Biological Psychiatry: CNNI

Archival Report

Long-term Influences of Prenatal Maternal Depressive Symptoms on the Amygdala–Prefrontal Circuitry of the Offspring From Birth to Early Childhood

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ABSTRACT

BACKGROUND: Prenatal maternal depression may have long-term impacts on amygdala-cortical development. This study explored associations of prenatal maternal depressive symptoms on the amygdala-cortical structural covariance of the offspring from birth to early childhood, derived from a longitudinal birth cohort.

METHODS: Structural magnetic resonance imaging was performed to obtain the amygdala volume and cortical thickness at each time point. Prenatal maternal depressive symptoms were measured using the Edinburgh Postnatal Depression Scale at 26 weeks of pregnancy. Regression analysis was used to examine the effects of the Edinburgh Postnatal Depression Scale on a structural coupling between the amygdala volume and cortical thickness at birth (n = 167) and 4.5 years of age (n = 199).

RESULTS: Girls whose mothers had high prenatal maternal depressive symptoms showed a positive coupling between the amygdala volume and insula thickness at birth (β = .617, p = .001) but showed a negative coupling between the amygdala volume and inferior frontal thickness at 4.5 years of age (β = −.369, p = .008). No findings were revealed in boys at any time point.

CONCLUSIONS: The development of the amygdala–prefrontal circuitry is vulnerable to environmental factors related to depression. Such a vulnerability might be sex dependent.

Keywords: Amygdala–cortical circuitry, Cortical thickness, Prenatal maternal depressive symptoms, Structural covariance, Structural magnetic resonance imaging, Structural network

https://doi.org/10.1016/j.bpsc.2019.05.006

Prenatal maternal depression has long-term impacts on emotional (1), behavioral (2), and cognitive outcomes (3) and increases the later risk for depression in the offspring (4). Prenatal maternal depressive symptoms are associated with alterations of the emotion-related circuitry in infants and children (5–8). Greater prenatal depressive symptoms are related to higher functional connectivity of the amygdala with cortical regions involved in emotion regulation in 6-month-old infants (6). Greater prenatal maternal depressive symptoms are related to larger right amygdala volume in young girls but not in young boys (7,9). These findings suggest that there is a potential influence of prenatal maternal depression on offsprings' amygdala–cortical circuitry.

Recently, Holmes *et al.* (10) employed structural magnetic resonance imaging (MRI) and investigated the relationship between the amygdala and the cortex. They found an inverse relationship between the amygdala volume and prefrontal cortex thickness in adults with extreme negative affect. In addition, reduced functional connectivity between the amygdala and prefrontal cortex, representing the disruption of the functional networks involved in emotion regulation, is found in both adolescents (11) and adults (12) with depression in comparison with healthy control subjects. These structural and functional findings are in line with Mayberg's neural model of depression that is characterized as hypoactivity of the prefrontal regions and hyperactivity of the amygdala in depression (13). Together, these findings may suggest poor control of the prefrontal cortex over the amygdala output (top-down regulation) in depression (10). However, owing to lack of imaging studies on infants and young children, it remains unclear whether the aforementioned top-down regulation of the amygdala–prefrontal neural mechanism applies to infants and young children with exposure to maternal depressive symptoms.

The current study explored the above two questions by examining influences of prenatal maternal depressive symptoms on structural covariance of the amygdala and the cortex in neonates and 4.5-year-old children who participated in a longitudinal birth cohort in Singapore. Structural covariance analysis has recently been employed to examine brain

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structural organization via the assessment of the correlation between anatomical measures, such as cortical thickness and structural volumes of the two brain regions (14). Such analysis has shown significant overlaps with the brain's resting state functional organization (15) and reflects anatomical connectivity of white matter pathways (16). We expected that prenatal maternal depression might disturb the amygdala–cortical development relevant to emotional regulation from birth to early childhood. Given that prenatal maternal depression is associated with alterations in brain structure (7) and function (5) in girls, we separately investigated the relations in girls and boys. We thus considered this study as an observational study rather than a specific hypothesis-driven study.

METHODS AND MATERIALS

Subjects

The longitudinal birth cohort study, Growing Up in Singapore Towards Healthy Outcomes (GUSTO) [see (17) for further details], was approved by the National Healthcare Group Domain Specific Review Board and the Sing Health Centralized Institutional Review Board. Written informed consent was obtained from mothers.

Children participating in GUSTO were invited to this neuroimaging study at birth and at 4.5 years of age. The GUSTO cohort consisted of pregnant Asian women who received their first trimester antenatal ultrasound scan at the National University Hospital and KK Women's and Children's Hospital in Singapore. Birth outcome and pregnancy measures were obtained from hospital records. The parents were Singapore citizens or permanent residents of Chinese, Malay, or Indian ethnic background. More detailed recruitment criteria are stated elsewhere (18).

