Chapter 5
Ontogeny of Stress Reactivity in the Human Child: Phenotypic Flexibility, Trade-Offs, and Pathology

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Abstract We humans are highly sensitive to our social environments. Our brains have special abilities such as empathy and social foresight that allow us to understand each other's feelings and communicate in ways that are unique among all living organisms. Our extraordinary social minds, however, come with some significant strings attached. Our emotional states can be strongly influenced by what others say and do. Our hearts can soar, but they also can be broken. Our bodies use internal chemical messengers—hormones and neurotransmitters—to help guide responses to our social worlds. From romantic daydreams to jealous rage, from orgasm to lactation and parent–child bonding, the powerful molecules produced and released by tiny and otherwise seemingly insignificant cells and glands help orchestrate our thoughts and actions. Understanding this chemical language is important for many research questions in human health. Here we focus on the question of why social relationships can affect health—why it is that words can hurt children. Stress hormones appear to play important roles in this puzzle.

The hypothalamic–pituitary–adrenal axis (HPAA) is highly responsive to traumatic experiences including social challenges. For the past 23 years we have conducted a field study of child stress and family environment in a rural community in Dominica. The primary objective is to document hormonal responses of children to

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everyday interactions with their parents and other care providers, concomitant with longitudinal assessment of developmental and health outcomes. Results indicate that difficult family environments and traumatic social events are associated with temporal elevations of cortisol and elevated morbidity. The long-term effects of traumatic early experiences on cortisol profiles are complex and indicate domain-specific effects, with normal recovery from physical stressors, but some heightened response to negative-affect social challenges. These results are consistent with the hypothesis that developmental programming of the HPAA and other neuroendocrine systems associated with stress responses may facilitate cognitive targeting to salient social challenges in specific environmental contexts.

5.1 Introduction

Living organisms are flexible; they can respond to changing conditions with a variety of morphological, physiological, and behavioral mechanisms. The processes that organisms use to change and respond to environmental challenges are posited to be evolved adaptations (West-Eberhard 2003). Flexibility involves both immediate, temporary responses and longer-term developmental changes. A classic example of adaptive developmental response is exhibited by the water flea, Daphnia ambigua, which grows a "helmet" of protective spikes if exposed during juvenile stages to chemicals released by one of its common predators, Chaoborus flavicans (Hanazato 1990). In the absence of the chemical signal of the Chaoborus predator, the juvenile Daphnia economize and allocate the resources that would have been used to grow the protective helmet into other somatic functions (Agrawal et al. 1999).

The human child does not grow spikes or other such dramatic morphological options. He or she nonetheless exhibits a most complex form of phenotypic plasticity. For the child must master the dynamics of social networks and the near-infinitely shifting sands of culture, supported by the extraordinary information-processing capacities of the human brain (Flinn 2006c; Rilling and Sanfey 2011) and its socio-cognitive and linguistic programs. Instead of growing a helmet, the human child can acquire the information necessary to build one out of animal skins or even duct tape.

We are especially interested in the unusual sensitivity of the fetus and child to the social environment—interpersonal relationships—and the consequent changes that occur in physiological stress systems. Our curiosity is piqued by both the paradoxical nature of this phenomenon—for physiological stress response has attendant somatic costs—and its importance for human health. Adverse conditions in utero appear to have a wide range of negative effects on child development and well-being with grave health consequences throughout the life span. Maternal stress during gestation has been reported to affect child development and postnatal behavior, mood, and mental and physical health (Seckl and Meaney 2004; Van den Bergh et al. 2008; Glover 2011; Brand et al. 2011; Hatzinger et al. 2012). For example, maternal depression and high levels of social anxiety during pregnancy are associated with low birth weight, elevated stress reactivity, and subsequent disease risk for

offspring (Gluckman and Hanson 2006; Weinstock 2005). The processes that underlay this biological embedding of information from the social environment in humans remain obscure. Our objective here is to use evolutionary theory to evaluate possible mechanisms and developmental trajectories that link early life events to physiological stress response, psychological development, and health outcomes.

Here we use an evolutionary framework to discuss the role of stress as a critical adaptation. First, we briefly review the general evolutionary logic of what is commonly termed "developmental programming" and discuss the effects of social environment on the ontogeny of neuroendocrine stress response and subsequent health outcomes. We evaluate our ideas with a brief overview of our field study of child stress and family environment in Bwa Mawego, Dominica. In our discussion we translate our interpretations of the results from this basic research into concepts with potential clinical application. We conclude with some evolutionary perspectives on the rather unusual life history and ontogeny of the human fetus and child.

5.2 Alternative Phenotypes

Waddington (1956) termed the mysteries of the translation of information from genetic materials during the development of the phenotype as the "great gap in biology." Ontogeny is an astonishingly complex process. Multi cellular organisms such as humans have significant portions of their genomes that perform developmental "regulatory" functions—in effect, switches that turn some genes off and others on during development. To complete their development takes humans nearly three decades. Physical and reproductive maturation take roughly two decades, while the brain continues its development for up to another decade (Bogin 1999; Fox et al. 2010). Throughout these periods, environmental exposures including social, energetic, and immune challenges can alter an individual's developmental trajectory in a variety of ways (Fig. 5.1a). Social, environmental, and physical challenges have been associated with mental health outcomes, academic performance, memory capabilities, sexual behavior, energy metabolism, immune response, aging patterns, and life-span length (Felitti et al. 1998; Harkonmaki et al. 2007; Thomas et al. 2008) (Fig. 5.1e). Consequently, the quality of the environment during development may affect an individual's health and well-being across their life span (Glover 2011; Flinn et al. 2011; Nepomnaschy and Flinn 2009; Swain et al. 2007; Talge et al. 2007). Importantly, the effects of those environmental exposures on ontogenesis appear to be more intense and extensive earlier during development that the exposure takes place (Van den Bergh and Marcoen 2004; Weinstock 2008; Laplante et al. 2004). This inverse relationship between the timing of an exposure and the intensity and breadth of its effects may potentially be explained by the mediating mechanisms involved.

