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RESEARCH ARTICLE

Early infant white matter tract microstructure predictors of subsequent change in emotionality and emotional regulation

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There are rapid changes in negative and positive emotionality (NE, PE) and emotional regulation (e.g., soothability) during the first year of life. Understanding the neural basis of these changes during maturation can enhance the understanding of the etiology of early psychopathology. Our goal was to determine how measures of white matter (WM) microstructure in tracts connecting key emotion-related neural networks, including the forceps minor (FM), cingulum bundle (CB), and uncinate fasciculus interconnecting the default mode network (DMN), salience network (SN), and central executive network (CEN), can predict developmental change in infant emotionality and emotional regulation. We used Neurite Orientation Dispersion and Density Imaging (NODDI) measures together with conventional diffusion tensor metrics to examine WM tract microstructure and fiber collinearity in the primary sample ($n = 95$), and modeled each WM feature with caregiver-reported infant NE, PE, and soothability, with infant and caregiver sociodemographic factors as covariates. In 3-month infants, higher neurite dispersion and lower longitudinal fiber alignment in the FM were associated with a larger increase in NE from 3 to 9 months of age, suggesting that greater integration of the DMN, SN, and CEN leads to a larger subsequent increase in NE; while higher neurite density and dispersion as well as lower WM longitudinal alignment in the left CB were associated with a larger increase in PE, suggesting that greater integration within the CEN leads to increasing PE over time. In addition, higher neurite dispersion and lower WM longitudinal alignment in the left CB were associated with a larger increase in soothability. Associations among diffusion tensor measures and changes in infant emotionality and emotional regulation measures were replicated in an independent test sample ($n = 44$). These findings suggest that early infant WM microstructural features support infant emotionality and emotional regulation development and could represent early biomarkers of future emotional and behavioral disorders.

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Introduction

Negative and positive forms of emotionality, along with emotional regulation capacities such as soothability, can be reliably assessed in infants within the first months of life. The development of negative emotionality (NE) tends to show relative stability with a trend to increase throughout the first year (1–7); positive emotionality (PE) undergoes rapid increase during this period (8); whereas emotional regulation capacities develop most dramatically in the first few years (9) and continue into adulthood (10). Previous research has shown that these early indices of emotionality and emotional regulation can predict future emotional behavioral outcomes (11–15). For example, high NE is associated with an increased risk for future affective and behavioral disorders (16–22), low PE is linked to a higher risk for future behavioral inhibition and depression (23–28), and low soothability has been linked to future aggression, disruptive behavior, and social engagement problems (29–31). Therefore, identifying objective markers of emotionality and emotional regulation development could provide valuable insights into the etiology of early psychopathology.

White matter (WM) tracts are identifiable early in neonates and undergo rapid development throughout infancy. Several WM tracts connect key regions within large-scale networks that are critical to emotional processing and regulation, including the default mode network (DMN), which supports self-referential processing (32, 33), the salience network (SN), which guides attention toward salient stimuli (33, 34), and the central executive network (CEN), subserving cognitive control (35). These WM tracts include the cingulum bundle (CB), interconnecting prefrontal, cingulate, and parietal cortices, which form connections within and between the DMN and CEN; the uncinate fasciculus (UF), interconnecting prefrontal and anterior temporal structures with the amygdala, and integrating pathways within the DMN and SN; and the forceps minor (FM) of the corpus callosum, interconnecting prefrontal cortical regions, and connecting the DMN, SN, and CEN across hemispheres (36, 37).

Neurite Orientation Dispersion and Density Imaging (NODDI) is a relatively new method of measuring WM tract microstructure. This method uses a multicompartmental model of multishell diffusion MRI (dMRI) that provides higher intracellular specificity than traditional diffusion tensor models by separating intraneuritic and extraneuritic components and free water within a dMRI voxel (38). This method provides estimations of microstructural integrity and myelination using the neurite density index (NDI) and pruning and dispersion using the orientation dispersion index (ODI). Very few studies have examined relationships among NODDI metrics of WM tract microstructure and emotionality or other clinical outcomes in infant, children, or adults. One previous study in young adults showed that first episode psychosis patients had lower NDI in the FM and higher ODI in the UF and FM (39). Furthermore, lower NDI in the FM and CB, along with higher ODI in the CB, were linked with a longer duration of untreated psychosis (39), a dimension of psychopathology characterized by disrupted cognitive and emotional processing. Another study in infants reported that lower 1-month infant UF microstructure, assessed using combined conventional diffusion tensor and NODDI metrics (including NDI, ODI, FA, MD, AD, and RD), was associated with higher 6-month infant fear before correcting for multiple comparisons (40). These findings highlight the potential of using NODDI metrics as proxies for microstructural features in emotion-related WM tracts. Given the above findings linking

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Table 1. Summary of infant-caregiver dyads characteristics for analyses

	Primary		Test	
	3-month Mean ± SD (Min–Max)	9-month Mean ± SD (Min–Max)	3-month Mean ± SD (Min–Max)	9-month Mean ± SD (Min–Max)
Total infant-caregiver pairs	95		44	
Infant				
Age, weeks	14.74 ± 2.72 (10–22)	41.68 ± 4.74 (35–67)	13.59 ± 2.66 (9–19)	39.2 ± 3.14 (36–48)
Biological sex, male/female	56/39		20/24	
Caregiver				
Caregiver age, years	31.80 ± 4.67 (18–42)	—	22.66 ± 1.41 (19–25)	—
Sum of public assistance types	0.94 ± 1.43 (0–5)	—	3.25 ± 1.43 (0–7)	—
EPDS depressed mood	5.27 ± 4.8 (0–22)	5.41 ± 4.52 (0–18)	5.98 ± 5.87 (0–24)	5.55 ± 4.60 (0–22)
PAI BOR affective instability	4.00 ± 3.34 (0–13)	4.32 ± 3.79 (0–16)	6.53 ± 2.81 (0–12)	—
STAI state anxiety	29.16 ± 8.81 (20–61)	27.57 ± 8.45 (20–58)	31.66 ± 9.52 (20–67)	27.89 ± 6.77 (20–50)
STAI trait anxiety	34.01 ± 10.87 (20–69)	33.79 ± 10.64 (21–70)	34.66 ± 8.41 (21–59)	35.05 ± 7.82 (22–55)
Emotional outcomes				
IBQ NE	2.90 ± 0.67 (1.63–4.38)	3.18 ± 0.72 (1.67–5.35)	3.00 ± 0.71 (1.49–4.38)	3.56 ± 0.76 (1.85–5.51)
IBQ PE	3.62 ± 1.27 (1–7)	5.50 ± 0.62 (3.79–6.93)	4.90 ± 1.16 (1.93–6.79)	5.49 ± 0.97 (1.55–6.79)
IBQ soothability	5.41 ± 0.71 (3.71–7)	5.58 ± 0.84 (3.29–7)	5.01 ± 0.78 (3.86–7)	5.12 ± 0.73 (4–6.71)

lower NDI and higher ODI in WM tracts with worse emotional outcomes, it is possible that lower NDI and higher ODI in WM tracts connecting neural regions important for emotional regulation might be associated with higher levels of infant emotionality, especially higher NE. While diffusion tensor imaging has been more commonly used in research to examine WM tract microstructure and fiber collinearity, more research is needed to examine how NODDI and diffusion tensor metrics can be used in infancy to identify indices of WM tract microstructure and fiber collinearity associated with emotional behaviors that represent transdiagnostic risk factors.

