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RESEARCH ARTICLE

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Prenatal depressive symptoms and childhood development of brain limbic and default mode network structure

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Abstract

Prenatal depressive symptoms are linked to negative child behavioral and cognitive outcomes and predict later psychopathology in adolescent children. Prior work links prenatal depressive symptoms to child brain structure in regions like the amygdala; however, the relationship between symptoms and the development of brain structure over time remains unclear. We measured maternal depressive symptoms during pregnancy and acquired longitudinal T1-weighted and diffusion imaging data in children ($n = 111$; 60 females) between 2.6 and 8 years of age. Controlling for postnatal symptoms, we used linear mixed effects models to test relationships between prenatal depressive symptoms and age-related changes in (i) amygdala and hippocampal volume and (ii) structural properties of the limbic and default-mode networks using graph theory. Higher prenatal depressive symptoms in the second trimester were associated with more curvilinear trajectories of left amygdala volume changes. Higher prenatal depressive symptoms in the third trimester were associated with slower age-related changes in limbic global efficiency and average node degree across childhood. Our work provides evidence that moderate symptoms of prenatal depression in a low sociodemographic risk sample are associated with structural brain development in regions and networks implicated in emotion processing.

KEYWORDS
APrON, graph theory, MRI, prenatal depression, structural networks, white matter

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1 | INTRODUCTION

Approximately 12% of pregnant individuals experience clinical levels of depressive symptoms during their pregnancy and many others are affected by subclinical symptoms that go unrecognized and untreated (Bernard-Bonnin et al., 2004; CDC, 2020; Woody et al., 2017). Children born to individuals experiencing depression are at risk for negative birth outcomes including low birth weight, preterm birth, and low Apgar scores (O'Donnell & Meaney, 2017). Prenatal depression is also associated with problems across social–emotional (poor self-regulation and internalizing and externalizing behaviors), cognitive, language, and motor domains in infancy and childhood (Fransson et al., 2020; Kingston et al., 2018; Letourneau et al., 2019; Madigan et al., 2018; Rogers et al., 2020). Notably, prenatal depressive symptoms are associated with depression in adolescent children (Pearson et al., 2013; Tirumalaraju et al., 2020), suggesting that exposure to maternal depression during early, critical periods of brain growth can confer risk for mental illness much later in development.

Prenatal depression is associated with brain structure across childhood, most commonly in regions of the limbic system and the default mode network (DMN), which are both involved in emotion regulation (Alves et al., 2019; Vasung et al., 2010). For example, elevated prenatal maternal depressive symptoms and maternal cortisol are associated with larger amygdala volumes across childhood (Buss et al., 2012; Jones et al., 2019; Wen et al., 2017), with some studies suggesting this relationship is more prominent in girls (Buss et al., 2012; Wen et al., 2017). Correlations between higher prenatal depression and smaller amygdala volumes in male infants (Lehtola et al., 2020) and 4-year-old children (Acosta et al., 2019) have also been reported. Larger amygdala volumes appear to partially mediate the relationship between prenatal depression/stress and affective problems or externalizing behaviors in children (Buss et al., 2012; Jones et al., 2019).

Often comorbid with depression (Farr et al., 2014), maternal stress and anxiety are associated with smaller hippocampal volumes in fetuses (Wu et al., 2020) and infants (Moog et al., 2021), as well as slower hippocampal growth in infancy (Qiu et al., 2013). Left hippocampal volume partially mediated the (negative) relationship between prenatal maternal stress and infant cognitive performance (Wu et al., 2022), and the relationship between maternal stress and infant social–emotional development (Moog et al., 2021).

Relationships between prenatal depression or stress and white matter connectivity have also been reported. Higher prenatal maternal depressive symptoms in late gestation were related to decreased structural connectivity between the amygdala and prefrontal cortex in both newborns and 3–6-year-old children (Hay et al., 2020; Posner et al., 2016). Further, higher MD mediated the relationship between prenatal maternal depression symptoms and externalizing behaviors in male children (Hay et al., 2020). More symptoms of depression in late pregnancy have also been linked to lower fractional anisotropy (FA) in the fornix, middle frontal gyrus, prefrontal and superior-parietal cortices, external and internal capsules, and the corona radiata of infants (Dean et al., 2018; Graham et al., 2020). Depressive symptoms in mid and later gestation were related to higher MD and/or lower FA of the uncinate fasciculus and cingulum in young children (El Marroun et al., 2018; Hay et al., 2020).

Previous work has focused on individual white matter tracts or regions, though there are networks of tracts and regions that support mental health and behavior. Only one study has examined prenatal maternal stress and brain networks, showing lower degree centrality of the amygdala in young adults exposed to higher prenatal stress (Mareckova et al., 2022). This suggests that network properties may be altered by prenatal distress, though no work to date has looked at relationships between prenatal maternal depression and structural networks in children.

Cross-sectional analyses are important for identifying relationships between perinatal depression and child brain structure at specific ages and with larger samples; however, they cannot capture the rapid brain development that occurs during infancy and childhood (Mills et al., 2016). Discrepancies across existing cross-sectional studies may reflect the dynamic nature of brain development and suggest that results vary by age. Longitudinal studies can provide an understanding of trajectories of brain growth across childhood (Lebel & Beaulieu, 2011; Reynolds et al., 2019). Studying the relationships between prenatal maternal depression and the development of default mode and limbic networks in childhood may provide insight into the mechanisms via which maternal depression confers risk of mental health difficulties for children (Tirumalaraju et al., 2020). Here, we aimed to investigate associations between prenatal maternal depressive symptoms and age-related changes in amygdala and hippocampal volume, as well as network characteristics of the limbic and default mode networks.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

Children were recruited from the ongoing Alberta Pregnancy Outcomes and Nutrition (APrON) study (Kaplan et al., 2014). Children of mothers in the APrON study who lived in Calgary were recruited for neuroimaging between ages 2–6 years. Children were invited to return approximately every 6 months, providing longitudinal data. 111 children (with 370 high quality neuroimaging data sets; mean = 3.3 data sets/participant) whose mothers provided prenatal and postnatal depression symptom information were included in this study (Figure 1). Children (60 females) ranged in age from 2.6 to 8.0 years (mean = 4.8; SD = 1.2 years) at the time of scanning (Table 1). Mothers were between the ages of 20 and 42 years during their pregnancy. All mothers in this sample identified as cisgender women at the time of questionnaire completion and 87% self-reported their ethnicity as White. The median income level was >$100,000. Most women (77%) had a university undergraduate education or higher and 95% were married or cohabitating (Table 1). Twenty of 111 (18%) mothers had a BMI ≥30 before pregnancy and 5 of 111 (4.5%) mothers developed gestational diabetes by their third trimester. There

