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Regular Article

Maternal mood entropy and children's hippocampal development: Enduring versus transient effects

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Abstract

Recent research suggests that maternal mood entropy, a novel measure of mood dysfunction, is associated with child outcomes. However, the link between maternal mood entropy and children's structural brain development, and how this association may change across childhood, remains unclear. In a longitudinal study with neuroimaging data collected at ages 4.5, 6, 7.5, and 10.5 years ($n = 1{,}498$; $n = 674$ with neuroimaging), we examined whether maternal mood entropy is associated with children's hippocampal and amygdala volumes over time. Mothers reported on negative mood symptoms at several assessments between ages 3 months and 4.5 years. We calculated maternal mood levels as the sum of mood symptoms and computed maternal mood entropy by applying Shannon's entropy to the distributions of mood questionnaire responses. Maternal mood measures were not associated with amygdala volumes; however, mood entropy was directly associated with smaller hippocampal volumes at age 4.5 years and indirectly associated with smaller hippocampal volumes at 10.5 years through rank-order stability over time. These effects were present beyond the effects of socioeconomic status and intracranial volume and were specific to mood entropy, not mood levels. Our findings indicate that patterns of maternal mood are embedded in early childhood brain structure, setting the stage for subsequent neurodevelopment.

Keywords: biological embedding; hippocampus; maternal mood; enduring effects; revisionist effects

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Introduction

Disorders characterized by difficulties regulating mood, such as anxiety and depression, are highly prevalent and recurring (Gotlib et al., 2020; Kessler et al., 2012; Scholten et al., 2023). In fact, recent research indicates that mood difficulties have increased during and since the COVID-19 pandemic, with mothers being disproportionately affected (Racine et al., 2021). This carries important implications not only for mothers' own well-being but also for how they interact with their offspring (MacNeill et al., 2022; Rao et al., 2021). Children exposed to more severe and frequent maternal mood difficulties are at increased risk for experiencing a range of negative developmental outcomes (Barker et al., 2011; Behrendt et al., 2020; Gotlib et al., 2023; M. M. Weissman et al., 2016). For example, maternal anxiety has been associated with increased risk for children's social-emotional problems (Behrendt et al., 2020), reduced cognitive and language development (Keim et al., 2011,) and more severe symptoms of psychopathology (Barker et al., 2011).

Consistent with the focus of developmental psychopathology on multiple levels of analysis (Cicchetti & Toth, 2009), recent research has examined maternal mood in the context of child neurodevelopmental outcomes, including alterations in brain structure (Donnici et al., 2021; Gotlib et al., 2023; Qiu et al., 2013; Rifkin-Graboi et al., 2013, 2015). In particular, potential associations of difficulties in maternal mood with children's hippocampal

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and amygdala volume have garnered significant attention (Gotlib et al., 2023; Qiu et al., 2013; Rifkin-Graboi et al., 2013). These brain regions are often conceptualized as "stress sensitive," with abundant glucocorticoid receptors that are important for regulating children's response to environmental stressors (McEwen et al., 2016). In fact, researchers have proposed that early adverse psychosocial experiences, including maternal mood difficulties, are biologically embedded in the structural development of these regions (Berens et al., 2017). However, prior studies have yielded inconsistent findings regarding the nature of the relations between maternal mental health and children's subcortical volumes. Some studies have reported that maternal mood difficulties are associated with reduced hippocampal or amygdala volume in offspring (Acosta et al., 2020; Chen et al., 2010; Moog et al., 2021), findings that align with other research indicating that exposure to adversity, broadly defined, is associated with reduced subcortical volumes, particularly the hippocampus (Calem et al., 2017). Conversely, other studies have found larger amygdala or hippocampal volumes in offspring exposed to maternal mood difficulties (Donnici et al., 2021; Lupien et al., 2011) or have not documented statistically significant associations with either region (Lupien et al., 2011; Wylie et al., 2024). It is also important to note that most of these studies have focused on maternal depression, especially during the perinatal period. Fewer studies have considered maternal anxiety during early childhood (Kemp et al., 2022), despite the fact that this is a period during which offspring may be particularly sensitive to the adverse effects of maternal anxiety (Gjerde et al., 2020). One significant challenge within the field is establishing how maternal mood dysfunction is best conceptualized to test associations with offspring neurodevelopment. Researchers have historically focused on average or total levels of symptom severity, frequency, or number of symptoms based on maternal responses to questionnaires. Although there are well-established relations between traditional assessments of maternal mood symptom levels and child adjustment, it is unclear whether summing symptom scores is the optimal approach for considering maternal mood in relation to offspring brain development. Assessing mood based on the sum symptom scores ignores information about variability in mood. In fact, researchers have proposed that intraindividual inconsistencies in caregiver mood states reflect unpredictable, fragmented signals that shape offspring brain development (Davis & Glynn, 2024; Glynn & Baram, 2019). This perspective is consistent with models that conceptualize unpredictability, or fluctuation in environmental conditions, as a core dimension of early life adversity, with neurodevelopment evolving to be sensitive to the statistical structure of the environment (Ellis et al., 2022). Interestingly, in rodent offspring, fragmented maternal signals have been linked to impoverished dendritic trees in the hippocampus (Brunson et al., 2005) and to alterations in hippocampus-dependent memory (Davis et al., 2017). Further, unpredictable maternal signals have been associated with altered expression of stress response genes in the amygdala of rodent offspring (Demaestri, 2023) and with altered structural connectivity between the amygdala and prefrontal cortex in human offspring (Granger et al., 2021). Together, these findings with rodent models provide a foundation for considering predictable versus unpredictable aspects of maternal mood and hippocampal and amygdala development in humans as a cross-species comparison.

Recently, researchers have used a novel approach to assess this aspect of maternal mood dysfunction, drawing on Shannon's entropy, which measures the "randomness or unpredictability of the probability distribution of a random variable" (Howland et al., 2021, p. 490). Thus, mood entropy reflects the randomness or unpredictability of an individual's responses to mood questionnaire items. For example, if a participant endorsed always feeling rested and never feeling nervous or restless on a questionnaire assessing anxiety, their item responses would be considered predictable and consistent and would yield a low entropy score. Conversely, a participant who completed the questionnaire at random would be considered highly unpredictable and, thus, obtain a high entropy score. Importantly, mood entropy based on questionnaire measures has shown to have convergent validity with variability in daily affect measured by ecological momentary assessments (Glynn et al., 2018; Ugarte, 2023). Thus, entropy provides a sensitive index of intraindividual inconsistencies in mood states as assessed by questionnaire items. Although there are other approaches to quantifying unpredictability (Ellis et al., 2022; Ugarte & Hastings, 2023), entropy aligns with our guiding framework (Davis & Glynn, 2024) and our aim to assess unpredictability specifically in maternal mood (Glynn et al., 2018; Howland et al., 2021). Entropy also quantifies unpredictability in a manner consistent with information theory, rather than defining it simply as variability (within-person standard deviation) or as deviations from model predictions (residual approach), neither of which directly indexes the unpredictability of mood symptoms.

