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Review

The programming of individual differences in defensive responses and reproductive strategies in the rat through variations in maternal care

Nicole M. Cameron, Frances A. Champagne, Carine Parent, Eric W. Fish, Kumi Ozaki-Kuroda, Michael J. Meaney*

McGill Program for the Study of Behavior, Genes and Environment, Departments of Psychiatry and Neurology & Neurosurgery, Douglas Hospital Research Centre, McGill University, 6875 Boulevard LaSalle, Montréal, Que., Canada H4H 1R3

Abstract

There are profound maternal effects on individual differences in defensive responses and reproductive strategies in species ranging literally from plants to insects to birds. Maternal effects commonly reflect the quality of the environment and are most likely mediated by the quality of the maternal provision (egg, propagule, etc.), which in turn determines growth rates and adult phenotype. In this paper, we review data from the rat that suggest comparable forms of maternal effects on both defensive responses to threat and reproductive behavior and which are mediated by variations in maternal behavior.

Ultimately, we will need to contend with the reality that neural development, function and health are defined by social and economic influences.

Keywords: Maternal behavior; Gene expression; Reproduction; Defensive behaviors; Stress; Environmental programming; Epigenetics

Contents

The quality of mental health over the lifespan varies as a function of socioeconomic status (SES). Individuals from lower SES are at greater risk for childhood behavioral disorders, depression, neurotic disorders, and drug abuse (Lewis et al., 1998; Miech et al., 1998; Turner and Lloyd, 1999; Breeze et al., 2001; Rios et al., 2001; Muntaner et al., 2003; Muramatsu, 2003; Schneiders et al., 2003;

* Corresponding author. Tel.: +1 514 761 6131x3938; fax: +1 514 762 3034.
E-mail address: michael.meaney@mcgill.ca (M.J. Meaney).

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Goodman et al., 2003; Costello et al., 2003; Stansfeld et al., 2003). Social selection has been advanced as one explanation and suggests that poor mental function determines SES rather than the other way around. This argument may have merit for schizophrenia, but is untenable for depression, anxiety and even substance abuse (Stansfeld et al., 2003) and can hardly account for the relation between adult health and SES in childhood (see below). Moreover, the influence of SES on mental health, as previously reported for heart disease and overall mortality, cuts across SES gradients such that individuals in the middle range fare more poorly that individuals than those in the upper-middle classes. Adler et al., 1993; Fuhrer et al., 2002; Power and Hertzman, 1997). Even relatively small variations in SES have significant impact on health and all-cause morbidity and these effects are apparent across the entire range of social classes. While factors as complex as SES are not easily disentangled, recent studies on the effects of SES reveal that (1) not surprisingly, low SES is associated with an increased exposure to chronic stressors (Turner and Lloyd, 1999; Power and Hertzman, 1997; Grzywacz et al., 2004; Turner and Avison, 2003) and to increased activity of biological systems associated with stressors (i.e. adrenal glucocorticoids and sympathetic catecholamines (Power and Hertzman, 1997; Seeman et al., 2004; Lupien et al., 2000), (2) low SES in early childhood has a sustained and independent effect on the risk for mental health and for certain outcomes may be an even better predictor than SES in adulthood, and (3) the effects of low SES on emotional and cognitive development are, in part at least, mediated by variations in parental care (Eisenberg and Earls, 1975; Conger et al., 1994; McLloyd, 1998). Taken together, these findings form the basis for an understanding of how social and economic forces may become 'biological embedded' in early life and thus define a developmental origin for adult disease.

The influence of adult SES on mental health is probably not surprising considering the established link between stress and disorders such as depression or drug abuse, but it is important to understand that such effects are not limited to the extreme lower echelons. There are graded effects of SES on depression, anxiety and substance abuse that cut linearly across multiple SES categories and are similar to earlier findings with cardiovascular and metabolic outcomes (Stansfeld et al., 2003; Kessler et al., 1997). These findings defy any simple model of deprivation (Poulton et al., 2002). Such graded SES effects emerge even controlling for health status at birth and are apparent in countries with universal health-care where access to medical services is less affected by SES. Indeed, effects of SES in adulthood on health are more closely associated with education than with income, and related to factors such as control and self-esteem (Stansfeld et al., 2003; Chang et al., 2002; Stansfeld et al., 1998; Bosma et al., 1998; Stansfeld et al., 1999).

The early studies of SES and mental health made no distinction between SES during early development and that of adulthood. More recent studies, including those using prospective analyses, reveal very significant effects of SES during childhood that are statistically independent of those associated with adult SES. These studies show significant effects of childhood SES on adult mortality (Kaplan and Salonen, 1990; Davey Smith et al., 1998; Marmot et al., 2001), metabolic (e.g. body mass index, hip:waist ratio) and cardiovascular (Poulton et al., 2002; Kaplan and Salonen, 1990; Blane et al., 1996; Brunner et al., 1996; Barker, 1992; Rahkonen et al., 1997; Bosma et al., 1999). Effects on psychological function and mental health are somewhat more complex, but no less impressive. Childhood SES affects alcohol dependence in adulthood and the effects are not reversed with subsequent upward mobility (Poulton et al., 2002). An extensive, prospective study by Gilman et al. (2003) found a clear effect of childhood SES on depression (Kessler et al., 1997; Sadowki et al., 1999; Ritsher et al., 2001). In other studies the effect is less obvious, but even in those studies (Seckl and Meaney, 1993) there is a very pronounced effect of childhood SES on hostility and hopelessness. Likewise, Bosma et al. (1999) found effects of childhood SES, that are independent of adult SES, on locus of control, neuroticism and coping style. These states predict an increased risk for depression and it may be that the effect of childhood SES is more apparent on measures of vulnerability for depression, while the actual emergence of depression is associated with both developmental determinants and contemporaneous burden as suggested in stress diathesis models (Seckl and Meaney, 1993; Meaney, 2001; Plotsky et al., 1998; Francis and Meaney, 1999; Luecken and Lemery, 2004). In summary, these findings reveal a strong association between childhood SES and health in adulthood, including mental health. The critical question is why and how such pervasive effects of socioeconomic conditions in early development might occur. In this paper, we argue that (1) the effects of variations in social relations and access to economic resources in early development (i.e. childhood SES) on health are mediated through environmentally-determined variations in parental care, (2) these parental effects are, in turn, mediated by alterations in gene expression in brain regions that regulate defensive responses to threat and reproductive behavior; these effects on gene expression thus represent, in part, the process by which variations in SES are 'biologically embedded', (3) the effects on reproductive behavior contribute to the transmission of vulnerability across generations (Johnson et al., 2001), while (4) the effects of defensive responses represent a vulnerability for mental illness over the lifespan. Finally, we suggest that the major features of the process by which SES in childhood influences vulnerability for illness in adulthood are apparent in far simpler species, suggesting a common adaptation strategy to conditions of adversity in early life that has been conserved across evolution.

Research in health sciences underscores the importance of family function and early life events as predictors of

health in adulthood (Repetti et al., 2002). Such studies show that the quality of family life influences the development of individual differences in vulnerability to illness throughout life. As adults, victims of childhood physical or sexual abuse are at considerably greater risk for mental illness, as well as for obesity, gastrointestinal illness, diabetes and heart disease (Bifulco et al., 1991; Brown and Anderson, 1991; McCauley et al., 1997; Felitti et al., 1998; Heim et al., 2002a; Newport et al., 2002; Leserman et al., 1996). Children need not be beaten, to be compromised. Persistent emotional neglect, family conflict and conditions of harsh, inconsistent discipline all serve to compromise growth (Montgomery et al., 1997), intellectual development (Ammerman et al., 1986; Trickett and McBride-Chang, 1995) and to increase the risk for adult obesity (Lissau and Sorensen, 1994), depression and anxiety disorders (Johnson et al., 2001; Holmes and Robins, 1987, 1988; Gottman, 1998; Canetti et al., 1997) to a level comparable to that for abuse. More subtle relationships exist. Cold, distant parent–child relationships are associated with a significantly increased the risk of chronic illness in later life (Canetti et al., 1997; Parker, 1981; Russak and Schwartz, 1997).

Family dysfunction and forms of parental care that endanger the health of the offspring are more prevalent under conditions of socioeconomic hardship (Repetti et al., 2002; Eggebeen and Lichter, 1991). Such findings are not surprising. Poverty imposes considerable stress on the family unit and stressors seriously compromise the quality of parental care (Repetti et al., 2002; Hart and Risley, 2005). In humans, high levels of maternal stress during the transition to parenthood are associated with depressed/anxious mood states and less sensitive parent–child interactions that, in turn, influence the quality of parent–child attachment (Dix, 1991; Fleming, 1998; Goldstein et al., 1996). Unstable/stressful environments, such as those prevailing under conditions of poverty, are associated with greater variability in the quality of infant–mother attachments (Vaughn et al., 1979). Parents rearing children under conditions of poverty, more frequently experience negative emotions such as irritability, depressed, and anxious moods, which can then lead to more punitive forms parenting (Conger et al., 1984; Grolnick et al., 2002; Belsky, 1997a). Reduced education of parents, low income, multiple children, the absence of social support, and single parenthood predict forms of parenting (verbal threats, pushing or grabbing the child, emotional neglect, overt physical abuse, and more controlling attitudes toward child) that compromise cognitive development and result in more anxious and behaviorally inhibited children (see Repetti et al., 2002 for a review).

The evidence for parental mediation is critical. Importantly, the effects of poverty on emotional and cognitive development are, in part, mediated by variations in parent–offspring interactions. Indeed, if parental care factors are statistically controlled, there no longer remains any discernible effect of poverty of child development (Conger et al., 1994; McLloyd, 1998). Moreover, parents and parenting style are highly effective targets for intervention studies aimed at child development outcomes (Olds et al., 1998; Van den Boom, 1994; Fisher et al., 2000). Such considerations also explain why the effects of interventions targeting parent–child interactions are more pronounced in disrupted families (Belsky, 1997a).