The underlying mechanisms through which environmental challenges "get under the skin" and influence physical and mental health and behavior are the subject of much scientific scrutiny. Epigenetic processes have emerged as important candidate

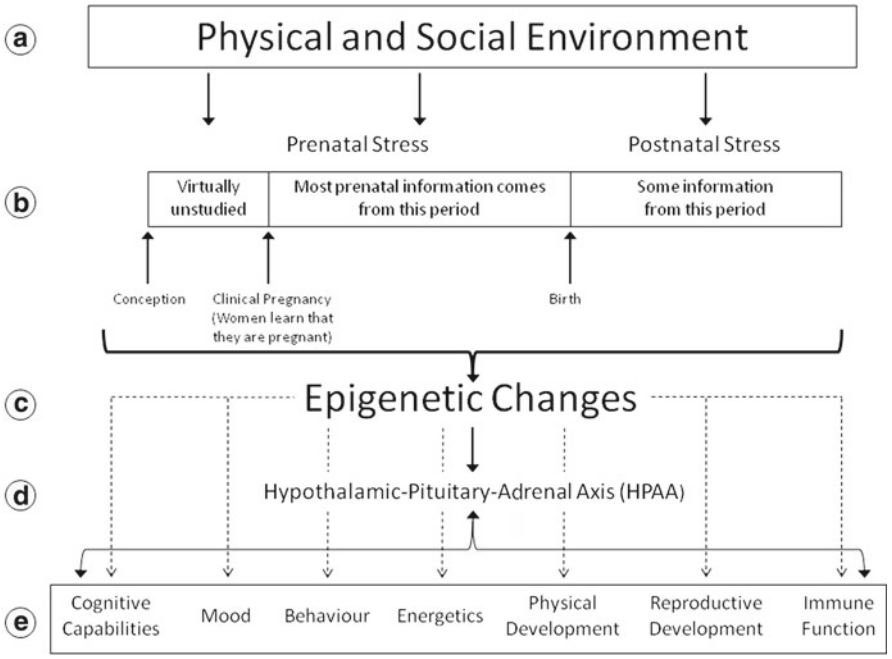

Fig. 5.1 The "great gap" in understanding the ontogeny of the human child

mechanisms. The expression of every gene depends on the individual's epigenome. The epigenome consists of methylations, histone acetylations, and other chemical "marks" that influence gene expression by affecting the extent to which specific sequences of DNA are accessible for transcription. The differential transcription of particular genes and the translation of their encoded proteins ultimately contribute to the observable traits in an individual (phenotype). DNA methylation, the addition of a methyl group to a cytosine base, is considered to be one of the more important and representative epigenetic modifications. Environmental challenges can affect the enzymatic pathways that regulate DNA methylation patterns, which can lead to specific changes in endocrine and metabolic regulation. These changes can in turn modify a wide range of critical outcomes, including growth trajectory, energy metabolism, reactivity, developmental pace, cancer risk, behavioral profiles, long-term memory capabilities, and neurological function (Fig. 5.1).

Although not without cost, these regulatory epigenetic switches are expected to result in phenotypic modifications that aid an organism to survive environmental challenges (West-Eberhard 2003). For example, food availability and crowding determine development of wingless grasshopper Phaulacridium vittatum nymphs into two distinct adult morphs. Scarce food and overcrowding result in a migratory, winged morph, whereas the opposite conditions result in the strikingly different wingless morph. Each morph appears well suited to their respective environmental challenges. Plants also exhibit strategic modifications of phenotype in response to

cues of future environmental conditions such as light availability and herbivore density. For example, thale cress (Arabidopsis thaliana) increases production of chemicals that deter caterpillars and other insects in response to loss of foliage (van Hulten et al. 2006; for general review, see Agrawal 2001, 2007).

Neurological processes provide for more rapid temporal adjustments of phenotype. For example, a young rat rapidly elevates pulse rate when it sees a cat to prepare for the energetic demands of a potential chase. Frequent exposure to cats results in more permanent changes to parts of the rat's brain—in particular the amygdala—that enhances predator anxiety and wariness in the future (Ademec et al. 2005; see also Amaral 2003; Sabatini et al. 2007). Human studies focused on epigenetic modifications are still scarce. Essex and colleagues recently published the results of a retrospective study where they report to have found an association between DNA methylation patterns in adolescents and adversity levels during infancy and preschool. These effects appear to depend on whether the stressor was maternal or paternal and were modulated by the individual's gender (Essex et al. 2012). Importantly, the ultimate effects of life events on the stress response system and their reversibility seem to be linked to the specific timing of their occurrence during ontogeny.

The general objective of developmental plasticity is to modify the phenotype so as to better meet future challenges. The key problem is predictability. How reliable are the cues that are used to assess future contingencies? The difficulty of prediction increases with distances in time and space. Dark clouds, thunder, and lightning are good indicators of oncoming rain in the immediate future. Cues for next week's or next year's weather conditions are less certain. Nonetheless we build roofs on our houses to protect us from future rains. Early preparation allows for more specialization and economy of development. The sooner one can adjust development to fit future environments, the better; in this way, resources need not be wasted covering other options. The balance between predictability and specialization during development influences the ontogenetic trajectories of phenotypic plasticity. "Critical periods" for environmental input involve this inherent temporal trade-off between the reliability of cues and the advantages of earlier specialization.

5.3 What Is Special About the Fetal and Infant Environments for Ontogeny?

The fetus has a unique source of information upon which to guide development of its phenotype: via the placenta, it can monitor its mother's neuroendocrine systems, including levels of cortisol, oxytocin, epinephrine, and other bioactive molecules. This hormonal data can provide cues to maternal condition and how the mother responds to different environmental stimuli, invaluable knowledge for decisions about ontogenetic trajectories. After birth the offspring loses this direct link to maternal neuroendocrine response and must instead rely upon breast milk and external cues—such as behavior and olfactory signals—to monitor levels of maternal hormones such as cortisol.

