Frontiers in Neuroendocrinology 53 (2019) 100736

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

The influence of unpredictable, fragmented parental signals on the developing brain

Laura M. Glynn[a,*], Tallie Z. Baram[b,c,d]

[a] Department of Psychology, Chapman University, Orange, CA, USA
[b] Department of Anatomy/Neurobiology, University of California-Irvine, Irvine, CA, USA
[c] Department of Pediatrics, University of California-Irvine, Irvine, CA, USA
[d] Department of Neurology, University of California-Irvine, Irvine, CA, USA

ARTICLE INFO

Keywords:
Brain circuits
Maternal care
Entropy
Neurodevelopment
Depression
Anhedonia
Prenatal
Postnatal
Unpredictability
Adversity

ABSTRACT

Mental illnesses originate early in life, governed by environmental and genetic factors. Because parents are a dominant source of signals to the developing child, parental signals - beginning with maternal signals *in utero* - are primary contributors to children's mental health. Existing literature on maternal signals has focused almost exclusively on their quality and valence (e.g. maternal depression, sensitivity). Here we identify a novel dimension of maternal signals: their patterns and especially their predictability/unpredictability, as an important determinant of children's neurodevelopment. We find that unpredictable maternal mood and behavior presage risk for child and adolescent psychopathology. In experimental models, fragmented/unpredictable maternal care patterns directly induce aberrant synaptic connectivity and disturbed maturation of cognitive and emotional brain circuits, with commensurate memory problems and anhedonia-like behaviors. Together, our findings across species demonstrate that patterns of maternal signals influence brain circuit maturation, promoting resilience or vulnerability to mental illness.

1. Introduction: Why parental (especially maternal) signals?

Parental care (particularly that from the mother) is a primary determinant of child survival in humans (Pavard et al., 2005; Sear et al., 2002; Willführ and Gagnon, 2013); so central is this care for the survival of the species, some have argued that the development of parental behavior may be one of the primary forces shaping the evolution of the mammalian brain (c.f. Hrdy, 2000; MacLean, 1990). Sensitive periods in early life largely overlap with developmental stages in which the child is dependent on the mother, thus providing a pathway through which maternal signals shape development (Kuzawa and Quinn, 2009). Not only does the mother facilitate the survival of her young through the provisioning of sustenance and protection, but beginning in the prenatal period, maternal signals influence the developing brain, shaping its maturation, with implications for the child's future cognitive and emotional function and trajectory of health or disease. Thus, the influence of maternal signals prenatally and postnatally on numerous aspects of brain development has far-reaching implications for mental health.

2. What maternal signals are salient to brain maturation? Current knowledge and novel principles

A robust empirical literature indicates that pre and postnatal maternal behaviors and emotional states are important determinants of risk for psychiatric disease. For example, building on the foundational work of Bowlby (1950), the importance of a secure attachment relationship, which is scaffolded by sensitive maternal behavior, has widespread implications for cognitive and emotional development (Belsky and Fearon, 2002; Masur et al., 2005; NICHD ECCRN, 1999a, 1999b, 2003, 2006; Hane et al., 2010; Feldman, 2007, 2015). Similarly, the profound adverse consequences of a lack of maternal care, and exposures to maternal depression during the pre and postnatal periods are well-established (Goodman, 2007; Gunnar, 2010; Murray et al., 2011; Dawson et al., 2003; Feldman et al., 2009; Halligan et al., 2004; Beck, 1998; Verbeek et al., 2012; Nelson et al., 2007). The documented effects on mental health are associated with altered maturation of neural circuits, which persists until adulthood (Soe et al., 2018; Wen et al., 2017; Lebel et al., 2016; Posner et al., 2016; Sandman et al., 2015). The accumulating evidence relating maternal behavior and psychological distress during the pre and postnatal periods to risk for

* Corresponding author at: Department of Psychology, Chapman University, One University Dr., Orange, CA 92866, USA.
E-mail address: lglynn@chapman.edu (L.M. Glynn).

