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Application of a Diathesis-Stress Model to the Interplay of Cortical Structural Development and Emerging Depression in Youth

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Abstract

Cross-sectional studies in adults have long identified differences in cortical structure in adults with depression compared to healthy adults, with most studies identifying reductions in grey matter volume, cortical thickness, and surface area in primarily frontal cortical regions including the OFC, ACC, and variable sub-regions of the PFC. However, *when*, *why*, and *for whom* these neural correlates of depression emerge remains poorly understood, necessitating *developmental* study of associations between depression and cortical structure. We systematically reviewed studies examining these associations in child/adolescent samples, and applied a developmentally-focused diathesis-stress model to understand the impacts of depressogenic risk-factors and stressors on the development of structural neural correlates of depression. Cross-sectional findings in youth are generally similar to those found in adults, but vary in magnitude and direction of effects. Preliminary evidence suggests that age, sex, severity, and comorbidity moderate these associations. Longitudinal studies show depression prospectively predicting cortical structure *and* structure predicting emerging depression. Consistent with a diathesis-stress model, associations have been noted between risk-factors for depression (e.g., genetic risk, family risk) and environmental stressors (e.g., early life stress) and structural neural correlates. Further investigation of these associations across development with attention to vulnerability factors and stressors is indicated.

Keywords

Depression; Developmental Psychopathology; Neurodevelopment; Cortical Structure

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Overview

Numerous studies, primarily in adults, find differences in brain structure between depressed and non-depressed individuals, as well as dimensional associations between brain structure and depressive symptoms. Associations between cortical structure and heritable risk for depression (e.g., genetic polymorphisms and family history of depressive disorders), known depressogenic risk factors (e.g., cognitive and temperamental vulnerability), and depressogenic stressors (e.g., early adversity) have also been examined. Understanding of the nature of these neurostructural differences in the cortex is further complicated by the use of multiple methodologies to index distinct anatomical features of the cortical grey matter including volume, thickness, and surface area. Here, a model is proposed that *integrates* this extant literature in a developmental psychopathology framework to understand 1) the development of depression and cortical structural features in childhood and adolescence and 2) the contribution of depressogenic vulnerability and stressors to this complex and dynamic process.

Reductions in cortical grey matter volume and thickness in primarily, but not only, frontal cortical regions have been consistently documented in adults with Major Depressive Disorder (MDD) across numerous individual studies and summarized in multiple meta-analyses (see Section 1). What is not yet understood is when or how this pattern of cortical structural characteristics emerges. Therefore, we first present a systematic review of the developmental literature of brain structure and depression (see Section 2). Cross-sectional studies in child and adolescent samples find associations between cortical structure and depression at different points of development. Longitudinal studies in youth explore the directionality of these associations between depressive symptomology and cortical structure. Early published evidence suggests that there are bidirectional relationships between cortical structure and depression. Furthermore, variability in these findings suggest the involvement of multiple other factors including, but not limited to, age, sex, symptom presentation and severity, and comorbid psychopathology.

Following this systematic review of the developmental literature, we additionally present *selective* reviews of the processes that may contribute to the development of depression and frontal cortical structure. We focus on multiple risk factors that demonstrate associations with depression and cortical structure, including high risk gene variants, familial history of depression (see Section 3), prenatal exposure to maternal depression, and early life stress (see Section 4). Finally, we consider the interactions between depressogenic risk factors and stressors on cortical structure to further elucidate when and for whom these outcomes emerge (see Section 5).

Introduction

Recently, research has sought to understand Major Depressive Disorder (MDD) through behavioral and neurobiological features across multiple units of analysis, including neural circuitry (Woody & Gibb, 2015). A rapidly expanding body of work has identified differences in both brain structure and function across subcortical and cortical systems associated with MDD (for review see Kaltenboeck & Harmer, 2018). Examination of

structural differences in *subcortical* structures have identified reduced grey matter volume in a number of regions. Findings from recent meta-analyses have most consistently documented reduced grey matter volume in subcortical regions, including the hippocampus, and less consistently the putamen, caudate nucleus and amygdala (Schmaal et al., 2016; Koolschijn et al., 2009; Bora et al., 2012). Studies of *cortical* structural differences associated with MDD reveal heterogenous findings that are due, in part, to variability in methodology and units of analysis. Specifically, the neuroanatomy of the cerebral cortex, marked by the folded gyri and sulci, contributes unique measurement challenges that have motivated the development of new analytic approaches (Winkler et al., 2010; Vijayakumar, Mills, Alexander-Bloch, Tamnes, & Whittle, 2018).

Measurement and Methodological Challenges

The first magnetic resonance imaging (MRI) metric to be developed and widely applied to the study of brain structure was grey matter volume. Volumetric techniques estimate the number of voxels comprising the 3-dimensionial volume of neuroanatomical structures, and can be applied to the measurement of both subcortical and cortical structures. However, the application of these voxel-by-voxel processing techniques (e.g. voxel-based morphometry), which are highly reliant on the accuracy of registration, smoothing, and atlas, to the folded cortical surface poses an increased risk of misalignment and misclassification (Winkler et al., 2010). In response to these challenges, MRI processing approaches that take a 2-dimensional, surface-based approach to quantifying the cortical surface have been developed (e.g. FreeSurfer) and provide rich additional information about neurostructural features unique to the cortex, including cortical thickness, surface area, and morphometry (for review see Vijayakumar et al., 2018). Grey matter volume may additionally be estimated as the product of cortical thickness and surface area. However, recent studies suggest that cortical thickness and surface area are influenced by different genetic processes and thus, poorly correlated with one another, though the biological underpinnings of their independence remains unclear (Winkler et al., 2010). These findings emphasize the value of considering *both* cortical thickness and surface area as independent outcomes of interest in studies of cortical structure, as opposed to restricting focus to their composite (grey matter volume).

Across metrics and methods, differences in cortical structure between individuals with and without MDD have been identified across the cortex, with studies implicating frontal, temporal, parietal, and occipital regions. In meta-analyses, specific frontal cortical regions such as the orbitofrontal cortex (OFC; Drevets, 2007), prefrontal cortex (PFC; George, Ketter, & Post, 1994), and the anterior cingulate cortex (ACC; Bush, Luu, & Posner, 2000) have emerged as areas of particular importance, consistent with the disruption of numerous “frontal lobe” neurocognitive functions observed in depression (Snyder, 2013). The following review focuses on studies examining cortical grey matter structure, with a particular emphasis on the comparison and integration of patterns of findings across the diverse array of structural characteristics (e.g., grey matter volume, cortical thickness, surface area, and morphometry) unique to the anatomy of the cortex.

Developmental Context

Finally, it is important to note that adolescence, the developmental period associated with heightened risk for depression, is also a time of prolific cortical structural development. Cortical maturation, particularly in frontal regions, continues into early to mid-adulthood and is marked by reductions in cortical thickness and grey matter volume and expansion of cortical surface area (Gogtay et al., 2004). The extension of the findings from cross-sectional, primarily adult, studies into *longitudinal* studies and research in child and adolescent populations is critical given that *both* depression and cortical structure are observed to develop and change through childhood and adolescence. Therefore, this review will primarily review studies in youth in order to highlight findings in the extant literature which not only establish the existence of cortical structural characteristics of MDD, but elucidate when, why, or how these structural features may emerge.

Methods

A systematic review of cross-sectional and longitudinal studies of associations between brain structure and depression was conducted following PRISMA guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). In September 2018, a search of three databases (PsychINFO, PubMed, and Web of Science) was conducted using the following search terms: “depress*” AND “brain” AND [“magnetic resonance imaging” OR “MRI” OR “cortical thickness” OR “cortical thinning” OR “surface area” OR “volume*” OR “morphometry”]. Search and screening results are documented in a PRISMA Flow Chart (Figure 2). Eligible studies included at least one assessment of depression diagnosis or symptoms, at least one assessment of brain structure using magnetic resonance imaging (MRI), and report volumetric or surface-based analysis of cortical structure. Across youth and adult samples, 680 articles examining cortical grey matter and depression were identified, including 142 reviews, 29 meta-analyses, and 509 empirical studies. However, the majority of studies to date have been conducted in adult populations. Given the developmental focus of the current review, systematic review was further limited to studies in *youth* samples. “Youth” was defined as studies with an upper-bound age range no higher than 25 years old, consistent with developmental frameworks that define adolescence as spanning through age 25 (Curtis, 2002). Thus, while studies with age ranges spanning childhood and adolescence (e.g., ages 8–25; Bos et al., 2018) were reviewed, those spanning broader developmental periods (e.g., ages 6–54; Bansal et al., 2016) were excluded. When restricted to youth samples, one meta-analysis and 42 empirical studies were identified. These studies are systematically reviewed in Section 2 and described in Tables S1–S3.

In addition to the work conducted in youth samples, many studies not meeting inclusion criteria for the systematic review are highly relevant to understanding brain-depression relationships from a developmental psychopathology perspective. Following systematic review of the developmental literature (see Section 2), we integrate evidence from heterogenous yet relevant studies in youth (e.g., infants with prenatal exposure to depression symptoms) and adults (e.g., retrospective report of early life stress, family history) to review processes that may contribute to the development of depression and frontal cortical structure in the following sections. It is important to acknowledge that full systematic

reviews of these literatures (e.g., cortical structure and early life stress, genetic risk for depression and cortical structure, etc.,) were not completed. Rather, we provide a brief *selective* review of relevant risk factors that demonstrate associations with depression and cortical structure. In support of a diathesis-stress model (Figure 1), we present emerging evidence exploring the contribution of genetic risk factors (e.g., high risk gene variants, familial history of depression; Section 3), environmental stressors (e.g., prenatal exposure to maternal depression, early life stress; Section 4), and their interactions (Section 5)."

Section 1 – Frontal Cortical Structure and Depression: Findings in Adults

Meta-analytic studies comparing cortical structure between adults with and without MDD have found differences in grey matter volume as well as cortical thickness, surface area, and morphology, though findings vary across methodology and sample characteristics. Numerous meta-analyses in adults have examined differences in cortical grey matter volume in adults with MDD compared to healthy controls, and confer evidence for a relatively consistent pattern of reduced grey matter volume in frontal cortical and, to a lesser extent, temporal regions. A comprehensive effect-size based meta-analysis examining differences in grey matter volume across 2,148 individuals with MDD and 1,947 healthy controls identified reduced grey matter volume in the OFC (d = 0.43), ACC (d = 0.77) and PFC (d = 0.34; Koolschijn, van Haren, Lensvelt-Mulders, Pol, & Kahn, 2009). These findings were replicated in a meta-analysis focused strictly on the cortico-striatal-pallidal-thalamic circuit, which found volume reductions in the OFC (d = 0.37), ACC (d = 0.34), and PFC (d = 0.27) in individuals with MDD compared to controls (Bora, Harrison, Davey, Yucel, & Pantelis, 2012). Studies using voxelwise metanalytic techniques, including signed differential mapping (Bora et al., 2012; Lai, 2013), activation likelihood estimation (Du et al., 2012), and computational meta-analysis of statistical parametric maps (Arnone et al., 2016), have also identified reduced grey matter volume in the ACC (Bora et al., 2012; Du et al., 2012; Lai, 2013), prefrontal cortex (Bora et al., 2012; Du et al., 2012; Arnone et al., 2016) and temporal lobes (Arnone et al., 2016). Smaller meta-analyses focused on subgroups of individuals with MDD describe reductions in grey matter volume in frontal and temporal regions in individuals experiencing first depressive episodes (Peng, Chen, Yin, Jia, & Gong, 2016; Wang et al., 2017), anti-depressant medication naïve individuals with MDD (Zhao et al., 2014), and individuals with late life depression (Du et al., 2014).

Relatively fewer studies have examined differences in cortical thickness and surface area between individuals with and without MDD. The largest meta-analysis to date found that across 2,148 individuals with MDD and 7,957 healthy controls, adults with MDD had thinner cortical grey matter in the OFC, anterior and posterior cingulate, insula, and temporal lobes (ds range between −.10 to −.14 across regions), but no differences in surface area (Schmaal et al., 2017a). A second meta-analysis examining only cortical thickness identified somewhat consistent findings; while MDD was similarly associated with significantly thinner bilateral OFC and left pars opercularis region of the PFC, reduced cortical thickness was also identified in the occipital region of the left calcarine fissure/ lingual gyrus, and thicker cortex was noted in the parietal region of the supramarginal gyrus (Suh et al., 2019). Taken together, meta-analyses in adults implicate similar regions (frontal, temporal) across metrics, and most often find that MDD is associated with reductions in

cortical thickness and grey matter volume. However, the directionality and localization of differences in cortical thickness are more variable (e.g., reductions thickness in the occipital lobe, increases in the parietal lobe). Meta-analytic differences in surface area and cortical folding patterns have not yet been reported, likely owing to a limited number of studies.

Individual studies in adults have additionally considered the contribution of age of onset to cortical structural differences associated in MDD. An array of studies have examined cortical structural differences between adults with MDD onset in youth and in adulthood. In adults, onset before age 25 has been shown to be associated with reduced cortical thickness in frontal (frontal pole, Jaworska et al., 2014; precentral gyrus, Truong et al., 2013), parietal (post central gyrus) and occipital (lingual gyrus) regions (Truong et al., 2013), as well as increased cortical thickness in the transverse temporal cortices (Jaworska et al., 2014). However, another study comparing individuals with late adolescent onset (18–23 years) and adult onset MDD (>24 years) did not differ on frontal cortical grey matter (Botterton et al., 2002). These limited yet complex findings highlight the need for further study of experiences of depression across development, and emphasize the relevance of developmentally focused study in understanding the cortical structural correlates of MDD seen in adulthood.