We previously reported that lower UF and FM structural integrity measured using normalized quantitative anisotropy, a proxy of directional diffusion, and fractional anisotropy (FA), a proxy measure of WM fiber density in the longitudinal relative to the transverse direction, in 3-month infants predicted greater NE at 9 months (41). Moreover, our recent work demonstrates that greater increases in right UF, FM, and left CB ODI from 3 to 9 months are associated with disrupted development of emotional regulation during the same period, while a greater increase in right UF NDI is linked to a smaller increase in PE in the same timeframe (42). To our knowledge, however, no study has examined the extent to which infant WM tract microstructure predicts developmental changes in emotionality or emotional regulation. The aim of our study was thus to determine the extent to which NODDI indices of WM microstructure predict change in emotionality and emotional regulation from 3 to 9 months of age. Given that early manifestations of emotionality and emotional regulation (43), as well as the onset of neural functional specialization for negative emotion processing (44), are observable in 3-month infants, and emotional dysregulation at 9 months of age can serve as an early indicator of future behavioral and emotional problems (45–49), we chose to study developmental changes in emotionality and emotional regulation within this 3- to 9-month period. Based on the small number of extant findings examining NODDI indices in infancy, we hypothesized that lower NDI and/or higher ODI in the CB, UF, and FM in 3-month-old infants would be associated with a greater increase in NE, a larger decrease or a smaller increase in PE, and/or a larger decrease or a smaller increase in soothability, from 3 to 9 months of age. We used diffusion tensor indices, that is, axial diffusivity (AD) as an indicator of longitudinal fiber alignment, radial diffusivity (RD) as a measure of myelination integrity, and FA to assess WM integrity measured as the balance between axial and radial diffusion, as secondary measures of WM tract microstructure and fiber collinearity to examine relationships among WM measures and changes in emotionality and emotional regulation. We next examined relationships among NODDI and diffusion tensor indices of WM microstructure to determine congruence among the microstructure-emotionality and emotional regulation relationships measured using these different indices. Diffusion tensor measures were then examined in an independent test sample in order to determine the extent to which WM microstructure-emotionality/emotional regulation relationships could be replicated.

To account for external factors that impact WM neurodevelopment (9, 50–57), we included sociodemographic and clinical measures, specifically, caregiver age, and affective states (depression, anxiety, and affective instability), along with infant age and biological sex, as covariates when modeling the relationships between indices of WM tract microstructure and the development of infant emotionality and emotional regulation.

Results

A total of 95 consented infant-caregiver dyads from the primary sample and 44 from the test sample meeting exclusion criteria had usable 3-month dMRI scans. Infant-caregiver dyads characteristics for analyses were summarized in Table 1. Change in infant NE, PE, and soothability from 3 to 9 months are plotted in Figure 1.

Associations Between 3-month WM NODDI Measures and the 3-to-9-month Change in Infant Emotionality

Three-month FM ODI was positively correlated with the 3-to-9-month change in NE ($\beta = 0.334$, $r^2 = 0.112$, $p = 0.0010$, $q = 0.020$; Figure 2A; parameters of models adjusted for covariates in Supplement), indicating that higher FM ODI was associated with a smaller decrease or larger increase in NE. Three-month FM NDI was also positively correlated with the 3-to-9-month change in NE ($\beta = 0.224$, $r^2 = 0.050$, $p = 0.0303$; Supplement Figure S1), but it did not survive the correction for multiple comparisons.

Three-month left CB ODI was positively correlated with the 3-to-9-month change in PE ($\beta = 0.300$, $r^2 = 0.090$, $p = 0.0037$, $q = 0.037$; Figure 2B; Supplement), indicating that higher left CB ODI was associated with a larger increase in PE. Three-month left CB NDI was positively correlated with the 3-to-9-month change in PE ($\beta = 0.283$, $r^2 = 0.080$, $p = 0.0062$, $q = 0.042$; Figure 2C; Supplement), indicating that higher left CB NDI was associated with a larger increase in PE.

Associations Between 3-month WM NODDI Measures and the 3-to-9-month Change in Infant Emotional Regulation

Three-month left CB ODI was positively correlated with the 3-to-9-month change in soothability ($\beta = 0.218$, $r^2 = 0.048$, $p = 0.0369$; Figure 2D; Supplement), indicating that higher left CB ODI was associated with a larger increase in soothability.

Associations Between 3-month WM Diffusion Tensor Measures and the 3-to-9-month Change in Infant Emotionality

Three-month FM AD was negatively correlated with the 3-to-9-month change in NE ($\beta = -0.295$, $r^2 = 0.087$, $p = 0.0039$; Figure 3A), indicating

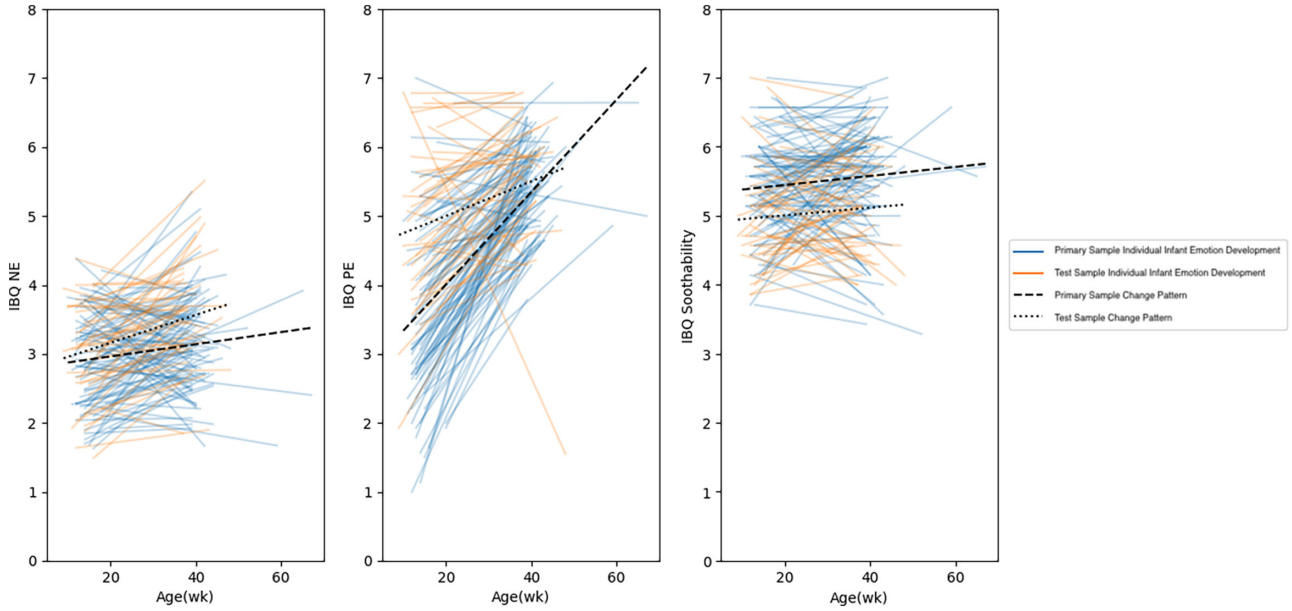

Figure 1. The 3-to-9-month development of infant NE, PE, and soothability.

that lower FM AD was associated with a smaller decrease or a larger increase in NE.

