NEW RESEARCH

Cortical Development Mediates Association of Prenatal Maternal Depressive Symptoms and Child Reward Sensitivity: A Longitudinal Study

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Objective: Maternal depression during pregnancy has long-term impacts on offspring. This study used neuroimaging and behavioral data from children aged 4 to 6 years and investigated whether prenatal maternal depressive symptoms (pre-MDS) associated with child cortical morphological development and subsequent reward-related behaviors in preschoolers.

Method: Pre-MDS was measured using the Edinburgh Postnatal Depression Scale at 26 weeks of pregnancy. Children (n = 130) underwent structural magnetic resonance imaging (MRI) at both 4 and 6 years of age. Child sensitivity to reward and punishment was reported by mothers when children were 6 years of age. Linear mixed-effect models examined pre-MDS associations with child cortical thickness and surface area. Mediation analysis examined whether cortical development mediated associations between pre-MDS and child sensitivity to reward and punishment.

Results: The 3-way interactions of pre-MDS, age, and sex on cortical thickness and surface area were not statistically significant. We found a significant interaction of pre-MDS with sex on the cortical surface area but not on thickness or their growth from 4 to 6 years, adjusting for ethnicity, socioeconomic status, baseline age, and postnatal MDS as covariates. Higher pre-MDS scores were associated with larger surface areas in the prefrontal cortex, superior temporal gyrus, and superior parietal lobe (SPL) in boys, whereas the opposite pattern was seen in girls. The SPL surface area mediated the relationship between pre-MDS and sensitivity to reward in girls.

Conclusion: Prenatal maternal depression alters the cortical morphology of pre-schoolers in a sex-dependent manner.

Key words: cortical development, child behavior, structural MRI, maternal depression during pregnancy, cortical morphology

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Depressive symptoms affect approximately 7% to 12% of pregnant women.[1] It is now well recognized that prenatal maternal depressive symptoms are associated with fetal neurobehavioral development,[2] offspring socio-emotional development,[3] and an increased risk of psychopathology in the offspring.[4] Furthermore, prenatal maternal depressive symptoms (Pre-MDS) are associated with the right amygdala microstructure of neonates[5] and the right frontal area of 1-month-old infants.[6] Pre-MDS is also related to cortical thinning in the right inferior frontal and middle temporal regions in offspring approximately 2.5 to 5.0 years of age[7] and in the prefrontal and somatosensory cortex in children 6 to 9 years of age.[8] Therefore, prenatal maternal depression can shape fetal brain development that may persist into childhood and form the basis for the transgenerational transmission of vulnerability for depression.[6-9] Nevertheless, it is not well understood how maternal depression during pregnancy shapes the neural developmental trajectory in early life, which may modulate child behaviors.

Biological mechanisms linking prenatal maternal depressive symptoms with child brain development and behaviors remain unclear. One of the most promising hypotheses involves prenatal programming of the hypothalamic–pituitary–adrenal (HPA) axis functioning.[4] Nevertheless, there are mixed findings.[4,10,11] Several studies failed to find an association between maternal depressive symptoms and cortisol levels during pregnancy,[10,11] which may be partially because of the severity of maternal depression. Other studies suggest sex differences in HPA axis programming. Female offspring exposed to prenatal stressors shows increased HPA axis reactivity compared with male offspring.[12] Human brain imaging

studies also have shown that maternal cortisol during pregnancy is related to an increased amygdala volume in 7-year-old girls.[13] Pre-MDS is associated with the volume[14] and white matter microstructure[6] of the amygdala, as well as the coupling between the amygdala volume and frontal thickness[14,15] in girls, but not boys. These findings suggest that such fetal programming enhances sex-specific neurodevelopment of the offspring, particularly in the prefrontal and limbic regions.

Another promising mechanism is proposed to be related to inflammation. Mothers with depressive symptoms during pregnancy exhibit altered inflammatory signals[10,16] and hence may influence fetal development. Maternal inflammatory proteins, such as interleukin (IL)−1β, IL-8, IL-6, IL-10, and tumor necrosis factor−α (TNF-α), interfere with neurogenesis, neural migration, and synaptogenesis in the prefrontal cortex, hippocampus, and amygdala of the offspring.[17-19] Maternal IL-6 levels during pregnancy are associated with the neonatal amygdala volume and functional connectivity with the hippocampus and sensory cortex that, in turn, predict subsequent behavior of 2-year-old children.[19,20] Similarly, transforming growth factor−β (TGF-β) signaling and other inflammatory signaling modulate the relationship of prenatal maternal depressive symptoms with neonatal brain and amygdala development in early life even if maternal depressive symptoms are mild.[21]