https://doi.org/10.1016/j.yfrne.2019.01.002
Received 5 September 2018; Received in revised form 4 January 2019; Accepted 29 January 2019
Available online 31 January 2019
0091-3022/

mental health disorders demands the identification of specific components of maternal signals that shape the developing brain. Whereas a clearly identified role for valence of maternal signals- empathy, sensitivity, availability, etc., has been established as described above, recent work in both humans and animal models highlights the importance of *patterns* of maternal-derived cues to the developing brain in shaping the maturation of brain circuits (Davis et al., 2017; Baram et al., 2012; Molet et al., 2016a, 2016b; Evans et al., 2005).

Thus, in addition to the well-established roles of maternal mood levels and sensitive maternal behavior, patterns of maternal signals seem to influence the maturation and organization of brain circuitries. Notably, in both rodent models and humans, the effects of patterns and especially of unpredictable, fragmented maternal signals on brain and behavior appear to be additional to *the quantity and quality of the same signals*, underscoring the importance of *patterns*. *Below we will illustrate these principles by describing new findings in human and experimental model studies, and* propose that unpredictable, fragmented signals from the mother (FRAG) represent a critical influence on the developing brain with implications for mental health outcomes (Baram et al., 2012; Glynn et al., 2018a; Risbrough et al., 2018).

Our work with humans, presented in the following paragraphs, has focused on patterns of maternal inputs in two domains: maternal behavior and maternal mood. We find that aberrant patterns of these domains influence cognitive and emotional maturation including memory, self-control and risk for internalizing disorders in children (Glynn et al., 2018b; Davis et al., 2017). Emerging information suggests that the mechanisms involved in such behavioral phenotypes include aberrant maturation of the underlying brain circuits (Kopala-Sibley et al., 2018; Bolton et al., 2018a; Molet et al., 2016b; Fareri et al., 2017).

2.1. Patterns of maternal behavior and their fragmentation and unpredictability (Sensory FRAG)

Mental and cognitive capabilities are a result of the development and maturation of underlying brain circuits. These, built of neurons and neuronal ensembles connected via synapses perform the complex computational tasks underlying specific brain functions including memory, decision making, and emotion regulation. During development, these circuits are immature, and certain synaptic connections formed early are strengthened to become permanent whereas others are eliminated. In sensory circuits such as vision and hearing, important neurobiological principles have been established demonstrating the role of modality-specific patterns of sensory signals are required for the maturation of the circuit. Lack of sensory signals (e.g., sight) or aberrant sensory patterns (auditory) during sensitive developmental periods disrupt the sculpting and maturation of visual, somatosensory and auditory brain circuits, with commensurate functional deficits (Espinosa and Stryker, 2012; Khazipov et al., 2004; Singh-Taylor et al., 2015; Wiesel and Hubel, 1963; Hackett et al., 2011). However, it is not known whether analogous sensory signals and their patterns are important for the maturation of cognitive and emotional brain circuits. Because the dominant sensory signals to the developing organism are generated by the mother, and because maternal care per se has been shown as critical for neurodevelopmental outcomes, we tested the hypothesis that patterns of maternal-derived signals might influence the maturation of brain circuits underlying cognitive functions such as memory and related circuits underlying pleasure reward and affective functioning.

