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Newborn Brain Function and Early Emerging Callous-Unemotional Traits

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IMPORTANCE Children with high callous-unemotional traits are more likely to develop severe and persistent conduct problems; however, the newborn neurobiology underlying early callous-unemotional traits remains unknown. Understanding the neural mechanisms that precede the development of callous-unemotional traits could help identify at-risk children and encourage development of novel treatments.

OBJECTIVE To determine whether newborn brain function is associated with early-emerging empathy, prosociality, and callous-unemotional traits.

DESIGN, SETTING, AND PARTICIPANTS In this prospective, longitudinal cohort study, pregnant women were recruited from obstetric clinics in St Louis, Missouri, from September 1, 2017, to February 28, 2020, with longitudinal data collected until March 20, 2023. Mothers were recruited during pregnancy. Newborns underwent brain magnetic resonance imaging shortly after birth. Mothers completed longitudinal follow-up when the children were aged 1, 2, and 3 years.

EXPOSURES The sample was enriched for exposure to socioeconomic disadvantage.

MAIN OUTCOME AND MEASURE Functional connectivity between hypothesized brain regions was assessed using newborn-specific networks and voxel-based connectivity analyses. Children's callous-unemotional traits were measured using the Inventory of Callous-Unemotional Traits. Empathy and prosociality were assessed using the Infant and Toddler Socio-Emotional Assessment.

RESULTS A total of 283 children (mean [SD] gestational age, 38 [2] weeks; 159 male [56.2%]; 2 Asian [0.7%], 171 Black [60%], 7 Hispanic or Latino [2.5%], 106 White [38%], 4 other racial or ethnic group [1.4%]) were included in the analysis. Stronger newborn functional connectivity between the cingulo-opercular network (CO) and medial prefrontal cortex (mPFC) was associated with higher callous-unemotional traits at age 3 years (β = 0.31; 95% CI, 0.17-0.41; $P < .001$). Results persisted when accounting for parental callous-unemotional traits and child externalizing symptoms. Stronger newborn CO-mPFC connectivity was also associated with lower empathy and lower prosociality at ages 1, 2, and 3 years using multilevel models (β = −0.12; 95% CI, −0.21 to −0.04; $P = .004$ and β = −0.20; 95% CI, −0.30 to −0.10; $P < .001$, respectively).

CONCLUSIONS AND RELEVANCE Newborn functional connectivity was associated with early-emerging empathy, prosociality, and callous-unemotional traits, even when accounting for parental callous-unemotional traits and child externalizing symptoms. Understanding the neurobiological underpinnings of empathy, prosociality, and callous-unemotional traits at the earliest developmental point may help early risk stratification and novel intervention development.

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Supplemental content

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Callous-unemotional traits, defined by limited empathy, guilt, and prosociality,[1] are a risk factor for severe aggression, low educational achievement, substance use, and criminality.[2,3] Callous-unemotional traits have been linked to difficulties recognizing others' emotions[4,5] and responding to others' distress.[1,6] These difficulties lead children to engage in fewer prosocial actions and feel less remorse about hurting others.[6,7] Importantly, callous-unemotional traits can be reliably measured by age 3 years,[8] when they similarly signal risk for later aggression and rule breaking.[9-11] Like older children, preschoolers with callous-unemotional traits show difficulties recognizing fear[12] and relating to others' emotional states.[13] It is imperative to understand the pathophysiology underlying the development of callous-unemotional traits as this knowledge could promote earlier detection and discovery of biologically informed interventions.

In older children and adolescents, callous-unemotional traits are commonly associated with alterations in frontolimbic connectivity between the amygdala or anterior insula and the medial prefrontal, anterior cingulate, and/or orbitofrontal cortices.[14-21] Higher callous-unemotional traits have also been related to weaker within-network default mode connectivity[20,22] and stronger default mode-salience network connectivity (including the anterior insula).[20] These neural alterations may arise early in development, with evidence of a link between callous-unemotional traits and reduced evoked response potentials to fearful faces in preschoolers aged 3 to 5 years.[23] However, it remains unclear whether the brain alterations in frontolimbic regions (ie, connectivity between the prefrontal cortex, amygdala, and anterior insula) seen in older children with callous-unemotional traits[14-22] precede the development of symptoms (ie, are a cause) or occur downstream of negative interactions with others because of callous-unemotional traits (ie, are a consequence).

