

UC Irvine

UC Irvine Previously Published Works

Title

Exposure to unpredictable maternal sensory signals influences cognitive development across species

Permalink

<https://escholarship.org/uc/item/97n5z10t>

Journal

Proceedings of the National Academy of Sciences of the United States of America, 114(39)

ISSN

0027-8424

Authors

Davis, Elysia Poggi
Stout, Stephanie A
Molet, Jenny
et al.

Publication Date

2017-09-26

DOI

10.1073/pnas.1703444114

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed



Exposure to unpredictable maternal sensory signals influences cognitive development across species

Elysia Poggi Davis^{a,b,1}, Stephanie A. Stout^a, Jenny Molet^c, Brian Vegetabile^d, Laura M. Glynn^{b,e}, Curt A. Sandman^b, Kevin Heins^d, Hal Stern^d, and Tallie Z. Baram^{c,f,g}

^aDepartment of Psychology, University of Denver, Denver, CO 80208; ^bDepartment of Psychiatry and Human Behavior, University of California, Irvine, CA 92697; ^cDepartment of Anatomy and Neurobiology, University of California, Irvine, CA 92697; ^dDepartment of Statistics, University of California, Irvine, CA 92697; ^eDepartment of Psychology, Chapman University, Orange, CA 92866; ^fDepartment of Pediatrics, University of California, Irvine, CA 92697; and ^gDepartment of Neurology, University of California, Irvine, CA 92697

Edited by Bruce S. McEwen, The Rockefeller University, New York, NY, and approved August 8, 2017 (received for review March 2, 2017)

Maternal care is a critical determinant of child development. However, our understanding of processes and mechanisms by which maternal behavior influences the developing human brain remains limited. Animal research has illustrated that patterns of sensory information is important in shaping neural circuits during development. Here we examined the relation between degree of predictability of maternal sensory signals early in life and subsequent cognitive function in both humans ($n = 128$ mother/infant dyads) and rats ($n = 12$ dams; 28 adolescents). Behaviors of mothers interacting with their offspring were observed in both species, and an entropy rate was calculated as a quantitative measure of degree of predictability of transitions among maternal sensory signals (visual, auditory, and tactile). Human cognitive function was assessed at age 2 y with the Bayley Scales of Infant Development and at age 6.5 y with a hippocampus-dependent delayed-recall task. Rat hippocampus-dependent spatial memory was evaluated on postnatal days 49–60. Early life exposure to unpredictable sensory signals portended poor cognitive performance in both species. The present study provides evidence that predictability of maternal sensory signals early in life impacts cognitive function in both rats and humans. The parallel between experimental animal and observational human data lends support to the argument that predictability of maternal sensory signals causally influences cognitive development.

cross-species | maternal care | cognition | brain development | early experiences

Decades of research establish the primacy of maternal care as a vital determinant of development that predicts a broad range of outcomes including emotional and behavioral problems as well as cognitive and social development (1–6). Quality of maternal caregiving including maternal sensitivity, warmth, and responsiveness plays a fundamental role in defining the developmental course of the offspring. There is a need, however, for research evaluating the specific processes by which maternal care shapes biological mechanisms underlying neurodevelopment.

Classic research by Ainsworth and others demonstrates that predictable and appropriate maternal responses to infant signals are foundational to the development of a secure attachment relationship (7). In contrast, unpredictable maternal care leads to the development of an insecure or, in the extreme, disorganized attachment relationship (8). Attachment quality in turn exerts wide-ranging influences on infant development with long-term effects on cognitive functions, emotional well-being, and social adjustment (7). Recent human research evaluating moment-to-moment maternal–infant interactions supports the importance of contingencies within the dyadic relationship and indicates that dyadic synchrony is a potent predictor of child development (4, 5, 9, 10). Together, these studies provide insight into the importance of maternal predictability and elucidate characteristics of maternal–infant dyadic interactions, such as synchrony, that promote development. Given evidence from the attachment literature illustrating the importance of predictable maternal care, we propose an alternative way of thinking about patterns of maternal sensory signals as a process by which mothering influences child neurodevelopment. We suggest

that the degree of predictability of maternal sensory signals on a moment-to-moment time-scale may be a pathway by which high-quality maternal care exerts its benefit on developing brain synapses and circuits.

Our hypothesis is supported by evidence from the rodent illustrating that, in addition to quality and quantity of care (11–13), specific maternal sensory (e.g., tactile and olfactory) signals to the pup regulate the development of biological systems (14, 15). More recent work documents that patterns of sensory information shape the development of brain synapses and circuits including visual (16), somatosensory (17), and stress-responsive hypothalamic circuits (18, 19). Because sensory input programs the development and potentiation of synapses, the building blocks of neuronal communication and networks, sensory signals from the mother are a plausible process by which maternal care may regulate brain development. Building on this research, we test the hypothesis that moment-to-moment patterns of sensory information from the mother similarly influence offspring brain circuits involved in higher-order cognitive functions.

Using a cross-species approach, we evaluate whether the degree of predictability of maternal sensory signals in early life, assessed using a common quantitative measure in the two species, predicts memory functions at later ages. Maternal sensory signals were assessed in both species through observation and coding of behaviors during a 10-min semistructured play episode in humans and during two 50-min/d periods in rats. Maternal behaviors that provide sensory input to the offspring (e.g., vocalizations and touching in humans, nursing and licking/grooming in rats) were coded continuously in real time. The entropy rate of

Significance

The receipt of high-quality maternal care is an established promoter of optimal neurodevelopment, but the processes by which maternal care influences development remain unclear. Using a cross-species approach, we probe the possibility that predictability of sensory signals from the mother is a process by which maternal behavior influences cognitive circuits within the developing brain. This is in accord with established roles of patterns of sensory information in the organization of visual and auditory systems of the brain during sensitive periods. Our data support the argument that the degree of predictability of maternal sensory signals affects subsequent cognitive function in both rats and humans and suggest that these signals contribute to the shaping of the underlying neural circuits, including the hippocampus.