To characterize patterns of sensory signals to the developing human infant, we applied a unique behavioral coding scheme to observations of mothers interacting with their infants in a prospective longitudinal cohort. Briefly, mothers were video-recorded interacting with their infants in a semi-structured 10-minute play episode in which they were given a standard set of age-appropriate toys and are instructed to play with their infant as they would at home (Davis et al., 2017). Using the Observer XT (Noldus Information Technology, 2008), maternal sensory signals were characterized in three domains: auditory (all maternal vocalizations, e.g., laughing, talking), tactile (all instances of physical contact, e.g. holding, touch) and visual (maternal manipulation of a toy or object while the infant was visually attending, Davis et al., 2017). Rather than coding these interactions for quality or valence (e.g. positive versus negative regard or sensitive versus intrusive), we classified the behaviors by sensory modality (auditory tactile, visual), coding behaviors in these three domains continuously in real time. We then analyzed the patterns of these behaviors, which allows the determination of whether for a given mother if specific patterns recur (e.g., holding a toy then smiling then putting the toy down) and the degree to which the patterns are random or unpredictable. The sequence of behaviors for each mother can be summarized by considering how often specific *transitions* occur; e.g., how many times touch is followed by speaking or speaking is following by concurrent touch and visual inputs. This summary index, termed sensory FRAG, is derived as follows: we focused on the conditional probabilities of transitioning between the visual, auditory and tactile signals. Predictability of a given transition from one behavior to another was examined considering all of the possible permutations, and quantified through an entropy rate (Vegetabile et al., in press). The entropy rate measures the randomness and unpredictability of the distribution of transitions with higher values indicating less predictable maternal signals (i.e., more sensory FRAG).

An initial examination of unpredictable maternal behavior was conducted in a prospective longitudinal study of 128 mother–child pairs in which sensory FRAG was assessed at 1-year year and cognitive development through six years of age (Davis et al., 2017). Children who were exposed to higher sensory FRAG during the first year of life exhibited less optimal cognitive development at 2-years of age ($r = -0.34$; $p < .01$) and evidence of poorer performance on a hippocampus-dependent memory task at 6 years of age ($r = -0.27$; $p < .05$). Importantly, these associations were independent of the quantity of sensory signals (i.e., the number of transitions) and persisted after consideration of possible third variable explanations including: maternal sensitivity, postpartum depression, duration of breastfeeding and family socioeconomic status. Additional analyses tested the hypothesis that sensory FRAG might partially mediate the relation between a more global observational measure of quality of maternal care (the widely used assessment of maternal sensitivity developed by the NICHD Study of Early Child Care and Youth Development (NICHD ECCRN, 1999a). These analyses revealed that sensory FRAG might partially mediate the relation between maternal sensitivity and child cognitive function. Taken together, our findings provide evidence that predictability of maternal sensory signals evaluated on short time scales is associated with cognitive development and raise the possibility that sensory FRAG might also represent a more proximal process by which some previously established indicators of quality of maternal care may shape development.

2.2. Patterns of maternal mood (Mood FRAG)

The valence of maternal mood (e.g. depression), is clearly a critical determinant of children's mental health. However, it is likely that variability or unpredictability of maternal mood influences children's emotional and cognitive development, in addition to the effects of mood levels. Therefore, we have begun to examine patterns or predictability of maternal mood. Additional support for the premise of this approach is derived from work in the fields of emotion and personality psychology emphasizing the importance of intra-individual variability in mood (independent from level or valence) as a central component of affective experience (Wessman and Ricks, 1966; Larsen and Diener, 1987; Mischel and Shoda, 1995; Fiske and Rice, 1955) and from documented links between mood variability and mental health (Depue et al., 1981; Bonsall et al., 2012; Kuppens et al., 2007; Thompson, Berenbaum, and Bredemeier, 2011). Interestingly, despite increasing interest in the role of emotion regulation and patterns of mood for

mental health (c.f. Aldao et al., 2010; Fernandez et al., 2016; Kring and Sloan, 2010), the potential impact of this domain of maternal affective function and hence signals to her child—on cognitive and emotional development has received little attention.