Section 2 – Depression and the Developing Brain: Findings in Children and Adolescents

In contrast to the wealth of studies in adults, the study of cortical structure and depression in children and adolescents is a newer and smaller literature. Over the past two decades, a quickly increasing body of cross-sectional and longitudinal work has examined cortical structural correlates of depression in childhood and adolescence.

2.1 – Meta-Analyses in Youth with Depression.

To date, no comprehensive meta-analytic studies of neurostructural differences in MDD in child/adolescent populations have been conducted. The ENIGMA working group included both adolescents and adults in their voxel-wise meta-analysis of grey matter volume, cortical thickness, and surface area. Whereas adults with MDD demonstrated reduced cortical thickness in multiple frontal and temporal cortical regions, no such differences in cortical thickness were found between adolescents with and without MDD (Schmaal et al., 2017a). Additionally, while no significant differences in cortical surface area were observed in adults with and without MDD, adolescents with MDD exhibited lower overall surface area compared to healthy controls. Adolescents with MDD demonstrated reduced grey matter volume in the medial OFC and superior frontal gyrus of the PFC, which is consistent with volumetric findings observed in adult populations. Regional grey matter reductions were also observed in primary and higher order visual, somatosensory, and motor areas.

2.2 – Cross-Sectional Studies of Brain Structure and Depression in Youth.

Cross-sectional studies of the relationship between depression and brain structure in childhood and adolescence have examined whether the structural differences in MDD described in adults replicate in younger populations. While cross-sectional studies are by

design limited in their ability to inform the directionality or possible underlying causal mechanisms, they evince associations between brain structure and depression and highlight unique features of these relationships at different developmental stages. Reviewed studies are summarized in Table S1.

Grey Matter Volume.—Similar to the adult literature, there is some evidence that MDD in youth is associated with reduced grey matter volume in frontal cortical regions. A number of cross-sectional volumetric studies in adolescents have found reduced grey matter volume in youth with MDD compared to healthy controls in the ACC (Pannekoek et al., 2014; MacMaster, Carrey, Langevin, Jaworska, & Crawford, 2014), the frontal lobes (Shad, Muddasani, & Rao, 2012; MacMaster et al., 2014), and the superior and middle temporal gyri (Shad et al., 2012). However, some studies have failed to identify significant associations between cortical grey matter volume and adolescent MDD (Redlich et al., 2018; Chen et al., 2008).

Other cross-sectional studies incorporated additional factors, such as age, symptom severity, and comorbid psychopathology, into their work to explain mixed findings. Hagan and colleagues (2015) examined whether age moderated the associations between MDD and cortical structure. The authors reported a significant interaction between depression status and age on grey matter volume of the ACC, such that age was inversely associated with ACC volume for non-depressed adolescents, but no associations were found between age and ACC volume for depressed adolescents (Hagan et al., 2015).

Depression severity is another important factor to consider. In some cross-sectional studies, despite significant group differences in cortical structure between youth with and without MDD, youth self-reported depressive symptoms were not significantly associated with cortical grey matter volume (Pannekoek et al., 2014; Hagan et al., 2015; Shad et al., 2012). However, in healthy youth, subclinical depressive symptoms have been found to be inversely correlated with grey matter volume of the rostral ACC (Boes, McCormick, Coryell, & Nopoulos, 2008). Additionally, severe symptoms of MDD such as suicidality have also been associated with grey matter volume. Youth with MDD who have a history of suicide attempt demonstrated reduced grey matter volume in the superior temporal gyrus (McLellan et al., 2018) and more suicide attempts have been inversely associated with grey matter volume in the ACC (Goodman et al., 2011). While findings concerning severity and brain structure are mixed, there is some evidence to suggest that the severity of depressive symptoms, even at subclinical levels, is associated with the degree of cortical structural changes.

Depression is often comorbid with other psychiatric diagnoses (Merikangas et al., 2010; Angold, Costello, & Erkanli, 1999) and studies have begun exploring the influence of comorbid disorders on brain structure. In youth with comorbid MDD and borderline personality disorder, reduced grey matter volume in the ACC was inversely associated with borderline personality symptom severity and number of suicide attempts, but was *not* associated with depressive symptoms (Goodman et al., 2011). In a study comparing youth with MDD with and without comorbid anxiety disorders, youth with comorbid anxiety had reduced dorsolateral PFC thickness compared to youth with MDD alone (Wehry et al., 2015). Results from this small literature suggest that comorbidity may affect cortical

structure in youth with depression, though our understanding is limited by a limited number of studies in small samples.

Consistent with findings in adults, studies of associations between MDD and grey matter volume in children and adolescents generally identify *reduced* grey matter volume in frontal and temporal regions, with the ACC emerging as a strong ROI. In some studies, depression also moderated the effect of age on cortical structure and highlights the need for attending to how depression influences neural development. The severity of MDD, including symptom severity, suicidality, and comorbidity, may also influence cortical structure.

Surface Characteristics.—Consistent with the adult literature, the most frequently used surface-based index of cortical structure in studies of youth depression is cortical thickness. Whereas adults demonstrate a reasonably consistent pattern of reduced cortical thickness in frontal regions, particularly the OFC and ACC, findings in youth have been more variable. Studies have found that children with MDD have had decreased cortical thickness in the pericalcarine gyrus, postcentral gyrus, supramarginal gyrus and superior parietal gyrus, but increased cortical thickness in the temporal pole (Fallucca et al., 2011), the ACC, and rostral middle frontal gyrus of the PFC (Koenig et al., 2018). However, other studies have failed to identify differences between adolescents with MDD and healthy controls (Fradkin et al., 2017). In adolescents with MDD, Reynolds and colleagues (2014) found an interaction between MDD and age, such that for adolescents with MDD, but not healthy controls, there was a significant inverse association between age and cortical thickness of the left middle frontal gyrus.

Cortical morphology (e.g., curvature; sulcogyral folding patterns) is also associated with depression in adolescence. Specifically, differences in cortical morphology have been identified in adolescents with MDD compared to healthy controls (Ramezani et al., 2014) and have demonstrated associations with self-reported symptom severity (Ramezani et al., 2014; Whittle, Bartholomeusz, et al., 2014). Cortical folding patterns have also distinguished between children with and without depression. Using support vector machine pattern classification modeling, cortical thickness, grey matter volume, and cortical folding patterns were able to successfully predict group membership with 78.4% accuracy, 76% sensitivity, and 80% specificity across children with MDD and demographically matched healthy controls (Wu et al., 2015).

Cross-sectional studies have begun to examine associations between cortical surface characteristics and symptoms of depression. In a large community sample of children and adolescents (ages 7–21), depressive symptoms were significantly inversely related to cortical thickness, but not surface area, in the ventromedial PFC/medial OFC (Merz, He, & Noble, 2018). However, in a sample limited to adolescents, self-reported depressive symptoms were *positively* associated with ACC, right medial OFC, and frontal pole cortical thickness (Koenig et al., 2018).

In summary, youth with MDD show *reduced* cortical thickness compared to non-depressed youth, though null and opposite findings have also been identified. These effects are observed primarily in the ACC and frontal cortical regions, but have also been observed

in temporal regions associated with the limbic system, as well as parietal and occipital regions that are less frequently implicated in volumetric studies. Subclinical depressive symptoms also are associated with reduced cortical thickness and cortical morphology. Furthermore, surface-based features can be used to predict diagnostic classification of MDD with reasonable accuracy.

Conclusions.—Cross-sectional studies of MDD in youth are generally consistent with the adult literature in identifying structural differences between MDD and healthy adolescents. However, findings in youth are highly variable, with cortical thickness, surface area, and morphology demonstrating heterogenous direction and location of effects. The degree to which heterogeneity in findings may be explained by factors such as age, sex, and comorbidity is not well understood. The implications of these findings are also limited owing to the cross-sectional designs. While the results from cross-sectional designs provide initial evidence for associations, they do not inform directionality of effects. Longitudinal studies can help inform whether alterations in brain structure are causes, correlates, or consequences of depression.

2.3 – Longitudinal Studies of Brain Structure and Depression in Youth.

Prospective longitudinal studies of the development of depression in childhood and adolescence provide opportunities to examine the directionality of associations between the development and course of MDD and cortical structure. Studies including *longitudinal* assessments of depression and *single* assessments of brain structure evince depressive symptomology as a possible predictor and outcome of cortical structural differences, but remain unable to inform causal claims. A novel and limited body of studies including multiple assessments of *both* depression and brain structure is beginning to elucidate the interplay of emerging depression and cortical structure throughout childhood and adolescence. Reviewed studies are summarized in Tables S2 and S3.

Longitudinal Assessments of Depression, Single Assessment of Brain Structure.—In some studies, depressive symptoms in childhood have prospectively predicted cortical structure later in development (Figure 1: Path A). As part of a longitudinal study of depression, children who were preschool age (3–5 years old) at baseline completed multiple assessments of depressive symptomology over a 10-year follow-up period, as well as a single MRI assessment in middle childhood (6–12 years old; e.g., Marrus et al., 2015; Belden et al., 2015). Longitudinal analyses found that MDD symptoms and diagnosis were prospectively associated with surface-based (Marrus et al., 2015) and volumetric (Belden et al., 2015) structural characteristics. Children with a prior diagnosis of MDD demonstrated reduced cortical thickness in the ventromedial PFC (Marrus et al., 2015) and reduced grey matter volume in the insula (Belden et al., 2015) compared to children with no history of MDD. Furthermore, early childhood depressive symptoms (3–5 years old), independent of current/school age symptoms (6–12 years old), also significantly inversely predicted cortical thickness in the ventromedial PFC in this sample (Marrus et al., 2015). Depressive symptoms in childhood also prospectively predict brain structure in late adolescence: in a large male community sample, internalizing symptoms in childhood (7–13 years old) were inversely associated with grey matter volume and surface area in the superior frontal

gyrus, and positively associated with grey matter volume and cortical thickness in the precuneus, in early adulthood (18–21 years old; Jensen et al., 2015). These findings provide preliminary evidence to suggest that history of depressive symptoms may predict structural characteristics associated with MDD.

Studies have also examined whether brain structure predicts later depressive symptoms (Figure 1: Path B). Belden et al. (2015) found that reduced grey matter volume in the insula predicted a future diagnosis of MDD (OR = 0.96; 95% CI, 0.01–0.75) across a 10-year follow-up period when controlling for past episodes. Other studies in adolescent samples have also found that cortical structure prospectively predicts future depressive symptoms (e.g., Vulser et al., 2015) and diagnosis of MDD (Foland-Ross et al., 2015b). In an adolescent community sample, grey matter volume in the ventromedial PFC and ACC was inversely associated with subclinical depressive symptoms at the time of a baseline MRI (14 years old) and at a follow-up assessment of depressive symptoms two years later (Vulser et al., 2015). Cortical thickness in early adolescence (10–15 years old) has also been shown to predict diagnosis of MDD across a 5 year follow up period with 70% accuracy in a support vector machine learning model, with the right medial OFC, right precentral gyrus, left ACC, and bilateral insula contributing most strongly (Foland-Ross et al., 2015b). However, other studies have failed to find associations between cortical thickness and depression. Specifically, in a sample of adolescents (15–20 years old) there were no significant predictions to depressive symptoms at 2-year follow up from cortical thickness at baseline (Busso et al., 2017). Similarly, Little and colleagues (2014) found that OFC volume at age 12 did not significantly predict onset of MDD in adolescence (13–19 years old).

In sum, there is evidence supporting reciprocal longitudinal relationships between youth depression and grey matter volume and cortical thickness. However, a number of studies have also failed to identify links between depressive symptoms and cortical structure, with null findings appearing most frequently in older adolescent samples. Thus, the nature, directionality and causal mechanisms of the relationship between depression and brain structure remain unclear. The above studies are limited by the use of only a single measure of cortical structure and therefore provide preliminary evidence for bidirectional effects. Without longitudinal measures of cortical structure, claims about causality or directionality of associations between depression and cortical structure are unable to be substantiated.

Longitudinal Assessments of Depression *and* Brain Structure.—A number of longitudinal studies have examined associations between trajectories of cortical development and trajectories of depressive symptoms in youth (e.g., Bos, Peters, van de Kamp, Crone, & Tamnes, 2018; Schmaal et al., 2017b; Luby et al., 2016), as well as constructs strongly associated with depression, such as irritability (Pagliaccio, Pine, Barch, Luby, & Leibenluft, 2018) and anhedonia (Luby et al., 2018). This emerging literature is beginning to elucidate the complex relationship between emerging depressive symptoms and neural structure.

Examination of the course of depressive symptomology throughout childhood and adolescence has revealed associations between emerging symptoms and brain structure. In Bos et al. (2018), a broad sample including children, adolescents, and early adults (8–

25 years old) completed three MRI assessments over five years, as well as self-reports of depression. The authors found that, controlling for baseline symptoms, accelerated cortical thinning in the OFC and PFC was associated with depressive symptoms at the third assessment (Bos et al., 2018). Study samples focusing on more specific developmental periods offer some insight into the progression of these relationships across time.

