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Challenges to the parental brain: Neuroethological and translational considerations

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ABSTRACT

Extending from research documenting adaptive parental responses in nonthreatening contexts, the influences of various neuroethological and physiological challenges on effective parenting responses are considered in the current review. In natural habitats, rodent family units are exposed to predators, compromised resources, and other environmental stressors that disrupt HPA axis functions. With the additional physiological demands associated with caring for offspring, alterations in stress-related neuroendocrine responsiveness contribute to adaptive responses in many challenging contexts. Some environmental contexts, however, such as restricted nesting resources, result in disrupted maternal responses that have a negative impact on offspring wellbeing. Additionally, parental dysregulation associated with exposure to environmental chemicals or pharmacological substances, also compromise maternal responses with effects that often extend to future generations. Continued preclinical and clinical research elucidating parental responses to various stressors and physiological disruptors is necessary to provide valuable translational information identifying threats to effective parenting outcomes.

1. Introduction: The dynamic parental brain

It is a commonly held belief that a woman's intellectual capacity diminishes during pregnancy. Indeed, the term "baby brain" refers to the memory lapses and cognitive failures reported by many women not only during pregnancy, but also during the postpartum period. A recent meta-analysis indicated a significant decline in cognitive function, particularly during the third trimester, between pregnant and non-pregnant women (Davies et al., 2018). Such effects are likely due to the dramatic reorganization of the maternal brain occurring during pregnancy to prepare for the physiological and behavioral changes associated with becoming a mother. Yet, the experience of motherhood greatly expands the behavioral repertoire of the female and may even improve cognitive capacity. Findings from both rodents and non-human primates suggest that new mothers are more vigilant (Kinsley et al., 1999), better at multitasking (Bardi et al., 2014), and bolder in their pursuit of food than their virgin counterparts (Lambert et al., 2005; Kinsley et al., 2014). In other words, when challenged, mothers engage in complex responses to nurture their genetic investments, and this new orientation to the external environment is predicated upon a fundamental internal transition from nulliparity to motherhood (Kinsley et al., 1999; Wartella et al., 2003; Love et al., 2005; Kinsley et al., 2014). The consideration of adaptive maternal responses, observed in challenging and stressful contexts both in laboratory and natural settings, is of central importance in this review.

As female rats transform from a nulliparous to primiparous animal, many neurobehavioral changes occur to facilitate caregiving responses promoting the well-being of offspring. In contrast to humans who benefit from diagnostic tests that allow them to cognitively prepare for impending parenthood, most mammals rely exclusively on neurophysiological changes triggered by alterations in key reproductive hormones. Critical to preparing the female for her new role, prolactin and associated placental lactogens facilitate the transformation from the nulliparous to the maternal brain (Grattan 2011), a response that is swift and consistent among maternal rodents (Fleming and Rosenblatt, 1974). Prolactin, perhaps best known for its role in milk production and lactation, is essential for the emergence of maternal behavior. When prolactin receptors are compromised in the medial preoptic area of the hypothalamus (MPOA), aspects of maternal behavior, including pup retrieval and nursing, are diminished (Brown et al., 2017). Additionally, both oxytocin and vasopressin, neuropeptides thought to have evolved from the ancient precursor vasotocin (Francis et al., 2002), facilitate maternal and paternal affiliative responses directed toward offspring and their care (Russell et al., 2001; Leng et al., 2008; Lambert et al., 2013; Bendesky et al., 2017).

These neurochemical changes, as well as others, influence the emerging maternal neuroarchitecture, altering synaptic plasticity and consolidating neural circuits that support parental care. In addition to the MPOA, the amygdala, medial prefrontal cortex, nucleus accumbens, superior-temporal gyrus, insula and areas of the parietal and frontal

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gyrus have been implicated in human parental behavior, with structural changes in the form of increased gray matter observed in the prefrontal cortex, parietal lobe and midbrain areas (Kim et al., 2010; Atzil et al., 2012). With regard to long-term changes associated with motherhood, reductions in gray matter in brain structures associated with social cognition have been reported, including changes in the superior temporal sulcus, medial and frontal cortex, hippocampus and cortical fusiform areas (Barha and Galea, 2017; Hoekzema et al., 2017). Further, rodent research has indicated structural changes associated with cell proliferation, including neurogenesis, within regions of the hippocampus across the peripartum period. Such changes may facilitate the changing responses associated with effective maternal care (Galea et al., 2014).

Thus, many neurobiological transformations underlie the transition to parenthood. It is interesting to consider that the same transformations marking the evolution from nonparental to parental responses, including trasitions from nulliparity to primiparity, serve as signature characteristics for the evolution of mammals. In his book *The Triune Brain*, pioneering neuroanatomist Paul MacLean observed the importance of this transformational shift as he identifited three behaviors that separated mammals from other vertebrates, including nursing, audiovocal maternal-offspring communications and the emergence of play behavior. Interestingly, all of these behaviors are associated with the emergence of maternal behavior (MacLean, 1990; Lambert, 2003). MacLean's observations were recently corroborated by evidencethat a mammalian fore-runner species, *Kayentatherium wellesi*, a plant-eating animal the size of a small dog that lived approximately 185 million years ago in the era of dinosaurs, gave birth to large litters of offspring without the facial and cranial enlargements typical of mammalian morphology. Preserved fossils of one clutch revealed 38 offspring in this stem-mammalian perinate indicating that the offspring skulls had the same proportions as the adult *K. wellesi* (but approximately 1/10th the size) as opposed to the bulbous skulls in mammals necessary to cradle the signature enlarged mammalian brains (Hoffman and Rowe, 2018). It was suggested that, as mammals entered the evolutionary scene and adopted the role of nurturer and caregiver, large brood size was replaced with large brain size and more complex behaviors emerged to sustain the necessary care of offspring (Hoffman and Rowe 2018). Consequently, mammalian brains are the largest brains in proportion to body size across the animal kingdom (Rowe et al., 2011). Focusing on humans, maternal behavior may have influenced the development of right-hand dominance and hemisphere lateralization when mothers used their left hands to hold their infants close to their hearts to calm them, leaving their right hands free to manipulate objects in the environment (MacLean, 1996). When describing this evolutionary transition, MacLean commented, "For more than 100 million years, the female has played the central role in mammalian evolution (Maclean, 1996, p. 422). Thus, throughout mammalian evolution, the parental brain adapted to properly care for its genetic investments, now in much smaller numbers, to assure their survival. To provide optimal care for offspring, early mammalian mothers incorporated both on-the-nest and off-the-nest survival strategies to protect their broods. As suggested by Craig Kinsley, "Arguably, no other developmental milestone is exemplified by, nor more reliant on, the sudden and dramatic behavioral alterations observed in the maternal mammal (Kinsley et al., 2014).

