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# Maternal Prenatal Social Disadvantage and Neonatal Functional Connectivity: Associations With Psychopathology Symptoms at Age 12 Months

Max P. Herzberg[1], Ashley N. Nielsen[2], Rebecca Brady[2], Sydney Kaplan[2], Dimitrios Alexopoulos[2], Dominique Meyer[2], Jyoti Arora[3], J. Philip Miller[3], Tara A. Smyser[1], Deanna M. Barch[1, 4, 5], Cynthia E. Rogers[1, 6], Barbara B. Warner[6], Christopher D. Smyser[2, 5, 6], and Joan L. Luby[1]

[1] Department of Psychiatry, Washington University in St. Louis
[2] Department of Neurology, Washington University in St. Louis
[3] Department of Biostatistics, Washington University in St. Louis
[4] Department of Psychological and Brain Sciences, Washington University in St. Louis
[5] Department of Radiology, Washington University in St. Louis
[6] Department of Pediatrics, Washington University in St. Louis

Recent research has reported effects of socioeconomic status on neurobehavioral development as early as infancy, including positive associations between income and brain structure, functional connectivity, and behavior later in childhood (Ramphal, Whalen, et al., 2020; Triplett et al., 2022). This study extends this literature by investigating the relation of maternal prenatal social disadvantage (PSD) to neonatal amygdala and hippocampus functional connectivity and whether socioeconomic-related alterations in functional connectivity subsequently predict behavior at age 12 months in a large, socioeconomically diverse sample ($N = 261$ mother–infant dyads). PSD was assessed across gestation; neonatal magnetic resonance imaging was completed within the first weeks of life; and infant internalizing and externalizing symptoms were evaluated using the Infant–Toddler Social and Emotional Assessment at age 12 months. The results showed that PSD was significantly related to neonatal right amygdala and left hippocampus functional connectivity with prefrontal and motor-related regions. Social disadvantage-related right amygdala and left hippocampus functional connectivity with these regions was subsequently related to infant externalizing and internalizing symptoms at age 12 months. Building off an emerging literature exploring prenatal impacts on neonatal functional connectivity, this study further emphasizes the important role of the maternal environment during gestation on infant brain function and its relationship with externalizing and internalizing behavior in the first years of life. The results suggest that the prenatal socioeconomic environment may be a promising target for interventions aimed at improving infant neurobehavioral outcomes.



Max P. Herzberg https://orcid.org/0000-0003-3177-7966

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Max P. Herzberg served as lead for conceptualization, formal analysis, visualization, writing–original draft, and writing–review and editing. Ashley N. Nielsen served in a supporting role for writing–review and editing. Rebecca Brady served in a supporting role for writing–review and editing. Sydney Kaplan served in a supporting role for writing–review and editing. J. Philip Miller served in a supporting role for data curation, formal analysis, and writing–review and editing. Tara A. Smyser contributed equally to project administration and served in a supporting role for writing–review and editing. Deanna M. Barch served in a supporting role for conceptualization, funding acquisition, and writing–review and editing. Cynthia E. Rogers served in a supporting role for conceptualization, funding acquisition, and writing–review and editing. Barbara B. Warner served as lead for funding acquisition and served in a supporting role for writing–review and editing. Christopher D. Smyser served as lead for funding acquisition and served in a supporting role for conceptualization and writing–review and editing. Joan L. Luby served as lead for funding acquisition and served in a supporting role for conceptualization and writing–review and editing. Sydney Kaplan, Dimitrios Alexopoulos, Dominique Meyer, and Jyoti Arora contributed equally to data curation. Dimitrios Alexopoulos and Dominique Meyer contributed equally to software. Deanna M. Barch and Joan L. Luby contributed equally to supervision.

Correspondence concerning this article should be addressed to Max P. Herzberg, Department of Psychiatry, Washington University in St. Louis, 660 South Euclid Avenue, St. Louis, MO 63110, United States. Email: maxherzberg@wustl.edu

***Public Significance Statement***
This study suggests that mothers' prenatal social disadvantage (PSD) impacts the brain function of their infants in the weeks shortly after birth. Additionally, the study reports a link between infant brain function shortly after birth and infant behavior 1 year later. The study results suggest that mother's PSD may be a promising target for interventions that improve infant health.

*Keywords:* neonatal imaging, functional connectivity, externalizing, socioeconomic status



Experiences that occur early in life influence trajectories of brain and behavior development across the lifespan. These experiences have greater influence on development during early-life sensitive periods when neurobiological systems are particularly open to the impact of environmental exposures (Luby et al., 2020). In recent years, a large body of research focusing on these early life experiences has investigated the widespread impacts of socioeconomic status, including on brain development (Herzberg & Gunnar, 2020; Johnson et al., 2016). Importantly, the impact of these experiences begins in the prenatal period with implications for protection or vulnerability to psychopathology (Monk et al., 2019). Given that more than 40% of infants and children live at or near the poverty line in the United States (e.g., below 200% of the federal poverty line; Koball & Jiang, 2018) and known associations between low socioeconomic status and child psychopathology (Peverill et al., 2021), understanding the impacts of prenatal socioeconomic status on brain and behavior development at birth may be crucial for future prevention and intervention efforts in psychopathology.

Socioeconomic status has been consistently related to brain development both pre- and postnatally (Johnson et al., 2016; Lean et al., 2022; Triplett et al., 2022). Various measures of socioeconomic status (e.g., family income and caregiver education) have been positively associated with total gray matter, white matter, and subcortical volumes during the adolescent period, though regional differences in the direction of effect have been reported (Johnson et al., 2016; Mackey et al., 2015; McDermott et al., 2019). Importantly, similar relationships have been reported earlier in development, with infant or prenatal socioeconomic exposures exhibiting positive associations with global brain volumes and subcortical brain volumes including in the amygdala and hippocampus (Betancourt et al., 2016; Hanson et al., 2015; Knickmeyer et al., 2017; Triplett et al., 2022). Structural connectivity measures, derived from diffusion-weighted imaging further support the substantial impact of socioeconomic status on brain structure, including altered medial diffusion and fractional anisotropy in frontolimbic tracts, including the uncinate fasciculus, as a function of social disadvantage or risk (Lean et al., 2022; Thompson et al., 2019).

Like brain structure, functional connectivity has been associated with socioeconomic status postnatally, including during middle childhood, adolescence, and early adulthood (e.g., Dejoseph et al., 2022; Rakesh et al., 2021; Ramphal, DeSerisy, et al., 2020). These investigations have shed light on the associations between socioeconomic status, functional connectivity, and psychopathology, emphasizing the potential impact of better understanding these relationships early in development. Functional connectivity development, including the connectivity of the amygdala and hippocampus, begins around mid-gestation and continues throughout the pre- and postnatal periods (van den Heuvel & Thomason, 2016), with maternal experience effects on amygdala connectivity reported during the second and third trimesters (van den Heuvel et al., 2023). During the first year of life, higher socioeconomic status in the prenatal period has been related to greater infant resting-state functional connectivity within the somatomotor network and decreased connectivity between the default mode network and all other regions of the brain, though these effects did not survive correction for multiple comparisons (Gao et al., 2015). The functional connectivity of subcortical regions, including the amygdala, has also been shown to be sensitive to the prenatal environment. Maternal prenatal depression symptoms have been associated with increased amygdala–anterior cingulate cortex functional connectivity (Qiu et al., 2015). Neonatal amygdala functional connectivity has also been associated with later infant behavior, including positive associations between the connectivity of frontolimbic regions (e.g., amygdala—medial prefrontal cortex, amygdala—superior frontal cortex) and infant internalizing symptoms at age 2 years (Rogers et al., 2017). Research combining measures of perinatal socioeconomic status, neonatal functional connectivity, and subsequent infant behavior has been limited. In one study combining all of these elements, left striatum functional connectivity with the prefrontal cortex was greater in newborns with public health insurance compared to their peers with private health insurance (Ramphal, Whalen, et al., 2020). This functional connectivity was shown to mediate the association between public insurance at birth and increased externalizing at 2 years such that left striatum–right frontopolar connectivity associated with public insurance strengthened the association with externalizing symptoms.

As these studies illustrate, infant functional connectivity is impacted by the perinatal maternal environment and may affect infant behavior through this neural mechanism. Given the still limited normative research to date, interpreting neonatal functional connectivity in a direction can be difficult as the expected developmental trajectories are yet to be established. Despite this challenge, the previous literature suggests that studying the associations between prenatal environmental exposures and neonatal functional connectivity may elucidate important mechanisms that underlie adversity-related behaviors later in infancy. Theoretical perspectives, such as the developmental origins of health and disease, support this possibility by characterizing prenatal development as a period of preparing the fetus and the precursors of functional brain organization for the environment into which the offspring will be born (Monk et al., 2019; Van den Bergh et al., 2020). In the original conception of this framework, mismatches between the prenatal and postnatal environment were theorized to confer risk for maladaptive outcomes (Barker, 1995). Furthermore, prior empirical research emphasizes the importance of subcortical structures, including effects on the amygdala and hippocampus, as potential links between perinatal socioeconomic status and infant internalizing and externalizing behavior (Hanson et al., 2015; Ramphal, Whalen, et al., 2020; Rogers et al., 2017; Triplett et al., 2022). As such, research evaluating the effects of maternal prenatal experiences, such as social disadvantage, on neonatal brain

connectivity and subsequent behavior is consistent with prenatal programming perspectives and the prior literature. Importantly, maternal prenatal social disadvantage (PSD), which is used here in place of socioeconomic status, incorporates both the effects of traditional measures of income and caregiver education with accompanying factors including neighborhood resource and access to healthy food which further contribute to the environmental signals transmitted to the fetus.