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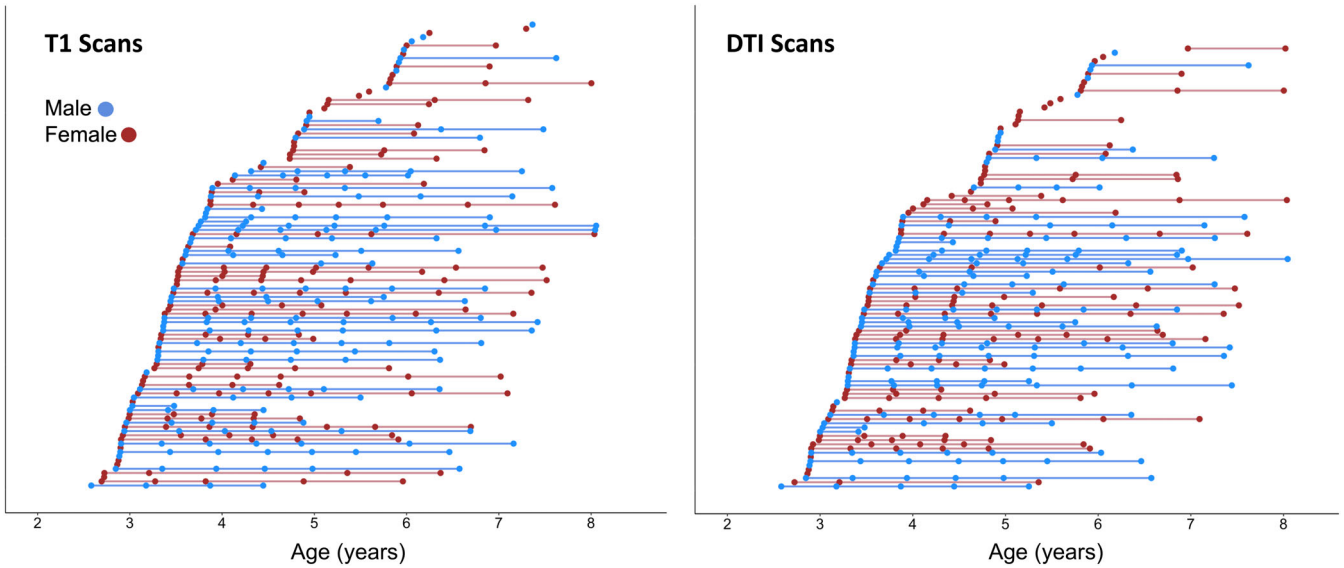


FIGURE 1 Age of participants at each childhood T1-weighted and diffusion tensor imaging (DTI) scan. Individual participant scans are represented by points on the plot and lines connecting the points in each row represent one participant. There were 370 T1-weighted scans from 111 participants (60 females). 67% (74/111) of participants had more than one T1-weighted scan. There were 349 DTI scans from 105 participants (58 females). 67% (70/105) of participants had more than one DTI scan. Number of scans per participant ranged from 1 to 7.

were no participants who reported smoking during pregnancy. Nine participants reported drinking small amounts of alcohol at one point during pregnancy. Not all mothers had depression information available from all three time points (second trimester, third trimester, postpartum), thus the number of participants included in each analysis varied. Three participants were taking antidepressant medication in the second trimester of their pregnancy; only one continued their medication in the third trimester.

This study was approved by the University of Calgary Conjoint Health Research Ethics Board. Informed consent was obtained from mothers and informed parental consent on behalf of the child was obtained at the time of MRI data collection. Parents received consent forms before attending the scan, and the MRI procedure and consent process was thoroughly outlined before scanning began. Parents and their children could withdraw consent at any time. A cross-sectional subset of these data has been previously published in relation to prenatal depressive symptoms (Hay et al., 2020; Lebel et al., 2016).

2.2 | Measures of depression symptoms

Maternal depression symptoms were measured using the Edinburgh Postnatal Depression Scale (EPDS) during the second and third trimesters of pregnancy and at 12 weeks postpartum. Most women in the study did not enroll until the second trimester of pregnancy; therefore, first trimester scores are not considered here. The EPDS is a 10-item self-report questionnaire validated for use during and after pregnancy (Cox et al., 1987). Although the EPDS is not diagnostic, a score of 10–12 is consistent with "possible depression" and a score ≥13 is consistent with clinical levels of depressive symptoms or a diagnosis of major depressive disorder (Cox et al., 1987). There were 15 women (15%) in this sample with scores ≥10 and 5 women (5.1%) with scores ≥13 in the second trimester ($n = 98$). When looking at third trimester symptoms ($n = 108$), there were 11 women (10%) who had scores ≥10 and 6 women (5.6%) with scores ≥13. Postnatal depressive symptoms were significantly associated with prenatal depressive symptoms in the second ($r = .51$, $p < .001$) and third ($r = .62$, $p < .001$) trimesters. There was no significant change in depressive symptoms across pregnancy and postpartum (Figure S1; estimate ±SE = −0.1 ± 0.2; $t = -0.6$; $p = .6$).

2.3 | Structural and diffusion tensor imaging

Structural and diffusion MRI data were obtained using a GE 3T MR750w (General Electric, Waukesha, WI) scanner with a 32-channel head coil at the Alberta Children's Hospital in Calgary, Alberta. During the scan, children were awake and watching a self-selected movie or sleeping naturally. The scanning protocol included T1 and whole brain diffusion weighted imaging (DWI). T1-weighted images were obtained using a FSPGR BRAVO sequence (flip angle = 12°, 210 slices, TR = 8.23 ms, TE = 3.76 ms, spatial resolution = 0.9 × 0.9 × 0.9 mm^3 resampled in the scanner to 0.45 × 0.45 × 0.9 mm^3, matrix size = 512 × 512, inversion time = 540 ms). Whole brain diffusion weighted images were obtained using single-shot spin echo echo-planar imaging in 30 gradient encoding directions at $b = 750$ s/mm^2 (flip angle = 90°, TR = 6750 ms, TE = 79 ms, FOV = 200 mm × 200 mm, matrix size: 256 × 256 × 54). Images were acquired at 1.6 × 1.6 × 2.2 mm resolution, which was resampled to

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TABLE 1 Demographic information of participants

	Range	Mean ± SD
Children ($n = 111$)		
Age at scan (years)	2.6–8.0	4.8 ± 1.2
Sex	51 males/60 females	
Birth weight (g)	2215–4610	3351 ± 489
Gestational age at birth (weeks)	35.0–42.0	39.4 ± 1.4
Mothers ($n = 111$)		
Maternal age (years)	20–42	31.8 ± 3.5
EPDS (second trimester; $n = 98$)	0–19	4.9 ± 4.2
EPDS (third trimester; $n = 108$)	0–19	5.7 ± 3.8
EPDS (3 months postpartum; $n = 111$)	0–19	4.6 ± 4.0
	N	**(%)**
Marital status		
Married/cohabitating	106	95
Ethnicity		
Asian or Pacific Islander	5	4.5
Latinx/Hispanic	1	0.9
Mixed race	3	2.7
White	96	86.5
Not reported	6	5.4
Household income		
<$20,000	3	2.7
$20,000–$40,000	4	3.6
$40,000–$60,000	7	6.3
$70,000–$100,000	28	25.2
>$100,000	69	62.2
Education		
Completed high school	4	3.6
Completed trade, technical, vocational school	22	19.8
Bachelor's degree	50	45.0
Postgraduate training	35	31.5
Health		
Prepregnancy BMI ≥30	20	18
Gestational diabetes	5	4.5

0.78 × 0.78 × 2.2 mm on the scanner. The total T1 acquisition time was 4:12 min and the total DWI acquisition time was 4:03 min. Further information about the data set and protocol can be found elsewhere (Reynolds et al., 2020).

2.4 | Image processing

2.4.1 | T1 image segmentation

T1-weighted images were segmented using Multi-atlas Cortical Reconstruction Using Implicit Surface Evolution (MaCRUISE) software at the Vanderbilt University Institute of Imaging Science, Center for Computational Imaging. MaCRUISE produces self-consistent brain segmentations of 132 regions including the right and left amygdala and hippocampus (Figure 2) (Huo et al., 2016). All segmentations were quality checked and manually edited, where necessary, in ITK-SNAP software to ensure completeness and accuracy of segmentation results (Yushkevich et al., 2006). Volumes from limbic structures including the left and right amygdala and hippocampus were extracted from volumetric labels.