Maternal education, ethnicity, and age were extracted from survey questionnaires conducted as part of a scheduled appointment during the 26th week of pregnancy. Birth outcomes—including gestational age; birth weight; Apgar score; and sex—were obtained from hospital records. This study included only children with maternal reports on depression scales and with gestational age ≥34 weeks, birth weight ≥2 kg, and a 5-minute Apgar score ≥8 to avoid potential effects of birth complications on brain development.

This neuroimaging study recruited 189 and 342 children shortly after their birth and at 4.5 years of age, respectively. There were no MRI scans performed during the period from birth to 4.5 years of age mainly because of challenges in imaging children at this young age and subject burden. Of the 189 neonatal subjects who underwent MRI, 6 subjects had unusable T2 data owing to poor image quality, and 3 subjects did not meet the inclusion criteria. The neonatal sample thus comprised 180 subjects. Moreover, 11 mothers of neonates did not complete depression (i.e., Edinburgh Postnatal Depression Scale [EPDS]) or demographic (i.e., maternal education status) questionnaires, and 2 outliers on the amygdala volume were found. Hence, the neonatal sample consisted of 167 subjects, of which 79 were girls and 88 were boys. Of the 342 4.5-year-old subjects who underwent MRI, 113 subjects had unusable T1 data owing to poor image quality and 4 subjects did not meet the inclusion criteria. The 4.5-year-old sample thus comprised 225 subjects. Among them, 25 mothers of infants did not complete depression or demographic questionnaires, and 1 outlier on the amygdala volume was found. Hence, the 4.5-year-old sample consisted of 199 subjects, of which 106 were girls and 93 were boys.

Owing to challenges in imaging young children, only 21 subjects had good T1-weighted MRI images at the two time points.

Maternal Depression Scale

The EPDS questionnaire (19) was administered to mothers at 26 weeks of pregnancy to assess depressive symptomatology. The EPDS is a widely used 10-item self-report scale designed as a screening instrument for postnatal depression and is valid for use in prenatal and early postnatal depression. Each item of the EPDS is scored on a 4-point scale (0–3), and items 3 and 5 to 10 are reverse scored.

The Beck Depression Inventory-II (BDI-II) and EPDS were also administered to mothers at 3 months, 1 year, 2 years, 3 years, and 4.5 years postpartum. The BDI-II is a widely used 21-item questionnaire that assesses the existence and severity of symptoms of depression and predicts the severity of clinical depressive symptoms (20). Each item of the BDI-II is scored on a 4-point scale (0–3). Higher total scores indicate more severe depressive symptoms.

Prorated imputation was performed when 8 or 9 questions were answered on the EPDS and 19 or 20 questions were answered on the BDI-II. To incorporate the EPDS and BDI-II scores, each EPDS/BDI-II score at each time point was first standardized. The standardization analysis was not restricted in the sample of this imaging study; rather, it was applied to the whole GUSTO sample (n = 1162). This study quantified postnatal maternal depressive symptoms using the average value over the course of the first 4.5 years postpartum (5) to represent the severity of postnatal maternal depressive symptoms in the following statistical analysis.

MRI Acquisition and Analysis

Neonatal Brain. A total of 189 neonates underwent axial fast spin-echo T2-weighted MRI (repetition time = 3500 ms, echo time = 110 ms, field of view = 256 × 256 mm, matrix size = 256 × 256, 50 axial slices with 2.0-mm thickness) at 5 to 17 days of life using a 1.5T GE scanner (GE Medical Systems, Milwaukee, WI) at the Department of Diagnostic and Interventional Imaging of the KK Women's and Children's Hospital. We obtained 2 acquisitions of the axial T2-weighted MRI while subjects were sleeping in the scanner. No sedation was used, and precautions were taken to reduce exposure to the MRI scanner noise. A neonatologist was present during each scan. A pulse oximeter was used to monitor heart rate and oxygen saturation throughout the scans. All brain scans were reviewed by a neuroradiologist (MVF). All axial slices of the T2-weighted MRI data were visually inspected to ensure no cross-slice motion or checkerboard patterns.

The neonatal brain tissue segmentation was based on a Markov random field model as detailed in Qiu *et al.* (21). The accuracies of the automated segmentation for the gray matter, white matter, and amygdala were 0.793, 0.862, and 0.75, respectively, evaluated based on a volume overlap ratio between the manual and automated segmentations of 20

Table 1. Demographics of Children With the Good Imaging Data

Measure	Neonatal Sample (n = 167)	4.5-Year-Old Sample (n = 199)
Child Characteristics		
Gestational age, weeks, mean (SD)	38.868 (1.133)	38.814 (1.272)
Birth weight, g, mean (SD)	3117.413 (390.636)	3114.910 (424.445)
Apgar score, mean (SD)	9.006 (0.077)	9.000 (0.101)
Sex, male/female, *n*	88/79	93/106
Age, years, mean (SD)	0.027 (0.006)	4.585 (0.083)
Total brain volume, cm^3, mean (SD)	547.737 (46.559)	1082.940 (94.487)
Left amygdala volume, mm^3, mean (SD)	210.497 (33.988)	1478.487 (167.960)
Right amygdala volume, mm^3, mean (SD)	185.449 (31.183)	1616.513 (181.060)
Mother Characteristics		
Prenatal maternal depression, mean (SD), [range]	8.623 (4.452), [0–21]	7.889 (4.620), [0–21]
Average (standardized) postnatal maternal depression, mean (SD)	–	0.022 (0.908)
Maternal ethnicity, %		
Chinese	45.51	49.25
Malay	41.32	31.66
Indian	13.17	19.09
Maternal education, %		
Primary school	3.59	6.03
Secondary school	34.13	31.16
Preuniversity, diploma, or technical course	44.91	38.20
University undergraduate level	13.77	22.11
Above university undergraduate level	3.59	2.50

