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Across ages and places: Unpredictability of maternal sensory signals and child internalizing behaviors

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ABSTRACT

Background: Patterns of sensory inputs early in life play an integral role in shaping the maturation of neural circuits, including those implicated in emotion and cognition. In both experimental animal models and observational human research, unpredictable sensory signals have been linked to aberrant developmental outcomes, including poor memory and effortful control. These findings suggest that sensitivity to unpredictable sensory signals is conserved across species and sculpts the developing brain. The current study provides a novel investigation of unpredictable maternal sensory signals in early life and child internalizing behaviors. We tested these associations in three independent cohorts to probe the generalizability of associations across continents and cultures.

Method: The three prospective longitudinal cohorts were based in Orange, USA (n = 163, 47.2 % female, Mage = 1 year); Turku, Finland (n = 239, 44.8 % female, Mage = 5 years); and Irvine, USA (n = 129, 43.4 % female, Mage = 9.6 years). Unpredictability of maternal sensory signals was quantified during free-play interactions. Child internalizing behaviors were measured via parent report (Orange & Turku) and child self-report (Irvine).

Results: Early life exposure to unpredictable maternal sensory signals was associated with greater child fearfulness/anxiety in all three cohorts, above and beyond maternal sensitivity and sociodemographic factors. The association between unpredictable maternal sensory signals and child sadness/depression was relatively weaker and did not reach traditional thresholds for statistical significance.

Limitations: The correlational design limits our ability to make causal inferences.

Conclusions: Findings across the three diverse cohorts suggest that unpredictable maternal signals early in life shape the development of internalizing behaviors, particularly fearfulness and anxiety.

1. Introduction

Emerging brain circuits are shaped during sensitive periods in early life, as certain synaptic connections are strengthened by repeated activation, whereas less frequently used connections are eliminated. These processes of synaptic pruning are heavily influenced by early environmental inputs (Dulac et al., 2014; Faust et al., 2021). It is established that patterns of sensory signals sculpt maturation of neural circuits involved in sensory processing including audition and vision (Espinosa and Stryker, 2012; Takesian et al., 2018). More recent cross-species work demonstrates that patterns of sensory signals additionally play an integral role in the development of higher order neural brain circuitry involved in cognitive and emotional processing (Birnie and Baram, 2022; Baram et al., 2012; Bolton et al., 2020; Davis et al., 2017; Granger et al., 2021). Patterns of parental sensory signals early in life thus may have wide reaching consequences for child brain development, which may promote risk or resilience for later emotional dysfunction (Birnie and Baram, 2022; Davis et al., 2017; Glynn and Baram, 2019; Luby et al., 2020).

The pervasive impact of quality of parental care, including sensitivity, warmth, responsiveness, and dyadic synchrony, as well as the formation of a secure attachment relationship have been documented across species (Ainsworth et al., 1978; Bowlby, 1950; Feldman, 2007, 2015; Hennessy et al., 1980; Howell et al., 2017; Landers and Sullivan, 2012). Much less is known about how patterns and sequences of parental sensory signals may influence development. Recent work from our group has quantified these patterns of parental-derived sensory signals to the child by computing the entropy rate, an index of the unpredictability of transitions between visual, auditory, and tactile inputs provided by the parent to their child during dyadic interactions (Davis et al., 2017, 2022; Glynn and Baram, 2019; Holmberg et al., 2020, 2022a, 2022b; Vegetabile et al., 2019). Low entropy indicates predictable patterns of sensory signals during parent-child interactions (e.g., auditory vocalizations repeatedly followed by visual stimulation). In contrast, high entropy reflects unpredictable patterns of sensory signals (e.g., a variable sequence of transitions among these signals).

Cross-species research demonstrates that unpredictable patterns of maternal sensory behaviors disrupt offspring development (Bolton et al., 2022; Chen and Baram, 2016; Noroña-Zhou et al., 2020; Short and Baram, 2019; Davis et al., 2017; Davis et al., 2019). For example, more unpredictable maternal sensory signals (i.e., greater entropy) lead to worse performance on

memory tasks in rodents and non-human primates (Chen and Baram, 2016; Davis et al., 2017, 2022) as well as decreases in hippocampal volume and dendritic arborization in rodents (Molet et al., 2016b). Similarly in humans, we find that unpredictable maternal sensory signals during the first year of life predicts poorer child cognitive function on a standard developmental assessment at 2 years of age and on two different memory tasks at 6.5 years of age (Davis et al., 2017, 2022). In humans, unpredictable maternal signals also presage lower effortful control from infancy through childhood, as indexed by parent report, neuropsychological tasks, and behavioral evaluation (Davis et al., 2019; Holmberg et al., 2022a). Consistent observation of unpredictable maternal sensory inputs impacting child neurodevelopment across experimental rodent research as well as studies with non-human primates, and humans suggests that unpredictable signals are an evolutionarily conserved mechanistic process with deep phylogenetic roots (Bolton et al., 2018, 2020, 2022; Chen and Baram, 2016; Davis et al., 2017, 2022; Davis and Glynn, 2024; Molet et al., 2016a). However, despite growing evidence that exposure to unpredictable parental sensory signals shapes child development, a paucity of work has explored the relation between unpredictable sensory signals and child emotional outcomes.

Internalizing behaviors are inwardly directed behavioral patterns reflecting an individual's emotional or psychological state (Achenbach, 1978; Achenbach and Rescorla, 2001; Liu et al., 2011; Rothbart, 2007), such as sadness and depression or fearfulness and anxiety. Although the relation between unpredictable maternal sensory signals and internalizing behaviors has yet to be examined in humans, two lines of evidence suggest that emotional systems implicated in the etiology of internalizing disorders may be susceptible to early life unpredictable sensory signals. First, beyond sensory signals, unpredictable life experiences broadly contribute to poor emotional outcomes in humans (Baram et al., 2012; Deater-Deckard et al., 2019; Gee and Cohodes, 2021; Glynn et al., 2018; Glynn and Baram, 2019; Jisaraie et al., in press; Lippold et al., 2021; Wilhoit et al., 2021). For instance, both unpredictable maternal mood (Glynn et al., 2018) and unpredictable household and family environments (Ellis et al., 2022; Glynn et al., 2019, 2021; Hartman et al., 2018; Kolak et al., 2018; Lindert et al., 2022; Risbrough et al., 2018; Spadoni et al., 2022) relate to internalizing symptoms in children and adults, including anxiety and depression. Second, experimental animal work documents that unpredictable maternal sensory signals disrupt the development of circuits involved in emotion processing in rodents (Birnie and Baram, 2022; Bolton et al., 2018; Gunn et al., 2013). Unpredictable sensory signals from the dam to the pup also cause anhedonic behaviors in the offspring, demonstrated by reduced sucrose or opioid preference, and altered behavior in peer-play (Kangas et al., 2022; Levis et al., 2022; Molet et al., 2016a). Notably, the impact of unpredictable maternal sensory signals on child emotional outcomes, including internalizing behaviors, has not been explored in humans.