2.4.2 | Diffusion images

Diffusion tensor imaging (DTI) data were visually checked to identify volumes with artifacts or motion, which were then removed. Data sets were excluded from analysis if <18 diffusion-weighted and <2 b0 high quality/low-motion volumes remained. All remaining preprocessing was completed in ExploreDTI (MATLAB version 2019a) (Leemans et al., 2009), including correction for signal drift, Gibbs ringing, subject motion, and eddy current and EPI distortions. N4 bias field correction and resampling to 1 mm isotropic resolution was first performed on T1-weighted images to correct for low frequency intensity nonuniformity artifacts before beginning the EPI correction with registration. FA maps were calculated and whole brain tractography was performed on the preprocessing outputs to obtain information about white matter tracts in the brain. The minimum FA threshold was 0.20 and the angle threshold was 30°.

Networks of interest (limbic and default mode) were identified from the functional networks defined by Thomas Yeo et al. (2011), which were also fully structurally connected in the majority of our data. The DMN consisted of 18 regions from the automated anatomical labeling (AAL) atlas (Figure 3; (Tzourio-Mazoyer et al., 2002)): left and right inferior frontal gyrus (orbital), superior frontal gyrus (orbital and medial-orbital), the anterior cingulate, posterior cingulate, hippocampus, angular gyrus, precuneus, and middle temporal gyrus. The limbic network (Figure 3) consisted of 14 regions: the left and right superior frontal gyrus (orbital), olfactory cortex, gyrus rectus, parahippocampal gyrus, amygdala, and temporal pole (superior temporal gyrus and middle temporal gyrus). A standard FA template from FSL (FMRIB58_FA_1mm.nii) and corresponding AAL regions of interest in MNI space were nonlinearly registered to individual FA maps using FSL and AFNI to create individual participant network maps in DTI space (Cox, 1996; Jenkinson et al., 2012).

Individual AAL maps, whole brain tractography data, and preprocessed diffusion files were input into the ExploreDTI "Network analysis tools" plugin to create connectivity matrices from the predefined labels (regions of interest). Connections between regions were evaluated according to the "PASS" definition (Leemans et al., 2009), which considers regions that tracts pass through to be points of connection. Connectivity matrices were binarized and matrices were excluded from analyses if they did not form fully connected networks (one or more isolated nodes). Simple graph theory metrics (clustering coefficient, node degree, and local and global efficiency) were calculated for

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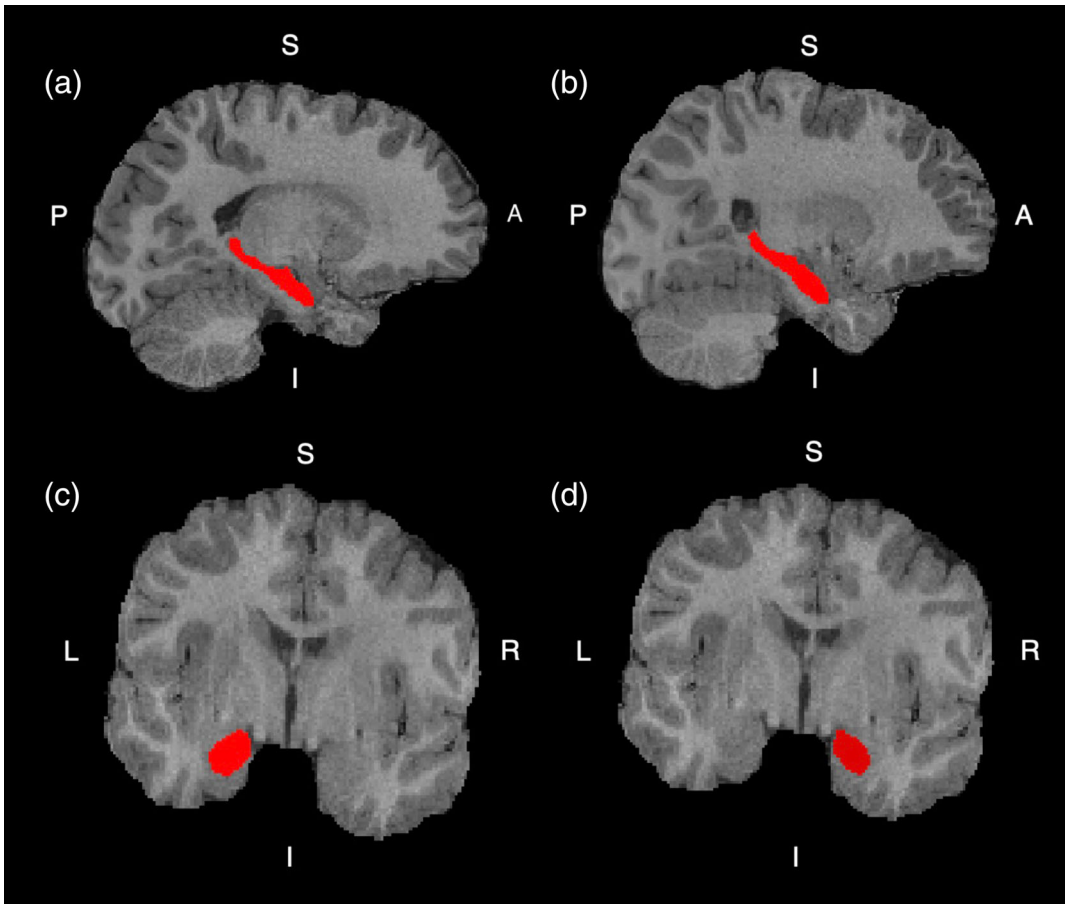


FIGURE 2 Segmentation of hippocampi and amygdalae. (a) Left and (b) right hippocampus and (c) left and (d) right amygdala segmentations were obtained using Multi-atlas Cortical Reconstruction Using Implicit Surface Evolution (MaCRUISE) software. Segmentations were performed on raw T1 images and were used to study volume of these structures. S—superior; I—inferior; R—right; L—left; P—posterior; A—anterior

each region in the independent networks using the Brain Connectivity toolbox and then averaged (Rubinov & Sporns, 2010).

2.5 | Statistical analysis

Statistical analysis was performed in RStudio version 4.0.5 using the lme4 (Bates et al., 2015) and lmerTest (Kuznetsova et al., 2017) packages to evaluate linear mixed effects models. Before examining prenatal depressive symptoms and age-related changes, we determined whether volumes and networks had linear or quadratic changes across childhood using chi square tests with the ANOVA function in R. We tested only linear and quadratic terms based on previous work suggesting linear or quadratic relationships with age in the amygdala, hippocampus and white matter tracts underlying the DMN and limbic network (Herting et al., 2018; Reynolds et al., 2019; Uematsu et al., 2012).

Bilateral amygdala and hippocampal volumes appeared to follow quadratic trajectories, so quadratic age terms and interactions were retained (Supplementary Table 1). Quadratic age terms were not significant for graph theory metrics and therefore were not included in those overall models (Supplementary Table 1).

We then tested prenatal maternal depressive symptoms, age, and the interaction between prenatal depressive symptoms and age, as predictors of child brain structure, controlling for child sex (and its interactions), household income, birth weight, and postnatal maternal depressive symptoms. Participant was modeled as a random factor. Second and third trimester scores were placed in separate models to avoid collinearity. Terms in brackets were exploratory interactions and were removed if not significant.

2.5.1 | Volume and graph theory models

Volume $\sim$ age + age^2 + sex + (age $\times$ sex) + (age^2 $\times$ sex) + intracranial volume (ICV) + income + birth weight + prenatal depression + prenatal depression $\times$ age + prenatal depression $\times$ age^2 + postnatal depression + (sex $\times$ prenatal depression) + (postnatal depression $\times$ age) + postnatal depression $\times$ age^2 + (age^2 $\times$ sex $\times$ prenatal depression).