Understanding the neurobiology of empathy and prosociality, 2 core developmental skills that have gone awry among children with callous-unemotional traits,[24] may also shed light on early-emerging symptoms. Empathy and prosociality emerge in the first year of life, with 1 study[25] showing that over 80% of infants help retrieve out-of-reach objects by 12 months old. Empathy and prosociality are also linked to neural activity in similar brain regions to callous-unemotional traits, including the amygdala, anterior insula, anterior cingulate cortex, and ventral medial prefrontal cortex, based on neuroimaging,[26-28] lesion,[29] and preclinical studies.[7] Examining whether these brain regions are associated with empathy and prosociality during infancy and toddlerhood may enhance knowledge about the development of callous-unemotional traits, before the construct can be reliably measured behaviorally.

Parental factors are also important to the development of callous-unemotional traits. Twin and adoption studies[30-34] suggest that callous-unemotional traits are moderately to highly heritable. Additionally, warm parenting protects against the development of callous-unemotional traits, whereas harsh parenting exacerbates risk for callous-unemotional traits.[35-39] Controlling for parental callous-unemotional traits may account for some of the shared genetic risk between parents and children, as well as early caregiving influences, thus allowing for stronger conclusions to be drawn about links between newborn functional connectivity and callous-unemotional traits.

Key Points

Question Do alterations in newborn brain function precede the development of callous-unemotional traits and associate with later symptom severity?

Findings In this longitudinal cohort study of 283 mother-infant dyads recruited during pregnancy, stronger functional connectivity between the cingulo-opercular network and the medial prefrontal cortex was associated with higher callous-unemotional traits at age 3 years, as well as lower empathy and prosociality at ages 1, 2, and 3 years.

Meaning Frontolimbic brain connectivity in newborns may be associated with the development of callous-unemotional traits in preschoolers and, therefore, precede increased symptom severity.

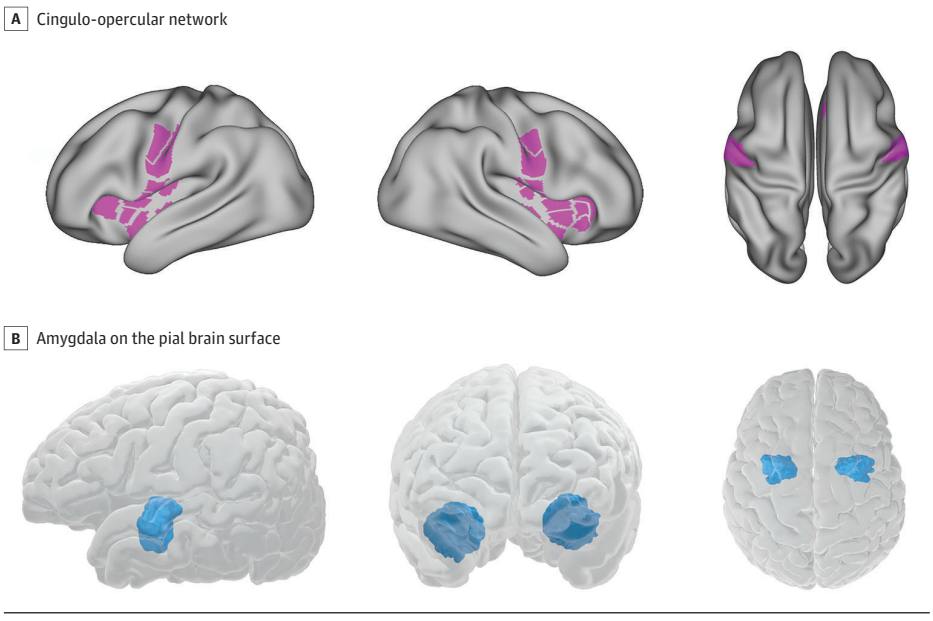
We aimed to understand the early neurobiology of callous-unemotional traits using resting-state functional magnetic resonance imaging (MRI), as prior work suggests that newborn functional brain connectivity is associated with psychiatric symptoms in early childhood.[40,41] First, we investigated whether newborn functional connectivity in frontolimbic regions was associated with callous-unemotional traits at age 3 years, including after accounting for parental callous-unemotional traits and externalizing symptoms. Second, we investigated whether the same newborn frontolimbic connectivity alterations were associated with low empathy or prosociality at ages 1, 2, and 3 years. Our analyses aimed to address whether functional brain connectivity precedes the development of callous-unemotional traits, which represents a first step in defining biomarkers to identify high-risk children before the behavioral manifestations of callous-unemotional traits. A better understanding of the role of functional brain alterations in callous-unemotional traits could ultimately enable the development of biologically informed interventions that improve outcomes for children at risk for severe conduct problems.

