Maternal Care, Gene Expression, and the Development of Individual Differences in Stress Reactivity

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PARENTAL CARE AND THE HEALTH OF OFFSPRING

The quality of family life influences the development of individual differences in vulnerability to illness throughout later life. As adults, victims of childhood physical or sexual abuse are at considerably greater risk for mental illness, as well as for diabetes and heart disease (e.g., Refs. 1–3). Children need not be beaten to be compromised. Persistent emotional neglect or conditions of harsh, inconsistent discipline serve to increase the risk of depression and anxiety disorders to a level comparable to that observed in cases of abuse.[4] Indeed, for certain outcomes, the consequences of persistent neglect exceed those of abuse.[5,6]

More subtle relationships exist. Low scores on parental bonding scales, reflecting cold, distant parent–child relationships, significantly increase the risk of depression and anxiety in later life (e.g., Refs. 7,8). And the risk is not unique to mental health. Russak and Schwartz[9] found that by midlife those individuals who, as undergraduate students, rated their relationship with parents as cold and detached, had a fourfold greater risk of chronic illness, including depression and alcoholism as well as heart disease and diabetes.

Parental factors also serve to mediate the effects of environmental adversity on development. For example, the effects of poverty on emotional and cognitive development are mediated by parental factors, to the extent that if such factors are controlled, there is no discernible effect of poverty on child development.[10,11] Moreover, treatment outcomes associated with early intervention programs are routinely correlated with changes in parental behavior: In cases where parental behavior proves resistant to change, treatment outcomes are seriously limited. These findings suggest that variations in parental care mediate, in part at least, the effects of environmental adversity on child development. One of the more common findings here is that maternal depression associated with environmental conditions not only compromises parent–child interactions, but also limits the efficacy of early intervention programs.

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The sword cuts both ways. Family life can also serve as a source of resilience in the face of chronic stress.[12] Thus, warm, nurturing families tend to promote resistance to stress and to diminish vulnerability to stress-induced illness.[13]

The critical question concerns the nature of these parental influences on the health of the offspring. What are the factors that mediate such enduring effects? We have argued that the relationship between early life events and health in adulthood is mediated by parental influences on the development of neural systems that underlie the expression of behavioral and endocrine responses to stress (see Ref. 14). There are two critical assumptions here: First, that prolonged activation of neural and hormonal responses to stress can promote illness and second that early environmental events influence the development of these responses. There is strong evidence in favor of both ideas.

RESPONSES TO STRESS

Stress is a risk factor for a variety of illnesses, ranging from autoimmune disorders to mental illness. The pathways by which stressful events can promote the development of such divergent forms of illness involve the same hormones that ensure survival during a period of stress.[15,16] These effects can, in part, be understood in terms of the responses elicited by stressors.[17,18] The increased adrenal release of catecholamines, adrenaline and noradrenaline, as well as the glucocorticoids, orchestrate a move to catabolism, increasing lipolysis and mobilizing glucose reserves and insulin antagonism (see TABLE 1). These actions serve to increase the availability and distribution of energy substrates. At the same time the increase in circulating levels of catecholamines and glucocorticoids is associated with increased cardiovascular tone. Prolonged activation of these pathways provides an obvious risk for decreased sensitivity to insulin and a risk of steroid-induced diabetes, hypertension, hyperlipidemia, hypercholesterolemia, abdominal fat deposition, and arterial

TABLE 1. Summary of major metabolic/cardiovascular effects of stress-induced increases in catecholamines and glucocorticoids[a]

Target	Effect	Function
Liver	Increased gluconeogenesis	Defend blood sugar level
	Decreased HDL synthesis	Increased plasma cholesterol
Selected macromolecular storage sites	Glygogenolysis, lipolysis substrates (glucose, fat metabolites)	Increased available energy
Heart circulatory system	Enhanced AC drive over heart rate, blood pressure	Increased blood flow
GH target tissue	Decreased sensitivity to GH; increase IGF binding protein	Dampened anabolic processes

ABBREVIATIONS: HDL, high density lipoprotein; CA, catecholamine; GH, growth hormone; IGF, insulin-like growth factor.

[a]See references 15–19.

wear and tear (see Ref. 19), all of which are associated with an increased risk for heart disease (see Ref. 20).