Despite prior empirical research and theoretical perspectives on the potential impact of prenatal maternal socioeconomic status and associated social disadvantage on neonatal connectivity, few studies to date have shed light on subsequent infant behavior and how neonatal connectivity may contribute to behavioral trajectories of adaptation and risk. The current study extended the prior literature and aimed to characterize the associations between social disadvantage and neonatal resting-state functional connectivity seeded from the amygdala and hippocampus, as well as subsequent behavioral development when infants reached age 12 months. Prior literature in infants and children suggests that frontolimbic connectivity, particularly between the amygdala and regions of the medial prefrontal cortex, is associated with maternal stress and psychopathology symptoms (Gao et al., 2015; Gee et al., 2013; Rogers et al., 2017). As such, we expected neonatal functional connectivity in the frontolimbic circuits to be related to prenatal maternal social disadvantage and subsequently associated with infant internalizing and externalizing symptoms. Given the nascent state of the neonatal functional connectivity literature, however, we tested this hypothesis using whole-brain methods using permutation-based control for false positives. The resulting connectivity estimates were extracted and submitted to further statistical testing to examine the relation of socioeconomic-related connectivity to infant behavior.

# Method

## Participants

The study sample included 261 mother–infant dyads from a large prospective study of pregnant women in Saint Louis, MO metropolitan area (full study sample $N = 399$ dyads, see Figure A1). More details about the larger sample can be found in previous publications (Luby et al., 2023; Stout et al., 2022). Infant inclusion criteria included full-term birth (≥37 weeks estimated gestational age), singleton pregnancy, birthweight ≥2,000 g, neonatal intensive care unit (NICU) stay of 7 days or less, no brain injury on magnetic resonance imaging (MRI), and 10 or more minutes of low-motion MRI data. Birth-related measures, such as infant postmenstrual age and birthweight were collected from infant medical records at delivery. Mothers with diagnosed infections known to cause congenital disease or who used alcohol or drugs during pregnancy (excluding marijuana and tobacco) were excluded from the study sample. Neonatal imaging scans took place within the first 6 weeks of life and medical data were collected using participant questionnaires and chart review. Participating dyads also completed a behavioral follow-up assessment when the infants were approximately 12 months of age. All procedures were approved by the Institutional Review Board of Washington University in Saint Louis (protocol ID 201703145; early life adversity, biological embedding, and risk for developmental precursors of mental disorders). Each participant provided informed consent and parental informed consent was obtained for each infant prior to participation. Detailed information about the sample can be found in Table 1.

## Measures

### PSD

Maternal PSD was the predictor of interest in the resting-state analyses and was operationalized as a latent factor score that included income-to-needs ratio, area deprivation index, insurance status, education, and maternal nutrition, each assessed during pregnancy (see Luby et al., 2023 for detailed information about this factor score and the model from which it was generated). The model fit indices for the factor analyses used to generate this score had good model fit (root-mean-square error of approximation [RMSEA] = .043, standardized root-mean-square residual [SRMR] = .055, comparative fit index [CFI]/Tucker–Lewis index [TLI] = .954/.944). Higher scores on this factor score indicate greater PSD. Family income-to-needs ratio and maternal education, collected at the first prenatal visit, are also included in Table 1 in order to contextualize the level of social disadvantage indicated by the prenatal maternal social disadvantage factor score.

### Resting-State Functional Magnetic Resonance Imaging (fMRI) Acquisition

MRI data were acquired using a 3T Prisma scanner (Siemens Corporation) with a 64-channel head coil. Structural scans for registration

**Table 1**
*Demographic Characteristics of Participating Mothers and Infants*

| Variable | Overall ($N = 261$) |
|---|---|
| Infant sex | |
| Male | 141 (54.0%) |
| Female | 120 (46.0%) |
| First trimester INR | |
| *M* (*SD*) | 2.95 (3.07) |
| *Mdn* (min, max) | 1.25 (0.430, 12.2) |
| Missing | 9 (3.4%) |
| Infant age at scan | |
| *M* (*SD*) | 41.3 (1.28) |
| *Mdn* (min, max) | 41.0 (38.0, 45.0) |
| Infant birthweight | |
| *M* (*SD*) | 3,270 (491) |
| *Mdn* (min, max) | 3,210 (2,200, 4,630) |
| Missing | 1 (0.4%) |
| Race/ethnicity | |
| Black | 157 (60.2%) |
| White | 98 (37.5%) |
| Asian | 2 (0.8%) |
| Native Hawaiian/Pacific Islander | 0 (0%) |
| American Indian Alaskan Native | 0 (0%) |
| Other | 4 (1.5%) |
| Unknown | 0 (0%) |
| Socioeconomic advantage factor score | |
| *M* (*SD*) | 0.0553 (0.977) |
| *Mdn* (min, max) | −0.352 (−1.47, 2.15) |
| Infant externalizing at 12 months | |
| *M* (*SD*) | 52.5 (11.7) |
| *Mdn* (min, max) | 50.0 (34.0, 93.0) |
| Missing | 64 (24.5%) |
| Maternal postnatal depression | |
| *M* (*SD*) | 5.66 (4.28) |
| *Mdn* (min, max) | 5.00 (0, 21.0) |
| Missing | 18 (6.9%) |

*Note.* INR = income-to-needs ratio; min = minimum; max = maximum.

were collected using a T2-weighted scanning sequence (0.8 mm isotropic voxels, 208 slices in the sagittal plane, echo time = 563 ms, tissue T2 = 160 ms, repetition time = 3,200 or 4,500 ms) and resting-state functional imaging data were collected using a blood oxygen-level dependent (BOLD) gradient-recalled echo-planar multiband sequence (72 slices, 2.0 mm isotropic voxels, echo time = 37 ms, repetition time = 800 ms, multiband factor = 8). Real-time participant movement was monitored using Framewise Integrated Real-time MRI Monitoring (Badke D'Andrea et al., 2022; Dosenbach et al., 2017).

### Resting-State fMRI Preprocessing

The resting-state fMRI data were preprocessed using a standard neonatal preprocessing pipeline for BOLD data that were composed of FMRIB Software Library tools (Jenkinson et al., 2012) and the 4 dfp tool suite (ftp://imaging.wustl.edu/pub/raichlab/4dfp_tools/). Briefly, the BOLD data were slice-timing corrected, debanded, motion corrected using rigid body realignment, bias field corrected, and normalized to a whole-brain mode of 1,000. The time series data were then corrected for readout distortion and linearly registered to the 711-2N Talairach atlas space via individual T2w images, a cohort-specific T2w atlas, and finally the 711-2N Talairach atlas. All linear registrations were completed in the same step with 12 degrees of freedom. Image censoring was completed so that only data with at least three consecutive frames with a framewise displacement (FD) <0.25 mm were used. BOLD runs were demeaned, detrended, and nuisance regression was completed with white matter, cerebrospinal fluid, and whole brain time series as predictors. The 24-Friston motion parameters (i.e., motion in the *x*, *y*, *z*, pitch, roll, and yaw directions from the current frame, the previous frame, and the squares of these parameters) were also included in nuisance regression. Finally, the data were bandpass filtered (0.005–0.1 Hz) and spatially smoothed using a 3-mm full width at half maximum Gaussian kernel. Only infants with 10 min or more usable fMRI data were included in the analysis and the resulting sample had low mean FD. See Table 1 for summary statistics on the average FD in the sample. Further description of the volume space processing can be found in Sylvester et al. (2023).

### Internalizing and Externalizing Symptoms

Parent-reported internalizing and externalizing scores at age 12 months were collected using the Infant–Toddler Social Emotional Assessment (ITSEA; Carter et al., 2003). The ITSEA includes 179 total items and assesses seven domains of which only the externalizing and internalizing domains were used in this analysis. The externalizing symptoms domain includes activity/impulsivity (e.g., "Is restless and can't sit still"), aggression/defiance (e.g., "Has temper tantrums"), and peer aggression (e.g., "Misbehaves to get attention from adults") subscales. Internalizing symptoms scores are made up of four subscales, including depression/withdrawal (e.g., "Avoids physical contact"), general anxiety (e.g., "Seems nervous, tense, or fearful"), separation distress (e.g., "Demands a lot of attention"), and inhibition to novelty ("Is shy with new adults"). Parents replied to each item ranking their child's behavior on a scale from 0 (*rarely/never*) to 2 (*often*) or with their general feelings about their child's behavior on a scale ranging from 0 (*not at all worried*) to 3 (*very worried*). The externalizing and internalizing domain scores were calculated as the mean of all items in each domain and converted to standardized *t* scores, which were adjusted for infant age and sex, prior to analysis. Higher scores indicate more reported internalizing and externalizing behaviors. Both the externalizing and internalizing scales of the ITSEA show high internal validity (Cronbach's $\alpha = .87$ and $\alpha = .80$, respectively; Carter et al., 2003).

### Maternal Postnatal Depression Symptoms

Maternal postnatal depression was assessed using the Edinburgh Postnatal Depression Scale (EPDS; J. L. Cox et al., 1987) when infants were age 4 and 12 months. The EPDS is made up of 10 items probing depression symptoms experienced in the previous 7 days. Responses range from *never* to *quite often* or *most of the time* and are scored on a scale of 0–3, with increasing sum scores indicating more depression symptoms. Total scores from the 4- and 12-month assessments were averaged to create a maternal postnatal depression score. Maternal postnatal depression scores were included as a covariate in models examining psychopathology outcomes as studies examining maternal depression have shown that both internalizing and externalizing symptoms are heritable (Grabow et al., 2017; Viktorin et al., 2016).

## Data Analysis Plan

### Seed-Based Functional Connectivity

Seed-based resting-state connectivity analysis was completed using amygdala and hippocampus seed regions of interest, analyzed separately for the left and right hemispheres. The seed regions of interest were created using the Melbourne Children's Regional Infant Brain Surface based pipeline (Adamson et al., 2020). Hippocampal regions of interest were manually edited to improve accuracy using the ITKsnap imaging software tool. Mean time series were then extracted from the region of interest masks using AFNI's 3dmaskave tool (Version 20.3.03 "Vespasian"; R. W. Cox, 1996; R. W. Cox & Hyde, 1997) and entered into a whole-brain seed-based regression analysis using 3dDeconvolve. Images exceeding the motion thresholds described above were censored at the subject level. The resulting subject-level correlation maps were Fisher *r*-to-*z* transformed using AFNI's 3dcalc command prior to group-level analysis. Group-level linear regression analyses using the subject-level correlation maps were then completed using 3dttest++ and included the PSD latent factor as the predictor of interest. Postmenstrual age at scan (which combines infant gestational age at birth and chronological age at scan), infant birthweight, infant sex, and mean FD were used as covariates. These covariates were chosen a priori given previous work in this sample, as well as known associations between postmenstrual age, birthweight, and sex on neurodevelopment (Triplett et al., 2022). Mean FD was included to provide additional assurance that the observed results were not attributable to participant head motion. All predictors were mean centered prior to analysis. A voxel-wise $p < .005$ significance threshold and nonparametric cluster correction from Clustsim were used to identify significant clusters of functional connectivity associated with PSD (R. W. Cox et al., 2017a, 2017b).

