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Primary parental preoccupation: circuits, genes, and the crucial role of the environment

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Summary. Parental caregiving includes a set of highly conserved behaviors and mental states that may reflect both an individual's genetic endowment and the early experience of being cared for as a child. This review first examines the mental and behavioral elements of early parental caregiving in humans. Second, we consider what is known about the neurobiological substrates of maternal behaviors in mammalian species including some limited human data. Third, we briefly review the evidence that specific genes encode proteins that are crucial for the development of the neural substrates that underlie specific features of maternal behavior. Fourth, we review the emerging literature on the "programming" role of the intrauterine environment and postnatal caregiving environment in shaping subsequent maternal behavior. 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 individual's responsivity to psychosocial stressors and their resiliency or vulnerability to various forms of human psychopathology later in life.

Keywords: Maternal behavior, gene-environment interactions, stress response, psychopathology, resiliency, intrauterine environment, early intervention programs.

"What fascinated me most was how intimate relationships and the desire for being with the other precede the rest of cognitive development, and that this social motivation moves these other achievements forward, including

meta-representation and theories about other minds. This intuitive, deeply encoded social orientation is first expressed in the mother's arms and then forms the basis for all future I-Thou relationships."

Donald J. Cohen, 2001

Introduction

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. 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 consideration of the normative developmental trajectory of parenting (Feldman, 1999; Fraiberg et al., 1975; Kreisler et al., 1974; Leckman et al., 1999; Stern et al., 1997; Zeanah et al., 1994).

This review focuses initially on recent efforts to characterize further early parental preoccupations and the caretaking behaviors they engender. Next, we consider recent advances in our understanding of the genetic, epigenetic, and neurobiological substrates of maternal behavioral in model mammalian species and their potential relevance for understanding human 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 intrauterine environment and 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 (Francis et al., 1999, 2003; Ladd et al., 2000). If similar mechanisms are at work in human populations, they may provide a basis for successful early intervention programs (Olds et al., 1999; Eckenrode et al., 2000) and may deepen our understanding of why some individuals are more vulnerable, or conversely more resilient, to certain forms of psychopathology (Werner et al., 1997, 2001).

Point-of-view and initial caveats

Before reviewing any specific findings, it may be useful to articulate our 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 appearance of our species dates to less than 100,000 years ago. In the struggle for life, certain traits have come to predominate. We might surmise that elements in our mental and behavioral repertoire related to successful reproduction were certainly the focus of intense 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 (Leckman and Mayes, 1998).

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, reciprocity and direct physical contact 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 (Bornstein, 1995; Dunn, 1977; Feldman et al., 2003; Stern, 1974; Trevarthan, 1979). Developmental researchers 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 (Egeland and Sroufe, 1981; Carlson et al., 1989; Rogosch et al., 1995; Heinicke, 1995). The major theoretical perspectives, psychoanalysis and attachment theory, emphasize both the link between the nature of early parent-infant relationship and adaptation across the lifespan as well as the interconnectedness of the physiological, behavioral, and representational components of parent-infant attachment. 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 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 near exclusion of all else. 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.

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 (Leckman et al., 1999). 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 two weeks after delivery mothers of normal infants, on average, reported spending nearly 14 hours per day focused exclusively on the infant, while fathers reported spending approximately half that amount of time.

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 three months of age. These idealizing thoughts may be especially important in the establishment of resiliency and the perception of self efficacy. Results from studies of at-risk infants confirm the centrality of the mother's positive perceptions in shaping the mother-infant relationship. Mothers of premature infants who reported positive feelings toward their infants, expressed confidence in their ability to parent, and perceived their infant as not very different from an ''ideal'' baby were more sensitive to their infants' signals during interactions, provided more affectionate touch, and the infants were more socially alert and involved during play (Keren et al., 2003).