There are also cognitive responses to stressors that include systems which mediate attentional processes as well as learning and memory.[21] During stress individuals become hypervigilant; the level of attention directed to the surrounding environment is increased at the expense of our ability to concentrate on a focused set of tasks that are not essential for survival. As a function of these changes in attentional processes, as well as the effects of glucocoticoids on brain structures such as the hippocampus, episodic memory is less functional during periods of stress (see Refs. 22–24). At the same time, glucocorticoids act on areas of the brain such as the amygdala to enhance learning and memory for emotional stimuli (see Refs. 25–27). These changes in psychological arousal are also associated with altered emotional states: Feelings of apprehension and fear predominate during a stressful experience. While these responses are highly adaptive, chronic activation of these systems can promote the emergence of specific forms of congitive impairments, states of anxiety and dysphoria, sleep disorders, and so forth.[28]

Herein lies the dilemma: The same stress hormones that permit survival during stress can ultimately lead to disease. In human and nonhuman populations, individuals that show exaggerated hypothalamic–pituitary–adrenal (HPA) responses to stress are at increased risk for a variety of disorders including heart disease and diabetes, as well as anxiety, depression, and drug addiction.

Corticotropin-Releasing Hormone

In large measure these reactions are governed by central corticotropin-releasing hormone (CRH) systems that coordinate behavioral, emotional, autonomic, and endocrine responses to stressors. There are two major CRH pathways regulating the expression of stress responses. First a CRH pathway from the parvocellular regions of the paraventricular nucleus of the hypothalamus (PVNh) to the hypophysial–portal system of the anterior pituitary, a system that serves as a principal network for the transduction of a neural signal into a pituitary–adrenal response.[29] In responses to stressors, CRH, as well as cosecretagogues such as arginine vasopressin, is released from PVNh neurons into the portal blood supply of the anterior pituitary where it provokes the synthesis and release of adrenocorticotropic hormone (ACTH). Pituitary ACTH, in turn, causes the release of glucocorticoids from the adrenal gland.

CRF neurons in the central nucleus of the amygdala (CnAmy) project to the locus ceruleus (LC) and increase the firing rate of LC neurons, resulting in increased noradrenaline release in the vast terminal fields of this ascending noradrenergic system (see Refs. 30–32). One of the principal noradrenergic targets here is actually the CRF neurons of the PVNh. Noradrenaline is the major known source of driveover CRF release from PVNh neurons during stress.[29,33] The amygdaloid CRF projection to the locus ceruleus[34-36] is also critical for the expression of behavioral responses to stress: Microinjections of the CRF receptor antagonist, α-helical CRF, into the LC attenuate fear-related behaviors.[37–39] Hence, the CRF neurons in the PVNh and the central nucleus of the amygdala serve as important mediators of both behavioral and endocrine responses to stress. Not surprisingly, increased CRF levels have been associated with serious mood disorders.[28]

These findings have provided a basis for understanding how stress can influence health. Yet the influence of stress can only really be fully appreciated when we factor into the equation some appreciation of the individual's response to stress. The hypothesis, which guides a major research effort on the development of psychopathology, focuses on the role of early life events in determining individual differences in vulnerability to stress. This hypothesis rests on the assumption that chronic activation of central and endocrine stress responses can promote illness (see references cited above). Thus, early life events that increase stress reactivity result in a greater vulnerability for stress-induced illness over the lifespan.

Environmental Regulation of HPA and Behavioral Responses to Stress

One of the strongest models for environmental regulation of the development of responses to stress is the postnatal handling research with rodents. Handling involves a brief (i.e., 3–15 min) daily period of separation of the pup from the mother. In the rat and mouse, postnatal handling decreases the magnitude of behavioral and endocrine responses to stress in adulthood.[40–50] In contrast, longer periods (i.e., 3–6 hours) of daily separation from the mother increase behavioral and endocrine responses to stress.[51–53] These effects persist through the life of the animal (e.g., Ref. 54) and are associated with health outcomes.[55,56]

The central CRF systems are critical targets for these effects (see TABLE 2). Predictably, handling decreases and maternal separation increases CRF gene expression in the PVNh and the CnAmy. Moreover, there are also potent effects on systems that

TABLE 2. Summary of the effects of postnatal handling or maternal separation on neural mediators of behavioral and HPA responses to stress in the rat[a]

Target	Postnatal handling	Maternal separation
CRF mRNA (PVNh)	decreased	increased
CRF mRNA (CnAmy)	decreased	increased
CRFir (locus ceruleus)	decreased	increased
CRF rec binding (locus ceruleus, raphé)	decreased	increased
GR mRNA (hippocampus)	increased	decreased
GR mRNA (PVNh)	no effect	decreased
GC feedback inhibition of CRF	increased	decreased
GABAA receptor	increased	decreased
CBZ receptor/g2 mRNA (amygdala, locus ceruleus, nucleus tractus solitarius)	increased	decreased

ABBREVIATIONS: CRF, corticotropin-releasing factor; PVNh, paraventricular nucleus of the hypothalamus; CnAmy, central nucleus of the amygdala; GR, glucocorticoid; CBZ, central benzodiazepine. (The g2 subunit of the GABAA receptor complex is thought to encode for the CBZ receptor site.)

