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The parental brain: Transformations and adaptations

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ABSTRACT

Few evolutionary transformations rival the complex neurobiological modifications accompanying the mammalian transition to parenthood. Research conducted primarily in maternal rodents highlights the engagement of multiple areas of the brain to initiate and maintain interest in resource-depleting vulnerable pups throughout lactation. Interestingly, many modifications marking the transition to motherhood result in adaptive response options that persist well beyond the weaning of pups; specifically, adaptations such as cognitive flexibility, emotional regulation and enhanced social attentiveness coincide with the parenthood transition and have emerged as defining characteristics of the most adaptive mammalian species. The paternal brain also results in interesting modifications that, in some biparental species, mimic the effects observed in females. Taken together, research suggests that the designation of “parent” is less of a categorical variable and more of a continuous variable, with the quality of nurturing responses directed toward offspring influenced by many factors such as predisposed sensitivity to reproductive hormones, nature and duration of exposure to offspring, number of reproductive experiences, adequate resources, and composition of the social environment. Indeed, the transition from an animal focused on self-preservation to one that is responsive to the needs of other animals, and the accompanying increases in reproductive fitness, represent a significant evolutionary transition, or upgrade of sorts, leading to a more diverse array of response options to meet the challenging demands of changing environmental and social terrains.

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1. Introduction

With our society's current fascination with upgrades, revisions and extreme makeovers, it is interesting to consider the context of the most significant upgrades in the evolution of the mammalian brain. As suggested by anthropologist and author Sarah Hrdy [1], although glimpses of parental care have been observed in mammalian terrestrial predecessors such as reptiles, the evolution of mammalian maternal care “marked a watershed in the way animals perceived other animals, with profound implications for the way vertebrate brains were structured.” (p. 39).

The mammalian maternal brain likely began around 220 million years ago when offspring first emerged in a form so altricial that sustained maternal care was necessary for their survival. Critical to the success of these vulnerable offspring was the provisioning of nutrients for their growing bodies. Although not known for certain, it has been theorized that mammalian predecessors excreted fluids from sweat glands or apocrine glands, perhaps to provide a protective coating or cooling agent for eggs. Regardless of its source, the nutrient exchange between the maternal animals and offspring required the dramatic transformation of the maternal animal's body fluids to nature's original “baby formula”. An additional challenge involved the

transfer of this essential fluid from mother to offspring. It is thought that vasotocin, the ancient precursor of OT and AVP involved in mating and egg laying in amphibians, initially facilitated this fluid regulatory challenge; interestingly, AVP and OT, involved in the regulation of minerals and water in terrestrial animals, also contribute to parental responses [2–4]. Although both neuropeptides are present in males and females, OT is known for its involvement in birth and lactation in maternal animals (additionally, the reproductive hormone, prolactin, plays a significant role in lactation) [5–8] and AVP, in addition to fluid regulation (e.g., blood pressure), is associated with social recognition in the paternal animal [9,10]. Thus, in addition to prolactin, neuropeptide oxytocin and vasopressin may represent essential neurochemicals that set mammals on the path of parenthood.

Once pregnant, many adaptations must occur to prepare the mammalian mother to respond appropriately to her impending delivery. In the absence of parenting classes, most mammals rely solely on physiological changes initiated and maintained by key reproductive hormones such as prolactin's activation of receptors widely distributed throughout the brain. Further, prolactin stimulates maternal behavior upon the arrival of the offspring and plays a role in modulating the stress response during pregnancy [5].

In addition to the adaptations required for prenatal development and postnatal nourishment, of interest in the current review is the transformation of the mammalian brain, the largest brains relative to body size in the animal kingdom, as it adopted the job description of nurturing parent. Recent research suggests that the initial brain

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adaptation in early mammals involved the expansion of the olfactory bulb, perhaps facilitating communications between maternal animals and offspring or honing the animals' ability to hunt at night when the larger predators were less of a threat [11]. As nature transformed the maternal, and on occasion, the paternal brain, mammals were forced to direct their awareness and attention away from exclusive self-care toward the care of another animal, from social tentativeness to social attentiveness. With helpless offspring to care for, mammalian parents needed to anticipate and subsequently meet their many needs to assure survival to reproductive maturity [1].

As discussed below, the parental neurobiological transformation is characterized by (1) the acquisition of *on-the-nest* responses directed to helpless offspring and (2) modifications and adaptations of responses beyond the scope of traditionally viewed parental responses (i.e., *off-the-nest* responses such as foraging) to provide adequate resources for the metabolically expensive offspring. Although not intended as a thorough review of the neurobiology of parental responses, the current review focuses on factors hypothesized as integral to the necessary transformations and adaptations for the provision of nurturing responses directed toward offspring.

