Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Biol Psychol. Author manuscript; available in PMC 2024 January 03.

Published in final edited form as:

Biol Psychol. 2023 November ; 184: 108717. doi:10.1016/j.biopsycho.2023.108717.

Concurrent and Prospective Associations Between Infant Frontoparietal and Default Mode Network Connectivity and Negative Affectivity

Sanjana Ravi[1,*], **M. Catalina Camacho**[2,*], **Brooke Fleming**[1], **Michael R. Scudder**[1], **Kathryn L. Humphreys**[1]

[1]Vanderbilt University, 230 Appleton Place, #552, Nashville, TN 37204

[2]Washington University in St. Louis, One Brookings Drive, Campus Box 1125, St. Louis, MO 63130

Introduction

Emotion dysregulation is associated with differences in neurobiological functioning in adults, however the etiology is not well understood. Adult resting state and task-based functional magnetic resonance imaging (fMRI) meta-analyses have identified connectivity in two cognitive networks, the default mode network (DMN) and frontoparietal network (FPN), to be linked to psychopathology (e.g., reduced DMN and FPN connectivity for anxiety (Sylvester et al., 2012); increased DMN connectivity, decreased FPN connectivity, and increased DMN–FPN connectivity for depression (Kaiser et al., 2015); and decreased DMN connectivity for bipolar disorder (Wang et al., 2020)). New work also suggests that the global efficiency–the average inverse connectivity distance between all region pairs, which is thought to reflect capacity for parallel information processing–of the DMN and FPN during frustration is increased in youth with high irritability (Linke et al., 2022). Taken together, this suggests that differences in DMN and FPN functioning may be closely linked to emotion dysregulation.

Importantly, both DMN and FPN have a protracted development as compared to other cognitive networks, with the adult-like functional architecture emerging in late infancy (Gao et al., 2009, 2015; Gao & Lin, 2012) and connectivity patterns continuing to mature well into adolescence (Camacho et al., 2020; Fan et al., 2021; Grayson & Fair, 2017; Uddin, 2010). It is possible that early differences in the functioning of these networks may offer the ability to identify risk for disorder before the onset of symptoms. Further, these networks are associated with higher level emotion processing such that they are implicated in emotion cognition and experience (Satpute & Lindquist, 2019), social processing (Buckner & DiNicola, 2019), and self-regulation (Marek & Dosenbach, 2018). There is some evidence to suggest that explicit emotion regulation (i.e., needing conscious effort and active monitoring

*Denotes equal contribution

Corresponding Author: Sanjana Ravi. Phone: 615-322-8141. sanjana.ravi@vanderbilt.edu. Address: 230 Appleton Place, #552, Nashville, TN 37204

Declaration of Interests: none

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

of emotion) is associated with activation of the FPN, including the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and parietal cortex, and implicit emotion regulation (i.e., evoked automatically by the stimulus and involves no conscious monitoring of emotion) is associated with the DMN (Etkin et al., 2015). Differences in DMN and FPN function may precede the development of emotion dysregulation symptoms in youth. For instance, recent work has found that decreases in DMN connectivity and activation as well as decreases in FPN connectivity predict greater depression and anxiety symptoms at follow-up in previously undiagnosed youth (Ernst et al., 2019; Shapero et al., 2019). Further, adolescent girls with a parental history of mood dysregulation have been shown to have lower within-network connectivity of the FPN relative to low-risk comparison groups (Clasen et al., 2014). Disorders of emotion dysregulation are influenced by negative affect —which has both state (i.e., temporary discomfort caused by uncertain events) and trait (i.e., baseline) features. DMN within and between network functional connectivity has been positively associated with trait rather than state negative affectivity (Y. Li et al., 2022). Thus, characterizing associations between DMN and FPN connectivity and trait-like negative affectivity (i.e., precursors to psychopathology)–before symptoms emerge–in infancy could therefore yield important insight to the early etiology of emotion dysregulation.

Temperamental negative affectivity—which includes fearful, crying, anger/frustration, and shy behaviors—assessed in early life is a strong predictor of later emotion dysregulation, increasing the odds of developing a related disorder by up to seven times (Clauss & Blackford, 2012; Dougherty et al., 2013; Michelini et al., 2022). For example, maternal reports of early behavioral inhibition, defined as signs of fear, reticence, and wariness to unfamiliar situations and withdrawal from unfamiliar individuals, has been associated with nearly four times increased odds of a lifetime social anxiety disorder diagnosis (Chronis-Tuscano et al., 2009). Similarly, other studies examining child negative affectivity indicate that increased child fear and distress is associated with higher levels of later depression and anxiety symptoms (Crawford et al., 2011; Dougherty et al., 2010; Michelini et al., 2022). Toddler and preschool anger and frustration, fear, and distress have also been associated with later depression, bipolar disorder, and clinical irritability (Luby & Navsaria, 2010; Wakschlag et al., 2015; Wiggins et al., 2018). Thus, child trait-like negative affectivity may be an important early indicator of vulnerability.

Recent work suggests that the neurobiological correlates of early emotional functioning may be present at birth, before the emergence of emotion dysregulation. Specifically, neonatal amygdala resting-state connectivity was positively associated with parent-reported internalizing symptoms at age two-years (Rogers et al., 2017) and DMN resting-state connectivity at birth was negatively associated with parent-reported behavioral inhibition at age two-years (Sylvester et al., 2018). Another study found that newborn amygdala–DMN connectivity was positively associated with parent-reported fearful behaviors at six-months of age (Graham et al., 2016). Considering how rapidly the brain develops during gestation and across the first year of life (Gilmore et al., 2018; Grayson & Fair, 2017; Thomason, 2020), early infancy is a uniquely vulnerable period for perturbations in foundational brain development that could portend long-term consequences for infant mental health. Thus, fully understanding how infant brain networks at birth are associated with later functioning would provide important insight to risk and intervention for emotion dysregulation. Further,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

examining brain network connectivity and negative affectivity in early infancy enables examination of markers for emerging psychopathology prior to postnatal influences on brain and behavior development.

In this preregistered study (https://osf.io/5dkqt/?view_only=328aa68fab124631ba288acfff8d838b), we aim to characterize concurrent and longitudinal associations between one-month DMN and FPN intra- and internetwork connectivity and negative affectivity. The DMN and FPN were selected as networks of interest as, (1) along with their protracted developmental course as noted above, we aim to examine trait-like emotion processing (Pan et al., 2018) as opposed to visceral sensation processing that are associated with limbic structure networks (Aziz et al., 2000); (2) less is known about how these two networks in particular are associated with negative affectivity in infancy; and (3) these cortical networks have high signal-to-noise ratio, thereby enabling more accurate estimation of functional connectivity (Maugeri et al., 2018). We use multiple methods for indexing negative affectivity, including both parent-report and objective measures of infant behavior (audio recordings). Based on our preliminary data analyses (presented in the preregistration) and past literature, we hypothesized that functional connectivity both within and between these networks would be positively associated with negative affectivity.

Methods

Participants

Families were recruited during pregnancy from the greater Nashville area from obstetrics clinics and through social media advertisements on Facebook and Instagram to take part in a longitudinal study of infant brain and behavioral development. All study procedures were approved by the Vanderbilt University Institutional Review Board. Interested individuals were first screened via phone to confirm eligibility. Eligibility included being 18 years or older, currently pregnant with a singleton pregnancy, fluent in English, a U.S. Citizen or permanent resident, and having no immediate plans to move out of the greater Nashville area given the longitudinal nature of the study. After their due date, participants were screened again to assess their infant's eligibility for MRI scanning. Exclusion criteria were parent-report of severe complications during birth, infant head trauma, infant premature birth (prior to 36 weeks gestation) and any infant MRI contraindication (e.g., metal implant). Informed consent was obtained from all participants prior to their participation, including for their infant to participate following birth. While data collection and processing are ongoing, at the time of manuscript preparation, scanning was attempted on 137 infants and usable T1-weighted, T2-weighted, and resting-state functional connectivity data was obtained from 79 infants. Five out of the 79 subjects with functional MRI data were excluded due to poor data quality (e.g., significant motion during the fieldmap scan). Two participants with less than five minutes of resting-state functional data (<0.2mm framewise displacement) at this stage were removed, leaving 72 infants for data analysis (See Table 1 for detailed sample characteristics). There were no statistically significant differences ($p<.05$) in demographic characteristics (i.e., infant sex, infant age at assessment (corrected for due date), infant race, infant ethnicity, caregiver education, income-to-needs ratio), negative affectivity measures

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

(i.e., age 1 month recorded and parent-report crying, age 6 months recorded and parent-report crying, and age 6 months temperamental negative affectivity), and age 18 months internalizing and externalizing symptoms between the final sample and those excluded (See Supplemental Table 1 for results on group differences)."

Procedures

Eligible infants underwent MRI scanning during natural sleep when they were between four and six weeks of age while parents completed a battery of questionnaires. Mother–infant dyads were subsequently invited back for a follow-up assessment at infant age six-months and eighteen-months during which parents were asked to complete a battery of questionnaires as well.

At both the one- and six-month assessments, families were asked to collect audio recordings of their infant's home environment via the Language Environment Analysis (LENA) digital language processors (DLPs). The LENA DLPs are small wearable devices that record audio continuously and the LENA software is designed to detect audio events (e.g., infant crying, words, conversations, etc.) in the child's environment. Families were provided with two LENA DLPs along with vests, in which the devices were placed, for the infants to wear. Participants were asked to record using the LENA for two days, 16 hours each day (most often one weekday and one weekend day). Participants were instructed to begin recording at the start of the day and to keep the devices on the child or near the child when removal was necessary (e.g., bath time).

