8-14-2019

Across Continents and Demographics, Unpredictable Maternal Signals are Associated with Children's Cognitive Function

Elysia Poggi Davis
University of Denver, University of California Irvine

Riikka Korja
University of Turku

Linnea Karlsson
University of Turku

Laura M. Glynn
University of California-Irvine, Chapman University

Curt A. Sandman
University of California-Irvine

See next page for additional authors

Publication Statement

Copyright is held by Authors. User is responsible for all copyright compliance. This article was originally published by Elsevier B.V. as:

Davis, E. P., Korja, R., Karlsson, L., Glynn, L. M., Sandman, C. A., Vegetabile, B., . . . Baram, T. Z. (2019). Across continents and demographics, unpredictable maternal signals are associated with children's cognitive function. *EBioMedicine, 46*, 256-263. https://doi.org/10.1016/j.ebiom.2019.07.025

EBioMedicine 46 (2019) 256–263

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Across continents and demographics, unpredictable maternal signals are associated with children's cognitive function

Elysia Poggi Davis [a,b,*], Riikka Korja [c,d], Linnea Karlsson [d,e], Laura M. Glynn [b,f], Curt A. Sandman [b], Brian Vegetabile [g], Eeva-Leena Kataja [d,c], Saara Nolvi [d], Eija Sinervä [d], Juho Pelto [d], Hasse Karlsson [d,h], Hal S. Stern [g], Tallie Z. Baram [i,j,k]

[a] Department of Psychology, University of Denver, Denver, CO, USA
[b] Department of Psychiatry and Human Behavior, University of California-Irvine, Hewitt Hall, Irvine, CA 92697, USA
[c] Department of Psychology, University of Turku, Turku, Finland
[d] Institute of Clinical Medicine, Turku Brain and Mind Center, FinnBrain Birth Cohort Study, University of Turku, Turku, Finland
[e] Institute of Clinical Medicine, Department of Child Psychiatry, University of Turku and Turku University Hospital, Turku, Finland
[f] Department of Psychology, Chapman University, 544 N. Cypress St., Orange, CA 92867, USA
[g] Department of Statistics, University of California-Irvine, Bren Hall, Irvine, CA 92697, USA
[h] Department of Psychiatry, University of Turku and Turku University Hospital, Turku, Finland
[i] Department of Pediatrics, University of California-Irvine, Hewitt, Hall Irvine, CA 92697, USA
[j] Department of Anatomy and Neurobiology, University of California-Irvine, Hewitt Hall, Irvine, CA 92697, USA
[k] Department of Neurology, University of California-Irvine, Hewitt Hall, Irvine, CA 92697, USA

ARTICLE INFO

Article history:
Received 19 June 2019
Accepted 9 July 2019
Available online 27 July 2019

Keywords:
Predictability
Early adversity
Development
Cognition
Maternal care

ABSTRACT

Background: Early life experiences have persisting influence on brain function throughout life. Maternal signals constitute a primary source of early life experiences, and their quantity and quality during sensitive developmental periods exert enduring effects on cognitive function and emotional and social behaviors. Here we examined if, in addition to established qualitative dimensions of maternal behavior during her interactions with her infant and child, *patterns* of maternal signals may contribute to the maturation of children's executive functions. We focused primarily on effortful control, a potent predictor of mental health outcomes later in life.
Methods: In two independent prospective cohorts in Turku, Finland ($N = 135$), and Irvine, CA, USA ($N = 192$) that differed significantly in race/ethnicity and sociodemographic parameters, we assessed whether infant exposure to unpredictable patterns of maternal-derived sensory signals portended poor effortful control.
Outcomes: In both the Irvine and Turku cohorts, unpredictable sequences of maternal behavior during infancy were associated with worse effortful control at one year of age. Longitudinal analyses demonstrated that this association persisted for as long as each cohort was assessed-until two years of age in the Turku cohort and to 9.5 years in the Irvine cohort. The relation of unpredictable maternal signals during infancy and the measures of executive function persisted after adjusting for covariates.
Interpretations: The consistency of our findings across two cohorts from different demographic backgrounds substantiated the finding that patterns, and specifically unpredictable sequences, of maternal behaviors may influence the development of executive functions which may be associated with vulnerability to subsequent psychopathology.
Fund: This research was supported by the National Institutes of Health (NIH) awards P50MH096889, HD051852, NS041298, HD02413, HD050662, HD065823, and by the FinnBrain funders: Academy of Finland (129839, 134950, 253270, 286829, 287908, 308176, 308252), Jane and Aatos Erkko Foundation, Signe and Ane Gyllenberg Foundation, Yrjö Jahnsson Foundation, and State Research Grants (P3498, P3654).

1. Introduction

Early experiences profoundly impact brain function and structure [1–3]. Maternal signals constitute a primary influence in early life, and their quantity and quality during sensitive developmental periods

* Corresponding author at: Department of Psychology, 2155 South Race Street, University of Denver, Denver, CO 80208-3500, USA.
E-mail address: Elysia.Davis@du.edu (E.P. Davis).

https://doi.org/10.1016/j.ebiom.2019.07.025

Research in Context

Evidence before this study

The evidence that early experiences including maternal mental health and quality of maternal care profoundly influence a child's neurodevelopment is undisputed. Notably, existing literature focuses primarily on quality of maternal signals, including sensitivity and responsiveness, but not on their patterns. It also is known that patterned sensory signals to the developing brain are necessary for the maturation of sensory circuits (e.g., auditory, visual), but it is not established if sensory signals and their patterns influence the maturation of circuits underlying cognitive and emotional functions. There is now evidence in experimental animals that exposure to unpredictable maternal signals has long-term consequences on cognitive and emotional brain systems. Indeed, we recently found that exposure to unpredictability early in life impacts memory in both human children and experimental systems (rats).

Added value of this study

There are three major contributions of the current study. First, rather than assessing only quantity or quality of maternal care, we evaluated how ***patterns*** of maternal signals to the infant predict developmental outcomes. Second, we demonstrate the novel relation of patterns of maternal signals with infant and child outcome in two independent cohorts in California and Finland. Third, we provide important support for the emerging concept that unpredictable patterns of sensory signals are related to effortful control, an aspect of executive function that has broad consequences for mental health.

