

# Early Family Trauma and the Ontogeny of Glucocorticoid Stress Response in the Human Child: Grandmother as a Secure Base

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**Abstract:** *Loss of a parent by death or divorce is among the most traumatic experiences faced by a human child. Exposure to early family trauma (EFT) can have long-term effects on the limbic hypothalamic-anterior pituitary-adrenal cortex (HPA) axis and other components of neuroendocrine stress response. Because the HPA system has important immunomodulatory functions, children that have endured difficult family social conditions during development may be at higher risk for immune dysfunction and other health problems. Here we investigate the mediating effects of grandparental relationships, mostly maternal grandmothers, on the ontogeny of HPA stress response among EFT children.*

**Sample and methods:** A longitudinal eighteen-year study (1988–2006) of child health in a rural community on the island of Dominica provides sequential biyearly data on salivary cortisol, morbidity, growth, and social environment (N= 282 children, 26,738 saliva samples from children + 5,470 saliva samples from their parents and other kin, 89,109 health observations, 46,788 anthropometric measurements, 42 months of residence in the community studying social environment). Patterns of cortisol response, extent of care from grandparents, morbidity, growth, and immune function are examined for associations with trauma at different periods during development.

**Results:** Grandparents are a common and important mediator of child wellbeing in this community. EFT children with extensive grandparental care are more likely to recover normal HPA function than are EFT children with little or no grandparental care. Lengthy informal discussions with children and their caregivers over the past 18 years suggest that grandparents are important components of their social worlds, including roles as temporary and permanent replacements for parents. EFT children with low contact rates with grandparents have more erratic cortisol profiles, higher morbidity, more growth disruptions, and more behavioral problems than EFT children with extensive grandparental care.

**Summary and conclusions:** Grandparents appear to have significant mediating effects on child development in this population. Intensive grandparental care is positively associated with lower average cortisol, normal growth, and lower morbidity. No significant associations were found between grandparental care and parasite loads or average fluctuating asymmetry. Overall these results suggest the importance of grandparents, especially maternal grandmothers, for children who have experienced early trauma in their family environments.

## Introduction: Grandparenting as an Evolved Human Adaptation

“I love my granbaby more than anything God put here on this earth” . . . “I love Mama”<sup>1</sup> . . . mutual hug and laugh. (Bwa Mawego<sup>2</sup> grandmother and her granddaughter, from MVF fieldnotes, Oct. 10, 1992).

Grandparents and grandoffspring share 25% of their genes identical by descent, a significant opportunity for kin selection. Few species, however, live in groups with multiple overlapping generations of kin. Fewer still have significant social relationships among individuals two or more generations apart—such as elephants (Lee, 1987), some cetaceans (Mesnick, Evans, Taylor, Hyde, Escorza-Trevino, & Dizon, 2003; Whitehead, 2003), and some primates (Goodall, 1986; Lancaster & King, 1992). Humans appear rather exceptional in this regard. Grandparenting is cross-culturally ubiquitous and pervasive (Murdock, 1967; e.g., Clarke, 1957; Sear, Mace, & McGregor, 2000). Our life histories allow for significant generational overlaps, including an apparent extended post-reproductive stage facilitated by the unique human physiological adaptation of menopause (Alexander, 1974, 1987; Hawkes, 2003; Williams, 1957).

The neuroendocrinological mechanisms guiding attachment processes in grand-relationships—such as the intense affiliation described in the anecdote above—are uncertain. The maternal neuropeptide oxytocin is a likely candidate. Regardless, the significance of emotional bonding between grandparents and grandchildren is beyond doubt. The evolved functions are uncertain, but likely involve the extraordinary importance of long-term extensive and intensive investment for the human child. The emotional and cognitive processes that guide grand-relationships evolved because they enhanced survival and eventual reproductive success of grandchildren.

Throughout human evolution, most children were likely to have benefited from the extra care provided by grandparents in addition to the investment by the immediate family. Children that for whatever reasons were not receiving much care from one or both parents were at risk, and, therefore, especially dependent upon help from grandparents. In addition to the physical basics of food, protection, and hygienic care, development of the human child is strongly influenced by the dynamics of the social environment (Dunn, 2004; Hetherington, 2003a, 2003b; Hinde & Stevenson-Hinde, 1987; Konner, 1991). Monitoring neuroendocrine stress response systems can provide useful insights into how children are coping with social challenges. Here we first re-

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1. This three year-old child referred to her grandmother as “Mama,” and her mother by her given name.

2. All place names and research participant names used here are pseudonyms to protect privacy rights.

view the potential functions of physiological stress response to stimuli in the social environment. We then investigate the effects of grandparents on the ontogeny of stress response among children that have endured the loss of a parent by death or separation.

### **The Paradox of Psychosocial Stress**

Humans elevate levels of the stress hormone cortisol in response to social challenges (Dickerson & Kemeny, 2004; Gunnar, Bruce, & Donzella, 2000). The magnitude and temporal pattern of cortisol release by the limbic hypothalamic-anterior pituitary-adrenal cortex (HPA) system can be altered by traumatic early experiences (Heim, Newport, Heit, Graham, Wilcox, Bonsall, Miller, & Nemeroff, 2000; Mirescu, Peters, & Gould, 2004; Weaver, Cervoni, Champagne, D'Alessio, Sharma, Seckl, Dymov, Szyf, & Meaney, 2004). High levels of the primary stress hormones cortisol, corticotropin releasing hormone (CRH), and epinephrine may be toxic to developing dendrites, neurons, and receptors in the hippocampus and other brain regions that are involved in the negative feedback loop for cortisol regulation (Chen, Bender, Brunson, Pomper, Grigoriadis, Wurst, & Baram, 2004; Sapolsky, Romero, & Munck, 2000). High levels of cortisol may also affect sensitivity of fear responses mediated by the amygdala. Hence early trauma may lead to permanent HPA-cortisol dysregulation. Because the HPA system has important immuno-modulatory functions (Ader, Felten, & Cohen, 2006; Sapolsky, 2005), children that have endured difficult social conditions during development may be at higher risk for immune dysfunction and other health problems.

The sensitivity of the HPA system to social stimuli presents an evolutionary paradox: why release cortisol if it has negative effects on health? We do not have good explanations for why natural selection favored links between the neuropsychological mechanisms involved with assessment of the social environment and the neuroendocrine mechanisms that regulate stress hormones. We also do not understand why these links are modifiable during development, such that early traumatic experiences may permanently alter hormone response to social challenges. And finally, we do not understand what factors, such as social support, may subsequently ameliorate the negative effects of early trauma on stress response (Caldji, Tannenbaum, Sharma, Francis, Plotsky, & Meaney, 1998; Cameron, Champagne, Parent, Fish, Ozaki-Kuroda, & Meaney, 2005; Francis, Diorio, Plotsky, & Meaney, 2002; Lupien, Fiocco, Wan, Maheu, Lord, Schramek, & Thanh Tu, 2005).

We approach these questions from an evolutionary paradigm that integrates proximate physiological explanations with ontogeny, phylogeny, and adaptive function (Tinbergen, 1963). Here we first briefly review the idea that childhood is an adaptation for coping with an increasingly complex and dynamic social and cultural environment. We then explore relations between physiological stress response and the ontogeny of social competencies. We posit that one of the important functions of the stress response system, in connection with emotional states such as fear or anxiety, is to manage the direction of mental processes to solving specific problems (Ademec, Blundell, & Burton, 2005; Flinn, 2006b, 2006d; Huether, 1998; Kaiser & Sachser,

2005; Meaney, 2001; Pitman, 1989; Rodriguez Manzanares, Isoari, Carrer, & Molina, 2005). For example, in the relatively straightforward prey-predator situation of a gazelle smelling a lion, a “freeze” response, focused sensory acuities, and neurological circuits for escape behaviors may be enabled. The human child may face more cognitively challenging problems that use more information processing capacity, such as complex social interactions (Roth & Dicke, 2005). For example, when dealing with the challenge of making friends on the first day of school, a child needs to allocate her cognitive efforts to the tasks at hand: prepare for immediate contingencies by recalling salient information, enhancing relevant sensory input, and pre-activating circuits for appropriate actions. Stress hormones may enable not only the acute responses to such challenges, but facilitate their modification during development as well. Parents and grandparents may play an important role in this dynamic interplay between stress response to social challenges and the ontogeny of a child’s coping mechanisms by providing both security and information.

Hypotheses are evaluated with analyses of data from an 18-year study of child stress in a rural community on the island of Dominica. The longitudinal depth, large sample size (30,122 salivary cortisol measures from 282 children and their caregivers), and naturalistic paradigm provide a unique research design for investigating relations between social environment and ontogeny of stress response. Empirical analysis is complicated by the pleiotropic nature of the key stress hormone cortisol. Moreover, the Dominica study does not have neurological data, hence direct or strong demonstrations of causal links among stress response, neural plasticity, family environment, grandparental care, and ontogeny of social competencies are not possible.

Our initial objective here is to review a plausible model that links stress response to the neural plasticity that enables adaptation to the dynamic human social environment. We then assess the effects of early family trauma on the ontogeny of stress response, and the potentially ameliorative effects of grandparental care. Understanding these relations may have significant consequences for child development and public health because it could provide new insights into associations among stress response, social disparities, and perinatal programming, among other outcomes (Barker, 1998; Dressler, Oths, & Gravely, 2005; Heim & Nemeroff, 2001; Maccari, Darnaudery, Morley-Fletcher, Zuena, Cinque, & Van Reeth, 2003; Marmot, 2004).

