is scored by the participant on a scale of 0-3. The GAD is well validated

and converges well with clinician ratings (Spitzer et al., 2006). In the current study, internal consistency was excellent (alpha = .91).

MRI Acquisition

Structural neuroimaging data were acquired in the sagittal plane on a GE 3T 750 Siemens scanner with a T1 weighted BRAVO pulse sequence and a 12-channel radiofrequency coil (flip angle of 15^{o}, slice thickness was 1.0mm, 180 sagittal slices, no overlap, FOV 24.0 mm, TE of 3.06ms and TR of 7.90ms).

Brain Structure Data Analysis

Images were extracted and analyzed using FreeSurfer version 6.0 (Fischl, 2012). The FreeSurfer hippocampal module uses a probabilistic atlas to produce automated segmentation of the hippocampal substructures and amygdala nuclei that reduces risk of overlap or gaps between the structures. Processing of the images included the following: removal of non-brain tissue and the skull (Fischl et al., 2002; F. Ségonne et al., 2004), segmentation of white and deep grey matter structures (Fischl et al., 2004), intensity normalization (Sled et al., 1998), tessellation of grey and white matter boundaries (Fischl et al., 2001; Florent Ségonne et al., 2007), surface deformation and tissue calcification (Dale et al., 1999), surface inflation and registration to spherical atlas (Dale et al., 1999; Fischl et al., 1999) and cortex parcellation (Fischl et al., 2004). Subcortical volumes and cortical thickness for parcellated regions were extracted using ENIGMA (ENIGMA, 2021), and ENIGMA scripts were used to check for outliers using R-package.

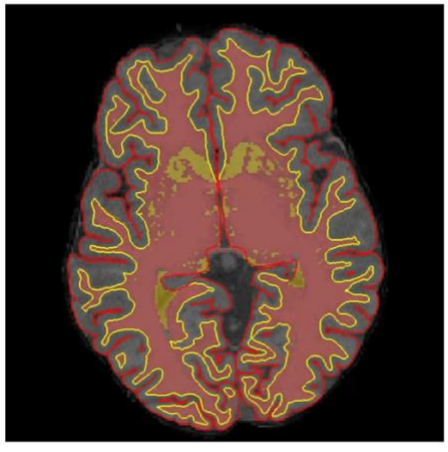
Each scan went through a manual visual quality check to ensure proper segmentation and parcellations were performed. Each scan was assigned a value from 0-2 (0= fail, 1=moderate, 2=pass) and notes were made about regions that looked incorrect (i.e., did not correspond to the ENIGMA protocol with examples of typical segmentation and parcellation). Because we used the

Freesurfer hippocampal module which ensures quality parcellation and segmentation of the hippocampal subfields and amygdala nuclei (Iglesias et al., 2015), we only made manual edits to cortical regions. This process was completed by two independent raters with 98% agreement. In the case of discrepancy, raters re-rated the scans together. If scans were rated as moderate, the same independent raters conducted manual edits to the pial surface and the border between grey and white matter using the Freeview function within FreeSurfer (See Figure 1). There were initially 139 scans; after image processing and analysis of outliers, 135 participants' scans remained in the effective sample.

Additionally, while a history of depressive disorders as well as GAD and social anxiety disorder in youth was an exclusionary criterion, 11 youth participants met criteria for these disorders. This may have been because initial screening calls took place over the phone, where the child may have been within ear shot of a parent, and perhaps did not feel comfortable disclosing symptoms of depression or anxiety in front of their parent, although we cannot be certain. As such, analyses excluded those 11 youth, resulting in an effective sample of 124

