Sex Steroid Hormone Determination of the Maternal Brain: Effects Beyond Reproduction

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Abstract: Herein we discuss the effects of hormones on reproduction, but with a focus on the ripples that emanate from the main effects. That is, the role of hormones in reproductive events is both well-known and well accepted; less studied and understood are effects that appear to be ancillary to the primary objectives of the hormonal effects, which support, complement and extend their primary effects. We present evidence for how the hormonal stimulation of pregnancy constructs the maternal brain; makes it more efficient; enhances cognition; regulates stress responsiveness; modifies sensory systems (we discuss mainly olfaction); neurogenesis; and learning. Thus, steroid and other hormones and neuropeptides restructure the nervous system, particularly of females, to produce and regulate maternal behavior as well as behaviors and physiological systems that contribute to and support what is arguably the primary function of the hormones: survival and effective nurturance of the female's metabolic and genetic investment.

Keywords: Dendritic spines, hippocampus, medial preoptic area (mPOA), parity, predation, prospective memory, spatial Memory.

A. PROXIMAL HORMONAL EXPOSURE DURING PREGNANCY

The developmental transformation that occurs as a female becomes a mother represents changes at many different levels. Furthermore, the effects appear to mark the female for her lifetime. Thus, reproductive experience (RE; pregnancy/lactation/motherhood) is a significant event on a par with sexual differentiation and puberty. The requisite processes involve a combination of hormones, neuropeptides, and neurotransmitters, and a host of neural regions that are modified through interactions with this neurochemical environment. The hormones and neurochemicals involved with parturition play key roles in the preparation of the maternal brain--including prolactin (PRL), estrogen/estradiol (E_2), progesterone (P), dopamine (DA), oxytocin (OXY) and the stress hormone cortisol/corticosterone (CORT). The actions of these substances on neural circuits cause long-lasting structural and functional modifications including cognitive enhancements that summate to increase the probability of maternal and offspring survival [1-5]. We believe that the study of motherhood and the associated reproductive states will provide insights into the consequences of long-lived effects on cognition. Together the neurochemical/hormonal interactions ensure adequate maternal care and successful reproduction, but they also affect many other necessary systems. A clear understanding of the long-term effects of reproductive experience on these systems will likely connect formerly disparate areas of study.

Maternal behavior -- broadly defined and as reported in many mammalian species -- in the rat involves a myriad of new, pup-directed behaviors, in addition to significant modifications of existing ones [6,7]. For instance, the new mother must construct and provision a more elaborate nest; be able to engage in the discrete acts of maternal care, such as retrieving, grouping, crouching-over and licking her young. She must be capable of distinguishing her young and friendly/hostile conspecifics and be capable of defending her nest and her young from predators. She must eat, drink and sleep in a pattern different than before; forage more efficiently; and remember the location of both food and water caches and potential dangers. In short, there is a marked difference between what the mother knew (or had to know) before her pups were born, and what she is required to learn and remember in order to care for them, a demanding and insistent group. As we and others have reported, cognition is enhanced in parous female rats [8]. This development of ancillary (i.e., maternal supportive) responsiveness is accompanied by significant neuronal changes [3-5, 8-13] in brain regions critical for the expression of maternal behavior, such as the medial preoptic area (mPOA), damage to which can compromise maternal behavior [2].

The medial preoptic area (MPOA) regulates maternal behavior, and also has a high concentration of E_2 and P receptors [14-17]. Gubernick *et al.* [18] reported that mPOA neuron somal size increased in female mice following pregnancy, parturition, and the initiation of maternal behavior. We have likewise observed increased somal size in mPOA neurons in pregnant rats, as well as in virgin female rats administered a pregnancy-pattern of hormone stimulation [19-21]. Further, E_2 binding is very high in diencephalon of late-pregnant and lactating females [22,23], and in males [24]. The acute decline in P just before parturition may render E_2 receptors hypersensitive to estrogen [25]. Such hormonal patterns stimulate neurons

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[26], and affect the proliferation (and subsequent regression) of hippocampal and amygdala dendritic spines [27-31]. We have reported that hippocampal neurons increase in dendritic spine density following exposure to pregnancy, pregnancy-like levels of E_2 and P, and during lactation [13], effects that impinge on many aspects of the mother's behavior, including foraging and resource acquisition [5-8,10], and, perhaps, spatial learning.

