



Full-length Article

Inflammatory biomarkers as predictors of fetal brain resilience or vulnerability to prenatal maternal anxiety

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ABSTRACT

Prenatal maternal anxiety has been associated with altered neurodevelopmental outcomes in offspring, yet the biological mechanisms underlying this relationship remain poorly understood. This study investigated whether maternal inflammatory biomarkers moderate the association between prenatal anxiety and offspring brain and behavioral development. Using data from a prospective longitudinal cohort, we assessed maternal anxiety and circulating inflammatory markers at late mid-pregnancy, followed by neonatal brain MRI ($n = 159$) and cognitive assessments at 24 months ($n = 340$). Our findings revealed that interferon-gamma (IFN- γ) moderated the association between prenatal maternal anxiety and neonatal right globus pallidus volume, with higher IFN- γ levels linked to a larger pallidus volume and better cognitive outcomes at 24 months, even in the context of elevated anxiety. Similarly, both high and low levels of maternal monocyte chemoattractant protein-1 (MCP-1) altered the relationship between prenatal anxiety and neonatal brain morphology within the striatal-cortical circuit, including bilateral caudate volumes and cortical thickness in the sensorimotor and temporal regions. These results suggest that extreme MCP-1 levels may amplify vulnerability or promote resilience in fetal brain development. Higher MCP-1 levels were also associated with improved language development at 24 months. Together, these findings highlight the potential roles of inflammatory biomarkers in shaping the fetal brain's sensitivity to maternal anxiety, offering potential mechanisms for early risk identification and intervention strategies.

1. Introduction

Prenatal maternal anxiety affects approximately 21% to 25% of pregnant women (Field, 2017). Growing evidence from observational human studies indicates that fetal exposure to maternal anxiety during pregnancy can have long-term effects on neurobehaviors and brain development of the offspring, particularly in brain regions implicated in affective disorders (Qiu et al., 2013, Buss et al., 2010, Rifkin-Graboi et al., 2015). Exposure to prenatal maternal anxiety predicts altered microstructure of the neonatal hippocampus, sensorimotor, frontal, and temporal cortices (Rifkin-Graboi et al., 2015). Infants born to mothers reporting higher anxiety during pregnancy have exhibited slower

bilateral hippocampal growth over the first six months of life (Qiu et al., 2013). Additionally, reduced gray matter volumes in the frontal and temporal regions have been reported in children exposed to elevated maternal anxiety during gestation (Buss et al., 2010). These findings underscore the importance of understanding the mechanisms through which maternal anxiety impacts early brain development.

One promising mechanism is maternal immune activation, which may moderate the effects of prenatal psychological distress on fetal neurodevelopment. Cytokines—immune signaling proteins such as interleukin-6 (IL-6), IL-1 β , IL-10, and tumor necrosis factor-alpha (TNF- α)—which respond to environmental stressors, may influence fetal brain development (Graham et al., 2018, Buss, 2021, Osborne et al., 2022). In

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humans, elevated levels of pro-inflammatory cytokines have been observed in pregnant women experiencing depression or anxiety during the third trimester (Leff Gelman et al., 2019). Higher maternal IL-6 levels during pregnancy have been linked to changes in neonatal amygdala volume and connectivity (Graham et al., 2018), and have been shown to predict poorer impulse control in toddlers (Rudolph et al., 2018, Rasmussen et al., 2019). Furthermore, the microglial-mediated pathway provides a mechanistic explanation for how these cytokine-induced disruptions occur, as microglia are the primary effector cells responsible for executing immune responses within the developing brain and regulating key developmental processes like synaptic refinement (Fitzgerald et al., 2024). These findings suggest that immune signaling plays a key role in shaping the fetal brain's response to maternal psychological stress.

Despite this growing body of evidence, current human research has largely focused on a limited set of inflammatory markers—primarily IL-6 and TNF- α —leaving other potentially important cytokines underexplored. Moreover, relatively little is known about how immune activity at the maternal-fetal interface, particularly during the mid-to-late pregnancy, influences fetal neurodevelopment. This period is marked by critical neurodevelopmental processes, such as neuronal migration, synaptogenesis, and early circuit formation (Tau and Peterson, 2010). Dysregulation of maternal immune signaling during this window—especially elevated levels of pro-inflammatory cytokines such as interferon-gamma (IFN- γ) and monocyte chemoattractant protein-1 (MCP-1)—may disrupt placental function and fetal brain maturation, increasing susceptibility to long-term neurodevelopmental challenges.

To address this gap, the present study leveraged data from a well-characterized prospective longitudinal birth cohort to investigate whether maternal inflammatory biomarkers in mid-pregnancy moderate the relationship between prenatal maternal anxiety and neonatal brain structure, as well as subsequent behavioral development at 24 months of age. Specifically, the study aimed to: (1) determine whether maternal inflammation moderates the association between prenatal anxiety and neonatal brain morphology; and (2) examine whether these moderating effects persist to influence early cognitive and behavioral outcomes. We hypothesized that inflammation-related pathways involving vascular endothelial growth factor (VEGF), tumor necrosis factor- α (TNF- α), monocyte chemoattractant protein-1 (MCP-1), and interferon- γ (IFN- γ) would modulate the fetal brain's sensitivity or resilience to maternal psychological distress. This biomarker panel captures both systemic inflammatory activity and pathway-specific processes relevant to neurogenesis, synaptic plasticity, and blood-brain barrier integrity. By linking maternal psychological and immune profiles with infant neurodevelopmental trajectories, this study offers novel insights into the biological embedding of prenatal experiences and identifies potential targets for early identification and intervention to foster resilience in children exposed to prenatal maternal anxiety.