2. *On-the-nest* parental responses

The traditional maternal responses assessed in rodent maternal models typically include retrieving, nursing and grooming behaviors, all necessary for successfully nurturing altricial offspring to reproductive maturity [12]. With the exception of nursing, these responses are also observed in male parents, although at a less consistent rate. As described below, the variability of paternal responses provides an opportunity to determine neurobiological mechanisms accompanying the acquisition of parental responses. Although specific mechanisms related to differential parental investments between mothers and fathers have yet to be clarified, rodent research focused on manipulations of the *Peg3* gene suggests that the mutation of this gene is associated with diminished maternal care (e.g., *Peg3*-knock out females exhibit less licking/grooming and spend less time nursing their offspring). Contributing to the perceived inequity in parental investment between males and females is the observation that only the father's *Peg3* gene, located on proximal chromosome 7 in the mouse, is selected while the mother's copy is turned off in the offspring [13]. Further research is required to elucidate how both genomic and nongenomic mechanisms are translated into nurturing responses in male and female parents.

2.1. *The maternal brain: no room for error*

Although opportunities exist for errors, in general, the maternal brain is amazingly reliable and consistent. Considering that, among the world's 5400 mammalian species, a majority of fathers exhibit little interest in the female and impending family following copulation, the female is essential for offspring survival. Thus, in nature's popular single mother family model, the female's parental response is required for the survival of the mammalian species, leaving little room for errors. In transforming from the vertebrate maternal model requiring no parental attention (as observed in most reptiles) to one requiring maximal attention, key modifications in the brain were necessary. As observed by Paul MacLean, three behaviors differentiating mammalian brains from reptilian brains included nursing, audiovocal communications between the mother and offspring and social play [12]. Thus, as the maternal mammal shifted her attention away from herself to her offspring, the fundamental neuroarchitecture was established for complex, affiliative social responses [14]. As seen in Fig. 1, a more complex brain accompanied characteristic behavioral – including parental behavioral – shifts from reptiles to mammals [15]. The squirrel monkey mother, as depicted in the figure, remains in constant contact with her offspring for the first month, ultimately carrying the offspring dorsally because



Fig. 1. Artistic representation of the transformations that have taken place throughout the evolution of the neomammalian brain of the squirrel monkey. As the paleomammalian brain evolved from reptiles (shown as the brainstem), more complex social interactions began to emerge and these responses continued to become more sophisticated with the emergence of the paleomammalian (shown as the limbic areas) and neomammalian brain (characterized by a complex cortex). This image was originally published in a special edition of *Physiology and Behavior* devoted to the lifetime contributions of Paul MacLean [15]. Design by Kelly Lambert; artwork by Jacqueline Berry.

the infant is too large to carry ventrally without impeding her movement. For this maternal animal, caring for offspring represents a significant energy investment [16].

Concerning neurobiological mechanisms accompanying the acquisition of maternal behavior, transformative events likely begin prior to mating. During the brief time of the estrous cycle when progesterone and estrogen levels peak, dendritic spines emerge on the pyramidal cells of the hippocampus CA1 area, perhaps to facilitate the location of a potential mate or to begin the process of preparing the brain for the increased demands accompanying motherhood [17,18]. Beyond the hippocampus, estrogen receptors are localized throughout the CNS and, when activated, result in rapid effects that are mediated by receptors associated with either the plasma membrane or intracellular signaling cascades [19]. Focusing on specific brain structures involved in the preparation for impending motherhood, research with rodents has identified several modifications necessary to bias the females' attention toward the pups that, to the virgin female, were viewed as aversive stimuli [20]. Specifically, the important role of the medial preoptic area (MPOA) of the hypothalamus, an area involved in other behaviors such as sexual behavior, has been established. Acting as a primary integrative hub for maternal responsiveness, the MPOA has rich connections with the ventral tegmental area, the nucleus accumbens, and the medial prefrontal cortex. When the MPOA is temporarily deactivated early during lactation, females trained in a conditioned place preference test with compartments associated with either pups or cocaine cease to prefer the pup compartment, selecting the cocaine chamber as observed in later stages of lactation [21]. In addition to the initial motivation

to interact with the pups, the maternal response incorporates the brain's reward neurocircuitry to motivate maternal mammals to continue to care for demanding pups over sustained durations. Consequently, the ventral tegmental area, when temporarily deactivated, also blocked pup preference but, interestingly, inactivation of the nucleus accumbens had no impact on pup chamber preferences. The nucleus accumbens, however, has been shown to be important in other assessments of maternal motivation; specifically, dopamine antagonism or accumbens DA depletion interferes with postpartum maternal motivation, although nursing remains intact [22,23]. Elevated extracellular levels of dopamine, involved in reward neurocircuitry, have also been observed when the maternal animals interact with the pups [24]. Interestingly, when female lactating rats were assessed via functional magnetic resonance imaging, nucleus accumbens activity was increased, as well as other components of the reward circuitry including the prefrontal cortex, caudate/putamen and ventral pallidum [25].