Figure 1

Freeview Segmentation Indicating the Border Between Grey and White Matter



Statistical Analysis

Analyses were done in SPSS version 25 (Bolin, 2014). Bivariate correlations examined associations of parental depressive and anxiety severity with youth grey matter thickness and volume in our a priori regions of interest (ROIs). We also examined associations of adolescent age and sex with brain structure. If associations between brain structure and offspring sex or age were significant, they were controlled for in subsequent analyses. Additionally, we controlled for intracranial volume (ICV) because it was significantly associated with parental anxiety symptoms as well as subcortical regions and the fusiform. As such, controlling for ICV will allow us to ensure that effects are not due to larger or smaller total brain volume. We also examined whether parental anxiety versus depression was uniquely associated with brain regions via partial correlation analyses. The 11 youth with baseline depressive or anxiety disorders, were excluded from analyses (i.e., youth with anxiety disorders at baseline were excluded from anxiety analyses and youth with depressive disorders at baseline were excluded from depression analyses). We used the Benjamini-Hochberg method of false discovery rate (FDR) adjustment to correct for type 1 error. FDR correction was applied to each subset of analyses (i.e., Parental depression and subcortical regions controlling for sex, GAD, and ICV; parental depression and cortical regions controlling for age, GAD and ICV; parental anxiety and subcortical regions controlling for BDI, sex, and ICV; parental anxiety and cortical regions, controlling for BDI, age, and ICV). Given that we expected a specific direction of effects a priori for our ROIs, we examined one-tailed p-values in our correlations.

Results

Demographic Variables and associations of adolescent brain structure with age and sex.

Bivariate correlations (Table 3 and 4) indicated that grey matter volume in subcortical brain regions (i.e., amygdala, hippocampus) was significantly associated with adolescent sex, such that males showed larger brain volumes in subcortical regions. Thickness in cortical regions (i.e., middle temporal gyrus, inferior parietal region, fusiform) was negatively associated with adolescent age (Table 3 and 4), suggesting that as age increases, grey matter in these regions decreases. Intracranial volume (ICV) was also significantly associated with parental anxiety (Table 4) and child age (Table 3 and 4), such that higher parental anxiety was associated with lesser total brain volume and older age in offspring was associated with greater total brain volume. As such, when examining associations between parental psychopathology and offspring cortical regions, we controlled for offspring age, and when examining associations between parental psychopathology and offspring subcortical regions, we controlled for offspring sex.

Table 3

Zero Order Correlations for Parental Depression and Offspring Brain Structure

	1	2	3
1. BDI Scores	1		
2. Child Sex	-.034	1	
3. Child Age	-.006	.170*	1
4. Left Amygdala	.13	.508**	.063
5. Right Amygdala	-.072	.422**	.139
6. Left Hippocampus	-.095	.436**	.080
7. Right Hippocampus	-.089	.545**	.100
8. Left Middle Temporal Gyrus	.162*	.112	-.210*
9. Right Middle Temporal Gyrus	.105	.005	-.162*
10. Left Inferior Parietal Region	.056	.080	-.316**

11. Right Inferior Parietal Region	.075	-.001	-.241**
12. Left Fusiform	.138	.095	-.208**
13. Right Fusiform	.127	.052	-.153*
14. ICV	-.031	.557**	.095
Mean	15.29	1.38	13.59
SD	10.7	.487	1.5

** p < .01

* p< .05

Table 4

Zero Order Correlations for Parental Anxiety and Offspring Brain Structure

	1	2	3
1. GAD Scores	1		
2. Child Sex	-.178*	1	
3. Child Age	-.086	.175*	1
4. Left Amygdala	-.010	.529**	.075
5. Right Amygdala	-.077	.434**	.138
6. Left Hippocampus	-.121	.425**	.112
7. Right Hippocampus	-.117	.449**	.119
8. Left Middle Temporal Gyrus	-.019	.126	-.232**
9. Right Middle Temporal Gyrus	.170*	.007	-.178*
10. Left Inferior Parietal Region	-.115	.081	-.342**
11. Right Inferior Parietal Region	.048	-.001	-.242**
12. Left Fusiform	.099	.089	-.197**
13. Right Fusiform	.136	.059	-.158*
14. ICV	-.193*	.567**	.118
Mean	6.23	1.38	13.59
SD	5.46	.487	1.5

** p < .01

* p< .05

Parental Depressive Symptoms and Offspring Brain Structure

In our zero order correlations, higher parental depression scores were significantly associated with higher levels of grey matter in offspring's left middle temporal gyrus (*r =.162, p=.034*) (Table 2). There were no significant associations between any subcortical regions and parental depressive severity (Table 5). Controlling for sex and offspring ICV, the left middle temporal gyrus (*r=.149, p=.049*) (Figure 2A) remained significantly associated with parental depressive severity (Table 6). This effect, however, did not survive FDR correction (*FDRp =.294)*.