2. Methods

2.1. Participants

This neuroimaging study included mother-child dyads enrolled in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) longitudinal cohort (Soh et al., 2012). Mothers were recruited when attending their first-trimester prenatal ultrasound scans at either the National University Hospital (NUH) or KK Women's and Children's Hospital (KKH) in Singapore. Eligible participants and their parents were Singapore citizens or Permanent Residents of Chinese, Malay, or Indian ethnicity. The detailed recruitment protocol is described elsewhere (Soh et al., 2012).

This neuroimaging study included mother-child dyads who participated in neonatal brain imaging within the first two weeks of life and behavioral measures at 24 months of age. The study included neonates with gestational age greater than 34 weeks and mothers who completed

mood questionnaires and blood sample collection at 26 ~ 28 weeks of pregnancy. As a result, the study included 159 mother-child dyads for neonatal imaging analysis and 340 for infant behavioral analysis.

The GUSTO cohort study was approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB) and the SingHealth Centralized Institutional Review Board (CIRB). Written informed consent was obtained from the mothers.

2.2. State-Trait Anxiety Inventory scale

The State-Trait Anxiety Inventory (STAI, Form Y-2) was administered at 26 weeks of pregnancy and again at 24 months postpartum to assess maternal anxiety levels during the prenatal and postnatal periods. The STAI is a widely used self-report instrument that measures anxiety through two subscales: state anxiety and trait anxiety, each comprising 20 items rated on a 4-point scale. Items reflecting the absence of anxiety are reverse-scored. Total anxiety scores are calculated by summing responses across all items, with higher scores indicating greater anxiety. In perinatal populations, the STAI has been demonstrated to have good construct validity (Meades and Ayers, 2011).

2.3. Maternal inflammatory biomarkers during pregnancy

Plasma sample preparation was detailed elsewhere (Chia et al., 2020). Briefly, prenatal maternal plasma samples were collected between the 26th and 28th weeks of gestation. Plasma levels of four inflammatory biomarkers, including interferon-gamma (IFN- γ), vascular endothelial growth factor (VEGF), tumor necrosis factor alpha (TNF- α), and monocyte chemoattractant protein-1 (MCP-1/CCL2), were quantified using a Human Luminex Cytokine panel, a high-throughput technique that allows the simultaneous measurement of multiple analytes within a single sample. Biomarker concentrations were natural log-transformed for statistical analyses; for figures, untransformed values are displayed to aid understanding.

This study included these four biomarkers because of their relevance to maternal immune activation during pregnancy and brain development. MCP-1 (CCL2) functions via CCR2 receptor activation to initiate inflammatory cascades and regulate microglial activation during normal brain development (Yang et al., 2011), while IFN- γ signals through the JAK/STAT1 pathway to regulate immune responses while simultaneously modulating neurogenesis by inhibiting neuronal differentiation of neural progenitor cells (Filiano et al., 2016). VEGF signals through VEGFR2-mediated PI3K/Akt and MAPK/ERK pathways to promote angiogenesis while supporting neurovascular development (Rosenstein et al., 2010). TNF- α operates through TNFR1/2 receptors, triggering NF- κ B and MAPK pathways mediating inflammatory responses while regulating synaptic plasticity and neuronal survival during development (Kim et al., 2018). These distinct molecular cascades may explain the differential effects observed across brain regions and developmental outcomes, as each pathway influences specific aspects of neurogenesis, synaptogenesis, and neural circuit formation.

2.4. Neonatal brain image acquisition and analysis

Axial fast spin-echo T2-weighted MRI was acquired for neonates at 5 to 14 days of age using a 1.5-Tesla GE scanner at the Department of Diagnostic and Interventional Imaging of the KK Women's and Children's Hospital. Detailed acquisition and image quality check procedures were previously reported (Qiu et al., 2013, Qiu et al., 2015). A Markov random field model (MRF) was used to automatically delineate gray matter, white matter, cerebrospinal fluid (CSF), and subcortical regions from the neonatal T2-weighted MRI data. The image acquisition, quality check, and segmentation accuracy was previously reported in (Qiu et al., 2013, Qiu et al., 2015, Fischl et al., 2002).

The cortical thickness was measured as the distance between the cortical surface and gray matter voxels along the boundary between gray

matter and CSF. The cortical thickness was smoothed using the Laplace-Beltrami basis functions on the cortical surface. For group comparison of the cortical thickness, we employed a large deformation diffeomorphic metric mapping (LDDMM) algorithm (Zhong and Qiu, 2010) to align individual cortical surfaces to the atlas that was generated based on the cortical anatomy of the same twenty subjects (Bai et al., 2012, Joshi et al., 2004) and transferred the thickness of each individual subject to the atlas.

2.5. Bayley scales of infant and toddler development

The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III), was administered at 24 months during home visits to assess five developmental domains: cognitive (91 items in the ability to process information, problem-solve, and develop memory skills), language (49 items in the receptive and 48 items in the expressive domain), motor (66 items in the fine motor and 72 items in the gross motor domain), social-emotional (derived from Greenspan chart), and adaptive behavior (derived from Adaptive behavior assessment system). This comprehensive assessment enabled the early identification of developmental concerns. Lower scores indicate poorer developmental outcomes.

2.6. Covariates

Sociodemographic information, including maternal ethnicity and education level, was collected during enrolment through an interviewer-administered questionnaire. Maternal education, categorized into five levels (primary, secondary, tertiary, university, post-graduate), was recorded at 26 ~ 28 weeks of pregnancy and used as a continuous indicator of socioeconomic status (SES). Gestational diabetes mellitus (GDM) was diagnosed following the IADPSG 2018 criteria, with fasting plasma glucose (PG) ≥ 5.1 mmol/L or 2-hour PG > 8.8 mmol/L marked as GDM. Birth outcomes and pregnancy measures were extracted from hospital records in this study, as previous studies indicated the correlation of maternal inflammation biomarker levels with parity, exposure to smoking, and GDM (Gaillard et al., 2016, Kennelly et al., 2022).