Regarding childhood, the study with the earliest assessments involved a sample of children who were preschool age (3–6 years old) at baseline and completed three MRI assessments at three year intervals (Luby et al., 2018; Luby et al., 2016). Depression in early childhood was associated with accelerated cortical thinning and grey matter volume loss globally across the three MRI assessments (Luby et al., 2016). In the same sample, specific examination of trajectories of change in cortical thickness and volume in the OFC found that change in this region did *not* prospectively predict depression in adolescence (13–18 years old; Luby et al., 2018). Null findings have also been reported in a study examining associations between internalizing symptoms at ages 6 or 10 and changes in overall cortical volume from age 8 to 10, which found no significant associations between symptoms and structure (Muetzel et al., 2018). The limited studies in early and middle childhood highlight early depressive symptoms as a risk factor for accelerated cortical thinning and volume loss in later childhood. However, more studies are necessary to replicate these findings.

In contrast to childhood, more longitudinal studies of cortical development have focused on adolescence. Some studies restricted to adolescence have failed to identify associations between cortical development and depression. Specifically, in a sample of older adolescents and early adults (16–25 years old), changes in cortical grey matter volume over a two-year follow-up period were not associated with MDD symptoms and failed to predict onset of MDD (Nickson et al., 2016). Additionally, in a sample of adolescents at high familial risk for depression, change in cortical thickness in the PFC from age 12 to age 16 was not associated with the first onset of MDD before age 18 (Whittle, Lichter, et al., 2014b). Schmaal and colleagues (2017b) examined the association between cortical structural changes and depression symptom using group-based trajectory modeling. Adolescents were grouped based on symptom trajectory as low-stable (consistently low depressive symptoms), early decreasing (high symptom levels in early adolescence which decreased over time), or late increasing (early symptom levels in early adolescence which increased over time). While there were no main effect group differences in brain structure related to trajectories, significant group differences in surface area were moderated by sex. Females with early-decreasing symptoms had less ACC and OFC surface area over time as compared to the other trajectory groups, while males with early-decreasing symptoms demonstrated an increase in surface area in the OFC. Given the well-documented emergence of sex differences in depression during adolescence (Hankin et al., 1998; Cyranowski, Frank, Young, & Shear, 2000), continued study of the effects of sex on relationships between brain structure and emerging depression will be critical to understand the interplay between these complex processes. Studies examining potential moderating factors, such as sex, of the associations between trajectories of depressive symptoms in adolescence and changes in brain structure may provide some insight into the increased variability of findings in adolescent populations compared to findings in children and adults.

Constructs associated with depression (anhedonia; irritability) have also been studied in relation to emerging cortical structural differences. Anhedonia is a core symptom of MDD marked by a lack of interest and pleasure in enjoyed activities (DSM-5; American Psychiatric Association, 2013). Higher anhedonia ratings over time have been associated with steeper decline in OFC volume across childhood and early adolescence (Luby et al., 2018). Irritability is a criterion for depression in youth (Egger & Angold, 2006). In an examination of associations between group-based trajectories of irritability, depressive symptoms and cortical structure, children with elevated irritability (consistently high trajectory) demonstrated higher depressive symptoms and *increased* cortical thickness in the superior frontal and temporal gyri and the right inferior parietal lobule (Pagliaccio et al., 2018). This finding is inconsistent with the prevailing pattern of *decreased* cortical thickness and volume in the context of depression.

A few studies have also identified *positive* associations between emerging depression and cortical structure, as opposed to the *negative* associations reported by the majority of studies in youth and adults. Ducharme and colleagues (2014) found that the directionality of associations between depressive symptoms and cortical thickness in the ventromedial PFC was moderated by age, such that anxious/depressed symptoms were *negatively* associated with cortical thickness in children (< 9 years old), but *positively* associated with thickness in older adolescents (15–22 years old). The change of direction in effects at different points in development noted by Ducharme and colleagues suggest that positive associations with cortical thickness emerge in older youth. This surprising effect may be secondary to a slower rate of cortical thinning in youth with higher levels of anxious/depressed symptoms. These results highlight the need to study the relationship between brain structure and depression at *all* points of development.

Conclusions.—Existing longitudinal data have yet to comprehensively examine the complex and dynamic relationship between brain structure and depression. Overall, there is evidence that trajectories of cortical development and depressive symptoms covary, but the directionality of effects is not clear. Findings from Ducharme et al. (2014) suggest the sign of the association between depression and cortical structure may change from negative to positive in middle childhood. Thus, depression and brain structure may have different relationships across neural development that may be reflected in the inconsistent findings across other studies. Despite these mixed results, implicated regions continue to be largely consistent with findings in the adult and cross-sectional literature (e.g., OFC, ACC, frontal cortical regions). Longitudinal studies confer more evidence that earlier depressive symptoms predict to later structure (Figure 1: Path A). Studies exploring predictions of structure to later onset of depression (Figure 1: Path B) more frequently reported null results, but were also fewer in number.

Taken together, the longitudinal studies directly examining changes in brain structure across development, as well as the developmental psychopathology of depression comprise a budding literature addressing the still unclear neural developmental pathways underlying MDD. There is preliminary evidence that the relationship between depression and cortical structure may be mediated and/or moderated by age and/or gender, but replication is needed. Preliminary evidence suggests that cortical structure may mediate the relationship

between past and future symptoms of depression. Vulser and colleagues (2015) found that, for girls only, the relationship between subclinical depressive symptoms at baseline and increased depressive symptoms at follow-up was mediated by lower grey matter volume in the ventromedial PFC. Continued longitudinal study that considers the differential effects of age and gender, and explores possible mediators and underlying mechanisms of these relationships, are indicated.

Section 3 – Associations between Family History, Single Nucleotide Polymorphisms (SNPs), and Cognitive Vulnerabilities as Risk Factors for Depression and Cortical Structure

The complex and heterogeneous findings in the developmental literature raise many questions about additional factors that influence the emergence of depression, altered brain structure, and the relationships between these outcomes. In order to clarify the nature of the relationship between depression and cortical structure, it is important to consider possible shared risk factors. The following section presents a selective review of the associations between cortical structure and known vulnerabilities to MDD, including genetic (Figure 1: Path C) and familial risk (Figure 1: Path D). and temperamental/cognitive traits (Figure 1: Paths E, F) known to confer vulnerability to MDD.

3.1 – Genetic Risk for Depression and Cortical Structure

Recent reviews of neuroimaging twin studies have begun to describe genetic influences on cortical structure broadly (Peper, Brouwer, Boomsma, Kahn, & Pol, 2007) and specifically within the context of MDD (Pigoni et al., 2018). A recent review of neuroimaging twin studies in MDD described a small number of adult studies with minimal conclusive findings (Pigoni et al., 2018). In the one study that describing differences in cortical structure, reduced grey matter volume in the fusiform gyrus was identified in monozygotic twin pairs with concordant MDD compared to healthy controls, but there were no intra-twin differences among twins discordant for MDD (Alemany et al., 2013). This is consistent with a genetically driven effect.

In addition to research in twins, there is great interest in identifying genetic risk factors for multiple processes related to the development of depression (Woody & Gibb, 2015), though evidence of contribution of genetic risk factors to depression remains limited (Dunn et al., 2015). While a large genome wide association study (GWAS) failed to identify any significantly different SNPs across 5763 adults with MDD and 6901 healthy controls (Wray et al., 2012), individual studies have identified associations between MDD and SNPs related to serotonin (Risch et al., 2009), BDNF (Verhagen et al., 2010), and immune responding (e.g., FKBP5 gene; Rao et al., 2016). A meta-analysis of studies of genetic risk and brain structure in the context of MDD found the BDNF Val66Met “Met” allele was associated with increased grey matter volume in the right middle frontal gyrus, though no other findings were statistically significant (Pereira et al., 2018). Additionally, individual studies in adults have found that variants of the FKBP5 gene associated with depression are also associated with reduced grey matter volume in the OFC (Hirakawa et al., 2016; Tozzi et al., 2018). In the one existing study of genetic risk, brain structure, and MDD in adolescents,

increasing copies of the 5-HTTLPR “s” alleles were associated with reduced grey matter volume in the OFC (Little et al., 2014), but this association failed to prospectively predict the onset of MDD during adolescence.

These studies, though limited in number, suggest that genetic risk for depression, depressive symptomatology, and cortical structure are likely associated. Despite the dearth of main effects specifically relevant to MDD, genetic risk may contribute a more complex role in the associations between MDD and its related cortical structural characteristics; an emerging body of studies (reviewed in Section 5 below) indicate that genetic risk may moderate associations between environmental stressors and cortical structure in the context of MDD (Figure 1: Path I).

3.2 – Familial Risk for Depression and Cortical Structure.

Comparison of brain structure in individuals at high and low familial risk for depression find differences in cortical structure in both healthy and depressed populations. Comparisons in adults show that MDD and high-risk groups demonstrated similarly reduced grey matter volume in the insula (Opel et al., 2016), OFC (Opel et al., 2016), and dorsolateral PFC (Amico et al., 2011), as well as reduced cortical thickness in the left inferior frontal, parahippocampal, precentral, and fusiform gyri (Papmeyer et al., 2015) compared to low-risk groups, though null findings have also been reported (Carballedo et al., 2012). Among adolescents with MDD, Nolan et al. (2002) found that those with a family history of MDD had reduced left prefrontal cortical grey matter volume. In a sample of both youth and adults (6–54 years old), healthy individuals at high familial risk for MDD demonstrated significantly reduced cortical thickness broadly across the right hemisphere (Peterson et al., 2009). Examinations of cortical structure in mothers with and without MDD and their healthy daughters have also identified associations between familial risk and cortical structure as indexed by both grey matter volume and cortical thickness. Mothers with MDD and their healthy daughters demonstrate reduced cortical thickness in the fusiform and inferior temporal gyri (Foland-Ross, Behzadian, LeMoult, & Gotlib, 2016) and reduced grey matter volume in the dorsomedial PFC as well as temporal and parietal cortical regions (Ozalay et al., 2016) compared to mothers/daughters without MDD.

More complex relationships between familial risk, dimensional symptoms of depression, and cortical structure have also been examined. Peterson and colleagues (2009) examined cortical thickness as a mediator of the associations between familial risk and MDD symptoms and cognitive functioning. In this study, cortical thickness was inversely associated with current MDD symptom severity and cognitive functioning (e.g., inattention and visual memory) and significantly mediated the associations between familial risk and symptoms/cognitive functioning. Familial risk has also been found to *moderate* the association between depressive symptoms and rostral ACC volume in a sample of youth (ages 7–17), such that high-risk youth demonstrated a stronger negative association than low-risk youth, who demonstrated a smaller, but still significant, negative association (Boes et al., 2008).

In conclusion, the brain structure of healthy individuals at high family risk of MDD mirrors patterns of cortical structural characteristics seen in those with MDD. Furthermore, youth

at high risk for MDD demonstrate associations between depressive symptoms/depressogenic stressors and cortical thickness in regions implicated in depression (e.g., ACC, insula), and these are similar to the associations seen in their depressed parents. Future research should continue to explore the specific mechanisms of family history of MDD on cortical structure and emerging depression in youth. Prior studies have suggested that changes to parenting behavior and parent-child relationships also contribute to the development of depression in offspring of depressed parents beyond the possible genetic risk associated with having a parent with MDD (for review see Franić et al., 2010).

3.3 – Cognitive Risk for Depression and Cortical Structure.

Depression is associated with deficits in a number of cognitive functions including executive functions (EF; Snyder, 2013), emotion regulation (Aldao, Nolen-Hoeksema, & Schweizer, 2010), and certain maladaptive cognitive attributional and coping styles (Beevers, 2005). Many cognitive factors, particularly executive functions/cognitive control, are housed in the frontal lobe (Duncan & Owen, 2000). Thus, a working hypothesis is that frontal lobe structural abnormalities may give rise to cognitive deficits (Figure 1: Path E) that increase risk for depression (Figure 1: Path F).

A small number of studies in youth have examined associations between frontal cortical structure and depression-related cognitive processes (Figure 1: Path E). Studies of cognitive development and cortical maturation in healthy youth link changes in cortical thickness and grey matter volume with change in cognitive functions, particularly executive functions such as behavioral inhibition and working memory (for review see Paus, 2005). However, few studies have explicitly studied associations between cognitive functions and brain structure in the context of emerging depression. One related construct associated with frontal cortical structure is impulsivity, or the tendency to act prematurely (Dalley, Everitt, & Robbins, 2011). In a large community sample of children and adolescents, impulsivity was associated with reduced cortical thickness in the medial OFC, frontal pole, rostral middle frontal gyrus, and pars orbitalis (Merz et al., 2018). Effortful control, a temperament dimension with close conceptual links to executive functioning (Zhou, Chen, & Main, 2012), was found by Vijayakumar and colleagues (2014) to significantly mediate the relationship between changes in cortical thickness and changes in depressive symptoms across a four-year period in early adolescence.

