

Epigenetic Transmission of Maternal Behavior: Impact on the Neurobiological System of Healthy Mothers

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Abstract

Quality of maternal caregiving not only impacts children's development but can also result in heritable changes in gene expression (i.e., in an epigenetic manner). Consequently, when women become mothers, they adopt parenting behavior similar to that they received at family of origin. This transgenerational transmission of maternal behavior may also be associated with changes in the neurobiological system of future mothers. This review aims to highlight the effect quality of perceived parenting has on maternal behavior and the neurobiological system of mothers, specifically the oxytocin system, brain morphology and brain function. This would likely help in finding biomarkers that profile the impact of perceived parenting on mothers, and thus allow identification of mothers who experience poor-quality parenting for intervention.

Keywords: Epigenetic, maternal behavior, mothers, oxytocin, perceived parenting, transgenerational

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INTRODUCTION

Sensitive and responsive maternal caregiving behavior is important for promoting secure attachment^[1] and healthy emotional, cognitive and social development of a child.^[2] On the contrary, poor maternal caregiving is associated with poorer outcomes in infants,^[3] such as emotional and behavioral problems during childhood^[4] and mental health disorders later in life.^[5] Evidence from both animal and human studies have shown that the quality of upbringing received is reflected in the care provided to offspring;^[6,7] therefore, the quality of parenting mothers offer to their children may impact the quality of parenting these children later provide to their offspring. Such transfer of upbringing behavior from one generation to another is through the non-traditional way of inheritance known as "epigenetic."

Consistent with the findings in animals, studies using imaging technique in humans have shown that experiencing adverse parenting during the early years of life can change the brain morphology.^[8,9] In addition, functional imaging studies have provided concrete evidence that the responses of maternal brain to their infant's signal (auditory or visual stimuli) may also reflect the quality of perceived parenting.^[7,10]

Hormones, such as vasopressin, testosterone, cortisol, oxytocin (OT) and prolactin have been found to play significant roles in shaping maternal caregiving behavior.^[11] The influence of these hormones may be affected by the quality of upbringing.^[12] Here, the authors focus on OT as a key factor implicated in social behavior and parenting^[13] as well as in brain adaptation to quality of perceived parenting.^[14]

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This review aims to contribute to the current literature by highlighting neurobiological changes in mothers in relation to quality of upbringing they received. Specifically, the review focusses on the structural and functional changes in the brain or the brain reactivity in response to infant signals and the pattern for OT reactivity in response to interactive behavior with own infant. By highlighting neurobiological changes related to early experience, the authors hope to pave the way for studies to identify biomarkers in mothers who experienced adverse experience of upbringing so that they could be targeted by interventions. Such intervention would aim to alleviate the impact of early experience on maternal behavior toward own child, thereby improving a mother's parenting behavior and a child's outcome.

IMPACT OF OWN PERCEIVED PARENTING ON MATERNAL CAREGIVING BEHAVIOR

Cross-fostering animal studies have demonstrated the role of early environment in shaping maternal caregiving behavior toward own offspring.^[15-17] In rodent, for example, female pups who were born to mothers with “low” quality of maternal caregiving (i.e., licking and grooming [LG]) but reared by “high” LG foster mothers were found to show high levels of parental care when they handled their own pups.^[18] Similarly, when offspring of high LG mothers were reared by low LG foster mothers, they showed low quality of caregiving when handling their pups.^[15,18,19]

In humans, earlier studies suggest a positive relationship between perceived parenting and maternal sensitivity (i.e., accurate and prompt responses to infant signals). In a study of 60 mothers, using the adult attachment interview, it was found that mothers with secure attachment to parents were more sensitive to their infant than nonsecure mothers.^[20,21] Similar findings were also found when parenting bonding instrument (PBI), a self-reporting measure, was used.^[22]