Fetal and infant development, therefore, present somewhat of a paradox: on the one hand, it is very difficult to predict what conditions will be like in 10 or 20 years. On the other hand, this period offers a wealth of information about the mother's internal states that can be used to adaptively modify ontogenetic trajectories. In preparation for his or her future postnatal environment, it may be advantageous for the fetus to adjust the baseline functioning of its own HPA axis to that of its mother. Following a similar logic, sudden alterations to the mother's HPA baseline functioning (acute stress) could also indicate relevant changes in the conditions to be faced postnatally, and the fetus should benefit from adjusting its stress response to those changes as well. A simple example of this type of scenario could concern the loss of a contributing partner/father taking place during gestation. Such an event could trigger modifications in the mother's HPA functioning and also affect the prenatal and postnatal environments of development for the fetus. Neurophysiological changes that help the developing fetus to survive a fatherless gestation, first, and a fatherless childhood, second, should be positively selected. Whether the resulting adult phenotype enjoys his or her life or whether peers deem the individual a carrier of one pathology or another is irrelevant to the process of natural selection. Some of the undesirable outcomes associated with stress may represent the unavoidable costs of adaptations that allowed the individual to survive exogenous challenges at some point during development or to be better adapted for the current environment. Labeling all stress outcomes as pathologies ignores the adaptive role of stress function, reduces our ability to achieve a complete understanding of the role stress plays in the unusual life history and ontogeny of the human fetus and child, and fails to help us curtail environments that lead to those undesirable outcomes.

5.4 Mother–Infant Synchrony

One interesting aspect of infant–mother relations involves synchrony or entrainment (Feldman et al. 2011, 2012). Some mother–infant pairs have activity and hormone levels that are highly correlated (Fig. 5.2a). Other pairs are more discordant (Fig. 5.2b).

Disruptions in child development as identified by delays in the Denver developmental assessment are associated with synchrony of cortisol response in mother–infant pairs (Fig. 5.3) and with reported and observed attachment behavior (Fig. 5.4).

The reasons why synchrony of cortisol levels between mother and infant is associated with positive outcomes for child development are uncertain. We speculate, based largely on 23 years of ethnographic study of this community, that mothers with fewer constraints on child care (such as separation from infant due to work and other outside demands) are more likely to be engaged in mutual activities (e.g., sleeping together, eating together, regular breastfeeding schedule, and playing together) and therefore have more similar cortisol levels. Additionally, as cortisol levels are lower in infants than in adults and there is much variation in the timing at which the circadian pattern of cortisol secretion is established during infancy (Hucklebridge et al. 2005; Laakso et al. 1994; Shimada et al. 1995; Touitou and Haus 2000; Touitou et al. 1983), it is possible that the observed synchrony between

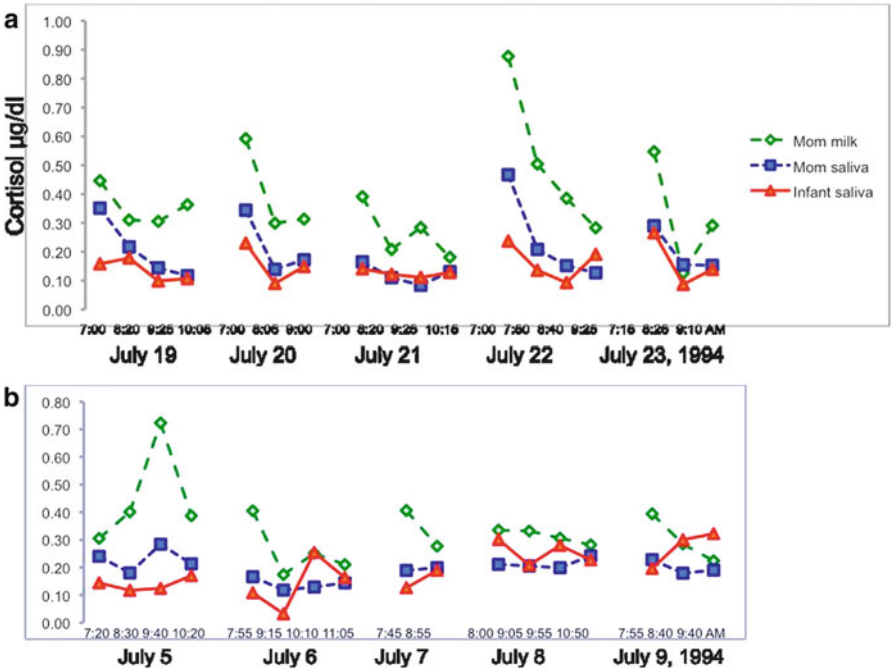

Fig. 5.2 Synchrony of mothers and their 8-month-old infants cortisol levels. Case #5 (**a**) exhibits moderate relation between a mother's salivary and breast milk cortisol levels and the salivary cortisol levels of her infant ($r=0.743$ for saliva). Case #12 (**b**) ($r=-0.182$ for saliva) exhibits lower levels of relation (Data from Flinn et al. 2011. Biological samples collected by Mark Turner)

mothers and their nursing infants is just reflecting the mothers' circadian profiles as maternal cortisol is transmitted through mothers' milk (Brummelte et al. 2010). Hence the synchrony relation may be an incidental (noncausal) marker of the intensity and quality of parental care.

The information that is conveyed by neuroendocrine response between mothers and infants is an understudied research area. The shift from the enormous amount of neuroendocrine information available in utero to postpartum may represent an important life history transition. At a minimum the postpartum transition presents new communicative challenges for both mothers and infants.