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 six months after birth, women reported increasing levels of worry toward the end of their pregnancy and 25 to 30% described being preoccupied with worries about caring for the infant postpartum (Entwisle and Doering, 1981). 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 eight months of gestation. In the weeks following delivery this percentage declined only slightly, and at three months these figures were unchanged. After delivery and on returning home, the most frequently cited concerns were one's adequacy as a new parent, concerns about feeding the baby, about the baby's crying, and thoughts about the infant's well-being. Conditions such as these are especially commonly reported among parents of very sick preterm infants, infants with serious congenital disorders or malformations or infants with serious birth complications (Feldman et al., 1999). Less commonly, intrusive thoughts of injuring the child may beset the new mother (or father) and can in turn lead to postpartum obsessive-compulsive disorder or depression or both (Winter, 1970).

Nursing, feeding, and affectionate touch and contact (parallel to grooming in other mammalian species) 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 (Bretherton, 1987). 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. Breast-feeding contributes to the mother's caregiving behavior and breast-feeding mothers were shown to be more sensitive to their infants' cues during a feeding session, pointing to the importance of maternal-infant intimacy in shaping maternal behavior (Brandt et al., 1998). Recent studies of direct skin-to-skin contact between premature newborns and their parents (Kangaroo care) also emphasize the beneficial effects of physical touch in facilitating more sensitive and affectionate interactions as the child grows older (Feldman et al., 2003). The physical intimacy afforded by the kangaroo experience increases nursing volume (Hurst et al., 1997) and contributes to infant resiliency, arousal modulation, stress reactivity, and cognitive competencies across infancy (Feldman et al., 2002a, b).

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. This sense of heightened responsibility leads parents to check on the baby frequently, even at times when they know the baby is fine (Leckman et al., 1999).

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. 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 100/1,000 live births in 1900 to about 10/1,000 in 1984 (Corsini and Viazzo, 1997). 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 and reordering of what is important in life. Caregiving 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 parents' hedonic homeostasis as they establish lasting reciprocal social bonds and make room in their inner lives for a new family member (Clutton-Brock, 1991).

Finally, too much or too little primary parental preoccupation may be problematic. Too much can lead to obsessive-compulsive-like states (Maina et al., 1999) and too little may set the stage for abuse or neglect in vulnerable, high-risk families (Eckenrode et al., 2000). 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 post-partum depression (Field, 1992; Goodman and Gottlieb, 1999). 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 (Feldman et al., 1999b). These data suggest that the function impaired by depression is the behavioral and mental investment in forming a relationship with the new infant. On the other hand, physical intimacy with the infant – in terms of kangaroo care and breastfeeding – were found to be effective in reducing maternal depression, increasing the mother's investment in the relationship, and improving the mother's attachment behaviors toward the infant (Feldman et al., 2002a; Feldman and Eidelman, 2003).

Neural circuitry of maternal behavior

Although the central nervous system events that accompany parental care and characteristic parental mental states in humans are largely unknown, it is likely that there is a substantial degree of conservation across mammalian species (Fleming et al., 1997). 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 (Leckman and Herman, 2002; Numan, 1994; Numan and Sheehan, 1997). Estrogen, prolactin, and oxytocin can act on the MPOA to promote maternal behavior (Bridges et al., 1990; Numan et al., 1997; Pedersen and Prange, 1979). 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 (Sofroniew and Weindl, 1981).

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 (Pedersen and Prange, 1979). 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 (Van Leegoed et al., 1987). 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 (Pedersen, 1997).

Data on the role of oxytocin in maternal behavior in humans is scarce. Mother-infant touch and contact have been shown to stimulate oxytocin release. Newborn infants placed on the mother's chest stimulate oxytocin release by hand movement and suckling (Matthiesen et al., 2001), and mother-infant skin-to-skin contact immediately after birth elevates maternal oxytocin levels (Nissen et al., 1995). Breast pumping and breastfeeding are related to a comparable increase in oxytocin levels (Zinaman et al., 1992) and thus measuring exact amounts of expressed milk may serve as a proxy of oxytocin levels. Mothers of premature infants who expressed higher quantities of breast-milk showed more optimal maternal behavior, in terms of higher sensitivity and more affectionate touch during interactions. The amount of breast-milk also predicted the infant's cognitive and motor development and negatively correlated with maternal depression (Feldman and Eidelman, 2003). Since oxytocin functions as an anti-depressant agent, reducing anxiety and elevating social activity in humans (Carter, 1998; Uvnas-Moberg, 1998) and is increased with touch and contact, it is likely to play a role in the general complex of behavior and mental representations related to maternal caregiving.