Author contributions: E.P.D., L.M.G., C.A.S., and T.Z.B. designed research; E.P.D., J.M., L.M.G., and C.A.S. performed research; B.V., K.H., and H.S. contributed new reagents/analytic tools; E.P.D., S.A.S., J.M., B.V., K.H., H.S., and T.Z.B. analyzed data; and E.P.D., B.V., H.S., and T.Z.B. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

¹To whom correspondence should be addressed. Email: elysia.davis@du.edu.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1703444114/-DCSupplemental.

this series of actions was then calculated as a quantitative measure of the degree of predictability of maternal sensory signals to the infant. In both species, entropy rate was associated with subsequent cognitive performance.

Results

Degree of Predictability of Maternal Sensory Signals Predicts Offspring Cognitive Development in Children and Rats. In both rats and humans the degree of predictability of maternal sensory signals was quantified using entropy rate and was associated with subsequent cognitive performance. See *SI Appendix* for additional information on behavioral coding and calculation of entropy rate.

Rats. The experimental manipulation, limited bedding and nesting material (LBN) in the cages, generated unpredictable maternal behavior. Behavior of mothers in the LBN cages was characterized by a higher entropy rate (1.81 ± 0.033) compared with the control dams (1.61 ± 0.043 ; $t_8 = -5.081$; $P < 0.01$), as described elsewhere (20). As shown in Fig. 1, memory performance was impaired in late adolescent male rats exposed to less-predictable maternal behavior (high entropy rate) during postnatal days (P)2–9. Specifically, in a task testing spatial memory (object location), control rats raised by mothers exhibiting a higher degree of predictability performed better than rats raised in LBN cages that received less-predictable maternal care: The control rats explored an object that had been moved to a new location significantly longer than an object that was not moved, indicating that they remembered the original locations of both objects. This is quantified as the ratio of time spent exploring novel/familiar locations (N/F ratio: 1.79 ± 0.11 controls; 1.18 ± 0.23 LBN; $t = 2.416$, $P = 0.023$) (Fig. 1). Exploration times of both objects during both training and testing did not differ between groups (*SI Appendix*, Fig. S7).

Children: Age 2 and 6.5 y. As with rat maternal behavior, entropy rate was calculated to characterize the degree of predictability of human maternal sensory signals (*SI Appendix*, section S1). Fig. 2A shows reduced cognitive function among children exposed to less-predictable maternal sensory signals (higher entropy rate) at 1 y of age. Specifically, a higher entropy rate predicted poorer cognitive performance (Mental Development Index; MDI) at 2 y of age ($r = -0.34$, $P < 0.001$). Less-predictable maternal sensory signals (high entropy rate) predicted lower child cognitive performance at age 2 y, even after accounting for covariates [$\beta = -0.18$, $t(122) = -2.23$, $P < 0.05$] (Table 1). The degree of predictability of maternal sensory signals was not significantly correlated with the child Psychomotor Development

Index (PDI) at age 2 y ($r = -0.02$, $P = 0.79$). We assessed children's recall memory at age 6.5 y to evaluate whether the association between entropy rate and cognitive performance persisted. As shown in Fig. 2B, unpredictable maternal sensory signals (high entropy rate) at age 1 y predicted poor performance on a hippocampus-dependent memory task at age 6.5 y ($r = -0.27$, $P < 0.05$; as described in *Methods*, *Statistical Analysis*, no covariates met criteria for inclusion in analyses of delayed-recall memory). Sex did not significantly moderate the relation between unpredictable maternal behavior and child cognitive performance at either age ($P > 0.20$ for both ages).

Predictability of Maternal Sensory Signals. In rats, we evaluated the possible alternative explanation that any differences in cognitive development might be due to quantity of maternal care rather than predictability of maternal signals. Consistent with previous findings (20, 21), the quantity of typical maternal nurturing behaviors, including nursing, arched-back nursing, and licking/grooming, was similar across the two groups. For example, in the low- and high-predictability groups, respectively, total nursing durations ($3,460 \pm 213$ and $3,508 \pm 166$ min; $t = 1.36$, $P = 0.21$), total licking and grooming durations (832 ± 83 and $1,101 \pm 126$ min; $t = 1.73$, $P = 0.11$), and total arched-back nursing duration ($1,640 \pm 263$ and $1,822 \pm 260$ min; $t = 0.49$, $P = 0.63$) did not differ (20).

In humans, we examined whether the degree of predictability of maternal signals explains unique variance in child cognition after accounting for a key global indicator of quality of maternal care: maternal sensitivity. Mothers who were low in maternal sensitivity also were lower in predictability (higher entropy rate) during the observed interaction with their child ($r = -0.32$, $P < 0.001$). Further, greater maternal sensitivity was associated with higher cognitive performance in the child at age 2 y ($r = 0.47$, $P < 0.05$) but not with delayed-recall memory at age 6.5 y ($r = 0.07$, $P = 0.60$). Importantly, predictability of maternal signals was associated with enhanced child cognitive function at age 2 y ($r = -0.23$, $P < 0.01$) and 6.5 y ($r = -0.26$, $P < 0.05$), even after adjusting for maternal sensitivity. Tests of indirect effects indicate that entropy rate partially mediated the relation between maternal sensitivity and child cognitive function indicator at age 2 y (bootstrapped 95% CI: 0.14, 1.61) (Fig. 3) but did not meet criteria for statistical significance at age 6.5 y (bootstrapped 95% CI: -0.001 , 0.49). As detailed in the *SI Appendix*, the entropy rate was a better indicator of cognitive outcomes than the amount of each sensory signal (auditor, tactile, and visual) or the total number of transitions, suggesting that the degree of predictability rather than quantity accounts for the observed associations.