Table 5

Associations Between Parental Depressive Severity and Offspring Subcortical Regions Controlling for ICV and Sex

	Pearson's R	FDR Corrected p-values
1. BDI Scores	1	
2. Left Amygdala	.009	0.459
3. Right Amygdala	-.117	0.194
4. Left Hippocampus	-.095	0.194
5. Right Hippocampus	-.119	0.38

** p < .01

* p < .05

Table 6

Associations Between Parental Depressive Severity and Offspring Cortical Regions Controlling for ICV and Age

	Pearson's R	FDR Corrected p-values
1. BDI Scores	1	

2. Left Middle Temporal	.149*	0.294
3. Right Middle Temporal	.085	0.262
4. Left Inferior Parietal	.033	0.358
5. Right Inferior Parietal	.049	0.351
6. Left Fusiform	.134	0.204
7. Right Fusiform	.112	0.214

** p < .01

* p < .05

Parental Anxiety Symptoms and Offspring Brain Structure

In our zero order correlations, higher parental anxiety scores were significantly associated with greater grey matter in the right middle temporal gyrus *(r=.170, p=.027)* and decreased ICV (*r=-.193, p=015*). (Table 4). There were no significant associations between parental anxiety and offspring subcortical structures (Table 7). When controlling for offspring age and ICV, higher parental anxiety scores were associated with reduced grey matter in the left inferior parietal region *(r=-.175, p=.026)* (Table 8). Neither of these findings survived FDR correction.

Table 7

Associations Between Parental Anxiety Severity and Offspring Subcortical Regions Controlling for ICV and Sex

	Pearson's R	FDR Corrected p-values
1. GAD Scores	1	
3. Left Amygdala	.077	0.394
4. Right Amygdala	-.061	0.332
5. Left Hippocampus	-.048	0.3
6. Right Hippocampus	-.095	0.584

** p < .01

* p < .05

Table 8

Associations Between Parental Anxiety Severity and Offspring Cortical Regions Controlling for ICV and Age

	Pearson's R	FDR Corrected p-values
1. GAD Scores	1	
2.. Left Middle Temporal	-.046	0.368
3. Right Middle Temporal	.128	0.234
4. Left Inferior Parietal	-.175*	0.156
5. Right Inferior Parietal	.005	0.477
6. Left Fusiform	.105	0.183
7. Right Fusiform	.117	0.194

** p < .01

* p < .05

Brain Regions Uniquely Associated with Parental Depressive versus Anxiety Severity

Controlling for offspring age, and parental symptoms of anxiety, cortical thickness in the left middle temporal gyrus (*r=.170, p=.030)* was uniquely associated with parental depressive severity (Table 10) (Figure 2A). However, this did not remain significantly associated with depression after FDR correction.

Figure 2

Significant Associations Between Increased Parental Depressive (A) and Anxiety (B) Scores and Offspring Brain Structure