When studying emotion dynamics it is possible to examine patterns over time (e.g. across days or weeks) or to focus on the dynamics at a single point in time, capturing a snapshot of emotional experience (Kuppens and Verduyn, 2015). We chose the latter approach and quantified fragmentation and unpredictability of the item-by-item responses to standardized assessments of mood states (mood FRAG). Specifically, our measure of mood FRAG comprises an application of Shannon's entropy to the distribution of responses on mood questionnaires (Cover and Thomas, 2006). The responses at a single assessment of mood states (e.g. the Center for Epidemiologic Studies Depression Scale or the Profile of Mood States) were tabulated over the items within each scale into probability distributions based on the relative frequency of each response choice, and these distributions represent empirical estimates of the propensity of a participant to respond across items in a consistent way. In this sense, mood FRAG quantifies the degree of predictability or unpredictability of the item-specific response, with higher values denoting less predictability. As shown in Table 1, a participant who generally reports "never worried" or "always secure" on a state anxiety scale, for example, would be considered very predictable and thus have a very low entropy score (low mood FRAG), whereas a participant who completes the anxiety items entirely at random would have a very high entropy score (high mood FRAG). We have tested the convergent validity of mood FRAG by examining its association with affective instability, a time-based, momentary measure of mood variability. Importantly, we have shown that the measure of mood FRAG is positively associated with variability in mood as assessed in real time across hours and days with the use of ecological momentary assessments ($r = 0.42$; $p < .01$; Glynn et al., 2018b).

Employing this instrument, we examined the predictive utility of the mood FRAG index in two independent, prospectively studied cohorts of mothers and children (N's = 227 and 180, Glynn et al., 2018b). Risk for internalizing disorders was assessed by maternal report of fearful temperament (a prodromal risk factor for the development of internalizing disorders) at 1, 2 and 7 years and by child report of his or her own anxiety symptoms at 10 years of age and depressive symptoms at 13 years of age. Higher prenatal maternal mood FRAG predicted increased child negative affectivity at 12-months ($r = 0.36$; $p < .01$).

Table 1
Item responses for three hypothetical respondents on a standardized mood scale demonstrating the concept of mood FRAG.

	1	2	3	4	5	6	7	8	9	10
Participant 1	a	a	a	a	a	a	a	a	a	a
Participant 2	b	a	a	c	b	a	b	d	c	c
Participant 3	d	c	c	d	d	d	d	c	d	c

Note: Suppose that a mood scale has a set of possible responses given by the letters a, b, c and d. This table shows simulated outcomes for three hypothetical respondents on such a scale. These participant responses are tabulated over items into probability distributions based on the relative frequency of each choice (i.e., the relative frequency of endorsing a, b, c or d), and we view these distributions as empirical estimates of the propensity of a participant to respond to mood items in a particular way. For example, if this were a state anxiety scale, a respondent who reports "never worried," and "always secure" (similar to Participant 1) may be said to respond particularly consistently across items, while a respondent who reports "never worried", "sometimes calm," and "rarely secure" (similar to Participant 2) responds less consistently. Shannon's entropy of these probability distributions are then calculated for each respondent and normalized to provide an index of mood FRAG. In our hypothetical example, Participant 1 would have a normalized entropy score of 0 (low mood FRAG), Participant 2 would have a normalized entropy score of 0.95 (high mood FRAG) and Participant 3 would be assigned a score of 0.49 (moderate mood FRAG).

The positive association was also observed at 24 months ($r = 0.31$, $p < .01$) and at 7 years of age ($r = 0.32$, $p < .01$). Consistent with these maternal reports, higher prenatal mood FRAG predicted increased child self-report of anxiety symptoms at age 10 ($r = 0.24$, $p < 01$) and depressive symptoms at 13 ($r = 0.29$; $p < .01$). It is important to note that all of these effects persisted *after statistical adjustment for both pre and postnatal mood levels (e.g., depressive symptoms)*, as well as after adjusting for other established indicators of early life adversity including gestational age at birth, socioeconomic status, cohabitation with the child's father. A further point worth underscoring (Glynn et al., 2018b), is that these effects are specific to mood FRAG – we calculated an entropy score from answers given on a non-mood related questionnaire (one related to physical activity) and these entropy scores did not predict child outcomes at any age. Additionally, *both pre and postnatal mood FRAG* were independent and statistically significant predictors of risk for anxiety and depression, suggesting that exposures to mood FRAG in both periods may meaningfully influence emotional development. Thus, in a prospective sample followed for 13 years from pregnancy through early adolescence, unpredictable maternal mood was associated with internalizing problems during infancy and childhood and symptoms of anxiety and depression in adolescence.