### **HPA Stress Response to Social Events**

Danny was roaming the Fond Vert area of the village with two of his closest friends, James and Isaiah, on a rainy Saturday morning. They had eaten their fill of mangoes, after pelting a heavily laden tree with stones for nearly an hour, taking turns testing their skill at knocking down breakfast. Now Danny was up the cashew tree in Mr. Pascal’s yard, tossing the yellow and red fruits to the smaller children below who had gathered to benefit from this kindness. Suddenly the sharp voice of his stepfather rang out from the nearby footpath. The bird-like chatter and laughter of the children immediately stopped. Danny’s hand froze mid-way to its next prize, and his head turned to face the direction of the yell with a mixed expression of surprise and fright.

Ordered down from the tree, Danny headed quickly home, head bowed in apparent numb submission (vignette from MVF field notes, July 14, 1994). Danny's salivary cortisol level rose from 2.2 to 3.8  $\mu\text{g}/\text{dl}$  in little more than an hour. That afternoon, his secretory immunoglobulin-A levels dropped from 5.70 to 3.83  $\text{mg}/\text{dl}$ . Three days later he had common cold symptoms: runny nose, headache, and fever. His two companions resumed their morning play, exhibiting a normal circadian decline in cortisol, and remained healthy over the next two weeks (Figure 1).

Danny had lost his father in a fishing accident when he was 3 years old. His relationships with his grandparents were not close; he visited them less than one hour a week. His friend James also did not have a co-resident father, as a consequence of a conjugal separation, but in contrast with Danny's situation, James' relationship with his maternal grandmother was very close, as illustrated by the following vignette. James was sitting contentedly sorting rice with Ma Tee-Jean, his maternal grandmother. He startled when I (MVF) kicked a rock on the path to forewarn them of my approach into the household yard, and he inched closer to grandma, who put her arm around him. James was dressed and ready for school. He had left his mother's house when an argument had broken out between his mother and stepfather last night, walking the 200 meters up the hill in the dark with his sister (MVF field notes, Sept 14, 1992). He was accustomed to this situation; James slept 44 out of 62 nights there in this summer of 1992, splitting his time between both households for most of the past

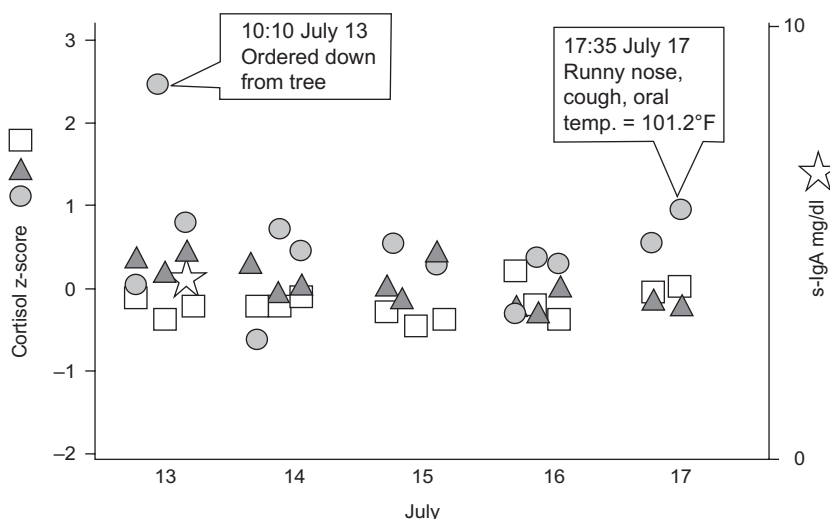


FIGURE 1. Morning, mid-morning, and afternoon cortisol levels of Danny and his two friends during summer 1994. Danny's cortisol levels were elevated and his s-IgA levels diminished after being reprimanded by his stepfather on the morning of July 13. Cortisol z-scores are standardized by five-minute intervals since wake-up time to control for the circadian patterns of cortisol; s-IgA levels are the raw values. Danny exhibits symptoms of an upper respiratory infection with slight fever on the afternoon of July 20.

four years, since his father had left when James was three years old and his stepfather had slowly moved in. James had always been close to his grandmother—whom he called “Mama”—as well as his mother—whom he called by her given name Lily. James’ cortisol levels were often elevated by family conflicts, but the solace he usually found at his grandmother’s often resulted in a return to normal levels.

These anecdotal case examples contribute to a common pattern. Children in this rural Dominican community are more than twice as likely to become ill during the week following a stressful event than during a week when they had not recently experienced any significant stressors (Flinn & England, 2003). Chronic elevation of cortisol levels may have negative consequences for health (Cohen, Doyle, Turner, Alper & Skoner, 2003; Maier, Watkins, & Fleschner, 1994; Marmot & Wilkinson, 1999; Mason, Buescher, Belfer, Artenstein, & Mougey, 1979). Morbidity and mortality rates for children in the stressful environments of orphanages and hospitals, if lacking the evolutionarily-normal intimacy and social contact of the family, can be a significant public health concern worldwide. It is not lack of food or hygienic care, nor just the occurrence of traumatic events that affect child health, but the lack of social support, including parental warmth and other factors that influence emotional states (Belsky, 1997; Davidson, Jackson, & Kalin, 2001; Field, Diego, Hernandez-Reif, Schanberg, & Kuhn, 2003). Why should this be so? Why do social interactions, and a child’s perceptions of them, affect stress physiology and morbidity? And, more generally, why is the social environment of such paramount importance in a child’s world? From the Tinbergen perspective, these “why?” questions ultimately involve understanding the evolutionary design of the ontogeny of the mind and brain of the human child (e.g., Belsky, 1997; Bjorklund & Pellegrini, 2002; Gilbert, 2005).

In Danny and James’ village, located on the east coast of the island of Dominica where I have lived and studied part-time over the past eighteen years, most of a child’s mental efforts seem focused on negotiating social relationships with parents, siblings, grandparents, cousins and other kin, friends, teachers, bus drivers, neighbors, shop owners, and so forth. Foraging for mangoes and guavas, hunting birds, or even fishing in the sea from rock cliffs, are relatively simple cognitive enterprises, complicated by conflicts with property owners, and decisions about which companions to garner and share calories with. The mind of the child seems more concerned with solving social puzzles than with utilitarian concerns of collecting food. Other populations may have more difficult subsistence practices that require more extensive learning (e.g., Bock, 2005), but the social chess game nonetheless appears ubiquitous and cognitively demanding in all cultures (Blurton-Jones & Marlowe, 2002; Hewlett & Lamb, 2005), as it likely was during human evolutionary history (Adolphs, 2003; Alexander, 1979, 1989; Baumeister, 2005; Bowlby, 1969, 1973; Flinn, Geary, & Ward, 2005; Hinde, 1974).

Complex sociality appears to have been an important selective pressure shaping the uniquely human combination of physically altricial but mentally and linguistically precocial infancy, extended childhood, and extended adolescence, enabled by extensive bi-parental and kin care (Alexander, 2005; Geary & Flinn, 2002; Flinn & Ward, 2005). Physiological stress response may help guide both the acute and long-term neurological plasticity (Huether, Doering, Ruger, & Schussler, 1999) necessary for adapting to the dynamic aspects of human sociality (Flinn, 2006b). Grandparents may pro-

vide important advice and enhance a secure base for the stressful tasks involved in the development of social competencies.

### **Evolution of the Extended Family as a Nest for the Child's Social Mind**

The human family is extraordinary and unique in many respects (Alexander, 1989, 2005; Flinn, Ward, & Noone, 2005; Geary & Flinn, 2001; Lancaster & Lancaster, 1987). Humans are the only primate species to live in multi-male groups with complex coalitions and extensive paternal care. The altricial infant is indicative of a protective environment provided by intense parental and alloparental care in the context of kin groups (Alexander, 1990a; Chisholm, 1999; Hrdy, 1999, 2005; e.g., Ivey, 2000). The human baby does not need to be physically precocial. Rather than investing in the development of locomotion, defense, and food acquisition systems that function early in ontogeny, the infant can work instead towards building a more effective adult phenotype. The brain continues rapid growth, and the corresponding cognitive competencies largely direct attention toward the social environment. Plastic neural systems adapt to the nuances of the local community (Alexander, 1990b; Bjorklund & Pellegrini, 2002; Geary & Bjorklund, 2000; Geary & Huffman, 2002). In contrast to the slow development of ecological skills of movement, fighting, and feeding, the human infant rapidly acquires skill with the complex communication system of human language (Bloom, 2000; Fisher, 2005; Pinker, 1994; Sakai, 2005). The extraordinary information-transfer abilities enabled by linguistic competency provide a conduit to the knowledge available in other human minds. This emergent capability for intensive and extensive communication potentiates (and presumably co-evolved with) the social dynamics characteristic of human groups (Deacon, 1997a, 1997b; Dunbar, 1997, 1998). The recursive pattern recognition and abstract symbolic representation central to linguistic competencies enable the open-ended, creative, and flexible information-processing characteristic of humans—especially of children.

Parents and other kin such as grandparents may be especially important for the child's mental development of social and cultural maps because they can 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 more as a nest from which social skills may be acquired than just as an economic unit centered on the sexual division of labor. An integration of the attachment paradigm (Bowlby, 1969; Lamb, 2005; Lamb, Bornstein, & Teti, 2002) with approaches emphasizing relationship networks (e.g., Kerr & Bowen, 1988; Suomi, 2005) would be congruent with this evolutionary logic (Belsky, 1997).

