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Maternal Childhood Adversity Associates With Frontoamygdala Connectivity in Neonates

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ABSTRACT

BACKGROUND: It is well established that exposure to adversity, especially during sensitive periods of development such as childhood, has both behavioral (e.g., increasing one's risk for psychiatric illnesses) and neurobiological consequences. But could these effects of early-life exposure to adversity also be transmitted across generations? We directly address this question, investigating the associations between maternal exposure to adversity during her own childhood and neural connectivity in her neonate.

METHODS: Mothers from a sample of Black mother–neonate dyads (n = 48)—a group that is disproportionately affected by early-life adversity—completed questionnaires assessing their current distress (i.e., a composite measure of anxiety, depression, and perceived stress) during the first and third trimesters of pregnancy and retrospectively reported on their own childhood experiences of abuse and neglect. At 1 month postpartum, neonatal offspring of these women underwent a resting-state functional magnetic resonance imaging scan during natural sleep.

RESULTS: Greater maternal exposure to emotional neglect during her own childhood correlated with stronger functional connectivity of two different frontoamygdala circuits in these neonates, as early as 1 month after birth. This effect was specific to early experiences of emotional neglect and was not explained by maternal exposure to other forms of childhood maltreatment or by maternal distress during pregnancy.

CONCLUSIONS: These results provide novel evidence that the absence of emotional support early in a mother's life, years before conception, are associated with neural changes—namely, in functional connectivity between the amygdala and medial prefrontal regions—in her offspring shortly after birth.

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Early-life adversity is linked to a number of negative health outcomes in one's own life, including increased risk for neuropsychiatric illnesses such as depression and anxiety (1). This risk is conferred in part via adversity-induced alterations in the hypothalamic-pituitary-adrenal (HPA) axis, one of the body's main stress response systems. Although some of these alterations are adaptive in the context of an acute stressor, persistent HPA axis alterations can have detrimental long-term effects, including increased risk for psychiatric illness (2). Moreover, HPA axis alterations may have particularly potent effects if they occur early in life, for instance, as a consequence of parental deprivation or other adverse experiences during childhood (3).

Recent behavioral work suggests that adversity-associated risk may additionally be transmitted across generations, even if the stress occurs years before a child is born (4). For example, maternal experiences of physical and sexual abuse during her own childhood increase her child's risk for anxiety (5). In addition, maternal exposure to adversity early in life further predicts altered HPA axis functioning both in abused mothers and in their infants (6). Together, this work suggests that adversity occurring years before a child is born can influence that child's neuropsychiatric risk from very early in life. Thus, to create effective preventative interventions, understanding how adversity becomes biologically embedded to increase risk for neuropsychiatric disorders across generations is of the utmost importance.

The fetal stage of development has been proposed as a time when the intergenerational transmission of early-life adversity in the mother may be particularly likely to occur (7,8). Early-life adversity may lead to long-term alterations in an individual's HPA axis, immune functioning, and epigenome, all of which may have cascading effects on the eventual uterine environment in which a fetus develops during gestation. These biological alterations may lead to increased fetal exposure to circulating glucocorticoids, the final hormonal output of the HPA axis. In turn, fetal brain development, which occurs rapidly across gestation, may be affected, particularly in regions that are rich in glucocorticoid receptors (e.g., the amygdala and the medial prefrontal cortex (mPFC). Although this theoretical model clearly identifies the intrauterine environment as a developmental stage when early-life adversity in mothers may influence offspring development, empirical work is needed to provide support for this model of transmission in

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humans and to identify the biological sequelae of inheriting maternal adversity.

Of particular importance, it has been difficult to tease apart the influence of adversity that occurred during a mother's childhood from the effects of prenatal adversity or adversity that occurs during the child's lifetime. Preventative interventions depend on our understanding of how timing and type of maternal stress exposure affect child risk; similarly, determining how early in development we can observe the effects of maternal adversity on child stress regulation and emotional development is necessary, given that these are early precursors of neuropsychiatric health (9). Fortunately, recent technological advances in functional magnetic resonance imaging (fMRI), such as resting-state fMRI (rsfMRI), can aid in this effort by enabling us to noninvasively examine brain functioning very early in life. The use of this methodology with neonates who have limited postnatal exposures additionally allows us to better parse the respective roles of maternal preconception, prenatal, and postnatal stress in shaping child development.

At least one recent study found that maltreatment during a mother's childhood correlated with global volumetric differences in the brains of newborn babies, even after controlling for prenatal experiences of stress and depression (10). This work raises the possibility that experiencing adversity during a sensitive period of development (i.e., a mother's own childhood) could have potent intergenerational effects that are not fully explained by continued stress into the perinatal period or by the child's postnatal exposure to maltreatment-induced parenting alterations. Additional studies are needed to replicate this effect and, importantly, to determine whether maternal early-life adversity affects brain function into the next generation, especially because certain disorders may result from impaired functional circuitry rather than from gross volumetric differences (11). Determining whether any observable effects are driven by particular types of childhood adversity (e.g., neglect vs. abuse) is also necessary to better understand potential moderators of risk transmission.

