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Neuroanatomical Correlates Underlying the Association Between Maternal Interleukin-6 Concentration During Pregnancy and Offspring Fluid Reasoning Performance in Early Childhood

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Abstract

Background—Maternal inflammation during pregnancy can alter offspring brain development and influence risk for disorders commonly accompanied by deficits in cognitive functioning. We therefore examined associations between maternal interleukin [IL]-6 concentrations during pregnancy and offspring cognitive ability and concurrent MRI-based measures of brain anatomy in early childhood. We further examined *newborn* brain anatomy in secondary analyses to consider

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whether effects are evident already soon after birth, and increase capacity to differentiate effects of pre- versus postnatal exposures.

Methods—IL-6 concentrations were quantified in early (12.6±2.8 weeks), mid (20.4±1.5 weeks) and late (30.3±1.3 weeks) pregnancy. Offspring nonverbal fluid intelligence (Gf) was assessed at 5.2±0.6 yrs using a spatial reasoning task (WPPSI-Matrix) (n=49). T1-weighted MRI scans were acquired at birth (n=89, postmenstrual age=42.9±2.0 weeks) and in early childhood (n=42, scan age=5.1±1.0 years). Regional cortical volumes were examined for a joint association between maternal IL-6 and offspring Gf performance.

Results—Average maternal IL-6 concentration during pregnancy was inversely associated with offspring Gf performance after adjusting for socioeconomic status and the quality of the caregiving and learning environment (R^2=13%; p=.02). *Early-childhood* pars triangularis (PT) volume was jointly associated with maternal IL-6 and childhood Gf (p-corrected<0.001). An association also was observed between maternal IL-6 and newborn PT volume (R^2=6%; p=.02).

Conclusions—These findings suggest that the origins of variation in child cognitive ability can, in part, trace back to maternal conditions during the intrauterine period of life and support the role of inflammation as an important component of this putative biological pathway.

Keywords

Longitudinal MRI; Newborn; Pars Triangularis; Inferior Frontal Gyrus; Interleukin-6; Inflammation; Fluid Reasoning; Fluid Intelligence

Introduction

Identifying the early determinants of neurodevelopmental cognitive phenotypes is of considerable individual and societal interest because these phenotypes form the basis of future academic success (1) and creativity (2). In this context, fluid reasoning skills (or fluid intelligence [Gf]) are particularly salient as they strongly relate to the complex skills that support the ability to learn and problem solve (3). A rapidly growing and convergent body of epidemiological, clinical and experimental evidence across species suggests that inter-individual variation in cognitive function can, in part, be traced back to the influence(s) of developmental conditions during the intrauterine period of life (*i.e.*, the concept of fetal programming) (4,5). This, from a developmental perspective, is expected, because gestation represents a period of particularly rapid embryonic and fetal brain development, during which time cues from the maternal compartment guide the specification of the neuroanatomical characteristics that underlie cognition.

Epidemiological and clinical evidence has identified several specific maternal conditions in pregnancy including obesity (6–8), infection, (9), poor diet (10,11), and high psychosocial stress (12,13) as being associated with an increased risk for offspring neurodevelopmental disorders and cognitive impairment (14–19). A common, though not requisite, feature across these prenatal conditions is that each of them is associated with a heightened state of inflammation. Indeed, we and others have postulated that inflammation may represent a key maternal-placental-fetal signaling pathway that impacts all aspects of fetal brain development, including offspring complex cognitive function (20). However, the majority

of this research has been limited to either human studies using *proxies* of inflammatory conditions during pregnancy (*e.g.* high pre-pregnancy BMI, maternal infection), or *animal* studies in which the maternal prenatal immune system is experimentally manipulated in a manner that may not have clear clinical application (21–23). Thus, there is a fundamental knowledge gap between epidemiological and preclinical lines of evidence regarding the role of prenatal maternal inflammation on offspring complex cognitive development.

Recent attempts to address this gap include observational studies suggesting that markers of inflammation during pregnancy (e.g. C-Reactive Protein, TNF-α) are associated with offspring neurodevelopmental delay (14), executive functioning (24), and full-scale IQ (68) in children. In addition, we and others have recently reported that maternal levels in pregnancy of pro-inflammatory cytokines such as interleukin [IL]-6 are associated with offspring brain morphology, functional connectivity (25), and structural connectivity at birth and during infancy (26). However, the specific role of maternal IL-6 in the ontogeny of variation in offspring complex cognitive traits that emerge *later* in development (i.e. fluid intelligence), and its neuroanatomical substrates, is largely unexplored. We, therefore, aim here to examine the relationship between maternal IL-6 concentration during pregnancy and offspring fluid reasoning performance and to identify its underlying neuroanatomical substrate(s).

Concentrations of IL-6 in maternal circulation in early, mid and late gestation were quantified as an indicator of maternal systemic inflammation during pregnancy. IL-6 features prominently among the key biological mediators in the maternal-placental-fetal (MPF) immune/inflammatory pathway because it acts as a *sensor*, *transducer,* and *effector* of gestational conditions on the developing fetal brain (27). Elevated IL-6 concentrations have been observed among pregnant women with conditions that increase risk for offspring neurodevelopmental disorders, including obesity, infection, and high psychosocial stress (*sensor*) (28,29). Such conditions are also characterized by higher IL-6 and other pro-inflammatory cytokines in the placental, intra-amniotic and fetal compartments, including cord blood and the fetal brain (*transducer*) (30–33). While IL-6 plays a requisite role in normal healthy fetal brain development (34), elevated levels can adversely affect cellular survival, proliferation and differentiation, as well as axonal growth and synaptogenesis (*effector*) (35–38). Moreover, animal models have suggested that IL-6 is both *necessary* and *sufficient* to activate this pathway (39,40).