### **Grandparental Relationships**

Caregiving by individuals other than parents provides important benefits for infants and juveniles in a variety of taxa. "Helpers" in birds, rodents, social carnivores,

elephants, and non-human primates enhance growth and survival (e.g., Alexander, Noonan, & Crespi, 1991; Brown, 1987; Clutton-Brock, 2002; Lee, 1987; Mitani & Watts, 1997). Kin selection and reciprocity appear to provide the evolutionary functions for non-parental care providers. Among primates, intensive allomaternal caregiving (e.g., feeding, carrying) is common in the callitrichids (e.g., Goldizen, 1987) and the colobines. Allomaternal care among the cercopithecines (e.g., Fairbanks, 1990; Maestripieri, 1994) and hominoids (e.g., Goodall, 1986; Nishida, 1990) is usually limited to protection from conspecifics and predators. Practice care is generally common among nulliparous females in social species (e.g., Hrdy, 1999). The prevalence of extensive alloparental care among humans (e.g., Flinn, 1989; Lahdenpera, Lummaa, Helle, Tremblay, & Russell, 2004; McKenna, 1982; Sear, Mace, & McGregor, 2000, 2003; Silk, 1990; Strassmann & Clarke, 1998; Tronick, Morelli, & Winn, 1987; Tronick, Morelli, & Ivey, 1992), particularly the importance of grandparents for direct care (Alexander, 1979; Hawkes, 2003), represents a strong divergence from our closest primate relatives.

The conditions responsible for the evolution of extensive alloparental care in humans are likely to include the importance of localized kin groups, altricial infants, prolonged childhood, extended generational overlap, and the cultural transmission of information (Alexander, 1989; Coe, 2003; Flinn & Ward, 2005; Geary & Flinn, 2001; Hrdy, 2005). Grandparents appear to be the most significant of potential alloparental caregivers (Hrdy, 2005).

The informational arms race that characterizes human social competition involves substantial novelty (Flinn, 2004, 2006a; Flinn & Alexander, 2006; Flinn & Coe, 2006) and hence requires unusual phenotypic plasticity. Although knowledge of the basic neuroanatomical structures involved with human social aptitudes has increased dramatically (e.g., Allman, 1999; Damasio, 2003; Gallese, 2005; Moll, Zahn, de Oliveira-Souza, Krueger, & Grafman, 2005), the mechanisms that guide their ontogeny remain uncertain. Neuroendocrine stress response to stimuli in the social environment may provide important clues.

### **Stress Hormone Profiles as an Assessment of Caretaking Environment**

Changing, unpredictable environments require adjustment of priorities. Growth, immunity, digestion, and sex are irrelevant while being chased by a predator (Sapolsky 1994), or coping with a traumatic social event. Emergencies—large and small, good and bad—perceived by the brain stimulate a variety of neuroendocrine systems. Hundreds of different endogenous chemicals—steroid and peptide hormones, neurotransmitters, cytokines, and so forth—are released from secretory glands and cells in response to information received and processed by the central nervous system (CNS). The movement of these chemicals in plasma and other intercellular fluids communicates information among cells and tissues, helping the body to respond appropriately to varying environmental demands.

Physiological stress responses affect the allocation of energetic and other somatic resources to different bodily functions via a complex assortment of endocrine and neu-

roendocrine mechanisms. Stress hormones help shunt blood, glucose, products of the immune system, and other resources to cells and tissues necessary for the task at hand. Chronic and traumatic stress can diminish long-term health, evidently because resources are diverted away from important health functions, including cellular repair, building muscle mass, immune response, and neuromodulation (Korte, Koolhaas, Wingfield, & McEwen, 2005; Selye, 1976). Stress during childhood may be particularly harmful because of the additional demands of growth and development, especially of the CNS (Rutter, 1991).

During the first few years of life the human brain more than doubles in size via an extraordinary spurt of cell growth, migration, specialization, remodeling, and pruning. The brain consumes almost half of the infant's resting caloric requirements. The thymus and other parts of the immune system undergo a similarly dramatic transformation, preparing defenses against a nearly infinite variety of pathogens, while selecting out responses to the numerous molecular fingerprints of self-tissues. Even under the best of circumstances successful outcome of these complex ontogenetic trajectories would seem miraculous; the developing child, however, often faces a most imperfect environment. Emotional and physical stressors—such as abuse, neglect, parental divorce, strenuous work, exogenous toxins, inconsistent punishment, infectious disease, and malnutrition—are powerful stimulants of physiological stress response with potential effects on brain and immune development (e.g., Boyce, Adams, Tschann, Cohen, Wara, & Gunnar, 1995; Fukunaga, Mizoi, Yamashita, Yamada, Yamamoto, Tatsuno, & Nishi, 1992; Maccari et al., 2003; McEwen, 1995, 1998). But even common, everyday activities may be important.

Physiological responses to environmental stimuli that are cognitively perceived as “stressful” are modulated by the limbic system (amygdala and hippocampus) and basal ganglia that interact with the sympathetic and parasympathetic nervous systems and several neuroendocrine axes. Here we are primarily concerned with what has traditionally been termed the limbic hypothalamic-anterior pituitary-adrenal cortex system (HPA). The HPA system affects a wide range of physiological functions in concert with other neuroendocrine mechanisms and involves complex feedback regulation. The HPA system regulates glucocorticoids, primarily cortisol, which is normally released in seven to fifteen pulses during a 24-hour period (for reviews see: de Kloet, Sibug, Helmerhorst, & Schmidt, 2005; Ellis, Essex, & Boyce, 2005; Gold & Chrousos, 2002; Gray, 1982, 1987; McEwen, 1995; Sapolsky, 1992a, 1992b; Weiner, 1992).

Cortisol is a key hormone produced in response to physical and psychosocial stressors in humans. Cortisol modulates a wide range of somatic functions, including: (a) energy release (e.g., stimulation of hepatic gluconeogenesis in concert with glucagon and inhibition of some effects of insulin), (b) immune activity (e.g., control of inflammatory response and the cytokine cascade, particularly Il-2), (c) mental activity (e.g., alertness, memory, and learning), (d) neural modification, (e) growth (e.g., inhibition of growth hormone and somatomedins), and (f) reproductive function (e.g., inhibition of gonadal steroids, including testosterone). These complex multiple effects of cortisol muddle understanding of its adaptive functions. The demands of energy regulation must orchestrate with those of immune function, and so forth. Receptor differentiation, competition with mineralocorticoids for binding sites, and other mechanisms enable localized targeting (e.g., glucose uptake by active *versus* inactive

muscle tissues, neuropeptide directed immune response, modulation by antiglucocorticoids, and cell-specific interactions with macrophages) of the above general physiological effects (e.g., de Kloet et al., 2005). Cortisol regulation allows the body to respond to changing environmental conditions by preparing for, and recovering from, *specific* short term demands (Mason, 1971; Munck, Guyre, & Holbrook, 1984).

These temporary beneficial effects of glucocorticoid stress response, however, are not without costs. Persistent activation of the HPA system is associated with immune deficiency, cognitive impairment, inhibited growth, delayed sexual maturity, damage to the hippocampus, enhanced sensitivity of amygdala fear circuits, and psychological maladjustment (Ader, 2001; Dunn, 1995; McEwen & Magarinos, 1997; Sapolsky, 1996). Deleterious effects of high cortisol to neurons in the hippocampus appear to occur after saturation of the high affinity mineralocorticoid receptors (MRs) and subsequent extensive binding of the glucocorticoid receptors (GRs) (de Kloet et al., 2005; Reul & de Kloet, 1985). Chronic stress may diminish cellular energy (Sapolsky, 1991; Sapolsky & Stein, 1989) and produce complications for autoimmune protection (Munck & Guyre, 1991). Stressful life events—such as divorce, death of a family member, change of residence, or loss of a job—are associated with infectious disease and other health problems during adulthood (Cohen et al., 2003; Maier et al., 1994; Marmot & Wilkinson, 1999).

Current psychosocial stress research suggests that cortisol response is stimulated by uncertainty that is perceived as significant and for which behavioral responses will have unknown effects (Dickerson & Kemeny, 2004; Kemeny, 2003; Kirschbaum & Hellhammer, 1994). In a child's world, important events are going to happen. The child does not know how to react so as to achieve desired outcomes, but is highly motivated to figure out what should be done. Cortisol release is associated with unpredictable, uncontrollable events that require full alert readiness and mental anticipation. In appropriate circumstances, temporary moderate increases in stress hormones (and associated neurotransmitters such as dopamine) may enhance mental activity for short periods in localized areas and prime memory storage, hence improving cognitive processes for responding to social challenges (Beylin & Shors, 2003; Boyce & Ellis, 2005; Domes, Heinrichs, Reichwald, & Hautzinger, 2002; LeDoux, 2000, 2003; cf. McEwen & Sapolsky, 1995; McGaugh, 2004). Mental processes unnecessary for appropriate response may be inhibited, perhaps to reduce external and internal "noise" (Servan-Schreiber, Prinz, & Cohen, 1990; cf. Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996; Lupien et al., 2005).