Brain areas comprising the medial prefrontal cortex area (e.g., the cingulate, paralimbic, and infralimbic cortical areas) communicate with both the MPOA and the reward/motivation circuitry; additionally, the medial prefrontal cortex processes sensory information necessary for pup recognition. This area is also known for contributing to executive functions such as directing attention toward salient and meaningful cues, planning, cognitive and behavioral flexibility and decision-making. Accordingly, lesions of the cingulate cortex component of the medial prefrontal cortex area resulted in disorganized maternal responses [20,21]. Based on findings obtained with rodent models, the maternal brain appears to have developed several response strategies including: (1) a predisposed preference for pups (2) reward and/or pleasure associated with interacting with the pups, and (3) efficient planning and cognitive abilities required to meet the many demands of the growing offspring.

Focusing on imaging studies of human mothers, when first-time mothers listen to their own versus other-baby cries, increased activity is observed in several brain regions such as the insula, amygdala, cingulate, striatum, midbrain, and orbitofrontal cortex. It is also thought that increases in dopamine serve as a key neurochemical response to the baby cry that allows the mother to focus her attention on the necessary parental response [26,27]. From the first weeks postpartum to about the third month, increased gray matter has been found in the prefrontal cortex, pre- and post-central gyrus, the parietal lobe, thalamus and insula. Further, the human mother's positive perception of her baby during the early postpartum phase was correlated with increased gray matter volume, this time in a cluster of midbrain areas including the substantia nigra, amygdala and hypothalamus [28].

When compared to the maternal circuits identified in the rodent data, the human imaging data confirm that the maternal response is a highly conserved response incorporating *hypothalamic–midbrain–limbic–paralimbic–cortical circuits* in support of parental responses directed to offspring [29]. Considering the pervasive neurochemical and neuroanatomical mechanisms accompanying the transition from the virgin female exhibiting an aversion to pup cues to a maternal female exhibiting a preference for pups over cocaine, the shift to a nurturing parent requires a substantial neural transformation.

2.2. The paternal brain: built for flexibility

Whereas a dysfunctional maternal brain results in the death of offspring, in most mammalian species, paternal responses toward offspring have more variable consequences for the offspring. In the rats, for example, maternal animals successfully raise large litters of pups with no paternal assistance. Although maternal mammals successfully raise their young as single mothers, or with assistance from alloparents, about 5% of mammalian species exhibit variable forms of paternal care [30]. Paternal care ranges from the occasional babysitting observed in baboons to almost exclusive care without help from other family members as observed in the owl monkey [31]. Focusing exclusively on

humans, paternal responses may be extremely facultative, expressed only under the most demanding situations, or obligate, with infants typically not surviving without the contributions of fathers [1]. Accordingly, males, even males designated as *paternal*, may contribute a little, a lot or no paternal care toward their offspring. The offspring of human fathers who have been deserted by their fathers may still fare well due to attention from alloparents [1]. However, recent research suggests that, in young children, higher mortality rates are observed in single parent households compared to families with married parents. Although these mortality rates were also affected by low education level and socioeconomic status, the number of parents was also influential [32]. Thus, paternal investment isn't always related to offspring survival in species such as humans in which paternal care is not required for offspring survival, but evidence suggests that young children have an advantage in two-parent households.

Although a product of a different evolutionary path, a vivid example of paternal flexibility has been observed in the blue-footed booby bird. As is the case with most birds, booby birds are biparental with the males incubating the eggs and, once hatched, feeding and defending their brood for up to six months. When young male parents are sick their energy is diverted from the chicks to self-care to assure the male's health for raising future broods. However, when senescent male parents are sick, they exhibit a very different response. Instead of turning away, they become somewhat of a superdad and focus all their attention on the brood, which will likely be their last brood. Obviously, the genetic stakes are different for these two age groups and the paternal response reflects the differential outcome probabilities [33]. This avian example corroborates with mammalian data emphasizing the point that paternal responses directed toward offspring depend on several variables such as age, immunological competence, resource availability and the probability of future parenting opportunities.

