Behavioral/Cognitive

Amygdala-Prefrontal Structural Connectivity Mediates the Relationship between Prenatal Depression and Behavior in Preschool Boys

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Prenatal depression is common, underrecognized, and undertreated. It has negative consequences on child behavior and brain development, yet the relationships among prenatal depression, child behavior, and children's brain structure remain unclear. The aim of this study was to determine whether altered brain connectivity mediates relationships between prenatal maternal depressive symptoms and child behavior. This study included 54 human mother-child pairs. Mothers completed the Edinburgh Postnatal Depression Scale during the second and third trimesters of pregnancy and 3 months postpartum. Their children had diffusion MRI at age 4.1 ± 0.8 years, and children's behavior was assessed using the Child Behavior Checklist within 6 months of their MRI scan. Structural brain connectivity of the amygdala, fornix, uncinate fasciculus, and cingulum was assessed using fractional anisotropy and mean diffusivity and analyzed with maternal prenatal depressive symptoms as well as child behavior. Third trimester maternal Edinburgh Postnatal Depression Scale scores were positively associated with mean diffusivity in the amygdala-frontal tract and the cingulum, controlling for postpartum depression. Externalizing behavior had a sex interaction in the amygdala-frontal pathway; weaker connectivity (lower fractional anisotropy, higher mean diffusivity) was associated with worse behavior in boys. Amygdala-frontal connectivity mediated the relationship between third trimester depressive symptoms and child externalizing behavior in males. These findings suggest that altered brain structure is a mechanism via which prenatal depressive symptoms can impact child behavior, highlighting the importance of both recognition and intervention in prenatal depression.

Key words: amygdala; brain development; depression; externalizing behavior; MRI; pregnancy

Significance Statement

Understanding how prenatal maternal depression impacts child behavior is critical for appropriately treating prenatal maternal mental health problems and improving child outcomes. Here, we show white matter changes in young children exposed to maternal prenatal depressive symptoms. Children of mothers with worse depressive symptoms had weaker white matter connectivity between areas related to emotional processing. Furthermore, connectivity between the amygdala and prefrontal cortex mediated the relationship between maternal depressive symptoms and externalizing behavior in boys, showing that altered brain structure is a possible mechanism via which maternal prenatal depression impacts children's behavior. This provides important information for understanding why children of depressed mothers may be more vulnerable to depression themselves and may help shape future guidelines on maternal prenatal care.

Received Apr. 1, 2020; revised June 11, 2020; accepted June 18, 2020.

Author contributions: R.E.H., G.F.G., N.L., D.D., and C.L. designed research; R.E.H., J.E.R., M.N.G., D.P., and C.L. performed research; R.E.H. and J.E.R. analyzed data; R.E.H. wrote the first draft of the paper; R.E.H., J.E.R., M.N.G., D.P., G.F.G., N.L., D.D., and C.L. edited the paper.

This work was supported by the Canadian Institute of Health Research IHD-134090, MOP-136797, and MOP-123535 and Postdoctoral Fellowship to J.E.R., Alberta Innovates–Health Solutions, the Alberta Children's Hospital Foundation, and National Institute of Environmental Health Sciences 5R21ES021295-03. R.E.H. was supported by a Mach-Gaensslen Foundation award. J.E.R. was supported by an Eyes High University of Calgary Postdoctoral Scholarship and the T. Chen Fong Postdoctoral Fellowship. M.N.G. was supported by a University of Calgary Queen Elizabeth II Graduate Studentship award and funding provided by the Department of Pediatrics. C.L. was supported (salary) by the Canada Research Chair program. We thank the members of the Alberta Pregnancy Outcomes and Nutrition study team.

The authors declare no competing financial interests.

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https://doi.org/10.1523/JNEUROSCI.0481-20.2020

Introduction

Depressive symptoms affect up to 20% of women in pregnancy (Josefsson et al., 2001; Leung and Kaplan, 2009), yet prenatal depression is underrecognized and undertreated (Leung and Kaplan, 2009; Earls et al., 2010). Prenatal depression, independent of postnatal depression and anxiety, is associated with lower child intelligence (Barker et al., 2011; Evans et al., 2012), higher infant generalized anxiety and sleep problems (Gerardin et al., 2011), increased internalizing (e.g., anxiety and depression) and externalizing (e.g., aggression and hyperactivity) behavior in preschool children (Dawson et al., 2003), and increased risk for depression at 18 years (Pearson et al., 2013). Research has also suggested that outcomes are sex-specific: male infants exposed to prenatal depression tend to have poorer motor skills, higher generalized anxiety, and sleep problems than females (Gerardin et al., 2011). Evidence indicates that effective treatment of maternal prenatal depression improves child outcomes and is associated with lower levels of internalizing behavior (Foster et al., 2008).