Experimental studies that expose subjects to acute temporal stressors such as public speaking or parachute jumping reliably elevate stress hormones (Dickerson & Kemeny, 2004). Relations between cortisol production and emotional distress in natural settings, however, are difficult to assess because of temporal and interindividual variation in HPA response (Dabbs & Hopper, 1990; Ellis, Jackson, & Boyce, 2006; Kagan, 1992; Pollard, 1995; Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996; Tennes & Mason, 1982). Habituation may occur to repeated events for which a child or adult acquires an effective mental model. Apparently "stressful" job environments may not stimulate increased levels of stress hormones if individuals have adjusted to them. Expressions of behavioral distress (e.g., crying) among children are not reliably associ-

ated with elevated cortisol (Gunnar, 1992; cf. Ahnert, Gunnar, Lamb, & Barthel, 2004; Flinn, 2006c), and some studies suggest that phobic individuals exhibit only moderate rises in cortisol during clinical phobic episodes (Nesse, Curtis, Thyer, McCann, Huber-Smith, & Knopf, 1985). Attenuation and below-normal levels of cortisol may follow a day or more after emotionally charged events. Personality may affect HPA response (and *vice versa*), because children with inhibited, anxious, or fearful temperaments tend to have higher cortisol levels than extroverted children (Kagan, Resnick, & Snidman, 1988; cf. Suomi, 1991; Hart, Gunnar, & Cicchetti, 1995; Higley & Suomi, 1996; Nachmias et al., 1996).

Chronically stressed children may develop abnormal cortisol response, possibly via changes in binding globulin levels, and/or reduced affinity or density of glucocorticoid, CRH, oxytocin and vasopressin receptors in the brain (De Kloet, 1991; Fuchs & Flugge, 1995). Early experience—such as perinatal stimulation of rats (Meaney, Mitchell, Aitken, Bhat Agar, Bodnoff, Ivy, & Sarriev, 1991; Takahashi, 1992; Weaver et al., 2004), some types of prenatal stress of rhesus macaques (Schneider, Coe, & Lubach, 1992; Clarke 1993), maternal-infant attachment among humans (Spangler & Grossmann, 1993), and sexual abuse among humans (De Bellis, Chrousos, Dorn, Burke, Helmers, Kling, Trickett, & Putman, 1994; Heim et al., 2002)—may permanently alter HPA response.

Further complications arise from interaction between HPA stress response and a wide variety of other neuroendocrine and neuroimmune activities, including modulation of catecholamines, melatonin, testosterone, serotonin,  $\beta$ -endorphins, cytokines, and enkephalins (de Kloet, 1991; Miller, Cohen, & Ritchey, 2002; Sapolsky, 1990b, 1992b). Changes in cortisol for energy allocation and modulation of immune function may be confused with effects of psychosocial stress. Cortisol may be a co-factor priming dopamine, oxytocin, and vasopressin intracerebral binding sites that are associated with the neuroplasticity of familial attachment in mammals (Carter, 2005; Fleming, Steiner, & Corter, 1997), and hence may influence distress involving caretaker-child relationships (see also Aragona, Liu, Yu, Curtis, Detwiler, Insel, & Wang, 2006; Carter, 2003; Cushing & Kramer, 2005; Porges, 1998; Tennes, 1982; Wismer Fries, Ziegler, Kurian, Jacoris, & Pollak, 2005). Synergistically, oxytocin has important effects on social cognition and fear (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Kirsch, Esslinger, Chen, Mier, Lis, Siddhanti, Gruppe, Mattay, Gallhofer, & Meyer-Lindenberg, 2005). Other components of the HPA axis, such as corticotropin releasing hormone (CRH) and melanocyte stimulating hormone, have additional stress-related effects that are distinct from cortisol. Finally, a variety of hormones such as estrogens and other endogenous chemicals—including “antiglucocorticoids”—mediate specific actions of cortisol (e.g., Kaufer, Ogle, Pincus, Clark, Nicholas, Dinkel, Dumas, Ferguson, Lee, Winters, & Sapolsky, 2004). Concurrent monitoring of all these neuroendocrine activities would provide important information about stress response, but is not possible in a non-clinical setting with current techniques.

Relations between stress-induced cortisol response and immunosuppression are perhaps even more complex and enigmatic (Coe & Lubach, 2005; McEwen, 1998; Sapolsky, 2005). Stress is associated with a variety of illness, including infectious disease, reactivation of latent herpes virus, cancer, and cardio-vascular problems. The

wide range of health effects of stress suggests that a number of immune mechanisms are involved. Cortisol influences many functions of lymphocytes, macrophages, and leukocytes, and as with energy use, may direct their movement to specific locations and even modulate apoptosis (Costas et al., 1996). Cortisol also inhibits the production of some cytokines (e.g., interleukin-1) and mediates several components of the inflammatory response. In concert with the sympathetic system, which generally down-modulates lymphocyte and monocyte functions, HPA stress response affects all of the major components of the immune system. However, the effects of neuroendocrine stress response are not all inhibitory, and involve temporary up-regulation and/or localized enhancement of some immune functions (Dhabbar & McEwen, 2001; Jefferies, 1991; Coe & Lubach, 2005).

Stress response involves an optimal allocation problem (Sapolsky, 1990a, 1994). Energy resources are diverted to muscular and immediate immune functions and other short-term (stress emergency) functions, at cost to long-term functions of growth, development, and building immunity. Under normal conditions of temporary stress, there would be little effect on health. Indeed, there may be brief enhancement and directed trafficking of immune (Dhabbar & McEwen, 2001) and cognitive function. Persistent stress and associated hyper- or hypo-cortisolemia, however, is posited to result in pathological immunosuppression, depletion of energy reserves, and damage to or inhibition of neurogenesis in parts of the hippocampus (e.g., Gould & Tanapat, 1999; Santarelli, Saxe, Gross, Surget, Battaglia, Dulawa, Weistaub, Lee, Duman, Arancio, Belzung, & Hen, 2003; Sheline, Gado, & Kraemer, 2003). This perspective highlights the problems with a stress response system that evolved to cope with short-term emergencies. The chronic stress produced by modern human—or other primates with complex relationships—social environments may present novel challenges that the system is not designed to handle, hence potentially resulting in maladaptive pathology (Sapolsky, 1994, 2003).

This strict version of an environmental novelty hypothesis, however, is difficult to reconcile with the long evolutionary histories of complex sociality in primates, and especially humans, accompanied by dramatic changes in the brain. Why, given all the extensive modifications of the human brain over the past several million years, would selection not have weeded out this apparent big mistake? Modern human environments have many novelties that elicit stress response, but social challenges in general seem to have a much more ancient evolutionary depth, and may be a key selective pressure for the large human brain. One possibility is that the demands of preparing for potential dangers are an unavoidable costly insurance, akin to expensive febrile response to pathogens that are usually benign—the “smoke-detector” principle (Nesse & Young, 2000). The idea is that although physiological stress response to social challenges is costly, and most often wasteful, it may have helped our ancestors cope with rare and unpredictable serious conflicts often enough to be maintained by selection. The benefit/cost ratio could be improved by fine-tuning stress mechanisms in response to environmental conditions during ontogeny.

A complementary approach suggests that neuroendocrine stress response may guide adaptive neural reorganization, such as enhancing predator detection and avoidance mechanisms (Buwalda, Kole, Veenema, Huininga, De Boer, Korte, & Koolhas, 2005; Dal Zatto, Marti, & Armario, 2003; LeDoux, 2000; Rodriguez Manzanares

et al., 2005; Meaney, 2001; Wiedenmayer, 2004). Exposure to cats that elevates glucocorticoid levels can have long-term effects on the central amygdala (right side) in mice, resulting in increased fear sensitization (Ademec et al., 2005; see also Knight, Nguyen, & Bandettini, 2005). The potential evolutionary advantages of this neural phenotypic plasticity are apparent (Rodriguez Manzanares et al., 2005). Prey benefit from adjusting alertness to match the level of risk from predators in their environments. Post-Traumatic Stress Disorder (PTSD) appears analogous to these fear conditioning models, and involves similar effects of noradrenergic (Pitman et al., 2002) and glucocorticoid systems (Roozendaal, 2002; Roozendaal, Quirarte, & McGaugh, 2002) on associative long-term potentiation of the amygdala. Social defeat also affects the amygdala and hippocampus, but in different locations (Bartolomucci, Palanza, Sacerdote, Panerai, Sgoifo, Dantzar, Parmigiani, 2005; Buwalda, Felszhegy, Horvath, Nyakas, de Boer, & Bohus, 2001; Koolhaas, de Boer, de Ruiter, Meerlo, & Sgoifo, 1997), suggesting that neural remodeling and LTP is targeted and domain-specific (e.g., Pham, McEwen, Ledoux, & Nader, 2005; Rumpel, LeDoux, Zador, & Malinow, 2005). Glucocorticoids, perhaps in combination with peptide hormones and catecholamines, appear to facilitate the targeting of domain-specific remodeling and long-term potentiation (Huang & Herbert, 2006). The potentiating effects of cortisol on emotional memories and other socially salient information may be of special significance in humans (Fenker, Schott, Richardson-Klavehn, Heinze, & Düzel, 2005; Jackson, Payne, Nadel, & Jacobs, 2006; Lupien et al., 2005; Pitman, 1989). The neurological effects of stress response may underlie adaptation to both short-term contingencies and guide long-term ontogenetic adjustments of behavioral strategies.

If physiological stress response promotes adaptive modification of neural circuits in the limbic and higher associative centers that function to solve psychosocial problems (Huether et al., 1999), then the paradox of psychosocial stress would be partly resolved. Temporary elevations of cortisol in response to social challenges could have advantageous developmental effects involving synaptogenesis and neural reorganization (Buchanan & Lovallo, 2001; Huether, 1996, 1998) if such changes are useful and necessary for coping with the demands of an unpredictable and dynamic social environment. Elevating stress hormones in response to social challenges makes evolutionary sense if it enhances specific acute mental functions and helps guide cortical remodeling of “developmental exuberance” (Flinn, 2006b; Innocenti & Price, 2005; Sur & Rubenstein, 2005).