Methods

Participants

Participants included mother-infant dyads recruited from outpatient obstetrics clinics at Washington University in St Louis, Missouri. Mothers were overrecruited for socioeconomic disadvantage, with 68% of the families in the sample living in poverty (defined by income to needs ratio [INR] <2). Participants from the following parent-identified race and ethnicity categories were included: Asian, Black, Hispanic or Latino, White, or other, which included multiracial. Race and ethnicity were collected to more fully characterize the socioeconomically disadvantaged sample. All study procedures were approved by Washington University institutional review board. Written informed consent was obtained from the mothers before participation. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Figure 1. Functional Connectivity Seed Regions in the Newborn Brain



Seed regions for the whole-brain, voxelwide analysis, are shown. A, The cingulo-opercular network is highlighted in purple on an average surface of the newborn brain. B, The amygdala on an individual's pial brain surface is shown, with the transparency altered for visualization purposes.

Newborn MRI scanning was performed shortly after birth. Mothers of participants filled out surveys assessing empathy and prosociality at 1 year, 2 years, and 3 years, as well as callous-unemotional traits at 3 years. Inclusion criteria were speaking English, maternal age of 18 years or older, and singleton birth. Exclusion criteria were self-reported alcohol or substance use during pregnancy (except tobacco or marijuana), maternal congenital infections, or fetal abnormalities including intrauterine growth restriction. Newborns were excluded if they had any parenchymal abnormality detected on newborn MRI as reviewed by a neuroradiologist (J.S.S.) and pediatric neurologist (C.D.S.).

Functional MRI

Imaging was performed in sleeping, nonsedated infants using a Siemens 3-T PRISMA scanner and 64-channel head coil. T2-weighted images (208 slices, 0.8 × 0.8 × 0.8 mm^3 voxels, time to echo [TE] = 563 milliseconds, T2 = 160 milliseconds, repetition time [TR] = 3200 milliseconds or 4500 milliseconds) were collected. Sleep-wake state was monitored continuously during data collection using an MRI-compatible camera to ensure that the infants were asleep.[42] Resting-state functional MRI data were collected using a blood oxygen level-dependent (BOLD) gradient-recalled echo-planar multiband sequence (72 slices, 2.0 × 2.0 × 2.0 mm^3 isotropic resolution, TE = 37 milliseconds, TR = 800 milliseconds, MB factor = 8). MRI data underwent standard BOLD preprocessing and functional connectivity processing (eAppendix in Supplement 1). A minimum of 10 minutes of low-motion (framewise displacement <0.25 mm) data were required for inclusion. Resting-state functional connectivity measures were computed as Fisher *z*-transformed Pearson correlation between time courses from pairs of surface vertices or parcels. Values were arranged into a connectivity matrix based on age-specific resting-state network assignments that were validated previously (eFigure 1 in Supplement 1).[43,44] Given that the amygdala and anterior insula are most commonly associated with callous-unemotional traits in older children and adults,[14-21] as well as in neuroimaging, lesion, and preclinical studies that assess empathy and prosocial behavior,[7,14,27-29] the cingulo-opercular network (CO), which captures functionally relevant portions of the anterior insula and associated regions in the newborn brain, and amygdala were investigated in hypothesis-driven analyses and used as seed regions for whole-brain, voxel-based analyses. The CO and amygdala are visualized in **Figure 1**. Based on prior literature, we hypothesized that connectivity between these regions and frontal regions of the brain, including the medial prefrontal cortex (mPFC), would be associated with callous-unemotional traits.[7,14-22,26,27,29]

