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# Maternal Systemic Interleukin-6 During Pregnancy is Associated with Newborn Amygdala Phenotypes and Subsequent Behavior at 2-years-of-age

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## Abstract

**Background—**Maternal inflammation during pregnancy increases risk for offspring psychiatric disorders and other adverse long-term health outcomes. The influence of inflammation on the developing fetal brain is hypothesized as one potential mechanism, but has not been examined in humans.

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**Methods—**Participants were N=86 adult women recruited in early pregnancy, and their infants born after 34-weeks gestation. A biological indicator of maternal inflammation (interleukin-6 [IL-6]), which has been shown to influence fetal brain development in animal models, was quantified serially in early, mid and late pregnancy. Structural and functional brain MRI was acquired in neonates shortly after birth. Infants' amygdalae were individually segmented for measures of volume and as seeds for resting state functional connectivity. At 24-months-of-age, children completed a snack delay task to assess impulse control.

**Results—**Higher average maternal IL-6 concentration during pregnancy was prospectively associated with larger right amygdala volume and stronger bilateral amygdala connectivity to brain regions involved in sensory processing and integration (fusiform, somatosensory cortex, thalamus), salience detection (anterior insula), and learning and memory (caudate and parahippocampal gyrus). Larger newborn right amygdala volume and stronger left amygdala connectivity were in turn associated with lower impulse control at 24-months-of-age, and mediated the association between higher maternal IL-6 concentrations and lower impulse control.

**Conclusions—**These findings provide new evidence in humans linking maternal inflammation during pregnancy with newborn brain and emerging behavioral phenotypes relevant for psychiatric disorders. A better understanding of intrauterine conditions that influence offspring disease susceptibility is warranted to inform targeted early intervention and prevention efforts.

### Keywords

Inflammation; pregnancy; neonates; neuroimaging; amygdala; resting state functional connectivity MRI

## Introduction

Maternal inflammation during pregnancy appears to increase risk for offspring neuropsychiatric disorders and adverse physical health outcomes.(1–3) Strong epidemiological evidence identifies connections between common conditions associated with heightened inflammation during pregnancy, including infection,(4–15) high maternal body mass index (BMI)(16–18), maternal psychopathology(19), increased psychosocial stress,(20) and elevated risk for offspring developing schizophrenia, autism, attention-deficit hyperactivity disorder (ADHD)(21) and other neurological and psychiatric disorders(12). Thus, maternal inflammation during pregnancy is a strong candidate for mediating effects of diverse conditions on offspring neurodevelopment with implications for long-term health. However, to our knowledge, the influence of maternal inflammation during pregnancy on developing brain systems implicated in psychiatric disorders has not yet been examined in humans.

Animal models support a key role for cytokines, inflammatory signaling proteins, as *sensors, transducers*, and *effectors* of environmental conditions on the developing embryonic and fetal brain. Maternal pro-inflammatory cytokine levels are elevated across a range of diverse high-risk conditions (*sensors*),(20, 22, 23) with accompanying increases in pro-inflammatory cytokines in placental tissue, amniotic fluid and the fetal brain (*transducers*). (24–27) Cytokines are also expressed in the fetal brain as part of typical neurodevelopmental

processes,(28) and facilitate cellular survival, proliferation and differentiation, axonal growth and synaptogenesis.(29–32) Elevated cytokine levels in the fetal brain (such as in response to maternal inflammation) trigger alterations in these aspects of neurodevelopment(33–35) (*effectors*). Interleukin-6 (IL-6), a pro-inflammatory cytokine, (36) exemplifies this tripartite role. Heightened IL-6 concentrations are evident across various maternal gestational conditions (e.g., obesity, psychosocial stress, depression and infection) that, in turn, have been shown to increase susceptibility for psychiatric disorders in offspring.(15, 20, 37, 38) Administration of IL-6 to pregnant dams mimics effects of maternal immune activation on upregulation of genes implicated in autism and schizophrenia in fetal brain tissue.(39) Moreover, effects of maternal immune activation on inflammation and gene expression in the fetal brain, and subsequent behavioral deficits, are eliminated by blocking IL-6 in the pregnant dam(40), or the placenta(41). Thus, examination of maternal IL-6 in relation to human fetal brain development represents an important step towards elucidating pathways by which maternal inflammation during pregnancy influences offspring risk for psychiatric disorders.

The present study seeks to advance understanding in this area by examining associations between systemic maternal IL-6 concentrations during pregnancy, newborn amygdala volume and functional connectivity, and emerging behavioral phenotypes at 24-months-of-age. The amygdala is of specific interest due to the relevance for offspring phenotypes associated with heightened maternal inflammation during pregnancy in animal models, including social deficits, increased emotional and stress reactivity (26, 42–44), heightened aggression (45), and decreased appetitive control(46, 47). Moreover, psychiatric disorders linked to maternal inflammation during pregnancy (e.g. schizophrenia, autism and ADHD) are also characterized by social deficits, and difficulty regulating emotions and behaviors. (15, 48–50) Alterations in amygdala integrity identified at the onset of these disorders suggest a potential causal role in pathogenesis(51, 52). Lastly, evidence that maternal inflammation during pregnancy enhances risk for psychiatric disorders by sensitizing offspring to adverse postnatal events (e.g. "a second hit"(15, 53)), further implicates stress sensitive brain regions, such as the amygdala.

The capacity to control impulses in service of working towards a goal, also referred to as inhibitory or effortful control, is foundational for regulating emotions and behaviors.(54–56) Impulse control can already be measured reliably during toddlerhood,(57, 58) and predicts subsequent behavioral, emotional and health outcomes during childhood(57, 59–61), adolescence(62) and adulthood(63). Difficulty regulating emotions and behaviors is a common feature across psychiatric disorders linked to maternal inflammation during pregnancy. We therefore examine impulse control at 24-months-of-age as an early emerging indicator of the balance between children’s reactivity/impulsivity and regulatory capacity. (64) We test whether aspects of newborn amygdala phenotypes linked to maternal IL-6 concentrations during pregnancy also relate to children’s impulse control, to examine the relevance of alterations in the newborn amygdala for subsequent behavior. Further, we test whether maternal IL-6 concentrations during pregnancy relate to children’s impulse control via alterations in the newborn amygdala (statistical mediation).

## Methods and Materials

### Participants

Mothers and children (N=86 with newborn structural MRI and N=70 with functional MRI data) were part of an ongoing, longitudinal study, conducted at the University of California, Irvine, for which mothers were recruited during the first trimester of pregnancy. Exclusionary criteria were as follows: maternal use of psychotropic medications or systemic corticosteroids during pregnancy; infant birth before 34 weeks gestation; and infant congenital, genetic, or neurologic disorder. Demographic characteristics are presented in Table 1 (N=86). A very small portion of mothers reported a mental health diagnosis at study entry (N=2). Behavioral data at 24-months-of-age ($M$=24.65 months, $SD$=.757) was available for a subset of children (N=52 with structural MRI and N=45 with functional MRI data). There were no significant differences in demographics for the full sample versus the sample with functional MRI data (N=70), or behavioral data. All procedures were approved by the Institutional Review Board at the University of California, Irvine, and written informed consent was obtained from all mothers.

### Maternal Interleukin 6 (IL-6) concentrations

Maternal antecubital venous blood samples were collected in serum tubes in early, mid and late pregnancy (see Table 2). Serum IL-6 concentrations were determined using a commercial high sensitivity ELISA (eBioscience). See Supplementary Material for details. IL-6 concentrations (reported in Table 2) were significantly correlated across trimesters ($r$'s=0.55 to 0.68, $p < .001$), and were therefore averaged to form a composite of maternal IL-6 during pregnancy. The composite was base 2 logarithm transformed to bring outliers closer to the mean and normalize the distribution.

### MRI and fMRI Data Acquisition and Processing

**Data acquisition—**Neuroimaging data was collected at approximately 4 weeks-of-age (M=3.79, SD=1.84) during natural sleep on a TIM Trio, Siemens 3.0T scanner. High resolution T2- (TR=3200ms, echo time=255ms, resolution=1×1×1mm, 4.18 mins) and T1-weighted scans (MP-RAGE TR=2400ms, inversion time=1200ms, echo time=3.16ms, flip angle=8°, resolution=1×1×1mm, 6.18 mins) were collected. Images for resting state functional connectivity MRI (rs-fcMRI) were obtained using a gradient-echo, echoplanar imaging (EPI) sequence sensitive to blood oxygen level-dependent (BOLD) contrast (TR=2000ms; TE=30ms; FOV=220×220×160mm; flip angle=77°).

