Molecular and Genetic Bases of Mammalian Maternal Behavior

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Abstract
New mammalian mothers undergo an increase in their maternal responsiveness with the birth of their infants. Associated with changes in responsiveness are how attracted mothers are to infant cues, mothers’ affective state, and their cognitive and executive function. In comparison to nonmothers, new mothers are more attracted to infant odors and are more easily alerted to their vocalizations; they undergo a reduction in withdrawal behaviors and anxiety, but increased lability. Their maternal sensitivity (human or licking intensity, rat) is associated with higher levels of attention and working memory. Maternal responsiveness and these associated behaviors are associated with large shifts in maternal hormones across parturition. Changes in expression of neuropeptides and neurotransmitters are affected by mothers’ prior experiences, including their very early experiences in their families of origin. The present review describes the regulation of mothering and associated behaviors by the neurotransmitters, oxytocin, dopamine, and serotonin, in a rat model and in humans. Emphasis is then given to studies that focus on the role of genes and what we know about their expression in the functioning of these 3 neurochemical systems in new mothers. Studies of early experience, genetics, and human mothering show gene-by-environment interplays (interactions) for a number of DNA single-nucleotide polymorphism within both the oxytocin and serotonin systems, where associations between mothers’ early experiences and mothering/affect depend on mothers’ genotype. Studies also show associations between different dopamine genes and many aspects of both mothering and maternal affect. Where known, we also discuss evidence that the relation between early experience and mothering is often an indirect one, mediated through an effect of experience on mothers’ affect or executive function. In many cases, mothers’ genetic profile moderates these relations. Finally, preliminary evidence suggests a role of epigenetic mechanisms in these processes.

Keywords
maternal behavior, psychobiology, humans, rats, depression, executive function, neurotransmitters, dopamine, oxytocin, serotonin

Introduction
This brief review explores the environmental and biological bases of early mothering. In the spirit of the goals of the conference, “The Environment Writes on the Body,” the present review emphasizes genetic influences on mothering. However, to understand the role of genetics in mothering, we are helped by knowing some of the physiological and behavioral factors that contribute to mothering in both nonhuman animals and/or humans. These include the hormones of parturition, the hormones of lactation, the known and relevant brain and neurotransmitter systems, and the psychological processes that are recruited when a woman becomes a mother and engages with her offspring. By looking at all these physiologic and psychological factors, we can make some educated guesses as to which candidate genes and pathways could reasonably be a focus for the study of the genetics of mothering. Our approach in this brief review is to explore the various factors that affect mothers’ motivation to care for young when they are born and during the postpartum and the role of genes in these processes. This review is selective, not exhaustive, giving undue emphasis to our own work on this topic, focusing primarily on 3 neurochemical systems: dopamine (DA), oxytocin (OT), and serotonin (5HT).¹ ⁵ However, we direct the reader to other more up-to-date studies and reviews of the epigenetics of mothering that describe the very exciting work that is presently ongoing in...
Levels of Analysis

Parental Psychology and Probable Genetic Foundations

The levels of analysis at which mothering has and continues to be studied begin historically with investigation of (1) nature and psychological characteristics of postpartum onset of maternal behavior and its continuation; (2) the endocrinology and neuroendocrinology of pre- and postpartum mothers that contribute to mothering and associated behaviors; (3) the autonomic/visceral and subcortical mechanisms of co (mother-infant) -conditioning based on an early Pavlovian framework; and (4) underlying genetic and epigenetic mechanisms contributing to each of the psychoneurobiological mechanisms. We argue that the individual's genetic endowment, as embodied in 23 pairs of chromosomes, does not determine the individual's biological characteristics at the system level in the absence of interaction with the environment. Or, stated the other way around, the expression of the biological systems and capabilities of the individual depends on an expression of the genome in relation to the demands and opportunities presented by the physical and social environments in which the individual exists or has existed in early life.

Mother–Infant Interactions

Rat maternal behavior. Animals (including humans) exhibit natural variations in the types and quantities of species-specific maternal care they exhibit. One of the most widely studied animal models of parenting is the rat. Rats exhibit stereotyped maternal behaviors: They nurse, lick, and groom their pups, build a nest, and retrieve the pups back to the nest. The mother and the nest provide nutrition, warmth, and protection. They also provide social and other stimuli that affect pups' neural and endocrine development and later behavior. Moreover, with postpartum exposure, the young learn to prefer their mother's odor that guides subsequent social interactions and even their responses to their own offspring later on. Maternal licking has a particularly pronounced effect on offspring development and long-term effects on the quality of mothering pups adopt toward their own young. The most effective period for transmission of licking effects seems to be in the first postpartum week when the rat brain is still rapidly developing. Licking and grooming (LG) during early life thus have a non-genetic influence on the next generations and are therefore crucial for optimal development. The absence or disruption of LG, such as during maternal separation or deprivation, has documented developmental consequences as well.

Human maternal behavior. The obvious similarities among mammalian species include nursing and a posture designed to enhance the neonates' access to the teat, some form of communication system between mother and offspring to indicate "needs" of both, a way of transporting offspring, especially if they are altricial or immature at birth, and some form of maternal "protective" defense of offspring. Most mothers also keep their offspring clean by grooming and provide a home base or "nest site" either in the environment or on their bodies where the young can sleep. In addition to performing these functions, human mothers normally develop feelings of nurturance and warmth (or "love") toward the baby, anxiety in response to distress or unexpected separations from the baby, and grief with his or her loss or death.

The differences among species in the typology, timing, and duration of the behaviors, their developmental trajectory, and the range of proximal causal mechanisms are vast. The differences emerge as a function of the developmental maturity of the young. In most mammalian species, the young are altricial, often born with their eyes and ears closed and with immature nervous systems; these young require extensive care and are very dependent on the mother for early survival. Other species are much more mature, or precocial, at birth and are more independent early on (as with ungulates where the young can stand within minutes of birth and ambulate behind the mother within days).

Nonhuman primates vary across species on the precocial-altricial dimension. Neonates must be able to cling to their mother using hands and feet postpartum. Most species have vision, hearing, olfactory, and somatosensory proprioceptive competence within the first month after birth. Beyond this commonality, offspring achieve independent mobility and are weaned over substantially different durations and stages of maturation. Humans are mostly altricial: Although they can see and hear at birth, they require a long period of care before they can fend for themselves (some would say this takes 2 decades or more!!). More intriguing—or less well understood—than cross-species differences are individual differences within a species.

The behavior of new human mothers toward their offspring shows both marked similarities and considerable differences within cultures, across cultures, and certainly in comparison to other species. Among the modal similarities are included nursing, singing, and contingent responding to infant cues and distress. However, in the absence of explicit practice, first-time mothers exhibit a range of different responses to their infants: Some look at them directly while others gaze avert; some keep their babies unclothed and stroke their bodies; others swaddle them instead. Some talk or sing to their babies; others do not. Some sleep with their babies while others keep their babies in a cot next to them or in their own rooms. Babies are also transported in different ways—some on the front of the body, others on the back; some on cradle boards and others still, in a vehicle.

More subtly, within a culture mothers show large variations in the postpartum development of nurturant feelings, from minutes to months. Once "attached" or emotionally committed, mothers vary in the intensity with which they exhibit different caregiving behaviors. More extremely, some are...
motivated to provide warmth, shelter, and food to the infant while others neglect or even abuse their infants.\textsuperscript{37-40}

In many of the studies that explore genetic associations to mothering, mothers’ sensitivity while interacting with infants constitutes an important phenotype that shows large variation in most populations. Maternal sensitivity is assessed (measured) by observation and recording of mother–infant interactions, and coding of mothers’ behavior in response to infant behaviors. In North America and other industrialized cultures, mothers described as showing high sensitivity (using the Ainsworth scales and maternal Behavior Q Sort) respond promptly, appropriately, and contingently to individual infant behaviors and cues and express “warmth” toward the infant.\textsuperscript{32,41}

**Postpartum Depression and Maternal Behavior: Psychological Effects on Offspring**

Parturition often brings about changes in maternal mood: Mothers become more labile, experiencing periods of elation alternating with tearfulness.\textsuperscript{42} Many mothers experience a period of “postpartum blues,” which is also characterized by emotional lability, but tends to involve more dysphoria, anxiety, and depression that is time limited and usually remits by the end of the first month.\textsuperscript{43} Other mothers experience a real postpartum depression, which is similar in some—but not all respects—to depression occurring during other periods of life. Postpartum depression is far more prevalent than is appreciated, with estimates of incidence rates of between 10\% and 13\% in developed countries, including Canada. Depression can start during the first 6 postpartum months and can persist on and off for years.\textsuperscript{43} However, peri- and postpartum depression most often remit within the first postpartum year, although one major predictor of depression during this period is depression outside the postpartum period in which case the depression may be present at other times and deepen during either pregnancy and/or the postpartum.\textsuperscript{44} Depressed mothers, like depressed nonmothers, often experience extreme fatigue, dysphoric mood, anxiety, tearfulness, and feelings of low self-esteem.\textsuperscript{44}

Unlike depression outside the peripartum period, maternal depression can have profound consequences for mother–child interactions and child development. Maternal depression often impairs the mothers’ attention, sensitivity, and “bonding” with the baby.\textsuperscript{44,49} These changes may also alter maternal perceptions of infant/child cues and her attention to them, which can, in turn, influence the salience of the infant/child to the mother and hence her motivation and competence.\textsuperscript{45-49} Although these studies focus on the first postpartum year, there is a substantial literature that suggests that outside the postpartum period, depressed individuals find various social stimuli to be less rewarding and that there is reduced neural activation in the striatum among depressed patients.\textsuperscript{50} Indeed, depression associates with states of anhedonia and impairments in executive functions, both of which may serve as the basis for later parenting difficulties.