A small body of research suggests that maternal mood entropy has associations with child outcomes that are unique from maternal mood levels (Glynn et al., 2018; Howland et al., 2021; Jirsaraie et al., 2024). For example, Glynn and colleagues (2018) found that maternal mood entropy was a unique predictor of maternal reports of negative affectivity in infancy and childhood and of child and adolescent self-reports of anxiety and depressive symptoms. Only one prior study, however, has focused on maternal mood entropy and the neurodevelopment of offspring: Jisaraie and colleagues (2024) found that prenatal maternal mood entropy, but not mood symptom level, was associated with salience network integrity in children. Whether maternal mood entropy is associated with the structural development of children's hippocampus and amygdala in a way that suggests biological embedding, and whether these associations are unique from maternal mood levels, is not yet known.

Another important limitation of the literature examining maternal mood and child neurodevelopment is that most studies have conducted a neuroimaging assessment at only a single point in time. However, developmental psychopathology frameworks posit that early risk factors, such as maternal mood difficulties, trigger developmental cascades that unfold over time and influence subsequent neurodevelopment (Masten & Cicchetti, 2010). Thus, longitudinal data with repeated neuroimaging assessments are essential for examining how the effects of early life experiences, such as exposure to maternal mood difficulties, unfold across childhood. Developmental psychologists have formulated models for testing two competing perspectives regarding how early experience shapes adaptation over time (Haltigan et al., 2013; Magro et al., 2020; Raby et al., 2015), but have not applied these models to longitudinal neuroimaging data. The *revisionist* perspective posits that early experiences are related to early developmental outcomes, but that their direct effects fade over time and are increasingly accounted for by the stability in the outcome (Fraley et al., 2013; Fraley & Roisman, 2015). Within this framework, this pattern is called a "transient" effect, referring specifically to the direct association fading over time. From this perspective, exposure to maternal mood difficulties in early childhood may have a transient direct association with brain structure in early

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childhood while still exerting indirect effects at later assessments via rank-order stability of brain development over time (i.e., consistently high, moderate, or low ranking relative to others). The formal model for testing this perspective would demonstrate that maternal mood difficulties are associated directly with children's early brain structure but only indirectly with brain structure at subsequent assessments through stability in brain development. Thus, the revisionist model suggests that maternal mood plays a transient but potentially foundational role in early neurodevelopment. It is important to note that the term "transient" in this context does not imply that the effect is developmentally unimportant; it refers specifically to the fading over time of the direct association. Because transient direct effects may be carried forward indirectly through the stability of brain development, they may nonetheless have lasting implications.

In contrast, the *enduring* perspective suggests that some early experiences continue to directly shape adaptation across development, not only during early childhood. An example of the enduring model comes from the proposition of attachment theory that early relationships with caregivers organize early development and that this history continues to play an important role in shaping development over time (Sroufe et al., 1990). From this perspective, early life interpersonal experiences are both foundational for early child development and serve as a direct scaffold for future development (Fraley et al., 2013; Fraley & Roisman, 2015). Thus, the enduring effects perspective would posit that early maternal mood difficulties have lasting and direct predictive significance for subcortical volumes across childhood (over and above the stability of these outcomes).

The current study had two aims. First, we examined whether maternal mood levels (sum of item responses) and entropy (unpredictability of item responses) are independently associated with children's hippocampal and amygdala volumes. Given that risk factors have frequently been associated with smaller hippocampal volume in children (Humphreys et al., 2019; Miller et al., 2024; D. G. Weissman et al., 2020a), we expected to observe smaller hippocampal volumes in the context of maternal mood difficulties. We did not have *a priori* hypotheses, however, regarding whether this association would be specific to maternal mood levels or entropy. Given inconsistent findings in the literature (Calem et al., 2017), we also did not have specific hypotheses about whether maternal mood would be related to smaller or larger amygdala volume. Second, we explored whether early patterns of maternal mood have transient associations with offspring neurodevelopment in early childhood or enduring effects that extend into late childhood. We tested models of transient versus enduring effects that have been developed in other areas of research (Fraley et al., 2013; Fraley & Roisman, 2015; Haltigan et al., 2013; Raby et al., 2015) but have yet to be applied to longitudinal neuroimaging data.

Methods

Participants and study design

Participants were drawn from the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) birth cohort study. The original GUSTO study design, including details regarding procedures and study exclusion criteria, is described in Soh et al. (2012). Participants were included in our analyses if they provided data on maternal mood symptoms at the age 3 months, years 1, 2, 3, and 4.5 assessments, and/or usable T1-weighted neuroimaging scans at any of the age 4.5, 6, 7.5, or 10.5 year assessments ($n = 1{,}425$ total; $n = 674$ children with neuroimaging; 47.8% female, Chinese 54.8%, Malay 26.5%, and Indian 18.7%). All demographic data were provided by mothers at 26 weeks' gestation. GUSTO was approved by the National Healthcare Group Domain Specific Review Board and the SingHealth Centralized Institutional Review Board in Singapore. Parents provided informed consent for participation and received compensation.

Measures

Maternal mood level and entropy

Mothers completed the State-Trait Anxiety Inventory (STAI; Spielberger, 1983) at 3 months and 1, 2, 3, and 4.5 years after the child's birth. The STAI measures current anxiety and "general" feelings of anxiety and has been used in prior studies comparing maternal mood levels and entropy (Howland et al., 2021). The STAI consists of 40 questions assessing severity and frequency of symptoms on a 1–4 scale. Following the scoring protocol for the STAI, 17 questions were reverse-scored (Bee Seok et al., 2018). To compute maternal mood *level*, item responses were summed, yielding a score between 40 and 160. The sum of responses to these 40 questions represents the *level* of maternal mood. These maternal mood level scores were averaged across assessment waves to create a composite score representing maternal mood level.

Maternal mood variability was calculated using Shannon's entropy formula. Consistent with Glynn et al. (2018), we applied Shannon's entropy formula to STAI responses.

This yields probability distributions reflecting a given participant's propensity to respond to STAI items in a consistent versus inconsistent manner, thus creating a measure of the unpredictability of mood states by entropic item responses. Entropy scores were calculated in R Studio (2023) utilizing code provided by Kelm, 2023, which can be found at https://contecenter.uci.edu/measuring-maternal-mood/. Mood entropy and mood level scores were auto-correlated across assessments (all $rs > .29$, $ps < .001$ for mood entropy, and all $rs > .48$, $ps < .001$ for mood levels). These correlations are presented in Supplemental Table S3. An overall maternal mood entropy score was calculated in the same manner as maternal mood level, averaging entropy scores across assessment waves.

Magnetic resonance imaging at ages 4.5, 6.0, 7.5, and 10.5 years

Participants completed magnetic resonance imaging (MRI) using a 3 T Siemens Skyra scanner at ages 4.5 and 6 years and using a 3 T Siemens Magnetom Prisma scanner at age 7.5 and 10.5 years. As reported in prior in prior analyses of GUSTO data (Miller et al., 2024), high-resolution T1-weighted structural scans were collected using a Magnetization-Prepared Rapid Gradient-Echo (MP-RAGE) sequence with the following parameters: 192 slices, repetition time = 2000 ms, echo time = 2.08 ms, 1 mm isotropic voxels, and matrix size = 192 × 192. Data harmonization using longitudinal ComBat v.0.0.0.90 (Beer et al., 2020) was done with two batches – (1) ages 4.5 and 6 years and (2) age 7.5 years.