**MRI and fMRI data preprocessing—**Processing followed established procedures for neuroimaging with neonates as described in our previous work(65) and detailed in the Supplementary Materials. Briefly, brain images were separated from the rest of the head tissue, and functional images were preprocessed to reduce artifacts.(66) Atlas transformation involved calculation of a single matrix to facilitate registration to a standard infant template (0- to 2-month age range; MRI Study of Normal Brain Development)(67, 68), and to the Talairach coordinate system(69) (by aligning the infant template to a custom atlas-transformed(70) target template [711-2B] using a series of affine transforms).(71)

**rs-fcMRI preprocessing—**Additional preprocessing steps for rs-fcMRI were conducted to account for signal stemming from non-neuronal processes.(72, 73) These steps followed established procedures(73–75) including, temporal low-pass filtering (0 $f < 0.1$ Hz), regression of rigid body head motion parameters in 6 directions, regression of whole brain signal, regression of average ventricular signal, regression of white matter signal, and regression of first order derivative terms for the whole brain, ventricular, and white matter signals.(73–75) Volume censoring was employed to reduce effects of motion determined by framewise displacement (FD)(76) of .3mm. Remaining mean FD was subsequently examined as a potential confound (see Supplementary Materials).

**Amygdala regions of interest—**Amygdalae were individually segmented using a multi-modality, multi-template based automatic method combining T1 and T2 weighted high-resolution images,(77) followed by manual correction in ITK-Snap(78) (see Supplementary Materials). Mean volumes were 279.95mm$^3$ (SD=31.59) and 270.55mm$^3$ (SD=31.07) for right and left amygdala respectively. For rs-fcMRI analyses, amygdalae were transformed to atlas space based on the atlas transform previously computed. For volumetric analyses, amygdalae volumes were adjusted for intracranial volume (ICV) to account for differences in overall brain size.

## Potential Confounds Relevant for Maternal IL-6 and Newborn Brain Outcomes

Potential confounds relevant to maternal inflammation and neurodevelopmental outcomes were examined to determine whether any identified associations between maternal IL-6 and the newborn amygdala could be better explained by other aspects of the prenatal environment. These included maternal pre-pregnancy body mass index (BMI), maternal cigarette smoking during pregnancy, obstetric (OB) risk, annual household income, and infant sex (see Supplementary Materials).

## Impulse Control at 24-months-of-age

Impulse control was measured with the snack delay task.(79, 80) Children were instructed to wait until an experimenter rang a bell before eating a desired snack placed on the table in front of them. Four trials were conducted with each trial involving a longer wait time (10, 15, 20 and 30 seconds). Scoring was consistent with the procedure established by Kochanska and colleagues,(79, 80) with higher scores indicative of waiting longer to reach for or eat the snack (i.e. better impulse control; see Supplementary Materials).

## Attachment as an Indicator of the Postnatal Caregiving Environment

In examining the newborn amygdala in relation to impulse control at 24-months-of-age, it is important to consider the postnatal caregiving environment, which has been shown to influence development of regulatory skills(81–83). Children's attachment security with their primary caregiver is indicative of the quality of caregiving, *and* the child's capacity to use their caregiver to effectively regulate emotions and explore the environment.(84) Attachment was assessed with the well-established Strange Situation Paradigm (SSP)(84, 85) when children were 12-months-of-age. SSP administration and coding followed established procedures(85, 86) detailed in the Supplementary Materials. Analyses focused on a

dichotomous variable indicating secure (51.9%) versus insecure attachment classification (48,1%).

### Analyses

Left and right amygdalae were examined separately due to evidence for lateralized effects of prenatal influences(87) and asymmetry in relation to psychiatric outcomes.(88) Mean maternal IL-6served as the independent variable, infant gestational age at birth (GA) and age at scan as covariates, and either amygdala volume or whole-brain voxel-wise connectivity as the dependent variable in regression models. For the rs-fcMRI analyses, multiple comparisons correction for $p<0.05$ voxel clusters required a threshold of 53 contiguous voxels with a Z-value> 2.25 based on Monte Carlo simulation(89)(see Supplementary Materials). Post-hoc analyses included mean maternal IL-6, infant GA at birth, age at scan, sex, mean remaining FD (for functional connectivity only), and all potential confounds entered together in the first step of a multiple regression model with the newborn amygdala phenotype as the dependent variable (see Supplementary Materials for further details). In the second step of the model, the moderating effect of infant sex was tested(90).

Newborn amygdala phenotypes which remained significantly associated with maternal IL-6 after considering potential confounds, were examined in relation to impulse control. For functional connectivity, we only examined the strongest right and left amygdala connection associated with maternal IL-6 (based on Z-value) to reduce the number of statistical tests. We included a covariate for attachment status, and tested for interactive effects between the newborn amygdala phenotypes and attachment in predicting impulse control. A structural equation modeling framework was used to test for mediation by examining the indirect path from maternal IL-6 to impulse control via the newborn amygdala phenotype (see Supplementary Materials for details).

## Results

### Amygdala Volume

After adjusting for GA and scan age, higher mean maternal IL-6 was significantly associated with larger right amygdala volume ($\beta=.245$, $p=.016$; $R^2$ change=.06; Figure 1). Mean maternal IL-6 was not significantly associated with left amygdala volume ($\beta=-.023$, $p=.831$).

### Amygdala Connectivity

Mean maternal IL-6 concentrations were significantly associated with newborn amygdala connectivity, with different connectivity patterns evident for the left and right amygdala. For the right amygdala, higher IL-6 was associated with stronger positive connectivity to right anterior insula (aI), fusiform gyrus/inferior temporal gyrus (ITG), caudate and thalamus. Higher mean IL-6 was additionally associated with stronger right amygdala connectivity to the left brainstem, and weaker connectivity to left superior occipital gyrus. For the left amygdala, higher mean IL-6 was associated with stronger connectivity to the right fusiform/ITG, parietal/somatosensory cortex, and parahippocampal gyrus (PHG), and weaker connectivity to a region encompassing ITG and ventral temporal cortex (Table 3, Figure 2).

## Post-hoc Analyses of Potential Confounds for Maternal IL-6 Concentrations and Newborn Amygdala Associations

**Amygdala Volume—**The association between mean IL-6 and right amygdala volume remained significant (β=.273, p=.015) after adjusting for all of the potential confounds in the same model, and was not moderated by infant sex (See Supplementary Table 1). Variation in maternal IL-6 concentrations continued to explain approximately 6% of the variance in right amygdala volume ($R^2$ change=.059).

**Amygdala Connectivity—**For all the identified amygdala connections, the effect of IL-6 remained significant (p < .05) after adjusting for the potential confounds with the exception of right amygdala-fusiform gyrus/ITG connectivity. For this connection, the effect of IL-6 became a trend (β=.208, p=.063), and higher pre-pregnancy BMI significantly predicted stronger connectivity (β=.432, p=.000). The associations between IL-6 and the right and left amygdala connections were not moderated by infant sex (See Supplementary Table 1).

## Relevance of Amygdala Phenotypes for Impulse Control at 24-months-of-age

**Amygdala Volume—**Larger newborn right amygdala volume was associated with lower impulse control at 24 months age (β= −.261, p=.036) in the model including covariates for GA at birth (β=.165, p=.217), age at scan (β=.053, p=.709) and attachment security (β=.176, p=.228). The associated between right amygdala volume and impulse control was not moderated by attachment security (β=.157, p = .426). Adding maternal IL-6 concentrations to the model revealed no direct association with impulse control (β=.083, p=.569). However, larger newborn right amygdala volume mediated an association between higher maternal IL-6, and lower impulse control (indirect effect= −.148 ; 95% CI: −.345, −.005; based on 5,000 bootstrap samples). Thus, higher systemic maternal IL-6 levels during pregnancy were associated with lower impulse control in children, via larger newborn right amygdala volume.

**Amygdala Connectivity—**The strongest right amygdala functional connection associated with maternal IL-6, right amygdala-aI connectivity, was not significantly associated with impulse control either independently or in interaction with attachment security (p > .10). The strongest left amygdala connection associated with IL-6, left amygdala-fusiform gyrus connectivity, was significantly associated with impulse control (β= −.406, p=.001) in the model including covariates for GA at birth (β=.093, p=.472), age at scan (β=.016, p=.904) and attachment security (β=.334, p=.007). Thus stronger connectivity was associated with lower impulse control, while a secure attachment was independently associated with better impulse control in this model. There was no moderated effect of attachment security (β= −.022, p = .909). Adding maternal IL-6 to the model again revealed no direct association with impulse control (β=.083, p=.569). However, stronger newborn left amygdala-fusiform connectivity mediated an association between higher maternal IL-6, and lower impulse control (indirect effect= −.245 ; 95% CI: −.490, −.069; based on 5,000 bootstrap samples). These analyses thus identified another pathway from higher maternal IL-6 to lower impulse control at 24-months-of-age via stronger newborn left amygdala-fusiform connectivity.