Implications of all the available evidence

Patterns of maternal signals to her infant may play a fundamental role in shaping brain development. Because unpredictable maternal sensory signals may be a form of early adversity they may contribute to the established effects of previously defined early-life adversity. The enduring associations between early-life unpredictability and executive function through 9 years of age suggests that this early exposure contributes to a developmental trajectory leading to increased vulnerability to subsequent psychopathology.

exert enduring effects on infant, child and adult emotional, cognitive and social behaviors in humans, nonhuman primates and rodents [4–6]. An extensive literature documents the critical importance of sensitive and responsive care and a secure attachment relationship [4,5,7], including dyadic synchrony, as critical determinants of optimal development of cognitive and emotional brain functions [8,9]. We evaluated the novel possibility that patterns of maternally derived sensory signals are associated with the development of executive functions.

Sensory signals from the environment are required for the maturation of brain circuits that underlie specific functions [10,11]. For example, light and visual patterns during a sensitive developmental period are mandatory for normal maturation of the visual system [10], and sound and tone-patterns are required for the full development of hearing and the auditory circuit [12]. However, it is unknown whether specific patterns of sensory signals are required for normative maturation of emotional and cognitive circuits in humans. In experimental animals we have discovered that patterns and specifically unpredictability and fragmentation of maternal signals during infancy impaired cognitive function and promoted anhedonia in adolescent rats [13–15]. Recently we showed that unpredictable maternal sensory signals during infancy led to subsequent cognitive impairments in both humans and rodents [16].

Here we evaluated whether infant exposure to unpredictable maternal signals was associated with reduced effortful control during infancy and childhood. This key element of executive function, effortful control, involves the ability to regulate behavior and attention [17,18]. The beginnings of executive function/effortful control emerge around 10–12 months of age and executive functions rapidly develop during childhood [19,20]. We focused on effortful control because it is influenced by early experiences [21] and deficits in effortful control are a significant predictor of later psychopathology [17,22]. In two human cohorts that differ socio-demographically followed prospectively in Turku, Finland and Irvine, California, we examined whether patterns of maternal signals to her infant influenced child effortful control.

2. Methods

We evaluated the relation between degree of unpredictability of maternal sensory signals and subsequent effortful control of the infants and children in two cohorts (see Fig. 1 for overview of study protocol). Degree of unpredictability of maternal sensory signals was evaluated in the context of a free-play interaction at 6 and 12 months (Irvine Cohort) and 8 months (Turku Cohort). Unpredictability of maternal signals to her infant was defined in terms of entropy rates [16]. The entropy rate was computed from real-time observations of maternal behaviors that convey sensory information to the infant. To evaluate the relation between early maternal unpredictability on child effortful control, children were assessed in the Irvine and Turku Cohorts at one year of age followed by assessments in the Turku Cohort at 2 years of age and in the Irvine Cohort at 5, 6.5 and 9.5 years of age.

2.1. Participants

Irvine Cohort: Study participants included 192 mothers and their children (91 girls, 101 boys) 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 for whose children we had at least one effortful control measure. Descriptive information for the sample appears in Table 1. Unpredictability of maternal sensory signals was evaluated when children were 6 months (Mean age = 6.09, SD = 0.3) and 1 year (Mean age = 1.02, SD = 0.05) of age and then averaged as an index of exposure to maternal unpredictability throughout infancy. 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 time points. Child effortful control was assessed initially at the 1-year visit ($n = 166$). Longitudinal evaluation of effortful 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 135 mothers and their children (68 male, 67 female) that were a subset of the large FinnBrain Birth Cohort Study and its Focus Cohort, a nested case-control population [23]. The subset comprised 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 having high prenatal psychological distress.

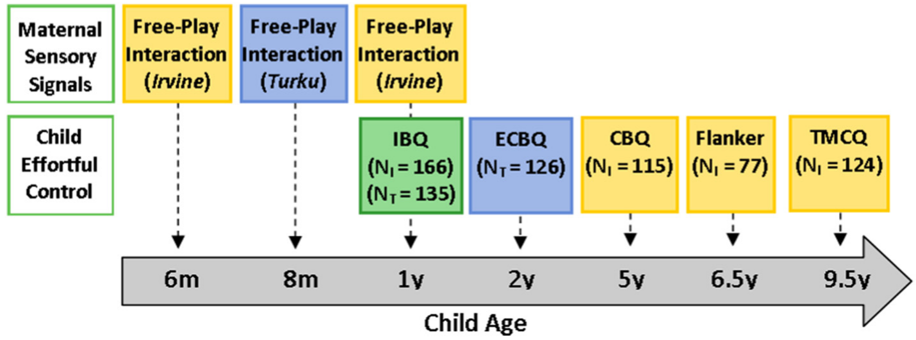

Fig. 1. Study overview and time for data collection for the Irvine and the Turku cohorts.

Three selected cut-points were employed: First, depression on the Edinburgh Postnatal Depression Scale (EPDS) that is widely used during pregnancy and postpartum [24,25] (> 11 points/max score 30); second, anxiety on the Symptom Checklist-90 (SCL-90) [26] (anxiety scale >9 points /max score 40); third, pregnancy-anxiety on the Pregnancy-Related Anxiety Questionnaire-Revised (PRAQ-R) [27] (> 33 points/ max score 50). Controls represented mothers who scored below the following thresholds in the same questionnaires at all time points for all measures: EPDS <7 points, SCL < 5 points, PRAQ-*R* < 26 points. 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 FinnBrain Cohort (Table 1). Participants in the present investigation were the 135 women for whom video recordings of maternal-child interactions and child outcomes were available. Unpredictability of maternal sensory signals was evaluated when children were 8 months old. Child effortful control was assessed at 1 year (M age = 1.04 years, SD = 0.03, n = 126) and 2 years (M age = 2.13 years, SD = 0.11, n = 112). All procedures were approved by the Ethics Committee of the Hospital District of Southwest Finland. Each mother provided written and informed consent for herself and her child.