Emotion regulation skills are another domain of cognitive skills with close ties to executive functions (Ochsner & Gross, 2005) and neural bases in the frontal lobe (Ochsner, Silvers, & Buhle, 2012). Initial findings suggest that depression-related emotion regulation deficits are associated with frontal cortical structure. In psychiatrically healthy 8–12 year old children, smaller grey matter volume in the insula was associated with decreased self-reported emotion regulation skills (Pagliaccio, Luby, Luking, Belden, & Barch, 2014). Additionally, reduced cortical thickness in the ACC is associated with more difficulty managing negative emotions such as sadness in healthy female adolescents at high familial risk for depression (Foland-Ross, Gilbert, et al., 2015). These cross-sectional findings have been replicated in longitudinal designs. Pagliaccio et al. (2014) found that larger insula volumes were positively associated with emotion regulation skills at an 18 month follow up above and

beyond concurrent emotion regulation skills. Emotion regulation skills were also associated with increasing subclinical depressive symptoms over time, but formal tests of mediation were not conducted.

Further evidence for the relationship between cortical structure, cognitive functioning, and depressive symptoms comes from intervention studies targeting executive functioning. In a 15-week creative arts program of a small sample of healthy children (n=29), positive changes in measures of executive function (e.g., Wisconsin Card Sorting Task) and reductions in depressive symptoms following intervention were associated with *increased* cortical thickness in the left postcentral gyrus and superior parietal lobule compared to baseline (Park et al., 2015). These results suggest that cortical structural differences may be plastic in response to intervention.

A recent study by Fradkin and colleagues (2017) examined whether MDD moderates the relationship between cortical structure and cognitive functioning. MDD diagnosis moderated the association between cortical thickness of frontal cortical regions and self-reported impulsivity. Specifically, cortical thickness of the middle frontal gyrus was *positively* associated with impulsivity in healthy adolescents, but frontal cortical thickness was *inversely* associated with impulsivity for youth with MDD. This study suggests that the relationship between cortical structure and neurocognitive outcomes may differ in the context of MDD.

The studies above present a relatively clear pattern of effects in which deficits in cognitive control, emotion regulation, executive functions, and related cognitive risk factors for depression are associated with cortical structural differences also implicated in depression. Furthermore, emerging evidence suggests that resilient cognitive coping styles are associated with *increased* grey matter volume in the ACC (Holz et al., 2016). More studies in larger samples which examine a greater variety of neurocognitive functions will be critical to understanding the associations between brain structure, cognitive functioning, and depression.

Section 4 – Stress: Depressogenic Stressors and Cortical Structure

Associations between cortical structure and depressogenic stressors contribute to additional understanding of the relationship between cortical structure and depression. Stressors experienced both in the prenatal (Figure 1: Path G) and early developmental environments (Figure 1: Path H) are associated with cortical structure, though few studies have been conducted in youth populations. While some of these stressors (child abuse, maltreatment) have been well studied in adult populations, others (e.g. SES, peer victimization) have yet to be explored. The following section presents a selective review of depressogenic stressors and associations with cortical structure.

4.1 – Prenatal Environment.

An emerging body of literature has examined associations between prenatal risk factors for depression and later cortical structure (Figure 1: Path G), with study designs including retrospective cross-sectional and prospective longitudinal designs. Results of prospective

longitudinal studies have identified associations between maternal depressive symptoms during pregnancy and cortical thickness in preschool (2–5 years old; Lebel et al., 2016) and school age children (6–9 years old; Sandman, Buss, Head, & Davis, 2015; El Marroun et al., 2016). Across studies, maternal depressive symptoms during the second trimester, but not the first or third, were inversely associated with cortical thickness in regions of the frontal cortex including the inferior PFC (Lebel et. al, 2016), superior PFC (Sandman et al., 2015; El Marroun et al., 2016), medial OFC (Sandman et al., 2015), frontal pole (Sandman et al., 2015). Furthermore, cortical thickness in these regions has been shown to mediate the relationship between prenatal maternal depressive symptoms and child externalizing, but not internalizing, symptoms (Sandman et al., 2015). The findings highlight the second trimester as a sensitive period for the effects of depression on the developing brain.

Peripartum depressive symptoms have demonstrated mixed associations with offspring cortical thickness, with inverse associations reported for the right superior frontal gyrus (Lebel et al., 2016) and a positive association between antenatal depressive symptoms and thickness in the left caudal middle frontal gyrus (El Marroun et al., 2016). In an isolated study, paternal depression was not significantly associated with offspring brain structure (El Marroun et al., 2016). The specificity of the effects on offspring cortical structure to depressive symptoms experienced by the mother during pregnancy, and particularly the second trimester, confer preliminary evidence for a possible biological or epigenetic mechanism.

In the one study (Jha et al., 2016) examining associations between prenatal exposure to depression and grey matter volume, no differences in grey matter volume at one month postpartum were identified across infants whose mothers experienced no depression, untreated depression, and depression treated with SSRIs during pregnancy. It is important to note that in this study brain structure was assessed in infancy, unlike the above studies in which brain structure was assessed in early or middle childhood.

In addition to prenatal exposure to depressive symptoms, studies in adults using retrospective reports and medical record reviews have documented associations between maternal stress during pregnancy and cortical structure. In adults, maternal stress assessed via retrospective self-reports (Mareckova et al., 2018) and medical record reviews (Favaro, Tenconi, Degortes, Manara, & Santonastaso, 2015) was found to be associated with reduced overall grey matter volume (Mareckova et al., 2018), as well as regional reductions in the frontal lobe (e.g., left dorsolateral PFC, right ACC, right precuneus; Mareckova et al., 2018), and medial temporal lobe (Favaro et al., 2015). Furthermore, reductions in grey matter volume were in turn associated with greater mood dysregulation (Mareckova et al., 2018) and depressive symptoms (Favaro et al., 2015), suggesting that cortical structure may mediate associations between prenatal stress and experience of depressive symptoms in adulthood.

The above studies suggest that exposure to maternal stress and depressive symptoms in utero is associated with cortical thickness and grey matter volume in offspring (Figure 1: Path G). These differences manifest at multiple developmental points, including early and middle childhood. Multiple studies suggest that the impact of depression is most significant during

the second trimester. Paternal depressive symptoms do not demonstrate these associations. However, it is unclear whether exposure to prenatal depression is the only agent of change in these relationships, as other factors present later in development may account for the relationship between prenatal exposure to depression and depressive cortical structural features. Additionally, no prospective studies to date of the effects of prenatal exposure to depressive symptoms on brain structure beyond middle childhood have been conducted; continued study of these effects into adolescence and adulthood are critical to understanding their stability across development.

4.2 – Early Life Environment.

Parenting.—A limited number of studies have examined the effects of negative parenting behaviors on cortical structure in the context of depression. In those that have explored these relationships, results suggest that adolescent children of parents who express infrequent positivity and frequent aggression tend to demonstrate disruptions to cortical and subcortical development and demonstrate greater risk for depression (Schwartz et al., 2017). Additionally, in a sample of pre-teens (11–13 years old), maternal aggressive behavior moderated the association between grey matter volume in the ACC and depressive symptoms such that at low levels of maternal aggression, ACC volumes were associated with depressive symptoms, but at high levels of maternal aggression no associations were observed (Yap et al., 2008). Results of these studies provide preliminary evidence that maladaptive parenting may not only affect cortical development, but may exacerbate risk for depression in the context of the cortical structural features often seen in MDD (e.g., reduced grey matter volume in the ACC).

Early Adversity.—Comparisons of youth who have experienced abuse/maltreatment in childhood and non-maltreated peers have found cortical structural differences including reduced grey matter volume in the OFC (De Brito et al., 2013) and medial temporal lobe (De Brito et al., 2013; Walsh et al., 2014). In longitudinal studies of youth, experience of adverse life events in early childhood (< 6 years old) was associated with reduced grey matter volume in the ACC (Jensen et al., 2015) and inferior frontal gyrus (Luby, Barch, Whalen, Tillman, & Belden, 2017), and increased grey matter volume in the precuneus (Jensen et al., 2015). In adults with MDD, retrospective report of abuse in childhood was associated with reduced grey matter volume in the OFC (Ahn et al., 2016; Saleh et al., 2017; Dannlowski et al., 2012), ACC (Dannlowski et al., 2012; Malykhin, Carter, Hegadoren, Seres, & Coupland, 2012), insula (Ansell, Rando, Tuit, Guarnaccia, & Sinha, 2012; Dannlowski et al., 2012), and frontal cortical regions more broadly (Yang et al., 2017; Frodl, Reinhold, Koutsouleris, Reiser, & Meisenzahl, 2010).

Preliminary studies also suggest that cortical structure may mediate the relationship between early adversity and depression. In a sample of youth at high risk for depression, reduced grey matter volume in the inferior frontal gyrus mediated the relationship between the experience of adverse events in early childhood and the severity of later depressive symptoms (Luby et al., 2017). Conversely, evidence also suggests that depressive symptoms may mediate the association between adversity and brain structure; in Jensen et al. (2015), stressful experiences in the first six years of life predicted internalizing symptoms in

adolescence, which were in turn associated with reduced grey matter volume in the ACC in early adulthood (Jensen et al., 2015). Other studies have failed to identify mediating effects (Kuhn et al., 2016). Thus, the relationship between early adversity, cortical structure, and depression remains poorly understood.

Some evidence suggests that stress and adversity may differentially effect cortical structure across development. In one sample of adolescents, while adversity in early childhood was associated with *decreased* grey matter volume in the medial temporal lobe, experience of negative/stressful life events in adolescence (14–17 years old) was associated with *increased* grey matter volume in the ACC (Walsh et al., 2014). In another sample of adolescents and young adults (17–24 years old), recent stress, but not abuse in childhood, was associated with *reduced* cortical thickness of the of the right rostral ACC (Paquola, Bennett, Hatton, Hermens, & Lagopoulos, 2017). Studies in adults confer additional evidence for early childhood as a critical period for stress exposure (Kuhn et al., 2016). While evidence to date suggests that early childhood events demonstrate effects that are more consistent with cortical structural characteristics of depression, they have also been more thoroughly studied than recent stressors. Continued studies are needed to clarify the effects of environmental stress in difference developmental periods on MDD and cortical structure.

Conclusions.—There is emerging evidence that exposure to environmental stress in childhood is associated with both volumetric and surface-based structural differences that persist into adulthood (Figure 1: Path H). In children, adolescents, and young adults, poor parenting and early childhood adversity demonstrates fairly consistent associations with reduced grey matter volume or cortical thickness in the ACC, OFC, and frontal and temporal cortical regions. In adults, retrospective reports of early childhood adversity also demonstrate fairly consistent associations with depression-related cortical structural outcomes, and are consistent with those seen in children and youth (with more proximal scans and non-retrospective assessment). Stress in adolescence may have different effects on structure than early childhood stress, with early childhood events being both more thoroughly studied and demonstrating effects that are more consistent with depressive cortical structural endophenotypes. Emerging evidence suggests that mediating and moderating relationships between early life stress, cortical structure, and depression likely exist and contribute to the neural and developmental processes underlying emerging depression, but the nature and directionality of these relationships remains to be elucidated. It is important to acknowledge that the impacts of environmental stress/early adversity on brain development has been widely studied, and broader reviews of this area (e.g., McLaughlin, Sheridan, & Lambert, 2014), highlight multiple impacts of adversity beyond the scope of those examined specifically in the context of MDD. Continued exploration of the diverse forms of early life adversity (e.g., socioeconomic status, adoption, parental psychopathology) and their contribution to the neurodevelopment of the neurostructural characteristics of depression is an important area in need of future study.

Section 5: Diathesis – Stress in Action: Interactions between Risk for Depression and Environmental Stressors

The previous two sections have explored the evidence from the literature examining genetic and familial risk factors and stressors to the development of depression and its associated cortical structure. However, there is no one clear risk factor or stressor that results in these outcomes (equifinality), nor are depressive symptomatology or depressive cortical structure the sole outcomes of any of these factors (multifinality). The following section presents a selective review of studies examining the *interaction* between risk factors (e.g., familial, genetic, and cognitive risk) and exposure to stressors (e.g., prenatal exposure to depressive symptoms, early life stress), which may inform *when* and *for whom* these outcomes are most likely to emerge (Figure 1: Path I).

The interaction of genetic risk factors and exposure to maternal depressive symptoms in utero has been found to predict cortical structure in offspring. Qiu and colleagues (2017) examined the interaction of prenatal exposure to depression and genetic risk for depression (indexed through a genomic risk score composed of multiple genetic markers) on cortical structure in 168 Asian and 85 American mother-child dyads. The interaction between maternal depressive symptoms during pregnancy and risk for depression significantly predicted cortical thickness of the OFC such that higher exposure to maternal depression in utero was associated with *increased* thickness of the OFC in infants at high, but not low, genetic risk for depression. These results suggest that the effects of prenatal exposure to depressive symptoms on the developing cortex and future risk for depression in youth may be exacerbated in those who carry high risk variants of genes associated with depression.

