Across continents and demographics, unpredictable maternal signals impact children's neurodevelopment

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Acknowledgements: This research was supported by the National Institutes of Health (NIH) awards P50MH096889, HD051852, NS041298, HD02413, HD050662, HD065823, and FinnBrain funders: Finnish Academy (No. 129839, 134950, 253270, 286829, 287908, 308176, 308252), Jane and Aatos Erkko Foundation, Signe and Ane Gyllenberg Foundation, Yrjö Jahnsson Foundation, and State Research Grants (No. P3498, P3654).

Abstract

Early life experiences influence brain function and structure throughout life¹⁻³. Maternal signals constitute a major source of early life experiences, and their quantity and qualities during sensitive developmental periods exert enduring effects on infant, child and adult emotional and social behaviors in humans, primates and rodents⁴⁻⁶. Existing studies probing the salient qualities of maternal signals to the infant have centered primarily on measures of their valence⁶⁻⁸. Here we report that in addition to these established qualitative dimensions, patterns of maternal signals⁹⁻¹² contribute greatly to infants and children's self-control, a potent predictor of mental health outcomes¹³. In two large, independent and disparate prospective cohorts in Turku, Finland, and Irvine, CA, USA, unpredictable sequences of maternal care portended worse child self-control. Specifically, less predictable maternal signals to the infant during the first postnatal months¹¹ were associated with poor self-control at the end of the first year of life. The correlation between unpredictable patterns of maternal signals and self-control persisted to school age in the cohort (Irvine) that was followed long-term. The consistency of these findings across two distinct demographic and cultural cohorts substantiates the finding that, in addition to the quality of maternal care, patterns and specifically unpredictable sequences of maternal care behaviors influence the maturation of circuits in the developing brain involved in the regulation of emotion and behavior, in a manner indicative of vulnerability to subsequent psychopathology.

Early life experiences influence brain function and structure throughout life¹⁻³. Maternal signals constitute a major source of early life experiences, and their quantity and qualities during sensitive developmental periods exert enduring effects on infant, child and adult emotional, cognitive and social behaviors in humans, non human primates and rodents⁴⁻⁶. We evaluate how patterns of maternally derived sensory signals influence child brain development.

Sensory signals from the environment are required for the maturation of brain circuits that underlie specific functions¹⁴⁻¹⁶. For example, light and visual patterns during a sensitive developmental period are mandatory for normal maturation of the visual system¹⁴, and sound and tone-patterns are required for the full development of hearing and the auditory circuit¹⁷. However, it is unknown which sensory signals are crucial for the normal maturation of emotional and cognitive circuits, and whether specific patterns of these signals are required for optimal neurodevelopment. It has been well established in several species that sensory signals from the mother are a major influence on the evolution of emotional and social brain functions^{9,18}. To date, the major emphasis has centered on the study of valence of these signals, such as maternal sensitivity, synchrony and depressed mood, as well as on the quantity of maternal care^{4,9,19}. In rodents, we previously found that patterns and specifically unpredictability and fragmentation of maternal signals can promote adolescent anhedonia in the offspring, a measure of aberrant pleasure/reward brain circuit function^{10,20}. Further, in both humans and rodents unpredictable maternal sensory signals during infancy portend subsequent cognitive impairments¹¹.

In two human cohorts that differ culturally as well as in risk factors for brain and behavioral outcomes, followed prospectively in Turku, Finland and Irvine, California, we examined if the patterns of maternal signals to the human infant influenced child self-control. Self-control involves the ability to regulate behavior and attention¹³. We focused on this outcome measure because extensive literature establishes poor self-control as a potent risk factor for later psychopathology^{13,21}. Here we found that infant exposure to unpredictable maternal signals

predicts subsequent poor self-control during infancy and childhood in two independent, diverse cohorts from two different continents.