In the current study, we address this key gap and evaluate how unpredictable maternal sensory signals in early life relate to child internalizing behaviors (i.e., depression/sadness and anxiety/fear) in infancy, early, and middle childhood. To probe the hypothesis that the impact of unpredictable maternal signals on internalizing behavior is generalizable, we test these associations in three distinct longitudinal cohorts of mothers and children which vary in key socio-demographic and cultural characteristics and reside in Turku, Finland (Turku cohort), Irvine, California, USA (Irvine cohort), and Orange, California, USA (Orange cohort). We hypothesize that more unpredictable maternal sensory signals relate to greater internalizing behaviors across development.

2. Method

2.1. Participants and procedure

All demographic data were collected via maternal report. Unpredictability of maternal sensory signals was quantified from mother-child free-play interactions and internalizing behaviors were assessed in all three cohorts. See Fig. 1 for an overview of the study protocol and assessment timepoints. Descriptive statistics for the study samples are provided in Table 1. Mothers across cohorts were approximately 30 years old when they delivered and majority of them were married or cohabitating with a partner. The Orange cohort was lower in income and education as indicated by 56.4 % living at or near the federal poverty line and 64.5 % having less than a college degree. The Turku cohort had a relatively high educational level with 70 % having a college degree and higher income (in part due to access to support such as state sponsored parental leave and healthcare).
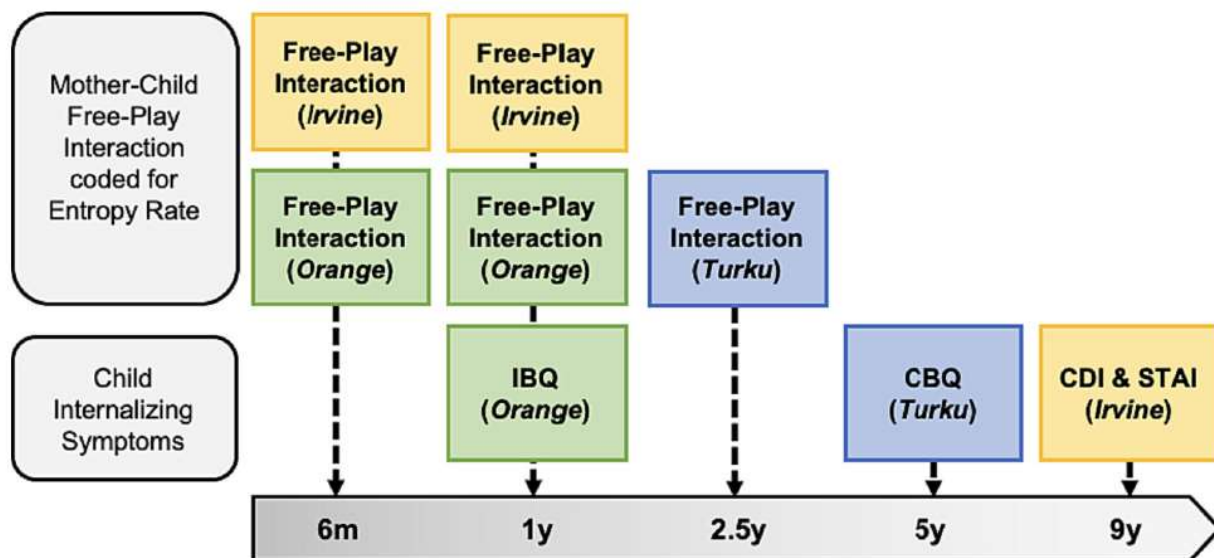

Fig. 1. Study overview and timeline for data collection.
Notes. Mother-child free play interactions were coded for maternal unpredictable sensory signals and maternal sensitivity.

2.1.1. Orange cohort

Participants in the Orange cohort were 163 mother-child dyads participating in a longitudinal study of prenatal and early life influences on development. Initial recruitment criteria for study consisted of the following: (a) English-speaking, (b) over the age of 18, (c) singleton pregnancies. Women were excluded if they had any uterine or cervical abnormalities, neuroendocrine dysfunction, or if they self-reported tobacco, alcohol, or drug use during pregnancy. Mothers identified as African American/Black (3.1 %), Asian (10.4 %), Latinx White (48.5 %), Multi-Ethnic (8.0 %), and Non-Latinx White (30.1 %). Infants were African American/Black (1.2 %), Asian (7.4 %), Latinx White (49.7 %), Multi-Ethnic (17.8 %), and Non-Latinx White (23.9 %). All study procedures were approved by the Institutional Review

Board for the protection of human subjects at the University of California, Irvine, and all mothers provided written and informed consent for themselves and their infants.

Table 1
Sample characteristics.