Segmentation

Segmentation was previously described in Miller et al. (2024). Briefly, MP-RAGE images underwent the standard FeeSurfer recon-all stream (v.7.0, http://surfer.nmr.mgh.harvard.edu). FreeSurfer outputs were inspected for registration between the structural images and atlas. Images showing poor registration were manually edited and reprocessed to ensure good correspondence with the atlas. Segmented hippocampal and amygdala masks were then used to estimate the volume measurements at each scan

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assessment. Quality control of scan data was performed at the raw MP-RAGE data and FreeSurfer recon-all output stages. For raw data, this involved a scoring system of pass (no or minimal visible motion lines, clear WM/GM distinction), good (visible motion lines that may be persistent with clear WM/GM distinction), questionable (visible motion lines that may be persistent with poor WM/GM distinction), or fail (ripples of motion lines that are prominent and persistent – integrity of WM/GM distinction are almost lost). Following our quality check, the number of scans that failed were 98 at age 4.5, 67 at age 6, 16 at age 7, and 3 at age 10.5. The numbers of children with 0, 1, 2, 3, and 4 scans are presented in Supplemental Table S2.

Data analysis

Brain volume data within each neuroimaging assessment timepoint were winsorized such that values higher and lower than the 95% and 5% quantile were replaced by those values, respectively. Bivariate correlations were conducted to assess the relations among maternal mood level, maternal mood entropy, and brain volumes. For hippocampal or amygdala volumes that showed significant associations with maternal mood levels or entropy, we then conducted a path analysis to formally investigate whether maternal mood variables showed transient associations specific to the region of interest in early childhood (i.e., significant direct effects at ages 4.5 and 6 years) or enduring associations with the region that continued across childhood (i.e., significant direct effects at all ages from 4.5 through 10.5 years). We tested separate models for the left and right hippocampus and amygdala volumes. After evaluating whether associations conformed more to a transient or enduring model, we tested whether the associations between maternal mood and brain volumes persisted after adjusting for covariates. Given that socioeconomic status is related to both maternal mental health and child neurodevelopment (Hair et al., 2015; Masarik & Conger, 2017), covariates included a latent factor score for socioeconomic status based on maternal education level and household income, both of which were assessed during a prenatal assessment. In addition, covariate-adjusted models included biological sex assigned at birth, intracranial volume to isolate region-specific variability, and both maternal mood levels and mood entropy as predictors to test their unique effects. This approach is consistent with prior studies that examined maternal mood levels and entropy in the same model (Glynn et al., 2018; Howland et al., 2021). Within the adjusted models, these covariates were included for every path between maternal mood and brain volume across the four neuroimaging assessments. All statistical models were conducted using the lavaan package in R (2023). We conducted Little's MCAR (missing completely at random) test to assess systematic missingness. The test failed to reject the null hypothesis ($p = .163$), indicating that the data are consistent with the assumption of MCAR. We used full information maximum likelihood (FIML) to handle missing data and to estimate model parameters. As a result, model parameters are informed by different numbers of participants depending on patterns of missingness across variables. To assess model fit, we used χ^2, the Comparative Fit Index (CFI), and the root mean square error of approximation (RMSEA) with a 90% confidence interval (CI).

Results

Descriptive statistics and correlations

Table 1 presents descriptive statistics, and Figure 1 presents a plot of the zero-order correlations among our variables of interest (see Table S1 for descriptive statistics using non-winsorized data). Maternal mood level and entropy were positively correlated with each other ($r = .66$, $p < .001$, 95% CI = 0.624, 0.695). Maternal mood entropy was negatively correlated with left and right hippocampal volume at ages 4.5 and 6 (all $rs > -.12$, $ps < .04$), but not at ages 7.5 and 10.5 (all $rs < -.07$, all $ps > .153$). Maternal mood level was not significantly correlated with any brain volume metric (all $rs < -.09$, all $ps > .185$). All brain volume metrics were positively associated with each other across regions, hemispheres, and

Table 1. Descriptive statistics

Variable	$N = 1,498$	Mean	*SD*	Min	Max
Infant sex	1,095	52% Female		0	1
Household income	1,244	3.581	1.096	1	5
Maternal education	1,319	4.486	1.345	1	6
No education	2	0.13%			
Primary	80	5.34%			
Secondary	357	23.8%			
Junior college	134	8.95%			
Polytechnic	328	21.9%			
University	418	27.9%			
Entropy	978	57.512	18.831	0	98.171
Level	978	70.088	17.883	18	138
R Hip 4.5	262	3,836.388	329.312	3,283.22	4,422.7
R Hip 6	350	4,007.084	330.142	3,411.35	46,37.375
R Hip 7.5	486	4,070.968	345.774	3,463.085	4,705.045
R Hip 10.5	467	4,279.702	351.206	3,640.05	4,896.175
L Hip 4.5	262	3,634.171	304.679	3,094.84	4,183.11
L Hip 6	486	3,782.875	315.731	3,214.675	4,390.675
L Hip 7.5	502	3,907.939	310.999	3,373.2	4,477.68
L Hip 10.5	467	4,054.739	320.457	3,510.95	4,657.655
R Amg 4.5	262	1,596.803	166.805	1,307.51	1,915.22
R Amg 6	350	1,683.412	173.279	1,387.7	2,031.15
R Amg 7.5	486	1,650.868	176.528	1,350.4	1,984.58
R Amg 10.5	467	1,770.497	183.63	1,448.47	2,130.075
L Amg 4.5	262	1,452.629	148.572	1,150.82	1,724.3
L Amg 6	350	1,517.335	159.233	1,230.8	1,794
L Amg 7.5	486	1,489.298	162.780	1,223.12	1,811.93
L Amg 10.5	467	1,643.314	170.857	1,354.245	1,956.01
ICV 4.5	262	1,405.824	119.384	1,199.845	1,640.257
ICV 6	350	1,481.724	131.015	1,272.251	1,735.983
ICV 7.5	486	1,490.896	116.386	1,281.382	1,708.621
ICV 10.5	467	1,507.343	118.212	1,301.909	1,737.232

Note. All brain metric units are in mm^3; ICV = intracranial volume (scaled by dividing ICV values by 1,000); Hip = hippocampus; Amg = amygdala; Entropy = mood entropy; Level = mood level; R = right; L = left. Household Income reported in Singapore dollars per month: $0–$999, $1,000–$1999, $2000–$3999, $4000–$5999, more than $6000. For Maternal Education, 1 = No education, 2 = Primary, 3 = Secondary, 4 = Junior college or Institute of Technical Education, 5 = Polytechnic, 6 = University (Bachelor's, Graduate degree).