Three-month left CB AD was negatively correlated with the 3-to-9-month change in PE ($\beta = -0.353$, $r^2 = 0.125$, $p = 0.0006$; Figure 3B), indicating that lower left CB AD was associated with a larger increase in PE.

Associations Between 3-month WM Diffusion Tensor Measures and the 3-to-9-month Change in Infant Emotional Regulation

Three-month left CB AD was negatively correlated with the 3-to-9-month change in soothability ($\beta = -0.254$, $r^2 = 0.065$, $p = 0.0144$; Figure 3C), indicating that lower left CB AD was associated with a larger increase in soothability over time.

Correlations Between 3-month NODDI and Diffusion Tensor Measures in WM Tracts in Which Significant Relationships were Shown Among NODDI Measures and Changes in NE, PE, and Soothability

FM ODI was negatively correlated with FM AD ($\rho = -0.843$, $p < 0.0001$), and left CB ODI and NDI were negatively correlated with left CB AD ($\rho = -0.812$, $p < 0.0001$; $\rho = -0.733$, $p < 0.0001$).

Validation of Significant WM Tract Measures—NE, PE, and Soothability Development Relationships

The modeling accuracies in the test sample were: 3-month FM AD – 3-to-9-month NE change root mean square error (RMSE) = 1.488; 3-month left CB AD—3-to-9-month PE change RMSE = 1.027; 3-month left CB AD—3-to-9-month soothability change RMSE = 1.282. These RMSE values reflect good fits of the models in the test sample.

Discussion

In this study, we examined the extent to which early infant WM microstructure may shape changes in emotionality and emotional regulation. Understanding the neural mechanisms underlying these changes can provide neural markers to better predict future behavioral and emotional challenges, as well as informing new intervention strategies and providing objective markers for monitoring response to these interventions. Our main finding for NE development was that higher neurite dispersion in the FM was associated with a smaller decrease or larger increase in NE from 3 to 9 months of age. Regarding PE development, higher neurite density and dispersion in the left CB were associated with a larger increase in PE. These findings indicate that specific microstructural features of WM tracts interconnecting emotion-related neural regions can help predict the subsequent development of emotionality and emotional regulation in infancy.

Greater 3-month neurite dispersion, as indicated by greater ODI, within the FM was significantly associated with a smaller decrease or larger subsequent increase in NE. Greater 3-month FM ODI, a marker of delayed pruning, can lead to greater functional integration of prefrontal cortical regions within the DMN, SN, and CEN. This pattern of greater integration among prefrontal regions across hemispheres at 3 months might then result in an increased influence of the DMN, supporting internalizing and attention to emotionally salient stimuli, on cognitive processes such as executive function supported by the CEN, leading to reduced capacity for emotional regulation. This maladaptive increase in integration across prefrontal regions, parallels our previous findings showing relationships between measures of functional integration among these large-scale neural networks and future depression and mania risk in young adults (58, 59), and children (60), and indicate that these relationships emerge early in infancy.

Greater 3-month microstructural complexity, as indicated by higher NDI and ODI, in the left CB was significantly associated with a larger subsequent increase in PE. Tractography was performed predominantly on the frontoparietal segment of the CB, which connects prefrontal, cingulate, and parietal cortices within the CEN (36, 37), making the anterior part of the CB a major interconnecting bundle of the CEN. One interpretation of this finding is thus that a greater extent of anatomical connectivity and associated functional integration across prefrontal, cingulate, and parietal cortices within the CEN at 3 months can enhance executive function and emotional regulation capacity, resulting in higher levels of PE longer-term. By contrast, lower neurite density and dispersion in the anterior CB at this early age might reduce the ability to process positive emotional experiences and might result in lower levels of PE longer-term. Similarly, greater 3-month left CB ODI was associated with a larger 3-to-9-month increase in soothability, providing further evidence that greater integration within the frontoparietal region of the CB is associated with a greater future capacity for emotional regulation, while lower integration within this region of the CEN at 3 months of age can result in longer-term impairments in emotional regulation capacity.

We previously reported that a greater 3-to-9-month increase in left CB ODI is associated with a greater decrease rather than a greater increase in soothability during the same period (42). Considering these and the present findings together, we hypothesize that as the left CB tract continues to develop during 3 to 9 months of age, there is an anterior to posterior shift in microstructural development of the CB, during which the posterior parietal portion of the CB increasingly integrates the DMN