The interaction between a number of genetic risk factors and early childhood stress and maltreatment has also been found to predict depression-related cortical structural outcomes. Genes related to the modulation of serotonin (e.g., 5HTTLPR, HTR3A) have been shown to interact with environmental risk factors such as early childhood stress and maltreatment to predict frontal cortical structure in the context of MDD. In adults with MDD, only carriers of the serotonin transporter gene *s* allele showed inverse associations between retrospective report of childhood stress and grey matter volume in the PFC (Frodl, Reinhold, Koutsouleris, Donohoe, et al., 2010a). A similar effect has also been observed for the HTR3A serotonin receptor gene; only carriers of the CC allele who also reported early life stress demonstrated reduced grey matter volume in the frontal cortex (Gatt et al., 2010). BDNF genotype also moderates the relationship between early adversity, depressive symptoms, and cortical structure in adults. Carriers of the Met allele of the BDNF gene who report early life stress have been found to demonstrate *decreased* grey matter volume in the lateral PFC (Gatt et al., 2009) and the ACC (Gerritsen et al., 2012). Other studies have also found that the val/val allele of the BDNF gene is associated with *reduced* cortical thickness in the OFC in the context of early life stress (van Velzen et al., 2016). Evidence that the FKBP5 genotype moderates the association between early life stress and cortical structure has also been found in adults with MDD; only those with the TT genotype demonstrate associations between childhood maltreatment and reduced grey matter volume in the insula (Grabe et al., 2016), ACC (Grabe et al., 2016), and OFC (Tozzi et al., 2018). Finally, familial

risk for depression has also been found to moderate the association between self-reported emotional abuse in early childhood and cortical structure such that adults at high, but not low, familial risk for depression demonstrated inverse associations between emotional abuse and grey matter volume in the dorsolateral PFC, ACC, and medial PFC (Carballedo et al., 2012).

Taken together, these studies confer substantial evidence that genetic and familial risk factors for depression may moderate associations between environmental stressors and the pattern of cortical structural outcomes often seen in MDD. This literature is consistent with a diathesis-stress model, suggesting that carriers of specific genetic variants, as well as individuals at high familial risk for depression, are more likely to experience cortical structural differences and symptoms of MDD in the face of environmental stressors such as abuse or maltreatment. However, most of the existing studies are cross-sectional and in adult populations. It will be critical to continue to examine the interaction of depressive risk and stressors longitudinally, and in child/adolescent populations, to understand these effects in the context of neural development.

Conclusions and Future Directions

Overall, findings in the adult literature provide compelling evidence that depression in adulthood is associated with cortical structure. Though there is considerable heterogeneity in findings, study methodology, and sample characteristics across individual studies, large and comprehensive meta-analyses consistently document *reductions* in cortical grey matter volume and thickness in primarily frontal cortical regions including the OFC, ACC, and variable sub-regions of the PFC (e.g., Schmaal et al., 2017a; Bora et al., 2012; Koolschijn et al., 2009). While individual studies have detected differences across the brain, non-frontal areas of interest that emerge across multiple studies highlight regions including the insula and temporal lobes. These differences emerge when using both volumetric and surface based methods of analysis, but there may be more variability in surface-based characteristics (cortical thickness, surface area).

It is important to consider the variability in findings across grey matter volume, cortical thickness, and cortical surface area in the context of the neurobiological and developmental processes that underlie these metrics. Reductions in grey matter volume observed on an MRI are most commonly understood to reflect increased in synaptic pruning (Gogtay & Thompson, 2010), though it has also been suggested that encroaching myelination of white matter may also contribute to the changes in grey matter volume observed on MRI (Paus, 2005). Furthermore, grey matter volume represents a composite of cortical thickness and surface area, processes that are genetically distinct (Panizzon et al., 2009) and demonstrate different developmental trajectories (Raznahan et al., 2011). Cortical thickness has been understood to more specifically represent neuronal density, while surface area and other morphometric outcomes (e.g., curvature, shape, pose, folding type) describe the degree and pattern of gyrification and expansion of the cortex (Houston, Hertig, & Sowell, 2013). The robust cross sectional finding of reduced cortical thickness and grey matter volume in adults with MDD may indicate increases in synaptic pruning resulting in excessive cortical thinning/grey matter volume loss over time. However, the variability in the

developmental literature, as well as the increased findings related to surface area, suggest that the neurodevelopmental pathways to these outcomes are complex and likely influenced by distinct neurobiological maturation processes.

The past two decades has seen a proliferation of empirical studies examining cortical structural characteristics of depression in *childhood and adolescence*, and reveal an inconsistent set of findings that are complicated by the effects of age, severity, and comorbidity. Longitudinal findings have yet to clarify the directionality or possible causality underlying the relationships between depression and cortical structural outcomes. In general, *earlier* experiences of depression, as well as exposure to early life stressors, seem to be more robustly associated with cortical structure later in development (Figure 1: Path A). However, there is also some, but less robust, evidence that structure predicts depression course and/or onset (Figure 1: Path B). Some studies have also found that the directionality of the relationship between depressive symptoms and cortical structure may differ across age (e.g., Ducharme et al., 2014). Substantial future work will be needed to tease apart the emergence of cortical structural features of depression in the context of typical neurodevelopment and the numerous psychosocial and cognitive factors that are in flux throughout childhood and adolescence.

Familial and genetic risk for depression are also associated with MDD cortical structure endophenotypes (Figure 1: Path C, D), though main effect findings are highly variable. More consistently, familial/genetic risk factors significantly *moderate* associations between cortical structure and depressive symptoms, such that those at higher genetic/familial risk are more likely to demonstrate associations between cortical structure and depressive symptomatology (Figure 1: Path I). Additionally, cortical structural deficits, particularly in the frontal lobe, may confer further vulnerability to future depression via impacts on cognitive and emotion regulation skills that may make it harder for youth to cope effectively with stressors (Figure 1: Path E, F).

Furthermore, exposure to depressogenic environmental stressors including prenatal exposure to depression, poor parenting, and early life adversity are also associated with MDD cortical structure endophenotypes (Figure 1: Path G, H). There is evidence suggesting that genetic and environmental risk factors and environmental stressors likely interact and contribute to the cortical structure brain differences seen in depression. Numerous studies in adults with early child abuse and genetic and familial risk have begun to elucidate one way these mechanisms influence the relationship between brain structure and depression. However, studies in *youth* are needed to test the interplay of these factors longitudinally in samples of both healthy and depressed youth. Examination of dimensional as well as categorical measures of depression and associated constructs is also necessary to clarify these complex and dynamic associations, which likely differ across stages of neural, cognitive, and psychosocial development.

Thus, vulnerabilities to depression may be independently associated with depressive cortical structural features (e.g., healthy but high-risk youth still show similar features), but the experience of depressogenic stressors and/or depression symptoms may exacerbate cortical structural outcomes, possibly by interrupting typical cortical development or stimulating

excessive cortical thinning or gray matter volume loss. Biological processes such as cortisol (Treadway et al., 2009) or inflammation (Harrison, 2017) which may explain associations between MDDs and/or environmental stressors and structure should be a focus of future studies.

It is important to acknowledge that while the current review focused on depression, the pathways described may be transdiagnositically relevant. Diathesis-stress models have been broadly applied to understand the developmental processes contributing to multiple domains of psychopathology including schizophrenia (Pruessner, Cullen, Aas, & Walker, 2017) and anxiety (Gazelle & Ladd, 2003). Furthermore, consistent with the principle of multifinality, many of the risk and stress processes that were identified to be relevant to the cortical structural changes seen in MDD are additionally associated with multiple adverse outcomes and psychological symptoms/disorders (e.g., early life stress: Hoppen & Chandler, 2018; cognitive control: McTeague, Goodkind, & Etkin, 2016). Finally, while there is some evidence to suggest from case-comparison studies that the neurostructural characteristics associated with MDD are distinct from other DSM diagnoses (e.g., MacMaster et al., 2014; Fallucca et al., 2011), recent research examining associations between cortical structure and hierarchical models of psychopathology suggest that reductions in grey matter volume (Snyder et al., 2017) and cortical thickness (Romer et al., 2020) are associated with a general psychopathology factor. Continued study is needed to parse the transdiagnostic and domain specific effects and processes that contribute to the neurostructural changes associated with depression and other forms of psychopathology.

Additionally, this review focused solely on associations between cortical structure and depression. However, associations between subcortical development and depression have also been well established, and should be considered in order to fully understand the neurodevelopmental processes underlying depression. Evidence also suggests that the synchrony of cortical and subcortical development throughout in adolescence has important consequences for emerging depression. Vijayakumar et al. (2017) examined associations between change in amygdala volume and cortical thinning in a sample of adolescents (11–20 years old) who underwent three assessments of depressive symptoms and brain structure. This study found that positive maturational coupling of the right amygdala and prefrontal and temporal cortical thickness was associated with reductions in depressive symptoms over time. These findings highlight the need to consider the synchrony of development across multiple neural systems when trying to understand the emergence of depression in the context of neural maturation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Ahn SJ, Kyeong S, Suh SH, Kim J-J, Chung T-S, & Seok J-H (2016). What is the impact of child abuse on gray matter abnormalities in individuals with major depressive disorder: a case control study. BMC Psychiatry, 16(1), 397. [PubMed: 27842522]

Aldao A, Nolen-Hoeksema S, & Schweizer S. (2010). Emotion-regulation strategies across psychopathology: A meta-analytic review. Clinical Psychology Review, 30(2), 217–237. [PubMed: 20015584]

Alemany S, Mas A, Goldberg X, Falcón C, Fatjó-Vilas M, Arias B, ... & Fañanás L. (2013). Regional gray matter reductions are associated with genetic liability for anxiety and depression: an MRI twin study. Journal of Affective Disorders, 149(1–3), 175–181. [PubMed: 23433857]

American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub.

Amico F, Meisenzahl E, Koutsouleris N, Reiser M, Moller H-J, & Frodl T. (2011). Structural MRI correlates for vulnerability and resilience to major depressive disorder. Journal of Psychiatry & Neuroscience, 36(1), 15–22. [PubMed: 20964952]

Angold A, Costello EJ, & Erkanli A. (1999). Comorbidity. Journal of Child Psychology and Psychiatry, 40(1), 57–87. [PubMed: 10102726]

Ansell EB, Rando K, Tuit K, Guarnaccia J, & Sinha R. (2012). Cumulative adversity and smaller gray matter volume in medial prefrontal, anterior cingulate, and insula regions. Biological Psychiatry, 72(1), 57–64. [PubMed: 22218286]

Arnone D, Job D, Selvaraj S, Abe O, Amico F, Cheng Y, … McIntosh AM (2016). Computational meta-analysis of statistical parametric maps in major depression. Human Brain Mapping, 37(4), 1393–1404. [PubMed: 26854015]

Beevers CG (2005). Cognitive vulnerability to depression: A dual process model. Clinical Psychology Review, 25(7), 975–1002. [PubMed: 15905008]

Belden AC, Barch DM, Oakberg TJ, April LM, Harms MP, Botteron KN, & Luby JL (2015). Anterior insula volume and guilt: Neurobehavioral markers of recurrence after early childhood major depressive disorder. JAMA Psychiatry, 72(1), 40–48. [PubMed: 25390502]

Boes AD, McCormick LM, Coryell WH, & Nopoulos P (2008). Rostral anterior cingulate cortex volume correlates with depressed mood in normal healthy children. Biological Psychiatry, 63(4), 391–397. [PubMed: 17916329]

Bora E, Harrison BJ, Davey CG, Yucel M, & Pantelis C. (2012). Meta-analysis of volumetric abnormalities in cortico-striatal-pallidal-thalamic circuits in major depressive disorder. Psychological Medicine, 42(4), 671–681. [PubMed: 21910935]

Bos MGN, Peters S, van de Kamp FC, Crone EA, & Tamnes CK (2018). Emerging depression in adolescence coincides with accelerated frontal cortical thinning. Journal of Child Psychology and Psychiatry, 59(9), 994–1002. [PubMed: 29577280]

Botteron KN, Raichle ME, Drevets WC, Heath AC, & Todd RD (2002). Volumetric reduction in left subgenual prefrontal cortex in early onset depression. Biological Psychiatry, 51(4), 342–344. [PubMed: 11958786]

Bush G, Luu P, & Posner MI (2000). Cognitive and emotional influences in anterior cingulate cortex. Trends in Cognitive Sciences, 4(6), 215–222. [PubMed: 10827444]

Busso DS, McLaughlin KA, Brueck S, Peverill M, Gold AL, & Sheridan MA (2017). Child Abuse, Neural Structure, and Adolescent Psychopathology: A Longitudinal Study. Journal of the American Academy of Child and Adolescent Psychiatry, 56(4), 321–328. [PubMed: 28335876]

Carballedo A, Lisiecka D, Fagan A, Saleh K, Ferguson Y, Connolly G, … Frodl T. (2012). Early life adversity is associated with brain changes in subjects at family risk for depression. Journal of Biological Psychiatry, 13(8), 569–578.

Chen H-H, Rosenberg DR, MacMaster FP, Easter PC, Caetano SC, Nicoletti M, … Soares JC (2008). Orbitofrontal cortex volumes in medication naive children with major depressive disorder: A magnetic resonance imaging study. Journal of Child and Adolescent Psychopharmacology, 18(6), 551–556. [PubMed: 19108659]

Curtis AC (2015). Defining adolescence. Journal of Adolescent and Family Health, 7(2), 2.