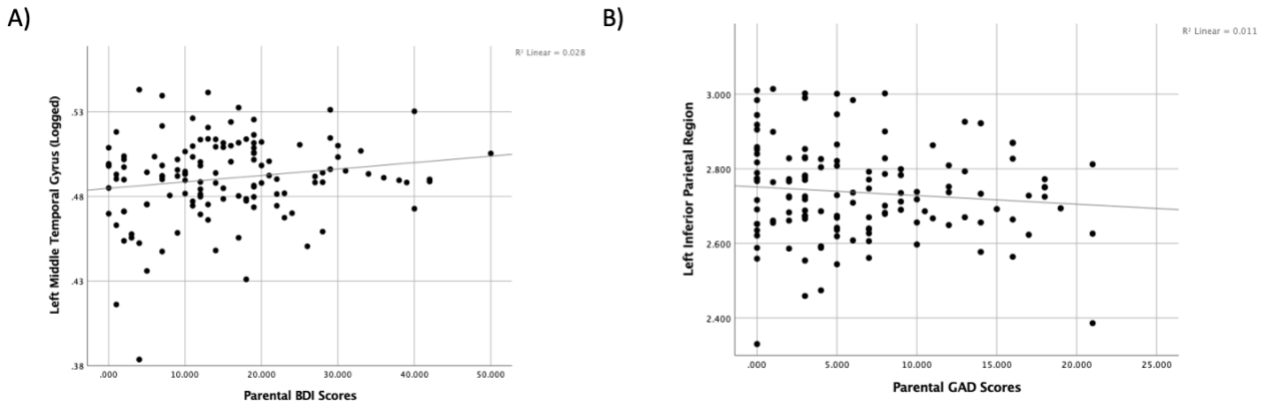


Table 9

Associations Between Parental Depressive Severity and Offspring Subcortical Regions Controlling for Sex, ICV, and Parental Anxiety Symptoms

	Pearson's R	FDR Corrected p-values
1. BDI Scores	1	
3. Left Amygdala	-.004	0.484
4. Right Amygdala	-.086	0.516
5. Left Hippocampus	-.062	0.442
6. Right Hippocampus	-.072	0.49

** p < .01

* p < .05

Table 10

Associations Between Parental Depressive Severity and Offspring Cortical Regions Controlling for Sex, ICV, and Parental Anxiety Symptoms

	Pearson's R	FDR Corrected p-values
1. BDI Scores	1	
2.. Left Middle Temporal	.170*	0.18
3. Right Middle Temporal	.046	0.306
4. Left Inferior Parietal	.116	0.3
5. Right Inferior Parietal	.067	0.277
6. Left Fusiform	.116	0.2
7. Right Fusiform	.073	0.316
** p < .01		
* p < .05		

Conversely, examining associations between parental anxiety severity and offspring brain structure, and controlling for offspring sex, age, and parental symptoms of depression, revealed that cortical thickness in the left inferior parietal region (*r=-.214, p=.009) (*Figure 2B) was uniquely associated with parental anxiety severity (Table 12). However, after FDR correction, this finding remained significant only at the trend level (*FDRp= .054)*.

Table 11

Associations Between Parental Anxiety Severity and Offspring Subcortical Regions Controlling for Sex, ICV, and Parental Depressive Symptoms

	Pearson's R	FDR Corrected p-values
1. GAD Scores	1	
3. Left Amygdala	.067	0.92
4. Right Amygdala	-.026	0.516
5. Left Hippocampus	-.013	0.442
6. Right Hippocampus	-.063	0.49
** p < .01		
* p < .05		

Table 12

Associations Between Parental Anxiety and Offspring Cortical Regions Controlling for Age, ICV, and Parental Depressive Symptoms

	Pearson's R	FDR Corrected p-values
1. GAD Scores	1	
2.. Left Middle Temporal	-.120	0.276
3. Right Middle Temporal	.099	0.274
4. Left Inferior Parietal	-.214**	0.054
5. Right Inferior Parietal	-.026	0.389
6. Left Fusiform	.057	0.316
7. Right Fusiform	.075	0.304