	Orange (n = 163)	Turku (n = 239)	Irvine (n = 129)
Maternal characteristics		*M ± SD; Range,* or %	
Age at delivery (years)	29.7 ± 5.6; 18.6–42.8	30.9 ± 4.4; 20.0–42.0	30.3 ± 5.2; 19.2–40.7
Cohabitating with a partner	90.8 %	97.1 %	89.1 %
Income			
Income-to-needs ratio (median)	157.0 ± 342.3; 14–2737	–	404.0 ± 230.6; 10–852
Annual income (€)	–		–
12,000–24,000		18.3 %	
24,000–36,000		48.1 %	
36,000–48,000		30.1 %	
48,000–60,000		4 %	
Education			
Highschool degree or less	23.4 %	12.8 %	13.2 %
Technical/Vocational school, Certificate, Some College, or Associate degree	41.1 %	10.9 %	34.9 %
College degree	16.6 %	29.2 %	31.8 %
Graduate degree	19.0 %	43.1 %	20.2 %
Child characteristics		*M ± SD;Range,* or %	
Age at internalizing assessment (years)	1.0 ± 0.1; 0.8–1.3	5.0 ± 0.1, 4.9–5.4	9.6 ± 0.7; 8–11
Biological sex at birth (% female)	47.2 %	44.8 %	43.4 %
Gestational age at birth (weeks)	39.0 ± 1.7; 29.9–41.7	39.8 ± 1.4; 32.9–42.4	39.4 ± 1.8; 28.4–42.6
Primary predictors and outcomes		*M ± SD; Range*	
Unpredictable maternal sensory signals (Entropy rate)	0.9 ± 0.1; 0.5–1.3	0.8 ± 0.1; 0.3–1.3	0.8 ± 0.2; 0.4–1.2
Maternal sensitivity[a]	8.3 ± 0.9; 5–10.5	5.2 ± 1.2; 2–7	9.9 ± 1.1; 6–12
Child fearfulness	3.4 ± 1.1; 1.1–6	3.7 ± 1.1; 1–6.5	–
Child sadness	3.6 ± 1.0; 1.1–6.1	3.8 ± 0.9; 1.3–6.8	–
Child depression symptoms	–	–	3.9 ± 3; 0–13
Child anxiety symptoms	–	–	35.4 ± 6.6; 23–52

[a] Maternal sensitivity scales ranged from 3 to 12 for the Orange and Irvine cohorts and 1 to 9 for the Turku cohort. See materials section for further details.

2.1.2. Turku cohort

Participants in the Turku cohort were 239 mother-child dyads in the Focus Cohort of FinnBrain Birth Cohort study, a longitudinal study of child development and parenting (Karlsson et al., 2018). Among this sample, the Focus Cohort participants were selected to be representative of the highest and lowest psychological distress experience at 14, 24, and 34 gestational weeks (see Karlsson et al., 2018 for further details). The recruitment criteria for the overall the Focus Cohort consisted of the following: (a) Finnish- or Swedish-speaking, (b) over the age of 18, (c) singleton pregnancy. Only individuals who had normal screening results following pregnancy ultrasonography were included. Race and ethnicity data were not collected in the Turku cohort. Study procedures were approved by the Ethics Committee of the Hospital District of Southwest Finland, and each mother provided written and informed consent for themselves and their infants.

2.1.3. Irvine cohort

Participants in the Irvine cohort were 129 mother-child dyads participating in a longitudinal study examining the influence of early life experiences on development. Initial recruitment criteria consisted of the following: (a) English-speaking, (b) over the age of 18, (c) singleton pregnancies. Women were excluded if they had any uterine or cervical abnormalities, neuroendocrine dysfunction, or if they self-reported tobacco, alcohol, or drug use during

pregnancy. Mothers identified as African American/Black (0.8 %), Asian (9.3 %), Latinx White (31.8 %), Multi-Ethnic (11.6 %), and Non-Latinx White (46.5 %). Infants were African American/Black (0.8 %), Asian (4.7 %), Latinx White (34.1 %), Multi-Ethnic (16.3 %), and Non-Latinx White (44.2 %). All study procedures were approved by the Institutional Review Board for the protection of human subjects at the University of California, Irvine, and all mothers provided written and informed consent for themselves and their children. Children also provided written assent at assessment in middle childhood.

2.2. Measures

2.2.1. Maternal measures

2.2.1.1. Mother-child interaction. Mothers and their children participated in a 10-min semi-structured free play interaction when their child was 6 months of age and 1 year of age in the Orange and Irvine cohorts, and at 30 months of age in the Turku cohort. During the interactions, mothers were provided with a standardized set of age-appropriate toys and were instructed to play with their child as they would at home. 2.2.1.2. Unpredictable maternal sensory signals (entropy rate). Video recordings of the mother-child interaction were coded to determine the unpredictability of maternal sensory signals. Videos were coded on a moment-to-moment basis using The Observer XT 11 (Noldus Information Technology, 2011). Maternal behaviors were coded to indicate when mothers were providing auditory, visual, and/or tactile sensory signals to their infants. Auditory signals include maternal vocalizations (e.g., talking, laughing). Visual signals include maternal physical manipulation of a toy or object while the infant is visually attending (e.g., shaking a rattle in front of the infant). Tactile signals include any instance of physical contact that is initiated by the mother (e.g., holding, touching). Raters continuously coded the onset and offset of all auditory, visual, and tactile maternal behaviors throughout the interaction and were blind to any additional information on study participants. Interrater reliability was calculated for 20 % of the videos in Orange and Irvine, and for 10 % of videos in Turku. Interrater reliability rating was 84 % for the Turku cohort and the averaged interrater reliability ratings of the two assessments were 91 % for the Orange and 89 % for the Irvine cohorts. The coded data indicate which of eight possible combinations of visual, auditory, and tactile sensory signals mothers were providing to their infant at any given time (i.e., the combination of the presence or absence of each type of sensory signal). For example, a mother who was speaking to her infant while also showing the infant a toy was coded as providing both auditory and visual stimulation simultaneously. When she picked up her infant, she was then also providing tactile stimulation, and this was coded as a new sensory state (i.e., auditory, visual, and tactile).