neonatal brain datasets (21,22). A cortical surface was constructed at the boundary between gray and white matter using a graph-based topology correction algorithm (23). The cortical thickness was measured as the distance between the cortical surface and gray matter voxels at the boundary between gray matter and cerebrospinal fluid. The cortical thickness was smoothed using the Laplace–Beltrami basis functions on the cortical surface (24). For group comparison of the cortical thickness, we employed a large deformation diffeomorphic metric mapping algorithm (25,26) to align individual cortical surfaces to the atlas that was generated based on the cortical anatomy of the same 20 subjects (27,28) and transferred the thickness of each subject to the atlas.

Child Brain. Children underwent MRI scans at 4.5 years (± 5 months) of age using a 3T Siemens Skyra scanner (Siemens AG, Erlangen, Germany) with a 32-channel head coil at KK Women's and Children's hospital. Children went through an MRI home training program before the MRI visit and on-site MRI training [see details in (7)]. High-resolution isotropic T1-weighted magnetization prepared rapid acquisition gradient-echo was acquired with the protocol (192 slices, 1-mm thickness, in-plane resolution = 1 mm, sagittal acquisition, field of view = 192 × 192 mm, matrix = 192 × 192, repetition time = 2000 ms, echo time = 2.08 ms, inversion time = 877 ms, flip angle = 9°, scanning time = 3.5 minutes). The image quality was verified immediately after the acquisition through visual inspection when children were still in the scanner. A scan was repeated if ring-like artifacts owing to the head motion were observed on T1-weighted images. The image was removed from the study if no acceptable image was acquired after 3 repetitions.

To eliminate potential profound effects of head motion on our statistical results, we manually checked image quality based on the stringent criteria in Ducharme *et al.* (29). Disqualified images were excluded from this study. FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/) was then used to label each voxel in the usable T1-weighted image as gray matter, white matter, cerebrospinal fluid, or subcortical structures (e.g., hippocampus, amygdala, thalamus, caudate, putamen, globus pallidus) (30). FreeSurfer employed a Markov random field model that requests a prior probability obtained from a training dataset with T1-weighted images and their manual structural labels. In this study, we reconstructed the prior probability in the Markov random field model based on the manual segmentation of 30 Asian children and embedded it in FreeSurfer (replacing RB_all_2008-03-26.gca under freesurfer/average). A postprocessing quality check was conducted following by the instruction in https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/TroubleshootingData. The segmentation accuracy was assessed using a volume overlap ratio between the automated and manual segmentations. The accuracies of the automated segmentation for the gray matter, white matter, and amygdala were 0.93, 0.92, and 0.90, respectively.

For group comparison of the cortical thickness, we employed large deformation diffeomorphic metric mapping (25,26) to align individual cortical surfaces to the atlas and transferred the thickness of each subject to the atlas.