[a]See references 40–55.

are known to regulate CRF gene expression in the PVNh and the CnAmy (see above). These include glucocorticoid receptor systems that serve to inhibit CRF synthesis and release in the PVNh neurons, as well as GABAergic/central benzodiazepine systems that regulate both amygdaloid CRF activity as well as effects at the level of the noradrenergic neurons of the LC and NTS.[57] Predictably, stress-induced activation of ascending noradrenergic systems in adult animals is enhanced by maternal separation and decreased by handling in early life.[53] Thus, environmental manipulations can alter the expression of behavioral and endocrine responses to stress by altering the development of central CRF systems.

In addition, maternal separation in early life alters the development of ascending serotonergic systems in both monkey (see especially the studies of Higley and colleagues[58] and rat.[52] Kraemer *et al.*[59] have shown that repeated periods of maternal separation in early life increase CSF measures of central noradrenaline and serotonin (5-HT) responses to stress in the rhesus monkey. Considering the importance of the ascending NA and 5-HT systems in depression, these findings suggest a mechanism whereby early life events might predispose an individual to depression in later life.

The decreased mother–infant contact resulting from long periods of maternal separation seems likely to be a critical variable in understanding how this procedure increases behavioral and HPA responses to stress. But does this imply that under normal conditions maternal care actively contributes to the development of neural systems that mediate stress responses, or simply that the absence of the mother is so disruptive to pup physiology that it affects the development of these systems? If maternal care is relevant, then what are the relevant features of mother–pup interactions, and how do they influence neural development?

What Are the Critical Features of These Environmental Manipulations?

Handling, although a brief interlude in the routine of mother–pup interactions, does alter the behavior of the mother towards the offspring.[60,61] Overall, mothers of handled (H) pups spend the same amount of time with their litters as mothers of non-handled (NH) pups; however, mothers of H litters spend significantly more time licking/grooming their pups.[61,62] The question, then, is whether this altered pattern of maternal behavior serves as a critical stimulus for the environmental effects on the development of endocrine and behavioral responses to stress.

Interestingly, there are substantial, naturally occurring variations in maternal licking/grooming in rat dams. Maternal licking/grooming of pups occurs most frequently before or during periods in which the mother nurses her young in the arched-back position. As you might imagine, the frequency of the two behaviors are closely correlated ($r = +0.91$[62]) across mothers. Thus, it is feasible to characterize mothers as high or low on licking/grooming and arched-back nursing (LG-ABN). Such naturally occurring variations were first described by Myers and colleagues[63] using behavioral observations of mothers with their pups in the home cages. Moreover, these individual differences are stable across multiple litters.[64]

In one series of studies, mothers were divided into two groups, high or low in licking/grooming and arched-back nursing (LG-ABN), on the basis of behavioral observations performed over the first 10 days of life (6–8 hours of observation per day). It is important to note that there were no differences between these groups in

the overall amount of time in contact with pups.[62,64,65] The logic here is simple. If handling-induced differences in licking/grooming or arched-back nursing are relevant for effects on HPA development, then the offspring of high LG-ABN mothers should resemble the H animals. This is exactly what was found.[62] As adults, the offspring of high LG-ABN mothers showed reduced plasma ACTH and corticosterone responses to restraint stress. These animals also showed significantly increased hippocampal GC receptor mRNA expression, enhanced GC negative feedback sensitivity, and decreased hypothalamic CRH mRNA levels. Moreover, the magnitude of the corticosterone response to acute stress was significantly correlated with the frequency of both maternal licking/grooming ($r = 0.61$) and arched-back nursing ($r = -0.64$) during the first 10 days of life, as was the level of hippocampal GC receptor mRNA and hypothalamic CRH mRNA expression (in all cases $r > 0.70$; see Liu *et al.*[62]). In addition, we also found that the adult offspring of low LG-ABN mothers showed significantly increased noradrenergic responses to stress at the level of the PVNh.[66] These studies suggest that the critical feature for the handling effect on HPA development involves an increase in maternal licking/grooming.

The offspring of the high and low LG-ABN mothers also differed in behavioral responses to novelty.[65] As adults, the offspring of the low LG-ABN showed increased startle responses, decreased open-field exploration, and longer latencies to eat food provided in a novel environment. These animals also showed increased CRF receptor levels in the locus ceruleus and decreased CBZ receptor levels in the basolateral and central nucleus of the amygdala, as well as in the locus ceruleus[65] and increased CRF mRNA expression in the CnAmy (D.D. Francis, J. Diorio, and