Cyranowski JM, Frank E, Young E, & Shear MK (2000). Adolescent Onset of the Gender Difference in Lifetime Rates of Major Depression: A Theoretical Model. Archives of General Psychiatry, 57(1), 21–27. [PubMed: 10632229]

Dalley JW, Everitt BJ, & Robbins TW (2011). Impulsivity, Compulsivity, and Top-Down Cognitive Control. Neuron, 69(4), 680–694. [PubMed: 21338879]

Dannlowski U, Stuhrmann A, Beutelmann V, Zwanzger P, Lenzen T, Grotegerd D, … Kugel H. (2012). Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. Biological Psychiatry, 71(4), 286–293. [PubMed: 22112927]

De Brito SA, Viding E, Sebastian CL, Kelly PA, Mechelli A, Maris H, & McCrory EJ (2013). Reduced orbitofrontal and temporal grey matter in a community sample of maltreated children. Journal of Child Psychology and Psychiatry, 54(1), 105–112. [PubMed: 22880630]

Drevets WC (2007). Orbitofrontal Cortex Function and Structure in Depression. Annals of the New York Academy of Sciences, 1121(1), 499–527. [PubMed: 17872395]

Du M, Liu J, Chen Z, Huang X, Li J, Kuang W, … Gong Q. (2014). Brain grey matter volume alterations in late-life depression. Journal of Psychiatry, 39(6), 397–406.

Du M-Y, Wu Q-Z, Yue Q, Li J, Liao Y, Kuang W-H, … Gong Q-Y (2012). Voxelwise meta-analysis of gray matter reduction in major depressive disorder. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 36(1), 11–16. [PubMed: 22001316]

Ducharme S, Albaugh MD, Hudziak JJ, Botteron KN, Nguyen T-V, Truong C, … Karama S. (2014). Anxious/depressed symptoms are linked to right ventromedial prefrontal cortical thickness maturation in healthy children and young adults. Cerebral Cortex, 24(11), 2941–2950. [PubMed: 23749874]

Duncan J, & Owen AM (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends in Neurosciences, 23(10), 475–483. [PubMed: 11006464]

Dunn EC, Brown RC, Dai Y, Rosand J, Nugent NR, Amstadter AB, & Smoller JW (2015). Genetic determinants of depression: Recent findings and future directions. Harvard Review of Psychiatry, 23(1), 1–18. [PubMed: 25563565]

Egger HL, & Angold A. (2006). Common emotional and behavioral disorders in preschool children: presentation, nosology, and epidemiology. Journal of Child Psychology & Psychiatry, 47(3/4), 313–337. [PubMed: 16492262]

El Marroun H, Tiemeier H, Muetzel RL, Thijssen S, van der Knaap NJF, Jaddoe VWV, … White TJH (2016). Prenatal exposure to maternal and paternal depressive symptoms and brain morphology: A population-based prospective neuroimaging study in young children. Depression and Anxiety, 33(7), 658–666. [PubMed: 27163186]

Fallucca E, MacMaster FP, Haddad J, Easter P, Dick R, May G, … Rosenberg DR (2011). Distinguishing between major depressive disorder and obsessive-compulsive disorder in children by measuring regional cortical thickness. Archives of General Psychiatry, 68(5), 527–533. [PubMed: 21536980]

Favaro A, Tenconi E, Degortes D, Manara R, & Santonastaso P. (2015). Neural correlates of prenatal stress in young women. Psychological Medicine, 45(12), 2533–2543. [PubMed: 25786412]

Foland-Ross LC, Behzadian N, LeMoult J, & Gotlib IH (2016). Concordant patterns of brain structure in mothers with recurrent depression and their never-depressed daughters. Developmental Neuroscience, 38(2), 115–123. [PubMed: 27198667]

Foland-Ross LC, Gilbert BL, Joormann J, & Gotlib IH (2015). Neural markers of familial risk for depression: An investigation of cortical thickness abnormalities in healthy adolescent daughters of mothers with recurrent depression. Journal of Abnormal Psychology, 124(3), 476–485. [PubMed: 25894441]

Foland-Ross LC, Sacchet MD, Prasad G, Gilbert B, Thompson PM, & Gotlib IH (2015). Cortical thickness predicts the first onset of major depression in adolescence. Journal of Developmental Neuroscience, 125–131.

Fradkin Y, Khadka S, Bessette KL, & Stevens MC (2017). The relationship of impulsivity and cortical thickness in depressed and non-depressed adolescents. Brain Imaging and Behavior, 11(5), 1515–1525. [PubMed: 27738995]

Franić S, Middeldorp CM, Dolan CV, Ligthart L, & Boomsma DI (2010). Childhood and adolescent anxiety and depression: beyond heritability. Journal of the American Academy of Child & Adolescent Psychiatry, 49(8), 820–829. [PubMed: 20643315]

Frodl T, Reinhold E, Koutsouleris N, Donohoe G, Bondy B, Reiser M, … Meisenzahl EM (2010). Childhood stress, serotonin transporter gene and brain structures in major depression. Neuropsychopharmacology, 35(6), 1383–1390. [PubMed: 20147891]

Frodl T, Reinhold E, Koutsouleris N, Reiser M, & Meisenzahl EM (2010). Interaction of childhood stress with hippocampus and prefrontal cortex volume reduction in major depression. Journal of Psychiatric Research, 44(13), 799–807. [PubMed: 20122698]

Gatt JM, Nemeroff CB, Dobson-Stone C, Paul RH, Bryant RA, Schofield PR, … Williams LM (2009). Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. Molecular Psychiatry, 14(7), 681–695. [PubMed: 19153574]

Gatt Justine M., Williams LM, Schofield PR, Dobson-Stone C, Paul RH, Grieve SM, … Nemeroff CB (2010). Impact of the HTR3A gene with early life trauma on emotional brain networks and depressed mood. Depression and Anxiety, 27(8), 752–759. [PubMed: 20694966]

Gazelle H, & Ladd GW (2003). Anxious solitude and peer exclusion: A diathesis–stress model of internalizing trajectories in childhood. Child Development, 74(1), 257–278. [PubMed: 12625449]

George MS, Ketter TA, & Post RM (1994). Prefrontal cortex dysfunction in clinical depression. Depression, 2(2), 59–72.

Gerritsen L, Tendolkar I, Franke B, Vasquez AA, Kooijman S, Buitelaar J, … Rijpkema M. (2012). BDNF Val66Met genotype modulates the effect of childhood adversity on subgenual anterior cingulate cortex volume in healthy subjects. Molecular Psychiatry, 17(6), 597–603. [PubMed: 21577214]

Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, … Thompson PM (2004). Dynamic mapping of human cortical development during childhood through early adulthood. Proceedings of the National Academy of Sciences, 101(21), 8174–8179.

Gogtay N, & Thompson PM (2010). Mapping gray matter development: implications for typical development and vulnerability to psychopathology. Brain and cognition, 72(1), 6–15. [PubMed: 19796863]

Goodman M, Hazlett EA, Avedon JB, Siever DR, Chu K-W, & New AS (2011). Anterior cingulate volume reduction in adolescents with borderline personality disorder and co-morbid major depression. Journal of Psychiatric Research, 45(6), 803–807. [PubMed: 21145068]

Grabe HJ, Wittfeld K, Van der Auwera S, Janowitz D, Hegenscheid K, Habes M, … Hosten N. (2016). Effect of the interaction between childhood abuse and rs1360780 of the FKBP5 gene on gray matter volume in a general population sample. Human Brain Mapping, 37(4), 1602–1613. [PubMed: 26813705]

Hagan CC, Graham JME, Tait R, Widmer B, van Nieuwenhuizen AO, Ooi C, … Suckling J. (2015). Adolescents with current major depressive disorder show dissimilar patterns of age-related differences in ACC and thalamus. Neuroimage-Clinical, 7, 391–399. [PubMed: 25685707]

Hankin BL, Abramson LY, Moffitt TE, Silva PA, McGee R, & Angell KE (1998). Development of depression from preadolescence to young adulthood: Emerging gender differences in a 10-year longitudinal study. Journal of Abnormal Psychology, 107(1), 128–140. [PubMed: 9505045]

Harrison NA (2017). Brain Structures Implicated in Inflammation-Associated Depression. Current Topics in Behavioral Neurosciences, 31, 221–248. [PubMed: 27272069]

Hirakawa H, Akiyoshi J, Muronaga M, Tanaka Y, Ishitobi Y, Inoue A, … Kawano Y. (2016). FKBP5 is associated with amygdala volume in the human brain and mood state: A voxel-based morphometry (VBM) study. Journal of Psychiatry in Clinical Practice, 20(2), 106–115.

Holz NE, Boecker R, Jennen-Steinmetz C, Buchmann AF, Blomeyer D, Baumeister S, … Laucht M. (2016). Positive coping styles and perigenual ACC volume: Two related mechanisms for conferring resilience? Social Cognitive and Affective Neuroscience, 11(5), 813–820. [PubMed: 26743466]

Hoppen TH, & Chalder T. (2018). Childhood adversity as a transdiagnostic risk factor for affective disorders in adulthood: a systematic review focusing on biopsychosocial moderating and mediating variables. Clinical Psychology Review, 65, 81–151. [PubMed: 30189342]

Houston SM, Herting MM, & Sowell ER (2013). The neurobiology of childhood structural brain development: conception through adulthood. In The Neurobiology of Childhood (pp. 3–17). Springer, Berlin, Heidelberg.

Jaworska N, MacMaster FP, Gaxiola I, Cortese F, Goodyear B, & Ramasubbu R. (2014). A preliminary study of the influence of age of onset and childhood trauma on cortical thickness in major depressive disorder. BioMed Research International, 2014, 410472. [PubMed: 24734233]

Jensen SKG, Dickie EW, Schwartz DH, Evans CJ, Dumontheil I, Paus T, & Barker ED (2015). Effect of Early Adversity and Childhood Internalizing Symptoms on Brain Structure in Young Men. JAMA Pediatrics, 169(10), 938–946. [PubMed: 26280410]

Jha SC, Meltzer-Brody S, Steiner RJ, Cornea E, Woolson S, Ahn M, … Knickmeyer RC (2016). Antenatal depression, treatment with selective serotonin reuptake inhibitors, and neonatal brain structure: A propensity-matched cohort study. Psychiatry Research: Neuroimaging, 43–53.

Kaltenboeck A, & Harmer C. (2018). The neuroscience of depressive disorders: A brief review of the past and some considerations about the future. Brain and Neuroscience Advances, 2, 239821281879926.

Koenig J, Schreiner MW, Klimes-Dougan B, Ubani B, Mueller B, Kaess M, & Cullen KR (2018). Brain structural thickness and resting state autonomic function in adolescents with major depression. Social Cognitive and Affective Neuroscience, 13(7), 741–753. [PubMed: 29939340]

Koolschijn PCMP, van Haren NEM, Lensvelt-Mulders GJLM, Pol HEH, & Kahn RS (2009). Brain volume abnormalities in major depressive disorder: A meta-analysis of magnetic resonance imaging studies. Human Brain Mapping, 30(11), 3719–3735. [PubMed: 19441021]

Kuhn M, Scharfenort R, Schumann D, Schiele MA, Munsterkotter AL, Deckert J, … Lonsdorf TB (2016). Mismatch or allostatic load? Timing of life adversity differentially shapes gray matter volume and anxious temperament. Social Cognitive and Affective Neuroscience, 11(4), 537–547. [PubMed: 26568620]

Lai C-H (2013). Gray matter volume in major depressive disorder: A meta-analysis of voxel-based morphometry studies. Psychiatry Research: Neuroimaging, 211(1), 37–46.

Lebel C, Walton M, Letourneau N, Giesbrecht GF, Kaplan BJ, & Dewey D. (2016). Prepartum and postpartum maternal depressive symptoms are related to children's brain structure in preschool. Biological Psychiatry, 80(11), 859–868. [PubMed: 26822800]

Little K, Olsson CA, Whittle S, Youssef GJ, Byrne ML, Simmons JG, … Allen NB (2014). Association between serotonin transporter genotype, brain structure and adolescent-onset major depressive disorder: a longitudinal prospective study. Translational Psychiatry, 4.

Luby JL, Agrawal A, Belden A, Whalen D, Tillman R, & Barch DM (2018). Developmental Trajectories of the Orbitofrontal Cortex and Anhedonia in Middle Childhood and Risk for Substance Use in Adolescence in a Longitudinal Sample of Depressed and Healthy Preschoolers. The American Journal of Psychiatry, appiajp201817070777.

Luby JL, Barch D, Whalen D, Tillman R, & Belden A. (2017). Association Between Early Life Adversity and Risk for Poor Emotional and Physical Health in Adolescence A Putative Mechanistic Neurodevelopmental Pathway. JAMA Pediatrics, 171(12), 1168–1175. [PubMed: 29084329]

Luby JL, Belden AC, Jackson JJ, Lessov-Schlaggar CN, Harms MP, Tillman R, … Barch DM (2016). Early childhood depression and alterations in the trajectory of gray matter maturation in middle childhood and early adolescence. JAMA Psychiatry, 73(1), 31–38. [PubMed: 26676835]

MacMaster FP, Carrey N, Langevin LM, Jaworska N, & Crawford S. (2014). Disorder-specific volumetric brain difference in adolescent major depressive disorder and bipolar depression. Brain Imaging and Behavior, 8(1), 119–127. [PubMed: 24158718]

Malykhin NV, Carter R, Hegadoren KM, Seres P, & Coupland NJ (2012). Frontolimbic volumetric changes in major depressive disorder. Journal of Affective Disorders, 136(3), 1104–1113. [PubMed: 22134041]

Mareckova K, Klasnja A, Bencurova P, Andryskova L, Brazdil M, & Paus T. (2018). Prenatal Stress, Mood, and Gray Matter Volume in Young Adulthood. Cerebral Cortex 29(3), 1244–1250.