Children's Callous-Unemotional Traits

Children's callous-unemotional traits at 3 years were measured using the 24-item parent-reported preschool version of the Inventory of Callous-Unemotional Traits, which was specifically designed for young children.[45-48] This questionnaire has been previously validated in community samples aged 3 to 5 years, paralleling the current study design.[8,35,48-50]

Children's Empathy and Prosocial Behaviors

Empathy and prosociality were assessed using the parent-reported Infant-Toddler Social and Emotional Assessment (ITSEA), which measures socioemotional problems and behavioral competencies from ages 1 to 3 years.[51] We used the empathy and prosocial peer relations subscales, which demonstrate good test-retest reliability and construct validity.[51] To complete the prosocial peer relations subscale, child participants needed to have contact with other young children, excluding siblings, reducing the availability of data for this subscale at younger ages.

Children's Externalizing Symptoms

We assessed parent reports on the externalizing problems subscale (ie, aggression, noncompliance) of the Child Behavior Checklist for ages 1.5 to 5 (CBCL 1.5-5).[52] The CBCL 1.5-5 has been validated for use in diverse samples, including children from low socioeconomic status backgrounds and racial and ethnic minoritized groups.[53,54] We reran analyses controlling for externalizing symptoms to establish the specificity of any brain-behavior associations with callous-unemotional traits rather than general severity of externalizing symptomatology.

Parental Callous-Unemotional Traits

Mothers completed a self-report version of the Inventory of Callous-Unemotional Traits (ICU)[47] and an observer-report version to assess the child's biological father's callous-unemotional traits at year 2.[46,47,55] Mothers also completed a self-report and observer report (for child's biological father) of the 26-item Levenson Self Report of Psychopathy (LSRP) scale to assess the broader construct of psychopathy at year 3.[56,57] Prior studies[58-61] demonstrate high concordance between self and other reports for the LSRP. To create a stable estimate of parental callous-unemotional traits over time, we computed an average of the primary factor of the LSRP measuring the interpersonal and affective components of psychopathy and ICU total scores for mothers and fathers. The eAppendix and eTables 10 and 11 in Supplement 1 contain statistics and analyses examining maternal and paternal scores separately.

Adversity Controls

Self-reported family income and household size compared with the Federal Poverty Level (ie, INR) was assessed during pregnancy, shortly after birth, and every 4 months until age 3 years and averaged to capture INR across time. Mother's self-reported experiences of racism were assessed using the Everyday Discrimination Survey.[62] We averaged participants' experienced discrimination attributed to race or skin color. Experiences of racial discrimination were included in analyses instead of race.

Statistical Analysis

Analyses were conducted using Permutation Analysis of Linear Models (PALM) software (Winkler et al),[63,64] R, and RStudio (R Core Team).[65] For the first aim, PALM was used to conduct whole-brain, voxel-based analyses using the CO network or amygdala as a hypothesized seed region. PALM conducts nonparametric tests to determine whether connectivity between the seed region and each voxel of the brain is associated with the outcome of interest, CU traits at age 3 years, when controlling for gestational age at birth, postmenstrual age at scan, sex, age at survey completion, INR, and racial discrimination. All of the voxel-level connections between the seed region and the rest of the brain were corrected for multiple comparisons using a family-wise error rate correction procedure that involves permutation testing as described by Westfall-Young.[66] Connectivity between the CO and significant regions was exported for use in subsequent models. Additional specificity analyses controlled for concurrent externalizing symptoms and parental callous-unemotional traits. Post hoc analyses were run to determine which brain areas within the CO were most important (eAppendix and eFigure 5 in Supplement 1). For our second aim, we conducted within-person, multilevel models associating significant newborn brain connections with empathy and prosociality at ages 1, 2, and 3 years using the lme4 package (Bates et al),[67] controlling for gestational age at birth, postmenstrual age at scan, sex, age at survey completion, INR, and racial discrimination. All analyses were corrected for multiple comparisons using a Holm-Bonferroni correction, which is a conservative family-wise error rate correction approach.[68] Additional post hoc specificity analyses addressing network-level connectivity (eAppendix, eFigure 4, and eTable 4-9 in Supplement 1), prematurity (eAppendix in Supplement 1), comorbid or preexisting psychopathology (eAppendix in Supplement 1), and missing data (eAppendix in Supplement 1) are described in the supplemental files. All P values were 2-sided, and $P < .05$ was considered statistically significant.