## Discussion

A growing body of research has established associations between a maternal inflammatory state during pregnancy and increased risk for offspring psychiatric disorders. To the best of our knowledge, this study provides the first evidence in humans linking a specific mediator of maternal inflammation, elevated maternal serum IL-6 concentrations, with the newborn brain. Examining the brain shortly after birth reduces potential confounding influences of the postnatal environment, thereby increasing capacity to differentiate pre- from postnatal influences on the developing brain. The findings of greater right amygdala volume and increased bilateral amygdala connectivity to regions involved in sensory processing and integration (fusiform, somatosensory cortex, thalamus), salience detection (insula), and learning and memory (caudate and PHG), have potential implications for offspring susceptibility for psychiatric disorders. Consistent with this interpretation, the newborn amygdala phenotypes mediated an association between higher maternal IL-6 during pregnancy and lower impulse control at 24 months-of-age, a behavioral phenotype repeatedly linked to difficulties regulating emotions and behaviors at later developmental stages.(57, 59–62) This provides support for a pathway from heightened maternal IL-6 concentrations during pregnancy to an altered balance between offspring impulsivity and regulatory capacity through alterations in the developing amygdala.

Previous research shows that both heightened maternal cortisol during pregnancy(91), and high levels of stress in the early postnatal environment (92–94) are associated with increased amygdala volume in children. The current findings indicate an additional role for inflammation in shaping the developing amygdala. This is consistent with previous findings linking maternal inflammation during pregnancy with increased risk for offspring psychiatric disorders in humans,(12, 15, 53) and amplified stress reactivity and social deficits in animal models,(26, 42–44) phenotypes that larger amygdala volumes have been shown to underlie. Variation in maternal IL-6 during pregnancy explained approximately 6% of the variance in right amygdala volume. While this effect seems modest, it may be clinically meaningful, as suggested by the association with lower impulse control at 24-months-of-age. A modest effect size at this early age is also in line with developmental trajectories of altered amygdala growth in relation to psychiatric disorders. For example, amygdala enlargement in relation to autism becomes more pronounced over early development with a 6% enlargement compared to typically developing controls noted at 3-years-of-age(51, 95) and a 9–12% enlargement by 4-years-of-age.(51, 96)

Increased functional integration of the newborn amygdala with regions implicated in detecting and processing stimuli, determining personal relevance of stimuli, and engaging learning and memory systems was also observed in relation to higher maternal IL-6 concentrations during pregnancy. The connections identified are of interest in the context of research in adults focused on stress responsivity and vulnerability to psychiatric disorders. The pattern of stronger amygdala-aI(97–99) and amygdala-caudate connectivity(100, 101) are in concordance with observations in adults after chronic and acute stress exposure. Increased strength of these connections has in turn been associated with higher perception of threat,(102) elevated anxiety,(103) and engagement of more rigid learning and memory strategies.(100, 101) Increased amygdala connectivity to brain regions involved in sensory

processing and integration is of interest in light of deficits in early (pre-attentive) filtering of sensory stimuli in psychiatric disorders linked to maternal inflammation during pregnancy.(15) Such filtering deficits involve a network of regions including the amygdala and thalamus.(104, 105) Interestingly, amygdala-fusiform gyrus connectivity has been specifically implicated in the core and early emerging face processing deficits in autism.(106–109)

Larger newborn amygdala volume and increased connectivity were prospectively associated with lower impulse control at 2-years-of-age after accounting for variation in the infant-caregiver relationship. Amygdala activity, functional connectivity and morphology has previously been associated with impulse control difficulties, including risk for substance use disorders(110–112) and ADHD(113–117) in human adults. These associations are likely related to the role of the amygdala in processing salient stimuli(118–120) and anticipating rewards(121, 122). The specific association between stronger newborn amygdala-fusiform gyrus connectivity and lower impulse control may relate to the role of the amygdala in modulating visual processing based on salience and emotional properties of stimuli(123–126). For example, enhanced amygdala and fusiform gyrus activity has been observed during visual presentation of highly salient or craved stimuli in adults(127). From a developmental perspective, the visual system, and specifically attentional control of vision, is foundational in developing cognition and emotion regulation(128, 129). It is therefore not surprising that coordinated functioning of the amygdala to an extrastriate visual region would be associated with emerging capacity to regulate response to a desired stimulus.

Whether directly mediated via placental transfer into the fetal compartment(130) or indirect effects mediated by placental inflammation,(39, 131) elevated maternal IL-6 concentrations can trigger inflammatory processes in the fetal brain, including, increased expression of IL-6 and other cytokines.(41, 132, 133) These cytokines in the fetal brain activate Janus Kinases (JAKs) and associated signal transducers and activators of transcription (STAT).(134, 135) Activation of the JAK/STAT pathway regulates the transition from neurogenesis to gliogenesis.(136) Stimulation or inhibition of this pathway can lead to earlier or delayed onset of gliogenesis(136) and processes guided by glial cells, including neuronal migration, axon growth, synapse formation,(137, 138) and myelination.(139) IL-6 and other proinflammatory cytokines also influence developing neurotransmitter systems relevant to amygdala development, including effects on decreased survival of fetal serotonin neurons in the rostral raphe,(34) and increased expression of GABA receptors in the amygdala.(140) These effects of cytokines on developing neurons, glia and neurotransmitter systems suggest multiple potential mechanisms through which maternal inflammation during pregnancy can alter fetal amygdala anatomy and coordinated functioning with implications for ongoing behavioral and neurological development.

The findings indicate potential hemispheric differences in vulnerability to intrauterine inflammation. Regarding anatomy, vulnerability seemed to be greatest for the right amygdala, while the functional connectivity results suggest bilateral consequences of intrauterine inflammation, with distinct alterations for the left versus right amygdala. Previous work showed that elevated maternal cortisol concentrations during pregnancy were specifically associated with right amygdala volume.(91) Findings of larger amygdala volume

in association with autism at early developmental stages are also most consistent for the right amygdala.(51, 95, 141) With regard to connectivity, the findings for the right amygdala involved a slightly more extensive set of brain regions, including amygdala-aI connectivity. These lateralized findings are interesting in light of a potentially disproportionate role for the right amygdala in contributing to anxiety and processing negatively valenced stimuli,(142–146) and for right amygdala-aI connectivity in vulnerability to stress-related disorders.(98)

Interestingly, while larger newborn right amygdala volume was associated with lower impulse control, right amygdala-aI connectivity was not associated with impulse control. This connection may be more relevant for normative and pathological variation in fear(64, 120, 140). Although impulse control is relevant for fear and anxiety disorders, the associations are not straightforward.(148) The sample size of the current study makes it difficult to investigate interactive processes between emotionality and impulse control at present, but this is an important topic for future work to understand the implications of these newborn amygdala phenotypes for subsequent development. It should also be noted that our measure of impulse control does not distinguish motivation, reactivity and inhibitory control processes, but reflects an estimate of the balance between these components.(64) More nuanced investigation of these processes will also be important for advancing understanding of how the observed neural phenotypes relate to subsequent risk and protective factors.

Some additional limitations of the study warrant attention. First, while systemic IL-6 represents an important marker of inflammation, we do not attribute the observed effects to the influence of IL-6 alone. Future research would benefit from consideration of different markers of inflammation, and identification of the triggers for heightened maternal inflammation(20, 22, 149). It will also be important to consider higher risk groups, such as mothers with psychiatric diagnoses, who may show distinct profiles of inflammation during pregnancy. We also note that while we considered a range of potential confounds, these variables are only considered in relation to newborn amygdala phenotypes associated with maternal IL-6, and are therefore not unbiased tests of the influence of these other variables on the newborn amygdala. This study therefore does not address the more general question of how these other aspects of the prenatal environment relate to the newborn amygdala. Finally, the present study focused on the amygdala as a starting point due to the behavioral phenotypes associated with maternal inflammation during pregnancy. However, given the ubiquitous role of cytokines in fetal brain development, identifying associations between maternal inflammation and multiple brain systems represents an important target of future research.

Despite the limitations, these results provide the first evidence to date in humans for an association between intrauterine inflammation, fetal brain development and emerging behavior. From a risk perspective, we have considered the extent to which similar amygdala phenotypes have been observed in psychiatric disorders. Consistent with this perspective, we have shown that these amygdala phenotypes are associated with lower impulse control, which has been linked to elevated risk for behavioral and emotional problems during childhood. This perspective includes a role for the postnatal environment because the connection between maternal inflammation and offspring psychiatric disorders is not deterministic,(15) and likely involves increased vulnerability to postnatal stress ("a second

hit").(15, 53) An adaptive, evolutionary perspective further suggests potential survival advantages of the observed brain phenotypes.(150) Specifically, if heightened maternal inflammation during pregnancy signals a more adverse, or dangerous environment, heightened vigilance and reactivity conferred by alterations in the amygdala could be adaptive depending on the match between the pre- and postnatal environment.(150–152) The current findings provide a foundation for ongoing investigation in this area by advancing understanding of the role of maternal inflammation in influencing newborn amygdala phenotypes and subsequent behavior.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References