Marrus N, Belden A, Nishino T, Handler T, Ratnanather JT, Miller M, … Botteron K. (2015). Ventromedial prefrontal cortex thinning in preschool-onset depression. Journal of Affective Disorders, 180, 79–86. [PubMed: 25881284]

McLaughlin KA, Sheridan MA, & Lambert HK (2014). Childhood adversity and neural development: deprivation and threat as distinct dimensions of early experience. Neuroscience & Biobehavioral Reviews, 47, 578–591. [PubMed: 25454359]

McLellan Q, Wilkes TC, Swansburg R, Jaworska N, Langevin LM, & MacMaster FP (2018). History of suicide attempt and right superior temporal gyrus volume in youth with treatment-resistant major depressive disorder. Journal of Affective Disorders, 239, 291–294. [PubMed: 30031248]

McTeague LM, Goodkind MS, & Etkin A. (2016). Transdiagnostic impairment of cognitive control in mental illness. Journal of psychiatric research, 83, 37–46. [PubMed: 27552532]

Merikangas KR, He J, Burstein M, Swanson SA, Avenevoli S, Cui L, … Swendsen J. (2010). Lifetime Prevalence of Mental Disorders in US Adolescents: Results from the National Comorbidity Study-Adolescent Supplement (NCS-A). Journal of the American Academy of Child and Adolescent Psychiatry, 49(10), 980–989. [PubMed: 20855043]

Merz EC, He X, & Noble KG (2018). Anxiety, depression, impulsivity, and brain structure in children and adolescents. NeuroImage-Clinical, 20, 243–251. [PubMed: 30094172]

Muetzel RL, Blanken LME, van der Ende J, El Marroun H, Shaw P, Sudre G, … White T. (2018). Tracking Brain Development and Dimensional Psychiatric Symptoms in Children: A Longitudinal Population-Based Neuroimaging Study. American Journal of Psychiatry, 175(1), 54–62.

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 [PubMed: 19621072]

Nickson T, Chan SWY, Papmeyer M, Romaniuk L, Macdonald A, Stewart T, … Whalley HC (2016). Prospective longitudinal voxel-based morphometry study of major depressive disorder in young individuals at high familial risk. Psychological Medicine, 46(11), 2351–2361. [PubMed: 27282778]

Nolan CL, Moore GJ, Madden R, Farchione T, Bartoi M, Lorch E, … Rosenberg DR (2002). Prefrontal cortical volume in childhood-onset major depression: Preliminary findings. Archives of General Psychiatry, 59(2), 173–179. [PubMed: 11825139]

Ochsner KN, & Gross JJ (2005). The cognitive control of emotion. Trends in Cognitive Sciences, 9(5), 242–249. [PubMed: 15866151]

Ochsner KN, Silvers JA, & Buhle JT (2012). Functional imaging studies of emotion regulation: A synthetic review and evolving model of the cognitive control of emotion. Annals of the New York Academy of Sciences, 1251, E1–24. [PubMed: 23025352]

Opel N, Zwanzger P, Redlich R, Grotegerd D, Dohm K, Arolt V, … Dannlowski U. (2016). Differing brain structural correlates of familial and environmental risk for major depressive disorder revealed by a combined VBM/pattern recognition approach. Psychological Medicine, 46(2), 277–290. [PubMed: 26355299]

Ozalay O, Aksoy B, Tunay S, Simsek F, Chandhoke S, Kitis O, … Gonul AS (2016). Cortical thickness and VBM in young women at risk for familial depression and their depressed mothers with positive family history. Psychiatry Research: Neuroimaging, 1–9.

Pagliaccio D, Luby JL, Luking KR, Belden AC, & Barch DM (2014). Brain-behavior relationships in the experience and regulation of negative emotion in healthy children: Implications for risk for childhood depression. Development and Psychopathology, 4(2), 1289–1303.

Pagliaccio D, Pine DS, Barch DM, Luby JL, & Leibenluft E. (2018). Irritability Trajectories, Cortical Thickness, and Clinical Outcomes in a Sample Enriched for Preschool Depression. Journal of the American Academy of Child and Adolescent Psychiatry, 57(5), 336+. [PubMed: 29706163]

Panizzon MS, Fennema-Notestine C, Eyler LT, Jernigan TL, Prom-Wormley E, Neale M, ... & Xian H. (2009). Distinct genetic influences on cortical surface area and cortical thickness. Cerebral cortex, 19(11), 2728–2735. [PubMed: 19299253]

Pannekoek JN, van der Werff SJA, van den Bulk BG, van Lang NDJ, Rombouts SARB, van Buchem MA, … van der Wee NJA (2014). Reduced anterior cingulate gray matter volume in treatment-naive clinically depressed adolescents. NeuroImage-Clinical, 4, 336–342. [PubMed: 24501702]

Papmeyer M, Giles S, Sussmann JE, Kielty S, Stewart T, Lawrie SM, … McIntosh AM (2015). Cortical thickness in individuals at high familial risk of mood disorders as they develop major depressive disorder. Biological Psychiatry, 78(1), 58–66. [PubMed: 25534753]

Paquola C, Bennett MR, Hatton SN, Hermens DF, & Lagopoulos J. (2017). Utility of the cumulative stress and mismatch hypotheses in understanding the neurobiological impacts of childhood abuse and recent stress in youth with emerging mental disorder. Human Brain Mapping, 38(5), 2709–2721. [PubMed: 28256777]

Park S, Lee J-M, Baik Y, Kim K, Yun HJ, Kwon H, … Kim B-N (2015). A preliminary study of the effects of an arts education program on executive function, behavior, and brain structure in a sample of nonclinical school-aged children. Journal of Child Neurology, 30(13), 1757–1766. [PubMed: 25862737]

Paus T. (2005). Mapping brain maturation and cognitive development during adolescence. Trends in Cognitive Sciences, 9(2), 60–68. [PubMed: 15668098]

Peng W, Chen Z, Yin L, Jia Z, & Gong Q. (2016). Essential brain structural alterations in major depressive disorder: A voxel-wise meta-analysis on first episode, medication-naive patients. Journal of Affective Disorders, 114–123.

Peper JS, Brouwer RM, Boomsma DI, Kahn RS, & Pol HEH (2007). Genetic influences on human brain structure: A review of brain imaging studies in twins. Human Brain Mapping, 28(6), 464–473. [PubMed: 17415783]

Pereira LP, Kohler CA, Stubbs B, Miskowiak KW, Morris G, de Freitas BP, … Carvalho AF (2018). Imaging genetics paradigms in depression research: Systematic review and meta-analysis. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 102–113.

Peterson BS, Warner V, Bansal R, Zhu H, Hao X, Liu J, … Weissman MM (2009). Cortical thinning in persons at increased familial risk for major depression. PNAS Proceedings of the National Academy of Sciences of the United States of America, 106(15), 6273–6278. [PubMed: 19329490]

Pigoni A, Delvecchio G, Altamura AC, Soares JC, Fagnani C, & Brambilla P. (2018). The role of genes and environment on brain alterations in Major Depressive Disorder: A review of twin studies: Special Section on “Translational and Neuroscience Studies in Affective Disorders”. Journal of Affective Disorders, 234, 346–350. [PubMed: 29100658]

Pruessner M, Cullen AE, Aas M, & Walker EF (2017). The neural diathesis-stress model of schizophrenia revisited: an update on recent findings considering illness stage and neurobiological and methodological complexities. Neuroscience & Biobehavioral Reviews, 73, 191–218. [PubMed: 27993603]

Qiu A, Shen M, Buss C, Chong Y-S, Kwek K, Saw S-M, … Meaney MJ (2017). Effects of antenatal maternal depressive symptoms and socio-economic status on neonatal brain development are modulated by genetic risk. Cerebral Cortex, 27(5), 3080–3092. [PubMed: 28334351]

Ramezani M, Johnsrude I, Rasoulian A, Bosma R, Tong R, Hollenstein T, … Abolmaesumi P. (2014). Temporal-lobe morphology differs between healthy adolescents and those with early-onset of depression. NeuroImage-Clinical, 6, 145–155. [PubMed: 25379426]

Rao S, Yao Y, Ryan J, Li T, Wang D, Zheng C, … Xu Q. (2016). Common variants in FKBP5 gene and major depressive disorder (MDD) susceptibility: a comprehensive meta-analysis. Scientific Reports, 6, 32687. [PubMed: 27601205]

Raznahan A, Shaw P, Lalonde F, Stockman M, Wallace GL, Greenstein D, ... & Giedd JN (2011). How does your cortex grow?. Journal of Neuroscience, 31(19), 7174–7177. [PubMed: 21562281]

Redlich R, Opel N, Burger C, Dohm K, Grotegerd D, Forster K, … Dannlowski U. (2018). The Limbic System in Youth Depression: Brain Structural and Functional Alterations in Adolescent In-patients with Severe Depression. Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology, 43(3), 546–554. [PubMed: 29039414]

Reynolds S, Carrey N, Jaworska N, Langevin LM, Yang X-R, & MacMaster FP (2014). Cortical thickness in youth with major depressive disorder. BMC Psychiatry, 14.

Risch N, Herrell R, Lehner T, Liang K-Y, Eaves L, Hoh J, … Merikangas KR (2009). Interaction Between the Serotonin Transporter Gene (5-HTTLPR), Stressful Life Events, and Risk of Depression. JAMA : The Journal of the American Medical Association, 301(23), 2462–2471. [PubMed: 19531786]

Romer AL, Elliott ML, Knodt AR, Sison ML, Ireland D, Houts R, ... & Moffitt TE (2019). A pervasively thinner neocortex is a transdiagnostic feature of general psychopathology. BioRxiv, 788232.

Saleh A, Potter GG, McQuoid DR, Boyd B, Turner R, MacFall JR, & Taylor WD (2017). Effects of early life stress on depression, cognitive performance and brain morphology. Psychological Medicine, 47(1), 171–181. [PubMed: 27682320]

Sandman CA, Buss C, Head K, & Davis EP (2015). Fetal Exposure to Maternal Depressive Symptoms Is Associated With Cortical Thickness in Late Childhood. Biological Psychiatry, 77(4), 324–334. [PubMed: 25129235]

Schmaal L, Hibar DP, Samann PG, Hall GB, Baune BT, Jahanshad N, … Veltman DJ (2017a). Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA Major Depressive Disorder Working Group. Molecular Psychiatry, 22(6), 900–909. [PubMed: 27137745]

Schmaal L, Hibar DP, Sämann PG, Hall GB, Baune BT, Jahanshad N, ... & Vernooij MW (2017). Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA Major Depressive Disorder Working Group. Molecular psychiatry, 22(6), 900–909. [PubMed: 27137745]

Schmaal Lianne, Yucel M, Ellis R, Vijayakumar N, Simmons JG, Allen NB, & Whittle S. (2017b). Brain structural signatures of adolescent depressive symptom trajectories: A longitudinal magnetic resonance imaging study. Journal of the American Academy of Child, 56(7), 593–601.

Schwartz OS, Simmons JG, Whittle S, Byrne ML, Yap MBH, Sheeber LB, & Allen NB (2017). Affective parenting behaviors, adolescent depression, and brain development: A review of findings from the orygen adolescent development study. Child Development Perspectives, 11(2), 90–96.

Shad MU, Muddasani S, & Rao U. (2012). Gray matter differences between healthy and depressed adolescents: a voxel-based morphometry study. Journal of Child and Adolescent Psychopharmacology, 22(3), 190–197. [PubMed: 22537357]

Shen Y, Yao J, Jiang X, Zhang L, Xu L, Feng R, … Chen W. (2015). Sub-hubs of baseline functional brain networks are related to early improvement following two-week pharmacological therapy for major depressive disorder. Human Brain Mapping, 36(8), 2915–2927. [PubMed: 25930660]

Snyder HR (2013). Major Depressive Disorder is Associated with Broad Impairments on Neuropsychological Measures of Executive Function: A Meta-Analysis and Review. Psychological Bulletin, 139(1), 81–132. [PubMed: 22642228]

Snyder HR, Hankin BL, Sandman CA, Head K, & Davis EP (2017). Distinct patterns of reduced prefrontal and limbic gray matter volume in childhood general and internalizing psychopathology. Clinical Psychological Science, 5(6), 1001–1013. [PubMed: 29399423]

Steingard RJ, Renshaw PF, Yurgelun-Todd D, Appelmans KE, Lyoo IK, Shorrock KL, … Barnes P. (1996). Structural abnormalities in brain magnetic resonance images of depressed children. Journal of the American Academy of Child and Adolescent Psychiatry, 35(3), 307–311. [PubMed: 8714318]

Suh JS, Schneider MA, Minuzzi L, MacQueen GM, Strother SC, Kennedy SH, & Frey BN (2019). Cortical thickness in major depressive disorder: A systematic review and meta-analysis. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 88, 287–302. [PubMed: 30118825]

Tozzi L, Farrell C, Booij L, Doolin K, Nemoda Z, Szyf M, … Frodl T. (2018). Epigenetic Changes of FKBP5 as a Link Connecting Genetic and Environmental Risk Factors with Structural and Functional Brain Changes in Major Depression. Neuropsychopharmacology, 43(5), 1138–1145. [PubMed: 29182159]

Treadway MT, Grant MM, Ding Z, Hollon SD, Gore JC, & Shelton RC (2009). Early adverse events, HPA activity and rostral anterior cingulate volume in MDD. PloS One, 4(3), e4887. [PubMed: 19325704]

Truong W, Minuzzi L, Soares CN, Frey BN, Evans AC, MacQueen GM, & Hall GBC (2013). Changes in cortical thickness across the lifespan in major depressive disorder. Psychiatry Research: Neuroimaging, 214(3), 204–211.

van Velzen LS, Schmaal L, Jansen R, Milaneschi Y, Opmeer EM, Elzinga BM, … Penninx BWJH (2016). Effect of childhood maltreatment and brain-derived neurotrophic factor on brain morphology. Social Cognitive and Affective Neuroscience, 11(11), 1841–1852. [PubMed: 27405617]

Verhagen M, van der Meij A, van Deurzen P. a. M., Janzing JGE, Arias-Vásquez A, Buitelaar JK, & Franke B. (2010). Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: effects of gender and ethnicity. Molecular Psychiatry, 15(3), 260–271. [PubMed: 18852698]

Vijayakumar N, Allen NB, Dennison M, Byrne ML, Simmons JG, & Whittle S. (2017). Cortico-amygdalar maturational coupling is associated with depressive symptom trajectories during adolescence. NeuroImage, 403–411.

