

The Construction of the Maternal Brain: Theoretical Comment on Kim et al. (2010)

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Recently, there has been a spate of articles detailing the many and multifaceted alterations that define the Maternal Brain. The article by Kim et al. (2010) has provided a new “window” into the brain of the mother by the use of MRI showing structural changes in major regions over the period of the first few months, during which the intimate relationship between mother and infant forms. In this accompanying Commentary, we explore some connections between the animal work and the human data, and suggest some common pathways. In the end, it appears that maternal motivation, far from the intrinsic or instinctual state that many believe it to be, may, in fact, be attributable to many active processes “building” a responsive neural substrate. Like early brain development, itself a marvel of interacting genetic and environmental forces, the Maternal Brain may represent another developmental epoch in the life of the female. In this case, the alterations occur to promote the survival of subsequent generations and the care and protection of a most expensive mammalian metabolic and genetic investment. If so, is it possible that just as there are edifices that are poorly constructed and crumble at the first challenge by earthquake or hurricane, there may be defectively assembled maternal brains that fail in their task of caring adequately for young?

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Anyone with a mother can appreciate the fundamental alterations necessary to produce that remarkable creature that unconditionally loves, sacrifices for, slaves over, and dutifully frets about her offspring. The dramatic transformation that renders the nulliparous female a mother suggests changes both widespread and sturdy. In a relatively brief period of time, investigators have begun to catalog the nervous system accompaniments that define the maternal animal. The current article, by Kim et al. (2010), adds significantly to this burgeoning database and adds another interesting species to the list: humans. Here, the authors describe a remarkable anatomical change in the volume of gray matter in prefrontal cortex, parietal lobes and midbrain areas in human mothers. The implications are that the set of defining characteristics associated with motherhood may, in fact, be the consequence of the construction of the maternal brain. Among the components being augmented/developed are significant alterations to olfactory systems and cognitive functions, including fear responses. Both indicate substantial neural reorganization and will be discussed below. In total, the data suggest that the mammalian mother is the cumulative result of neural modifications, culminating in an offspring-responsive parental organ. If so, an interesting corollary arises: if the maternal brain does not develop the way it should, does not achieve its potential neural horizon, does that produce a bad or indifferent mother? Those data are yet to be gathered but,

notwithstanding, the Kim et al. article (2010) raises many fascinating issues about how mothers are fashioned.

Numan and Insel (2003) document the many maternal behaviors characteristic of the mammal, and regulatory neural sites that are necessary and, in some cases, sufficient, for their proper display. Among these areas, the medial preoptic area (mPOA), a dorsal hypothalamic structure, appears to play a major role in the display of maternal behavior. Its destruction virtually eliminates maternal behavior, whereas placement of pregnancy-relevant hormones into it (e.g., estrogen and progesterone) stimulates the behavior. Keyser et al. (2001), in a demonstration of individual mPOA neuronal dynamics, showed that as parturition approached, neuronal somata here increased in volume, an indication of enhanced protein synthesis (Miller & Erskine, 1995). At the cellular level, the up-tick in activity suggests a large increase in neuronal activity in preparation for the arrival of young. The metaphor that has been used to describe this ramping-up of activity in mPOA neurons is that of a revving race car (Kinsley & Franssen, 2010), as the vehicle strains at its tethers before being released. The brain undergoes a significant set of changes in advance of the presence of the young, being readied for the demands about to be placed on the mother. Thereafter, the new mother, and her new-found motivation, finds satisfaction and reinforcement in the interaction with her infant.

Other work has demonstrated enhancements to the set of behaviors that supports maternal behavior, namely, foraging. That is, the suite of responses formally referred-to as maternal behavior includes retrieving, grouping, and crouching over pups, pup-licking, nest-building, and nest defense. This latter set of responses is considered “pup-directed.” In addition, however, the mother relies on foraging, predation, opportunistic caching, as well as other strategies to fill her larders for her young; the perils that daily accompany such activities would be greatly diminished by en-

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hanced efficiencies in their conduct. That is, very simply, any behavioral enhancements that would reduce foraging costs would likely translate into less time away from vulnerable young. Furthermore, given the uncertainty that the environment holds—the predator is just as likely to become the prey—the mother's ability to defend herself becomes paramount. Hence, alterations in the mother's ability to withstand stress and anxiety (Wartella et al., 2003), which convert into a form of behavioral resiliency, steel her against the hazards of caring for and provisioning her young—or worse, inaction. Cognitive alterations may reduce the costs and increase the benefits of natural maternal interactions. Again, the net result would be a greater likelihood of offspring survival and flourishing.