Although research with rodents confirms that males experience hormonal alterations during copulation, pair-bonding and paternal care, the physiological effects are less extreme than experienced by maternal animals. The variability of the paternal responses, therefore, contributes to the value of the paternal model for obtaining information about the neurobiology of nurturing, parental responses [34]. Thus, males exhibiting high levels of paternal care provide a unique behavioral window to discern critical variables associated with heightened paternal and parental responsiveness. Even so, compared to the extensive research conducted on the maternal brain, mostly on the rat single parent model, relatively little research has been conducted on the paternal brain [35].

From the work that has been conducted on the paternal brain, both neuroendocrine and neuroanatomical factors have been identified as important in the maintenance of the male's nurturing responses. Focusing on biparental rodent species, prairie voles (*Microtus ochrogaster*), California deer mice (*Peromyscus californicus*), and degus (*Octodon degus*) have been the subjects used in a majority of the paternal brain research studies. Additionally, brain imaging has revealed neurobiological trends in human fathers (discussed below).

The comparative species approach is often used in rodent models to enable researchers to compare the paternal species to a closely related nonpaternal species (see Fig. 2). In *P. californicus*, castration reduced paternal responsiveness but, interestingly, had no impact on aggression; additionally, increased levels of prolactin and oxytocin have been observed in paternal males [10,36,37]. Arginine vasopressin (AVP), especially mediation of the AVP 1a receptor, is known for its role in social responses in mammals and, consequently, has been investigated in paternal models [38,39]. In prairie voles, paternal males exhibit altered densities of AVP-immunoreactive fibers in the lateral septum and habenular nucleus [40]; accordingly, V1aR antagonists suppress paternal care, an effect reversed by AVP agonists injected into the lateral septum [41]. Manipulation of the AVP system has been observed to enhance paternal responsiveness in the nonpaternal meadow vole species [42]. Thus, the distribution of AVP 1a receptor binding sites may underlie



Fig. 2. Comparative species paternal model. When male *Peromyscus californicus* mice with paternal experience encounter an unfamiliar conspecific pup they exhibit nurturing responses such as retrieval, grooming and crouching over the pup (above); male *Peromyscus maniculatus* mice with paternal experience, however, exhibit anxiety and escape responses in the presence of an unfamiliar conspecific pup (see below).

paternal care in various mammalian species [43,44]. Modifications in hormone levels also exist in human fathers; for example, circulating prolactin levels are higher in second-time fathers than in less experienced fathers [45].

Similar to the maternal model, the MPOA is involved in the paternal *P. californicus* mouse; specifically, lesions disrupt paternal responses [46,47]. Exploration of AVP fibers in this species has also implicated the bed nucleus of the stria terminalis (BNST), as decreased AVP immunoreactivity was associated with decreased paternal responsiveness [48]. Further, in our laboratory, we have compared *P. californicus* biological fathers to nonpaternal *Peromyscus maniculatus* biological fathers in

a family reunion scenario in which a pup is reintroduced after a 24 hour separation. As depicted in Fig. 3, biparental *P. californicus* males had more AVP-immunoreactive cells and fibers in the paraventricular and supraoptic nuclei than uniparental *P. maniculatus* males, an effect not observed in the BNST. Further, certain brain areas involved in fear and social stress such as the paraventricular nucleus of the hypothalamus, medial amygdala, and pyriform cortex were inhibited (as indicated by less fos immunoreactivity) in paternal *P. californicus* biological fathers compared to the nonpaternal *P. maniculatus* biological fathers [34]. Interestingly, the *Peg3* knockout female mice (described above) that exhibited less maternal behavior were also characterized as having increased