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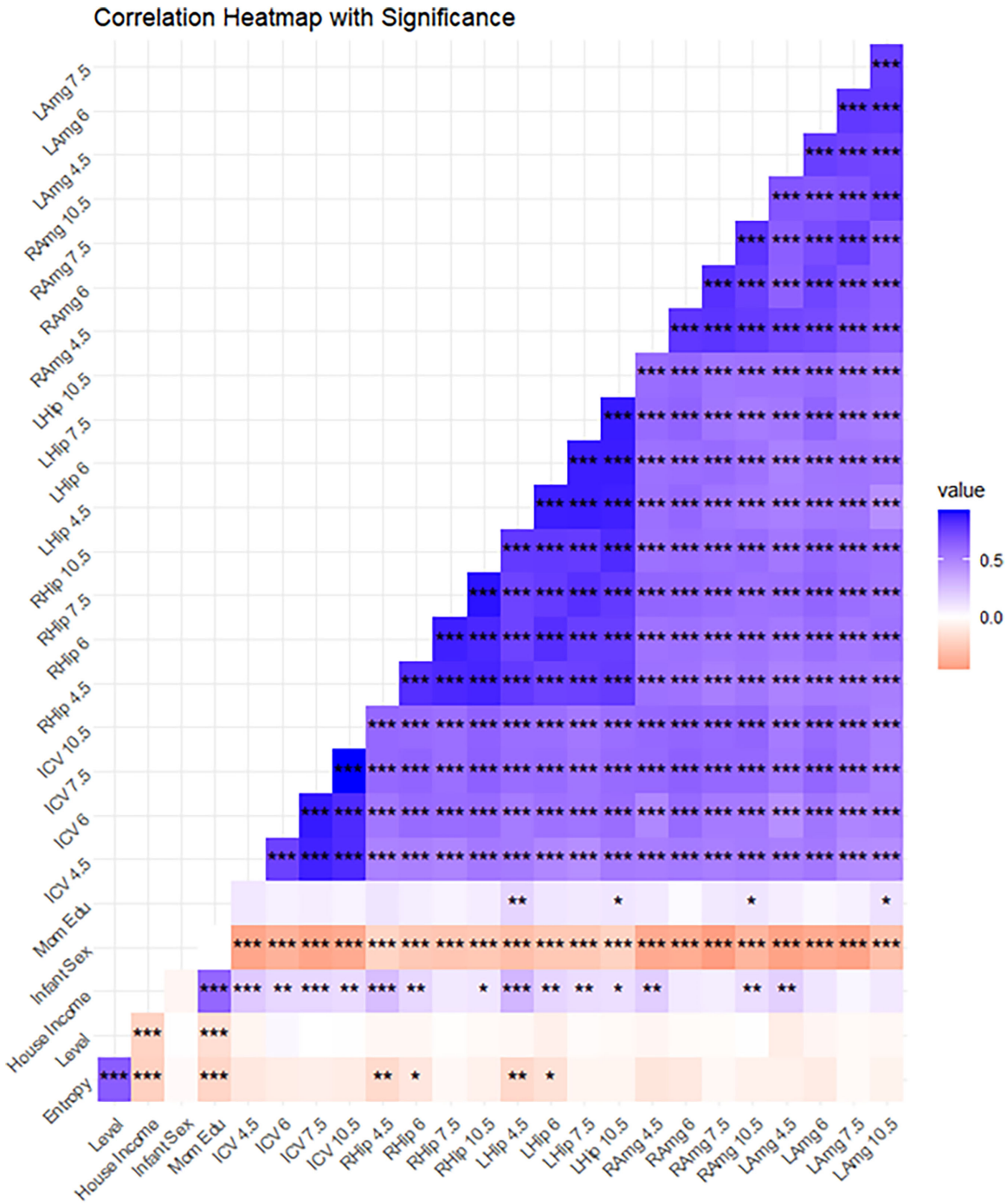


Figure 1. Correlations. *Note*. Squares in blue represent positive correlations, squares in red represent negative correlations. Stronger correlations are represented by darker squares. Mom Edu = maternal education; Sex coded as 0 = male and 1 = female. ***p <.001, **p <.01, *p <.05.

timepoints (all $rs > .49$, $ps < .001$). Each measurement of brain volume showed strong rank-order stability over time (all $rs > .76$, all $ps < .001$). Females had smaller brain volumes across regions and ICV compared to males (all $rs > -.38$, all $ps < .001$). Household income was significantly positively correlated with most measurements of brain volumes (all $rs > .10$, all $ps < .044$), except for right and left amygdala at ages 6 and 7.5, left amygdala at age 10.5, and right hippocampal volume at age 7.5 (all $rs < .10$, all $ps > .075$). Maternal education was significantly positively associated with left and right amygdala and left hippocampal volumes at 10.5 and left hippocampal volume at 4.5 (all $rs > .10$, all $ps <$ .038), but not any other brain metric (all $rs < .10$, all $ps > .066$). A table of all correlations and their respective p-values is presented in Supplemental Table S4.

Path analysis models of maternal mood entropy and hippocampal volume

The correlations showed that maternal mood entropy, but not level, was negatively associated with hippocampal volumes at ages 4.5 and 6. Therefore, we conducted path analysis models focused on maternal mood entropy as a predictor of hippocampal volumes,

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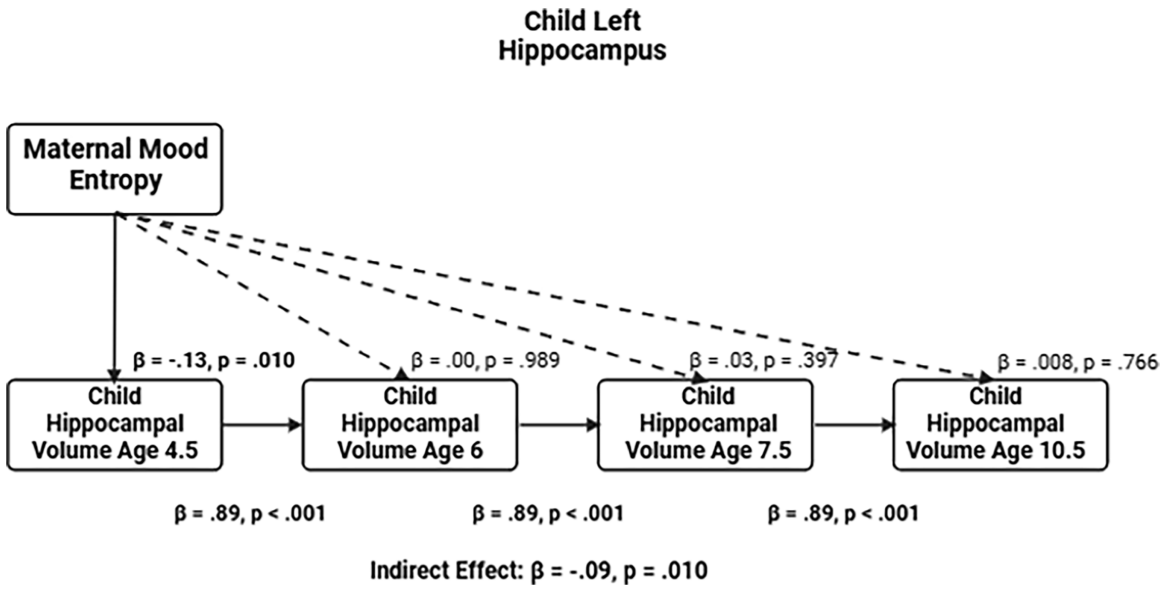


Figure 2. Entropy and left hippocampal volume model. *Note.* Solid lines are paths significant at $p < .05$.