The unpredictability of maternal sensory signals was determined by calculating the conditional probabilities of transitioning between each of these eight possible combinations of maternal sensory signals. The transitions between these states were modeled as changes in the state of a discrete-state first-order Markov process, and the entropy rate of the process was taken as a measure of unpredictability, as described in Davis et al. (2017). Alternative Markov chain models (2nd order and 3rd order), as well as non-parametric approaches confirmed the reliability of the entropy measures (Spearman's rank correlations for the resulting entropy measures ranging from 0.91 to 0.98; Vegetabile et al., 2019). The entropy rate of a sequence of behaviors can be conceptualized as a measure of how random or unpredictable a mother's next behavior

would appear to an observer who was making a guess based only on the most recently observed behavior. If one behavior was always followed by another behavior (e.g., speech was always followed by touch), then this transition would be highly predictable and there would be little uncertainty for the observer (low entropy rate). In contrast, if one behavior was followed by a random choice of another behavior, this would be highly unpredictable (high entropy rate). Entropy rate can vary between a minimum value of zero (low unpredictability) to a maximum value of 2.807 (the logarithm [base two] of the number of possible transitions of sensory signals at each step; high unpredictability), when all possible transitions in this coding scheme are equally likely and maternal signals are most unpredictable. The entropy rates of maternal sensory signals at the 6- and 12-month visits were correlated in the both the Orange cohort ($r = 0.24$, $p = .003$) and the Irvine cohort ($r = 0.47$, $p < .001$) and were averaged together to create a composite measure of unpredictable sensory signals in infancy, providing a more representative indicator of the infants' exposure to unpredictability during the first postnatal year (Davis et al., 2019). If a child was missing an entropy rate measure at one of the time points, the missing value was imputed from a regression model relating the entropy rate between the two timepoints. Entropy rate was assessed at one time point in Turku cohort.

Additional details regarding the behavioral coding, calculation of entropy, and a description of an R software package for calculating entropy rate are provided in Davis et al. (2017) and are available at https://contecenter.uci.edu/shared-resources/.

2.2.1.3. Maternal sensitivity. In the Orange and Irvine cohorts, maternal sensitivity also was assessed from the same 10-min video recordings of mother-child interactions. The videos were coded using the NICHD Study of Early Child Care and Youth Development coding system (NICHD Early Child Care Research Network, 1999). Coders provided global ratings of maternal sensitivity to non-distress, positive regard, and intrusiveness on a 4-point Likert scale. A composite rating of maternal sensitivity was created by summing ratings of sensitivity to non-distress, positive regard, and intrusiveness (reverse coded). The range for the composite score can be between 3 and 12. Maternal sensitivity scores at the 6- and 12-month visits were correlated (Orange cohort: $r = 0.35$, $p < .001$; Irvine cohort: $r = 0.40$, $p < .001$) and were averaged to create an index of maternal sensitivity across the first postnatal year. All coders were blind to other data gathered on study participants. Twenty percent of the videos were selected at random, without coder knowledge, and were coded again by an independent coder to obtain an index of interrater reliability. Reliability values for each of the subscales were above 90 % in the Orange cohort: sensitivity to nondistress (98 %), intrusiveness (93 %) and positive regard (95 %) and 90 % in the Irvine cohort: sensitivity to nondistress (90 %), intrusiveness (90 %) and positive regard (93 %).

In the Turku cohort, maternal sensitivity was assessed during 15-min mother-child interaction at 30 months with the Emotional Availability Scales (EA; Biringen et al., 2008). EA consists of four scales regarding maternal emotional interaction (sensitivity, structuring, non-intrusiveness, and non-hostility). The scale of maternal sensitivity was used in the current analyses. Sensitivity coding characterized the mother's ability to be emotionally connected with the child, to recognize the child's interaction cues, and to respond to them appropriately and promptly. Scores range between 1 and 9 with higher scores indicating greater levels of sensitivity. Ten percent of videos were coded by independent coders to assess interrater reliability. The reliability for the sensitivity scale was 87 % at 30 months.

2.2.1.4. Maternal postpartum depression symptoms. Maternal symptoms of depression were assessed at the time of each mother-child interaction.

In the Orange and Irvine cohorts, maternal postpartum depression symptoms were assessed at 6 and 12 months using the revised Center for Epidemiological Studies-Depression scale (CES–D; Radloff, 1977). The CES-D is a 9-item self-report measure of depression symptoms for the general population. Mothers responded to items on a 4-point scale (ranging from 0 to 3) to indicate how they have felt over the past 7 days. Total scores could range from 0 to 27. The CES-D has high content validity (Okun et al., 1996) and is appropriate to use both in clinical and non-clinical populations (Knight et al., 1997; Morin et al., 2011). The internal consistency of the CES-D in this study was high for both time months; Irvine cohort: $\alpha = 0.90$ for 6 months, and $\alpha = 0.88$ for 12-months). CES-D ratings at 6- and 12-months were correlated (Orange cohort: $r = 0.57$, $p < .001$; Irvine cohort: $r = 0.69$, $p < .001$) and were averaged across the two time points to create a composite score of maternal postpartum depression symptoms in both cohorts. Composite CES-D scores were log transformed in the Irvine cohort due to data skewness.

In the Turku cohort, maternal postpartum depression symptoms were assessed at 24 months using the Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987). The EPDS is a 10-item self-report measure for the screening of perinatal depression (Cox et al., 1987). Mothers responded to items on a 0 to 3 scale to indicate how they have felt over the past two weeks. Total scores could range from 0 to 30, with higher scores reflecting greater levels of depressive symptoms. The internal consistency of the EPDS sum score was high ($\alpha = 0.87$). There were 122 missing values for the EPDS score in the Turku cohort and thus the data were imputed using multivariate imputation by chained equation method (MICE; van Buuren and Groothuis-Oudshoorn, 2011) with 100 imputed datasets. The imputation model included the biological sex of the child, maternal income, maternal sensitivity, unpredictable sensory signals, child fearfulness and child sadness.

2.2.2. Child internalizing measures

Age-appropriate measures of child internalizing behaviors (fearfulness/anxiety and sadness/depression) were administered in each cohort.