Results

Descriptive Statistics

Participants included 382 mother-infant dyads recruited from outpatient obstetrics clinics at Washington University. Mothers were overrecruited for socioeconomic disadvantage, with 258 families (68% of the sample) living in poverty. Newborn MRI was performed shortly after birth (mean [range] postmenstrual age, 41 [37-45] weeks). Mothers of participants filled out surveys assessing empathy and prosociality at 1 year (mean [range] age, 13 [11-21] months), 2 years (mean [range] age, 25 [23-31] months), and 3 years (mean [range] age, 36 [35-41]), as well as callous-unemotional traits at 3 years.

Of these 382 participants, 319 had usable functional MRI scans with 10 minutes or more of high-quality data (84% usable scans). Sixty-three participants (16.5%) were missing functional MRI data for the following reasons: no MRI scan due to COVID-19 restrictions (n = 14), no functional MRI data collected (n = 1), no usable T2 for registration (n = 30), less than 10 minutes of low-motion data after motion censoring (n = 11), and visible artifacts (n = 7). For longitudinal follow-up, 282 participants (74%) had survey data at 1 year, 259 participants (68%) had survey data at 2 years, and 250 participants (65%) had survey data at 3 years.

After accounting for missing functional MRI and survey data, the final number of participants in analyses was 283 (mean [SD] gestational age, 38 [2] weeks; 159 male [56.2%]; 124 female [43.8%]; 2 Asian [0.7%], 171 Black [60%], 7 Hispanic or Latino [2.5%], 106 White [38%], 4 other racial or ethnic group [1.4%]). Of the analyzed participants, 180 families (64%) lived in poverty. Forty-three infants were born prematurely. Thirty-four infants were born in the late preterm period (34-36 weeks), 2 infants were born moderately preterm (32-24 weeks), and 7 infants were born very preterm (28-31 weeks). Parent-child dyads with missing data did not differ from parent-child dyads with complete data on child sex, maternal education, racial discrimination, gestational age at birth, postmenstrual age at scan, callous-unemotional traits, empathy, or prosociality; how-

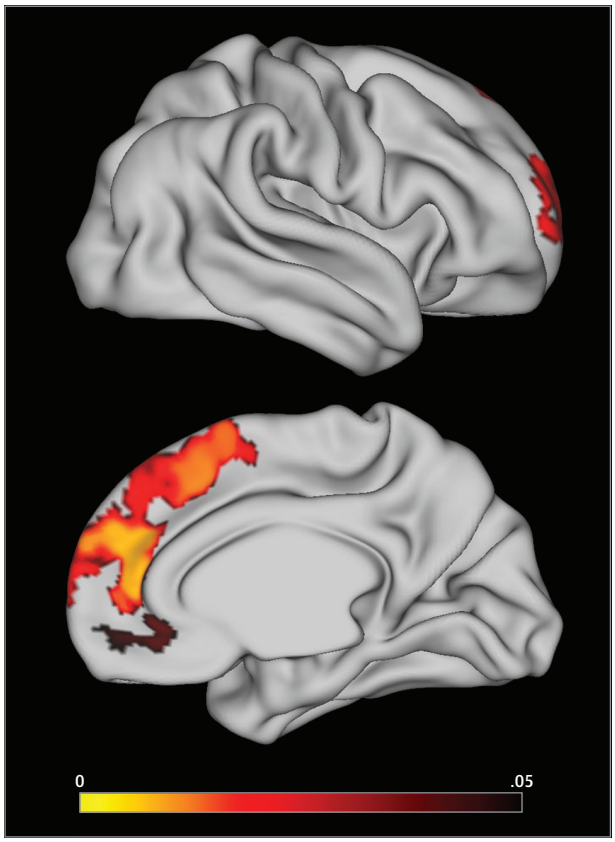
Table 1. Sample Demographics (N = 283)