Using a prospective longitudinal design and rsfMRI in neonates as young as 1 month, we asked just these questions, examining whether and how different maternal experiences of adversity during childhood yield intergenerational effects on neonatal frontoamygdala connectivity, a circuit that is often disrupted in the context of depression and anxiety. Specifically, we examined amygdala connectivity with two distinct regions within the mPFC—the dorsal anterior cingulate cortex (dACC) and the ventromedial PFC (vmPFC). We selected these regions for two primary reasons. First, they share differential connections to the amygdala (12) and may be affected differentially by maternal prenatal distress (13). For instance, higher levels of maternal prenatal depression have been linked to stronger amygdala–dACC connectivity but weaker amygdala–vmPFC connectivity in sleeping neonates (13). Second, these mPFC regions are functionally distinct (14) and likely support different aspects of stress processing. As an example, functional connectivity (FC) between the amygdala and the dACC increases during fear acquisition in adults (15), and enhanced amygdala–vmPFC connectivity is linked to inhibited fear learning (16). Whether maternal childhood adversity differentially associates with this neural circuitry in neonates has not yet been tested—the very question asked here.

METHODS AND MATERIALS

Participants

Mothers were recruited from an ongoing longitudinal study that follows Black women through pregnancy (R01NR014800) (17) and across the first 18 months postpartum (R01MD009746) (18). Women were recruited for the larger ongoing study during the first trimester of pregnancy (mean = 11.5 weeks; SD = 2.5) from a public hospital and a private hospital in the Atlanta area, resulting in a socioeconomically diverse sample (Table 1). Most of the women (>85%) additionally completed a second prenatal visit during the late second/early third trimester (mean = 26.4 weeks; SD = 2.7). Forty-eight mother–neonate dyads (n = 27 female infants) enrolled in the current study, which involved the neonate completing a 30-minute MRI scan at approximately 1 month postpartum (mean = 40 days; SD = 15). Seven enrolled dyads were excluded from final analyses owing to unusable data (Figure 1), resulting in a final sample size of 41 neonates. As shown in Table 1, no differences were found in demographics or on measures of maternal adversity between dyads who were and were not included in final analyses.

Measures

Maternal Childhood Adversity. Mothers' experiences of childhood adversity were assessed via retrospective report during the first trimester of pregnancy, using the Childhood Trauma Questionnaire–Short Form (CTQ) (19). The CTQ comprises five subscales: Sexual Abuse, Physical Abuse, Emotional Abuse, Physical Neglect, and Emotional Neglect. High scores are indicative of more severe neglect and abuse.

Nearly 45% (n = 21) of women in the sample experienced at least one form of moderate to severe abuse or neglect during childhood, which is consistent with national prevalence rates of childhood trauma exposure among Black women (20). Although experiences of neglect were common in this sample, few women reported childhood physical, emotional, or sexual abuse, resulting in restricted range for these variables (Figure S1). As such, these variables were dichotomized and combined into a single variable that reflected whether a mother was the victim of any sexual, physical, or emotional abuse as a child (21). In contrast, physical neglect and emotional neglect showed a broad range in our sample and were therefore used in their continuous form to examine potential dosage effects.

Maternal Prenatal Stress. Maternal prenatal distress was measured via multiple self-report measures that were completed during the first trimester of pregnancy and again during the third trimester. The Perceived Stress Scale assesses the degree of stress an individual perceives in their current life and has demonstrated construct validity (22–24). Mothers also completed the Spielberger State-Trait Anxiety Inventory, a 20-item measure that assesses state and trait-like anxiety and stress (25,26). Finally, mothers completed the Edinburgh Depression Scale to assess current depressive symptoms (27). A composite prenatal distress variable was

Table 1. Demographics of Sample and Differences Between Included and Excluded Dyads