2.2.2.1. Infancy and early childhood assessment. The developmentally appropriate version of the Rothbart Temperament questionnaires, a standardized, parent report measure of infant temperament, was used to assess fear and sadness during infancy and early childhood. The fear and sadness subscales of the Infant Behavior Questionnaire-Revised (IBQ-R; Gartstein and Rothbart, 2003; fear: 16 items and sadness: 14 items) at 12 months in the Orange cohort, and the Finnish translation of the Children's Behavior Questionnaire – Short Form (CBQ-SF; Putnam and Rothbart, 2006; fear: 6 items and sadness: 7 items) at 5 years in the Turku cohort were included. The fear subscale measures the startle and distress responses to novel or surprising stimuli during infancy and negative emotions such as worry or nervousness in the case of threat or distress in early childhood. The sadness subscale assesses the extent to which the infant experiences a lowered mood or activity level due to physical pain or discomfort, object loss, or disappointment. Both the IBQ-R and CBQ-SF have strong psychometric properties, including internal consistency and stability over development (Gartstein and Rothbart, 2003; Putnam et al., 2008; Putnam and Rothbart, 2006; Worobey and Blajda, 1989). Cronbach's alphas in the current

sample were moderate to excellent (αIBQ = 0.91 and αCBQ = 0.72 for the fearfulness subscales; αIBQ = 0.84 and αCBQ = 0.61 for the sadness subscales).

2.2.2.2. Middle childhood assessment. Children in the Irvine cohort completed self-report measures of their anxiety and depression symptoms at 9 years.

Children reported on their anxiety symptoms with the trait form of the State-Trait Anxiety Inventory for Children (STAIC; Spielberger et al., 1973). The 20 items are rated on a 3-point Likert scale with higher scores indicating elevated symptoms of anxiety. The STAIC is a reliable and well validated measure among youth across cultures (Chaiyawat and Brown, 2000; Turgeon and Chartrand, 2003). In the current sample Cronbach's alpha for the STAIC was good (α = 0.81).

Children reported on their depression symptoms in using the Children's Depression Inventory-Short Form (CDI Short; Kovacs and Saint-Laurent, 2003). There are 12 items in the CDI-Short rated on a 3-point Likert scale and children rated the items depending on how they had felt within the last two weeks. The CDI is a reliable and well validated measure of depression symptoms among youth (Kovacs, 2015; Tobin, 2016). Within the current sample, Cronbach's alpha for the CDI was moderate (α = 0.67).

2.3. Statistical analysis

Linear regression models were conducted to test whether unpredictable maternal sensory signals (entropy rate) predicted child internalizing behaviors and subsequently, whether associations remained after consideration of covariates. SPSS, version 25.0 (IBM Corp, 2017) was used in the Orange and Irvine cohorts and R, version 4.2.2 (R Core Team, 2022) was used in the Turku cohort.

Factors that have been shown to influence maternal behaviors or child internalizing behaviors in prior literature were included as covariates in all models in all cohorts (Goodman et al., 2011; Hankin and Abramson, 2009; Letourneau et al., 2013; McLean and Anderson, 2009; Piccinelli and Wilkinson, 2000). These selected factors are household income, maternal postpartum depression symptoms, and child sex at birth. See Table 2 for interrelations among covariates and study variables.

3. Results

3.1. Unpredictable maternal sensory signals and child fearfulness/anxiety

Unpredictable maternal sensory signals were positively associated with child fearfulness/anxiety (see Fig. 2 & Table 2). More unpredictable maternal sensory signals were associated with elevated fear and anxiety in all three cohorts. High entropy rate was associated with elevated fear in the Orange cohort at 12 months ($\beta = 0.16$, $p = .042$) and the Turku cohort at 5 years ($\beta = 0.16$, $p = .014$), as well as elevated child anxiety symptoms in the Irvine cohort at 9 years ($\beta = 0.23$, $p = .009$). Notably, these patterns of associations remained after covarying maternal sensitivity and other key maternal and sociodemographic factors (i.e., income, infant sex, and maternal postpartum depression symptoms) (see Table 3 for additional details).

Table 2
Bivariate correlations among study variables across three cohorts

Study variables	1	2	3	4	5	6
Orange (12 months)						
1. Entropy rate						
2. Maternal sensitivity	−0.23**					
3. Child fearfulness	0.16*	−0.13				
4. Child sadness	0.07	0.08	0.49***			
5. Income	−0.16*	0.17*	−0.15	−0.04		
6. Depression symptoms	−0.05	0.05	0.17*	0.21**	−0.11	
7. Child sex at birth	−0.03	−0.02	0.16*	−0.04	−0.12	0.01
Turku (5 years)						
1. Entropy rate						
2. Maternal sensitivity	−0.11*					
3. Child fearfulness	0.16*	−0.01				
4. Child sadness	0.12^	−0.02	0.39***			
5. Income	−0.07	0.10*	−0.25***	−0.14*		
6. Depression symptoms	−0.04	−0.10	0.19*	0.33**	−0.13*	
7. Child sex at birth	−0.08	0.14**	0.06	0.12^	0.06	−0.03
Irvine (9 years)						
1. Entropy rate						
2. Maternal sensitivity	−0.35***					
3. Child anxiety symptoms	0.23**	−0.13				
4. Child depression symptoms	0.16	−0.24**	0.45***			
5. Income	−0.30***	0.36***	−0.12	−0.10		
6. Depression symptoms	0.14	−0.08	0.12	0.08	−0.24**	
7. Child sex at birth	−0.10	0.10	0.04	0.04	0.14	−0.10

Notes. Child sex at birth was coded as 0 = male, 1 = female in all cohorts.
^ $p < .10$.
* $p < .05$.
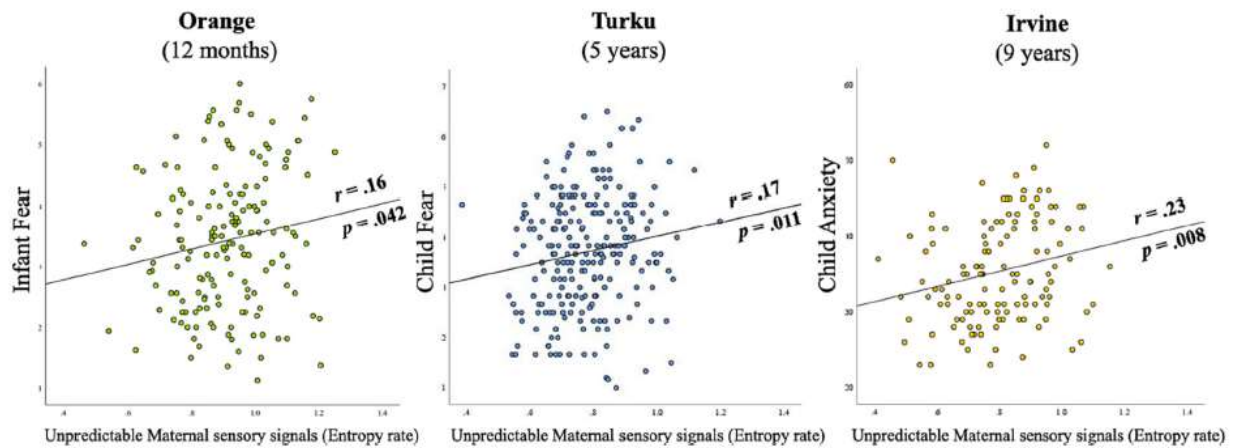** $p < .01$.
*** $p < .001$