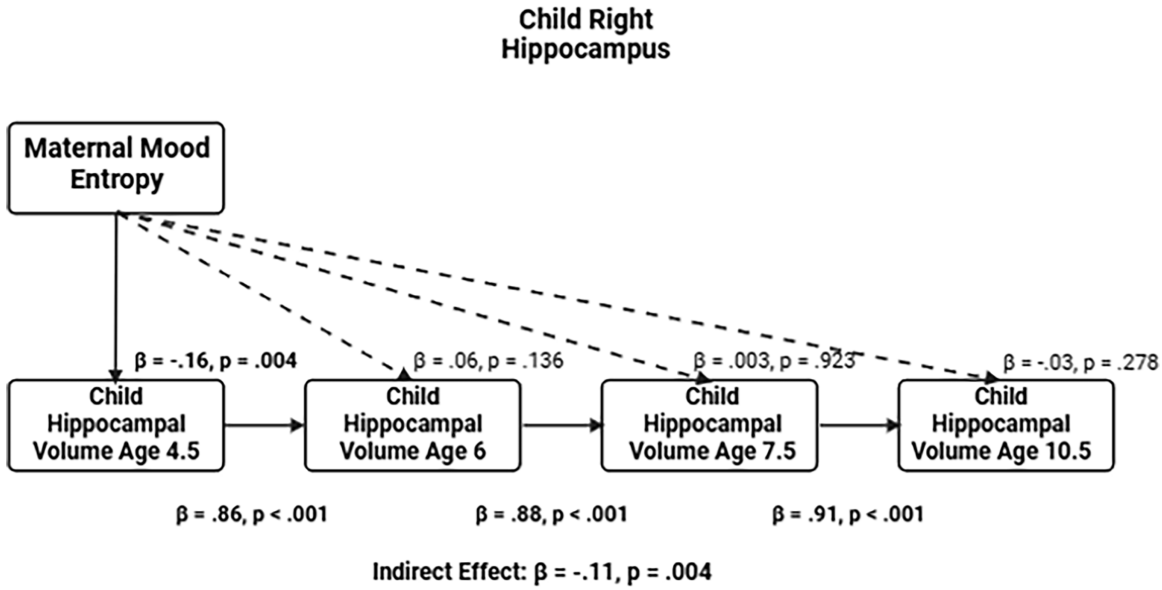


Figure 3. Entropy and right hippocampal volume model. *Note.* Solid lines are paths significant at $p < .05$.

controlling for rank-order stability over time, to examine the degree to which this association was transient versus enduring. The left and right hippocampal volume models (not adjusted for covariates) are presented in Figures 2 and 3, respectively (see Tables 2 and 3 for parameter estimates).

These models showed acceptable fit to the data (left hippocampus model: $\chi^2(13) = 174.134$, $p < .001$; CFI = .924; RMSEA = .094, CI [0.082, 0.106]; right hippocampus model: $\chi^2(13) = 140.861$, $p < .001$; CFI = .938; RMSEA = .083, CI [0.071, 0.096]). Our results were more consistent with a transient effect than enduring effect model. Specifically, maternal mood entropy was negatively associated with child left and right hippocampal volume at age 4.5 years ($\beta = -.13$, $p = .010$ and $\beta = -.16$, $p = .004$); however, after controlling for rank-order stability of hippocampal volume over time, maternal mood entropy was no longer associated with left or right hippocampal volume at age 6 years (both βs < .07, ps > .136). Maternal mood entropy was also not associated with hippocampal volumes at 7.5 and 10.5 years (all βs < .04, ps > .278). Additionally, maternal mood entropy was indirectly associated with reduced hippocampal volume at 10.5 years through rank-order stability of hippocampal volume over time (serial indirect $\beta = -.09$, $p = .010$, and serial indirect $\beta = -.11$, $p = .004$ for left and right hippocampal volumes, respectively).

Path analysis with covariates

In our previous models, we determined that maternal mood entropy was specifically associated with child hippocampal volume. After adjusting for covariates (see Figures 4 and 5 and Tables 4 and 5), the direct associations of maternal mood entropy with hippocampal volumes at age 4.5 remained statistically significant (both ps < .040 for left and right hippocampal volume).

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Table 2. Entropy and left hippocampal volume model

Paths	*β*	*SE*	*p*	95% CI
Outcome: left hippocampal volume at age 4.5				
Entropy	−0.13	0.05	0.010**	−0.235, −0.033
Outcome: left hippocampal volume at age 6				
Entropy	0.00	0.04	0.989	−0.070, 0.071
Left hippocampal volume age 4.5	0.89	0.01	< .001***	0.861, 0.915
Outcome: left hippocampal volume at age 7.5				
Entropy	0.03	0.030	0.397	−0.033, 0.084
Left hippocampal volume age 6	0.89	0.01	< .001***	0.871, 0.914
Outcome: left hippocampal volume at age 10.5				
Entropy	0.008	0.03	0.766	−0.042, 0.057
Left hippocampal volume age 7.5	0.89	0.01	< .001***	0.875, 0.913
Outcome: indirect effect				
	−0.09	0.04	0.010**	−0.167, −0.022

Note. ***p < .001, **p < .01, *p < .05. *β* = standardized beta; *SE* = standard error; CI = confidence interval.

Table 3. Entropy and right hippocampal volume model

Paths	*β*	*SE*	*p*	95% CI
Outcome: right hippocampal volume at age 4.5				
Entropy	−0.16	0.05	0.004**	−0.260, −0.051
Outcome: right hippocampal volume at age 6				
Entropy	0.06	0.04	0.136	−0.019, 0.138
Right hippocampal volume age 4.5	0.86	0.02	< .0 001 ***	0.819, 0.891
Outcome: right hippocampal volume at age 7.5				
Entropy	0.003	0.03	0.923	−0.060, 0.066
Right hippocampal volume age 6	0.88	0.01	< .001***	0.865, 0.909
Outcome: right hippocampal volume at age 10.5				
Entropy	−0.03	0.02	0.278	−0.070, 0.020
Right hippocampal volume age 7.5	0.91	0.01	< .001***	0.892, 0.925
Outcome: indirect effect				
	−0.11	0.04	0.004**	−0.180, −0.034

Note. ***p < .001, **p < .01, *p < .05. *β* = standardized beta; *SE* = standard error; CI = confidence interval.

These associations were present over and above the effects of socioeconomic status (both *β*s < .12, *p*s < .021) and intracranial volume (both *β*s < .54, *p*s < .001) and were specific to maternal mood entropy (not levels). The indirect effect of maternal mood entropy on left and right hippocampal volume at 10.5 was also still significant in a covariate-adjusted model.

In the covariate-adjusted model for the right hippocampus, maternal mood entropy was significantly and positively associated with right hippocampal volume at age 6 (*β*=.11, *p*=.036). Given that the zero-order correlations between maternal mood entropy and right hippocampal volume at ages 4.5 and 6 were negative and significant, it is possible that the positive association at age 6 in the covariate-adjusted model is a suppression effect; therefore, we did not interpret this effect. See Tables S5 and S6 for results using non-winsorized data.

