



Propagation of maternal behavior across generations is associated with changes in non-maternal cognitive and behavioral processes

Vedran Lovic^{a,*}, Alison S. Fleming^b

^a Department of Brain and Cognitive Sciences, McGovern Institute for Brain Research, Massachusetts Institute of Technology, USA

^b Department of Psychology, University of Toronto Mississauga, Canada



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ABSTRACT

Over a number of years we have studied the phenomenology of maternal behavior from endocrine, neural, experiential, and ontogenetic perspectives. Here, we focus on the effects of early life experiences with and without the mother on subsequent maternal and non-maternal behaviors of the offspring. We have used an artificial rearing procedure, which entails removing rat pups from their mother and raising them in isolation, while controlling and manipulating several aspects of their upbringing. As adults, mother-reared (MR) and artificially-reared (AR) rats are assessed on their own maternal behavior, as well several other behaviors. While both AR and MR rats nurse and successfully wean their young, the AR rats spend less time licking, grooming, and crouching over their young. Hence, being raised in social isolation does not seem to affect primary maternal motivational dynamics. Instead, isolation rearing produces alterations in the ongoing execution of the behavior and its effective organization. Here, we present evidence that changes in maternal behavior, as a result of social isolation from mother and siblings, are due to changes in top-down (e.g., sustained attention, flexibility) and bottom-up process (e.g., increased stimulus-driven behavior). These changes are likely due to alterations in brain dopamine systems, which are sensitive to early life manipulations and are modulators of bottom-up and top-down processes. Finally, we draw parallels between the rat and human maternal behavior.

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1. Forward

When I (ASF) first arrived at University of Toronto in 1975, Jerry Hogan was among the first people I met and I recall feeling quite intimidated by him. He attended my job talk and asked all the hard questions I wanted to avoid. But doing so, he was also an influence on my decision to come to University of Toronto. I could see that he both questioned and sympathized with my need to unpack 'innate' behaviors and to dissect the complex behavioral mechanisms that underlie species-characteristic behavior. His work focused on learning, but not in the traditional laboratory animals, but rather in a variety of 'exotic' species, such as jungle-fowl, chickens, and paradise fish. He did not study them in strictly artificial settings, but in settings and stimulus contexts with ecologic

validity. I admired his behavioral and more ethologic approach to science and his belief in the role of experience in the development of species-characteristic behavior. The years in the 'chicken house' reinforced my admiration for his science and for his keen mind.

There are numerous differences between mammals and other types of animals, but perhaps the most salient differences relate to the quality and quantity of parental care mammalian parents provide to their young. Mammalian offspring require significant parental care, such as food, warmth, and protection, in order for the young to survive and thrive. However, there are significant intra- and interspecies variations in the extent and quality of parental care provided (see Rosenblatt and Snowdon, 1996). Perhaps the biggest interspecies differences relate to the involvement of both parents in the care of the offspring. In the vast majority of species, males are seldom involved in rearing of the young and it is the mothers who take on the primary responsibility of parental care (Kinsley and Amori-Meyer, 2011; Numan and Insel, 2003; Mann and Bridges, 2001; Rosenblatt and Snowdon, 1996; Stern and Lonstein, 2001).

* Corresponding author at: Department of Psychology, University of Calgary, Canada.

E-mail address: vedran.lovic@ucalgary.ca (V. Lovic).

Over several decades of research, we have examined the role of hormones, neural structures, and experience on maternal behavior. Early postpartum period is characterized by pronounced plasticity for the new mother but also for her offspring. Alterations in the mother-offspring relationship can produce acute and long-term changes in the offspring's behavior and physiology. Here we review findings from our laboratory, as well as by others, examining the effects of early life manipulations on brain and behavior. We provide evidence that early life manipulations of the quality and quantity of maternal care offspring receive from their mother subsequently alters the maternal behavior offspring show toward their own young. Therefore, we see a propagation of maternal behavior across generations. However, these early life experiences with one's mother not only alter future display of maternal behavior toward the next generation of young, but they also alter some general functions, such as impulsivity, attention, behavioral flexibility, and attraction to reward-related stimuli or cues (Lovic et al., 2001, 2006, 2011a; Lovic and Fleming, 2004). We argue that, although mothering alters mothering of the next generation, mothering also changes general cognitive-behavioral profile of the offspring and these changes in turn change maternal 'styles' in the offspring.