We conducted a prospective, longitudinal study of maternal-child dyads from early pregnancy through early childhood, with characterization of maternal IL-6 across pregnancy and quantification of offspring Gf performance and brain anatomy in early childhood. We note the early childhood time point represents the *earliest* age at which fluid intelligence can be reliably measured (72). The hypothesis that maternal IL-6 concentration in pregnancy is prospectively and inversely associated with offspring Gf performance is based on the above considerations that maternal inflammation often accompanies risk factors for offspring cognitive impairment, that maternal IL-6 likely represents a key biological mediator in the MPF inflammatory pathway, and that Gf, in contrast to learned intelligence, represents a construct modifiable by biological factors (71). Here, we examined the *independent* association of maternal IL-6 with offspring Gf after accounting for the effects of other

key sociodemographic and postnatal determinants of Gf, including the quality of the postnatal environment. Next, we elucidated the neuroanatomical substrate(s) that may underlie this association using the child brain magnetic resonance imaging (MRI) data collected concurrent to Gf assessment. To do so, we employed an ROI-based approach to examine the *joint* cross-sectional associations between: *a*) child regional brain volumes and Gf, and *b*) maternal IL-6 and child regional brain volumes. We note that any relationship between a maternal state that is restricted to the duration of pregnancy (e.g. maternal IL-6) and an offspring outcome at any postnatal age/time point (e.g. offspring neuroanatomy in early childhood) will represent a sum of prenatal and postnatal effects. For example, maternal inflammation during pregnancy can affect fetal brain development directly while simultaneously affecting postnatal physiology (e.g., infant immune function (73)), that, in turn, can impact postnatal brain maturation. Thus, in order to address the question of whether any observed effects of maternal IL-6 on offspring Gf-related brain regions might have been established during the fetal period of development (*i.e.*, fetal programming), we leveraged *newborn* brain imaging data and performed an exploratory/preliminary analysis. We quantified the presence and magnitude of associations between maternal IL-6 and newborn brain regions and restricted this analysis to only those brain regions that had been identified at the early childhood age as being correlated with child Gf performance. The logic of using the newborn time point is that any observed effects on the child's brain at this time could not be attributable to postnatal influences; they necessarily originate during fetal life (26). Furthermore, the importance of addressing this question (of whether the influence of maternal IL-6 on the child's brain may have begun during the fetal period of development) derives from the consideration that its answer may identify criticial periods for intervention (prenatal vs. postnatal, or both).

Methods

Sample

Mother-child dyads were part of a longitudinal study, conducted at the University of California, Irvine, for which mothers were recruited during the first trimester of pregnancy and provided serial blood samples in early, mid and late pregnancy (N=153; Table 1). MRI was performed in the offspring near birth (N=89, postmenstrual age=42.9±2.0 weeks) and again in early childhood (N=42, scan age=5.1±1.0 years; N=29 with longitudinal MRI data). Gf measures were available in N=49 children (N=31 with concurrent Gf and MRI measures). Exclusionary criteria included maternal use of psychotropic medications or systemic corticosteroids during pregnancy; infant birth before 34 weeks gestation; and infant congenital, genetic, or neurologic disorder. All procedures were approved by the Institutional Review Board at the University of California, Irvine, and written informed consent was obtained from all mothers.

Measurement of Maternal IL-6 Concentration during Pregnancy

Maternal antecubital venous blood samples were collected in serum tubes (BD Vacutainer) in early (12.6±2.8 weeks), mid (20.4±1.5 weeks) and late (30.3±1.3 weeks) pregnancy. Serum IL-6 concentration was determined using a commercial high sensitivity ELISA (eBioscience) with a sensitivity of 0.03 pg/ml. IL-6 concentration was moderately stable

across pregnancy (ICC=0.45). Thus, IL-6 was averaged across pregnancy and base 2 logarithm transformed to normalize the distribution.

Measurement of Offspring Fluid Reasoning Performance (Gf)

Offspring children (5.2+/−0.6 years) completed the matrix reasoning subscale of the Wechsler Preschool & Primary Scale of Intelligence (WPPSI)-IV (67). This subtest prompts children to complete the missing piece of a colored puzzle/pattern of increasing difficulty. These problems require the complex reasoning and abstract, spatial perception commonly used to measure Gf (41). Matrix reasoning scores were scaled for age and sex per WPPSI guidelines. Of note, N=18 children were not assessed for Gf due to age-based exclusion (<4 years of age).

MRI Acquisition and Processing

A detailed description of the MRI acquisition and processing steps are provided as Supplementary Materials. In short, T1-weighted MRI scans were processed using FreeSurfer resulting in 34 bi-laterally averaged regions of interest (ROI). ROI-based volume was used in the primary analysis, while surface area and cortical thickness were used in supplementary analyses.

At the newborn time point, T1- and T2-weighted MRI scans were acquired during natural sleep. Images were processed using a framework based off of the Freesurfer-based Human Connectome Project pipeline but adapted for infant imaging (https://github.com/DCAN-Labs/infant-abcd-bids-pipeline/tree/master/app, see Supplementary Materials), providing regional volumes consistent with the early childhood time point. Of note, the term “volume” is used throughout to denote what would be more accurately defined as “apparent volume as measured by MRI” (56).

Measurement of Potentially Confounding Factors

Socioeconomic status (SES), quality of the caregiving/learning environment (Home Observation for Measurement of the Environment [HOME], Home Learning Environment [HLE]), gestational age at birth, birthweight (percentile), obstetric risk, and measures of maternal perceptual reasoning (PRI) were considered based on their potential either for confounding effects or as covariates of non-interest (see Supplementary Material).

