

# Parental attachment systems: neural circuits, genes, and experiential contributions to parental engagement

Linda C. Mayes\*, James E. Swain, James F. Leckman

*Yale Child Study Center, 230 S. Frontage Road, New Haven, CT 06520, USA*

## Abstract

Parental caregiving includes a set of highly conserved set of behaviors and mental states that may reflect both an individual's genetic endowment and the early experience of being cared for as a child. We consider the mental and behavioral elements of early parental caregiving in humans and what is known of the neurobiological substrates of maternal behaviors in mammalian species including some limited human data. Also reviewed briefly is the evidence that specific genes encode proteins that are crucial for the development of the neural substrates that underlie specific features of maternal behavior. Finally, we review the literature on the "programming" role of epigenetic factors in shaping subsequent maternal behavior. Drawing also from recent neuroimaging data, we conclude that there are critical developmental windows during which the genetically determined microcircuitry of key limbic-hypothalamic-midbrain structures are susceptible to early environmental influences and that these influences powerfully shape an individuals responsivity to psychosocial stressors and their resiliency or vulnerability to various forms of human psychopathology later in life.

© 2005 Published by Elsevier B.V. on behalf of Association for Research in Nervous and Mental Disease.

*Keywords:* Maternal behavior; Gene-environment interactions; Stress response; Psychopathology; Resiliency; Early intervention programs

## 1. Introduction

Parenting is a stage in life, a personal choice, a psychological transition, a psychobiological condition, a cultural creation, a necessity for the species, a political icon, a state of mind. For some, the word conjures up memories of the past, for others the anticipated and desired, and for many an idealization. While each of these characterizations draw on a different discipline and different perspective on how adults care for children, their multiplicity underscores how the real and imagined roles of parents are woven through our developmental and psychological landscape. Much of the study of parenting has focused on how parents care for their infants and young children; less often is the focus on how adults become parents, how they make the normative psychological (and necessarily biological) adjustment and reorganization that takes place when an adult is either pregnant or anticipating the birth of their child.

In 1956 Donald Winnicott, a pediatrician and psychoanalyst, drew attention to 'primary maternal preoccupations'. He described this state as 'almost an illness' that a mother must experience and recover from in order to create and sustain an environment that can meet the physical and psychological needs of her infant ([29] [1956]). Winnicott speculated that this special state began towards the end of the pregnancy and continued through the first months of the infant's life. Although this concept has been incorporated into subsequent clinical formulations of disordered mother–infant interactions, it has received relatively little scientific attention especially in considerations of the normative developmental trajectory of parenting [31–39].

This chapter focuses initially on efforts to characterize further in normative groups of adults—early parental preoccupations—and the care taking behaviors they engender. In particular, we present an empirical line of work on parental preoccupation that addresses a classical and clinically relevant psychoanalytic construct. Next, we consider recent advances in our understanding of the genetic, epigenetic, and neurobiological substrates of maternal

\* Corresponding author. Tel.: +1 203 785 7211; fax: +1 203 785 7926.  
E-mail address: linda.mayes@yale.edu (L.C. Mayes).

behavioral in model mammalian species and their potential relevance for understanding risk and resiliency. For example, some of the studies reviewed suggest that aspects of maternal behavior are non-genomically transmitted from one generation to the next and that the nature of the maternal care received in infancy may ‘program’ aspects of infant’s response to stress later in life and have enduring consequences in their approach to the world [40,41]. If similar mechanisms are at work in human populations, they may provide a basis for successful early intervention programs [42,43] and may deepen our understanding why some individuals are more vulnerable, or conversely more resilient, to certain forms of psychopathology [44,45]. Further, these studies of the intergenerational transmission of parenting behaviors are very relevant to psychoanalytic developmental theories regarding the internalization of parenting experiences and the clinical appreciation of how enduring and powerful are internalized representations of parental care.

### *1.1. Point-of-view and initial caveats*

Before reviewing any specific findings, it may be useful to articulate an evolutionary point-of-view concerning developmental psychopathology. The human brain is a remarkable product of evolution. While the basic machinery of the vertebrate brain has been in place for more than 450 million years, the exploration of variations leads to the appearance of our species less than 100,000 years ago. In the struggle for life, certain traits have come to predominate. Elements in our mental and behavioral repertoire related to successful reproduction were certainly the focus of the greatest selective pressures. The selection of a mate, bearing of viable offspring, and the formation of parental commitments that will sustain an infant through a lengthy period of dependency are just a few of the crucial complex, interdependent processes needed for individual survival and hence, species viability. Although most of our biological and behavioral potentialities are likely called upon at one point or another in the service of these goals, there must be highly conserved brain-based systems that are specifically activated at developmentally appropriate moments to achieve and sustain these processes. We hypothesize that a thorough understanding of these ‘normal’ processes will also lead to deeper insights into our vulnerability to develop a range of psychopathological outcomes [46].

Despite the intuitive appeal of evolutionary explanations, it is also worth noting a few caveats. First, these explanations typically are population-based and fail to account for why a particular individual is affected. Any adequate account of disease pathogenesis requires that environmental events that impinge on CNS development be considered. Second, species and strain differences can be pronounced so that generalizations across species can be misleading. Finally, the empirical testing of specific evolutionary theories may prove to be difficult, if not

impossible. Nonetheless, even if only from a sentimentally historical point of view, there is a parallel between the early roots of psychoanalysis and Freud’s interests in Darwin and evolutionary perspectives and this more contemporary view regarding the conservation of highly salient behavioral and mental repertoires that subservise social adaptation and both the propagation and nurturing of infants.

## **2. Early parental love**

For the most part, empirical studies of the early parent–child relationship have been child centered. Most reports have focused on the development of attachment behaviors in the child and on the moment-to-moment observable, behavioral functioning of the parent–infant dyad. These points of focus have revealed the highly specialized nature of parental verbal and non-verbal behaviors with very young infants, and the importance of early synchrony and reciprocity in parent–child interactions, and the critical impact of early experiences on the child’s subsequent attachment behaviors toward the parent—and later in other intimate relationships [47–51]. They have underscored the potential negative impact of early parental deprivation and neglect on the development of socialization capacities and the importance of parental marital adjustment, self-esteem, and social supports for successful adaptation to parenting a newborn and infant [51–55]. However, relatively neglected in these lines of research have been the thoughts of the parents regarding their roles as parents and the place of the infant in their inner lives, and the relationship of these thoughts to their behaviors with the infant.

As noted above, Winnicott described an altered mental state that he termed ‘primary maternal preoccupation’ that characterizes the first weeks of a mother’s relationship with the infant. Suggesting that such a state of preoccupation or a state of ‘heightened sensitivity’ develops toward the end of pregnancy and lasts for the first few postnatal weeks, he likened it to a withdrawn or dissociated state that in the absence of pregnancy and a newborn would resemble a mental illness of acute onset. In this period, mothers are deeply focused on the infant to the apparent conscious exclusion of all else, and this preoccupation heightens their ability to anticipate the infant’s needs, learn his/her unique signals, and over time to develop a sense of the infant as an individual. Winnicott emphasizes the crucial importance of such a stage for the infant’s self-development and the developmental consequences for infants when mothers are unable to tolerate such a level of intense preoccupation.

Similar to the notion of primary maternal preoccupation, others have suggested that for both mothers and fathers, there is an initial critical period of ‘engrossment’ with the infant in which all other concerns and realities assume a lesser role in day to day life [56]. In a prospective longitudinal study of 82 parents, we have documented the course of early preoccupations and found that they peak around the time of delivery

[38]. Although fathers and mothers displayed a similar time course, the degree of preoccupation was significantly less for the fathers in our study. For example, at 2 weeks after delivery mothers of normal infants, on average, reported spending nearly 14 h per day focused exclusively on the infant, while fathers reported spending approximately half that amount of time [38].

The mental content of these preoccupations includes thoughts of reciprocity and unity with the infant, as well as thoughts about the perfection of the infant. For example, we found that 73% of the mothers and 66% of the fathers reported having the thought that their baby was 'perfect' at 3-months of age [38]. These idealizing thoughts may be especially important in the establishment of resiliency and the perception of self-efficacy.