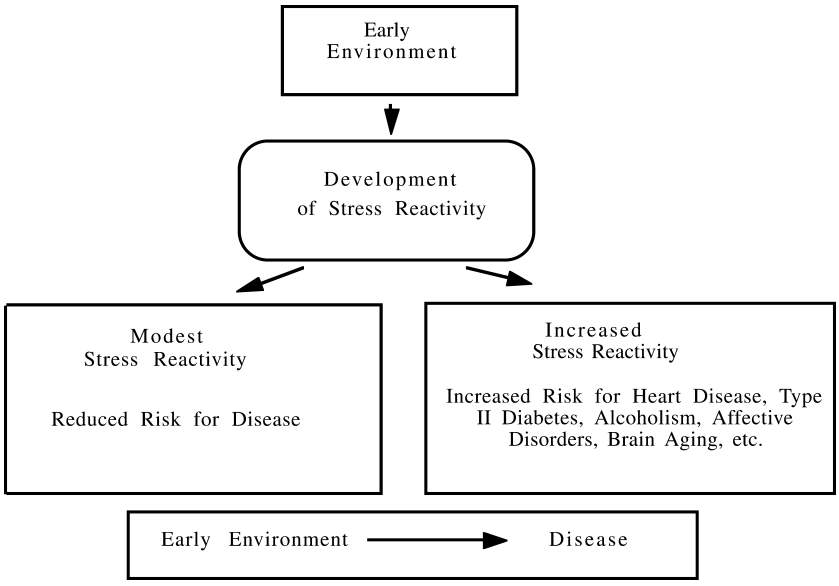

FIGURE 1

Meaney, unpublished). These differences map perfectly onto the differences in H and NH animals and provide support for the idea that the effects of handling are mediated by changes in maternal behavior.

It may surprise the reader that rather subtle variations in maternal behavior have such a profound impact on development. However, for a rat pup, the first weeks of life do not hold a great deal of stimulus diversity. Stability is the theme of the burrow, and the social environment in the first days of life is defined by the mother and littermates. The mother, then, serves as a primary link between the environment and the developing animal. It seems reasonable that variations in mother–pup interaction would serve to carry so much importance for development.

The Transmission of Individual Differences in Maternal Care to the Offspring

Interestingly, individual differences in maternal behavior show intergenerational transmission. The female offspring of high LG-ABN mothers showed significantly more mother licking/grooming and arched-back nursing than did the female offspring of low LG-ABN mothers.[67] The intergenerational transmission of parental behavior has also been reported in primates. In rhesus monkeys there is clear evidence for family lineages expressing child abuse.[68] There is also evidence for transmission of individual differences in parental styles falling within the normal range. Fairbanks[69] found that daughters who were reared by mothers who consistently spent a higher amount of time in physical contact with their offspring became mothers who were similarly more attentive to their offspring. In rhesus monkeys, Berman[70] found that the rate of rejecting the infant by mothers was correlated with the rejection rate of their mothers. In primates, such individual differences in maternal behavior may be revealed in juvenile, nulliparous females. Thus, among juvenile female vervet monkeys, time spent in proximity to nonrelated infants was associated with the maternal behavior of their mothers.[71] In all cases these findings were independent of the social rank of the mother. Equally impressive findings exist in humans, where Miller *et al.*[72] found that scores on parental bonding measures between a mother and her daughter were highly correlated with the same measures of bonding between the daughter and her child. These findings suggest a perhaps common process of intergenerational transmission of maternal behavior. The critical question here concerns the mechanism underlying this intergenerational transmission of individual differences in behavior.

We[67] have provided evidence for a nongenomic transmission of individual differences in maternal behavior. In one study, we performed reciprocal cross-fostering of the offspring of low and high LG-ABN mothers. The primary concern here was that the wholesale fostering of litters between mothers is known to affect maternal behavior.[73] In order to avert this problem and maintain the original character of the host litter, no more than 2 of 12 pups were fostered into or from any one litter.[74] The critical groups of interest are the biological offspring of low LG-ABN mothers fostered onto high LG-ABN dams, and *vice versa.* The control groups included (1) the offspring of low LG-ABN onto other low LG-ABN mothers as well as offspring of high LG-ABN dams fostered onto other high LG-ABN mothers; (2) sham-adoption animals that were simply removed from the nest and fostered back to their biological mothers; and (3) unmanipulated pups. The limited cross-fostering design did not result in any effect on group differences in maternal behavior. Hence, the frequency of

pup licking/grooming and arched-back nursing across all groups of high LG-ABN mothers was significantly higher than that for any of the low LG-ABN dams regardless of litter composition.