In both the Irvine and Finnish Cohorts ($n = 192$ and 126 , respectively), self-control during infancy and childhood, assessed via maternal report, was lower in those exposed to less predictable sensory signals from the mother (higher entropy rate) in infancy (Turku: $r = -.28$, $p < .01$; Irvine: $r = -.16$, $p < .05$; Figure 1). The longevity of the association between unpredictable maternal sensory signals and self-control was measured in the Irvine Cohort. The results of a mixed linear model analysis that incorporates all 3 time points illustrates that infant exposure to unpredictable maternal sensory signals presaged poor self-control over time (1 year to 9.5 years; see Table 2A). Boys exhibit lower self-control than girls, however, the interaction between sex and entropy rate is not significant. Further, in a subset of children from the Irvine Cohort who participated in a direct assessment of self-control via the Flanker test, unpredictable maternal sensory signals (high entropy rate) portended poor self-control on this task at 6.5 years of age ($r = -.34$, $p < .01$). Thus, the predictive value of higher entropy rate of sensory signals from the mother to the child's self-control was enduring, lasting, at a minimum, to school age.

We next examined in each population additional factors that might influence the relation between predictability of maternal signals to the infant and the infant/child's self-control. In the Irvine cohort, mothers with lower household income ($r = -.31$, $p < .01$), with higher psychological distress (i.e., depressive and anxious symptoms; $r = .14$, $p < .05$), or younger age ($r = -.16$, $p < .05$), provided less predictable sensory signals to their infants. Marital status, race/ethnicity, and child sex were not related to predictability. In contrast to the Irvine cohort, maternal psychological distress was not significantly associated with predictability of maternal signals in the Turku cohort. Younger mothers ($r = -.18$, $p < .05$) and mothers with lower income ($r = -.16$, $p < .05$) provided less predictable maternal sensory signals to their infants.

We next probed further the role of income, psychological distress and maternal age in both cohorts by including them as covariates. The association between predictability of maternal signals and self-control at 1 year remained statistically significant in the Turku cohort when income and age were included ($\beta = -.28$, $t = -3.22$, $p < .01$ and $\beta = -.27$, $t = -3.1$, $p < .01$, respectively). In the Turku cohort, not only did the association between maternal entropy rate and self-control remain when maternal distress (anxiety and depression) was co-varied ($\beta = -.25$, $t = -2.7$, $p < .01$), but the association between predictability of maternal signals and child self-control was significant when women with high and low psychological distress were evaluated separately ($r = -.31$, $p < .05$ and $r = -.27$, $p < .05$, respectively). In the Irvine cohort the association between predictability of maternal signals and child self-control remained when income, maternal psychological distress, and maternal age were incorporated in the mixed linear model (Table 2B). Further, when the direct behavioral measure of children's self-control (response inhibition on a computerized Flanker task) was evaluated, the relation between predictability of maternal signals and self-control remained significant after co-varying household income, psychological distress and maternal age ($\beta = -.27$, $t = -2.2$, $p < .05$).

In summary, our studies demonstrate a novel relation of patterns of maternal signals and infant and child outcomes. Predictability of maternal signals had robust effects on a crucial measure of brain development, self-control, which predicts mental health throughout life¹³. Importantly, in studying two very different populations on different continents, with discrepant cultural and demographic characteristics, covariates of maternal unpredictability diverged, yet this predictive association survived. The findings attest to the fundamental importance of predictable sequences of maternal-derived signals to her infant in sculpting functional brain development.

Methods

In two cohorts, we evaluated the relation between degree of predictability of maternal sensory signals and subsequent self-control of the infants and children (see Figure 2 for overview of study protocol). Degree of predictability of maternal sensory signals was evaluated in the context of a free-play interaction at 6 and 12 months (Irvine Cohort) and 8 months of age (Turku Cohort). Predictability of maternal signals to her infant was defined in terms of entropy rates¹¹. The entropy rate was computed based on real-time observations of maternal behaviors that convey sensory information to the infant to characterize degree of predictability. To evaluate the influence of early maternal care on child self-control, children were assessed in the Irvine and Turku Cohorts at one year of age and in the Irvine Cohort at 5 years and at 9.5 years of age. Additionally, child self-control was measured in the Irvine Cohort at 6.5 years of age using a computerized Flanker task²².