These parental preoccupations also include anxious intrusive thoughts about the infant. In a longitudinal study of 120 couples during their first pregnancy and in the 6 months after birth, women reported increasing levels of worry toward the end of their pregnancy and 25–30% described being preoccupied with worries about caring for the infant postpartum [57]. Immediately before and after birth this figure may be substantially higher. In our study, we found that 95% of the mothers and 80% of the fathers had such recurrent thoughts about the possibility of something bad happening to their baby at 8 months of gestation. In the weeks following delivery this percentage declined only slightly to 80 and 73% for mothers and fathers, respectively, and at 3 months these figures were unchanged [38]. After delivery and on returning home, most frequently cited were concerns about feeding the baby, about the baby's crying, one's adequacy as a new parent, and thoughts about the infant's well-being [38]. Conditions such as these are more commonly reported among parents of very sick preterm infants, infants with serious congenital disorders or malformations or infants with serious birth complications [39].

Less commonly, intrusive thoughts of injuring the child beset the new mother (or father) that can in turn lead to postpartum obsessive-compulsive disorder or depression or both [58]. Parents also endorse fantasies or worries that they may in some way inadvertently harm their infant, for example, by dropping the baby or in a time of exhaustion or frustration, more actively ignoring or injuring the baby. Surely, such persistent worries, even those of harming the infant, are commonly observed among parents of, for example, preterm infants or infants with serious birth complications or congenital disorders or malformations [3,18]. And among many mental health clinicians, such worries are often taken as concerning clues of potential disturbances in early parent–infant attachment. But normative studies suggest that in late pregnancy and in the first months after delivery, these preoccupations with more negative, anxiety provoking content are common and normative. It is their persistence beyond the first 3–6 months that may signal difficulties in the parent–infant relationship.

Nursing and feeding are the parental behaviors that are

perhaps most associated with a new infant. Women describe breast feeding as a uniquely close, very physical, at times sensual experience and one that brings a particular unity between the mother and her infant [59]. In some instances, mothers appear not to experience breast feeding as an interpersonal event, but rather as a moment when they and the infant are joined as one. Grooming and dressing behaviors carry a special valence inasmuch as they permit the closeness between parent and infant and are times for close inspection of the details of the infant's body and appearance.

Even before the child is born parents preoccupy themselves with creating a safe, clean, and secure environment for the infant. Major cleaning and renovation projects are commonplace as the human form of nest building unfolds. After birth, unimpeded access and safety are among the parents' uppermost concerns. Safety issues include the cleanliness of the infant and the infant's immediate environment, taking extra care not to drop the infant, as well as protection from potential external threats. Parents also report feeling compelled to these actions and anxious if prevented from accomplishing them even though they recognize that their behaviors may be extreme, exaggerated or even unwarranted (e.g. that the baby is safe, the room and clothes thoroughly clean and warm). Community and cultural rituals (baby showers, baptism) not only mark the infant's arrival into a larger community, but also have an element of safe-guarding and protective actions. After birth this same sense of heightened responsibility lead parents to check on the baby frequently, even at times when they know the baby is fine [38].

Similarly, preoccupation with the baby's physical perfection is given behavioral voice not only in the already mentioned detailed reveries about the details of his body and appearance, but also in the choice of clothes that may have special meanings. Parents often choose clothing that indicates their wishes and fantasies for their child or bears a special relationship to their family, such as the clothes they wore as an infant, or clothing made by one or more grandparents. Special oils, shampoos, and perfumes only further adorn the infant's perfection and add to his physical comfort. Again, in and of themselves, these behaviors are not unusual in the commonality, but they are part and parcel of the intense state of preoccupation characterizing the first months after a baby is born. These behavioral sets lessen in intensity after the first 6 months when, we might say, the baby is safe and, if all has gone well, has a firm place in the parents' psychological structure.

Viewed from an evolutionary perspective, it seems nearly self-evident that the behavioral repertoires associated with early parenting skills would be subject to intense selective pressure [60–64]. For one's genes to self-replicate, sexual intimacy must occur and the progeny of such unions must survive. Pregnancy and the early years of an infant's life are fraught with mortal dangers. Indeed, it has only been during the past century that infant mortality rates have fallen from over 100/1000 live births in 1900 to about 10/1000 in

1984 [65]. Little wonder then that a specific state of heightened sensitivity on the part of new parents would be evolutionarily conserved.

It is also worth noting that becoming a new parent often comes at high physiological and mental cost. For nursing mothers there is the need to increase their caloric intake as well as to remain well hydrated. There is also a revaluing of what is important in life. Care giving is just one of several competing motivational systems for parents. Parents must also consider the needs of the other children in the family, their occupational duties, the needs of the marital relationship and the demands of the larger social group so that the advent of a new infant involves an adjustment in the parent's hedonic homeostasis as they establish lasting reciprocal social bonds and make room in their inner lives for a new family member [66].

Finally, too much or too little primary parental preoccupation may be problematic. Too much can lead to obsessive-compulsive-like states [43] and too little may set the stage for abuse or neglect in vulnerable, high-risk families [9]. One condition that has been repeatedly associated with disrupted mother–infant attachment and poses a risk factor for children's development across life is maternal postpartum depression [11,12]. In terms of the primary parental preoccupations, depressed mothers reported lower levels of preoccupations, particularly the aspect relating to the building of a meaningful relationship with the infant, such as interacting with the infant in a special way, calling him/her by a nickname, imagining the infant's future, or idealizing the child [10]. These data suggest that the function impaired by depression is the behavioral and mental investment in forming a relationship with the new infant.

### 3. Neural circuitry of maternal behavior

Although the central nervous system events that accompany parental care in humans are largely unknown, it is likely that there is a substantial degree of conservation across mammalian species [67]. Classical lesion studies done in rodent model systems (rats, mice, and voles) have implicated the medial preoptic area (MPOA) of the hypothalamus, the ventral part of the bed nucleus of the stria terminalis (BNST), and the lateral septum (LS) as regions pivotal for regulation of pup-directed maternal behavior [68–70]. Estrogen, prolactin, and oxytocin can act on the MPOA to promote maternal behavior [71–73]. Oxytocin is primarily synthesized in the magnocellular secretory neurons of two hypothalamic nuclei, the paraventricular (PVN) and the supraoptic (SON) nuclei. The PVN and SON project to the posterior pituitary gland. Pituitary release of oxytocin into the bloodstream results in milk ejection during nursing and uterine contraction during labor. It has also been shown that oxytocin fibers, which arise from

parvocellular neurons in the PVN, project to areas of the limbic system including the amygdala, BNST, and LS [74].

There are several reports that oxytocin facilitates maternal behavior (sensitization) in estrogen-primed nulliparous female rats. Intracerebroventricular (ICV) administration of oxytocin in virgin female rats induces full maternal behavior within minutes [75]. Conversely, central injection of an oxytocin antagonist, or a lesion of oxytocin-producing cells in the PVN, suppresses the onset of maternal behavior in postpartum female rats [76,77]. However, these manipulations have no effect on maternal behavior in animals permitted several days of postpartum mothering. This result suggests that oxytocin plays an important role in facilitating the onset, rather than the maintenance, of maternal attachment to pups [78].

Brain areas that may inhibit maternal behavior in rats have been identified [79]. For example, the vomeronasal and primary olfactory systems have been identified as brain regions that mediate avoidance behavior in virgin female rats exposed to the odor cues of pups [80].

Ascending dopaminergic and noradrenergic systems associated with reward pathways also appear to play a crucial role in facilitating maternal behavior [81]. For example, rat dams given microinfusions of the neurotoxin 6-hydroxydopamine (6-OHDA) in the ventral tegmental area (VTA) to destroy catecholaminergic neurons during lactation showed a persistent deficit in pup retrieval, but were not impaired with respect to nursing, nest building, or maternal aggression [82]. There also appears to be an important interaction between dopaminergic neurons and oxytocin pathways. Specifically, pup retrieval and assuming a nursing posture over pups were blocked in parturient dams by infusions of an oxytocin antagonist into either the VTA or MPOA [72].

In summary, the initiation and maintenance of maternal behavior involves a specific neural circuit. With pregnancy or with repeated exposure to pups, structural and molecular changes occur, most of which are not yet completely understood, in specific limbic, hypothalamic, and midbrain regions that reflect, in part, an adaptation to the various homeostatic demands associated with maternal care.