Cognition and maternal behavior. Mother rats that naturally show high levels of pup licking perform better on a variety of attention tasks, including attention set-shifting and prepulse inhibition (PPI) of the acoustic startle response.\textsuperscript{51} Mothers reared apart from their own mothers, show both reduced licking and correlated decrements in attention set-shifting, PPI, and enhanced action impulsivity.\textsuperscript{51-53}

Numan and Insel\textsuperscript{54} argue that in primates, as compared to rodents, the balance between size and role of the medial preoptic area (MPOA) and the neocortex in regulating maternal behavior has shifted in favor of the latter, reflecting the greater importance of the prefrontal function in human parenting. This expanded role of the neocortex is consistent with the extended period of parental care in humans, as well as with the demands of parenting children at very different developmental stages.\textsuperscript{54} The DA neurochemical input into the prefrontal cortex (PFC) is closely associated with attentional and executive function systems critical for quality parenting.\textsuperscript{55-57}

Dyadic synchrony between a mother and her infant, which often develops over the first postpartum months, consists of crucial individual components, including positive affect, physiological synchrony, a shared focus of attention, and temporal coordination and contingency; all controlled primarily by the caregiver. Our studies with human mothers confirm the importance of cognitive flexibility, mother–child synchrony, and emotional well-being for maternal behaviour.\textsuperscript{45,58-60}

Mothers with disturbed attachments to their own caregivers (disorganized/unresolved), and to their own infants (irrational fear of loss of the infant), and mothers of disorganized infants (infants whose attachment strategies collapse under stress), show attentional difficulties when assessed with emotional Stroop tasks.\textsuperscript{61} Mothers with slow Stroop reactivity are slower to respond to infant signals.\textsuperscript{60} Furthermore, we found that mothers with fewer errors on extradimensional shift and spatial working memory tasks at 2 to 6 months postpartum are more sensitive in their interactions with their infants and show more contingent responding to infant cues.\textsuperscript{56} Finally, a recent randomized controlled intervention study Family Nurture Intervention shows that additional guided support to promote contingent interactions between mothers and newborns, especially in the neonatal intensive care unit, enhances mothers’ self-confidence, positive touch, and interactional sensitivity and reduces the probability of PPD in these mothers; it also (and thereby?) has positive effects on the infant’s own behaviors as well as its growth and development.\textsuperscript{62,63}

**Maternal experience, early adversity, and maternal behavior.** Parturitional hormones in rats are critical during the early postpartum period for attraction to pups. However, throughout lactation and the accompanying interactions with young, associative learning processes render the pups highly rewarding, a characteristic sustained following weaning as mothers remain responsive to young for many months.\textsuperscript{24} In the absence of these usual interactions with mother and siblings, as in situations of early social isolation, rat pups grow up to show reduced licking of their own young and reduced interest in them.\textsuperscript{18,64,65} In
monkeys, maternally deprived mothers are more likely to reject infant suckling attempts and engage in more physical aggression toward their infants, are less likely to “retrieve” a crying infant.96,97

Human mothers who experienced early adversity may also show suboptimal mothering; they are more likely to be abusive and neglectful, and/or less sensitive and responsive to their babies.98 In the absence of a subsequent positive social support during development, negative parenting experiences tend to be transmitted across generations.18,69,70 However, along the way, supportive positive experiences including by family and/or friend support networks, or a supportive spouse may act as protective factors that ameliorate the effect of negative early experiences in the family of origin.27,71-73

Hence, as we have seen, optimal mothering requires efficient emotion regulation, cognition, learning/experience/, and executive function. Human mothers must be sensitive to infant cues and respond appropriately and in synchrony with the needs of the infant. Infant cues must be attractive and salient for the mother, recruiting attentional systems. Mothers must be emotionally prepared and positively motivated to engage socially with the infant. They must selectively attend to the offspring in the context of competing stimuli and be consistent in their responsiveness. Finally, and not surprisingly, optimal mothering and its psychological profile are affected by mothers’ early and other life experiences and their effects can be transmitted to the next generation of mothers.56,74-76

Looking to the animal work and to human studies, and by understanding the phenomenology of mothering and its neurochemistry and neurobiology, we are in a good position to choose candidate genes. We look both to the animal work on the role of gene expression and gene products on maternal and associated behaviors, especially in rodents but extending up to nonhuman primates and humans. Within the past 2 decades, an extensive literature on gene polymorphisms related to neurobiological function in animals and to maternal psychological function in humans has emerged. In general, genetic studies exploring these functions focus on their dysfunction and look for gene polymorphisms that relate to conditions such as postpartum depression, impulsivity, memory disorders, and so on. Hence, in what follows we discuss not only what is known about the genetics of mothering per se but also the genetics of behavioral maladaptation and disorders in psychobiological domains that contribute to mothering. Before addressing maternal behavior at the genetic level, the biology and neurobiology of mothering will briefly be reviewed.

**Neurobiological Effects of Mothering Experience on the Mother: Hormones and Gene Expression**

Genes associated with the hormones that undergo change during later pregnancy and at parturition are good candidates for investigation. These include genes associated with the ovarian or placental reproductive hormones (estrogen and progesterone), the peptide prolactin, and the neuropeptides OT and arginine vasopressin (AVP).54 Hormonal changes in the final trimester of pregnancy, including elevations in estradiol and a decline in progesterone, form the basis for the onset of maternal behavior following parturition in the rat.77-80 These changes have been implicated in the regulation of maternal behavior in many mammalian species.2,54

Three neurochemical systems and gene pathways have been associated with mothering and associated cognition, attention, and affect. These include those associated with OT, DA, and 5HT.4 While no single neural system operates in isolation to regulate a complex phenotype like maternal and associated behavior, all 3 systems are likely to be implicated in different aspects of maternal behavior. Genes for the hormones, such as estrogen, prolactin, and indeed cortisol, are relevant to early licking effects in rats and probably play a role in human maternal behavior as well. They have yet to be studied—or have been studied minimally—in this context in humans and are not discussed further in the present review (except to note that an orthologue of a gene first identified in Drosophila melanogaster, the Foraging Gene, has recently been associated with maternal behavior in humans81). Below we review findings relevant to the 3 neurochemical systems (OT, DA, and 5HT), and their genetic precursors, to mothering and associated behaviors.

**Oxytocin**

**Oxytocin physiology and mothering.** Oxytocin is a neuropeptide hormone involved in parturition and milk let-down across all mammals.82 Estrogen enhances OT receptor (OTR) binding in the MPOA, a brain region critical to maternal behavior across mammals.83,84 Central administration of OT stimulates maternal behavior, while OTR blockers reduce maternal behavior in virgin rats.85,86 Moreover, individual differences in specific forms of maternal behavior, such as pup LG, correlate with OTR expression in the MPOA, and intracerebral infusion of an OTR antagonist eliminates individual differences in pup LG among lactating rats.87

The role of OT is more ambiguous in women. A number of studies show that OT is closely related to affiliative relationships, being a neuropeptide that “acts to enhance the perceptual salience of social and emotional stimuli in general.”88,89 However, whether OT has effects (or associations) is not always straightforward, varying as a function of the context in which their effects (or associations) are assessed as well as the person’s gender, maternal status, personality, attachment style, general stress reactivity, and early life experiences to name a few.88,90-93 Given the importance of these variables, our analysis of the role of any of the hormones, neuropeptides, or neurotransmitters in human mothering needs to keep in mind the potential role of other factors that could influence whether or not these brain chemicals have effects on maternal behavior and affect. In prospective mothers, OT levels in the first trimester predict postpartum characteristics of the expression of maternal behavior and coordination with infant state.94 The OT levels in mothers have also been associated with affectation, rather than stimulatory parenting.95 Interestingly, OT is
anxiolytic, reducing the impact of stress on emotional states, although often effects of OT on depressive symptomatology and maternal sensitivity depend on mothers’ psychosocial stress 99; among highly stressed individuals (but not among women with low levels of psychosocial stress), plasma OT levels are associated positively with maternal sensitivity and inversely with depression. 93 An intriguing analysis of OT nasal spray effects in humans suggests that OT may promote positive affective states within social interactions and the recognition of emotional states in others. 96,97

Within the maternal context, and when it has positive effects, OT seems to be mostly associated with the onset of maternal behavior, “maternal motivation,” and warmth. It is likely to be of greatest direct relevance in the early stages of maternal responding when close contact behaviors predominate, and nursing may still be occurring. 98 The OT may also be related to mothers’ depression after birth. For instance, low OT levels during pregnancy are associated with the development of postpartum depression. 98 On the other hand, as Zelkowitz et al99 point out, OT levels during pregnancy are only related to maternal symptoms of depression at 2 months postpartum among mothers experiencing high levels of psychosocial stress. Further, in nonmothers, plasma OT levels are higher in patients with major depression than in healthy controls. 99 The relationship between plasma OT measures and mood states in women is not straightforward and depends on multiple moderating influences.