Data Statement: Data from the Irvine Cohort are publically available. Current Finnish legislation does not allow publication of datasets from medical research. The anonymized dataset is available upon request. Requests should be submitted to statistician Juho Pelto (juho.pelto@utu.fi).

Table 1
Demographic characteristics for the Irvine and Turku Cohorts.

	Irvine cohort (N = 192)	Turku cohort (*N* = 135)
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 (years)	30.2 (5.47)	31.2 (4.07)
Education in years	15.52 (2.37)	
Education (%)		
High School or Less	13.5	8
Some College, Associates or Vocational Degree	40.7	12
4-year College Degree	28.6	43
Graduate Degree	17.2	37
Income	60,778 (33,770) dollars	20,187 (8333) Euros
Cohabitation Status (% Married or cohabitating)	88	93
Maternal anxiety[a]	17.0 (5.0)	3.68 (5.27)
Maternal Depressive symptoms[a]	4.4 (4.6)	5.20 (5.11)
Child Sex (% female)	47.4	49.6
Entropy Rate (mean)	0.82 (0.16)	0.88 (0.17)
Effortful Control 1 yr.	4.8 (0.62)	5.06 (0.67)
Effortful Control 2 yrs.	N/A	4.99 (0.57)
Effortful Control 5 yrs.	5.2 (0.6)	N/A
Effortful Control 9.5 yrs.	3.4 (5)[b]	N/A
Flanker Task	76.7% (22.7)	N/A

[a] Maternal anxiety was evaluated with the STAI and maternal depressive symptoms with the EPDS in the Irvine Cohort. In the Turku cohort maternal anxiety was evaluated with the SCL anxiety scale and maternal depressive symptoms with the EPDS scale. For details on these measures see the Methods.

[b] The Likert scale is 1–5 at 9 years and 1–7 at all other ages-based on validated versions of these measures. Data were standardized within each age for all analyses.

2.2. Measuring the degree of unpredictability of maternal sensory signals

Coding maternal sensory signals. The degree of unpredictability of maternal sensory signals was quantified using the entropy rate of a sequence of behavioral observations derived from behavioral coding of a play interaction of mother and child as previously described (see [16]). Briefly, mothers were video-recorded interacting with their infants in a semi-structured 10-min play episode at 6 months and 1 year 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 infants as they would at home. Maternal behaviors that provide auditory, visual, or tactile sensory signals to the child were coded *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. Additional information on the details of behavioral coding, including the training manual are found in [16] and at https://contecenter.uci.edu/shared-resources.

Quantifying unpredictability of maternal sensory signals (entropy rate). Identical procedures were used in the two cohorts to quantify the extent to which sequences of maternal sensory signals were unpredictable, as described in Davis et al., 2017 [16]. Our approach focused on the conditional probabilities of transitioning between different combinations of maternal visual, auditory and tactile sensory signals, considering 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 were modeled as changes in the state of a discrete-state Markov process and the entropy rate of the process was taken as a measure of unpredictability. Notably, the use of alternative Markov chain models (2nd order and 3rd order), as well as a non-parametric approaches based on theoretical results relating data compression to entropy, led to highly consistent results (Spearman's rank correlations for the resulting entropy measures ranged from 0.91 to 0.98) [28]. We therefore used the entropy rate of a sequence of behaviors as a measure of how random or uncertain a mother's next behavior would appear to an observer (including her infant) who was making a guess based on the most recently observed behavior. If one behavior always followed another (e.g., speech was always followed by touch), than this would be highly predictable and there would be little uncertainty for the observer (low entropy rate). In contrast, if the likelihood of one behavior following another is random than this would be unpredictable (high entropy rate). Entropy rate can vary between a minimum value of zero, when a process is perfectly predictable, to a maximum value of 2.807 (the logarithm (base two) of the number of possible transitions (7) of sensory signals at each step), 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., 2017 [16] and available at https://contecenter.uci.edu/shared-resources/.

2.3. Measuring effortful control in children

2.3.1. Maternal report

The infant and child temperament questionnaires employed in this investigation were selected as developmentally and age appropriate measures designed to evaluate individual differences in effortful control throughout infancy and childhood. The authors created age appropriate versions of this temperament measure for each of the ages assessed in this study. Each version was designed to measure the same underlying temperament construct at different ages [29].

Infant assessment: Child Orienting/Regulation, as a precursor to effortful control, was assessed at one year of age in both the Irvine and Turku Cohorts using the 60-item Orienting/Regulation scale of the Infant Behavior Questionnaire - Revised (IBQ-R) [29]. This measure has been used extensively in developmental research and items probe infant responses to specific and frequently occurring situations to reduce observer bias. The IBQ-R psychometric properties provide evidence of the instrument's reliability and validity [29]. The Orientating/Regulation scale assesses regulatory functions that are consistent with the development of executive function [30]. There are shifts in regulatory function from infancy through childhood and thus, the infant scales assess early components (or precursors) to the development of more mature executive function abilities during childhood [29].

Childhood assessments: During childhood as frontal regions involved in executive function mature, the ability to engage in effortful regulation of attention and behavior increase. The temperament questionnaires employed probe effortful control abilities with age appropriate items [18]. Child effortful control was measured at 2 years with the 32-item Effortful Control scale of the Early Childhood Behavior Questionnaire – Revised (ECBQ-R) in the Turku cohort [18]. At 5 years, the 60-item Effortful Control scale of the Children's Behavior Questionnaire (CBQ) was employed (in the Irvine Cohort), and at 9.5 years we used the 48-item Effortful Control scale of the Temperament in Early Childhood Questionnaire (TMCQ; also in the Irvine Cohort).