Remarkably, many of the same cell groups implicated in the control of maternal behavior have been implicated in the control of ingestive (eating and drinking) behavior, thermoregulatory (energy homeostasis), social (defensive and sexual) behaviors, as well as general exploratory or foraging behaviors (with locomotor and orienting components) that are required for obtaining any particular goal object. Many of these same structures are also intimately involved in stress response [83]. Swanson has conceptualized this set of limbic, hypothalamic, and midbrain nuclei as being the 'behavioral control column' that is voluntarily regulated by cerebral projections [84]. Consistent with this formulation, it is readily apparent that motherhood presents a major homeostatic challenge within each of these behavioral domains.

While information about these circuits in humans and other primate species is sparse, the available data are consistent with the same circuitry being involved [85]. For example, Fleming and co-workers have found that first-time mothers with high levels of circulating cortisol were better able to identify their own infant's odors. In these same primiparous mothers, the level of affectionate contact with the infant (affectionate burping, stroking, poking and hugging) by the mother was associated with higher levels of salivary cortisol [67]. Both of these findings support the hypothesis that our stress response systems are adaptively activated during the period of heightened maternal sensitivity surrounding the birth of a new infant.

#### 4. Parent–infant neuroimaging studies

Functional brain imaging studies examining brain responses to emotionally charged infant stimuli are beginning to uncover the neural substrates of normal parenting [23]. Investigators have begun to use non-invasive neuroimaging techniques such as functional magnetic resonance imaging to measure brain activity parameters while healthy parents are exposed to baby stimuli. This approach to parental neurophysiology was begun by Lorberbaum et al. [16,17] using baby cries as stimuli. Building on the thalamocingulate theory of maternal behavior in animals developed by MacLean (1990), Lorberbaum predicted that baby cries would selectively activate cingulate, thalamus, medial and orbitofrontal prefrontal cortex. They first exposed mothers who were less than 3.5 years postpartum to blocks of 30 s of a standard baby cry versus white noise stimuli [16]. In this small sample of four, they found increased activity in anterior cingulate and right medial prefrontal cortex. In the follow-up study [17], brain activity in breastfeeding first-time mothers ( $n=10$ ) 4–8 weeks postpartum was measured while listening to standard baby cry compared with intensity and pattern matched white noise. In this more methodologically stringent study, with respect to subject selection and stimulus, all of the hypothesized regions as well as midbrain, hypothalamus, striatum and septal regions—known to be important for rodent maternal behavior [69,70].

Other important considerations include whether parental neural responses to baby sounds would be different for mother and fathers, whether parents are first-time or veteran, whether the noises (discussed in [24]) or at different times in the postpartum as the parent–infant relationship develops. Hypothesizing that gender and experience would affect the neural responses to baby cry and laughter, Seifritz et al. [22], studied four groups: mothers and fathers of children under age 3, and non-parent males and females with 10 subjects in each group. Using an event-related design, which measures the response to brief 6-s events, it was found that over the entire sample, crying and laughing baby stimuli produced more activity in Heschl's gyrus. Further, it was

reported that women were found to have a decrease in activity to both baby cry and laughter in the anterior cingulate to these brief signals, which was not present in males. This is contrary to other studies [16,17,24], which may mean that 6-s stimuli have a different meaning to new parents compared to 30-s blocks. Finally, looking at parental status, Seifritz et al. [22] reported that non-parents activated right amygdala with baby laugh stimuli, but parents did not; while with baby cry stimuli, non-parents activated right amygdala, but parents did not. These data represent the first steps into the study of gender and experience-dependant aspects of parental brain circuitry.

With the transforming experience of having a baby and the tendency for parents to be highly preoccupied in the immediate postpartum [38], we [24] have hypothesized that parental responses to baby cries might produce selective activations in thalamus–cortical–basal ganglia circuits akin to those seen in humans relating to ritualistic behaviors such as with obsessive-compulsive disorder [2,14], in addition to emotional alarm centers including amygdala and insula. Using own baby cry stimuli compared with other baby cry, Swain et al. [24] reported regions of relative activation in a group of first-time mothers ( $n=9$ ) at 2–4 weeks postpartum which included midbrain, basal ganglia, cingulate, amygdala and insula. Preliminary analysis of the parenting interview data showed that mothers were significantly more preoccupied than fathers, which may be reflected in the relative lack of activation for fathers in amygdala and basal ganglia [25]. In the group of primiparous mothers, given the same stimuli at 3–4 months postpartum, amygdala and insular activations were not observed and instead, medial prefrontal cortical and hypothalamic activations [26] were seen, perhaps reflecting a change in regional brain responses as the parent–infant relationship develops.

In addition to baby cry stimuli, several groups are using baby visual stimuli [1,15,19,24]. Hypothesizing that reward and emotion circuits, which are important for aspects of romantic love, might also be involved in maternal love (Bartels and Zeki [1] are using photographs of own, familiar and unfamiliar infants (9 months to 6 years of age) as stimuli for parental brain circuits. They reported relative activations in anterior cingulate, insula, basal ganglia (striatum) and midbrain (periaqueductal gray). These regions may mediate the emotionally rewarding aspects of maternal behavior. Bartels and Zeki [1] also reported decreases in activity in areas important for negative emotions, avoidance behavior and social assessment. They suggest a push-pull mechanism for maternal behavior in which child stimuli activate reward and shut down avoidance circuits.

In another study of mothers brains using pictures, Nitschke et al. [19] looked at six primiparous mothers responding to pictures of their own infants compared to age-matched controls 2–4 months postpartum. They reported bilateral orbitofrontal cortex activations, which were correlated with ratings of pleasant mood. These data point

to the orbitofrontal cortex as a center important for positive attachment of mother and child. Using photographs of older children (5–12 years old), Leibenluft et al. [15] found that own versus other comparison in a sample of seven mothers activated amygdala, insula and anterior paracingulate regions, which they interpret as emotion and theory-of-mind regions relating to the ability to predict and explain other peoples behaviors. Using 40-s blocks of silent video of own versus other infants (4–8 months old) as stimuli for nine mothers, Ranote et al. [21], reported activations in amygdala, temporal pole and occipital regions. To own versus infant photographs, both mothers and fathers 2–4 weeks postpartum activated a familiar set of regions including brainstem, amygdala, basal ganglia, cingulate and occipital cortices [24]. It appears that there may be significant differences between parental responses to baby signals across sensory modalities. This rapidly growing field does seem to indicate at least that emotion-control centers are activated by baby signals. Combinations of well-controlled stimuli and sensitive psychometric data may clarify the specific importance of these brain circuits to mediate normal parental behavior, and allow us to study abnormalities of parental circuitry that may be manifest in postpartum depression and anxiety. Such understanding will suggest optimal detection and treatment strategies for these conditions that may have profound deleterious effects on the quality of parent–infant interactions, and the subsequent long-term health risks and resiliencies of infants.

## 5. Genetic determinants of maternal behavior

Gene knockout technology has provided new insights into the molecular basis of maternal behavior that are congruent with the existing neurobiological literature. At least nine genes have been identified that are necessary for the expression of one or more aspects of maternal behavior. These genes encode for three transcription factors: three enzymes, including dopamine beta hydroxylase and neuronal nitric oxide synthase; two receptors, including the prolactin and the estrogen  $\alpha$  receptor; and one neuropeptide, oxytocin [70]. By way of illustration, we briefly review two of these genes, Paternally expressed gene-3 (*Peg3*) and dopamine beta hydroxylase (*Dbh*).

### 5.1. Paternally expressed gene-3

*Peg3* is an imprinted gene. Imprinted genes display differential expression according to their parental origin. Normally, only the paternally derived *Peg3* allele is expressed. *Peg3* contains two zinc finger motifs and likely acts as a transcription factor. Li and co-workers disrupted *Peg3* by inserting a  $\beta$ geo selection cassette into its 5' coding exon [86]. Pups born to *Peg3*  $-/-$  mutant mothers failed to survive. While only 8% of litters born to mutant mothers grew to weaning age, 83% of litters born to wild-type

females survived. The offspring of mutant females and wild-type males ( $+/- \times +/+$ ) also failed to thrive, suggesting that the genotype of the mother, not the father, was relevant for their survival. Since these pups inherited the active paternal *Peg3* allele and the silent maternal allele, they should develop as normal adults. The fact that so few pups survived suggested that there was a defect in maternal behavior. Mutant primiparous mothers were subjected to a behavioral assay of nurturing behaviors. These animals were deficient in nest building, pup retrieval, and nursing.