The results of the behavioral studies are consistent with the idea that the variations in maternal care are causally related to individual differences in the behavior of the offspring. The biological offspring of low LG-ABN dams reared by high LG-ABN mothers were significantly less fearful under conditions of novelty than were any of the offspring reared by low LG-ABN mothers, including the biological offspring of high LG-ABN mothers. A separate group of female offspring was then mated, allowed to give birth, and observed for differences in maternal behavior. The effect on maternal behavior followed the same pattern as that for differences in fearfulness. As adults, the female offspring of low LG-ABN dams reared by high LG-ABN mothers did not differ from normal, high LG/ABN offspring in the frequency of pup licking/grooming or arched-back nursing. The frequency of licking/grooming and arched-back nursing in animals reared by high LG-ABN mothers was significantly higher than in any of the low LG-ABN groups, and again this included female pups originally born to high LG-ABN mothers but reared by low LG-ABN dams. Individual differences in fearfulness or maternal behavior mapped onto those of the rearing mother, rather than the biological mother.

A second series of studies was designed to examine the intergenerational effects of an "early intervention" program. Handling increases maternal licking/grooming and arched-back nursing. Handling pups, in fact, turns low LG-ABN dams into high LG-ABN mothers.[67] As adults, the handled offspring of such mothers resemble the offspring of high LG-ABN mothers, a finding that is consistent with the nongenomic transmission hypothesis. We then studied the F_3 generation, focusing on the handled and nonhandled offspring of low LG-ABN mothers. These animals were completely unmanipulated. Bear in mind, we refer to these mothers as low LG-ABN because they are derived from low LG-ABN mothers themselves. The low LG-ABN mothers with handled pups behave in a manner that is indistinguishable from high LG-ABN dams. Importantly, their female offspring (F_2 animals) also behave as high LG-ABN.

As shown in TABLE 2, the F_3 offspring of handled/low LG-ABN mothers resemble the offspring of high LG-ABN dams on measures of hypothalamic CRF and hippocampal glucocorticoid receptor mRNA expression, as well as CBZ receptor binding (see also Ref. 67). These findings suggest that individual differences in gene expression in brain regions that result in behavioral and endocrine responses to stress can also be transmitted across generations via a nongenomic mechanism.

These findings are consistent with the results of studies using the cross-fostering technique as a test for maternal-mediation hypotheses. For example, the spontaneously hypertensive rat (SHR) is a strain bred for hypertension, which appears in adolescence. Although the selective breeding suggests a genetic background, the expression of the hypertensive trait is also influenced by epigenetic factors (see Ref. 75). SHR pups reared by wild-type, WKY mothers do exhibit hypertension to the extent of kin reared by SHR dams. When borderline hypertensive rats (BHR), a hybrid formed by SHR-WKY matings, are reared by WKY mothers, they do not express the spontaneous hypertensive phenotype.

The Potential Effects of Maternal Behavior on the Development of Behavior and Endocrine Responses to Stress in BALBc Mice

The BALBc is normally a strain that is very fearful and shows elevated HPA responses to stress. However, BALBc mice cross-fostered to C57 mothers are significantly less fearful, with lower HPA responses to stress.[76] Importantly, C57 mothers normally lick and groom their pups about twice as frequently as BALBc mothers.[77] Comparable findings have emerged with rat strains. Typically, Fisher 344 rats are more responsive to novelty and have increased HPA responses to acute stress in comparison to Long-Evans rats. Moore and Lux[78] reported that Long-Evans darns lick/groom their offspring significantly more often than do Fisher 344 mothers.

Under normal circumstances, of course, BALBc mice are reared by BALBc mothers. The genetic and environmental factors conspire to produce an excessively fearful animal. This is usually the reality of nature and nurture. Genetic and environmental factors work in concert, and are often correlated (see Ref. 79). Because parents provide both genes and environment for their biological offspring, the offspring's environment is therefore, in part, correlated with their genes. The offspring's genes are correlated with those of the parents, and the parents' genes influence the environment they provide for the offspring. The reason why many epidemiological studies based on linear regression models often find that the epigenetic factors, such as parental care, do not add predictive value above that of genetic inheritance is because of this correlation. The environment the parent provides commonly serves to enhance the genetic differences—they are redundant mechanisms. The knowledge of an animal's BALBc pedigree is sufficient to predict a high level of timidity in adulthood. Additional information on maternal care would statistically add little to the predictability—the two factors work in the same direction. But this is clearly different from concluding that the maternal care is not relevant, and the results of the cross-fostering studies attest to the importance of such epigenetic influences.

The value of this process is that it can provide for variation. If the genetically determined trajectory is not adaptive for the animal, then development that can move in the direction of the current environmental signal would be of adaptive value. Hence, environmental events can alter the path of the genetically established trajectory in favor of more adaptive outcomes. This, of course, is the adaptive value of plasticity.