### Brain–Behavior Associations

Descriptive and inferential statistics following the seed-based resting-state functional connectivity analyses were completed in R Version 4.2.1 (R Core Team, 2020). The associations between seed-based resting-state connectivity and infant internalizing and externalizing symptoms were estimated using linear regression models that included maternal postnatal depression symptoms as a covariate.

Children's age and sex were controlled for by using age- and sex-normed *t* scores. Significant brain–behavior associations were followed up with a mediation analysis investigating whether neonatal functional connectivity mediated the relationship between prenatal maternal social disadvantage and infant internalizing or externalizing symptoms at 12 months. These analyses were completed using the mediation package in R, nonparametrically bootstrapped using 1,000 simulations, and controlled for maternal postnatal depression symptoms (Tingley et al., 2014). Follow-up exploratory analyses evaluated whether or not sex differences were present in the associations between prenatal maternal social disadvantage, neonatal functional connectivity, and infant internalizing and externalizing symptoms at 12 months. With all covariates and behavioral variables included, the final brain-behavior sample size was 197 mother–infant dyads. Table A1 in the Appendix includes the correlations among all the predictor variables and Table A2 includes demographic information for those with and without behavioral data, including differences in social disadvantage between groups. This study was not preregistered. Data are available upon request to the authors and the establishment of a data use agreement, while the analysis code is available from the corresponding author upon request.

## Results

### Maternal PSD Associated With Functional Connectivity

Right amygdala and left hippocampus neonatal functional connectivity were significantly associated with PSD when controlling for postmenstrual age at scan, infant sex, infant birthweight, and mean FD. Functional connectivity between the right amygdala and a large cluster spanning the ventromedial prefrontal cortex and dorsal anterior cingulate was negatively associated with PSD (cluster-corrected $p < .01$; cluster size $k = 678$ voxels; critical $k = 144$ voxels; see Figure 1A). A second cluster of connectivity between the right amygdala and the right precentral gyrus was positively associated with PSD (cluster-corrected $p < .01$, cluster size $k = 425$ voxels; critical $k = 144$ voxels; see Figure 1B). Similarly, two significant clusters were evident using the left hippocampus as the seed region: left hippocampus–right inferior frontal gyrus connectivity was negatively associated with PSD (cluster-corrected $p < .03$; cluster size $k = 172$ voxels; critical $k = 135$ voxels; see Figure 2A), while left hippocampus connectivity with the right precentral gyrus was positively associated with social disadvantage (cluster-corrected $p < .01$; cluster size $k = 251$ voxels; critical $k = 135$ voxels; see Figure 2B). Despite similar spatial patterns, there were no associations between PSD and functional connectivity patterns of the left amygdala or right hippocampus that survived cluster correction. No evidence of sex differences in the association between prenatal maternal social disadvantage and neonatal functional connectivity was observed.

### Maternal PSD and Infant Behavior at 12 Months

PSD was positively associated with both infant externalizing ($r = .22$, $p = .001$) and internalizing ($r = .16$, $p = .02$) symptoms at 12 months of age.

### Associations Between Functional Connectivity and Infant Behavior

A series of follow-up models investigated associations between PSD-related right amygdala and left hippocampus functional connectivity estimates with infant externalizing and internalizing behaviors at the 12-month assessment (see Tables A3–A10 for full regression results). Mean maternal postnatal depression symptoms were a covariate in all models. Functional connectivity between the right amygdala and the bilateral ventromedial prefrontal cortex/dorsal anterior cingulate related to PSD was negatively associated with infant externalizing behaviors (standardized beta = −.18; 95% CI [−0.31, −0.04]) and internalizing behaviors (standardized beta = −.16, 95% CI [−0.30, −0.03]) at age 12 months. Right amygdala–right precentral gyrus connectivity associated with PSD was positively associated with 12-month infant internalizing behaviors (standardized beta = .18, 95% CI [0.05, 0.32]; see Figure 3A) but was not associated with infant externalizing (standardized beta = .07, 95% CI [−0.07, 0.21]). In a follow-up analysis to assess specificity, right amygdala connectivity with the right precentral gyrus remained positively associated with infant 12-month internalizing behavior when concurrent infant externalizing symptoms were added as a covariate in the model (standardized beta = .13, 95% CI [0.01, 0.25]). Neither of the clusters of functional connectivity with the left hippocampus that showed significant associations with PSD was subsequently associated with infant externalizing (right inferior frontal gyrus: standardized beta = −.04, 95% CI [−0.17, 0.10]; right precentral gyrus: standardized beta = .06, 95% CI [−0.08, 0.20]). Conversely, left hippocampus connectivity with the right precentral gyrus related to PSD was positively associated with internalizing behavior at the 12-month assessment (standardized beta = .17, 95% CI [0.04, 0.31]; see Figure 3B). No association with infant internalizing was observed for left hippocampus connectivity with the right inferior frontal gyrus (standardized beta = .10, 95% CI [−0.04, 0.23]).

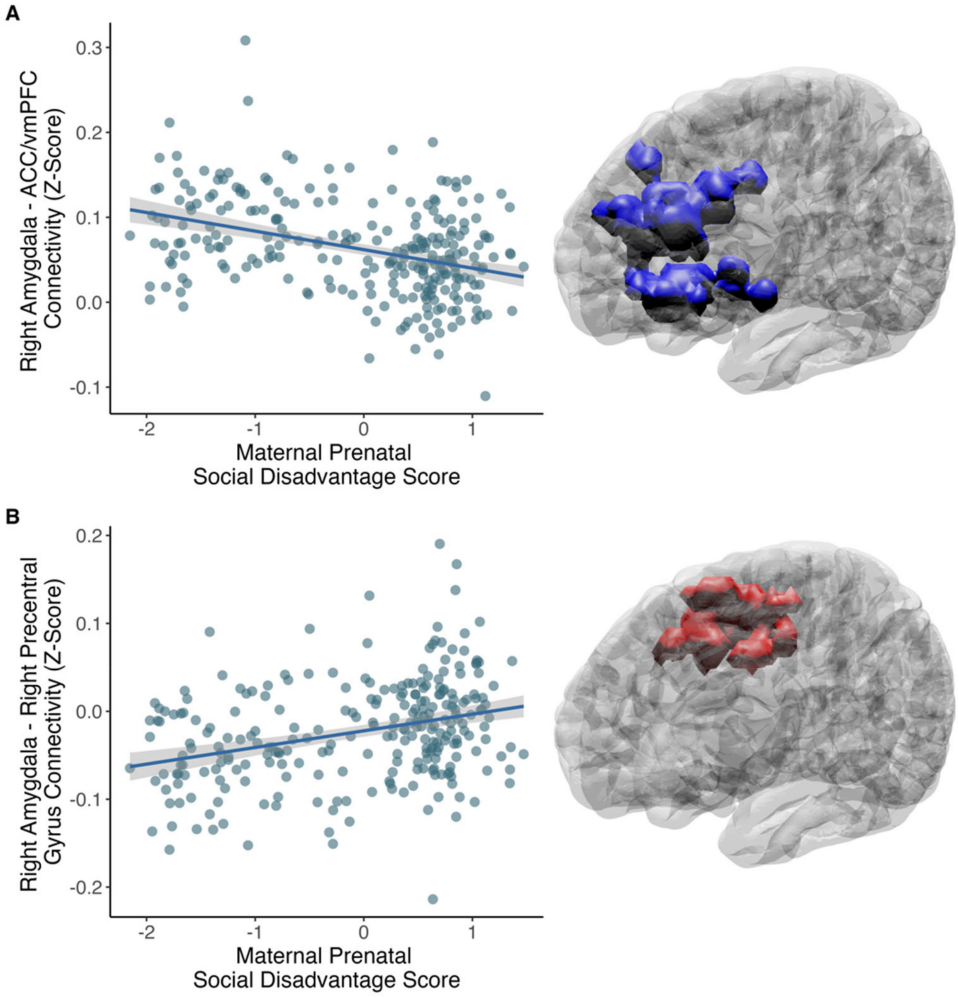
Exploratory models examining the potential for sex differences in the association between neonatal functional connectivity and externalizing and internalizing scores at age 12 months revealed significant moderation effects (see Tables A11 and A12). Right amygdala–ventromedial prefrontal and dorsal anterior cingulate cortex functional connectivity was associated with externalizing symptoms in female infants (standardized beta = −.32, 95% CI [−0.52, −0.13]) but not male infants (standardized beta = −.02, 95% CI [−0.21, 0.18]; see Figure 4A and Table A13). A similar pattern of results was observed when predicting internalizing symptoms at age 12 months (female-only standardized beta = −.30, 95% CI [−0.49, −0.11] and male-only standardized beta = −.01, 95% CI [−0.20, 0.19]; see Figure 4B and Table A14). Each of these models included postnatal maternal depression symptoms as a covariate. Conversely, the association between PSD-related connectivity between the right amygdala and right precentral gyrus and infant internalizing symptoms was not moderated by infant sex (standardized beta = .13, 95% CI [0.00, 0.26]; see Table A15). The association between PSD-related left hippocampus–right precentral gyrus functional connectivity and internalizing behavior was also not moderated by infant sex (standardized beta = .07, 95% CI [−0.06, 0.21]; see Table A16).