Although the environment is typically safe and consistent in the laboratory where most of the parental neurobiological research on rodents has been conducted, the natural environment for these animals is characterized by unpredictable threats and challenges. The goal of the current review is to explore the maternal and, in some cases, paternal response to the many challenges—ranging from environmental stress to neurochemical disruptions—that threaten the quality of parental care and the well-being of offspring. An enhanced understanding of parental functions in the face of adversity will further elucidate our understanding of the neurobiological mechanisms that sustain the parental brain, providing more information about vulnerabilities that compromise adequate care and the well-being of offspring. Although the emphasis of this review is on the maternal brain, where appropriate, paternal responses will also be considered.

2. Detecting Threats: The maternal stress response

With the arrival of pregnancy, the neurobiological cost-benefit evaluations shift to ensure the survival of both mother and offspring. At a time when there is more to lose from the perspective of genetic investments, it is informative to consider alterations in the maternal animals' stress response system. It has been known for over half a century that the hypothalamic–pituitaryadrenal (HPA) response is attenuated, rather than enhanced, during a time when it seems that a heightened HPA response may be necessary for sufficient protection of the offspring (Thoman et al., 1970; Barlow et al., 1975). Subsequent research has indicated that circadian variations in HPA activity are muted (Atkinson and Waddell, 1995; Brunton et al., 2005), coincident with an attenuated response to many environmental stressors (Douglas et al., 1995; Brunton et al., 2008), which may serve to limit the energetic costs associated with sympathetic activation during a time of increased energy expenditure for the mother. Further, attenuated glucocorticoid production serves to limit fetal exposure thereby avoiding any potential adverse neurodevelopmental effects of these potent steroidal hormones (Brunton and Russell, 2008; Brunton et al., 2008).

In addition to the endocrine modifications accompanying pregnancy and lactation, maternal experience itself alters behavioral responses to stress. For example, when pup-sensitized (e.g., virgin females conditioned to care for pups) were exposed to a brightly-lit, noisy, open field arena, they exhibited decreased anxiety-like behaviors similar to that observed in animals that had previously experienced pregnancy and lactation . Interestingly, this shift toward more risk-taking, less anxiety-like pattern of behavior, occurred in the absence of altered HPA axis responsivity that is usually observed in maternal animals, indicating that these behavioral changes occur independent of HPA alterations (Agrati et al., 2008).

Similarly, when either pregnant or virgin rats are exposed to an open field, decreased anxiety-like behaviors are observed in the pregnant rats. When c-fos protein immunoreactivity, a marker of neuronal activation in contexts such as stress exposure, is measured following testing, lower expression levels are observed in the basolateral amygdala and CA3 region of the hippocampus. When these same groups are exposed to restraint stress, reduced fos immunoreactivity is also observed in these same limbic areas (Wartella et al., 2003). These results corroborate earlier work indicating that lactating rats exhibited less anxiety-like behavior in the elevated plus maze (Neumann, 2001). Regarding long-term effects, when anxiety-like behaviors in the elevated plus maze were assessed at approximately four month intervals, primiparous animals spent more time in the open arms at 10, 14, 18, and 22 month assessments (Love et al., 2005). Thus, these findings indicating how parous females perceive and respond to environmental challenges suggest persistent effects on systems that regulate the stress response well beyond weaning of their pups and, perhaps, for the duration of the animal's lives (Gatewood et al., 2005; Byrnes and Bridges, 2006).

In humans, systematic neural responses haven't been observed during severe maternal threats, however increased stress responses (e.g., heightened HPA reactivity) in the presence of infant stimuli is associated with poor maternal functions (Laurent et al., 2011). In another study in which fMRI scans were evaluated in mothers, activation of the orbitofrontal cortex was observed to be negatively correlated with perceived maternal stress during exposure to videos of daily caretaking activities such as feeding children. Further, co-activation of the OFC with the anterior insular cortex, ventral pallidum, periaqueductal gray and cerebellum, brain areas associated with maternal motivation, was also associated with reduced maternal stress responses (i.e., self-reported emotional responses; (Noriuchi et al., 2019)). In agreement with Paul MacLean's comments about maternal responses influencing the lateralization of brain responses, activation of the *right* anterior insular cortex is associated with emotional responses associated with heightened maternal motivation and lower parental stress (Craig, 2009). Thus, both rodent and human research provide evidence of the necessity of a well-balanced brain in the maintenance of both stress regulation and maternal motivation in adaptive maternal responses.

One benefit of a muted response to stress-provoking environmental stimuli in maternal animals may be sustained attention during foraging tasks at a time when energy consumption is especially critical for lactating mothers. Indeed, previous studies demonstrate that maternal rodents exhibit enhanced foraging abilities when compared to their virgin counterparts (Kinsley et al., 1999) and these effects are maintained when foraging in competitive and food-related attention set-shifting tasks (Love et al., 2005) as well as in a predatory cricket-hunting task (Kinsley et al., 2014). Focusing on a primate model, male and female owl monkeys with reproductive experience performed more efficiently (by 4-fold) in a foraging task than animals with no parenting experience (Bardi et al., 2014). Further, these animals had a higher dehydroepiandrosterone (DHEA) to cortisol ratio in urinary samples; higher DHEA/Cortisol ratios have been associated with adaptive coping during stress exposure (Charney, 2004, Morgan et al., 2009; Lambert et al., 2014). Even in traditionally viewed nonpaternal male primate species, i.e., *Maccaca fascicularis*, positive correlations are observed between DHEA/Cortisol levels and the amount of time spent with juvenile animals (Bardi et al., 2017).