Recently, in a sample of 80 healthy British mothers, maternal perceived parental care (assessed using PBI) was found to be positively correlated with rating of maternal sensitivity when mothers interacted with their 4–6-month-old infants.^[12] Similar findings were also reported in another study where 192 British couples were followed up for 2 years after childbirth. The couples' interactive behavior with their child and perception of own perceived parenting were assessed and it was found that a “controlling” mother at family of origin was positively associated with decreased “engagement” with own infant.^[23]

EPIGENETIC TRANSMISSION OF MATERNAL CAREGIVING BEHAVIOR

Cross-generational transmission of maternal behavior is suggested to occur in an epigenetic manner, and this can be passed down for generations.^[24] Mechanism involved in epigenetic changes vary, but generally involve chemical changes (e.g., DNA methylation) in genes that either silence or enhance it.^[16,25] Epigenetic transmission of maternal behavior is due to alterations in the hypothalamic estrogen receptors through methylation.^[26] This, in turn, leads to neurobiological changes with respect to social attachments and stress reactivity.^[15,27] The effects of these epigenetic changes can be modified by life experiences (e.g., mother–infant interaction).^[28]

The above-discussed findings are in line with the “internal working model” of the attachment theory,^[29] according to which positive care experiences in the early years of life provide individuals with the emotional and cognitive resources that enhance their social learning to subsequently provide high-quality caregiving.^[30] Transgenerational transmission of parental behavior is related with interaction between environment (i.e., quality of caregiving received) and genotypes, resulting in heritable changes in gene expression.

NEUROBIOLOGICAL IMPLICATIONS OF PERCEIVED PARENTING

Oxytocin system

Direct examination for the associations between OT and perceived parenting experience has been the focus of OT studies in adults and children.^[12,13,31-33] In one study, attachment representations with own mothers were assessed in those who were securely ($n = 15$) and insecurely attached ($n = 14$). Plasma OT was examined before (baseline) and after play interaction with their 4-month-old infants and it was found that although the baseline plasma OT did not differ, secure mothers had higher post-interaction OT levels than insecure mothers.^[13]

Two studies have shown that the impact of perceived parenting on an individual's OT profile may also reflect the role of OT in stress regulation.^[12,31] Feldman *et al.*'s^[31] study comprised 71 mothers, 41 fathers and their 4–6-month-old infants. Interestingly, the urinary OT levels showed a trend for “negative” correlation with reported perceived care only among mothers. Elmadih *et al.*'s^[12] study comprised a cohort of 80 mothers who were rated for maternal sensitivity following observed interaction with their infant at 4–6 months postpartum. Comparison was made between mothers who were rated as high sensitivity mothers (HSMs) and those rated as low

sensitivity mothers (LSMs) (15 in each group). Although quality of perceived parenting (assessed using PBI) did not differ between HSMs and LSMs, plasma OT levels among LSMs were positively correlated with negative perceived parenting experience at all times, but especially with “maternal overprotection.” It is possible that adverse parenting received by these mothers created stress that made it challenging to adapt to the new maternal role and handle their own infant. Findings from these two studies support the current evidence that OT could be released as a modality for regulating social stress to moderate or even decrease stress responsiveness,^[34,35] which is, in general, higher among women than men.^[34,36-40]

Interestingly, the relationship between OT and quality of upbringing is not only apparent among parents but may also appear in nonparents and children. In a study that included men and women who were not parents ($n = 45$), a positive correlation was reported between plasma OT levels and the individual's reported parental care scores.^[33] In another study among children, Wismer Fries *et al.*^[32] compared urinary OT levels of children who were raised in orphanages (adopted at the start of the study; $n = 18$) and those who were raised by their biological mothers ($n = 21$). Children interacted with their mothers (foster or biological) for 30 min while playing video games sitting on their lap. They repeated the same session with an unfamiliar adult (i.e., mother of another child). Despite the absence of differences in the baseline OT between adopted and biological children, children raised by their parents showed borderline higher postinteraction urinary OT ($P = 0.06$), irrespective of with whom they interacted. This suggests that OT may not always represent affiliation and it likely has a more complex role. This was highlighted in a study on mothers where maternal brain activation in response to their infant's video was negatively correlated with their plasma OT levels.^[41]

Based on the studies discussed, it can be stated that in addition to its role in parental affiliative behavior, OT is positively correlated with attachment representation to own parents and to memory about own parental care. Recent evidence suggests that the quality of perceived parenting may correlate with OT both positively and negatively, supporting a dual role of OT in the overall affiliation and stress regulation.