** $p < .01$

* $p < .05$

Discussion

The aim of this study was to identify relationships between severity of parental depressive and anxiety disorders and their offspring's cortical and subcortical grey matter in a sample of adolescents whose parents have a history of mood and anxiety disorders. Furthermore, we examined whether differences in cortical and subcortical grey matter in offspring were unique to parental symptoms of depression versus anxiety. Consistent with hypotheses, our results indicated that higher parental depressive scores were associated with greater cortical thickness in offspring's left middle temporal gyrus, which remained significant when controlling for offspring age and ICV. Likewise, higher parental anxiety scores were associated with greater cortical thickness in the right middle temporal gyrus, although this finding was no longer significant when controlling for offspring age and ICV. However, lesser grey matter in the inferior parietal region became significantly associated with higher parental anxiety scores when controlling for offspring age and ICV. Higher parental anxiety was also associated with lower

total brain volume. Greater cortical thickness in the left middle temporal gyrus was uniquely associated with parental depression, and lesser cortical thickness in the left inferior parietal region was uniquely associated with parental anxiety. It should be noted, however, that after FDR correction for multiple comparisons, the left inferior parietal region remained significant only at the trend level, and the left middle temporal gyrus was no longer significant.

Parental mood and anxiety psychopathology and offspring brain structure.

Results were partially consistent with our hypotheses, which we based on the findings of the extant literature examining brain structure in high-risk offspring (Kemp et al., 2022). For example, Lebel et al (2016) reported cortical thinning in the middle temporal region associated with parental depression, but like Ozalay et al (2016), our results indicated cortical thickening of the middle temporal gyrus was associated with parental depression severity. The difference in direction of effects may be explained by the differing age groups, as Lebel (2016) examined children aged 2-5, whereas Ozalay (2016) examined young adults aged 18-26, and we examined adolescents aged 11-18. Peak grey matter density occurs first in sensorimotor regions such as various temporal gyri (Giedd & Rapoport, 2010), so reduced cortical thickness of the middle temporal gyrus may represent aberrant development during childhood, whereas greater cortical thickness in the same region during adolescence and adulthood may represent aberrant development due to delayed cortical thinning which usually takes place during adolescence (Giedd & Rapoport, 2010). Results also revealed associations between elevated levels of parental anxiety and cortical thinning in the inferior parietal region. This corresponds with previous literature that identified significant negative associations between parental depression and offspring's inferior parietal region (Hao et al., 2017; Ozalay et al., 2016; Peterson et al., 2009).

The extant literature has reported associations between amygdala volumes and parental depression and anxiety, but results are not always consistent; some report larger amygdala volumes (Nickson et al., 2016) in association with parental depression, some report smaller (Chai et al., 2015), and some studies found no significant differences (Shapero et al., 2019). However, Nickson et al (2016) reported that high-risk offspring who developed depression showed smaller amygdalae at baseline and at follow-up, whereas high-risk offspring who did not develop depression showed larger amygdala volume at follow-up. This indicates that larger amygdala size may be protective against depression. Nonetheless, our results did not detect any associations between the amygdala and parental depression or anxiety severity. We may have been underpowered to detect small effect sizes in this region; we also did not employ manual quality control methods for correcting subcortical segmentation and parcellation errors, so it is possible that there was increased variance in this region that was not accounted for.

Based on previous studies, we expected to see increased parental psychopathology associated with thinning of the fusiform region, as the majority of studies to date have found this pattern of effect (Foland-Ross et al., 2015, 2016; Ozalay et al., 2016; Papmeyer et al., 2015). However, we did not find any significant associations between parental depression or anxiety severity and offspring fusiform thickness. The fusiform borders the temporal pole and upon review of our manual quality control procedures, it appears that the temporal pole was the region most affected by MRI artifacts. Because we chose not to examine the temporal pole as one of our ROIs, we did not edit this region. Therefore, due to the proximity between the temporal pole and fusiform, fusiform parcellation and segmentation may not have been reliable, which produced results contrary to previous literature.

Mechanisms Linking Parental Mental Health and Offspring Brain Structure

One potential mechanism linking parental mental health and offspring brain structure is alterations in parenting behaviours. Parental psychopathology is significantly associated with suboptimal parenting behaviour including a lack of parental energy, irritability (Errázuriz Arellano et al., 2012; Leinonen et al., 2003), negative attitudes, and flat affect (Dix & Meunier, 2009; Leinonen et al., 2003; Smith, 2004), or indirectly via marital problems (Leinonen et al., 2003; Smith, 2004), lower socioeconomic status (Smith, 2004; Waylen & Stewart-Brown, 2010), or having the child be exposed to stressful events associated with parental symptom severity such as marital disharmony, domestic violence, separation or divorce, and poverty (Smith, 2004).