Study data were collected and managed using REDCap electronic data capture tools hosted at Vanderbilt University (Harris et al., 2009, 2019). Participants were compensated $20/hour for participation at each timepoint.

MRI Acquisition

MR images were acquired at infant age of ~one-month at the Vanderbilt University Institute of Imaging Science (VUIIS) Center for Human Imaging using a Philips Ingenia Elition 3.0T equipped with a 32-channel head coil. Infants were prepared using the "swaddle and soothe" method and scanned during natural sleep in the evenings (for more details, see Camacho et al., 2020). Families arrived at the imaging suite typically between 5:30pm and 7:30pm. The infant was changed into a disposable diaper and swaddled using a muslin blanket before being wrapped by a MedVac immobilizer designed for infants. The infant was then fitted with hearing protection which included placing silicone ear putty in their ears secured with skin-safe medical tape and covering their ears with Natus MiniMuffs (Styrofoam pads with adhesives) for additional noise reduction. Parents were then encouraged to feed their infant and put their infant to sleep. Once the infant was asleep for at least 20 minutes, the infant was transferred to the scanner bed and slim-fit headphones playing pink noise intermixed with rain sounds were placed on their ears. The infant's head and the headphones were secured with foam pads to fill out the head coil space and reduce likelihood of motion during scanning. If the infant remained soundly asleep, acquisition was initiated, otherwise the infant was given additional time to move back into a deep sleep before starting the scan. A trained research assistant remained with the infant during the scan to monitor the infant

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

and alert the scan technician if the infant woke up. The researcher soothed the infant back to a deep sleep if the infant woke up before resuming scanning. This process was repeated until either all data were collected or the family decided to end the session.

The scans collected included a T1-weighted anatomical image (TR=10ms, TE=4.6ms, TI=700ms, flip angle=8 degrees, FOV=256×256×150mm, resolution = $1\times1\times1mm^3$), T2-weighted anatomical image (TR=2500ms, TE=310ms, flip angle=90 degrees, FOV=220×220×144mm, resolution=$0.8\times0.8\times0.8mm^3$), and resting-state fMRI (resolution=$2.0\times1.9\times1.9\ mm^3$, 54 axial slices, 96×96 acquisition matrix, flip angle=60 degrees, TR=1410 ms, TE=30 ms, 3 simultaneous slices, 270 contiguous volumes). Framewise Integrated Real-time MRI monitoring (FIRMM) software was installed by VUIIS partway through data collection and, since its installation, was used to monitor motion in real time for the resting-state scan and the sequence was repeated until approximately 10-minutes of fMRI data under 0.2mm framewise displacement was collected. All MR images were visually inspected for artifacts prior to processing.

MRI Processing

Anatomical processing.—MR image preprocessing was conducted using Nibabies (https://nibabies.readthedocs.io/en/latest/), an open-source software pipeline designed and optimized to process anatomical and functional magnetic resonance imaging data from human infants between 0–2 years old. Nibabies utilizes Infant FreeSurfer (https://surfer.nmr.mgh.harvard.edu/fswiki/infantFS) to process T1-weighted and T2-weighted anatomical images (Zöllei et al., 2020). Registration of each participant's anatomical image to the template (MNIInfant:cohort-1) was inspected for accuracy before subsequent processing.

Functional connectivity processing.—The fMRI data preprocessing was performed using fMRIPrep 21.0.1+0.g0c07d63.dirty (Esteban et al., 2019), which is based on Nipype 1.6.1 (Gorgolewski et al., 2011). A B_0-nonuniformity map (or *fieldmap*) was estimated based on two (or more) echo-planar imaging (EPI) references with topup (FSL 5.0.11). BOLD runs were slice-time corrected to 0.666s (0.5 of slice acquisition range 0s-1.33s) using 3dTshift from AFNI (Cox & Hyde, 1997). Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using mcflirt (FSL 5.0.11, Jenkinson et al., 2002). The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying the transforms to correct for head-motion. These resampled BOLD time-series will be referred to as preprocessed BOLD in original space, or just preprocessed BOLD. The BOLD reference was then co-registered to the T1-weighted reference using flirt (FSL 5.0.11, Jenkinson & Smith, 2001) with the boundary-based registration (Greve & Fischl, 2009) cost-function. Co-registration was configured with nine degrees of freedom to account for distortions remaining in the BOLD reference. First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. Several confounding time-series were calculated based on the preprocessed BOLD: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed using two formulations

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

following Power (absolute sum of relative motions; Power et al., 2014) and Jenkinson (relative root mean square displacement between affines; Jenkinson et al., 2002). FD and DVARS are calculated for each functional run, both using their implementations in Nipype (following the definitions by Power et al., 2014). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al., 2013). The BOLD time-series were resampled into standard space, generating a preprocessed BOLD run in MNIInfant:cohort-1 space. First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. All resamplings can be performed with a single interpolation step by composing all the pertinent transformations (i.e., head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using antsApplyTransforms (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos, 1964). Registration of each participant's functional MRI image to the anatomical image and to the template was inspected for accuracy before subsequent processing. 5 out of the 79 subjects with functional MRI data were excluded due to errors in processing.

Preprocessed functional MRI data were denoised, bandpass filtered, and high motion volumes dropped before functional connectivity analysis. Specifically, motion metrics obtained during rigid realignment were notch filtered at 30–60 breaths per minute to remove breathing artifacts from head motion estimates (Fair et al., 2020; Kaplan et al., 2022). Nuisance regressors removed during denoising included global signal, filtered motion estimates, Volterra expansion of the first derivative of filtered motion estimates (lagged 6 times), and censoring of volumes that exceeded 0.09 filtered FD, for a total of 43 nuisance regressors plus censoring. Denoised data were next bandpass filtered (0.009–0.1 Hz) and volumes that were censored were dropped from the timeseries. 2 participants with less than 5-minutes of data at this stage were removed, leaving 72 infants for the connectivity analysis. We included global signal regression because it has been found to reduce artifacts, including motion-related and respiratory-related artifacts, thereby enhancing brain–behavior associations (Ciric et al., 2017; J. Li et al., 2019; Zhang et al., 2019). Regression of global signal shifts connectivity correlations across the brain from positive values to being centered at approximately zero (Murphy et al., 2009; Murphy & Fox, 2017) and thus negative correlations should be interpreted as relatively less connectivity as opposed to negative connectivity.

Connectivity analysis.—The DMN and FPN were defined using a recently published volume space regions of interest (ROI) and network designations (Seitzman et al., 2020). We chose to use an adult network schema due to recent evidence suggesting that the functional architecture of these networks may be present but weak at one-month of age (Sylvester et al., 2022) and because we are interested in connectivity of regions that will become the networks identified in adults. Specifically, the volume space 5mm ROIs were warped to the infant template and manually corrected for accuracy (Figure 1). For each infant, intra- and inter-network connectivity was computed as the Pearson correlation between ROIs, which

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

was then z-scored (Fisher Z) and averaged across parcels, resulting in a single measure for each infant for each DMN intranetwork, FPN intranetwork, and DMN–FPN internetwork connectivity.

Negative Affectivity

Infant crying.—Infant crying estimates were obtained using two methods at ages one- and six-month assessments. First, parents completed a brief questionnaire that asked them to provide estimates of the number of hours, on average, that their infant cried over each 24-hour period over the past week (e.g., “Approximately how many hours did your baby cry today”, “Approximately how many hours did your baby cry yesterday”, “Approximately how many hours did your baby cry two days ago”, etc.). The reported hours of crying were then averaged across the one-week period to obtain a single estimate of parent-reported infant crying for both age one-month (N=72, M=1.62, SD=1.04) and six-month timepoints (N=55, M=1.12, SD=0.92). Parent-reported infant crying demonstrated excellent internal consistency with Cronbach’s α=.97 and .96 for age one- and six-months respectively.

Second, we obtained an estimate of infant crying from approximately 32 hours of home audio recordings collected across two days (~16 hours per day) using the LENA recording devices using the crying detection model developed by Yao et al. (2022) and obtained from github.com/AgnesMayYao/Infant-Crying-Detection. Infant crying noises have a mean F0 range of 441.8 to 502.9 Hz (Rothgänger, 2003). LENA recordings were first preprocessed to filter out any acoustic events that were not crying noises (e.g., segments that were silent above a 350 Hz threshold). The remaining audio segments were then analyzed for crying noises. Estimates were produced for one-second intervals and filtered as either “crying” or “not crying.” These one-second intervals were then concatenated into five-minute segments. To ensure accuracy of the crying estimates, a random five-minute segment from each of four random subjects was manually annotated at the second-by-second level. Automatic labeling was then compared to the manually labeled data for accuracy and precision of crying labels. The automatic labeling had a 94.25% accuracy with 71.49% precision, lending confidence in our crying estimates. Average crying estimate per hour for one- (N=24, M=185.59 seconds, SD=104.93 seconds) and six-month (N=42, M=225.83 seconds, SD=102.72 seconds) timepoints were used for further analysis.