### Mediation Model

Longitudinal mediation models were used to examine whether neonatal functional connectivity mediated the associations between PSD and externalizing and internalizing symptoms at age 12 months. Right amygdala–ventromedial prefrontal cortex/dorsal anterior cingulate

**Figure 1**

*Right Amygdala Functional Connectivity Associated With Maternal Prenatal Social Disadvantage*




*Note.* PSD was (A) negatively associated with right amygdala connectivity with a cluster spanning the ventromedial prefrontal cortex and anterior cingulate (peak voxel: $x = 1.5$, $y = -27$, $z = -6$, cluster-corrected $p < .01$) and (B) positively associated with connectivity between the right amygdala and right precentral gyrus (peak voxel: $x = -7.5$, $y = 27$, $z = 48$, cluster-corrected $p < .01$). Individual data points represent raw data with the model-predicted trend plotted with a confidence envelope representing the 95% confidence interval. PSD = prenatal social disadvantage; ACC = anterior cingulate cortex; vmPFC = ventromedial prefrontal cortex. See the online article for the color version of this figure.

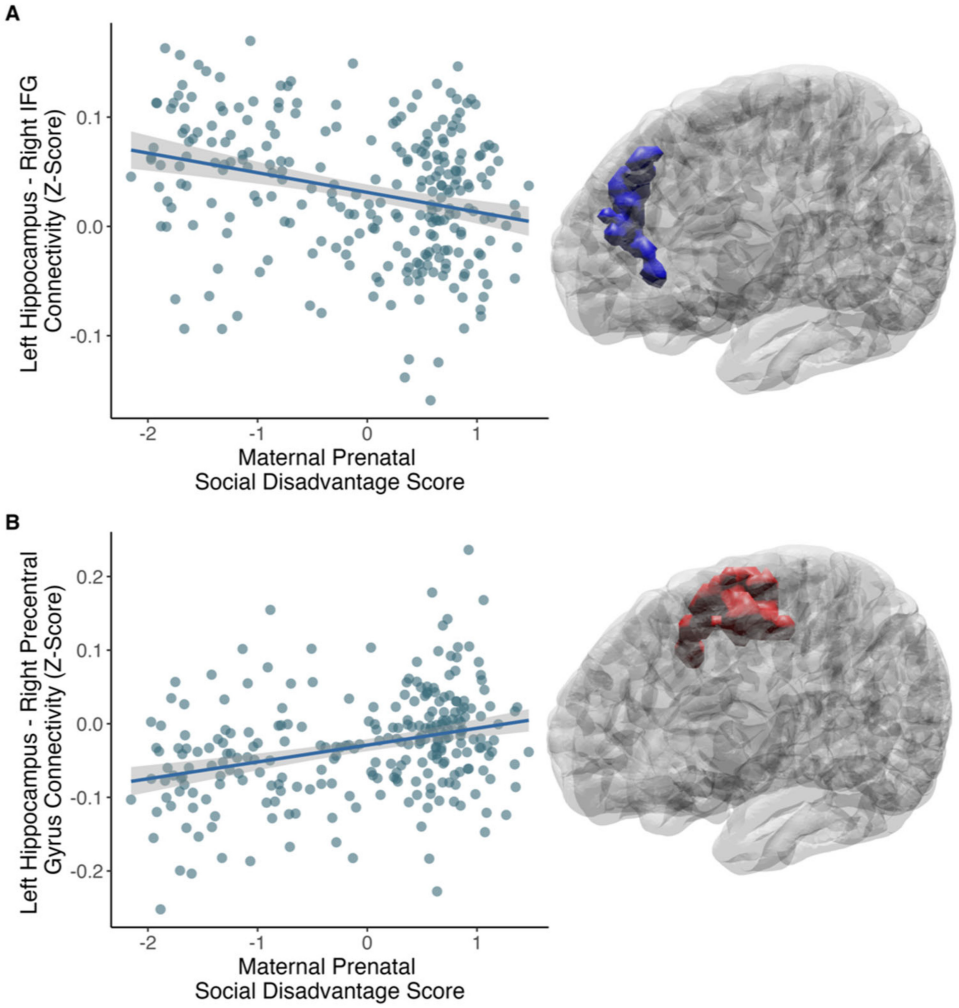
functional connectivity did not mediate the relationship between PSD and 12-month externalizing symptoms when controlling for postnatal maternal depression symptoms in the full sample or in male and female infants separately (see Figure A2). Infant 12 -month internalizing symptoms, which were also significantly associated with amygdala–ventromedial prefrontal cortex/dorsal anterior cingulate connectivity in female infants, did not show a significant mediation effect in female infants (see Figure A3). Conversely, both right amygdala–right precentral gyrus connectivity and left hippocampus–right precentral gyrus connectivity associated with PSD significantly mediated the association between PSD and 12-month internalizing behavior (right amygdala indirect effect $p = .04$; left hippocampus indirect effect $p = .04$; see Figure 5) with maternal depression symptoms included as a covariate.

## Discussion

In this study, PSD was associated with neonatal functional connectivity using hemisphere-specific amygdala and hippocampus seeds and with infant externalizing and internalizing behavior at age 12 months. Specifically, neonatal right amygdala functional connectivity with a large cluster in the ventromedial prefrontal and dorsal anterior cingulate cortex was negatively associated with maternal social disadvantage. The same association was observed for left hippocampus–left inferior frontal gyrus connectivity. Conversely, both neonatal right amygdala–right precentral gyrus and left hippocampus–right precentral gyrus connectivity was positively associated with PSD. Right amygdala–ventromedial prefrontal/dorsal anterior cingulate connectivity associated with PSD was subsequently negatively

**Figure 2**

*Left Hippocampus Functional Connectivity Associated With Maternal Prenatal Social Disadvantage*



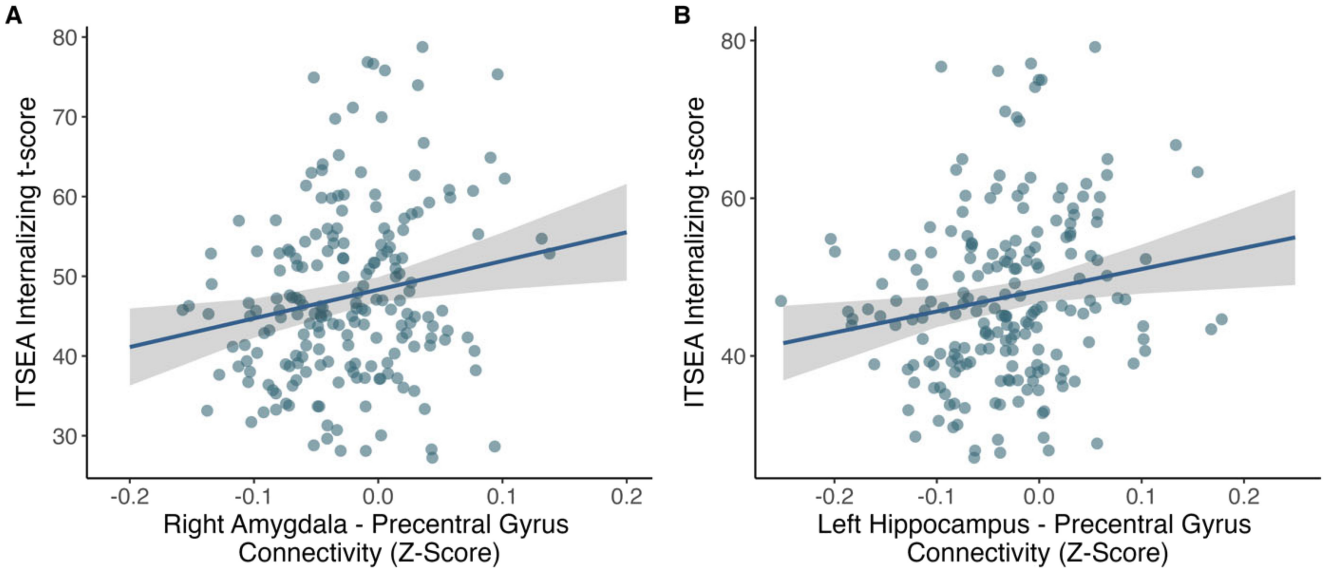

*Note.* PSD was (A) negatively correlated with neonatal left hippocampus–right IFG functional connectivity (cluster-corrected $p < .03$; peak voxel: $x = -49.5$, $y = -12.0$, $z = 9.0$) and (B) positively correlated with a cluster in the right precentral gyrus (cluster-corrected $p < .01$; peak voxel: $x = -22.5$, $y = 21.0$, $z = 54.0$). Individual data points represent raw data with the model-predicted trend plotted with a confidence envelope representing the 95% confidence interval. PSD = prenatal social disadvantage; IFG = inferior frontal gyrus. See the online article for the color version of this figure.

associated with infant externalizing and internalizing behavior at 12 months, though this effect was specific to female infants. Interestingly, both the right amygdala and left hippocampus functional connectivity with the right precentral gyrus associated with PSD were positively associated with internalizing, but not externalizing, symptoms when infants were age 12 months. No differences by infant sex were observed for PSD-related precentral gyrus connectivity. Given known heritability of maternal psychopathology in offspring behavioral development, the models producing these results included maternal postnatal depression scores as a covariate because no genetic data were available and the study did not leverage an adoption or twin design. Finally, both right amygdala–and left hippocampus–right precentral gyrus connectivity mediated the association between PSD and 12-month internalizing behavior.