Amygdala model

In models controlling for rank-order stability (i.e., autocorrelation) and covariates, maternal mood entropy was not significantly associated with amygdala volume at any timepoint for either hemisphere (all absolute *β*s < .10, *p*s < .110).

Testing a latent factor model of maternal mood dysregulation

The significant correlation between maternal mood entropy and mood levels raises the possibility that these measures are manifestations of a broader construct of mood dysregulation that may be implicated in children's neurodevelopment. Therefore, we tested whether a latent factor based on mood entropy and mood levels was associated with children's hippocampal and amygdala

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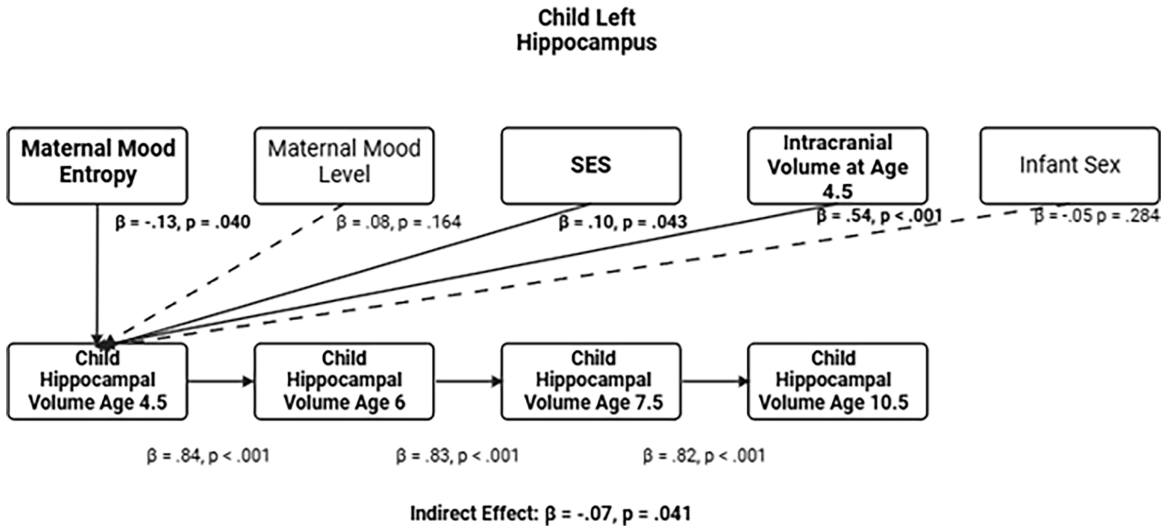


Figure 4. Entropy and left hippocampal model after adjusting for covariates. *Note.* Solid lines are paths significant at $p < .05$. Maternal mood level, SES, ICV, and sex were included as covariates at all time points but are omitted from the plot for clarity. Further statistical details regarding these results are presented in Table 4.

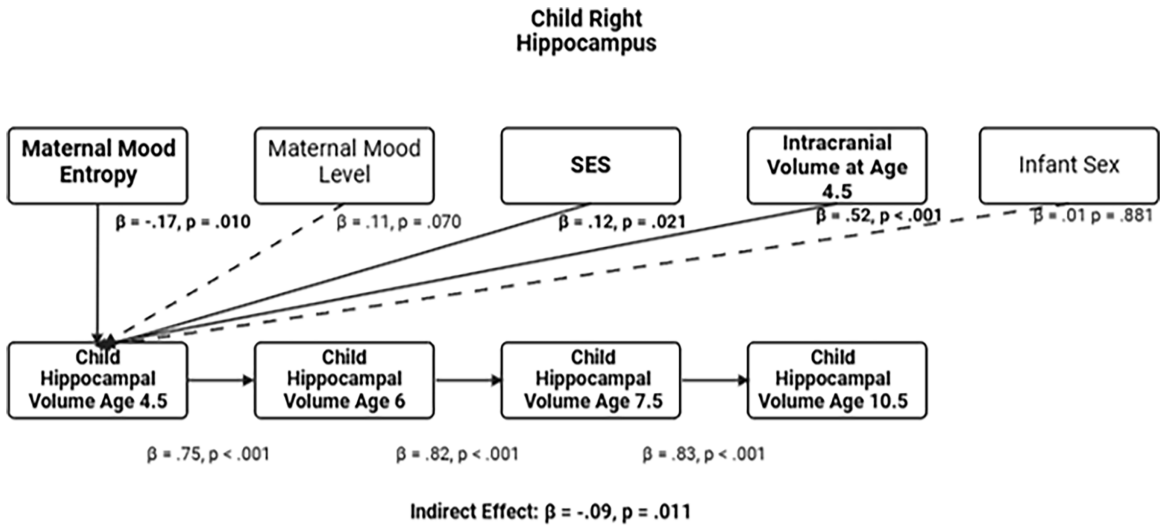


Figure 5. Entropy and right hippocampal model after adjusting for covariates. *Note.* Solid lines are paths significant at $p < .05$. Maternal mood level, SES, ICV, and sex were included as covariates at all time points but are omitted from the plot for clarity. Further statistical details regarding these results are presented in Table 5.

volumes. We did not find that this latent factor was significantly associated with left or right volumes at any time point (all βs < 0.05, ps $> .332$). Further details on these results for the hippocampus are presented in the supplemental materials, Tables S7 and S8.

Testing sex differences

Prior work suggests that there are sex-specific subcortical alterations in offspring exposed to difficulties in maternal mood (Wen et al., 2017). To examine whether similar patterns of findings are found in the context of maternal mood entropy, we tested whether the effects of maternal mood entropy (and mood level) on subcortical volumes differed by sex. Specifically, we added interaction terms of sex and maternal mood entropy, as well as sex and maternal mood level, to our path analysis models. One model yielded significant sex moderation for the association of maternal mood entropy with right hippocampal volume ($\beta = -.07$, $p = .045$) at age 10.5 years. To probe these effects, we reran our models separately in males and females. For both right hippocampal and left amygdala volume at age 10.5, the direct effect of maternal mood entropy was not statistically significant for either females or males (all βs $< -.11$, ps $> .115$). Thus, although the associations of maternal mood entropy with right hippocampal and left amygdala volumes at 10.5 differed significantly for males and females, they did not differ from zero for either sex. Consequently, we do not interpret these interactions further. We present additional details about these results in Supplemental Tables S9 and S10. We also provide in Figure S1 a visualization of average changes in hippocampal and amygdala volumes across time.