Analytical Approach

1. **Maternal IL-6 Concentration and Offspring Early Childhood Fluid Reasoning Performance (Gf)—**Linear Regression models were used to examine the relationship between maternal IL-6 concentrations during pregnancy and early childhood Gf. We first tested the hypothesis that maternal IL-6 would be negatively associated with offspring Gf using a parsimonious bi-variate regression analysis. Post-hoc tests for potentially confounding factors leveraged a Multiple Imputation method (50 iterations using predictive mean matching) (42–44) to account for missing data (N_{NA}=3 maternal cognition, N_{NA}=1 6-month HOME score, N_{NA}=8 5-year HLE score) using the *mice* package in R.

2. Neuroanatomical Substrates of the Association Between Maternal IL-6 Concentration and Offspring Early Childhood Fluid Reasoning Performance (Gf)—We considered regional brain volumes associated with both the predictor (IL-6) and the outcome (Gf) using stratified models and testing for joint significance: 1) offspring regional brain volume and Gf, and 2) maternal IL-6 and offspring regional brain volume. The associations between maternal IL-6 concentration, regional gray matter volumes, and Gf were tested using a parsimonious linear regression correcting for child age at scan, sex, total GM volume, and quality control (QC). Follow-up tests were performed post-hoc to assess the influence of confounding factors. Multiple comparisons corrections were performed using a permutation test of joint (e.g. associated with IL-6 *and* Gf) significance (45). Based on initial findings, statistical mediation of the association between maternal IL-6 in pregnancy and child Gf via two regional brain volumes (rostral middle frontal gyrus (RMFG) and pars triangularis (PT) selected based on the joint significance test) were assessed using causal mediation and nonparametric bootstrapping (N=10,000) in the *mediation* package in R (46).

3. Newborn Brain Volumes—To address the question of whether any influence of maternal IL-6 on Gf-relevant child brain region(s) could have been established during the fetal period of life, we explored the relationships between inter-individual variation in *newborn* regional brain volume, maternal IL-6 and childhood outcomes (regional brain volume and Gf performance). Specifically, we tested the association between newborn and early childhood brain volume (restricted to those identified in the above joint significance and mediation analyses with the early childhood data) correcting for age, sex, and global GM volume. Next, we examined whether newborn brain volume was associated with childhood Gf performance, and whether maternal IL-6 was associated with newborn brain volume. These secondary analyses were identical to the early childhood models, with the exception that number of surface holes (QC) were not included in the model as this measure was not available. Of note, all post-hoc analyses were considered exploratory in nature and thus should only be interpreted as such.

Results

1. Descriptive Findings

Median raw IL-6 across pregnancy was 0.76 pg/ml (Q_1/Q_3=0.47/1.34 pg/ml). The base 2 logarithm values of mean IL-6 across pregnancy were −0.36±1.05, normally distributed, correlated across pregnancy trimesters ($r_{1st,2nd}$=.70; $r_{2nd,3rd}$=.59; $r_{1st,3rd}$=.54), and consistent with prior studies (47). The mean scaled matrix reasoning performance (Gf) score was 8.8±3.1 (median=9, Q_1/Q_3=6/11). The scaled score was not associated with age or sex (p>.2), and the distribution of percentile ranks were roughly in accordance with expectations (mean percentile rank=40.1, Q_1/Q_3=16/75).

2. Maternal IL-6 Concentration During Pregnancy and Early Childhood Fluid Reasoning Performance (Gf)

Maternal IL-6 concentration during pregnancy was inversely associated with early childhood Gf ($\beta_{IL\text{-}6}$ = −.38; p = .013; N = 49; Figure 1). Post-hoc testing using multiple imputation

(N=50) with missing value replacement suggested that maternal IL-6 remained significant when accounting for potential pre- and postnatal confounding factors (t = −2.36; p = .023). Maternal IL-6 in pregnancy independently explained 13% of the variance in child Gf performance.

3. Neuroanatomical Substrates of the Association Between Maternal IL-6 Concentration and Offspring Early Childhood Fluid Reasoning Performance (Gf)

We accounted for global size by including total GM volume as a covariate in the primary models. Thus, we first tested the association between maternal IL-6 concentration, Gf, and early childhood global GM volume (see Supplementary Materials for details). Total GM values were 737+/−79cm^3 on average. There was a trend for an inverse association between maternal IL-6 concentration during pregnancy and total GM volume ($\hat{\beta} = -.24$, p = .07; N=42) in the parsimonious linear regression model including age at scan, sex, and QC. Similarly, there was a trend for a positive association between total GM volume and early childhood Gf ($\hat{\beta} = .29$, p = .10; N=31).

3A. Brain Volume in Early Childhood, Gf in Early Childhood and Maternal IL-6—Early childhood PT and RMFG volumes were negatively associated with early childhood Gf (see Figure 2, left panel). Separately, maternal IL-6 concentration during pregnancy was associated with early childhood brain volume in three regions (positive association with PT and RMFG; negative association with parahippocampal gyrus; Figure 2, middle panel). Further descriptives of these associations are given as Supplementary Materials. An omnibus non-parametric multiple comparisons (n=34 ROIs) test of joint significance between maternal IL-6 concentration during pregnancy, ROI-based measures of volume, *and* early childhood Gf identified two potential ROIs – PT (p-corrected < .001) and RMFG (p-corrected = .046) (Figure 2, right panel) – as being along the indirect pathway between maternal IL-6 and offspring Gf.