2. Rat maternal behavior

Rat maternal behavior is relatively stereotyped yet complex, as it consists of a constellation of behaviors that are influenced by numerous sensory, hormonal, and experiential factors. Typically, virgin female rats are not responsive to pups and will avoid them, bury them, or even attack them. Pregnant female rats become responsive to pups in the latter third of the 21-day pregnancy period. During parturition female rats will pull pups out of the vaginal canal, clean them by removing the placenta, and retrieve the pups to the nest site. Soon after, the female will crouch over the pups allowing them to nurse while keeping them warm and protected from the environment. New mothers will lick pups' anogenital regions to stimulate urination and defecation. Mothers will also lick and groom pups non-anogenital skin (see Rosenblatt and Snowdon, 1996). Given that pups are born blind and deaf, maternal licking is a major sensory stimulation for newborn pups (see Rosenblatt and Snowdon, 1996). However, it is important to note that in addition to receiving somatosensory stimulation from the mother, pups also receive considerable somatosensory from each other as well (e.g., Alberts, 1978). While virtually all postpartum rats show maternal behavior, there are significant individual differences in the amount of licking and grooming mothers provide to their pups. These differences have long-lasting effects on pups' physiology and behavior.

The change from the virgin, maternally non-responsiveness state, to the postpartum, maternally responsive state, is associated with hormonal alterations characterizing the end of pregnancy – namely, declining levels of progesterone and rising levels of estrogen and prolactin (see Bridges, 2008; Mann and Bridges, 2001). These hormones act on numerous brain areas, but the most relevant is their action on the medial preoptic area of the hypothalamus (MPOA) (Numan, 1974; Stern and Lonstein, 2001). The MPOA, along with several other brain areas, is the ultimate neural node controlling rat maternal behavior. Lesions of the MPOA rapidly abolish many features of maternal behavior (Numan, 1974). The hormonal profile of postpartum females changes rapidly and within days their hormonal profile is similar to that of the virgin female (Orpen and Fleming, 1987). Hence, the importance of hormones diminishes and maternal behavior is maintained by sheer experience of being maternal. In fact, as little as 30 min of postpartum experience is enough to make the female rat responsive to pups for a long period of time (Orpen and Fleming, 1987). In a number of

studies, we have demonstrated that maternal experience effect is dependent on the functional integrity of the nucleus accumbens (Li and Fleming, 2003a,b). This area of the ventral striatum receives rich dopaminergic input from the ventral tegmental area and dopaminergic blockade in the accumbens can block the maternal experience effect (Parada et al., 2008). Overall, rat maternal behavior, while stereotypic, is highly complex and is modulated by motivational, affective, and as will be evident below, cognitive processes.

3. From maternal separation to individual variations in maternal behavior

In 1956, Levine et al. (1956) made a surprising discovery. Their experiment examined the effects of early life 'trauma' on adult 'emotionality' (stress responses). The experimental group consisted of rat pups, removed daily from their mother and nest, and subsequently given mild electric shocks over a 3-min period. The control groups consisted of undisturbed pups and pups that were removed from the nest but not given mild shock. The pups were allowed to grow up and their 'emotionality' was assessed. Surprisingly, pups that were removed from their mother and electrically stimulated were not significantly different from the pups that were removed from their mothers but not given shocks. Importantly, both of these groups were less 'emotional' compared to the non-manipulated (control) group of rats. This was one of the first studies showing that relatively brief separations from the mother can have long-term effects on offspring's responses to stressor. However, the mechanisms by which these effects come to be were not known for some time.