Normally in rodent brain, high levels of *Peg3* expression are present in a number of hypothalamic nuclei (MPOA and PVN) as well as the MA, BNST, hippocampus, and olfactory bulb. Further, histological examination revealed that the *Peg3*  $-/-$  mothers had fewer oxytocin-positive neurons in the PVN.

### 5.2. Dopamine beta hydroxylase

Noradrenergic neurons in the brain project from brainstem nuclei and innervate virtually all areas of the brain and spinal cord. The enzyme *Dbh* synthesizes the adrenergic receptor ligands norepinephrine (NE) and epinephrine. Thomas et al. [87] disrupted the *Dbh* gene in mice. Mice homozygous for the *Dbh* mutation (*Dbh*  $-/-$ ) died *in utero*, of apparent cardiovascular failure. *Dbh*  $-/-$  mice could be rescued at birth by provision of adrenergic agonists or a synthetic precursor of NE, L-threo-3, 4-dihydroxyphenylserine (DOPS), in the maternal drinking water from embryonic day 9.5 until birth [87]. The majority of these rescued animals became viable adults. When subjected to behavioral tests, the *Dbh*  $-/-$  mice displayed some difficulty learning an active avoidance paradigm and a simple motor task.

In a subsequent study, Thomas and Palmiter [88] demonstrated impaired maternal behavior across virtually all domains evaluated. Pups were observed scattered within the bedding around the nest. Often pups were not cleaned, and their placentas remained attached. Milk was not detected in the stomachs of most pups born to *Dbh*  $-/-$  females, which suggests that the pups were not nursing despite the presence of normal mammary gland tissue. Cross-fostering experiments revealed that almost all litters in which *Dbh*  $-/-$  dams were paired with experienced wild-type pups were raised to weaning. This observation demonstrates that the *Dbh*  $-/-$  dams can nurse and that lactation is not impaired.

The impairment in maternal behavior in the *Dbh*  $-/-$  animals could reflect a developmental deficit caused by NE deficiency or it could represent a physiological deficit. To distinguish between these possibilities DOPS was used to restore transiently NE to the mutant females. When mutant females were injected with DOPS on the morning after birth, maternal behavior was not restored, and all pups subsequently died. However, when mutant females were injected with DOPS on the evening prior to birth, over half of the litters survived. Even more pups survived when

DOPS was injected both in the evening before and on the morning after birth.

These findings suggest that NE may play a key role in initiating a realignment of the dam's sense of what is salient and important in the environment. Interestingly, in 85% of the mutant females, the rescue of maternal behavior by DOPS extended to the mother's subsequent pregnancies even in the absence of DOPS injections. However, DOPS injections did not significantly enhance pup retrieval by mutant virgin females.

In sum, gene-targeting studies have demonstrated that at least nine certain genes including *Peg3* and *Dbh* are necessary for the development of maternal behavior. We conclude that the basic microcircuitry responsible for mediating maternal behavior is at least, in part, genetically determined. Indeed, the limbic–hypothalamic–midbrain circuit implicated by the gene knockout studies is the same circuit identified by the classical lesion studies. Strikingly, some of the genetically mediated deficits in maternal behavior can be restored through early environmental manipulations.

## 6. Non-genomic influences on maternal behavior

Thus far, several experimental interventions have been shown to have effects on aspects of maternal behavior including licking and grooming, high arched-backed nursing, and aggression towards an intruder. More recently, other rodent maternal behaviors have also been systematically evaluated [89]. In general, these findings suggest that maternal behavior in the days following birth serves to program the subsequent maternal behavior of the adult offspring as well as establishing the pups' level of hypothalamic–pituitary–adrenal responsiveness to stress [40,90,91]. This complex programming also appears to influence aspects of learning and memory. Further, many of the brain regions are implicated in these experimental interventions are the same as those identified in the knockout gene and earlier lesioning studies. Although we review in detail a series of recent rodent studies, investigations in social primates also highlight the importance of early mothering in determining how the daughters will mother [92,93]. It is also clear that the effects of early maternal deprivation in primates may be difficult to reverse, such that many maternally deprived monkeys as adults are able to function normally under normal conditions, but are unable to cope with psychosocial stressors [94].

### 6.1. Handling and brief separations (15 min per day) from pups

Repeated handling of pups in conjunction with brief maternal separations induces more licking and grooming by the rat dams [95]. The handling procedure used in the Liu study involved removing the mother and then rat pups from

their cage, placing the pups together in a small container, and returning the animals 15 min later to their cage and their mothers. The manipulation was performed daily for the first 21 days of life. This manipulation resulted in more than a doubling of the time the dam spent licking and grooming her pups. The licking and grooming behavior is also highly correlated with high arched-back nursing postures.

As adults, the offspring of mothers that exhibited more licking and grooming of pups during the first 10 days of life showed reduced plasma adrenocorticotrophic hormone (ACTH) and corticosterone responses to acute restraint stress, as well as increased hippocampal glucocorticoid receptor mRNA expression, and decreased levels of hypothalamic corticotropin-releasing factor (CRF) mRNA [95,96]. Subsequent studies by the same group of investigators, have shown that the offspring of these high licking and grooming mothers also show reduced acoustic startle responses, and enhanced spatial learning and memory [41,97].

### 6.2. Handling and prolonged separations (3 h per day) from pups

In contrast, repeated handling of pups in conjunction with prolonged maternal separations induces deranged maternal behavior including a reduction in licking and grooming by the rat dams and reduced maternal aggression [41,98]. Similarly, the adult offspring show increased neuroendocrine responses to acute restraint stress and airpuff startle including elevated levels of PVN CRF mRNA and elevated plasma levels of ACTH and corticosterone [41,97]. These animals also show as an increased acoustic startle response, and enhanced anxiety or fearfulness to novel environments [41].

### 6.3. Handling and early adoption within first 3–6 h

Early adoption has been found to be associated with increased maternal licking behavior [99]. In the same study, early adoption within the first 3–6 h after birth was found to prevent the prolonged stress-induced secretion of corticosterone evident in early separated offspring that were returned to the nest with their biological mother. Similarly, as adults the early adopted pups demonstrated lower novelty-induced locomotion and improved recognition performance in a Y-maze compared to the early separated offspring. However, later adoption at either 5 or 10 days resulted in a prolonged stress-induced corticosterone secretion, increased the locomotor response to novelty, and disrupted cognitive performance in the adult offspring. This has been further supported by work on maternal separation of mice which suggests a role for nerve growth factor to mediate the effects of external manipulations on the developing brain (reviewed in [6]).

#### 6.4. Cross-fostering studies

It has been observed that rodent mothers display naturally occurring variations in maternal licking/grooming and arched-back nursing [40]. Since the licking/grooming behavior occurs most frequently before or during arched-back nursing, the frequencies of these two behaviors are closely correlated among mothers. In a subsequent cross-fostering study, investigators determined that the amount of licking and grooming that a female pup receives in infancy is associated with how much licking and grooming she provides to her offspring as a new mother [40]. They also reported that the low licking and grooming dams could be transformed into high licking and grooming dams by handling. Most impressively they also found that this change was passed on to the next generation—that is that the female offspring of the low licking and grooming dams became high licking and grooming mothers if they were either cross-fostered by high licking and grooming dams or if they were handled. The converse was also true, namely that the female offspring of the high licking and grooming dams became low licking and grooming mothers if they were cross-fostered by low licking and grooming dams.

These naturally occurring variations in licking, grooming, and arched-back nursing have also been associated with the development of individual differences in behavioral responses to novelty in adult offspring. Adult offspring of the low licking, grooming, and arched-back nursing mothers' show increased startle responses, decreased open-field exploration, and longer latencies to eat food provided in a novel environment [40].