3B. Exploring Mediation of the Association Between Brain Volume and Gf in Early Childhood by Maternal IL-6—Based on the consideration that maternal IL-6 concentration during pregnancy was prospectively associated with both early childhood PT volume *and* Gf, we explored whether regional brain volume (PT or RMFG) supported statistical mediation of the association between maternal IL-6 concentration during pregnancy and early childhood Gf. Using a bias-corrected bootstrap analysis there was supporting evidence for PT, but not RMFG (p=0.30), volume statistically mediating the association between maternal IL-6 concentration during pregnancy and early childhood Gf (95% CI = [−1.33, −0.08]; p-indirect = .02; Figure 3).

Further, in a supplementary analysis, we also tested whether the above findings held when substituting volume for cortical surface area and thickness. In short, we found that ROI-based measures of cortical surface area, but not cortical thickness (all p>0.10), largely recapitulated the above PT volume associations with maternal IL-6 concentration during pregnancy and early childhood Gf (see Supplementary Materials).

4. Newborn Brain Volumes

We first tested the longitudinal association between newborn and early childhood PT volume, as that region had been identified above as jointly significant (associated with IL-6 *and* Gf), survived adjustment for potentially confounding factors, and demonstrated evidence of statistically mediating the association between maternal IL-6 and Gf. Newborn PT volume was significantly associated with early childhood PT volume, in the limited sample of children (N=29) with longitudinal neuroimaging data (R_{PT}^2=46%, p<0.001).

In order to further explore the association between maternal IL-6 and the developing fetal brain we tested whether maternal IL-6 concentration during pregnancy was associated with *newborn* PT volume. Maternal IL-6 concentration during pregnancy was significantly associated with newborn PT (p<0.05) volume after controlling for age at scan, gestational age at birth, sex, and total GM volume (Figure 4, top left panel). The effect size of maternal IL-6 on newborn brain volume was smaller relative to the effect on early childhood brain volume ($\hat{\beta}_{neonatal,\,IL-6} = 0.15$, $\hat{\beta}_{5yr,\,IL-6} = 0.39$). While *newborn* PT volume was not significantly (p=0.12) associated with early childhood Gf performance (Figure 4, top right panel), the same direction of association ($\hat{\beta}_{neonatal,\,Gf} = -0.24$, $\hat{\beta}_{5yr,\,Gf} = -0.47$) was observed as between early childhood PT volume and early childhood Gf (Figure 4, bottom right panel).

Discussion

In this prospective, longitudinal study we present evidence of an inverse association between maternal IL-6 concentration during pregnancy and early childhood Gf performance. We further identify two brain regions in early childhood, PT and RMFG, whose volumes were significantly associated with both maternal IL-6 concentration and offspring Gf performance. Furthermore, exploratory mediation analyses suggest PT volume (but not RMFG) is a significant mediator of the association between maternal IL-6 concentration and offspring Gf performance. By leveraging brain imaging data acquired at the newborn time point, we were also able to demonstrate that inter-individual variation in newborn PT brain volume was associated with this same measure in early childhood, and that maternal IL-6 was associated with *newborn* PT volume. Thus, these findings suggest that the origins of variation in fluid reasoning ability may, in part, trace back to the intrauterine period of life, and they provide evidence for prenatal inflammation as a putative biological mechanism with the potential to influence fetal brain development.

The direction of association between maternal IL-6 during pregnancy and early childhood Gf performance is consistent with preexisting epidemiological, observational, and preclinical evidence demonstrating cognitive deficits in offspring exposed to a heightened pro-inflammatory state *in utero*. The effect size is substantial, with maternal IL-6 in pregnancy accounting for 13% of the variance in child Gf performance. Further, based on the premise that fluid reasoning partially underlies learning and academic achievement (1,41) (e.g. GPA and SAT scores); early learning reinforces the motivation to learn more; early mastery of skills makes future learning more efficient (48); and interventions that begin earlier afford greater benefits (48,49) at lower cost, it is reasonable to infer that primary interventions

aimed at controlling maternal inflammation during pregnancy may confer a high rate of return to investment in terms of learning and academic potential.

Early childhood PT volume was observed in this study to be inversely associated with Gf performance. Based on existing literature we might have *a priori* hypothesized a positive (50,51) association consistent with the trend positive association ($p<0.10$) observed between *total* gray matter volume and Gf. Because all analyses were adjusted for total gray matter volume, our observation should be interpreted in the context of PT volume *relative* to gray matter volume. However, because brain development at this age is a relatively understudied (52,53) and spatiotemporally dynamic process with known context-dependent (54,55) and tissue-dependent (56) changes, the mechanisms underlying the direction of these effects ought to be the focus of future studies.

Average maternal IL-6 during pregnancy was positively associated with PT volume in early childhood (medium effect size). There exists a large and convergent preclinical body of evidence that supports altered offspring frontal and limbic morphological development in the context of in utero exposure to maternal inflammation (69,79,80). However, due to the lack of a clear PT homologue in rodents (74), it is difficult to fully place the specific anatomic association with maternal inflammation into this context. In humans, the current finding is regionally consistent with previous observations demonstrating an association between newborn functional connectivity between the amygdala and the inferior frontal gyrus and cognition at 6-months age (75). In addition, maternal IL-6 concentration during pregnancy has previously been associated with newborn offspring functional connectivity between the cingulate and medial prefrontal cortex (76), two regions previously implicated in the parieto-frontal integration theory of intelligence (61, 62, 77). The direction of the effect observed here is conceptually consistent with recent literature in lambs (57) demonstrating cortical surface area expansion in prenatally LPS-exposed offspring, and is attributed to edema. In *post-hoc* analyses we observed that maternal inflammation (and Gf performance) is more strongly related to cortical surface area than cortical thickness. Thus, these findings are consistent with the concept of inflammation-driven cortical surface area expansion. However, we emphasize that the underlying cellular underpinnings of structural MRI are not possible to disentangle based on MRI measurements alone (56) and that this topic warrants future investigation.