5.5 Why Is the Human Child so Sensitive to the Social Environment?

Human behavioral plasticity is unusual in its potential for novelty and for cumulative directional changes occurring over lifetimes and multiple generations. Natural selection equipped humans with rather special abilities to adjust and respond to the current environment and, in some circumstances, to struggle to improve upon the current

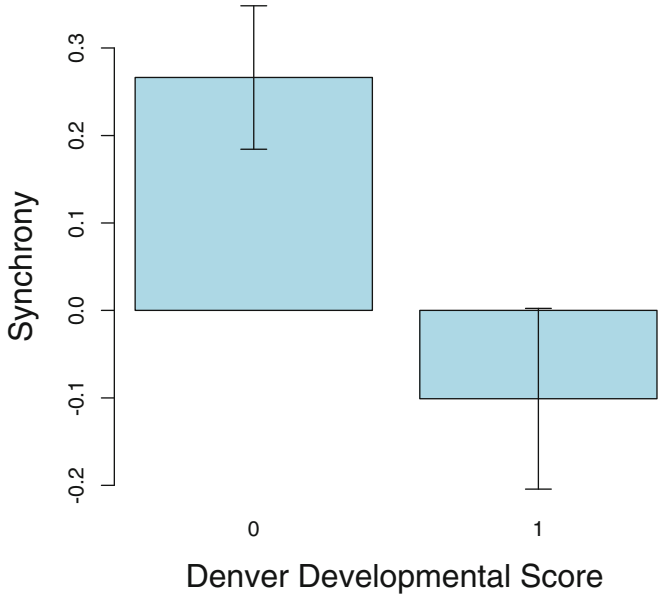

Fig. 5.3 Mother–infant cortisol synchrony (*r* values as in Fig. 5.1) and Denver developmental scores (0 = no risks or delays; 1 = one or more risks or delays). *N* = 22 and 9, respectively

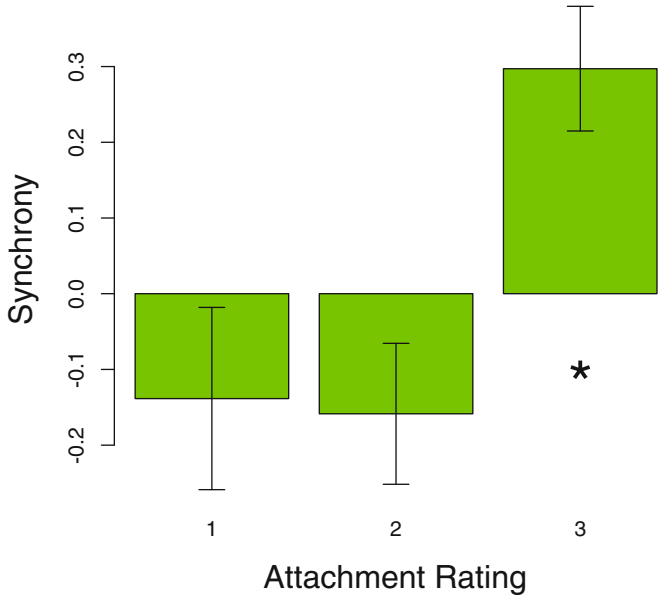

Fig. 5.4 Mother–infant cortisol synchrony (*r* values as in Fig. 5.1) and attachment (physical and emotional closeness: composite measure of reported and observed affection and care, including shared attention, nuzzling, and response to distress). *N* = 6, 12, and 13, respectively. Mother–infant pairs with attachment rating 3 had higher synchrony than those with attachment ratings of 1 or 2

strategies, that is, to be creative, to develop a way of doing something that is different, and potentially better, than the way that it is currently being done by others.

Novelty is a risky business in the evolutionary game. Mutation is organic evolution's source of variability, new genetic information that may alter the phenotype in beneficial or, much more likely, deleterious ways. Hence organisms have evolved mechanisms to protect and correct their DNA if it has been damaged. Changes, especially random ones, to a machine/organism that have been finely honed over millions of generations are not a good bet. And yet the human mind does so regularly and persistently with the information bits that it processes. It seems to have a system of filters and checks that improve the odds of hitting upon a good idea, a better mousetrap.

One cognitive area in which humans are truly extraordinary is social relationships. Humans are able to mentally represent the feelings and thoughts of others. Humans have unusually well-developed mechanisms for theory of mind (Amodio and Frith 2006; Gallese et al. 2004; Leslie et al. 2004) and associated specific pathologies in this domain (Baron-Cohen 1995; Gilbert 2001, 2005). We have exceptional linguistic abilities for transferring information from one brain to another (Pinker 1994), enabling complex social learning. Social and linguistic competencies are roughly equivalent in both males and females, although human mothers appear to have especially important roles in the development of their offspring's sociocognitive development (Deater-Deckard et al. 2004; Simons et al. 2001). In apparent contrast with chimpanzees and gorillas, human females have substantial social influence or power, based not only on modeling a behavior but on the use of information transmitted via language (e.g., Hess and Hagen 2006).

The human child is an extraordinarily social creature, motivated by and highly sensitive to interpersonal relationships (Gopnik et al. 1999). The life history stage of human childhood enables the development of necessary social skills (Muehlenbein and Flinn 2011), including emotional regulation. Learning, practice, and experience are imperative for social success. The information-processing capacity used in human social competition and cooperation is considerable and perhaps significantly greater than that involved with foraging skills (Roth and Dicke 2005). An extended human childhood may be attributed to the selection for development and necessity of a social brain that requires a lengthy ontogeny to master complex dynamic tasks such as learning the personalities, social biases, and so forth of peers and adults in the local community and developing appropriate emotional responses to these challenges (Battaglia et al. 2004; Bugental 2000). The learning environments that facilitate and channel these astonishing aspects of human mental phenotypic plasticity appear to take on a special importance.

Parents and other kin may be especially important for the child's mental development of social and cultural maps due to their level of emotional involvement/attachment and because they may be relied upon as landmarks who provide relatively honest information. From this perspective, the evolutionary significance of the human family in regard to child development is viewed as a nest from which social skills may be acquired and emotional regulation developed (Flinn et al. 2005a, b, 2007; Flinn and Coe 2007), in addition to its importance as an economic unit centered on

the sexual division of labor. The links among psychosocial stimuli, emotions, and physiological stress response may guide both the acute and long-term neurological plasticity necessary for adapting to the dynamic aspects of human sociality. Adjustments to developmental trajectories begin with the zygote's adaptation to the maternal uterine environment and continue throughout pregnancy, infancy, and childhood. The family appears to play a key role in this adaptive process.