Participants

Irvine Cohort: Study participants included 192 mothers and their children (91 female, 101 male) participating in a longitudinal study evaluating the role of early life experiences on development. Women who were English-speaking, non-smokers, over the age of 18, with a singleton pregnancy, and for whom there was no evidence of drug or alcohol use during pregnancy were eligible. The study participants included in these analyses were the 192 women for whom video recordings of maternal-child interactions and child outcomes were available and videos were of sufficient quality to assess predictability of maternal sensory information (9 women for whom less than 90% of the video was of good quality were excluded from this investigation) and for whose children we had at least one self-control measure. Descriptive information for the sample appears in Table 1. Predictability of maternal sensory signals was evaluated when children were 6 months ($M = 6.09$, $SD = 0.3$) and 12 months ($M = 12.16$, $SD = 0.45$) of age and then averaged as an index of exposure to maternal predictability in infancy. If a child was missing an entropy measure at one of the time points, the missing value was imputed

from a regression model relating the entropy rate at the two time points. At the 12-month assessment child self-control additionally was assessed (N = 166). Longitudinal evaluation of self-control continued at 5 years (M = 5.28, SD = 0.49, N = 115), 6.5 years (M = 6.52, SD = 0.15, N = 77), and 9.5 years (M = 9.60, SD = 0.70, N = 124). All procedures were approved by the Institutional Review Board for Protection of Human Subjects at the University of California-Irvine. Each mother provided written and informed consent for herself and her child, and children provided written assent at the study visit at 9.5 years of age.

Turku Cohort: Study participants included 126 mother-infant dyads that are a subset of the large FinnBrain Birth Cohort Study and its Focus Cohort, a nested case-control population²³. The subset was comprised of mothers with high or low psychological distress based on self-report measures collected during gestational weeks 14, 24 and 34. Women with at least two positive screens for distress (i.e., twice by the same instrument or once in two different instruments) were identified as high prenatal psychological distress. The selected cut points were: depression, Edinburgh Postnatal Depression Scale (EPDS)²⁴ > 11 points / max score 30; anxiety, Symptom Checklist-90 (SCL-90)^{25,26} anxiety scale > 9 points / max score 40; and pregnancy-anxiety, Pregnancy-Related Anxiety Questionnaire-Revised (PRAQ-R)²⁷ > 33 points / max score 50. Controls represent those scoring below the following thresholds in the same questionnaires at all time points: EPDS < 7 points, SCL < 5 points, PRAQ-R < 26 points. The categories are mutually exclusive. The criteria for the Focus Cohort were initially determined by using the first 500 FinnBrain Birth Cohort Study participant mothers' questionnaire data in exploratory analyses and establishing cut-points for the approximately highest and lowest 25th percentiles of maternal psychological distress during pregnancy. After the collection of the pregnancy data of the whole FinnBrain Birth Cohort, the psychological distress group eventually comprised 20% and the control group 27% of all women in the Cohort.

Measuring the Degree of Predictability of Maternal Sensory Signals to her infant

The degree of predictability of maternal sensory signals was quantified using entropy rate derived from behavioral coding of a play interaction of mother and child as previously described (see¹¹). Briefly, mothers were video-recorded interacting with their infants in a semi-structured 10-minute play episode at 6 and 12 months in the Irvine Cohort and at 8 months in the Turku Cohort. During this play interaction, mothers were given a standard set of age-appropriate toys and instructed to play with their infant as they would at home. Maternal behaviors that provide auditory, visual, or tactile sensory signals to the child were coded *continuously, on a moment-to-moment basis* from digital video recordings using The Observer XT 11 (Noldus). Auditory signals included all maternal vocalizations (e.g., talking, laughing). Visual signals included maternal manipulation of a toy or object while the infant was visually attending. Tactile signals involved all instances of physical contact (e.g., holding, touching) initiated by the mother. Coders were blind to all other information on study participants. Interrater reliability was calculated for 20% of the videos and averaged 89% for the Irvine Cohort and 86% for the Turku Cohort. See Davis et al., 2017¹¹ and <https://contecenter.uci.edu/shared-resources> for additional information on details of behavioral coding, including the training manual.