Once established, ongoing maternal behavior is displayed independent of hormonal regulation [32,33]. During lactation, the pups provide direct sensory stimulation to the mother that may be considered a form of environmental enrichment, as we have proposed [8,34]. The behavioral differences among nulliparous females (i.e., no reproductive experience; NULL) and primiparous (one reproductive experience; PRIM) and multiparous females (two or more reproductive experiences; MULT) brought about by motherhood are long-lasting or permanent [32,35,36] and are believed to include significant structural alterations. Modney and Hatton [37] found that postpartum females had extensively reorganized cell-cell interactions with new specialized synapses forming on the dendrites of magnocellular neurons, effects reminiscent of neural structural events associated with or governing learning [38-40]. These observations suggest that the neuronal changes may be caused by stimulation provided by pups, similar to our data demonstrating significant increases in pup-supportive behaviors and hippocampal CA1 neuronal dendritic spine concentrations in lactating females compared to age-matched and non pup-exposed NULL females [8,13]. Conceivably the marked sensory stimulation a postpartum female receives from young can affect learning and memory [8,34,41-44], perhaps permanently [35,36], through significant alterations of brain structure and function [13,31,45-47]. Our published work and preliminary data suggest that this is the case.

As Bridges [48] has so convincingly demonstrated for the hormonal profile characteristic of pregnancy, it is the prolonged exposure to E_2 and P that plays the significant role in the transition from non-responsiveness to rapid-onset maternal behavior. In part, this transition occurs because of the structure of the temporal pattern of exposure to those powerful hormones during pregnancy; in particular, the progressive alteration of the ratio of P to E_2 appears to dictate the onset of maternal responsiveness. Pregnancy lasts approximately 22-23 days in the rat (with day of conception = 0), during which time the levels of E_2 and P steadily increase; by day three of pregnancy, P levels have risen substantially, undergo an additional peak by day 15, well into the final trimester, and decline precipitously as parturition approaches. This abrupt reduction in levels of circulating P is associated with, and appears to be required for, parturition, lactogenesis, the onset of parental behavior, and additional facets of the formation of the maternal brain. As P declines near parturition, E_2 rises slightly, which contributes to the initiation of maternal behavior [49].

Therefore, the pattern of a decline in P coupled to an increase in E_2 stimulates, in part, the display of appropriate maternal behaviors. (Other hormones are involved, as mentioned above, which all play important roles in the totality of the maternal response, but the principal ones, the *primum mobile*, is E_2 and P.) This novel set of responses involves a myriad of new, pup-directed behaviors, in addition to significant modifications of existing ones [7,50,51]. That is, the mother is confronted with a set of challenges that must be met and bettered, as we mentioned above in terms of nest building and direct, that is, pup-direct, maternal responses, some of which pose risks for the mother and which involve overcoming fear and anxiety. As mentioned, the mother must feed and be active in a pattern different than before, as her schedule changes because of the pups'. She must forage more efficiently and warily in a hostile environment in order to provision both the offspring and herself. And invaluable food and water sources each have their unique hazards, all of which may determine the mother's and her offspring's fates. In short, we argue that there is a patent difference between her behavioral repertoire before her pups were born, and that which follows in order to care for them. These changes are likely permanent, both for maternal behaviors (so called maternal memory: [43]) and ancillary responses: [35,36].