We have demonstrated parity-enhanced spatial memory in the female rat (Kinsley et al., 1999) that would support the above. Employing two different spatial tasks (an eight-arm radial maze, and a dry land maze [DLM; a Morris water maze analog; Kesner & Dakis, 1995]), and two different strains of rats (albino Sprague-Dawley and hooded Long-Evans), we showed that parous females were significantly faster at remembering the location of preferred food rewards. Pawluski, Vanderbyl, Ragan, and Galea (2006a) and Pawluski, Walker, and Galea (2006b) replicated this spatial memory-enhancing effect, showing a difference between working and reference memory. Bodensteiner, Cain, Ray, and Hamula (2006) reported no effect during pregnancy, but subsequent enhancements do occur, again favoring reference memory. Collectively, these data suggest neural changes that affect behavior, and consequently benefit the female at a time when she most needs it (Kinsley et al., 2006; Pawluski et al., 2006a, 2006b). In the Kim et al. (2010) data, the suggestion is that the brain is altered both in response to, and in preparation for, the arrival of the baby and the duties required, as well as to underscore the motivation/affect for the offspring. Like the rat, the human mother needs to care for the infant, as well as to provision it, in a largely unpredictable environment.

Work in humans shows similar learning effects (Buckwalter et al., 1999). The data for postpartum females demonstrated by Kim et al. and others raises questions regarding the interplay between mother and the receipt of cues from the offspring. Lambert et al. (2005) have reported that the offspring play a significant (and likely enriching) role in the memory enhancements. Pup-sensitized nulliparous females were significantly better in the DLM than nulliparous, and almost as good as lactating females with pups (Kinsley et al., 1999). The enhanced spatial memory effect persists well into senescence (24 months+) in the female rat, with multiparous females showing the greatest effects on both behavior (maze learning and memory) and brain (healthier, with fewer hippocampal deposits of the deleterious substance, amyloid precursor protein; Gatewood et al., 2005). There are also significant alterations of hippocampal neuronal microarchitecture, in particular, the concentration of CA1 dendritic spines is increased in late-pregnant, lactating, and pregnancy hormone-treated females (Kinsley et al., 2006). Such changes/improvements would contribute to spending less time away from the nest and a more secure nest, overall. As intimated by the Kim et al. (2010) data, the potent steroidal cocktail characteristic of pregnancy (estrogen, progesterone), other hormones (prolactin, cortisol), followed by the intricate array of the babies's multisensory inputs to their mother's brains, may produce the manifest alterations, and express the inherent

neuroplasticity, described here. The *mélange* of sights, smells, sounds, suckling stimulation and somatosensory cues from young may have a significant impact on the way the maternal brain unfolds. The “enriched environment” represented hereby, could contribute to the substantial neural alterations that have been reported.

The maternal behavioral data, too, may be managed through neural mechanisms that govern enhanced attention toward young and supporting behaviors; so, too, as Kim et al. (2010, p. 695) suggest, the “maternal positive perception” that accompanied the mothers' brain structural changes. For example, Tomizawa et al. (2003), in mice, examined the role of neuron-hormone interactions in the mediation of enhanced spatial ability. They showed that oxytocin, which undergoes dramatic fluctuations coincident with the various stages of pre-and-post motherhood, enhances hippocampal MAP kinase activity. Hippocampal tissue treated with oxytocin facilitated both long term potentiation (LTP) and phosphorylation of cyclic AMP-response element binding protein, the latter effect being antagonized by inhibition of MAP kinase. Further, untreated hippocampal tissue from multiparous animals resembled that of the oxytocin-treated virgin tissues. Lastly, infusion of oxytocin into nulliparous mice (*icv*), improved their spatial memory, whereas an oxytocin agonist, administered to multiparous females, interfered with spatial memory. Oxytocin, therefore, in addition to its other well-described social actions, appears to play a significant role in the enhancements of spatial memory in the parous female. As we will see later, oxytocin in olfactory systems may also play a role.

Reproductive experience exerts strong and persistent effects on pup-directed responses, spatial learning and foraging behavior, as well as on stress and anxiety regulation. The Kim et al. (2010) data highlight changes to sites such as prefrontal cortex, parietal lobes and midbrain areas, which also receive and process significant amounts of olfactory-related information, and because a primary entryway to the subsequent neural landscape is olfactory input. A new mother is exposed to significant olfactory stimuli, and as we will see, recent evidence suggests stimulation of neurogenesis in and around olfactory structures.