2.7. Statistical analysis

Student's t-tests and χ^2 tests were respectively used to examine the difference of continuous and discrete demographic characteristics between the whole GUSTO sample and samples with neonatal brain imaging and behavior records.

Linear regression was conducted to examine the interactive effects of plasma inflammatory biomarker levels with prenatal maternal anxiety on neonatal cortical thickness or subcortical volumes. The primary factors in regression were prenatal maternal anxiety and inflammatory biomarkers. In the first block of the regression, these primary factors were entered alongside covariates: neonatal sex, gestational age, maternal education level, ethnicity, GDM, exposure to smoking, and parity. To assess potential interaction effects, the interaction term between prenatal maternal anxiety and inflammatory biomarkers was added in the second block of the model. Statistical significance was determined using cluster-level correction for multiple comparisons based on random field theory (Chung et al., 2010), with a threshold of $p < 0.05$ and a minimum cluster size >1000 mm².

Johnson-Neyman technique was performed to examine the range of inflammation biomarker levels, where prenatal maternal anxiety was significantly associated with neonatal cortical thickness. Mean cortical thickness was calculated within the brain regions with significant interactive effects, offering a more detailed understanding of how prenatal maternal anxiety and inflammatory biomarkers jointly shape neonatal brain morphology.

The same linear regression model was used to examine the interactive effects of inflammatory biomarker levels and prenatal maternal anxiety on child behavioral outcomes, as assessed by the BSID-III.

Maternal anxiety symptoms at 24 months postpartum were included as an additional covariate.

3. Results

3.1. Demographic characteristics

Table 1 lists the demographic characteristics of the study populations with neonatal brain imaging data ($n = 159$) and 24-month behavioral data ($n = 340$). The two samples showed comparable profiles across most measurements, with maternal ethnicity, educational level, smoking exposure, and prenatal anxiety scales showing modest variation ($p < 0.05$). Birth weight, gestational age, infant sex, maternal parity, gestational diabetes mellitus (GDM), postnatal anxiety scales, and all maternal inflammatory biomarker levels were consistent between the two samples (all $p > 0.05$).

3.2. Maternal inflammatory biomarkers moderate the relationship between prenatal maternal anxiety and neonatal subcortical volumes

Maternal plasma MCP-1 level significantly moderated the relationship between prenatal maternal anxiety and the bilateral caudate volumes (left: $t = 2.49$, $p = 0.014$, $df = 148$; right: $t = 2.74$, $p = 0.007$, $df = 148$). In the high MCP-1 group, prenatal maternal anxiety was positively associated with the caudate volume (left: $\beta = 2.85$, $p = 0.032$, $df = 148$, Fig. 1A; right: $\beta = 2.91$, $p = 0.275$, $df = 148$, Fig. 1C), while in the low MCP-1 group, this association was negative (left: $\beta = -3.03$, $p = 0.028$, $df = 148$, Fig. 1A; right: $\beta = -3.48$, $p = 0.011$, $df = 148$, Fig. 1C). Johnson-Neyman analysis indicated significant interaction effects when MCP-1 levels fell below 113 pg/ml for the left caudate (Fig. 1B), and when levels fell below 141 pg/ml for the right caudate (Fig. 1D).

Table 1
Demographics.

	Neonatal MRI sample (n=159)	24-Month behavioral sample (n=340)
Birth Weight (kg)	3.08 ± 0.38	3.06 ± 0.37
Gestational Age (weeks)	38.9 ± 1.10	38.9 ± 1.17
Near-term (<37 weeks)	2.50%	5.00%
Sex (%)		
Female	46.5	48.5
Male	53.5	51.5
Parous (%)	61.6	55
Smoking Exposure During Pregnancy (%)	52.1	37.4
Gestational diabetes mellitus (%)	14.5	14.4
Maternal Ethnicity (%)		
Chinese	45.9	57.1
Malay	41.5	26.5
Indian	12.6	16.4
Maternal education (%)		
Primary school and below	5.7	5.6
Secondary school	35.2	21.5
Pre-university, diploma or technical source	17.6	10.6
University undergraduate level	26.4	24.7
Above university undergraduate level	15.1	37.6
State-Trait Anxiety Inventory (prenatal week 26)	73.75 ± 18.34	70.09 ± 18.34
State-Trait Anxiety Inventory (postnatal 24 months)	\	70.03 ± 19.78
Maternal Inflammation Biomarker (median [25th 75th])		
TNF- α (pg/ml)	5.82 [3.28 10.67]	4.96 [2.65 10.05]
IFN- γ (pg/ml)	13.26 [5.64 29.70]	10.98 [2.23 28.19]
VEGF (pg/ml)	409.10 [176.02 800.34]	416.48 [200.20 802.70]
MCP-1 (pg/ml)	218.04 [153.53 284.76]	203.61 [149.05 266.71]