The development of maternal behavioral responsiveness may be accompanied by long-lasting or permanent neuronal changes [11,12,50]. The mPOA largely regulates maternal behavior, has a high concentration of E_2 and P receptors [14-17], and displays interesting plasticity: The data from Gubernick *et al*. [18], showing that mPOA neuron somal size increased in females following pregnancy, parturition and the initiation of maternal behavior suggests that hormonal stimulation of neurons in specific areas of the brain -- in this case, an area which regulates maternal behavior -- results in behavior-relevant alterations. Using Golgi-Cox analyses, we have found somal size increases in mPOA neurons in the female rat following a pregnancy-pattern of hormone stimulation [20], suggesting enhanced protein synthesis [21] in maternal-behavior related neurons in preparation for the presence of young. Because E_2 binding is upregulated in the diencephalon of late-pregnant and lactating females [22,23], real-time modifications in estrogen sensitivity may regulate, in part, maternal responsiveness, together with the effects of P on E_2 receptors [25]. The outcome is similar to the relationship described above (E_2 followed by a rise in P that subsequently declines) that affects the hippocampal dendritic spines [27-29]. Given the changes to hormones and their responsiveness, it follows, then, that we might expect to see alterations of hippocampal neuronal structure in females exposed to the primary hormones of pregnancy: there are reports of hippocampal neuronal dendritic spine density increases, and their implications, following exposure to pregnancy (PREG) and PREG-like levels of E_2 and P [13,31]. These effects may contribute to the enhancement of cognition that has been reported in younger parous females [8,34,41,44], as well as very old ones (two years+; [35,36]; see below).

Once established, maternal behavior is preserved independent of hormonal regulation, as pups may serve as both stimulus and enriched environment, as we have reported (see below). Olfactory pathways appear to play a primary role in the mother's response to her young, as we discuss below in the section on "Hormonal Effects on

Olfaction and Olfactory Activity." Once neuronal networks that elicit maternal behavior are hormonally activated, the behavior is retained or easily activated [32,33], again, through what appear to be permanent alterations of underlying pathways. Bridges and colleagues refer to this phenomenon as "maternal memory" [52-54]. Such "adult organizational" neural differences among NULL and PRIM or multiparous females (two or more reproductive experiences; MULT) are long-lasting or permanent. They are believed to represent significant structural alterations. Modney and Hatton [37] found that postpartum females had extensively reorganized cell-cell interactions with new specialized synapses forming on the dendrites of magnocellular neurons, effects reminiscent of neural structural events associated with learning [38-40]. Modney and Hatton's [37] observations suggest that the neuronal changes are caused by stimulation provided by pups, as do our data demonstrating significant increases in hippocampal CA1 neuronal dendritic spine concentrations in lactating females compared to age-matched and non pup-exposed NULL females [8,31]. As discussed above, there is a marked sensory load that falls on the maternal female – sights, smells, sounds, suckling stimulation – and, like a enriched environment, that stimulation a postpartum female receives from young may affect learning and memory [8,34,41,44]. The effects are robust and persistent, too [35,36]. Together, these data suggest that hormones do have actions well beyond their normally ascribed actions in these maternal models.

B. DISTAL EFFECTS OF REPRODUCTIVE EXPERIENCE ON HORMONAL SYSTEMS REGULATION OF STRESS

We and others have demonstrated that, in the female rat and other species, reproductive experience results in long-lasting and vast alterations in neuroendocrine activities. Interestingly, Byrnes and colleagues have reported reductions in circulating E_2 levels in primiparous (which they define as one pregnancy+21 days of lactation/ mothering, with testing occurring six-weeks after weaning) compared to age-matched, nulliparous females, effects which persist well into middle-age. In younger, cycling rats, they report that such effects are observed only during the proestrus phase, wherein estradiol levels [55] are highest (in the non-pregnant female). Likewise, across species, including reproductively-experienced humans, reductions in circulating estrogens during the luteal phase of the menstrual cycle have been reported [56]. What do these fluctuations and altered physiological parameters mean for the female?