IMPACT OF PERCEIVED PARENTING ON MATERNAL BRAIN MORPHOLOGY AND BRAIN RESPONSES TO OWN INFANT

In both animal and human studies, it has been found that the plasticity of a maternal brain allows it to undergo

numerous changes and remodeling related to previous maternal care experience to facilitate the adaptation to environment while raising offspring.^[26,42] For example, in rodents, offspring of mothers who show high LG were found to have increased glucocorticoid receptor expression in the hippocampus, which enhanced their learning and memory ability.^[42] On the other hand, female reared by low LG mothers had lower levels of glucocorticoid receptor gene expression in the hippocampus.^[43] However, similar corresponding evidence is relatively limited in human studies because of the challenges associated with conducting such studies. Nonetheless, the authors discuss neurological changes related to transmission of early perceived parenting in humans, with particular attention to morphological changes in the brain or responses shown by mothers who experienced low quality of upbringing.

Hippocampus

In humans, magnetic resonance imaging studies have reported that women who received low maternal care at family of origin had smaller hippocampal volume,^[44] which is associated with reduced ability to regulate stress and emotions.^[45] This is possibly because the hippocampus is known to receive OT projections and contribute to decoding emotional memories.^[46] Furthermore, mothers who experienced adverse parenting may show stronger hippocampal activation in response to their infant crying, similar to that observed when individuals were shown distressing pictures.^[47] Collectively, this volumetric reduction and increased activation in the hippocampus are suggestive of chronic stress in these mothers.^[45]

Kim *et al.*^[48] classified mothers as having high or low perceived maternal care using PBI ($n = 13$ each) and examined brain responses to their infant crying. Mothers who received high maternal care showed greater activation in frontal areas implicated in parenting, including the precentral gyrus, dorsolateral prefrontal cortex, superior temporal gyrus, middle frontal gyrus, fusiform gyrus and lingual gyrus. On the other hand, only the hippocampus, which is implicated in stress regulation, was found to have higher activation in mothers who received low maternal care. This suggests that mothers who received poor-quality parenting may have higher stress to their infant crying compared with mothers who received high-quality parenting. It is also possible that chronic exposure to stress may increase cortisol levels, which can reduce the maternal brain responses to infant's cry in other areas involved in parenting.^[48]

Nigrostriatal pathways

In a study by Strathearn *et al.*,^[13] when insecurely attached mothers were shown the smiling face of their infant,

there was increased activation in the brain regions implicated in executive functions and empathy, specifically the nigrostriatal pathways, which includes dorsolateral prefrontal cortex, dorsal striatum and substantia nigra of the midbrain.^[49] In contrast, mothers with secure attachment had higher activation in brain regions implicated in secretion of OT and dopamine, which plays a role in reward processing, namely, the mesolimbic pathway including medial prefrontal cortex, ventral striatum and ventral tegmental area. These mothers also had activation in the hypothalamus and pituitary region, which was positively correlated with rise in their plasma OT levels.

Insula

In mothers who are insecurely attached, activation of insula has been reported in response to seeing an image of their infant's sad face.^[13] In mothers who reported parental neglect during childhood, a similar activation was observed in response to seeing their infant cry.^[9] Such activation of insula suggest avoidance or rejection of negative infant cues by these mothers.