Ascending dopaminergic and noradrengeric systems associated with reward pathways also appear to play a crucial role in facilitating maternal behavior (Koob and LeMoal, 1997). 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 (Hansen et al., 1991). 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 (Pedersen et al., 1994).

Brain areas that may inhibit maternal behavior in rats have been identified (Sheehan et al., 2000). 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 (Fleming et al., 1980).

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. Swanson has conceptualized this set of limbic, hypothalamic, and midbrain nuclei as being the "behavioral control column" that is voluntarily regulated by cerebral projections (Swanson, 2000). 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 (Fleming et al., 1999; Lorberbaum et al., 2002). 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 (Fleming et al., 1997). Likewise, Lorberbaum and colleagues (2002) found increased levels of activity in the cingulate cortex as well as the midbrain, hypothalamus, dorsal and ventral striatum, and the lateral septal region. Each of these findings supports the hypothesis that our stress response systems are adaptively activated during the period of heightened maternal sensitivity surrounding the birth of a new infant.

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 α receptor; and one neuropeptide, oxytocin (Leckman and Herman, 2002). By way of illustration, we briefly review one of these genes, *Dopamine beta hydroxylase* (*Dbh*).

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 and colleagues disrupted the *Dbh* gene in mice. Mice homozygous for the *Dbh* mutation (*Dbh* –/–) died *in utero*, of apparent cardiovascular failure (Thomas et al., 1995). *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. The majority of these rescued animals became viable adults.

In a subsequent study, Thomas and Palmiter (1997) 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 NE transiently 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 specific genes including *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.

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 (Pryce et al., 2001). In general, these findings suggest that the intrauterine environment (Francis et al., 2003) and maternal experience and 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 (Denenberg et al., 1969; Francis et al., 1999, 2002; Levine, 1975). This complex programming also appears to influence aspects of learning and memory. Further, many of the brain regions implicated in these experimental interventions are the same as those identified in the knockout gene and earlier lesioning studies. Investigations of social primates also highlight the importance of early mothering in determining how the daughters will mother (Harlow, 1963; Suomi and Ripp, 1983). It is also clear that the effects of early maternal deprivation in primates may be difficult to reverse, as many maternally deprived monkeys, as adults, are able to function normally under usual conditions but are unable to cope with psychosocial stressors (Suomi et al., 1976). Alternatively, in rodent models environmental enrichment in the peripubertal period appears to compensate for the effects of early maternal separation (Francis et al., 2002).

Embryonic transfer

Francis and colleagues (2003) recently investigated the effects of prenatal (embryo transfer) and postnatal (cross-fostering) environments in two strains of inbred mice with profound and reliable differences in behavior. They found that some robust strain-related behavioral differences including fearfulness in novel environments may result from environmental factors during development rather than genetic differences between the offspring.

Postnatal cross-fostering studies

It has been observed that rodent mothers display naturally occurring variations in maternal licking/grooming and arched-back nursing (Francis et al., 1999). 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. They 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.

Furthermore, Francis and coworkers 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. In the amygdala there are increased central benzodiazepine receptor levels in the central and basolateral nuclei. There is decreased CRF mRNA in the PVN. These adult pups also show a number of changes in receptor density in the locus coeruleus including: increased alpha2 adrenoreceptors, reduced GABA A receptors, and decreased CRF receptors (Caldji et al., 1998, 2000).

In another 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 (Francis et al., 2000). 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. 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 the final section of this review we consider whether there is any evidence in human studies of similar effects.

Early life experience, risk and resiliency

Increasing clinical and epidemiological data supports the view that exposure to early adverse environments underlies vulnerability to altered physiological responses to stress and the later expression of mood and anxiety disorders (Ambelas, 1990; Brown et al., 1987; Kendler et al., 1993). 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 colleagues (2000), 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 (Cassidy and Shaver, 1999). 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 (Sroufe et al., 1999). 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 (Werner and Smith, 2001).