The regulation of the hormonal effects may occur at central and peripheral sites. Byrnes and colleagues interesting work shows significant increases in expression of estrogen receptor α (ERα) mRNA within the anterior pituitary of RE females [55], as well as within the mPOA and medial amygdala (MeA), suggesting modulation by both RE and the estrus cycle [57]. They report that ERα expression in the mPOA was significantly increased in RE (primiparous) females on the afternoon of proestrus, whereas nulliparous females were not affected. They also showed that nulliparous females in proestrous expressed higher levels of ERα expression in the MeA, compared to primiparous females, which evinced reduced levels. Older females (middle-aged) failed to show differences in ERα expression in these same brain regions, suggesting the superimposition of developmental regulation. Whereas alterations in ERα receptor expression in the mPOA and MeA are observed only in cycling, proestrous females, long-lasting or permanent reductions in circulating estradiol are observed in young and middle-aged females. Thus, the implications for the regulation of diverse types of behavior in the female would be expected to be vast. For example, give the above effects on amygdala, emotional regulation might be expected to change.

As Byrnes's work shows, in addition to endocrine effects, RE alters related behaviors, with changes and enhancements to, and alterations of, anxiety-like behavioral responses and spatial learning and memory [8,35,36,58]. As to the former, there are significant parity effects on the elevated plus maze (EPM) and open field tasks [59], with PRIM females spending increased time exploring the open, unprotected (and, hence, anxiogenic) arms of the maze, which suggest reduced anxiety-like behavior. Still, the latter effects [59] were limited to the proestrus phase of the females' cycle. Middle-aged PRIMs showed *increased* anxiety in the same test, the differential effects of which are likely tied to RE-related alterations in circulating E2 and/or ERα. Because stress sensitivity interacts with the above behaviors, and others, many of the long-lasting RE effects may thus color the manner in which basal regulation of stress responses occur, coupled to estrogens and HPA axis interactions. That is, the basal "tone" of the animal's behavioral responsiveness is labile, overlain by such a physiological governor. It is worth pointing out that though studies examining the anxiolytic effects of estrogen receptor beta (ERβ) have been conducted mainly in virgin females [60,61], some work in ERα knock-out mice suggest that the receptor may regulate the extent of the anxiogenic response along with effects on sexual, pup-induced maternal, and other behaviors. Both sets of behaviors are strongly affected by RE and, again, such effects demonstrate hormonal effects beyond the baseline action of hormones, actions complementary to, and supernumerary to, their normal reproductive actions.

The distribution of ERα positive neurons suggest their importance to, and regulation by, RE. For example, they can be found in neural circuits that regulate pregnancy and its consequences. Studies examining c-fos activation show co-localization with ERα [62]. Effective mothers (*viz.*, those displaying high levels of pup licking and grooming and attention) reportedly have an increased number of mPOA double labeled cells [63], which may influence the binding properties of oxytocin on neurons in the mPOA [64]. There are direct projections between oxytocin-ir neurons in the mPOA and the parvocellular region of the PVN [65], which suggests that mPOA-oxytocin neuronal modifications may determine, in part, HPA axis activity. mPOA ERα expression owing to RE occurs during periods of elevated estradiol (such as proestrus), making it likely that estrogenic regulation of the HPA axis could modify oxytocin projections to/from the mPOA of RE-females. These actions illustrate issues related to the manner in which hormones

extend their effects beyond regular, well-described events, as well as to novel sites of action.