Characteristic	No. (%)	Range
Sex assigned at birth		
Female	124 (43.8)	NA
Male	159 (56.2)	
Race		
Asian	2 (0.7)	NA
Black	171 (60.4)	
White	106 (37.5)	
Other[a]	4 (1.4)	
Ethnicity		
Hispanic or Latino	7 (2.5)	NA
Not Hispanic or Latino	274 (96.8)	
Unspecified	2 (0.7)	
Infant characteristics, mean (SD)		
Gestational age at birth, wk	37.9 (2.0)	28-41
Postmenstrual age at MRI scan, wk	41.2 (1.5)	37-45
1 y ITSEA score, mean (SD)		
Empathy (n = 247)	0.68 (0.49)	0-2
Prosocial peer relations (n = 179)	0.75 (0.41)	0-2
2 y ITSEA score, mean (SD)		
Empathy (n = 221)	1.19 (0.45)	0-2
Prosocial peer relations (n = 179)	1.13 (0.45)	0-2
3 y ITSEA score, mean (SD)		
Empathy (n = 213)	1.52 (0.41)	0-2
Prosocial peer relations (n = 188)	1.39 (0.45)	0-2
3 y ICU total score (n = 205)	17.6 (8.3)	0-62
3 y CBCL externalizing problems (n = 177)	48.5 (9.6)	28-85
Maternal characteristics, mean (SD)		
ICU self-report total score (n = 242)	15.2 (7.1)	1-39
LSRP self-report primary factor (n = 199)	24.6 (5.8)	16-49
Racial discrimination (n = 278)	1.5 (0.9)	1-6
Paternal characteristics, mean (SD)		
ICU observer-report total score (n = 229)	21.8 (12.0)	1-62
LSRP observer-report primary factor (n = 189)	32.7 (11.5)	16-64
Family characteristics, mean (SD)		
Income to needs ratio (n = 283)	2.6 (2.6)	0.3-11.8

Abbreviations: CBCL, Child Behavior Checklist; ICU, Inventory of Callous-Unemotional Traits; ITSEA, Infant-Toddler Social and Emotional Assessment, LSRP, Levenson Self-Report Psychopathy Scale; MRI, magnetic resonance imaging; NA, not applicable.

[a] Other includes 2 individuals of Asian and White race and 2 individuals of Black and White race.

Figure 2. Newborn Cingulo-Opercular Network (CO)–Medial Prefrontal Cortex Connectivity Associated With Preschool Callous-Unemotional Traits



The red-to-yellow areas of the brain are colored based on their Westfall-Young corrected *P* values, which represent a positive association between the CO network and the warm-colored region that significantly associates with callous-unemotional traits at age 3 years, after controlling for gestational age at birth, postmenstrual age at scan, sex, age at survey completion, income to needs ratio, and racial discrimination. All areas of the brain that are colored gray are not significant (ie, negative results).

ever, they did differ in regard to INR values (included sample mean [SD] INR, 2.6 [2.6]; missing sample mean [SD] INR, 1.8 [1.9]; $P = .002$) and race.

Descriptive statistics for all study variables are reported in **Table 1**. Child callous-unemotional traits were normally distributed (eFigure 2 in Supplement 1) and correlated with lower empathy and prosociality at every time point (Pearson r, range = −0.27 to −0.64; all $P < .001$) (eTable 1 in Supplement 1). Higher parental callous-unemotional traits were correlated with higher child callous-unemotional traits at age 3 (Pearson $r = 0.31$; $P < .001$) (eFigure 3 in Supplement 1).