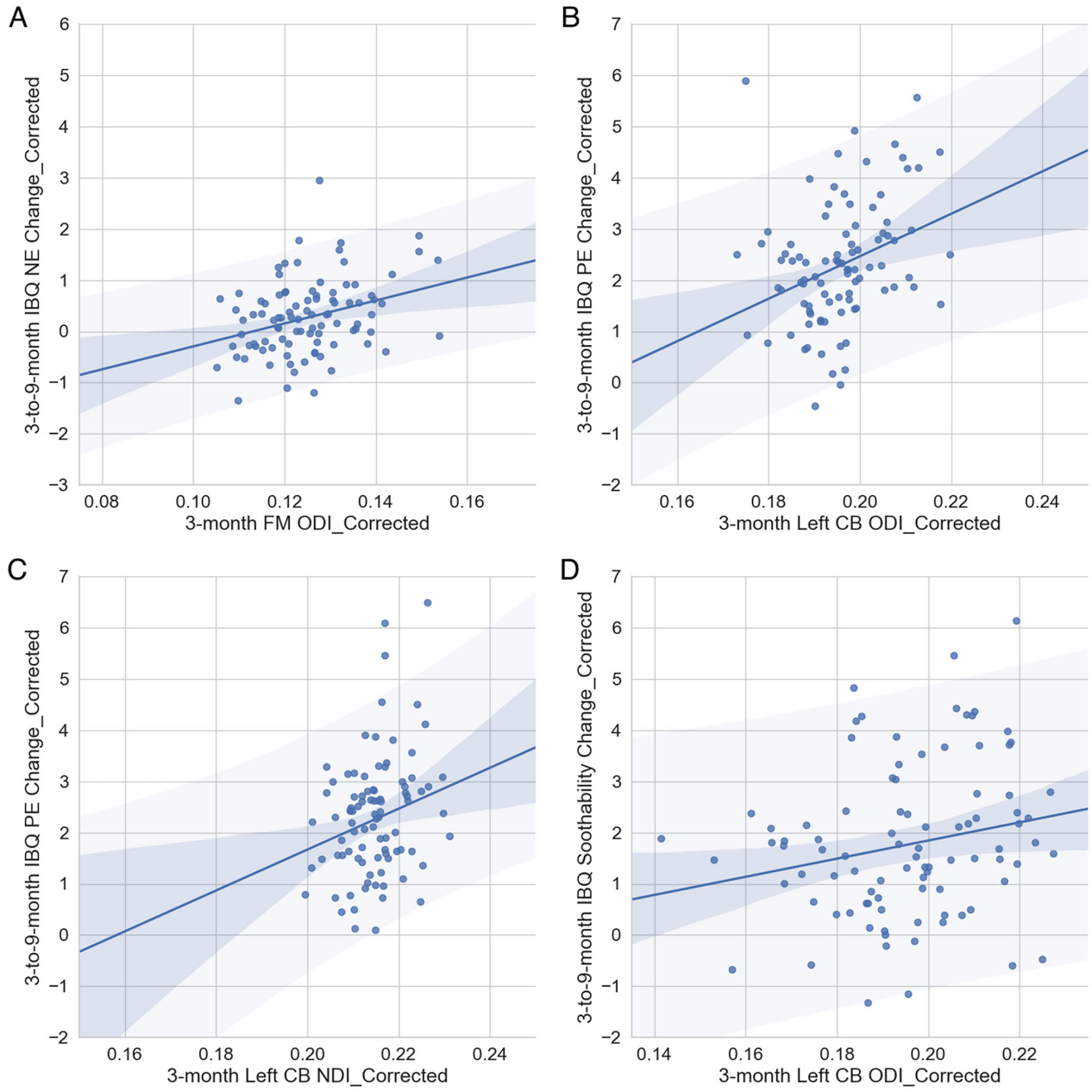

Figure 2. Covariate-corrected relationships between WM NODDI measures and the infant emotionality and emotional regulation development (solid lines as regression lines, brighter shadowed area as prediction interval, and darker shadowed areas as corresponding 95% confidence intervals). (A) Association between 3-month FM ODI and 3-to-9-month NE changes. (B) Association between 3-month left CB ODI and 3-to-9-month PE changes. (C) Association between 3-month left CB NDI and 3-to-9-month PE changes. (D) Association between 3-month left CB ODI and 3-to-9-month soothablity changes.

with the CEN, and other neural networks, resulting in greater interference with emotional regulation capacity. Thus, our findings from the present and this previous study together suggest a nonlinear relationship among CB ODI and emotional regulation capacity during 3 to 9 months of age, whereby greater left CB ODI at 3 months followed by a smaller increase, or greater decrease, in ODI from 3 to 9 months are necessary for the development of higher levels of emotional regulation capacity.

Significant negative correlations were observed among FM ODI and AD, as well as left CB ODI and NDI with AD, suggesting that greater NDI and ODI together might be associated with lower AD. These findings parallel previous reports that ODI may be negatively associated, while NDI may show a smaller but positive correlation, with FA (38). This is because higher ODI, indicating a greater extent of neurite dispersion, is associated with a lower level of longitudinally aligned WM fiber, that is, lower AD and lower AD can contribute to lower FA. Our findings regarding relationships among FM and left CB AD and 3-to-9-month changes in NE, PE and soothability were therefore in the opposite direction from those among FM and left CB ODI and NDI and these emotionality and emotional regulation outcome measures. Furthermore, these AD—outcome measure relationships were replicated in our test sample, indicating the robust nature of these relationships.

We acknowledge several limitations of this study. The sample size of the present study was relatively small with the exclusion of infants who were unable to remain still during scans, and the replication was

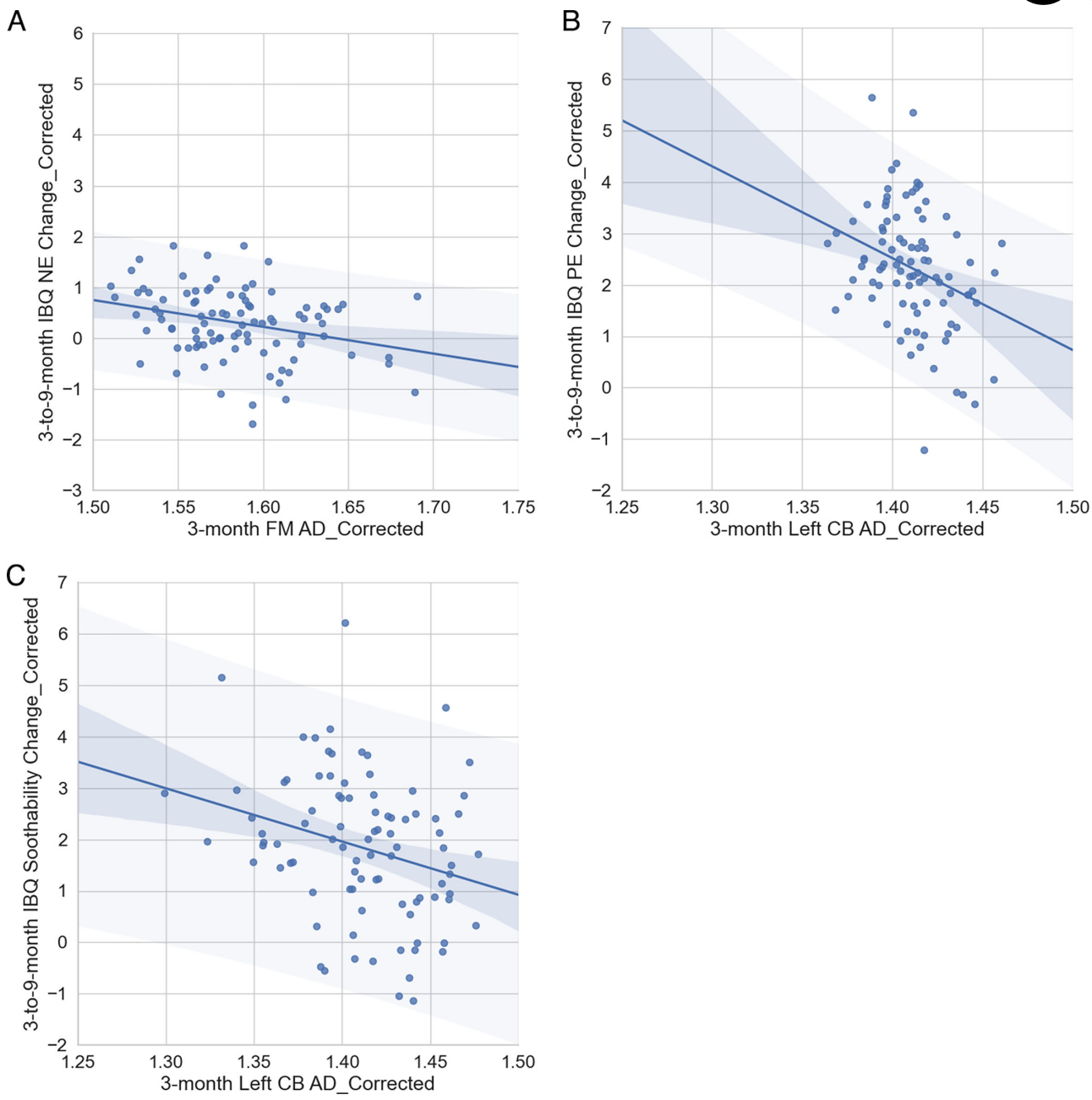

Figure 3. Covariate-corrected relationships between WM diffusion tensor measures and the infant emotionality and emotional regulation development (solid lines as regression lines, brighter shadowed area as prediction interval, and darker shadowed areas as corresponding 95% confidence intervals). (A) Association between 3-month FM AD and 3-to-9-month NE changes. (B) Association between 3-month left CB AD and 3-to-9-month PE changes. (C) Association between 3-month left CB AD and 3-to-9-month soothablity changes.