C. INFLUENCES ON MATERNAL NEUROGENESIS

The events that surround reproduction are significant, multi-layered, and enduring, and also represent an example of hormones acting beyond their main effects on reproduction, in the forthcoming case, to influence the structure of the hippocampus and olfactory bulb. For example, among the effects reported are elements of enriched environments, exercise, social contact, steroid hormones, etc. Interestingly, these same facets have been reported to regulate neurogenesis [66]. Does RE, therefore, affect neurogenesis? Despite reports of altered CA1 pyramidal cell morphology during pregnancy and postpartum [13,44], there is little evidence that the reported spatial memory enhancements are accompanied by an increased hippocampal neurogenesis, although this is a compelling hypothesis [67]. In contrast, there are reports of decreased hippocampal volume in pregnant compared to non-pregnant females [68], and no increases in hippocampal cell proliferation during late pregnancy, when compared with estrus-cycling females [69-71]. There are reports, however, of neurogenesis (increased cell proliferation) in the subventricular zone (SVZ) of the forebrain [70-71]. Further, these data suggest that pregnancy-associated neurogenesis may be region-specific [72]. Neurogenesis also appears to be altered in the postpartum period and after the offspring are weaned, as Darnaudery *et al*. [73] report. In particular, they report decreases in cell proliferation (defined as the number of cells containing bromodeoxyuridine [BrdU]) in the hippocampal dentate gyrus of early postpartum period females; longer-term cell survival does not appear to differ either, as 14 days after injection, BrdU staining did not differ between NULL and lactating females [73].

Multiple reproductive experiences also affect cell proliferation. MULTs have greater neurogenesis in the hippocampus than either PRIMs or NULLs [74]. And again, similar to an enriched environment, these differences in cell proliferation are greatly influenced by exposure to pups after parturition, with pup exposure maintaining or elevating [74,75] the number of new hippocampal neurons. The pup sensory load – sight, smells, sounds, suckling stimulation, etc. – presented to the mother is substantial. Therefore, changes in hippocampal cell morphology (*via* dendritic spines), themselves apparently maintained in the postpartum period through pup stimulation [13], and possibly, number of cells, may be important in regulating the transition from NULL to mother. Furthermore, these and other data indicate a role for both hormones [13,31] and pup exposure [8,75] in hippocampal cell and behavioral modifications. It is likely that the union of hormones and pup stimuli alter the hippocampus, stimulating some of the effects of parity. The hippocampal neurogenesis story, underlain by changes in but a small number of neurons – which are, notably, unlike any other cell in the body and are capable of immense plasticity as a function of miniscule changes themselves in quality or quantity – may regulate large alterations in behavior (see [76]).

D. HORMONAL EFFECTS ON OLFACTION AND OLFACTORY ACTIVITY

That the olfactory system plays an essential role in many reproductive activities, ranging from mate selection to maintenance of the resulting pregnancy is well established. The proper functioning of this system is highly reliant on hormonal activity in male and female animals but the effects also travel beyond reproduction. Mak & Weiss [77] recently examined paternal recognition of young and the associated changes in the brain. They found that newly born olfactory interneurons in males were preferentially activated by their offspring's odors and that the interruption of prolactin stopped the production of new neurons thus inhibiting offspring recognition. Further, the recognition behavior was restored with the return of neurogenesis [77]. Though this may seem to over-simplify the complex system of parental behavior, it nonetheless indicates how hormones play a significant role in male, as well as female parenting behaviors.

Steroid hormones play a large role in social recognition and learning mediated by the olfactory system (for complete review see [78]). Ferguson, Aldag, Insel, and Young [79] found that olfactory stimuli driven social recognition is modulated by oxytocin and oxytocin receptors in the medial amygdala and olfactory bulbs but only if there is adequate priming by estrogen. Specifically, the effects of estrogen on social learning appears to be mediated by only one of the two estrogen receptors, ERα, as shown with experiments with ER knockout mice [78]. The activation of ERα, estrogen may be modulating the oxytocin system which, as mentioned earlier, controls social recognition [80] and a host of anxiolytic regulators. Last, testosterone increases activity in the rat main olfactory bulb when a male is exposed to female chemosignals [81]; when these males are subsequently castrated, the female-induced activity diminishes, which results in substantially impaired social recognition memory [82].

E. DIVERSE TYPES OF LEARNING AFFECTED BY REPRODUCTIVE EXPERIENCE

Fittingly, as we are learning, the reproductive hormones, the role for which was once thought to be confined to the preparation of the body for pregnancy and maternity, appear to contribute strongly to the neurophysiological changes linked to learning. As a female advances through the stages of pregnancy, the hormones that enable her to carry her young also enhance her cognitive processes ([8]; see above).