The mechanisms through which unpredictable patterns of maternal signals (sensory and mood FRAG) lead to alterations in children's cognitive and emotional phenotypes have yet to be established and these types of mechanistic studies are challenging in human cohorts. An exciting aspect of our findings in infants and children are the robust parallels with observations in controlled experimental systems. In these rodent models, we can design studies that allow detailed probing of both causality and mechanisms, providing a strong translational system in which to further our understanding of the role of early life unpredictability and fragmentation of maternal-derived signals in brain maturation.

3. How do maternal signals influence the developing brain?: insight from experimental models

Brain maturation spans prenatal and early postnatal (infancy) periods, and the sculpting of a number of important brain circuits continues to adulthood. Processes involved in brain circuit-maturation include axonal and dendritic growth, synaptic formation, stabilization and pruning (Garey, 1984; Speh and Moore, 1993; Hoeijmakers et al., 2014; Woo et al., 1997; Maras and Baram, 2012; Neniskyte and Gross, 2017). The perinatal period therefore represents a critical stage of development, rendering the brain particularly vulnerable environmental influences (Chen and Baram, 2016). Environmental signals critically contribute to the evolution of brain circuits. Thus, light and visual patterns, and sound and tones are required for the establishment and refinement of visual and auditory circuits, respectively (Espinosa and Stryker, 2012; Sun et al., 2018). However, the environmental signals that might drive the maturation of 'cognitive' and 'emotional' circuits remain unknown.

In mammals, including humans, monkeys and rodents, maternal input has perhaps the most significant influence on the type of environment experienced during development (Rincon-Cortes and Sullivan, 2014; Baram et al., 2012; Bowlby, 1950; Sanchez et al., 2015; Kundakovic and Champagne, 2015; Seay et al., 1962). The role of parental and especially maternal care in influencing offspring outcome has been a topic of intense study in humans (Gunnar, 2010; Nelson et al., 2007; Heim and Binder, 2012), primates (Drury et al., 2016; Seay et al., 1962) and rodents (Malter Cohen et al., 2013; Raineki et al., 2012; Dalle Molle et al., 2012; Rice et al., 2008; Champagne et al., 2003). Specifically, a compelling existing body of work has linked the presence (Gunnar, 2010; Nelson et al., 2007) and certain features of maternal care (Rilling and Young, 2014) to emotional outcome in both children and rodents. Thus, it is tempting to consider that maternal signals might contribute to the maturation of emotional and cognitive

brain circuits. However, the fundamental properties of maternal signals that are perceived by the developing brain and influence the developing limbic networks to promote advantageous versus pathological outcomes remain enigmatic (Bale et al., 2010; Baram et al., 2012; Champagne et al., 2003; Heim and Binder, 2012; NIMH Workgroup, 2009). Our recent findings in experimental models support a direct causal and relation of maternal signals and their patterns in the maturation of cognitive and emotional brain circuits (Ivy et al., 2010; Molet et al., 2016a, 2016b; Bolton et al., 2018a, 2018b).

We have employed a paradigm rearing mice or rats for one postnatal week in 'simulated poverty', using cages with limited bedding and nesting, and observed both maternal behaviors and the outcomes of the pups (Molet et al., 2014; Molet et al., 2016a; Rice et al., 2008; Ivy et al., 2008). To analyze dam behavior we assessed the durations of maternal nurturing behaviors as well as several qualitative aspects of dam behavior known to influence outcome (Champagne et al., 2003). In addition, we analyzed the patterns and sequences of maternal care and examined their predictability and fragmentation. We employed analyses of entropy rates similar to those reported above for human sensory FRAG.