Consistent with our expectations, we observed negative associations between PSD and neonatal frontolimbic connectivity, particularly between right amygdala and a large bilateral cluster including ventromedial prefrontal and dorsal anterior cingulate connectivity. These findings are concordant with a small but growing literature that has established associations between maternal prenatal socioeconomic status and somatomotor network connectivity, default mode network connectivity, and striatum–prefrontal cortex connectivity (Gao et al., 2015; Ramphal, Whalen, et al., 2020). The results presented here extend these associations to include amygdala and hippocampus connectivity with the prefrontal cortex, while also emphasizing the impacts of both social disadvantage and functional connectivity on infant mental health. Importantly, a limited literature has also directly observed associations between maternal stress prior to and during

**Figure 3**

*Infant Internalizing Symptoms as a Function of Amygdala and Hippocampus Functional Connectivity*

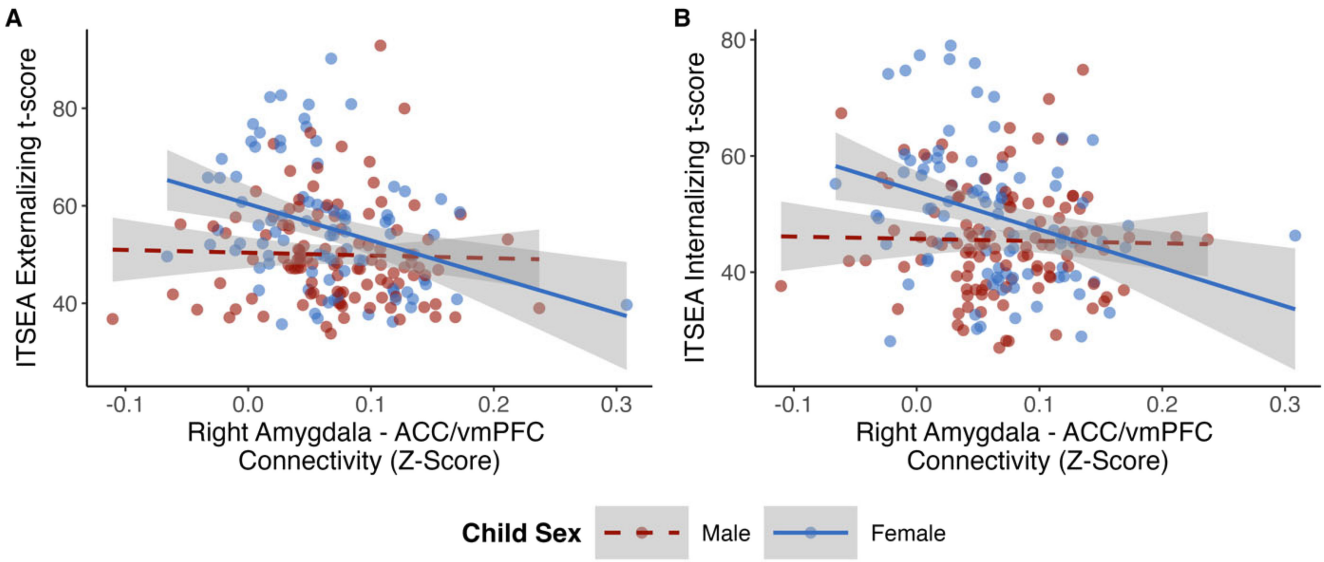



*Note.* (A) Extracted neonatal functional connectivity estimates between the right amygdala and the right precentral gyrus related to PSD were positively associated with infant internalizing behaviors at the 12-month follow-up assessment. (B) A similar positive association between internalizing symptoms at age 12 months with left hippocampus–right precentral gyrus connectivity associated with PSD was also observed. Mean maternal postnatal depression symptoms were a covariate in each model. The ITSEA internalizing t score is normed for age and sex. Individual data points represent raw data with the model-predicted trend plotted with a confidence envelope representing the 95% confidence interval. PSD = prenatal social disadvantage; ITSEA = Infant–Toddler Social and Emotional Assessment. See the online article for the color version of this figure.

pregnancy with fetal connectivity of the amygdala and hippocampus. Fetal amygdala–prefrontal cortex connectivity has been positively associated with maternal childhood maltreatment exposure while hippocampus–prefrontal cortex connectivity has been positively and negatively associated with state anxiety during gestation (De Asis-Cruz et al., 2020; Hendrix et al., 2022; van den Heuvel et al., 2023).

**Figure 4**

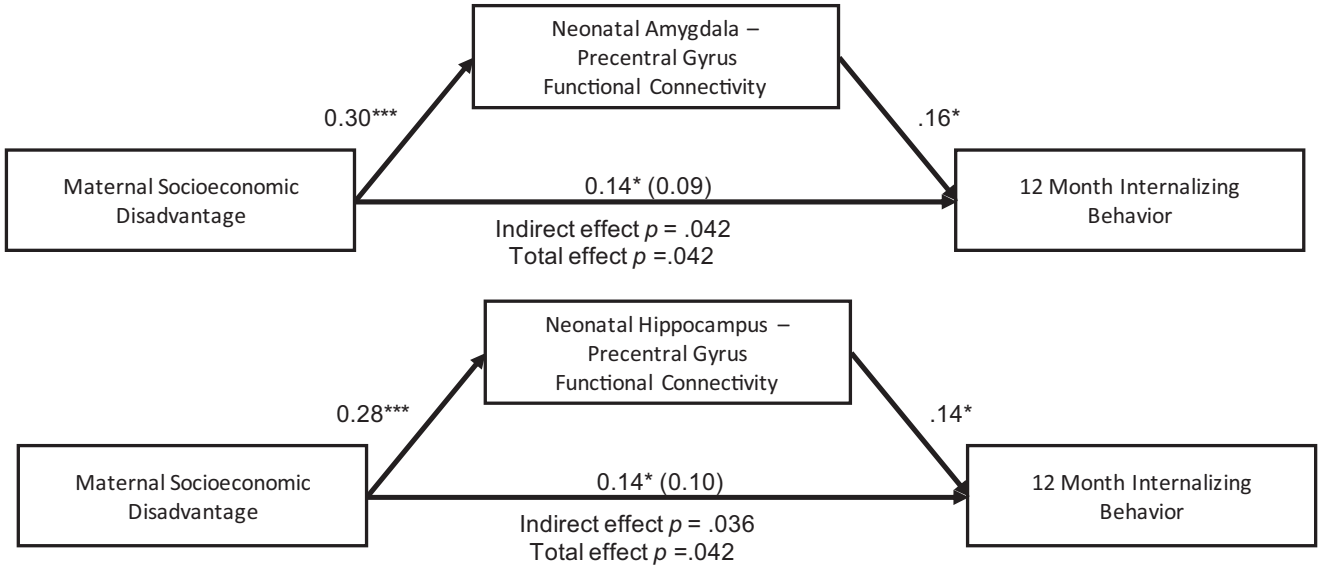
*Infant Externalizing and Internalizing Symptoms as a Function of Right Amygdala Functional Connectivity*




*Note.* Neonatal right ACC and vmPFC connectivity related to PSD is negatively associated with externalizing (A) and internalizing (B) scores in female, but not male infants. Individual data points represent raw data with the model-predicted trend plotted with a confidence envelope representing the 95% confidence interval. ITSEA = Infant–Toddler Social and Emotional Assessment; ACC = anterior cingulate cortex; vmPFC = ventromedial prefrontal cortex; PSD = prenatal social disadvantage. See the online article for the color version of this figure.

**Figure 5**

*Mediation Diagrams of Functional Connectivity Mediating the Association Between Prenatal Disadvantage and Infant Internalizing*




*Note.* Longitudinal mediation models investigating whether neonatal right amygdala connectivity with the right precentral gyrus (top panel) and neonatal left hippocampus connectivity with the right precentral gyrus (bottom panel) mediates the association between PSD and internalizing behavior at age 12 months. Coefficients are standardized beta estimates with the c′ path in parentheses. A bootstrapping analysis with 1,000 simulations was used to generate *p* values when controlling for maternal postnatal depression symptoms. PSD = prenatal social disadvantage.
* $p < .05$. *** $p < .001$.



Despite inconsistency in the direction of effect, these previously reported results support the notion that maternal stress during pregnancy is associated with fetal functional connectivity development. The direction of results in amygdala–ventromedial prefrontal/dorsal anterior cingulate cortex connectivity and infant behavior observed in this study, in contrast, were consistent with our expectations. Prior literature in older populations has established the structure, function, and connectivity of the amygdala as being sensitive to stressful environments and has linked these characteristics with behavioral development that may confer risk for later psychopathology (Gee & Casey, 2015; Gee et al., 2013; Heleniak et al., 2016; McEwen et al., 2016; Smith & Pollak, 2020). Future research that continues to characterize the impacts of prenatal exposures on infant functional connectivity, including improved characterization of normative trajectories of connectivity development is needed to better understand these effects in the context of the literature.

With one exception, the prior literature linking prenatal environmental conditions to neonatal functional connectivity has not assessed the subsequent behavioral consequences of this association, which is a crucial step toward generating clinically translatable solutions. Our results are a first step toward filling this gap in the literature as the PSD-related right amygdala–ventromedial prefrontal/dorsal anterior cingulate cortex functional connectivity was subsequently negatively associated with both externalizing and internalizing symptoms 12 months later. Left hippocampus connectivity with the right inferior frontal gyrus was also negatively associated with PSD but was not associated with infant behavior at age 12 months. In prior literature examining the links between neonatal connectivity with infant behavior, amygdala connectivity with several regions, including medial frontal cortex was positively associated with internalizing symptoms at 2 years of age in a sample of full-term or very preterm infants (Rogers et al., 2017). In another sample of very preterm neonates, amygdala functional connectivity with regions of occipital cortex, the parahippocampal gyrus, and the thalamus was associated with a factor score encompassing negative affectivity and effortful control at a 5-year follow-up (Kanel et al., 2022). While these prior findings converge with our results to demonstrate the predictive role of neonatal amygdala functional connectivity for infant externalizing and internalizing behavior development, the possibility of preceding environmental effects was not directly assessed. Like our study, one prior study has demonstrated that neonatal amygdala connectivity with the prefrontal cortex associated with prenatal maternal stress (as indexed by cortisol) was associated with subsequent internalizing behavior, with this connectivity mediating the association between maternal prenatal stress and symptoms in female infants only (Graham et al., 2019). Our results also indicated female-specific effects, though unlike the previous research, these effects were specific to the association between neonatal functional connectivity and subsequent externalizing and internalizing behavior. While some previous literature has suggested sex differences in the vulnerability to psychopathology following prenatal stress exposure (Hicks et al., 2019; Hodes & Epperson, 2019), more research is needed to fully understand the implications of the sex differences in the association between neonatal functional connectivity and psychopathology-related behaviors observed here.