Fig. 2. Unpredictable maternal sensory signals (entropy rate) and child fearfulness/anxiety.

3.2. Unpredictable Maternal Sensory Signals and Child Sadness/Depression

Unpredictable maternal sensory signals were positively associated with child sadness/depression symptoms (see Fig. S1 & Table 2). However, the correlations with sadness/depression symptoms did not reach traditional thresholds for statistical significance. The association between unpredictable maternal sensory signals and child sadness/depression was weaker than fear/anxiety in the Orange cohort at 12 months ($\beta = 0.07$, $p = .376$), the Turku cohort at 5 years ($\beta = 0.12$, $p = .062$), or the Irvine cohort at 9 years ($\beta = 0.16$, $p = .068$) (see Table 3 for additional details).

Table 3
Regression models of unpredictable maternal sensory signals (entropy rate) and child internalizing behaviors.

Model	Predictors	Fearfulness						Sadness					
		B	SE	β	t	p	R^2	B	SE	β	t	p	R^2
Orange (12 months)													
1	Entropy rate	1.27	0.62	0.16	2.04	.043*	0.02	0.51	0.57	0.07	0.88	.378	−0.001
2	Entropy rate	1.10	0.64	0.14	1.73	.086	0.02	0.66	0.59	0.09	1.13	.259	0.001
	Maternal sensitivity	−0.11	0.10	−0.09	−1.18	.240		0.11	0.09	0.10	1.19	.235	
3	Entropy rate	1.11	0.63	0.14	1.77	.078	0.07	0.69	0.58	0.10	1.18	.238	0.03
	Maternal sensitivity	−0.11	0.10	−0.09	−1.11	.269		0.10	0.09	0.09	1.11	.268	
	Household income	0.00	0.00	−0.08	−0.98	.328		0.00	0.00	−0.02	−0.27	.789	
	Child sex	0.33	0.17	0.15	1.93	.055		−0.08	0.16	−0.04	−0.47	.640	
	Depression symptoms	0.05	0.02	0.18	2.28	.024*		0.05	0.02	0.21	2.62	.010**	
Turku (5 years)													
1	Entropy rate	1.43	0.58	0.16	2.47	.014*	0.03	0.81	0.43	0.12	1.87	.062	0.02
2	Entropy rate	1.43	0.59	0.16	2.43	.015*	0.03	0.80	0.44	0.12	1.82	.070	0.02
	Maternal sensitivity	−0.04	0.07	−0.04	−0.64	.525		−0.03	0.05	−0.04	−0.56	.57	
3	Entropy rate	1.36	0.57	0.15	2.39	.017*	0.11	0.79	0.42	0.12	6.59	.062	0.11
	Maternal sensitivity	0.04	0.06	−0.0.03	−0.55	.58		−0.00	0.05	−0.04	−0.62	.537	
	Household income	−0.14	0.05	−0.18	−2.85	<.001***		−0.06	0.04	−0.09	−1.42	.156	
	Child sex	0.27	0.14	0.12	1.88	.062		0.28	0.11	0.17	2.61	.009	
	Depression symptoms	0.04	0.02	0.16	2.60	.009**		0.05	0.04	0.25	3.92	<.001 ***	
Irvine (9 years)													
1	Entropy rate	10.12	3.80	0.23	2.67	.009**	0.05	3.23	1.76	0.16	1.84	.068	0.03
2	Entropy rate	9.27	4.07	0.21	2.28	.024*	0.06	1.82	1.85	0.09	0.99	.327	0.06
	Maternal sensitivity	−0.32	0.54	−0.06	−0.60	.552		−0.54	0.25	−0.20	−2.18	.031*	
3	Entropy rate	9.08	4.20	0.21	2.16	.033*	0.06	1.64	1.90	0.08	0.87	.389	0.08
	Maternal sensitivity	−0.32	0.57	−0.06	−0.57	.573		−0.54	0.26	−0.20	−2.07	.040*	
	Household income	−0.00	0.00	−0.01	−0.13	.902		0.00	0.00	−0.01	−0.12	.908	
	Child sex	−0.93	1.19	−0.07	−0.787	.433		−0.48	0.54	−0.08	−0.88	.379	
	Depression symptoms	0.45	0.74	0.06	0.60	.548		0.35	0.34	0.10	1.05	.295	

Note. Unpredictable maternal sensory signals and child sadness/depression.
^ $p < .10$.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

4. Discussion

Unpredictable sensory signals early in life have robust implications for development of neurocircuitry (Birnie and Baram, 2022; Birnie et al., 2023; Bolton et al., 2022; Granger et al., 2021). Our findings suggest that exposure to unpredictable maternal sensory inputs may increase vulnerability to psychopathology related to fear and anxiety. The consistency of the association between sensory signal unpredictability (entropy rate) and fearfulness/anxiety during infancy and