Child internalizing and externalizing behavioral deficits associated with prenatal maternal depression might be explained, at least in part, by alterations to underlying neurologic structure and function. The stress response is regulated by the limbic circuit, including the cingulate cortex, hippocampus, and amygdala (Rajmohan and Mohandas, 2007; Sheikh et al., 2014). Dysfunction of these brain regions is associated with hyperactivity and aggression in children (Noordermeer et al., 2016), as well as the development of depression and stress disorders in youth and adults (Drevets et al., 2008). The amygdala is particularly important for emotional processing (Bjorkquist et al., 2016) through its connections to the frontal cortex (Banks et al., 2007). Altered connectivity between the amygdala and frontal cortex is associated with disruptive behaviors (Ibrahim et al., 2019), vulnerability to depression (van Eijndhoven et al., 2009; Price and Drevets, 2010; Holmes et al., 2012; Malykhin et al., 2012), anxiety, and increased stress reactivity (Prater et al., 2013; Fowler et al., 2017).

Maternal prenatal depression may impact child behavior by altering this neurologic circuit *in utero*. Indeed, prenatal depression is associated with altered amygdala functional connectivity in 6-month-old infants and 4.5-year-old children (Qiu et al., 2015; Wen et al., 2017), altered right amygdala microstructure at birth (Rifkin-Graboi et al., 2013), lower frontal and parietal brain activation (Dawson et al., 2003), altered uncinate fasciculus connectivity in neonates (Lautarescu et al., 2020), lower right frontal white matter microstructure at 1-month-old (Dean et al., 2018), and significant right frontal cortical thinning in children (Sandman et al., 2015; Lebel et al., 2016).

Together, these findings suggest that maternal prenatal depression affects child behavior by impacting neurologic development. However, to our knowledge, no study has investigated whether altered white matter mediates the relationship between prenatal depression and child behavior, which would provide more concrete evidence of a mechanism. The goal of this study was to determine the relationship between prenatal depression and child brain and behavior outcomes and investigate whether relationships between maternal depression and child behavior are mediated by alterations to structural connectivity, and if these effects are sex specific.

Materials and Methods

Participants

Fifty-four mothers and their children (24 female; 4.1 ± 0.8 years at MRI scan) were enrolled from an ongoing, prospective study (Kaplan et al., 2014). All participants provided informed consent, and this project was approved by the University of Calgary Health Research Ethics Board. Exclusion criteria for children included diagnosed neurologic disorders, history of head trauma, genetic disorders impacting cognitive or motor function, and contraindications to MRI. Two mothers were previously diagnosed with depression, one of whom was taking a moderate dose of a selective serotonin receptor inhibitor daily during pregnancy. Two women reported anxiety at enrollment; all women were screened. Prenatal medical comorbidities included celiac disease ($n = 1$), treated hypothyroidism ($n = 5$), and gestational diabetes ($n = 5$). For demographic information, see Table 1.

Table 1. Demographic characteristics of mothers and children enrolled in the study[a]

	Range	Mean (±SD)
Mothers		
Maternal age at child's birth (yr)	26–38	32.3 ± 2.8
Postsecondary education (yr)	0–12	5.53 ± 2.8
EPDS first trimester ($n = 27$)	0–16	4.85 ± 3.7
EPDS second trimester ($n = 47$)	0–16	4.47 ± 4.0
EPDS third trimester ($n = 53$)	0–18	4.83 ± 3.5
EPDS 3 months postpartum ($n = 54$)	0–19	4.72 ± 4.7
Children		
Sex	24 female/30 male	
Gestational age at birth (wk)	35–41.86	39.3 ± 1.4
Birth weight (g)	2230–4150	3344.9 ± 451.8
Age at scan (yr)	2.85–6.00	4.12 ± 0.8
CBCL Externalizing behavior T scores	28–68	44.81 ± 9.4
CBCL Internalizing behavior T scores	20–69	44.80 ± 9.2

[a]$N = 54$ unless otherwise specified. EPDS, Edinburgh postnatal depression scale; CBCL, Child behavior checklist.

Depressive symptoms

Maternal depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987; Bergink et al., 2011). Higher scores indicate worse symptoms; scores ≥12 are usually consistent with a diagnosis of major depressive disorder (MDD) (Cox et al., 1987). Women completed the EPDS up to three times in pregnancy (first trimester: 11.0 ± 2.8 weeks, $n = 27$; second trimester: 16.8 ± 2.2 weeks, $n = 47$; third trimester: 31.5 ± 1.1 weeks, $n = 53$) and at 3 months postpartum (11.5 ± 2.8 weeks, $n = 54$). Two women (7.4%) scored ≥12 on the EPDS in the first trimester, 4 women (8.5%) in the second trimester, 2 (3.8%) in the third trimester, and 5 (9.3%) postpartum. There were no significant associations between EPDS scores at each trimester.

Behavioral measures

Within 6 months of their MRI scan (average was 6 ± 4 d before the MRI), each child's parent (52 completed by mothers, 2 by fathers) completed the Child Behavior Checklist (CBCL) (Rescorla, 2005), a 118-item measure of child behavior that includes composite scores for internalizing and externalizing behavior (Table 1). Two children had T scores >60 (considered "at risk") in internalizing, and 6 children had scores >60 on externalizing. No children were >70 (considered clinically significant) in either domain. CBCL scoring is stable over time, with high reliability for up to 1 year (Frizzo et al., 2015).