Similar to the IBQ, these instruments (ECBQ, 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. Prior research suggests that these scales exhibit good internal reliability and validity [29,31], consistency between parent report and home and laboratory observations [32,33], as well as good stability over time [18]. Indeed, in our study effortful control was correlated over time with moderate stability from infancy to childhood [Irvine Cohort (r(age 1, age 5) = 0.28, r(age 1, age 9.5) = 0.39, Turku Cohort (r(age 1, age 2) = 0.56] and a high degree of stability within childhood [r(age 5, age 9.5) = 0.71)]; all of these were statistically significant ($p < .01$).

2.3.2. Direct behavioral evaluation

Child effortful control was assessed at 6.5 years using the Flanker task [34]. 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 5000 ms) 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 at age 6.5 years was associated with maternal report of effortful control at ages 5 ($r = 0.21$) and 9.5 years ($r = 0.37$), but not at 1 year ($r = -0.02$).

2.3.3. Assessment of maternal mental health

Maternal symptoms of anxiety and depression were assessed in both cohorts during the postnatal period when patterns of maternal behavior were assessed. In the Irvine cohort, the EPDS and the State Anxiety Inventory (STAI) were administered at 6 and 12 months. Scores were highly correlated ($r = 0.80$, $p < .01$) for the EPDS and STAI and thus were averaged to create an index of maternal mental health. In the Turku cohort, SCL and EPDS scores at 6 months were highly correlated ($r = 0.68$, $p < .01$) and an average score for the index of maternal health was used in the analyses.

2.4. Analysis plan

For all outcome measures our analysis strategy initially considered associations without adjusting for covariates. Next, linear model analyses with covariates (as discussed below) were used to investigate the contribution of unpredictability to effortful control after covarying for other risk factors. A priori power analyses for the Irvine Cohort suggested that entropy rate was associated with an increase in the proportion of explained variance for cognitive scores from 0.29 to 0.32. The sample size of the Irvine Cohort ($N = 192$) provides power 0.80 to detect the effect. The validation/replication Turku Cohort required a smaller sample size ($N = 135$).

2.4.1. Covariates and possible confounding factors

Several factors that might influence maternal behaviors based on the prior literature were investigated as covariates. *These factors include* maternal mental health (anxiety and depression), maternal age, maternal marital status, race/ethnicity, education and income. Additional factors such as sex have been shown to be related to a child's effortful control. Covariates that were significantly associated with unpredictability or effortful control (see supplement Tables 1 and 2) were included in the linear regression analyses described below. In the Irvine cohort, mothers with higher psychological distress (i.e., depression and anxiety symptoms), lower household income, lower education, not married or cohabitating and younger age, provided more unpredictable sensory signals to their infants. Consistent sex differences also were observed in effortful control, and maternal age, income and education were related to this measure (supplement Tables 1 and 2). In the Turku Cohort, younger mothers and mothers with lower income provided more unpredictable sensory signals to their infants. In this cohort, maternal psychological distress was related to effortful control (supplement Table 1). Income and education were highly correlated ($r > 0.6$); therefore, to reduce issues related to co-linearity we included income in the final model. These final regression models for both cohorts thus tested covariates evaluating sociodemographic (income and maternal age), maternal psychological distress (depression and anxiety) and child (sex) factors.

2.4.2. Relating degree of unpredictability of maternal sensory signals to effortful control in children

Unpredictability and effortful control at 1 year of age. Pearson correlations were used to assess the bivariate relation between unpredictability of maternal sensory signals (entropy rate), and child effortful control.

2.4.3. Unpredictability of maternal sensory signals and effortful control longitudinal analysis

The relation between unpredictable maternal sensory signals and effortful control across infancy and childhood was assessed using a mixed linear model [35] treating effortful control as the dependent variable. In the Irvine cohort, to include all three time points (1 year, 5 years and 9.5 years) in a single analysis we first z-transformed each effortful control score within time point (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 unpredictability (entropy rate). A similar model was used in the Turku Cohort with effortful control assessed at ages 1 and 2 years. The effortful control scores were similarly z-transformed within each age. The independent variables included in the model were time period (age 1 served as the reference group and indicator for the age 2 measurement), sex (female = 0, male = 1), and unpredictability (entropy rate). The correlation resulting from having repeated observations of the same individuals was addressed through incorporation of random intercepts for individuals. The mixed models were fit using the lme4 package [36] in the R statistical computing environment [37]. Longitudinal analyses were repeated with the inclusion of covariates as described above.

Unpredictability of maternal sensory signals and effortful control Flanker task. First, Pearson correlations were used to assess the strength of the relation between unpredictability of sensory signals (entropy rate) and performance on the Flanker task. Next, regression analyses were implemented to test the relation between predictability and the Flanker task after consideration of covariates as described above.

2.5. Role of the funding source

Study funding sources had no influence on study design, on the collection, analysis, and interpretation of data, on the writing of the report or in the decision to submit the paper for publication.

3. Results

Unpredictability of maternal signals and effortful control at 1 year of age. In both the Irvine and Finnish Cohorts, bivariate correlations revealed that unpredictable maternal sensory signals (higher entropy rate) were associated with low effortful control in infancy (Turku: $r = -0.28$, $p < .01$; Irvine: $r = -0.16$, $p = .04$). Fig. 2 illustrates the distribution of all data points.

Unpredictability of maternal signals and effortful control - longitudinal analysis. The results of a mixed linear model analysis that incorporated the longitudinal data in each cohort demonstrated that infant exposure to unpredictable maternal sensory signals was associated with poor effortful control using data from infancy and childhood (1 year to 9.5 years in Irvine Cohort and 1 year to 2 years in the Turku Cohort; see Table 2A). Boys in both cohorts exhibited lower effortful control than girls. The sex effect was statistically significant in the Irvine cohort ($p < .01$); it trended in the same direction ($p = .14$) in the Turku Cohort (see Table 2A).

Unpredictability of maternal signals and effortful control - Flanker task. Exposure to unpredictable maternal sensory signals (high entropy rate) was associated with poor effortful control on the Flanker task at 6.5 years of age ($r = -0.34$, $p < .01$).

Including this direct assessment, Fig. 3 illustrates that the relation between unpredictable sensory signals and effortful control in the Irvine Cohort persisted longitudinally throughout the four ages.