The transition from the independence of virginity to the responsibility of rearing young is one of the most significant challenges in the female mammal's life. To restructure her cognition from a self-centered basis to one focused on the well-being of a dependent individual(s) requires drastic and elaborate changes in the cognitive outputs of the mother's brain. Arguably, at no other point in her lifetime are the immediate enhancements to learning so important to her and her offspring [83]. Too long a "learning curve" may spell doom for the offspring. Either the mother learns quickly to care for her young, and provide for their nurturance, or her offspring may not survive and she must absorb a significant

loss. The energetic costliness of mating, pregnancy, and offspring delivery and rearing necessitates a adaptation. Reproduction is simply too valuable a process to jeopardize through lack of rapid learning and, thus, when a female transitions to motherhood, it becomes apparent that she may rely more on enhanced cognition than her virgin counterparts. During the intense period of time between pregnancy and caring for young, neural reorganization may allow for improvements in the many types of mother-requisite learning. Over recent years, evidence has been building to suggest that this plasticity, which is central to shaping a virgin into a good mother, is controlled by reproductive hormones and extends well beyond reproduction.

Pregnancy hormones reshape the brain in preparation for a more difficult behavioral landscape. Dramatic increases in estradiol and progesterone promote dendritic spine growth in the hippocampus [8,13,84]. As the hormones increase the density of dendritic spines, the surface area for synapses builds, which in turn allows for more efficient learning. Additionally, long-term potentiation in the hippocampus, which regulates learning and memory, is induced by gonadal hormones [85], and regulated by reproductive experience through oxytocin stimulation of basic neuronal mechanisms of learning [86].

There is an extraordinary diversity of learning types that are improved through reproductive experience, representing the range of extra-hormonal actions. Although the primary purpose for enhanced learning abilities, it can be argued, is successful parenting, these cognitive increases confer advantages useful in other aspects of life outside of or post-reproduction, which provides for an organism to be better equipped to survive the many exigencies of a harsh, competitive, and unpredictable environment. Many of the studies providing evidence of enhanced maternal learning draw on evidence from mice and rat models.

Spatial learning, or the ability to orient oneself in space in relation to the location of objects in the environment, was one of the first learning enhancements to be observed in mother rats. Kinsley *et al*. [8] demonstrated that mother rats more successfully navigated an 8-arm radial maze and a large dry land maze, equivalent to the Morris water maze, compared to non-mothers. The mothers had a more finely tuned ability to learn spatial information in various environments, more quickly and with fewer errors. That is, in the radial arm maze, mothers learned faster where to find food and were able to remember the location of food between trials [83]. This increased sensitivity to spatial information is fundamental to a mother's capacity to locate her young, remember where to find food, and know and remember the location of possible threats such as predators. Spatial learning increases a mother's efficiency while foraging, reducing the time that she must spend away from her pups in search of food, and thus decreasing the probability that she or her pups will be harmed while away from the nesting area. The complete dependence of the offspring on their mother pressures her to increase the efficiency with which she navigates her environment, and her elevated pregnancy hormone levels provides for the expression of her inherent learning-sharpening neuroplasticity. For example, the increases in dendritic spine density that are triggered by the soaring pregnancy estrogen levels enrich her neural functioning by increasing the surface area available for synapses.