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Table 4. Entropy and left hippocampal volume model with covariates

Paths	*β*	*SE*	*p*	95% CI
Outcome: left hippocampal volume at age 4.5				
Entropy	−0.13	0.06	0.040*	−0.251, −0.006
Level	0.08	0.06	0.164	−0.034, 0.198
SES	0.10	0.05	0.043*	0.003, 0.187
Infant sex	−0.05	0.05	0.284	−0.143, 0.042
ICV at 4.5	0.54	0.04	< .001***	0.466, 0.618
Outcome: left hippocampal volume at age 6				
Entropy	0.05	0.05	0.252	−0.038, 0.146
Level	−0.08	0.05	0.107	−0.148, 0.014
SES	0.01	0.03	0.808	−0.058, 0.074
Infant sex	0.04	0.03	0.245	−0.027, 0.104
ICV at 6	0.12	0.04	< .001***	0.052, 0.197
Left hippocampal volume age 4.5	0.84	0.03	< .001***	0.790, 0.887
Outcome: left hippocampal volume at age 7.5				
Entropy	0.01	0.04	0.763	−0.063, 0.085
Level	0.02	0.04	0.576	−0.050, 0.089
SES	−0.02	0.03	0.420	−0.075, 0.047
Infant sex	−0.05	0.03	0.070	−0.105, 0.004
ICV at 7.5	0.09	0.03	0.007**	0.023, 0.148
Left hippocampal volume age 6	0.83	0.02	< .001***	0.794, 0.875
Outcome: left hippocampal volume at age 10.5				
Entropy	0.03	0.03	0.276	−0.027, 0.096
Level	−0.01	0.03	0.685	−0.068, 0.045
SES	0.03	0.02	0.166	−0.014, 0.081
Infant sex	0.09	0.02	< .001***	0.037, 0.132
ICV at 10.5	0.18	0.03	< .001***	0.123, 0.231
Left hippocampal volume age 7.5	0.82	0.02	< .001***	0.788, 0.860
Indirect effect				
	−0.07	0.04	0.041*	−0.145, −0.003

Note. ***$p < .001$, **$p < .01$, *$p < .05$. β = standardized beta; *SE* = standard error; CI = confidence interval; ICV = intracranial volume (scaled by dividing ICV values by 1,000); Sex coded as 0 = male and 1 = female.

Further sensitivity analyses

Analyses incorporating a measure of maternal depression (Beck Depression Inventory II; BDI-II) did not yield significant associations with offspring neurodevelopment. We considered BDI-based measures of entropy and levels and an aggregate measures of BDI with STAI. Maternal mood entropy and mood levels based on BDI were not associated with hippocampal volumes (all βs < .13 ps > .128), with the exception of entropy predicting left hippocampal volume at age 10.5 ($\beta = .12$, $p = .008$). Although an aggregate measure of BDI entropy and STAI entropy had small but significant zero-order correlations with both left and right hippocampal volumes at age 4.5 (both rs > −.14, both ps < .023), these associations were no longer statistically significant after adjusting for covariates (both rs < −.05, both ps > .466).

We also conducted analyses testing our covariate-adjusted models but limited to the subset of participants who had at least one neuroimaging timepoint ($n = 674$). These analyses yielded the same pattern of findings as models based on the full sample. Specifically, mood entropy, but not mood level, was associated with right hippocampal volume at age 4.5 ($\beta = -.16$, $p = .010$), and this association was carried forward indirectly to right hippocampal volume at age 10.5 via the rank-order stability of hippocampal volume over time ($\beta = -.08$, $p = .011$). Our left hippocampal model showed the same pattern of results. Model estimates are presented in Supplemental Tables S11 and S12.

Discussion

This study had two primary aims. First, to determine whether early maternal mood symptoms are implicated in offspring hippocampal and amygdala volume development, testing whether these associations were specific to maternal mood symptom levels or entropy. Second, we explored two competing perspectives regarding how the effects of early experiences on subcortical development unfold across time. Our results demonstrate that

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Table 5. Entropy and right hippocampal model with covariates

Paths	β	*SE*	*p*	95% CI
Outcome: right hippocampal volume at age 4.5				
Entropy	−0.17	0.07	0.010*	−0.303, −0.042
Level	0.11	0.06	0.070	−0.010, 0.238
SES	0.12	0.05	0.021*	0.017, 0.215
Infant sex	0.01	0.05	0.881	−0.092, 0.108
ICV at 4.5	0.52	0.04	< .001***	0.437, 0.603
Outcome: right hippocampal volume at age 6				
Entropy	0.11	0.05	0.036*	0.007, 0.207
Level	−0.07	0.05	0.140	−0.166, 0.023
SES	−0.02	0.04	0.609	−0.091, 0.053
Infant sex	−0.03	0.04	0.455	−0.097, 0.043
ICV at 6	0.21	0.04	< .001***	0.132, 0.290
Right hippocampal volume age 4.5	0.75	0.03	< .001***	0.692, 0.810
Outcome: right hippocampal volume at age 7.5				
Entropy	0.01	0.04	0.799	−0.069, 0.090
Level	−0.03	0.04	0.493	−0.100, 0.048
SES	−0.06	0.03	0.039*	−0.110, −0.003
Infant sex	−0.03	0.03	0.237	−0.089, 0.022
ICV at 7.5	0.11	0.03	< .001***	0.045, 0.173
Right hippocampal volume age 6	0.82	0.02	< .001***	0.775, 0.861
Outcome: right hippocampal volume at age 10.5				
Entropy	−0.01	0.03	0.677	−0.068, 0.044
Level	0.006	0.03	0.831	−0.046, 0.057
SES	0.02	0.02	0.424	−0.026, 0.062
Infant sex	0.05	0.02	0.020*	0.008, 0.097
ICV at 10.5	0.19	0.03	< .001***	0.127, 0.229
Right hippocampal volume age 7.5	0.83	0.02	< .001***	0.791, 0.862
Indirect effect				
	−0.09	0.03	0.011	−0.155, −0.020

Note. ***$p < .001$, **$p < .01$, *$p < .05$. β = standardized beta; *SE* = standard error; CI = confidence interval; ICV = intracranial volume (scaled by dividing ICV values by 1,000); Sex coded as 0 = male and 1 = female.

early patterns of maternal mood dysregulation are implicated in early childhood brain structure, laying the foundation for subsequent neurodevelopment. Early maternal mood entropy, which may reflect intraindividual patterns of mood instability or variability, is implicated in the underdevelopment of offspring's hippocampi that predisposes them to continue showing this pattern in the future. Our findings both contribute to a developing body of research that entropy is an independent and meaningful component of mood dysregulation (Glynn et al., 2018; Howland et al., 2021; Jirsaraie et al., 2024) and suggest a specific developmental process that comprises the changing association between early maternal mood entropy and children's hippocampal volume across childhood. Consistent with prior research on maternal mood entropy in relation to other child outcomes, our results indicate that maternal mood entropy is uniquely implicated in child hippocampal volume over and above mood level. Our prediction that maternal mood abnormalities are negatively associated with hippocampal development was also confirmed. We did not find effects of maternal mood entropy or levels on children's amygdala volume, which fits with the inconsistencies reported in previous studies of early life adversity more broadly (Calem et al., 2017). Lastly, we found inconsistent evidence for sex differences within our models. Maternal mood entropy only significantly interacted with sex to directly predict hippocampal volume at age 10.5. However, the effects of mood entropy were not significantly different from zero for either males or females.