Numerous studies have similarly confirmed associations between parental mental health and increased maladaptive broad parenting styles (see Lovejoy et al., 2000a for a review). For example, Leinonen et al. (2003) collected information about both parent and child mental health, quality of parenting, quality of marital interactions, and children's peer relationships and academic performance, and found that parental mental health symptom severity was associated with child outcomes via their parenting style. Fathers' depressive symptoms were associated with daughters' internalizing behaviour via punitive parenting, and mother's social dysfunction symptoms were associated with daughters externalizing symptoms via less authoritative parenting. Furthermore, Dix & Meunier (2009) discuss how various types and levels of severity of depression symptoms predict parenting styles including withdrawal of interest in the child, low responsiveness and involvement, maternal intrusiveness, and flat and negative affect towards self and child. Indeed, Kopala-Sibley et al. (2017) found that parents with a history of depression showed increased permissiveness, a maladaptive parenting style characterized by providing few guidelines or rules to the child, which was in turn associated with children's externalizing

behaviours later in childhood. There is substantial evidence that parenting in turn influences offspring structural brain development (for reviews see Bhanot et al., 2021; Belsky & De Haan, 2011; Whittle et al., 2014). For example, children who are maltreated have smaller intercranial and cerebral volumes compared to controls (Belsky & De Haan, 2011). Conversely, Whittle et al (2014) showed that positive maternal interactions predicted amygdala growth in school-aged children. Another study indicated that alterations in male hippocampus volumes are predicted by neglect, whereas female hippocampus volumes are predicted by abuse (Teicher et al., 2016).

While there are likely numerous mechanisms through which parental psychopathology may influence offspring brain structure via altered parenting, the influence of stress on brain development is likely an important consideration given that adverse parenting is likely a substantial source of stress for children and adolescents. Indeed, brain structures associated with emotion regulation such as the amygdala, hippocampus (Phillips et al., 2003; Rao et al., 2010), prefrontal and parietal regions (Parnham et al., 2016) are highly plastic and vulnerable to volumetric changes during critical development periods (Dahmen et al., 2018; Lupien et al., 2011). Stress during development can cause upregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which results in sustained increases of circulating glucocorticoids. Sustained elevation of glucocorticoids such as the stress hormone, cortisol, can disrupt hippocampal cell functioning which disrupts the negative feedback mechanism responsible for shutting down the HPA axis (Carpenter et al., 2010; Tyrka et al., 2012). Both the amygdala and hippocampus are rich in glucocorticoid receptors (Dahmen et al., 2018; Pechtel et al., 2014), and elevated levels of glucocorticoids can prevent neuronal growth in the hippocampus (Tyrka et al., 2012). Furthermore, elevated glucocorticoids drive dendritic arborization in the amygdala (Hanson et al., 2015). Van Marle et al (2009) suggests that the amygdala is also thought to facilitate

enhanced sensory processing in other regions such as the fusiform. This occurs in the face of stress, when circulating catecholamines and glucocorticoids increase the cellular excitability in the amygdala, which then lowers the perceptual threshold of other sensory regions (ie. the fusiform), leading to enhanced vigilance and threat detection (van Marle et al., 2009). As a result, the impact of stress on these structures may result in semi-permanent upregulation and volumetric changes (Dahmen et al., 2018; Lupien et al., 2011; Pechtel et al., 2014; van Marle et al., 2009).