In our minds, these are adaptive processes. Children inherit not only genes from their parents, but also an environment[80]: Englishmen inherit England, as Francis Galton remarked. We believe that the transmission of individual differences in stress reactivity from mother to offspring can provide an adaptive level of "preparedness" for the offspring. Under conditions of increased environmental demand, it is commonly in the animal's interest to enhance behavioral (e.g., vigilance, fearfulness) and endocrine (HPA and metabolic/cardiovascular) responsivity to stress. These responses promote detection of potential threats, avoidance learning, and the mobilization of energy reserves, which are essential under the increased demands of the stressor. Because the offspring usually inhabit a niche that is similar to their parents, the transmission of these traits from parent to offspring could serve to be adaptive. In this context it is understandable that parents inhabiting a very demanding environmental niche might "transmit" a high level of stress reactivity to their offspring.

MATERNAL RESPONSIVITY IN HIGH AND LOW LG-ABN MOTHERS

One question certainly concerns the neural basis for these individual differences in maternal behavior as well as the mechanisms that underlie this apparent transmission of parental behavior from one generation to the next. We believe that these questions can, to some degree, be addressed in nonhuman populations, and the focus of our work lies in the findings of Allison Fleming,[81] showing a direct relationship between fearfulness and maternal behavior.

In the rat, maternal behavior emerges as a resolution of an interesting conflict.[82] Females rats, unless they are in late pregnancy or lactating, exhibit a fearful, neophobic reaction to pups. Habituation through continuous exposure to pups renders females more likely to exhibit maternal behavior. In the classic behavioral test for "maternal responsivity," virgin females are exposed continuously to pups of 3–6 days of age (see Refs. 83,84). After a number of days most females begin to show active care of the pups, including crouching over the pups in a nursing posture and licking/grooming. Thus, habituation through continuous exposure to pups renders females less neophobic and more likely to exhibit maternal behavior. In general, procedures that reduce fearfulness, including amygdaloid lesions, enhance maternal responsivity, reducing the amount of time for females to exhibit maternal behavior.[85] Such findings may apply to the human condition. Fleming[86] reported that many factors contribute to the quality of the mother's attitude towards her newborn, but none are correlated more highly than the women's level of anxiety. More anxious, depressed mothers are, not surprisingly, less positive towards their babies (also see Ref. 87). Behaviorally, more fearful mothers, such as the low LG-ABN dams, appear to be less maternally responsive towards their offspring.

Considering the differences in fearfulness in the female offspring of high and low LG-ABN, we expected to see differences in the maternal responsivity test in these animals. This was exactly what occurred (Champagne and Meaney, unpublished). The virgin female offspring of high LG-ABN mothers exhibited the full pattern of maternal behavior in about one-half the exposure time of the offspring of low LG-ABN (4.4 vs. 8.9 days exposure). These findings suggest that naturally occurring variations in maternal care are reflected in differences in the maternal responsivity test. Moreover, variations in maternal responsivity in the female offspring of high and low LG-ABN mothers are apparent even in nulipars.

If naturally occurring variations in maternal care are associated with differences in maternal responsivity, then we should be able to screen a population of nulliparous females with the pup sensitization paradigm and use data on individual differences in the latency to express maternal behavior to predict variations in actual maternal care. This admittedly obvious hypothesis has, to the best of our knowledge, never actually been tested. This seems surprising, considering the degree to which our knowledge of the neural basis of maternal behavior rests on the use of the pup-sensitization paradigm. We found that the frequency of licking/grooming over the first 10 days post-partum in primaparous females was highly correlated to the latency in which females exhibited maternal behavior in the maternal responsivity test (Champagne and Meaney, unpublished).

NEURAL BASIS FOR INDIVIDUAL DIFFERENCES IN MATERNAL BEHAVIOR

The onset of maternal care in the rat is mediated by hormonal events before and during parturition,[82,83] including critical variations in circulating levels of progesterone and estrogen. Estrogen acts at the level of the medial preoptic area (MPOA) to enhance maternal behavior.[82] The MPOA is also a site of action for the effects of placental lactogens, including prolactin, on maternal behavior.[83]

The influence of ovarian hormones on maternal behavior in the rat is mediated, in part, by effects on central oxytocinergic systems (see Ref. 88). Estrogen induces oxytocin receptor gene expression.[89] Administration (i.c.v.) of oxytocin rapidly stimulates maternal behavior in virgin rats.[90,91] The effect of oxytocin is abolished by ovariectomy and reinstated with estrogen treatment. Moreover, treatment with oxytocin antiserum or receptor antagonists blocks the effects of ovarian steroid treatments on maternal behavior.[92,93]

Oxytocin receptor levels are enriched in sites such the MPOA, the ventral tegmental area (VTA) and the CnAmy and increase following parturition in each of these regions.[85,93] Oxytocin infusion into the MPOA or the VTA increases the expression of maternal behavior (e.g., Refs. 88,90–92). Oxytocinergic neurons that project to the VTA have been located in the ventral bed nucleus of the stria terminalis–lateral preoptic area as well as the PVNh,[88] and lesions of these areas inhibit maternal behavior.[94,95] The VTA is, of course, the source for the mesocorticolimbic dopamine system, and dopamine receptor blockers suppress the expression of pup licking/grooming.[97]