In an attempt to delve further into the mechanisms of altered HPA responses in maternal animals, a recent study reported reduced glucocorticoid receptor immunoreactivity, and enhanced BDNF-immunoreactivity, in the hippocampus of primiparous rats compared to their nulliparous counterparts. As expected, higher DHEA/corticosterone levels were also observed in the primiparous animals, accompanied by evidence of more resilient foraging responses in a spatial task probe trial (Sullivan et al., 2017). Focusing on a different timepoint, modifications in GR density were observed in late pregnant animals, providing additional evidence of dynamic properties of the stress response in maternal animals (Pawluski et al., 2015). Given findings of varied responses, however, more research focused on contextual-dependent modifications in various aspects of the HPA axis are necessary to further understand the nature of stress responsivity changes across pregnancy and lactation.

Interestingly, although a diminished maternal stress response is adaptive in some environmental contexts, in other contexts a rigorous stress response may be adaptive for offspring. Maternal aggression, for example, is coincident with maternal responses in rodents and serves the important role of protecting offspring (Rosenblatt et al., 1994). It has been hypothesized that maternal stress responses may program offspring HPA responses so that they are better prepared to survive in the environmental context to which they are born (Sheriff et al., 2017). According to the proposed *Environmental Maternal-Matching Hypothesis*, optimal survival may be achieved if the degree of stress is comparable for the maternal and offspring environments (Gluckman et al., 2005; Sheriff and Love, 2013). Recent investigation of the maternal-matching hypothesis in wrens, however, suggests the presence of complex interactions between maternal and offspring stress exposure. Although maternal wrens given corticosterone-enhanced mealworms produced offspring with larger body weights, greater survival was observed when the stress-exposed offspring were raised by control mothers that were not exposed to corticosterone-injected worms (Weber et al., 2018). Hence, although a full discussion of this issue is outside of the purview of the current review, maternal programming of the offspring HPA axis can be achieved through *in ovo*, *in utero* or postnatal activational and/or organizational effects and may be mediated through epigenetic modifications in the offspring genome (Heijmans et al., 2008; Cao-Lei et al., 2014). This hypothesis is consistent with heightened attention currently directed toward the proposed transgenerational effects that enable animals to adapt optimally to relevant environmental contexts (Levins, 1968; Leimar and McNamara, 2015).

Thus, with the dramatic modifications that accompany the transformation of the maternal brain, there are many opportunities for dysregulation of circuits critical for emotional resilience and mental health. The impact of impaired or disrupted maternal care ultimately affects the development of offspring and can lead to negative transgenerational effects (Curley et al., 2009; Brummelte and Galea, 2010). More research is necessary to elucidate the most prevalent risk factors for mental illness susceptibility during this critical time for both the mother and offspring. More specifically, appropriate behavioral models of depression are necessary to investigate disorders such as depression in females (Brummelte and Galea, 2010). As more ethologically relevant and species appropriate assessments are developed for females across the reproductive stages, increased opportunities for interventions and treatment will be made available to human females, enhancing the translational value of the preclinical work.

3. Parental challenges

3.1. Beyond the nest

Even when all the necessary neurobiological adjustments occur to maximize parental attention toward the offspring, threats to this symbiotic relationship present themselves in many forms. With a larger genetic investment at stake when there are additional offspring to care for, a heightened vigilance for external threats is necessary. Maternal California ground squirrels, for example, exhibit more risk assessment behaviors when presented with sounds of rattling from their natural predators, Northern Pacific rattlesnakes, than virgin or male ground squirrels. The intensity of risk assessment in the form of bipedal stands and tail flagging is enhanced in proportion to the level of danger associated with the snake cues, as well as the vulnerability and age of the offspring (Swaisgood et al., 2003).

Laboratory work with maternal rodents corroborates these findings of heightened vigilance and responsiveness to provide protection against threats to the nest and offspring. Specifically, as previously described, maternal rodent aggression, viewed as the dam's defense against a threatening intruder, becomes much more intense as a female transitions from virgin to a primiparous female. Whereas it is rare for a nulliparous female to attack an intruder, attacks are frequent in late pregnant and lactating female rodents (Flannelly and Flannelly, 1987). The neuropeptides oxytocin and vasopressin, both chemical mediators of social interactions and anxiety, as well as brain areas such as the paraventricular nucleus, central amygdala, septum and bed nucleus of the stria terminalis (BNST), have been implicated in rodent maternal aggression (Bosch et al., 2010; Bosch, 2013). These findings are corroborated by the observation of changes in oxytocin and vasopression receptor expression in postpartum females during a time of heightened maternal aggression (Nephew et al., 2009).

The sophisticated maternal detection of impending threat was examined in a study investigating the impact of predator odor exposure on maternal responsiveness and neural activation in dams on the day of parturition. Additionally, the impact of transport stress was assessed, as knowledge of movement in the laboratory increases the likelihood of the cage being in an unfamiliar territory. Interestingly, maternal responses (e.g., nursing duration, frequency of licking/grooming) weren't impacted by the presence of predator odor; however, when predator odor was presented in addition to transport stress, maternal responsiveness was reduced early in the pup exposure assessment. Further, whereas fos activation in the BNST was observed following exposure to predator odor (regardless of the presence of transport stress), no effects were observed in the medial preoptic area, suggesting that the BNST may integrate environmental cues to determine compensatory responses toward the offspring (Kenny et al., 2014).