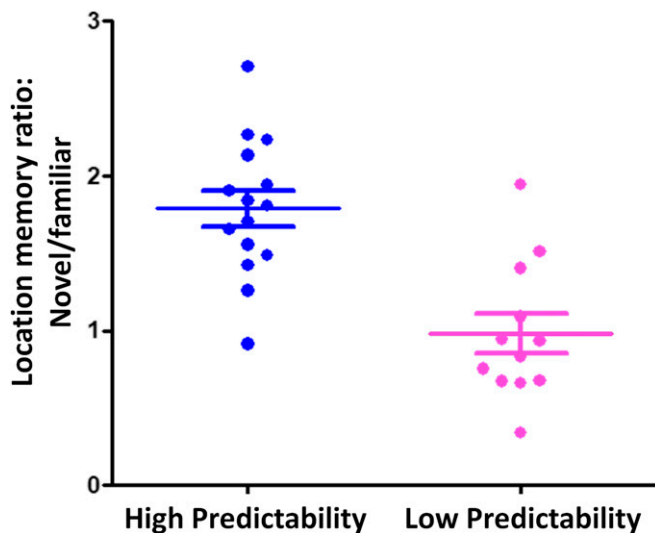


Fig. 1. Rats reared by dams providing less-predictable maternal sensory signals performed poorly on a spatial memory task (reduced ratio of time spent exploring objects in a novel vs. familiar location) during adolescence.

Discussion

As demonstrated in the classic studies by Hubel and Wiesel, sensory signals during sensitive periods regulate organization of the developing brain (17, 22, 23). Consistent with the importance of sensory information during sensitive periods, the major finding of the present cross-species research is that infant exposure to less-predictable maternal sensory signals results in subsequent impairments in cognitive development in both humans and rats. The parallel between our experimental evidence that unpredictable maternal sensory signals to the pup causally impact cognitive development in the rat and observational links between these signals and human cognitive functioning supports the argument that predictability of maternal sensory signals influences cognitive development in both species. Thus, these findings suggest that the predictability of maternal sensory signals is one of the processes by which maternal care regulates neurodevelopment.

The present findings complement a rich literature illustrating that maternal care early in life is a potent environmental signal that exerts pervasive and long-lasting effects on offspring health and development. In addition to the extensive human literature documenting the importance of predictability of maternal care for attachment security (7), classical experimental studies with nonhuman primates (24, 25) have demonstrated that environmental unpredictability impairs offspring development. Consistent with the

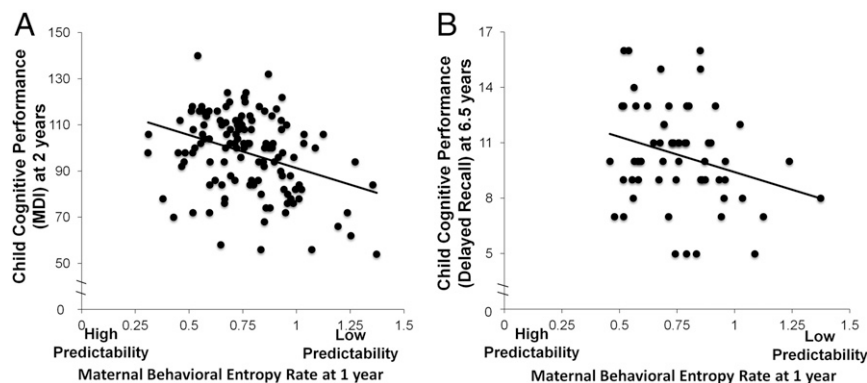


Fig. 2. Infants exposed to less-predictable maternal sensory signals (high entropy rate) at 1 y of age have (A) lower child MDI scores at 2 y of age ($r = -0.34$, $P < 0.001$) and (B) poor child delayed-recall scores on the WRAML at 6.5 y of age ($r = -0.27$, $P < 0.05$).

importance of understanding maternal signals in real time, recent human research shows that moment-to-moment dyadic processes, such as gaze synchrony, are profoundly important for human development (4, 5, 9, 10). We provide evidence that predictability of maternal sensory signals evaluated on short time scales of seconds to minutes is associated with subsequent cognitive functioning in both rats and human children. Importantly, in our human study, predictability of maternal sensory signals is associated with cognitive function even after adjusting for maternal, parenting, and socio-demographic factors such as level of maternal depressive symptoms, maternal sensitivity, and socioeconomic status (SES) as well as after accounting for quantity of signals (e.g., number of transitions). Although predictability uniquely contributes to cognitive function, it also is the case that parenting characteristics, such as maternal sensitivity, are associated with the predictability of sensory information to the child and with general cognitive development assessed with the MDI. Findings from mediational analyses are consistent with the possibility that entropy rate (degree of predictability of sensory signals) is a more proximal process by which well-established indicators of quality of maternal care such as maternal sensitivity and secure attachment influence the infant.