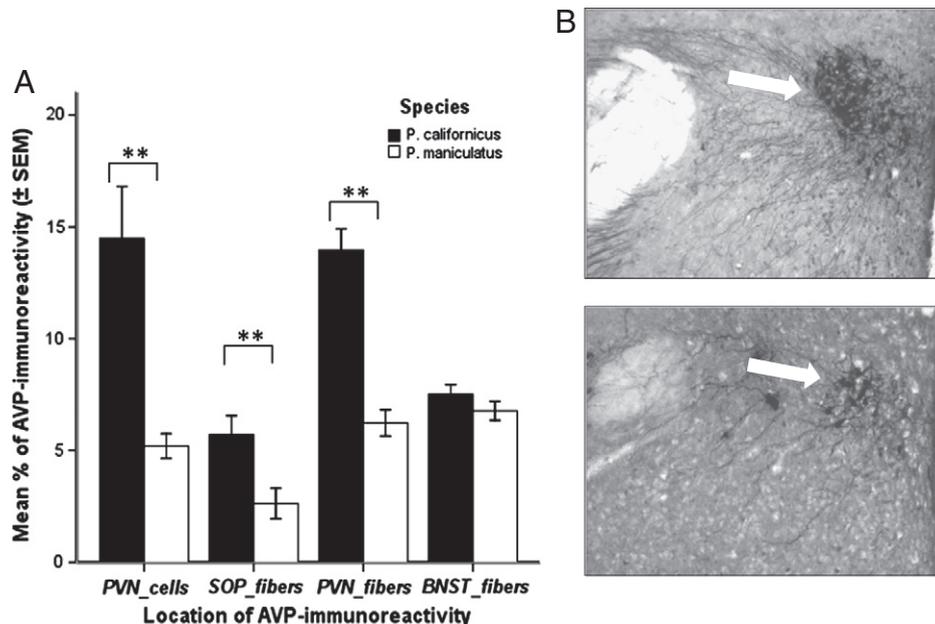


Fig. 3. Vasopressin immunoreactivity in peromyscus males. Mean percent (%) of AVP-ir in various brain locations. (A) *P. californicus* males had more AVP-ir in the PVN cell bodies (PVN cells; $t_{31} = 2.97$, $p = .009$); in fibers extending from this area (PVN fibers; $t_{56} = 6.71$, $p < .0001$); and fibers extended in the direction of the supraoptic nucleus (SON; $t_{57} = 2.79$, $p = .008$). (B) Photomicrographs of PVN and lateral fibers in *P. californicus* (above) and *P. maniculatus* (below).

fear and neophobia, suggesting that modified emotional responses to novel stimuli, including social stimuli, may represent a fundamental adaptation in parental animals [13]. Further, these data partially support a theory proposed to explain human imaging data suggesting that the parental response is a push–pull system in which reward circuits are activated whereas the avoidance circuits are less active [49].

In a recent preliminary study, *P. californicus* paternal mice exposed to a conspecific alien pup placed in a small mesh enclosure in our laboratory exhibited interest in the pup and, upon sacrifice, their brains exhibited less fos-immunoreactivity in the anterior cingulate cortex, insular cortex and nucleus accumbens than *P. maniculatus*, the nonpaternal species that exhibited little interest in the pups. The cingulate and insular data suggest that altered sensory gating may be involved in a threatening paternal experience, as the processing of less relevant sensory information may be decreased to optimize neural recruitment for the resolution of the impending cognitive or emotional challenge (i.e., rescuing the distressed pup from the enclosure) [50].

The cingulate cortex has also been implicated in human neuroimaging data; specifically, it has been suggested that the cingulate cortex, in this case the posterior cingulate, remains in a continuous state of arousal gathering information about the environment until a specific task requires more specific attention, resulting in decreased activity [51]. Interestingly, women, but not men, exhibited less activation in the anterior cingulate cortex when exposed to infant crying (regardless of their parental status), suggesting that this sensory-gating effect extends to the parental situation [52]. Also interesting is the observation in human subjects that the medial prefrontal cortex, which, as described above, contains the anterior cingulate cortex and has been implicated in the maternal response, exhibits reduced activation when subjects anticipate anxiety [53], a response likely associated with a crying child. Although comparisons of the frontal cortex between rodents and humans are controversial, behavioral and neurocytoarchitectural evidence suggests that, although distinctions exist, the rodent medial prefrontal cortex serves as a valuable model for the human prefrontal cortex [54]. When the brains of human fathers have been scanned, similar to mothers, activation has been observed in areas such as the amygdala, basal ganglia, cingulate, and occipital cortices while gazing at their infants [55]. However, compared to mothers hearing their babies cry, fathers exhibited less activity in the amygdala and basal ganglia [56].

Exhibiting very different parenting strategies than mothers, fathers employ varying levels of interest in their offspring. Considering that newborns frequently require more parental care than a mother can provide, the variability of the father's contribution, along with the potential of alloparenting in some species, adds to the complexity of the parental brain [57].

3. Off-the-nest parental responses: value-added applications for parental mammals?

Working with collaborator Craig Kinsley and our many students over the years, we have been interested in looking beyond the “on-the-nest” parental behaviors discussed above to focus on the myriad additional responses the maternal mammal performs to successfully raise her offspring. She must be an efficient forager so that she can return to her vulnerable pups before they are harmed by predators. And she should expend minimal energy in her foraging forays considering that she typically has about 10 pups to feed and tend. She also needs to exhibit enhanced social vigilance to distinguish friend from foe as both conspecifics and potential predation species gain proximity to her pups [58]. Thus, the maternal rat brain must transform in many ways to assure optimal care and survival of helpless pups.