1. Estes ML, McAllister AK. Maternal immune activation: Implications for neuropsychiatric disorders. Science (80-). 2016; 353:772–777.
2. Gaillard R, Rifas-Shiman SL, Perng W, Oken E, Gillman MW. Maternal inflammation during pregnancy and childhood adiposity. Obesity. 2016; 24:1320–1327. [PubMed: 27094573]
3. O'Reilly JR, Reynolds RM. The risk of maternal obesity to the long-term health of the offspring. Clin Endocrinol (Oxf). 2013; 78:9–16. [PubMed: 23009645]
4. Khandaker GM, Zimbron J, Lewis G, Jones P. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. Psychol Med. 2013; 43:239–257. [PubMed: 22717193]
5. Brown AS, Begg MD, Gravenstein S, Schaefer CA, Wyatt RJ, Bresnahan M, et al. Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch Gen Psychiatry. 2004; 61:774–780. [PubMed: 15289276]
6. Brown AS, Patterson PH. Maternal infection and schizophrenia: Implications for prevention. Schizophr Bull. 2011; 37:284–290. [PubMed: 21134972]
7. Brown AS, Derkits EJ. Prenatal infection and schizophrenia: A review of epidemiologic and translational studies. Am J Psychiatry. 2010; 167:261–280. [PubMed: 20123911]
8. Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Bernstein D, Yolken RH. Maternal Infections and Subsequent Psychosis Among Offspring. Arch Gen Psychiatry. 2001; 58:1032–1037. [PubMed: 11695949]
9. Fang SY, Wang S, Huang N, Yeh HH, Chen CY. Prenatal Infection and Autism Spectrum Disorders in Childhood: A Population-Based Case-Control Study in Taiwan. Paediatr Perinat Epidemiol. 2015; 29:307–316. [PubMed: 25989831]
10. Lee BK, Magnusson C, Gardner RM, Blomstrom A, Newschaffer CJ, Burstyn I, et al. Maternal hospitalization with infection during pregnancy and risk of autism spectrum disorders. Brain Behav Immun. 2015; 44:100–105. [PubMed: 25218900]
11. Atladóttir HÓ, Henriksen TB, Schendel DE, Parner ET. Autism After Infection, Febrole Episodes, and Antibiotic Use During Pregancy: An Exploration Study. 2012; 130:1447–1454.
12. Knuesel I, Chicha L, Britschgi M, Schobel SA, Bodmer M, Hellings JA, et al. Maternal immune activation and abnormal brain development across CNS disorders. Nat Rev Neurol. 2014; 10:643–60. [PubMed: 25311587]

13. Machon RA, Mednick SA, Huttunen MO. Adult Major Affective Disorder After Prenatal Exposure to an Influenza Epidemic. Arch Gen Psychiatry. 1997; 54:322–328. [PubMed: 9107148]
14. Cannon M, Cotter D, Coffey VP, Sham PC, Takei N, Larkin C, et al. Prenatal exposure to the 1957 influenza epidemic and adult schizophrenia: a follow-up study. Br J Psychiatry. 1996; 168:368–371. [PubMed: 8833694]
15. Meyer U, Feldon J, Dammann O. Schizophrenia and autism: both shared and disorder-specific pathogenesis via perinatal inflammation? Pediatr Res. 2011; 69:26R–33R.
16. Li Y-M, Ou J-J, Liu L, Zhang D, Zhao J-P, Tang S-Y. Association Between Maternal Obesity and Autism Spectrum Disorder in Offspring: A Meta-analysis. J Autism Dev Disord. 2016; 46:95–102. [PubMed: 26254893]
17. Krakowiak P, Walker CK, Bremer AA, Baker AS, Ozonoff S, Hansen RL, Hertz-Picciotto I. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. Pediatrics. 2012; 129:e1121–8. [PubMed: 22492772]
18. Reynolds LC, Inder TE, Neil JJ, Pineda RG, Rogers CE. Maternal obesity and increased risk for autism and developmental delay among very preterm infants. J Perinatol. 2014; 34:688–92. [PubMed: 24811227]
19. Pearson RM, Evans J, Kounali D, Lewis G, Heron J, Ramchandani PG, et al. Maternal Depression During Pregnancy and the Postnatal Period. JAMA Psychiatry. 2013; 70:1312. [PubMed: 24108418]
20. Coussons-Read ME, Okun ML, Schmitt MP, Giese S. Prenatal stress alters cytokine levels in a manner that may endanger human pregnancy. Psychosom Med. 2005; 67:625–631. [PubMed: 16046378]
21. Instanes JT, Halmøy A, Engeland A, Haavik J, Furu K, Klungsøyr K. Attention-Deficit/Hyperactivity Disorder in Offspring of Mothers With Inflammatory and Immune System Diseases. Biol Psychiatry. 2015; 81:452–459. [PubMed: 26809250]
22. Madan JC, Davis JM, Craig WY, Collins M, Allan W, Quinn R, Dammann O. Maternal obesity and markers of inflammation in pregnancy. Cytokine. 2009; 47:61–64. [PubMed: 19505831]
23. Challis JR, Lockwood CJ, Myatt L, Norman JE, Strauss JF, Petraglia F. Inflammation and pregnancy. Reprod Sci. 2009; 16:206–215. [PubMed: 19208789]
24. Gayle DA, Beloosesky R, Desai M, Amidi F, Nuñez SE, Ross MG. Maternal LPS induces cytokines in the amniotic fluid and corticotropin releasing hormone in the fetal rat brain. Am J Physiol Regul Integr Comp Physiol. 2004; 286:R1024–9. [PubMed: 14988088]
25. Urakubo A, Jarskog LF, Lieberman JA, Gilmore JH. Prenatal exposure to maternal infection alters cytokine expression in the placenta, amniotic fluid, and fetal brain. Schizophr Res. 2001; 47:27–36. [PubMed: 11163542]
26. Meyer U. The Time of Prenatal Immune Challenge Determines the Specificity of Inflammation-Mediated Brain and Behavioral Pathology. J Neurosci. 2006; 26:4752–4762. [PubMed: 16672647]
27. Mandal M, Marzouk AC, Donnelly R, Ponzio NM. Maternal immune stimulation during pregnancy affects adaptive immunity in offspring to promote development of TH17 cells. Brain Behav Immun. 2011; 25:863–871. [PubMed: 20854892]
28. Burns T, Clough J, Klein R, Wood G, Berman N. Developmental regulation of cytokine expression in the mouse brain. Growth Factors. 1993; 9:253–8. [PubMed: 8148154]
29. Mehler MF, Kessler JA. Hematolymphopoietic and inflammatory cytokines in neural development. Trends Neurosci. 1997; 20:357–365. [PubMed: 9246730]
30. Deverman BE, Patterson PH. Cytokines and CNS Development. Neuron. 2009; 64:61–78. [PubMed: 19840550]
31. Boulanger LM. Immune proteins in brain development and synaptic plasticity. Neuron. 2009; 64:93–109. [PubMed: 19840552]
32. Zhao B, Schwartz JP. Involvement of cytokines in normal CNS development and neurological diseases: Recent progress and perspectives. J Neurosci Res. 1998; 52:7–16. [PubMed: 9556025]
33. Rousset CI, Chalon S, Cantagrel S, Bodard S, Andres C, Gressens P, Saliba E. Maternal exposure to LPS induces hypomyelination in the internal capsule and programmed cell death in the deep gray matter in newborn rats. Pediatr Res. 2006; 59:428–433. [PubMed: 16492984]