In humans, maternal sensitivity and depressive symptomatology as well as the degree of predictability of maternal sensory signals are associated with overall cognitive function at age 2 y (MDI score). However, of these measures, only the degree of predictability is associated with performance on the hippocampus-dependent delayed-recall task at 6.5 y of age. In addition, it is notable that the degree of predictability of maternal sensory signals influences hippocampus-dependent memory function in the rat offspring. Together, these data suggest that the predictability of sensory input early in life may be a common biological parameter influencing hippocampal circuit maturation across species. In rats, exposure to disruptions in maternal care early in life leads to reduced dorsal hippocampal volume and corresponding microstructural deficits, including reduced dendritic

arborization (26). Future studies will examine if similar deficits are detectable in children.

There are several strengths of the present investigation, which employs a prospective and longitudinal design to characterize the effects of infant exposure to varying degrees of predictability of maternal sensory signals on subsequent cognitive performance in both rats and humans. We quantify the degree of predictability of maternal sensory signals using entropy rate in both species. The cross-species approach overcomes a primary limitation of observational studies in humans. In observational human studies, the effect of maternal behavior cannot be completely disentangled from other factors such as prenatal influences, shared genes, or shared environments that may influence both maternal behavior and child neurodevelopment. In addition to these study strengths, several limitations exist. First, cross-species comparability is limited by the fact that maternal behavior was characterized as two distinct experimental groups in the rat but was observed as continuous variation in typical maternal behavior in humans. Second, only male rats were evaluated. However, in humans, sex did not moderate the observed association between the degree of maternal predictability and cognitive function. Third, cognitive function was assessed during childhood in humans and at a developmentally older age corresponding to late adolescence in the rat. Although ages of the offspring are not parallel in the two species, the benefit of assessment of human children longitudinally from infancy to middle childhood allows consideration of the effects of predictability on the developmental trajectories of cognitive abilities.

The mechanisms by which the degree of predictability of maternal sensory signals influences subsequent cognitive functioning in the offspring remain unknown. Cognitive function is predicated on the normal development and maturation of brain neuronal circuits. The development of these circuits and their synaptic connections is ongoing during the developmental periods when maternal care was examined in both humans and rats. It is well established that patterns

Table 1. Multiple regression demonstrating that unpredictable maternal sensory signals at 1 y postpartum account for unique variance in child MDI scores 1 y later at 2 y of age, after considering relevant covariates

Regression model	R^2	F	B	SE(B)	β	Partial r
Overall model	0.32	11.24***				
Maternal age at delivery			-0.19	0.29	-0.06	-0.06
Maternal EPDS, child age 1 y			-0.04	0.30	-0.01	-0.01
Breastfeeding duration			0.35	0.24	0.12	0.13
SES composite score			4.22***	0.88	0.44	0.40
Maternal behavioral entropy rate			-15.35*	6.88	-0.18	-0.20

Significance: * $P < 0.05$, *** $P < 0.001$; dependent variable is child MDI score at 2 y of age. β , standardized beta coefficient; B, unstandardized beta coefficient; F, F statistic/regression result; SE(B), standard error of the unstandardized beta coefficient.

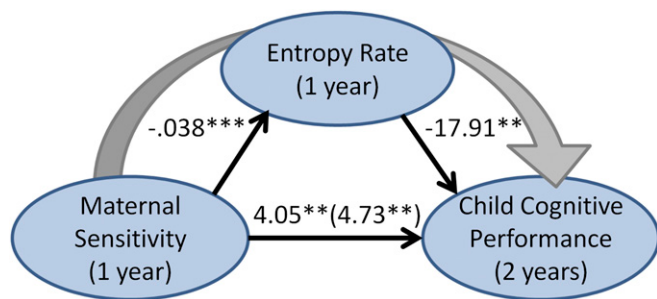


Fig. 3. Mediation model of maternal sensitivity, entropy rate, and child MDI scores. All coefficients are unstandardized. Test of indirect effects indicates that entropy rate partially mediates the relation between maternal sensitivity and child cognitive performance. The value in parentheses is the coefficient describing the relation between maternal sensitivity and child MDI scores not accounting for entropy rate. $^{**}P < 0.01$, $^{***}P < 0.001$.

of afferent stimulation govern the development and potentiation of single synapses in these circuits (27). Thus, it is tempting to speculate that consistent, predictable patterns of sensory stimulation from the mother will influence synaptic differentiation in an analogous manner. Indeed, in rats that received experimentally enhanced predictable maternal care there was reduced excitatory innervation of specific cell populations in the hypothalamus (28), whereas rats that received unpredictable maternal care displayed increases in excitatory innervation of the same stress-sensitive neurons (19, 29). Although these proposed mechanisms remain speculative, the cross-species findings reported here enable future testing across species using common methodologies such as MRI (26) with both species. These imaging studies could then be augmented with evaluation of molecular and synaptic changes in the rat to precisely test these proposed mechanisms. Thus, the finding presented here should promote innovative and important studies throughout the field of developmental neuroscience. The identification of the predictability of maternal sensory signals as a process by which maternal behavior shapes her offspring's developing brain is a critical first step toward the testing of hypothesized mechanisms at the neural, molecular, and genetic levels.

Methods

Study Overview. We evaluated the relation between degree of predictability of maternal sensory signals and subsequent cognitive functioning of the offspring in both humans and rats. In rats, predictability of maternal sensory signals was experimentally manipulated between days P2 and P9. The effect of unpredictable maternal sensory signals on subsequent cognitive function in the offspring was evaluated using a hippocampus-dependent spatial memory task at an age when spatial memory can be reliably assessed (between days P49 and P60). In humans, the degree of predictability of maternal sensory signals was evaluated in the context of a free-play interaction at 1 y of age. To evaluate the influence of early maternal care on subsequent child cognitive development, cognition was assessed at age 2 y using the Bayley Scales of Infant Development (BSID-II) (30) and at age 6.5 y using the Wide Range Assessment of Memory and Learning (WRAML-2) (31) to evaluate delayed-recall memory. The entropy rate for both species was computed based on real-time observations of maternal sensory behavior to characterize the degree of predictability.