Variable	Included in Final Sample (n = 41)	Excluded[a] (n = 7)
Demographics		
Gestational age at birth, weeks	38.7 (1.4)	38.5 (2.1)
Preterm	3 (7.3%)	1 (14.3%)
Infant gestational age at scan, weeks	44.5 (2.8)	44.2 (0.9)
Infant age at scan, days	41.2 (17.1)	40.9 (15.8)
Infant sex, female	23 (56.1%)	5 (71.4%)
Cohabitating with partner	16 (39.0%)	2 (28.6%)
Mother race, Black	41 (100%)	7 (100%)
Mother education, some college or more	13 (31.7%)	2 (28.6%)
Insurance type, low-income Medicaid	8 (19.5%)	0 (0%)
Maternal Childhood Adversity		
CTQ emotional neglect	9.9 (5.5)	9.4 (5.2)
CTQ physical neglect	8.2 (3.6)	6.4 (2.7)
CTQ sexual abuse	6.9 (4.3)	11.7 (9.2)
CTQ physical abuse	6.8 (2.8)	7.4 (1.8)
CTQ emotional abuse	6.8 (4.2)	9.9 (6.9)
CTQ overall score	38.9 (15.6)	44.9 (23.4)
CTQ any moderate to severe abuse or neglect	20 (48.8%)	3 (42.9%)
CTQ any sexual, physical, or emotional abuse	15 (36.6%)	4 (57.1%)
Maternal Prenatal Distress		
First trimester EDS	7.1 (5.8)	5.6 (5.4)
First trimester PSS	23.0 (7.8)	19.4 (6.2)
First trimester STAI	33.4 (11.1)	30.3 (10.8)
Third trimester EDS	7.6 (5.6)	6.2 (8.7)
Third trimester PSS	22.9 (7.0)	21.6 (10.7)
Third trimester STAI	34.3 (10.7)	33.2 (11.3)

Values are presented as mean (SD) or n (%). There were no significant differences between mother–infant dyads who were and were not included in the final analyses. Preterm birth was defined as less than 37 weeks' gestational age.

CTQ, Childhood Trauma Questionnaire; EDS, Edinburgh Depression Scale; FD, framewise displacement; MRI, magnetic resonance imaging; PSS, Perceived Stress Scale; STAI, State-Trait Anxiety Inventory.

[a]Dyads were excluded from the final sample because they did not sleep through the MRI scan (n = 2), they had too much motion during the scan (>1 mm FD, n = 2), data were lost owing to technical malfunction (n = 1), or there was an incidental finding that indicated non-normative neural development (n = 2).

created from these three measures of prenatal adversity by standardizing and averaging the total score of the Perceived Stress Scale, Spielberger State-Trait Anxiety Inventory, and Edinburgh Depression Scale. The creation of this composite score was based on a principal components analysis completed with the full prenatal study cohort ($n > 500$) (17) and visual inspection of correlations between the Perceived Stress Scale, Edinburgh Depression Scale, and Spielberger State-Trait Anxiety Inventory (Table 2). A number of our infants (n = 33) were not included in the principal components analysis, so we validated our composite score in the larger prenatal cohort by correlating our composite score with the composite scores produced by the principal components analysis. The two composite scores were highly correlated ($r > .99$).

Infant MRI. All scanning procedures were completed by two trained research assistants and an MRI technician (see Supplemental Methods). While the infant was in natural sleep, the following scans were collected using a standard 32-channel head matrix coil: at least one echo planar imaging resting-state scan (repetition time = 1000 ms, echo time = 31.4, acquisition matrix = 72 × 72 × 39, and voxel size = 2.5 × 2.5 × 2.5 mm^3, 300 volumes), a T1 structural scan (repetition time = 1900 ms, echo time = 2.28 ms, 192 slices, field of view = 192, voxel size = 1 × 1 × 1 mm^3), or a T2w structural scan (repetition time = 2000 ms, echo time = 376 ms, 176 slices, field of view = 192, voxel size = 1 × 1 × 1 mm^3).

Preprocessing and Data Analysis

FSL (5.0.11) was used to analyze functional data. Preprocessing included motion correction, detrending, slice time correction, intensity normalization, and spatial smoothing using an 8-mm full width at half maximum Gaussian kernel. The first 20 volumes were discarded to account for scanner start, and images were bandpass filtered (0.01–0.08 Hz) to retain low-frequency signal. Signal from 6 motion parameters, signal from a 3-mm sphere surrounding a voxel that was manually placed within the ventricle, signal from a 3-mm white matter sphere, and the mean global signal were included as nuisance regressors.

Resting-State Correlation

Resting-state functional correlations were operationally defined as the correlation of the time-varying blood oxygen

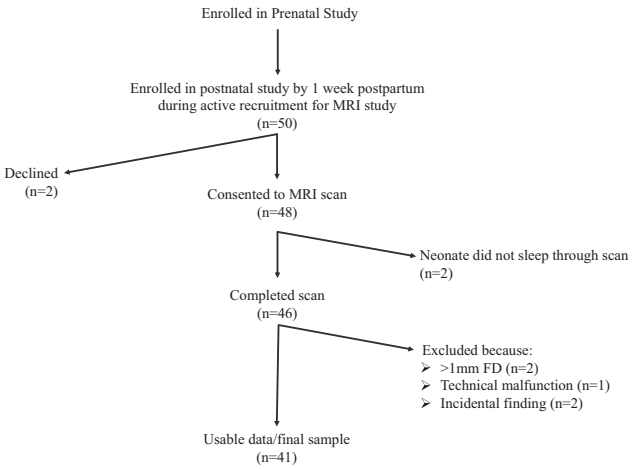

Figure 1. Recruitment flow chart. FD, framewise displacement; MRI, magnetic resonance imaging.