limited to diffusion metrics. That noted, we were able to replicate our findings in an independent test sample, which is a major strength of the present study. In addition, the test sample in this study was recruited from a higher-risk group, which may have introduced demographic differences between the two samples. However, the high modeling accuracies achieved on the test sample provide further evidence of the consistency of our findings. Future studies aiming to replicate our NODDI metric findings in larger multisite infant imaging cohorts, for example, the HEALthy Brain and Child Development (HBCD) dataset (61), can be performed when these datasets become publicly available. Potential interaction effects between baseline infant emotionality and emotional regulation and caregiver affective states may also be examined with these larger longitudinal datasets. One future direction is to investigate how microstructural features within tracts can predict emotionality and emotional regulation development. Microstructural features extracted from tract subregions may be analyzed in longitudinal infant imaging data to offer insights into tract-specific developmental trajectories, and their relationships with infant emotional behavior.

The present study highlights the important role of FM and left CB ODI and NDI in 3-month-old infants, reflecting integration of critical emotion-related large-scale networks at this age, as predictors of the future development of emotionality and emotional regulation. These insights enhance understanding of the neural mechanisms underlying the development of emotionality and emotional regulation during this critical

developmental period, and provide potential early neural targets to monitor the effectiveness of interventions to mitigate future psychopathology risk.

Materials and Methods

Participants and Measures

The University of Pittsburgh Human Research Protection Office approved all study procedures. Infant-caregiver dyads for the primary sample were identified using three recruitment sources: the University of Pittsburgh Clinical and Translational Science Institute Newborn Research Support Service (NuRSERy) and Community Pediatric Service (Pediatric PittNet), and the University of Pittsburgh Pitt + Me website. The test sample was recruited from the population-based, longitudinal Pittsburgh Girls Study (MH106570). Exclusion criteria for both samples were: (1) infant: preterm birth (<37 weeks postgestational age), low birth weight (<5.5 lb), Apgar score <7 (5 min after birth), abnormal brain morphometry (occipitofrontal circumference <32 cm), extended hospitalization due to physical health problems, and MRI contraindications (pacemakers, aneurysm clips, or non-removable ferromagnetic implants); (2) caregiver: <18 years, prenatal or concurrent illicit substance use (measured via obstetric records or self-report), and <2 h/day care of the infant.

At 3 and 9 months, caregiver report on the Infant Behavior Questionnaire-Revised (IBQ-R) Short Form (1) provided measures of infant NE (i.e., composite of Sadness, Distress to Limitations, Fear, and reverse coded Falling Reactivity/Rate of Recovery from Distress subscales), PE (i.e., composite of Smiling/Laughter and High-Intensity Pleasure subscales), and Soothability. To control for sociodemographic variables that may impact infant brain and/or emotional behaviors infant biological sex and age (weeks) at each research visit, caregiver age (years) and the sum of the types of governmental household public assistance received (a proxy for financial strain) at 3 months were used as covariates. Additionally, caregiver postpartum depression using the Edinburgh Postnatal Depression Scale (EPDS) (62), affective lability using the Personality Assessment Inventory-Borderline Features Scale (PAI-BOR) (63), and state and trait anxiety using the Spielberger State-Trait Anxiety Inventory (STAI) (64) at the 3- and 9-month visits were used as clinical covariates.

Image Acquisition and Processing

MRI scanning procedures were conducted with 3-month-old infants during natural sleep (65) using a 3T Siemens MAGNETOM Skyra MRI system (Siemens Healthcare AG, Erlangen, Germany) with a 32-channel head coil at Children's Hospital of Pittsburgh. Multishell echo planar (EPI) diffusion MRI (dMRI) data were acquired under the following parameters: (1) primary sample: FOV = 200 mm, voxel dimensions = 2.0 × 2.0 × 2.0 mm^3, anterior to posterior phase encoding: TE/TR = 98/2800 ms, 9 reference volumes with b = 0 s/mm^2, 50 volumes with b = 750 s/mm^2 and 100 volumes with 2000 s/mm^2; posterior to anterior phase encoding for EPI distortion correction: TE/TR = 80/2500 ms, 10 reference volumes with b = 0 s/mm^2. (2) Test sample: FOV = 256 mm, voxel dimensions = 2.0 × 2.0 × 2.0 mm^3, TE/TR = 83/10,600 ms, 7 reference volumes with b = 0 s/mm^2, 42 volumes with b = 1000 s/mm^2.

Three-month infant multishell diffusion MRI scans first underwent manual removal of volumes with motion artifacts for quality control, followed by correction for eddy current, motion and EPI distortion with FMRIB Software Library (FSL) 6.0 toolbox's eddy and topup (66, 67). For scans from the primary sample, tissue weight–modulated NODDI metrics were estimated using the NODDI Matlab toolbox following our previous protocol in native space (68). Mean NDI, ODI, FA, AD, and RD were extracted from the forceps minor (FM) and the left and right cingulum bundle (CB) and UF tracts generated using AutoTrack in DSI Studio (version June 7, 2020 build) (Supplemental Table S1) (69, 70). Intracranial volume was based on the brain mask volume. For the test data, tractography of each scan was generated using the same parameter in DSI Studio. FA, AD, and RD maps were harmonized with the primary sample using the neuroComBat (71). Mean harmonized FA, AD, and RD extracted from each WM tract were used for further analysis.

Data Analysis

NODDI (NDI, ODI) measures of each WM tract from the primary sample were modeled with 3-to-9-month changes of infant NE and PE in order to examine relationships among 3-month microstructural features of each WM tract of interest and change in emotionality during this developmental period. Infant and caregiver sociodemographic/clinical variables (i.e., 3- and 9-month infant age in weeks, biological sex, 3-month intracranial volume, 3-month corresponding NE, PE, or soothability baseline; caregiver age, financial strain at 3 months, 3- and 9-month caregiver EPDS, PAI-BOR affective instability, STAI state and trait anxiety) were included as covariates. Multiple comparisons were addressed using false discovery rate for each outcome independently (72). Specifically, 20 comparisons were conducted, corresponding to two NODDI measures for each of five tracts for two outcomes. Soothability was examined as an additional outcome separately from NE and PE, as the 3-to-9-month change in soothability was collinear with the 3-to-9-month change in NE (Supplement Figure S2).