For decades now, Numan's fine work has demonstrated that the hormonally primed mPOA regulates maternal behavior. Recently, new data suggest that the mPOA may direct maternal care through subjective reinforcement associated with interactions with young. Together with dopamine (DA)-containing neurons (mesolimbic and incerto-hypothalamic), DA and the mPOA interact to regulate maternal behavior in rats through interactions with nucleus accumbens (Numan & Stolzenberg, 2009). According to this work, the steroid-sensitized mPOA directs the more appetitive or reinforcing components of maternal behavior through activation of mesolimbic DA projections to the nucleus accumbens (especially, the shell portion). The authors speculate that mPOA output is modified by both hormones (estradiol) and peptides, and oxytocin, which may regulate neuronal activity by gating the flow of action potentials. The culmination of these many levels of activation may be to regulate the maternal memory for the pups as pups (thereby affecting maternal responses), and/or as specific offspring (the recognition of pups as own vs. strange). As we discuss in more detail, such responses would depend heavily on olfactory information.

Levy, Keller, and Poindron (2004) highlight the crucial nature of the olfactory information provided by pups to the maternal-infant bond and interaction. The virgin transitions from a pup-indifferent female to a highly motivated one, largely through hormone-induced changes to olfactory inputs and responses. Furthermore, the odors allow for an extremely refined recognition mechanism focusing maternal attention on the appropriate recipients. The odors also determine the strength of maternal responses toward pups. Morphine, which disrupts maternal behavior (Bridges & Grimm, 1982), does so through a naloxone-reversible action in the POA of lactating females (Rubin & Bridges, 1984). Kinsley and Bridges (1990) demonstrated the olfactory-mediating aspects of the morphine effect. When exposed to a choice between bedding soiled by pups or plain bedding, lactating females showed a clear preference for the odors of pups (significantly more time spent out of 300s investigating the odors). When, however, these same females were injected with a small dose of morphine, they spent significantly more time investigating the plain chips. The data suggest that the morphine creates an aversion for the odors of pups, which likewise explains the reduction of maternal behavior that has been reliably reported in morphine-treated females: such animals may be rendered temporarily averse to the odors of pups and, hence, the pups themselves.

In humans and animals alike, the olfactory system is an instigator of change in the brain circuitry associated with maternal behavior, and is, for the rat, its primary sensory input. For example, olfactory cues from young elicit maternal responses from the new mother, physically and emotionally. Whereas olfactory cues inhibit maternal behavior in virgin animals, new mothers develop a state of hyper-responsiveness to olfactory cues emanating from newborns (Levy et al., 2004), often showing a preference for pup-soiled bedding versus clean bedding; this is opposite behavior to their virgin counterparts (Kinsley & Bridges, 1990). Further, olfaction seems to play an integral role in specific maternal behaviors. A series of studies has indicated that specific olfactory cues radiating from the pups regulate anogenital licking, a behavior crucial to the survival of the offspring (Brouette-Lahlou, Vernet-Maury, & Cjanel, 1991; Levy et al., 2004). Additionally, maternal rats will retrieve their own young first if given the choice to between their own or alien pups (Brouette-Lahlou et al., 1991; Levy et al., 2004). This discriminatory ability may be essential for directing appropriate care toward one's own genetic relatives.

The Kim et al. article (2010) reported an increase in gray matter in several brain regions that eventually receive and process olfactory and somatosensory information. Although they did not examine the olfactory cortex specifically, the areas mentioned above receive input from the olfactory system, thus likely playing a significant role in maternal behavior. The changes Kim et al. observed in gray matter are consistent with observations of positive human maternal behavior. Here, new mothers were much more likely to rate "infant odors" as pleasant compared with nulliparous women (Fleming, Steiner, & Corter, 1993). Further, humans have demonstrated olfactory identification of newborns several days following birth (see Levy et al., 2004), indicating an enhanced perception of the unique olfactory properties of their infant together with the nascent development of the emotional bond between the two. Of interest, higher levels of cortisol increased odor sensitivity to the mother's own infant (Fleming et al., 1997; Levy et al., 2004). These data suggest that local changes in

olfactory sensitivity, coupled to hypothalamic-pituitary-adrenal axis activation, may interact to create a "better," more motivated mom. With a well developed sense of smell, the cocktail of hormones involved during pregnancy, birth and lactation, and projections to emotion-regulating centers of the brain, the new mother associates positive emotions with regards to her offspring and their odors, and is ready to lavish attention upon them. The Kim et al. data (2010) reinforce the sensory system-emotion connections.