'Stress diathesis' models have emerged as explanations for the relation between the quality of early life and health in adulthood. These models suggest that adversity in early life alters the development of neural and endocrine systems in a manner that predisposes individuals to disease in adulthood. The relation between the quality of the early environment and health in adulthood appears to be mediated by parental influences on the development of neural systems that underlie the expression of behavioral and endocrine responses to stress (Seckl and Meaney, 1993; Meaney, 2001; Plotsky et al., 1998; Francis and Meaney, 1999; Luecken and Lemery, 2004; Newport et al., 2002; Heim et al., 2000). Adversity or decreased quality of parental investment increases the magnitude of emotional, autonomic and HPA responses to stress in adulthood. 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. In humans, physical and/or sexual abuse in early life, for example, increases endocrine and autonomic responses to stress in adulthood (Luecken and Lemery, 2004; Heim et al., 2000; De Bellis et al., 1994). Children from high-conflict homes show increased cardiovascular reactivity (El-Sheikh and Harger, 2001) and elevated basal cortisol (Flinn and England, 1995). Among adults, early parental loss is associated with increased cardiovascular and HPA responses to stress, an effect that is mediated by the quality of the relation with the surviving parent (Leucken, 1998, 2000). Even more subtle measures, such as variations in parent–offspring bonding predict individual differences in HPA and central catecholamine responses to stress in humans (Pruessner et al., 2004a). There is considerable evidence for the sustained effects of disruptions to mother–infant relations on HPA responses to stress in primates (Bennett et al., 2002; Higley et al., 1991) and rodents (Plotsky et al., 1998; Plotsky and Meaney, 1993). Moreover, prolonged exposure to elevated levels of stress hormones, including corticotrophin-releasing factor (CRF), catecholamines, most notably norepinepherine, and glucocorticoids directly promote the development of a diverse range of high risk conditions, such as visceral obesity, hypertension and insulin resistance, and thus contribute to overt pathology, including diabetes, depression, drug addiction and multiple forms of coronary heart disease (Seeman et al., 1997; Dallman et al., 1995; McEwen, 1998; Chrousos and Gold, 1992; Agrawal, 2001). In essence, stress diathesis models suggest that the quality of the early environment influences the development of individual differences in HPA and autonomic responses to

stress and that these effects form a basis for vulnerability/resistance to chronic illness in adulthood. The emergence of illness in later life occurs as a function of the current level of environmental demand and a developmentally-defined vulnerability.

Support for the basic elements stress diathesis models appears compelling. Adversity during perinatal life alters development in a manner that seems likely to promote vulnerability, especially for stress-related diseases. Diathesis describes the interaction between development, including the potential influence of genetic factors, and the prevailing level of stress in predicting health outcomes. Such models have considerable appeal, and could identify both the origins and the nature of vulnerability. At the same time, there is a troubling aspect to the discussion surrounding these developmental models. Within health sciences, such models are often assumed to imply an ideal form of phenotypic development and, by implication, ideal forms of early environment. For example, dampened stress reactivity and enhanced capacity for declarative memory are considered indicators of 'positive' development. By such criteria postnatal handling or environmental enrichment are thought to be beneficial for development. Stressors, such as neglect or prolonged separation of mother and offspring, in early life are thought to compromise development and lead to negative functional outcomes, such as increased stress reactivity and decreased hippocampal synaptic development. But positive or negative, in relation to what? In an evolutionary sense, health outcomes are a relevant consideration only to the extent that they influence reproduction. Fitness is defined by success in the arena of reproductive competition; health and well being over the life cycle is of importance only to the extent that it bears on survival and reproduction.

We certainly do not dispute the idea that there are predictable relations between certain forms of early experience and specific health outcomes (see above). It is critical to identify risk factors for illness and thus provide an empirical basis for prevention. Nevertheless, the idea that any form of phenotypic variation in and of itself is necessarily positive or negative is an anathema to biology. The merit of any variation in phenotype is understandable only in terms of the degree to which it serves to enhance adaptation to environmental demands with respect to reproductive outcomes. Traits that enhance survival (through periods of active reproduction) and reproduction within any specific environmental context are favored. The value of any trait is therefore contextually determined. This argument may seem slightly inane for those interested in the health outcomes. However, we argue that if science is to meaningfully understand the relation between SES in early life and health in adulthood, then we must consider the question of why adversity in early life alters phenotypic development in such a predictable and persistent manner and why parental investment in the offspring varies so greatly; if parental 'nurturance' is so beneficial for neural development, then why would not all parents invest heavily in each individual offspring?

In this paper, we offer a perspective that attempts to understand the alterations in defensive responses and reproductive behavior commonly associated with dysfunctional family life as an adaptive developmental strategy. We present evidence from a wide range of species that suggests that enhanced defensive responses to threat and altered reproductive behavior/physiology are very common and predictable outcomes of early life adversity. The benefits of this strategy are to increase survival under conditions of adversity and to increase the likelihood of reproduction; the cost is reflected in an increase in the vulnerability for psychopathology. Finally, we argue that these sustained, epigenetic effects of early life adversity on adult behavior and physiology are, in part, mediated by alterations in the chemistry of the DNA. We do not intend this explanation to stand in opposition to those focusing on effects at the level of parent–offspring attachment, but rather as a complimentary level of analysis, and perhaps an understanding how attachment in early life is translated into adult biology and health.

1. Phenotypic plasticity

Modern evolutionary biology reflects the idea that adaptation is not limited to the process of natural selection (i.e. adaptation at the level of the species), but includes adaptation of the individual organism to its ecological niche. This view is reflected in studies of 'phenotypic plasticity' which refers to variation in phenotype as a result of environmental conditions (Agrawal, 2001). In some of the cases cited below, such variation emerges across individuals of a species living within a group in which the members are actually identical clones: these findings provide clear evidence of variation in phenotype emerging from a common genotype as a function of variation in environmental conditions. Indeed, it is commonly thought that the capacity for phenotypic plasticity evolved to permit variation in genotype–phenotype relations in response to variations in the level of environmental demands. Such phenotypic variation reflects complex gene–environment interactions that likely involve protein–DNA interactions at sites (promoters, enhancers, suppressors) that regulate the expression of the coding regions of the genome. It is interesting to note that across species, increasing complexity is associated not so much with an increase in the number of genes that actively code for proteins, but rather in the size of the non-coding region of the genome. We presume that this difference reflects the increased complexity of the regulatory regions of the DNA that, in turn, confers enhanced capacity for tissue-specific regulation of gene expression in multi-organ animals. In addition, the increased size of the regulatory region of the genome should also correspond to an increased capacity for environmental regulation of gene

expression—a process whereby an increasing range of phenotypes might emerge from a common genotype: an increased capacity for phenotypic plasticity.

Nevertheless, while the potential for phenotypic plasticity associated with factors such as parental investment may be greater in more complex species, evidence for this process is apparent in reptiles, insects and even plants (Qvarnstrom and Price, 2001; Rossiter, 1999; Mousseau and Fox, 1998). There is a common theme across all species. Exposure of the mother to environmental adversity alters the nature of mother–offspring interaction, which, in turn, influences the development of defensive responses to threat as well as reproductive strategies in the progeny. We propose that (1) environmental effects on the development of individual differences in defensive reactions to threat or reproductive strategies represent adaptations, or developmental strategies, that serve to refine the function of various organs to an anticipated level of environmental demand and (2) that such environmental effects on development are mediated by variations in parental care.

Before going further, we would point out that it is doubtful that any single component of what you are about to read is original. At best, we are integrating ideas from multiple fields of study including evolutionary biology, ecology, developmental psychology, anthropology, physiology and endocrinology. Indeed, the two main tenets of this paper (see above) can be easily traced to the writings of Gig Levine in his discussions of the effects postnatal handling and to John Bowlby's writings on human development and subsequent revisions of Hinde (Levine, 1994; Lehrman, 1996; Hinde, 1986; Gottlieb, 1991; Denenberg, 1964; Belsky, 1997b).

1.1. Developmental strategies

Development occurs as a result of adaptations to growth and increasing independence from the parent and the parent-controlled environment. Development occurs within an environmental context that ultimately shapes the function of the brain and other organs in the juvenile and adult animal. These effects ultimately define individual differences in multiple traits, and thus vulnerability for illness over the lifespan. For example, environmental adversity in early life alters the development of behavioral and endocrine responses to stress. And the resulting increase in stress reactivity and behavioral inhibition can serve as a risk factor for many forms of chronic illness. However, we argue that such effects should not be considered as examples of impoverished or impaired development. Rather, these effects reflect adaptations to an anticipated level of demand. In most species, the level of environmental demand at birth reliably predicts the quality of the adult environment. As Galton observed, Englishmen inherit England (West and King, 1987). Adversity during perinatal development could be expected to forecast an increased level of demand in adulthood. The resulting effects on the development of individual differences in defensive responses and in reproductive strategies could then be viewed as adaptive responses to adversity: adaptive with respect to survival and/or reproduction, not necessarily with respect to health and well-being. Simply put, the primary objective of phenotypic plasticity is to fine-tune the development of specific biological systems so as to enhance the match between phenotype and environmental demand, and thus increase the probability of successful reproduction.

1.2. Parental mediation

The second feature of this argument is that the effects of environmental quality on development are mediated by variations in parental investment. We are using the term 'investment' in a very generic sense, such that it might refer to the nutrient supply provided by the parent as well as to behavioral interactions. Of course, the nature of parental investment will vary dramatically across species. For insects, parental investment may be reflected in the quality of the ova or the propagule (the nutritional source left for the offspring by the mother. Variations in parental investment in mammals commonly involve the quantity and quality of behavioral interactions between parent and offspring. The actual form of the variation in parental investment will vary, but the effects on phenotypic plasticity are common and in each case affect the development of (1) defensive responses and (2) reproductive strategies. We argue that across a remarkable range of species variations in parental investment is associated with phenotypic plasticity in defensive and reproductive systems. We propose that environmental adversity alters parent–offspring interactions and that these effects serve as the basis for phenotypic plasticity. The variations in parent–offspring interactions are, in effect, the forecast of environmental quality for the offspring. There is, of course, one critical premise. If parental care serves as the mediator for the effects of environmental adversity on development, then there must be a predictable relation between the quality of the environment and parental care.