childhood in three cohorts with very different cultural and socioeconomic backgrounds provides strong evidence for the universality of this signal (see Fig. 3). This claim is further bolstered by experimental and cross-species work documenting the neurodevelopmental impact of unpredictability in rodents, non-human primates, and humans (Bolton et al., 2017; Davis et al., 2017, 2022).
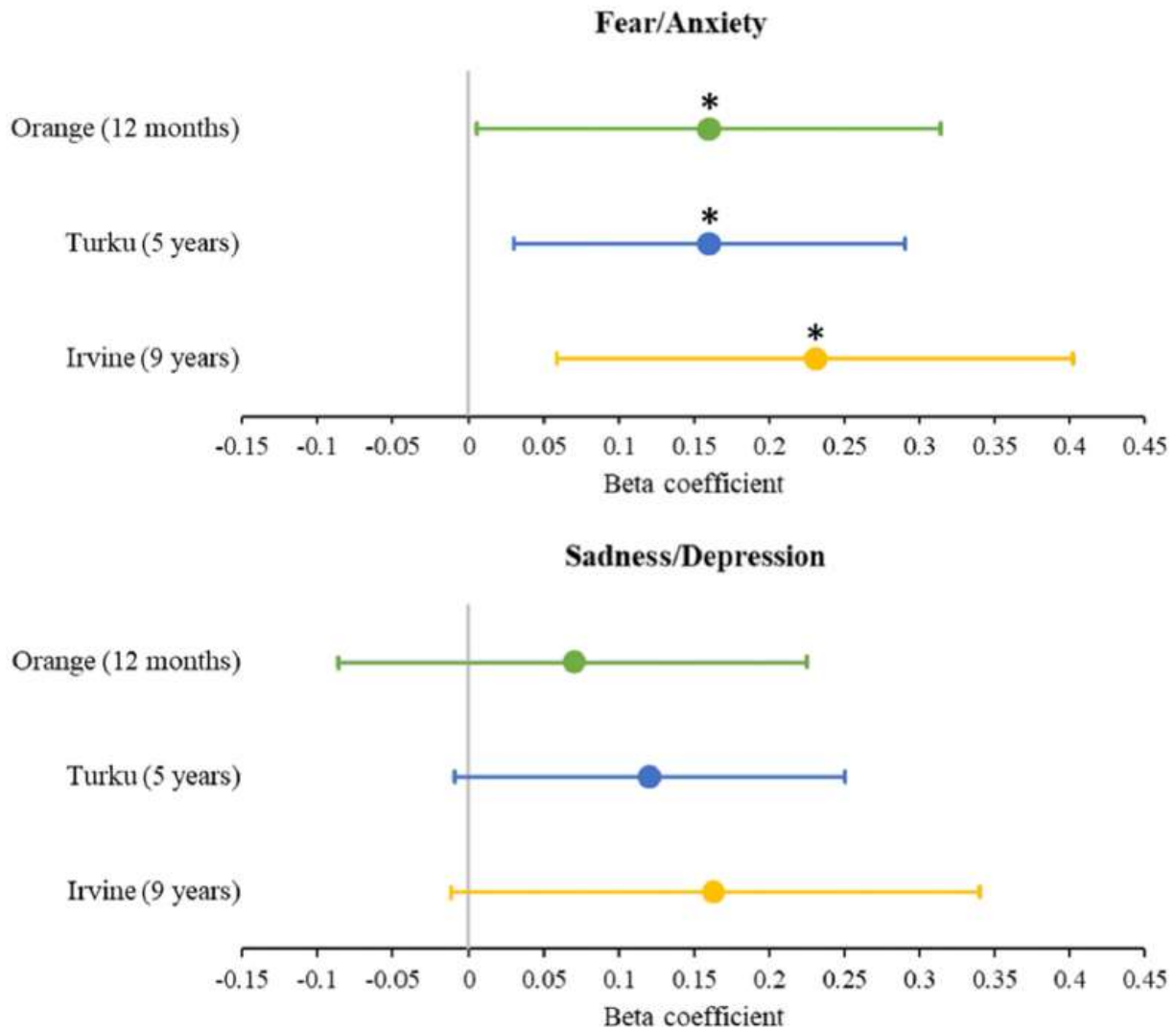

Fig. 3. Associations between unpredictable maternal sensory signals (entropy rate) and child internalizing behaviors across cohorts (effect sizes and confidence intervals are shown).
Notes. *$p < .05$. Standardized beta coefficients indicating the relation between unpredictable maternal sensory signals and child internalizing outcomes are graphed with 95 % confidence intervals.

The link between unpredictable maternal sensory signals and child internalizing behaviors was consistently observed for fearfulness/anxiety outcomes. Specifically, across ages and cohorts, children exposed to greater maternal sensory signal unpredictability in early life were more fearful and anxious. Although the associations between unpredictable maternal sensory signals and child sadness/depression were also positive, they did not reach traditional thresholds for statistical significance. There are several potential explanations which might explain this finding that the associations are stronger for anxiety outcomes. First, it is possible that unpredictable sensory signals may have a particularly potent impact on anxious phenotypes, particularly as past work in humans suggests that environmental unpredictability and uncertainty broadly activate anxiety-related brain circuits and are particularly relevant for the emergence of anxiety symptoms (Hirsh et al., 2012). Indeed, within the attachment literature, greater unpredictability in the mother-child relationship has been linked to an anxious-ambivalent attachment style in the child (Szepsenwol and Simpson, 2019) and increased risk for later anxiety disorders (B¨ogels and Brechman-Toussaint, 2006; Kerns and Brumariu, 2014). Second, it is plausible that a weak relation between maternal unpredictable sensory signals and depression outcomes could be attributed to the developmental timing of child assessments. Although anxiety and depression are highly comorbid across development, the onset of anxiety disorders typically precedes the emergence of depression disorders in youth (Cole et al., 1998; Costello et al., 2003; Kalin, 2021). Anxiety disorders are more prevalent than depression and other mood disorders in young children (Merikangas et al., 2009), whereas depression more frequently emerges during adolescence (Kalin, 2021). It is therefore possible that the emergence of internalizing symptoms following unpredictable sensory signals early in life could more commonly manifest as anxious phenotypes in infancy and childhood, whereas depression phenotypes may be more robustly detected later in adolescence and adulthood (Glynn et al., 2019). More work is needed to continue evaluating the long-term impact of unpredictable maternal sensory signals on internalizing symptoms into adolescence and adulthood.