Imaging

MRI data were collected at the Alberta Children Hospital on a GE 3T MR750w (General Electric) using a 32-channel head coil. Children were watching a movie of their choice during the scan; some ($n = 3$) fell asleep during the scan. Whole-brain diffusion tensor imaging (DTI) was collected using single-shot spin echo EPI with 30 diffusion encoding gradient directions at $b = 750$ s/mm^2 and 5 images at $b = 0$ s/mm^2, TR = 6750 ms, TE = 79 ms, and spatial resolution of $1.6 \times 1.6 \times 2.2$ mm^3 (resampled on scanner to $0.78 \times 0.78 \times 2.2$ mm); total time was 4:03. DTI was collected as part of a larger protocol that also included T1-weighted anatomic imaging, passive viewing fMRI, and arterial spin labeling (Reynolds et al., 2020).

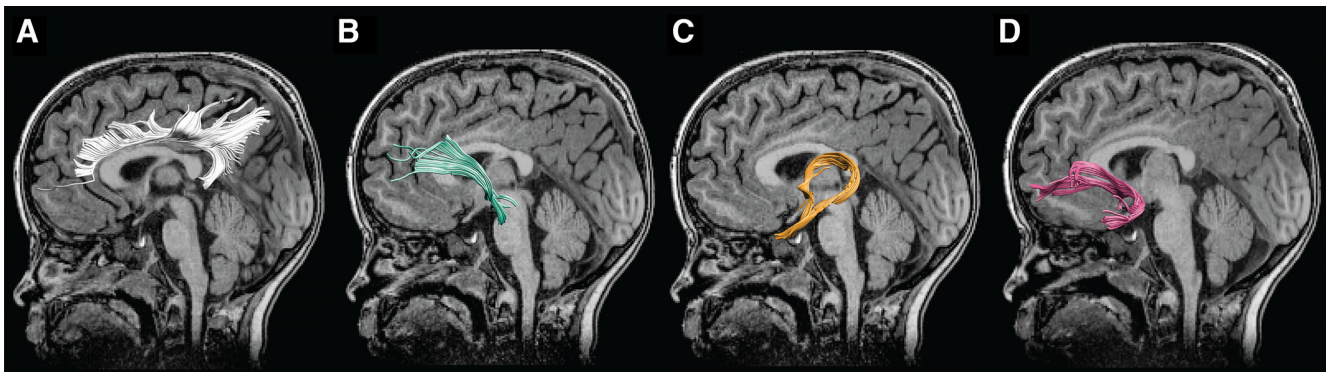

Figure 1. White matter tracts examined in this study. ***A***, Cingulum. ***B***, Amygdala pathway. ***C***, Fornix. ***D***, Uncinate fasciculus. Tracts did not overlap.

Image processing and analysis

Images were manually checked and volumes with artifacts or motion corruption were removed (Reynolds et al., 2019b). Participants with fewer than 22 volumes remaining were excluded from analysis. On average, participants had 32 ± 4 volumes remaining (of 35 original volumes; range 22-35). The average number of non–diffusion-weighted (b = 0 s/mm^2) images removed was 0.2 ± 0.5 (range 0-2); the average number of diffusion-weighted images removed was 3.24 ± 3.3 (range 0-12). The number of volumes remaining was not significantly related to depressive symptoms or child behavior (all $p > 0.4$). Preprocessing in ExploreDTI (Leemans et al., 2009) included correction for signal drift, Gibbs ringing, eddy currents, and motion. Semiautomated deterministic streamline tractography (Reynolds et al., 2019a) was used to delineate the fornix, cingulum, uncinate fasciculus, and white matter connectivity from the amygdala to the PFC (Hay et al., 2019). A representative scan (a 3.68-year-old female) was identified using the tract-based spatial statistics nonlinear registration step in FSL for use as a target (Smith et al., 2006; for further details, see Reynolds et al., 2019b). All other subjects' fractional anisotropy (FA) maps were registered to this template. ROIs were drawn in the left and right hemispheres on the template and warped to fit each subject using the inverse registration parameters calculated from the previous step (Lebel et al., 2008a). Tractography was conducted in native space for each participant. Tracts were visually inspected to ensure accuracy, and spurious fibers were removed if necessary. Mean FA and mean diffusivity (MD) were extracted for each tract. Left and right tracts were examined separately for the amygdala tract, the uncinate fasciculus, and the cingulum; the fornix was analyzed as a whole, as it is a continuous tract across hemispheres. Tracts did not overlap and are shown in Figure 1.