Temperamental negative affectivity.—Parents completed the Infant Behavior Questionnaire-Short Form Revised (IBQ-SF-R; Putnam et al., 2014) at age six-month assessment (N=54). This 91-item questionnaire has excellent interrater and test-retest reliability (Putnam et al., 2014). The IBQ-SF-R comprises 13 subscales which assess infants’ tendencies toward reactivity, emotionality, and regulation. Our analyses focused on the Negative Affectivity domain, which included the following subscales: Sadness, Distress to Limitations, Fear, and Falling Reactivity (reverse scored).

Toddler Emotion Dysregulation Symptoms

Parent-report of child emotion dysregulation (internalizing symptoms) were obtained using the preschool version of the Child Behavior Checklist for ages 1.5–5 (CBCL; Achenbach & Edelbrock, 1983) at age eighteen-month assessment (N=25). We asked parents to reflect

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

on their child's behavior over the past six months and to rate each of the items on the questionnaire (preschool vision consisted of 99 items) on a 3-point Likert scale (0 = not true; 1 = somewhat or sometimes true; 2 = very true/often). The CBCL demonstrates strong psychometric properties (Achenbach & Edelbrock, 1983; Warnick et al., 2008). The ratings yield scores on internalizing symptoms, externalizing symptoms, and overall difficulties (i.e., total problems score). The internalizing and externalizing symptoms scores were used for exploratory analysis.

Pre-registered Data Analytic Plan

Robust linear regression was used to test the pairwise associations among one-month DMN and FPN intra- and internetwork resting-state functional connectivity and one- and six-months infant negative affectivity as it de-weights potential outliers. Infant age at assessment (corrected for due date) and average motion were entered as covariates. Additional potential covariates (i.e., parity [first child vs. not], sex of the infant, maternal age, and income-to-needs ratio) were evaluated using a model fitting approach to determine whether to also include in the final model. Specifically, to preserve model parsimony, only covariates that were significantly associated with functional connectivity, as determined by the Pillai's test statistic with p-value of less than .05, in the multivariate multiple regression model were included.

Exploratory analysis examined associations among one-month DMN and FPN intra- and internetwork resting-state functional connectivity, ages one- and six-month negative affectivity, and internalizing and externalizing symptoms at age eighteen-months.

Deviations from the Pre-registration

We deviated from our pre-registered plan (https://osf.io/5dkqt/?view_only=328aa68fab124631ba288acfff8d838b) in four ways. First, we had originally planned to analyze the data in surface space using parcels. Given a delay in the availability of usable surfaces, we chose to analyze the brain data using volume space—and ROIs defined for volume space analyses—instead. Second, we had stated that we would extract average crying per day from the LENA recordings. Due to some subjects having two days of recordings while others only had one, we chose to use average crying per hour instead. Third, correlation analysis was conducted in place of the Pillai's test to determine which covariates to include in the regression analyses. Finally, while data collection and processing are ongoing, at the time of manuscript preparation, scanning was attempted on 137 infants and usable T1-weighted, T2-weighted, and resting-state functional connectivity data was obtained from 79 infants. Five out of the 79 subjects with functional MRI data were excluded due to poor data quality (e.g., significant motion during the fieldmap scan). Two participants with less than five minutes of resting-state functional data at this stage were removed, leaving 72 infants for the connectivity analysis.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Results

Associations among variables of interest

Distribution of all variables of interest were examined using histogram plots and given outliers in recorded crying estimates, Spearman bivariate correlation analysis was conducted to examine associations among variables (Table 2). Results revealed that DMN connectivity was positively and statistically associated with FPN and internetwork connectivity, and FPN connectivity was positively and statistically associated with internetwork connectivity. Parent-reported crying at age one-month was positively and statistically associated with parent-reported crying at age six-months, temperamental negative affectivity at age six-months, and internalizing symptoms at age eighteen-months. Parent-reported crying at age six-months was positively and statistically associated with temperamental negative affectivity at age six-months. Recorded crying at age six-months was positively and statistically associated with externalizing symptoms at age eighteen-months. Temperamental negative affectivity at age six-months was positively and statistically associated with internalizing symptoms at age eighteen-months. Internalizing symptoms and externalizing symptoms were positively and statistically associated at age eighteen-months.

Spearman bivariate correlation analyses with covariates of non-interest revealed that maternal age was negatively and statistically associated with temperamental negative affectivity at age six-months and internalizing symptoms at age eighteen-months. Income-to-needs ratio was negatively and statistically associated with DMN and FPN intra- and internetwork connectivity as well as temperamental negative affectivity at age six-months.

Concurrent associations between one-month DMN and FPN connectivity and Negative Affectivity

Robust linear regression models included infant age at assessment (corrected for due date), average motion, income-to-needs ratio, and infant sex as covariates of non-interest. In contrast to our hypotheses, DMN connectivity at one-month was *negatively* associated with parent-reported crying (β=−0.36, 95% CI [−0.62, −0.11], p=.006, N=66; Figure 2). In the subset of infants with DMN and recorded crying, the magnitude of the effect was similar although not statistically significant (β=−0.27, 95% CI [−0.83, 0.28], p=.341, N=19). Further, contrary to our hypotheses, FPN intra- and internetwork connectivity were not statistically associated with concurrent negative affectivity (βs<−0.03, ps>.713, Ns>19). See Table 3 for full model statistics for significant associations.

Longitudinal associations between one-month DMN and FPN connectivity and age six-months negative affectivity

Robust linear regression models included infant age at assessment (corrected for due date), average motion, income-to-needs ratio, and infant sex as covariates of non-interest. For the regression model with recorded crying at age six-months, parity was included as an additional covariate of non-interest due to statistically significant group differences, $t(24)$=−3.35, p<.01 (Cohen's d=−1.16, 95% CI [−1.82, −0.49]), such that first-born infants cried less than those infants with older siblings. DMN connectivity at one-month was negatively and statistically associated with age six-months temperamental negative

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

affectivity (β=−0.35, 95% CI= [−0.66, −0.05], p=.025, *N*=49; Figure 2) but not with recorded or parent-reported crying (βs<0.16, ps>.280, *Ns*>36). See Table 3 for full model statistics for significant associations.

Exploratory analyses with eighteen-month symptoms

Robust linear regression models included infant age at assessment (corrected for due date), average motion, income-to-needs ratio, and infant sex as covariates of non-interest. DMN connectivity at one-month was negatively and statistically associated with age eighteen-months internalizing symptoms (β=−0.58, 95% CI= [−0.99, −0.16], p=.012, *N*=20; Figure 3). The association was in the same direction but weaker in magnitude for externalizing symptoms, and was not statistically significant (β=−0.28, 95% CI= [−0.66, 0.09], p=.165, *N*=20). FPN intra- and internetwork connectivity were not statistically associated with age eighteen-months symptoms (βs<0.03, ps>.225). See Table 3 for full model statistics for significant associations.

Discussion

In this study, we sought to characterize the longitudinal associations between one-month FPN and DMN connectivity and concurrent and age six-months negative affectivity. We used multiple measures of negative affectivity, including parent-reported temperament and crying, as well as quantitative measures of crying from naturalistic recordings. In contrast to our preregistered hypotheses, we found evidence for a negative association between connectivity within DMN and age one- and six-months negative affectivity measures as well as with age eighteen-months internalizing symptoms. We also found no associations among one-month FPN connectivity and negative affectivity. This work furthers a neurodevelopmental model of emotion dysregulation by suggesting that infant brain connectivity is associated with later emotional functioning.

Our findings suggest that DMN brain functioning at birth is associated with future socio-emotional behavior. Research in adult populations indicates that the DMN plays a strong role in affective experience (Satpute & Lindquist, 2019) and social processing (Brandman et al., 2021; Buckner & DiNicola, 2019). Specifically, the DMN is composed of regions that integrate sensory stimuli and regions that interface with each saliency and executive function processing networks of the brain, which dynamically shift in connectivity strength during social processing (Yeshurun et al., 2021). Though there is little research examining infant DMN functional connectivity in relation to negative affectivity, a recent study found that functional connectivity of the amygdala–superior frontal gyrus (a region of the DMN) functional connectivity at four months of age was positively correlated with negative affectivity concurrently (Filippi et al., 2020). Another study examining amygdala–DMN functional connectivity found that newborn connectivity was positively associated with fearful behaviors at six months of age (Graham et al., 2016), though concurrent negative affectivity was not examined. Together, these findings suggest a link between DMN connectivity and socio-emotional functioning from birth. Notably, in contrast to these findings and to our hypotheses, our results revealed a negative association between intra-network DMN connectivity, and negative affectivity and internalizing symptom measures.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Past work suggests that adolescents and adults at high versus low familial risk for depression exhibit increased DMN intra-network connectivity and these findings remain statistically significant even after excluding individuals with a current or lifetime history of depression (Posner et al., 2016). There is also evidence to suggest increased connectivity between the PCC and DMN regions in children with known depression during the preschool period (Gaffrey et al., 2012). However, in youth age 9–15 years who were followed annually over a 3-year period, greater depressive symptomatology was found to be associated with significant decreases in within-network DMN connectivity over time (Son et al., 2023). Thus, it is possible for the associations to change over time as the DMN is understood to reach maturity in adulthood (Grayson & Fair, 2017).

Our results also revealed that DMN and FPN intranetwork connectivity were positively associated with one another. Past work on brain development in early life examined correlations between these networks across three timepoints in infancy (neonates, 1-year-olds, and 2-year-olds); these networks were positively correlated in neonates but, by age 1 year they were negatively, and further the magnitude of the negative correlation was larger still at age 2 years (Gao et al., 2013). This suggests these networks segregate across the first year or life. Results from our work adds to this body of literature and underscores the importance of future work examining longitudinal changes in connectivity in the first year of life.