Unlike the frontolimbic results, the effects of PSD on right amygdala and left hippocampus functional connectivity with the precentral gyrus and subsequent associations with infant internalizing were not

expected outcomes. The precentral gyrus is a critical component of the somatomotor system and has been shown to be functionally connected with the amygdala early in infant development (Gabard-Durnam et al., 2018; Qiu et al., 2015). Connectivity between the amygdala and precentral gyrus has previously been shown to be negatively associated with maternal prenatal anxiety (Donnici et al., 2021). Furthermore, preliminary evidence suggests that greater neonatal amygdala connectivity with a number of regions including the precentral gyrus is associated with higher levels of infant fearfulness at age 6 months (Graham et al., 2016), consistent with the brain–behavior associations observed in this study. Other prior literature has shown the opposite pattern, that increasing amygdala connectivity with sensorimotor regions is associated with fewer internalizing symptoms, though the behavioral assessments occurred later in development than those examined here (2 and 4 years of age, respectively; Rogers et al., 2017; Salzwedel et al., 2019). Later in development, differences in the functional connectivity between the amygdala and precentral gyrus have also been observed between youth with bipolar disorder and autism spectrum disorder (Fishman et al., 2018; Singh et al., 2015), further supporting a potentially impactful role for the connectivity of these two regions for adaptive behavioral development. Substantially less is known about hippocampus–precentral gyrus connectivity during the perinatal period and its associations with behavioral development. Future research dedicated to addressing this gap may be an important step toward understanding the associations between limbic functional connectivity and adaptive development across development.

In addition to the main effects observed between PSD, amygdala and hippocampus connectivity, and infant externalizing and internalizing behavior, we also observed significant mediation effects. These results indicated that increasing PSD is associated with infant internalizing symptoms at age 12 months via increased connectivity between the right amygdala and left hippocampus with the precentral gyrus. This result is in the same direction as the results of Graham et al. (2016) discussed above, as increasing connectivity was associated with greater levels of internalizing symptoms including infant fearfulness. Our results extend this prior finding to include the prenatal maternal exposures and elucidate one potential mechanistic pathway by which PSD may lead to increased risk for psychopathology in infants and children. Research replicating this result and investigating interventions that target this series of relations will be important next steps toward facilitating healthy development for youth whose caregivers experience social disadvantage.

Taken together, our findings relating PSD with neonatal connectivity and subsequent behavior suggest heterogenous effects of prenatal exposures on functional connectivity and distinct implications for developmental trajectories of adaptation and risk. The frontolimbic effects observed here, including negative associations between PSD and functional connectivity within the circuit are consistent with prior literature and further suggest that differences in frontolimbic connectivity may be a female-specific risk factor for externalizing and internalizing symptoms in infancy. In contrast, the association between PSD and the functional connectivity of the amygdala and hippocampus with the precentral gyrus was positive and appeared to play a mechanistic role in the conferral of risk from maternal prenatal exposures to behavioral development in male and female infants alike. These opposing effects in connectivity with the prefrontal cortex and motor-related areas are particularly interesting in the context of early psychopathology given the rapid development of the motor symptoms early in life, suggesting that rapidly developing circuits may be especially important for understanding perinatal psychopathology risk. The prenatal period has been emphasized as a particularly sensitive period in which signals from the maternal environment can affect the developing fetus, with implications for postnatal physical and behavioral health (Monk et al., 2019; Sandman et al., 2016). Our results align closely with this conceptualization of prenatal development and provide a plausible mechanism by which PSD is associated with early infant internalizing behaviors, an early risk factor for later maladaptive outcomes (Cicchetti & Toth, 1998; Luby, 2010). Importantly, these and other prior findings emphasize the potentially large impact that policy or care interventions focused on providing positive environmental contexts to gestating persons could have on infant neurobehavioral outcomes. Furthermore, it is important to note that effects related social disadvantage should not be seen as evidence of inherent poverty-related deficits but instead the profound impact that the environmental exposures associated with poverty (e.g., food insecurity, neighborhood crime, and disrupted sleep) can have on the developing child.

Several limitations should also be considered when interpreting the results presented in this study. As mentioned previously, it is still unclear what the normative maturational trajectories of functional connectivity are across early development, making it difficult to interpret the direction of the effects reported here. Future research will be needed to better characterize the normative maturational course of functional connectivity in the perinatal period to clarify whether stronger frontolimbic connectivity is consistently associated with more adaptive behavior in infancy. While the social disadvantage score used here incorporated several domains of socioeconomic context, it may obscure specific effects associated with maternal nutrition, exposure to environmental toxins, or disruptions to maternal and infant sleep. More specific assessment of these environmental and individual factors may be an important component of generating translational evidence for the associations between the perinatal environment, brain function, and infant mental health. In addition, the subsample used to examine brain–behavior associations differed significantly from the neuroimaging sample on dimensions of social disadvantage, limiting the generalizability of these results to dyads without extremely high levels of social disadvantage. Furthermore, there was data loss from the larger study related to the need for high-quality neuroimaging data which may result in a healthier sample in the behavioral domains of interest. It should be noted, however, that the data loss due to other exclusion criteria (e.g., preterm birth, time in NICU, and brain injury) was much greater than the loss attributable to imaging data quality, a high retention rate that may be attributable, in part, to real-time monitoring of head motion during scanning. Finally, while we were able to adjust for maternal postnatal depression symptoms in our brain–behavior associations, no measure of maternal externalizing during the first year of life was available. In light of these limitations and the results presented here, two additional future directions for research emerge from the findings in this study. While we did find a significant mediating role for amygdala and hippocampus functional connectivity in the relationship between PSD and infant internalizing behavior at 12 months, future research in large, longitudinal samples should formally investigate whether other neonatal neurodevelopmental metrics can be identified as mechanisms that give rise to psychopathology risk early in life at extremely low levels

of disadvantage. It will also be important for future research investigating prenatal impacts on neonatal functional connectivity and subsequent behavior to consider additional individual differences factors, such as genetic or heritable risk, as important moderators of the pathway from prenatal exposure to postnatal risk for, or protection from, psychopathology.

The results of this study reveal associations between PSD, neonatal amygdala and hippocampus functional connectivity, and subsequent infant externalizing and internalizing behavior. Along with a growing body of literature, these results continue to emphasize the importance of PSD in shaping infant brain and behavior development. Given that early externalizing and internalizing problems may portend risk for future psychopathology, and that our results indicate a mechanistic pathway extending from social disadvantage to internalizing symptoms through amygdala and hippocampus connectivity with the precentral gyrus, it is important that future research investigate approaches to ameliorating the risk that may be conferred by high levels of social disadvantage. Better understanding of these effects may provide the foundation needed to develop more specific intervention targets during the prenatal period, whether socioeconomic or psychosocial, that will contribute to improving infant and child neurobehavioral outcomes.



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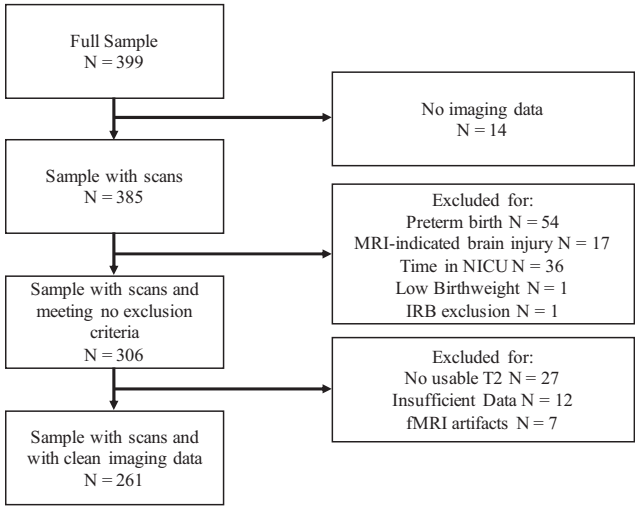
## Appendix

## Missing Data Accounting and Additional Tables and Figures

**Figure A1**

*Diagram of Exclusion Reasons From the Full eLABE Sample to the Functional Imaging Subsample Included in the Current Study*

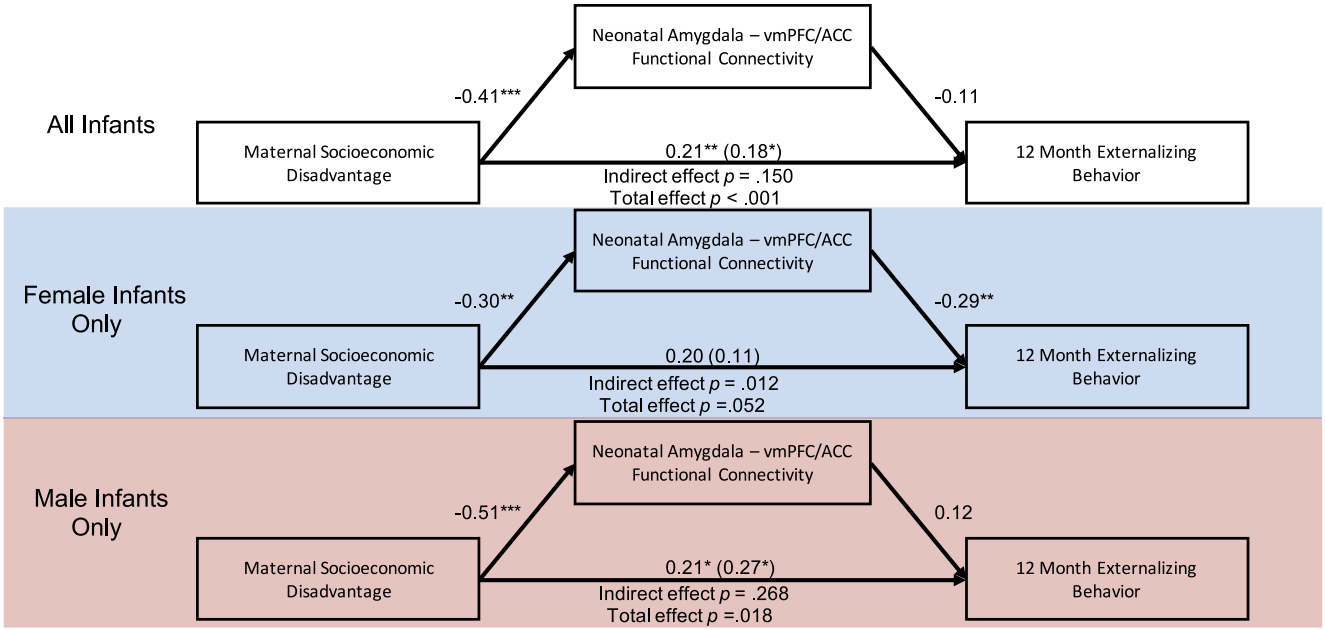



*Note.* The sample used in this study was a subset of a larger prospective longitudinal study that included 399 mother–infant dyads. Of those, 261 provided usable imaging data and did not meet criteria for nonimaging exclusions. Exclusion criteria overlapped in some infants. MRI = magnetic resonance imaging; NICU = neonatal intensive care unit; IRB = Institutional Review Board; T2 = structural MRI scan; fMRI = functional magnetic resonance imaging.