Bell et al. (1971) found that manipulating or 'handling' pups altered their ultrasonic vocalizations and Levine (1975) proposed that handling of the pups alters the behavior of mother and pups and that this alteration in mother-pup interaction then produces the effects of handling. This turned out to be the case. Mothers of pups that have been handled show increased pup licking and arched-back nursing (Liu et al., 1997). Therefore, solely manipulating the pups can alter maternal behavior, which was hypothesized to then, in turn, alter the pups' long-term neurophysiology, such as expression of several biomarkers involved in stress responses (Meaney et al., 1996, 2000; Meaney, 2001).

If handling is mediated by alterations in mother-pup interactions, namely the amount of licking that pups receive and the type of nursing posture that the mother exhibits, then it is conceivable that naturally occurring differences in these two behaviors will produce effects associated with handling experiments. Liu et al. (1997) tested this hypothesis. They observed and recorded maternal behavior of rat mothers during the first ten days of the postpartum period. They separated the mothers, based on the mean of licking and arched-back nursing, into those that were one standard deviation above the mean (i.e., high licking arched-back nursing) and those that were one standard deviation below the mean (i.e., low licking arched-back nursing). Once the offspring of these animals reached adulthood their physiological responses to stress were assessed. They found a significant negative correlation between the amount of licking and arched-back nursing administered to the pups by dams and pups' physiological indicators of emotionality. That is, pups that are licked more are less 'emotional'. Furthermore, we and others have found that the amount of licking and grooming mother rats provide to their offspring is correlated with the amount of licking grown offspring show toward their own offspring (Francis et al., 1999). Hence, there is a propagation of individual differences in maternal behavior across generations. However, the causal effects from these observational and correlational studies are not self-evident.

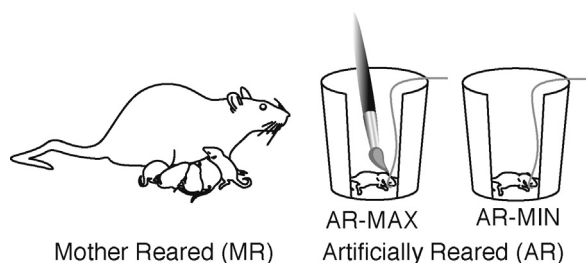


Fig. 1. Overview of Artificial Rearing Procedure. Pup siblings are either mother-reared (MR) or artificially-reared (AR). AR-MIN pups receive 2 (morning and evening) anogenital stimulations. AR-MAX pups receive 5 daily maternal licking-like (general body) stimulations in addition to 2 anogenital stimulations.

4. Artificial rearing

We have adopted a different strategy to manipulate early life experiences and examine the role of maternal stimulation (e.g., maternal licking) in the development of later maternal and non-maternal behaviors. Our experimental procedure involves ‘artificial rearing’ of rats pups. In this procedure, rat pups are removed from the nest on postnatal day (PND) 2–4 and are implanted with either cheek or gastric cannula. The procedure is brief, lasting no more than 2 min. Pups are fed artificial formula consisting of evaporated milk, proteins, minerals and vitamins through the implanted cannula. The pups reside in weighted plastic cups, which float in a warm water bath. Hence, the artificially reared (AR) pups receive nutrition and warmth and are compared to a control group of maternally reared (MR) pup siblings. The MR group, in turn, consists of two different subgroups. In one of these MR groups, pups are left undisturbed and in the other, they are given sham surgeries similar to the experimental AR rats but are reared by their mothers. In general, there are no differences in outcomes between the two MR groups.