Chronic destabilization of neuronal networks in the hippocampus or cerebral cortex, combined with enhanced fear circuits in the amygdala (e.g., Bauer, LeDoux, & Nader, 2001; Phan, Fitzgerald, Nathan, & Tancer, 2006), however, could result in apparently pathological conditions such as PTSD (Tupler & DeBellis, 2006; Yehuda, 2002) and some types of depression (Preussner, Baldwin, Dedovic, Renwick, Khalili Mahani, Lord, Meaney, & Lupien, 2005). Even normal (but rather novel) everyday stressors in modern societies, such as social discordance between what we desire and what we have (Dressler & Bindon, 2000), might generate maladaptive HPA response. Individual differences in perception, emotional control, rumination, reappraisal, self-esteem, and social support networks seem likely co-factors (see also Ellis, Jackson, & Boyce, 2006).

Testing these ideas about relations between physiological stress response, neural remodeling, and adaptation to the social environment is not a simple or easy task (e.g., Pine, Fyer, Grun, Phelps, Szesko, & Koda, 2001). Cortisol can affect cognitive functioning, and cognitive processing can affect cortisol response, all in an ongoing ontogenetic dance. Teasing out the causes and effects in ontogenetic sequence requires sequential data on physiological response profiles, environmental context, and perception. Extensive research on hormonal stress response has been conducted in clinical, experimental, school, and work settings (Dickerson & Kemeny, 2004; Gunnar, Tout, de Haan, Pierce, & Stansbury, 1997; Panter-Brick & Pollard, 1999; Stansbury & Gunnar, 1994; Weiner, 1992). We know relatively little, however, about stress neuroendocrinology among children in normal everyday (“naturalistic”) environments, particularly in non-industrial societies (Panter-Brick, 1998). Investigation of childhood stress and its effects on development has been hampered by the lack of non-invasive techniques for measurement of stress hormones. Frequent collection of plasma samples in non-clinical settings is not feasible. The development of saliva immunoassay techniques, however, presents new opportunities for research on stress response to everyday life. Saliva is relatively easy to collect and store, especially under adverse field conditions faced by anthropologists and psychologists working in naturalistic research settings (Ellison, 1988). Longitudinal monitoring of a child’s daily activities, stress hormones, and psychological conditions provides a powerful research design for investigating naturally occurring stressors. Analyzing hormone levels from saliva can be a useful tool for examining the child’s imperfect world and its developmental consequences, especially when accompanied by detailed ethnographic, medical, and psychological information. Unfortunately, we do not yet have field techniques for assessment of corresponding ontogenetic changes in the relevant neurological mechanisms.

### **Social Worlds and the Ontogeny of Stress Response: The Dominica Study**

Assessment of relations among psychosocial stressors, hormonal stress response, family environment, and health during child development is complex, requiring (a) longitudinal monitoring of social environment, emotional states, hormone levels, immune measures, and health, (b) control of extraneous effects from physical activity, circadian rhythms, and food consumption, (c) knowledge of individual differences in temperament, experience, and perception, and (d) awareness of specific social and cultural contexts. Multi-disciplinary research that integrates human biology, psychology, and ethnography is particularly well suited to these demands (Bogin, 1999; Panter-Brick, 1998). Physiological and medical assessment in concert with ethnography and coresidence with children and their families in anthropological study populations can provide intimate, prospective, longitudinal, naturalistic information that is not feasible to collect in clinical studies. For the past eighteen years (1988–present) we have conducted such research with the help of many colleagues and students and the extraordinary cooperation of a wonderful study population.

## **The Study Village**

“Bwa Mawego” is a rural community located on the east coast of Dominica. About 500 residents live in 160 structures/households that are loosely clumped into five “hamlets” or neighborhoods. The population is of mixed African, Carib, and European descent. The community is isolated because it sits at the dead-end of a rough road. Part-time residence is common, with many individuals emigrating for temporary work to other parts of Dominica, other Caribbean islands, the United States, the United Kingdom, or Canada. Most residents cultivate bananas and/or bay leaves as cash crops, and plantains, dasheen, and a variety of fruits and vegetables as subsistence crops. Fish are caught by free-diving with spear-guns and from small boats (hand-built wooden “canoes” of Carib design) using lines and nets. Land is communally “owned” by kin groups, but parceled for long-term individual use.

Most village houses are strung close together along roads and tracks. Older homes are constructed of wooden planks and shingles hewn by hand from local forest trees; concrete block and galvanized roofing are more popular today. Most houses have one or two sleeping rooms, with the kitchen and toilet as outbuildings. Children usually sleep together on foam or rag mats. Wealthier households typically have “parlors” with sitting furniture. Electricity became available in 1988; during the summer of 1995 about 70% of homes had “current,” 41% had telephones, 11% had refrigerators, and 7% had televisions. Water is obtained from streams, spring catchments, and run-off from roofs; public piped water became available in June 1999, but few households are connected.

The community of Bwa Mawego is appropriate for the study of relations between a child’s social environment and physiological stress response for the following reasons: (1) there is substantial variability among individuals in the factors under study (i.e., family environments, social challenges, and stress response), (2) the village and housing are relatively open, hence behavior is easily observable, (3) kin tend to reside locally, (4) the number of economic variables is reduced relative to urban areas, (5) the language and culture are familiar to the investigator, (6) there are useful medical records, and (7) local residents welcome the research and are most helpful.

The study involved 282 children and their caregivers residing in 84 households. This is a nearly complete sample (> 98%) of all children living in four of the five village hamlets during the period of fieldwork.

### *Methods and Field Techniques*

“. . . we finished getting the spit today! . . . maybe we should collect a couple more [duplicate] samples tomorrow from a few of the kids . . . just to make sure the lab measures are reliable . . . and to double-check that cortisol levels do not change much from day to day.”  
(MVF field notes, July 18, 1989)

Our initial objective, back in 1989, was to assess what each child’s general stress level was, as determined by a single measure of the level of cortisol in their saliva. The idea was to see how this hormone was associated with a child’s family environment. We assumed, rather naively, but in good academic company, that salivary cortisol

levels were a fairly stable “trait” character. What seemed like an unnecessarily cautious decision at the time to collect and assay additional saliva samples from several of the children resulted in a rather more complex study. We were quite surprised when the results of the additional sample assays indicated that a child’s cortisol levels varied substantially from one day to the next. Serendipity provided samples from two siblings in good spirits one day, but sad and upset by a family quarrel the next, in concert with field notes detailing the events. This temporal link between cortisol levels and psychosocial states suggested a dramatic revision of research design. We also were fortunate to have saliva samples from different times of day in this initial collection, and quickly recognized that very precise control of circadian patterns—in particular sleep schedules and wake-up times—was critical to accurate assessment of HPA stress response (Flinn & England, 1992). More than 30,000 saliva samples later, it seems we have more questions than answers.

In this study, sequential longitudinal monitoring is used to assess physiological stress response to everyday events, including social challenges. Saliva is collected from children by members of the research team at least twice a day, wherever the children happen to be (usually at their household). This direct collection and observation procedure avoids errors that can occur with at-home self- or parent-collection and report protocols. The large sample size of cortisol measures for each child (>100 samples for most children) in a variety of naturalistic contexts provides a more extensive and complex picture of HPA stress response than small sample designs.

Data analyses examine both long term (ten+ years) and short term (day-to-day, hour-by-hour) associations among cortisol levels, family composition, socioeconomic conditions, behavioral activities, events, temperament, growth, medical history, immune measures, and illness. *Physiological stress response* is assessed by radioimmunoassay (RIA) of cortisol levels in saliva. Analyses include mean values, variation, and day-to-day and hour-by-hour profiles of standardized (circadian control by 5-minute intervals from wake-up time) cortisol data (Flinn & England, 2003; Flinn & Quinlan, in prep.). *Family composition* is assessed by age, sex, genealogical relationship, and number of individuals in the caretaking household. *Socioeconomic conditions* include household income, material possessions, land ownership, occupations, and educational attainment. *Caretaking* is assessed by (a) frequencies and types of behavioral interaction, (b) informant ratings of caretaking that children received, and (c) informant interviews. Here we use a dichotomous (above median, below median) composite measure of caretaking by grandparents (“GPC”). *Immune response* is assessed by turbidimetric immunoassay of secretory-immunoglobulin A from saliva; however, relatively few samples have been assayed (N = 212), and interpretation is uncertain so inferences are preliminary. *Health* is assessed by (a) observed type, frequency, and severity of medical problems (diarrhea, influenza, common cold, asthma, abrasions, rashes, etc.), (b) informant (parents, teachers, neighbors) ratings, (c) medical records, (d) growth (standard anthropometric measures, including height, weight, and skinfolds) and fluctuating asymmetry patterns (Flinn, Leone, & Quinlan, 1999; Leone, 2005) and (e) physical examination by a medical doctor. The primary measure of health used is *percentage of days ill*, the proportion of days that a child was observed (directly by researchers) with common benign temporary infectious disease

(89% were common-cold upper respiratory tract infections with nasal discharge, cough, or myalgia—e.g., rhinovirus, adenovirus, parainfluenza, and influenza; 6% were diarrheal; 5% were miscellaneous indeterminate—e.g., febrile without other symptoms). *Daily activities* and *emotional states* are assessed from (a) caretaker and child self-report questionnaires, and (b) systematic behavioral observation (focal follow and instantaneous scan sampling). Multiple sources of information are cross-checked to assess reliability (Bernard, Killwoth, Kronenfield, & Sailer, 1984).