3.2. On the nest

Focusing closer to the nest, laboratory investigations of maternal separation, in which the pups are repeatedly removed from the nest have revealed vulnerabilities to anxiety-prone responses and addiction in the offspring (Francis et al., 1999; Caldji et al., 2000). However, in one study, maternal compensatory responses appeared to diminish long-lasting effects in the pups. Specifically, pups were repeatedly separated from the maternal nest for four hours during postnatal days 1–14. When compared to controls separated for only 5 min daily, offspring from the extended separated group exhibited no differences in opiate immunoreactivity or plasma corticosterone levels, nor were changes observed in a battery of behavioral assessments for anxiety. This surprising resilience in the pups was attributed to altered caregiving responses in the females; for example, the maternal rats in the extended separation group spent more time with the pups upon their return to the nest after the four-hour separation than the maternal rats in the brief separation group (Marmendal et al., 2004). One factor leading to the unexpected findings of no evidence of vulnerabilities in the extended separation group is likely the lack of an undisturbed control group; regardless, the flexibility and compensation of the maternal response is interesting. This maternal adaptation has also been observed in a briefer maternal-pup separation protocol in which maternal rats separated from pups for 15 min during postnatal days 1–22 exhibited increased maternal behavior (as observed in the previous mentioned study) and diminished anxiety in the elevated plus maze. Further, the separated mothers exhibited higher levels of estrogen and oxytocin receptors, and lower levels of serotonin receptors, throughout the limbic areas of the brain (hippocampus, prefrontal cortex, amygdala, medial preoptic area and the nucleus accumbens). Thus, transient changes in relevant neurochemicals may be an underlying mechanism for the maintenance of flexible maternal responses when challenged by being separated from offspring (Stamatakis et al., 2015). It is worth noting, however, that maternal rats in their natural habitats leave their pups for necessary foraging excursions to maintain appropriate energy levels for nurturing the growing pups. Further, in some cases, communal nursing is observed in natural habitats (Mannella et al., 1990). Research characterizing HPA regulation during these required maternal-offspring separations would inform laboratory findings associated with forced maternal separations.

Transient compensatory responses have also been observed in an experimental manipulation of anxiety-like behavior in postpartum rats in which the drinking water was punished by electric shocks. Compared to virgin rats, the maternal rats consumed more water. Even when the nulliparous rats were water deprived twice as long as the maternal rats (48 hrs vs 24 hrs), the maternal rats still consumed more water. Explorations of GABA sensitivity in brain tissue throughout the limbic system, hypothesized to be a mechanism for an increased tolerance to pain (Enna and McCarson, 2006), failed to identify any differences between the maternal and virgin animals. Although the specific mechanism wasn't identified, the maternal rats responded to this experimental version of conflict-induced anxiety with more robust consumption of fluids, critical for lactation, than their nulliparous counterparts (Ferreira et al., 1989).

Although rats in the previous study tolerated negative outcomes associated with shock punishment, maternal rodents' responses to modifications in the physical resources that contribute to nest quality appear to present more threats to their maternal responsiveness. One experimental approach, referred to as early life stress or limited nesting stress, involves inserting a plastic mesh surface in the dams' cages so that they don't have direct access to bedding. Additionally, less nesting material, in the form of a portion of a paper towel, is provided to the restricted resource group. In one study, when Sprague-Dawley dams were exposed to these restricted resources during the first week following parturition, they exhibited disrupted maternal care (e.g., less time engaged in licking and grooming the pups) and evidence of anxiety in the open-field test (Ivy et al., 2008). This disrupted maternal behavior was replicated with Wistar female rats; specifically, the frequency of pups observed to be out of the nest increased. Further, the limited resource rats spent more time building the nest and self-grooming than the control condition maternal rats, with no effects observed in time directed toward licking and grooming the pups. The pups exhibited evidence of delayed maturation of the HPA axis around postnatal day 10 (Moussaoui et al., 2016). Interestingly, sex-dependent effects have been observed in the offspring of maternal rats exposed to this early-life stress, with males exhibiting more vulnerability than female offspring (Walker et al., 2017).

Different from previous studies, researchers have also investigated low resources by providing 25% of typically provisioned bedding and nesting material, as opposed to a plastic grid for the floor surface used in previous studies. Initial reports indicate that the limited resource dams exhibit poorer nest quality and spend less time crouching over their pups. Further, when exposed to a pup-retrieval challenge test in which three pups were separated from the dam by a novel barrier in an unfamiliar cage, the limited resource rats exhibited longer retrieval times than the standard housed maternal rats (Scarola et al., unpublished data, 2017). More research is necessary, however, to further elucidate the effects of limited nest resources on both maternal responsiveness and offspring outcomes. One limitation of these studies is that the behavioral observations typically monitor diurnal behaviors; thus, it would be informative to conduct these behavioral assessments during the dark phase to complement the light phase findings.

Past research has also targeted the impact of immunological threats on maternal responsiveness. Although immunological challenges during pregnancy have been linked to offspring exhibiting phenotypes consistent with psychiatric illnesses such as autism (Estes and McAllister, 2016), research exposing maternal animals to immunological challenges postpartum are limited. One study, however, generated immune activation by administering the viral mimic polyriboinosinic-polyribocytidilic acid (PolyI:C) to pregnant dams. This immunological challenge led to fragmented maternal care in the form of diminished attention to the pups (i.e., licking and grooming) and increased attention to nest building (Schwendener et al., 2009). Transgenerational effects of maternal immunological threats using the PolyI:C model have been observed in depression-like symptoms (i.e, behavioral despair in the forced swim task and anhedonia in the sucrose preference task) in second-generation F2 offspring (Ronovsky et al., 2017). Although the significant impact of maternal infections such as the Zika virus have recently been in the spotlight, the preclinical animal models suggest that any infections that disrupt maternal care should be thoroughly investigated (Meyer et al., 2009; Ronovsky et al., 2017). Focusing on paternal behavior modifications during immune challenges, interesting findings have been observed between mature and senescent male blue-footed booby birds after experiencing lipopolysaccharide (LPS)-induced sickness. Whereas older males typically produce fewer fledglings, when the senescent males were immunologically challenged, they produced more healthy fledglings than their younger counterparts—increasing their reproductive success by 98% compared to healthy, but senescent, birds who had not been immunologically challenged (Velando et al., 2006). Thus, in a natural illustration of neuroeconomics, both age and health status factors impacted the neural processing that accompanies parental decision-making/response outcomes in the blue-footed booby birds.