Prenatal stress−induced alterations in the prefrontal cortex and limbic brain regions in infants and children have been implicated in major depressive disorder and may increase the risk of psychopathology in children.[22,23] Early life maternal stress is associated with alternations in neural systems that regulate stress response and affect reward processing, suggesting that the neurobiology of response to early stress and reward processing substantially overlap.[24] Alterations in neural correlates of reward processes are a risk factor for depression and attention-deficit/hyperactivity disorder (ADHD) in preschool- and school-aged children.[25-27] Preschoolers with depression show a blunted event-related potential (ERP) amplitude in a rewarding task compared to healthy controls.[26] Children with ADHD symptoms show decreased brain activity during reward processing and increased reward sensitivity in daily life.[28] Taking these findings together, we expected a possible neural basis to support the relationship between prenatal maternal depressive symptoms and reward sensitivity of children.

This study aimed to examine the following: (1) the potential associations of pre-MDS with cortical brain development from age 4 to 6 years, a critical period for neurodevelopment; and (2) the potential role of cortical development in mediating the association between pre-MDS and child sensitivity to reward and punishment. We expected that the associations between pre-MDS and cortical development are sex dependent, which may in turn mediate child sensitivity to reward and punishment. We used data from a longitudinal cohort study, Growing Up in Singapore Towards Healthy Outcomes (GUSTO), in which pre-MDS was assessed during the third trimester. Cortical thickness and surface area were used to characterize cortical development derived from structural magnetic resonance imaging (MRI) data in children at 4 and 6 years of age. In addition, child behavior was measured via the Sensitivity to Punishment and Sensitivity to Reward Questionnaire for Children (SPSRQ-C) at 6 years of age. It has been shown that SPSRQ-C sensitivity to reward/punishment scores largely correlate with anxiety−depression, as well as internalizing and externalizing problems in young children from general populations.[29] This prospective longitudinal study allows the evaluation of putative associations among pre-MDS, cortical development, and child behaviors. The examination of mediation roles of cortical development can potentially shed light on neural pathways linking maternal factors and child behaviors, which might facilitate clinical intervention and treatment.

METHOD

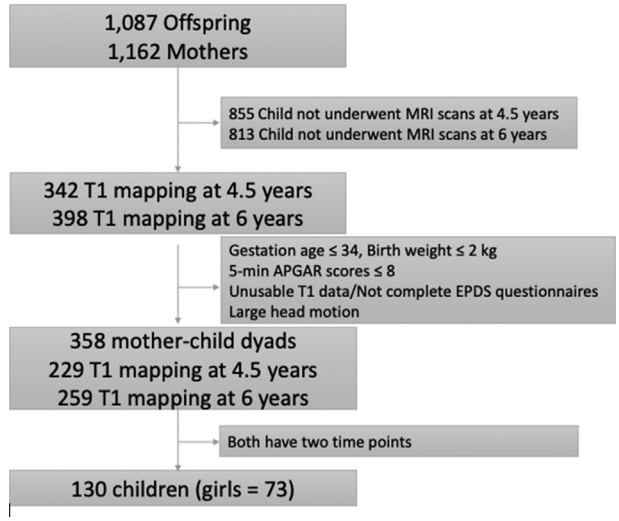
Participants

Growing Up in Singapore Towards Healthy Outcomes (GUSTO), a prospective longitudinal birth cohort study (http://www.gusto.sg), was approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB) and the Sing Health Centralized Institutional Review Board (CIRB). Recruitment commenced in 2009 with a cohort of 1,163 pregnant mothers in their first trimester. The mothers and children were followed throughout pregnancy. Mothers on chemotherapy, psychotropic drugs, or with type 1 diabetes mellitus were excluded from the study. The recruitment procedure of the cohort was detailed in Soh *et al.*[30] Maternal education level, family income, and maternal ethnicity were obtained from survey questionnaires conducted as part of a scheduled appointment during the 26th week of pregnancy. Socioeconomic status (SES) was computed as the averaged value of household income and maternal education, where household income and maternal education were standardized to z scores.[31] Birth outcomes, such as gestational age, birth weight, Appearance, Pulse, Grimace, Activity, Respiration (APGAR) score, and sex, as well as pregnancy measures, were obtained from the hospital record.