We also found that DMN and FPN intra- and internetwork connectivity was not associated with age six-months crying. One possible explanation is the change in how infants communicate—and, by extension, how their caregivers respond—over the first six months of life. Our naturalistic recordings indicate that infants cried, on average, about the same amount at one- and six-months, which is consistent with other research (Wolke et al., 2017). However, while overall levels are consistent, the reasons for crying–as well as how caregivers interpret crying– shifts from birth to middle infancy. In early infancy, humans are not yet capable of speech and have limited vision and motor control. As a result, their primary means of signaling to their caregivers is through crying (Keller & Schölmerich, 1987; Wolke et al., 2017). Early crying may not, therefore, be a product of distress so much as it is a signal for caregiver attention, resulting in caregivers typically responding by troubleshooting what the infant needs (T. G. Power et al., 1990). In contrast, by six months of age, infants typically have a more diverse repertoire in terms of types of vocalizations (Keller & Schölmerich, 1987; Oller et al., 2013), can reach (Berthier, 1996; Kirk et al., 2022), have control of their upper bodies, and otherwise use social signals to communicate with caregivers. Further, colic represents a larger proportion of crying observed at six-months than at newborn (Wolke et al., 2017). As a result, caregivers may be more likely to interpret crying in older infants as fussiness (T. G. Power et al., 1990), eliciting more diverse reactions that are dependent on the caregivers own attitudes, mood state, and parenting style.

The foundations of the networks supporting cognitive development, including the DMN, at one month of age are thus likely associated with how the infant interacts with their caregivers as well as how they receive the scaffolding that caregivers provide to deal with negative mood states, which in turn may be associated with how the infant expresses

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

themselves later in life. It is therefore possible that while associations between DMN connectivity near birth and crying do not persist, each infant's unique DMN functioning near birth may still be associated with emotion functioning more broadly. Further research is needed to characterize how early postnatal experiences interact with foundational brain development to shape emotional development. For instance, future work could examine associations between functional connectivity at age one-month and caregiving behavior at age six-months as well as whether caregiving behavior mediates associations between functional connectivity at age one-month and negative affectivity at age eighteen-months months. Moreover, given that six-month-olds with older siblings exhibited more crying than first-born infants, it is possible amount of crying may be influenced by the presence of siblings such that multiple children result in competing caregiving demands and reduced responsiveness to the infant. A not-mutually exclusive alternative is that older siblings may engage in behaviors that elicits greater crying. Our findings differ from evidence from Wikander and Theorell (1995) which found that infants with two or more siblings cried significantly less than other infants. However, in this study crying estimates were obtained solely via parent-report. Taken together, examining transactional associations between postnatal influences such as, caregiving behavior and presence of siblings, and functional connectivity and negative affectivity is critical to elucidating pathways implicated in the development of early indicators of emerging psychopathology.

We found evidence for associations between the functional architecture of the DMN near birth and emotional functioning. It is possible that these early brain connectivity metrics are under genetic control. However, it is also possible that experience prenatally may be shaping neurodevelopment. Recent research has found that prenatal cortisol and inflammation (Graham et al., 2018, 2019; Rudolph et al., 2018; Spann et al., 2018), prenatal stress and mental health (Humphreys et al., 2020; Rifkin-Graboi et al., 2013, 2015; Scheinost et al., 2020), and prenatal socioeconomic status and environmental stressors (Brady et al., 2022; Lean et al., 2022) have all been associated with newborn infant brain structure and function, with a principle focus on the so-called limbic system (amygdala, hippocampus, insula, and cingulate). It is thus possible that the associations between DMN connectivity near birth and later functioning may be, in part, due to the prenatal environment shaping top–down systems with protracted development such as the DMN. Another consideration is genetic influences which may influence foundational (and prospective) infant brain development. For instance, adoption studies have demonstrated that genetic offspring of individuals with emotion dysregulation are at an elevated and transdiagnostic risk (Shih et al., 2009), indicating a partial genetic component to such disorders. A careful examination of to what degree genetic, prenatal, and postnatal factors contribute to functional network and infant emotional development will be critical for teasing apart the unique influences of each.

This study has several strengths, including both the use of a longitudinal sample with multiple measures of negative affectivity and the use of both objective (crying estimates from LENA audio recordings) and subjective (parent-report) measures of infant negative affectivity. There are also several limitations to this work. First, while the sample size is larger than most previous work examining infant functional connectivity (Pollatou et al., 2022), recent work conducted in older children and adults suggest that much larger sample sizes are needed to find replicable brain–behavior associations (Marek et al., 2022).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Though finding the same association across multiple measures of negative affectivity lends confidence to our results, this finding must be replicated in a separate sample before strong conclusions can be made. Second, given the novelty of using a crying detection algorithm on LENA recordings to obtain crying estimates, it is unclear how reliable it may be in capturing infant crying. While preliminary examination of accuracy by manually coding a random five-minute segment from each of four random subjects at each of the timepoints revealed high accuracy with acceptable precision, future work utilizing such crying detection models might benefit from other tools to capture crying to compare with the estimates obtained from the algorithm as well as examining correlations with other forms of crying measures. Third, although not all participants in our sample shared the same racial identity or were from the same social class, relative to the U.S. population our sample was more likely to identify their infants as White and to report annual household incomes that were middle-class or higher. Fourth, due to time constraints and the difficulties associated with processing infant MRI data (Korom et al., 2022), we ultimately processed the data in volume space, which is known to have poorer participant–participant registration than surface space analysis in children (Ghosh et al., 2010). Future research will aim to use new tools that enable more accurate segmentation of infant brains and allow for surface-based registration across participants. Finally, while there is an established literature linking infant negative affectivity and increased risk for later psychiatric diagnoses, no psychiatric diagnoses were assessed given the age of the toddlers at follow-up. As a result, it is unclear whether there is clinical significance to the associations and levels of functioning demonstrated in this sample. Future work replicating this work in large longitudinal datasets such as, the HEALthy Brain and Child Development study will be crucial in shedding light on the degree to which these associations may be adaptive or maladaptive across development.

In summary, we found evidence that DMN connectivity at one-month was associated with greater negative affectivity at ages one and six months, as well as with internalizing symptoms at age 18 months, suggesting that infant functional connectivity at rest is associated with later emotional functioning. Given this association is present shortly after birth, it suggests that factors such as genetics and/or prenatal environment may account for some of the variance in the neural circuitry and negative affectivity. Our study adds to a growing body of research suggesting that brain functioning as early as near birth may be pertinent to young children's emotional development, thus rendering itself to be a critical time for potential early interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the families who contributed their time to BABIES (Brain and Behavior: Infant Experiences Study). We thank the study staff and students who assisted with recruitment, data collection, and data cleaning.

Funding

This work was supported by the Jacobs Foundation Early Career Research Fellowship (2017-1261-05); National Science Foundation CAREER Award (2042285); National Institutes of Health (F32 MH132185); John and Polly

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Sparks Foundation Investigator Award from the Brain and Behavior Research Foundation (29593); Vanderbilt Institute for Clinical and Translational Research Grant (VR53419); Vanderbilt Strong Grant; Vanderbilt Kennedy Center Grant; National Center for Advancing Translational Sciences (UL1 TR000445).

References

Achenbach TM, & Edelbrock CS (1983). Manual for the child behavior checklist and revised child behavior profile. Burlington: University of Vermont.

Berthier NE (1996). Learning to reach: A mathematical model. Developmental Psychology, 32(5), 811–823. Scopus. 10.1037/0012-1649.32.5.811

Brady RG, Rogers CE, Prochaska T, Kaplan S, Lean RE, Smyser TA, Shimony JS, Slavich GM, Warner BB, Barch DM, Luby JL, & Smyser CD (2022). The Effects of Prenatal Exposure to Neighborhood Crime on Neonatal Functional Connectivity. Biological Psychiatry, 92(2), 139–148. 10.1016/j.biopsych.2022.01.020 [PubMed: 35428496]

Brandman T, Malach R, & Simony E (2021). The surprising role of the default mode network in naturalistic perception. Communications Biology, 4(1), 79. 10.1038/s42003-020-01602-z [PubMed: 33469113]

Buckner RL, & DiNicola LM (2019). The brain's default network: Updated anatomy, physiology and evolving insights. Nature Reviews Neuroscience, 20(10), 593–608. 10.1038/s41583-019-0212-7 [PubMed: 31492945]

Camacho MC, Quiñones-Camacho LE, & Perlman SB (2020). Does the child brain rest?: An examination and interpretation of resting cognition in developmental cognitive neuroscience. NeuroImage. 10.1016/j.neuroimage.2020.116688

Chronis-Tuscano A, Degnan KA, Pine DS, Perez-Edgar K, Henderson HA, Diaz Y, Raggi VL, & Fox NA (2009). Stable Early Maternal Report of Behavioral Inhibition Predicts Lifetime Social Anxiety Disorder in Adolescence. Journal of the American Academy of Child & Adolescent *Psychiatry*, 48(9), 928–935. 10.1097/CHI.0b013e3181ae09df [PubMed: 19625982]