4. Chemical threats to maternal circuits

4.1. Endocrine disrupting chemicals

Chemicals that diminish reproductive competency pose a significant threat to species survival, particularly if such chemicals dramatically decrease either fertility or fecundity. Similarly, teratogens inducing gross developmental defects that have a discernable impact on reproductive success, also present a clear threat. Many chemicals, however, induce more subtle effects on reproductive processes. And yet, over time such chemicals can negatively impact not only the health of the affected individual, but their future progeny as well. For example, persistent organic pollutants (POP), which include chemicals such as polychlorinated biphenyls (PCBs) and dioxins, negatively impact a number of reproductive processes and are considered a significant environmental threat. The effects of PCBs have been well-documented in avian species (Ottinger et al., 2009) and like many POPs, are likely due to effects on the endocrine system.

It is now understood that many environmental chemicals have the potential to act as endocrine disruptors (endocrine-disrupting chemicals; EDCs), and as such can modify the normal development of the neuroendocrine axis (Gore et al., 2015). Thus, while rarely toxic to the fetus or neonate, exposure to EDCs can lead to significant alterations in neuroendocrine development and overall reproductive health in both males and females. Importantly, effects of EDCs involve unconventional dose response relationships, including significant effects that may only be observed at low doses, and developmental periods of increased vulnerability. Such unique characteristics initially complicated interpretation of EDCs studies, but are now recognized as important factors to consider when evaluating effects of these chemicals. Thus, the available clinical literature suggests increased risk for neurobehavioral disorders and increased adiposity/obesity associated with early exposure to a variety of EDCs (Braun, 2017).

While preclinical studies specifically examining the effects of EDCs on parental behaviors are more limited, a number of findings demonstrate that developmental exposure can result in significant effects on parenting. For example, exposure to low dose Bisphenol A (BPA) in Wistar rats throughout pre- and postnatal development, decreased the amount of time exposed females (F1) spent nursing their own young (F2) when tested as adults. Moreover, these F2 males and females demonstrated significantly increased body mass as adults, suggesting a multigenerational effect of BPA exposure (Boudalia et al., 2014). Similarly, in mice, exposure to the synthetic estrogen 17alpha-ethinyl estradiol (EE2) modified the maternal behavior of exposed females. Specifically, adult females exposed to EE2 during fetal and perinatal development displayed altered pup retrieval behaviors during the early postpartum period which was associated with decreased estrogen receptor α (ERα) expression in the MPOA. In biparental California mice, developmental exposure to either BPA or EE2 disrupts maternal care displayed by adult F1 females with no significant effects on paternal behavior displayed by exposed F1 males. However, unexposed females partnered with exposed F1 males, also demonstrated decreased maternal investment in the care of pups (Johnson et al., 2015). These findings suggest that even exposure in the males was not without impact on the care of their offspring. While specific mechanisms underlying these effects remain to be determined, EDCs likely modify normal development of neuroendocrine circuits underlying the hormonal regulation of maternal behavior. While a large body of literature suggests adverse effects on reproductive organs and tissues in humans (Karwacka et al., 2017), currently there are no data demonstrating adverse effects of EDCs on maternal behaviors in women. Given the potential multigenerational impact of such exposure, studies examining the effects of EDCs on maternal responsiveness in human populations are needed.

4.2. Drugs of abuse

Substance abuse represents a significant threat to the appropriate display of maternal behavior in humans. Yet, the relationship between substance use disorders (SUD) and the regulation of the mother-infant dyad is complex. Indeed, while correlations between parental substance use and child maltreatment exist, childhood abuse and neglect are also risk factors for the development of a SUD. This relationship makes it difficult to disentangle multigenerational patterns of both maltreatment and SUD. Thus, rather than simply reporting associations between maternal SUD and neglect, studies are currently attempting to better understand how drugs of abuse alter neural circuits to influence certain aspects of maternal care. In humans, imaging studies have revealed significant differences in critical maternal pathways in women with SUD. For example, data suggest that substance using mothers may have reduced activation of reward circuits associated with images of their own baby's face (Kim et al., 2017). Additionally, women with SUD appear to have increased activation of stress circuits in response to infant cries. Such findings suggest a fundamental shift in the relationship between reward- and stress-related circuits regulating maternal behavior as a consequence of SUD (Rutherford et al., 2011). However, even these more mechanistic studies are still unable to dissociate the neurobiological effects of the drugs from the numerous genetic, environmental, and experiential factors that led to the initiation and escalation of substance use. In contrast, preclinical studies are able to directly examine the effects of specific substances on maternal circuits and associated maternal behaviors.