Experimental research on the emergence and organization of brain circuits in early life provides a plausible mechanistic explanation for the link between unpredictable maternal sensory signals and child internalizing outcomes. In translational rodent studies, patterns of sensory inputs early in life play a critical role in shaping emotional brain circuits (Birnie and Baram, 2022; Bolton et al., 2022). It is plausible that exposure to unpredictable maternal sensory signals during this sensitive window of development can therefore disrupt these systems, which may persist and manifest as internalizing problems throughout the lifespan in humans. Evidence from experimental studies demonstrates that rodents exposed to unpredictable maternal sensory signals show increased secretion of corticotropin-releasing hormone (CRH) in the hippocampus (Ivy et al., 2010) and amygdala (Bolton et al., 2018). Rodent pups raised by dams with unpredictable care also show greater density of excitatory synapses in CRH expressing hypothalamic neurons (Bolton et al., 2022; Gunn et al., 2013), changes which have been linked to a reduction in phagocytic (synapse engulfing) microglial Mer tyrosine kinase receptor (MERTK). Collectively, these alterations in synaptic connectivity in the pup result in altered behavioral and hormonal stress responses in later years. Taken together, these studies suggest that early exposure to unpredictable sensory signals may affect the trajectory of socioemotional development in humans through these neural, mechanistic pathways. Given this translational evidence that unpredictable patterns of maternal signals sculpt circuit development in experimental systems and humans (Birnie and Baram, 2022; Bolton et al., 2022), it is plausible that unpredictable sensory signals are a pathway by which other aspects of early life adversity

(e.g., parental mental health or poverty) shape development (Davis and Glynn, 2024). In the rodent models, manipulating the physical environment through limited bedding and nesting, results in unpredictable care among dams. Similarly, it can be speculated that among humans limited resources and sociocultural stressors may contribute to unpredictable care expressed through sensory signals. Indeed, in the current study with higher levels of income, unpredictability of sensory signals was significantly lower in the Orange and Irvine cohorts (see Table 2). Future work is needed to understand what drives unpredictability of parental behavior to support opportunities for prevention and intervention.

Unpredictability of maternal sensory signals was assessed at 6 and 12 months in the Orange and Irvine cohorts and at 30 months in the Turku cohort. Future studies should continue to explore the developmental timing of these mechanistic pathways. It is possible that both infancy and toddlerhood are part of a sensitive window in which unpredictable maternal sensory signals impact brain circuits underlying emotional development (Gee and Cohodes, 2021). Alternatively, it is also possible that the assessment in toddlerhood could be a proxy measure of unpredictable maternal sensory signals during infancy, as past work demonstrates that unpredictable maternal sensory signals are correlated across infancy and toddlerhood (Holmberg et al., 2022b). Future work in both experimental animal models and human observational studies should continue to identify sensitive periods of susceptibility to unpredictable signals for specific outcomes.

The current study should be evaluated in the context of both strengths and limitations. A key strength of the study protocol is that we tested the association between unpredictable maternal sensory signals and child internalizing behaviors at multiple ages (i.e., infancy, early and middle childhood) and across three international cohorts with varying demographic characteristics. Specifically, mothers in all cohorts were similar age but they differed in income and education such that the Turku cohort consisted of participants from slightly higher income and educational backgrounds and the participants in the Orange cohort had lower income and education levels. The results of the current study thus demonstrate that the associations between unpredictable maternal sensory signals and child internalizing behaviors are replicable and consistent across development stages and different sociocultural contexts, further underscoring the generalizability of study findings. Another key study strength is that our results persisted above and beyond established sociodemographic and other parenting predictors of child internalizing behaviors, highlighting the unique contributions of unpredictable sensory signals to child internalizing behaviors. As we utilized an observational design, we cannot draw causal inferences from these data alone. However, because the study measure of unpredictable maternal sensory signals can be applied in both animal and human models, cross-species work can directly probe these causal pathways and further disentangle the effect of unpredictable maternal sensory signals from genetic and other environmental influences. Indeed, existing evidence from experimental rodent studies shows that rodents exposed to unpredictable maternal sensory signals in early life continue exhibiting anxiety and depression-like behaviors in adulthood (Kangas et al., 2022; Molet et al., 2016a). Future work may therefore continue to assess the impact of unpredictable sensory signals on child development via this cross-species framework. Additionally, unpredictability was assessed specifically in the context of the mother-child dyad in the current study. Future studies should expand upon this work by going beyond birthing parents and including all parents and caregivers who play a pivotal role in shaping child development.

5. Conclusion

The findings of the current study suggest that experiencing unpredictable maternal sensory signals during early life is linked to children's emotional development, especially anxious phenotypes. Results of the current investigation support the accumulating evidence that unpredictability of sensory signals is an important form of adversity and document its unique contribution to risk for internalizing disorders among children. Notably, unpredictable parenting behaviors can be seen as an actionable form of adversity that is amenable to early intervention (Glynn et al., 2021; Davis and Glynn, 2024). Unpredictable maternal signals therefore may be a biologically plausible target due to its effects on brain circuit maturation for the prevention and treatment of internalizing disorders in youth.

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CRediT authorship contribution statement

Ö. Aran and D. A. Swales formulated the research question, performed statistical analyses, and wrote the initial draft of the manuscript. E. P. Davis formulated the research question, designed, and oversaw data collection for the Irvine cohort, and provided critical feedback. L. M. Glynn and C. A. Sandman formulated the research question, designed, and oversaw data collection for the Irvine and Orange cohorts, and provided critical feedback. H. S. Stern is the statistician who developed and computed the measure of entropy rate. N. Bailey conducted statistical analyses and contributed to drafting method and results in the Orange cohort. T. Z. Baram provided critical feedback. R. Korja, H. Karlsson, and L. Karlsson designed, and oversaw data collection for the Turku cohort (FinnBrain study) and provided critical feedback. E. Eskola designed and oversaw data collection at 30 months years for the Turku cohort, and E. Holmberg, S. Nolvi, and E. Nordenswan designed, and oversaw data collection at 5 years for the Turku cohort. L. Perasto, conducted statistical analyses and contributed to drafting method and results in the Turku cohort. All authors provided feedback and approved the final manuscript.

Declaration of competing interest

No conflicts of interests were reported by the authors.

Data availability

Acknowledgements

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