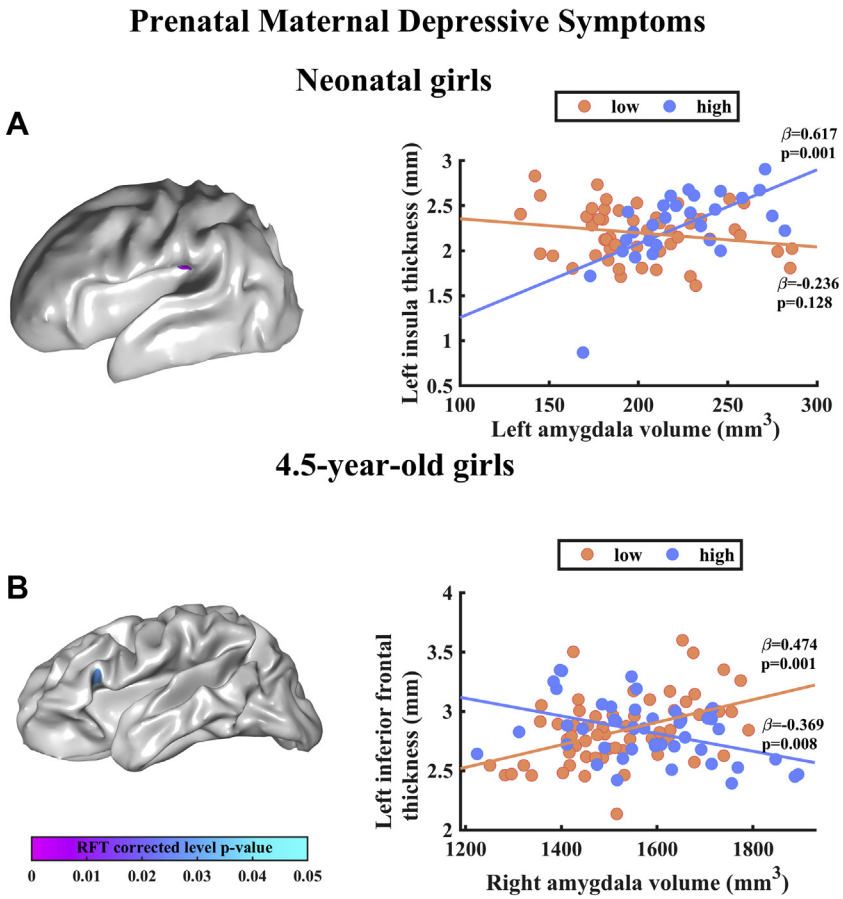

Figure 1. Influence of prenatal maternal depressive symptoms on amygdala volume–cortical thickness structural covariance in girls. **(A)** Influence of prenatal maternal depression on left amygdala volume–cortical thickness structural covariance in neonatal girls. **(B)** Influence of prenatal maternal depression on left amygdala volume–cortical thickness structural covariance in 4.5-year-old girls. Standardized β values and *p* values of the regression analysis in each group after adjustment for covariates are reported in scatterplots. Inflated cortical surface was used in the two panels. RFT, random field theory.

Statistical Analysis

Owing to the limited MRI sample size with all the 2-time points, our analysis in this study was done in a cross-sectional manner. Associations of prenatal maternal depressive symptoms with the amygdala volume–cortical thickness structural covariance at each time point were examined with a regression model,

$$Y \sim \text{covariates} + \text{amygdala\_volume} + \text{prenatal maternal depressive symptoms} + \text{amygdala\_volume} \times \text{prenatal maternal depressive symptoms},$$

where Y denotes cortical thickness at each vertex of the cortical surface. An F contrast was used to examine the effect of amygdala_volume × prenatal maternal depressive symptoms. The regression analysis was run for all the vertices on the cortical surface. Multiple comparisons across the vertices on the cortical surface were corrected based on random field theory (31) with a vertex-level $p < .001$, a cluster level of significance $p < .05$, and cluster size (cortical surface area) > 100 mm^2 for 4.5-year-old data and > 24 mm^2 for the neonatal brain. The thresholds were different because of the difference in the cortical surface areas at birth and 4.5 years of age. The above regression model was examined for girls and boys.

This study considered variables that were related to either the brain structure or prenatal maternal depressive symptoms as covariates in the above regression analysis. Hence, age at MRI and maternal ethnicity and education were included as covariates. The score of postnatal maternal depressive symptoms was also considered as a covariate for 4.5-year-old data in the regression model.

Post hoc analyses were further performed to examine the coupling of the right or left amygdala volume with the cortical thickness in groups, with a prenatal maternal depression score greater than its median value (high group) and equal to or lower than the median value (low group). The median values of the prenatal maternal depression score were computed based on the whole sample for the robustness of statistics. The cortical thickness used in this post hoc analysis was computed as the average value of thickness over the cortical regions within each significant cluster identified in the above regression model.

RESULTS

Demographics

Table 1 lists the demographic information of the samples at birth and 4.5-year-old time points. The two samples did not differ in gestational age (t = 0.427, p = .670), birth weight

Table 2. Effects of Prenatal Maternal Depressive Symptoms on Amygdala–Cortical Thickness Structural Covariance in Neonatal and 4.5-Year-Old Girls

Sample	Amygdala–Cortical Region Association	Corrected *p* Value	Surface Area, mm^2
Neonatal	L amygdala–L insula	<.001	31.1
4.5-Year-Old	R amygdala–L inferior frontal	.029	115.6

Surface area and random field theory–corrected cluster *p* values are presented.

L, left; R, right.

(t = 0.058, p = .954), Apgar score (t = 0.629, p = .530), maternal education (χ^2 = 6.139, p = .189), sex (χ^2 = 1.291, p = .256), maternal ethnicity (χ^2 = 4.558 p = .102), and prenatal maternal depressive symptoms (t = 1.701, p = .090). Among the samples at birth (n = 167) and 4.5-year-old (n = 199) time points, 25 mothers had a score of prenatal maternal depressive symptoms (EPDS score) greater than 13.

Among the subjects who underwent the MRI scanning, the prenatal maternal depression scores were not significantly different between neonates with and without usable brain image data (t = −0.425, p = .671). Similarly, there was no difference between 4.5-year-old children with and without usable brain image data (t = 0.183, p = .855). Moreover, there was no statistically significant difference in prenatal maternal depressive symptoms between boys and girls in the neonatal (t = −0.062, p = .951) and 4.5-year-old (t = 1.556, p = .121) samples with usable MRI data. Prenatal maternal depressive symptoms were associated with maternal education (r = −.121, p < .001), maternal ethnicity (F = 7.490, p = .001), sex (t = −1.991, p = .047), and postnatal maternal depressive symptoms (r = .469, p < .001). Hence, maternal education and ethnicity were considered as covariates in our statistical analysis. The postnatal maternal depressive symptoms were considered as covariates for the 4.5-year-old time point.