2. Perinatal life and the development of stress responses

As recently as the 1950s, this entire subject was considered moot. Defensive responses to stress, including behavioral, endocrine and autonomic responses, were considered innate. Although few attempted to clearly describe what the term 'innate' actually meant in a developmental sense, it implied a measure of universality in form and expression across members of the same species, and independence from environmental influence. Such responses, however they might emerge over development, were considered invariant. Surely, biology would never leave the development of such essential processes to the caprice of environmental suggestion! However, by the late 1950s and early 1960s the pages of Science and Nature were

frequently dedicated to articles reporting the effects of postnatal handling (aka, infantile stimulation) on the development of responses to adverse stimuli, or stressors (Levine, 1994; Denenberg, 1964). In infant rats and mice, handling during infancy was commonly found to decrease the magnitude of both behavioral and hypothalamic–pituitary–adrenal (HPA) responses to stress in adulthood. These findings clearly demonstrated that even rudimentary defensive responses to threat were influenced by the early environment.

By the mid-1970s Levine and others (Levine, 1994) suggested that the effects of handling were actually mediated by changes in maternal care. Indeed, handling was reported to increase the licking/grooming of pups by the mother (Lee and Williams, 1975; Liu et al., 1997). Subsequent studies supported the maternal-mediation hypothesis. One approach was to examine the consequences of naturally-occurring variations in maternal licking/grooming. These studies indicate that the adult offspring of High licking/grooming (LG) mothers resembled postnatally-handled animals on measures of behavioral and endocrine responses to stress, while those of Low LG mothers were comparable to nonhandled animals. Cross-fostering studies, where pups born to High LG mothers were fostered at birth to Low LG mothers (and vice versa), suggest a direct relationship between maternal care and the postnatal development of individual differences in behavioral and HPA responses to stress (Francis et al., 1999a; Caldji et al., 2003). Finally, these studies suggest that variations within a normal range of parental care can dramatically alter development. Parental care need not include forms of overt abuse or extreme neglect in order to influence the development offspring. In large measure, this is likely due to the fact that natural selection has shaped offspring to respond to subtle variations in parental behaviors as a forecast of the environmental conditions they will ultimately face following independence from the parent (Hinde, 1986).

2.1. Maternal care in the rat: behavioral and HPA responses to stress

Central corticotropin-releasing factor (CRF) systems furnish the critical signal for the activation of behavioral, emotional, autonomic and endocrine responses to stressors. There are two major CRF pathways regulating the expression of these stress responses. First, a CRF pathway from the parvocellular regions of the paraventricular nucleus of the hypothalamus (PVNh) to the hypophysial-portal system of the anterior pituitary, which serves as the principal mechanism for the transduction of a neural signal into a pituitary–adrenal response (Rivier and Plotsky, 1986; Plotsky, 1991; Antoni, 1993; Whitnall, 1993). In responses to stressors, CRF, as well as co-secretagogues such as arginine vasopressin, are released from PVNh neurons into the portal blood supply of the anterior pituitary where it stimulates the synthesis and release of adrenocorticotropin hormone (ACTH). Pituitary ACTH, in turn, causes the release of glucocorticoids from the adrenal gland. CRF synthesis and release is subsequently inhibited through a glucocorticoid negative-feedback system mediated by both mineralocorticoid and glucocorticoid receptors in a number of brain regions including and perhaps especially in the hippocampus.

CRF neurons in the central nucleus of the amygdala project directly to the locus coeruleus and increase the firing rate of locus coeruleus neurons, resulting in increased noradrenaline release in the vast terminal fields of this ascending noradrenergic system. Thus, icv infusion of CRF increases extracellular noradrenaline levels (Lavicky and Dunn, 1993; Emoto et al., 1993; Page and Valentino, 1994; Valentino et al., 1998). The amygdaloid (BNST) CRF projection to the locus coeruleus (Valentino et al., 1998; Moga and Gray, 1989; Koegler-Muly et al., 1993; Van Bockstaele et al., 1996; Gray and Bingaman, 1996) is also critical for the expression of behavioral responses to stress (Butler et al., 1990; Liang et al., 1992; Swiergiel et al., 1993; Koob et al., 1994; Schulkin et al., 1994; Stenzel-Poore et al., 1994; Bakshi et al., 2000; Davis and Whalen, 2001). 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.

We examine the relation between maternal care and the development of behavioral and endocrine responses to stress using a rather simple model of naturally-occurring variations in maternal behavior over the first 8 days after birth (Champagne et al., 2003a). Individual differences in maternal behavior are characterized through direct observation of mother–pup interactions in normally-reared animals. These observations reveal considerable variation in two forms of maternal behavior—LG of pups and arched-back nursing (Stern, 1997). Licking/grooming includes both body as well as anogenital licking. Arched-back nursing, also referred to as 'crouching', is characterized by a dam nursing her pups with her back conspicuously arched and legs splayed outward. While common, it is not the only posture from which dams nurse. A blanket posture represents a more relaxed version of the arched-back position where the mother is almost lying on the suckling pups. As you can imagine, it provides substantially less opportunity for movement by the pups such as nipple-switching. Dams also nurse from their sides and often will move from one posture to another over the course of a nursing bout. Interestingly, the frequency of LG and arched-back nursing (ABN) is correlated across animals and thus we are able to define mothers according to both behaviors as High or Low LG–ABN mothers. For the sake of most of the studies described here, High and Low LG–ABN mothers are females whose scores on both measures were ± 1 SD above (High) or below (Low) the mean for their cohort. Importantly, High and Low LG–ABN mothers do not differ in the amount of contact time with pups; differences in

the frequency of LG or ABN do not occur simply as a function of time in contact with pups. High and Low LG–ABN mothers raise a comparable number of pups to weaning and there are no differences in the weaning weights of the pups, suggesting an adequate level of maternal care across the groups. These findings also suggest that we are examining the consequences of variations in maternal care that occur within a normal range. Indeed, the frequency of both pup LG and ABN are normally distributed across large populations of lactating female rats (Champagne et al., 2003a).

The critical question concerns the potential consequences of these differences in maternal behavior for the development of behavioral and neuroendocrine responses to stress (Liu et al., 1997). As adults, the offspring of High LG–ABN mothers show reduced plasma ACTH and corticosterone responses to acute stress by comparison to the adult offspring of Low LG–ABN mothers. Circulating glucocorticoids act at glucocorticoid and mineralocorticoid receptor sites in corticolimbic structures, such as the hippocampus, to regulate HPA activity. Such feedback effects commonly target CRF synthesis and release at the level of the PVNh. The High LG–ABN offspring show significantly increased hippocampal glucocorticoid receptor mRNA expression, enhanced glucocorticoid negative feedback sensitivity and decreased hypothalamic CRH mRNA levels. Moreover, Liu et al. (1997) found that the magnitude of the corticosterone response to acute stress is significantly correlated with the frequency of both maternal LG ($r = -0.61$) and ABN ($r = -0.64$) during the first week of life, as is the level of hippocampal glucocorticoid receptor mRNA and hypothalamic CRH mRNA expression (all $rs > 0.70$).

The offspring of the High and Low LG–ABN mothers also differ in behavioral responses to novelty (Francis et al., 1999a; Caldji et al., 1998). As adults, the offspring of the High LG–ABN showed decreased startle responses, increased open-field exploration, and shorter latencies to eat food provided in a novel environment. The offspring of Low LG–ABN mothers show greater burying in the defensive burying paradigm (Menard et al., submitted for publication) which involves an active response to a threat. The offspring of the High LG–ABN mothers also show decreased CRF receptor levels in the locus coeruleus and increased $GABA_A$/BZ receptor levels in the basolateral and central nucleus of the amygdala, as well as in the locus coeruleus (Caldji et al., 1998, 2003) and decreased CRF mRNA expression in the central nucleus of the amygdala (Francis, Diorio, and Meaney, unpublished). BZ agonists suppress CRF expression in the amygdala (Owens et al., 1991). Predictably, stress-induced increases in PVNh levels of noradrenaline that are normally stimulated by CRF are significantly higher in the offspring of the Low LG–ABN offspring (Francis et al., 1999b).

Maternal care during the first week of life is associated with stable individual differences in $GABA_A$ receptor sub-unit expression in brain regions that regulate stress reactivity. The adult offspring of High also LG–ABN mothers show significantly higher levels of $GABA_A$/BZ receptor binding in the basolateral and central nucleus of the amygdala as well as the locus coeruleus. These findings provide a mechanism for increased GABAergic inhibition of amygdala-locus coeruleus activity. A series of in situ hybridization studies (Caldji et al., 2003) illustrate the molecular mechanism for these differences in receptor binding and suggest that variations in maternal care might actually permanently alter the sub-unit composition of the $GABA_A$ receptor complex in the offspring. The offspring of the High LG–ABN mothers show increased levels of the mRNAs for the $\gamma 1$ and $\gamma 2$ sub-units, contribute to the formation of a functional BZ binding site. Such differences are not unique to the γ sub-units. Levels of mRNA for the $\alpha 1$ sub-unit of the $GABA_A$/BZ receptor complex are significantly higher in the amygdala and locus coeruleus of High compared with Low LG–ABN offspring. The $\alpha 1$ sub-unit appears to confer higher affinity for GABA, providing the most efficient form of the $GABA_A$ receptor complex, through increased receptor affinity for GABA. The adult offspring of the Low LG–ABN mothers actually show increased expression of the mRNAs for the $\alpha 3$ and $\alpha 4$ sub-units in the amygdala and the locus coeruleus. Interestingly, $GABA_A$/CBZ receptor composed of the $\alpha 3$ and $\alpha 4$ sub-units show a reduced affinity for GABA, by comparison to the $\alpha 1$ sub-unit. Moreover, the $\alpha 4$ sub-unit does not contribute to the formation of a BZ receptor site. These differences in sub-unit expression are tissue specific; no such differences are apparent in the hippocampus, hypothalamus or cortex. Thus, differences in $GABA_A$/BZ receptor binding are not simply due to a deficit in sub-unit expression in the offspring of the Low LG–ABN mothers, but of an apparently 'active' attempt to maintain a specific $GABA_A$/BZ receptor profile in selected brain regions.