In terms of OT and early-life experience, OT levels in cerebrospinal fluid (CSF) are negatively correlated with anxiety in women who have experienced early childhood trauma. 100 In fact, there are differences among women in their susceptibility to early childhood experiences, which may be passed on across generations and which may also relate to individual differences in genetic profile. 101-107

**Oxytocin genetics and mothering.** Very few studies have explored the association between genetics within the OT system and mothering and they are predominantly human studies. 11,98,106-110 Hence, we know more about the role of OT neuroendocrinology in mothering from the animal work and about OT genetics and mothering from human studies. Among new human mothers, evidence shows that the presence of a C allele on 1 OT gene single-nucleotide polymorphism (SNP) is associated with higher stress-induced anxiety and lower emotional well-being. 11 Variations in OT-related genes modulate both non-postpartum depression and anxiety and, possibly, maternal mood and sensitivity in mother–infant interactions. 11 Genetic variations within the OT system also interact with mothers’ own childhood experiences of adverse rearing and current stressors to influence mothering. 11 These effects are often mediated through alterations in mothers’ affective state.

Specifically, Mileva-Seitz et al11 examined 2 polymorphisms in the OT peptide gene SNP, OT (rs2740210 and rs4813627), and one polymorphism in the oxytocin receptor gene OTR (rs237885) in 187 Caucasian mothers at 6 months postpartum. For OT, both rs2740210 and rs4813627 were significantly associated with maternal vocalizing to the infant. These polymorphisms also interacted with the quality of care mothers experienced in early life to predict variation in maternal instrumental care and postpartum depression. However, postpartum depression did not mediate the gene–environment (G×E) effects of the OT SNPs on instrumental care. In contrast, the OTR SNP rs237885 did not associate with maternal behavior, but it did associate with prenatal (but not postnatal) depression scores. These findings illustrate the importance of variation in OT genes as predictors of individual differences in human mothering, both alone and in interaction with early environment. Depression does not appear to have a causal role in the variation we report in instrumental care of the infant. This suggests that variation in instrumental care varies in association with an effect of gene by early environment interaction regardless of the magnitude of ongoing depressive symptomatology.

Finally, our findings highlight the importance of examining multiple dimensions of human maternal behavior in studies of genetic associations. Mothers who experienced early adversity in their family of origin and who showed increased depression, also showed reduced length of breastfeeding if they possessed the CC genotype of OT rs2740210 but not if they possessed the A allele (AA/AC genotypes). 98 In the case of breastfeeding, then, depression apparently does play a role in mediating the relationship between early adversity and breastfeeding outcome, but only among women who are homozygous for the C allele. 98 In this case, the gene variants have a moderating effect on the association between adversity and breastfeeding, reflected in a clear G×E interaction (OT genotype × level of early adversity). However, in a meta-analysis of the role of genes in the OTR system (as opposed to the OT ligand system, including AVP, for example), Bakermans-Kranenburg and van Ijzendoorn111 found that there was no evidence to support an association between 2 of the most frequently studied OTR coding region SNPs (rs53576, rs2254298) and 5 domains of human behavior. This meta-analysis was limited, however, by its focus on only 2 SNPs and a broad definition of human behaviors that included personality, psychopathology, and autism.

In a more recent analyses of the Maternal Adversity Vulnerability and Neurodevelopment sample, we tested and tagged 2 SNPs, OTR rs237885, which was not explored by the Bakermans-Kranenburg group111 and OTR rs2254298 (which was) against executive function at 48 months postpartum. 57 Executive functions were assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB; Attentional set-shifting, Spatial working memory, Stop signal task, and Decision-making). A mother–child interpersonal interaction at 48 months postpartum, the Etch-a-Sketch task, was coded and factored into Physical Controlling Parenting and Positive Parenting. OTR rs2254298A had an indirect effect on Positive Parenting mediated through parental performance on Decision-making. Further, OTR rs2254298A had both direct and indirect effects on Physically Controlling parenting, in this
case, also mediated through enhanced performance on CANTAB Decision-making.57

Although OT has previously been associated with only the onset of maternal behavior, “maternal motivation,” and warmth, involved in bonding, close contact, and nursing during the early postpartum period, we now know that OTR polymorphisms are associated with maternal behavior at 48 months postpartum via associations with the mothers’ executive functions. These studies highlight the importance of the OT system to maternal sensitivity at birth and beyond infancy and the role in these associations of mothers’ executive function.

**Dopamine**

**Dopamine physiology and mothering.** Oxytocin does not act alone. Dopamine is also a central neurochemical for the expression of mothering in the rodent model. In fact, OT is one regulator of DA release and activity in the nucleus accumbens (nACC), and nACC and DA are important for the maternal attraction to young112,113 and to consolidation of maternal experience.114,115 Over the first postpartum week, rat mothers become increasingly attracted to the young.116 This effect is dependent on the interactions of the OT and DA systems. The OT infused into the midbrain region stimulates DA release in a forebrain region (the nACC) involved in experience-enhanced stimulus salience and reward.117 Forebrain DA levels increase during both nursing bouts and licking or sniffing interactions with pups not only in newly parturient female rats but also in response to foster pups in multiparous experienced animals and virgins induced to become maternal by continuous exposure to pups.113,117-121

Chemical lesions of DA neurons or infusions of DA receptor (D1, D2) or DA transporter (DAT) antagonists, profoundly disrupt maternal behavior in the mother.113,117-124 Agonists produce the opposite effect.24 Moreover, the magnitude of DA release in the forebrain in the mother is directly related to the level of pup LG by rat mothers and to the experience level of mothers.119,120,125 The DA release in the cortex also occurs and is implicated in the mediation of cortical executive function.126,127 Microarray studies show that genes for DA receptors show differential expression in the brains of virgin and postpartum animals.125 Together, these studies suggest that the mesocorticolimbic DA system regulates maternal behavior in part by acting on the forebrain to influence incentive motivation, reward, and lower level attentional processes, and in part by acting on the PFC to influence executive function (eg, working memory, attention). Lesions to brain regions that receive DA input disrupt approach responding and sequential organization of behavior, respectively.128

There is no direct evidence relating intracerebral levels of DA to human mothering, or mothers’ responses to infant cues. However, functional magnetic resonance imaging and positron emission tomography (PET) studies reveal that activity along DA pathways in forebrain, limbic system, and cortex is associated with individual differences in responsiveness to infant stimuli assessed through blood-oxygen-level-dependent contrasts. Increased activity within these systems is associated with enhanced executive function and selective attention functions necessary for maternal responsiveness.23,129-133 Not surprisingly, these same regions are also activated when women view pictures of their own versus other children or hear infant cries.134-137 The DA system may differ from the OT system in becoming more involved when the reward, attentional systems, and memory come to be more strongly involved in maternal behavior as mothers gain experience with infants. This starts soon after birth but demands on these capacities increase over the ensuing months and years (6-60 months).

**Dopamine genetics and mothering.** What is the role of the DA-related genes to mothering? One of the first DA genetic association studies of maternal behavior in humans found no direct association between the DA D2 receptor Taq1 polymorphism and maternal sensitivity, parenting stress, negativity, or depressive symptoms.138 When environmental influences were also considered, however, it was found that DA D4 receptor and catechol-O-methyltransferase (COMT) Val158 Met polymorphisms in mothers were found to interact with daily stresses, or “hassles,” to predict maternal sensitivity.138 Consistent with these findings, mothers with a DA D4 receptor 7-repeat allele behaved more sensitively to fussier infants and less sensitively to less fussy infants compared to mothers without the 7-repeat allele, suggesting that mothers are differentially sensitive to their infants’ fussiness dependent on their own DA genotypes.139 As well, DAT polymorphisms in mothers were associated with “negative” maternal behaviors during a structured mother–child interaction task; an effect that was particularly strong if the infants were being disruptive during the interactions.140 Finally, in a recent series of studies relating DA genes to mothering at 6 months postpartum, we found that 2 DA D1 receptor SNPs were significantly associated with time mothers spent attending to the infant.9

These findings are consistent with the idea that DA acts at the D1 receptor to enhance the salience and thus attention toward infant stimuli. Mothers who are heterozygous for the DA D1 receptor SNP oriented away from their infants significantly less than either homozygote group, showing evidence of heterosis for the DA D1 receptor haplotypes. In contrast, 2 DA D2 receptor haplotypes were significantly associated with maternal vocalizing/speech to the infant.9 Our findings provide important evidence that genetic variation in receptors critical for mothering in nonhuman species also affects human maternal behaviors. This also highlights the importance of exploring multiple dimensions of the complex human mothering phenotype. In contrast, in terms of incentive salience or “reward,” no studies to date have explored genetic influences on mothers’ attraction to infants or positive stimulus salience in general. Most of the genetic studies have examined genetic predictors of neuropsychopathologies in the reward system, including impulsivity, addiction, and gambling, where polymorphisms within the DA receptor systems have been associated with variations in a variety of addictive traits or reward deficiency conditions.141-143 In terms of depression, to our knowledge,
there are no studies on genetic variation in DA systems relating to postpartum depression. However, genetic variants in the DA-related genes, COMT, and monoamine-oxidase A all appear to be important predictors of depression.\textsuperscript{144-147}