Diffusion graph theory measure $\sim$ age + sex + (age $\times$ sex) + income + birth weight + prenatal depression + postnatal depression + prenatal depression $\times$ age + (sex $\times$ prenatal depression) + postnatal depression $\times$ age + (age $\times$ sex $\times$ prenatal depression).

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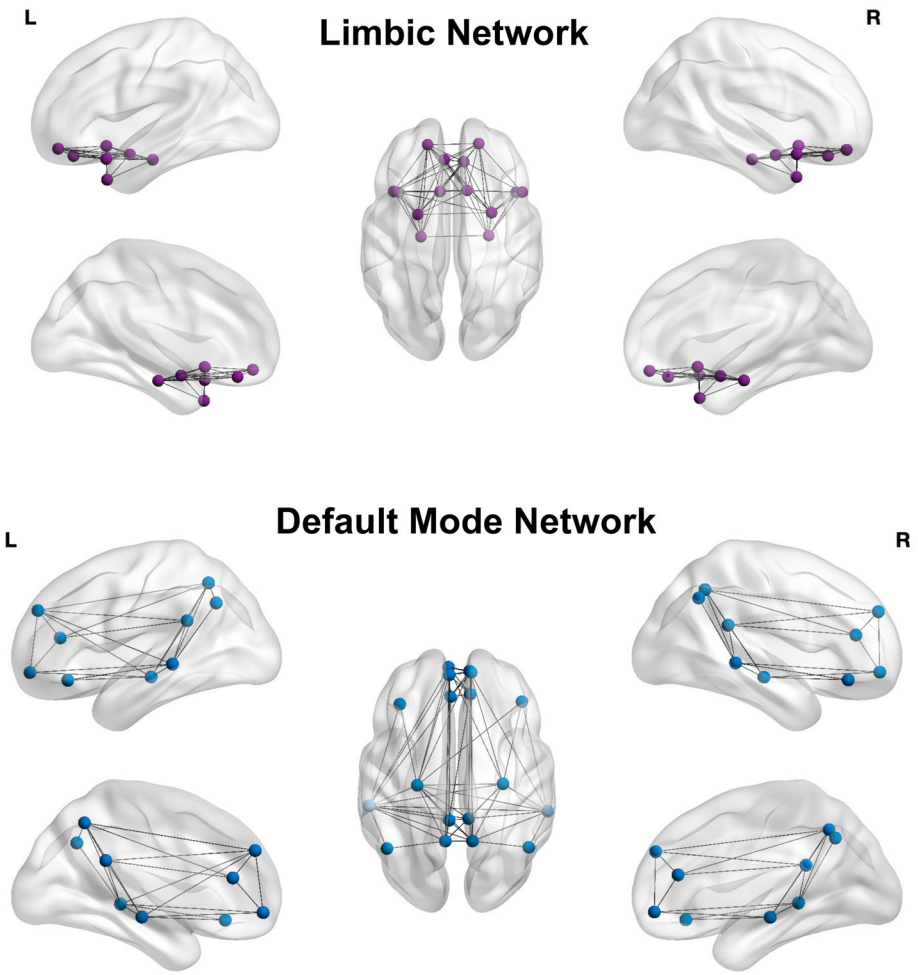


FIGURE 3 Networks of interest. Regions of the limbic (top) and default mode (bottom) networks are represented as nodes according to their positions defined by the Automated Anatomical Labeling (AAL) atlas. The limbic network included the left and right superior frontal gyrus (orbital part), olfactory cortex, gyrus rectus, parahippocampal gyrus, amygdala, and temporal pole (superior and middle temporal regions). The default mode network included the left and right inferior frontal gyrus (orbital part), superior frontal gyrus (medial and medial orbital regions), anterior cingulate and paracingulate gyri, posterior cingulate gyrus, hippocampus, angular gyrus, precuneus, and middle temporal gyrus. Lines represent examples of how regions may be connected based on data from a participant

ICV was included as a covariate in models looking at amygdala and hippocampal volume. We also tested total gray matter volume instead of ICV based on work advocating for this approach to achieve consistency across segmentation methods (Zhou et al., 2021); there was no difference in optimal model fits when controlling for total gray matter over ICV.

As follow-up to each analysis, we removed participants who consumed alcohol or used antidepressants to observe if our results differed. We also added alcohol use, gestational diabetes, and prepregnancy BMI as covariates to identify if these influenced our results.

2.5.2 | Multiple comparison correction

The Benjamin and Hochberg false discovery rate was used to correct for multiple comparisons across each measure (regional volume, clustering coefficient, local efficiency, global efficiency, and node degree) at $q < 0.05$.

3 | RESULTS

3.1 | Amygdala and hippocampal volumes

There was a significant interaction between age^2 and maternal depressive symptoms in the second but not third trimester, such that children exposed to higher prenatal depressive symptoms had more curvilinear left amygdala volume trajectories than children exposed to lower symptoms (Figure 4a; Table 2; $t = -2.7$; $p = .01$, $q = .04$). A nominally significant similar relationship was observed for the right amygdala, though this did not survive multiple comparison correction (Figure 4b; Table 2; $t = -2.2$; $p = .03$, $q = 0.06$). There were no significant relationships between prenatal depressive symptoms and age-related changes in hippocampal volume.

3.2 | Limbic and default mode networks

Participant data were excluded from analysis if networks on a scan were not fully connected (limbic: $n = 24$; DMN: $n = 18$). Based on these differences and missing depression scores at some time points, different analyses (structural vs. diffusion data and DMN vs. limbic network) included slightly different numbers of participants (Tables 2 and 3).

All graph theory metrics of the DMN increased across age ($p < .001$). Limbic global efficiency ($p < .001$) and average node degree ($p = .003$), were significantly positively associated with age but limbic clustering coefficient and local efficiency did not show significant age-related changes (Supplementary Table 1).

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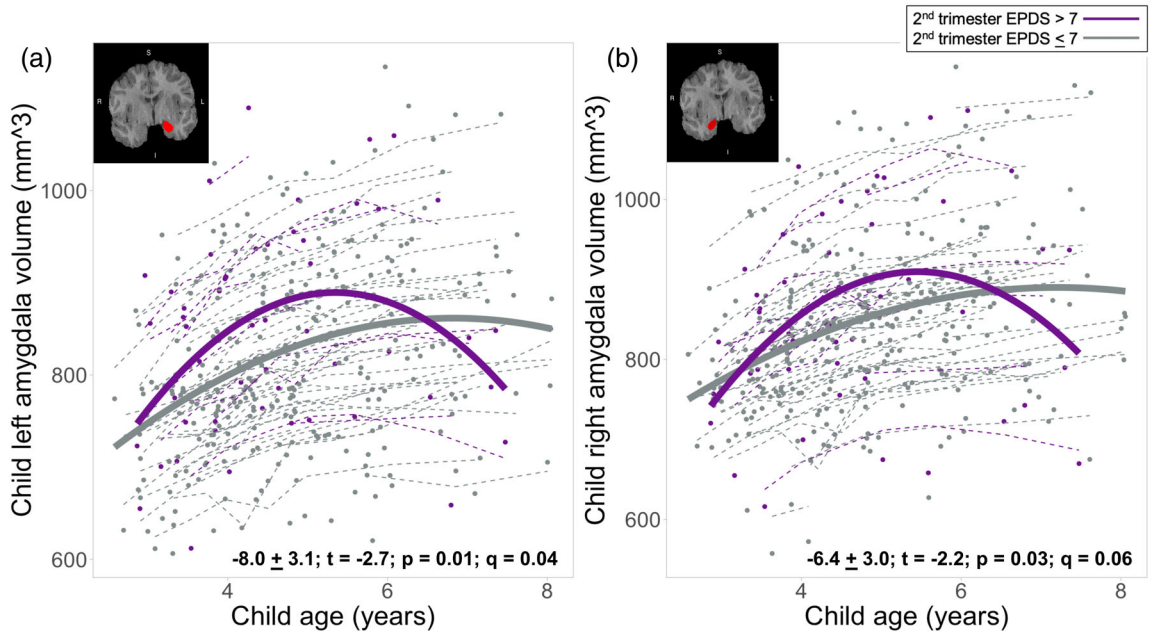