Influences of Prenatal Maternal Depressive Symptoms on the Amygdala–Cortical Circuitry

Girls. At birth, there was a significant association of prenatal maternal depressive symptoms with the left amygdala–left insula structural covariance in girls (corrected p < .001) (Figure 1A and Table 2). Post hoc analysis revealed a significant positive coupling between the left amygdala volume and left insula thickness in the group with prenatal maternal depressive symptom scores greater than 9 (median score) (β_{22} = .617, p = .001), and no significant coupling in the group with prenatal maternal depressive symptom scores less than or equal to 9 (β_{45} = −.236, p = .128).

At 4.5 years of age, there was a significant association of prenatal maternal depressive symptoms with the right amygdala–left inferior frontal structural covariance in girls (corrected p = .029) (Figure 1B and Table 2). Post hoc analysis revealed a significant negative coupling between the right amygdala volume and left inferior frontal thickness in the group with prenatal maternal depressive symptom scores greater than 8 (median score) (β_{47} = −.369, p = .008) and a significant positive coupling in the group with prenatal maternal depressive symptom scores less than or equal to 8 (β_{45} = .474, p = .001).

Boys. Prenatal maternal depressive symptoms were not associated with the amygdala–cortical structural covariance in neonatal or 4.5-year-old boys.

DISCUSSION

The current study investigated the associations of prenatal maternal depressive symptoms with the amygdala–cortical structural covariance in neonatal and 4.5-year-old girls and boys. Girls whose mothers had high prenatal maternal depressive symptoms showed a positive coupling between the amygdala volume and insula thickness at birth but showed a negative coupling between the amygdala volume and inferior frontal thickness at 4.5 years of age. These findings suggest that maternal mental health plays an essential role in the modulation of amygdala–prefrontal development during early life. Such associations are dependent on the timing of brain development and happen mostly in girls.

The amygdala, along with other subcortical structures, typically develops early and becomes mature during childhood, while the cortex, particularly the prefrontal cortex, has a later maturation period (32,33). During typical development, the amygdala functional coupling with the subcortical regions is stable. However, the amygdala functional coupling with the prefrontal cortex, insula, and posterior cortex exhibits vast changes from early childhood through adulthood, characterized by the appearance of both positively and negatively correlated coupling (34). Our findings significantly overlap with these cortical regions, suggesting that these developmental changes could be modulated by prenatal environmental risks.

Our findings showed a positive coupling of the amygdala with the insula at birth but showed a negative coupling with the inferior frontal cortex at 4.5 years of age in girls with high prenatal maternal depressive symptoms. The amygdala and insula share roles in processing emotion and saliency (35,36), while the inferior frontal cortex plays a role in evaluating emotional information, response inhibition, and emotion regulation through the modulation of the amygdala's response (37–40). A higher amygdala–insula functional connectivity in neonates was associated with greater fear in 6-month-old infants (41). A higher amygdala–insula functional connectivity in neonates was also associated with greater internalizing symptoms at 2 years of age (42). Moreover, altered amygdala and inferior frontal functional connectivity has been found in youths (43,44) and adults (12) with major depressive disorder. Greater prenatal maternal depressive symptoms were associated with greater development of the white matter tracts connecting the amygdala and inferior frontal region (i.e., uncinate fasciculus) in 2.6- to 5.1-year-old children (8). Our amygdala–prefrontal structural covariance findings in relation with prenatal maternal depressive symptoms are consistent with our previous findings on the amygdala functional networks, derived from resting-state functional MRI of the same cohort, in terms of brain regions, timing, and association directions (5,6). Greater prenatal maternal depressive symptoms are associated with greater left amygdala–left insula functional connectivity in 6-month-old infants (6) and with right amygdala–left prefrontal cortex in 4.5-year-old girls (5). It is unclear why our findings were shown at the specific laterality of the amygdala and the cortex. The literature regarding the

laterality of the amygdala dysfunction in depression is also mixed (12,45). Nonetheless, our findings derived from both structural and functional MRI data showed the same trend of the amygdala–cortical lateralization at each time point.

Prenatal maternal depressive symptoms were positively associated with the structural coupling of the amygdala–prefrontal circuits at birth but were negatively associated with the structural coupling of the amygdala–prefrontal circuits during early childhood. Such a shift was also observed across typical brain development from early childhood to early adulthood, implicating an intriguing model for the general development of regulatory connections between the amygdala and the prefrontal cortex (34,46). In other words, earlier amygdala development may drive heavier bottom-up signaling early in life, accelerating prefrontal development. As top-down signaling increasingly emerges over time, the prefrontal cortex plays a role in regulating signals from the amygdala (34,46). Nevertheless, in typical development, this shift of a positive connectivity to a negative connectivity occurs around the transition from childhood to adolescence. In our study, this shift happened much earlier, suggesting that prolonged exposure to maternal adversity might modulate the typical development of the amygdala–prefrontal cortex. In other words, early childhood is a critical and malleable period in the amygdala–cortical formation, along with increased vulnerability to environmental influences.