Our finding that maternal mood entropy was uniquely associated with child hippocampal development highlights the importance of considering intraindividual inconsistencies in mood in understanding associations between maternal functioning and child neurodevelopment. Research examining alterations in maternal mood in relation to offspring neurodevelopment may benefit from focusing on entropy, which is not captured by traditional approaches that focus on frequency and severity of mood

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difficulties. Our findings are consistent with the perspective that unpredictable maternal signals shape offspring neurodevelopment (Davis & Glynn, 2024) and with findings from recent studies with rodents suggesting that offspring hippocampal structure is sensitive to these signals (Davis et al., 2017). Further, our findings support broader models that frame environmental unpredictability as an evolutionarily meaningful dimension of early life adversity (Ellis et al., 2022). The current study provides the first evidence in humans that early patterns of maternal mood entropy are associated with altered hippocampal volume and development in offspring. Importantly, reduced hippocampal volume has been observed in the context of other early life adversities (Humphreys et al., 2019; Miller et al., 2024) and has been associated with children's heightened stress sensitivity and psychopathology (Durham et al., 2021; D. G. Weissman et al., 2020b). These relations, in combination with the current findings, suggest that reduced hippocampal volumes are one neurodevelopmental mechanism by which exposure to maternal mood entropy increases children's risk for mental health difficulties.

Our findings also contribute to our understanding of the legacy of early childhood experiences for neurodevelopment across childhood. We used a developmental modeling approach, with repeated neuroimaging observations, to formally test whether the association between maternal mood patterns and offspring neurodevelopment changes over time. A key statistical distinction between enduring and revisionist models is whether early life experiences are associated directly with future development (i.e., Enduring) or indirectly through the stability of development over time (i.e., Revisionist) (Fraley et al., 2013; Fraley & Roisman, 2015). Our findings provide support for a revisionist model of biological embedding. That is, exposure to early maternal mood entropy appears to have a significant but transient direct association with reduced hippocampal volume in early childhood. Although maternal mood entropy did not have enduring direct predictive significance, an indirect effect was carried forward through rank-order stability of hippocampal volumes, leading to underdevelopment of the hippocampus in late childhood. Taken together, maternal mood entropy serves as a foundational experience that is directly associated with early child hippocampal volume (age 4.5) and continues indirectly throughout childhood (out to age 10.5). Many researchers endorse the biological embedding perspective, which posits that early life experiences organize neurobiological structure and function (Berens et al., 2017; Shonkoff, 2012). It is important to note, however, that most studies have used cross-sectional designs and retrospective reporting of early life experiences or have focused on associations with future neural outcomes assessed at a single timepoint. Fewer studies have utilized longitudinal modeling to characterize biological embedding of early life experience as a developmental process that shapes neurodevelopment across time. Early maternal mood entropy appears to predispose children to develop smaller hippocampal volumes, which leads to reduced volumes in the future, a finding that would have gone unnoticed using an approach that focused on a prospective association with future hippocampal volumes at a single timepoint. We believe that our work serves as a call for more longitudinal neuroimaging data given that these study designs are necessary for modeling developmental processes (Roisman & Fraley, 2013).

Although it was not an aim of our study, we also found that family SES was positively associated with hippocampal volume in early childhood, suggesting that higher SES serves as a compensatory resilience factor that offsets the effects of maternal mood entropy on hippocampal development. Conversely, lower SES and higher maternal mood entropy appear to have additive effects on children's reduced hippocampal volume. Collectively, these findings are consistent with prior research suggesting that family SES is related to variability in neuroanatomy (Colich et al., 2020; Hair et al., 2015; Miller et al., 2022) and promotes resilient developmental outcomes in the context of various risk factors (Fergus & Zimmerman, 2005).

It is also worth noting that our findings were specific to maternal anxiety; using a measure of maternal depression (BDI-II) in our analyses did not replicate our findings. It is unclear whether this is due to differences between the constructs of anxiety and depression and/or to differences between the STAI and BDI-II. For example, there was more variability in responses to the STAI than to the BDI-II, which may be related to the fact that the BDI-II items include relatively extreme and less prevalent symptoms (e.g., suicidal ideation). As a result, participants may have been less likely to use the full range of response options on the BDI-II items. The BDI-II is also shorter than the STAI, potentially further limiting opportunities to show unpredictable responding. These features of the BDI-II and/or depression as a construct may have constrained our ability to uncover associations with offspring neurodevelopment. Although prior studies of mood entropy included the STAI and BDI, they combined these measures with other questionnaires (Glynn et al., 2018; Howland et al., 2021). Further research is needed to determine if integrating multiple measures of symptoms of psychopathology yields a more robust index of entropy or whether associations with entropy are driven by specific measures.

We should note four limitations of this study. First, GUSTO is a birth cohort study in Singapore, and the generalizability of the current findings to other populations and sociocultural contexts is unclear. Second, our earliest measurement of child neuroimaging data was at age 4.5 years. In our longitudinal models, we treated the hippocampal and amygdala volume data at this timepoint differently than we did at subsequent assessments, which included paths to control for rank-order stability. It is possible that had we been able to model hippocampal volume at age 4.5 years as being predicted by volumes at earlier ages, we would not have observed an association with maternal mood entropy at this timepoint. In this context, however, it is important to note that maternal mood entropy was associated specifically with hippocampal volume at age 4.5 (and age 6) in our zero-order correlation analyses, which is consistent with the path analyses. Nonetheless, it is possible that maternal mood entropy is directly related to offspring structural neurodevelopment at even earlier ages. Third, there are alternative methods for quantifying maternal mood, each of which captures a different aspect of unpredictability. Our findings are specific to mood entropy, and operationalizing unpredictability in other ways may yield different results. Future research should examine and compare systematically the strengths and limitations of various quantitative approaches, as well as the operationalization of unpredictability reflected by each approach. Finally, our models did not include potential mechanisms linking maternal mood entropy to hippocampal volumes. Although it is not clear precisely how exposure to mood entropy might be related to reduced hippocampal volume, theoretical and empirical work points to fragmented sensory signals as one possibility (Davis et al., 2017; Davis & Glynn, 2024). Fluctuations in maternal emotions and moods, corresponding to changes in emotion-specific behaviors (Keltner & Gross, 1999), may lead to increased inconsistencies in auditory, tactile, and visual input to the child from the caregiver which, in

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turn, may be a more proximal factor influencing maturation of the developing brain.

Despite these limitations, our data show that maternal mood entropy is uniquely associated with reduced hippocampal volume in early childhood, which sets the stage for continued structural underdevelopment of the hippocampus across childhood. This study is the first to link early maternal mood entropy to structural development of the hippocampus in humans. It will be important for future longitudinal neuroimaging research to consider other measures of maternal mood and caregiving unpredictability in order to build on our findings and advance our understanding of the biological embedding of early life experiences in neurodevelopment.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0954579426101291.

Data availability statement. The data for this paper are derived from the GUSTO longitudinal birth cohort study. Restrictions apply to data availability. However, the data can be requested at (https://gustodatavault.sg/), which will require a project description and scientific reasoning.

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Competing interests. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Pre-registration statement. These analyses were largely exploratory and were not pre-registered.

AI statement. ChatGPT was used to assist with troubleshooting and developing R code for analyses and to edit grammar and punctuation while drafting the manuscript.

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