\section*{Serotonin}

\textbf{Serotonin Physiology and mothering.} Serotonin influences mood, emotion, and cognition, as well as regulatory functions like sleep.\textsuperscript{148} Central 5HT release occurs primarily in the hindbrain of the brainstem, with axons projecting to the entire brain. The 5HT has multiple effects on maternal behaviors, depending on which receptor systems and brain regions are affected.\textsuperscript{115} The 5HT brain levels in rats are associated with maternal aggression and maternal behavior; different 5HT receptor agonists increase maternal aggression and disrupt expression of many maternal behaviors, without affecting maternal motivation, affection, or stimulus salience per se,\textsuperscript{149} although some 5HT agonists seem to disrupt aspects of maternal startle and attention.\textsuperscript{150-152} In primates, 5HT is implicated in anxiety arousal of mothers\textsuperscript{153} and lower CSF 5HIAA levels associate with more restrictive and rejecting maternal behaviors.\textsuperscript{154} Female monkeys raised by abusive mothers have lower levels of 5HIAA and are more likely to abuse their own offspring.\textsuperscript{154}

There are no studies of 5HT and mothering in humans, although 5HT dysregulation is thought to be related to postpartum depression and other affective disorders and is associated with increased aggressive behaviours.\textsuperscript{148,155} There is also a substantial literature that suggests that outside the postpartum period, depressed individuals find various social stimuli to be less rewarding and that there is reduced neural activation in the striatum among depressed patients.\textsuperscript{30} Indeed, depression associates with states of anhedonia and impairments in executive functions, both of which serve as the basis for later parenting difficulties. Although DA, OT, and 5HT are implicated in major depression, the 5HT system seems to take precedence, likely in conjunction with the other systems in different aspects or symptoms of depression.\textsuperscript{155-158} In fact, DAergic agents appear particularly useful as adjunct treatments targeting hedonic processes and the quality of life.\textsuperscript{159} The PET studies show decreased brain 5HT2A receptor density in drug-naive depressed patients.\textsuperscript{160} Therapeutic action of antidepressants is associated with the increase and/or normalization in brain 5HT2A receptor density.\textsuperscript{161,162}

In terms of 5HT gene polymorphisms and mothering, one gene has received wide attention in the developmental literature and that is the serotonin transporter (\textit{5HTT}) gene.\textsuperscript{163,164} We examined the influences of 5HTT gene polymorphism and early-life experience on the expression of individual differences in 3 dimensions of maternal responsiveness in 6-month postpartum mothers: These included maternal sensitivity, maternal behavior (orienting away from the infant), and maternal attitudes (perceived attachment).\textsuperscript{10} Mother’s 5HTT gene polymorphisms are characterized by 1 of 3 allele types designated S (short), L (Long), and Lg (Long as well but Lg is functionally similar to S allele in terms of 5HTT expression).\textsuperscript{165} We found that mothers carrying an S, or the functionally similar Lg allele, were more sensitive than those lacking these alleles. We also found a highly significant G×E interaction effect on 2 other mothering dimensions. With increasing quality of care, mothers with an S, or Lg allele, tended to orient away from their babies less often and score higher on ratings of perceived attachment whereas mothers lacking an S (or Lg) allele tend to exhibit increased frequency of orienting away and lower ratings on perceived attachment with increased early care quality.\textsuperscript{10}

These results are not consistent with an earlier study by Bakermans-Kranenburg and van Ijzendoorn\textsuperscript{108} who report that independent of daily stress levels, S-carrying mothers are less maternally sensitive, which is opposite to the present findings. However, there were many differences between these 2 studies, including the age of the young at time of assessment (6 months vs 2 years) and the location of the assessment (less stressful home environment vs more stressful laboratory setting). It is possible that S-carrying mothers are more sensitive than non-S-carrying mothers under conditions of low stress, but less sensitive under conditions of high stress. This hypothesis is consistent with arguments that genetic influences depend on environmental conditions\textsuperscript{103} and fits well with the emerging theory that the S allele confers greater sensitivity to environmental signals, both good and bad, rather than acting only as a “vulnerability” allele.\textsuperscript{166} Rather than a susceptibility (or vulnerability) allele, the S allele may be viewed as a plasticity allele.\textsuperscript{167,168}

These interactions between early experience and genotype may be related to underlying neural and cognitive evidence that the S allele predicts improved attentional processes\textsuperscript{169} and social cognition,\textsuperscript{170} which as indicated above are important components of mothering.\textsuperscript{23,61,171} In terms of physiological mechanisms, the 5HTTLPR serotonin transporter genotype in humans is also directly associated with differences in 5HTT binding in a variety of brain sites important for DA and mothering.\textsuperscript{172-175} This is consistent with the theory that the neurotransmitter 5HT inhibits dopaminergic neuron signalling.\textsuperscript{176}

\section*{Epigenetic Mechanisms Relating to Mothering}

The environment could affect later mothering through direct effects on gene expression. This has been demonstrated in the cortisol–hypothalamic–pituitary–adrenal system rats.\textsuperscript{7,177-179} Unfortunately to date, we have no information about epigenetic processes acting on the \textit{DA} or \textit{5HT} genes that we have argued are important for mothering. However, such effects have been found for other gene products that affect mothering, especially for some of the steroid receptors. As earlier described for the rat model, in comparison to high-licking mother rats, mothers who lick their pups less have female offspring who as adults lick their offspring less.\textsuperscript{17,18,180,181} In the MPOA (the area crucial to mothering), these female offspring show both reduced expression of the estrogen receptor \textit{\alpha} gene (and hence are less sensitive to estrogen action) and an increased DNA methylation of its promoter region, which functionally reduces gene
expression. A similar epigenetic process may also affect the BDNF gene under adverse early experiences. The reduction in the demethylation (or a retention of methylation) is a mechanism by which the early adverse experience, as opposed to a positive and healthy experience, could have a long-term impact on mechanisms through which mothering behavior is mediated. Finally, as early adversity effects on methylation patterns in the human (postmortem) brains have also been reported, it would be important to know whether the gene-by-early experience interactions reported in relation to mothering involve differential methylation patterns of the relevant OT, DA, and 5HT genes. These studies are ongoing in the rat model.

Summary and Conclusions
We know considerably more about the endocrine and neurochemical bases of mothering in nonhuman mammals than in humans. In rodents, we have determined their effects on brain mechanisms of maternal behavior directly and on mechanisms regulating other behavioral systems that affect mothering. In both nonhuman and human studies, many behavioral systems and experiences affect how mothers interact with their offspring. In a number of mammalian species, the quality of mothering is influenced by the mother’s affective state, attention, impulse control, cognitive learning function, executive function, and the salience of stimuli mothers attribute to their environments including infant cues and related stimuli. We also know from both animal and human studies that early-life experiences, current stressors, and surrounding social and physical environments impact the quality of mothers’ behavior and the effects of hormones and neurochemicals on mothering affect and behavior. What we have tried to briefly review but clearly know less about is the role of genetics in this process and how the environment affects the expression of potential gene products. What is the role of genes in mothers’ transition to parenting and in the quality of mothering shown? How do early stressors affect mothers with different genetic profiles? These are questions that will guide future research in this area.

What we have attempted to do is describe studies that show, primarily in human research, a potential role for certain gene systems in the regulation of early postpartum mothering, choosing those systems assiduously, and based on our knowledge of the relevant biochemistries shown to be important for nonhuman rat mothering. What is missing from our review is an extensive description of the multiple genes involved in the regulation of mothering, which can occur now through use of gene-wide arrays and predicted signaling pathways (as in DA, OT, and 5HT pathways) and the role of epigenetics in their action. Also understudied are the myriad of environmental and experiential influences that moderate the effects of these signaling pathways and their genetic bases. Clearly, one mechanism for the G×E interaction or interplay is through processes of epigenetics-methylation, histone acetylation, chromatin modification—which we know occur when the environment impinges on the genes and which regulates gene expression. Clearly, an epigenetic analysis would provide us with a mechanism through which G×Es could occur, that is, how experiences, both early and recent, could exert their effects on gene expression to affect the brain mechanisms of mothering. We look forward to future explorations involving very large longitudinal samples of mothers (and fathers!) who have been deeply phenotyped (assessed for their lifetime family and social experiences, their own and child characteristics, their demographics, and their behavioral interactions with offspring). This program of research would focus on hypothesized gene systems that are derived from our knowledge of the underlying physiology of mothering/parenting and associated neurobiological affective and cognitive characteristics.