The same modeling approach was applied using diffusion tensor (FA, AD, and RD) measures of WM tract microstructure and fiber collinearity in the primary sample. Correlation analyses were then conducted in the primary sample to examine relationships between 3-month NODDI and diffusion tensor measures, in order to assess the potential congruence of these measures in characterizing WM microstructure.

All significant WM tract index—outcome of interest (change in NE, PE, or soothability) relationships using diffusion tensor measures of WM microstructure and fiber collinearity in the primary sample were then evaluated in the test sample. Here, the modeling accuracy of each significant WM tract index—outcome of interest relationship in the independent test sample was evaluated using the RMSE. Significant relationships among NODDI indices and 3-to-9-month changes in NE, PE and/or soothability in the primary sample were not validated in the independent test sample because the scanning parameters in the latter sample were not optimized for extraction of NODDI indices.

Data Availability

The data analyzed in this study are available upon reasonable request from the corresponding author, subject to applicable regulations and approval.

Author Contributions

Y.Z. conducted image processing, performed data modeling and analysis, wrote the original draft, and reviewed and edited the manuscript. L.B. provided mentorship and oversight, conducted image processing, and reviewed and edited the manuscript. A.V. provided mentorship and reviewed and edited the manuscript. A.S. conducted infant scan visits, managed image storage, and conducted image quality check. M.A. contributed to image processing. M.T. and G.E. conducted infant behavioral and caregiver sociodemographic and clinical data collection. V.J.S. and V.K.L. facilitated study start-up and infant scanning. R.S. managed the data and reviewed and edited the manuscript. H.A. managed the data. A.E.H. acquired funding, provided mentorship, and reviewed and edited the manuscript. M.L.P. acquired funding, provided mentorship, oversight, and resources, and reviewed and edited the manuscript.

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Author Disclosures

The authors have no conflicts of interest related to this work.

References

1. Gartstein MA, Rothbart MK. Studying infant temperament via the revised infant behavior questionnaire. Infant Behav Dev. 2003;26(1):64–86. DOI: 10.1016/j.infbeh.2016.04.001. PMID: 27088863; PMCID: PMC4909571