(*Appendix continues*)

**Figure A2**

*Mediation Diagrams of Functional Connectivity Mediating the Association Between Prenatal Disadvantage and Infant Externalizing by Sex*

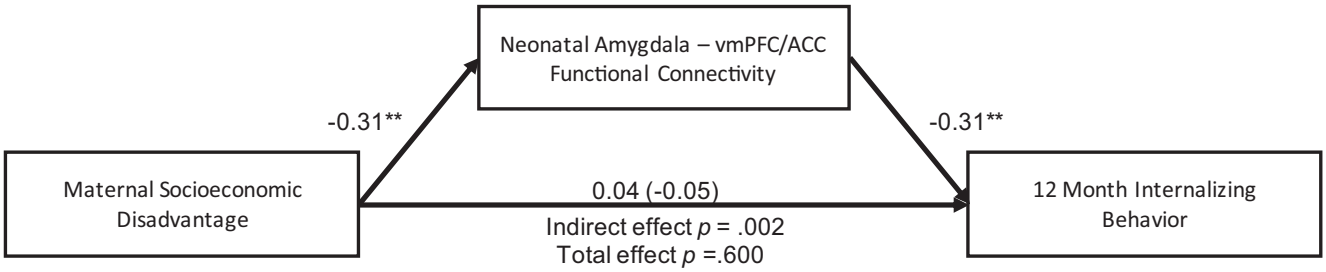



*Note.* Longitudinal mediation models investigating whether neonatal right amygdala connectivity mediates the association between maternal prenatal socioeconomic advantage and externalizing behavior at age 12 months in all infants (top panel), female infants only (middle panel), and male infants (bottom panel) only. Coefficients are standardized beta estimates with the c′ path in parentheses. A bootstrapping analysis with 1,000 simulations was used to generate p values when controlling for maternal postnatal depression symptoms. ACC = anterior cingulate cortex; vmPFC = ventromedial prefrontal cortex. See the online article for the color version of this figure.

* $p < .05$. ** $p < .01$. *** $p < .001$.

**Figure A3**

*Longitudinal Mediation Model Investigating Whether Neonatal Right Amygdala Connectivity Mediates the Association Between Maternal Prenatal Socioeconomic Advantage and Internalizing Behavior at Age 12 Months in Female Infants Only*




*Note.* Coefficients are standardized beta estimates with the $c'$ path in parentheses. A bootstrapping analysis with 1,000 simulations was used to generate $p$ values when controlling for maternal postnatal depression symptoms. ACC = anterior cingulate cortex; vmPFC = ventromedial prefrontal cortex.

** $p < .01$.

(*Appendix continues*)

**Table A1**
*Correlations Amongst All Predictor Variables*

| Variable | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| 1. Disadvantage factor | — | | | | | | | | |
| 2. Right amygdala–dACC/vmPFC rsFC | −.38** [−.48, −.27] | — | | | | | | | |
| 3. Left hippocampus–IFG rsFC | −.29** [−.39, −.17] | .32** [.20, .42] | — | | | | | | |
| 4. Left hippocampus–precentral gyrus rsFC | .32** [.20, .42] | −.29** [−.40, −.18] | −.23** [−.34, −.11] | — | | | | | |
| 5. Postmenstrual age at scan | −.21** [−.32, −.09] | .01 [−0.11, 0.13] | −.08 [−0.20, 0.04] | −.13* [−.25, −.01] | — | | | | |
| 6. Infant sex | .04 [−0.08, 0.16] | −.09 [−0.21, 0.04] | −.07 [−0.19, 0.05] | .09 [−0.03, 0.21] | −.08 [−0.20, 0.04] | — | | | |
| 7. Infant birthweight | −.33** [−.44, −.22] | .06 [−0.06, 0.18] | −.04 [−0.17, 0.08] | −.08 [−0.20, 0.04] | .21** [.09, .32] | −.11 [−0.23, 0.01] | — | | |
| 8. ITSEA internalizing *t* score | .16* [.02, .29] | −.19** [−.32, −.05] | .05 [−0.09, 0.19] | .18** [.05, .31] | .08 [−0.06, 0.21] | .20** [0.06, 0.33] | −.01 [−0.15, 0.12] | — | |
| 9. ITSEA externalizing *t* score | .22** [.09, .35] | −.20** [−.33, −.06] | −.07 [−0.20, 0.07] | .07 [−0.07, 0.21] | .04 [−0.10, 0.18] | .24** [.11, .37] | −.15* [−.29, −.01] | .49** [.37, .59] | — |
| 10. Maternal depression score | .14* [.02, .26] | −.01 [−0.14, 0.12] | −.09 [−0.21, 0.04] | .07 [−0.06, 0.19] | .04 [−0.08, 0.17] | .14* [.02, .27] | .03 [−0.09, 0.16] | .28** [.14, .40] | .22** [.08, .35] |

*Note*. Values in square brackets indicate the 95% confidence interval for each correlation. dACC = dorsal anterior cingulate cortex; vmPFC = ventromedial prefrontal cortex; IFG = inferior frontal gyrus; rsFC = resting-state functional connectivity; ITSEA = Infant–Toddler Social and Emotional Assessment.
* $p < .05$. ** $p < .01$.

**Table A2**
*Demographics of Participants With and Without ITSEA Scores*

| Variable | With ITSEA ($N = 197$) | Without ITSEA ($N = 64$) | *p* |
|---|---|---|---|
| Infant sex | | | |
| Male | 110 (55.8%) | 31 (48.4%) | .37 |
| Female | 87 (44.2%) | 33 (51.6%) | |
| First trimester INR | | | |
| *M* (*SD*) | 3.30 (3.24) | 1.82 (2.11) | <.01 |
| Median (min, max) | 1.63 (0.430, 12.2) | 1.21 (0.440, 9.92) | |
| Missing | 5 (2.5%) | 4 (6.3%) | |
| Socioeconomic disadvantage factor score | | | |
| *M* (*SD*) | −0.180 (1.02) | 0.330 (0.703) | <.01 |
| *Mdn* (min, max) | 0.110 (−2.15, 1.47) | 0.580 (−1.83, 1.14) | |
| Caregiver education | | | |
| <12th grade | 15 (7.6%) | 5 (7.8%) | <.01 |
| High school degree/GED | 82 (41.6%) | 41 (64.1%) | |
| Some college/vocational school | 31 (15.7%) | 5 (7.8%) | |
| College degree (4 years) | 50 (25.4%) | 3 (4.7%) | |
| Missing | 19 (9.6%) | 10 (15.6%) | |
| Infant postmenstrual age at scan (weeks) | | | |
| *M* (*SD*) | 41.4 (1.23) | 41.3 (1.46) | .97 |
| Median (min, max) | 41.0 (38.0, 45.0) | 41.5 (38.0, 44.0) | |
| Infant birthweight (grams) | | | |
| *M* (*SD*) | 3,290 (493) | 3,240 (484) | .49 |
| *Mdn* (min, max) | 3,220 (2,200, 4,630) | 3,160 (2,280, 4,610) | |
| Missing | 0 (0%) | 1 (1.6%) | |
| race/ethnicity | | | |
| Black | 107 (54.3%) | 50 (78.1%) | .01 |
| White | 84 (42.6%) | 14 (21.9%) | |
| Asian | 2 (1.0%) | 0 (0%) | |
| Native Hawaiian/Pacific Islander | 0 (0%) | 0 (0%) | |
| American Indian/Alaskan Native | 0 (0%) | 0 (0%) | |
| Other | 4 (2.0%) | 0 (0%) | |
| Maternal postnatal depression | | | |
| *M* (*SD*) | 5.52 (4.01) | 6.23 (5.26) | .39 |
| *Mdn* (min, max) | 5.50 (0, 18.0) | 4.50 (0, 21.0) | |
| Missing | 2 (1.0%) | 16 (25.0%) | |

*Note.* Significant *p* values indicate meaningful differences between groups with and without ITSEA scores. Statistics were generated using *t* tests for continuous outcome measures while categorical outcomes were assessed using chi-square tests. ITSEA = Infant–Toddler Social and Emotional Assessment; min = minimum; max = maximum; INR = income-to-needs ratio; GED = general educational diploma.

(*Appendix continues*)

**Table A3**
*Regression Model Predicting Infant Externalizing at Age 12 Months*

| Parameter | Standardized beta | *SE* | 95% CI | Statistic | *p* |
|---|---|---|---|---|---|
| Intercept | .000 | 1.714 | [−0.1363, 0.1363] | 30.135 | <.001 |
| Amygdala–ACC/vmPFC connectivity | −.177 | 14.231 | [−0.3144, −0.0405] | −2.556 | .011 |
| Postnatal EPDS score | .205 | 0.203 | [0.0685, 0.3423] | 2.959 | .003 |

*Note.* CI = confidence interval; ACC = anterior cingulate cortex; vmPFC = ventromedial prefrontal cortex; EPDS = Edinburgh Postnatal Depression Scale.

**Table A4**
*Regression Model Predicting Infant Internalizing at Age 12 Months*

| Parameter | Standardized beta | *SE* | 95% CI | Statistic | *p* |
|---|---|---|---|---|---|
| Intercept | .000 | 1.550 | [−0.1337, 0.1337] | 29.338 | <.001 |
| Amygdala–ACC/vmPFC connectivity | −.161 | 12.860 | [−0.2956, −0.0269] | −2.367 | .019 |
| postnatal EPDS score | .268 | 0.182 | [0.1341, 0.4028] | 3.941 | <.001 |

*Note.* CI = confidence interval; ACC = anterior cingulate cortex; vmPFC = ventromedial prefrontal cortex; EPDS = Edinburgh Postnatal Depression Scale.