level–dependent signal between two regions of interest (ROIs). After preprocessing, the continuous time series for each voxel within an ROI was extracted and averaged together to create an average time series. The average time series for one ROI was then correlated with the average time series from another ROI. The resulting correlation coefficient (r) was transformed to Gaussian-distributed z-scores using Fisher's transformation, and these z-scores were used as our measure of FC in further analyses (28,29). We examined ipsilateral left and right hemispheric connections separately to determine whether any associations with maternal adversity were lateralized, given that previous research has found stronger associations between maternal stress and left hemispheric alterations in offspring (13,30). Exploratory contralateral analyses are included in the Supplement.

Data Analysis Plan

Descriptives and measures of variability were examined for all variables. Physical neglect and emotional neglect subscales from the CTQ were log-transformed to correct for positive skew (physical skew = 0.76; emotional skew = 1.14), which was effective at improving distribution normality (log-transformed physical skew = 0.43; emotional skew = 0.63). We also repeated our analyses using the nontransformed neglect variables, and our results were unchanged. Hierarchical linear regressions were used to test study hypotheses, with relevant covariates (see Supplemental Methods) entered in the first step and the primary predictor variable entered in the second step. Cohen's f^2 was calculated as an additional measure of effect size (31), with cutoffs for small (f^2 = 0.02), medium (f^2 = 0.15), and large (f^2 = 0.35) effect sizes (32). Linear regression assumptions were assessed in several ways. Unstandardized residuals were visually examined, using histograms to determine normality, and residuals were plotted against predicted values to ensure homoscedasticity. Finally, Cook's D was used to identify potential outliers because it considers both leverage

Table 2. Intercorrelations Between Primary Measures of Adversity

	Childhood Maternal Adversity		First Trimester Maternal Distress				Third Trimester Maternal Distress		
	Emotional Neglect	Physical Neglect	PSS	STAI	EDS	Composite Distress	PSS	STAI	EDS
Maternal Childhood Adversity									
Physical Neglect	r = .69 p < .001	–	–	–	–	–	–	–	–
First Trimester Maternal Prenatal Distress									
PSS	r = .50 p = .01	r = .39 p = .01	–	–	–	–	–	–	–
STAI	r = .74 p < .001	r = .58 p < .001	r = .55 p < .001	–	–	–	–	–	–
EDS	r = .52 p = .001	r = .42 p = .008	r = .64 p < .001	r = .59 p < .001	–	–	–	–	–
Composite Distress	r = .69 p < .001	r = .54 p < .001	r = .86 p < .001	r = .83 p < .001	r = .89 p < .001	–	–	–	–
Third Trimester Maternal Prenatal Distress									
PSS	r = .29 p = .08	r = .35 p = .03	r = .63 p < .001	r = .55 p < .001	r = .48 p = .002	r = .64 p < .001	–	–	–
STAI	r = .53 p = .001	r = .51 p < .01	r = .51 p = .001	r = .74 p < .001	r = .60 p < .001	r = .70 p < .001	r = .66 p < .001	–	–
EDS	r = .24 p = .14	r = .44 p = .003	r = .45 p = .004	r = .55 p < .001	r = .69 p < .001	r = .64 p < .001	r = .58 p < .001	r = .66 p < .001	–
Composite Distress	r = .41 p = .01	r = .50 p = .01	r = .61 p < .001	r = .71 p < .001	r = .68 p < .001	r = .76 p < .001	r = .85 p < .001	r = .89 p < .001	r = .86 p < .001

All measures of maternal prenatal distress (i.e., the PSS, STAI, and EDS) were positively correlated with each other in our final sample (n = 41), supporting the creation of two composite measures of maternal prenatal distress: prenatal distress during the first trimester and prenatal distress during the third trimester. Composite distress refers to composite prenatal distress (i.e., the average of PSS, STAI, and EDS standardized scores).

CTQ, Childhood Trauma Questionnaire; EDS, Edinburgh Depression Scale; PSS, Perceived Stress Scale; STAI, State-Trait Anxiety Inventory.

and discrepancy. Univariate analyses of covariance were used for analyses examining childhood abuse history as a predictor of neonatal connectivity.