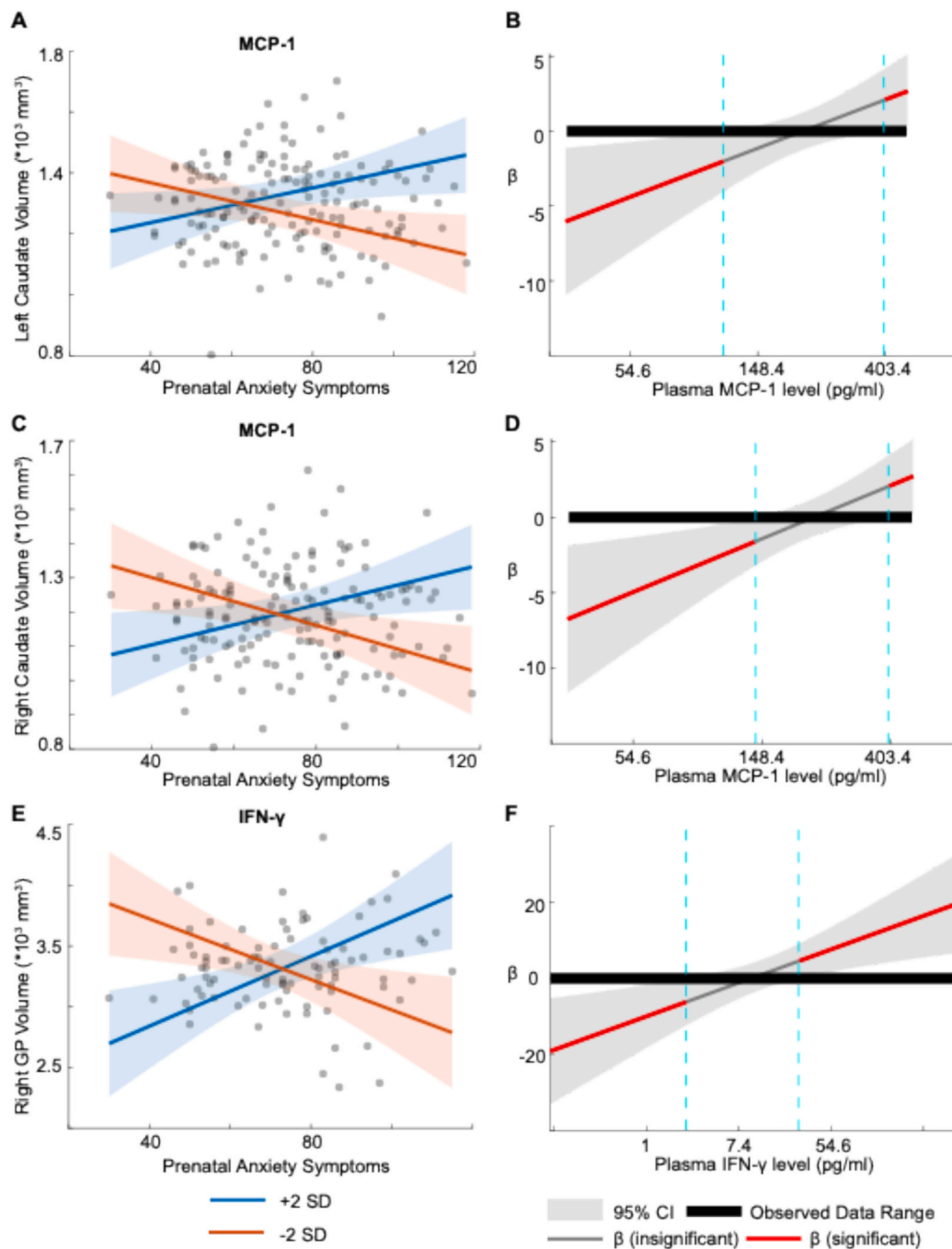


Fig. 1. Moderating effects of maternal inflammatory biomarkers on the association between prenatal maternal anxiety and neonatal subcortical volumes. Scatter plots in panels (A, C, E) illustrate the interaction effects. Blue lines depict the association between prenatal maternal anxiety and neonatal subcortical volumes at high biomarker levels (+2 standard deviations above the mean), while red lines represent this relationship at low biomarker levels (–2 standard deviations below the mean). Johnson-Neyman plots in panels (B, D, F) identify specific biomarker threshold values at which the association between maternal anxiety and neonatal subcortical volume becomes statistically significant. The x-axis is presented on a natural logarithmic scale, and the y-axis shows the conditional effect (slope) of prenatal maternal anxiety on neonatal subcortical volume across varying biomarker levels. The gray shaded area represents the 95% confidence interval, and vertical dotted lines indicate regions where the association becomes statistically significant ($p < 0.05$).

Significant interaction between prenatal maternal anxiety and IFN- γ level was observed primarily in the right globus pallidus (GP) volume ($t = 3.00$, $p = 0.004$, $df = 82$). In the high IFN- γ group, prenatal maternal anxiety was positively associated with the GP volume ($\beta = 14.36$, $p = 0.004$, $df = 82$), while in the low IFN- γ group, this association was negative ($\beta = -12.50$, $p = 0.013$; Fig. 1E). Johnson-Neyman analysis identified significant interaction effects when IFN- γ levels exceeded 27 pg/ml or fell below 2.38 pg/ml (Fig. 1F). No significant moderation effects were observed for TNF- α or VEGF.

We then assessed whether the observed interactions between total anxiety scores and cytokine levels were also shown in state or trait anxiety dimensions. Trait anxiety exhibited interaction patterns comparable to those identified with total anxiety scores, whereas state anxiety interactions did not reach statistical significance in the basal ganglia volume (see Fig. S1 and the Supplementary Material for details).

3.3. Maternal inflammatory biomarkers moderate the relationship between prenatal maternal anxiety and neonatal cortical morphology

Interaction effects between prenatal maternal anxiety and MCP-1 levels were observed in the left and right sensory-motor cortex (left: $cluster\ p = 0.031$, $df = 148$, Fig. 2A; right: $cluster\ p = 0.006$, $df = 148$, Fig. 2D), as well as in the right medial and inferior temporal cortex ($cluster\ p = 0.003$, $df = 148$, Fig. 2G). At high MCP-1 levels, greater prenatal maternal anxiety was significantly associated with reduced cortical thickness (left sensory-motor: $\beta = -0.007$, $p = 0.001$, Fig. 2B; right sensory-motor: $\beta = -0.009$, $p < 0.001$, Fig. 2E; right temporal cortex: $\beta = -0.013$, $p < 0.001$, Fig. 3H). In contrast, at low MCP-1 levels, greater prenatal maternal anxiety was significantly associated with increased cortical thickness (left sensory-motor: $\beta = 0.006$, $p = 0.004$, Fig. 2B; right sensory-motor: $\beta = 0.007$, $p = 0.004$, Fig. 2E; right temporal cortex: $\beta = 0.008$, $p = 0.015$, Fig. 2H).