Statistical analysis

Regression. Data met assumptions for regression (linearity, homoscedasticity, independence, normality). Brain measures (FA and MD for 7 different white matter tracts) were tested separately as dependent variables using linear regression, with maternal prenatal EPDS and an EPDS-sex interaction. Based on previously established relationships with maternal depressive symptoms and/or child brain, the following potential confounding variables were also included in the regression model: child age at MRI, child sex, gestational age at birth, birth weight, maternal age, maternal postsecondary education, and postnatal EPDS. Second and third trimester EPDS symptoms were tested separately; first trimester EPDS was not assessed because of low numbers. Results were corrected for multiple comparisons using false discovery rate (FDR) based on 7 white matter tracts (left and right amygdala pathway, left and right cingulum, left and right uncinate, and fornix), 2 values each (FA and MD), and 2 trimesters (second and third) for a total of 28 comparisons.

Tracts with significant (after correction) relationships with prenatal maternal depressive symptoms were then analyzed for relationships with behavioral scores. CBCL scores (Internalizing T score and Externalizing T score) were tested using linear regression with the brain measure and a brain-sex interaction. The same confounders as above were included in the model: child age at MRI, child sex, gestational age at birth, birth weight, maternal age, maternal postsecondary education, and postnatal EPDS. For both models, if interaction terms were not significant, they were removed from the model and the analysis was rerun. There was one outlying EPDS score; analysis was run without that person with no change in results. Similarly, the analysis was run with and without the individual on a selective serotonin receptor inhibitor, with no change in results.

Mediation. Tracts that were significantly related to both CBCL and EPDS scores were selected for mediation analysis. When sex interactions in the EPDS or CBCL regression models were significant, mediation was analyzed separately for males and females. Maternal depressive symptoms (EPDS) were entered as the independent variable (X), brain measures as the mediator (M), and CBCL scores as the outcome variable (Y). Nonparametric mediation tests were run on in-house Python using statsmodels version 0.11.1 with percentile bootstrapping, given the validation of this model on the non-normal distribution of mediating variables (Taylor and MacKinnon, 2012).

Results

FA and MD values were in the typical range for children this age: left amygdala FA (mean: 0.42 ± 0.01; range: 0.36–0.46), MD (0.88×10^{-3} mm^2/s ± 0.03×10^{-3}, 0.8×10^{-3}- 1.0×10^{-3} mm^2/s); right amygdala FA (0.42 ± 0.02, 0.35–0.46), MD (0.88×10^{-3} mm^2/s ± 0.03×10^{-3}, 0.8×10^{-3} to 1.0×10^{-3} mm^2/s); left cingulum FA (0.42 ± 0.02, 0.36–0.48), MD (0.87×10^{-3} mm^2/s ± 0.03×10^{-3}, 0.8×10^{-3} to 0.9×10^{-3} mm^2/s); right cingulum FA (0.40 ± 0.03, 0.35–0.44), MD (0.86×10^{-3} mm^2/s ± 0.03×10^{-3}, 0.8×10^{-3}-0.9×10^{-3} mm^2/s); left uncinate fasciculus FA (0.40 ± 0.02, 0.34–0.42), MD (0.93×10^{-3} mm^2/s ± 0.03×10^{-3}, 0.9×10^{-3}-1.0×10^{-3} mm^2/s); right uncinate fasciculus FA (0.38 ± 0.02, 0.34–0.43), MD (0.91×10^{-3} mm^2/s ± 0.03×10^{-3}, 0.9×10^{-3}-1.0×10^{-3} mm^2/s); and fornix FA (0.40 ± 0.02, 0.33–0.40), MD (1.42×10^{-3} mm^2/s ± 0.1×10^{-3}, 1.2×10^{-3}-1.8×10^{-3} mm^2/s).

Cingulum

Second trimester maternal EPDS scores had a positive main effect on left cingulum FA ($F = 4.871$, $p = 0.033$; Table 2), such that children of women with higher prenatal depressive symptoms tended to have higher FA. This result did not survive FDR correction (corrected p value: $q = 0.143$). There was a significant sex × third trimester EPDS interaction in right cingulum FA ($F = 4.417$, $p = 0.042$), such that higher maternal depressive symptoms were associated with lower FA in males; this did not survive FDR correction ($q = 0.143$). Third trimester EPDS had a main effect on left cingulum MD ($F = 10.593$, $p = 0.002$) and a sex × EPDS interaction ($F = 5.725$ $p = 0.021$). Specifically, higher

Table 2. Associations between prenatal depressive symptoms and white matter measures[a]