Together, with the findings from earlier handling studies (Levine, 1994), the results of these studies suggest that the behavior of the mother towards her offspring can 'program' behavioral and neuroendocrine responses to stress in adulthood. These effects are associated with sustained changes in the expression of genes in brain regions that mediate responses to stress, and form the basis for stable individual differences in stress reactivity. These findings provide a potential mechanism for the influence of parental care on vulnerability/resistance to stress-induced illness over the lifespan.

Individual differences in behavioral and neuroendocrine responses to stress in the rat are correlated with naturally-occurring variations in maternal care. Such effects might serve as a possible mechanism by which selected traits might be transmitted from one generation to another. Indeed, Low LG–ABN mothers are more fearful and show increased HPA responses to stress by comparison to High LG–ABN dams (Francis et al., 2000). Individual differences in stress reactivity are apparently transmitted across

generations: Fearful mothers beget more stress reactive offspring. The obvious question is whether the transmission of these traits occurs only as a function of genomic-based inheritance. If this is the case, then the differences in maternal behavior may be simply an epiphenomena, and not causally related to the development of individual differences in stress responses. The issue is not one of inheritance, but the mode of inheritance.

The results of recent studies provide evidence for a nongenomic transmission of individual differences in stress reactivity and maternal behavior (Francis et al., 1999a). One study involved a 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 (Maccari et al., 1995). 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 (McCarty and Lee, 1996). The critical groups of interest are the biological offspring of Low LG–ABN mothers fostered onto High LG–ABN dams, and vice versa. 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 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 the offspring reared by Low LG–ABN mothers, including the biological offspring of High LG–ABN mothers (Francis et al., 1999a). Subsequent studies have revealed similar findings for hippocampal glucocorticoid receptor expression (Weaver et al., 2001). and for the differences in both the $\alpha 1$ and $\gamma 2$ $GABA_A$ receptor subunit expression in the amygdala (Caldji et al., 2003). These findings suggest that individual differences in patterns of gene expression and behavior can be directly linked to maternal care over the first week of life.

2.2. Parental effects on defensive responses in an evolutionary context

What is perhaps surprising here is that developmental effects of such magnitude derive from variations in parental care that appear to lie within a normal range for the species. As Hinde (1986) suggested, this is likely due to the fact that natural selection has shaped offspring to respond to subtle variations in parental behaviors as a forecast of the environmental conditions they will ultimately face following independence from the parent. The critical question of why such developmental effects might exist is best considered within an evolutionary context. Studies on the long-term effects of maternal care on defensive responses to threat in the rat are examples of what evolutionary biologists refer to as 'maternal effects' (Qvarnstrom and Price, 2001; Rossiter, 1999; Mousseau and Fox, 1998). Within evolutionary biology, maternal or parental effects are defined as sustained influences on any component of the phenotype of the offspring that is derived from either the mother or the father, apart from nuclear genes. Such parental effects have been described across a variety of species and the results clearly indicate that environmentally-induced modifications of the parental phenotype can be transmitted to offspring.

Studies of the effects of childhood SES on development suggest that environmental adversity alters parent–offspring interactions and thus influences the phenotype of the offspring. Studies with humans, nonhuman primates and rodents suggest that these effects are, in part, revealed as individual differences in stress responses. The fundamental theme is that of parental influences over the development of defensive responses. This is a stunningly common theme in biology. Not only are maternal effects on defensive responses not unique to mammals, they are not even unique to animals. Plants also show maternal effects, with basically the same characteristics as those reported in mammals (although we assume through very difference mechanisms of transmission). In a remarkable paper, Agrawal et al. (1999) provided evidence for transgenerational, maternal effects in two models. The first of these models described maternal effects on the development of defensive responses in the offspring—in the radish. Herbivory commonly results in the expression of 'inducible' defenses in plants. In the case of the radish, damage from a caterpillar, *Pieris rapae*, induces an increase in the production of mustard oil glycosides and higher densities of setose trichomes on newly formed leaves. The defense is termed 'inducible' since its expression occurs only in response to a specific form of threat (Tollrian and Harvell, 1999). In contrast, a constitutive defense is constantly and invariably operative. Inducible defenses triggered by herbivory protect against subsequent predator attack. Under conditions where there is a prevailing threat of herbivory, plants expressing inducible defenses show a significantly greater lifetime seed production than did controls (Agrawal, 1999; Agrawal et al., in press)

To examine the consequences of herbivory of the maternal plant for the next generation. Agrawal et al. examined seeds from control and caterpillar-damaged plants. The seedlings from the damaged radishes showed significant changes in glycosinolate profiles. Herbivory of the maternal plant also altered trichome expression: the number of trichomes per leaf are increased in seedlings as a function of maternal herbivory. Such changes were adaptive. Caterpillars gained significantly less weight, presumably from reduced consumption, when exposed to seedlings from damaged versus undamaged mothers.

Maternal effects have been reported with inducible defensives in many invertebrate species (Mousseau and Fox, 1999). Inducible defensives, as opposed to constitutive

defensives, emerge or develop to full strength in response to signals from environmental threats, such as those associated with predators. For example, in response to chemosignals, or kairomones, from aquatic predators, water fleas (Daphnia) form impressive, helmet-like growths on their necks and spines along their tails (Tollrian, 1995). These morphological changes render the animals less likely to be captured and successfully ingested (Gilbert, 1999; Tollrain and Dodson, 1999). This is an inducible, morphological defense. There is evidence for transgenerational effects, comparable to those reported in the behavioral and endocrine responses to stress in the rat. In the rat, Low LG–ABN mothers are more fearful, and beget more fearful, stress reactive offspring. The mechanism for this transgenerational effect involves variations in maternal behavior. In *Daphnia*, the mechanism is unknown, but the evidence for intergenerational transmission is no less compelling. The F1 and F2 generations of mothers exposed to kairomones up until pregnancy, and clean water thereafter, exhibited significantly larger helmets than those of mothers consistently maintained in clean water environments (Agrawal et al., 1999). Kairomone exposure of the mother was sufficient to alter the morphology of the completely kairomone-naïve offspring.

Larger scincid lizards with longer tails are less successfully preyed upon by snakes. Again, there is evidence for plasticity in morphological defenses, and for the transmission across generations. Female scincid lizards (*Pseudomoia pagenstecheri*) exposed to the scent of lizard-eating snakes during gestation, but not thereafter, gave birth to offspring that were heavier, had unusually long tails and were significantly more sensitive to the odor of the predator (Shine and Downes, 1999). Thus the anti-predator responses to the offspring are modified by the experience of the mother. Functionally, such effects reflect an influence of the mother over the vulnerability of the offspring to predatory snakes—presumably an adaptive modification of the offspring's phenotype.

These examples provide compelling evidence for maternal effects on defensive responses and yield a common theme: exposure of the mother to environmental adversity influences the phenotype of the offspring. In each case, exposure of the mother to conditions that threaten survival, results in variations in the phenotype of the offspring that increase the capacity of the offspring to avoid predators. We argue that the effects of maternal behavior on the development of individual differences in defensive responses in the rat represent similar examples of maternal effects, in this case mediated by variations in maternal behavior. It is not surprising that among mammals, with extended periods of postnatal care, parental behavior should emerge as a critical mechanism for such effects. If this is indeed the case then at least two basic features of this effect should be apparent: (1) environmental adversity should have a significant effect on maternal behavior and (2) the alterations in the defensive responses of the offspring should be adaptive.

2.3. The effects of stress on maternal behavior in mammals

If parental care is to serve as the mediator for the effects of environmental adversity on development, then there must be a predictable relation between the quality of the environment and parental care. There is considerable evidence for a relationship between environmental adversity and parental care in humans (Repetti et al., 2002; Fleming, 1999). Such studies are, of course, correlational. Perhaps the most compelling evidence for a direct effect of environmental adversity on parent–infant interactions emerges from the studies of Rosenblum, Coplan and colleagues with nonhuman primates (Rosenblum and Andrews, 1994; Coplan et al., 1996, 1998). 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) 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, following 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 show signs of depression commonly observed in maternally-separated macaque infants. Remarkably, these reactions are apparent even when the infants are in contact with their mothers. As adolescents, the infants reared in the VFD conditions are more fearful, submissive and showed less social play behavior.

More recent studies demonstrate the effects of these conditions on the development of neural systems that mediate behavioral and endocrine response to stress. As adults, monkeys reared under VFD conditions showed increased CSF levels of CRF (Coplan et al., 1996, 1998). 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. It will be fascinating to see if these traits are then transmitted to the next generation.