Genetics

While there is substantial evidence supporting environmental factors (e.g., parenting styles) as a link between parental psychopathology and offspring brain structure, genes also undoubtedly play a role. A recent review of the heritability of brain morphology suggests sizable estimates of heritability in cortical thickness, grey and white matter volume, and cortical surface area ranging from 60-80% (Jansen et al., 2015). Moreover, a study looking at heritability of brain structure in nine-year-old twins revealed that structures in the posterior fronto-occipital, corpus callosum, and superior longitudinal fascicles were up to 93% heritable, and structures in the amygdala and superior frontal and middle temporal cortices were up to 83% heritable (Peper et al., 2009). Knickmeyer et al., (2014) examined whether polymorphisms in psychiatric risk genes are associated with brain structure at birth. They found that grey matter in neonates was significantly associated with polymorphisms in various psychiatric risk genes (ie., DISC1 (rs821616), COMT, NRG1, APOE, ESR1 (rs9340799), and BDNF) (Knickmeyer et al., 2014), suggesting that genes associated with psychiatric illness may also influence grey matter.

A key consideration in interpreting evidence to date is that there are likely interactions between the environment provided by the parents and the genes they pass to their children (Jami

et al., 2021). Therefore, if a child shares a psychiatric risk allele with their parent, both the risk allele itself and the effects of mental health on parenting behavior (Lovejoy et al., 2000b) may interact to alter offspring brain structure. In a recent review, Jami et al. (2021) note that while genetically informed studies confirm the substantial role of genetics in offspring psychosocial outcomes, factors such as parental psychopathology and parenting also play an important role. With considerable evidence for both environmental factors (parenting) and genetic contributions (risk alleles and heritability), there is a significant gap in the literature exploring the relative contributions of genes versus parenting to offspring brain development. Moreover, there is no literature of which we are aware examining interactions between children's genes and the parenting they experience in predicting offspring brain structure.

Clinical Implications

The findings of the current study build on the growing body of literature identifying premorbid risk factors for depression and anxiety in high versus low-risk adolescents. Although previous studies have identified changes in brain structure that differentiate high risk versus low-risk adolescents, our results indicate that even within high-risk youth, increased severity of parental psychopathology is linked to alterations in brain structure, although results should be interpreted with caution, given they did not survive correction for multiple comparisons. To our knowledge, this is the first study to look at parental symptom severity's effect on adolescent offspring brain structure in a clinical sample. Results may elucidate alterations in brain structure that may confer premorbid risk for future depression or anxiety among youth already at high risk based on their family history. Extant literature on the pathophysiology of depression and anxiety points to various brain regions that are altered throughout the course of each disease (Baumann et al., 1999; Shad et al., 2012), with the caveat being that most of these studies examine patients

after the onset of psychopathology. As such, identifying whether these same brain regions are altered in people at high risk for affective disorders may inform early interventions and may improve the prognosis of disease course, as early treatment may alter development in these specific brain regions. Such associations may have implications for our understanding of which youth, among youth at risk based on their family history, are at particularly high risk for affective disorders.

Strengths and Limitations

To date, few studies have examined whether severity of parental psychopathology, as opposed to the presence or absence of a disorder, is linked to offspring brain structure. The only such studies examined maternal peri- or post-natal mental health, assessed dimensionally, and early childhood brain structure. Further, these studies were conducted in a non-clinical sample of parents (Buss et al., 2010; Qiu et al., 2013). Related to this, it is unclear if links between parental anxiety and depression during or post-pregnancy and children's brain structure persist into adolescence or adulthood. That is, it is possible that links between adult or adolescent brain structure and parental mental health are a continuation of effects that began prenatally or in early childhood. As such, a key strength of the current study was having parents with confirmed clinical diagnoses, which allowed us to account for comorbidities and measure symptoms dimensionally (i.e., symptom severity) rather than only use a categorical measure of diagnosis. This provided a novel approach to interpreting associations between parental psychopathology and offspring brain structure, as it allows us to tentatively identify those youth most at risk, in an already high-risk group of adolescents. Another strength of the current study was having a moderate sample size. This enabled us to employ manual quality control strategies to process our MRI data, which is known to be the most reliable way to reduce unexplained variance in

morphological data, and is the gold standard for quality control of brain segmentation and parcellation (Monereo-Sánchez et al., 2021). This type of quality control is generally not feasible for larger neuroimaging studies because of the time commitment required for each individual scan. Additionally, this study benefitted from having a sample of risk enriched offspring who were clinically naive at baseline (had no clinically significant symptoms of psychopathology), which allows us to tentatively suggest that offspring's own history of depression or anxiety is not influencing their brain structure in our sample.