3.1. Cognitive advantages

Initially we investigated spatial memory in two different foraging tasks, a radial arm maze and a dry land maze (a dry land version of

the Morris water maze in which animals learn which of eight previously baited wells will remain baited throughout testing trials) [18]. In both studies, the maternal animals exhibited enhanced spatial memory; further, pup-sensitized virgin females also experienced an advantage. In another version of the dry land maze, we placed groups of three females in the arena at the same time (a virgin, pup-sensitized, and maternal animal of comparable age and size) and required the animals to compete for the food reward—i.e., to cope efficiently with the anxiety associated with being placed with unfamiliar conspecifics and focus on the task of locating the food reward. Although all animals were placed on the same food restriction schedule, the maternal animals consistently obtained the reward faster than the other animals (60% success rate for maternal animals vs 7% success rate for virgin females [58–60]). In several studies we assessed animals approximately two weeks past lactation to avoid any confounds related to altered metabolic rates in the lactating females; once again, the maternal animals performed better throughout testing in the dry land maze task, as well as the probe trial where no well was baited and the memory for the task was assessed by recording the amount of time spent in proximity to the previously baited well [61]. These improvements in spatial memory also appeared to be long-term as older animals with maternal experience continued to exhibit enhanced foraging skills and spatial memory [59,62].

Another cognitive modification that we have observed in maternal rats is associated with cognitive flexibility. In an unpublished study assessing virgin, primiparous and multiparous animals in the attention-set shifting paradigm, task requiring animals to initially learn a salient cue associated with reward (e.g., coconut smell predicts reward in digging pot) and subsequently shift their response strategies when a new salient cue is introduced. Thus, the animals have to assess current information about likely “payoffs” in the context of ignoring previously reinforced stimuli (e.g., intra-dimensional shifts to another smell or interdimensional shifts from smell to tactile stimuli). In the more challenging tasks, especially the interdimensional shift, the primiparous rats performed better than the virgins and the multiparous rats exhibited fewer errors than the primiparous animals. In general, the multiparous animals maintained scores close to 100% accuracy whereas the nulliparous animals were closer to 50% accuracy shifts throughout testing [58,63].

Following up on the observed changes in spine densities coinciding with the rat's brief estrous cycle, we have observed changes following the more prolonged state of altered steroid hormones, i.e., pregnancy and lactation. Specifically, multiparous animals have denser populations of spines in the CA1 area of the hippocampus during late pregnancy and lactation [64]. Glial cells also exhibit increases in size, based on gfap-immunoreactive tissue [60]. Further, less amyloid precursor protein (associated with cognitive decline) was observed in senescent females with maternal experience [62]. Focusing on biparental marmosets, increased spine density on pyramidal neurons located in the prefrontal cortex was observed in first time fathers [65]. These modifications in the hippocampus and prefrontal cortex likely contribute to the cognitive effects observed in parental mammals.

To investigate the effects of maternal experience on recovery from brain injury, nulliparous and multiparous rats were recently trained in the dry land maze and injected with kainic acid, a naturally-occurring analog of the excitatory amino acid neurotransmitter glutamate known to damage the CA3 area of the hippocampus [66,67]. Animals were assessed in the task one day following the brain injury by exposing them to a probe test. Among animals receiving the KA injection, maternal rats spent a similar amount of time in proximity to the previously baited well as the saline injected mothers (the group exhibiting the strongest memory); regardless of injection, the virgins spent less time in proximity to the previously baited well. On the next day, maternal females also exhibited protection against performance deficits in the novel object test assessing the animal's memory of an object they had previously investigated. In an accompanying experiment in which

degenerating cells were assessed, no differences were observed between the maternal and virgin animals receiving KA injections; thus, in spite of similar levels of neural insult, the maternal animals were partially protected against the behavioral deficits associated with hippocampal damage [68]. These preliminary results were especially interesting considering research suggesting that the reproductive hormone progesterone has been found to offer resilience in traumatic brain injury [69,70]. Further, previous research has shown that lactating females also experience protection against neural insult in the hippocampus following excitotoxicity [71].

We have also assessed spatial memory in the paternal *P. californicus* and have found that fathers performed better than the pup exposed and pup-naïve virgin groups on the key transition day of training, during which animals learn that only one well is baited. This behavioral effect was complemented by increased fos-immunoreactivity in the fathers' hippocampal CA1 and CA3 areas [72]. Focusing on neuroplasticity, increased nestin (an intermediate neurofilament expressed during CNS development as well as during restructuring phases of mature neurons [73–75]) was observed in the pup exposed virgins, suggesting that pup exposure, in the absence of a pregnant female, alters hippocampal neurons [72,76]. The potential behavioral plasticity observed in the pup-exposed males is in agreement with enhanced spatial memory in pup-exposed females [18,61], suggesting that the pups may provide a form of enriched environment for parental (and nonparental) rodents.