Johnson-Neyman analysis revealed that prenatal maternal anxiety had a significant effect on left sensorimotor cortical thickness when MCP-1 levels exceeded 270 pg/ml or fell below 140 pg/ml (Fig. 2C). In the right sensorimotor cortex, significant effects were observed when MCP-1 levels were above 250 pg/ml or below 135 pg/ml (Fig. 2F), and in the right medial and inferior temporal cortex, when levels exceeded 215 pg/ml or dropped below 105 pg/ml (Fig. 2I). These findings suggest that both elevated and reduced MCP-1 levels heighten the fetal brain's sensitivity to maternal anxiety, amplifying either vulnerability or resilience in cortical development depending on the inflammatory context. No significant interaction effects of prenatal maternal anxiety were detected for IFN- γ , TNF- α , or VEGF.

We subsequently assessed whether the observed interactions between total anxiety scores and cytokine levels were shown in state or trait anxiety or both. State anxiety exhibited interaction patterns comparable to those identified with total anxiety scores (Fig. S2). In contrast, trait anxiety interactions did not reach statistical significance in the right cortical thickness (see Fig. S2 and the Supplementary Material for details). These differential findings suggest potentially distinct neurobiological mechanisms through which acute (state) versus chronic (trait) anxiety dimensions may interact with maternal inflammatory markers to influence fetal brain morphology.

3.4. Maternal plasma levels of inflammatory biomarkers moderate the relationship between prenatal maternal anxiety and behaviors

Only maternal MCP-1 and IFN- γ levels significantly moderated the relationship between prenatal maternal anxiety and child behavioral outcomes at 24 months (Fig. 3). No significant moderation effects were observed for VEGF, or TNF- α .

Language function at 24 months was significantly affected by the interaction between prenatal maternal anxiety and MCP-1 levels ($t = 2.01$, $p = 0.045$, $df = 322$; Fig. 3A). Post-hoc analysis showed a trend of significance but did not reach statistical significance: a positive trend in the high MCP-1 group ($\beta = 0.19$, $p = 0.058$, $df = 322$; Fig. 3A), and a negative, nonsignificant association in the low MCP-1 group ($\beta = -0.17$, $p = 0.11$, $df = 322$; Fig. 3A). Johnson-Neyman analysis revealed significant interaction effects when MCP-1 levels exceeded 601 pg/ml (Fig. 3B).

Cognitive function at 24 months was significantly affected by the interaction between prenatal maternal anxiety and IFN- γ levels ($t = 2.62$, $p = 0.010$, $df = 199$; Fig. 3C). Post-hoc analysis revealed opposing patterns between prenatal maternal anxiety and cognitive function in high versus low IFN- γ groups (high: $\beta = 0.25$, $p = 0.031$, $df = 199$; low: $\beta = -0.28$, $p = 0.019$, $df = 199$; Fig. 3C). Significant moderation effects emerged when IFN- γ levels exceeded 114 pg/ml or fell below 1.6 pg/ml (Fig. 3D). High IFN- γ levels could buffer the impact of prenatal maternal anxiety on cognitive function, and low IFN- γ levels could amplify the impact of prenatal anxiety on cognitive function in offspring.

Next, we assessed whether the observed interactions between total

anxiety scores and cytokine levels were shown in state or trait anxiety or both. State anxiety exhibited interaction patterns comparable to those identified with total anxiety scores, while trait anxiety interactions did not reach statistical significance in language function (see Fig. S3 and the Supplementary Material for details). These findings suggest differential associations between acute versus chronic maternal anxiety and inflammatory markers in relation to toddler behaviors, especially language function.

4. Discussion

The study found that maternal inflammatory biomarkers, particularly IFN- γ and MCP-1, significantly moderated the relationship between prenatal maternal anxiety and offspring neurodevelopment. IFN- γ influenced the association between prenatal anxiety and neonatal right globus pallidus volume, with higher maternal IFN- γ levels linked to better cognitive outcomes at 24 months despite elevated anxiety. Similarly, both elevated and reduced levels of maternal MCP-1 modified the relationship between prenatal anxiety and neonatal brain morphology within the striatal-cortical circuit, including caudate volume and cortical thickness in sensorimotor and temporal regions. These findings suggest that extreme MCP-1 levels may either heighten vulnerability or enhance resilience in fetal brain development. Notably, higher MCP-1 levels were also associated with improved language development at 24 months despite elevated anxiety. No significant moderating effects were observed for TNF- α or VEGF. Overall, the results highlight the potential roles of inflammatory biomarkers that modulate the fetal brain's sensitivity to maternal anxiety, with lasting implications for neurodevelopment and potential targets for early intervention.