RESULTS

First, given that motion is a known confound of rsfMRI, we limited the effects of motion in several ways. In addition to correcting for motion during preprocessing as described earlier and in the Supplement, we confirmed that the number of frames included in analysis was not correlated with amygdala–dACC (left: $r = -.13$, $p = .40$; right: $r = .03$, $p = .86$) or amygdala–vmPFC connectivity (left: $r = -.12$, $p = .45$; right: $r < .01$, $p = .99$). We additionally confirmed that frame to frame motion displacement was not associated with amygdala–dACC FC (left: $r = .22$, $p = .16$; right: $r = .13$, $p = .41$) or amygdala–vmPFC FC (left: $r = -.01$, $p = .95$; right: $r = -.02$, $p = .92$) in our final sample. Neonatal framewise displacement was also unrelated to our measures of maternal adversity ($p > .14$).

Next, we examined our question of whether maternal experiences of neglect and abuse from her own childhood correlated with frontoamygdala circuitry in neonates (Tables 3 and 4). After controlling for relevant covariates and maternal distress during the first trimester of pregnancy, emotional neglect from the mother's childhood robustly correlated with amygdala–dACC FC in neonates ($\Delta R^2 = .20$, $f^2 = 0.25$) (Table 3). That is, the more emotional neglect mothers experienced during their own childhood, the stronger the functional coupling was between the amygdala and dACC in her neonate across both the left and right hemispheres (Figure 2). This association was only significant after controlling for maternal prenatal distress (see Supplement). Neither physical neglect nor abuse from the mother's childhood was associated with amygdala–dACC FC in neonates after controlling for relevant covariates and maternal prenatal distress (Table 3).

Similarly, being emotionally neglected during a mother's own childhood explained 11% of the variance in left hemisphere amygdala–vmPFC FC in neonates beyond relevant covariates and maternal prenatal distress ($f^2 = 0.11$) (Figure 2). Again, the effect of emotional neglect only emerged after controlling for maternal prenatal distress. A similar pattern of results emerged for right neonatal amygdala–vmPFC connectivity, but this association was only marginally significant (Table 4). Moreover, the effect on left amygdala–vmPFC FC was also specific to emotional neglect from the mother's childhood. Maternal experiences of physical neglect did not associate with amygdala–vmPFC FC in neonates, nor did experiencing abuse during childhood. These results suggest strong specificity for an intergenerational effect of childhood emotional neglect on frontoamygdala circuitry into the next generation (see also Supplemental Results). Controlling for maternal distress during the third trimester of pregnancy also yielded similar results across both of these frontoamygdala circuits.

Finally, we conducted post hoc analyses to determine the specificity of associations with frontoamygdala circuitry. For these control analyses, we examined whether experiences of emotional neglect from the mother's childhood correlated with alterations in neonatal FC between our two frontal regions of interest, and between the amygdala and a more lateral prefrontal region, the inferior frontal gyrus. As shown in Figure 2, mothers' childhood emotional neglect did not associate with neonatal dACC–vmPFC FC (left: $\beta = -.17$, $\Delta R^2 = .01$, $f^2 = 0.01$, $p = .54$; right: $\beta = .02$, $\Delta R^2 < .01$, $f^2 < 0.01$, $p = .94$) or with neonatal amygdala–inferior frontal gyrus FC (left: $\beta = .15$, $\Delta R^2 = .01$, $f^2 = 0.01$, $p = .53$; right: $\beta = .25$, $\Delta R^2 = .03$, $f^2 = 0.03$, $p = .22$) after controlling for relevant covariates and first trimester prenatal distress. Together these results suggest that the intergenerational impact of early-life emotional neglect is specific to communication between the amygdala and the mPFC, at least at this early stage of development.

DISCUSSION

This study is to our knowledge the first to examine associations between maternal experiences of early-life adversity and neonatal neural connectivity. We found that maternal childhood experiences of emotional neglect robustly correlate with stronger functional coupling between the amygdala and the

Table 3. Correlates of Neonatal Ipsilateral Connectivity Between the Amygdala and dACC

	β	*t*	b 95% CI	*p*	R^2	Δ*F*	ΔR^2
Outcome: Left Neonatal Amygdala-dACC FC							
Maternal childhood emotional neglect	.68	3.40	0.01, 0.04	.002	.53	11.57	.20
Maternal childhood physical neglect	.14	0.62	−0.36, 0.67	.54	.40	0.39	.01
Maternal any childhood abuse	.22	1.23	−0.07, 0.26	.23	.32	1.52	.04
Outcome: Right Neonatal Amygdala-dACC FC							
Maternal childhood emotional neglect	.46	2.24	0.001, 0.04	.04	.56	5.0	.09
Maternal childhood physical neglect	.09	0.44	−0.41, 0.62	.67	.47	0.19	<.01
Maternal any childhood abuse	.17	0.98	−0.09, 0.25	.34	.36	0.97	.03

We examined different types of maternal adversity as predictors of neonatal amygdala-dACC connectivity separately for ipsilateral connections within the left and right hemispheres. Mothers' experiences of emotional neglect from their childhood correlated with stronger positive functional coupling of the amygdala and dACC in neonates on average 1 month after birth. This effect emerged only after controlling for maternal distress during the first trimester of pregnancy. Results are similar when controlling for maternal distress during the third trimester instead of during the first trimester. All analyses also control for number of included frames, framewise displacement, neonatal age at scan, neonate sex, neonate head circumference at scan, birth weight, gestational age at birth, maternal education, private insurance vs. low-income Medicaid, maternal age, cohabitation with partner, and number of people living in the home in the first step of the model.