Consideration of confounding factors. As described in detail in the Methods section, we evaluated the consequences of unpredictability on effortful control at all ages after co-varying potential confounding factors. Focusing initially on socio-demographic factors that were related to unpredictable maternal signals (entropy rate) or effortful control, we examined income and maternal age. When these were included as covariates the association between unpredictability of maternal signals and report of effortful control remained at the level of a trend ($p = .08$) in the Irvine Cohort and remained significant ($p < .01$) in the Turku Cohort (see Table 2B for results of the mixed linear model). Similarly, the relation between unpredictability of maternal signals and effortful control assessed with the Flanker task in the Irvine Cohort remained significant after co-varying household income and maternal age ($\beta = -0.27$, $t = -2.5$, $p = .01$). Next, we evaluated maternal psychological distress. In both cohorts the association between unpredictability of maternal signals and child effortful control remained significant (Irvine $p = .04$; Turku $p = .02$) when maternal psychological distress was incorporated in the mixed linear model (Table 2C). Similarly, the relation between unpredictability of maternal signals and effortful control assessed with the Flanker task remained significant after co-varying maternal distress ($\beta = -0.33$, $t = -3.0$, $p < .01$). Thus, in cohorts from California, USA, and Turku, Finland, unpredictable sequences of maternal behavior towards her infant were associated with a reduction in executive function in her child, even after consideration of socio-demographic factors and maternal mental health (anxiety and depressive symptoms).

4. Discussion

There are two key findings of this series of studies. First, in two prospective and longitudinal cohorts, one from Turku, Finland and the other from Irvine, California, infant exposure to unpredictable maternal sensory signals predicted poor effortful control. In the Irvine Cohort in which data was available through 9.5 years, this association persisted through childhood. Second, in both populations, the association between unpredictability of maternal signals persisted after covarying maternal mental health and other potential contributing factors such as socioeconomic status and sex of the child. Thus, unpredictable patterns of maternal signals may predict a crucial measure of executive function, effortful control, which contributes to mental health throughout life [17]. Importantly, the demonstration of this association in two different populations on different continents, with varying cultural and demographic characteristics increases confidence in the findings and attests to the importance of unpredictable sequences of maternal-derived signals to her infant in relation to development of executive functions.

Decades of empirical research have documented the importance of quality and quantity of maternal care, including dyadic synchrony, in shaping child development [4,5,7]. Here we added a novel parameter of maternal care that influences infant development: patterns. We applied an analytic method from information theory, entropy rate [38], where unpredictable sequences of maternal sensory signals to the infant are characterized by high entropy rate [16], and demonstrated that unpredictability of maternal sensory signals to the infant contributed to measures of executive function across infancy and childhood, even after accounting for maternal mental health and socioeconomic factors in two cohorts.

The theoretical basis of the impact of unpredictable patterns on executive function derives from our evolving understanding of the maturation of brain circuits that execute complex behavior. Sensory signals early in life are critical for the maturation of sensory brain circuits

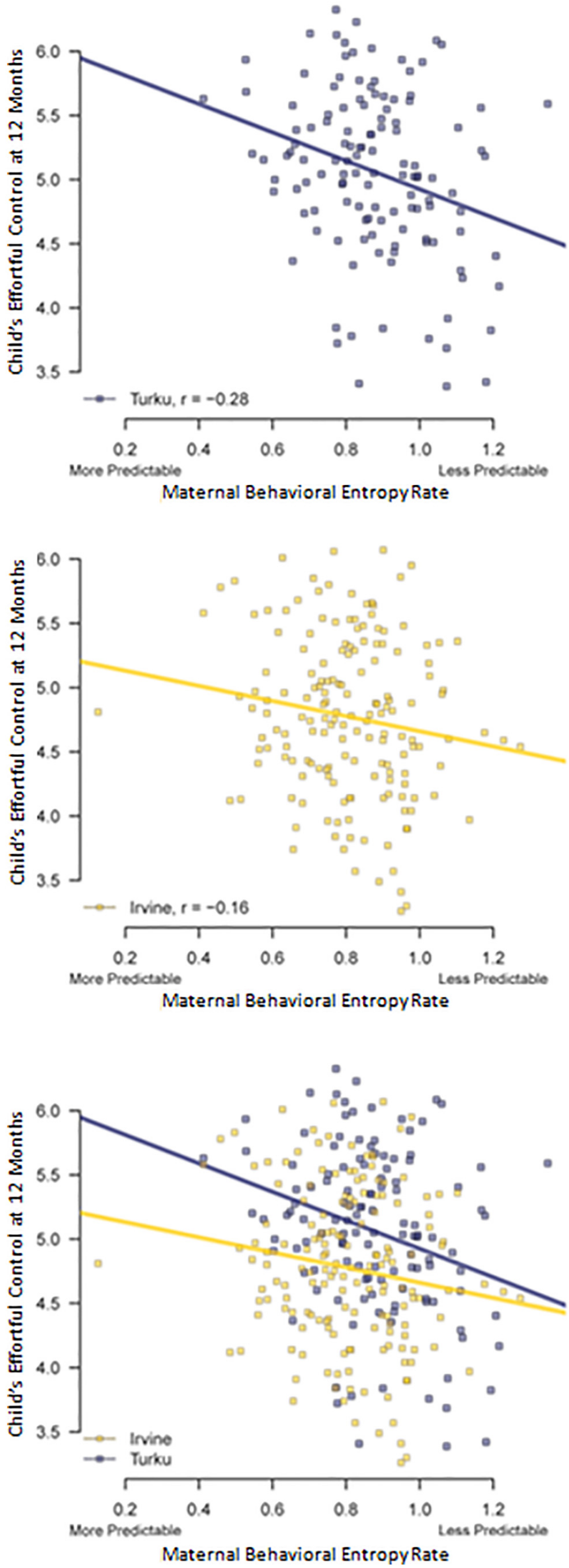

Table 2A
Results of mixed linear model for effortful control in Irvine and in Turku cohorts.