Typical brain development during the fetal period is characterized by a rapid increase in cortical thickness and subcortical volumes (Bethlehem et al., 2022). Larger basal ganglia volumes and greater cortical thickness in neonates have been associated with more favorable developmental outcomes (Loh et al., 2017, Girault et al., 2020, Dabbs et al., 2013). Building upon this framework of typical brain development, our findings suggested that IFN- γ during pregnancy may moderate the vulnerability of fetal neurodevelopment to maternal anxiety. IFN- γ is a pro-inflammatory cytokine primarily produced by natural killer (NK) cells and T lymphocytes. IFN- γ helps modulate the immune balance at the maternal-fetal interface, encourages immune tolerance of the fetus by promoting regulatory immune responses, and provides immune surveillance to protect the fetus and placenta from infections (Yockey and Iwasaki, 2018). Its beneficial effects are dose- and context-dependent (Ko et al., 2023, Mendes-Monteiro and Viejo-Borbolla, 2025)—excessive or prolonged IFN- γ signaling can trigger inflammatory cascades that manipulate placental function and fetal development. During fetal brain development, IFN- γ plays a critical role in shaping neural connectivity and immune signaling, particularly within subcortical regions, such as the basal ganglia (Filiano et al., 2016, Estes and McAllister, 2016). In the context of maternal anxiety, IFN- γ may act as a key moderator at the maternal-fetal interface, influencing how stress-related immune changes impact the developing fetal brain (O'Connor et al., 2013). The basal ganglia—central to motor, emotional, and cognitive functions—are especially sensitive to neuroimmune modulation during gestation (Javed and Cascella, 2025). IFN- γ can regulate microglial activation and synaptic pruning within these regions, processes essential for refining basal ganglia circuitry. Moderate IFN- γ levels may support healthy development by promoting appropriate synaptic refinement and neuroprotection (Filiano et al., 2016). However, dysregulated IFN- γ signaling, either excessive or deficient, may disrupt the formation of basal ganglia pathways by altering neuronal differentiation or inducing neuroinflammation. Our findings suggested that under maternal anxiety, elevated IFN- γ levels may buffer the fetus against anxiety-related neurodevelopmental disruptions, whereas low levels may increase vulnerability, potentially leading to long-term

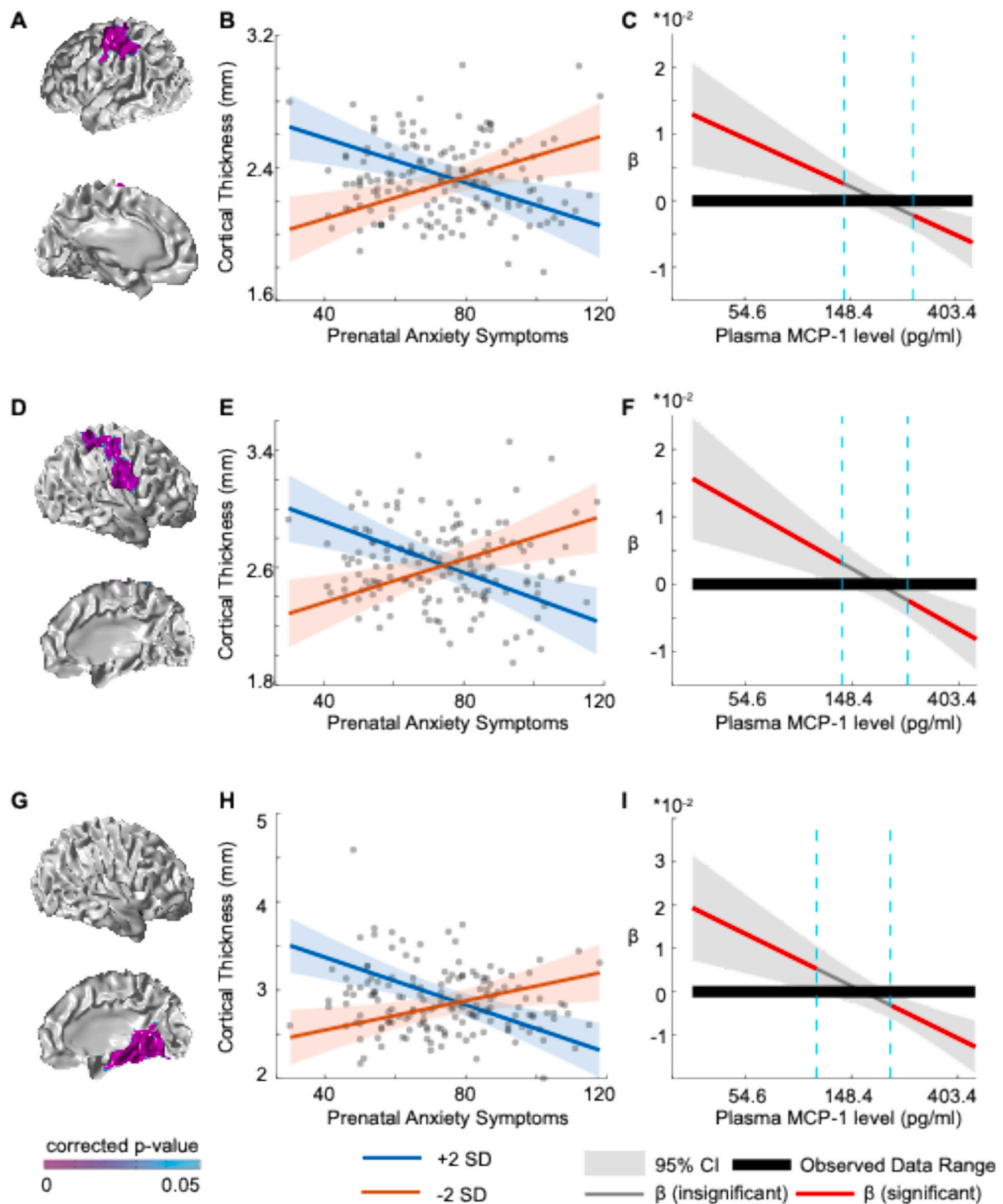


Fig. 2. Moderating effects of maternal MCP-1 on the association between prenatal maternal anxiety and neonatal cortical thickness. Panels (A, D, G) illustrate how maternal MCP-1 levels moderate the relationship between prenatal maternal anxiety and neonatal cortical thickness. Colored regions indicate significant clusters in the left precentral/postcentral gyrus (A, D) and right medial and inferior temporal cortex (G). Panels (B, E, H) display scatter plots of the interaction effects. Blue lines represent the association between prenatal maternal anxiety and cortical thickness in mothers with high MCP-1 levels (+2 standard deviations above the mean), and red lines represent the association in mothers with low MCP-1 levels (-2 standard deviations below the mean). Panels (C, F, I) present Johnson-Neyman plots identifying the specific MCP-1 threshold values where the association between prenatal maternal anxiety and cortical thickness transitions from non-significant to significant. The x-axis shows the natural log-transformed MCP-1 concentration (pg/mL), and the y-axis depicts the conditional effect (slope) of prenatal maternal anxiety on cortical thickness. The gray shaded area indicates the 95% confidence interval, and vertical dotted lines mark regions where the association becomes statistically significant ($p < 0.05$).