Additional research suggests that the recognition of these pup odors is driven by maternal hormones. For example, just as oxytocin may play a role in other areas of the brain to modify maternal behavior, evidence suggests it is working on the olfactory system as well. Infusion of oxytocin into the main olfactory bulb of rats produces a rapid onset of maternal behavior, a possible result of a decrease in mitral cell activity herein (Yu, Kaba, Okutani, Takahashi, & Higuchi, 1996). Additional fMRI work in lactating rodents has indicated that oxytocinergic neurotransmission contributes to a reduction of anxiety and fear levels (Febo, Shields, Ferris, & King, 2009). Investigators saw a reduced level of blood oxygen level dependant (BOLD) signal in the anterior olfactory nucleus (AON), a secondary olfactory structure shown to express oxytocin-like immunoreactivity (Brunjes, Illig, & Meyer, 2005; Iqbal & Jacobson, 1995). As odor information passes through the nasal epithelium, it is received by the olfactory bulbs and subsequently sent on to the AON and piriform cortex. Whereas it has been well established that the main olfactory bulb plays a role in maternal behavior (and likewise receives input from the amygdala), little work has examined the AON and what role it may be playing in maternal behavior. We do know that the AON receives projections from the medial amygdala (Brunjes et al., 2005), and lesions to the latter area in virgin rats facilitate maternal behavior (Numan, 2006). Thus, perhaps this system would have to be suppressed in order for maternal behavior to occur in new moms (amygdala-mediated induction of fearfulness (Numan, 2006). Furthermore, in virgins, novel olfactory stimuli from pups delays maternal behavior because the input may activate amygdalar "fear-inducing" mechanisms (Numan, 2006). Inhibiting the aversive properties of the odors or otherwise modifying them may be important, right at the front end, for the adequate display of maternal responsiveness.

As mentioned in the Kim et al. article (2010), there are changes in several hormones during the postpartum period. These same hormones, estrogen and prolactin for example, have all been shown to enhance neurogenesis in adult animals. Prolactin stimulates neurogenesis in olfactory bulb of adult females (Shingo et al., 2003) and estrogen has been shown to have neuroprotective effects on neurons (Suzuki et al., 2001; Wise et al., 2001). Therefore if the maternal brain is protected from cell death while increasing the number of existing cells, one might expect see subtle changes in two other critical brain areas involved in maternal behavior, the olfactory system and the hippocampus. For the former, in the vole, some alterations of oxytocin immunoreactivity have been reported. More specifically, administration of estradiol resulted in an increase in oxytocin receptor binding in the anterior olfactory nucleus alone compared with the hypothalamus, bed nucleus of the stria terminalis, or the amygdala (Witt, Carter, & Insel, 1991). This change in oxytocin receptors may prepare this area of the brain for a faster and more efficient display of maternal behavior. For the latter, in the rat, some reproduction-related structural changes have

been observed (Kinsley et al., 2006; Pawluski & Galea, 2006). Again, these anatomical data may relate to those changes reported by Kim et al. Last, recent data show changes to another (some consider it “the”) primary human sensory system, vision, and the manner in which emotionally laden faces may be perceived (Pearson, Lightman, & Evans, 2009). The picture that emerges is one of a heightened, sensitive, acute and focused maternal system directed toward the infant.

Last but not least: what about the paternal brain? Is the male merely a benchwarmer in the game of parenthood? Would one expect to see changes in the gray matter of paternal animals using MRI? Few studies have examined the paternal brain. Mak & Weiss (2009) 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 (Mak & Weiss, 2010). Although this may seem to oversimplify the complex system of parental behavior, it nonetheless indicates how hormones play a significant role in male, as well as female parenting behaviors. Recent work by Kelly Lambert and Catherine Franssen is showing that the male brain in biparental species expresses some of the same neuroplasticity upon interactions with young that has been described in those species’s mothers (Unpublished observations/personal communication as the manuscript is under review.).

In closing, the Kim et al. data (2010) raise many interesting questions. Bridging what we know from basic research with laboratory animals to cutting-edge techniques in the human model of the maternal brain, represents a big leap forward in our understanding of the many forces at play in ensuring propagation and offspring survival. The changes we and others observe summate to protect the organisms’ metabolic and genetic investments. The many forces arrayed to ensure success—like a NASA space launch with primary, secondary, tertiary, quaternary and so forth systems and backup systems—come to fruition in this most simple, basic and life-defining event. Work such as Kim et al.’s expands our understanding of the mechanisms that underlie normal Maternal Brain formation. It would be of interest to examine similar sites in the brains of inattentive, or worse, mothers in an effort to elucidate the structural and functional differences that must lie at the base of such behavioral anomalies.

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