5.6 Social Brain and the Human Family

One of the most remarkable developments in the evolution of life has been the dramatic growth of brain size and complexity found among primates over the past several million years. The adaptive advantage in this spurt in brain growth may be related to the complex and highly integrated social lives found among primates (Alexander 1990; Byrne and Suomi 2002; Flinn and Ward 2005). The size of the neocortex relative to the rest of the brain is correlated with the size of the social group in which a particular primate species lives (Dunbar 1997, 2007; Dunbar and Schultz 2007). The primary selective pressures that led to the rapid evolution of the human brain may have involved competition in the social world of our hominid ancestors and the cognitive skills required to successfully manage the kin- and reciprocity-based coalitions (Alexander 1990; Flinn and Alexander 2007).

The selection for brain size and complexity found among primates also occurred in tandem with the selection for prolonged parental care (Allman 1999; Geary and Flinn 2001; Kaplan et al. 2003; Flinn et al. 2005a, b). The coevolution of the brain and the family permitted both a protective environment in which brain growth after birth could occur and a structure in which information beyond that encoded in DNA could be transmitted over the generations. A lengthened period of parental care also allowed the developing brain to adapt to a more complex social environment, with the family providing a social realm in which a child could learn the competitive and cooperative relationship skills needed to successfully navigate in the larger world (Flinn 2004; Kaplan et al. 2003).

The prolonged period of protective development necessary for the growth of the human brain, then, entails more than the mother–child dyad. In Evolving Brains (1999) Allman states, "Without the extended family, big brains would not have evolved in hominids. … The human evolutionary success story depends on two great buffers against misfortune, large brains and extended families, with each supporting and enhancing the adaptive value of the other" (pp. 202–203; see also Hrdy 2005; Walker et al. 2010, 2011).

The brain/family coevolution also entailed the selection of the powerful neuroendocrine mechanisms required for the attachments involved in human mating, parenting, and extended family bonds (Carter 2005; Flinn 2011; Panksepp 1998). For not only were highly sophisticated cognitive skills required to observe, remember, analyze, and respond to complex social scenarios, the emotional forces forging intricate and enduring bonds among family and larger social groups were also required. Although the family provided the protective environment in which a complex brain

can develop, the attachments entailed also exerted pressures on family members to which they must have had to continuously respond. The strong bonds, required for prolonged pair bonding, parental investment, and connections in the larger family and social systems, can generate intense emotional states. Since such bonds are vital to individual and family well-being, disturbances in important relationships can be perceived as threatening and activate the fear or stress response. The evolution of the "social mind" required the integration of increasingly complex cognitive and emotional functions, allowing the individual not only to attend to the external social world but to regulate the intense emotional reactions stimulated by events in the relationship environment.

5.7 Parental Care and Stress Reactivity

One aspect of how well individuals respond and adapt to challenges over the course of their lives is related to the effectiveness of their stress response systems. This entails how accurately they are able to perceive social stressors as well as how effectively they respond to them (Del Giudice 2012; Huether 1996, 1998; McEwen and Seeman 1999). Over the past several decades significant knowledge has been gained about the mammalian neuroendocrine stress response system and the influence parental care has on its development.

Much research has focused on the limbic–hypothalamic–pituitary–adrenal (L-HPA) system and the release of "stress hormones" into the bloodstream, which help to regulate the mind–body's response to challenge. The stress response is designed to release and channel energy to allow individuals to adapt to changing conditions and threats. This mobilization is aimed at facilitating cognitive, emotional, physiological, and behavioral responses. Those responses are mediated in part by the release of the catecholamines (epinephrine and norepinephrine) and the stress hormones corticotropin-releasing hormone (CRH) and cortisol. The "stress hormones" help to coordinate a system-wide response, involving the brain, cardiovascular, immune, digestive, and reproductive systems, in order to respond to the challenge or threat at hand. This automatic response is vital to survival. However, while the short-term elevation of cortisol in the bloodstream results in adaptive responses chronic elevations can lead to impairment in one or more of biological systems (Huether 1996, 1998; LeDoux 1996; Lupien and McEwen 1997; McEwen 1995, 1998; Sapolsky 1992). Prolonged heightened L-HPA responses to stress have been found to be associated with autoimmune and cardiovascular illnesses as well as anxiety, depressive, and addictive disorders (Heim and Nemeroff 2001; McEwen 1998; McEwen et al. 1997).

Individuals differ in how they respond to stress including their behavioral, emotional, and physiological resilience in the face of life pressures. The L-HPA system of individuals is not equally influenced by all stressors, but primarily by those that are seen as uncontrolled and as having a social-evaluative aspect (Dickerson and Kemeny 2004). Entailed in the phenotypic plasticity of the human are the significant and enduring effects the parental–offspring relationship has on the offspring's

responsiveness to stress throughout life. Animal studies have demonstrated that subjecting one generation to uncontrollable stress results in observable behavioral and physiological changes in their offspring.

5.7.1 Prenatal Stage

The parental influence on the development of an offspring's physical and behavioral responsiveness to stress begins even prior to birth. The stressing of pregnant mammals can result in changes among offspring that persist into adulthood. Among rodents such stressing has been found to influence their offspring's neurotransmitter functioning (Fride and Weinstock 1988; Moyer et al. 1978; Takahashi et al. 1992); opiate and benzodiazepine receptors (Insel et al. 1990; Fride et al. 1985); maternal and sexual behavior (Champagne and Meaney 2006; Fride et al. 1985; Kinsley and Bridges 1988); exploratory, cognitive, and aggressive behaviors (Grimm and Frieder 1987; Kinsley and Svare 1986); and reactivity to stressful situations (D'Amato et al. 1988; Pollard 1984; Takahashi 1992). In a review, O'Regan et al. (2001) cite further findings of prenatal exposure to exogenous or endogenous stress hormones associated with hypertension, hyperglycemia, hyperinsulinemia, as well as altered behavior and neuroendocrine responses into adulthood. Cross-fostering and adoption studies have demonstrated that some of the effects of prenatal stressing can be moderated during postnatal development (Maccari et al. 1995; Weinstock 1997).