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References
1. Brett ZH, Humphreys KL, Fleming AS, Kraemer GW, Drury SS. Using cross-species comparisons and a neurobiological framework to understand early social deprivation effects on behavioral development. Dev Psychopathol. 2015;27(2):347-367.
2. Fleming AS, Lonstein JS, Levy F. Introduction to this special issue on parental behavior in honor of Jay S. Rosenblatt. Horm Behav. 2016;77:1-2.
3. Lomanowska AM, Boivin M, Hertzman C, Fleming AS. Parenting begets parenting: a neurobiological perspective on early adversity and the transmission of parenting styles across generations. Neuroscience. 2017;342:120-139.
4. Lonstein JS, Levy F, Fleming AS. Common and divergent psychobiological mechanisms underlying maternal behaviors in nonhuman and human mammals. Horm Behav. 2015;73:156-185.
5. Mileva-Seitz VR, Bakermans-Kranenburg MJ, van Ijzendoorn MH. Genetic mechanisms of parenting. Horm Behav. 2016;77:211-223.
6. King L, Robins S, Chen G, et al. Perinatal depression and DNA methylation of oxytocin-related genes: a study of mothers and their children. Horm Behav. 2017;96:84-94.
7. Stolzenberg DS, Champagne FA. Hormonal and non-hormonal bases of maternal behavior: the role of experience and epigenetic mechanisms. Horm Behav. 2016;77:204-210.
8. McGowan PO, Roth TL. Epigenetic pathways through which experiences become linked with biology. Dev Psychopathol. 2015;27(2):637-648.
9. Mileva-Seitz V, Fleming AS, Meaney MJ, et al. Dopamine receptors D1 and D2 are related to observed maternal behavior. Genes Brain Behav. 2012;11(6):684-694.
10. Mileva-Seitz V, Kennedy J, Atkinson L, et al. Serotonin transporter allelic variation in mothers predicts maternal sensitivity,
behavior and attitudes toward 6-month-old infants. *Genes Brain Behav.* 2011;10(3):325-333.

11. Mileva-Seitz V, Steiner M, Atkinson L, et al. Interaction between oxytocin genotypes and early experience predicts quality of mothering and postpartum mood. *PLoS One.* 2013;8(4):e61443.

12. Welch MG. Calming cycle theory: the role of visceral/autonomic learning in early mother and infant/child behaviour and development. *Acta Paediatr* (Oslo, Norway: 1992). 2016;105(11):1266-1274.

13. Abel RA, Ronca AE, Alberts JR. Perinatal stimulation facilitates suckling onset in newborn rats. *Dev Psychobiol.* 1998;32(2):91-99.

14. Hofer MA, Sullivan R. Toward a neurobiology of attachment. In: Hann MD, Gunner MR, eds. *Handbook MOF Parenting: Biology and Ecology of Parenting.* Vol 1. Mahwah, NJ: Lawrence Erlbaum; 1995.

15. Shah A, Oxley G, Lovic V, Fleming AS. Effects of preweaning exposure to novel maternal odors on maternal responsiveness and selectivity in adulthood. *Dev Psychobiol.* 2002;41(3):187-196.

16. Wilson DA, Sullivan RM. Neurobiology of associative learning in the neonate: early olfactory learning. *Behav Neural Biol.* 1994;61(1):1-18.

17. Champagne FA, Francis DD, Mar A, Meaney MJ. Variations in maternal care in the rat as a mediating influence for the effects of environment on development. *Physiol Behav.* 2003;79(3):359-371.

18. Gonzalez A, Lovic V, Ward GR, Wainwright PE, Fleming AS. Intergenerational effects of complete maternal deprivation and replacement stimulation on maternal behavior and emotionality in female rats. *Dev Psychobiol.* 2001;38(1):11-32.

19. Chatterjee D, Chatterjee-Chakraborty M, Rees S, et al. Maternal isolation alters the expression of neural proteins during development: ‘stroking’ stimulation reverses these effects. *Brain Res.* 2007;1158:11-27.

20. Bornstein MH, ed. *Handbook of Parenting: Biology and Ecology of Parenting.* Vol 1. Mahwah, NJ: Lawrence Erlbaum; 1995.

21. Bornstein MH. *Handbook of Parenting. Vols 1-5.* 2nd ed. Mahwah, NJ: Lawrence Erlbaum; 2002.

22. Corter C, Fleming AS. Psychobiology of maternal behavior in human beings. In: Bornstein MH, ed. *Handbook MOF Parenting: Biology and Ecology of Parenting.* Vol. 2. Mahwah, NJ: Lawrence Erlbaum; 2002:141-182.

23. Gonzalez AAL, Fleming AS. Attachment and the comparative psychobiology of parenting. In: Hann MD, Gunner MR, eds. *Handbook of Developmental Social Neuroscience.* New York, NY: The Guilford Press; 2009:225-245.

24. Numan M, Fleming AS, Levy F. Maternal behavior. In: Neill JD, ed. *Knobil and Neill’s Physiology of Reproduction.* London, England: Elsevier; 2006:1921-1923.

25. Altman J. *Baboon Mothers and Infants.* Cambridge, MA: Harvard University Press; 1980.

26. Hinde RA. *Biological Bases of Human Social Behaviour.* New York, NY: McGraw-Hill; 1974.

27. Hrdy SB. *Mothers and Others: The Evolutionary Origins of Mutual Understanding.* Cambridge, MA: Harvard University Press; 2011.

28. Leiderman P, Leiderman M. Economic change and infant care in an East African Agricultural Community. In: Leiderman PH, Tulkin SR, Rosenfeld A, eds. *Culture and Infancy: Variations in Human Experience.* New York, NY: Academic Press; 1977: 405-438.

29. Trehub SE. Cross-cultural convergence of musical features. *Proc Natl Acad Sci U S A.* 2015;112(29):8809-8810.

30. Trehub SE, Ghazban N, Corbeil M. Musical affect regulation in infancy. *Ann N Y Acad Sci.* 2015;1337:186-192.

31. Ainsworth MDS. *Infancy in Uganda: Infant Care and the Growth of Love.* Baltimore, MD: Johns Hopkins University Press; 1967.

32. Pederson DR, Moran G, Sitko C, Campbell K, Ghosquire K, Acton H. Maternal sensitivity and the security of infant–mother attachment: a Q-sort study. *Child Dev.* 1990;61(6):1974-1983.

33. Brazelton TB. The Brazelton Neonatal Behavior Assessment Scale: introduction. *Monogr Soc Res Child Dev.* 1978;43(5-6):1-13.

34. Thomans EB. Co-sleeping, an ancient practice: issues of the past and present, and possibilities for the future. *Sleep Med Rev.* 2006;10(6):407-417.

35. Bornstein MH, Tamis-LeMonda CS, Tal J, et al. Maternal responsiveness to infants in three societies: the United States, France, and Japan. *Child Dev.* 1992;63(4):808-821.

36. Bornstein MH, Hahn CS, Haynes OM, et al. Maternal personality and parenting cognitions in cross-cultural perspective. *Int J Behav Dev.* 2007;31(3):193-209.

37. Leifer M. Psychological effects of motherhood: a study of first pregnancy. *Genet Psychol Monogr.* 1980;95:55-96.

38. Moss HA, Jones SJ. Relations between maternal attitudes and maternal behavior as a function of social class. In: Leiderman PH, Tulkin SR, Rosenfeld A, eds. *Culture and Infancy: Variations in Human Experience.* New York, NY: Academic Press; 1977: 439-468.

39. Rohson KM, Kumar R. Delayed onset of maternal affection after childbirth. *Br J Psychiatry.* 1980;136:347-353.

40. Trevathan WR. Maternal “en face” orientation during the first hour after birth. *Am J Orthopsychiatry.* 1983;53(1):92-99.

41. Bohr Y, Putnick DL, Lee Y, Bornstein MH. Evaluating caregiver sensitivity to infants: measures matter. *Infancy.* 2018;23(5):730-747.

42. O’Hara MW, Zekoski EM, Philipp LH, Wright EJ. Controlled prospective study of postpartum mood disorders: comparison of childbirth and nonchildbearing women. *J Abnorm Psychol.* 1990;99(1):3-15.

43. Cox JL, Murray D, Chapman G. A controlled study of the onset, duration and prevalence of postnatal depression. *Br J Psychiatry.* 1993;163:27-31.

44. Brummelte S, Galea LA. Postpartum depression: etiology, treatment and consequences for maternal care. *Horm Behav.* 2016;77:153-166.

45. Field T, Healy BT, Goldstein S, Guthertz M. Behavior-state matching and synchrony in mother–infant interactions of nondepressed versus depressed dyads. *Dev Psychol.* 1990;26(1):7-14.