Mother−child dyads who were enrolled in this prospective GUSTO birth cohort study were asked to participate in this neuroimaging study when children were at birth (5−17 days), at age 4 years (mean age = 4.6 years), and at

age 6 years (mean age = 6.1 years). Because of large differences in MRI scanners and image acquisition (T2-weighted MRI at birth and T1-weighted MRI in childhood) between neonates and children, we did not include the neonatal scans in this longitudinal study. This study recruited 342 and 398 children at 4 and 6 years of age, respectively, from the GUSTO sample. This study included children with the following: gestational age ≥34 weeks; birth weight ≥2 kg; 5-minute APGAR score ≥8 to avoid potential impacts on brain development; mothers who completed maternal questionnaires; and good MRI data at both time points. Figure 1 provides a flow chart of subject selection based on the above inclusion criteria. This resulted in 130 children who fulfilled the above-mentioned inclusion criteria. Table 1 lists the demographic information of these 130 children. Table S1, available online, provides demographic information of 358 children who had at least 1 good MRI scan.

FIGURE 1 Flow Chart of Subject Selection



Maternal Depression Scales

Pre-MDS was assessed among mothers at 26 weeks of pregnancy using the Edinburgh Postnatal Depression Scale (EPDS). The EPDS is a widely used, 10-item self-report scale designed as a screening instrument for postnatal depression and valid for use in prenatal and early postnatal depression.[32,33] Each item of the EPDS is scored on a 4-point scale (0−3), and items 3 and 5 to 10 are reverse scored. Points of all items are summed as the total score. A higher score of EPDS indicates greater severity of depression.

The Beck Depression Inventory−II (BDI-II) was also administered to the mother at 3 months, 12 months, 24 months, 36 months, and 54 months 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.[34] Each item of the BDI-II is scored on a 4-point scale (0−3). Points of all items are summed as the total score. A higher score of BDI-II indicates more severe depressive symptoms. The postnatal maternal depressive score was averaged for the scores of BDI-II at 3 to 54 months and was considered as a control variable of postnatal maternal depressive symptoms in statistical analysis because of their stability across time.[35]

Child Behavior Checklist

Child internalizing and externalizing behavior problems were assessed using the maternal report of the CBCL/1.5-5[36] at 4 years of age (48−50 months). This study used these only to indicate whether children in this study had behavioral problems.

Sensitivity to Reward and Punishment in Children

The Sensitivity to Punishment and Sensitivity to Reward Questionnaire for Children (SPSRQ-C) was completed by mothers when children were 6 years of age. The SPSRQ-C measures converge with the measures of temperament and *DSM-5* disorders.[29] The SPSRQ-C is a widely used, 33-item questionnaire that assesses sensitivity to reward and punishment behaviors in children based on the Gray sensitivity to reinforcement model.[37,38] Each item is scored on a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree). The SPSRQ-C is divided into punishment and reward sensitivity scales.[39] Reward sensitivity, in general, quantifies impulsivity/fun-seeking (eg, "your child often does things to be praised"), reward responsivity (eg, "your child engages in risky behavior for a quick reward"), and drive (eg, "your child likes to compete and do everything they can to win"). This study used the raw scores of sensitivity to reward and punishment. A higher score means higher sensitivity to punishment or reward. The reliability was 0.87 for punishment sensitivity and 0.69 for reward responsivity using Cronbach analysis based on our data.

Magnetic Resonance Image Acquisition and Analysis

The MRI data were acquired when children were at 4 years (range, 4.36−4.75 years) and 6 years (range, 5.83−6.61 years) of age. Children underwent MRI scans using a 3T scanner (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil at KK Women's and Children's hospital. The T_1-weighted imaging protocol was as follows: high-resolution isotropic T_1-weighted Magnetization Prepared Rapid Gradient Recalled Echo (MPRAGE; 192 slices, 1-mm thickness, in-plane resolution 1 mm, sagittal acquisition, field-of-view 192 × 192 × 192 mm^2,

TABLE 1 Demographic Characteristics and Birth Outcomes of Study Sample

Measures	Boys (n = 57)	Girls (n = 73)	*P*
Birth weight, g, mean (SD)	3,223 (399)	2,993 (412)	.002**
Gestational age (week), mean (SD)	38.6 (1.51)	39 (1.33)	.089
APGAR score, mean (SD)	9.0 (0.01)	9.0 (0.12)	.380
Baseline age, mean (SD)	4.65 (0.09)	4.64 (0.07)	.690
Follow-up age, mean (SD)	6.13 (0.09)	6.13 (0.14)	.970
Maternal ethnicity, %			
Chinese	40.3	49.3	.420
Malay	43.9	35.6	
Indian	15.8	15.1	
Socioeconomic status (*z* score)	0.13 (0.86)	−0.19 (0.78)	.031*
Frequency of smoking exposure, %	40.4	50.7	0.120
Pregnancy complications, n			
Gestational diabetes	8	6	—
Hypertension	2	1	—
Hypoglycemia	5	2	—
Prenatal MDS, mean (SD)	6.8 (3.9)	8.1 (4.8)	.120
Postnatal MDS, mean (SD)			
3-monBDI score	6.5 (5.9)	7.4 (6.9)	.420
12-mo BDI score	6.4 (6.4)	7.1 (6.8)	.610
24-mo BDI score	5.7 (4.2)	7.7 (6.5)	.040*
36-mo BDI score	6.4 (4.4)	8.0 (6.4)	.120
54-mo BDI score	5.2 (4.1)	6.9 (7.7)	.150
4-y Internalizing *T* score, mean (SD),	51.2 (7.1)	54.5 (8.7)	.023*
4-y Externalizing *T* score, mean (SD)	49.2 (7.8)	50.5 (7.7)	.360
4-y Internalizing *T* score >65, n	0	10	—
4-y Externalizing T score >65, n	1	1	—
BAS-BIS scales			
Sensitivity to Punishment	47.7(5.9)	47.1(5.3)	.500
Sensitivity to Reward	52.7(6.3)	53.1(7.1)	.790