	EPDS			EPDS × sex			
Cingulum	*F*	*p* (*q*)	PES	*F*	*p* (*q*)	PES	R^2
Second trimester EPDS							
Left cingulum FA	4.871	0.033* (0.143)	0.114				0.309
Left cingulum MD	0.203	0.655	0.005				0.203
Right cingulum FA	0.100	0.753	0.003				0.155
Right cingulum MD	0.121	0.729	0.003				0.188
Third trimester EPDS							
Left cingulum FA	0.298	0.588	0.007				0.257
Left cingulum MD	10.593	0.002[b]* (0.028)	0.201	5.725	0.021* (0.143)	0.126	0.483
Right cingulum FA	0.161	0.690	0.004	4.417	0.042* (0.143)	0.095	0.295
Right cingulum MD	5.527	0.023* (0.143)	0.114				0.267
Amygdala pathway							
Second trimester EPDS							
Left amygdala pathway FA	0.079	0.780	0.002				0.294
Left amygdala pathway MD	0.000	1.000	0.000				0.059
Right amygdala pathway FA	0.220	0.642	0.006				0.217
Right amygdala pathway MD	0.502	0.483	0.013				0.097
Third trimester EPDS							
Left amygdala pathway FA	0.067	0.797	0.002				0.349
Left amygdala pathway MD	4.319	0.044* (0.143)	0.091				0.138
Right amygdala pathway FA	0.222	0.640	0.005				0.216
Right amygdala pathway MD	11.568	0.001[b]* (0.028)	0.212				0.262
Uncinate fasciculus							
Second trimester EPDS							
Left uncinate fasciculus FA	1.340	0.254	0.034				0.391
Left uncinate fasciculus MD	0.712	0.404	0.019	9.911	0.003[b]* (0.028)	0.211	0.406
Right uncinate fasciculus FA	0.010	0.923	0.000				0.299
Right uncinate fasciculus MD	2.032	0.162	0.052	4.249	0.046* (0.143)	0.103	0.358
Third trimester EPDS							
Left uncinate fasciculus FA	0.937	0.339	0.021				0.415
Left uncinate fasciculus MD	2.392	0.129	0.052				0.231
Right uncinate fasciculus FA	0.759	0.388	0.017				0.409
Right uncinate fasciculus MD	6.725	0.013	0.135				0.304
Fornix							
Second trimester EPDS							
Fornix FA	0.161	0.690	0.004				0.338
Fornix MD	0.027	0.871	0.001				0.146
Third trimester EPDS							
Fornix FA	0.217	0.644	0.005				0.332
Fornix MD	4.986	0.031* (0.143)	0.104				0.258

[a]Covariates were child age, sex, gestational age, birth weight, maternal age, maternal postsecondary education, and postpartum depressive symptoms. If the EPDS × sex interaction was nonsignificant, it was removed from the model, and these cells are blank. df values in EPDS2 are (9, 37); df values in EPDS3 are (9, 42) with interactions in the model. PES, Partial eta squared; EPDS, Edinburgh postnatal depression scale; FA, fractional anisotropy; MD, mean diffusivity.
[b]Results that survive FDR correction for multiple comparisons.
*Significant results.

maternal depressive symptoms were associated with higher MD in males (Fig. 2). The main effect survived FDR correction ($q = 0.028$).

Neither CBCL Externalizing nor Internalizing behavior was significantly associated with cingulum microstructure (Table 3).

Amygdala pathway

Third trimester maternal depressive symptoms had a positive main effect on right amygdala pathway MD ($F = 11.568$, $p = 0.001$) and left amygdala pathway MD ($F = 4.319$, $p = 0.044$) (Table 2; Fig. 2). Results for the right amygdala pathway, but not the left, survived FDR correction ($q = 0.028$ and $q = 0.143$, respectively).

The sex × brain interactions on CBCL Externalizing behavior were significant for the right amygdala pathway MD ($F = 6.638$, $p = 0.015$). Higher FA and lower MD in females were associated with higher externalizing behaviors, whereas lower FA and higher MD in males were associated with higher externalizing behavior (Table 3).

Uncinate fasciculus

Second trimester maternal depressive symptoms had a significant sex interaction on left and right uncinate MD (left: $F = 9.911$, $p = 0.003$; right: $F = 4.249$, $p = 0.046$) with males having a higher MD with higher maternal depressive symptoms (Table 2; Fig. 2). The positive relationship in the left uncinate, but not the right, survived multiple comparison correction ($q = 0.028$ and $q = 0.143$, respectively). Neither CBCL Externalizing nor Internalizing behavior was associated with uncinate microstructure (Table 3).

Fornix

Fornix MD was positively associated with third trimester EPDS ($F = 4.986$, $p = 0.031$); this result did not survive multiple comparison ($q = 0.143$).

Mediation analysis

MD of the right amygdala significantly mediated the relationship between third trimester depressive symptoms and externalizing behavior in males (95% CI: [0.013, 2.05] Fig. 3).