Similar findings have been found in studies with nonhuman primates (Clarke et al. 1994; Clarke and Schneider 1993; Schneider 1992; Schneider and Coe 1993). Though most of the primate studies focused on the behavioral and physiological functioning of infants, Clarke and Schneider (1993, 1994) studied the long-term effects of prenatal stressing of rhesus monkeys and found that the offspring continued to demonstrate more anxious social behavior and more elevated ACTH and cortisol levels when stressed than did controls.

Human studies are consistent with the prenatal stress findings of the nonhuman animal studies. Glover and O'Connor (2002), for example, reported in an epidemiological study that a strong relationship existed between maternal anxiety during the third trimester and behavioral and emotional problems in those children at age 4. In a study of mothers who had been exposed to the World Trade Center collapse while pregnant, Yehuda et al. (2005) found that both the mothers who developed PTSD and their infants at age 1 had reduced cortisol levels as compared to the mothers who did not develop PTSD and their infants. Reduced cortisol levels had previously been found among individuals with PTSD.

5.7.2 Postnatal Stage

The study of the early postnatal period has also demonstrated that the parent–offspring relationship can have a lifelong influence in regulating an offspring's responsiveness to stress. In both human and nonhuman studies, the disruption of the

maternal–offspring relationship as well as overprotective, restrictive maternal behavior have been found to be associated with long-term cognitive, physiological, and behavioral effects on offspring (Anderson et al. 1999; Byrne and Suomi 2002; Essex et al. 2002; Fairbanks 1989; Fairbanks and McGuire 1988; Francis and Meaney 2002; Mirescu et al. 2004; Suomi 2002; Suomi et al. 1983).

The influence of the early parental relationship on an offspring's later responsiveness to stress appears to be shaped by the actual "programming" of the neuroendocrine stress response system. Investigators have demonstrated that variation in particular maternal behaviors (licking and grooming, arched-backed nursing) among rodents results in stable individual differences in the neural systems that mediate fearfulness in their offspring which persist into adulthood (Caldji et al. 1998; Francis et al. 1999; Liu et al. 1997). More specifically, higher or lower levels of these maternal behaviors influence gene expression of the stress hormone, CRH, in the hypothalamus and amygdala, which are involved in activating the HPA stress response system. These maternal behaviors also influence gene expression for glucocorticoid (cortisol in primates; corticosterone in rodents) receptors in the hippocampus, which is instrumental in down regulating the HPA stress response. Maternal behaviors, then, can shape individual differences among offspring in their reactivity to stress. Elegant cross-fostering methods determined that stress reactivity was influenced by nursing mothers, but not by biological mothers (Caldji et al. 1998; Francis et al. 1999; Liu et al. 1997).

Human studies also suggest that the early environment and parental care influence individual differences in the stress reactivity of children. Most of the studies have been retrospective and usually investigate the impact of either early life stressors and trauma or maternal depression. Several studies, for example, have found that early trauma or loss is associated with increased stress reactivity (Heim et al. 2002; Kaufman et al. 2000; Nicolson 2004). The experience of early life stress or maternal stress during childhood is related to the later development of depression or anxiety disorders (Brunson et al. 2001; Grossman et al. 2003; Heim and Nemeroff 2001), both of which may be related to dysregulation of the stress response system. Further, there is some evidence that the stress reactivity of children is influenced by depression in their mothers (Ashman et al. 2002; Harkness and Monroe 2002; Lupien et al. 2000). Maternal depression in a child's first 2 years of life, for example, was the best predictor of elevated cortisol levels at age 7 (Ashman et al. 2002).

Given the lengthy period of development and plasticity of the human brain (Sapolsky 2003), a number of studies highlight the importance of long-term developmental studies of children in order to determine the influence of early adverse experiences on the later functioning of the L-HPA stress response system. Gunnar and Donzella (2002) found that a child's L-HPA stress response system is to some degree regulated by parental care, thus mediating the influence of stressful events. In a longitudinal study, Flinn (2006a, 2009) found that the cortisol reactivity of children to stressful events was influenced by the family environment. Another longitudinal study (Essex et al. 2002) found higher cortisol levels among children exposed both during infancy and at 4.5 years, but not among children exposed only in infancy or at 4.5 years of age. Socioeconomic status and maternal depression

were associated with cortisol reactivity in a study of Quebec children, but SES effects emerged over time (Lupien et al. 2000). These studies suggest that while there are sensitive periods in development, during which the stress response system is more open to influence, in humans such periods may occur over a significant part of development.

The link between parental care and stress axis function is likely to be a primitive one. McGowan and colleagues compared methylation patterns between suicide victims with and without a history of childhood abuse and found that the postmortem hippocampus obtained from those who suffered abuse presented lower levels of glucocorticoid receptor mRNA and its transcripts (McGowan et al. 2009). These results are consistent with similar findings in nonhuman models. An ancient origin for the role of parental care on the epigenetic regulation of the functioning of the L-HPA stress response system, together with the obvious costs that some of the resulting behaviors have for the carriers in some contexts, strengthens the idea that under dire circumstances, traits such as anxiety and depression should provide a selective advantage.

The critical question is, what are those circumstances? And why can early programming of the L-HPA stress response system be reversed by later experience (Francis et al. 2002)? To answer those questions, it is necessary to have thorough understanding of the complexity of human society and its social units—communities, groups, and especially the human family—in which the mother–child relationship is embedded.

5.8 Family Influence on Children's Stress Reactivity

There is, then, a significant body of research which demonstrates that the quality of maternal care can influence the development of individual differences in stress reactivity among offspring and, as a result, their health and behavior (Caldji et al. 1998; Essex et al. 2002; Fairbanks and McGuire 1988; Flinn 1999, 2006b; Suomi 2003). The evidence suggests such differences occur due in part to the influence maternal care can have on the development of an offspring's L-HPA and CRH stress response systems (Brunson et al. 2001; Francis and Meaney 2002; Heim and Nemeroff 2001; Ladd et al. 2000; McEwen and Magarinos 2001; Weaver et al. 2004).