Investigations of neuroplasticity effects underlying behavioral plasticity in parental animals have produced somewhat confusing results. Tracking the impact of neurogenesis and other measures of neuroplasticity have suggested that, in some animals such as sheep, neurogenesis decreases during the perinatal period perhaps to favor the selection of neurons involved in olfactory recognition of offspring. Rodent research also suggests that rates of neural proliferation in the hippocampus are decreased or unaffected during pregnancy, parturition and the early postpartum period, depending on the specific phase investigated [77,78]. Wild pregnant meadow voles, for example, had lower levels of hippocampal cell proliferation than meadow voles captured during the non-breeding season [79]. Location within the brain also matters; increased rates of cellular proliferation have been observed in the subventricular zone of pregnant rats [80,81]. Nulliparous rats exposed to pups also exhibited increased cell proliferation in the hippocampus. In rodents with reproductive experience, the ratio of surviving cells at the time of weaning is higher in multiparous than primiparous females; thus, gains in neuroplasticity occurred in accordance with the number of reproductive experiences [77].

In biparental species, fathers have been shown to exhibit enhanced olfactory neurogenesis [82]. Although just 20 min of pup exposure resulted in increased rates of cell proliferation in male prairie voles [83]; reduced cell survival has been observed after three weeks of pup exposure in *P. californicus* mice [84]. Preliminary results in our laboratory suggest that five days of pup exposure have also been associated with increased nestin-immunoreactivity (cellular restructuring) in experienced fathers and increased rates of cellular proliferation (ki-67-immunoreactivity) in pup-exposed virgins [76]. Interestingly, higher rates of cellular proliferation in the pup-exposed virgins than in biological fathers appears to contradict the notion of parenting-induced neuroplasticity (as observed in some maternal studies as well); however, this finding could be explained by the presence of higher rates of cellular proliferation during the male partner's pregnancy in preparation for the arrival of the pups. Hence, the increased rate of cell proliferation could have occurred earlier in the biological fathers.

Considering the neuroplasticity research conducted on the parental brain thus far, in spite of the variable results related to neurogenesis, glial plasticity (as described earlier in this section) appears to be a bit more consistent. An up-regulation in glial plasticity, for example, has been observed in the cingulate cortex of rats as early as three hours postpartum; further, changes in MPOA cell volume appear during this early postpartum time as well [85,86]. Additionally, altered

spine density has been consistently observed suggesting that the restructuring of existing neuronal circuits plays a significant role in the transition to the parental brain [60,87]. Accordingly, we plan to extend the examination of neuroplasticity variables recently explored in the paternal brain (e.g., nestin-immunoreactivity) to the maternal brain in the near future.

3.2. Emotional advantages

Another off-the-nest advantage observed in experienced parents involves emotional responses. Considering the high energy demands required for lactation, energy devoted to the stress response may be especially costly during this time; correspondingly, the stress response is altered during lactation, conserving energy in order to meet the taxing metabolic demands experienced by lactating mammals. Comprising somewhat of a paradox of emotional expression in the female, lactating females are both hyper-responsive in terms of defensively protecting her offspring and hyporesponsive, considering her lower stress hormone levels during lactation [88,89].

When placed in a novel environment, primigravid, multigravid, and virgin rats were observed for 30 min and their brains were subsequently harvested for an analysis of fos-immunoreactivity. In addition to showing fewer signs of stress in the open field, lower levels of fos-immunoreactivity were observed in the basolateral amygdala and the hippocampus CA3 area. In a second experiment with nulliparous, primiparous, and multiparous animals, maternal animals exhibited less fos immunoreactivity in response to restraint stress [90].

Long-term effects on emotional responses were observed when multiparous, primiparous and nulliparous rats were repeatedly tested on an elevated plus maze every four months; although no differences were observed at six months, the primiparous animals exhibited less anxiety than the nulliparous animals at 10, 14, 18 and 22 month assessments and the multiparous animals spent more time in the open arms at 10 and 14 months [59].

The aforementioned research suggests that the maternal animals experience altered emotional responses throughout pregnancy, lactation and beyond the weaning of pups. More efficient stress responses may also serve a neuroprotection effect across the lifespan of the females, contributing to some of the neuroplasticity measures discussed above.