Furthermore, Francis and co-workers demonstrated that the influence of maternal care on the development of stress reactivity was mediated by changes in gene expression in regions of the brain that regulate stress responses. For example, adult offspring of high licking, grooming, and arched-back nursing dams showed increased hippocampal glucocorticoid receptor mRNA expression as well as increased expression of NMDA receptor subunit and brain-derived neurotrophic factor mRNA, and increased cholinergic innervation of the hippocampus [40]. In the amygdala there are increased central benzodiazepine receptor levels in the central and basolateral nuclei. In the PVN there is decreased CRF mRNA in the PVN. These adult pups also show a number of changes in receptor density in the locus ceruleus including: increased alpha2 adrenoreceptors, reduced GABA A receptors, and decreased CRF receptors [100,101].

In another recent study, oxytocin receptor binding levels were examined in brain sections from high and low licking, grooming, and arched-back nursing animals sacrificed either as non-lactating virgins or during lactation [102]. Examination of the MPOA and the intermediate and ventral regions of the lateral septum disclosed that oxytocin receptor levels were significantly higher in lactating females compared with non-lactating females. Lactation-induced

increases in oxytocin receptor binding were greater in high compared with low licking, grooming, and arched-back nursing females in the BNST and ventral region of the septum. Francis and colleagues suggest, therefore, that variations in maternal behavior in the rat may be reflected in, and influenced by differences in oxytocin receptor levels in the brain.

In sum, despite genetic constraints, the nature of early caregiving experiences can have enduring consequences on individual differences in subsequent maternal behavior, anxiety regulation and patterns of stress response through specific neuopharmacological mechanisms (reviewed in [28]). Data from animal studies indicate that the interval surrounding the birth of the rat pup or the rhesus infant is a critical period in the life of the animal that likely has enduring neurobiological and behavioral consequences.

In Section 8 of this review we consider whether there is any evidence in human studies of similar effects?

#### 7. Early life experience, risk and resiliency

Increasing clinical and epidemiological data supports the view that exposure to early adverse environments underlie vulnerability to altered physiological responses to stress and the later expression of mood and anxiety disorders [103–105]. Among the most important early environmental influences is the interaction between the primary caregiver and the infant. Building on the early work of Bowlby and co-workers [106], efforts to characterize this reciprocal interaction between caregiver and infant and to assess its impact have provided a powerful theoretical and empirical framework in the fields of social and emotional development [107]. Over the past 30 years, clear evidence has emerged that significant disturbances in the early parent–child relationship (reflected in such things as child abuse and neglect or insecure attachments) contribute to an increased risk for developing both internalizing and externalizing disorders [108]. While early adversity and insecure attachment may not be a proximal cause of later psychopathology, it appears to confer risk. Conversely, longitudinal studies of high-risk infants suggest that the formation of a special relationship with a caring adult in the perinatal period confers a degree of resiliency and protection against the development of psychopathology later in life [44].

Similar to the findings observed in rodents by Liu, Francis and co-workers [40,95], there is a growing body of evidence also indicates that human caregivers' levels of responsiveness to their children can be traced in part to the caregivers' own childrearing histories and attachment-related experiences [109]. Caregivers' attachment-related experiences are hypothesized to be encoded in 'internal working models' of self and others that establish styles of emotional communication that either buffer the individual in times of stress or that contribute to maladaptive patterns of



affect regulation and behavior [110]. In Section 7.1, we review the results of early intervention programs with high-risk families. The focus is primarily on interventions begun in the pre- or perinatal period and that included random assignment to either the experimental intervention group or to a comparison group.

### 7.1. Early interventions to reduce insecure attachments

Based on the empirical work suggesting the critical importance of early parent–infant relationships, at least six home visitation studies with random assignment have been reported that have aimed to reduce rate of relationship disturbances between high-risk mothers and their infants [4,111–116]. Five of the six studies focused on low SES populations, and one focused on mothers who adopted children of different nationalities. Five out of the six interventions reported reductions in the rates of insecure attachment and the sixth [110] reported fewer negative attachment behaviors. Four of these home visitation programs employed health care professionals as visitors, while the fifth employed a combination of nurses, para-professionals, and non-professionals. Three studies began in the prenatal period [111,113,116]. The duration of the programs varied with two programs lasting only 3–4 months, another lasting on average 8.5 months, and the remainder lasting between 12 and 24 months. Unfortunately, only one of these studies has examined long-term effects on child emotional and behavioral adjustment. Bor et al. [4] found that maternal attitude at 6 months is an independent risk factor for behavioral problems at 5 years in both boys and girls.

In sum, while it appears that the quality of infant–mother attachment is malleable, the long-term impact of such adjustments on risk and resiliency to later psychopathology remains in doubt. The results of the one adoption study are also difficult to interpret, as there was no assessment, antecedent or otherwise, of the biological parents.

### 7.2. Early interventions to improve child behavioral adjustment

Thus far there have been at least three selective intervention studies with *random assignment* and prenatal initiation and at least 1-year duration focused on child behavioral adjustment. The first set of studies was based on an intervention model that included home visits, parent meetings and medical care [117,118]. It showed early effects at 2 and 3 years of age that attenuated by 5 years of age. A second intervention that also included home visits by nurses, parent meetings, and medical care showed less of an effect early on at 4 years of age that became significant at 5 and 6 years of age [119,120]. Finally, a third set of studies that included home visits by nurses that began prenatally and continued for 30 months has shown a remarkable number of positive outcomes as late as 15 years of age [42,121,122]. For example, this nurse home visitation

program developed by Olds and co-workers reduced the number of subsequent pregnancies, the use of welfare, child abuse and neglect, and criminal behavior on the part of low-income, unmarried mothers for up to 15 years after the birth of the first child. These studies by Olds and colleagues provide some of the strongest evidence to date that early intervention can make a difference in the lives of high-risk children. Although the mechanism by which these effects are achieved remains in doubt, Olds and colleagues [42,43,123] have argued that one key element is the length of time between the first and second pregnancies by the mothers participating in the home visitation program. On average, the time to the second pregnancy was more than 60 months in the experimental group that participated in the home visitation program and less than 40 months in the comparison group. This suggests that there was a greater maternal investment in the children who were in the Nurse Home Visitation Program compared to the children born to the comparison mothers.

In sum, data from selective early intervention programs indicate that the interval surrounding the birth of the infant is a critical period in the life of the infant—that likely has enduring behavioral consequences. Thus far, the most compelling data suggest that these early intervention programs are likely to reduce a variety of maladaptive outcomes such as early involvement in the juvenile justice system. Less clear is the impact of these early interventions on the later rates of depression and anxiety disorders as the children reach maturity. Nor is it clear what effect these early intervention programs have on an individual's stress responsivity, susceptibility to drug abuse, or on their capacity as parental caregivers. It is also worth noting that none of these selective early intervention programs has monitored maternal preoccupations as a possible proximal predictor of individual differences in outcome.

## 8. Conclusions

Becoming a parent is about understanding the needs of those who are more dependent, less developmentally mature, and needful of the care and protection of an adult who has their interests and wants as a core preoccupation. How adults transition to being parents and parental caregiving includes a set of highly conserved set of behaviors and mental states that may reflect both an individual's genetic endowment and the early experience of being cared for as a child. Indeed, while we have focused on the process of adults' becoming pregnant and anticipating the birth of their child, there are many other forms of parenting—adoption, foster care, step-parenting, teaching, mentoring, grandparenting. Each involves understanding the needs of those who are more dependent, less developmentally mature, and needful of the care and protection of an adult who has their interests and wants as a core preoccupation, and each probably involving these

highly conserved affiliative systems that permit us to become preoccupied and focused on caring, love relations.

Behavioral, neurobiological, and genetic and neurobiological studies in model mammalian systems have to potential to inform clinical practice, particularly early intervention programs for high-risk expectant parents. To paraphrase Winnicott, ‘good enough’ genes combined with good enough parental care are needed to ensure positive outcomes in childhood and beyond. Among these positive outcomes is a resiliency to subsequent adversities in life and the capacity to be a good enough parent for the next generation. Consequently, it is possible that effective early intervention programs may have consequences for generations. Measures of ‘primary parental preoccupations’ may be useful in future early intervention programs as an index of change within a key domain of functioning.