34. Jarskog LF, Xiao H, Wilkie MB, Lauder JM, Gilmore JH. Cytokine regulation of embryonic rat dopamine and serotonin neuronal survival in vitro. Int J Dev Neurosci. 1997; 15:711–716. [PubMed: 9402221]
35. Pang Y, Zheng B, Fan L-W, Rhodes PG, Zhengwei C. IGF-1 Protects Oligodendrocyte Progenitors Against TNFa-Induced Damage by Activation of PI3K/Akt and Interruption of the Mitochondrial Apoptotic Pathway. Glia. 2007; 55:1099–1107. [PubMed: 17577243]
36. Ishihara K, Hirano T. IL-6 in autoimmune disease and chronic inflammatory proliferative disease. Cytokine Growth Factor Rev. 2002; 13:357–368. [PubMed: 12220549]
37. Eder K, Baffy N, Falus A, Fulop AK. The major inflammatory mediator interleukin-6 and obesity. Inflamm Res. 2009; 58:727–736. [PubMed: 19543691]
38. Haeri S, Baker AM, Ruano R. Do pregnant women with depression have a pro-inflammatory profile? J Obstet Gynaecol Res. 2013; 39:948–952. [PubMed: 23509887]
39. Garbett KA, Hsiao EY, Kálmán S, Patterson PH, Mirnics K. Effects of maternal immune activation on gene expression patterns in the fetal brain. Transl Psychiatry. 2012; 2:e98. [PubMed: 22832908]
40. Smith S, Li J, Garbett K, Mirnics K, Patterson P. Maternal immune activation alters fetal brain development through interleukin-6. J Neurosci. 2007; 27:10695–10702. [PubMed: 17913903]
41. Wu W-L, Hsiao EY, Yan Z, Mazmanian SK, Patterson PH. The placental interleukin-6 signaling controls fetal brain development and behavior. Brain Behav Immun. 2017; 62:11–23. [PubMed: 27838335]
42. Hava G, Vered L, Yael M, Mordechai H, Mahoud H. Alterations in behavior in adult offspring mice following maternal inflammation during pregnancy. Dev Psychobiol. 2006; 48:162–168. [PubMed: 16489598]
43. Sullivan EL, Grayson B, Takahashi D, Robertson N, Maier A, Bethea CL, et al. Chronic Consumption of a High-Fat Diet during Pregnancy Causes Perturbations in the Serotonergic System and Increased Anxiety-Like Behavior in Nonhuman Primate Offspring. J Neurosci. 2010; 30:3826–3830. [PubMed: 20220017]
44. Sasaki A, de Vega W, St-Cyr S, Pan P, McGowan P. Perinatal high fat diet alters glucocorticoid signaling and anxiety behavior in adulthood. Neuroscience. 2013; 240:1–12. [PubMed: 23454542]
45. Raygada M, Cho E, Hilakivi-Clarke L. High maternal intake of polyunsaturated fatty acids during pregnancy in mice alters offsprings' aggressive behavior, immobility in the swim test, locomotor activity and brain protein kinase C activity. J Nutr. 1998; 128:2505–2511. [PubMed: 9868200]
46. Bayol SA, Farrington SJ, Stickland NC. A maternal "junk food" diet in pregnancy and lactation promotes an exacerbated taste for "junk food" and a greater propensity for obesity in rat offspring. Br J Nutr. 2007; 98:843–851. [PubMed: 17697422]
47. Sullivan EL, Nousen EK, Chamlou KA, Grove KL. The Impact of Maternal High-Fat Diet Consumption on Neural Development and Behavior of Offspring. Int J Obes Suppl. 2012; 2:S7–S13. [PubMed: 26069734]
48. Beauchamp MH, Anderson V. SOCIAL: an integrative framework for the development of social skills. Psychol Bull. 2010; 136:39–64. [PubMed: 20063925]
49. Karalunas SL, Fair D, Musser ED, Aykes K, Iyer SP, Nigg JT. Subtyping Attention-Deficit/Hyperactivity Disorder Using Temperament Dimensions : Toward Biologically Based Nosologic Criteria. JAMA psychiatry. 2014; 97239:1–10.
50. Wehmeier PM, Schacht A, Barkley RA. Social and Emotional Impairment in Children and Adolescents with ADHD and the Impact on Quality of Life. J Adolesc Heal. 2010; 46:209–217.
51. Nordahl CW, Scholz R, Yang X, Buonocore MH, Simon T, Rogers S, Amaral DG. Increased rate of amygdala growth in children aged 2 to 4 years with autism spectrum disorders: A longitudinal study. Arch Gen Psychiatry. 2012; 69:53–61. [PubMed: 22213789]
52. Ganzola R, Maziade M, Duchesne S. Hippocampus and amygdala volumes in children and young adults at high-risk of schizophrenia: Research synthesis. Schizophr Res. 2014; 156:76–86. [PubMed: 24794883]
53. Meyer U. Developmental neuroinflammation and schizophrenia. Prog Neuro-Psychopharmacology Biol Psychiatry. 2013; 42:20–34.
54. Duckworth AL, Steinberg L. Unpacking self-control. Child Dev Perspect. 2015; 9:32–37. [PubMed: 25821515]

55. Zelazo, PD., Müller, U. Executive Function in Typical and Atypical Development. In: Goswami, U., editor. Handb Child Cogn Dev. Oxford: Blackwell Publishers Ltd; 2002. p. 445-469.
56. Murray KT, Kochanska G. Effortful control: factor structure and relation to externalizing and internalizing behaviors. J Abnorm Child Psychol. 2002; 30:503–14. [PubMed: 12403153]
57. Mulder H, Hoofs H, Verhagen J, van der Veen I, Leseman PPM. Psychometric properties and convergent and predictive validity of an executive function test battery for two-year-olds. Front Psychol. 2014; 5doi: 10.3389/fpsyg.2014.00733
58. Beck DM, Schaefer C, Pang K, Carlson SM. Executive Function in Preschool Children: Test-Retest Reliability. J Cogn Dev. 2011; 12:169–193. [PubMed: 21643523]
59. Lengua LJ, Moran L, Zalewski M, Ruberry E, Kiff C, Thompson S. Relations of Growth in Effortful Control to Family Income, Cumulative Risk, and Adjustment in Preschool-age Children. J Abnorm Child Psychol. 2015; 43:705–720. [PubMed: 25253079]
60. Kim S, Nordling JK, Yoon JE, Boldt LJ, Kochanska G. Effortful Control in "Hot" and "Cool" Tasks Differentially Predicts Children's Behavior Problems. J Abnorm Child Psychol. 2013; 41:43–56. [PubMed: 22798038]
61. Reuben JD, Shaw DS, Neiderhiser JM, Natsuaki MN, Reiss D, Leve LD. Warm Parenting and Effortful Control in Toddlerhood: Independent and Interactive Predictors of School-Age Externalizing Behavior. J Abnorm Child Psychol. 2016; 44:1083–1096. [PubMed: 26496906]
62. Duckworth AL, Tsukayama E, Kirby TA. Is it really self-control? Examining the predictive power of the delay of gratification task. Pers Soc Psychol Bull. 2013; 39:843–55. [PubMed: 23813422]
63. Moffitt TE, Arseneault L, Belsky D, Dickson N, Hancox RJ, Harrington H, et al. A gradient of childhood self-control predicts health, wealth, and public safety. Proc Natl Acad Sci U S A. 2011; 108:2693–8. [PubMed: 21262822]
64. Neuenschwander R, Blair C. Zooming in on children's behavior during delay of gratification: Disentangling impulsigenic and volitional processes underlying self-regulation. J Exp Child Psychol. 2017; 154:46–63. [PubMed: 27835753]
65. Graham AM, Buss C, Rasmussen JM, Rudolph MD, Demeter DV, Gilmore JH, et al. Implications of newborn amygdala connectivity for fear and cognitive development at 6-months-of-age. Dev Cogn Neurosci. 2016; 18:12–25. [PubMed: 26499255]
66. Miezin FM, Maccotta L, Ollinger JM, Petersen SE, Buckner RL. Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. Neuroimage. 2000; 11:735–59. [PubMed: 10860799]
67. Fonov VS, Evans AC, Botteron K, Almli CR, McKinstry RC, Collins DL. Unbiased average age-appropriate atlases for pediatric studies. Neuroimage. 2011; 54:313–27. [PubMed: 20656036]
68. Fonov VS, Evans AC, Mckinstry RC, Almli CR, Collins DL. Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. Neuroimage. 2009; 47:S102.
69. Talairach, P., Tournoux, J. Co-planar Stereotaxic Altas of the Human Brain. Stuttgart, Germany: Georg Thieme Verlag; 1988.
70. Lancaster JL, Glass TG, Lankipalli BR, Downs H, Mayberg H, Fox PT. A Modality-Independent Approach to Spatial Normalization of Tomographic Images of the Human Brain. Hum Brain Mapp. 1995; 3:209–223.
71. Michelon P, Snyder AZ, Buckner RL, McAvoy M, Zacks JM. Neural correlates of incongruous visual information An event-related fMRI study. Neuroimage. 2003; 19:1612–1626. [PubMed: 12948716]
72. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007; 8:700–11. [PubMed: 17704812]
73. Fair DA, Nigg JT, Iyer S, Bathula D, Mills KL, Dosenbach NUF, et al. Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data. Front Syst Neurosci. 2012; 6:80. [PubMed: 23382713]
74. Fair DA, Dosenbach NUF, Church JA, Cohen AL, Brahmbhatt S, Miezin FM, et al. Development of distinct control networks through segregation and integration. Proc Natl Acad Sci U S A. 2007; 104:13507–12. [PubMed: 17679691]

75. Fair DA, Cohen AL, Power JD, Dosenbach NUF, Church JA, Miezin FM, et al. Functional brain networks develop from a “local to distributed” organization. PLoS Comput Biol. 2009; 5:e1000381. [PubMed: 19412534]

76. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage. 2012; 59:2142–2154. [PubMed: 22019881]

77. Wang J, Vachet C, Rumple A, Gouttard S, Ouziel C, Perrot E, et al. Multi-atlas segmentation of subcortical brain structures via the AutoSeg software pipeline. Front Neuroinform. 2014; 8:1–11. [PubMed: 24501593]

78. Yushkevich, Pa, Piven, J., Hazlett, HC., Smith, RG., Ho, S., Gee, JC., Gerig, G. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. Neuroimage. 2006; 31:1116–28. [PubMed: 16545965]

79. Kochanska G, Murray KT, Harlan ET. Effortful Control in Early Childhood: Continuity and Change, Antecedents, and Implications for Social Development. Dev Psychol. 2000; 36:220–232. [PubMed: 10749079]

80. Kochanska G, Murray K, Jacques TY, Koenig AL, Vandegeest KA. Inhibitory Control in Young Children and Its Role in Emerging Internalization. Child Dev. 1996; 67:490–507. [PubMed: 8625724]

81. Bernier A, Carlson SM, Deschenes M, Matte-Gagne C. Social factors in the development of early executive functioning: A closer look at the caregiving environment. Dev Sci. 2012; 15:12–24. [PubMed: 22251288]

82. Bernier A, Carlson SM, Whipple N. From External Regulation to Self-Regulation: Early Parenting Precursors of Young Children’s Executive Functioning. Child Dev. 2010; 81:326–339. [PubMed: 20331670]

83. Hostinar CE, Stellern Sa, Schaefer C, Carlson SM, Gunnar MR. Associations between early life adversity and executive function in children adopted internationally from orphanages. Proc Natl Acad Sci U S A. 2012; 109(Suppl):17208–12. [PubMed: 23047689]

84. Ainsworth MDS, Bell SM. Attachment, exploration, and separation: Illustrated by the behavior of one-year-olds in a strange situation. Child Dev. 1970; 41:49–67. [PubMed: 5490680]

85. Ainsworth, MDS., Blehar, M., Waters, E., Wall, S. Patterns of attachment: A psychological study of the strange situation. Hillsdale, NJ: Erlbaum; 1978.