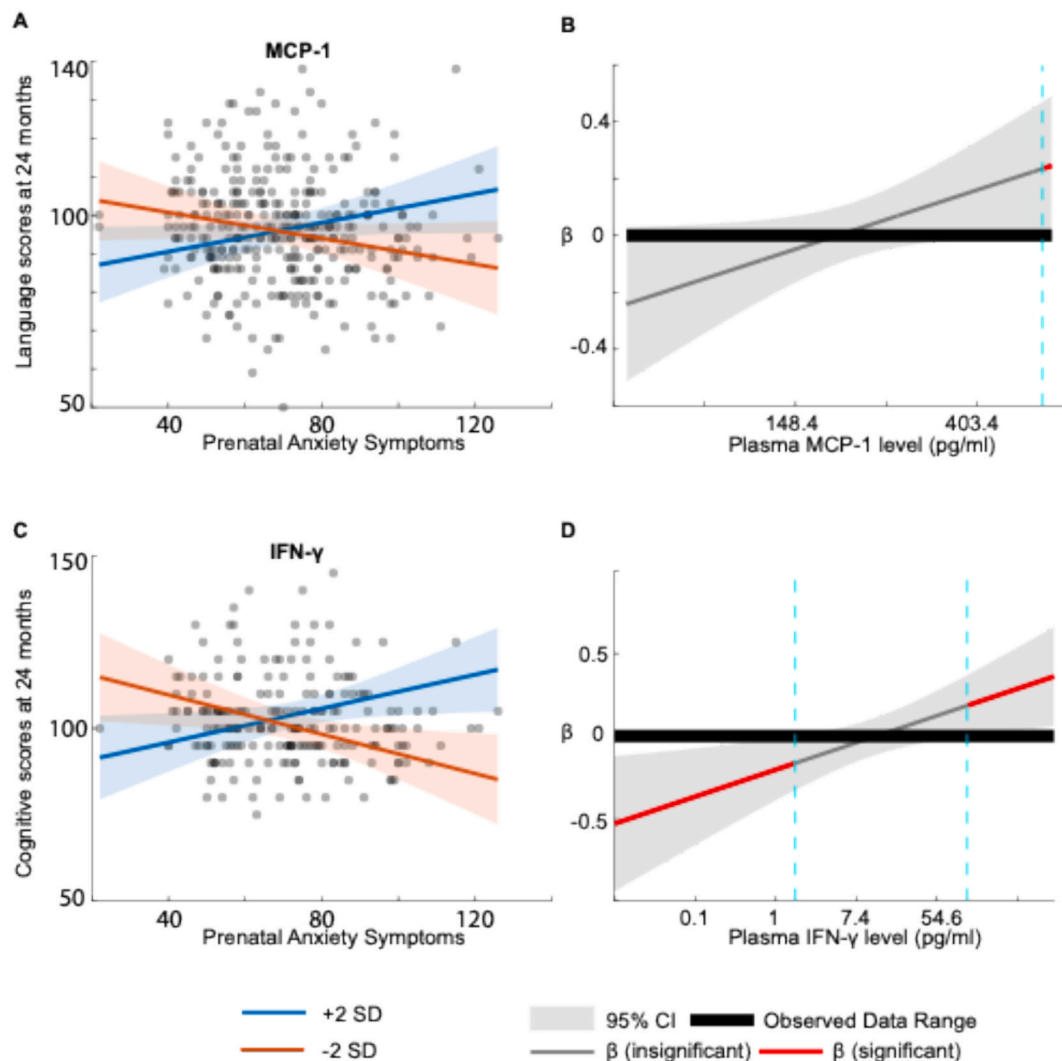


Fig. 3. Moderating effects of maternal inflammatory biomarkers on the association between prenatal maternal anxiety and offspring language and cognitive outcomes at 24 months. Panels (A, C) display scatter plots showing the interaction effects. Blue lines represent the association between prenatal maternal anxiety and developmental outcomes in mothers with higher biomarker levels (+2 SD above the mean), while red lines represent the association in mothers with lower biomarker levels (−2 SD below the mean). Panels (B, D) present Johnson-Neyman plots identifying specific biomarker threshold values at which the relationship between prenatal maternal anxiety and child outcomes transitions from non-significant to significant. The x-axis shows the natural log-transformed biomarker concentration (pg/mL), and the y-axis represents the conditional effect (slope) of prenatal maternal anxiety on cortical thickness across different biomarker levels. The gray shaded area indicates the 95% confidence interval, and vertical dotted lines mark regions where the association becomes statistically significant ($p < 0.05$).

alterations in basal ganglia-dependent functions such as affective regulation and cognitive processing.