46. Fleming AS, Ruble DN, Flett GL, Shaul D. Postpartum adjustment in first-time mothers: relations between mood, maternal
attitudes and mother–infant interactions. Dev Psychol. 1988;24:77-81.
47. Lovejoy MC, Graczyk PA, O’Hare E, Neuman G. Maternal depression and parenting behavior: a meta-analytic review. Clin Psychol Rev. 2000;20(5):561-592.
48. Mileva V, Fleming AS. How mothers are born. In: Booth A, McHale S, Landale N, eds. Biosocial Research Contributions to Understanding Family Processes and Problems. Berlin, Germany: Springer; 2010.
49. Milgrom J, Westley DT, McCloud PI. Do infants of depressed mothers cry more than other infants? J Paediatr Child Health. 1995;31(3):218-221.
50. Forbes EE, Dahl RE. Research review: altered reward function in adolescent depression: what, when and how? J Child Psychol Psychiatry. 2012;53(1):3-15.
51. Lovic V, Fleming AS. Artificially-reared female rats show reduced prepulse inhibition and deficits in the attentional set shifting task – reversal of effects with maternal-like licking stimulation. Behav Brain Res. 2004;148(1-2):209-219.
52. Lovic V, Keen D, Fletcher PJ, Fleming AS. Early-life maternal separation and social isolation produce an increase in impulsive action but not impulsive choice. Behav Neurosci. 2011;125(4):481-491.
53. Lovic V, Saunders BT, Yager LM, Robinson TE. Rats prone to attribute incentive salience to reward cues are also prone to impulsive action. Behav Brain Res. 2011;223(2):255-261.
54. Numan M, Insel T. The Neurobiology of Parental Behavior. New York, NY: Springer; 2003.
55. Chico E, Gonzalez A, Ali N, Steiner M, Fleming AS. Executive function and mothering: challenges faced by teenage mothers. Dev Psychobiol. 2014;56(5):1027-1035.
56. Gonzalez A, Jenkins JM, Steiner M, Fleming AS. Maternal early life experiences and parenting: the mediating role of cortisol and mothering behaviours. Development and behavioral processes. Dev Psychol. 2015;17:42-47.
57. Tombeau Cost K, Unternaehrer E, Plamondon A, et al. Thinking and the genome. Biochem J. 2018;51(7):673-682.
58. Bourvis N, Singer M, Saint Georges C, et al. Pre-linguistic infants employ complex communicative loops to engage mothers in social exchanges and repair interaction ruptures. R Soc Open Sci. 2018;5(1):170274.
59. Pratt M, Aptor-Levi Y, Yakart A, Kanat-Maymon Y, Zagoory-Sharon O, Feldman R. Mother–child adrenocortical synchrony; moderation by dyadic relational behavior. Horm Behav. 2017;89:167-175.
60. Atkinson L, Leung E, Goldberg S, et al. Attachment and selective attention: disinorganization and emotional Stroop reaction time. Dev Psychopathol. 2009;21(1):99-126.
61. Beebe B, Myers MM, Lee SH, et al. Family nurture intervention for preterm infants facilitates positive mother–infant face-to-face engagement at 4 months. Dev Psychol. 2018;54(11):2016-2031.
62. Welch MG, Myers MM. Advances in family-based interventions in the neonatal ICU. Curr Opin Pediatr. 2016;28(2):163-169.
63. Lomanowska AM, Melo AI. Deconstructing the function of maternal stimulation in offspring development: insights from the artificial rearing model in rats. Horm Behav. 2016;77:224-236.
64. Lovic V, Fleming AS. Propagation of maternal behavior across generations is associated with changes in non-maternal cognitive and behavioral processes. Behav Process. 2015;117:42-47.
65. Maestripieri D. Early experience affects the intergenerational transmission of infant abuse in rhesus monkeys. Proc Natl Acad Sci U S A. 2005;102(27):9726-9729.
66. Ruppenthal GC, Arling GL, Harlow HF, Sackett GP, Suomi SJ. A 10-year perspective of motherless-mother monkey behavior. J Abnorm Psychol. 1976;85(4):341-349.
67. Moehler E, Biringen Z, Poustka L. Emotional availability in a sample of mothers with a history of abuse. Am J Orthopsychiatry. 2007;77(4):624-628.
68. Belsky J, Conger R, Capaldi DM. The intergenerational transmission of parenting: introduction to the special section. Dev Psychol. 2009;45(5):1201-1204.
69. Champagne F, Meaney MJ. Like mother, like daughter: evidence for non-genomic transmission of parental behavior and stress responsivity. Prog Brain Res. 2001;133:287-302.
70. Egeland B, Bosquet M, Levy A. Continuities and discontinuities in the intergenerational transmission of child maltreatment: implications for breaking the cycle of abuse. In: Browne chkh H, Stratton P, eds. The Prediction and Prevention of Child Abuse: A Handbook. New York, NY: John Wiley and Sons; 2002.
71. Langeland W, Dijkstra S. Breaking the intergenerational transmission of child abuse: beyond the mother–child relationship. Child Abuse Rev. 1995;4(1):4-13.
72. Werner EE. The children of Kauai: resiliency and recovery in adolescence and adulthood. J Adolesc Health. 1992;13(4):262-268.
73. Gonzalez A, Catherine N, Boyle M, et al. Healthy foundations study: a randomized controlled trial to evaluate biological embedding of early-life experiences. BMJ Open. 2018;8(1):e018915.
74. Pereira M, Ludmer JA, Gonzalez A, Atkinson L. Mothers’ personal and interpersonal function as potential mediators between maternal maltreatment history and child behavior problems. Child Maltreat. 2018;23(2):147-156.
75. Almanza-Sepulveda ML, Chico E, Gonzalez A, Hall GB, Steiner M, Fleming AS. Executive function in teen and adult women: association with maternal status and early adversity. Dev Psychobiol. 2018;60(7):849-861.
76. Bridges RS. Biochemical basis of parental behavior in the rat. Advances Study Behavior. 1996;25:215-242.
77. Fleming AS, O’Day DH, Kraemer GW. Neurobiology of mother–infant interactions: experience and central nervous system plasticity across development and generations. Neurosci Biobehav Rev. 1999;23(5):673-685.
79. Moltz H, Lubin M, Leon M, Numan M. Hormonal induction of maternal behavior in the ovariectomized nulliparous rat. *Physiol Behav.* 1970;5(12):1373-1377.

80. Rosenblatt JS. Psychobiology of maternal behavior: contribution to the clinical understanding of maternal behavior among humans. *Acta Paediatr Suppl.* 1994;397:3-8.

81. Sokolowski HM, Vasquez OE, Unternaehrer E, et al. The drosophila foraging gene human orthologue PRKG1 predicts individual differences in the effects of early adversity on maternal sensitivity. *Cogn Dev.* 2017;42:62-73.

82. Jonas W, Woodside B. Physiological mechanisms, behavioral and psychological factors influencing the transfer of milk from mothers to their young. *Horm Behav.* 2016;77:167-181.

83. Pedersen CA. Oxytocin control of maternal behavior. Regulation by sex steroids and offspring stimuli. *Ann N Y Acad Sci.* 1997;807:126-145.

84. Young LJ, Wang Z, Donaldson R, Rissman EF. Estrogen receptor alpha is essential for induction of oxytocin receptor by estrogen. *Neuroreport.* 1998;9(5):933-936.

85. Fahrbach SE, Morrell JI, Pfaff DW. Possible role for endogenous oxytocin in estrogen-facilitated maternal behavior in rats. *Neuroendocrinology.* 1985;40(6):526-532.

86. Pedersen CA, Caldwell JD, Walker C, Ayers G, Mason GA. Oxytocin activates the postpartum onset of rat maternal behavior in the ventral tegmental and medial preoptic areas. *Behav Neurosci.* 1994;108(6):1163-1171.

87. Champagne F, Diorio J, Sharma S, Meaney MJ. Naturally occurring variations in maternal behavior in the rat are associated with differences in estrogen-inducible central oxytocin receptors. *Proc Natl Acad Sci U S A.* 2001;98(22):12736-12741.

88. Galbally M, Lewis AJ, Ijzendoorn M, Permezel M. The role of oxytocin in mother–infant relations: a systematic review of human studies. *Harv Rev Psychiatry.* 2011;19(1):1-14.

89. Peltola MJ, Strathnearn L, Puura K. Oxytocin promotes face-sensitive neural responses to infant and adult faces in mothers. *Psychoneuroendocrinology.* 2018;91:261-270.

90. Bartz JA, Lydon JE, Kolevzon A, et al. Differential effects of oxytocin on agency and communion for anxiously and avoidantly attached individuals. *Psychol Sci.* 2015;26(8):1177-1186.

91. Crowley SK, Pedersen CA, Leserman J, Girdler SS. The influence of early life sexual abuse on oxytocin concentrations and premenstrual symptomatology in women with a menstrually related mood disorder. *Biol Psychol.* 2015;109:1-9.

92. Pierrehumbert B, Torrisi R, Ansermet F, Borghini A, Halfon O. Adult attachment representations predict cortisol and oxytocin responses to stress. *Attach Hum Dev.* 2012;14(5):453-476.

93. Zelkowitz P, Gold I, Feeley N, et al. Psychosocial stress moderates the relationships between oxytocin, perinatal depression, and maternal behavior. *Horm Behav.* 2014;66(2):351-360.

94. Feldman R, Weller A, Zagoory-Sharon O, Levine A. Evidence for a neuroendocrinological foundation of human affiliation: plasma oxytocin levels across pregnancy and the postpartum period predict mother–infant bonding. *Psychol Sci.* 2007;18(11):965-970.

95. Gordon I, Zagoory-Sharon O, Leckman JF, Feldman R. Oxytocin, cortisol, and triadic family interactions. *Physiol Behav.* 2010;101(5):679-684.