Focusing on the paternal *P. californicus* mice, we exposed fathers, pup-exposed virgins and pup naïve virgins to two environments designed to elicit an anxiety response: a closed cage containing a sample of fox feces and an open field with a novel object placed in the center. In this particular study, the fathers had weaned their first litter and, along with one group of the virgin mice (i.e., the pup-exposed virgins) were exposed to three days of 10 minute exposure to an unfamiliar pup. Mice with paternal experience exhibited decreases in the occurrence of incomplete behavioral chains, in this case grooming, when exposed to the novel object environment, indicating fewer disruptions in functional responses in the paternal animals. Twelve hours following the final pup exposure, fecal samples were collected to assess levels of corticosteroid and dehydroepiandrosterone (DHEA), a steroid hormone released in parallel with CORT that has been associated with emotional resilience [91,92]. Increased CORT and DHEA levels were observed in paternal *P. californicus* whereas the pup exposed virgins exhibited the healthiest CORT/DHEA ratios. These results provide further evidence that parenting experience, in this case paternal experience, alters emotional responses [93].

3.3. Enhanced social responsiveness

The transition from an animal that deposits eggs to parental animals extending continued care to offspring, a hallmark of mammals, was accompanied by a heightened awareness and response bias toward others. According to philosopher and author Patricia Churchland, caring

for others was acquired as evolutionary pressures prompted mammals to extend their self-care behavioral strategies to other relevant individuals. As she states in her book *Braintrust*, "...the mother rat behaves as though the newborn pups are included in her basic homeostatic ambit—they must be fed, cleaned, and kept warm, as well as protected from the assorted dangers of the world, just as she must keep herself fed, warm, clean and safe from the dangers of the world. When the pups are threatened, their well-being matters to her in somewhat the same way her own well-being matters to her, and corrective behavior is taken. Pain and fear, her homeostatic emotions that are both feeling and motivation, are triggered when the well-being of her pups is at risk. It is as though the golden circle of me expands to include my helpless pups' [9], pp. 30.

Many examples of an extended range of self-care to other-care exist in the rodent maternal literature, ranging from the maternal rats' short latencies to group, groom and crouch over their offspring when pups have been strewn throughout her cage to the increased activation in a mother's brain upon the introduction of offspring. The cocktail of neurochemicals discussed above including oxytocin, vasopressin, endorphins and dopamine likely contribute to the increasing circle of social awareness in maternal mammals [20,94,95]. These neurobiological adjustments contribute to social cooperation and alloparenting responses often necessary for raising demanding offspring.

Despite the less extreme reproduction-induced changes reported in males, we have also investigated social attentiveness in paternal *P. californicus* mice. As previously mentioned, the high variability observed in male parental responses represents an ideal model to explore the specific mechanisms associated with the shift in attention to the pups. In the previously described distressed pup study, *P. californicus* males with parenting experience directed more behaviors toward a distressed unfamiliar pup than their *P. maniculatus* counterparts. Overall, *P. maniculatus* males engaged in more attempts to avoid the pup (e.g., trying to jump out of the cage). Coupled with enhanced social attentiveness toward the pups, *P. californicus* males with paternal experience exhibited less fos-immunoreactivity in the BNST (a brain area involved in anxiety), and cingulate cortex [50]. Thus, when *P. californicus* mice encountered a distressed unfamiliar pup, their brain response was different than a species exhibiting few overt signs of interest in the pup. As observed in the maternal research, experience with pups shapes these nurturing circuits, emphasizing the plastic nature of caring responses.

Thus, paternal mammals and their expansive continuum of nurturing responses, provide valuable models for the investigation of social attention and nurturing. As more research is conducted on social attentiveness and nurturing responses in both maternal and paternal models, key neurobiological mechanisms related to the acquisition of nurturing responses and social awareness will be identified. Such data will likely inform other social situations in which social attentiveness is dampened, as observed in the human condition autism.

4. Conclusions

As mammals transitioned into parental animals, a host of neurobiological mechanisms were responsible for maintaining this complex response. With these evolutionary upgrades, mammals acquired larger brains and transitioned into animals with response biases directing their attention toward pups. Modifications have also been observed in off-the-nest ancillary responses essential for efficient parenting. Consequently, modifications in cognition (e.g., enhanced spatial memory, flexibility in focus of attention, and cognitive resilience), emotional regulation (e.g., less anxiety in new environments, bolder exploratory responses, fewer disruptions in functional behavioral sequences) and social attentiveness (e.g., more attention focused on pups) have been observed in mammals with parenting experience. Thus, research suggests that parental sensitivity should be viewed as more of a continuum than a discrete categorical variable as various contextual variables contribute to the consistency and quality of nurturing responses in male and female animals. Taken together, these results suggest that

the parental brain, consisting of more complex responses than mere social reflexes in response to specific offspring cues paved the way for the acquisition of adaptive responses to environmental challenges including social cooperation and flexible problem solving. Considering that these effects are seen most dramatically in females with reproductive experience, the maternal mammal may have evolved the "mother of all brains".

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