Most studies on the interaction between maternal behavior and stress reactivity have focused on one or more of four areas: (1) maternal separation or early trauma (Anderson et al. 1999; Byrne and Suomi 2002; Heim and Nemeroff 2001; Huot et al. 2004; Kaufman et al. 2000; Mirescu et al. 2004), (2) maternal behavior (Ashman et al. 2002; Caldji et al. 1998; Fairbanks and McGuire 1988; Fleming et al. 1999; Halligan et al. 2004; Kraemer 1992), (3) maternal social and physical environment (Clarke and Schneider 1993; Coplan et al. 1998; Flinn 1999; Lupien et al. 2000; O'Connor et al. 2001), and (4) influence of the previous generation on parental care (Berman 1996; Champagne and Meaney 2001, 2006; Fairbanks 1989; Fleming 2005; Francis et al. 1999).

While the maternal–offspring dyad has been the principle focus in most of these studies, the latter two areas suggest that the broader relationship environment, particularly that of the family, plays a vital role in the development of an individual's responsiveness to stress. This broader relationship environment includes not only fathers and siblings but the extended families as well. From this perspective, the mother–child dyad represents a link in a larger, highly integrated family system, which is seen as playing a significant role in the shaping and regulation of the individual's neuroendocrine stress response system (Noone 2008).

The mother–child relationship is embedded in and influenced by the larger family relationship system that can serve as a mediator of environmental stress as well as a potential source of stress for its members (Carter 2005; Flinn 2006a; Lupien et al. 2000; Nicolson 2004; Uvnas-Moberg 1998). The human brain is highly sensitized to relationships and social behavior (Adolphs 2003), and this sensitivity is strongly influenced by the family relationship network.

5.9 Multigenerational Transmission of Reactivity to Stress

In addition to the influence of family interactions on maternal care and the development of an offspring's stress reactivity, there is evidence that the maternal caretaker's experience of being parented influences her own maternal care and the stress reactivity of her offspring. The previous generation, then, can be seen to influence the development of individual differences in stress reactivity. Rodent (Champagne and Meaney 2001; Francis and Meaney 2002), nonhuman primate (Fairbanks 1989; Suomi 2002), and human (Fleming 2005) studies provide evidence that maternal care can influence not only the stress reactivity of offspring but the quality of maternal care provided in the next generation as well. Maternal care is seen as influencing the development of L-HPA stress reactivity, which in turn affects neural systems involved in parental care.

A series of studies indicate that parental care influencing individual differences in the stress response systems of offspring can be transmitted nongenomically over the generations (Caldji et al. 1998; Francis et al. 1999). Champagne and Meaney (2001) state, "These findings suggest that for neurobiologists, the function of the family is an important level of analysis and the critical question is that of how environmental events regulate neural systems that mediate the expression of parental care."

The plasticity of the neural systems involved in stress reactivity and the evidence for epigenetic programming of maternal behaviors has been discussed in a number of recent studies (Champagne 2008; Francis et al. 1999, 2002; Lupien et al. 2000; Weaver et al. 2004; Zhang and Meaney 2010). Fleming (2005) describes a number of experiential factors during childhood and adolescence, such as alloparenting and maternal deprivation that may alter psychobiological mechanisms mediating parental behavior. Family instability prior to age 12, for example, leads to higher cortisol levels and long-lasting effects on maternal behavior (Krpan et al. 2005). While much remains to be learned, the existing animal and human research provide

evidence that the development of the neuroendocrine stress response systems in mammals is shaped by the parent–offspring relationship and that this influence can continue to have an effect in the next generation.

It has been suggested that the intergenerational regulation of parental care and stress reactivity may be adaptive (Champagne and Meaney 2001; Zhang et al. 2006). A phenomenon known as maternal or parental effects may evolve when there is some predictability between the parental and offspring environments. "Adaptive trans generational phenotypic plasticity" is observed when the maternal phenotype response to the environment stimulates phenotypic plasticity in offspring (Mousseau and Fox 1998). For example, parental reactivity to a threatening environment might stimulate offspring to respond with greater wariness and thereby enhance adaptiveness in a threatening environment. From this perspective, adverse environmental conditions may result in maternal behavior that "programs" gene expression for neuroendocrine systems more responsive to such conditions (Zhang et al. 2006).

This does not, however, account for within family variability of stress reactivity or the range of stress reactivity found in both highly stable and unstable environmental conditions. Increased stress reactivity increases vulnerability to stress-related illnesses, and higher levels of reactivity are associated with a decrease in the more recently evolved cognitive capacity to regulate social and emotional responsiveness to the environment. If prolonged, heightened reactivity of the L-HPA system can impair cognitive and other systems central to survival (McEwen 1998; McEwen and Seeman 1999) and so the adaptive value may be limited.

Another view is that while such programming may be detrimental to one or more offspring, it may have adaptive value to the other siblings and the family. While one child is likely to be the object of anxious parental involvement, the other children will be less involved, less constrained, and as a result more adaptive or resilient in their lives. More intense involvement with one child can take the form of either a positive or anxious emotional responsiveness, but each is seen as leading to the child's heightened responsiveness to other relationships. The containment of much of the parental anxiety in one relationship is seen as having a buffering effect for the other children. Among the factors observed to contribute to such positional effects on the functioning of children are birth order, nuclear family behavioral patterns, and family stressors occurring during pregnancy, early development, and adolescence (Kerr and Bowen 1988).

Differential parental involvement and other family interactions lead to individual differences in responsiveness to stress; such differences can influence mate selection and be transmitted into the next generation, hence affecting family interactional patterns resulting in a wide range of individual differences in functioning over the generations. From this perspective the "trans generational phenotypic plasticity" found in the human family would enhance the adaptiveness of some offspring, but be maladaptive for others.

Given the plasticity of the human brain, its extended development, and the complexity of the family environment, the degree to which individual differences in stress reactivity in the human population are shaped and transmitted by the family will require the long-term study of families over several generations.

As Fleming (2005) has remarked, "the role of epigenetics in the regulation of parental behavior and of the effects of experience on individual differences in development is totally uncharted territory in nonhuman mammals or humans" (2005, p. 162).