96. Di Simplicio M, Massey-Chase R, Cowen PJ, Harmer CJ. Oxytocin enhances processing of positive versus negative emotional information in healthy male volunteers. *J Psychopharmacol.* 2009;23(3):241-248.

97. Guastella AJ, Einfeld SL, Gray KM, et al. Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biol Psychiatry.* 2010;67(7):692-694.

98. Jonas W, Mileda-Seitz V, Girard AW, et al. Genetic variation in oxytocin rs2740210 and early adversity associated with postpartum depression and breastfeeding duration. *Genes Brain Behav.* 2013;12(7):681-694.

99. Parker KJ, Kemna HA, Zeitzer JM, et al. Preliminary evidence that plasma oxytocin levels are elevated in major depression. *Psychiatry Res.* 2010;178(2):359-362.

100. Heim C, Plotsky PM, Nemeroff CB. Importance of studying the contributions of early adverse experience to neurobiological findings in depression. *Psychiatry Res.* 2004;29(4):641-648.

101. Bailey JA, Hill KG, Oesterle S, Hawkins JD. Parenting practices and problem behavior across three generations: monitoring, harsh discipline, and drug use in the intergenerational transmission of externalizing behavior. *Dev Psychol.* 2009;45(5):1214-1226.

102. Belsky J, Jaffee SR, Sligo J, Woodward L, Silva PA. Intergenerational transmission of warm-sensitive-stimulating parenting: a prospective study of mothers and fathers of 3-year-olds. *Child Dev.* 2005;76(2):384-396.

103. Belsky J, Bakermans-Kranenburg MJ, van Ijzendoorn MH. For better and for worse: differential susceptibility to environmental influences. *Curr Direct Psychol Sci.* 2007;16:300-304.

104. Chen ZY, Kaplan HB. Intergenerational transmission of constructive parenting. *J Marriage Fam.* 2001;63:17-31.

105. Conger RD, Neppi T, Kim KJ, Scaramella L. Angry and aggressive behavior across three generations: a prospective, longitudinal study of parents and children. *J Abnorm Child Psychol.* 2003;31(2):143-160.

106. Neppi TK, Conger RD, Scaramella LV, Ontai LL. Intergenerational continuity in parenting behavior: mediating pathways and child effects. *Dev Psychol.* 2009;45(5):1241-1256.

107. Scaramella LV, Neppi TK, Ontai LL, Conger RD. Consequences of socioeconomic disadvantage across three generations: parenting behavior and child externalizing problems. *J Fam Psychol.* 2008;22(5):725-733.

108. Bakermans-Kranenburg MJ, van Ijzendoorn MH. Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting. *Soc Cogn Affect Neurosci.* 2008;3(2):128-134.

109. Feldman R, Zagoory-Sharon O, Weisman O, et al. Sensitive parenting is associated with plasma oxytocin and polymorphisms in the OXTR and CD38 genes. *Biol Psychiatry.* 2012;72(3):175-181.

110. Klahr AM, Klump K, Burt SA. A constructive replication of the association between the oxytocin receptor genotype and parenting. *J Fam Psychol.* 2014;29(1):91-99.

111. Bakermans-Kranenburg MJ, van Ijzendoorn MH. Research review: genetic vulnerability or differential susceptibility in
child development: the case of attachment. J Child Psychol Psychiatry. 2007;48(12):1160-1173.

Afonso VM, Grella SL, Chatterjee D, Fleming AS. Previous maternal experience affects accumbal dopaminergic responses to pup-stimuli. Brain Res. 2008;1198:115-123.

Afonso VM, Shams WM, Jin D, Fleming AS. Distal pup cues evoke dopamine responses in hormonally primed rats in the absence of pup experience or ongoing maternal behavior. J Neurosci. 2013;33(6):2305-2312.

Li M, Fleming AS. The nucleus accumbens shell is critical for normal expression of pup-retrieval in postpartum female rats. Behav Brain Res. 2003;145(1-2):99-111.

Li M, Fleming AS. Differential involvement of nucleus accumbens shell and core subregions in maternal memory in postpartum female rats. Behav Neurosci. 2003;117(3):426-445.

Fleming AS, Li M. Psychobiology of maternal behavior and its early determinants in nonhuman mammals. In: Bornstein MH, ed. Handbook of Parenting. Vol 2. 2nd ed. Mahwah, NJ: Lawrence Erlbaum; 2002:61-97.

Shahrokh DK, Zhang TY, Diorio J, Gratton A, Meaney MJ. Oxytocin–dopamine interactions mediate variations in maternal behavior in the rat. Endocrinology. 2010;151(5):2276-2286.

Afonso VM, King S, Chatterjee D, Fleming AS. Hormones that increase maternal responsiveness affect accumbal dopaminergic responses to pup- and food-stimuli in the female rat. Horm Behav. 2009;56(1):11-23.

Afonso VM, King SJ, Novakov M, Burton CL, Fleming AS. Accumbal dopamine function in postpartum rats that were raised without their mothers. Horm Behav. 2011;60(5):632-643.

Champagne FA, Chretien P, Stevenson CW, Zhang TY, Gratton A, Meaney MJ. Variations in nucleus accumbens dopamine associated with individual differences in maternal behavior in the rat. J Neurosci. 2004;24(17):4113-4123.

Hansen S, Harthon C, Wallin E, Loefberg L, Svensson K. Mesotelencephalic dopamine system and reproductive behavior in the female rat: effects of ventral tegmental 6-hydroxydopamine lesions on maternal and sexual responsiveness. Behav Neurosci. 1991;105(4):588-598.

Hansen S, Harthon C, Wallin E, Loefberg L, Svensson K. The effects of 6-OHDA-induced dopamine depletions in the ventral or dorsal striatum on maternal and sexual behavior in the female rat. Pharmacol Biochem Behav. 1991;39(1):71-77.

Numan M, Numan MJ, Pliakou N, et al. The effects of D1 or D2 dopamine receptor antagonism in the medial preoptic area, ventral pallidum, or nucleus accumbens on the maternal retrieval response and other aspects of maternal behavior in rats. Behav Neurosci. 2005;119(6):1588-1604.

Parada M, King S, Li M, Fleming AS. The roles of accumbal dopamine D1 and D2 receptors in maternal memory in rats. Behav Neurosci. 2008;122(2):368-376.

Akbari EM, Shams S, Belay HT, et al. The effects of parity and maternal behavior on gene expression in the medial preoptic area and the medial amygdala in postpartum and virgin female rats: a microarray study. Behav Neurosci. 2013;127(6):913-922.

Butts KA, Weinberg J, Young AH, Phillips AG. Glucocorticoid receptors in the prefrontal cortex regulate stress-evoked dopamine efflux and aspects of executive function. Proc Natl Acad Sci U S A. 2011;108(45):18459-18464.

Staiti AM, Morgane PJ, Galler JR, Grivetti JY, Bass DC, Mokler DJ. A microdialysis study of the medial prefrontal cortex of adolescent and adult rats. Neuropharmacology. 2011;61(3):544-549.

Afonso VM, Sison M, Lovic V, Fleming AS. Medial prefrontal cortex lesions in the female rat affect sexual and maternal behavior and their sequential organization. Behav Neurosci. 2007;121(3):515-526.

Alvarez JA, Emory E. Executive function and the frontal lobes: a meta-analytic review. Neuropsychol Rev. 2006;16(1):17-42.

Banich MT, Milham MP, Jacobson BL, et al. Attentional selection and the processing of task-irrelevant information: insights from fMRI examinations of the Stroop task. Prog Brain Res. 2001;134:459-470.

Cabeza R, Nyberg L. Neural bases of learning and memory: functional neuroimaging evidence. Curr Opin Neurol. 2000;13(4):415-421.

Compton RJ, Banich MT, Mohanty A, et al. Paying attention to emotion: an fMRI investigation of cognitive and emotional stroop tasks. Cogn Affect Behav Neurosci. 2003;3(2):81-96.

Rogers RD, Andrews TC, Grasby PM, Brooks DJ, Robbins TW. Contrasting cortical and subcortical activations produced by attentional-set shifting and reversal learning in humans. J Cogn Neurosci. 2002;12(1):142-162.

Barrett J, Fleming AS. Annual research review: all mothers are not created equal: neural and psychobiological perspectives on mothering and the importance of individual differences. J Child Psychol Psychiatry. 2011;52(4):368-397.

Leibenluft E, Gobbini MI, Harrison T, Haxby JV. Mothers’ neural activation in response to pictures of their children and other children. Biol Psychiatry. 2004;56(4):225-232.

Nitschke JB, Nelson EE, Rusch BD, Fox AS, Oakes TR, Davidson RJ. Orbitofrontal cortex tracks positive mood in mothers viewing pictures of their newborn infants. Neuroimage. 2004;21(2):583-592.

Pruessner JC, Champagne F, Meaney MJ, Dagher A. Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: a positron emission tomography study using [11C]raclopride. J Neurosci. 2004;24(11):2825-2831.

van Ijzendoorn MH, Bakermans-Kranenburg MJ, Mesman J. Dopamine system genes associated with parenting in the context of daily hassles. Behav Brain Res. 2008;7(4):403-410.