Given that numerous studies had provided indirect evidence to suggest that early experiences with the mother have an effect on subsequent maternal behavior in adulthood, we experimentally manipulated the amount of maternal licking-like stimulation AR pups receive. Half of AR pups receive only 2 anogenital stimulations per day (AR minimally stimulated pups; AR-MIN group). The other half of AR pups receive additional five (2 min) daily stimulations (AR maximally stimulated group; AR-MAX). These stimulations consist of brushing of general body surface with a soft camel-hair brush. On PND 21 all pups, MR and AR, are pair-housed with non-experimental conspecifics. Once adults their behavior is assessed in various tests (see Fig. 1 for experimental groups).

5. The effects of artificial rearing on maternal behavior

Based on previous studies, we hypothesized that differential and insufficient early life experience with the mother would affect subsequent maternal behavior that offspring show toward their own offspring. We found that all rats, MR and AR, are maternal (Gonzalez et al., 2001). Both MR and AR rats build nests prior to parturition and they deliver and subsequently clean their pups. They retrieve pups and they gather them in the nest, nurse them, and their pups survive. If pups are removed from the nest and are subsequently placed in the diagonally opposite corner from the nest, both MR and AR mothers will retrieve them. Therefore, AR procedure does not impair maternal motivation. So what is affected by the AR procedure? AR rats tend to spend less time on top of their pups and provide them with less somatosensory stimulation (i.e., less anogenital and body licking). They also, tend to be slower at retrieving their pups back to the nest and appear less organized in their behavior. For example, MR rats tend to efficiently pick up

pups and retrieve them to the nest in a single action sequence. In contrast, AR rats often pick up one pup but drop them halfway to the nest, and then go to the other pups. Their retrieval sequences tend to be more segmented, often interrupted by their orienting and attention to minor environmental stimuli. Importantly, we see the effects of early life maternal licking-like stimulation of pups on their subsequent mothering. AR-MAX rats engage in more pup licking and time spent on pups compared to AR-MIN rats. Therefore, maternal stimulation received early in life affects the expression of maternal behavior toward the next generation. However, as mentioned above, we have no evidence that artificial rearing, or low levels of intact maternal care, affects maternal motivation per se.

From here the question then arises, “why are artificially reared rats less maternal toward their own offspring?” One of two general possibilities is that the offspring of mothers that were artificially reared do not elicit normal maternal behavior (e.g., pups of AR mothers might vocalize less, etc.). We have tested this hypothesis and have found no evidence to support it (Palombo et al., 2010). Another possibility is that AR mothers differ in their hormonal profile and that this endocrine change alters their behavior. This is also not the case. Virgin AR and MR females were given the hormonal regimen (progesterone and estrogen) that normally activate mothering. The differences between AR and MR virgins, in response to foster pups, were similar to those observed in postpartum AR and MR rats. Hormonally-primed AR virgin rats become maternal as quickly as their MR counterparts, in terms of the latency to onset of their behavior; however once maternal, they show the same pattern of disrupted behavior described for the postpartum AR rats (Novakov and Fleming, 2005). What then is involved in AR effect on mothering behavior? The answer is likely in alterations in other behavioral systems that impact the quality of mothering.

6. AR changes attentional abilities

We have observed that AR animals, as adult mothers, tend to be easily distracted (Lovic and Fleming, 2004). That is, they orient toward and approach various environmental stimuli. This often comes at the expense of being maternal. For example, we observed that, in contrast to postpartum MR rats, AR mothers leave the nest to approach the front of the cage when experimenters enter their housing room. Furthermore, during brief tests of maternal behavior, which consisted of removing the pups from the nest and placing them in the diagonally opposite corner of the home cage, AR rats often pause pup retrieval to attend to other stimuli. Therefore, we hypothesized that AR rats might be hyperactive and have attentional deficits. We assessed the locomotor activity of AR and MR rats, and found that AR rats show greater levels of locomotor activity (Burton et al., 2006). Much like with the assessment of maternal behavior, AR-MAX rats showed an intermediate level (relative to AR-MIN and MR rats) of locomotor activity, suggesting that maternal-like licking stimulation is able to ‘normalize’ the behavior and deficits produced by social isolation are reduced.