Newborn Functional MRI and Callous-Unemotional Traits at Age 3 Years

Stronger connectivity between the CO network and the mPFC was associated with higher callous-unemotional traits at age 3 years (β = 0.31; 95% CI, 0.17-0.41; $P < .001$) (**Figure 2**). Connectivity between the amygdala and the rest of the brain was not associated with callous-unemotional traits, after correcting for multiple comparisons. Stronger newborn CO-mPFC connectivity continued to associate with higher callous-unemotional traits at age 3 years after controlling for concurrent externalizing (β = 0.25; 95% CI, 0.11 to 0.40; $P < .001$; adjusted $P = .003$) and withdrawn (β = 0.27; 95% CI, 0.12 to 0.41; $P < .001$; adjusted $P = .002$) symptoms in children, as well as externalizing symptoms in toddlers (eAppendix in Supplement 1). The association between the newborn CO-mPFC and callous-unemotional traits at year 3 was also significant after accounting for parental callous-unemotional traits (β = 0.28; 95% CI, 0.14 to 0.41; $P < .001$; adjusted $P<.001$) (eTable 2 and 3 in Supplement 1).

Table 2. Association of Newborn Functional Connectivity With Empathy and Prosociality at Age 1, 2, and 3 Years

	ITSEA empathy			ITSEA prosocial peer relations		
Predictors[a]	Estimates	95% CI	*P* value	Estimates	95% CI	*P* value
Intercept	−0.44	−0.56 to −0.32	<.001	−0.52	−0.66 to −0.38	<.001
Time	0.07	−0.35 to 0.48	.75	0.15	−0.31 to 0.62	.52
CO-mPFC connectivity	−0.12	−0.21 to −0.04	.004	−0.20	−0.30 to −0.10	<.001
Time × CO-mPFC connectivity	−0.01	−0.08 to 0.06	.71	0.04	−0.03 to 0.12	.26
Random effects						
σ^2	0.41	NA	NA	0.40	NA	NA
Participant, τ00	0.19			0.25		
ICC	0.32			0.38		
Participant, No.	262			230		
Observations, No.	579			463		
Marginal R^2/conditional R^2	0.386/.581			0.338/0.591		

Abbreviations: CO, Cingulo-Opercular Network; ICC, intraclass correlation coefficient; ITSEA, Infant-Toddler Social and Emotional Assessment; mPFC, medial prefrontal cortex; NA, not applicable.

[a] This model includes gestational age at birth, postmenstrual age at scan, sex (female), child age at survey completion, income to needs ratio, and racial discrimination as predictors.

Newborn Functional MRI and Empathy and Prosociality at Ages 1, 2, and 3 Years

Stronger newborn CO-mPFC connectivity was associated with lower empathy (β = −0.12; 95% CI, −0.21 to −0.04; *P* = .004; adjusted *P* = .01) and lower prosociality (β = −0.20; 95% CI, −0.30 to −0.10; *P* < .001; adjusted *P* < .001) at ages 1, 2, and 3 years using within-person, multilevel models to account for the longitudinal associations (**Table 2**). The interaction between time and CO-mPFC connectivity was not a significant predictor of empathy or prosociality (Table 2), indicating that the results were not driven by a single age point. Post hoc analyses demonstrated that newborn CO-mPFC predicted empathy, prosociality, and callous-unemotional traits in correlated dependent variable models (eAppendix and eTable 13 and 14 in Supplement 1).

Discussion

Study results suggest that stronger frontolimbic connectivity between the CO network and the mPFC in newborns was associated with callous-unemotional traits at age 3 years, even when controlling for externalizing symptoms and parental callous-unemotional traits. Stronger newborn CO-mPFC connectivity was also associated with lower empathy and prosociality throughout toddlerhood. These findings are consistent with prior work in older children and adults showing that the anterior insula and its connectivity to the mPFC are associated with callous-unemotional traits and empathy.[20,26,27] Using a prospective, longitudinal cohort, we advance prior knowledge by demonstrating that alterations in frontolimbic connectivity occurred early in life, before the behavioral manifestations of empathy, prosociality, and callous-unemotional traits.