Some of the earliest studies examining the effects of drugs of abuse on maternal behavior measured aspects of maternal responding following acute administration of the commonly prescribed opioid analgesic morphine. Indeed, morphine-induced deficits in maternal behavior were revealed several decades ago in rats and include significantly delayed pup retrieval (Bridges and Grimm, 1982; Grimm and Bridges, 1983), decreased preference for pup odors (Kinsley and Bridges, 1990) and decreased maternal aggression (Kinsley and Bridges, 1986), with similar effects observed in mice (Haney and Miczek, 1989). Additional findings suggest that morphine-induced activation of mu-opioid receptors in the MPOA underlies disruptions in maternal responding (Rubin and Bridges, 1984; Mann et al., 1991; Stafisso-Sandoz et al., 1998). More recent findings implicate the activation of opioid receptor subtypes within the PAG in regulating other aspects of maternal behavior, including predatory behaviors involved in hunting. Interestingly, while mu-opioid receptor agonists infused into the PAG disrupt maternal care, kappa receptor antagonism actually increases maternal predatory behaviors (Klein et al., 2014). These effects are likely due to opioid modulation of neurotransmission, including regulation of dopamine (Callahan et al., 1996; Yilmaz and Gilmore, 1999), serotonin (Tao and Auerbach, 1995), and relevant neuropeptides (Keverne and Kendrick, 1991; Sukikara et al., 2011). Indeed, inhibitory effects of opioids on oxytocin secretion in postpartum females have been reported in numerous mammalian species (Haldar and Sawyer, 1978; Haldar et al., 1982; Wright et al., 1983; Russell et al., 1991; Tancin et al., 2000), including humans (Lindow et al., 1999). Moreover, the role of endogenous opioids in attenuating the prosocial effects of oxytocin has been supported by data from both animals and humans (Dal Monte et al., 2017), suggesting that alterations in opioid receptor activation can influence affiliative behaviors in general and maternal behavior in particular. Effects of chronic opioid exposure during critical developmental windows on regulation of maternal circuits has also been examined in animal studies. For example, prenatal exposure to morphine can diminish maternal care and augment the disruptive effects of acute morphine during the postnatal period (Miranda-Paiva et al., 2001; Slamberova et al., 2001). Similarly, chronic infusion of the synthetic opioid methadone during gestation also negatively impacts maternal care (Hutchings et al., 1992). In contrast, prenatal exposure to morphine does not impair maternal behavior in adult exposed F1 females (Slamberova et al., 2003). Similarly, while adolescent exposure to morphine prior to pregnancy alters suckling-induced prolactin secretion (Byrnes, 2005; Byrnes, 2008), maternal behavior is not significantly disturbed (Byrnes et al., 2003; Johnson et al., 2011). There are fewer studies examining the effects of chronic exposure to commonly prescribed or misused opioids, such as oxycodone or fentanyl, on maternal behavior during the postpartum period. Recent data, however, suggest that withdrawal from oxycodone following self-administration throughout pregnancy can increase pup retrieval latencies

(Vassoler et al., 2018). Currently, most studies examining the effects of prenatal opioids focus on outcomes in the offspring and many of these studies have research design features that may limit their translational value (as discussed in (Byrnes and Vassoler, 2018)). Given the dramatic increase in the number of infants born to opioid dependent women (Gomez-Pomar and Finnegan, 2018), including those receiving medication assisted treatment (e.g. methadone or buprenorphine), understanding how chronic opioid exposure alters the maternal brain may assist in the development of interventions to improve outcomes for both mother and baby. To date, there are limited clinical data available regarding effects on maternal care specifically related to the use of medication assisted therapy; however, a meta-analysis of integrated treatment programs that include a parenting component, found that such programs demonstrate better outcomes with regard to decreasing both measures of parenting stress and future parental substance use (Moreland and McRae-Clark, 2018). Such findings, as well as more limited data from pregnant women and mothers in treatment for opioid use disorder (Kahn et al., 2017), highlight the critical role that educational programs that emphasize parenting skills can play in improving long-term outcomes associated with maternal substance use. Moreover, these data suggest that one mechanism underlying improved outcomes with regard to relapse may be decreasing the stress associated with parenting, which may be heightened in opioid using mothers.

Numerous preclinical studies have also examined the effects of both acute and chronic cocaine administration on parenting behaviors. Acutely, dose-dependent effects of cocaine are observed in postpartum females, with decreased pup-directed maternal behavior and suppression of maternal aggression (Johns et al., 1994; Vernotica et al., 1996; Johns et al., 1998). These effects appear to be transient and associated with increased locomotor activity. Chronic gestational treatment with doses of cocaine lower than 30 mg/kg are associated with few significant effects (Lubin et al., 2001), while doses at 30 mg/kg or higher, whether continued during the postpartum period or withdrawn one day prior to delivery, result in maternal neglect (Johns et al., 1994; Johns et al., 1997; Lubin et al., 2001). In contrast to findings following acute cocaine, chronic gestational treatment at the 30 mg/kg dose results in a dramatic increase in postpartum aggression, even towards a submissive intruder. This aggression is not associated with litter protection and should not be seen as adaptive as litter and mother are in increased danger during this period. While the mechanisms underlying these effects remain to be determined, several studies find strong correlations with oxytocin system dysregulation associated with cocaine treatment (Nephew and Febo, 2012; Williams and Johns, 2014). Other proposed mechanisms include cocaine-induced increases in dopamine, norepinephrine and serotonin release within the maternal circuit (Lubin et al., 2003) which may be further regulated by circulating levels of gonadal hormones across the postpartum period (Vernotica and Morrell, 1998; Perrotti et al., 2001; Tobiansky et al., 2016). Additional effects mediated by dysregulation of the HPA axis may also play a role in these effects (Zhou et al., 2003). Moreover, studies suggest that females that were not exposed to cocaine prenatally but were reared by cocaine-exposed dams, also demonstrate disrupted maternal behaviors (Johns et al., 2005), indicating behavioral transmission of a deficient maternal care phenotype to future generations. These findings suggest that cocaine exposure, particularly at chronic high doses, increases maternal neglect and heightened aggression. Interestingly, studies using conditioned place preference for either cocaine or pups, demonstrate that during the early postpartum period females have an increased preference for pups over cocaine, while the opposite is observed during the late postpartum period (Seip and Morrell, 2007). These maternal preferences were associated with differential gene expression in key nodes within the maternal circuit, including the MPOA, prefrontal cortex, nucleus accumbens and basolateral amygdala (Mattson and Morrell, 2005). Such findings highlight the highly rewarding nature of pups to maternal animals and suggest that the strength of this reward diminishes over the postpartum period, perhaps in response to a changing hormonal milieu and decreased response demands.