The critical issue here is that of the effect of environmental adversity on maternal behavior. Female rats exposed to stress during pregnancy show increased retrieval latencies (Fride et al., 1985; Moore and Power, 1986; Kinsley et al., 1988) a finding that would seem to reflect an effect of stress on maternal responsivity. Gestational stress in the rat decreases the frequency of pup licking/grooming during lactation (Smith et al., 2004;

Champagne and Meaney, 2000). We examined the effect of such gestational stress on maternal behavior in High and Low LG–ABN mothers (Champagne and Meaney, 2000). Females previously characterized as High or Low LG–ABN mothers with their first litter were exposed to restraint stress during the last half of gestation or to control conditions. Gestational stress decreased the frequency of maternal LG with the second litter in the High, but not in Low LG–ABN mothers. Thus, a stressful environmental signal during gestation was sufficient to completely reverse the pattern of maternal behavior in High LG–ABN mothers. The maternal behavior of High LG–ABN mothers exposed to gestational stress during an earlier pregnancy was indistinguishable from that of Low LG–ABN mothers. Of course, these effects on maternal behavior are apparent in the development of the offspring. As adults, the offspring of High LG–ABN/gestationally-stressed mothers were comparable to those of Low LG–ABN dams on measures of behavioral and HPA responses to stress. Of course, such effects might be associated with a classic 'prenatal stress' effects, since these animals were in utero during the imposition of the stressor. To address this question, we examined the offspring of a subsequent pregnancy over which time no experimental manipulations were imposed. As it turns out, the effects of gestational stress during the second pregnancy were apparent with a subsequent, third litter, even in the absence of any further stress. This finding enabled us to examine the effects of stressed-induced alterations in maternal behavior independent of the presence of the stressor during prenatal life. As with the second litter, the adult offspring of the High LG–ABN/gestationally-stressed mothers were again comparable to those of Low LG–ABN dams on measures of behavioral and HPA responses to stress.

The effects of gestational stress were also apparent in the maternal behavior of the female offspring. The female offspring of High LG mothers exposed to gestational stress behave towards their pups in a manner consistent with the behavior of their mothers; as adults, these females are Low LG–ABN mothers with reduced levels of oxytocin receptor binding in the medial preoptic area. Hence, the effects of environmental adversity are effectively transmitted from parent to offspring.

2.4. Adaptive value of enhanced stress reactivity in mammals

Environmental adversity influences fearfulness and stress reactivity in parents and these effects are reflected in alterations in parental care, commonly reflecting a decreased level of investment. The resulting patterns of parental behavior serve to enhance stress reactivity of the offspring. The anxiety of the parent is transmitted to the offspring. Such intergenerational transmission of individual differences in stress reactivity via maternal behavior could represent an adaptive approach to development. Since the offspring usually inhabit a niche that is similar to their parents, the transmission of individual differences in traits from parent to offspring could serve to be adaptive with respect to survival. Adversity over the adult life of the parent is thus likely to predict more of the same for the offspring. Under conditions of increased environmental demand, it is commonly in the animal's interest to enhance its behavioral (e.g. vigilance, fearfulness) and endocrine (HPA and metabolic/cardiovascular) responsivity to stress. These responses promote detection of potential threat, fear conditioning to stimuli associated with threat and avoidance learning (see above). Moreover, the hormonal effectors of sympathoadrenal and HPA stress responses mobilize energy reserves through effects of lipolysis, glycolysis and gluconeogenesis. These effects are the hallmark of the shift to catabolism that occurs during periods of stress and are essential for animals exposed to famine. Indeed, the ability to survive sustained periods of nutrient deprivation depends upon the capacity to increase circulating levels of glucocorticoids and catecholamines.

Impoverished environments are also commonly associated with multiple sources of infection. Under such conditions, adrenal glucocorticoids serve as a potent defense against septic shock (Munck et al., 1984). Among rats, animals with increased HPA responses to agents such as bacterial endotoxins are at reduced risk for sepsis (Mason, 1991). Interestingly, adults exposed to a bacterial endotoxin during the first week of life exhibit increased HPA responses to stress as well increased resistance to sepsis upon subsequent exposure to bacterial infection (Shanks et al., 1995, 2000). Conversely, postnatal handling, which increases maternal licking/grooming and dampens HPA responses to stress, serves to increase vulnerability to endotoxin-induced sepsis (Laban et al., 1995). Under conditions of increased risk for predation, more behaviorally fearful guppies with shorter escape latencies show increased survival (O'Steen et al., 2002). These findings underscore the potentially adaptive value of increased neuroendocrine and behavioral responses to threat.

A metaphor for this argument exists in the physiology of the thrifty phenotype in rodents (Neel, 1962; Hales and Barker, 1992). In response to the deprivation of energy substrates in fetal life, rodents show a pattern of development that favors energy conservation and an increased capacity for both gluconeogenesis and lipolysis in adulthood. Both effects appear to reflect 'anticipatory' patterns of development that would be adaptive under repeated periods of food shortages. Interestingly, these effects are mediated sustained changes in the expression of genes in hepatic tissues that mediate glucose and fat metabolism (Bauer et al., 1998; Seckl et al., 1999; Gluckman and Pinal, 2002; Seckl, 2001) as well as by increased HPA activity (Seckl, 2001; Phillips, 1998). Importantly, these effects occur as a result of changes in maternal HPA activity (Seckl, 2001). Effects on hepatic metabolism and HPA function in the offspring are reproduced if the mother is treated with

dexamethasone during gestation. In parallel are changes in HPA activity (Seckl, 2001). Protein deprivation, stress or dexamethasone exposure during gestation results in increased HPA reactivity to stress in the offspring, effects that are mediated by increased CRF gene expression in both the PVNh and the central nucleus of the amygdala. As mentioned above, the end-product of the HPA axis, the adrenal glucocorticoids, serve to increase energy substrates during stress, such as prolonged periods of food deprivation. Interestingly, maternal exposure to bacterial infection during the gestation has a comparable effect on HPA development in the offspring (Reul et al., 1994). In each case, exposure of the mother to environmental adversity, results in increased defensive responses to threat in the offspring. We believe that a similar argument applies to the effects of maternal care on behavioral responses to stress and suggest an adaptive advantage of the increased level of stress reactivity apparent in the offspring of Low LG–ABN mothers under appropriate conditions. The research of Farrington (Farrington et al., 1988) and Tremblay (Haapasap and Tremblay, 1994) on young males growing-up in a low SES, high crime urban environments provides an excellent illustration of the potential advantages of increased emotional stress reactivity. The males that were most successful in avoiding the pitfalls associated with such a 'criminogenic' environment were those that were shy and somewhat timid. Under such conditions a parental rearing style that favored the development of a greater level of stress reactivity to threat could be viewed as adaptive.

Impoverished environments are associated with nutritional deprivation, violence and infection: stress responses provide natural defenses against all three conditions. It is thus perhaps understandable that parents occupying a highly demanding environment would transmit to their young an enhanced level of stress reactivity in 'anticipation' of a high level of environmental adversity. Such a pessimistic developmental profile would be characterized by an increased level of hypothalamic and amygdaloid CRF gene expression, and in patterns of gene expression that dampen the capacity of inhibitory systems, such as the $GABA_A$/BZ receptor complex and the hippocampal glucocorticoid receptor system. In contrast, more favorable environments encourage an optimistic pattern of development, characterized by more modest levels of stress. The quality of the environment influences the behavior of the parent which, in turn, is the critical factor in determining whether development proceeds along an optimistic versus pessimistic pattern of development. The obvious conclusion is that there is no single ideal form of parenting: various levels of environmental demand require different traits in the offspring. It seems reasonable to suggest that parental is thus structured in a manner that enhances the adaptation of the offspring to the particular demands of the environment they are about to inherit. Indeed, this is a simple extension of the suggestion advanced by Hinde (1986) that natural selection might have shaped offspring to use variations in parental behaviors to forecast the environmental conditions they will ultimately face. Moreover, as discussed above, there is a predictable relationship between the quality of the environment and parental care.

2.4.1. Summary

These findings are entirely consistent with those revealing effects of low SES in childhood on vulnerability for chronic illness in adulthood, and further, support the idea that effects of childhood SES are, in part at least, mediated through variations in parent–offspring interactions. Recall that in humans 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 (Eisenberg and Earls, 1975; Conger et al., 1994; McLloyd, 1998). 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 for the children are seriously limited. Taken together, these findings suggest that environmental adversity alters the emotional well-being of the mother: chronic stress increases anxiety and fearfulness, and thus decreases maternal responsivity, which in turn influences the development of stress reactivity in the offspring. For humans, these are not isolated conditions: one in five teens and one in six adults, women experience abuse during pregnancy (Newberger et al., 1992; Parker et al., 1994). Also, in humans Fleming (1988) reported that many factors contribute to the quality of the mother's attitude towards her newborn, but none were correlated more highly than the women's level of anxiety. Mothers who felt depressed and anxious were, not surprisingly, less positive towards their baby (Field, 1998). Moreover, there is evidence for the behavioral transmission of anxiety. Highly anxious mothers are more likely to have children who are shy and timid, and the behavior of the mother predicts the level of such behavioral inhibition in the child (Hirschfeld et al., 1997a,b). Scores on parental bonding measures are correlated with autonomic, HPA and mesolimbic dopamine responses to stress (Pruessner et al., 2004b). Young, adult subjects that described a cold, distant relationship with their parents show increased glucocorticoid and cardiovascular responses to stress, as well as evidence for increased dopamine release in the ventral striatum. More extreme variations in parental care have predictable results. As adults, victims of abuse in early life show increased endocrine and autonomic responses to stress (Luecken and Lemery, 2004; Heim et al., 2002b). The increased stress reactivity apparent in individuals exposed to environmental adversity in early life may thus be seen as a developmental adaptation. The benefit is presumably an increased capacity to survive under conditions of continuous environmental hardship.

The cost is that of an increased vulnerability for pathology.