Findings suggest that the observed associations between maternal inflammation and regional brain volume differences were evident already soon after birth. The importance of this is two-fold. First, concurrent measurement of brain volume and Gf performance in early childhood constrains inference on the sequential order of development. Second, because unobserved postnatal factors (e.g. offspring immune function) may be programmed by maternal inflammation and potentially influence *postnatal* brain development (58), there is potential for hidden confounding by unobserved variables. Thus, while insufficiently powered for testing the mediation of the association between maternal IL-6 and childhood PT volume by newborn PT volume, these findings support the notion that the influence of maternal IL-6 may begin *in utero* by shaping aspects of fetal brain development.

The possibility that maternal inflammation during pregnancy may continue to exert an additional influence on postnatal brain development (via the effects of prenatal inflammation on offspring physiology), may account for the observation that the association between maternal IL-6 during pregnancy and offspring PT volume appears to get stronger with age (6% and 19% variance explained in infancy and early childhood, respectively). On the other hand, it cannot be ruled out that this observation is simply due to relative differences in signal variation (e.g. exponential/Gompertz (59) growth in early life) and noise/measurement error (e.g. point estimate precision, image/segmentation quality (60)) between newborn and early childhood measurements. These considerations highlight the challenge of studying the prenatal origins of neurophenotypes (due to the high degree of plasticity the brain maintains after birth), and they emphasize the high scientific potential of incorporating newborn assessments.

The PT and RMFG brain regions comprise key components of the fluid intelligence network specified under the parieto-frontal integration theory (P-FIT) of intelligence and are commonly operationalized in neuroimaging studies (61,62) as part of an *a priori* set of 10 ROIs. However, based on relative effect sizes, and in light of the absence of *post-hoc* RMFG findings (e.g. correction for potentially confounding factors, and statistical mediation), only the PT appears to be uniquely involved in the current framework. In support of this premise, recent evidence suggests that the PT is indeed distinctive within the P-FIT network due to its dense integration with brain regions and networks susceptible to elevated gestational inflammation. Specifically, the PT is densely connected to, and thus innervated by, limbic circuitry via the Uncinate Fasciculus (UF) (63). In our prior work, we have reported associations between maternal IL-6 concentrations and newborn offspring UF fractional anisotropy, limbic structure (amygdala volume), and limbic (amygdala) functional connectivity (25,26,64). Because tangential expansion on the cortex is partially guided by functional input (65), PT surface area expansion may be guided by limbic signaling that itself can be programmed by prenatal inflammation.

This work builds on and extends our previous reports on the association between maternal IL-6 concentration during pregnancy and offspring neurophenotypes (25,26,64) in two key ways. First, the current findings support the notion that the influence of maternal inflammation on neurodevelopmental outcomes reaches beyond the first year of life. This is of particular interest because the brain system highlighted here (PT) is generally considered to mature outside the developmental window of our previous observations. Specifically, this includes an estimated 122–142% increase in volume between birth and two years age (78), followed by decreases in volume spanning from early childhood to adolescence (66). Second, Gf extends our previous work into a higher-order cognitive domain that is difficult to index prior to early childhood (67). While we have previously identified associations between maternal IL-6 concentrations and offspring working memory at two years of age, the current study represents our first opportunity to examine the influence of maternal inflammation specifically on Gf.

Limitations of the current study include the tradeoff between power and specificity provided by our choice of morphometric analyses, sample size, and conceptualization of IL-6 in isolation. While the use of ROI-based measures increase sensitivity *via* reduced comparisons

and improved signal averaging, it also restricts anatomical specificity by constraining regions to *a priori* definitions. In addition, while morphometry-based measures are reflective of the gross underlying neurobiology, they lack the microstructural specificity (56) necessary for validating detailed microscopy outcomes. Thus, while the current findings address key knowledge gaps by extending existing preclinical paradigms through observations in humans that further demonstrate the physiological relevance of maternal inflammation during pregnancy for fetal brain development (69,79,80) and cognitive behavior (21–23) in later life, animal and/or human models that couple *in vivo* imaging modalities with outcomes at the cellular level remain of high translational importance. Although it is reasonable to assume that structure (PT volume) begets function (Gf performance) and model it accordingly (as in the above mediation analysis), in the context of development this is a cyclical process in which function/ability also affects structure (e.g. axonal connectivity). Thus, we note that the reverse mediation and conceptualization case also seems plausible and should be examined in future studies. While the current study, to our knowledge, is the largest to date with maternal IL-6 concentration sampling during pregnancy combined with newborn and early childhood imaging, it is underpowered for the testing of interaction effects (e.g. sex, quality of postnatal environment), which remain of high interest given the observation that the associations between maternal IL-6 and brain outcomes appear to strengthen throughout early brain development. Thus, replication in a larger sample size, ideally with repeated measures across early childhood in order to parse apart the ontogeny of observed effects, is warranted. Finally, it should be noted that IL-6 does not operate in isolation but within a complex network of immune (70) and endocrine mediators. Thus, efforts aimed at a greater understanding of the role of maternal stress and inflammation for altering fetal brain development and offspring behavior, from a systems perspective, are warranted.