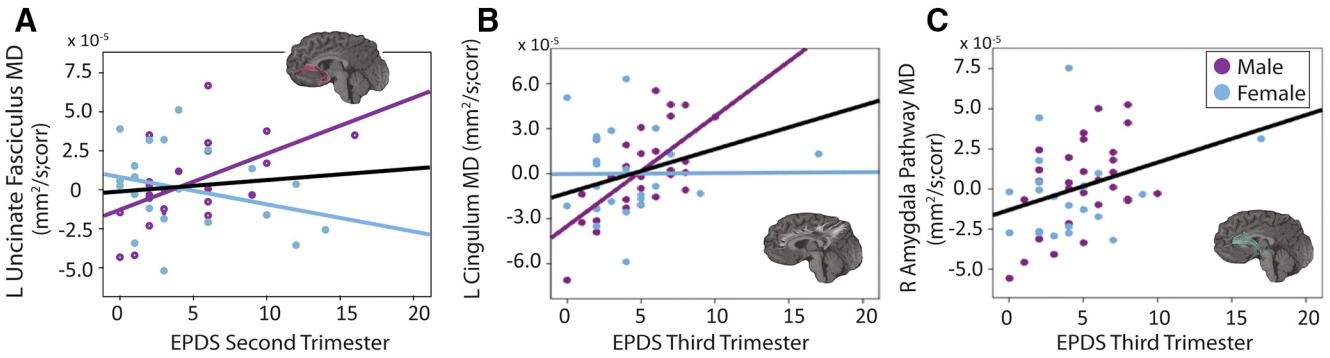

Figure 2. Relationships between white matter measures and prenatal maternal depressive symptoms. Black line indicates a main effect of Edinburgh postnatal depression scale (EPDS) scores. Lines color-coded by sex indicate an interaction between EPDS and sex. ***A***, Maternal depressive symptoms in the second trimester were positively associated with left uncinate fasciculus mean diffusivity (MD), with a significant sex interaction. Third trimester depressive symptoms were positively associated with (***B***) left cingulum MD and (***C***) right amygdala pathway MD. MD values are corrected for covariates.

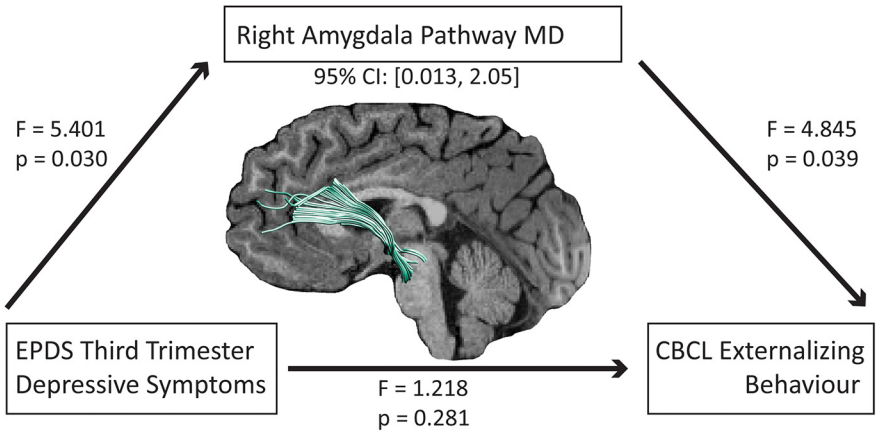

Figure 3. Mean diffusivity (MD) of the right amygdala pathway significantly mediated the relationship between third trimester depressive symptoms and externalizing behavior in males. The 95% CI for the indirect relationship was [0.013, 2.05].

Table 3. Associations between child behavior and white matter measures in tracts that had significant relationships with maternal depressive symptoms[a]

	MD			MD × sex			
Cingulum	*F*	*p*	PES	*F*	*p*	PES	R^2
Left cingulum							
CBCL Internalizing	2.393	0.129	0.052				0.137
CBCL Externalizing	0.438	0.512	0.010				0.065
Amygdala pathway							
Right amygdala pathway							
CBCL Internalizing	0.913	0.345	0.020				0.109
CBCL Externalizing	2.107	0.154	0.047	6.368	0.015*	0.129	0.186
Uncinate fasciculus							
Left uncinate fasciculus							
CBCL Internalizing	0.001	0.979	0.000				0.090
CBCL Externalizing	0.057	0.813	0.001				0.057

[a]Covariates were child age, sex, gestational age, birth weight, maternal age, maternal postsecondary education, and postpartum depressive symptoms. If the interaction was nonsignificant, it was removed from the model, and these cells are blank. df values are (9, 43) with interactions in the model. PES, Partial eta squared; MD, mean diffusivity; CBCL, child behavior checklist.
*Significant results.

Discussion

Here, we show that prenatal maternal depressive symptoms are associated with altered limbic-prefrontal connectivity in young children. Furthermore, reduced structural connectivity between the amygdala and PFC mediated the relationship between maternal depressive symptoms and externalizing behavior in boys. These results suggest that reduced brain connectivity within the stress network is a mechanism via which maternal depression symptoms impact children's behavior.

We found weaker structural connectivity (lower FA and higher MD) in the amygdala pathway and cingulum associated with higher prenatal maternal depressive symptoms. Because FA increases and MD decreases with age (Yoshida et al., 2013), lower FA and/or higher MD values may indicate underdeveloped white matter in young children exposed to higher maternal prenatal depression symptoms, which may in turn predispose these children to dysregulated emotional states. Previous functional imaging studies have reported weaker amygdala-PFC functional connectivity in children born to more depressed mothers (Rifkin-Graboi et al., 2013). Similarly, reduced functional connectivity from the amygdala to the PFC was observed in 4- to 7-year-old children exposed to early life stress, and weaker connectivity was associated with more aggression and attention difficulties (Park et al., 2018). On the other hand, Qiu et al. (2015) found greater functional connectivity from the left amygdala to frontal cortex in neonates exposed to maternal prenatal depression (Qiu et al., 2015), indicating a potentially complex picture that could depend on factors, such as child age and sex.