The amygdala–prefrontal structural covariance is a function of prenatal environment, which may appear to be sex dependent. This corroborates with evidence suggesting that sex-dependent associations of prenatal maternal depressive symptoms with early brain development are apparent only in girls (5,7,9). Furthermore, given that female individuals are more vulnerable to major depressive disorder (47,48), it is not surprising that the same risk factor, present in both male and female individuals, might predominantly alter the amygdala neurocircuitry in female individuals. Exact mechanisms that explain the presence of sex-dependent effects have yet to be clearly defined and need further investigation. One possible mechanism for such sex-dependent influences could be linked with stress. Female fetuses are more susceptible to changes in stress levels and the presence of sex-dependent time windows when the fetus is vulnerable to a maternal environment (49). The placenta appears to be responsive to changes in stress signals such as maternal glucocorticoid concentration (50). Elevated placental corticotropin-releasing hormone during pregnancy was associated with more fearful temperament and higher levels of distress behaviors in female infants (51). Prenatal exposure to maternal cortisol is associated with fearful temperament in female infants (51) and with a larger amygdala volume in 7-year-old girls (9). Despite this, some evidence suggests fetal exposure to maternal depression and stress as independent risk factors (50,52), which might need further investigation.

This study, to the best of our knowledge, is the first to investigate environmental (i.e., prenatal maternal depression) risk factor on the amygdala–cortical structural covariance in a relatively large sample across two time points (i.e., neonatal and 4.5-year-old girls and boys). While the neonatal and young children's neuroimaging datasets in this study are unique in their timing of acquisition and the number of subjects involved, it is nevertheless a modest sample size for our analysis on the amygdala–cortical structural covariance. Moreover, owing to challenges in imaging young children, our study had only 21 subjects with good MRI scans across the 2 time points. Hence, our study did not combine all brain data or employ longitudinal statistical models to examine associations of prenatal maternal depressive symptoms with the amygdala–cortical structural covariance from birth to early childhood. Last but not least, our assessment of maternal depressive symptoms was based on a standard screening tool intended to elicit a subjective report of emotional well-being, but it did not lead to a clinical diagnosis. The brain variations in the offspring are thus best considered as being associated with self-reported depressive symptoms and not with clinical depression per se.

To conclude, our study investigated the associations of prenatal maternal depressive symptoms with the amygdala–cortical neurocircuitry in girls from birth to early childhood. Our findings suggest that early childhood is a critical and malleable period in the formation of the amygdala–cortical network along with increased vulnerability to environmental influences. The vulnerability of the development of the amygdala–cortical circuitry to environmental factors related to depression might be sex dependent.

ACKNOWLEDGMENTS AND DISCLOSURES

This research was supported by the Singapore National Research Foundation under its Translational and Clinical Research (TCR) Flagship Programme and administered by the Singapore Ministry of Health's National Medical Research Council (NMRC) (Grant Nos. NMRC/TCR/004-NUS/2008 and NMRC/TCR/012-NUHS/2014 [to Y-SC, LPS, AQ]). Additional funding was provided by the Singapore Institute for Clinical Sciences, Agency for Science Technology and Research, Singapore Ministry of Education (Academic Research Fund Tier 1; Grant No. NUHSRO/2017/052/T1-SRP-Partnership/01 [to Y-SC, LPS, AQ]), and National University of Singapore Institute of Data Science (to Y-SC, LPS, AQ).

All authors report no biomedical financial interests or potential conflicts of interest.

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Received Mar 15, 2019; revised and accepted May 9, 2019.

REFERENCES

1. Davis EP, Snidman N, Wadhwa PD, Glynn LM, Schetter CD, Sandman CA (2004): Prenatal maternal anxiety and depression predict negative behavioral reactivity in infancy. Infancy 6:319–331.
2. Luoma I, Tamminen T, Kaukonen P, Laippala P, Puura K, Salmelin R, *et al.* (2001): Longitudinal study of maternal depressive symptoms and child well-being. J Am Acad Child Adolesc Psychiatry 40:1367–1374.
3. Sohr-Preston SL, Scaramella LV (2006): Implications of timing of maternal depressive symptoms for early cognitive and language development. Clin Child Fam Psychol Rev 9:65–83.