Clasen PC, Beevers CG, Mumford JA, & Schnyer DM (2014). Cognitive control network connectivity in adolescent women with and without a parental history of depression. Developmental Cognitive Neuroscience, 7, 13–22. 10.1016/j.dcn.2013.10.008 [PubMed: 24270043]

Clauss JA, & Blackford JU (2012). Behavioral Inhibition and Risk for Developing Social Anxiety Disorder: A Meta-Analytic Study. In JOURNAL OF THE AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY (Vol. 51, Issue 10, pp. 1066–1075). www.jaacap.org [PubMed: 23021481]

Cox RW, & Hyde JS (1997). Software tools for analysis and visualization of fMRI data. NMR in Biomedicine, 10(4–5), 171–178. 10.1002/(SICI)1099-1492(199706/08)10:4/5<171::AID-NBM453>3.0.CO;2-L [PubMed: 9430344]

Crawford NA, Schrock M, & Woodruff-Borden J (2011). Child Internalizing Symptoms: Contributions of Child Temperament, Maternal Negative Affect, and Family Functioning. Child Psychiatry & Human Development, 42(1), 53–64. 10.1007/s10578-010-0202-5 [PubMed: 20734130]

Dalili MN, Penton-Voak IS, Harmer CJ, & Munafò MR (2015). Meta-analysis of emotion recognition deficits in major depressive disorder. Psychological Medicine, 45(6), 1135–1144. 10.1017/S0033291714002591 [PubMed: 25395075]

Dougherty LR, Klein DN, Durbin CE, Hayden EP, & Olino TM (2010). Temperamental Positive and Negative Emotionality and Children's Depressive Symptoms: A Longitudinal Prospective Study from Age Three to Age Ten. Journal of Social and Clinical Psychology, 29(4), 462–488. 10.1521/jscp.2010.29.4.462

Dougherty LR, Smith VC, Bufferd SJ, Stringaris A, Leibenluft E, Carlson GA, & Klein DN (2013). Preschool Irritability: Longitudinal Associations With Psychiatric Disorders at Age 6 and Parental Psychopathology. Journal of the American Academy of Child & Adolescent Psychiatry, 52(12), 1304–1313. 10.1016/j.jaac.2013.09.007 [PubMed: 24290463]

Ernst M, Benson B, Artiges E, Gorka AX, Lemaitre H, Lago T, Miranda R, Banaschewski T, Bokde ALW, Bromberg U, Brühl R, Büchel C, Cattrell A, Conrod P, Desrivières S, Fadai T, Flor H, Grigis A, Gallinat J, … Martinot J-L (2019). Pubertal maturation and sex effects on the

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

default-mode network connectivity implicated in mood dysregulation. Translational Psychiatry, 9(1), Article 1. 10.1038/s41398-019-0433-6

Esteban O, Markiewicz CJ, Blair RW, Moodie CA, Isik AI, Erramuzpe A, Kent JD, Goncalves M, DuPre E, Snyder M, Oya H, Ghosh SS, Wright J, Durnez J, Poldrack RA, & Gorgolewski KJ (2019). fMRIPrep: A robust preprocessing pipeline for functional MRI. Nature Methods, 16(1), Article 1. 10.1038/s41592-018-0235-4

Fair DA, Miranda-Dominguez O, Snyder AZ, Perrone A, Earl EA, Van AN, Koller JM, Feczko E, Tisdall MD, van der Kouwe A, Klein RL, Mirro AE, Hampton JM, Adeyemo B, Laumann TO, Gratton C, Greene DJ, Schlaggar BL, Hagler DJ, … Dosenbach NUF (2020). Correction of respiratory artifacts in MRI head motion estimates. NeuroImage, 208. 10.1016/j.neuroimage.2019.116400

Fan F, Liao X, Lei T, Zhao T, Xia M, Men W, Wang Y, Hu M, Liu J, Qin S, Tan S, Gao J-H, Dong Q, Tao S, & He Y (2021). Development of the default-mode network during childhood and adolescence: A longitudinal resting-state fMRI study. NeuroImage, 226, 117581. 10.1016/j.neuroimage.2020.117581 [PubMed: 33221440]

Filippi CA, Ravi S, Bracy M, Winkler A, Sylvester CM, Pine DS, & Fox NA (2020). Amygdala Functional Connectivity and Negative Reactive Temperament at Age Four Months. Journal of the American Academy of Child & Adolescent Psychiatry. 10.1016/j.jaac.2020.11.021

Gao W, Alcauter S, Elton A, Hernandez-Castillo CR, Smith JK, Ramirez J, & Lin W (2015). Functional Network Development During the First Year: Relative Sequence and Socioeconomic Correlations. Cerebral Cortex, 25(9), 2919–2928. 10.1093/cercor/bhu088 [PubMed: 24812084]

Gao W, & Lin W (2012). Frontal parietal control network regulates the anti-correlated default and dorsal attention networks. Human Brain Mapping, 33(1), 192–202. 10.1002/hbm.21204 [PubMed: 21391263]

Gao W, Zhu H, Giovanello KS, Smith JK, Shen D, Gilmore JH, & Lin W (2009). Evidence on the emergence of the brain's default network from 2-week-old to 2-year-old healthy pediatric subjects. Proceedings of the National Academy of Sciences, 106(16), 6790–6795. 10.1073/pnas.0811221106

Ghosh SS, Kakunoori S, Augustinack J, Nieto-Castanon A, Kovelman I, Gaab N, Christodoulou JA, Triantafyllou C, Gabrieli JDE, & Fischl B (2010). Evaluating the validity of volume-based and surface-based brain image registration for developmental cognitive neuroscience studies in children 4 to 11years of age. NeuroImage, 53(1), 85–93. 10.1016/j.neuroimage.2010.05.075 [PubMed: 20621657]

Gilmore JH, Knickmeyer RC, & Gao W (2018). Imaging structural and functional brain development in early childhood. Nature Reviews Neuroscience, 19(3), 123–137. 10.1038/nrn.2018.1 [PubMed: 29449712]

Gorgolewski K, Burns CD, Madison C, Clark D, Halchenko YO, Waskom ML, & Ghosh SS (2011). Nipype: A Flexible, Lightweight and Extensible Neuroimaging Data Processing Framework in Python. Frontiers in Neuroinformatics, 5, 13. 10.3389/fninf.2011.00013 [PubMed: 21897815]

Graham AM, Buss C, Rasmussen JM, Rudolph MD, Demeter DV, Gilmore JH, Styner M, Entringer S, Wadhwa PD, & Fair DA (2016). Implications of newborn amygdala connectivity for fear and cognitive development at 6-months-of-age. Developmental Cognitive Neuroscience, 18, 12–25. 10.1016/j.dcn.2015.09.006 [PubMed: 26499255]

Graham AM, Rasmussen JM, Entringer S, Ben Ward E, Rudolph MD, Gilmore JH, Styner M, Wadhwa PD, Fair DA, & Buss C (2019). Maternal Cortisol Concentrations During Pregnancy and Sex-Specific Associations With Neonatal Amygdala Connectivity and Emerging Internalizing Behaviors. Biological Psychiatry. 10.1016/j.biopsych.2018.06.023

Graham AM, Rasmussen JM, Rudolph MD, Heim CM, Gilmore JH, Styner M, Potkin SG, Entringer S, Wadhwa PD, Fair DA, & Buss C (2018). Maternal Systemic Interleukin-6 During Pregnancy Is Associated With Newborn Amygdala Phenotypes and Subsequent Behavior at 2 Years of Age. Biological Psychiatry, 83(2), 109–119. 10.1016/j.biopsych.2017.05.027 [PubMed: 28754515]

Grayson DS, & Fair DA (2017). Development of large-scale functional networks from birth to adulthood: A guide to the neuroimaging literature. NeuroImage, 160, 15–31. 10.1016/j.neuroimage.2017.01.079 [PubMed: 28161313]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Greve DN, & Fischl B (2009). Accurate and robust brain image alignment using boundary-based registration. NeuroImage, 48(1), 63–72. 10.1016/j.neuroimage.2009.06.060 [PubMed: 19573611]

Hardi FA, Goetschius LG, McLoyd V, Lopez-Duran NL, Mitchell C, Hyde LW, Beltz AM, & Monk CS (2022). Adolescent functional network connectivity prospectively predicts adult anxiety symptoms related to perceived COVID-19 economic adversity. Journal of Child Psychology and Psychiatry, n/a(n/a). 10.1111/jcpp.13749

Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J, & Duda SN (2019). The REDCap consortium: Building an international community of software platform partners. Journal of Biomedical Informatics, 95, 103208. 10.1016/j.jbi.2019.103208 [PubMed: 31078660]

Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, & Conde JG (2009). Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics, 42(2), 377–381. 10.1016/j.jbi.2008.08.010 [PubMed: 18929686]

Humphreys KL, Camacho MC, Roth MC, & Estes EC (2020). Prenatal stress exposure and multimodal assessment of amygdala–medial prefrontal cortex connectivity in infants. Developmental Cognitive Neuroscience, 100877. 10.1016/j.dcn.2020.100877

Jenkinson M, Bannister P, Brady M, & Smith S (2002). Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. NeuroImage, 17, 825–841. 10.1006/nimg.2002.1132 [PubMed: 12377157]

Jenkinson M, & Smith S (2001). A global optimisation method for robust affine registration of brain images. Medical Image Analysis, 5(2), 143–156. 10.1016/S1361-8415(01)00036-6 [PubMed: 11516708]