Viewing parenting as an interaction among genes, past parenting, current experience, psychological state, neurobiological salience systems, and environmental constraints brings many disciplines to the study of parenting. No one discipline even within the social, or even basic, sciences can lay claim to studies of parenting as its primary domain of expertise. Parenting by its very nature is a multidisciplinary study. Close collaboration between clinicians and those who develop parent–infant intervention programs have been long standing. But the ‘new science’ of parenting brings together basic scientists—neurobiologists, geneticists, neuroimagers—with psychoanalysts, cognitive and social psychologists, social scientists studying attachment, anthropologists, obstetricians, pediatricians, and child. The special focus on how adults make room for their new infant is concerned not only with facilitating health babies, but also with helping adults make the transition to their new role and to understanding the genetic, biologic and psychological contributions to that transition. Future studies should permit the examination of how successful early intervention programs influence brain development, problem solving abilities, stress response, as well as vulnerability to later psychopathology.

### Acknowledgements

Aspects of this work were presented as the 20th Annual Daniel Prager Lecture (JFL), The George Washington University, May 2000, Washington, DC. (JFL), the Baltimore–Washington and Houston Psychoanalytic Institute (2002) (LCM), and the Weil Memorial Lecture, Boston, MA, 2003 (LCM). The Korczak and Harris Foundation and grants from the National Institutes of Health MH49351, HD03008, RR06022, and MH30929 supported this research for JFL. The work is also supported by a grant from the Irving Harris Foundation and grants from the National Institute on Drug Abuse (RO1 DA-06025) and by a Research Scientist Development Award to LCM (KO2 DA-00222). Material in this paper has also appeared in

chapters by our research group including Leckman et al. (2004) and Leckman and Herman (2002).

### References

- [1] Bartels A, Zeki S. The neural correlates of maternal and romantic love. *Neuroimage* 2004;21(3):1155–66.
- [2] Baxter Jr LR. Basal ganglia systems in ritualistic social displays: reptiles and humans; function and illness. *Physiol Behav* 2003;79(3):451–60.
- [3] Bidder R, Crowe E, Gray O. Mothers’ attitudes to preterm infants. *Arch Dis Child* 1974;49:766–70.
- [4] Bor W, Brennan PA, Williams GM, Najman JM, O’Callaghan M. A mother’s attitude towards her infant and child behaviour five years later. *Australian and New Zealand J Psychiatry* 2003;37:748–55.
- [6] Cirulli F, Berry A, Alleve E. Early disruption of the mother–infant relationship: effects on brain plasticity and implications for psychopathology. *Neurosci Biobehav Rev* 2003;27:73–82.
- [9] Eckenrode J, Ganzel B, Henderson Jr CR, Smith E, Olds DL, Powers J, et al. Preventing child abuse and neglect with a program of nurse home visitation: the limiting effects of domestic violence. *J Am Med Assoc* 2000;284(11):1385–91.
- [10] Feldman R, Weller A, Leckman JF, Kvint J, Eidelman AI. The nature of the mother’s tie to her infant: the formation of parent–infant bonding in healthy and at-risk dyads. *J Child Psychol Psychiatry* 1999;40:929–39.
- [11] Field T. Infants of depressed mothers. *Dev Psychopathol* 1992;4:49–66.
- [12] Goodman SH, Gotlib IH. Risk for psychopathology in the children of depressed mothers: a developmental model for understanding mechanisms of transmission. *Psychol Rev* 1999;106:458–90.
- [14] Leckman JF, Feldman R, Swain JE, Eicher V, Thompson N, Mayes LC. Primary parental preoccupation: circuits, genes, and the crucial role of the environment. *J Neural Transm* 2004;111:753–71.
- [15] Leibenluft E, Gobbi MI, Harrison T, Haxby JV. Mothers’ neural activation in response to pictures of their children and other children. *Biol Psychiatry* 2004;56(4):225–32.
- [16] Lorberbaum JP, Newman JD, Dubno JR, Horwitz AR, Nahas Z, Teneback C, et al. Feasibility of using fMRI to study mothers responding to infant cries. *Depression Anxiety* 1999;10:99–104.
- [17] Lorberbaum JP, Newman JD, Horwitz AR, Dubno JR, Lydiard RB, Hammer MB, et al. A potential role for thalamocingulate circuitry in human maternal behavior. *Biol Psychiatry* 2002;51(6):431–45.
- [18] Minde K, Shosenberg N, Thompson J, et al. Self-help groups in a premature nursery follow-up at one year. In: Call J, Galenson E, Tyson R, editors. *Frontiers of infant psychiatry*. New York: Basic Books; 1983. p. 264.
- [19] 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):583–92.
- [21] Ranote S, Elliott R, Abel, Mitchell R, Deakin JFW, Appleby L. The neural basis of maternal responsiveness to infants: an fMRI study. *Neuroreport* 2004;15(11):1825–9.
- [22] Seifritz E, Esposito F, Neuhoff JG, Luthi A, Mustovic H, Dammann G, et al. Differential sex-independent amygdala response to infant crying and laughing in parents versus nonparents. *Biol Psychiatry* 2003;54(12):1367–75.
- [23] Squire S, Stein A. Functional MRI and parental responsiveness: a new avenue into parental psychopathology and early parent–child interactions? *Br J Psychiatry* 2003;183:481–3.