Similar to the findings observed in rodents by Liu, Francis and colleagues, a growing body of evidence also indicates that human caregivers' levels of responsivity to their children can be traced in part to the caregivers' own child-rearing histories and attachment-related experiences (Miller et al., 1997). Caregivers' attachment-related experiences are hypothesized to be encoded as "internal working models" of self and others that establish styles of emotional communication that either buffer the individual in times of stress or contribute to maladaptive patterns of affect regulation and behavior (Bretherton and Munholland, 1999).

Of particular interest in this context is recent theoretical and empirical work on the role of secure attachment relationship in shaping the experience and expectancies of the infant (Fonagy et al., 2002). By entering into a synchronous affective communication with the infant, the caregiver provides an external support for the infant's emerging bioregulatory abilities and thus conveys resilience to stress coping capacities throughout life. The experience of caregiver and child's micro-level matching of affective states and level of arousal during face-to-face interactions emerging around the second month of life provides the basis for children's social development, empathy, and moral internalization (Feldman et al., 1999b). Maternal gaze matching, facial expressions, vocalizations, and regulation of arousal states during face-to-face play provide critical environmental inputs during the sensitive period of maturation of the visual cortex. Furthermore, by synchronizing with infant arousal state, mothers entrain the infant's biological rhythms (Lester et al., 1985; Feldman, 2003), providing a "resonance" (Trevarthan, 1994) of internal and external experience, self and other, brain and behavior. Disorganized attachment, on the other hand, is viewed as a model for the effects of relational trauma on affect dysregulation, propensity for PTSD, and reduced stress management (Lyons-Ruth and Jacobvitz, 1999).

In the next section, we review the results of early intervention programs with high-risk families. The focus is primarily on interventions initiated in the pre- or peri-natal period that included random assignment to either the experimental intervention group or to a comparison group.

Early interventions to increase parental sensitivity and child attachment security

Attachment security is a resiliency factor across the life-span. In a recent meta-analysis of 88 intervention studies Bakermans-Kranenburg and colleagues (2003) found that, overall, interventions were effective in enhancing parental sensitivity and child attachment security. Interventions focused on parenting skills, social supports, or maternal well-being were significantly more successful. So were interventions that included both mother and father. Thus, the body of research on early interventions underscores the importance of devising clear-cut, short-term, behavioral interventions for a variety of at-risk populations. One caveat of this important study is that the time since the termination of treatment was not systematically evaluated. It is thus impossible to determine whether the improvement observed immediately after treatment was short-lived or had a long-term impact on risk and resiliency to later psychopathology.

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 one-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 (Brooks-Gunn et al., 1993; McCarton et al., 1997). 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 (Gutelius et al., 1972, 1977). 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 (Olds et al., 1997, 1998, 1999, 2002). 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 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 a recent study based in Denver women visited by nurses had fewer subsequent pregnancies (29% vs 41%) and births (12% vs 19%); they delayed subsequent pregnancies for longer intervals; and during the second year after the birth of their first child, they worked more than women in the control group (6.83 vs 5.65 months). Nurse-visited mother-child pairs interacted with one another more responsively than those in the control group. At 6 months of age, nurse-visited infants were less likely to exhibit emotional vulnerability in response to fearful stimuli (16% vs 25). At 21 months, nurse-visited children born to women with low psychological resources were less likely to exhibit language delays (7% vs 18%); and at 24 months, they exhibited superior mental development to their control-group counterparts. Of interest for most outcomes on which either visitor produced significant effects, the paraprofessionals typically had effects that were about half the size of those produced by nurses.

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 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.

Conclusions

Behavioral, neurobiological, and genetic and neurobiological studies in model mammalian systems have the potential to inform clinical practice, particularly early intervention programs for high-risk expectant parents. "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.

Close collaborations between clinicians and the designers of model intervention programs have been long standing. These collaborations are now beginning to include neuroimagers, developmental neurobiologists, and geneticists. Our capacity to study genes and the development of the brain has never been stronger. 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.

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