5.10 Family and Stress Reactivity Among Children in a Caribbean Village

One of the few studies that have included family relationships as factors in maternal care and stress reactivity is a 23-year longitudinal study of children, their families, and health in a rural village on the Caribbean island of Dominica (Flinn 2006a; Flinn et al. 2005a, b). This study of stress reactivity and health includes over 300 children and their families and has entailed the collection of extensive family genealogies, medical histories, growth measures, household compositions, and detailed observations of behavior and daily routines. Utilizing noninvasive saliva immunoassay techniques, the physiological stress responses of children in the naturalistic settings of their families were obtained. Saliva is relatively easy to collect and store. Concomitant monitoring of a child's daily activities, stress hormones, and psychological conditions provides a powerful research design for investigating the effects of naturally occurring psychosocial events in the family environment.

In this study community, family household composition is related to the stress hormone levels of children (Flinn and England 1997). Children who lived with both parents or with single mothers who had grandparental or other kin support had lower mean cortisol levels than those children who lived with single parents without kin support or who lived in the households of more distant relatives or stepparents with half-siblings.

High-stress events (cortisol increases from 100 to 2,000%) were most commonly found to involve trauma from family conflict or change (Flinn and England 2003; Flinn et al. 1996). Punishment, quarreling, and residence change substantially increased cortisol levels, whereas calm affectionate contact was associated with diminished (−10 to−50%) cortisol levels. Of all cortisol values that were more than two standard deviations above mean levels (i.e., indicative of substantial stress), 19.2% were temporally associated with traumatic family events (residence change of child or parent/caretaker, punishment, "shame," serious quarreling, and/or fighting) within a 24-h period. Of all recorded traumatic family events, 42.1% were temporally associated with substantially elevated cortisol (i.e., at least one of the saliva samples collected within 24 h was >2 S.D. above mean levels).

It is important to note that there was considerable variability among children in cortisol response to family disturbances. Not all individuals had detectable changes in cortisol levels associated with family trauma. Some children had significantly elevated cortisol levels during some episodes of family trauma but not during others. Cortisol response is not a simple or uniform phenomenon. Numerous factors, including preceding events, habituation, specific individual histories, context, and temperament, might affect how children respond to particular situations.

Nonetheless, traumatic family events were associated with elevated cortisol levels for all ages of children more than any other factor examined. These results suggest that family interactions were a critical psychosocial stressor in most children's lives, although the sample collection during periods of intense family interaction (early morning and late afternoon) may have exaggerated this association.

Although elevated cortisol levels are associated with traumatic events such as family conflict, long-term stress may result in diminished cortisol response. In some cases chronically stressed children had blunted response to physical activities that normally evoked cortisol elevation. Comparison of cortisol levels during "non-stressful" periods (no reported or observed: crying, punishment, anxiety, residence change, family conflict, or health problem during 24-h period before saliva collection) indicates a striking reduction and, in many cases, reversal of the family environment–stress association Flinn 2007. Chronically stressed children sometimes had subnormal cortisol levels when they were not in stressful situations. For example, cortisol levels immediately after school (walking home from school) and during noncompetitive play were lower among some chronically stressed children (cf. Long et al. 1993). Some chronically stressed children appeared socially "tough" or withdrawn and exhibited little or no arousal to the novelty of the first few days of the saliva collection procedure.

Relations between family environment and cortisol stress response appear to result from a combination of factors. These include frequency of traumatic events, frequency of positive "affectionate" interactions, frequency of negative interactions such as irrational punishment, frequency of residence change, security of "attachment," development of coping abilities, and availability or intensity of caretaking attention. Probably the most important correlate of household composition that affects childhood stress is maternal care.

Mothers in socially "secure" households (i.e., permanent amiable co-residence with mate and/or other kin) appeared more able and more motivated to provide physical, social, and psychological care for their children (Fig. 5.4). Mothers without mate or kin support were likely to exert effort attracting potential mates and may have viewed dependent children as impediments to this. The mothers in such stable households may also be less socially isolated and thus less anxious. Hence co-residence of father may provide not only direct benefits from paternal care, but also affect maternal care (Konner 2010). Young mothers without mate support usually relied extensively upon their parents or other kin for help with child care (Quinlan and Flinn 2005; Quinlan et al. 2005).

While children who experienced early trauma prior to age 6 had significantly more elevated cortisol levels at age 10 than those children who did not, this did not hold true for those children whose mothers had high levels of maternal support (Flinn 2006a). Children experiencing early trauma whose mothers had social support did not differ significantly from children who had not experienced early trauma. The stress reactivity of children was also found to be mediated by significant contact with caretakers other than their mothers. Children with extensive alloparental care, especially by grandparents, were found to recover normal HPA function more quickly following social trauma than did those children who had fewer caretakers (Flinn and Leone 2006, 2009).

5.11 Discussion

The human brain represents one of the most extraordinary developments in the evolution of life on earth. It is extraordinary in terms of its complexity and rapid evolution. The brain and family coevolved and are intimately interconnected as the latter provides the protective environment required for the prolonged development of the brain. The prolonged postnatal development allows for the learning required to respond to and navigate through the complexity of the human social environment. A central element in the human's responsiveness to the social environment is the L-HPA stress response system, which heightens an individual's cognitive, emotional, and physiological responses to the challenges at hand. It plays a vital role in an individual's capacity to adapt throughout life.

The family not only provides a safe haven in which the infant and child's brain can observe and learn to respond to a changing social environment, it also plays a significant role in shaping this responsiveness. The neuroendocrine stress response systems, along with other neural systems, are shaped by the family relationship environment during both the prenatal and postnatal development. The study of the influence of the family on the developing brain and individual differences in responding to the complex social world of the human will continue to be enhanced by both animal and human studies. The study of mother–child dyadic relationships will also contribute to the knowledge of the family and individual development, but prospective, longitudinal studies of the larger family network in naturalistic settings will be required to observe the rich and complex role the larger family plays in mother–child relationships and individual development. A family system and an evolutionary theoretical framework will play a vital role in both the integration of emerging knowledge and the development of researchable questions in the growing field of social neuroscience.

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