The cingulum was also associated with prenatal depressive symptoms, consistent with a previous study that showed increased MD in the cingulum of school-aged year-old children exposed to prenatal maternal depressive symptoms (El Marroun et al., 2018). The cingulum is thought to be a structure susceptible to stress (Kim et al., 2006). Lower FA has been associated with dissociation and depression in young adults exposed to early life and prenatal stress (Choi et al., 2009; Marečková et al., 2019). The hippocampus receives serotonergic transmission from the midbrain raphe via the fornix and the cingulum (Patel et al., 1996), providing a potential means by which alterations in the cingulum could disrupt mood.

Higher MD in the left uncinate fasciculus was associated with greater severity of second trimester depressive symptoms. Higher MD, similar to lower FA, may indicate underdevelopment of this

tract; this interestingly corresponds to other data showing reduced structural white matter connectivity of the uncincate in young adults who experienced early life stress (Hanson et al., 2015), decreased uncinate and cingulum FA in depressed adults (Bhatia et al., 2018), and decreased FA in the uncinate and cingulum of neonates exposed to prenatal anxiety (Rifkin-Graboi et al., 2015). While the uncinate was not associated with behavioral symptoms in these young children, it is possible that altered development within it may predispose children to mood disorders later on in life given data strongly suggesting uncinate involvement in MDD (Steffens et al., 2011; Carballedo et al., 2012; Bhatia et al., 2018; Deng et al., 2018).

Previous results from our laboratory in an overlapping sample suggested an accelerated pattern of development (lower diffusivity) in right frontal-temporal white matter in children exposed to greater second trimester depressive symptoms (Lebel et al., 2016). Indeed, other data have found that accelerated development may predispose children to psychiatric conditions later in life (Ono et al., 2008; Gee et al., 2013; Jalbrzikowski et al., 2017). Different results found here for third trimester may be a product of timing and brain areas examined. Indeed, in this study, we found a similar pattern of accelerated development (higher right cingulum FA in females) associated with second trimester maternal depressive symptoms, although this finding did not survive multiple comparison. These results suggest complex associations between the prenatal environment and children's brain development, where outcomes vary by timing of exposure and child age.

Altered structural connectivity similar to that observed here is associated with depression. Decreased amygdala-PFC connectivity is seen in adolescents with MDD (Cullen et al., 2014) and individuals with a familial history of depression (Luking et al., 2011). Decreased functional and structural connectivity between the amygdala and frontal cortex may indicate loss of inhibitory control and subsequent increased amygdala reactivity. This idea is supported by data showing reduced amygdala-PFC connectivity in adults associated with impaired emotional responses (Banks et al., 2007; Bjorkquist et al., 2016), anxiety and depression (Chen et al., 2008; Prater et al., 2013; Cheng et al., 2018), and increased aggression and attention problems in children (Park et al., 2018). Increased amygdala reactivity is also seen in adolescents with MDD (Perlman et al., 2012). Medications and psychotherapy that treat depression increase functional coupling between the amygdala and the striatum, thalamus, right frontal, and cingulate cortex (Chen et al., 2008), likely resulting in increased prefrontal inhibition and regulation of amygdala responsivity. It is important to note that, although data consistently show altered amygdala-PFC connectivity associated with mood and anxiety disorders, it is unclear whether that dysfunction is because of hypo- or hyper-connectivity (Jalbrzikowski et al., 2017). Our results support the theory of weaker top-down amygdala inhibition in children who experienced higher prenatal maternal depressive symptoms, providing evidence of a structural basis for previously observed deficits in functional connectivity.

Structural connectivity of the amygdala pathway mediated the relationship between maternal prenatal depressive symptoms and externalizing behavior in boys. Children whose mothers experienced prenatal depression consistently have higher externalizing symptoms (Oberlander et al., 2007), and thus alterations to amygdala-PFC structural connectivity may be a mechanism via which maternal depression impacts children's behavior (Pearson et al., 2013). Furthermore, this altered connectivity may increase children's risk for later mental health difficulties, as higher childhood externalizing symptoms are associated with later risk of suicidality, substance use, and psychopathology in adolescence and adulthood (Holtmann et al., 2011; Bellani et al., 2012). While this is the first study to show a mediating role of white matter connectivity, previous studies have shown a mediating role for gray matter in school-aged children. Right prefrontal cortical thickness mediates the relationship between maternal prenatal depressive symptoms and externalizing behavior in school-aged children (Sandman et al., 2015); in an overlapping sample, frontal cortical thickness in children mediated the relationship between prenatal maternal stress and adolescent depressive symptoms (Davis et al., 2020). Another study showed that amygdala volumes mediate the effect of prenatal maternal stress on boys' externalizing behavior at age 11 years (Jones et al., 2019), supporting the idea of sex-specific mediation effects on behavior.