In summary, we have demonstrated an inverse association between average maternal IL-6 concentration during pregnancy and offspring fluid reasoning (Gf) performance. Because the variation in maternal inflammation studied here is within a normative range, and because fluid reasoning performance may underlie academic achievement, we posit that these findings are of potentially broad societal importance. In addition, we observed a brain region (PT) consistent with the P-FIT theory of intelligence to be associated with both maternal IL-6 concentration during pregnancy and early childhood Gf performance. Finally, we have provided evidence suggesting that aspects of the variation in this neuroanatomy are associated with maternal IL-6 concentration during pregnancy as early as birth. Collectively, we suggest that the influence of maternal IL-6 on fluid intelligence may begin *in utero* through the influence of fetal brain development in regions known to underlie fluid reasoning. Thus, this work supports the need for intervention research in determining the impact of the primary prevention of excess maternal inflammation on offspring academic performance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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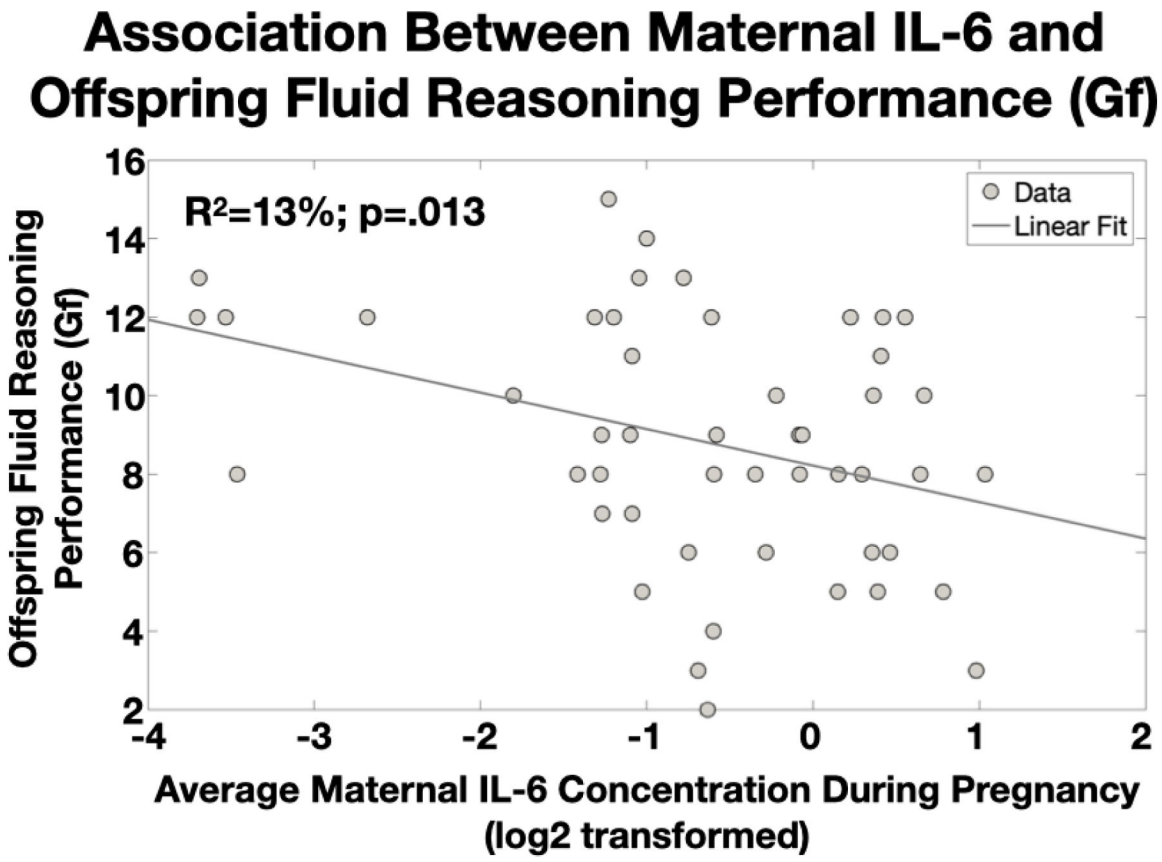

Figure 1. Maternal IL-6 Concentration During Pregnancy is Associated with Early Childhood Fluid Reasoning Performance (Gf).

Scatter plot of the negative association between maternal IL-6 concentration during pregnancy and offspring Gf.