Our study found that maternal MCP-1 levels were associated to neonatal brain structure in the context of prenatal maternal anxiety. In animal models, maternal immune activation induced by polyI:C injection increases MCP-1 not only in maternal circulation but also in the fetal brain (Arrode-Bruses and Bruses, 2012). It is also associated with altered cortical cell density (Smith et al., 2012, Hinojosa et al., 2011). MCP-1 plays a key role in mediating monocyte and macrophage recruitment at the maternal–fetal interface (Lin et al., 2022), and in regulating microglial activation within the developing brain (Zhang et al., 2018). Hofbauer cells—placental macrophages that share ontogeny and functional properties with microglia—are major producers of MCP-1 (Batorsky et al., 2024), and likely act as intermediaries in transducing prenatal immune signals to the fetus (Guglielmo et al., 2025). This positions MCP-1 as a plausible molecular mediator whose effects on neurodevelopment depend on both its concentration and the surrounding inflammatory milieu.

Although direct evidence for MCP-1 effects on fetal basal ganglia is

limited, cytokines interact with dopaminergic and glutamatergic signaling within basal ganglia circuits (Felger and Miller, 2012, Gnanavel et al., 2016), offering a plausible route to caudate vulnerability or compensation. For example, pro-inflammatory cytokines may have neuroprotective effects against glutamatergic excitotoxicity in the caudate (Gnanavel et al., 2016). Together, these data suggest that dysregulated maternal MCP-1—whether elevated in the context of anxiety/inflammation or abnormally low—may perturb microglial and neuronal processes, yielding atypical cortical thickness and subcortical volumes that increase neurodevelopmental risk.

The study revealed contrasting effects of prenatal maternal anxiety on the basal ganglia and temporal cortex in the presence of elevated maternal MCP-1 levels. Specifically, higher maternal anxiety was associated with larger bilateral caudate volumes but reduced cortical thickness in the medial and inferior temporal cortex. Although the mechanisms are not yet fully understood, previous studies have consistently shown associations between prenatal maternal anxiety and cortical thinning in the temporal regions (Buss et al., 2010, Wu et al., 2020) and white matter integrity in the sensorimotor and temporal

regions (Rifkin-Graboi et al., 2015). Notably, the mid-to-late pregnancy represents a critical window for microglial colonization to all cortical layers (Menassa et al., 2022). MCP-1 may play a role in synchronizing the maturation of the striatum and cortex by regulating microglial-mediated synaptic refinement. Under conditions of maternal anxiety or immune activation, elevated MCP-1 may alter the fetal brain environment—potentially mitigating the adverse effects of stress on basal ganglia morphology while simultaneously disrupting the timing and coordination of microglial activity across subcortical and cortical regions.

Our findings, which highlighted significant moderating effects of MCP-1 and IFN- γ —but not VEGF or TNF- α —may reflect fundamental differences in the biological functions, timing, and target pathways of these inflammatory markers during fetal brain development. VEGF primarily facilitates vascular development and angiogenesis, processes that exert their most pronounced effects earlier in gestation, particularly during placental implantation and early neurovascular formation (Polizzi and Mahajan, 2015, Sun et al., 2003). As such, VEGF may have limited direct influence on the later-developing neuroanatomical and behavioral outcomes assessed in this study, such as cortical thickness, subcortical volume, and cognitive function. TNF- α , while known for its role in inflammation and synaptic plasticity, typically exerts more acute and transient effects and may function synergistically with other cytokines (Zipp et al., 2023, Ross et al., 2022). Its influence may not align temporally or regionally with the striatal–cortical circuit alterations observed in relation to prenatal maternal anxiety.

We also reported several null findings. No significant interactions were observed between prenatal maternal anxiety and VEGF or TNF- α on neonatal brain morphology or later behavioral outcomes. They should not be interpreted as evidence that VEGF or TNF- α are uninvolved in fetal brain development, as both play established roles in placental function, vascular remodeling, and neurodevelopment (Wheeler et al., 1999; Potter et al., 2023). The lack of observed effects may reflect factors such as single time-point cytokine measurement, limited sensitivity of neurodevelopmental metrics, or sample size constraints.

Several limitations should be acknowledged. First, maternal inflammatory markers were measured at a single prenatal time point, the panel did not include certain cytokines (e.g., IL-6), and sampling time was not standardized. These factors may provide only a partial snapshot of the maternal immune milieu. Nevertheless, sampling during mid-to-late pregnancy captures a critical period of immunologic transition (Takacs et al., 2024, Jarmund et al., 2021), when inflammatory balance is essential for fetal brain development. Our panel also indexed key chemokine, angiogenic, and proinflammatory pathways relevant to this stage, coinciding with rapid neural migration and synaptogenesis (Tau and Peterson, 2010). Second, while the cohort's geographic and demographic homogeneity may limit generalizability, it enhances internal validity by minimizing environmental variability. Third, only the neonatal brain was examined in this study, limiting inference on brain developmental trajectories. Despite these limitations, this study uniquely integrates maternal cytokine profiling, prenatal anxiety assessment, and neonatal neuroimaging, providing rare prospective evidence that specific inflammatory pathways may moderate the effects of maternal mood on early brain development.

This study suggests that specific maternal inflammatory markers during mid-to-late pregnancy, particularly MCP-1 and IFN- γ , may moderate associations between prenatal maternal anxiety and fetal brain and later behavioral outcomes, indicating region- and biomarker-specific variability in susceptibility. These preliminary findings contribute to our understanding of the biological pathways that could connect maternal psychological state with offspring neurodevelopment. Our work highlights the importance of ongoing research into the interplay between maternal psychological health, inflammation, and offspring neurodevelopment.

CRediT authorship contribution statement

Xiang Zhou: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **Die Zhang:** Methodology. **Chaoqiang Liu:** Methodology. **Helen Chen:** Supervision. **Yap-Seng Chong:** Supervision. **Marielle V. Fortier:** Supervision. **Peter D. Gluckman:** Supervision. **Anqi Qiu:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

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

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Institutional review board statement

The study was conducted according to the National Healthcare Group Domain Specific Review Board (NHG DSRB) and the SingHealth Centralized Institutional Review Board (CIRB). Written informed consent was obtained from the mothers.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bbi.2026.106477>.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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