Functionally, the onset of maternal behavior emerges from the decreased fearful response of the female to pups and an increase in the attraction of the mother for her pups (see Refs. 82, 86, and 97 for reviews). The positive cues associated with pups emerge from tactile, gustatory, and auditory stimuli (see Ref. 97). Thus, pup stimuli can either be aversive, eliciting withdrawal, or positive, eliciting approach. The onset of maternal behavior clearly depends on decreasing the negative-withdrawal tendency, and increasing the positive-approach responses.

For virgin females, pups elicit withdrawal and avoidance associated with odor cues transduced via both the vomeronasal and accessory olfactory bulb projections to the MPOA. The vomeronasal projections arise via the amygdala. Thus, anosmic females are more readily maternal,[98] and lesions of the amygdala enhance maternal responsiveness in virgin females[99] (see also Ref. 95). These findings suggest that the cues that elicit withdrawal are transmitted through the amygdala. Morgan *et al.*[100] found that amygdaloid kindling, which enhances fearfulness in the rat, increases neophobia and decreases approaches to pup-related stimuli in virgin females. Additionally, oxytocin projections to the olfactory bulb may mediate a decrease in odor-induced fear responses to pups (see Ref. 101). Interestingly, Neumann *et al.*[102] reported that oxytocin infused directly into the CnAmy produced an anxiolytic effect in female rats. These findings suggest that oxytocin might promote the expression of maternal behavior, in part by inhibiting fear-related neural activity.

What is particularly interesting to consider is the possibility that neural systems involved in the expression of fearfulness, notably the CRF systems, can directly influence maternal behavior. Pederson *et al.*[104] reported that central CRF infusions

disrupt maternal behavior in the rat. Such CRF effects could then explain, in part at least, differences in the maternal behavior of high and low LG-ABN mothers. In addition, there may also be effects of maternal care on neural systems mediating attraction to pup-related stimuli. We found significantly reduced oxytocin receptor levels in the CnAmy of low LG-ABN mothers, as well as increased CRF receptors in this same region. Such findings are apparent even in virgin animals and underscore the relationship between neural systems mediating fear and those involved in maternal behavior. In addition to these differences in the amygdala, we also found differences in oxytocin receptors in the MPOA that were evident only during lactation.

Individual differences in maternal care could therefore be derived from early environmental effects on the development of neural systems mediating fearfulness as well as those involved in mediating the attraction of females towards pups. The net effects are differences in maternal responsivity between high and low LG-ABN mothers. These effects, in turn, provide the basis for stable individual differences in stress reactivity and maternal behavior in the offspring. This hypothesis could account, at least in part, for the stable transmission of individual differences in maternal behavior in the rat.

ENVIRONMENTAL REGULATION OF MATERNAL BEHAVIOR

A critical issue here is the relationship between the environment of the mother and the nature of her behavior toward her offspring. We propose that such individual differences are, in turn, functionally related to the level of environmental demand that confronts the animal. Under natural conditions, and the sanctity of the burrow, rat pups have little direct experience with the environment. Instead, conditions such as the scarcity of food, social instability, and low dominance status directly affect the status of the mother and, thus, maternal care. The effects of these environmental challenges on the development of the pups are then mediated by alterations in maternal care, which serve to transduce an environmental signal to the pups (see FIG. 2). The environmentally driven alterations in maternal care then influence the development of neural systems that mediate behavioral and HPA responses to stress. These effects can thus serve to increase or decrease stress reactivity in the offspring. We suggest that more fearful, anxious animals, such as the low LG-ABN mothers, are therefore more neophobic and lower in maternal responsivity to pups than are less fearful animals. Hence, these effects then serve as the basis for comparable patterns of maternal behavior in the offspring and for the transmission of these traits to the subsequent generation (see FIG. 2).

A critical assumption here is that variations in parental behavior are related to the level of environmental demand. Human research suggests that the social, emotional, and socioeconomic context are overriding determinants of the quality of the relationship between parent and child.[80] Human parental care is disturbed under conditions of chronic stress. Conditions that most commonly characterize abusive and neglectful homes involve economic hardship, marital strife, and a lack of social and emotional support (see Ref. 80). Such homes, in turn, breed neglectful parents such that individual differences in parental behavior are reliably transmitted across generations. Although this analysis may seem to be a parental indictment, it is important to

note that these same environments are also associated with considerable anxiety and depression. It is important to note that under a high level of environmental demand, increased fearfulness and hypervigilance might well be considered as adaptive. Of course, increased stress reactivity is also associated with enhanced vulnerability to stress-induced illness. Because individual differences in parental care can influence the development of stress reactivity and thus vulnerability for chronic illness in later life, vulnerability for chronic illness is also transmitted across generations. The assumption here is that variations in parental behavior reflect environmental demand.