In the following section we briefly review some of the results from this study that may provide useful insights into the ontogeny of stress response to psychosocial challenges. We then turn to examining the effects that grandparents have in guiding this aspect of child development.

### *Cortisol Response to Naturally Occurring Social Challenges*

Our analyses of naturally occurring stressors in children's lives in Bwa Mawego indicate that social challenges are important stressors, with the emphasis upon the family environment as both a primary source and mediator of stressful stimuli (Flinn & England, 1995, 2003; Flinn, Turner, Quinlan, Decker, & England, 1996; Turner, Flinn, & England, 1995). Temporary moderate increases in cortisol are associated with common activities such as eating meals, active play (e.g., cricket), and hard work (e.g., carrying loads of wood to bay oil stills) among healthy children. These moderate stressors—"arousers" might be a more appropriate term—usually have rapid attenuation, with cortisol levels diminished to normal within an hour or two (some stressors have characteristic temporal "signatures" of cortisol level and duration—see Figure 5 for an example).

High-stress events (cortisol increases from 100% to 2000%), however, most commonly involved trauma from family conflict or change (Flinn & England, 2003). Punishment, quarreling, and residence change substantially increased cortisol levels, whereas calm, affectionate contact is associated with diminished (–10% to –50%) cortisol levels. Of all cortisol values that are more than two standard deviations above mean levels (i.e., indicative of substantial stress), 19.2% are temporally associated with traumatic family events (residence change of child or parent/caretaker, punishment, "shame," serious quarreling, and/or fighting) within a 24-hour period—for comparison, 12% are associated with minor family conflicts, 9.2% with peer conflicts or school problems, 7.9% with illness, and 6.4% with physical exertion, the next highest categories; 43.4% have no recorded abnormal event. In addition, 42.1% of traumatic family events are temporally associated with substantially elevated cortisol (i.e., at least one of the saliva samples collected within 24 hours is  $> 2$  SD above mean levels)—other consistent predictors of elevated cortisol include illness with fever and high profile competitive sports events. Chronic elevations of cortisol levels, as in the example of the Franklin family (Figure 2), may also occur, but are more difficult to assess quantitatively.

There is considerable variability among children in cortisol response to family disturbances. Not all individuals have detectable changes in cortisol levels associated

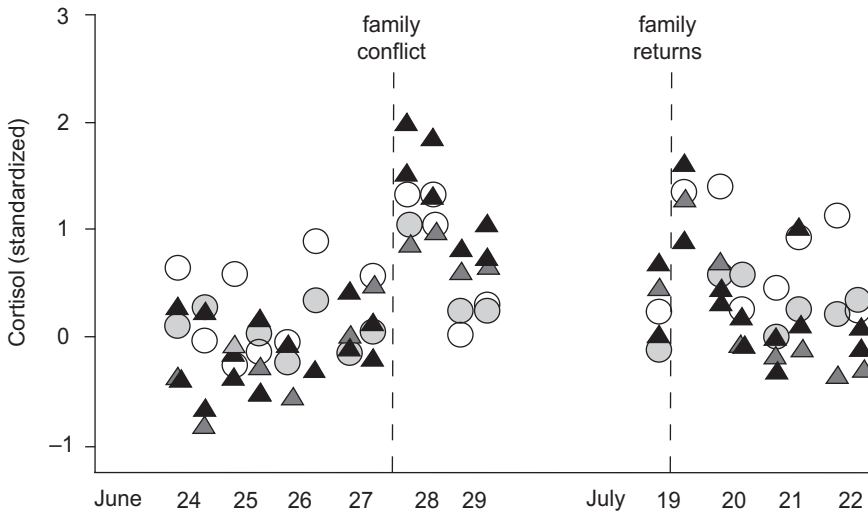


FIGURE 2. On June 28, 1992, a serious marital conflict erupted in the “Franklin” household. “Amanda” was a 34-year-old mother of six children, five of whom (ages 2, 3, 5, 8, and 14) were living with her and their father/stepfather, “Pierre Franklin.” Amanda was angry with Pierre for spending money on rum. Pierre was vexed with Amanda for “shaming” him in front of his friends. He left the village for several weeks, staying with a relative in town. His three genetic children (ages 2, 3, and 5) showed abnormal cortisol levels (in this case, elevated) for a prolonged period following their father’s departure. This pattern is typical: children usually became habituated to stressful events, but absence of a parent often resulted in abnormal patterns of elevated and/or subnormal cortisol levels. Following the return of their father, the Franklin children’s cortisol levels resumed a more normal profile. Again, this pattern is typical: children living in families with high levels of marital conflict (observed and reported serious quarreling, fighting, residence absence) were more likely to have abnormal cortisol profiles than children living in more amiable families were. Figure adapted from Flinn & England, 1997.

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 and social emotions such as guilt and shame (Flinn, 2006c) were associated with elevated cortisol levels for all ages of children more than any other factor that we examined. These results suggest that family interactions were a critical psychosocial stressor in most children’s lives, although the sample collection during periods of relatively intense family interaction (early morning and late afternoon) may have exaggerated this association.

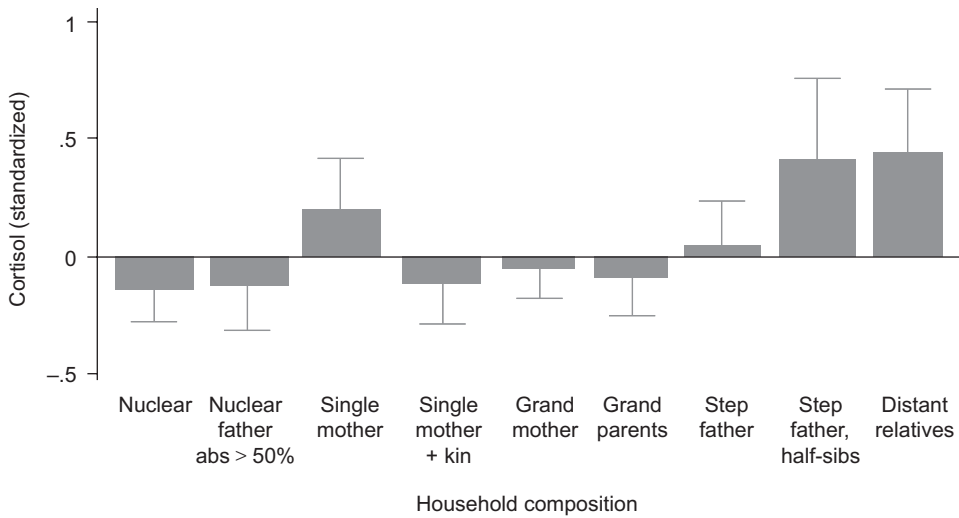


FIGURE 3. Household composition and average cortisol levels of children. Vertical lines represent 95% confidence intervals ( $1.97 \times SE$ ). Figure adapted from Flinn, 1999.

Children residing in bi-parental, single mother with kin, and grandparental households have moderate cortisol levels (Figure 3), with a higher proportion of elevations occurring in the context of positive affect situations such as competitive play, physical work, and excitement regarding novel situations.

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 “nonstressful” periods (no reported or observed crying, punishment, anxiety, residence change, family conflict, or health problem during the 24-hour period before saliva collection) indicates a striking reduction and, in many cases, reversal of the family environment-stress association (Flinn & England, 2003). 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 non-competitive play were lower among some chronically stressed children (cf. Long, Ungpakorn, & Harrison, 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. These subnormal profiles may be similar in some respects to those of individuals with Post-Traumatic Stress Disorder (e.g., Yehuda, Engel, Brand, Seckl, Marcus, & Berkowitz, 2005).

Although elevated cortisol levels in children are usually associated with negative affect, events that involve excitement and positive affect can also stimulate stress response (Flinn, 2006c). For example, cortisol levels on the day before Christmas were more than one standard deviation above normal, with some of the children from two-parent households and those having the most positive expectations exhibiting the

highest cortisol (Flinn, 2006e). Cortisol response appears sensitive to social challenges with different affective states. Other studies further suggest that the cognitive effects of cortisol may vary with affective states, such as perceived social support (Ahner et al., 2004; Quas, Bauer, & Boyce, 2004).

There are some age and sex differences in cortisol profiles, but it is difficult to assess the extent to which this is a consequence of neurological differences (e.g., Butler, Pan, Epstein, Protopopescu, Tuescher, Goldstein, Cloitre, Yang, Phelps, Gorman, LeDoux, Stern & Silbersweig, 2005), physical maturation processes, or the different social environments experienced, for example, during adolescence as compared with early childhood (Flinn, Turner, Quinlan, Decker, & England, 1996; Flinn & Quinlan, in preparation). For instance, young adult women have a higher incidence of depression and associated abnormal cortisol profiles than children or young men in this community.

The emerging picture of HPA stress response in naturalistic context from the Dominica study is one of sensitivity to social challenges, consistent with clinical and experimental studies. The results further suggest that family environments are an especially important source and mediator of stressful social challenges for children. In the next section, data on the longitudinal effects of early traumatic experiences are examined to assess the domain-specificity of changes in stress response.