An interesting interface between memory and performance is hunting ability. Catching prey requires good memory for spatial information, coupled to efficient and economical motor responses. Whereas rats are commonly thought to be scavengers, they possess impressive hunting abilities. Unpublished findings from our lab [10] have demonstrated that mothers are significantly better at catching prey compared to virgin animals. Mothers hunted, captured, and consumed crickets in a large open field maze in a significantly shorter amount of time than virgin females. For example, mothers averaged ~65 seconds to catch an insect (cricket), whereas non-mothers averaged ~270 seconds. Impressively, this effect held true even when virgin females were food-deprived for twice as long, suggesting that the difference is not due to metabolic differences. Improvements to motor skills and vision, prompted by the reproductive hormones coursing through the mother's body, make this advantage possible even though a new mother has not yet returned to her pre-pregnancy weight. A series of follow-up experiments examined specific sensory modalities was conducted to isolate the underlying cause for the improvement in predatory skills. The inhibition of olfaction, audition and somatosensation, failed to diminish the mothers' advantage in hunting ability. When vision was obstructed, however, through testing in a zero-lux environment, the mothers took a significantly longer time to catch the cricket than in the light. This increase in hunting ability comes at a time when a mother's skill at acquiring food is crucial to her pups' survival, and her hormone-driven motivation to effectively care for them guides her behavior.

Thus, a mother's hunting and foraging expertise may determine the degree to which she is able to provide for her young, a critical set of skills. Out of a new mother's need to attain nourishment for her and offspring, are the requisite adaptations, sharpening a combination of hunting and cognitive skills. The combination, then, of her increased hunting skills and decreased fear and anxiety increases the probability that she will provide successfully for herself and her offspring.

Recently, we have begun to examine another form of enhanced learning in mother rats involving prospective memory (PM). PM is defined, essentially, as the ability to remember to perform behaviors in the future. We have begun to show that maternal rats are better capable of such planning ahead compared to non-mothers. This ability to "project oneself forward in time" likely improves the mother's ability to acquire resources for her young, by anticipating a future environment. PM was explored in age-matched mother (primiparous) and non-mother (nulliparous) rats by first lightly water-depriving and then training them to acquire water in an open field maze. Individuals were then placed back into their home cages where they encountered either abundant or no water. Those lacking home cage water were thus predicted to find water more quickly and drink more than their counterparts. Thus, this behavior demonstrates PM in that such females should drink more in anticipation of the

future environment (*viz*., their home cage) not containing water. It had been predicted that mothers, being superior at various learning and memory tasks, and faced with the exigencies of an unpredictable environment, would be more likely to remember to drink in the maze than their nulliparous counterparts. Mother rats that were water-deprived in the home cage spent significantly more time drinking in the maze than control mothers, non-mothers, and male rats, signifying the use of prospective memory. They learned to drink more water in the maze in anticipation of not having water when they returned to the home cage. Control experiments are being conducted to verify the PM and to control for metabolic regulation.

The demonstration of PM suggests that mothers learn to plan ahead for an unpredictable environment, whereas non-mothers appear less capable of doing so. Compared with the other forms of learning described, mothers generally have an advantage compared to non-mothers. In the current study, however, the data suggest that reproductive hormones, in addition to enhancing the skills of mothers, may create an entirely new skill set previously described only in scrub jays and primates [87].

F. SUMMARY EFFECTS ON THE MATERNAL BRAIN

During the course of pregnancy and lactation, the female's responses to offspring change considerably---from avoidance to approach to focused attention and nurturing. As briefly reviewed above, several brain modifications have been documented to accompany the emergence of the maternal response profile (e.g., modifications in the mPOA, hippocampus, SVZ, amygdala); the dramatic shifts in responses to the same stimuli (i.e., pup-related stimuli), however, provide an opportunity to investigate alterations in non-traditional, but crucial, maternal behaviors such as memory enhancements and sustained attentional processes. Thus, the maternal brain provides a unique and valuable opportunity to explore processes accompanying decision-making and problem-solving, as the animal is required to modify response strategies during pregnancy and lactation to maximize inclusive fitness. In an attempt to understand modifications in cognitive strategies in the maternal rat, our labs have conducted numerous studies demonstrating dramatic changes in the maternal animal. Here, we will employ behavioral measures, a variety of neuronal and glial staining procedures, including multiple-fluorescence staining for neurogenesis, and gene expression analyses, extracting as much information as possible from our subjects as we investigate the formation and expression of the maternal brain.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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