While the majority of preclinical and clinical findings related to drugs of abuse and maternal neurocircuitry focus on opioids or cocaine, the impact of other drugs on the expression of maternal behaviors has also been examined. For example, acute alcohol intoxication disrupts the expression of maternal behavior, although these effects subside once the female develops metabolic tolerance to alcohol (Pepino et al., 2002). Prenatal exposure to alcohol, however, leads to disruption of maternal behavior in adult F1 females (Barron and Riley, 1985); once again highlighting critical developmental periods during which chemical exposures can significantly disrupt the future establishment of maternal behavior. Similarly, exposure of squirrel monkeys to tetrahydrocannabinol (THC) postpartum, dampens the pup-directed activity of mothers, particularly in response to separation distress (Kaplan, 1979). Meanwhile, F1 offspring exposed to THC prenatally demonstrate alterations in both reward and stress-related circuits (Murphy et al., 1995; Navarro et al., 1995) which ultimately could impact their own parental behavior. Beyond drugs of abuse, other pharmaceuticals may also impact maternal behavior circuitry. Indeed, a number of preclinical studies observed disruptive effects of several classes of antidepressants and antipsychotics on certain aspects of maternal care (Johns et al., 2005; Li et al., 2005), likely due to their effects on the biogenic amines and their receptors. Such findings, however, should not be used to suggest limiting the use of these medications in postpartum women, as both depression and psychosis present exponentially greater risk to the health of both the mother and infant (Mullick et al., 2001; Spinelli, 2004).

Overall, the current findings demonstrate significant interactions between commonly used and misused drugs on neural systems regulating maternal care. These effects are often dose-dependent and may be more dramatic when drugs are administered at high doses or in individuals with no prior exposure. Following chronic exposure, the impact of withdrawal and tolerance need to be considered. Perhaps most relevant to human exposure, effects that negatively impact the reward valence of the pup or which increase non-adaptive aggression are of greatest concern. Additional consideration should be given to adaptations in the HPA axis in both the mother and her offspring. As discussed previously, the HPA axis plays a critical role in regulating maternal care in response to different environmental challenges. All of the aforementioned drugs modulate the HPA axis and often induce long-lasting alterations in stress responsiveness (Armario, 2010; Jacobson, 2014). Thus, under certain environmental conditions, prior exposure to drugs of abuse may fundamentally alter the expression of maternal care. So, while the failure to observe significantly disrupted maternal care following drug exposure may demonstrate the robust nature of this critical behavioral repertoire, one must also consider the possibility that effects may only emerge in the presence of increased demand. Moreover, even studies that report limited disruptions in the maternal care in the drug-exposed dam, intergenerational effects are still feasible. Indeed, many studies report effects of prenatal drug exposure on the development of neural circuits critical for maternal responsiveness, including effects on the HPA (Rubio et al., 1995; Slamberova et al., 2004; Hamilton et al., 2005; Laborie et al., 2005; Williams et al., 2012) and HPG (Raum et al., 1990; Smith et al., 1995; Dutriez-Casteloot et al., 2001; Younes-Rapozoet al., 2013) axes, both of which play a critical role in neurodevelopment. Thus, in addition to behavioral transmission of impaired maternal behavior from one generation to the next, as observed in preclinical models of cocaine (Johns et al., 2005), neurodevelopmental effects on both reward- and stress-circuitry may underlie intergenerational vulnerabilities that lead to suboptimal maternal care under conditions of increased environmental demand. Similar to outcomes observed following exposure to EDCs, these findings suggest that the multigenerational impact of maternal drug use may propagate risks to this critical behavior across generations particularly under challenging environmental conditions.

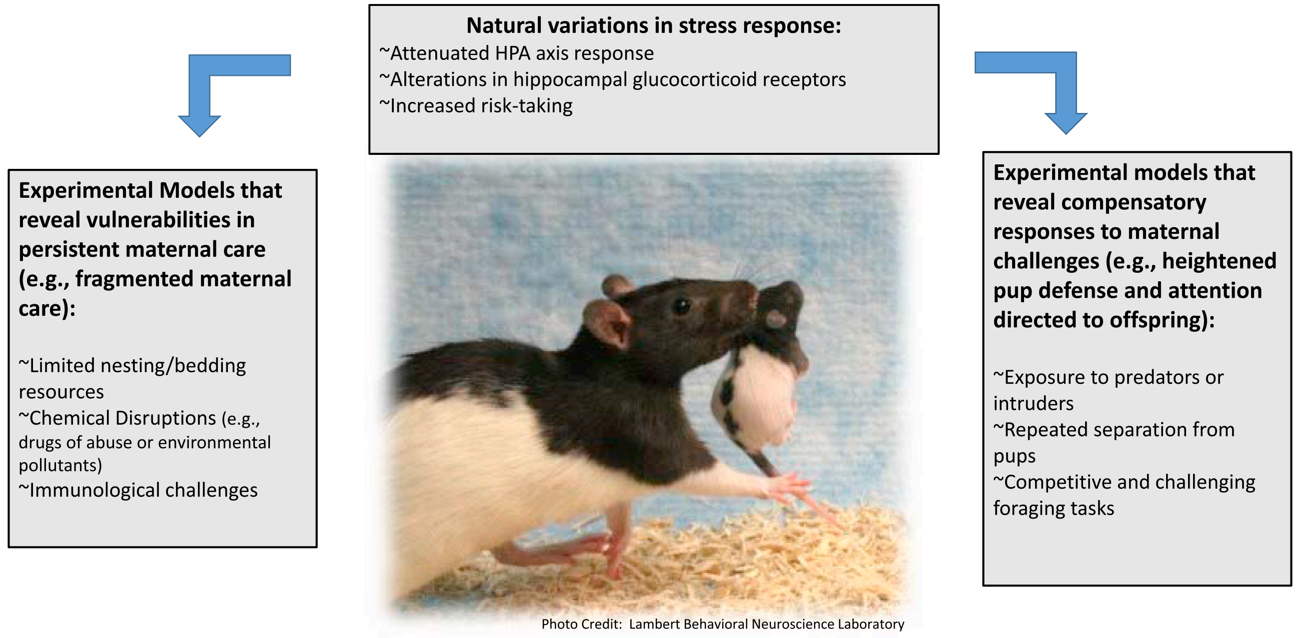

Fig. 1. Context-Specific Maternal Responses. Decades of laboratory rodent research have contributed to our understanding of the female's ability to care for offspring in the midst of external and internal challenges.