### **Ontogeny: The Early Trauma → HPA Dysfunction Hypothesis**

“. . . the development of individual differences in behavioral and neuroendocrine responses to stress can be influenced by events occurring at multiple stages in development . . .” (Francis, Diorio, Plotsky, & Meaney, 2002)

Early experiences can have profound and permanent effects on stress response. Exposure to prenatal maternal stress, or prolonged separation from mother in rodents and non-human primates, can result in lifelong changes in HPA stress response (MacCari et al., 2003; Meaney 2001; Suomi, 1997; cf. Levine, 2005). Research on the developmental pathways has targeted the homeostatic mechanisms of the HPA system, which appear sensitive to exposure to high levels of glucocorticoids during ontogeny. Glucocorticoid receptors (GRs) in the hippocampus that are part of the negative feedback loop regulating release of CRH and ACTH can be damaged by the neurotoxic levels of cortisol associated with traumatic events (Sapolsky, 1990b, 2005). Hence early trauma is posited to result in permanent HPA dysregulation and hypercortisolemia, with consequent deleterious effects on the hippocampus, thymus, and other key neural, metabolic, and immune system components (Mirescu et al., 2004; Zhang, Parent, Weaver, & Meaney, 2004). These effects have additional consequences resulting from high density of GRs in the pre-frontal cortex in primates (DeKloet, Oitzl, & Joels, 1999; Patel, Lopez, Lyons, Burke, Wallace, & Schatzberg, 2000; Sanchez, Young, Plotsky, & Insel, 2000).

Finer-grained analysis of the epigenetic mechanisms involved with maternal effects on glucocorticoid negative feedback on CRH release indicates that DNA methylation affects hippocampal GR exon 17 promoter activity (Weaver et al., 2004). The

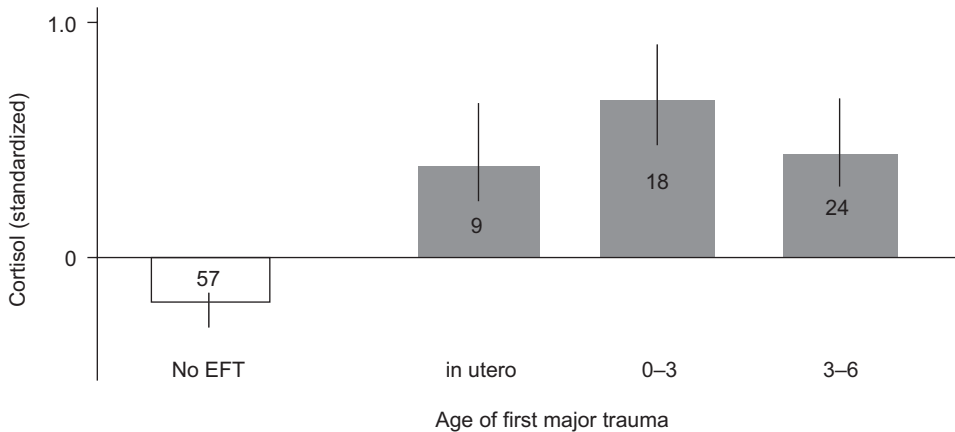


FIGURE 4. Children exposed to early family trauma *in utero* or post-natal have higher average (means for each child) cortisol levels at ages ten and above than children who were not exposed to early trauma (no EFT). Sample sizes (# of children) are in bars. Vertical lines represent 95% confidence intervals. Figure adapted from Flinn, 2006b.

permanence of DNA methylation, set during a sensitive period in the first week after birth in the rat, is a mechanism connecting diminished maternal care (e.g., licking, grooming, and arched-back nursing) with long-term elevations of HPA stress response.

The specific mechanisms affecting relations between exposure to trauma early in development and subsequent HPA system function in humans are not as well documented as in animal studies. Nonetheless, a similar causal linkage appears plausible (e.g., Essex, Klein, Cho, & Kalin, 2002; Heim et al., 2000; Lupien et al., 2005; O’Conner, Heron, Golding, Glover, & ALSPAC study team, 2003; Teicher, Andersen, Polcari, Anderson, Navalta, & Kim, 2003). Children in the Bwa Mawego study who were exposed to the stress of hurricanes and political upheavals during infancy or *in utero* do not have any apparent differences in cortisol profiles in comparison with children who were not exposed to such stressors. Children exposed to the stress of parental divorce, death, or abuse (hereafter “early family trauma” or EFT), however, have significantly higher cortisol (Figure 4) levels at age ten than other children. EFT children also have higher morbidity than non-EFT children (Flinn, 2006b). Based on analogy with the non-human research discussed previously, two key factors could be involved: (1) diminished hippocampal GR receptor functioning, resulting in less effective negative feedback regulation of cortisol levels; and (2) enhanced sensitivity to perceived social threats, perhaps as a consequence of lower social competencies. Children usually elevate cortisol in response to strenuous physical activity, but rapidly return to normal levels (Figure 5). If EFT has affected the negative feedback loop, then recovery to normal cortisol levels would be slower. Resumption of normal cortisol levels after physical stressors, however, appears similar regardless of early experience of family trauma (Flinn, 2006b). Cortisol profiles following social stressors, however,

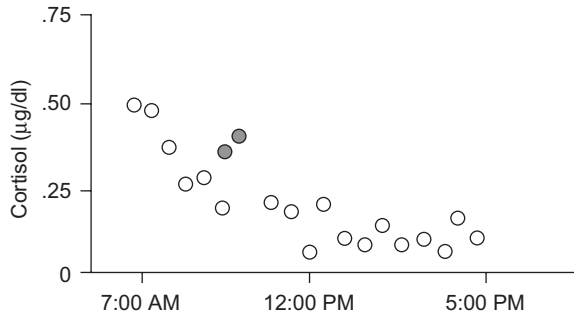


FIGURE 5. Ten-hour cortisol profile of a 12-year-old boy. Note elevation of cortisol levels at 10:00–10:30 AM when he was helping his father carry wood.

indicate that EFT children sustain elevated cortisol levels longer than non-EFT children (Flinn, 2006b).

The enhanced HPA stress response of children in this community that were exposed to EFT appears primarily focused on social challenges, suggesting that the ontogenetic effects of early trauma on stress response may be domain-specific and even context-specific. These results are consistent with studies of the effects of social defeat with non-human models (e.g., Kaiser & Sachser, 2005). In the following section we examine the effects of close grandparental relationships on the stress response of EFT children.

### **Ameliorative Effects of Grandparental Care on the Ontogeny of Stress Response**

Review of analyses of data in the previous section indicate that early family trauma is associated with higher cortisol levels among children in this community. The different cortisol response patterns to social and physical stressors suggest that domain-specific mechanisms have been affected. In this section we examine whether close relationships with grandparents during early childhood are associated with individual differences among EFT children in several outcome measures. The general hypothesis is that grandparental care (GPC) reduces psychosocial stress for grandchildren. The negative effects of early family trauma on child development are therefore expected to be moderated by GPC, as measured by cortisol levels, growth, and morbidity.

EFT children with high (above median) levels of GPC have lower average cortisol levels (Figure 6a), lower morbidity (Figure 6b), and higher growth percentiles (Figure 6c), than EFT children with low GPC. EFT children that have high rates of grandparental care (GPC), however, do not have lower average fluctuating asymmetry (FA)

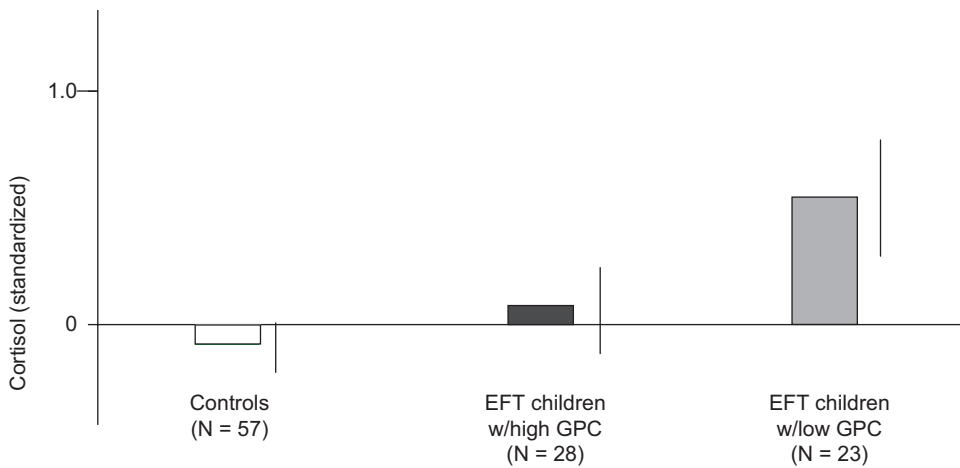


FIGURE 6a. EFT children with high grandparental care (GPC) have lower average cortisol levels than low GPC EFT children. Vertical lines represent 95% confidence intervals.

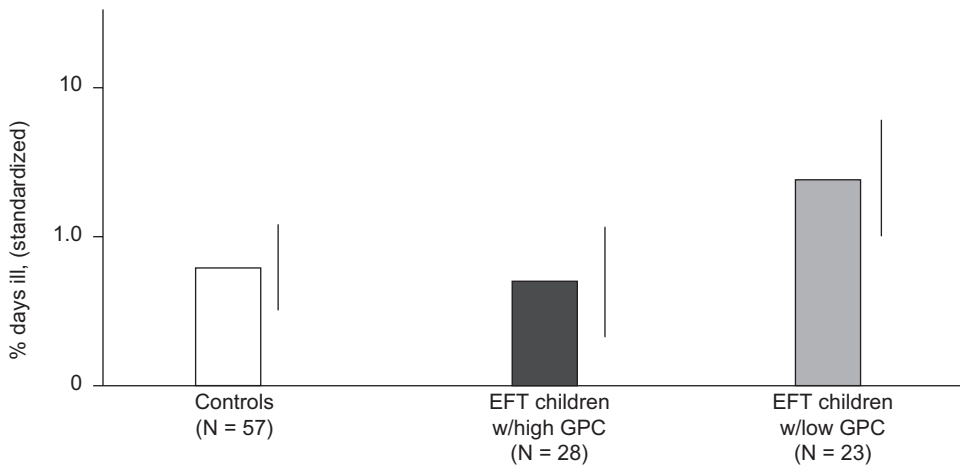


FIGURE 6b. EFT children with high grandparental care (GPC) have lower average morbidity levels than low GPC EFT children. Vertical lines represent 95% confidence intervals.