2. Putnam SP, Gartstein MA, Rothbart MK. Measurement of fine-grained aspects of toddler temperament: the Early Childhood Behavior Questionnaire. Infant Behav Dev. 2006;29(3):386–401. DOI: 10.1016/j.infbeh.2006.01.004. PMID: 17138293; PMCID: PMC4334385
3. Putnam SP, Rothbart MK, Gartstein MA. Homotypic and heterotypic continuity of fine-grained temperament during infancy, toddlerhood, and early childhood. Infant Child Develop. 2008;17(4):387–405. DOI: 10.1002/icd.582.
4. Rothbart MK, Derryberry D, Hershey K. Stability of temperament in childhood: laboratory infant assessment to parent report at seven years. Temperament and Personality Development Across the Life Span. Psychology Press: London, United Kingdom; 2000, 85–119.
5. Arterberry ME, Bornstein MH. Development in Infancy: A Contemporary Introduction. Psychology Press: London, United Kingdom; 2013.
6. Carranza Carnicero JA, Pérez-López J, Del Carmen GonzálezSalinas M, Martínez-Fuentes MT. A longitudinal study of temperament in infancy: stability and convergence of measures. Eur J Pers. 2000;14(1):21–37. DOI: 10.1002/(SICI)1099-0984(200001/02)14:1⟨21::AID-PER367⟩3.0.CO;2-A.
7. Partridge T, Lerner JV. A latent growth-curve approach to difficult temperament. Infant Child Dev. 2007;16(3):255–65. DOI: 10.1002/icd.465.
8. Belsky J, Fish M, Isabella RA. Continuity and discontinuity in infant negative and positive emotionality: Family antecedents and attachment consequences. Dev Psychol. 1991;27(3):421. DOI: 10.1037/0012-1649.27.3.421.
9. Crockenberg SC, Leerkes EM. Infant and maternal behaviors regulate infant reactivity to novelty at 6 months. Dev Psychol. 2004;40(6):1123. DOI: 10.1037/0012-1649.40.6.1123. PMID: 15535761
10. Charles ST, Carstensen LL. Emotion regulation and aging. Handbook of Emotion Regulation, vol. 307. Guilford Press: New York, NY; 2007, 327.
11. Fox NA, Henderson HA, Marshall PJ, Nichols KE, Ghera MM. Behavioral inhibition: linking biology and behavior within a developmental framework. Annu Rev Psychol. 2005;56:235–62. DOI: 10.1146/annurev.psych.55.090902.141532. PMID: 15709935
12. Gladstone GL, Parker GB, Mitchell PB, Wilhelm KA, Malhi GS. Relationship between self-reported childhood behavioral inhibition and lifetime anxiety disorders in a clinical sample. Depress Anxiety. 2005;22(3):103–13. DOI: 10.1002/da.20082. PMID: 16149043
13. Dougherty LR, Klein DN, Durbin CE, Hayden EP, Olino TM. Temperamental positive and negative emotionality and children's depressive symptoms: a longitudinal prospective study from age three to age ten. J Soc Clin Psychol. 2010;29(4):462–88. DOI: 10.1521/jscp.2010.29.4.462.
14. De Pauw SS, Mervielde I. The role of temperament and personality in problem behaviors of children with ADHD. Abnorm Child Psychol. 2011;39:277–91. DOI: 10.1007/s10802-010-9459-1. PMID: 20862537
15. Cicchetti D, Ackerman BP, Izard CE. Emotions and emotion regulation in developmental psychopathology. Dev Psychopathol. 1995;7(1):1–10.
16. Henderson HA, Wachs TD. Temperament theory and the study of cognition–emotion interactions across development. Dev Rev. 2007;27(3):396–427.
17. Sanson A, Hemphill SA, Smart D. Connections between temperament and social development: a review. Soc Dev. 2004;13(1):142–170.
18. Lonigan CJ, Phillips BM, Hooe ES. Relations of positive and negative affectivity to anxiety and depression in children: evidence from a latent variable longitudinal study. J Consult Clin Psychol. 2003;71(3):465–81. DOI: 10.1037/0022-006x.71.3.465. PMID: 12795571
19. Masse LC, Tremblay RE. Behavior of boys in kindergarten and the onset of substance use during adolescence. Arch Gen Psychiatry. 1997;54(1):62–8. DOI: 10.1001/archpsyc.1997.01830130068014. PMID: 9006402
20. Vitaro F, Barker ED, Boivin M, Brendgen M, Tremblay RE. Do early difficult temperament and harsh parenting differentially predict reactive and proactive aggression? J Abnorm Child Psychol. 2006;34:681–91. DOI: 10.1007/s10802-006-9055-6. PMID: 17048109
21. Eisenberg N, Valiente C, Spinrad TL, Cumberland A, Liew J, Reiser M, et al. Longitudinal relations of children's effortful control, impulsivity, and negative emotionality to their externalizing, internalizing, and co-occurring behavior problems. Dev Psychol. 2009;45(4):988. DOI: 10.1037/a0016213. PMID: 19586175; PMCID: PMC2775424
22. Slutske WS, Moffitt TE, Poulton R, Caspi A. Undercontrolled temperament at age 3 predicts disordered gambling at age 32: a longitudinal study of a complete birth cohort. Psychol Sci. 2012;23(5):510–6. DOI: 10.1177/0956797611429708. PMID: 22457426; PMCID: PMC3556900
23. Tellegen A. Structures of mood and personality and their relevance to assessing anxiety, with an emphasis on self-report. Anxiety and the Anxiety Disorders. Lawrence Erlbaum Associates, Inc: Hillsdale, NJ, US; 1985, 681–706.
24. Watson D, Wiese D, Vaidya J, Tellegen A. The two general activation systems of affect: structural findings, evolutionary considerations, and psychobiological evidence. J Pers Soc Psychol. 1999;76(5):820.
25. Park S-Y, Belsky J, Putnam S, Crnic K. Infant emotionality, parenting, and 3-year inhibition: exploring stability and lawful discontinuity in a male sample. Dev Psychol. 1997;33(2):218. DOI: 10.1037//0012-1649.33.2.218. PMID: 9147831
26. Shankman SA, Tenke CE, Bruder GE, Durbin CE, Hayden EP, Klein DN. Low positive emotionality in young children: association with EEG asymmetry. Dev Psychopathol. 2005;17(1):85–98. DOI: 10.1017/s0954579405050054. PMID: 15971761
27. Oldehinkel AJ, Hartman CA, De Winter AF, Veenstra R, Ormel J. Temperament profiles associated with internalizing and externalizing problems in preadolescence. Dev Psychopathol. 2004;16(2):421–40. DOI: 10.1017/s0954579404044591. PMID: 15487604
28. Hayden EP, Klein DN, Durbin CE, Olino TM. Positive emotionality at age 3 predicts cognitive styles in 7-year-old children. Dev Psychopathol. 2006;18(2):409–23. DOI: 10.1017/S0954579406060226. PMID: 16600061
29. Crockenberg SC, Leerkes EM, Bárrig Jó PS. Predicting aggressive behavior in the third year from infant reactivity and regulation as moderated by maternal behavior. Dev Psychopathol. 2008;20(1):37–54. DOI: 10.1017/S0954579408000023. PMID: 18211727
30. Kochanska G, Tjebkes JL, Fortnan DR. Children's emerging regulation of conduct: restraint, compliance, and internalization from infancy to the second year. Child Dev. 1998;69(5):1378–89. PMID: 9839422
31. Baumeister RF, Vohs KD. Handbook of Self-regulation. Guilford Press: New York; 2004.
32. Spreng RN, Mar RA, Kim AS. The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. J Cogn Neurosci. 2009;21(3):489–510. DOI: 10.1162/jocn.2008.21029. PMID: 18510452
33. Menon V. Developmental pathways to functional brain networks: emerging principles. Trends Cogn Sci. 2013;17(12):627–40. DOI: 10.1016/j.tics.2013.09.015. PMID: 24183779
34. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct. 2010;214(5-6):655–67. DOI: 10.1007/s00429-010-0262-0. PMID: 20512370; PMCID: PMC2899886
35. Dosenbach NU, Fair DA, Cohen AL, Schlaggar BL, Petersen SE. A dual-networks architecture of top-down control. Trends Cogn Sci. 2008;12(3):99–105. DOI: 10.1016/j.tics.2008.01.001. PMID: 18262825; PMCID: PMC3632449
36. Catani M, De Schotten MT. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. Cortex. 2008;44(8):1105–32. DOI: 10.1016/j.cortex.2008.05.004. PMID: 18619589
37. Nozais V, Forkel SJ, Petit L, Talozzi L, Corbetta M, Thiebaut de Schotten M, et al. Atlasing white matter and grey matter joint contributions to resting-state networks in the human brain. Commun Biol. 2023;6(1):726. DOI: 10.1038/s42003-023-05107-3. PMID: 37452124; PMCID: PMC10349117
38. Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. Neuroimage. 2012;61(4):1000–16. DOI: 10.1016/j.neuroimage.2012.03.072. PMID: 22484410
39. Kraguljac NV, Monroe WS, Anthony T, Jindal RD, Hill H, Lahti AC. Neurite orientation dispersion and density imaging (NODDI) and duration of untreated psychosis in antipsychotic medication-naïve first episode psychosis patients. Neuroimage Rep. 2021;1(1):100005. DOI: 10.1016/j.ynirp.2021.100005. PMID: 36969709; PMCID: PMC10038586
40. Planalp EM, Dowe KN, Alexander AL, Goldsmith HH, Davidson RJ, Dean DC III. White matter microstructure predicts individual differences in infant fear (but not anger and sadness). Dev Sci. 2023;26(3):e13340. DOI: 10.1111/desc.13340. PMID: 36367143; PMCID: PMC10079554
41. Banihashemi L, Bertocci MA, Alkhars HM, Versace A, Northrup JB, Lee VK, et al. Limbic white matter structural integrity at 3 months prospectively predicts negative emotionality in 9-month-old infants: a preliminary study. J Affect Disord. 2020;273:538–41. DOI: 10.1016/j.jad.2020.04.029. PMID: 32560951; PMCID: PMC7367553
42. Zhang Y, Banihashemi L, Versace A, Samolyk A, Abdelkader M, Taylor M, et al. Associations among white matter microstructural changes and the development of emotional reactivity and regulation in infancy. Mol Psychiatry. 2025. DOI: 10.1038/s41380-025-03025-w
43. Feldman R, Greenbaum CW, Yirmiya N, Mayes LC. Relations between cyclicity and regulation in mother-infant interaction at 3 and 9 months and cognition at 2 years. J App Develop Psychol. 1996;17(3):347–65.
44. Blasi A, Mercure E, Lloyd-Fox S, Thomson A, Brammer M, Sauter D, et al. Early specialization for voice and emotion processing in the infant brain. Curr Biol. 2011;21(14):1220–4. DOI: 10.1016/j.cub.2011.06.009. PMID: 21723130
45. Stifter CA, Jain A. Psychophysiological correlates of infant temperament: stability of behavior and autonomic patterning from 5 to 18 months. Dev Psychobiol. 1996;29(4):379–91. DOI: 10.1002/(SICI)1098-2302(199605)29:4⟨379::AID-DEV5⟩3.0.CO;2-N. PMID: 8732809