Participants.

Rat subjects. Dams ($n = 12$) were primiparous, timed-pregnant Sprague-Dawley rats maintained in uncrowded animal facilities on 12-h light/dark cycles with access to chow and water. Pups from several litters were gathered on day P2. Ten pups were assigned at random to each dam to obviate potential genetic and litter size confounders. Both males and females were included, and litters were matched for the number of males. In the current studies, only males were used ($n = 28$). After weaning, they were housed two or three mice per cage. All animal experiments were performed in accordance with NIH guidelines and were approved by the Institutional Animal Care and Use Committee at the University of California, Irvine.

Human participants. Study participants included 128 mothers and their children (62 female, 66 male) participating in a longitudinal study evaluating the role of early experiences on development. Women who were English-speaking,

nonsmokers, over the age of 18 y, with a singleton pregnancy, and for whom there was no evidence for drug or alcohol use during pregnancy were eligible. The study participants included in these analyses were the 128 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 (nine women for whom less than 90% of the video was of good quality were excluded). All children included in the present analyses were born at greater than 35 gestational weeks and had 5-min Apgar scores between 8 and 10. Descriptive information for the sample appears in Table 2. One hundred twenty-eight mother-child dyads were seen at child age of 1 y (mean = 1.01, SD = 0.03) and 2 y (mean = 2.01, SD = 0.03). A subset of 60 (27 males, 33 females) of these mother-child dyads additionally was seen at 6.5 y (mean = 6.51, SD = 0.14). As shown in Table 2, the subsample seen at child age 6.5 y is similar to the overall sample on sociodemographic factors. All human 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.

Measuring the Degree of Predictability of Maternal Sensory Signals to the Offspring.

Rat maternal behavior.

Experimental manipulation. Maternal behavior was manipulated by randomly assigning dams and litters to either "impoverished" cages (LBN condition) or standard cages from P2 through P9, as described previously (20). In the LBN condition, typical plastic cages were fitted with a plastic-coated mesh platform ~2.5 cm above the floor. Bedding was reduced to cover the cage floor sparsely, and one-half of a single paper towel was provided for nesting material. Control dams and litters resided in standard cages containing 0.33 ft³ of cob bedding. The LBN paradigm induces fragmented and unpredictable maternal care (20, 21). Control and experimental cages were undisturbed during P2–P9 and were housed in temperature-controlled rooms with laminar airflow preventing ammonia accumulation. LBN groups were transferred on day P10 to routine cages, where maternal behavior normalizes within hours (21). Rats were weaned on P21–22 and then were housed in group cages.

Assessment of rat maternal behavior. Maternal behaviors were recorded through direct and continuous observation of cages for 50-min periods twice each day, as described in ref. 20 and in *SI Appendix, section S1.1*. Mothers were identified as performing one of seven different behaviors: licking/grooming pups, carrying pups, eating, nursing (in high- or low-arched posture), nest building, off pups, or self-grooming. Two investigators coded behaviors, and coding reliability was established (20).

Quantifying predictability of maternal behavior in rats (entropy rate). The total amount of the individual nurturing behaviors (licking/grooming, nursing) in the control and LBN environments was assessed using four cohorts collected at different times. Each cohort consisted of two dams in control environments and two dams in LBN cages. Next, we assessed unpredictability of maternal behavior by modeling behavioral sequences as a first-order Markov chain and estimating the entropy rate of the process. This approach focused on transitions from one type of maternal behavior to another. For each mother a record was maintained of the frequency and conditional probability of transitions from each of the $K = 7$ behaviors described above (licking/grooming, nursing, and others) to all other behaviors. The entropy rate for the stochastic process describing maternal care was estimated as described below for the human study and in *SI Appendix, section S1.2*.

Human maternal behavior.

Observation. Mothers were video-recorded interacting with their 12-month-old infants in a semistructured 10-min play episode. During this play interaction, mothers were given a standard set of age-appropriate toys and were 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 in real time 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%. Additional details are provided in *SI Appendix, section S1.1*.

Quantifying predictability of maternal behavior in humans (entropy rate). To quantify the extent to which sequences of maternal sensory signals were predictable, we focused on the conditional probabilities of transitioning between maternal visual, auditory, and tactile sensory signals. We considered all $K = 8$ combinations of these 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 was then providing auditory, visual, and tactile input, then picking up the child would be considered a transition.