(Figure 6d) or lower gastrointestinal parasite loads (Figure 6e) than EFT children with low GPC. These results suggest that grandparental care may substantially ameliorate some of the negative consequences of difficult family environments. These findings are generally consistent with our subjective impressions from watching these children over nearly two decades: that grandparental relationships are often of great importance

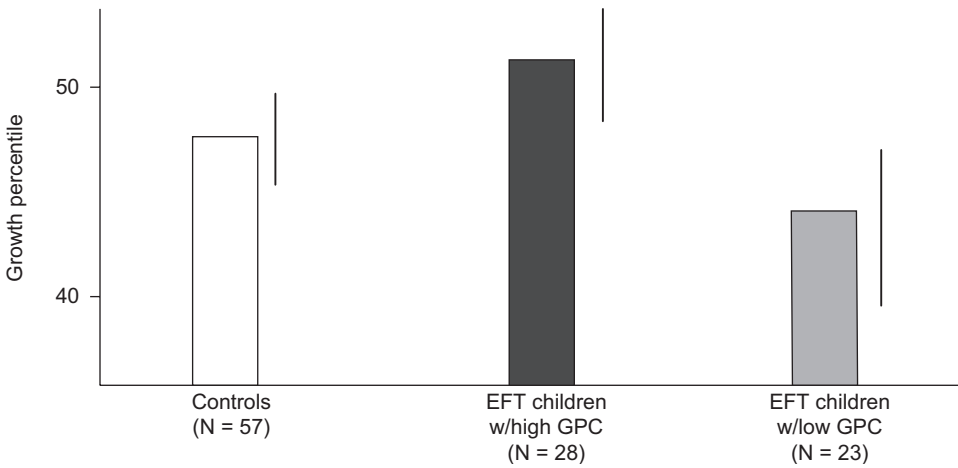


FIGURE 6c. EFT children with high grandparental care (GPC) have higher average growth percentiles than low GPC EFT children. Vertical lines represent 95% confidence intervals.

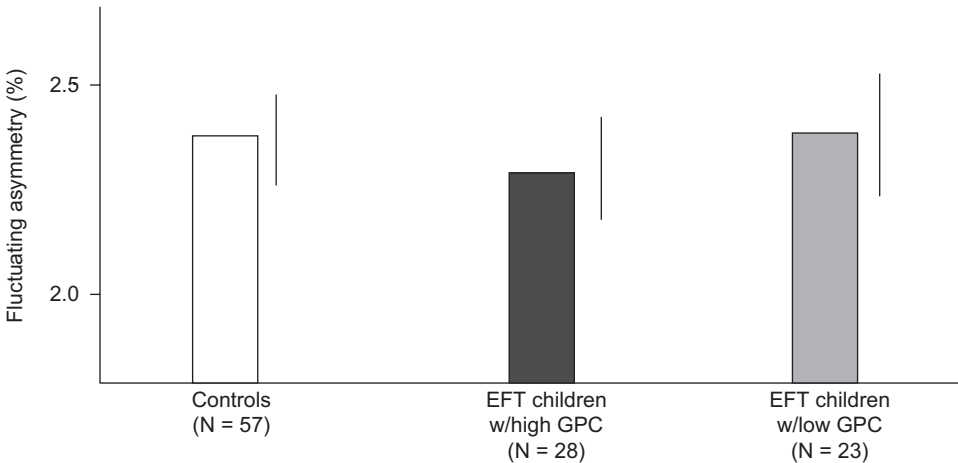


FIGURE 6d. EFT children with high grandparental care (GPC) do not have lower levels of fluctuating asymmetry (FA) than low GPC EFT children. Vertical lines represent 95% confidence intervals.

for the development of emotional regulation, social skills, and self-confidence, especially for children in difficult family environments. What the specific mechanisms are, and whether the effects are direct or indirect via support to the child's mother, are not discernable from these analyses.

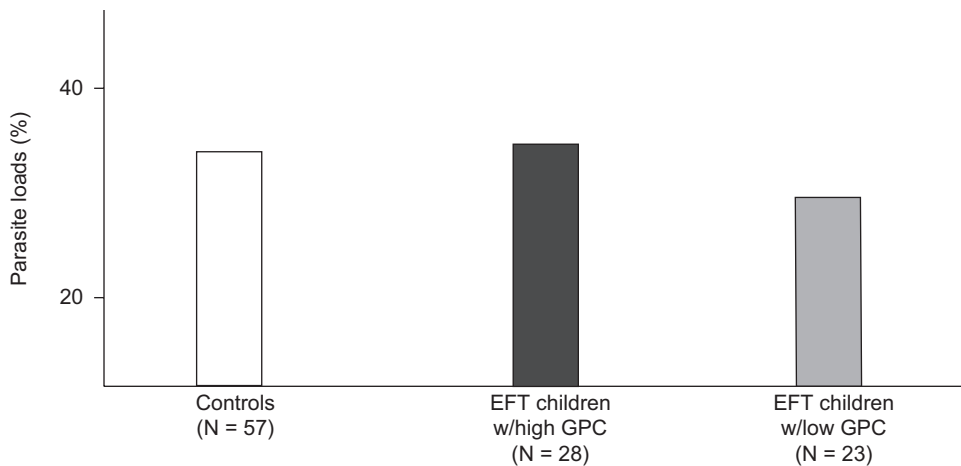


FIGURE 6e. EFT children with high grandparental care (GPC) do not have lower levels of parasite loads than low GPC EFT children.

## Conclusions

Grandparental care appears to be a significant mediator of HPA stress response and associated growth and health problems among children that have experienced early family trauma. Our observations suggest that maternal grandmothers are especially important mediators, (Quinlan & Flinn, 2005), although a variety of other kin (e.g., aunts, siblings, grandfathers) may also contribute, and in special cases, may be primary caregivers (Flinn & Leone, 2006). These results are likely to be specific to the context of the kin networks of this community (e.g., see Quinlan & Flinn, 2003), and are likely to vary contingent on the specific patterns of kinship, although grandparent-grandchild relationships appear to be broadly important (Lahdenpera et al., 2004; Sear et al., 2000; Voland & Biese, 2002). These results are consistent with the hypotheses that the importance of grandmothers in human evolution may involve their role as providers of social information (e.g., emotional comfort, social competencies, traditions) (Coe, 2003) in addition to providing calories and protection (Alexander, 1974; Hawkes, O'Connell, Blurton Jones, Alvarez, & Charnov, 1998).

Returning to the paradox of why natural selection favored sensitivity of stress response to social stimuli in the human child, several points emerge. Human childhood is a life history stage that appears necessary and useful for acquiring the information and practice to build and refine the mental algorithms critical for negotiating the social coalitions that are key to success in our species. Mastering the social environment presents special challenges for the human child. Social competence is difficult because the target is constantly changing and similarly equipped with theory of mind and other cognitive abilities. Results from the Dominica study indicate that family environment, including care from grandparents, is a primary source and mediator of stressful events

in a child's world. The sensitivity of stress physiology to the social environment may facilitate adaptive responses to this most salient and dynamic puzzle, aided by information and security provided by effective parental and grandparental care.

Children lacking such care may be at a disadvantage in developing the social competencies necessary for coping with social challenges, and consequently may be at increased risk for problems ranging from dysregulation of emotional control and increased risk of psychopathology (Gilbert, 2001; Nesse, 1999), to broader health issues associated with social and economic disparities (Adler, Boyce, Chesney, Cohen, Folkman, Kahn, & Syme, 1994; Dressler et al., 2005; Marmot & Wilkerson, 1999). The potential for intergenerational cycles that perpetuate social relationships that affect stress (Belsky, 2005; Belsky, Jaffee, Sligo, Woodward, & Silva, 2005; Fleming, Kraemer, Gonzalez, Lovic, Rees, & Melo, 2002; Fleming, O'Day, & Kraemer, 1999; Francis, Diorio, Liu, & Meaney, 1999; Maestripieri, Lindell, Ayala, Gold, & Higley, 2005) and poor health are especially concerning. Under such circumstances, grandparents helping their grandchildren cope with difficult events involving their parents, intervening during times of critical need and stabilizing development, may be of critical importance (e.g., Lussier, Deater-Deckard, Dunn, & Davies, 2002).

We are still far from identifying the specific mechanisms linking stress response to the ontogenetic plasticity of components of the limbic system and pre-frontal cortex that are involved with the acquisition of social competencies. An evolutionary developmental perspective can be useful in these efforts to understand this critical aspect of a child's world by integrating knowledge of physiological causes with the logic of adaptive design by natural selection (Worthman, 1999). It reminds us that our biology has been profoundly affected by our evolutionary history as fundamentally social creatures, including, perhaps, a special reliance upon grandparents. Indeed, the mind of the human child may have design features that enable its development as a group project, guided by the multitudinous informational contributions of its ancestors and co-descendants. Children without grandparental input may find themselves in worlds that are more stressful because they lack the advice, traditions, good humor, soft laps, and hugging arms by which to understand them.

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