FIGURE 4 Prenatal depressive symptoms and child amygdala volume growth. Child left (a) and right (b) amygdala volumes across age are shown for high (purple) and low (gray) maternal prenatal depressive symptoms in the second trimester. Scores were split at a value of 7 (top 20th percentile). ($n = 98$; 52 females; 2.6–8.0 years)

The interaction between child age and third trimester maternal depressive symptoms significantly predicted global efficiency (Figure 5a, Table 3; $t = -3.2$; $p = .002$, $q = 0.006$) and average node degree (Figure 5b, Table 3; $t = -2.8$; $p = .005$, $q = 0.02$) of the limbic network. There were also positive main effects of third trimester depressive symptoms on average node degree (Table 3; $t = 2.8$; $p = .005$, $q = 0.02$) and global efficiency (Table 3; $t = 3.4$; $p < .001$, $q = 0.003$). Local clustering metrics (average clustering coefficient, local efficiency) were not related to prenatal depressive symptoms. There were no significant effects of second trimester symptoms on age-related changes in the limbic network. Prenatal depressive symptoms were not related to graph theory measures of the DMN.

The interaction between second trimester depressive symptoms and sex was a significant predictor of limbic global efficiency (Figure 6a; $t = 2.6$; $p = .01$, $q = 0.04$) and average node degree (Figure 6b; $t = 2.7$; $p = .007$, $q = 0.03$). Female children showed a negative relationship between prenatal depressive symptoms and node degree/global efficiency, while males showed the opposite. No sex-depressive symptom interactions were found in the DMN.

When participants whose mothers used antidepressants or consumed alcohol during pregnancy were removed from analysis, results remained significant. Further, when alcohol consumption, gestational diabetes, and prepregnancy BMI were added as covariates, results also remained significant.

4 | DISCUSSION

Here, we show that prenatal depressive symptoms are associated with structural brain changes over time in young children. Higher prenatal depressive symptoms were associated with more curvilinear trajectories of amygdala volume and slower development of limbic network connections in young children. These results suggest that prenatal depressive symptoms have long-lasting effects not just on brain structure, but on its development throughout childhood, and may help explain previous discrepant findings of participants at different ages.

To our knowledge, this study is the first to report associations between age-related changes in amygdala volume and prenatal maternal depressive symptoms. In children exposed to higher depressive symptoms, left amygdala volume showed a more curvilinear trajectory, with faster increases from 3 to 6 years, followed by decreases after age 6 years. In contrast, children whose mothers had lower symptoms in pregnancy showed a less curved trajectory, with increases across most of this age range. Right amygdala volume followed a similar trend, though findings were not significant after correction for multiple comparisons. Previous work suggests that prenatal depression and stress are related to larger amygdala volumes throughout infancy and early childhood (Buss et al., 2012; Jones et al., 2019; Wen et al., 2017). Our results extend that work by showing prenatal depressive symptoms are also associated with altered development. Prenatal exposure to depression symptoms may resemble early postnatal adverse exposures like deprivation and reduced maternal sensitivity, which have also been related to larger amygdala volumes in young children (Rifkin-Graboi et al., 2015; Tottenham et al., 2010).

More depressive symptoms in the third trimester of pregnancy were associated with altered limbic network global efficiency and average node degree. Children exposed to higher symptoms had lower global efficiency and node degree, as well as slower development of these metrics with age. This suggests less network integration

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TABLE 2 Statistical parameters for analyses with second trimester depression. Linear mixed effects (fixed effects) parameters for relationships with second trimester and postnatal depressive symptoms. Parameters include coefficients/estimates, standard error, *p*, and *q* values

	Main effects		Interactions			
Brain region	**Prenatal depression (second trimester)**	**Postnatal depression**	**Age × prenatal depression (second trimester)**	**Age² × prenatal depression (second trimester)**	**Age × postnatal depression**	**Age² × postnatal depression**
Volumes						
Right amygdala volume[a]	10.4 ± 7.8	1.9 ± 7.9	3.5 ± 3.2	−6.4 ± 3.0	NA	1.1 ± 2.0
	$t = 1.3$	$t = 0.2$	$t = 1.2$	$t = -2.2$		$t = 0.5$
	$p = .18$	$p = .8$	$p = .3$	$p = .03$		$p = .6$
				$q = \mathbf{0.06}$		
Left amygdala volume[a,b]	15.6 ± 7.9	−2.17 ± 7.68	2.2 ± 3.4	−8.0 ± 3.1	NA	3.6 ± 2.1
	$t = 2.1$	$t = -0.2$	$t = 0.7$	$t = -2.7$		$t = 1.8$
	$p = .05$	$p = .8$	$p = .5$	$p = .01$		$p = .09$
	$q = 0.2$			$\boldsymbol{q = 0.04}$		
Right hippocampus volume[a]	−7.0 ± 32.1	22.6 ± 32.1	−12.3 ± 9.4	2.5 ± 7.8	NA	2.1 ± 5.7
	$t = -0.2$	$t = 0.7$	$t = -1.4$	$t = 0.1$		$t = 0.4$
	$p = .7$	$p = .5$	$p = .2$	$p = .8$		$p = .7$
Left hippocampus volume[a]	−5.6 ± 31.0	−4.1 ± 30.1	−3.9 ± 9.3	−2.0 ± 7.8	NA	1.8 ± 5.5
	$t = -0.2$	$t = -0.1$	$t = -0.5$	$t = -0.4$		$t = 0.4$
	$p = .7$	$p = .9$	$p = .7$	$p = .8$		$p = .7$
Graph theory measures						
Clustering coefficient DMN[b,c]	0.005 ± 0.005	−0.002 ± 0.005	−0.001 ± 0.001	NA	0.0007 ± 0.0009	NA
	$t = 1.0$	$t = -0.5$	$t = -1.4$		$t = 0.8$	
	$p = .3$	$p = .6$	$p = .2$		$p = .4$	
Clustering coefficient limbic[d]	0.006 ± 0.005	−0.002 ± 0.005	−0.0009 ± 0.001	NA	0.00006 ± 0.0009	NA
	$t = 1.1$	$t = -0.5$	$t = -0.82$		$t = 0.06$	
	$p = .3$	$p = .7$	$p = .4$		$p = .9$	
Local efficiency DMN[b,c]	0.005 ± 0.005	−0.002 ± 0.005	−0.001 ± 0.001	NA	0.0006 ± 0.0009	NA
	$t = 1.0$	$t = -0.4$	$t = -1.3$		$t = 0.7$	
	$p = .3$	$p = .7$	$p = .2$		$p = .5$	
Local efficiency limbic[d]	0.008 ± 0.005	−0.005 ± 0.004	−0.001 ± 0.0009	NA	0.0004 ± 0.0008	NA
	$t = 1.7$	$t = -1.2$	$t = -1.1$		$t = 0.5$	
	$p = .1$	$p = .2$	$p = .3$		$p = .6$	
Global efficiency DMN[c]	0.002 ± 0.003	0.002 ± 0.002	−0.0003 ± 0.0005	NA	−0.0005 ± 0.0004	NA
	$t = 0.7$	$t = 0.8$	$t = -0.6$		$t = -1.1$	
	$p = .5$	$p = .4$	$p = .6$		$p = .3$	
Global efficiency limbic[d]	0.003 ± 0.005	−0.003 ± 0.004	−0.0002 ± 0.001	NA	−0.00008 ± 0.0008	NA
	$t = 0.6$	$t = -0.7$	$t = -0.2$		$t = -0.1$	
	$p = .5$	$p = .5$	$p = .9$		$p = .9$	
Node degree DMN[c]	0.05 ± 0.05	−0.004 ± 0.04	−0.01 ± 0.01	NA	0.0006 ± 0.008	NA
	$t = 1.0$	$t = -0.1$	$t = -1.2$		$t = 0.08$	
	$p = .3$	$p = .9$	$p = .2$		$p = .9$	
Node degree limbic[d]	0.06 ± 0.07	−0.02 ± 0.06	−0.008 ± 0.01	NA	−0.004 ± 0.01	NA
	$t = 0.9$	$t = -0.4$	$t = -0.6$		$t = -0.3$	
	$p = .3$	$p = .7$	$p = .5$		$p = .7$	