Note: *APGAR = Appearance, Pulse, Grimace, Activity, and Respiration; BAS = Behavioural Activation System; BIS = Behavioural Inhibition System; BDI = Beck Depression Inventory; MDS = maternal depressive symptoms.*
*p < .05; **p < .01.

matrix = 192 × 192 × 192, repetition time = 2,000 milliseconds, echo time = 2.08 milliseconds, inversion time = 877 milliseconds, flip angle = 9°, scanning time = 3.5 minutes). The home training program for the magnetic resonance image acquisition and the image quality check protocol was detailed in supplementary material.[14] 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 head motion were observed on T_1-weighted images. The image was removed from the study if no acceptable image was acquired after 3 repetitions. To eliminate the potentially profound effects of head motion on our statistical results, we manually checked image quality based on the stringent criteria in Ducharme *et al.*[40]

The T_1-weighted image analysis was started when the data collection of the 4-year time point was completed. FreeSurfer longitudinal analysis pipeline (a bug-fixed version 5.3.0) was used to segment brain tissues into the following 3 tissue types: gray matter,[41] white matter,[42] and cerebrospinal fluid (CSF). FreeSurfer used a Markov random field (MRF) model that requests for a prior probability obtained from a training dataset with T_1-weighted images and their manual structural labels. This study

reconstructed the prior probability in the MRF 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 post-processing quality check was conducted by one well-trained researcher (based on the instruction given at https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/TroubleshootingData). The surface maps of cortical thickness and surface area were resampled, mapped to a standard surface, and smoothed using a circularly symmetric Gaussian kernel with a full-width at half-maximum of 10 mm as suggested in FreeSurfer.

Statistical Analysis

To examine sex-specific effects of pre-MDS on cortical development from 4 to 6 years of age, we used a spatio-temporal linear mixed effect model in MATLAB (2017b) on cortical thickness or surface area at each vertex.[43] This model included pre-MDS scores, postnatal BDI depressive scores, socioeconomic status (SES), baseline age, time (from baseline to follow-up), maternal ethnicity, sex, and all 2-way and 3-way interactions. A random intercept was included to capture individual variability in the baseline. Hence, the model was specified as follows, in MATLAB fitlme syntax: *Surface area/Cortical thickness ~ pre-MDS* + $BDI_{postnatal}$ + *SES* + $Age_{Baseline}$ + *Ethnicity* + *Sex* + *Time* + (*Time * sex * pre-MDS*) + (*sex * pre-MDS*) + (*Time * pre-MDS*) + (*Time*gender*) + 1 | *Subject*. The main measures of interest were the 3-way interaction (*Time * sex * pre-MDS*) and 2-way interactions (*Time * pre-MDS and sex * pre-MDS*) for the investigation of our research questions. We followed a hierarchical regression method such that when the 3-way interaction was not significant, the 2-way interactions of pre-MDS with time or sex were then tested. When the 2-way interactions were significant, *post hoc* analysis was then further examined. Based on this sequence of hierarchical testing, statistical findings were reported after correction for multiple comparisons at each hierarchical level. Statistical findings of the 3-way or 2-way interactions were corrected for multiple comparisons across all the vertices on the cortical surface via the false discovery rate (FDR) procedure in Bernal-Rusiel *et al.*,[43] and the results were thresholded at a corrected p value of .05.

The *post hoc* analysis then examined pre-MDS effects on cortical thickness or surface area in girls and boys if the 2-way interaction of pre-MDS and sex on the thickness or surface area was significant. Significant clusters were delineated and used as regions of interest.[44] The thickness or surface area of these regions of interest (ROIs) was imported into R, version 3.6.2 (https://www.R-project.org/) package lme4[45] for linear mixed regression analyses. Bonferroni correction was used for multiple comparisons of the *post hoc* analyses (corrected $p = .05$/number of ROIs).