4. Plant DT, Pariante CM, Sharp D, Pawlby S (2015): Maternal depression during pregnancy and offspring depression in adulthood: Role of child maltreatment. Br J Psychiatry 207:213–220.
5. Soe NN, Wen DJ, Poh JS, Chong YS, Broekman BF, Chen H, *et al.* (2018): Perinatal maternal depressive symptoms alter amygdala functional connectivity in girls. Hum Brain Mapp 39:680–690.
6. Qiu A, Anh TT, Li Y, Chen H, Rifkin-Graboi A, Broekman BFP, *et al.* (2015): Prenatal maternal depression alters amygdala functional connectivity in 6-month-old infants. Transl Psychiatry 5:e508.
7. Wen DJ, Poh JS, Ni SN, Chong Ys, Chen H, Kwek K, *et al.* (2017): Influences of prenatal and postnatal maternal depression on amygdala volume and microstructure in young children. Transl Psychiatry 7:e1103.
8. 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. Biol Psychiatry 80:859–868.
9. Buss C, Davis EP, Shahbaba B, Pruessner JC, Head K, Sandman CA (2012): Maternal cortisol over the course of pregnancy and subsequent child amygdala and hippocampus volumes and affective problems. Proc Natl Acad Sci U S A 109:E1312–E1319.
10. Holmes AJ, Lee PH, Hollinshead MO, Bakst L, Roffman JL, Smoller JW, *et al.* (2012): Individual differences in amygdala-medial prefrontal anatomy link negative affect, impaired social functioning, and polygenic depression risk. J Neurosci 32:18087–18100.
11. Connolly CG, Ho TC, Blom EH, LeWinn KZ, Sacchet MD, Tymofiyeva O, *et al.* (2017): Resting-state functional connectivity of the amygdala and longitudinal changes in depression severity in adolescent depression. J Affect Disord 207:86–94.
12. Ramasubbu R, Konduru N, Cortese F, Bray S, Gaxiola-Valdez I, Goodyear B (2014): Reduced intrinsic connectivity of amygdala in adults with major depressive disorder. Front Psychiatry 5:17.
13. Mayberg HS (1997): Limbic-cortical dysregulation: A proposed model of depression. J Neuropsychiatry Clin Neurosci 9:471–481.
14. Alexander-Bloch A, Giedd JN, Bullmore E (2013): Imaging structural co-variance between human brain regions. Nat Rev Neurosci 14:322–336.
15. Zielinski BA, Gennatas ED, Zhou J, Seeley WW, Raichle ME (2010): Network-level structural covariance in the developing brain. Proc Natl Acad Sci U S A 107:18191–18196.
16. Gong G, He Y, Chen ZJ, Evans AC (2012): Convergence and divergence of thickness correlations with diffusion connections across the human cerebral cortex. NeuroImage 59:1239–1248.
17. Soh SE, Lee SSM, Hoon SW, Tan MY, Goh A, Lee BW, *et al.* (2012): The methodology of the GUSTO cohort study: A novel approach in studying pediatric allergy. Asia Pac Allergy 2:144–148.
18. Soh S-E, Tint MT, Gluckman PD, Godfrey KM, Rifkin-Graboi A, Chan YH, *et al.* (2014): Cohort profile: Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort study. Int J Epidemiol 43:1401–1409.
19. Cox JL, Holden JM, Sagovsky R (1987): Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 150:782–786.
20. Beck AT, Ward CH, Mendelson MM, Mock JJ, Erbaugh JJ (1961): An inventory for measuring depression. Arch Gen Psychiatry 4:561–571.
21. Qiu A, Tuan TA, Ong ML, Li Y, Chen H, Rifkin-Graboi A, *et al.* (2015): COMT haplotypes modulate associations of antenatal maternal anxiety and neonatal cortical morphology. Am J Psychiatry 172:163–172.
22. Rifkin-Graboi A, Bai J, Chen H, Hameed WB, Sim LW, Tint MT, *et al.* (2013): Prenatal maternal depression associates with microstructure of right amygdala in neonates at birth. Biol Psychiatry 74:837–844.
23. Han X, Xu C, Braga-Neto U, Prince JL (2002): Topology correction in brain cortex segmentation using a multiscale, graph-based algorithm. IEEE Trans Med Imaging 21:109–121.
24. Tan M, Qiu A (2015): Spectral Laplace-Beltrami wavelets with applications in medical images. IEEE Trans Med Imaging 34:1005–1017.
25. Zhong J, Qiu A (2010): Multi-manifold diffeomorphic metric mapping for aligning cortical hemispheric surfaces. NeuroImage 49:355–365.
26. Tan M, Qiu A (2016): Large deformation multiresolution diffeomorphic metric mapping for multiresolution cortical surfaces: A coarse-to-fine approach. IEEE Trans Image Process 25:4061–4074.
27. Bai J, Abdul-Rahman MF, Rifkin-Graboi A, Chong YS, Kwek K, Saw SM, *et al.* (2012): Population differences in brain morphology and microstructure among Chinese, Malay, and Indian neonates. PLoS One 7:e47816.
28. Joshi S, Davis B, Jomier M, Gerig G (2004): Unbiased diffeomorphic atlas construction for computational anatomy. NeuroImage 23(suppl 1): S151–S160.
29. Ducharme S, Albaugh MD, Nguyen TV, Hudziak JJ, Mateos-Perez JM, Labbe A, *et al.* (2016): Trajectories of cortical thickness maturation in normal brain development—The importance of quality control procedures. NeuroImage 125:267–279.
30. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, *et al.* (2002): Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. Neuron 33:341–355.
31. Worsley KJ, Taylor JE, Tomaiuolo F, Lerch J (2004): Unified univariate and multivariate random field theory. NeuroImage 23:S189–S195.
32. Gee DG, Humphreys KL, Flannery J, Goff B, Telzer EH, Shapiro M, *et al.* (2013): A developmental shift from positive to negative connectivity in human amygdala-prefrontal circuitry. J Neurosci 33:4584–4593.
33. Gilmore JH, Shi F, Woolson SL, Knickmeyer RC, Short SJ, Lin W, *et al.* (2012): Longitudinal development of cortical and subcortical gray matter from birth to 2 years. Cereb Cortex 22:2478–2485.
34. Gabard-Durnam LJ, Flannery J, Goff B, Gee DG, Humphreys KL, Telzer E, *et al.* (2014): The development of human amygdala functional connectivity at rest from 4 to 23 years: A cross-sectional study. NeuroImage 95:193–207.
35. Menon V (2015): Salience network. In: Toga AW, editor. Brain Mapping: An Encyclopedic Reference. Waltham, MA: Academic Press, 597–611.
36. Lindquist KA, Wager TD, Kober H, Bliss-Moreau E, Barrett LF (2012): The brain basis of emotion: A meta-analytic review. Behav Brain Sci 35:121–143.
37. Swick D, Ashley V, Turken U (2008): Left inferior frontal gyrus is critical for response inhibition. BMC Neurosci 9:102.
38. Grecucci A, Giorgetta C, Bonini N, Sanfey AG (2013): Reappraising social emotions: The role of inferior frontal gyrus, temporo-parietal junction and insula in interpersonal emotion regulation. Front Hum Neurosci 7:523.
39. Beer JS, Knight RT, D'Esposito M (2006): Controlling the integration of emotion and cognition: The role of frontal cortex in distinguishing helpful from hurtful emotional information. Psychol Sci 17:448–453.
40. Hayes JP, Morey RA, Petty CM, Seth S, Smoski MJ, McCarthy G, *et al.* (2010): Staying cool when things get hot: Emotion regulation modulates neural mechanisms of memory encoding. Front Hum Neurosci 4:230.
41. Graham AM, Buss C, Rasmussen JM, Rudolph MD, Demeter DV, Gilmore JH, *et al.* (2016): Implications of newborn amygdala connectivity for fear and cognitive development at 6-months-of-age. Dev Cogn Neurosci 18:12–25.
42. Rogers CE, Sylvester CM, Mintz C, Kenley JK, Shimony JS, Barch DM, *et al.* (2017): Neonatal amygdala functional connectivity at rest in healthy and preterm infants and early internalizing symptoms. J Am Acad Child Adolesc Psychiatry 56:157–166.
43. Pannekoek JN, van der Werff SJA, Meens PHF, van den Bulk BG, Jolles DD, Veer IM, *et al.* (2014): Aberrant resting-state functional connectivity in limbic and salience networks in treatment-naive clinically depressed adolescents. J Child Psychol Psychiatry 55:1317–1327.
44. Fowler CH, Miernicki ME, Rudolph KD, Telzer EH (2017): Disrupted amygdala-prefrontal connectivity during emotion regulation links stress-reactive rumination and adolescent depressive symptoms. Dev Cogn Neurosci 27:99–106.