Based on our hypothesis that AR rats might have attentional impairments, we tested attentional abilities of AR and MR rats. This was done in two tests, prepulse inhibition (PPI) of the startle response and attentional set-shifting task. The attentional set shifting task for rats, tests higher level attentional functions—the ability to form and shift attentional sets. AR-MIN rats require a greater number of trials to reach criterion during the intradimensional shift (test of the ability to form an attentional set), extradimensional shift (test of the ability to shift attentional focus from irrelevant stimuli to relevant stimuli), and reversals (indicative of reduced behavioral flexibility) (Lovic and Fleming, 2004). That is, AR-MIN rats show difficulty maintaining attentional sets, shifting attentional sets, and disengaging from previous modes of responding. When we

correlated the number of trials to completion of the intradimensional shift with the amount of pup licking these rats displayed, we found that rats that were better able to sustain or form an attentional set (i.e., needed fewer trials to complete the intradimensional stage) also showed significantly more pup licking. Therefore, a higher-level attentional ability is related to the quality of maternal care displayed toward the pups (Lovic and Fleming, 2004). Performance on the attentional set shifting task is sensitive to lesions of several brain areas. For example, lesions of the medial prefrontal cortex produce deficits in extradimensional shifts (Birrell and Brown, 2000). We have found that lesions of the medial prefrontal cortex in postpartum rats do not abolish maternal behavior, but they do disrupt pup retrieval and reduce the amount of pup licking somewhat similar to AR rats (Afonso et al., 2007). Taken together, these findings suggest that AR-MIN rats might have compromised functioning of the prefrontal cortex and higher-level, top-down control of behavior. Indeed we have found that several biomarkers, such as NueN (neuronal marker) and synaptophysin (synaptic protein) are different in the medial prefrontal cortex between AR and MR rats (Chatterjee et al., 2007).

PPI is thought to test 'early' attentional processes or sensorimotor gating – the ability to filter out irrelevant stimuli. Greater levels of inhibition on this test reflect better sensorimotor gating or filtering ability. AR-MIN rats showed reduced levels of inhibition suggesting that they are less able to filter out irrelevant environmental stimuli. Next, we correlated all rats' PPI scores with maternal behavior scores found a positive correlation between PPI levels and quantity of maternal behavior. Rats that show greater levels of prepulse inhibition also lick their pups more (Lovic and Fleming, 2004). These correlational findings suggests that maternal behavior might require for mothers to have good filtering abilities, ignoring various environmental stimuli, and sufficiently processing pup relevant stimuli, which in turn could allow them to sustained maternal activity, such as licking.

7. AR rats are more impulsive

We have also noted that AR rats not only have attentional impairments, but also tend to act quickly toward stimuli and approach novel but irrelevant objects, leading us to hypothesize that they have deficient self-control and inhibition. Impulsivity is a multidimensional trait and consists of at least two psychological constructs: (1) impulsive action, or the tendency to act prematurely, and (2) impulsive choice, or the inability to delay gratification. We tested AR and MR rats on two operant schedules, differential reinforcement of low rate of responding (DRL-20 s) and delay discounting. These two operant schedules assess impulsive actions and impulsive choice, respectively. On DRL-20s schedule, rats can make operant responses (e.g., lever presses) and receive food pellets as a reward. However, responses have to be separated by at least 20 s in order for them to be followed by pellets as rewards. Making responses prior to the elapsing of 'waiting' time (in this case 20 s) does not result in pellet delivery and it resets the waiting time clock. The measure of impulsivity is efficiency or the ratio of responses made and pellets earned. A high degree of efficiency is indicative of good self-control. Conversely, low efficiency reveals high levels of impulsivity.