Note: NA—not applicable (i.e., not tested in model). Terms that were bolded (q values) represent significance.
Abbreviation: DMN, default mode network.
[a]Analysis of volumes included 98 participants (345 scans).
[b]Age × sex interaction terms were significant and included in the model.
[c]Analysis of DMN graph theory measures included 92 participants (313 scans).
[d]Analysis of limbic graph theory measures included 93 participants (308 scans).

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TABLE 3 Statistical parameters for analyses with third trimester depression. Linear mixed effects (fixed effects) parameters for relationships with third trimester and postnatal depressive symptoms. Parameters include coefficients/estimates, standard error, *p*, and *q* values

	Main effects		Interactions			
Brain region	**Prenatal depression (third trimester)**	**Postnatal depression**	**Age × prenatal depression (third trimester)**	**Age² × prenatal depression (third trimester)**	**Age × postnatal depression**	**Age² × postnatal depression**
Volumes						
Right amygdala volume[a]	5.8 ± 8.4	−3.0 ± 8.5	2.2 ± 3.4	−3.9 ± 3.0	NA	0.9 ± 2.3
	$t = 0.6$	$t = -0.3$	$t = 0.7$	$t = -1.3$		$t = 0.4$
	$p = .5$	$p = .7$	$p = .5$	$p = .2$		$p = .7$
Left amygdala volume[a,b]	8.1 ± 8.7	−1.5 ± 8.9	2.5 ± 3.6	−5.1 ± 3.3	NA	3.5 ± 2.4
	$t = 1.2$	$t = -0.5$	$t = 0.7$	$t = -1.8$		$t = 1.7$
	$p = .4$	$p = .9$	$p = .5$	$p = .1$		$p = .2$
Right hippocampus volume[a]	−19.5 ± 32.3	23.6 ± 33.2	6.8 ± 9.7	−14.4 ± 8.5	NA	6.3 ± 6.3
	$t = -0.5$	$t = 0.7$	$t = 0.6$	$t = -1.6$		$t = 0.9$
	$p = .5$	$p = .5$	$p = .5$	$p = .9$		$p = .3$
Left hippocampus volume[a]	38.8 ± 30.8	−38.4 ± 31.6	3.4 ± 9.4	−17.3 ± 8.3	NA	8.0 ± 6.1
	$t = 1.4$	$t = -1.3$	$t = 0.3$	$t = -2.0$		$t = 1.3$
	$p = .2$	$p = .2$	$p = .7$	$p = .04$		$p = .2$
				$q = 0.15$		
Graph theory measures						
Clustering coefficient DMN[b,c]	0.003 ± 0.006	−0.002 ± 0.005	−0.0007 ± 0.001	NA	0.0006 ± 0.001	NA
	$t = 0.5$	$t = -0.4$	$t = -0.5$		$t = 0.6$	
	$p = .6$	$p = .7$	$p = .6$		$p = .6$	
Clustering coefficient limbic[d]	−0.007 ± 0.006	0.004 ± 0.005	0.001 ± 0.001	NA	−0.001 ± 0.001	NA
	$t = -1.1$	$t = 0.8$	$t = 1.0$		$t = -0.9$	
	$p = .3$	$p = .4$	$p = .3$		$p = .4$	
Local efficiency DMN[b,c]	0.004 ± 0.006	−0.002 ± 0.005	−0.0008 ± 0.001	NA	0.0006 ± 0.001	NA
	$t = 0.6$	$t = -0.4$	$t = -0.6$		$t = 0.5$	
	$p = .6$	$p = .7$	$p = .6$		$p = .6$	
Local efficiency limbic[d]	0.0001 ± 0.006	−0.001 ± 0.005	0.0002 ± 0.001	NA	−0.0001 ± 0.0009	NA
	$t = 0.02$	$t = -0.3$	$t = 0.2$		$t = -0.2$	
	$p = .9$	$p = .8$	$p = .9$		$p = .9$	
Global efficiency DMN[c]	0.0007 ± 0.003	0.002 ± 0.003	−0.00003 ± 0.0006	NA	−0.0006 ± 0.0005	NA
	$t = 0.2$	$t = 0.9$	$t = -0.04$		$t = -1.2$	
	$p = .8$	$p = .4$	$p = .9$		$p = .2$	
Global efficiency limbic[d]	0.02 ± 0.005	−0.01 ± 0.005	−0.004 ± 0.001	NA	0.002 ± 0.0009	NA
	$t = 3.4$	$t = -2.5$	$t = -3.2$		$t = 2.0$	
	$p = .0007$	$p = .01$	$p = .002$		$p = .05$	
	$\mathbf{q = 0.003}$	$q = 0.05$	$\mathbf{q = 0.006}$		$q = 0.2$	
Node degree DMN[c]	−0.01 ± 0.06	0.02 ± 0.05	0.004 ± 0.01	NA	−0.007 ± 0.009	NA
	$t = -0.2$	$t = 0.5$	$t = 0.4$		$t = -0.7$	
	$p = .8$	$p = .6$	$p = .7$		$p = .5$	
Node degree limbic[d]	0.22 ± 0.08	−0.1 ± 0.07	−0.04 ± 0.02	NA	0.02 ± 0.01	NA
	$t = 2.8$	$t = -1.7$	$t = -2.8$		$t = 1.4$	
	$p = .005$	$p = .09$	$p = .005$		$p = .2$	
	$\mathbf{q = 0.02}$		$\mathbf{q = 0.02}$			

Note: NA—not applicable (i.e., not tested in model). Terms that were bolded (q values) represent significance.

Abbreviation: DMN, default mode network.

[a]Analysis of volumes included 108 participants (360 scans).

[b]Age × sex interaction terms were significant and included in the model.

[c]Analysis of DMN graph theory measures included 100 participants (321 scans).

[d]Analysis of limbic graph theory measures included 101 participants (316 scans).