We did not find an association between newborn amygdala connectivity and callous-unemotional traits at age 3 years. Although many studies have demonstrated that amygdala structure and function are associated with callous-unemotional traits,[15,69,70] more recent investigations report null associations.[71,72] Demographic and developmental factors could contribute to differences between our findings and prior studies, as our cohort is younger, predominantly impoverished, and includes a majority of Black participants. Additionally, we defined the amygdala by anatomic boundaries instead of functional boundaries due to its small size in newborns, which may have reduced signal to noise ratios and decreased our ability to detect significant associations. Finally, changes in amygdala connectivity may instead occur after the development of callous-unemotional traits, potentially as a consequence of negative or disrupted social interactions with others.

Importantly, we found that stronger newborn CO-mPFC connectivity was associated with lower emerging empathy/prosociality, in addition to callous-unemotional traits. The shared brain connectivity underlying these developmental processes points to convergent validity. Although callous-unemotional traits can only be reliably measured starting at age 3 years,[73] direct assessment of empathic and prosocial skills might identify high-risk children earlier in life. Earlier diagnosis and treatment may be crucial in alleviating the burdens associated with callous-unemotional traits. Treatment improvements are needed because children with callous-unemotional traits have stubbornly high conduct problems,[74] despite the success of early parent-child interaction therapy adapted for callous-unemotional traits.[75,76] Interventions that occur before symptom onset could also help reduce the stigma associated with early behavior problems, as strengths-based approaches could be implemented to promote empathy and prosociality. Future studies need to replicate these findings, further investigate the mechanisms, and potentially translate these findings into clinical practice.

Strengths and Limitations

Strengths of the study include a prospective, longitudinal data set with a relatively long newborn scan length (≥10 minutes) and controlling for parental callous-unemotional traits; al-

though residual genetic confounding likely remained. Some limitations of this study should be noted. First, callous-unemotional traits were normally distributed in our sample, likely reflecting that our sample was oversampled for multiple psychopathological risk factors. Another possible explanation for this distribution is that the ICU may have differential item functioning in our high-risk population. As such, our findings may not generalize to lower-risk samples or samples with positively skewed distributions of callous-unemotional traits. Second, it is unknown whether newborn brain function or our behavioral measure of callous-unemotional traits at age 3 predict callous-unemotional later in development. Although a meta-analysis of 10 studies indicated that callous-unemotional traits measured before age 5 years were associated with greater concurrent conduct problem severity,[10] and another study suggested that callous-unemotional traits measured at age 3 were associated with callous-unemotional traits in late childhood,[9] few studies have addressed whether early callous-unemotional traits are associated with outcomes across adolescence and into adulthood. Future prospective studies using the Early Life Adversity Biological Embedding, and Risk for Developmental Precursors of Mental Disorders (eLABE) sample or other longitudinal cohorts are needed to establish long-term predictive validity of early callous-unemotional traits. Third, we used maternal report of the biological father's callous-unemotional traits. Although observer reports have demonstrated reliability,[58-60] an ideal study design would have included the biological father's self-report. Findings may also have been influenced by the degree of contact between children and biological fathers (eAppendix, eFigure 6 and 7, and eTable 12 in Supplement 1). Fourth, we assessed parental callous-unemotional traits at ages 2 and 3 years. Although callous-unemotional traits among adults may be relatively stable,[77] the lack of data on parental characteristics before birth prevented investigation of the effects of prospectively assessed parental callous-unemotional traits on later newborn functional connectivity. Fifth, we investigated 2 regions of interest in a hypothesis-driven approach; however, it is possible that neonatal functional connectivity in other brain regions also contributes to the development of callous-unemotional traits. Finally, our longitudinal observational study design could not address causality. Future preclinical or intervention studies are needed to identify causal mechanisms.

Conclusions

Results of this prospective, longitudinal cohort study suggest that newborn frontolimbic connectivity was associated with callous-unemotional traits at age 3 years, as well as empathy and prosociality across toddlerhood. These findings may spur research into risk stratification as early as the newborn period and biologically informed therapies for children with callous-unemotional traits. Given that callous-unemotional traits can severely disrupt caregiving relationships, cause social problems, and impact educational opportunities, it is crucial to develop effective therapies that can be delivered early in life.

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