3. Phenotypic plasticity in reproductive behavior

The results of research on phenotypic plasticity in defensive responses suggest that the quality of the environment determines parental investment, which in turn influences the development of defensive responses in the offspring. Maternal effects on defensive responses of the offspring reflect alterations in the phenotype of the offspring that appear to anticipate a future level of adversity. These developmental effects are mediated by sustained, tissue-specific changes in gene expression and result in individual differences in defensive responses. This same theme emerges in studies on reproductive behavior. In animals, including humans, adversity in early life is defined by diminished access to economic resources and an increased risk for mortality, and leads to a very predictable reproductive strategy: reproduce early and often, and minimize the investment in any single offspring. The benefit of this strategy is to increase the probability of successful reproduction under conditions where the prospects for growth are poor and survival is uncertain. Once again the cost is revealed as an increased risk for pathology.

Neuroendocrine studies of the development of reproductive behaviors focus largely on differences *between* the sexes. However, over the past decade behavioral ecologists and psychologists have described considerable variation among individuals within the sexes in reproductive tactics. These studies reveal that rather than evolution giving rise to a single best male and female phenotype for each species, it has instead opted for phenotypic diversity (Gross, 1996).

There is compelling evidence for within-gender, individual differences in reproductive tactics across members of the same species (Gross, 1996; Rhen and Crews, 2002). In most instances, the existing reports reveal individual differences in courtship and mating behaviors among males. The issue of individual differences in reproductive behavior among females has been largely neglected (Rhen and Crews, 2002). Detailed examples of phenotypic plasticity in reproductive behavior have been described in insects, amphibians, fish, birds and mammals (Rhen and Crews, 2002). The most common variations studied are among males and involve the establishment and defense of territories, parental care of the young, and courtship tactics (e.g. vocalizations), although the causal mechanisms are known for only a few examples.

Variations in reproductive tactics, in some cases, are associated with genetic polymorphisms (Gross, 1996). For example, in the swordtail (*Xiphiphorus nigrensis*), three alleles at a single Y-locus appear to result in small, intermediate-sized and large males that respectively sneak, sneak and court, and court in order to gain access to females (Shuster and Wade, 1991). There are also examples of maternal effects on male reproductive tactics. In the ground-nesting bee (*Perdita portalis*), large larvae develop into males expressing a fighter phenotype that is flightless, has large mandibles, and mates within the nest. Smaller larvae develop into smaller, fully winged males that mate outside the nest: Presumably along the lines of a 'lose-shift' strategy. Maternal provisioning determines male larval size and thus adult reproductive tactic. The size and quality of the maternal provision (or propagule) among insects is commonly associated with the quality of the prevailing environment. This suggests that environmental conditions influence the development of reproductive tactics through effects on parental investment. Evidence for such an influence emerges from studies with guppies (*Poecilia reticulata*) housed in the presence of a model that simulates a predator. Under such conditions, the male guppy makes increase use of a sneaking tactic in access females as opposed to the more conspicuous courtship rituals. Presumably, the former is less likely to draw the attention of a predator and could be considered as adaptive.

The most definitive research (Bass, 1990) on proximal mechanisms underlying alternative mating tactics is with the plainfin midshipman fish (*Porichthys notatus*). Type I midshipman build nests and use courtship vocalizations to attract females. Type I males are parental. Type II males build no nests, but wander as 'satellite' males, sneaking mating opportunities, and are not parental. These tactics appear fixed over the lifespan. Type II males mature earlier, a common strategy under conditions of environmental adversity, are smaller, have a poorly developed vocal circuitry, as well as fewer GnRH neurons and lower androgen levels. Differences in the pattern of vocalizations are associated with the differential effects of the neuropeptides arginine vasotocin (AVT) and isotocin. In frogs, which show similar variations in vocalizations, such effects are associated with changes in AVT under the control of androgens and estrogens. Indeed, steroidal regulation of neuropeptide systems is a common mechanism underlying the activation of reproductive behaviors.

Moore (2005) argued that individual differences in reproductive behavior could be understood in terms of the organizational-activational effects of sex steroids (Pheonix et al., 1959). Androgens and estrogens act in early life to influence the differentiation of the brain regions involved in mating and gonadotropin-releasing hormone (GnRH) synthesis and release. Such effects are stable, if not irreversible, and represent organizational effects. Over the course of the lifespan, gonadal steroids also transiently regulate neuronal activity and behavior, and such effects are considered 'activational'. Moore proposed that individual differences in reproductive behavior occur when animals alternate between various tactics. Such effects were seen as arising from continuous activational influences in the relative absence of organizational effects in early development. Presumably, the absence of organization effects ensured sufficient plasticity for phenotypic variation in adulthood.

In contrast, organizational effects would prevail under conditions in which there is little or no variation across individuals in mating tactics. The distinction was between 'fixed' versus 'plastic' systems. This was a clever solution, presented at a time when little was actually known about underlying mechanisms. Indeed, there are many examples of species in which individuals alternate from one reproductive strategy to another in adulthood. Hermaphroditic fish mate first as one gender, and switch to the other. Variations in social hierarchies produce changes in mating tactics in primates, ungulates and other species. However, it now appears that fixed, organizational effects are apparent in many species even when there is considerable individual variation in reproductive tactics (Rhen and Crews, 2002). Alternative mating strategies may vary across individuals, but are stable over time. Moreover, the original thesis did not distinguish between the most prevalent cases, where phenotypic plasticity emerges from either genetic polymorphisms versus alternative phenotypes that are sensitive to environmental factors in early development, but not at later times points (Rhen and Crews, 2002). Maternal effects on reproductive strategies would be an example of the later condition. Thus, as exemplified in the case of the Midshipman, alternative reproductive tactics can emerge from the organizational effects in early life. We argue that this pattern also occurs in the female rat due to organizational effects on steroid–neuropeptide interactions.

3.1. Maternal programming of individual differences in reproductive behavior in the rat

The differences in maternal behavior in the High and Low LG–ABN mothers are not unique to the first litter (Champagne et al., 2003a). Across dams there was a correlation of +0.84 between the licking/grooming of the first and second litters and a correlation of +0.72 between the licking/grooming scores for the first and third litters. Thus, the variations in maternal behavior represent stable individual differences in a specific form of reproductive behavior. These findings are comparable to those of primate studies in which individual differences in maternal behavior remained consistent across infants (e.g. Fairbanks, 1996; Berman, 1990; Maestripieri, 1999). Moreover, in the rat and monkey, individual differences in maternal behavior are transmitted from mother to daughter. Likewise in humans, scores on the parental bonding index are correlated across generations in females (Miller et al., 1997). The issue is whether such findings might reflect maternal effects on maternal behavior. We examined this question using the same cross-fostering paradigm described above (Francis et al., 1999a). 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. These findings suggest that maternal–infant interactions program not only defensive responses to threat, but also reproductive behavior.

We recently extended these findings in studies examining the effects of maternal care over the first week of life on sexual behavior in the female offspring (Cameron et al., 2004). Females were tested in proestrus with males in the confinements of a traditional testing arena. Under these circumstances the female offspring of Low LG–ABN mothers exhibited an increased lordosis response to male mounts. The female offspring of Low LG–ABN dams also exhibited increased rates of proceptive behaviors (ear wiggling, hopping (Erskine, 1989)), that serve to attract the male and enhance male copulation. In contrast, the female offspring of High LG–ABN dams exhibited increased levels of agonistic behavior towards the males.

Solicitation behaviors in the female rat are highly dependent upon context. In smaller confines, the most common pattern of paracopulatory (or proceptive) behavior is that of hopping, darting and ear wiggling. However, when a receptive female is tested in a larger area that affords the opportunity to retreat from the male, the approach-withdrawal pattern prevails and results in the female pacing of mating (Erskine, 1989). Female rats pace the rate of male intromissions and thus ejaculation by withdrawal from the male following each intromission. The latency to return to the male is longer after ejaculation than after an intromission, which in turn, is longer than after a mount with an intromission (Bermant, 1961; Erskine et al., in press; Yang and Clemens, 1996). As testing proceeds over the courses of multiple ejaculatory sequences, the inter-intromission interval increases (Peirce and Nutall, 1961; Kreiger et al., 1976; Coopersmith et al., 1996). Testing in the pacing chamber revealed considerable differences in sexual behavior as a function of maternal care. We examined the adult offspring of Low, Mid and High LG mothers in order to examine the effect of postnatal maternal care over a wider range of the population. As in the previous test, the critical measure of receptivity (lordosis rating) suggested decreased sexual receptivity in the adult female offspring of High LG–ABN mothers by comparison to those reared by either Low or Mid LGABN dams. The most impressive differences in pacing were in the intervals between intromissions. Over the entire session the average inter-intromission interval was almost four times longer in the female offspring of High LG–ABN mothers, with no difference between females reared by Low or Mid LG–ABN dams. A similar effect was observed in the second half of the test session, when variation in intromission intervals is generally greater. Importantly, there were also significant group differences in the rate of pregnancy following mating in

the pacing chamber. While 50% of the female offspring of High LG–ABN mothers became pregnant, over 80% of those of Low LG–ABN mothers were pregnant. These findings suggest that, at least under certain conditions, the differences in sexual behavior between the offspring of High and Low LG–ABN mothers are indeed functionally relevant for reproductive success.

These findings reveal evidence for the maternal programming of sexual behavior in the female rat. Moreover, maternal care is associated not only with alterations in sexual behavior in the adult rat, but also in the timing of the onset of sexual behavior. The female offspring of Low LG–ABN mothers show vaginal opening (an unambiguous indication of pubertal development in the rat) significantly earlier in life than do the offspring of High LG–ABN dams. These findings provide a stunning parallel to the human literature (see below).