CI, confidence interval; dACC, dorsal anterior cingulate cortex; FC, functional connectivity.

Table 4. Correlates of Neonatal Ipsilateral Connectivity Between the Amygdala and vmPFC

	β	*t*	b 95% CI	*p*	R^2	Δ*F*	ΔR^2
Outcome: Left Neonatal Amygdala-vmPFC FC							
Maternal childhood emotional neglect	.49	2.35	0.002, 0.03	.03	.54	5.53	.11
Maternal childhood physical neglect	.19	0.91	−0.22, 0.55	.37	.46	0.82	.02
Maternal any childhood abuse	.21	1.19	−0.05, 0.20	.25	.36	1.41	.04
Outcome: Right Neonatal Amygdala-vmPFC FC							
Maternal childhood emotional neglect	.38	1.71	−0.003, 0.03	.10	.47	2.91	.06
Maternal childhood physical neglect	.06	0.27	−0.42, 0.55	.79	.41	0.07	<.01
Maternal any childhood abuse	.03	0.18	−0.14, 0.17	.86	.33	0.03	<.01

We examined predictors of neonatal amygdala-vmPFC connectivity separately for ipsilateral connections within the left and right hemispheres. Mothers' experiences of emotional neglect from childhood correlated with stronger positive functional coupling of the left amygdala and left vmPFC in neonates 1 month after birth. This effect emerged only after controlling for maternal distress during the first trimester of pregnancy. Results are similar when controlling for maternal distress during the third trimester instead of during the first trimester. All analyses also control for number of included frames, framewise displacement, neonatal age at scan, neonate sex, neonate head circumference at scan, birth weight, gestational age at birth, maternal education, private insurance vs. low-income Medicaid, maternal age, cohabitation with partner, and number of people living in the home in the first step of the model.

CI, confidence interval; FC, functional connectivity; vmPFC, ventromedial prefrontal cortex.

vmPFC and between the amygdala and the dACC in their infants after controlling for maternal prenatal distress. These effects were particularly robust with respect to amygdala–dACC connectivity. Changes in neonatal frontoamygdala connectivity were specific to emotional neglect. These novel findings illustrate that certain experiences from a mother's own childhood are associated with differences in the development of frontoamygdala circuitry in the next generation as early as 1 month after birth.

Being emotionally neglected during mothers' own childhoods correlated with strengthened functional coupling of the amygdala with the medial prefrontal regions in their newborns. This enhanced positive coupling is especially interesting given that connectivity between these regions increases in the context of fear learning (33) and after an acute stressor (15). Amygdala–mPFC connectivity also strengthens across childhood (34), so presuming that the same developmental pattern generalizes to infancy, the current results are consistent with the stress acceleration hypothesis (35), which posits that exposure to emotional neglect (e.g., parental deprivation) and other forms of early-life stress may lead to the early maturation of frontoamygdala circuitry. This accelerated development may predispose children to more readily detect threat or to self-regulate in an environment that lacks the buffering influence of an involved caregiver. However, this early acceleration also may come at the cost of decreasing neural plasticity (16) and increasing risk for certain neuropsychiatric disorders long-term. Indeed, descriptive research shows stronger resting-state FC between the amygdala and the mPFC among individuals with anxiety disorders (12), which is consistent with the observed neural phenotype we found in neonates of emotionally neglected mothers. Our findings contribute to extant research by showing that childhood experiences of emotional neglect may also strengthen frontoamygdala FC into the next generation. However, more work is needed to determine whether the current results represent accelerated development, transient increases in frontoamygdala connectivity, or persistently high functional correlations between frontoamygdala regions.