AR-MIN rats are more impulsive as they have lower efficiency scores. That is, they make more responses and fewer of them are followed by rewards (Lovic et al., 2011a). When correlated with maternal behavior, we have found that impulsive rats are less maternal (Lovic et al., 2011b). However, when tested on a delay discounting operant schedule, a test of impulsive choice, we found that AR rats are actually less impulsive. Therefore, AR procedure produces a specific impulsivity deficit – AR rats have difficulty

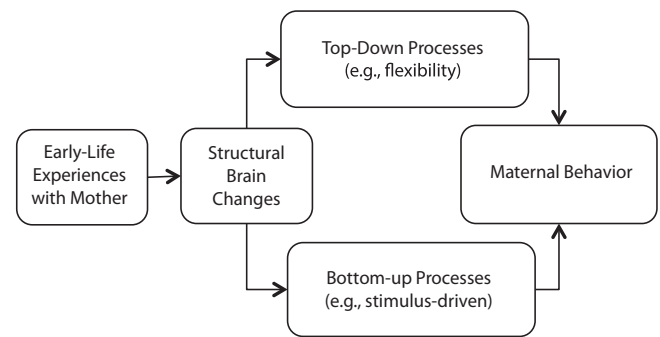


Fig. 2. Theoretical model connecting offspring experiences with the mother and the expression of maternal behavior offspring show towards their own young. According to this model, early experiences with the mother produce structural brain changes in the offspring (e.g., dopamine systems). In turn, these brain changes are associated with top-down (e.g., maintaining and shifting attentional sets) and bottom-up (e.g., responses to stimuli) cognitive-behavioral processes. Being reared without the mother, as a form of early life adversity, does not seem to alter basic maternal motivational dynamics.

withholding responses. This type of dissociation is also seen in rats with elevated levels of dopamine via amphetamine injections (see below).

8. Overall effects of artificial rearing

It is important to note that we have not found any general learning deficits in AR rats. Their ability to associate predictive cues with reward delivery (i.e., Pavlovian conditioning), spatial memory in the water maze, or ability to learn which actions lead to specific consequences (e.g., instrumental responding for food) is similar to that of MR rats (Lomanowska et al., 2011; Lovic and Fleming, 2004; Levy et al., 2003). We are arguing here that early life adversity, through artificial rearing, changes both top-down and bottom-up processing. That is, AR animals are stimulus-driven, impulsive, and have attentional impairments. In turn, these cognitive-behavioral impairments alter maternal behavior even though primary maternal motivational dynamics might not be changed (see Fig. 2).

Many of the deficits associated with AR that we have described here are associated with elevated or hyperactive dopamine systems. For example, drug sensitization, which alters dopamine systems (Robinson and Berridge, 1993), produces deficits in the attentional set shifting task (Fletcher et al., 2005) and it also increases impulsive actions (Fletcher et al., 2011). Amphetamine treatment, which potentially elevates dopamine levels, reduces prepulse inhibition (Mansbach et al., 1988). Furthermore, both maternal separation and artificial rearing are associated with elevated dopamine levels in the nucleus accumbens (Afonso et al., 2011; Meaney et al., 2002; Hall et al., 1999).

9. Relevance to human maternal behavior

The studies we have reviewed above apply to rats and tell us something about the behavioral mechanisms that underlie maternal behavior in *Rattus norvegicus*. But to what extent are these principles applicable to other animals and to humans? Oddly, we have little information regarding generalizable principles to other non-primate animals. However, among primates and, especially humans, there is a remarkable similarity in the behavioral and neurobiological changes that occur to the developing offspring with early social and/or maternal deprivation or insensitive parenting. Numan and Insel (2003) argue that in primates, as compared to rodents, the balance between size and role of the hypothalamus and the neocortex in regulating maternal behavior has shifted in favor of the latter (Keverne, 2001), reflecting the greater importance of the

prefrontal function in human parenting. This expanded role of the neocortex is consistent with the extended period of parental care in humans, as well as with the demands of parenting children at very different developmental stages. The dopamine input into the prefrontal cortex is closely associated with attentional and executive control systems, (Arnsten, 2006), function which are critical for quality parenting.