Finally, we performed mediation analysis to examine the role of cortical surface area/thickness in the relation between pre-MDS and child sensitivity to reward and punishment. In this analysis, the predictor variable was pre-MDS. The outcome variable was either sensitivity to reward or sensitivity to punishment, and the mediator was cortical thickness/surface area of brain regions that were significantly associated with both Pre-MDS and sensitivity to reward or punishment. Age, ethnicity, SES, and postnatal BDI were included as covariates. It should be noted that only the brain measures that were statistically significant for the above 2-way interaction analysis were included in this mediation analysis. We used the PROCESS test of indirect effect via SPSS version 22)[46] to examine the indirect effect of pre-MDS on sensitivity to reward or punishment in association with cortical thickness/surface area of the brain. Specifically, we examined the relationship between pre-MDS and cortical thickness/surface area (*a* path), the relationship between cortical thickness/surface area and sensitivity to reward or punishment (*b* path), and the effect of pre-MDS on sensitivity to reward or punishment after including cortical thickness/surface area as a mediator in the model (*c'* path). The significance of the indirect effect (*ab*) of pre-MDS on sensitivity to reward or punishment through the proposed mediator was tested using 95% bias-corrected confidence intervals with bootstrapping procedures (5,000 bootstrap resamples).[47]

RESULTS

Demographics

Table 1 lists the demographic information of the children with both MRI scans at 4 and 6 years of age (n = 130). Among 130 children, 10 had an internalizing score of >65, and 2 had an externalizing score of >65 at 4 years of age. Our assessment of prenatal depressive symptoms was based on a screening tool that intends to elicit a subjective self-report of emotional well-being but does not constitute a clinical diagnosis. Figure S1, available online, illustrates the distribution of prenatal maternal depressive scores in our final study sample. Mothers had relatively mild depressive symptoms, with 9.2% of women having EPDS scores of >13 and 32.3% of women having EPDS scores of >9. Table S1, available online, lists the demographic information of children with 1 or 2 MRI scans (N = 358). Table S2, available online, lists the clinical and social differences between subjects included in this study (n = 130) and those who underwent MRI but were not included in this study (n = 228). There were no significant differences between the 2 samples in Pre-MDS, mean postnatal BDI,

SES, gestational age, birth weight, internalizing and externalizing behaviors, and sensitivity to punishment and reward.

In our study sample, there were no significant sex differences in baseline age ($t = 0.4$, $p = .69$), gestational age ($t = -1.72$, $p = .09$), pre-MDS ($t = -1.56$, $p = .12$), mean postnatal maternal depressive scale (post-MDS; $t = -1.59$, $p = .11$), maternal ethnicity ($\chi^2 = 1.74$, $p = .42$), smoking exposure ($\chi^2 = 2.45$, $p = .12$), externalizing behaviors ($t = -0.92$, $p = .36$), sensitivity to punishment ($t = 0.67$, $p = 0.50$), and sensitivity to reward ($t = -0.27$, $p = .79$). Sex differences were observed in birth weight ($t = 3.2$, $p = .002$), SES ($t = 2.19$, $p = .031$), and internalizing behaviors ($t = -2.31$, $p = .023$). Moreover, pre-MDS was significantly correlated with mean post-MDS ($r = 0.5$, $p < .001$), but not with gestational age ($r = -0.04$, $p = .62$), birth weight ($r = 0.003$, $p = .98$), SES ($r = -0.16$, $p = .079$), or baseline age ($r = -0.04$, $p = .62$). Finally, the CBCL internalizing t score at 4 years of age was significantly correlated with the sensitivity to reward ($r = 0.3$, $p < .001$) and to punishment ($r = 0.22$, $p = .011$) scores at 6 years of age. The CBCL externalizing t score at 4 years of age was also significantly correlated with the sensitivity to punishment score ($r = 0.24$, $p = .006$) at 6 years of age, but was not significantly correlated with the sensitivity to reward score ($r = 0.086$, $p = .33$). These findings were largely consistent with those reported in children in a Spanish general population.[29]

Associations Between Pre-MDS and Growth of Cortical Surface Area and Thickness

Our statistical analysis examined pre-MDS scores with cortical measures while controlling for postnatal MDS and other covariates stated in the Statistical Analysis section. The 3-way interaction of pre-MDS, age (scan interval), and sex on surface area (Figure S2, available online) and cortical thickness (Figure S3, available online) was not statistically significant.

Neither the 2-way interactions between age and sex nor between pre-MDS and age on surface area and cortical thickness was statistically significant, suggesting that the relation of pre-MDS with the cortical development in terms of surface area and thickness from 4 to 6 years was not a function of age. Because it is an exploratory study, to show it more comprehensively, uncorrected p values ($p < .1$) of statistical maps are shown in Figures S4 and S5, available online, for cortical surface area, and Figures S6 and S7, available online, for cortical thickness.