**Table A5**
*Regression Model Predicting Infant Externalizing at Age 12 Months*

| Parameter | Standardized beta | *SE* | 95% CI | Statistic | *p* |
|---|---|---|---|---|---|
| Intercept | .000 | 1.488 | [−0.1382, 0.1382] | 33.325 | <.001 |
| Amygdala–precentral gyrus connectivity | .073 | 15.227 | [−0.0669, 0.2121] | 1.027 | .306 |
| postnatal EPDS score | .208 | 0.206 | [0.0686, 0.3476] | 2.943 | .004 |

*Note.* CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale.

**Table A6**
*Regression Model Predicting Infant Internalizing at Age 12 Months*

| Parameter | Standardized beta | *SE* | 95% CI | Statistic | *p* |
|---|---|---|---|---|---|
| Intercept | .000 | 1.321 | [−0.1332, 0.1332] | 33.682 | <.001 |
| Amygdala–precentral gyrus connectivity | .183 | 13.409 | [0.0485, 0.3176] | 2.683 | .008 |
| Postnatal EPDS score | .257 | 0.182 | [0.122, 0.3911] | 3.761 | <.001 |

*Note.* CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale.

**Table A7**
*Regression Model Predicting Infant Externalizing at Age 12 Months*

| Parameter | Standardized beta | *SE* | 95% CI | Statistic | *p* |
|---|---|---|---|---|---|
| Intercept | .000 | 1.581 | [−0.1385, 0.1385] | 31.285 | <.001 |
| Left hippocampus–IFG connectivity | −.038 | 14.356 | [−0.1797, 0.103] | −0.536 | .593 |
| Postnatal EPDS score | .209 | 0.209 | [0.0679, 0.3506] | 2.919 | .004 |

*Note.* CI = confidence interval; IFG = inferior frontal gyrus; EPDS = Edinburgh Postnatal Depression Scale.

**Table A8**
*Regression Model Predicting Infant Internalizing at Age 12 Months*

| Parameter | Standardized beta | *SE* | 95% CI | Statistic | *p* |
|---|---|---|---|---|---|
| Intercept | .000 | 1.424 | [−0.135, 0.135] | 29.765 | <.001 |
| Left Hippocampus–IFG connectivity | .096 | 12.917 | [−0.0417, 0.2342] | 1.376 | .171 |
| Postnatal EPDS score | .298 | 0.187 | [0.1599, 0.4359] | 4.258 | <.001 |

*Note.* CI = confidence interval; IFG = inferior frontal gyrus; EPDS = Edinburgh Postnatal Depression Scale.

(*Appendix continues*)

**Table A9**

*Regression Model Predicting Infant Externalizing at Age 12 Months*

| Parameter | Standardized beta | *SE* | 95% CI | Statistic | *p* |
|---|---|---|---|---|---|
| Intercept | .000 | 1.480 | [−0.1384, 0.1384] | 33.405 | <.001 |
| Left hippocampus–precentral gyrus connectivity | .058 | 11.884 | [−0.0817, 0.1967] | 0.815 | .416 |
| Postnatal EPDS score | .212 | 0.206 | [0.0725, 0.3509] | 3.000 | .003 |

*Note.* CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale.

**Table A10**

*Regression Model Predicting Infant Internalizing at Age 12 Months*

| Parameter | Standardized beta | *SE* | 95% CI | Statistic | *p* |
|---|---|---|---|---|---|
| Intercept | .000 | 1.317 | [−0.1334, 0.1334] | 33.692 | <.001 |
| Left hippocampus–precentral gyrus Connectivity | .172 | 10.598 | [0.0381, 0.3066] | 2.532 | .012 |
| Postnatal EPDS score | .265 | 0.182 | [0.1303, 0.3988] | 3.887 | <.001 |

*Note*. CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale.

**Table A11**

*Regression Model Predicting Infant Externalizing at Age 12 Months With Amygdala–ACC/vmPFC Connectivity Moderated by Child Sex*

| Parameter | Standardized beta | *SE* | 95% CI | Statistic | *p* |
|---|---|---|---|---|---|
| Intercept | −.010 | 3.837 | [−0.1424, 0.1221] | 10.058 | <.001 |
| Amygdala–ACC/vmPFC connectivity | −.161 | 42.672 | [−0.2941, −0.0283] | 1.582 | .115 |
| Child sex | .196 | 2.436 | [0.0614, 0.3309] | 3.803 | <.001 |
| Postnatal EPDS score | .167 | 0.199 | [0.0319, 0.3015] | 2.439 | .016 |
| Amygdala Connectivity × Child Sex | −.169 | 27.652 | [−0.3019, −0.037] | −2.523 | .012 |

*Note*. CI = confidence interval; ACC = anterior cingulate cortex; vmPFC = ventromedial prefrontal cortex; EPDS = Edinburgh Postnatal Depression Scale.

**Table A12**

*Regression Model Predicting Infant Internalizing at Age 12 Months With Amygdala–ACC/vmPFC Connectivity Moderated by Child Sex*

| Parameter | Standardized beta | *SE* | 95% CI | Statistic | *p* |
|---|---|---|---|---|---|
| Intercept | −.011 | 3.505 | [−0.1423, 0.1202] | 10.088 | <.001 |
| Amygdala–ACC/vmPFC connectivity | −.148 | 39.086 | [−0.2796, −0.0159] | 1.598 | .112 |
| Child sex | .137 | 2.219 | [0.0029, 0.271] | 3.200 | .002 |
| Postnatal EPDS score | .239 | 0.181 | [0.1045, 0.3726] | 3.510 | <.001 |
| Amygdala Connectivity × Child Sex | −.165 | 25.260 | [−0.2964, −0.0334] | −2.473 | .014 |

*Note*. CI = confidence interval; ACC = anterior cingulate cortex; vmPFC = ventromedial prefrontal cortex; EPDS = Edinburgh Postnatal Depression Scale.

**Table A13**

*Regression Model Predicting Infant Externalizing at Age 12 Months in Female and Male Infants Separately*

| Child sex | Parameter | Standardized beta | *SE* | 95% CI | Statistic | *p* |
|---|---|---|---|---|---|---|
| Female | Intercept | .000 | 2.670 | [−0.1943, 0.1943] | 20.503 | <.001 |
| | Amygdala–ACC/vmPFC connectivity | −.323 | 21.400 | [−0.5191, −0.1272] | −3.280 | .002 |
| | Postnatal EPDS score | .285 | 0.292 | [0.0889, 0.4807] | 2.891 | .005 |
| Male | Intercept | .000 | 2.092 | [−0.1915, 0.1915] | 23.796 | <.001 |
| | Amygdala–ACC/vmPFC connectivity | −.017 | 17.758 | [−0.2097, 0.1753] | −0.177 | .860 |
| | Postnatal EPDS score | .038 | 0.271 | [−0.1545, 0.2305] | 0.391 | .696 |

*Note*. CI = confidence interval; ACC = anterior cingulate cortex; vmPFC = ventromedial prefrontal cortex; EPDS = Edinburgh Postnatal Depression Scale.

(*Appendix continues*)

**Table A14**

*Regression Model Predicting Infant Internalizing at Age 12 Months in Female and Male Infants Separately*

| Child Sex | Parameter | Standardized beta | *SE* | 95% CI | Statistic | *p* |
|---|---|---|---|---|---|---|
| Female | Intercept | .000 | 2.450 | [−0.1886, 0.1886] | 19.285 | <.001 |
| | Amygdala–ACC/vmPFC connectivity | −.295 | 19.626 | [−0.4856, −0.1052] | −3.088 | .003 |
| | Postnatal EPDS score | .352 | 0.266 | [0.1615, 0.5419] | 3.676 | <.001 |
| Male | Intercept | .000 | 1.898 | [−0.1906, 0.1906] | 23.360 | <.001 |
| | Amygdala–ACC/vmPFC connectivity | −.005 | 16.114 | [−0.1967, 0.1866] | −0.052 | .959 |
| | Postnatal EPDS score | .104 | 0.246 | [−0.088, 0.2953] | 1.072 | .286 |

*Note*. CI = confidence interval; ACC = anterior cingulate cortex; vmPFC = ventromedial prefrontal cortex; EPDS = Edinburgh Postnatal Depression Scale.

**Table A15**

*Regression Model Predicting Infant Internalizing at Age 12 Months With Amygdala–Precentral Gyrus Connectivity Moderated by Child Sex*

| Parameter | Standardized beta | *SE* | 95% CI | Statistic | *p* |
|---|---|---|---|---|---|
| Intercept | −.017 | 2.548 | [−0.1496, 0.1157] | 15.331 | <.001 |
| Amygdala–precentral gyrus connectivity | .173 | 40.621 | [0.0394, 0.3068] | −0.980 | .328 |
| Child sex | .126 | 1.606 | [−0.0093, 0.2611] | 2.461 | .015 |
| Postnatal EPDS score | .223 | 0.183 | [0.0874, 0.3583] | 3.244 | 0.001 |
| Amygdala Connectivity × Child Sex | .129 | 26.820 | [−0.0047, 0.2636] | 1.903 | .058 |

*Note*. CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale.

**Table A16**

*Regression Model Predicting Infant Internalizing at Age 12 Months With Hippocampus–Precentral Gyrus Connectivity Moderated by Child Sex*

| Parameter | Standardized beta | *SE* | 95% CI | Statistic | *p* |
|---|---|---|---|---|---|
| Intercept | −.005 | 2.541 | [−0.1374, 0.1279] | 15.509 | <.001 |
| Hippocampus–precentral gyrus connectivity | .173 | 31.813 | [0.0389, 0.307] | −0.203 | .839 |
| Child sex | .138 | 1.636 | [0.0029, 0.2736] | 2.285 | .023 |
| Postnatal EPDS score | .233 | 0.184 | [0.0968, 0.3687] | 3.376 | <.001 |
| Hippocampus Connectivity × Child Sex | .074 | 21.488 | [−0.0618, 0.2096] | 1.074 | .284 |

*Note*. CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale.

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