Kaiser RH, Andrews-Hanna JR, Wager TD, & Pizzagalli DA (2015). Large-Scale Network Dysfunction in Major Depressive Disorder. JAMA Psychiatry, 72(6), 603. 10.1001/jamapsychiatry.2015.0071 [PubMed: 25785575]

Kaplan S, Meyer D, Miranda-Dominguez O, Perrone A, Earl E, Alexopoulos D, Barch DM, Day TKM, Dust J, Eggebrecht AT, Feczko E, Kardan O, Kenley JK, Rogers CE, Wheelock MD, Yacoub E, Rosenberg M, Elison JT, Fair DA, & Smyser CD (2022). Filtering respiratory motion artifact from resting state fMRI data in infant and toddler populations. NeuroImage, 247, 118838. 10.1016/j.neuroimage.2021.118838 [PubMed: 34942363]

Keller H, & Schölmerich A (1987). Infant vocalizations and parental reactions during the first 4 months of life. Developmental Psychology, 23, 62–67. 10.1037/0012-1649.23.1.62

Kirk E, Donnelly S, Furman R, Warmington M, Glanville J, & Eggleston A (2022). The relationship between infant pointing and language development: A meta-analytic review. Developmental Review, 64, 101023. 10.1016/j.dr.2022.101023

Korom M, Camacho MC, Filippi CA, Licandro R, Moore LA, Dufford A, Zöllei L, Graham AM, Spann M, Howell B, Shultz S, & Scheinost D (2022). Dear reviewers: Responses to common reviewer critiques about infant neuroimaging studies. Developmental Cognitive Neuroscience, 53, 101055. 10.1016/j.dcn.2021.101055 [PubMed: 34974250]

Lanczos C (1964). Evaluation of Noisy Data. Journal of the Society for Industrial and Applied Mathematics Series B Numerical Analysis, 1(1), 76–85. 10.1137/0701007

Lean RE, Smyser CD, Brady RG, Triplett RL, Kaplan S, Kenley JK, Shimony JS, Smyser TA, Miller JP, Barch DM, Luby JL, Warner BB, & Rogers CE (2022). Prenatal exposure to maternal social disadvantage and psychosocial stress and neonatal white matter connectivity at birth. Proceedings of the National Academy of Sciences, 119(42), e2204135119. 10.1073/pnas.2204135119

Linke JO, Haller SP, Xu E, Nguyen LT, Chue AE, Botz-Zapp C, Revzina O, Samantha P, Ross AJ, Tseng W-L, Shaw P, Brotman MA, Pine DS, Gotts SJ, Leibenluft E, & Kircanski K (2022). Persistent Frustration-Induced Reconfigurations of Brain Networks Predict Individual Differences in Irritability. Journal of the American Academy of Child & Adolescent Psychiatry. 10.1016/j.jaac.2022.11.009

Luby JL, & Navsaria N (2010). Pediatric bipolar disorder: Evidence for prodromal states and early markers. Journal of Child Psychology and Psychiatry, 51(4), 459–471. 10.1111/j.1469-7610.2010.02210.x [PubMed: 20085607]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Marek S, & Dosenbach NUF (2018). The frontoparietal network: Function, electrophysiology, and importance of individual precision mapping. Dialogues in Clinical Neuroscience, 20(2), 133–140. 10.31887/DCNS.2018.20.2/smarek [PubMed: 30250390]

Marek S, Tervo-Clemmens B, Calabro FJ, Montez DF, Kay BP, Hatoum AS, Donohue MR, Foran W, Miller RL, Hendrickson TJ, Malone SM, Kandala S, Feczko E, Miranda-Dominguez O, Graham AM, Earl EA, Perrone AJ, Cordova M, Doyle O, … Dosenbach NUF (2022). Reproducible brain-wide association studies require thousands of individuals. Nature, 603(7902), Article 7902. 10.1038/s41586-022-04492-9

Michelini G, Gair K, Tian Y, Miao J, Dougherty LR, Goldstein BL, MacNeill LA, Barch DM, Luby JL, Wakschlag LS, Klein DN, & Kotov R (2022). Do general and specific factors of preschool psychopathology predict preadolescent outcomes? A transdiagnostic hierarchical approach. Psychological Medicine, 1–10. 10.1017/S003329172200246X

Oller DK, Buder EH, Ramsdell HL, Warlaumont AS, Chorna L, & Bakeman R (2013). Functional flexibility of infant vocalization and the emergence of language. Proceedings of the National Academy of Sciences, 110(16), 6318–6323. 10.1073/pnas.1300337110

Pollatou A, Filippi CA, Aydin E, Vaughn K, Thompson D, Korom M, Dufford AJ, Howell B, Zöllei L, Martino AD, Graham A, Scheinost D, & Spann MN (2022). An ode to fetal, infant, and toddler neuroimaging: Chronicling early clinical to research applications with MRI, and an introduction to an academic society connecting the field. Developmental Cognitive Neuroscience, 54, 101083. 10.1016/j.dcn.2022.101083 [PubMed: 35184026]

Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, & Petersen SE (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. NeuroImage, 84, 320–341. 10.1016/j.neuroimage.2013.08.048 [PubMed: 23994314]

Power TG, Gershenhorn S, & Stafford D (1990). Maternal perceptions of infant difficultness: The influence of maternal attitudes and attributions. Infant Behavior and Development, 13(4), 421–437. 10.1016/0163-6383(90)90014-Y

Putnam SP, Helbig AL, Gartstein MA, Rothbart MK, & Leerkes E (2014). Development and Assessment of Short and Very Short Forms of the Infant Behavior Questionnaire–Revised. Journal of Personality Assessment, 96(4), 445–458. 10.1080/00223891.2013.841171 [PubMed: 24206185]

Rifkin-Graboi A, Bai J, Chen H, Hameed WBR, Sim LW, Tint MT, Leutscher-Broekman B, Chong YS, Gluckman PD, Fortier MV, Meaney MJ, & Qiu A (2013). Prenatal maternal depression associates with microstructure of right amygdala in neonates at birth. Biological Psychiatry, 74(11), 937–944. 10.1016/j.biopsych.2013.06.019

Rifkin-Graboi A, Meaney MJ, Chen H, Bai J, Hameed WBR, Tint MT, Broekman BFP, Chong YS, Gluckman PD, Fortier MV, & Qiu A (2015). Antenatal maternal anxiety predicts variations in neural structures implicated in anxiety disorders in newborns. Journal of the American Academy of Child and Adolescent Psychiatry, 54(4), 313–321.e2. 10.1016/j.jaac.2015.01.013 [PubMed: 25791148]

Rogers CE, Sylvester CM, Mintz C, Kenley JK, Shimony JS, Barch DM, & Smyser CD (2017). Neonatal Amygdala Functional Connectivity at Rest in Healthy and Preterm Infants and Early Internalizing Symptoms. Journal of the American Academy of Child & Adolescent Psychiatry, 56(2), 157–166. 10.1016/j.jaac.2016.11.005 [PubMed: 28117062]

Rothgänger H (2003). Analysis of the sounds of the child in the first year of age and a comparison to the language. Early Human Development, 75(1), 55–69. 10.1016/j.earlhumdev.2003.09.003 [PubMed: 14652159]

Rudolph MD, Graham AM, Feczko E, Miranda-Dominguez O, Rasmussen JM, Nardos R, Entringer S, Wadhwa PD, Buss C, & Fair DA (2018). Maternal IL-6 during pregnancy can be estimated from newborn brain connectivity and predicts future working memory in offspring. Nature Neuroscience, 21(5), 765–772. 10.1038/s41593-018-0128-y [PubMed: 29632361]

Satpute AB, & Lindquist KA (2019). The Default Mode Network's Role in Discrete Emotion. Trends in Cognitive Sciences. 10.1016/j.tics.2019.07.003

Satterthwaite TD, Elliott MA, Gerraty RT, Ruparel K, Loughead J, Calkins ME, Eickhoff SB, Hakonarson H, Gur RC, Gur RE, & Wolf DH (2013). An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

functional connectivity data. NeuroImage, 64, 240–256. 10.1016/j.neuroimage.2012.08.052 [PubMed: 22926292]

Scheinost D, Spann MN, McDonough L, Peterson BS, & Monk C (2020). Associations between different dimensions of prenatal distress, neonatal hippocampal connectivity, and infant memory. Neuropsychopharmacology. 10.1038/s41386-020

Seitzman BA, Gratton C, Marek S, Raut RV, Dosenbach NUF, Schlaggar BL, Petersen SE, & Greene DJ (2020). A set of functionally-defined brain regions with improved representation of the subcortex and cerebellum. NeuroImage, 206. 10.1016/j.neuroimage.2019.116290

Shapero BG, Chai XJ, Vangel M, Biederman J, Hoover CS, Whitfield-Gabrieli S, Gabrieli JDE, & Hirshfeld-Becker DR (2019). Neural markers of depression risk predict the onset of depression. Psychiatry Research: Neuroimaging, 285, 31–39. 10.1016/j.pscychresns.2019.01.006 [PubMed: 30716688]

Shih RA, Belmonte PL, & Zandi PP (2009). A review of the evidence from family, twin and adoption studies for a genetic contribution to adult psychiatric disorders. International Review of Psychiatry. 10.1080/09540260400014401

Spann MN, Monk C, Scheinost D, & Peterson BS (2018). Maternal immune activation during the third trimester is associated with neonatal functional connectivity of the salience network and fetal to toddler behavior. J. Neurosci, 2272–17. 10.1523/JNEUROSCI.2272-17.2018