Irvine cohort				Turku cohort			
Parameter	Estimate	Std. Error	p	Parameter	Estimate	Std. Error	p
Intercept	0.95	0.31	.02	Intercept	1.173	0.42	.006
Age 1 year (reference)	–			Age 1 year (reference)	–		
Age 5 years	−0.02	0.09	.84	Age 2 years	0.02	0.09	.81
Age 9.5 years	0.02	0.09	.82				
Sex (1 = M; 0 = F)	−0.41	0.12	.0005	Sex (1 = M; 0 = F)	−0.23	0.15	.14
Entropy Rate	−0.90	0.376	.01	Entropy Rate	−1.20	0.47	.01

[10,11,39]. For example, the requirement of patterned signals for refinement of auditory circuits has been demonstrated [12]. Recent information indicates that patterned signals from the environment and the generation of patterned neuronal activity also critically influence the maturation of association/high-order brain networks in experimental rodent research [40]. In experimental systems, environmental signals modulate circuit formation and refinement via activity-dependent strengthening of engaged synapses and pruning of others [41-43]. Unpredictable patterns similarly influence human behavior [44]. Here we posit that patterns of maternal behavior also may influence maturation of the brain circuits involved in executive functions, such as effortful control.

Executive functions, including effortful control, evolve with age and are executed by specific brain circuits [45,46]. These involve long-range associations of several regions of the prefrontal cortex (mPFC), including both medial and especially dorsal mPFC, with subcortical regions [47,48]. In analogy to behavioral studies demonstrating the evolution of effortful control in children and adolescents, functional MRI work has delineated the protracted maturation of the long-range effortful control pathways, and comparative studies have identified correlations between behavioral and imaging maturation [45]. Thus, in infants and young children, brain networks typically consist of short connections among neighboring regions [49,50]. In contrast, the long-range connections underlying aspects of effortful control, including the executive attention network, which includes the anterior cingulate cortex and adjacent mPFC, remain immature until young adulthood [51]. The present findings may indicate that early-life exposure to unpredictable signals impacts these brain networks resulting in the observed associations with effortful control.

The studies described here involved humans, where it is difficult to completely rule out alternative explanations. For example, genetics is difficult to control in human studies and a mother's genes both drive her behavior and are transmitted to the infant impacting development. Another factor that may have contributed to study findings are aspects of infant behavior and temperament that might influence maternal behavior patterns. Whereas these factors are difficult to experimentally manipulate in the human, they can be addressed in experimental animal models. In the controllable experimental animal system, we have minimized the effects of genetic and of infant contribution by mixing pups from several litters and randomly distributing them to dams. Then, dams were randomly assigned to typical cages or to those promoting unpredictable behaviors. Thus, any genetic effects of the dam or pups as well as intrinsic pup-generated influences are minimized. In these conditions, we have identified a striking influence of unpredictability and fragmentation of maternal behaviors on cognitive outcome in the pups, with deficits that persist to adulthood and middle age [16,52]; a finding that has been replicated extensively [53,54].

Fig. 2. Early-life exposure to unpredictable maternal sensory signals (high entropy rate) is associated with lower effortful control in 2 distinct prospective cohorts, in Turku, Finland (blue) and in Irvine, California (gold).

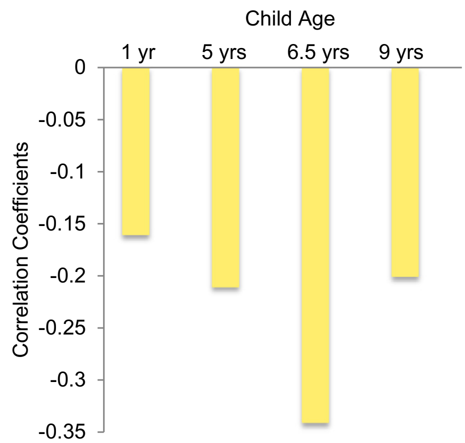

Fig. 3. Bivariate correlations between unpredictable maternal sensory signals and child effortful control illustrate that the relation between unpredictable maternal sensory signals and effortful control persists through 9.5 years of age.

Table 2B
Results of mixed linear model for effortful control with sociodemographic covariates in Irvine and in Turku cohorts.

Irvine cohort				Turku Cohort			
Parameter	Estimate	Std. Error	p	Parameter	Estimate	Std. Error	p
Intercept	0.74	0.31	.02	Intercept	1.06	0.79	.19
Age 1 year (reference)	–			Age 1 year (reference)	–		
Age 5 years	0.02	0.09	.83	Age 2 years	0.02	0.09	.81
Age 9.5 years	0.01	0.09	.87				
Sex (1 = M; 0 = F)	−0.42	0.12	.0003	Sex (1 = M; 0 = F)	−0.23	0.15	.14
Entropy Rate	−0.65	0.38	.08	Entropy Rate	−1.20	0.548	.01
Income	0.07	0.07	.29	Income	0.002	0.06	.97
Maternal Age	0.12	0.07	.08	Maternal Age	0.004	0.02	.86

Table 2C
Results of mixed linear model for effortful control with maternal psychological distress as a covariate.

Irvine cohort				Turku cohort			
Parameter	Estimate	Std. Error	p	Parameter	Estimate	Std. Error	p
Intercept	0.77	0.29	.01	Intercept	1.05	0.43	.02
Age 1 year (reference)	–			Age 1 year (reference)	–		
Age 5 years	0.03	0.09	.74	Age 2 years	0.02	0.09	.82
Age 9.5 years	0.02	0.09	.81				
Sex (1 = M; 0 = F)	−0.44	0.11	.0005	Sex (1 = M; 0 = F)	−0.19	0.15	.23
Entropy Rate	−0.71	0.35	.04	Entropy Rate	−1.09	0.47	.02
Maternal Psychological Distress	−0.26	0.06	.0001	Maternal Psychological Distress	−0.16	0.09	.07

The animal studies enable assessment of causality as well as of mechanisms. There is now evidence from cross species research that unpredictability of maternal signals influence the maturation of brain circuits involved in cognition (e.g., memory) in rats [53] and cognitive function (memory) in both rats and human children [16]. The current work demonstrates that the association of unpredictability of maternal signals and measures of cognitive function may also be important in human populations. For example, in the Turku sample all women were on paid parental leave, likely accounting for the smaller association between income and unpredictability as compared to the Irvine sample. However, in both samples, the association between unpredictability and effortful control was present and remained after covarying income.