Quantifying predictability of maternal behavior (entropy rate). In both cohorts identical procedures were used to quantify the extent to which sequences of maternal sensory signals were predictable, as described in Davis et al., 2017¹¹. Our approach focuses on the conditional probabilities of transitioning between different combinations of maternal visual, auditory and tactile sensory signals. We considered all eight possible combinations of these sensory signals (presence/absence of input of each of the three types of sensory signals). For example, a mother might be speaking to the child while showing her a toy (auditory and visual input). If she additionally picked up the child (tactile input) so that she now provides auditory, visual, and tactile input, then this would be considered a transition to a different combination of sensory signals. The transitions are modeled as changes in the state of a discrete-state Markov process

and the entropy rate of the process is taken as a measure of predictability. Entropy rate varies between a minimum value of zero, when a process is perfectly predictable, to a maximum value of 3 (the logarithm (base two) of the number of possible combinations of sensory signals), when all possible transitions are equally likely and maternal signals are most unpredictable.

Additional details regarding the calculation of entropy and a description of an R software package for calculating entropy rate are provided in Davis et al., 2017¹¹ and available at <https://contecenter.uci.edu/shared-resources/> .

Measuring Self-Control in Children:

Irvine and Turku Cohorts: Child self-control was assessed at one year of age using the 60 item Orienting/Regulation scale of the Infant Behavior Questionnaire - Revised (IBQ-R)²⁸.

Irvine Cohort: Child self-control was measured at 5 years with the 60 item scale of the Children's Behavior Questionnaire (CBQ)²⁹, and at 9.5 years with the 48 item scale of the Temperament in Early Childhood Questionnaire (TMCQ).

These instruments (IBQ, CBQ and TMCQ) were developed to reduce the possibility of maternal reporting bias by asking about specific behaviors in defined situations, rather than asking for judgments about child temperament or behaviors. Responses on each item range from 1 (never) to 7 (always). These scales exhibit good internal reliability and validity^{28,29}. As expected, self control using this measure was correlated over time in the Irvine Cohort ($r(\text{age } 1, \text{age } 5)=0.28$, $r(\text{age } 1, \text{age } 9.5)=.39$, $r(\text{age } 5, \text{age } 9.5)=.71$; all are statistically significant ($p < .01$).

Child self-control additionally was assessed at 6.5 years using the Flanker task²². The Flanker task is designed to measure response inhibition and requires the ability to resolve conflicts when competing information is present. Participants were presented with five arrows and were instructed to press the left or right response button based upon the direction of the center arrow (target). They were instructed to ignore the surrounding arrows (flankers), which were either congruent or incongruent with the center arrow. The task consisted of 24 congruent

and 24 incongruent trials. Each set of arrows was presented until the child responded (maximum of 5000ms) with a 750-ms inter-trial interval. Prior to the scored 48-trial task, 20 practice trials were completed which consisted of eight trials where only the middle arrow was presented, and 12 trials where all five arrows were presented (6 congruent, 6 incongruent). Percent correct on incongruent trials was used in analyses as the outcome measure of child response inhibition, with higher scores representing better inhibitory control. Flanker performance was associated with maternal report of self-control at ages 5 ($r=.21$) and 9.5 years ($r=.37$), but not at 1 year ($r=-.02$).