Surprisingly, the quantity and several typical qualitative measures of maternal nurturing behaviors (e.g. arched-back nursing; Champagne et al., 2003) did not predict emotional outcome in the pups. However, novel analyses of the patterns of maternal behavior revealed that individual nurtuing events were short and fragmented, and the sequences of distinct behaviors were unpredictable in the limited-beding cages (Molet et al., 2016a). These aberrant patterns were quantified using entropy rates as described for human behaviors (Molet et al., 2016a). Notably, these aberrant patterns of maternal caring behaviors- i.e., the major source of sensory input to the pups- led to abnormal emotional outcome in the pups as they reached adolescence Specifically, a reduced capacity to experience pleasure (anhedonia) was observed (Bolton et al., 2018b; Molet et al., 2016a). More recently, aberrant maturation of the pleasure-reward circuitry in these 'graduates' of unpredictable maternal care has been identified (Bolton et al., 2018a). Thus, it appears that at least one crucial brain circuit is directly modulated by the patterns of maternal–origin sensory signals during sensitive early-life periods.

The mechanisms by which environmental signals modulate circuit formation and refinement involve, in part, activity-dependent strengthening of engaged synapses and pruning of others (Woo et al., 1997; Neniskyte and Gross, 2017; Paolicelli et al., 2011; Schafer et al., 2012; Comery et al., 1997). It is not yet known of synaptic development or pruning are affected in the reward circuitry of pups exposed to unpredictable (high entropy) maternal care. Predictable sequences of events engage the dopaminergic reward system (Berns et al., 2001) that is not fully mature until the third postnatal week in rodents (Voorn et al., 1988) and is sensitive to the influence of early-life experiences (Pena et al., 2014; Ventura et al., 2013). Thus, we propose that predictable sensory-signals may be critical for the maturation of these circuits (Singh-Taylor et al., 2015; Singh-Taylor et al., 2018), and unpredictable early-life sensory signals may disrupt these developmental processes, provoking anhedonia (Molet et al., 2016a).

In addition to anhedonia, and congruent with findings described above in children, impaired memory was observed in graduates of the unpredictable maternal behaviors (Ivy et al., 2010; Molet et al., 2016b; Davis et al., 2017), associated with aberrantl maturation of hippocampal/limbic circuit organization (Molet et al., 2016b; Ivy et al., 2010). Further, there is also evidence that highly predictable maternal signals influence synaptic growth and persistence in brain circuits subserving stress-resilience (Singh-Taylor et al., 2018). Thus, there is converging evidence that patterns of maternal-derived sensory signals to the developing rodent brain influence synapse stabilization and circuit maturation in limbic and cognitive brain networks, with consequent cognitive and emotional sequelae. Importantly, these effects on brain and behavior are additional to those related to *the quantity and quality of the maternal signals*, underscoring the importance of *patterns* of unpredictability in shaping the immature brain.

4. Conclusions and therapeutic opportunities

Cognitive and emotional health, as well as vulnerability to cognitive and emotional disorders, derive from interactions between genes and environment, especially during sensitive developmental periods. We have limited control over genetic susceptibility. Thus, an emphasis on understanding and mitigating early-life environmental factors is warranted.

There is compelling evidence for broad and persisting consequences on mental health outcomes of exposure to early life adversity. Many of the circumstances of early-life adversity (war, displacement, poverty, discrimination) are difficult to modify. Here we identify aberrant patterns of sensory input from the mother as an important and potentially modifiable factor, and hence a feasible target for intervention. Future work will be required to assess and delineate the precise critical periods of vulnerability to unpredictable maternal signals, and to the crafting of interventions aimed to enhance patterns promoting optimal brain maturation and mental health outcomes.

Competing interests

The authors have no competing interests to declare.

Funding

The authors' work is supported by the National Institutes of Health (MH-096889; MH73136; NS28912).

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