In summary, the present findings provide cross-cultural evidence that early life exposure to unpredictability is an important influence on child development and adds significant variance to the prediction of outcomes beyond established factors.

Acknowledgements

This research was supported by the National Institutes of Health (NIH) awards P50 MH096889, R01 HD051852, R01 NS041298, R01 HD02413, R01 HD050662, R01 HD065823, and FinnBrain funders: Academy of Finland (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).

Author contributions

E.P.D., L.M.G., C.A.S., H.S., R.K., L.K., H.K. and T.Z.B. designed research; E.P.D., L.M.G., C.A.S., R.K., E.L.K, S.N., E.S., L.K. performed the research; B.V. and H.S. contributed new analytic tools; E.P.D., B.V., R.K., J.P. and H.S. analyzed data; and E.P.D., H.S., and T.Z.B. wrote the paper, and all authors provided critical evaluation of the manuscript.

Declaration of Competing Interest

Authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebiom.2019.07.025.

References

[1] Bale TL, Baram TZ, Brown AS, Goldstein JM, Insel TR, McCarthy MM, et al. Early life programming and neurodevelopmental disorders. Biol Psychiatry 2010;68(4):314–9.
[2] Russo SJ, Murrough JW, Han M, Charney DS, Nestler EJ. Neurobiology of resilience. Nat Neurosci 2012;15(11):1475.
[3] Sandi CH, Stress J. The social brain: behavioural effects and neurobiological mechanisms. Nature Reviews Neuroscience 2015;16(5):290.
[4] Bowlby J. Research into the origins of deliquent behaviour. Br Med J 1950;1:570–3.
[5] Landers MS, Sullivan RM. The development and neurobiology of infant attachment and fear. Dev Neurosci 2012;34(2–3):101–14.
[6] Tang AC, Reeb-Sutherland BC, Romeo RD, McEwen BS. On the causes of early life experience effects: evaluating the role of mom. Front Neuroendocrinol 2014;35(2):245–51.
[7] Ainsworth MDS, Blehar MC, Waters E, Wall S. Patterns of Attachment. A Psychological Study of the Strange Situation. Hillsdale: Earlbaum; 1978.
[8] Beebe B, Messinger D, Bahrick LE, Margolis A, Buck KA, Chen H. A systems view of mother-infant face-to-face communication. Dev Psychol 2016;52(4):556–71.
[9] Feldman R. 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 2015;27(4 Pt 1):1007–23.
[10] Espinosa JS, Stryker MP. Development and plasticity of the primary visual cortex. Neuron 2012;75(2):230–49.
[11] Khazipov R, Sirota A, Leinekugel X, Holmes GL, Ben-Ari Y, Buzsaki G. Early motor activity drives spindle bursts in the developing somatosensory cortex. Nature 2004;432(7018):758–61.
[12] Takesian AE, Bogart LJ, Lichtman JW, Hensch TK. Inhibitory circuit gating of auditory critical-period plasticity. Nat Neurosci 2018;21(2):218–27.
[13] Baram TZ, Davis EP, Obenaus A, Sandman CA, Small SL, Solodkin A, et al. Fragmentation and unpredictability of early-life experience in mental disorders. Am J Psychiatry 2012;169(9):907–15.
[14] Molet J, Heins K, Zhuo X, Mei YT, Regev L, Baram TZ, et al. Fragmentation and high entropy of neonatal experience predict adolescent emotional outcome. Transl Psychiatry 2016;6:e702.
[15] Bolton JL, Molet J, Regev L, Chen Y, Rismanchi N, Haddad E, et al. Anhedonia following early-life adversity involves aberrant interaction of reward and anxiety circuits and is reversed by partial silencing of amygdala corticotropin-releasing hormone gene. Biol Psychiatry 2018;83(2):137–47.