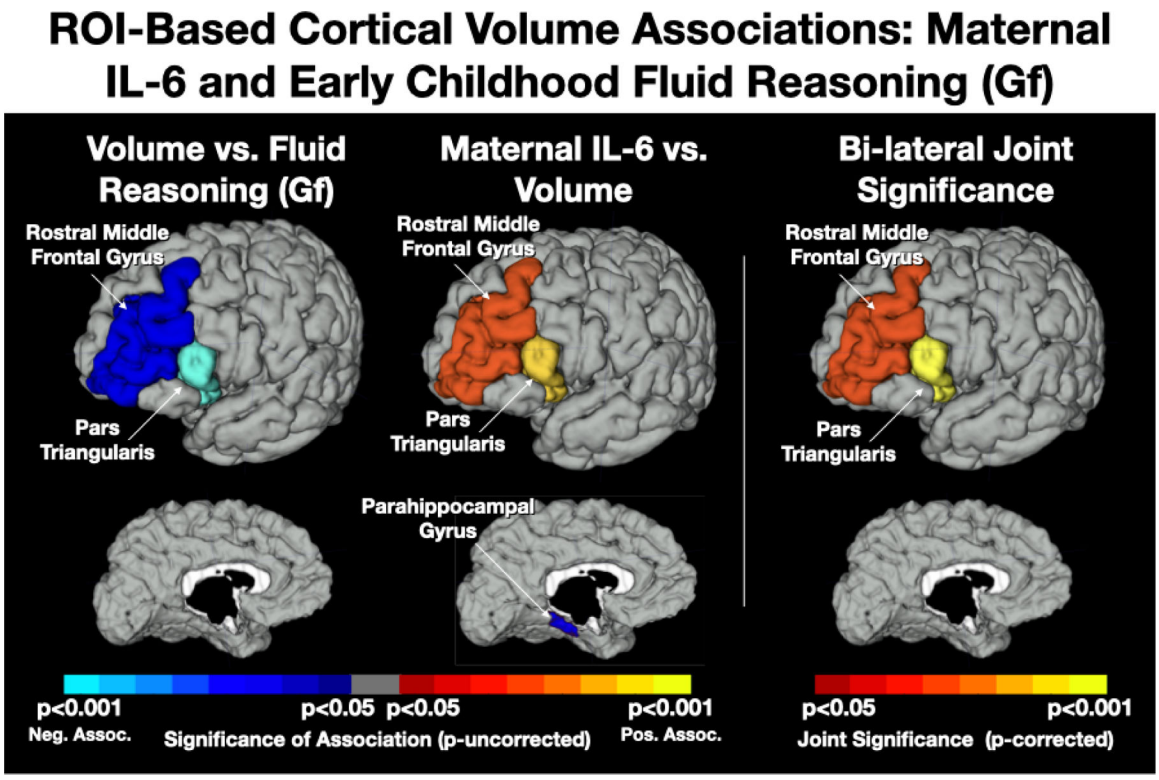

Figure 2. ROI-Based Cortical Volume Associations: Maternal IL-6 Concentration During Pregnancy and Early Childhood Fluid Reasoning Performance (Gf).

Left column depicts ROI-based gray matter volumes associated with Gf, middle column depicts ROI-based associations between maternal IL-6 concentration during pregnancy and gray matter volumes, right column depicts multiple comparisons corrected bi-lateral joint significance (maternal IL-6 *and* Gf performance associated with gray matter volume).

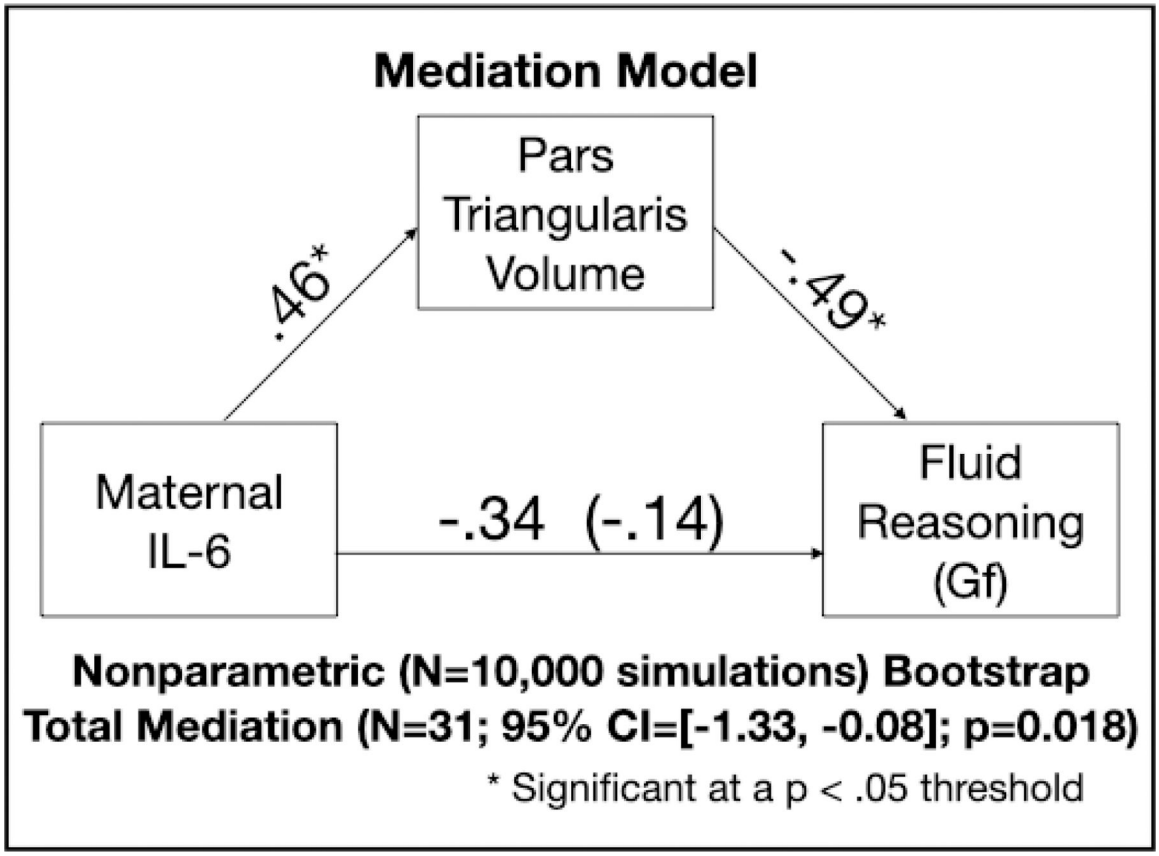

Figure 3. Pars Triangularis (PT) Volume in Early Childhood Mediates the Association Between Maternal IL-6 Concentration During Pregnancy and Early Childhood Fluid Reasoning Performance (Gf).