Moreover, there was no significant main effect of pre-MDS on cortical thickness when age, sex, maternal ethnicity, SES, and postnatal BDI were included as covariates (Figure S8, available online). The main effect of pre-MDS on the cortical surface area was sparse (Figure S9, available online).

Sex-Dependent Influences of Prenatal Maternal Depressive Symptoms on Cortical Surface Areas

Figure 2A and 2B show statistically significant 2-way interactions between pre-MDS and sex on the surface area of the left paracentral, anterior superior temporal gyrus (aSTG), dorsolateral prefrontal cortex (dlPFC), fusiform, and right superior parietal lobe (SPL), anterior inferior temporal gyrus (aITG), and lateral orbitofrontal cortex (lOFC). Figure 2C and 2D illustrate the effects of pre-MDS on cortical surface area in boys and girls, respectively. *Post hoc* analysis revealed that higher pre-MDS scores were associated with larger cortical surface areas in the right lOFC ($t = 2.84$, $p = .005$), aITG ($t = 4.44$, $p < 0.001$), SPL ($t = 1.99$, $p = .049$), and left fusiform ($t = 3.94$, $p < .001$), dlPFC ($t = 2.54$, $p = .012$), paracentral cortex ($t = 2.88$, $p = .005$), and aSTG ($t = 2.14$, $p = .034$) in boys. In contrast, girls showed negative associations of pre-MDS scores with the cortical surface areas of these regions, including the left dlDFC ($t = -2.28$, $p = .025$), aSTG ($t = -2.28$, $p = .025$), and right SPL ($t = -3.52$, $p < .001$). These results revealed an unprecedented sex dependency for the influence of pre-MDS on cortical surface area.

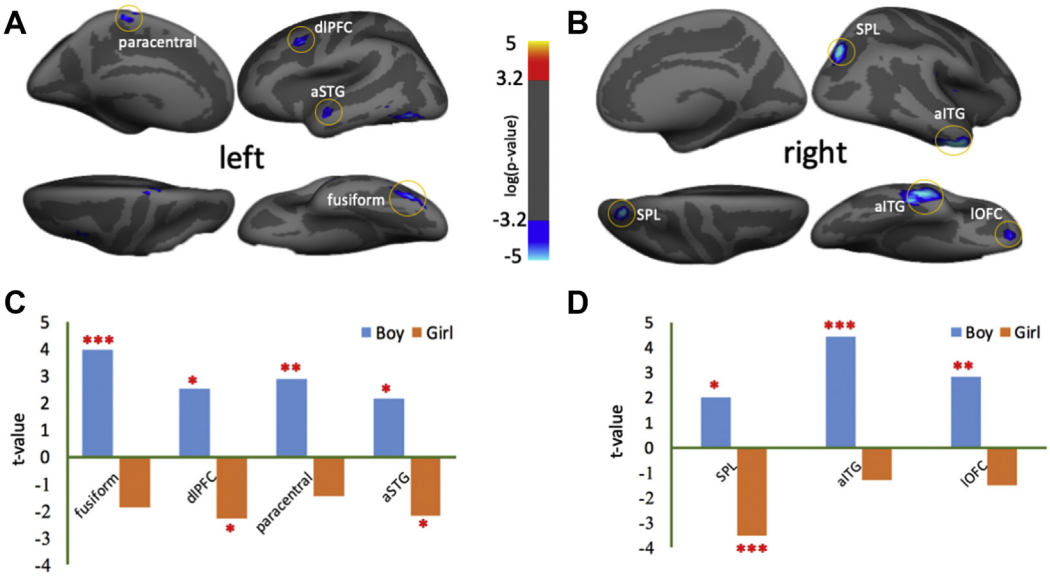
Additional longitudinal models were run when pregnancy complications (14 women with gestational diabetes, 3 women with hypertension, and 7 women with hypoglycemia in our sample) were also considered covariates. The above findings remained the same (Table S3, available online). Furthermore, our statistical findings shown in Figure 2 remained the same while controlling for postnatal maternal depressive symptoms at each time point (Figure S10, available online).

SPL Mediation in Relationship Between Pre-MDS and Child Sensitivity to Reward

Following the brain findings shown in Figure 2, we then examined the relationship between sensitivity to reward/punishment and cortical surface areas. A greater surface area of the right SPL was associated with lower sensitivity to reward ($\beta = -0.28$, $p = .016$) (Figure 3) in girls, but not in boys ($\beta = -0.13$, $p = 0.38$) after adjusting for age, postnatal MDS, maternal ethnicity, and SES. The rest of the cortical regions' surface areas shown in Figure 2 were not significantly correlated with sensitivity to reward or punishment in either boys or girls.