Kaitz M, Shalev I, Sapir N, et al. Mothers’ dopamine receptor polymorphism modulates the relation between infant fussiness and sensitive parenting. Dev Psychobiol. 2010;52(2):149-157.

Lee SS, Chronis-Tuscano A, Keenan K, et al. Association of maternal dopamine transporter genotype with negative parenting: evidence for gene × environment interaction with child disruptive behavior. Mol Psychiatry. 2010;15(5):548-558.

Chen D, Liu F, Shang Q, Song X, Miao X, Wang Z. Association between polymorphisms of DRD2 and DRD4 and opioid dependence: evidence from the current studies. Am J Med Genet B Neuropsychiatr Genet. 2011;156B(6):661-670.
142. Comings DE, Gade R, Wu S, et al. Studies of the potential role of the dopamine D1 receptor gene in addictive behaviors. *Mol Psychiatry*. 1997;2(1):44-56.

143. Smith L, Watson M, Gates S, Ball D, Foxcroft D. Meta-analysis of the association of the Taq1A polymorphism with the risk of alcohol dependency: a HuGE gene–disease association review. *Am J Epidemiol*. 2008;167(2):125-138.

144. Mitchell C, Notterman D, Brooks-Gunn J, et al. Role of mother’s genes and environment in postpartum depression. *Proc Natl Acad Sci U S A*. 2011;108(20):8189-8193.

145. Prins J, Olivier B, Korte SM. Triple reuptake inhibitors for treating subtypes of major depressive disorder: the monoamine hypothesis revisited. *Expert Opin Investig Drugs*. 2011;20(8):1107-1130.

146. Ruhe HG, Mason NS, Schene AH. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. *Mol Psychiatry*. 2007;12(4):331-359.

147. Sacher J, Wilson AA, Houle S, et al. Elevated brain monoamine oxidase A binding in the early postpartum period. *Arch Gen Psychiatry*. 2010;67(5):468-474.

148. Lucki I. The spectrum of behaviors influenced by serotonin. *Biol Psychiatry*. 1998;44(3):151-162.

149. Wu R, Davis C, Li M. Behavioral mechanisms underlying the maternal disruptive effect of serotonin 5-HT2A receptor activation in Sprague-Dawley rats. *J Neural Transm (Vienna)*. 2018;125(7):1065-1075.

150. Johns JM, Joyner PW, McMurray MS, et al. The effects of dopaminergic/serotonergic reuptake inhibition on maternal behavior, maternal aggression, and oxytocin in the rat. *Pharmacol Biochem Behav*. 2005;81(4):769-785.

151. Li X, Ding X, Wu R, et al. A behavioral mechanistic investigation of the role of 5-HT1A receptors in the mediation of rat maternal behavior. *Pharmacol Biochem Behav*. 2018;169:16-26.

152. Zhao C, Li M. C-Fos identification of neuroanatomical sites associated with haloperidol and clozapine disruption of maternal behavior in the rat. *Neuroscience*. 2010;166(4):1043-1055.

153. Maaestrieperi D. Emotions, stress, and maternal motivation in primates. *Am J Primatol*. 2011;73(6):516-529.

154. Maaestrieperi D, Lindell SG, Higley JD. Intergenerational transmission of maternal behavior in rhesus macaques and its underlying mechanisms. *Dev Psychobiol*. 2007;49(2):165-171.

155. Prange AJ Jr. The pharmacology and biochemistry of depression. *Dis Nerv Syst*. 1964;25:217-221.

156. Brown GW, Harris TO. Depression and the serotonin transporter 5-HTTLPR polymorphism: a review and a hypothesis concerning gene–environment interaction. *J Affect Disord*. 2008;111(1):1-12.

157. Risch N, Herrell R, Lehner T, et al. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. *JAMA*. 2009;301(23):2462-2471.

158. Rocha FL, Fuzikawa C, Riera R, Hara C. Combination of antidepressants in the treatment of major depressive disorder: a systematic review and meta-analysis. *J Clin Psychopharmacol*. 2012;32(2):278-281.

159. Ishak WW, Davis M, Jeffrey J, et al. The role of dopaminergic agents in improving quality of life in major depressive disorder. *Curr Psychiatry Rep*. 2009;11(6):503-508.

160. Messa C, Colombo C, Moresco RM, et al. 5-HT(2A) receptor binding is reduced in drug-naive and unchanged in SSRI-responder depressed patients compared to healthy controls: a PET study. *Psychopharmacology (Berl)*. 2003;167(1):72-78.

161. Bhagwagar Z, Hinz R, Taylor M, Fancy S, Cowen P, Grasby P. Increased 5-HT(2A) receptor binding in euthymic, medication-free patients recovered from depression: a positron emission study with [(11)C]MDL 100,907. *Am J Psychiatry*. 2006;163(9):1580-1587.

162. Massou JM, Trichard C, Attar-Levy D, et al. Frontal 5-HT2A receptors studied in depressed patients during chronic treatment by selective serotonin reuptake inhibitors. *Psychopharmacology (Berl)*. 1997;133(1):99-101.

163. Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE. Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. *Am J Psychiatry*. 2010;167(5):509-527.

164. Uher R, Caspi A, Houts R, et al. Serotonin transporter gene moderates childhood maltreatment’s effects on persistent but not single-episode depression: replications and implications for resolving inconsistent results. *J Affect Disord*. 2011;135(1-3):56-65.

165. Hu XZ, Lipsky RH, Zhu G, et al. Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *Am J Hum Genet*. 2006;78(5):815-826.

166. Taylor SE. Genetic contributions to sensitive parenting. *Soc Cogn Affect Neurosci*. 2008;3(2):89-90.

167. Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes? *Mol Psychiatry*. 2009;14(8):746-754.

168. Uher R, McGuffin P. The moderation by the serotonin transporter gene of environmental adversity in the aetiology of mental illness: review and methodological analysis. *Mol Psychiatry*. 2008;13(2):131-146.

169. Roiser JP, Muller U, Clark L, Sahakian BJ. The effects of acute tryptophan depletion and serotonin transporter polymorphism on emotional processing in memory and attention. *Int J Neuropsych*. 2010;17(4):449-461.

170. Canli T, Lesch KP. Long story short: the serotonin transporter in emotion regulation and social cognition. *Nat Neurosci*. 2007;10(9):1103-1109.

171. Donovan WL, Leavitt LA, Walsh RO. Cognitive set and coping strategy affect mothers’ sensitivity to infant cries: a signal detection approach. *Child Dev*. 1997;68(5):760-772.

172. Dremencov E, El Mansari M, Blier P. Effects of sustained serotonin reuptake inhibition on the firing of dopamine neurons in the rat ventral tegmental area. *J Psychiatry Neurosci*. 2009;34(3):223-229.

173. Herve D, Pickel VM, Joh TH, Beaudet A. Serotonin axon terminals in the ventral tegmental area of the rat: fine structure and synaptic input to dopaminergic neurons. *Brain Res*. 1987;435(1-2):71-83.
174. Praschak-Rieder N, Wilson AA, Hussey D, et al. Effects of tryptophan depletion on the serotonin transporter in healthy humans. *Biol Psychiatry*. 2005;58(10):825-830.

175. Reimold M, Smolka MN, Schumann G, et al. Midbrain serotonin transporter binding potential measured with [11C]DASB is affected by serotonin transporter genotype. *J Neural Transm (Vienna)*. 2007;114(5):635-639.

176. Guiard BP, El Mansari M, Merali Z, Blier P. Functional interactions between dopamine, serotonin and norepinephrine neurons: an in-vivo electrophysiological study in rats with monoaminergic lesions. *Int J Neuropsychopharmacol*. 2008;11(5):625-639.

177. Pan P, Lawson DO, Dudin A, et al. Both maternal care received and genotype influence stress-related phenotype in female rats. *Dev Psychobiol*. 2018;60(8):889-902.

178. Pan P, Fleming AS, Lawson D, Jenkins JM, McGowan PO. Within- and between-litter maternal care alter behavior and gene regulation in female offspring. *Behav Neurosci*. 2014;128(6):736-748.

179. Szyf M, Weaver IC, Champagne FA, Diorio J, Meaney MJ. Maternal programming of steroid receptor expression and phenotype through DNA methylation in the rat. *Front Neuroendocrinol*. 2005;26(3-4):139-162.

180. Francis DD, Champagne FA, Liu D, Meaney MJ. Maternal care, gene expression, and the development of individual differences in stress reactivity. *Ann N Y Acad Sci*. 1999;896:66-84.

181. Lovic V, Gonzalez A, Fleming AS. Maternally separated rats show deficits in maternal care in adulthood. *Dev Psychobiol*. 2001;39(1):19-33.

182. Champagne FA, Weaver IC, Diorio J, Dymov S, Szyf M, Meaney MJ. Maternal care associated with methylation of the estrogen receptor-alpha1b promoter and estrogen receptor-alpha expression in the medial preoptic area of female offspring. *Endocrinology*. 2006;147(6):2909-2915.

183. Roth TL, Sweatt JD. Epigenetic marking of the BDNF gene by early-life adverse experiences. *Horm Behav*. 2011;59(3):315-320.

184. McGowan PO, Sasaki A, D’Alessio AC, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci*. 2009;12(3):342-348.