Table 2. Descriptive information for mothers and children in the study sample

Sample characteristics	Full sample, <i>n</i> = 128	Subsample at child age 6.5 y, <i>n</i> = 60	Comparisons test statistic (<i>P</i>)
Maternal characteristics			
Age at delivery (M ± SD)	29.9 ± 5.2	30.1 ± 4.8	−0.41 (0.68)
Cohabiting with child's father, %	92	90	0.75 (0.39)
Ethnicity, %			4.08 (0.40)
Non-Hispanic white	49.2	46.7	
Hispanic	29.7	31.7	
Household income, in dollars, M ± SD	62,637 ± 34,223	66,250 ± 36,390	−1.12 (0.26)
Education in years, M ± SD	15.8 ± 2.5	16.02 ± 2.50	−0.93 (0.36)
High school or less, %	12.5	13.3	
Some college, %	36.7	30.0	
College graduate, %	50.8	56.7	
Entropy rate, M ± SD	0.77 ± 0.21	0.76 ± 0.19	0.56 (0.58)
Maternal depressive symptoms, EPDS	4.6 ± 4.5	4.3 ± 5.1	0.58 (0.56)
Maternal sensitivity at child age 1 y, M ± SD	9.72 ± 1.72 ^a	9.87 ± 1.64	−0.90 (0.37)
Child characteristics			
Sex, % male	51.6	45.0	1.95 (0.16)
Gestational age at birth, M ± SD	39.4 ± 1.3	39.5 ± 1.1	−1.09 (0.28)
Birth weight, g	3,409.9 ± 466.19	3,382.8 ± 451.6	0.62 (0.54)
First born, %	43.8	51.7	2.88* (0.09)
Duration of breastfeeding, M ± SD in months	7.9 ± 6.0	9.3 ± 6.5	−2.40** (0.02)
MDI at age 2 y, M ± SD	97.8 ± 17.1	101.1 ± 18.2	−2.02** (0.045)
PDI at age 2 y, M ± SD	97.9 ± 13.6	99.5 ± 15.5	−1.22 (0.23)
Delayed recall (WRAML) at age 6.5 y, M ± SD		10.3 ± 2.7	

Significance: **P* < 0.10, ***P* < 0.05 comparing those with 6.5-y follow-up and those without; all other *P*s > 0.10. M, mean.

These observed behavioral data were then summarized in an empirical transition matrix $P = \{p_{ij}\}$ for $i, j = 1, \dots, K$, where p_{ij} measures the proportion of times that a mother who was performing behavior i transitioned to behavior j . The likelihood of transitions was assumed to depend only on the current behavior and not on earlier behaviors in the sequence. This made the series of behaviors a Markov process (32). Row i of the transition matrix summarized the distribution of the next behavioral state from behavior i . Each row summed to one, $\sum_{j=1}^K p_{ij} = 1$, because these entries accounted for all possible transitions starting from state i . Additionally, $p_{ii} = 0$ for all i , indicating that it was not possible to transition to the same state.

To measure the predictability of the transitions between sensory signals (or combinations of signals), we applied measures from information theory (32). Entropy and entropy rate are measures of the randomness or unpredictability of random variables and stochastic processes, respectively (32). The range of values for both measures is from zero to the logarithm of the number of possible states of the process. For each row i of P we calculated the entropy (or predictability) of the distribution of the next maternal signal, $h = -\sum_{j=1}^K p_{ij} \log_2 p_{ij}$ (33). For a Markov process like our sequence of maternal signals, the entropy rate is a weighted average of these row entropies weighted by the stationary distribution of the process, $\pi = \{\pi_i\}$. The stationary distribution, $\pi = \{\pi_i\}$, $i = 1, \dots, K$, can be thought of as the proportion of time spent in each state if we were to observe a behavioral process governed by the transition matrix P over a long period (34). Once the stationary distribution was determined, the entropy rate was calculated as follows:

$H = -\sum_{i=1}^K \pi_i \sum_{j=1}^K p_{ij} \log_2 p_{ij}$. A higher entropy rate indicates more unpredictable maternal sensory signals. Additional details are provided in *SI Appendix, section S1.2*.

Characterizing global quality of maternal care: Maternal sensitivity. Maternal sensitivity was evaluated through observation of the same 10-min interaction to determine whether predictability of maternal behavior contributed to child cognitive function beyond measures of maternal care quality. Maternal behavior was coded using a protocol developed for the National Institute of Child Health and Human Development (NICHD) Study of Early Child Care and Youth Development (6). Maternal behavior was rated for sensitivity to nondistress, intrusiveness, and positive regard (1 = not at all characteristic to 4 = highly characteristic). A composite rating of maternal sensitivity was created by summing ratings of sensitivity to nondistress, positive regard, and intrusiveness (reverse-coded). Coders were blind to other data gathered on study participants. Interrater reliability was calculated for 20% of the videos, and reliability for subscales ranged from 90–93%.

Relating Degree of Predictability of Maternal Care to Cognition in Humans and Rats.

In both humans and rats the association between early degree of predictability of maternal sensory signals and subsequent cognitive functioning was evaluated.

Spatial memory in rats. Rats were tested with a hippocampus-dependent spatial memory task that evaluates the ability to remember the location of an object (35). This task consisted of two sessions conducted over 2 d and involved a training session and a testing session (24 h after training). Rats from each of the study groups were run concurrently and at the same time of day. Rats were assessed on days P49–P60.

During the training session, rats were placed in the experimental apparatus with two identical objects (250-mL beakers) and allowed to explore the objects for 10 min. During the testing session on day 2, rats were returned to the testing room, placed in the experimental apparatus, and presented with the two familiar objects from the training session with one object moved to a novel location. Exploration of the two objects was scored for 5 min. Both training and testing phases were video-recorded using an overhead camera, and the duration of exploration of each object (touching the object with the nose or sniffing with the nose <1 cm from objects) as well as total object exploration were scored by an observer who was blinded to condition. To assess recognition memory of the familiar location, exploration times for the novel and familiar locations were used to calculate a discrimination ratio, *N/F*. Because rats explore novelty, they will prefer an object moved to a new location over one in a familiar place (36, 37). Thus, a higher *N/F* ratio indicates better recognition memory.