The mediation finding was shown in Figure 4. After adjusting for age, postnatal MDS, maternal ethnicity, and SES, the pre-MDS score was significantly associated with the surface area of the right SPL (a path: $\beta = -0.47$, 95%

FIGURE 2 Statistical Maps of Interaction Between Prenatal Maternal Depressive Symptoms and Sex on Cortical Surface Areas



Note: *(A, B) Statistical maps for left and right hemispheres, respectively. (C, D) Relationship between pre-MDS and cortical surface areas in boys and girls, respectively. aITG = anterior inferior temporal gyrus; aSTG = anterior superior temporal gyrus; dlPFC = dorsal lateral prefrontal cortex; LOFC = lateral orbital frontal cortex; pre-MDS = prenatal maternal depressive symptoms; SPL = superior parietal lobe.*

*p < .05; **p < .01; ***p < .001.

CI = −0.72 to −0.22), the surface area of the right SPL was significantly correlated with sensitivity to reward (*b* path: $\beta = -0.29$, 95% CI = −0.55 to −0.03) in girls. Pre-MDS scores were not significantly associated with sensitivity to reward in girls after adjusting the surface area of the right SPL (*c*' path: $\beta = -0.005$, 95% CI = −0.29 to 0.28). The reduced surface area of the right SPL was found to mediate the positive relationship between pre-MDS scores and sensitivity to reward in girls (*ab* path: $\beta = 0.14$, 95% CI = 0.01 to 0.33).

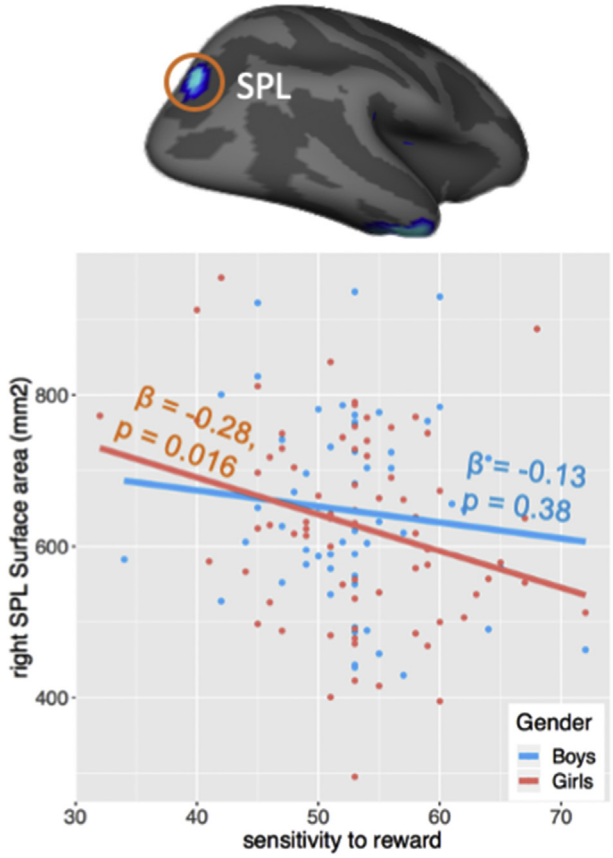
DISCUSSION

We examined the associations between pre-MDS scores and cortical development from 4 to 6 years. Our results showed that fetal exposure to prenatal maternal depressive symptoms was associated with alterations in the cortical surface area of several regions involved in cognitive control, attention, social perception, and social decision making. These associations were sex dependent. In particular, a higher pre-MDS score was associated with greater cortical surface areas in boys and smaller surface areas in girls. The smaller SPL surface area mediated the positive association between pre-MDS scores and sensitivity to reward in girls.

Individual variation in infant cortical surface area is strongly influenced by sex and obstetric history.[48] In our study, the sex-dependent association between pre-MDS and cortical surface area may indicate that prenatal maternal depression results in alterations in cortical surface area from the fetal period to early childhood, which increases the risk for general child psychopathology. This hypothesis needs to be tested in a longitudinal design with psychopathology assessments and individual variation in cortical surface area development from infancy to childhood.