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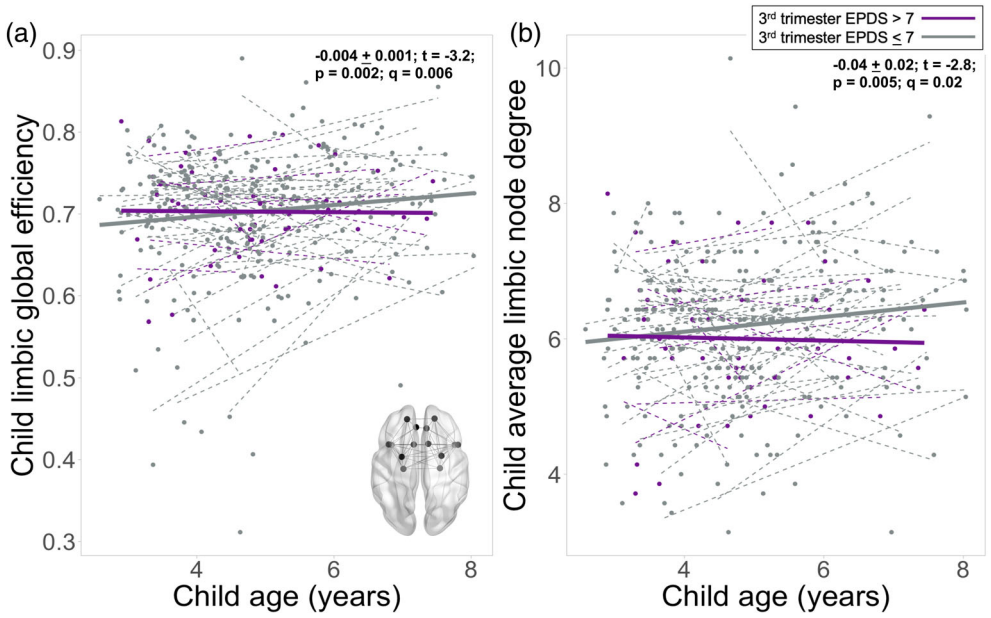


FIGURE 5 Prenatal depressive symptoms and age-related changes in child limbic connectivity. The interaction between third trimester depressive symptoms and child age was significantly associated with (a) child global efficiency and (b) average node degree of the limbic system (inset). For visualization, children are separated by maternal prenatal depressive symptoms split at an EPDS of 7 (top 20th percentile) ($n = 101$; 57 females; 2.6–8.0 years)

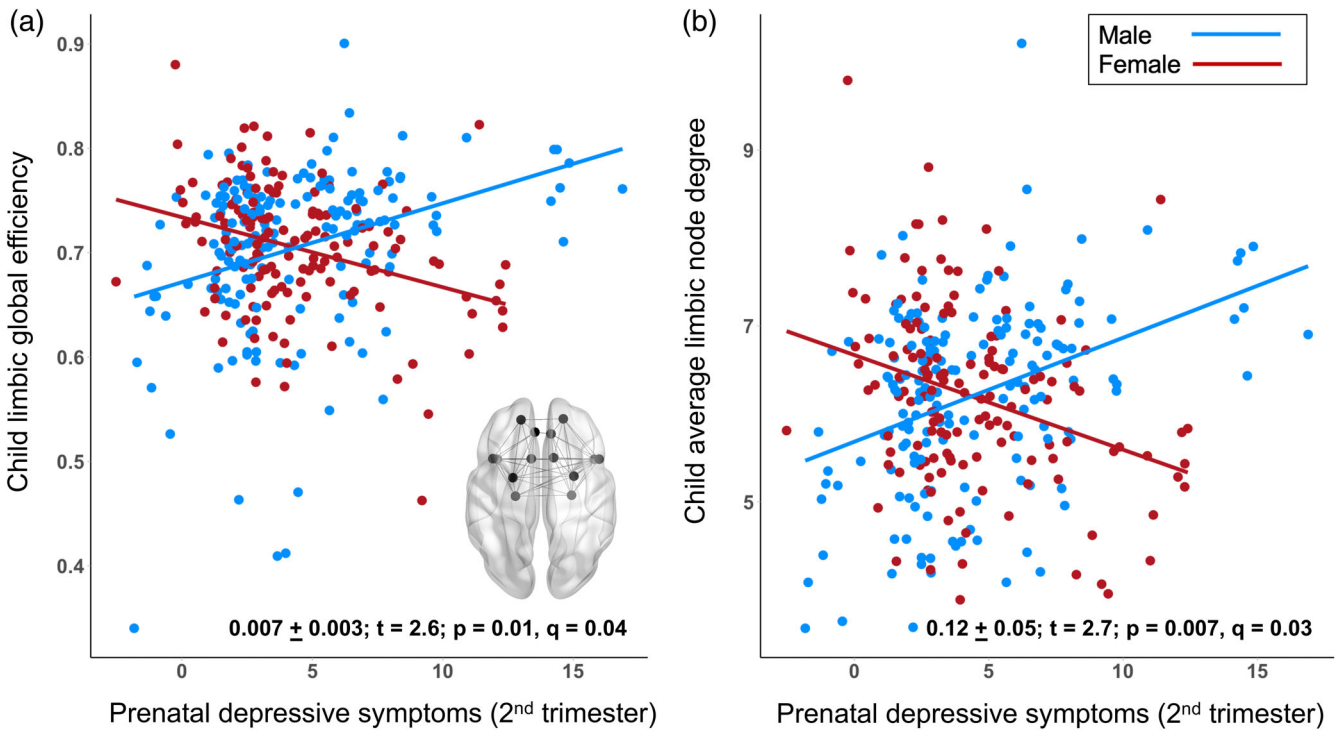


FIGURE 6 Prenatal depressive symptoms and sex differences in limbic global efficiency and node degree. In female children, higher prenatal depressive symptoms were associated with lower global efficiency (a) and average node degree (b), while the opposite was found in male children ($n = 93$; 308 scans; 52 females; 2.6–8.0 years). Plots represent residual values accounting for covariates (age, sex, income, birth weight, postnatal depressive symptoms)

across regions important for emotional control like the amygdala, orbitofrontal cortex, and temporal pole. This result is consistent with prior work showing lower degree centrality of the amygdala in young adults whose mothers experienced more symptoms of prenatal stress (Mareckova et al., 2022). Our findings also align with previous research suggesting weakened structural connectivity of individual connections of the limbic network (Dean et al., 2018; El Marroun et al., 2018; Hay et al., 2020; Posner et al., 2016). Importantly, weakened connectivity of similar networks has been observed in individuals with depression (Korgaonkar et al., 2014; Yun & Kim, 2021), suggesting that these brain changes may predispose children to later mental health challenges.

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The lack of associations between prenatal depressive symptoms and age-related changes in hippocampal volume aligns with previous work suggesting the amygdala may be more sensitive to prenatal depression than the hippocampus in children (Buss et al., 2012). Associations between prenatal stress and hippocampal volume growth have been observed in infancy (Moog et al., 2021; Qiu et al., 2013). These discrepancies may reflect a higher sensitivity of the hippocampus to forms of stress other than prenatal maternal depression. Postnatal adversity may have a more pronounced impact on hippocampal volumes than prenatal stress, as suggested by studies of early caregiving adversity (VanTieghem et al., 2021). It is also worth noting that the hippocampus may have more flexibility to correct its developmental course after exposure to environmental insult, as evidenced by research in animal models where chronic stress-related atrophy was reversed in the hippocampus, but not the amygdala (Vyas et al., 2004).

There were no significant effects of prenatal depressive symptoms on network measures in the DMN. Prior findings showed that prenatal maternal depressive symptoms were associated with structural connectivity of white matter tracts that make up edges of the structural DMN (e.g., uncinate fasciculus, cingulum) (El Marroun et al., 2018; Hay et al., 2020; Lebel et al., 2016). However, given the large number of tracts and fibers comprising the DMN, it is possible that altered connectivity in some tracts is compensated for by other tracts in the network to balance measures such as local and global efficiency overall.