Vijayakumar N, Mills KL, Alexander-Bloch A, Tamnes CK, & Whittle S. (2018). Structural brain development: A review of methodological approaches and best practices. Developmental Cognitive Neuroscience, 33, 129–148. [PubMed: 29221915]

Vijayakumar N, Whittle S, Dennison M, Yuecel M, Simmons J, & Allen NB (2014). Development of temperamental effortful control mediates the relationship between maturation of the prefrontal cortex and psychopathology during adolescence: A 4-year longitudinal study. Developmental Cognitive Neuroscience, 9, 30–43. [PubMed: 24486655]

Vulser H, Lemaitre H, Artiges E, Miranda R, Penttila J, Struve M, … Paillere-Martinot M-L (2015). Subthreshold depression and regional brain volumes in young community adolescents. Journal of the American Academy of Child and Adolescent Psychiatry, 54(10), 832–840. [PubMed: 26407493]

Walsh ND, Dalgleish T, Lombardo MV, Dunn VJ, Van Harmelen A-L, Ban M, & Goodyer IM (2014). General and specific effects of early-life psychosocial adversities on adolescent grey matter volume. NeuroImage-Clinical, 4, 308–318. [PubMed: 25061568]

Wang W, Zhao Y, Hu X, Huang X, Kuang W, Lui S, … Gong Q. (2017). Conjoint and dissociated structural and functional abnormalities in first-episode drug-naive patients with major depressive disorder: a multimodal meta-analysis. Scientific Reports, 7.

Wehry AM, McNamara RK, Adler CM, Eliassen JC, Croarkin P, Cerullo MA, … Strawn JR (2015). Neurostructural impact of co-occurring anxiety in pediatric patients with major depressive disorder: a voxel-based morphometry study. Journal of Affective Disorders, 171, 54–59. [PubMed: 25285899]

Wei M, Qin J, Yan R, Bi K, Liu C, Yao Z, & Lu Q. (2015). Association of resting-state network dysfunction with their dynamics of inter-network interactions in depression. Journal of Affective Disorders, 527–534. [PubMed: 25556670]

Whittle S, Bartholomeusz C, Yuecel M, Dennison M, Vijayakumar N, & Allen NB (2014). Orbitofrontal sulcogyral patterns are related to temperamental risk for psychopathology. Social Cognitive and Affective Neuroscience, 9(2), 232–239. [PubMed: 23160816]

Whittle S, Lichter R, Dennison M, Vijayakumar N, Schwartz O, Byrne ML, … Allen NB (2014). Structural brain development and depression onset during adolescence: a prospective longitudinal study. The American Journal of Psychiatry, 171(5), 564–571. [PubMed: 24577365]

Winkler AM, Kochunov P, Blangero J, Almasy L, Zilles K, Fox PT, … Glahn DC (2010). Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. NeuroImage, 53(3), 1135–1146. [PubMed: 20006715]

Woody ML, & Gibb BE (2015). Integrating NIMH Research Domain Criteria (RDoC) into depression research. Current Opinion in Psychology, 4, 6–12. [PubMed: 25642446]

Wray NR, Pergadia ML, Blackwood DHR, Penninx BWJH, Gordon SD, Nyholt DR, … Sullivan PF (2012). Genome-wide association study of major depressive disorder: new results, meta-analysis, and lessons learned. Molecular Psychiatry, 17(1), 36–48. [PubMed: 21042317]

Wu M-J, Wu HE, Mwangi B, Sanches M, Selvaraj S, Zunta-Soares GB, & Soares JC (2015). Prediction of pediatric unipolar depression using multiple neuromorphometric measurements: A pattern classification approach. Journal of Psychiatric Research, 62, 84–91. [PubMed: 25687738]

Yang S, Cheng Y, Mo Y, Bai Y, Shen Z, Liu F, … Xu X. (2017). Childhood maltreatment is associated with gray matter volume abnormalities in patients with first-episode depression. Psychiatry Research: Neuroimaging, 27–34.

Yap MBH, Whittle S, Yucel M, Sheeber L, Pantelis C, Simmons JG, & Allen NB (2008). Interaction of parenting experiences and brain structure in the prediction of depressive symptoms in adolescents. Archives of General Psychiatry, 65(12), 1377–1385. [PubMed: 19047524]

Zhao Y-J, Du M-Y, Huang X-Q, Lui S, Chen Z-Q, Liu J, … Gong Q-Y (2014). Brain grey matter abnormalities in medication-free patients with major depressive disorder: A meta-analysis. Psychological Medicine, 44(14), 2927–2937. [PubMed: 25065859]

Zhou Q, Chen SH, & Main A. (2012). Commonalities and Differences in the Research on Children's Effortful Control and Executive Function: A Call for an Integrated Model of Self-Regulation. Child Development Perspectives, 6(2), 112–121.

Highlights

- Adults with MDD demonstrate *reduced* cortical grey matter in the frontal cortex.
- Youth show associations from MDD to later brain structure *and* structure to later MDD.
- Moderators of effects remain unclear but may include sex, age and comorbidity.
- Relations between MDD risk factors and stressors and brain structure are reviewed.

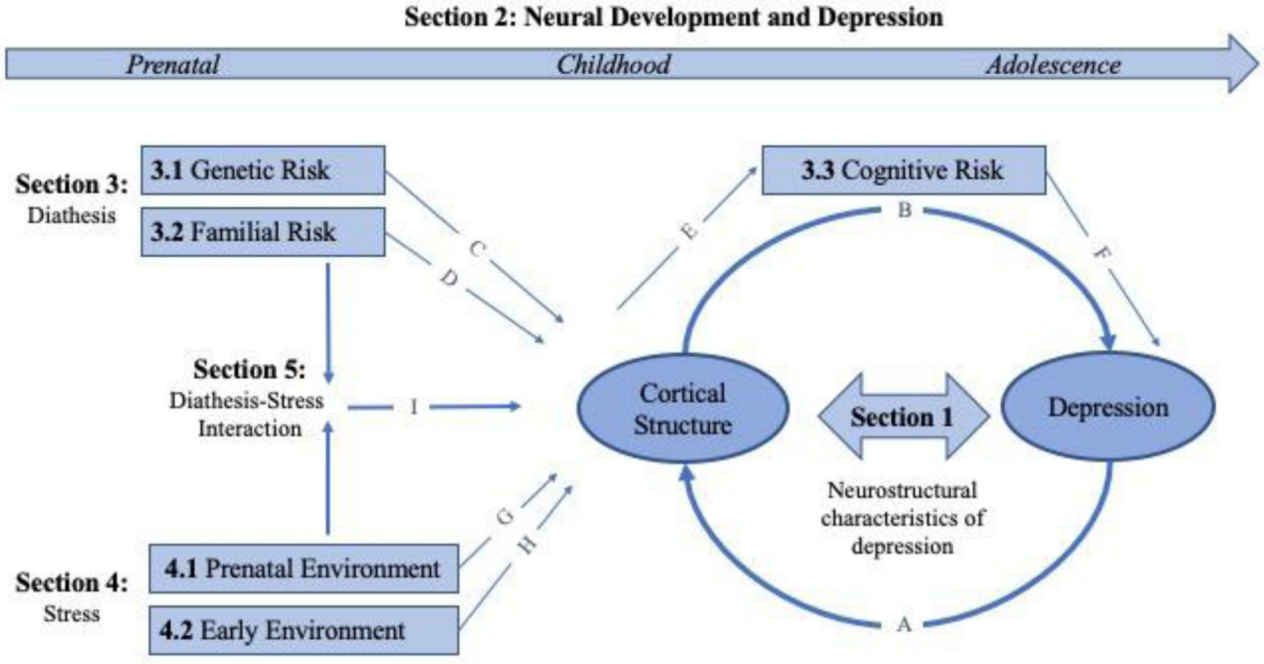

Figure 1.
Conceptual Figure.

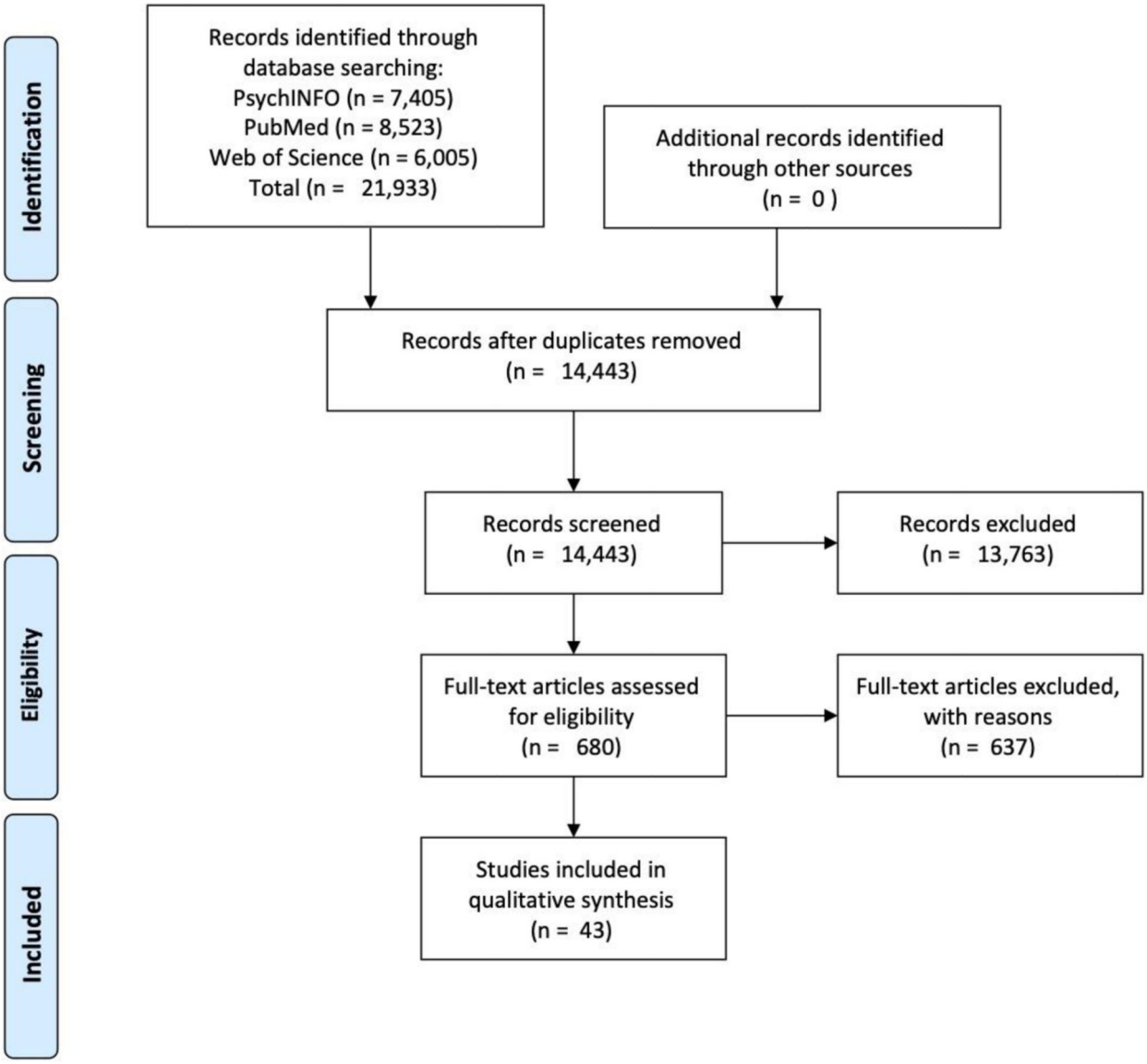

Figure 2.

PRISMA Flow Chart documenting the search results for the systematic review of studies examining cortical structure and depression in youth samples.