Amygdala

Mothers with insecure attachment show greater amygdala activation to their infant crying than mothers with secure attachment.^[50] However, activation of amygdala has also shown to be a healthy maternal response to infant stimuli.^[51] This reflects the importance of amygdala in parenting, given its complex role in emotional salience, detection of threat, processing of reward and biological valence that are required for social behavior.^[52]

Gray/white matter

Mothers who received high-quality maternal care may have larger grey matter volume than their counterparts who received low-quality maternal care. In turn, this larger grey matter volume helps them understand the emotional states of their infant, and thus respond more sensitively to their infant's signals. Interestingly, children who received institutional care and then moved to foster care setting had larger white matter volume compared with those who remained in institutional care, suggesting that a positive change in environment can improve adverse effects that result from poor upbringing.^[8]

The use of neuroimaging in parenting research has improved our understanding about maternal brain, including brain function and responses related to perceived parenting experience. However, research on structural or functional changes in maternal brain with respect to early life experiences is still limited and not without contradictions.^[53] For instance, activation of amygdala and

insula have been reported in mothers with low-quality and high-quality perceived parenting. In addition, increase in gray matter volume through skills' training was peculiarly associated with increase in hippocampal activation, similar to that seen in individuals with stress-related parenting experience.^[54] This inconsistency points toward the need for more experimental-based studies in humans despite its challenges.

CONCLUSION

Care experienced during the early years of life can have both positive and negative adaptation in the brain structure and function. Mounting evidence suggests that these changes and their associated quality of caregiving can be transmitted to next generations. Further, OT is both positively and negatively correlated with attachment representation and, subsequently, to parental care provided to own children. In addition, neuroimaging has provided better understanding of the maternal brain with respect to function and responses to perceived parenting. However, research on structural or functional changes in the brain based on early life experiences is limited and contradictory, thereby highlighting the need for more experimental studies on humans.

FUTURE DIRECTIONS

The negative impact of maternal adversity on offspring's development and well-being is now well-known from developmental literature. However, emerging evidence suggests that providing mothers (and/or their infants) with a supportive psychosocial environment may confer protection against adverse parenting received during early years of life and counter transmission of negative behavior to the next generations.^[26] Recently, in a human study, reorganization of attachment pattern toward security in mothers with unresolved trauma resulted in their children being securely attached.^[55] Similarly, there is sufficient evidence in animals demonstrating that epigenetic modifications can be changed or even reversed through environmental enrichment during prenatal or postnatal periods.^[17]

Strategies to alleviate the impact of adverse perceived parenting could be through prevention and/or intervention.^[53] However, given the well-established plasticity of maternal brain, interventions could employ coping strategies that aim to improve the capacity of parents to cease harmful behavior that resulted from adverse parenting.^[56] However, positive outcomes may be challenging. For example, although recent experimental

studies in humans have suggested that administration of OT can improve mother–infant bonding,^[14] positive outcomes in mothers who had negative childhood experiences or insecure attachment representations were not certain.^[57] Specifically, administering OT to individuals who had negative childhood parenting experience does not improve their response to infant cry, whereas individuals with a positive childhood parenting experience show decrease in their aggressive behavior in response to infant cry.^[58] Therefore, it is possible that such interventions may need to use a variety of different strategies, including strategies that focus on enriching the social environment of mothers, to alleviate the impact of stress related to parenting received in the early years of life.

Although this review is limited to discussing the impact of “perceived parenting”, impact of childhood adversity due to “abuse or maltreatment” from others (including parents) cannot be overlooked. Chronic exposure to stress due to experiencing abuse can result in lasting alterations in stress reactivity, including changes in the hypothalamic–pituitary–adrenal axis.^[34] Empirical evidence to support transgenerational transmission of these changes is currently limited.^[59] In mothers who experienced childhood abuse, studying the structural and functional changes in the brain due to abuse may help better understand the reason these mothers are more vulnerable to mental disorders.^[59]

Going forward, although the current knowledge on brain regions that could mirror adverse early parenting experiences is promising for early identification of mothers at risk of poor parenting, this knowledge is yet limited to guide advanced screening strategies.^[53] Charting a discrete profile of the maternal brain that is mediated by stress- and reward-related neural systems on its own is not enough to guide interventions. This should ideally be accompanied by relevant hormonal assessment, which could pave the way for therapeutic strategies to prevent the epigenetic transmission of negative maternal behavior.

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