Emotional neglect from the mother's childhood only correlated with strengthened amygdala–dACC and strengthened amygdala–vmPFC connectivity after, but not before, controlling for prenatal distress. This finding suggests that the influence of maternal childhood emotional neglect is separate and distinct from that of prenatal distress and from the reporting and recall differences that can accompany heightened distress. The emotional neglect subscale of the CTQ also contains some of the most subjective items (e.g., "I felt loved"). Recent research suggests that subjective reports of childhood maltreatment are 1) separable from concurrent neuropsychiatric illness and 2) more strongly linked to future neuropsychiatric symptomology compared with objective measures of maltreatment severity (e.g., court records) (36). Possibly the CTQ emotional neglect subscale best captures subjective maltreatment experiences, which is why it yielded the strongest intergenerational impacts in the current study. Alternatively, emotional neglect may be a particularly potent form of maltreatment that uniquely shapes early development, which aligns with work showing the long-lasting impacts of early parental deprivation on offspring brain development (37).

The behavioral consequences of strengthened connectivity between the amygdala and mPFC during the neonatal period remain unclear. Indeed, evidence suggests that certain regions do not develop functional selectivity before 6 months of age, but instead are refined after months, or even years, of postnatal experience (38). Although the functions of many brain regions during the neonatal period remain unknown, examining resting-state FC patterns offers important insight into the developing brain, given that connectivity between regions may precede the development of functional selectivity (39). Moreover, neural connectivity patterns early in life can be used to predict what a specific region will become selective for in the future (40) as well as future emotional functioning in children (41). In sum, the inputs of a given region (i.e., what it is connected to) may drive its specialization later in development, making infant resting-state connectivity patterns a promising tool for understanding the neural underpinnings of neuropsychiatric illness and risk transmission.

The association between maternal childhood emotional neglect and infant frontoamygdala connectivity was not explained by maternal prenatal distress in the current study.

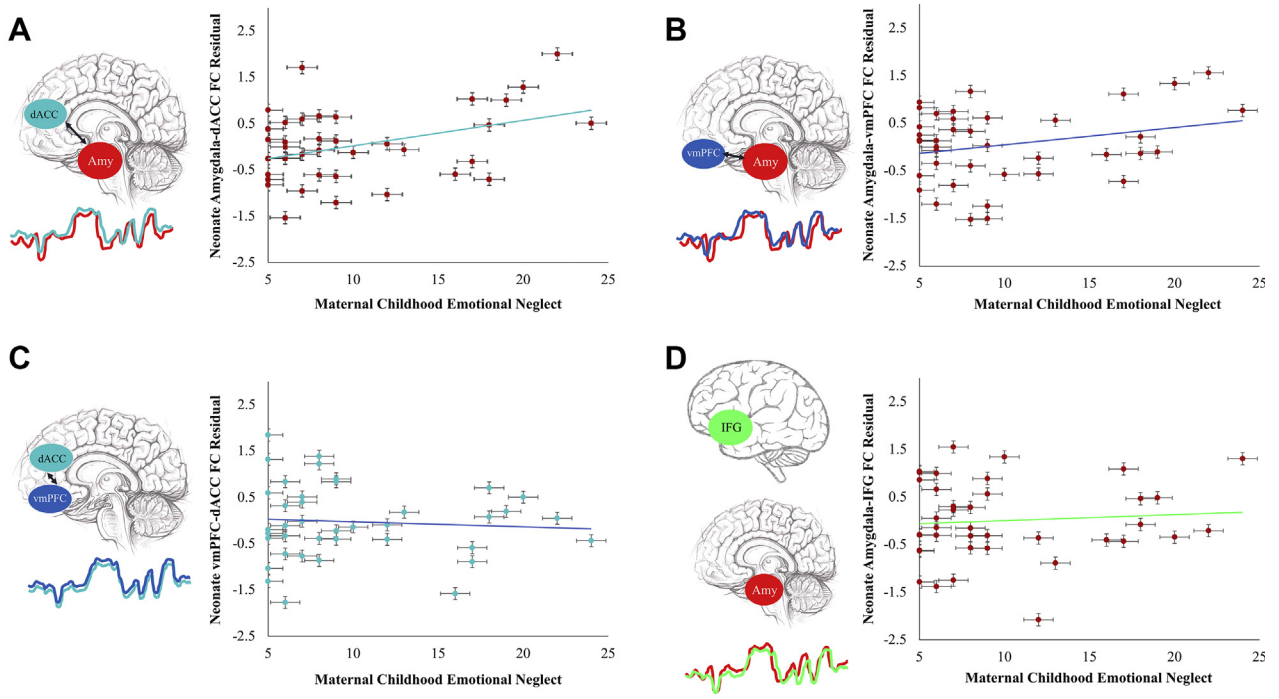

Figure 2. The functional correlation between the amygdala (Amy) and dorsal anterior cingulate cortex (dACC) in each neonate was calculated by averaging the blood oxygen level–dependent time series of each voxel within the region of interest mask and correlating the average time series of the amygdala with the average time series of the dACC. The same procedure was used to calculate the functional connectivity (FC) between the amygdala and ventromedial prefrontal cortex (vmPFC), between the dACC and vmPFC, and between the amygdala and inferior frontal gyrus (IFG). Next, maternal experiences of adversity were examined as predictors of these FCs in 1-month-old sleeping neonates. Emotional neglect from the mother's childhood was robustly associated with **(A)** stronger positive amygdala–dACC FC in neonates and **(B)** stronger positive amygdala–vmPFC FC. Maternal childhood emotional neglect did not associate with **(C)** neonatal vmPFC–dACC FC or **(D)** neonatal amygdala–IFG FC.