The sexual differentiation suggests that boys are more vulnerable to maternal depressive symptoms. Some studies show that males experience more prominent age-related gray (De Bellis et al., 2001) and white matter changes compared with females (Simmonds et al., 2014; Reynolds et al., 2019b), although other studies suggest similar development trajectories across sexes (Lebel et al., 2008b; Muftuler et al., 2012). More rapid development in males may underlie increased susceptibility to environmental factors, such as prenatal depression. In childhood, males have a higher prevalence of depression (Merikangas et al., 2009), and male but not female children of postnatally depressed mothers have poorer cognitive function (Murray et al., 2010). Male infants exposed to prenatal depression have lower motor skills, higher generalized anxiety, and sleep problems (Gerardin et al., 2011). Thus, our data highlight that it may be underlying brain vulnerability in males that predisposes them to behavior problems. Of note, previous data in adults showed no moderating effect of sex on the relationship between prenatal stress during the first half of pregnancy and FA of the cingulum (Marečková et al., 2019). However, differences in exposure periods and the age of the offspring may account for the contrasting results.

The mechanisms through which prenatal maternal depression influences child brain structure are not well understood. Theories include dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and increased cortisol during pregnancy, genetic heritability of mood disorders, epigenetic modification of preexisting genes, nutrition, and inflammation (Weinstock, 2005). Maternal stress and depression during pregnancy increase cortisol and corticotropin releasing hormone, which initiates signaling in the HPA axis and can cross the placenta (Weinstock, 2005). Depression is associated with HPA axis dysregulation, with increased and prolonged stress responses and higher circulating glucocorticoids (Wong et al., 2000), which activate receptors in the child's brain and induce epigenetic changes (Weinstock, 2008). Animal research shows that even brief stress induces structural remodeling of the PFC, increasing emotional dysregulation and reducing fear extinction (Holmes and Wellman, 2009). Indeed, early life stress and HPA-axis function predict later psychopathology, potentially through connections with the amygdala-ventromedial PFC (Burghy et al., 2012); thus, prenatal HPA axis dysregulation and cortisol exposure may induce similar changes in amygdala projections to the PFC. Additionally, high stress in late pregnancy is associated with reduced uterine blood flow, suggesting that fetuses experience periods of hypoxia (Weinstock, 2008) that may impact brain development. MDD is highly heritable (Lohoff, 2010), and preexisting genetic vulnerability likely plays an important role in child vulnerability. Poor nutrition during pregnancy increases the risk of perinatal depression and poor child cognitive outcomes (Leung and

Kaplan, 2009). Prenatal stress is associated with increased inflammation and cytokine activity, which may also impact child outcomes (Buitelaar et al., 2003). Higher depressive symptoms are associated with less social support (Ren et al., 2018), and decreased social support during pregnancy is associated with lower Apgar scores, worse labor progress, and increased prenatal and postpartum depression (Elsenbruch et al., 2007). Decreased social support and higher maternal depressive symptoms are also associated with a higher risk of developmental delay in children (Huang et al., 2014). It is likely a combination of biological and psychosocial factors that contribute to altered brain development and child outcomes.

This study has some limitations. Because of the timing of recruitment, limited first trimester depressive symptom data were available, and therefore were not analyzed. Greater severity of EPDS depressive symptom scores is associated with a diagnosis of depression, but the EPDS itself is not diagnostic. Therefore, we cannot say whether these women had a clinical diagnosis of depression. The relationships between even mild depressive symptoms and white matter and behavioral changes highlight the importance of even mild depressive symptoms for child outcomes. Furthermore, the EPDS only asks about the preceding 7 d, and thus may not represent symptoms across the entire trimester. The CBCL is a parent report measure, and therefore may be subject to parental bias and anxiety. Specific to the context of this study, women experiencing more depressive symptoms may answer the CBCL differently from many factors, including attachment and coping. Parental anxiety and social support contribute to child development and may play a role in our sample here. Brain development is known to be nonlinear in children (Reynolds et al., 2019b), although linear fits, as used here, can approximate trends over narrow age ranges. The age range in this study is 2.86–6 years; and so, it is possible that a linear fit is not ideal. Finally, our sample size was small for mediation, particularly in sex-specific analysis, which results in low power and may increase the FDR (Smaldino and McElreath, 2016). Thus, a significant mediation effect may also be present in girls but was not detected here. Future studies with larger sample sizes and wider age ranges may wish to include nonlinear age terms to better represent brain development.

In conclusion, we show altered structural connectivity of the amygdala in children of mothers with higher prenatal depressive symptoms, and these alterations mediate behavioral dysfunction in boys. These data present evidence of a structural basis for decreased top-down inhibition of the amygdala, resulting in altered behavior in children and may indicate structural abnormalities that predisposes children to develop affective disorders. Indeed, these data may help explain why children born to depressed mothers have a higher risk of developing depression themselves (Pearson et al., 2013). Additionally, we show sexual differentiation, suggesting that males have increased vulnerability to changes in early childhood. These findings suggest a need to improve prenatal care through programs that screen for perinatal depression and address prenatal depression as an important factor in future child health outcomes.

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