Sylvester CM, Corbetta M, Raichle ME, Rodebaugh TL, Schlaggar BL, Sheline YI, Zorumski CF, & Lenze EJ (2012). Functional network dysfunction in anxiety and anxiety disorders. Trends in Neurosciences, 35(9), 527–535. 10.1016/j.tins.2012.04.012 [PubMed: 22658924]

Sylvester CM, Kaplan S, Myers MJ, Gordon EM, Schwarzlose RF, Alexopoulos D, Nielsen AN, Kenley JK, Meyer D, Yu Q, Graham AM, Fair DA, Warner BB, Barch DM, Rogers CE, Luby JL, Petersen SE, & Smyser CD (2022). Network-specific selectivity of functional connections in the neonatal brain. Cerebral Cortex, bhac202. 10.1093/cercor/bhac202

Sylvester CM, Smyser CD, Smyser T, Kenley J, Ackerman JJ, Shimony JS, Petersen SE, & Rogers CE (2018). Cortical Functional Connectivity Evident After Birth and Behavioral Inhibition at Age 2. Am J Psychiatry, 175, 180–187. 10.1176/appi.ajp.2017.17010018 [PubMed: 28774192]

Thomason ME (2020). Development of Brain Networks In Utero: Relevance for Common Neural Disorders. Biological Psychiatry. 10.1016/j.biopsych.2020.02.007

Uddin LQ (2010). Typical and atypical development of functional human brain networks: Insights from resting-state fMRI. Frontiers in Systems Neuroscience. 10.3389/fnsys.2010.00021

Visintin E, De Panfilis C, Amore M, Balestrieri M, Wolf RC, & Sambataro F (2016). Mapping the brain correlates of borderline personality disorder: A functional neuroimaging meta-analysis of resting state studies. Journal of Affective Disorders, 204, 262–269. 10.1016/j.jad.2016.07.025 [PubMed: 27552444]

Wakschlag LS, Estabrook R, Petitclerc A, Henry D, Burns JL, Perlman SB, Voss JL, Pine DS, Leibenluft E, & Briggs-Gowan ML (2015). Clinical Implications of a Dimensional Approach: The Normal:Abnormal Spectrum of Early Irritability. Journal of the American Academy of Child & Adolescent *Psychiatry*, 54(8), 626–634. 10.1016/j.jaac.2015.05.016 [PubMed: 26210331]

Wang Y, Gao Y, Tang S, Lu L, Zhang L, Bu X, Li H, Hu X, Hu X, Jiang P, Jia Z, Gong Q, Sweeney JA, & Huang X (2020). Large-scale network dysfunction in the acute state compared to the remitted state of bipolar disorder: A meta-analysis of resting-state functional connectivity. EBioMedicine, 54, 102742. 10.1016/j.ebiom.2020.102742 [PubMed: 32259712]

Warnick EM, Bracken MB, & Kasl S (2008). Screening efficiency of the Child Behavior Checklist and Strengths and Difficulties Questionnaire: A systematic review. Child and Adolescent Mental Health, 13(3), 140–147. 10.1111/j.1475-3588.2007.00461.x [PubMed: 32847173]

Wiggins J, Briggs-Gowan M, Estabrook R, Brotman M, Pine D, Leibenluft E, & Wakschlag LS (2018). Identifying clinically significant irritability in early childhood. Journal of the American Academy of Child and Adolescent Psychiatry.

Wolke D, Bilgin A, & Samara M (2017). Systematic Review and Meta-Analysis: Fussing and Crying Durations and Prevalence of Colic in Infants. The Journal of Pediatrics, 185, 55–61.e4. 10.1016/j.jpeds.2017.02.020 [PubMed: 28385295]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Yao X, Micheletti M, Johnson M, Thomaz E, & de Barbaro K (2022). Infant Crying Detection in Real-World Environments. IEEE INternational Conference on Acoustics, Speech, and Signal Processing.

Yeshurun Y, Nguyen M, & Hasson U (2021). The default mode network: Where the idiosyncratic self meets the shared social world. Nature Reviews Neuroscience, 22(3), 181–192. 10.1038/s41583-020-00420-w [PubMed: 33483717]

Aziz Q, Schnitzler A, & Enck P (2000). Functional Neuroimaging of Visceral Sensation: Journal of Clinical Neurophysiology, 17(6), 604–612. 10.1097/00004691-200011000-00006 [PubMed: 11151978]

Ciric R, Wolf DH, Power JD, Roalf DR, Baum GL, Ruparel K, Shinohara RT, Elliott MA, Eickhoff SB, Davatzikos C, Gur RC, Gur RE, Bassett DS, & Satterthwaite TD (2017). Benchmarking of participant-level confound regression strategies for the control of motion artifact in studies of functional connectivity. NeuroImage, 154, 174–187. 10.1016/j.neuroimage.2017.03.020 [PubMed: 28302591]

Etkin A, Büchel C, & Gross JJ (2015). The neural bases of emotion regulation. Nature Reviews Neuroscience, 16(11), 693–700. 10.1038/nrn4044 [PubMed: 26481098]

Gaffrey MS, Luby JL, Botteron K, Repovš G, & Barch DM (2012). Default mode network connectivity in children with a history of preschool onset depression: Default mode network connectivity in preschool depression. Journal of Child Psychology and Psychiatry, 53(9), 964–972. 10.1111/j.1469-7610.2012.02552.x [PubMed: 22519864]

Li J, Kong R, Liégeois R, Orban C, Tan Y, Sun N, Holmes AJ, Sabuncu MR, Ge T, & Yeo BTT (2019). Global signal regression strengthens association between resting-state functional connectivity and behavior. NeuroImage, 196, 126–141. 10.1016/j.neuroimage.2019.04.016 [PubMed: 30974241]

Li Y, Zhuang K, Yi Z, Wei D, Sun J, & Qiu J (2022). The trait and state negative affect can be separately predicted by stable and variable resting-state functional connectivity. Psychological Medicine, 52(5), 813–823. 10.1017/S0033291720002391 [PubMed: 32654675]

Maugeri L, Moraschi M, Summers P, Favilla S, Mascali D, Cedola A, Porro CA, Giove F, & Fratini M (2018). Assessing denoising strategies to increase signal to noise ratio in spinal cord and in brain cortical and subcortical regions. Journal of Instrumentation, 13(02), C02028–C02028. 10.1088/1748-0221/13/02/C02028

Murphy K, Birn RM, Handwerker DA, Jones TB, & Bandettini PA (2009). The impact of global signal regression on resting state correlations: Are anti-correlated networks introduced? NeuroImage, 44(3), 893–905. 10.1016/j.neuroimage.2008.09.036 [PubMed: 18976716]

Murphy K, & Fox MD (2017). Towards a consensus regarding global signal regression for resting state functional connectivity MRI. NeuroImage, 154, 169–173. 10.1016/j.neuroimage.2016.11.052 [PubMed: 27888059]

Pan J, Zhan L, Hu C, Yang J, Wang C, Gu L, Zhong S, Huang Y, Wu Q, Xie X, Chen Q, Zhou H, Huang M, & Wu X (2018). Emotion Regulation and Complex Brain Networks: Association Between Expressive Suppression and Efficiency in the Fronto-Parietal Network and Default-Mode Network. Frontiers in Human Neuroscience, 12, 70. 10.3389/fnhum.2018.00070 [PubMed: 29662443]

Posner J, Cha J, Wang Z, Talati A, Warner V, Gerber A, Peterson BS, & Weissman M (2016). Increased Default Mode Network Connectivity in Individuals at High Familial Risk for Depression. Neuropsychopharmacology, 41(7), 1759–1767. 10.1038/npp.2015.342 [PubMed: 26593265]

Son JJ, Schantell M, Picci G, Wang Y-P, Stephen JM, Calhoun VD, Doucet GE, Taylor BK, & Wilson TW (2023). Altered longitudinal trajectory of default mode network connectivity in healthy youth with subclinical depressive and posttraumatic stress symptoms. Developmental Cognitive Neuroscience, 60, 101216. 10.1016/j.dcn.2023.101216 [PubMed: 36857850]

Wikander B, & Theorell T (1995). The crying infant: Understandable only in a multidisciplinary perspective. Scandinavian Journal of Social Welfare, 4(4), 246–254. 10.1111/j.1468-2397.1995.tb00110.x

Zhang J, Magioncalda P, Huang Z, Tan Z, Hu X, Hu Z, Conio B, Amore M, Inglese M, Martino M, & Northoff G (2019). Altered Global Signal Topography and Its Different Regional Localization

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

in Motor Cortex and Hippocampus in Mania and Depression. Schizophrenia Bulletin, 45(4), 902–910. 10.1093/schbul/sby138 [PubMed: 30285255]

Zöllei L, Iglesias JE, Ou Y, Grant PE, & Fischl B (2020). Infant FreeSurfer: An automated segmentation and surface extraction pipeline for T1-weighted neuroimaging data of infants 0–2 years. NeuroImage, 218, 116946. 10.1016/j.neuroimage.2020.116946 [PubMed: 32442637]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