In our study, girls of mothers with a higher level of prenatal depressive symptoms showed lower dlPFC and SPL surface areas, but boys showed larger lOFC, aITG, SPL, fusiform, dlPFC, and paracentral cortical areas. Our previous studies found sex-specific effects of pre-MDS on the amygdala volume,[14] functional connectivity with STG and OFC,[35] and structural coupling with the frontal regions[15] in newborns and young children. This sex difference may be attributed to placental and embryonic response to maternal stress and environmental perturbations during gestation. Lombardo *et al.* showed that fetal testosterone predicted sex-specific changes in superior parietal gyrus and lOFC gray matter volumes during childhood, with a greater individual increase in fetal testosterone relating to decreasing gray matter in female children compared to male children.[49] It has been suggested that depressed mood is associated with testosterone levels in pregnant women.[50] Moreover, given that sex difference in the expression level and distribution of androgen and estrogen receptors throughout the brain,[51] exposure to prenatal maternal depression may affect girls' and boys' HPA circuitry and brain in different ways. Further research, including

FIGURE 3 Association Between Brain Structure and Reward Sensitivity

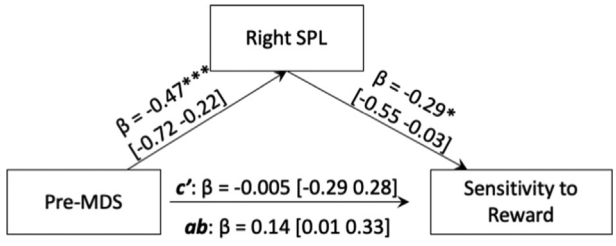


Note: *A significant negative linear relationship between reward sensitivity and the surface area of the right superior parietal lobe in girls (orange: β = –0.28, p = 0.016). SPL = Superior Parietal Lobe. Please note color figures are available online.*

comprehensive prenatal hormone assessment and depressed mood changes, is needed to confirm this speculation.

Interestingly, the smaller SPL surface area mediated the positive association between pre-MDS scores and girls' sensitivity to reward. Previous studies suggested that the SPL is also involved in selective attention and maintaining attention to novelty/reward-related visual.[52] Over-attention to rewarding stimuli or events may induce impulsive behavior for possible rewards in preschool-aged children. Moreover, altered sensitivity to reward has been reported in children,[37,53] and in adolescents[54] with ADHD. These findings suggest a potential pathway linking prenatal depressive symptoms to child's reward sensitivity through cortical development. Prenatal maternal depression may entail alterations in the neural circuitry of reward-related processes in offspring, particularly in the prefrontal and parietal areas, which may influence reward-related decision making in girls and heighten the risk of impulsive behavior. However, further research is needed to explore this possibility. Together, our findings provide evidence for pre-MDS sex-dependent associations with the cortical surface area in preschool-aged children.

FIGURE 4 Mediation of Prenatal Maternal Depressive Symptoms on the Reward Sensitivity by Brain Structure



Note: *The right superior parietal lobe mediation of the relationship between prenatal maternal depressive symptoms and reward sensitivity in girls (ab path: β = 0.14, 95% CI [0.01 0.33]). Pre-MDS = prenatal Maternal Depressive Symptoms; SPL = Superior Parietal Lobe.*
*p < .05; ***p < .001.

There are several strengths and limitations to this study. To the best of our knowledge, this study is the first longitudinal sample to investigate cortical morphology in relation to pre-MD and its role in linking pre-MDS with parental ratings of child behavior. Although the neuroimaging dataset in this study is unique in its timing of acquisition and the number of participants, it is a modest sample size for our interaction analysis. Because of challenges in imaging young children, our study included only 130 subjects with good MRI scans across the 2 time points, even though each time point had more than 200 scans. Hence, our study did not fully use the available image data. We did not conduct structured interviews with mothers for their trauma or stressor-related symptoms. Although postpartum depression was adjusted, the association between prenatal maternal depression and brain structure development of preschool-age children may be confounded by parenting behavior. Mothers with depression may demonstrate more unsupportive or intrusive parenting behaviors, which in turn shape brain development and socio-emotional outcome. Furthermore, our assessment of maternal depressive symptoms was based on a standard screening tool intended to elicit a subjective emotional well-being report but did not constitute clinical assessment. Thus, the brain variations in the offspring are best considered as being associated with self-reported depressive symptoms and not with clinical depression. Our study assessed pre-MDS only at 26 weeks' gestation. Although measurements at each trimester may have allowed for a better understanding of specificity in timing, previous studies suggested that the second and third trimesters were critical periods when pre-MDS showed the most substantial impact on child brain.[7,8] Child sensitivity to reward was assessed via questionnaires reported by parents, which may be prone to measurement bias by factors associated with parents' background. Finally, our study

did not explore potential genetic roles in this study, which require further investigation.

In conclusion, our findings suggest that the cortical surface area could be a brain morphological indicator relevant to the transgenerational transmission of mental health from mother to child in early childhood. The vulnerability of cortical morphology to environmental factors related to depression might be sex dependent.

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