46. Martin RP, Wisenbaker J, Baker J, Huttunen MO. Gender differences in temperament at six months and five years. Infant Behav Develop. 1997;20(3):339–47.
47. Bates JE, Bayles K, Bennett DS, Ridge B, Brown MM. Origins of externalizing behavior problems at eight years of age. In: Pepler Debra J., Rubin KH, editors. The Development and Treatment of Childhood Aggression, vol. 17. Lawrence Erlbaum Associates: Hillsdale, NJ; 1991, pp 93–120.
48. Teerikangas OM, Aronen ET, Martin RP, Huttunen MO. Effects of infant temperament and early intervention on the psychiatric symptoms of adolescents. J Am Acad Child Adolesc Psychiatry. 1998;37(10):1070–6. DOI: 10.1097/00004583-199810000-00017. PMID: 9785718
49. Moore GA, Cohn JF, Campbell SB. Infant affective responses to mother's still face at 6 months differentially predict externalizing and internalizing behaviors at 18 months. Dev Psychol. 2001;37(5):706–14. PMID: 11552765
50. Britton JR. Infant temperament and maternal anxiety and depressed mood in the early postpartum period. Women Health. 2011;51(1):55–71. DOI: 10.1080/03630242.2011.540741. PMID: 21391161
51. Feldman R, Granat A, Pariente C, Kanety H, Kuint J, Gilboa-Schechtman E. Maternal depression and anxiety across the postpartum year and infant social engagement, fear regulation, and stress reactivity. J Am Acad Child Adolesc Psychiatry. 2009;48(9):919–27. DOI: 10.1097/CHI.0b013e3181b21651. PMID: 19625979
52. Hane AA, Fox NA. Ordinary variations in maternal caregiving influence human infants' stress reactivity. Psychol Sci. 2006;17(6):550–6. DOI: 10.1111/j.1467-9280.2006.01742.x. PMID: 16771807
53. Tronick E, Reck C. Infants of depressed mothers. Harv Rev Psychiatry. 2009;17(2):147–56. DOI: 10.1080/10673220902899714. PMID: 19373622
54. Hobson RP, Patrick M, Crandell L, García–Pérez R, Lee A. Personal relatedness and attachment in infants of mothers with borderline personality disorder. Dev Psychopathol. 2005;17(2):329–47. DOI: 10.1017/s0954579405050169. PMID: 16761548
55. Crandell LE, Patrick MP, Hobson RP. 'Still-face' interactions between mothers with borderline personality disorder and their 2-month-old infants. Br J Psychiatry. 2003;183(3):239–47. DOI: 10.1192/bjp.183.3.239. PMID: 12948998
56. Apter G, Devouche E, Garez V, Valente M, Genet M-C, Gratier M, et al. The still-face: a greater challenge for infants of mothers with borderline personality disorder. J Pers Disord. 2017;31(2):156–69. DOI: 10.1521/pedi_2016_30_243. PMID: 27088165
57. Gratz KL, Kiel EJ, Latzman RD, Elkin TD, Moore SA, Tull MT. Emotion: empirical contribution: maternal borderline personality pathology and infant emotion regulation: examining the influence of maternal emotion-related difficulties and infant attachment. J Pers Disord. 2014;28(1):52–69. DOI: 10.1521/pedi.2014.28.1.52. PMID: 24344887
58. Bertocci MA, Afriyie-Agyemang Y, Rozovsky R, Iyengar S, Stiffler R, Aslam HA, et al. Altered patterns of central executive, default mode and salience network activity and connectivity are associated with current and future depression risk in two independent young adult samples. Mol Psychiatry. 2023;28(3):1046–56. DOI: 10.1038/s41380-022-01899-8. PMID: 36481935; PMCID: PMC10530634
59. Schumer MC, Bertocci MA, Aslam HA, Graur S, Bebko G, Stiffler RS, et al. Patterns of neural network functional connectivity associated with mania/hypomania and depression risk in 3 independent young adult samples. JAMA Psychiatry. 2024;81(2):167–77. DOI: 10.1001/jamapsychiatry.2023.4150. PMID: 37910117; PMCID: PMC10620679
60. Fournier JC, Bertocci M, Ladouceur CD, Bonar L, Monk K, Abdul-Waalee H, et al. Neural function during emotion regulation and future depressive symptoms in youth at risk for affective disorders. Neuropsychopharmacology. 2021;46(7):1340–7. DOI: 10.1038/s41386-021-01001-w. PMID: 33782511; PMCID: PMC8134479
61. Jordan CJ, Weiss SR, Howlett KD, Freund MP. Introduction to the special issue on "Informing longitudinal studies on the effects of maternal stress and substance use on child development: planning for the HEALthy brain and child development (HBCD) study". Adver Resil Sci. 2020;1(4):217–21. DOI: 10.1007/s42844-020-00022-6. PMID: 33106790; PMCID: PMC7578232
62. Cox J, Holden J. Perinatal Mental Health: A Guide to the Edinburgh Postnatal Depression Scale (EPDS). Royal College of Psychiatrists: London, United Kingdom; 2003.
63. Trull TJ. Borderline personality disorder features in nonclinical young adults: 1. Identification and validation. Psychol Assess. 1995;7(1):33–41.
64. Spielberger CD. Test anxiety inventory. Palo Alto, CA: Consulting Psychologists Press; 1980.
65. Haney B, Reavey D, Atchison L, Poull J, Dryer L, Anderson B, et al. Magnetic resonance imaging studies without sedation in the neonatal intensive care unit: safe and efficient. J Perinat Neonatal Nurs. 2010;24(3):256–66. DOI: 10.1097/JPN.0b013e3181e8d566. PMID: 20697244
66. Andersson JL, Skare S, Ashburner J. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. Neuroimage. 2003;20(2):870–88. DOI: 10.1016/S1053-8119(03)00336-7. PMID: 14568458
67. Andersson JL, Sotiropoulos SN. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. Neuroimage. 2016;125:1063–78. DOI: 10.1016/j.neuroimage.2015.10.019. PMID: 26481672; PMCID: PMC4692656
68. Zhang Y, Banihashemi L, Versace A, Samolyk A, Taylor M, English G, et al. Early infant prefrontal cortical microstructure predicts present and future emotionality. Biol Psychiatry. 2024;96(12):959–70. DOI: 10.1016/j.biopsych.2024.04.001. PMID: 38604525; PMCID: PMC11461701
69. Yeh F-C, Verstynen TD, Wang Y, Fernández-Miranda JC, Tseng W-YT. Deterministic diffusion fiber tracking improved by quantitative anisotropy. PLoS One. 2013;8(11):e80713. DOI: 10.1371/journal.pone.0080713. PMID: 24348913; PMCID: PMC3858183
70. Banihashemi L, Schmithorst VJ, Bertocci MA, Samolyk A, Zhang Y, Santos JPL, et al. Neural network functional interactions mediate or suppress white matter–Emotional behavior relationships in infants. Biol Psychiatry. 2023;94(1):57–67. DOI: 10.1016/j.biopsych.2023.03.004. PMID: 36918062; PMCID: PMC10365319
71. Fortin J-P, Cullen N, Sheline YI, Taylor WD, Aselcioglu I, Cook PA, et al. Harmonization of cortical thickness measurements across scanners and sites. Neuroimage. 2018;167:104–20. DOI: 10.1016/j.neuroimage.2017.11.024. PMID: 29155184; PMCID: PMC5845848
72. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Series B Stat Methodol. 1995;57(1):289–300.