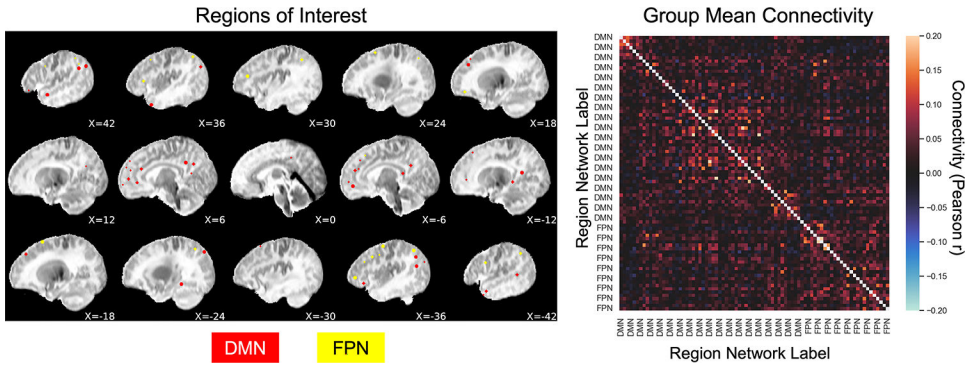

Figure 1:

FPN and DMN cortical regions of interest (ROIs) from the Seitzman atlas (Seitzman et al., 2020) and sample group mean connectivity. Each region was 5mm in diameter and manually edited to ensure placement consistent with adult template landmarks.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

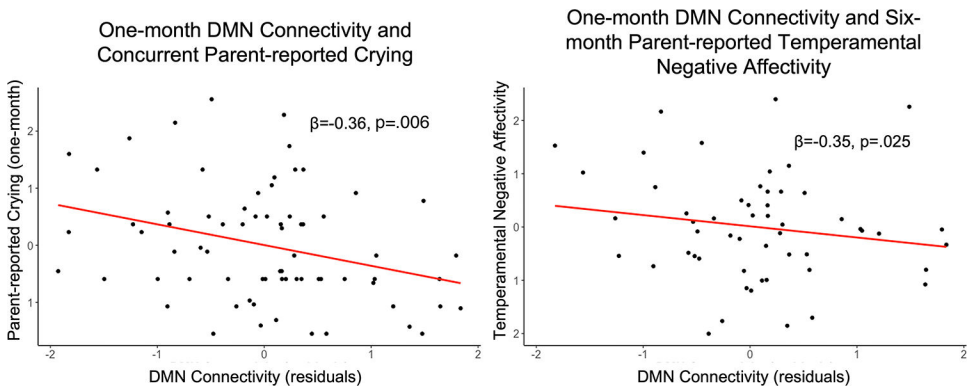

Figure 2:

Associations between one-month DMN connectivity and concurrent parent-reported crying (left) and six-month temperamental negative affectivity (right). Residualized DMN data statistically corrected for age at scan, sex, mean motion, and income-to-needs ratio.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

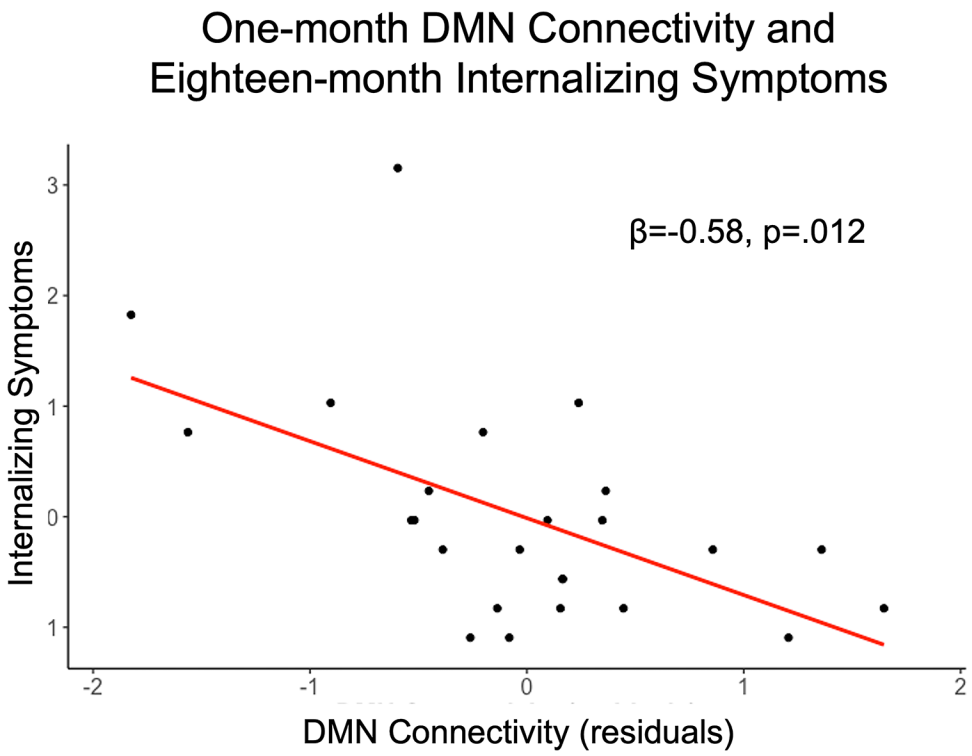

Figure 3:
Association between one-month DMN connectivity and eighteen-month internalizing symptoms.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Sample Demographic Characteristics

Infant sex	39 Males (54%)
Infant age at scan	4.90 weeks (3.43–6.86)
Infant race	
American Indian or Alaska Native	0 (0%)
Asian	1 (2%)
Black or African American	3 (4%)
Native Hawaiian or Other Pacific Islander	0 (0%)
White	57 (79%)
Other	11 (15%)
Infant ethnicity	5 Hispanic/Latinx (7%)
Caregiver education	
High school graduate or equivalent	2 (3%)
Trade/technical/vocational training	0 (0%)
Some college credit, no degree	7 (10%)
Associate’s degree	3 (4%)
Bachelor’s degree	26 (36%)
Graduate degree	34 (47%)
Income-to-needs ratio	1.61 (0.13–2.53)

Note. N (%) except for infant age at scan and income-to-needs ratio, in which mean (range) are provided.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2

Bivariate Spearman Correlations Between all Measures of Interest

		1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	DMN Connectivity	-													
2	FPN Connectivity	**0.29** *	-												
3	DMN-FPN Connectivity	**0.62** *	**0.59** *	-											
4	Parent-reported Crying at Age One-Month	−0.19	0.06	−0.10	-										
5	Parent-reported Crying at Age Six-Months	0.09	0.03	0.03	**0.47** *	-									
6	Recorded Crying at Age One-Month	−0.18	−0.05	−0.16	0.34	0.39	-								
7	Recorded Crying at Age Six-Months	0.11	−0.21	0.04	0.11	0.21	0.19	-							
8	Temperamental Negative Affectivity at Age Six-Months	0.03	0.06	0.18	**0.48** *	**0.48** *	0.25	0.02	-						
9	Internalizing Symptoms at Age Eighteen-Months	−0.35	0.01	−0.24	**0.45** *	−0.05	-	−0.08	**0.49** *	-					
10	Externalizing Symptoms at Age Eighteen-Months	−0.27	**−0.40** *	−0.25	0.19	−0.16	-	**0.49** *	0.28	**0.62** *	-				
11	Maternal Age	−0.22	−0.08	−0.11	−0.10	−0.16	−0.21	0.30	**−0.42** *	**−0.41** *	−0.22	-			
12	Infant Age	0.14	0.05	0.09	−0.14	0.09	−0.09	0.06	0.00	0.19	−0.16	−0.15	-		
13	Income-to-needs Ratio	**−0.40** *	**−0.25** *	**−0.24** *	−0.13	−0.18	−0.18	0.11	**−0.37** *	−0.23	−0.06	**0.63** *	0.00	-	
14	fMRI Motion	−0.22	−0.20	−0.24	−0.22	−0.15	−0.09	−0.15	−0.12	0.23	0.20	−0.08	−0.02	0.00	-

Note.

* p<.05. When bivariate associations were unavailable in participants, no value is provided.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 3

Robust Regression Results for DMN Connectivity Predicting Infant Crying at age one-month, Temperamental Negative Affectivity at age six-months, and Internalizing Symptoms at age eighteen-months

Model	β	se	t	Robust F-test
Dependent Variable: Infant Crying at age one-month				F=8.22, p=.006
Constant	0.40	0.36	1.12	
DMN Connectivity	−0.36	0.13	−2.84	
fMRI Motion	−0.34	0.12	−2.89	
Infant Age (weeks)	−0.13	0.11	−1.13	
Income-to-needs Ratio	−0.35	0.13	−2.67	
Infant Sex	−0.29	0.23	−1.23	
Dependent Variable: Temperamental Negative Affectivity at age six-months				F=5.37, p=.025
Constant	0.46	0.43	1.08	
DMN Connectivity	−0.35	0.16	−2.26	
fMRI Motion	−0.14	0.13	−1.08	
Infant Age (weeks)	−0.11	0.12	−0.92	
Income-to-needs Ratio	−0.59	0.16	−3.63	
Infant Sex	−0.34	0.29	−1.17	
Dependent Variable: Internalizing Symptoms at age eighteen-months				F=7.67, p=.012
Constant	0.08	0.53	0.14	
DMN Connectivity	−0.58	0.21	−2.74	
fMRI Motion	0.04	0.19	0.22	
Infant Age (weeks)	0.09	0.14	0.61	
Income-to-needs Ratio	−0.40	0.17	−2.29	
Infant Sex	−0.17	0.36	−0.48	