3.2. Neuroendocrine mechanisms

These findings are interesting to consider in light of what is known about the neuroendocrine mechanisms underlying the differences in maternal behavior in High and Low LG–ABN mothers. Throughout most of pregnancy, progesterone levels are high and accompanied by moderate levels of estrogen. Then, prior to parturition, progesterone levels fall and there occurs a surge in estrogen levels. Both events are obligatory for the onset of maternal behavior and of particular importance are the effects of estrogen at the level of the medial preoptic area [MPOA (Rosenblatt, 1994)]. The influence of ovarian hormones on the onset of maternal behavior in the rat is mediated in part by effects on central oxytocinergic systems (Pedersen, 1995). Estrogen increases oxytocin receptor gene expression and receptor binding (De Kloet et al., 1985; Johnson et al., 1989; Bale et al., 1995; Young et al., 1997). ICV administration of oxytocin rapidly stimulates maternal behavior in virgin rats (Pedersen and Prange, 1979; Fahrbach et al., 1984) and the MPOA appears to be a critical site. The effect of oxytocin is abolished by ovariectomy and re-instated with estrogen treatment. Moreover, treatment with oxytocin-antisera or receptor antagonists blocks the effects of ovarian steroid treatments on maternal behavior (Pedersen et al., 1985; Fahrbach et al., 1985). Among lactating females, there are significantly higher levels of oxytocin receptors in the MPOA, the bed nucleus of the stria terminalis and the lateral septum all animals (Pedersen, 1995), however, the lactation-induced increase in receptors levels is substantially greater in the High LG–ABN mothers (Francis et al., 2000). Each of these brain regions is implicated in the expression of maternal behavior in the rat (Pedersen, 1995; Numan and Sheehan, 1997). Not surprisingly, the oxytocin receptor binding levels are highly correlated with the frequency of pup licking/grooming (Champagne and Meaney, unpublished). Importantly, central infusion of an oxytocin receptor antagonist on day 3 of lactation completely eliminates the differences in maternal licking/grooming between High and Low LG–ABN mothers (Champagne et al., 2001). The ascending mesolimbic dopamine seems to be a relevant target for the effects of oxytocin. Oxytocin neurons project directly to the ventral tegmental area, the origin of the mesolimbic dopamine system, and facilitate dopamine release as well as dopamine-mediated behaviors. Dopamine levels in the nucleus accumbens are directly related to the frequency of pup licking/grooming (Champagne et al., in press). Not surprisingly, the magnitude of the dopamine signal in the nucleus accumbens accompanying pup licking/grooming is significantly greater in High LG–ABN mothers. Moreover, central infusion of a dopamine transporter blocker into lactating High and Low LG–ABN females completely eliminated the differences in both dopamine levels in the nucleus accumbens and pup licking/grooming.

Differences in estrogen sensitivity mediate the differential effects of lactation on the induction of oxytocin receptors in High and Low LG–ABN females. Among ovariectomized females given estrogen replacement, there is a significantly greater estrogen effect on oxytocin receptor levels in the MPOA in High compared with Low LG–ABN animals (Champagne et al., 2003b). The effect is apparent across a wide range of doses, and indeed there was little evidence for any effect of estrogen on oxytocin receptor levels in the MPOA of Low LG–ABN females. The fact that such differences occurred even in the non-lactating, ovariectomized state suggests the existence of stable differences in estrogen sensitivity. Indeed, among either lactating High LG mothers or in the virgin female offspring of High LG–ABN dams the expression of estrogen receptor α, but not estrogen receptor β, is significantly increased in the medial preoptic area (Champagne et al., 2003b).

The findings of a recent collaboration with Alison Fleming provide further evidence that maternal behavior can directly program estrogen receptor α expression in the MPOA. These studies exploit the 'pup-in-a-cup' model developed by Fleming and colleagues (Lovic and Fleming, in press) in which newborn rat pups are placed in thermal-controlled cups and reared artificially. Tactile stimulation derived from stroking with a brush comprises part of the care essential for sustaining life under these conditions. The stroking procedure, which mimics maternal licking/grooming, provides an opportunity to systematically vary the amount of tactile stimulation per day for each pup (e.g. 25 strokes $\times$ 5 times/day vs. 5 strokes $\times$ 5 times/day). As adults, the female pups reared artificially with a high level of stroking showed significantly higher levels of estrogen receptor α mRNA expression in the MPOA compared with pups reared under low levels of stroking (Rhees et al., submitted for publication).

In an effort to establish the regional specificity of the effect of maternal behavior, we examined estrogen receptor expression in multiple brain regions including hypothalamic sites. Much to our surprise, we found that estrogen receptor

α mRNA expression was significantly increased in the ventromedial nucleus of the hypothalamus (VMNh) in the offspring of Low LG–ABN mothers. Estrogen induces oxytocin receptor binding in both the VMNh as well as in the MPOA and, predictably, we found increased oxytocin receptor levels in the VMNh of the offspring of Low LG–ABN mothers. Rather impressive evidence for tissue specificity! In our minds, what potentially makes these findings so interesting is that while the estrogen–oxytocin circuit in the MPOA mediates the expression of maternal behavior, the same network in the VMNh regulates female sexual behavior, with no known effects on parental behavior. Infusion of a pseudorabies label into the lumbar epaxial muscles that execute the lordosis response resulted in considerable labeling in the oxytocin fiber tract within the VMH (Daniels and Flanagan-Cato, 2000). ICV infusion of oxytocin facilitates female sexual behavior in estradiol- and estradiol + progesterone treated female rats (Caldwell et al., 1990; Schumacher et al., 1990), while infusion of either an oxytocin receptor antagonist (Witt and Insel, 1991; Caldwell et al., 1994), or an antisense oligonucleotide sequence directed against the oxytocin receptor (McCarthy et al., 1994) into the VMNh decreases female sexual behavior. Interestingly, the central infusion of an oxytocin receptor antagonist, in this case the more selective OTA_2 version, not only reduced lordosis and paracopulatory behavior, but also increased agonistic behavior directed towards the male (Pedersen and Boccia, 2003). These behavioral findings are comparable to those observed in the female offspring of High LG mothers and are consistent with the idea that decreased oxytocin receptor levels in the VMNh, as a consequence of reduced estrogen receptor α expression, mediate the effect of maternal care on the expression of female sexual behaviors.

To summarize, the offspring of Low LG–ABN mothers show evidence for increased sexual receptivity and decreased maternal licking/grooming and arched-back nursing. The offspring of High LG–ABN mothers show precisely the opposite profile. And these differences in reproductive behaviors map onto those in estrogen receptor α mRNA expression, and thus oxytocin receptor binding. These finding suggest that maternal effects on reproductive behavior are mediated by tissue-specific differences in estrogen receptor α expression in brain regions that regulate maternal and sexual behaviors. The remarkable feature of this effect is that the same stimulus input (maternal care) regulates the expression of the same gene, the estrogen receptor α gene, in exactly the opposite manner depending upon brain region (MPOA vs. VMNh).

These patterns of reproductive behavior are reminiscent of well-known reproductive strategies; the *r* and *K* approaches to reproduction (McCarthy, 1965) Life represents a series of energy investments in four domains: growth, development, mating and parental care. The *r* and *K* reproductive strategies represent differential investment in mating versus parental care. The *r* strategy emphasizes a strategy that maximizes the quantity of offspring through earlier and more frequent mating. In contrast, the *K* strategy emphasizes the quality of offspring through parental investment in the offspring. The former approach involves increased investment in mating, the later in parental care. While originally conceived as descriptions of species differences, more recent studies focusing on phenotypic variation with species reveal that both strategies can be represented within the same species, depending upon the prevailing environment conditions (Chisholm, 1993; Coall and Chisholm, 2003; Hill et al., 1994). Indeed it is reasonable to consider the *r* and *K* approaches as lying along a continuum and that the point along this continuum is defined by the quality of parental investment (Chisholm, 1993; Coall and Chisholm, 2003; Hill et al., 1994; Belsky et al., 1991; Gangestad and Simpson, 2000). The reasoning is that if environmental demands are high and threaten survival, then the optimal reproductive approach is to decrease investment in individual offspring in favor of enhanced mating activity—the quantity above quality approach. In contrast, more propitious environmental conditions favor greater investment in individual offspring at the cost of mating. Maximizing offspring quality tends to reduce intergenerational variance in reproductive success, resulting in greater long-term fitness. Moreover, in favorable environments, competition for resources tends to determine success, and offspring quality is thus a relevant consideration in defining the reproductive fitness of the progeny. In contrast, under adverse environmental conditions with high risk and uncertainty, when the probability of extended periods of growth and survival are comparatively low, the optimal strategy is to maximize offspring quantity through early and more frequent mating. Maximizing reproductive output enhances the chances that at least some offspring will survive to sexual maturity. Moreover, since such adverse environments are characterized by uncertainty and often high, unavoidable risks, parental investment in offspring quality is seen as futile (Chisholm, 1993). Increased risk of mortality favors a shift in parental investment away from offspring quality and towards offspring quantity (Chisholm, 1993; Coall and Chisholm, 2003; Hill et al., 1994; Belsky et al., 1991). Moreover, decreased parental investment in the offspring may serve to program defensive responses in a manner that is adaptive for survival in high-risk environments. Under stable environmental conditions, the level of parental investment is then reflected in the reproductive behavior of the offspring. Hence, the same environmental conditions that 'program' enhanced defensive responses may also alter the development of reproductive strategies. The findings with the rat suggest that maternal behavior serves to actively program both defensive responses to threat as well as reproductive strategies. The argument here is that under conditions of stress, both might serve to be adaptive and thus as a logical outcome of environmental adversity in early life.

Trivers (1974) initially focused explanations of gender differences in mating strategies on the assumption that

women were more discriminating in mate choice and restricted in sexual behavior than men. However, more recent studies with humans and other species reveal considerable overlap between the sexes as well as considerable within-gender variation. Among humans, women and men shift between short- and long-term mating strategies with considerable within-gender variation. (Gangestad and Simpson, 2000). A recent meta-analysis found that gender accounted for only 10–20% of the variance in so-called 'casual sex'. More recent views suggest that evolutionary pressures should produce not a single optimal strategy for males or females, but rather a range of conditional strategies. These findings suggest considerable phenotypic plasticity in mating strategies across members of the same species. The critical question then becomes the origin of such phenotypic variation. Clearly some measure of variation is an adaptation to prevailing environmental conditions as well as the competitive position of the individual relative to other same-gender members of the group. However, we argue here that phenotypic variation in mating strategies can emerge as a result of developmental programming. Moreover, such effects are likely to be adaptive for the offspring.