Mental development in humans. Child cognitive ability was assessed at age 2 y using the BSID-II (30), a widely used instrument to assess infant and toddler cognitive development. The primary outcome of interest for this study was the MDI that assesses cognitive (e.g., sensory/perceptual acuities, problem-solving, acquisition of object constancy) and language skills. A second PDI that measures gross and fine motor skills was administered also. Conventional scoring created composite MDI and PDI scores (Table 2) that were then converted to a scaled score using a developmental reference table that adjusts for the age of the child. An independent observer scored 27% of the assessments, and interrater reliability was 93%.

Delayed-recall memory in humans. Because published rat literature focuses primarily on the effect of unpredictable care on memory (26), we evaluated the performance of older children on a hippocampus-dependent delayed-recall memory assessment. The verbal list-learning test from the second edition of the WRAML-2 (31) was used to assess children's verbal delayed-recall memory. This task includes an immediate and a delayed-recall condition. The delay condition was the outcome of interest because performance on delayed-memory tasks has been shown to be indicative of hippocampal function (36). The subtests have demonstrated validity and good internal consistency (31).

Possible Confounding Factors in the Human Study. Based on the published literature, we identified maternal, demographic, and child factors that may influence cognitive development for inclusion in analyses assessing possible confounding factors.

Maternal depression. Depressive symptoms were assessed concurrently with the evaluation of maternal behavior using the 10-item Edinburgh Postnatal Depression Scale (EPDS) (38). Data were imputed using regression imputation for two women who did not complete the EPDS.

Sociodemographic measures. Race/ethnicity, maternal cohabitation with baby's father, maternal education, and household income were assessed via maternal report. Education and household income were used to create a standardized SES composite score (39).

Child measures. Gestational age at birth, birth order, birth weight, and Apgar scores were abstracted from the medical record. Breastfeeding history was assessed via maternal report.

Statistical Analysis.

Degree of predictability of rat maternal sensory signals and offspring cognitive development. We used *t* tests to compare the discrimination ratio values and total exploration times of both groups. Two rats (out of 30) were excluded because of short exploration times (<40 s). One rat was considered an outlier and was removed from the discrimination ratio analysis based on the Grubb test (www.graphpad.com/quickcalcs/Grubbs1.cfm).

Identification of covariates (humans). Correlations, *t* tests, and ANOVA were used when appropriate to identify sociodemographic (i.e., race/ethnicity, cohabitation with baby's father, SES, depressive symptoms) and infant (i.e., birth order, sex, birth weight percentile, gestational age at birth, duration of breastfeeding) variables that might influence infant cognitive or motor development. The factors associated with both maternal behavioral entropy rate and child MDI, PDI, or delayed recall at the level of $P < 0.10$ were identified for inclusion as covariates in relevant analyses. Maternal age at delivery, maternal depressive symptoms, SES, and duration of breastfeeding

were associated with both maternal behavioral entropy rate at 1 y and child MDI scores at 2 y at $P < 0.10$ and thus were included as covariates in subsequent analyses with MDI. Maternal age at delivery, breast feeding duration, and SES were associated with both maternal behavioral entropy rate at 1 y and child PDI scores at 2 y at $P < 0.10$. No covariates were associated with both maternal behavioral entropy rate at 1 y and delayed recall at 6.5 y at $P < 0.10$.

Degree of predictability of human maternal sensory signals and child cognition. First, bivariate correlations were used to evaluate whether the degree of predictability of maternal sensory signals (entropy rate) was associated with child cognition. If significant correlations were observed, a regression model was implemented to determine whether maternal behavior patterns predicted child cognitive function after accounting for identified covariates. For both outcomes, subsequent analyses were conducted to determine if sex moderated the impact of early maternal behavior on subsequent child cognitive development.

Degree of predictability of maternal sensory signals and other maternal care indicators. Final analyses evaluated the relation between measures of degree of predictability (entropy rate) and global maternal care indicators. For rats we tested whether group differences associated with predictability were due to differences in quantity of care. For humans, the relation between degree of predictability of maternal sensory signals and maternal sensitivity was evaluated using Pearson correlations. Next, we included maternal sensitivity as a covariate in our model to determine whether entropy rate accounted for variance in child cognition after covarying maternal sensitivity. Finally, we assessed whether entropy rate partially mediated the relation between maternal sensitivity and child outcomes using a test of indirect effects (95% bias-corrected bootstrap CIs with 5,000 bootstrap resamples).

ACKNOWLEDGMENTS. We thank the families who participated in these projects and the dedicated staff at the Women and Children's Health and Well-Being Project. This research was supported by NIH Awards P50 MH096889, MH86062, HD51852, NS41298, HD40967, MH73136, and NS28192.