Dyadic synchrony between a mother and her infant, which often develops over the first postpartum months, consists of crucial individual components, including positive affect, a shared focus of attention, temporal coordination and contingency, which are all controlled primarily by the caregiver. Our studies with human mothers confirm the importance of cognitive flexibility and emotional well-being for maternal behavior. Mothers with disturbed attachments to their own caregivers (disorganized/unresolved) and to their own infants (irrational fear of loss of the infant), and mothers of disorganized infants (infants whose attachment strategies collapse under stress), show attentional difficulties when assessed with emotional Stroop tasks (Atkinson et al., 2009). In the conventional version of the Stroop task, participants are asked to name the color of printed words (e.g., the word RED presented in blue ink). Successful performance on this task requires allocation of attentional resources to be focused on one dimension of the stimulus (i.e., ink color) while the other stimulus properties are ignored (i.e., word meaning). In the emotion-assessing variant of the Stroop task, Atkinson and colleagues presented participants with 'emotional' words that pertain to attachment (e.g., ABANDON). Mothers with slow Stroop reactivity are slower to respond to infant signals (Steinhauer et al., 2009). Furthermore, we found that mothers with fewer errors on extra-dimensional shift and spatial working memory tasks at 2–6 months postpartum are more sensitive in their interactions with their infants and show more contingent responding to infant cues (Gonzalez et al., 2012). This is particularly the case with teenage mothers who tend to respond less sensitively to their infants. Teenagers in general, but teenage mothers especially, tend also to show much poorer attention, executive function, and impulse control (Chico et al., 2014; McAnarney, 2008; Sturman and Moghaddam, 2011; Geier et al., 2010; Rubia et al., 2010; Van Leijenhorst et al., 2010).

Moreover, executive function in humans is clearly affected by early experiences in the family of origin. Early adversity studies in children have found a stable relationship between abuse or neglect and executive function (Bos et al., 2009; De Bellis, 2005; Kreppner et al., 2001; Pears and Fisher, 2005a,b). Bos et al. (2009) investigated executive function in children that had a history of early deprivation due to institutionalization – a condition that shares properties with the AR regimen- and reported that early adversity is associated with deficits in performance on tasks that involve planning and working memory. Early adversity resulting from familial violence has also been associated with deficits in a wide range of executive functions, including working memory, problem solving, inhibition and attentional control (Fishbein et al., 2009; Nolin and Ethier, 2007; Pears et al., 2008). While we expect that these deficits continue into adulthood, less is known about the predictive relationship between early adversity and executive function in adulthood.

These functions, as we have seen, are closely related to appropriate mothering. Thus for both perceptual responsiveness and executive functions, there is evidence of a link between early adversity, defined as inappropriate or abusive parenting, and deficits in these cognitive functions. These cognitive functions are obviously relevant for parenting, but factual data linking early adversity (i.e., parenting), these cognitive functions, and later parenting is lacking at this point. However, based on the extensive animal literature reviewed above and the observation that in humans early adversity in the home is related to problems with executive function and

with social behavior in general, it would not be surprising to discover that people who have had unfortunate rearing experiences are at greater risk of having parenting problems related to cognitive challenges, inattention, and absence of impulse control.

Our arguments and evidence presented in this paper is largely based on correlational findings. Future studies need to establish a causal link between early-life adversity, changes in cognitive functions, and parental behavior. Researchers will need to show that temporally specific manipulations, not induced by early-life adversity, can lead to specific and transient impairments in parental behavior. These studies will need to show that selective functions, such as impulsivity, which are impaired as a result of early-life adversity, can be selectively 'repaired', pharmacologically, optogenetically or otherwise, and that these reversals in impairment will lead to specific changes in parental behavior. These findings will not only be relevant to basic understanding of the relationship between early-life adversity and parental behavior, but they also generate better prevention and treatment options for poor parental care.

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