86. Main, M., Solomon, J. Procedures for identifying infants as disorganized/disoriented during the Ainsworth Strange Situation. In: Greenberg, MT.Cicchetti, D., Cummings, EM., editors. Attach Presch years Theory, Res Interv. Chicago: University of Chicago Press; 1990. p. 121-160.

87. Qiu A, Anh TT, Li Y, Chen H, Rifkin-Graboi A, Broekman BFP, et al. Prenatal maternal depression alters amygdala functional connectivity in 6-month-old infants. Transl Psychiatry. 2015; 5:e508. [PubMed: 25689569]

88. Okada N, Fukunaga M, Yamashita F, Koshiyama D, Yamamori H, Ohi K, et al. Abnormal asymmetries in subcortical brain volume in schizophrenia. Mol Psychiatry. 2016:1–7. [PubMed: 26678307]

89. Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. Improved Assessment of Significant Activation in Functional Magnetic Resonance Imaging (fMRI): Use of a Cluster-Size Threshold. Magn Reson Med. 1995; 33:636–647. [PubMed: 7596267]

90. Bronson SL, Bale TL. Prenatal stress-induced increases in placental inflammation and offspring hyperactivity are male-specific and ameliorated by maternal antiinflammatory treatment. Endocrinology. 2014; 155:2635–2646. [PubMed: 24797632]

91. Buss C, Davis EP, Shahbaba B, Pruessner JC, Head K, Sandman CA. Maternal cortisol over the course of pregnancy and subsequent child amygdala and hippocampus volumes and affective problems. Proc Natl Acad Sci. 2012; 109:E1312–E1319. [PubMed: 22529357]

92. Tottenham N, Hare TA, Quinn BT, McCarry TW, Nurse M, Gilhooly T, et al. Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. Dev Sci. 2010; 13:46–61. [PubMed: 20121862]

93. Mehta MA, Golembo NI, Nosarti C, Colvert E, Mota A, Williams SCR, et al. Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: the English

and Romanian Adoptees study pilot. J Child Psychol Psychiatry. 2009; 50:943–51. [PubMed: 19457047]

94. Lupien SJ, Parent S, Evans AC, Tremblay RE, David P, Corbo V. Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. Proc Natl Acad Sci. 2011; 108:14324–14329. [PubMed: 21844357]
95. Schumann CM, Barnes CC, Lord C, Courchesne E. Amygdala Enlargement in Toddlers with Autism Related to Severity of Social and Communication Impairments. Biol Psychiatry. 2009; 66:942–949. [PubMed: 19726029]
96. Sparks BF, Friedman SD, Shaw DW, Aylward EH, Echelard D, Artru AA, et al. Brain structural abnormalities in young children with autism spectrum disorder. Neurology. 2002; 59:184–192. [PubMed: 12136055]
97. van Marle HJF, Hermans EJ, Qin S, Fernández G. Enhanced resting-state connectivity of amygdala in the immediate aftermath of acute psychological stress. Neuroimage. 2010; 53:348–54. [PubMed: 20621656]
98. Rabinak CA, Angstadt M, Welsh RC, Kenndy AE, Lyubkin M, Martis B, Phan KL. Altered amygdala resting-state functional connectivity in post-traumatic stress disorder. Front Psychiatry. 2011; 2:62. [PubMed: 22102841]
99. Sripada RK, King AP, Garfinkel SN, Wang X, Sripada CS, Welsh RC, Liberzon I. Altered resting-state amygdala functional connectivity in men with posttraumatic stress disorder. J Psychiatry Neurosci. 2012; 37:241–9. [PubMed: 22313617]
100. Schwabe L, Tegenthoff M, Höffken O, Wolf OT. Mineralocorticoid Receptor Blockade Prevents Stress-Induced Modulation of Multiple Memory Systems in the Human Brain. Biol Psychiatry. 2013; 74:801–808. [PubMed: 23871473]
101. Schwabe L, Wolf OT. Stress and multiple memory systems: From “thinking” to “doing”. Trends Cogn Sci. 2013; 17:68.
102. van Wingen GA, Geuze E, Vermetten E, Fernández G. Perceived threat predicts the neural sequelae of combat stress. Mol Psychiatry. 2011; 16:664–71. [PubMed: 21242990]
103. Baur V, Hänggi J, Langer N, Jäncke L. Resting-state functional and structural connectivity within an insula-amygdala route specifically index state and trait anxiety. Biol Psychiatry. 2013; 73:85–92. [PubMed: 22770651]
104. Butler PD, Chen Y, Ford JM, Geyer MA, Silverstein SM, Green MF. Perceptual measurement in schizophrenia: Promising electrophysiology and neuroimaging paradigms from CNTRICS. Schizophr Bull. 2012; 38:81–91. [PubMed: 21890745]
105. Kumari V, Antonova E, Geyer Ma, Ffytche D, Williams SCR, Sharma T. A fMRI investigation of startle gating deficits in schizophrenia patients treated with typical or atypical antipsychotics. Int J Neuropsychopharmacol. 2007; 10:463–477. [PubMed: 16923324]
106. Dziobek I, Bahnemann M, Convit A, Heekeren HR. The role of the fusiform-amygdala system in the pathophysiology of autism. Arch Gen Psychiatry. 2010; 67:397–405. [PubMed: 20368515]
107. Kleinhans NM, Richards T, Sterling L, Stegbauer KC, Mahurin R, Johnson LC, et al. Abnormal functional connectivity in autism spectrum disorders during face processing. Brain. 2008; 131:1000–1012. [PubMed: 18234695]
108. Dalton KM, Nacewicz BM, Alexander AL, Davidson RJ. Gaze-Fixation, Brain Activation, and Amygdala Volume in Unaffected Siblings of Individuals with Autism. Biol Psychiatry. 2007; 61:512–520. [PubMed: 17069771]
109. Dalton KM, Nacewicz BM, Johnstone T, Schaefer HS, Gernsbacher MA, Goldsmith HH, et al. Gaze fixation and the neural circuitry of face processing in autism. Nat Neurosci. 2005; 8:519–526. [PubMed: 15750588]
110. Cservenka A, Fair DA, Nagel BJ. Emotional processing and brain activity in youth at high risk for alcoholism. Alcohol Clin Exp Res. 2014; 38:1912–1923. [PubMed: 24890898]
111. Potenza MN, Hong KA, Lacadie CM, Fulbright RK, Tuit KL, Sinha R. Neural Correlates of Stress Induced and Cue-Induced Drug Craving: Influences of Sex and Cocaine Dependence. Am J Psychiatry. 2012; 169:406–414. [PubMed: 22294257]