Perhaps the most compelling evidence for this process emerges from the studies of Rosenblum and colleagues (see Ref. 104 for a review). Bonnet macaque mother–infant dyads were maintained under one of three foraging conditions: low foraging demand (LFD), where food was readily available; high foraging demand (HFD),

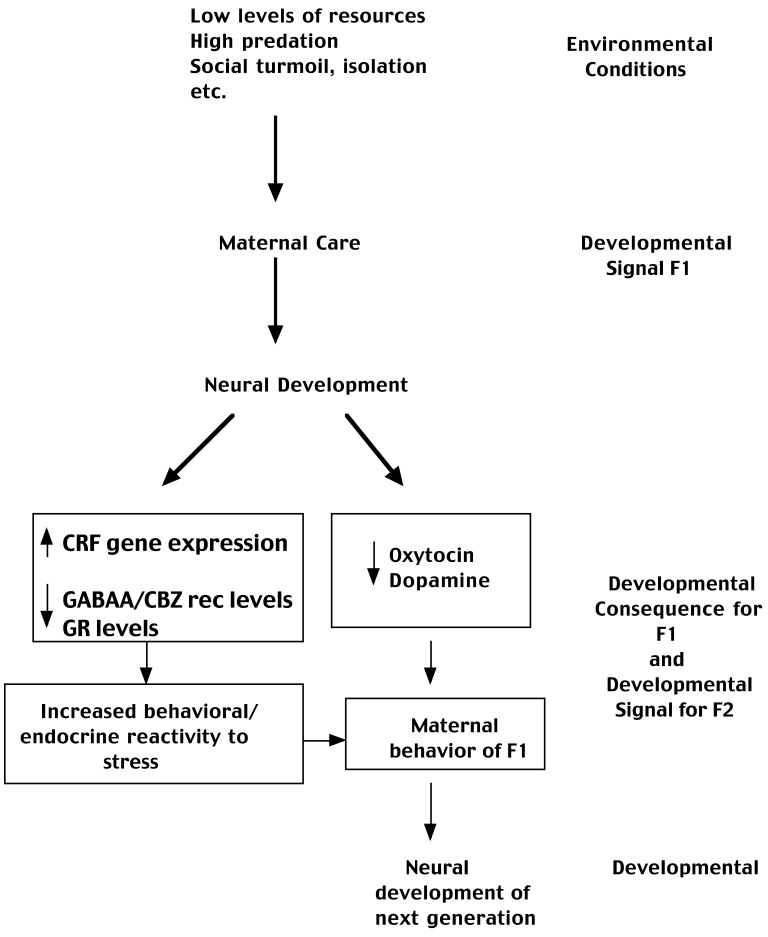

FIGURE 2

where ample food was available but required long periods of searching; and variable foraging demand (VFD), a mixture of the two conditions on a schedule that did not allow for predictability. At the time that these conditions were imposed, there were no differences in the nature of mother–infant interactions. However, after a number of months of these conditions, there were highly significant differences in mother–infant interactions. The VFD condition was clearly the most disruptive. Mother–infant conflict increased in the VFD condition. Infants of mothers housed under these conditions were significantly more timid and fearful. These infants showed signs of depression commonly observed in maternally separated macaque infants—remarkably, even while the infants were in contact with their mothers. As adolescents, the infants reared in the VFD conditions were more fearful and submissive and showed less social play behavior.

More recent studies have demonstrated the effects of these conditions on the development of neurobiological systems that mediate the organisms' behavioral and endocrine/metabolic responses to stress. Coplan *et al.*[105,106] showed that, as adults, monkeys reared under VFD conditions showed increased CSF levels of CRF. Increased central CRF drive would suggest altered noradrenergic and serotonergic responses to stress, and this is exactly what was seen in adolescent VFD-reared animals.[106] Predictably, these animals show increased fearfulness. We would predict that if the environmental conditions remained stable these differences would, in turn, be transmitted to the offspring (see FIG. 2).

These studies underscore two critically important points. First, variations in maternal care falling within the normal range of the species can have a profound influence on development. One does not need to appeal to the more extreme conditions of abuse and neglect to see evidence for the importance of parental care. Second, environmental demands can alter parental care, and thus infant development. Indeed, we hypothesize that environmentally induced alterations in maternal care mediate the effect of variations in the early postnatal environment on the development of specific neural systems that mediate the development of fearfulness. Such individual differences in fearfulness, in turn, influence the parental care of the offspring, providing a neurobiological basis for the intergenerational transmission of specific behavioral traits.

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