Belsky et al. (1991) argued for a comparable relation between the quality of the environment and reproduction in humans, citing parent–child attachment as the mediating variable. In brief, they argue that the quality of the environment influences parenting and thus the development of individual differences in the form of infant attachment. This proposal is obviously consistent with the ideas presented above in the section on defensive responses. As evidence for this idea, Belsky et al. (1991) cite the results of studies revealing that environmental conditions that are known to compromise parent–child interactions result in early puberty, an early onset of sexual activity and greater promiscuity among human females; insecure attachment is associated with earlier onset of puberty and sexual activity. There is considerable evidence for the relation between family stress, poor parent–child relations and early menarche in human females (Graber et al., 1995; Steinberg, 1988; Kim and Smith, 1998; Moffitt et al., 1992). Early menarche may be seen as adaptive, since in high-risk environments where survival is less certain, the best strategy may be to reproduce early as well as often (Chisholm and Burbank, 2001). Likewise, a poor parent–child relation, especially mother–child, is related to the early onset of sexual behavior, an increased number of sexual partners in adolescence and to an increased number of sexually-transmitted infections (Santelli et al., 2000; Parera and Suris, 2004). Not surprisingly, Low SES environments, where family stress is more common, are associated with early onset sexual behavior in females (Parera and Suris, 2004). Importantly, it is the quality of the family relation more so than the presence/absence of one parent that is critical. Resnick et al. (1993) report that the health and well being of adolescents living in dysfunctional intact nuclear families is worse than that of peers in stepfamilies or single-parent families after divorce. Thus, family stress is associated with insecure attachment and early menarche. There are important implications for health. Early menarche is also associated with poor levels of mental health. Early-maturing girls have more emotional problems, a lower self-image, and higher rates of depression, anxiety, and disordered eating than their peers (Ge et al., 1996). Familial dysfunction in early life is associated with a greater number of sexual partners in adolescence, reduced use of contraception and an increased risk for unintended pregnancy (Hertzman, 1999) and poorer general health in women (Rahkonen et al., 1999).

3.3. Summary

The quality of the environment in early development alters defensive responses to threat and reproductive strategies across a wide range of animals. These effects appear to be developmental adaptations that produce phenotypic variation in response to varying levels of environmental demand. Poorer quality environments result in increased defensive responses to threat, and, at least in females, early menarche and enhanced sexual behavior. This pattern is strikingly similar to that associated with a poor quality of parent–child relations in humans, which are commonly associated with conditions of impoverishment. Low socio-economic environments are associated with increased family stress, which, in turn, predicts an increased frequency of abuse, emotional neglect, lower parent–offspring bonding and harsh/inconsistent discipline. Each of these factors predicts an increased risk for depression, anxiety and drug abuse. Moreover, these conditions are also associated with increased defensive responses to threat (i.e. HPA and sympathetic responses), early menarche, and an earlier onset of sexual behavior with a larger number of sexual partners. Attachment is also associated with the expression of defensive responses in humans. Atkinson et al. (Goldberg et al., 2003) found that differences in attachment are associated with individual differences in HPA responses stress among children: Poorer attachment was associated with increased cortisol responses to stress (Luecken and Lemery, 2004; Essex et al., 2002). Parental bonding is associated with differences in both HPA and mesolimbic dopamine responses to stress in humans (Pruessner et al., 2004b). The common thread between the literature in developmental psychology and behavioral ecology is the emphasis on the importance of environmentally-driven variations in parental care and their importance for phenotypic plasticity in the offspring. Studies with nonhuman species suggest that such effects can occur as a direct result of variations in the quality of mother–offspring interactions.

Increased stress reactivity and precocious sexual behavior are associated with a risk for anxiety and depression in adolescence and adulthood. We believe that this relation explains why childhood SES predicts vulnerability for multiple forms of mental illness in adulthood

(Walker et al., 1999 and see references cited above). We suggest that the association between SES in early life and mental health in adolescence and adulthood is, in part at least, due to alterations in parent–offspring relations, which in turn program the expression of genes in selected brain regions that regulate defensive and reproductive behaviors. Thus, the origins of the effect of childhood SES are both social and biological; because variations in parental care produce sustained effects at the level of gene expression, explanations based on attachment theory and epigenetic variations in gene expression are complimentary, not oppositional. Indeed, the effects of parental care on gene expression explain how social relations in early life are 'biologically embedded' (Walker et al., 1999) and thus influence health over the lifespan.

3.4. Conclusions and implications

The central idea of this review is that impoverished environments are defined by an increased level of physical and psychological demand as well as inadequate levels of resources that produce alterations in parent–offspring interactions that program the development of gene expression in brain regions that regulate defensive and reproductive behaviors. The effect of poverty is to increase the reactivity of defensive systems and to favor reproductive strategies that maximize fecundity at the expense of parental investment. We emphasize the importance of understanding such effects as adaptations to prevailing socioeconomic hardship, and not as 'deficits' or 'impairments' in some idealized developmental trajectory. This perspective leads to an important conclusion for public health. Thus, the critical target for intervention is not the altered defensive or reproductive behavior of the individual, but rather the causal conditions of poverty and family dysfunction. This conclusion is supported by findings that intervention programs that target the family, as opposed to a unique focus on the individual child, are successful in altering developmental outcomes. The danger, of course, is that such interventions presuppose an improvement in the quality of the prevailing environment. To the extent that the effects of childhood impoverishment on defensive responses and reproduction are adaptive, intervention aimed at reversing such effects without providing adequate social or economic resources may be questioned. These considerations suggest that the health of individuals within a society must be supported by community-based programs as well as interventions targeting the individual.

While the effects of childhood adversity on adult function and health are compelling, they are best understood in models that consider the cumulative effects of disadvantage over the lifespan. The hypothesis that best fits current evidence is that the graded effect of SES on health is an 'emergent property' of the interaction 'between the developmental status of people and the material and psychosocial conditions they encounter over their life course' (Walker et al., 1999). Childhood SES influences the development of personality traits such as hostility and hopelessness, and thus the risk for depression (Rahkonen et al., 1997; Bosma et al., 1999; Sadowki et al., 1999; Ritsher et al., 2001; Harper et al., 2002). We propose that these effects are mediated by alterations in parent–offspring interactions that, in turn, produce alterations gene expression in selected brain regions (e.g. prefrontal cortex, amygdala, hippocampus (Liu et al., 1997; Francis et al., 1999a; Caldji et al., 2003, 1998; Liu et al., 2000)) that regulate cognitive–emotional responses to stress. These effects define an increased vulnerability for psychopathology over the life span. Yet even in studies that reveal a clear effect on such traits, childhood SES alone may not predict mortality independent of SES in adulthood (Lynch et al., 1994; Gilman, 2002). Of course childhood SES predicts SES in adulthood. There are multiple pathways that might serve to mediate this relationship and include effects of defensive responses and reproductive behaviors. Increased stress reactivity and early onset sexual behavior could serve to ensure reduced SES. Moreover, there are parental effects on the development of brain structures that mediate cognitive functions such as learning and memory. In the rat, enhanced maternal licking/grooming is associated with increased neuron survival and synaptic density within the hippocampus (Liu et al., 2000; Bredy et al., 2003a,b, 2004). These effects are mediated by increased hippocampal expression of the subunits for the NMDA and AMPA receptors (Bredy et al., 2004). Adults animals reared by Low LG–ABN mothers show reduced expression of the NMDA and AMPA receptor subunits, decreased hippocampal synaptic density and impaired performance on tests of hippocampal-dependent cognitive function (Liu et al., 2000; Bredy et al., 2003a,b, 2004). Each of these effects is eliminated with environmental enrichment over the peripubertal period (Bredy et al., 2004). These findings are of potential relevance in assessing the influence of lifetime SES on health in humans. Childhood SES predicts cognitive function in adulthood (Jefferis et al., 2002), and the effects of SES at birth on adult mortality are at least partially attenuated after adjustment for cognitive function (Osler et al., 2003). While such findings may appear dauntingly deterministic, rodent studies also reveal remarkable effects of environmental enrichment during the peripubertal period on emotional and cognitive outcomes (van Praag et al., 2000; Guilarte et al., 2003; Rampon et al., 2000; Francis et al., 2002). Interestingly, the effects of environmental enrichment are often most apparent in animals experiencing some form of deprivation in early life. In the rat, peripubertal environmental enrichment can serve to completely eliminate the effects of maternal care on measures of hippocampal development and function (Bredy et al., 2004). Again there are striking parallels to the human literature. Interventions targeting the cognitive development of children from impoverished environments show remarkable and sustained effects that are most apparent among children from the most disadvantaged homes (Ramey and Ramey, 1998). Indeed, the effects of adoption among

the severely deprived Romanian orphans suggest a remarkable capacity for the reversal of the effects of early life deprivation (Rutter, 1998). The ideal scenario would appear to be conditions in which the interventions occur within a context that offers a realistic opportunity for upward mobility in social and economic status. Increased SES should render valueless the otherwise adaptive effects of poverty on defensive and reproductive behavior. The counterproductive scenario would be instances in which therapies target adaptive effects of poverty on defensive and reproductive behavior without change in the social and economic conditions from which such behaviors very logically derive (Earls, 2001). Ultimately, we will need to contend with the reality that neural development, function and health are defined by social and economic influences, and that the success of interventions that ignore such forces will be seriously limited.

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Further reading

1. Bobak, M., Pikhart, H., Rose, R., Hertzman, C., Marmot, M. Socioeconomic factors, material inequalities, and perceived control in self-rated health: cross-sectional data from seven post-communist countries. Soc. Sci. Med. 51(9), 1343–1350.