Differences between findings related to second versus third trimester may reflect specific developmental processes occurring at these times. Second trimester network architecture is dependent on axon migration and synaptogenesis whereas the third trimester involves the beginning of myelination (Semple et al., 2013; Stiles & Jernigan, 2010). Age-related changes in limbic global efficiency may be linked to processes of brain development later in gestation such as the combination of synaptogenesis and early myelination (Semple et al., 2013; Stiles & Jernigan, 2010). Relationships between second trimester symptoms and amygdala volume likely relate back to neurogenesis, which is more prominent early in development and impacts subcortical volume (Semple et al., 2013; Stiles & Jernigan, 2010).

Some prior studies report sex-dependent effects of depressive symptoms on child brain white matter, which seem to be age and region-specific (Dean et al., 2018; Hay et al., 2020; Lebel et al., 2016). Sex differences have also been noted in associations between prenatal stress or depression and amygdala volume (Buss et al., 2012; Lehtola et al., 2020; Wen et al., 2017). Here, child sex was not a significant moderator of the depression-volume relationships in the amygdala or hippocampus. There is evidence that females and males have different amygdala and hippocampal volume trajectories (Uematsu et al., 2012), but more recent work has shown that growth rates do not appear to differ by sex (Zhou et al., 2021). Child sex did moderate the relationship between second trimester prenatal depressive symptoms and limbic global efficiency and average node degree. In females, we observed negative relationships with global efficiency and average node degree in the limbic network, whereas the opposite relationships were observed in males. This relationship did not interact with age, suggesting that while exposure to prenatal depressive symptoms may differentially influence network organization in male and female children, the sex differences remain stable across early childhood. Exploring sex differences alongside child behavior in future work will be important in determining if brain structure underlies differential susceptibility to behavioral and mental health concerns.

There are several possible mechanisms through which prenatal depressive symptoms may impact child brain development. Maternal glucocorticoid levels normally rise throughout pregnancy and glucocorticoid receptors are highly expressed in the placenta, mediating metabolic and anti-inflammatory effects (O'Donnell & Meaney, 2017). However, fetal glucocorticoid levels are lower than levels in maternal circulation because of a placental enzyme (11-beta-hydroxysteroid dehydrogenase type 2), which converts active glucocorticoids to an inert form (Chapman et al., 2013). This enzyme is regulated by pro-inflammatory cytokines (Chapman et al., 2013) and deficiencies or decreased activity in the enzyme can lead to overexposure of the fetus to cortisol, which can dysregulate the infant stress response (Newman et al., 2017). The right and left amygdala have glucocorticoid receptors that may be directly affected by cortisol release (McGowan & Matthews, 2018). Prenatal stressors like depressive symptoms may be associated with epigenetic regulation, for example, DNA methylation and histone modification of HPA-axis genes encoding cortisol binding receptors or the inactivating enzyme (Babenko et al., 2015; Conradt et al., 2013). It has been suggested that maternal anxiety and depression have a role in increased methylation of genes and subsequent increases in the salivary cortisol stress response in infants (Newman et al., 2017). Inflammation may also have a role. In humans, pro-inflammatory cytokine levels are elevated due to maternal depression and can reach and cross the placenta (Schepanski et al., 2018), where they may modulate other enzymes or processes (Chapman et al., 2013), or interfere with neurogenesis, neural migration, and synaptogenesis (Schepanski et al., 2018). Higher interleukin-6 (IL-6) is associated with larger right amygdala volume and stronger bilateral connectivity to brain regions involved in sensory processing, affect and learning and memory in offspring (Graham et al., 2018). Larger right amygdala volumes and left amygdala connectivity mediated the association between high maternal IL-6 concentration and low impulse control in 2-year-old children (Graham et al., 2018). Genes associated with the SNARE complex and brain-specific signaling pathways related to synaptic development appear to mediate the relationship between prenatal depressive symptoms and cortical–limbic development including amygdala volume (Qiu et al., 2017). Sex differences in global efficiency and average node degree observed here may be driven by interactions between prenatal depressive symptoms and genes that differ by sex (i.e., Y-linked genes) and have a role in network brain development in the second trimester (Reinius & Jazin, 2009).

It is important to note that few participants in this sample had clinically significant depressive symptoms (~5%), and/or high sociodemographic risk, as evidenced by higher incomes and education relative to the Canadian population (Table 1). This suggests that even subthreshold prenatal depressive symptoms may impact child brain development and are therefore important to consider. Associations between prenatal depressive symptoms and structural brain

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development may be even more prominent in people with worse depression symptoms; however, care should be taken in extrapolating these results as described below.

4.1 | Limitations

Women in this study were recruited from a larger community study and had generally low depressive symptoms and sociodemographic risk. Thus, it may not be appropriate to generalize these findings to a population with more sociodemographic diversity. We did not collect maternal depressive scores at each scan, and therefore we were unable to control for their possible influence on brain development, or their possible interactions with prenatal scores. Prior studies suggest that maternal depression prenatally is far more impactful than maternal depression in later childhood and young adulthood (Mareckova et al., 2020, 2022; Zou et al., 2019), though future studies should further evaluate the effects of maternal depression throughout childhood on brain structure. Prenatal and postnatal depressive symptoms can act through independent pathways (Osborne et al., 2018; Pearson et al., 2013); however, they are often significantly associated. Because we were not able to include maternal depression at each scan in our analyses, we are limited in our ability to ascertain prenatal vs. postnatal influences. We were unable to account for the potential effects of heritability as we did not measure genetic risk scores. Understanding that brain development is guided by both genetic and environmental factors (Stiles & Jernigan, 2010), this will be important to consider in future work. Individual and group metrics of structural and functional connectivity differ as a function of brain parcellation (Domhof et al., 2021; Rubinov & Sporns, 2010). Therefore, it is important to emphasize that while we chose definitions of the limbic network and DMN based on previous work using the AAL atlas (Thomas Yeo et al., 2011), our findings may differ with other parcellation schemes.

5 | CONCLUSIONS

This large longitudinal neuroimaging study shows that prenatal depressive symptoms are associated with age-related changes in amygdala volume and node degree and global efficiency of the structural limbic network in young children. Our sample included participants from low sociodemographic risk backgrounds with low to moderate depressive symptoms, providing evidence that in utero exposure to even low levels of symptoms could impact children's brain structure and organization in areas important for emotion regulation.

AUTHOR CONTRIBUTIONS

All authors had full access to the data in the study and take responsibility for the integrity of the data and accuracy of data analysis. Study concept and design: Catherine Lebel, Deborah Dewey, Nicole Letourneau, Gerald F. Giesbrecht, Claire Donnici, and Xiangyu Long. Formal analysis: Claire Donnici, Xiangyu Long, and Jess Reynolds. Data acquisition, analysis, or interpretation of data: all authors. Writing (original draft): Claire Donnici and Catherine Lebel. Writing (review and editing): all authors. Supervision: Catherine Lebel. Funding acquisition: Catherine Lebel, Deborah Dewey, Nicole Letourneau, and Gerald F. Giesbrecht.

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CONFLICT OF INTEREST

None of the authors have biomedical financial interests or potential conflicts of interest to report.

DATA AVAILABILITY STATEMENT

This project uses a neuroimaging data set collected by the Developmental Neuroimaging Lab (https://www.developmentalneuroimaginglab.ca) at the University of Calgary. This data set is publicly available: https://osf.io/axz5r/ (Reynolds et al., 2020).

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