45. Drevets WC, Price JL, Furey ML (2008): Brain structural and functional abnormalities in mood disorders: Implications for neurocircuitry models of depression. Brain Struct Funct 213:93–118.
46. Gee DG, Gabard-Durnam LJ, Flannery J, Goff B, Humphreys KL, Telzer EH, *et al.* (2013): Early developmental emergence of human amygdala-prefrontal connectivity after maternal deprivation. Proc Natl Acad Sci U S A 110:15638–15643.
47. Piccinelli M, Wilkinson G (2000): Gender differences in depression: Critical review. Br J Psychiatry 177:486–492.
48. Albert PR (2015): Why is depression more prevalent in women? J Psychiatry Neurosci 40:219–221.
49. Buss C, Davis EP, Class QA, Gierczak M, Pattillo C, Glynn LM, *et al.* (2009): Maturation of the human fetal startle response: Evidence for sex-specific maturation of the human fetus. Early Hum Dev 85:633–638.
50. Sandman CA, Davis EP, Buss C, Glynn LM (2012): Exposure to prenatal psychobiological stress exerts programming influences on the mother and her fetus. Neuroendocrinology 95:7–21.
51. Sandman CA, Glynn LM, Davis EP (2013): Is there a viability-vulnerability tradeoff? Sex differences in fetal programming. J Psychosom Res 75:327–335.
52. O'Donnell KJ, Meaney MJ (2017): Fetal origins of mental health: The developmental origins of health and disease hypothesis. Am J Psychiatry 174:319–328.