Analysis Plan

Possible Confounding Factors. Based on the published literature we identified maternal, demographic and child factors that may influence the development of child self-control, for inclusion in analyses assessing possible confounding factors. Potential covariates and confounders were identified by using correlations (continuous variables) or t-tests/F-tests (categorical variables) to determine the association with predictability. Potential covariates included child sex, race/ethnicity, maternal mental health (anxiety and depression), maternal age, maternal marital status, and income. Covariates that were significantly associated with predictability were included as covariates. In the Irvine cohort, mothers with lower household income ($r = -.31$, $p < .01$), with higher psychological distress (i.e., depressive and anxious symptoms; $r = .14$, $p < .05$), and younger age ($r = -.16$, $p < .05$), provided less predictable sensory signals to their infants. Marital status, race/ethnicity, and child sex were not related to predictability. In contrast to the Irvine cohort, maternal psychological distress was not significantly associated with predictability of maternal signals in the Turku cohort. Younger mothers ($r = -.18$, $p < .05$) and mothers with lower income ($r = -.16$, $p < .05$) provided less predictable maternal sensory signals to their infants.

Relating Degree of Predictability of Maternal Sensory Signals to Self-Control in Children.

Predictability and self-control at 1 year of age (Irvine and Turku cohorts). Pearson correlations were used to assess the strength of the relation between entropy rate, a measure of predictability of maternal care, and the various measures of child self-control

Predictability of maternal care and self-control longitudinal analysis (Irvine Cohort). The longevity of the association between unpredictable maternal sensory signals and self-control was assessed using a mixed linear model treating self-control as the dependent variable. To include all three time points (1 year, 5 years and 9.5 years) in a single analysis we first z-transformed each (to have mean zero and standard deviation one). The model included as independent variables time period (age 1 served as the reference group and indicators for the age 5 and age 9.5 measurements were included), sex (female = 0, male = 1), and predictability (entropy rate). There was no evidence of interactions of the predictors. The correlation due to having repeated observations of the same individuals was addressed through incorporation of random intercepts for individuals. The mixed models were fit using the lme4 package³⁰ in the R statistical package³¹.

Predictability of maternal care and self-control Flanker task (Irvine Cohort). Pearson correlations were used to assess the strength of the relation between predictability (entropy rate) and performance on the Flanker task.

Table 1. Demographic characteristics for the Irvine and Turku Cohorts.

	Irvine	Turku
	Cohort	Cohort
	(N = 192)	(N = 126)
Maternal Race/Ethnicity (%)		
Latina	27.1	0
Black	2.6	0
Asian	8.3	0
Non-Hispanic White	51.6	100
Other	10.4	0
Maternal Age at Delivery (mean years)	30.2	31.2
Education (%)		
High School or Less	13.5	0
Some College, Associates or Vocational Degree	40.7	19
4-year College Degree	28.6	40
Graduate Degree	17.2	41
Marital Status (% Married)	74.5	84
Child Sex (% female)	47.4	51.1
Entropy Rate (mean)	0.82	0.88

Table 2A. Results of mixed linear model for self-control

Parameter	Estimate	Std. Error
Intercept	0.95	0.31
Age 5 years	-0.01	0.10
Age 9.5 years	0.02	0.09
Sex (1=M; 0=F)	-0.42	0.12
Entropy Rate	-0.90	0.37

Table 2B. Results of mixed linear model for self-control with covariates

Parameter	Estimate	Std. Error
Intercept	0.73	0.31
Age 5 years	0.00	0.09
Age 9.5 years	0.02	0.09
Sex (1=M; 0=F)	-0.44	0.12
Entropy Rate	-0.63	0.37
Income	-0.02	0.07
Maternal Psychological Distress	-0.24	0.06
Maternal Age	0.13	0.07

Figure 1. Early life exposure to unpredictable maternal sensory signals (high entropy rate) is associated with poor self-control in 2 distinct cohorts, assessed in Irvine, California (gold) and in Turku, Finland (blue).

Figure 2. Study overview and time for data collection for the Irvine and the Turku cohorts.

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