- [24] Swain JE, Leckman JF, Mayes LC, Feldman R, Constable RT, Schultz RT. The neural circuitry of human parent–infant attachment in the early postpartum. *Proceedings of the American College of neuropsychopharmacology 42nd annual meeting* 2003;114:192.
- [25] Swain JE, Leckman JF, Mayes LC, Feldman R, Constable RT, Schultz RT. Neural substrates and psychology of human parent–infant attachment in the postpartum. *Biol Psychiatry* 2004;55(8):153S.
- [26] Swain JE, Leckman JF, Mayes LC, Feldman R, Constable RT, Schultz RT. Brain circuitry and psychology of human parent–infant attachment in the postpartum. *Proceedings of the international association for child and adolescent psychiatry and allied professions 16th world congress* 2004 p. 365. P-020-369.
- [28] Weaver IC, Diorio J, Seckl JR, Szyf M, Meaney MJ. Early environmental regulation of hippocampal glucocorticoid receptor gene expression: characterization of intracellular mediators and potential genomic target sites. *Ann NY Acad Sci* 2004;1024:182–212.
- [29] Winnicott DW. Primary maternal preoccupation. In: *Collected papers: through paediatrics to psycho-analysis*; 1975. New York: Basic Books. [1956]. p. 300–5.
- [31] Fraiberg S, Adelson E, Shapiro V. Ghosts in the nursery: a psychoanalytic approach to the problems of impaired infant–mother relationships. *J Am Acad Child Psychiatry* 1975;14:387–421.
- [32] Kreisler L, Fain M, Soulé M. *L'enfant et son corps*. Paris: Presses Universitaires de France; 1974.
- [33] Lebovici S. *Le nourrisson, la mère et le psychoanalyste: Les interventions précoces*. Paris: Le Centurion; 1983.
- [34] Stern DN. *The motherhood constellation: a unified view of parent–infant psychopathology*. New York: Basic Books; 1997.
- [35] Bretherton I, Waters E, editors. *Growing points of attachment theory and research. Monographs of the society for research in child development*, vol. 50, 1985. p. 1–2. Serial No. 209.
- [36] Benoit D, Parker KCH, Zeanah CH. Mothers' representations of their infants assessed prenatally: stability and association with infant-attachment classification. *J Child Psychol Psychiatry* 1997;38:307–13.
- [37] Zeanah CH, Benoit D, Hirshberg L, Barton MI, Regan C. Mothers' representations of their infants are concordant with infant attachment classifications. *Dev Issues Psychiatry Psychol* 1994;1:1–14.
- [38] Leckman JF, Mayes LC, Feldman R, Evans D, King RA, Cohen DJ. Early parental preoccupations and behaviors and their possible relationship to the symptoms of obsessive-compulsive disorder. *Acta Psychiatrica Scand* 1999;100(396):1–26.
- [39] Feldman R, Weller A, Leckman JF, Kvint J, Eidelman AI. The nature of the mother's tie to her infant: the formation of parent–infant bonding in healthy and at-risk dyads. *J Child Psychol Psychiatry* 1999;40:929–39.
- [40] Francis D, Diorio J, Liu D, Meaney MJ. Non-genomic transmission across generations of maternal behavior and stress responses in the rat. *Science* 1999;286:1155–8.
- [41] Ladd CO, Huot RL, Thiruvikraman KV, Nemeroff CB, Meaney MJ, Plotsky PM. Long-term behavioral and neuroendocrine adaptations to adverse early experience. In: Mayer EA, Saper CB, editors. *Progress in brain research: the biological basis for mind body interactions*, vol. 122. Amsterdam: Elsevier; 2000. p. 81–103.
- [42] Olds DL, Henderson Jr CR, Kitzman HJ, Eckenrode JJ, Cole RE, Tatelbaum RC. Prenatal and infancy home visitation by nurses: recent findings. *Future Child* 1999;9(1):190–1 see also p. 44–65.
- [43] Eckenrode J, Ganzel B, Henderson Jr CR, Smith E, Olds DL, Powers J, et al. Preventing child abuse and neglect with a program of nurse home visitation: the limiting effects of domestic violence. *J Am Med Assoc* 2000;284(11):1385–91.
- [44] Werner EE. Vulnerable but invincible: high-risk children from birth to adulthood. *Acta Paediatr Suppl* 1997;422:103–5.
- [45] Werner EE, Smith RS. *Journeys from childhood to midlife: risk, resilience, and recovery*. Ithaca, NY: Cornell University Press; 2001.
- [46] Leckman JF, Mayes LC. Understanding developmental psychopathology: how useful are evolutionary perspectives? *J Am Acad Child Adolesc Psychiatry* 1998;37:1011–21.
- [47] Stern DN. Mother and infant at play: the dyadic interaction involving facial, vocal, and gaze behaviors. In: Lewis M, Roseblum LA, editors. *The effect of the infant on its caregiver*. New York: Wiley; 1974.
- [48] Dunn JB. Patterns of early interaction: continuities and consequences. In: Schaffer HR, editor. *Studies in mother–infant interaction*. London: Academic Press; 1977. p. 438–56.
- [49] Trevarthan C. Communication and cooperation in early infancy: a description of primary intersubjectivity. In: Bullowa M, editor. *Before speech: the beginning of interpersonal communication*. Cambridge: Cambridge University Press; 1979. p. 321–47.
- [50] Bornstein MH. Parenting infants. In: Bornstein M, editor. *Handbook of parenting*, vol. 1. Mahwah, NJ: Erlbaum; 1995. p. 3–39.
- [51] Anderson BJ, Vietze P, Dodecki PR. Reciprocity in vocal interactions of mothers and infants. *Child Dev* 1997;48:1676–81.
- [52] Egeland B, Sroufe LA. Developmental sequelae of maltreatment in infancy. *New Dir Child Dev* 1981;11:77–92.
- [53] Carlson V, Cicchetti D, Barnett D, et al. Disorganized/disoriented attachment relationships in maltreated infants. *Dev Psychol* 1989;25:525–31.
- [54] Rogosch FA, Cicchetti D, Shields A, et al. Parenting dysfunction in child maltreatment. In: Bornstein M et al, editor. *Handbook of parenting*, vol. 4. Hillsdale, NJ: Erlbaum; 1995. p. 127–59.
- [55] Heinicke C. Determinants of the transition to parenting. In: Bornstein M, editor. *Handbook of parenting*, vol. 3. Hillsdale, NJ: Erlbaum; 1995. p. 277–303.
- [56] Greenberg M, Morris N. Engrossment: the newborn's impact upon the father. *Am J Orthopsychiatry* 1974;44:520–31.
- [57] Entwisle DR, Doering SG. *The first birth: a family turning point*. Baltimore, MD: Johns Hopkins University Press; 1981.
- [58] Winter SK. Fantasies at breast feeding time. *Psychol Today* 1970;3:31–2.
- [59] Sichel DA, Cohen LS, Dimmock JA, Rosenbaum JF. Postpartum obsessive-compulsive disorder: a case series. *J Clin Psychiatry* 1993;54:156–9.
- [60] Bretherton I. New perspectives on attachment relations: security, communication, and internal working models. In: Osofsky JD, editor. *Handbook of infant development*. New York: Wiley; 1987. p. 1061–100.
- [61] Hinde RA. *Biological bases of human social behavior*. New York: McGraw-Hill; 1974.
- [62] Stevenson-Hinde J. An ethological perspective. *Psychol Inq* 1994;5:62–5.
- [63] Hofer MA. An evolutionary perspective on anxiety. In: Rose SP et al, editor. *Anxiety as symptom and signal*. Hillsdale, NJ: The Analytic Press; 1995. p. 17–38.
- [64] Pryce CR. Determinants of motherhood in human and nonhuman primates. In: Pryce CR et al, editor. *Motherhood in human and nonhuman primates: biological and social determinants*. Basel: Karger; 1995. p. 1–15.
- [65] Corsini CA, Viazzo P. *The decline of infant and child mortality: the European experience, 1750–1990*. The Hague: Kluwer Law International; 1997.
- [66] Clutton-Brock TH. *The evolution of parental care*. Princeton, NJ: Princeton University Press; 1991.
- [67] Fleming AS, Steiner M, Corter C. Cortisol, hedonics, and maternal responsiveness in human mothers. *Horm Behav* 1997;32(2):85–98.
- [68] Numan M. In: Knobil E, Neill JF, editors. *The physiology of reproduction*. New York: Raven Press; 1994. p. 221–301.
- [69] Numan M, Sheehan TP. Neuroanatomical circuitry for mammalian maternal behavior. *Ann NY Acad Sci* 1997;807:101–25.