112. Charboneaua EJ, Dietricha MS, Park S, Caoa A, Watkinsa TJ, Blackford JU, et al. Cannabis cue-induced brain activation correlates with drug craving in limbic and visual salience regions: Preliminary results. Psychiatry Res. 2013; 214:122–131. [PubMed: 24035535]
113. Posner J, Nagel BJ, Maia TV, Mechling A, Oh M, Wang Z, Peterson BS. Abnormal amygdalar activation and connectivity in adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2011; 50doi: 10.1016/j.jaac.2011.05.010
114. Seymour KE, Reinblatt SP, Benson L, Carnell S. Overlapping neurobehavioral circuits in ADHD, obesity, and binge eating: evidence from neuroimaging research. CNS Spectr. 2015; 20:401–411. [PubMed: 26098969]
115. Elton A, Alcauter S, Gao W. Network connectivity abnormality profile supports a categorical-dimensional hybrid model of ADHD. Hum Brain Mapp. 2014; 35:4531–4543. [PubMed: 24615988]
116. Hulvershorn LA, Mennes M, Castellanos FX, Di Martino A, Milham MP, Hummer TA, Roy AK. Abnormal amygdala functional connectivity associated with emotional lability in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2014; 53:351–361. [PubMed: 24565362]
117. Frodl T, Skokauskas N. Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. Acta Psychiatr Scand. 2012; 125:114–126. [PubMed: 22118249]
118. van Marle HJF, Hermans EJ, Qin S, Fernández G. From specificity to sensitivity: how acute stress affects amygdala processing of biologically salient stimuli. Biol Psychiatry. 2009; 66:649–55. [PubMed: 19596123]
119. Davis M, Whalen PJ. The amygdala: vigilance and emotion. Mol Psychiatry. 2001; 6:13–34. [PubMed: 11244481]
120. Whalen PJ, Raila H, Bennett R, Mattek a, Brown a, Taylor J, et al. Neuroscience and Facial Expressions of Emotion: The Role of Amygdala-Prefrontal Interactions. Emot Rev. 2013; 5:78–83.
121. Bermudez MA, Göbel C, Schultz W. Sensitivity to temporal reward structure in amygdala neurons. Curr Biol. 2012; 22:1839–1844. [PubMed: 22959346]
122. Probst CC, Van Eimeren T. The functional anatomy of impulse control disorders topical collection on neuroimaging. Curr Neurol Neurosci Rep. 2013; 13doi: 10.1007/s11910-013-0386-8
123. Vuilleumier P, Driver J. Modulation of visual processing by attention and emotion: windows on causal interactions between human brain regions. Philos Trans R Soc B Biol Sci. 2007; 362:837–855.
124. Grimm O, Jacob MJ, Kroemer NB, Krebs L, Vollstädt-Klein S, Kobiella A, et al. The personality trait self-directedness predicts the amygdala's reaction to appetizing cues in fMRI. Appetite. 2012; 58:1023–1029. [PubMed: 22381514]
125. Wendt J, Weike AI, Lotze M, Hamm AO. The functional connectivity between amygdala and extrastriate visual cortex activity during emotional picture processing depends on stimulus novelty. Biol Psychol. 2011; 86:203–209. [PubMed: 21130141]
126. Herrington, Taylor JM, Grupe DW, Curby KM, Schultz RT. Bidirectional communication between amygdala and fusiform gyrus during facial recognition. Neuroimage. 2011; 56:2348–2355. [PubMed: 21497657]
127. Malik S, McGlone F, Dagher A. State of expectancy modulates the neural response to visual food stimuli in humans. Appetite. 2011; 56:302–309. [PubMed: 21232571]
128. Elison JT, Paterson SJ, Wolff JJ, Reznick JS, Sasson NJ, Gu H, et al. White matter microstructure and atypical visual orienting in 7-month-olds at risk for autism. Am J Psychiatry. 2013; 170:899–908. [PubMed: 23511344]
129. Leppänen JM, Nelson CA. Tuning the developing brain to social signals of emotions. Nat Rev Neurosci. 2009; 10:37–47. [PubMed: 19050711]
130. Dahlgren J, Samuelsson AM, Jansson T, Holmang A. Interleukin-6 in the maternal circulation reaches the rat fetus in mid-gestation. Pediatr Res. 2006; 60:147–151. [PubMed: 16864694]

131. Hsiao EY, Patterson PH. Placental regulation of maternal-fetal interactions and brain development. Dev Neurobiol. 2012; 72:1317–26. [PubMed: 22753006]

132. Samuelsson A-M, Jennische E, Hansson H-A, Holmäng A. Prenatal exposure to interleukin-6 results in inflammatory neurodegeneration in hippocampus with NMDA/GABA(A) dysregulation and impaired spatial learning. Am J Physiol Regul Integr Comp Physiol. 2006; 290:R1345–56. [PubMed: 16357100]

133. Patterson PH. Immune involvement in schizophrenia and autism: Etiology, pathology and animal models. Behav Brain Res. 2009; 204:313–321. [PubMed: 19136031]

134. Heinrich PC, Behrmann I, Haan S, Hermanns HM, Müller-Newen G, Schaper F. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. Biochem J. 2003; 374:1–20. [PubMed: 12773095]

135. Baker SJ, Rane SG, Reddy EP. Hematopoietic cytokine receptor signaling. Oncogene. 2007; 26:6724–37. [PubMed: 17934481]

136. He F, Ge W, Martinowich K, Becker-Catania S, Coskun V, Zhu W, et al. A positive autoregulatory loop of Jak-STAT signaling controls the onset of astrogliogenesis. Nat Neurosci. 2005; 8:616–625. [PubMed: 15852015]

137. Ullian EM. Control of Synapse Number by Glia. Science (80-). 2001; 291:657–661.

138. Shu T, Richards LJ. Cortical axon guidance by the glial wedge during the development of the corpus callosum. J Neurosci. 2001; 21:2749–58. [PubMed: 11306627]

139. Valerio A. Soluble Interleukin-6 (IL-6) Receptor/IL-6 Fusion Protein Enhances in Vitro Differentiation of Purified Rat Oligodendroglial Lineage Cells. Mol Cell Neurosci. 2002; 21:602–615. [PubMed: 12504593]

140. Nyffeler M, Meyer U, Yee B, Feldon J, Knuesel I. Maternal immune activation during pregnancy increases limbic GABAA receptor immunoreactivity in the adult offspring: Implications for schizophrenia. Neuroscience. 2006; 143:51–62. [PubMed: 17045750]

141. Mosconi MW, Hazlett HC, Poe MD, Gerig G, Smith RG, Piven J. Longitudinal study of amygdala volume and joint attention in 2-to 4-year-old children with autism. Arch Dis Child Fetal Neonatal Ed. 2009; 66:509–516.

142. Demaree HA. Brain Lateralization of Emotional Processing: Historical Roots and a Future Incorporating “Dominance”. Behav Cogn Neurosci Rev. 2005; 4:3–20. [PubMed: 15886400]

143. De Bellis MD, Casey BJ, Dahl RE, Birmaher B, Williamson DE, Thomas KM, et al. A pilot study of amygdala volumes in pediatric generalized anxiety disorder. Biol Psychiatry. 2000; 48:51–57. [PubMed: 10913507]

144. Juranek J, Filipek PA, Berenji GR, Modahl C, Osann K, Spence MA. Association Between Amygdala Volume and Anxiety Level : Magnetic Resonance Imaging (MRI) Study in Autistic Children. 2006:1051–1058.

145. Herrington JD, Heller W, Mohanty A, Engels AS, Banich MT, Webb AG, Miller GA. Localization of asymmetric brain function in emotion and depression. Psychophysiology. 2010; 47:442–54. [PubMed: 20070577]

146. Young EJ, Williams CL. Valence dependent asymmetric release of norepinephrine in the basolateral amygdala. Behav Neurosci. 2010; 124:633–644. [PubMed: 20939663]

147. Qin S, Young CB, Duan X, Chen T, Supekar K, Menon V. Amygdala subregional structure and intrinsic functional connectivity predicts individual differences in anxiety during early childhood. Biol Psychiatry. 2014; 75:892–900. [PubMed: 24268662]

148. White LK, McDermott JM, Degnan KA, Henderson HA, Fox NA. Behavioral inhibition and anxiety: the moderating roles of inhibitory control and attention shifting. J Abnorm Child Psychol. 2011; 39:735–747. [PubMed: 21301953]

149. Danese A, Caspi A, Williams B, Ambler A, Sugden K, Mika J, et al. Biological embedding of stress through inflammation processes in childhood. Mol Psychiatry. 2010:1–2. [PubMed: 20029403]

150. Wadhwa PD, Buss C, Entringer S, Swanson JM. Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. Semin Reprod Med. 2009; 27:358–368. [PubMed: 19711246]

151. Gillman MW, Barker D, Bier D, Cagampang F, Challis J, Fall C, et al. Meeting report on the 3rd international congress on developmental origins of health and disease (DOHaD). Pediatr Res. 2007; 61:625–629. [PubMed: 17413866]