Maternal IL-6 concentration during pregnancy is positively associated with early childhood PT volume and negatively associated with early childhood Gf. Early childhood PT volume is negatively associated with early childhood Gf. Early childhood PT volume mediates the association between maternal IL-6 concentration during pregnancy and early childhood Gf ($p<0.05$).

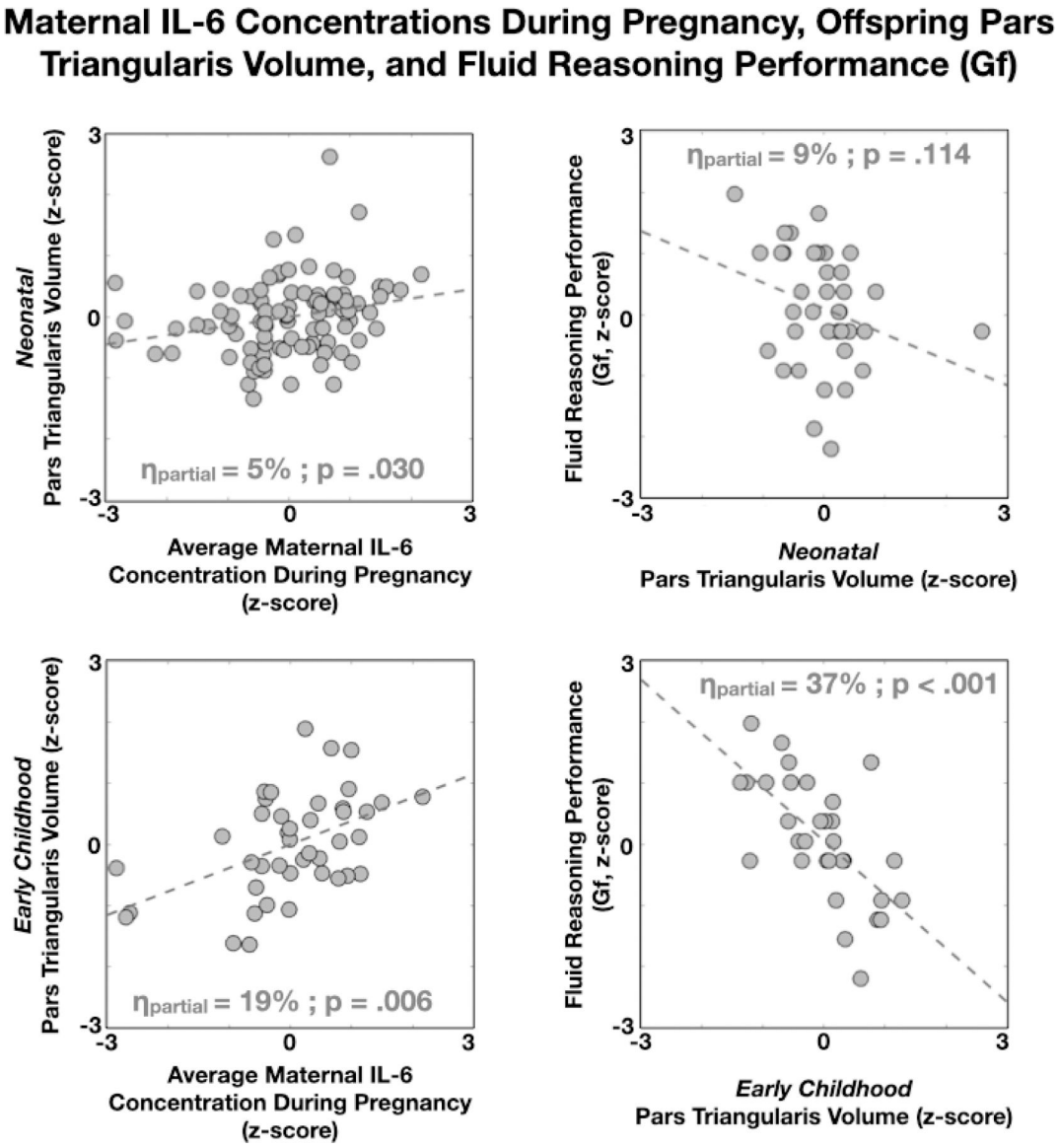

Figure 4. Maternal IL-6 Concentrations During Pregnancy, Offspring Pars Triangularis Volume, and Early Childhood Fluid Reasoning Performance (Gf).

Scatter plots depicting bi-variate associations between newborn (top row) and early childhood (bottom row) pars triangularis gray matter volume, and maternal IL-6 concentration during pregnancy (left column) and Gf (right column).

Table 1.

Demographic Information.

Demographic information of the full sample (N=153 mothers or the subset of children with MR imaging) with available maternal IL-6 measurements. There were no significant differences in key demographics between the full sample and the various subsets (those with neuroimaging and/or behavioral data) available for analyses.

Maternal Age [years (SD)]	27.8 (5.4)
Maternal Race/Ethnicity (%)	
White non-Hispanic	39.9
White Hispanic	37.2
Asian	8.5
Other	14.5
Household Highest Level of Maternal Education (%)	
High-School or Test Equivalent	22.2
Vocational School or Some College	41.2
Associates Degree	5.8
Bachelors or Graduate Level Degree	30.7
Gross Annual Household Income (%)	
< $15,000	10.3
$15,000 – 29,999	19.2
$30,000 – 49,999	21.2
$50,000 – 100,000	37.7
> $100,000	11.6
Newborn MRI	
Gestational Age at Birth [N=89,weeks (SD)]	39.2 (1.0)
Postnatal Age at Scan [N=89,weeks (SD)]	3.7 (1.8)
Childhood MRI	
Age at Scan [N=42,years (SD)]	5.1 (1.0)