- [70] Leckman JF, Herman A. Maternal behavior and developmental psychopathology. *Biol Psychiatry* 2002;51:27–43.
- [71] Bridges RS, Numan M, Ronsheim PM, Mann PE, Lupini CE. Central prolactin infusions stimulate maternal behavior in steroid-treated, nulliparous female rats. *Proc Natl Acad Sci USA* 1990;87:8003–7.
- [72] 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;108:1163–71.
- [73] Numan M, Rosenblatt JS, Kiminsaruk BR. Medial preoptic area and onset of maternal behavior in the rat. *J Comp Physiol Psychol* 1997; 91:146–64.
- [74] Sofroniew MV, Weindl A. Central nervous system distribution of vasopressin, oxytocin, and neurophysin. In: Martinex JL, Jensen RA, Messing RB, Rigter H, McGraugh JL, editors. *Endogenous peptides and learning and memory processes*. New York: Academic Press; 1981.
- [75] Pederson CA, Prange AJ. Induction of maternal behavior in virgin rats after intracerebroventricular administration of oxytocin. *Proc Natl Acad Sci USA* 1979;76:6661–5.
- [76] Van Leengoed E, Kerker E, Swanson HH. Inhibition of postpartum maternal behavior in the rat by injecting an oxytocin antagonist into the cerebral ventricles. *J Endocrinol* 1987;112:275–82.
- [77] Insel TR, Harbaugh CR. Lesions of the hypothalamic paraventricular nucleus disrupt the initiation of maternal behavior. *Physiol Behav* 1989;45:1033–41.
- [78] Pedersen CA. Oxytocin control of maternal behavior: regulation by sex steroids and offspring stimuli. *Ann NY Acad Sci* 1997;807: 126–45.
- [79] Sheehan TP, Cirrito J, Numan MJ, Numan M. Using c-Fos immunocyto-chemistry to identify forebrain regions that may inhibit maternal behavior in rats. *Behav Neurosci* 2000;114:337–52.
- [80] Fleming AS, Vaccarino F, Luebke C. Amygdaloid inhibition of maternal behavior in the nulliparous female rat. *Physiol Behav* 1980; 25:731–43.
- [81] Koob GF, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. *Science* 1997;278(5335):52–8.
- [82] Hansen S, Harthorn C, Wallin E, Lofberg L, Svensson K. Mesotelencephalic dopamine system and reproductive behavior in the female rat: effects of ventral tegmental 6-hydroxy-dopamine lesions on maternal and sexual responsiveness. *Behav Neurosci* 1991;105:588–98.
- [83] Lopez JF, Akil H, Watson SJ. Neural circuits mediating stress. *Biol Psychiatry* 1999;46(11):1461–71.
- [84] Swanson LW. Cerebral hemisphere regulation of motivated behavior. *Brain Res* 2000;886:113–64.
- [85] 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):673–85.
- [86] Li LL, Keverne EB, Aparicio SA, Ishino F, Barton SC, Surani MA. Regulation of maternal behavior and offspring growth by paternally expressed *Peg3*. *Science* 1999;284:330–3.
- [87] Thomas SA, Matsumoto AM, Palmiter RD. Noradrenaline is essential for mouse fetal development. *Nature* 1995;374:643–6.
- [88] Thomas SA, Palmiter RD. Impaired maternal behavior in mice lacking norepinephrine and epinephrine. *Cell* 1997;91:583–92.
- [89] Pryce CR, Bettschen D, Feldon J. Comparison of the effects of early handling and early deprivation on maternal care in the rat. *Dev Psychobiol* 2001;38(4):239–51.
- [90] Denenberg VH, Rosenberg KM, Paschke R, Zarrow MX. Mice reared with rat aunts: effects on plasma corticosterone and open-field activity. *Nature* 1969;221:73–4.
- [91] Levine S. Psychosocial factors in growth and development. In: Levi L, editor. *Society, stress and disease*. London: Oxford University Press; 1975. p. 43–50.
- [92] Harlow HF. The maternal affectional system of rhesus monkeys. In: Rheingold HL, editor. *Maternal behavior in mammals*. New York: Wiley; 1963. p. 254–81.
- [93] Suomi SJ, Ripp C. A history of motherless mothering at the University of Wisconsin Primate Laboratory. In: Reite M, Caine N, editors. *Child abuse: the non-human data*. New York: Alan R Liss; 1983. p. 49–78.
- [94] Suomi SJ, Delizio R, Harlow HF. Social rehabilitation of separation-induced depressive disorders in monkeys. *Am J Psychiatry* 1976; 133(11):1279–85.
- [95] Liu D, Diorio J, Tannenbaum B, Caldji C, Francis D, Freedman A, et al. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic–pituitary–adrenal responses to stress. *Science* 1997; 277:1659–62.
- [96] Plotsky PM, Meaney MJ. Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. *Brain Res Mol Brain Res* 1993;18(3):195–200.
- [97] Liu D, Diorio J, Day JC, Francis DD, Meaney MJ. Maternal care, hippocampal synaptogenesis and cognitive development in rats. *Nat Neurosci* 2000;3:799–806.
- [98] Huot R, Smith M, Plotsky PM. Alterations of maternal–infant interaction as a result of maternal separation in Long Evans rats and its behavioral and neuroendocrine consequences. *International Society of Psychoneuroendocrinology, XXVIIIth Congress, July 26–30, San Francisco, CA*.
- [99] Barbazanges A, Vallee M, Mayo W, Day J, Simon H, Le Moal M, et al. Early and later adoptions have different long-term effects on male rat offspring. *J Neurosci* 1996;16(23):7783–90.
- [100] Caldji C, Tannenbaum B, Sharma S, Francis D, Plotsky PM, Meaney MJ. Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. *Proc Natl Acad Sci USA* 1998;95(9):5335–40.
- [101] Caldji C, Francis D, Sharma S, Plotsky PM, Meaney MJ. The effects of early rearing environment on the development of GABAA and central benzodiazepine receptor levels and novelty-induced fearfulness in the rat. *Neuropsychopharmacology* 2000; 22(3):219–29.
- [102] Francis DD, Champagne FC, Meaney MJ. Variations in maternal behavior are associated with differences in oxytocin receptor levels in the rat. *J Neuroendocrinol* 2000;12:1145–8.
- [103] Brown GW, Bifulco A, Harris TO. Life events, vulnerability and onset of depression: some refinements. *Br J Psychiatry* 1987;150: 30–42.
- [104] Ambelas A. Life events and the onset of mania. *Br J Psychiatry* 1990;157:450–1.
- [105] Kendler KS, Kessler RC, Neale MC, Heath AC, Eaves LJ. The prediction of major depression in women: toward an integrated etiologic model. *Am J Psychiatry* 1993;150(8):1139–48.
- [106] Bowlby J. *Attachment*. 2nd ed. New York: Basic Books; 2000.
- [107] Cassidy J, Shaver PR, editors. *Handbook of attachment*. New York: Guilford Press; 1999.
- [108] Sroufe LA, Carlson EA, Egeland B. Implications of attachment theory for developmental psychopathology. *Dev Psychopathol* 1999;11(1):1–13.
- [109] Miller L, Kramer R, Warner V, Wickramaratne P, Weissman M. Intergenerational transmission of parental bonding among women. *J Am Acad Child Adolesc Psychiatry* 1997;36(8):1134–9.
- [110] Bretherton I, Munholland KA. Internal working models in attachment relations—a construct revisited. In: Cassidy J, Shaver PR, editors. *Handbook of attachment—theory, research, and clinical implications*. New York: The Guildford Press; 1999. p. 89–111.
- [111] Anisfeld E, Casper V, Nozyce M, Cunningham N. Does infant carrying promote attachment? An experimental study of the effects of increased physical contact on the development of attachment. *Child Dev* 1990;61(5):1617–27.

- [112] Lieberman AF, Weston DR, Pawl JH. Preventive intervention and outcome with anxiously attached dyads. *Child Dev* 1991;62(1):199–209.
- [113] Jacobson SW, Frye KF. Effect of maternal social support on attachment: experimental evidence. *Child Dev* 1991;62(3):572–82.
- [114] van den Boom DC. Do first-year intervention effects endure? Follow-up during toddlerhood of a sample of Dutch irritable infants. *Child Dev* 1995;66(6):1798–816.
- [115] Juffer F, Hoksbergen RA, Riksen-Walraven JM, Kohnstamm GA. Early intervention in adoptive families: supporting maternal sensitive responsiveness, infant–mother attachment, and infant competence. *J Child Psychol Psychiatry* 1997;38(8):1039–50.
- [116] Heinicke CM, Fineman NR, Ruth G, Recchia SL, Guthrie D, Rodning C. Relationship-based intervention with at-risk mothers: outcome in the first year of life. *Infant Mental Health J* 1999;20:349–74.
- [117] Brooks-Gunn J, Klebanov PK, Liaw F, Spiker D. Enhancing the development of low-birthweight, premature infants: changes in cognition and behavior over the first three years. *Child Dev* 1993;64(3):736–53.
- [118] McCarton CM, Brooks-Gunn J, Wallace IF, Bauer CR, Bennett FC, Bernbaum JC, et al. Results at age 8 years of early intervention for low-birth-weight premature infants. The infant health and development program. *J Am Med Assoc* 1997;277(2):126–32.
- [119] Guteilus MF, Kirsch AD, MacDonald S, Brooks MR, McErlean T, Newcomb C. Promising results from a cognitive stimulation program in infancy. A preliminary report. *Clin Pediatr (Phila)* 1972;11(10):585–93.
- [120] Guteilus MF, Kirsch AD, MacDonald S, Brooks MR, McErlean T. Controlled study of child health supervision: behavioral results. *Pediatrics* 1977;60(3):294–304.
- [121] Olds DL, Eckenrode J, Henderson Jr CR, Kitzman H, Powers J, Cole R, et al. Long-term effects of home visitation on maternal life course and child abuse and neglect. Fifteen-year follow-up of a randomized trial. *J Am Med Assoc* 1997;278(8):637–43.
- [122] Olds D, Henderson Jr CR, Cole R, Eckenrode J, Kitzman H, Luckey D, et al. Long-term effects of nurse home visitation on children's criminal and antisocial behavior: 15-year follow-up of a randomized controlled trial. *J Am Med Assoc* 1998;280(14):1238–44.
- [123] Kitzman H, Olds DL, Sidora K, Henderson Jr CR, Hanks C, Cole R, et al. Enduring effects of nurse home visitation on maternal life course: a 3-year follow-up of a randomized trial. *J Am Med Assoc* 2000;283(15):1983–9.