Several limitations of the current study design should also be noted. Firstly, it is possible that parental depressive severity is not directly influencing offspring's brain structure, but instead the parent is passing down risk allele(s) associated with depression that in turn influence offspring's brain structure. Additionally, this study was cross-sectional; it is therefore unknown how parental depression or anxiety influences offspring brain development over time. Future research may benefit from longitudinal designs that begin during the perinatal period and extend into adolescence or early adulthood in order to draw conclusions about how parental mental health affects offspring brain development across the early lifespan, although such a study would be highly time and resource intensive. This will clarify whether effects seen here are persisting from perinatal or early childhood exposure to parental depression or anxiety, or if they are unique to current parental depression or anxiety severity. Given evidence that children's behaviour influences parental mental health (Allmann et al., 2016), it is also possible that there are bidirectional relationships between youth brain structure and parental psychopathology.

Another important limitation is that while modest our sample size enabled us to perform manual quality control on structural brain images, it may have also resulted in low power to detect smaller effects, especially after correction for multiple comparisons. Larger imaging

studies such as the ABCD (Pagliaccio et al., 2020) study will be well-powered to detect small effects of parental psychopathology on offspring brain structure. To our knowledge, there has been one study published to date from the ABCD dataset on examining parental depression, assessed categorically, and offspring brain structure (Pagliaccio et al., 2020). However, smaller imaging studies will likely continue to be informative as they may examine unique populations and provide more thorough characterization of parental psychopathology as well as enable better quality control of structural brain images. Effect sizes in our study were also small, suggesting that parental depressive and anxiety severity is a significant, but weak predictor of offspring brain structure.

Furthermore, this study used an ROI design. Most prior studies have chosen ROI-based study designs given a priori predictions regarding brain regions associated with certain parental psychopathologies, as such, we derived our a priori predictions based on findings of our recent review (see Kemp et al. 2022). However, ROI-based study designs may exclude potential findings from other brain regions and potentially increase the likelihood of confirmation bias. There may, however, also be limitations of whole brain analyses; multiple comparisons increase risk for Type 1 error, and smaller sample sizes may be underpowered to correct for multiple comparisons.

Furthermore, this sample is drawn from a risk-enriched study assessing premorbid risk for development of clinical depression and anxiety, and so there was no control group of youth with no familial risk. It is therefore unclear whether subclinical parental depression and anxiety symptoms in parents with no diagnosable history of depression or anxiety would be associated with offspring brain structure, although perinatal research suggests there may be (Adamson et al., 2018; Donnici et al., 2021; Lebel et al., 2016). Furthermore, majority of parents in the current

study had history of either major depressive disorder and/or an anxiety disorder, with very few having only an anxiety disorder. In our secondary analysis, we found that the left middle temporal gyrus was uniquely associated with depression and the left inferior parietal region was uniquely associated with anxiety, although these findings did not survive correction for multiple comparisons. However, future studies may benefit from examining offspring brain structure of parents with only a history of depression versus only a history of anxiety.

Conclusions

Previous literature confirms a difference in grey matter volume and cortical thickness between people with versus without depression or anxiety in addition to grey matter differences between adolescents at high-risk for depression/anxiety and their non-high-risk peers. Our findings support these conclusions; the left middle temporal gyrus was significantly and uniquely associated with parental depression severity and the left inferior parietal region was significantly and uniquely associated with higher parental anxiety scores. Additionally, findings from the current study suggest that even within a group of adolescents with a family history of depression or anxiety, there may be elevated risk for altered grey matter volume and thickness depending on parent symptom severity. Results highlight potential early biomarkers of risk and resilience for mood and anxiety disorders in at risk youth which may facilitate early identification and intervention.

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