152. Barker DJP. In utero programming of chronic disease. Clin Sci. 1998; 95:115–28. [PubMed: 9680492]

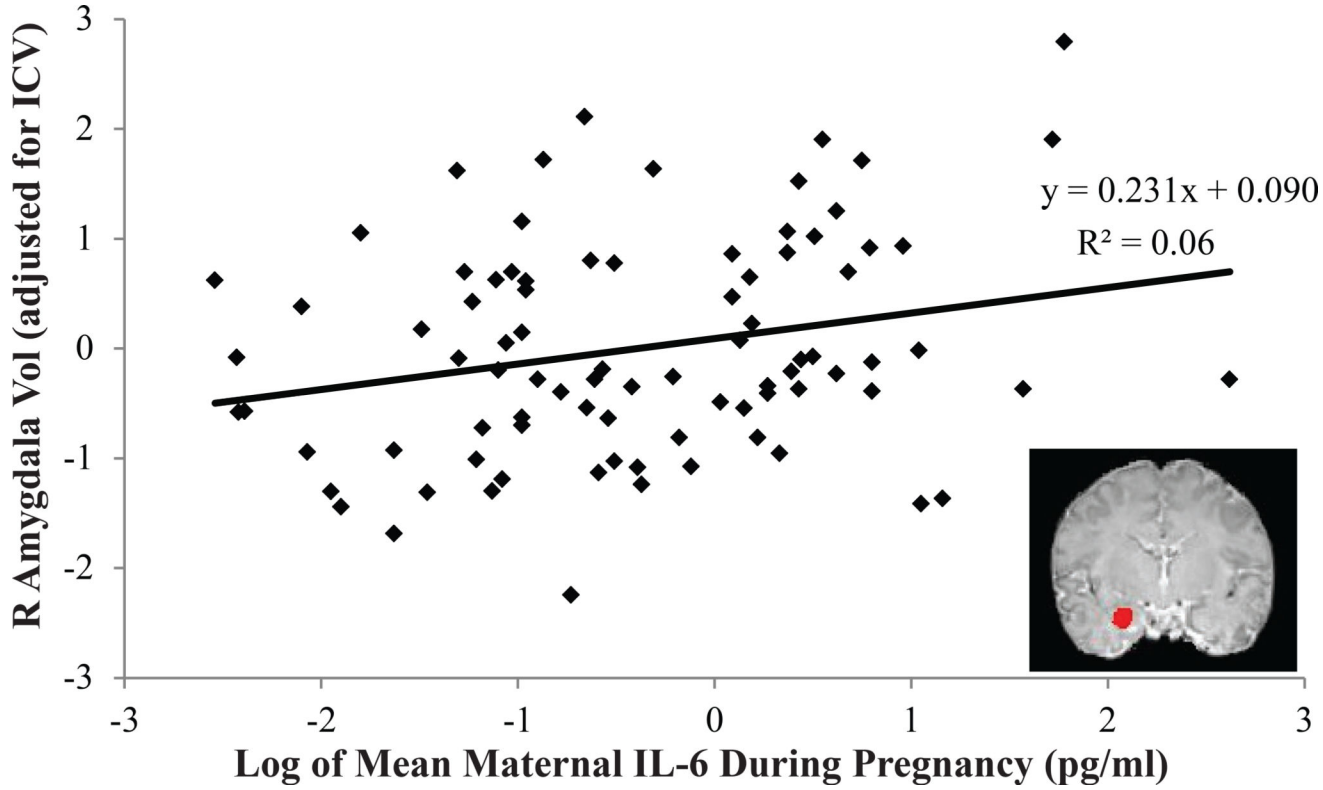


**Figure 1.**

Higher maternal *IL-6* concentrations during pregnancy are associated with greater newborn right amygdala volume.

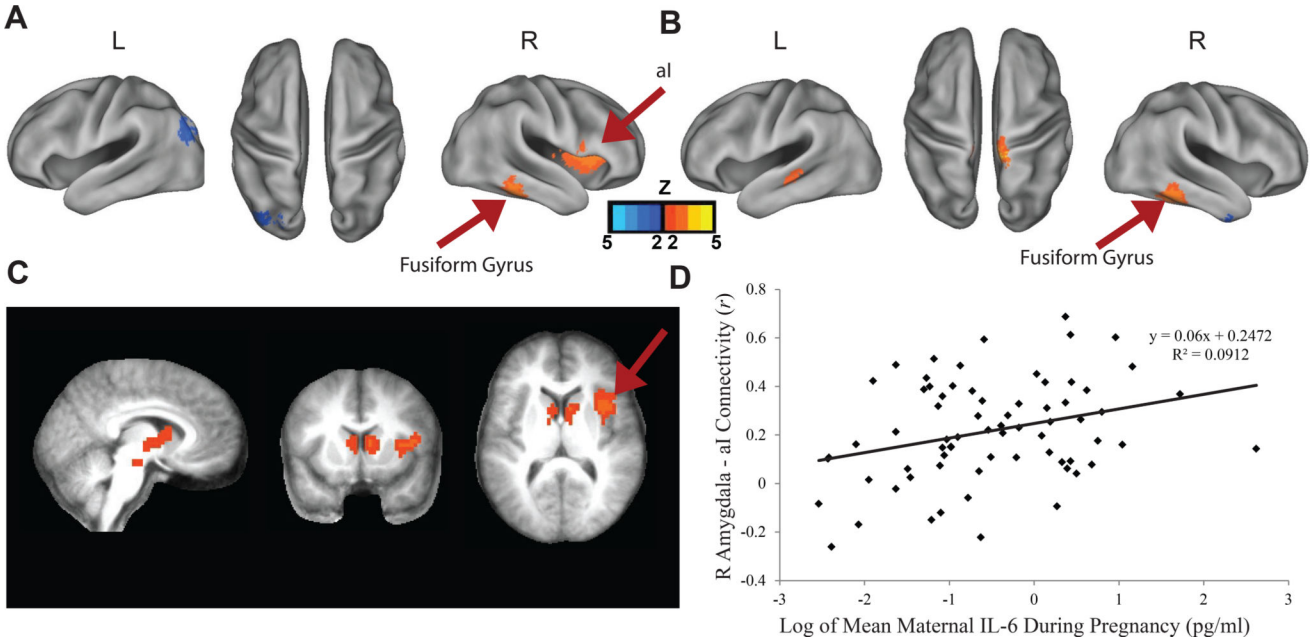


**Figure 2.**

Maternal *IL-6* concentrations during pregnancy are associated with newborn amygdala functional connectivity.

***Note.*** Mean maternal *IL-6* concentrations during pregnancy are prospectively associated with stronger newborn right (Panel A) and left (Panel B) amygdala connectivity to several cortical brain regions including fusiform gyrus. Panel C shows the associations between higher maternal IL-6 concentrations and stronger newborn right amygdala connectivity to anterior insula (aI), thalamus and caudate. Panel D illustrates the association between higher maternal *IL-6* concentrations and newborn right amygdala-aI connectivity (identified in the voxel-wise analyses and displayed on the brain in Panels A and C).

**Table 1**

Sample demographics

| | Mean (SD) |
|---|---|
| Maternal Age in 1st Trimester (years) | 28.2 (5.48) |
| Infant Age (weeks) | |
| Gestational Age at Birth | 39.2 (1.47) |
| Age at MRI Data Collection | 3.79 (1.84) |
| | **Percentage** |
| Infant Sex | |
| Male | 59.3 |
| Female | 40.7 |
| Race/Ethnicity | |
| Caucasian non-Hispanic | 37.5 |
| African American non-Hispanic | 2.50 |
| Asian non-Hispanic | 7.50 |
| Multi-racial non-Hispanic | 8.75 |
| Caucasian Hispanic | 35.0 |
| Asian Hispanic | 1.25 |
| Multi-racial Hispanic | 7.50 |
| Highest Level of Maternal Education | |
| High-School or Test Equivalent | 22.1 |
| Vocational School or Some College | 41.9 |
| Associates Degree | 4.65 |
| Bachelors or Graduate Level Degree | 31.4 |
| Gross Annual Household Income | |
| < $15,000 | 9.75 |
| $15,000 – 29,999 | 22.0 |
| $30,000 – 49,999 | 24.4 |
| $50,000 – 100,000 | 36.6 |
| > $100,000 | 7.32 |

**Table 2**

Mean and standard deviation of maternal IL-6 concentrations and gestational age at collection

| | 1st Trimester | 2nd Trimester | 3rd Trimester |
|---|---|---|---|
| Gestational Age | 12.7 (1.71) | 20.5 (1.39) | 30.4 (1.33) |
| IL-6 Concentration (pg/ml) | 0.79 (0.73) | 0.98 (1.06) | 1.23 (1.36) |

**Table 3**

Mean maternal IL-6 during pregnancy is prospectively associated with newborn amygdala connectivity

| **Right Amygdala** | | | | | | **Left Amygdala** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Region** | **Hem** | **x** | **y** | **z** | **Z** | **Region** | **Hem** | **x** | **y** | **z** | **Z** |
| Anterior insula | R | 35 | 11 | 11 | 2.89 | Fusiform gyrus/ITG | R | 52 | −47 | −22 | 3.09 |
| Fusiform gyrus/ITG | R | 53 | −43 | −23 | 2.87 | Parietal/somatosensory | R | 3 | −40 | 72 | 3.06 |
| Caudate | R | 8 | 5 | 10 | 2.63 | PHG | L | −24 | −29 | −4 | 2.69 |
| Brainstem | L | −2 | −22 | −15 | 2.63 | Temporal pole/ventral temporal cortex | R | 41 | −2 | −38 | −2.94 |
| Thalamus | R | 5 | −9 | 2 | 2.51 | | R | 47 | −20 | −34 | −2.65 |
| Superior Occipital Gyrus | L | −38 | −79 | 31 | −2.53 | | | | | | |

*Note*. Regions are in descending order based on highest Z value.

PHG=parahippocampal gyrus; ITG=inferior temporal gyrus.