5. Translational considerations

Although mammals have evolved various adaptive stress responses that contribute to the maintenance of both parental and offspring health, some stressful experiences result in allostatic load and compromised parental care. With the stress response so intricately involved in mental health, any fluctuations to this system in parental animals may have psychiatric outcomes—for both the parent and offspring. Up to 20% of women, for example, exhibit evidence of mental illness such as depression during pregnancy and the postpartum period (Bennett et al., 2004). Risk factors such as a prior history of depression, stressful lifestyle, and low socioeconomic status have been associated with increased maternal mental illness during the perinatal period (Lancaster et al., 2010; Stewart 2011; Pawluski et al., 2014). The previously described dysregulated neurogenesis in rodent models experiencing stress exposure during pregnancy provides an insight into what may be occurring in human mothers (Falconer and Galea, 2003; Shors et al., 2007), especially considering that low levels of neurogenesis have been associated with anxiety and depressive disorders (Pawluski et al., 2009; Wainwright and Galea 2013). Further, reduced dendritic spine length in the CA3 hippocampal area have been observed in rodent females stressed during the last two weeks of the pregnancy (Pawluski et al., 2012); if such effects occur in human mothers, then an increased susceptibility to cognitive and emotional disorders emerge. The reduced gray matter recently reported in human females suggests that these effects occur in both rodent and human maternal models (Barha and Galea, 2017; Hoekzema et al., 2017).

The symbiotic relationship between maternal stress dysregulation and offspring development presents additional translational considerations. Fragmented maternal care, observed in rodents with low resources [modeling low socioeconomic status (SES) in humans], or those predisposed to attend less to their offspring (e.g., low-licking mothers), has been associated with synergistically disrupted offspring HPA activity (Weaver et al., 2004; Ivy et al., 2008; Moussaoui et al., 2016; Walker et al., 2017). Another effect of low resources and fragmented maternal care in humans is delayed language development. Compromised parent–child interactions have been observed to result in diminished verbal interactions between parents and children, providing a model similar to the fragmented maternal care in rodents raised with restricted bedding resources (Huttenlocher et al., 2010). Further, intelligence scores in children raised in low SES contexts scored approximately 6 points lower than those raised in high SES backgrounds at two years of age, a difference that had tripled by age 16 years of age (von Stumm and Plomin, 2015). In addition to compromised intelligence, negative health benefits have also been observed in children raised in low SES environments that are characterized by fragmented parental care (Aber et al., 1997). Related to mental health, prenatal stress in the form of prenatal depression has far-reaching effects in offspring such as decreased activation in the prefrontal cortex and accompanying maladaptive coping (Reising et al., 2018). Hence, prenatal and postnatal stress that compromises parental care has long-lasting effects on offspring.

Similarly, dysregulation of parental care following exposure to exogenous chemicals can also induce persistent effects. Whether effects emerge in adults exposed pre- or postnatally to EDCs or are the result of ongoing drug use during the postpartum period, the outcome is the same, i.e. the influence of parental care on the well-being and development of offspring may be suboptimal. Certainly ongoing SUDs (including alcohol use disorders) negatively influence the continuity of parental care and are associated with increased reports of child neglect (Goldstein et al., 2013). Additional findings suggest that substance abusing women with a history of 5 or more adverse childhood events, report increased parenting stress and have children at increased risk for abuse and neglect (Nair et al., 2003). Thus, their own children are more likely to experience a significant number of adverse childhood events, which then increase their risk of developing a SUD; interestingly the effect of adverse childhood events on early initiation of substance use is only significant in females (Chatterjee et al. 2018). Studies in rodents also report effects of early life stress on drug intake patterns, suggesting face and perhaps construct validity (Kalinichev et al., 2003; Moffett et al., 2007), with more recent studies implicating epigenetic modifications within the nucleus accumbens in response to early life stress as a critical mediator of increase risk for substance abuse (Lewis et al., 2016). To break this cycle of early childhood adversity within the context of continuing SUD, interventions that focus on providing training and support around parenting are needed. Such interventions have shown some success (Donohue et al., 2017), however, their use is limited. Given the critical role of parental care in the future health and well-being of offspring across species, targeted interventions for parents may be the best mechanism for modulating risk factors in future generations.

6. Concluding thoughts

Pioneering neuroanatomist Paul MacLean suggested that social vocalizations evolved in mammals to facilitate a mother's location of separated offspring, since mammalian survival depends on continuous and reliable maternal care (MacLean, 1996; Lambert, 2003). Indeed, the altricial nature of mammalian offspring requires a sophisticated social system to sustain critical interactions to sufficiently care for offspring. As discussed in this review, disruptions in maternal and, in some cases, paternal, care most often result in negative consequences for parents and offspring. Perhaps to optimize offspring health and reproductive fitness, physiological adjustments have evolved to dampen the maternal energy-expensive stress responses in some contexts (e.g., when faced with acute stressors) and, alternatively, to heighten stress responses (e.g., maternal aggression) when a threat has been detected. In spite of the robustness of parental responses, laboratory explorations of rodents indicate that certain conditions, such as the restriction of bedding and nesting resources, can result in fragmented maternal care. Additionally, exposure to chemical disruptors (e.g. drugs of abuse) or environmental toxins, can disrupt the delicate balance of endocrine, physiological and neuroanatomical factors in ways that threaten the quality of parental care (see Fig. 1 for summary of maternal responses to various challenges). Both laboratory investigations and human clinical research confirm the sensitivity of healthy parental responses to exposure to chemical disruptors. Given the importance of parent-infant interactions to the development of healthy neural and physiological systems, compromises in the quality of these social responses has negative consequences. As evidence about the impact of threats to optimal familial interactions continues to emerge, it is imperative that more targeted preventative strategies for vulnerable parents are identified and translated into effective treatment approaches.

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Appendix A. Supplementary material

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