This result was surprising given that at least one study has reported that maternal prenatal depression (which was included in our composite prenatal distress measure) modulates amygdala–dACC and amygdala–vmPFC connectivity in neonates (13). Although we used similar analytic techniques, sampling differences may explain our inability to replicate this effect. Our sample is composed entirely of Black mother–neonate dyads, which is rare among neuroscientific research [e.g., in (14), Black dyads made up less than 13% of the study sample]. Early-life adversity may affect neonatal frontoamygdala connectivity more strongly than prenatal adversity specifically for Black mother–neonate dyads. Perhaps the buffering influence of sensitive caregiving is especially important in the context of unique race-related stressors that Black youth experience in the United States (42). Indeed, recent work suggests that Black individuals are more impacted by early-life adversity than their White counterparts and that these differences persist into adulthood (43). Such differences speak to the importance of increasing sample diversity in developmental neuroscience and are consistent with findings that suggest that sample ethnicity and socioeconomic status influence study findings related to brain development (44); again, ethnicity and socioeconomic status are differentially associated with adversity across the lifespan, with Black race and low socioeconomic status being associated with different types (45) and intensities (46) of adversity exposure, as well as differences in the stress response beginning very early in life (47). The current study makes an important contribution to the field by examining brain development in an underrepresented sample who may be disproportionately exposed to and affected by adversity, and it suggests the need for further empirical investigations regarding race-specific impacts of maternal stress.

Some mediating processes likely were not measured in the current study. Evidence suggests that early adversity may induce lasting epigenetic changes—such as alterations to DNA methylation, which in turn controls gene expression (48)—that can influence the uterine environment during pregnancy and shape offspring neurodevelopment. For example, increased methylation (and decreased expression) of the *11β-HSD-2* gene has been demonstrated in women exposed to early adversity (49). 11β-HSD-2 regulates fetal exposure to glucocorticoids by converting cortisol to its benign form (i.e., cortisone) as it crosses the placental barrier. Therefore, offspring of mothers with reduced 11β-HSD-2 expression are likely exposed to elevated levels of cortisol in utero, which has been associated with an increased risk for depression and anxiety across the lifespan (50). Elevated glucocorticoid levels also have been shown to mediate the association between early maternal separation (an extreme form of childhood emotional neglect) and increased frontoamygdala connectivity in children (51).

Notably, reduced 11β-HSD-2 expression is most strongly associated with women's exposure to early- versus later-life adversity (49). This aligns with the finding from the current study that maternal experiences of emotional neglect during her childhood were more closely associated with offspring frontoamygdala connectivity compared with maternal distress during pregnancy. Together, it is possible that emotional neglect during childhood enacts epigenetic alterations that lead to elevated fetal glucocorticoid exposure, which in turn strengthens frontoamygdala circuitry in neonates.

Although we identified effects on child neural connectivity strikingly early in development, these neonates were exposed to 1 month of parenting before completing the fMRI scan. This first month of parenting behavior, although limited, could mediate the relationship between maternal childhood emotional neglect and offspring neural development, because mothers who were emotionally neglected during their own childhood may engage in fewer behaviors that buffer their neonate from the effects of stress (52). For instance, these mothers may be slower to pick up their newborn infant when he or she cries, which offers the infant more opportunities to self-soothe. These repeated opportunities to self-soothe may contribute to the strengthened frontoamygdala connectivity observed in this study. Mothers who were emotionally neglected as children also may continue to lack emotional support during pregnancy and early in the postnatal period. This lack of emotional support may manifest as the infant's father being less involved and less available to offer sensitive parenting in the manner described earlier. Indeed, in our sample, only 39% of women cohabitated with a partner.

The findings from this novel study suggest that childhood experiences of emotional neglect may have potent intergenerational effects on infant neural connectivity and especially on left hemispheric frontoamygdala circuitry. This finding advances our knowledge of factors that shape the development of emotion-related neural circuits and highlights that certain maternal experiences that occur years before conception may shape child development in impactful ways. It will therefore be important to include measures of maternal early-life adversity in future research examining the effects of prenatal stress on child development to delineate cumulative, interactive, or competing effects. In turn, this will lay the groundwork for creating a comprehensive model that explains the intergenerational transmission of adversity and neuropsychiatric risk.

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