[16] Davis EP, Stout SA, Molet J, Vegetabile B, Glynn LM, Sandman CA, et al. Exposure to unpredictable maternal sensory signals influences cognitive development across species. Proc Natl Acad Sci 2017;114(39):10390–5.
[17] Moffitt TE, Arseneault L, Belsky D, Dickson N, Hancox RJ, Harrington H, et al. A gradient of childhood self-control predicts health, wealth, and public safety. Proc Natl Acad Sci 2011;108(7):2693–8.
[18] Putnam SP, Gartstein MA, Rothbart MK. Measurements of fine-grained aspects of toddler temperament: The Early Childhood Behavior Questionnaire. Infant Behav Dev 2006;29:386–401.
[19] Rueda MR, Rothbart MK, McCandliss BD, Saccomanno L, Posner MI. Training, maturation, and genetic influences on the development of executive attention. Proc Natl Acad Sci 2005;102(41):14931–6.
[20] Diamond A. The performance of human infants on a measure of frontal cortex function, the delayed response task. Dev Psychobiol 1989;22:271–94.
[21] Choe DE, Olson SL, Sameroff AJ. Effects of early maternal distress and parenting on the development of children's self-regulation and externalizing behavior. Dev Psychopathol 2013;25(2):437–53.
[22] Hankin BL, Snyder HR, Gulley LD. Cognitive risks in developmental psychopathology. In: Cicchetti D, editor. Developmental Psychopathology. Wiley; 2016.
[23] Karlsson L, Tolvanen M, Scheinin NM, Uusitupa H, Korja R, Ekholm E, et al. Cohort profile: the FinnBrain birth cohort study (FinnBrain). Int J Epidemiol 2018;47(1) (15-6j).
[24] Cox JL, Chapman G, Murray D, Jones P. Validation of the Edinburgh Postnatal Depression Scale (EPDS) in non-postnatal women. J Affect Disord 1996;39(3):185–9.
[25] Rubertsson C, Börjesson K, Berglund A, Josefsson A, Sydsjö G. The Swedish validation of Edinburgh Postnatal Depression Scale (EPDS) during pregnancy. Nord J Psychiatry 2011;65(6):414–8.
[26] Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale - preliminary report. Psychopharmacol Bull 1973;9:13–28.
[27] Huizink AC, Delforterie MJ, Scheinin NM, Tolvanen M, Karlsson L, Karlsson H. Adaption of pregnancy anxiety questionnaire–revised for all pregnant women regardless of parity: PRAQ-R2. Arch Womens Ment Health 2016;19(1):125–32.
[28] Vegetabile B, Stout SA, Davis EP, Baram TZ, Stern H. Estimating the entropy rate of finite Markov Chains with application to behavior studies. J Educ Behav Statis 2019;44(3):282–308.
[29] Gartstein MA, Rothbart MK. Studying infant temperament via the revised infant behavior questionnaire. Infant Behav Dev 2003;26(1):64–86.
[30] Posner MI, Rothbart MK. Attention mechanisms and conscious experience. In: Rugg M, Milner AD, editors. The neuropsychology of consciousness. Londun. Academic press; 1991. p. 91–112.
[31] Rothbart MK, Ahadi SA, Hershey KL, Fisher P. Investigations of temperament at three to seven years: The Children's Behavior Questionnaire. Child Dev 2001;72(5): 1394–408.
[32] Rothbart MK, Ahadi SA, Evans DE. Temperament and personality: origins and outcomes. J Pers Soc Psychol 2000;78(1):122–35.
[33] Kochanska G, Murray KT, Jacques TY, Koenig AL, Vandegeest KA. Inhibitory control in young children and its role in emerging internalization. Child Dev 1996;67:490–507.
[34] Eriksen BA, Eriksen CW, Hoffman JE. Recognition memory and attentional selection: serial scanning is not enough. J Exp Psychol Hum Percept Perform 1986;12(4): 476–83.
[35] Fitzmaurice G, Laird L, Ware J. Applied longitudinal data analysis. . 2nd ed.New York: Wiley; 2004.
[36] Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4, 67(1); 2015; 48.
[37] Team RC. R: A language and environment for statistical computing R. Vienna, Austria: Foundation for Statistical Computing; 2017.
[38] Cover TM, Thomas JA. Elements of information theory. . 2nd edition ed.Wiley-Interscience; 2006.
[39] Redish AD, Gordon JA. Computational psychiatry: new perspectives on mental illness. Cambridge, MA: MIT Press; 2016.
[40] Singh-Taylor A, Molet J, Jiang S, Korosi A, Bolton JL, Noam Y, et al. NRSF-dependent epigenetic mechanisms contribute to programming of stress-sensitive neurons by neonatal experience, promoting resilience. Mol Psychiatry 2018;23(3):648–57.
[41] Woo TU, Pucak ML, Kye CH, Matus CV, Lewis DA. Peripubertal refinement of the intrinsic and associational circuitry in monkey prefrontal cortex. Neuroscience 1997; 80(4):1149–58.
[42] Paolicelli RC, Bolasco G, Pagani F, Maggi L, Scianni M, Panzanelli P, et al. Synaptic pruning by microglia is necessary for normal brain development. Science 2011; 333(6048):1456–8.
[43] Schafer DP, Lehrman EK, Kautzman AG, Koyama R, Mardinly AR, Yamasaki R, et al. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. Neuron 2012;74(4):691–705.
[44] Glynn LM, Stern H, Howland VB, Risbrough DG, Baker CM, Nievergelt TZBaram, Davis EP. Measuring novel antecedents of mental illness: The questionnaire of unpredictability in childhood. Neuropsychopharmacology 2019;44(5):876–82.
[45] Casey B. Beyond simple models of self-control to circuit-based accounts of adolescent behavior. Annu Rev Psychol 2015;66:295–319.
[46] Misic B, Sporns O. From regions to connections and networks: new bridges between brain and behavior. Curr Opin Neurobiol 2016;40:1–7.
[47] Duncan J, Emslie H, Williams P, Johnson R, Freer C. Intelligence and the frontal lobe: the organization of goal-directed behavior. Cogn Psychol 1996;30(3):257–303.
[48] Dosenbach NU, Fair DA, Miezin FM, Cohen AL, Wenger KK, Dosenbach RA, et al. Distinct brain networks for adaptive and stable task control in humans. Proc Natl Acad Sci U S A 2007;104(26):11073–8.
[49] Gao W, Gilmore JH, Shen D, Smith JK, Zhu H, Lin W. The synchronization within and interaction between the default and dorsal attention networks in early infancy. Cereb Cortex 2013;23(3):594–603.
[50] Fair DA, Cohen AL, Power JD, Dosenbach NU, Church JA, Miezin FM, et al. Functional brain networks develop from a "local to distributed" organization. PLoS Comput Biol 2009;5(5):e1000381.
[51] Fjell AM, Walhovd KB, Brown TT, Kuperman JM, Chung Y, Hagler Jr DJ, et al. Multimodal imaging of the self-regulating developing brain. Proc Natl Acad Sci U S A 2012;109(48):19620–5.
[52] Brunson KL, Kramar E, Lin B, Chen Y, Colgin LL, Yanagihara TK, et al. Mechanisms of late-onset cognitive decline after early-life stress. J Neurosci 2005;25(41):9328–38.
[53] Molet J, Maras PM, Kinney-Lang E, Harris NG, Rashid F, Ivy AS, et al. MRI uncovers disrupted hippocampal microstructure that underlies memory impairments after early-life adversity. Hippocampus 2016;26(12):1618–32.
[54] Walker CD, Bath KG, Joels M, Korosi A, Larauche M, Lucassen PJ, et al. Chronic early life stress induced by limited bedding and nesting (LBN) material in rodents: critical considerations of methodology, outcomes and translational potential. Stress 2017; 20(5):421–8.