- Belsky J, Fearon RM (2002) Early attachment security, subsequent maternal sensitivity, and later child development: Does continuity in development depend upon continuity of caregiving? *Attach Hum Dev* 4:361–387.
- NICHD Early Care Research Network (2006) Infant-mother attachment classification: Risk and protection in relation to changing maternal caregiving quality. *Dev Psychol* 42:38–58.
- Hane AA, Henderson HA, Reeb-Sutherland BC, Fox NA (2010) Ordinary variations in human maternal caregiving in infancy and biobehavioral development in early childhood: A follow-up study. *Dev Psychobiol* 52:558–567.
- Feldman R (2007) Parent-infant synchrony and the construction of shared timing; physiological precursors, developmental outcomes, and risk conditions. *J Child Psychol Psychiatry* 48:329–354.
- Feldman R (2015) Mutual influences between child emotion regulation and parent-child reciprocity support development across the first 10 years of life: Implications for developmental psychopathology. *Dev Psychopathol* 27:1007–1023.
- NICHD Early Child Care Research Network (1999) Chronicity of maternal depressive symptoms, maternal sensitivity, and child functioning at 36 months. *Dev Psychol* 35:1297–1310.
- Sroufe LA (2005) Attachment and development: A prospective, longitudinal study from birth to adulthood. *Attach Hum Dev* 7:349–367.
- Groh AM, Roisman GI, van Ijzendoorn MH, Bakermans-Kranenburg MJ, Fearon RP (2012) The significance of insecure and disorganized attachment for children's internalizing symptoms: A meta-analytic study. *Child Dev* 83:591–610.
- Beebe B, et al. (2016) A systems view of mother-infant face-to-face communication. *Dev Psychol* 52:556–571.
- Beebe B, Steele M (2013) How does microanalysis of mother-infant communication inform maternal sensitivity and infant attachment? *Attach Hum Dev* 15:583–602.
- Sucecki D, Nelson DY, Van Oers H, Levine S (1995) Activation and inhibition of the hypothalamic-pituitary-adrenal axis of the neonatal rat: Effects of maternal deprivation. *Psychoneuroendocrinology* 20:169–182.
- Liu D, et al. (1997) Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. *Science* 277:1659–1662.
- Meaney MJ, Szyf M (2005) Maternal care as a model for experience-dependent chromatin plasticity? *Trends Neurosci* 28:456–463.
- Levine S (2002) Regulation of the hypothalamic-pituitary-adrenal axis in the neonatal rat: The role of maternal behavior. *Neurotox Res* 4:557–564.
- Shair HN, Hofer MA (1993) Afferent control of pressor responses to feeding in young rats. *Physiol Behav* 53:565–576.
- Espinosa JS, Stryker MP (2012) Development and plasticity of the primary visual cortex. *Neuron* 75:230–249.
- Khazipov R, et al. (2004) Early motor activity drives spindle bursts in the developing somatosensory cortex. *Nature* 432:758–761.
- Baram TZ, et al. (2012) Fragmentation and unpredictability of early-life experience in mental disorders. *Am J Psychiatry* 169:907–915.
- Singh-Taylor A, et al. (January 10, 2017) NRSF-dependent epigenetic mechanisms contribute to programming of stress-sensitive neurons by neonatal experience, promoting resilience. *Mol Psychiatry*, 10.1038/mp.2016.240.
- Molet J, et al. (2016) Fragmentation and high entropy of neonatal experience predict adolescent emotional outcome. *Transl Psychiatry* 6:e702.
- Ivy AS, Brunson KL, Sandman C, Baram TZ (2008) Dysfunctional nurturing behavior in rat dams with limited access to nesting material: A clinically relevant model for early-life stress. *Neuroscience* 154:1132–1142.
- Wiesel TN, Hubel DH (1963) Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J Neurophysiol* 26:1003–1017.
- Woo CC, Hingco EE, Taylor GE, Leon M (2006) Exposure to a broad range of odorants decreases cell mortality in the olfactory bulb. *Neuroreport* 17:817–821.
- Coplan JD, et al. (1996) Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult nonhuman primates exposed to early-life stressors: Implications for the pathophysiology of mood and anxiety disorders. *Proc Natl Acad Sci USA* 93:1619–1623.
- Rosenblum LA, Andrews MW (1994) Influences of environmental demand on maternal behavior and infant development. *Acta Paediatr Suppl* 397:57–63.
- Molet J, et al. (2016) MRI uncovers disrupted hippocampal microstructure that underlies memory impairments after early-life adversity. *Hippocampus* 26:1618–1632.
- Collingridge GL, Peineau S, Howland JG, Wang YT (2010) Long-term depression in the CNS. *Nat Rev Neurosci* 11:459–473.
- Korosi A, et al. (2010) Early-life experience reduces excitation to stress-responsive hypothalamic neurons and reprograms the expression of corticotropin-releasing hormone. *J Neurosci* 30:703–713.
- Gunn BG, et al. (2013) Dysfunctional astrocytic and synaptic regulation of hypothalamic glutamatergic transmission in a mouse model of early-life adversity: Relevance to neurosteroids and programming of the stress response. *J Neurosci* 33:19534–19554.
- Bayley N (1993) *Bayley Scales of Infant Development* (The Psychological Corporation, San Antonio, TX), 2nd Ed.
- Sheslow D, Adams W (2003) *Wide Range Assessment of Memory and Learning Administration and Technical Manual* (Psychological Assessment Resources, Lutz, FL), 2nd Ed.
- Cover TM, Thomas JA (2006) *Elements of Information Theory* (Wiley-Interscience, Hoboken, NJ), 2nd Ed.
- Shannon CE (1948) A mathematical theory of communication. *Bell Syst Tech J* 27:379–423.
- Levin DA, Peres Y, Wilmer EL (2009) *Markov Chains and Mixing Times* (American Mathematical Society, Providence, RI).
- McQuown SC, et al. (2011) HDAC3 is a critical negative regulator of long-term memory formation. *J Neurosci* 31:764–774.
- Squire LR, Wixted JT, Clark RE (2007) Recognition memory and the medial temporal lobe: A new perspective. *Nat Rev Neurosci* 8:872–883.
- Langston RF, Wood ER (2010) Associative recognition and the hippocampus: Differential effects of hippocampal lesions on object-place, object-context and object-place-context memory. *Hippocampus* 20:1139–1153.
- Cox JL, Holden JM, Sagovsky R (1987) Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry* 150:782–786.
- Cohen S, Doyle WJ, Baum A (2006) Socioeconomic status is associated with stress hormones. *Psychosom Med* 68:414–420.