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Biological sensitivity to context: I. An evolutionary–developmental theory of the origins and functions of stress reactivity

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Abstract

Biological reactivity to psychological stressors comprises a complex, integrated, and highly conserved repertoire of central neural and peripheral neuroendocrine responses designed to prepare the organism for challenge or threat. Developmental experience plays a role, along with heritable, polygenic variation, in calibrating the response dynamics of these systems, with early adversity biasing their combined effects toward a profile of heightened or prolonged reactivity. Conventional views of such high reactivity suggest that it is an atavistic and pathogenic legacy of an evolutionary past in which threats to survival were more prevalent and severe. Recent evidence, however, indicates that (a) stress reactivity is not a unitary process, but rather incorporates counterregulatory circuits serving to modify or temper physiological arousal, and (b) the effects of high reactivity phenotypes on psychiatric and biomedical outcomes are bivalent, rather than univalent, in character, exerting both risk-augmenting and risk-protective effects in a context-dependent manner. These observations suggest that heightened stress reactivity may reflect, not simply exaggerated arousal under challenge, but rather an increased *biological sensitivity to context*, with potential for negative health effects under conditions of adversity and positive effects under conditions of support and protection. From an evolutionary perspective, the developmental plasticity of the stress response systems, along with their structured, context-dependent effects, suggests that these systems may constitute *conditional adaptations*: evolved psychobiological mechanisms that monitor specific features of childhood environments as a basis for calibrating the development of stress response systems to adaptively match those environments. Taken together, these theoretical perspectives generate a novel hypothesis: that there is a curvilinear, U-shaped relation between early exposures to adversity and the development of stress-reactive profiles, with high reactivity phenotypes disproportionately emerging within *both* highly stressful and highly protected early social environments.

Biological reactivity to environmental stressors is now widely implicated in the processes linking psychological adversity to psychiatric and biomedical disorder. The neuroendocrine changes that reliably accompany stressful events, in humans and other species, are the physiological, homeostatic means by which survival under threat is protected, but are also among the dysregulatory pathways by which psychological trauma is transmuted into pathogenic biological processes. Individual differences in such "stress reactivity" are thought to underlie the broad variability in stress–illness associations and to reflect constitutional variation in susceptibility to stressful challenge. Highly reactive phenotypes, in which affected individuals mount vigorous and/or persistent

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autonomic, adrenocortical, or other biological responses to stressors, have been viewed as an atavistic health risk factor, a legacy of physiological responses more commensurate with the perils of prehistoric human environments. As such, exaggerated stress reactivity is generally viewed as a maladaptive, monotonically harmful heritage of an ancient preparedness for endangerment. High reactivity, so the argument goes, is a heritable response disposition, often unmasked by traumatic experiences in early life, which places individuals at heightened risk for disorders of mental and physical health. It is the central claim of this two-part series that this view, that high reactivity phenotypes are uniformly harmful psychobiological reversions to primitive and maladaptive modes of response, is mistaken.

Rather, an evolutionary reinterpretation of evidence regarding reactivity and health suggests that highly reactive phenotypes can be more usefully viewed as reflecting heightened *biological sensitivity to context* (BSC), an attribute that may have conferred selective advantages in certain social and ecological contexts during human evolution. Further, although a substantial literature documents the capacity of early developmental trauma to predispose an individual toward high biological reactivity, an evolutionary formulation of recent findings suggests a different and novel hypothesis: that the association between early adversity and reactivity is curvilinear in character, with *both* highly stressful and highly protective environments yielding disproportionate numbers of highly reactive children. In this paper, the theoretical and evidential grounds for this new hypothesis are presented, and in the second paper, exploratory data analyses in two studies of early development and psychopathology are used to generate empirical observations commensurate with the same hypothesis. Together, the papers present both theoretical and empirical lines of argument that converge upon a single thesis: that highly reactive phenotypes are forms of enhanced, neurobiologically mediated sensitivity to context, which have been favored by natural selection due to their fitness-enhancing effects in both minimally and maximally stressful environments. This evolutionary paradox, of reactive phenotypes being selected within two oppositional categories of environments, can be resolved, it will be argued, by the supposition that BSC increases adaptive competence in highly *stressful* environments by augmenting vigilance to threats and dangers and in highly *protective* environments by increasing susceptibility to social resources and ambient support. In the sections that follow, we (a) describe the structure and phylogeny of the neural circuits implicated in stress reactivity, (b) delineate genetic and environmental contributions to the calibration of such reactivity, (c) review past and recent findings linking stress reactivity and health, and (d) conclude that phenotypic expressions of unusually heightened reactivity reflect an underlying biological sensitivity to contextual signals. Finally, exploring this reconceptualization of exaggerated reactivity as context sensitivity, we construct an evolutionary–developmental theory of the origins and functions of the human stress response and formulate new hypotheses characterizing the relation between early adversity and the magnitude of biological responses to stress. This theory and derivative hypotheses are founded on the concept of conditional adaptation, in which a single genotype supports a range of environmentally contingent phenotypic expressions, enabling an adaptive correspondence between the developing organism and its environment.

The Structure and Phylogeny of the Human Stress Response

Environmental events signaling threats to survival or well being produce a set of complex, highly orchestrated responses within the neural circuitry of the brain and peripheral neuroendocrine pathways regulating metabolic, immunologic, and other physiological functions. As first described in the work of Claude Bernard on homeostasis (Bernard, 1878) and the subsequent research of 20th century stress physiologists Walter Cannon (1929) and Hans Selye (1950), this elaborate and tightly integrated repertoire of responses results in an immediate, relatively automatic

shift to a state of biological and behavioral preparedness, involving increases in heart rate and blood pressure, metabolic mobilization of cellular nutrients, preferential redirection of energy resources and perfusion to the brain, and the induction of behavioral vigilance and fear. Comprehensively detailed in the writings of neuroscientists such as Chrousos (1998), Meaney (2001), and McEwen (1998), the neural substrate for the organism's stress response comprises two anatomically distinct but functionally integrated circuits, the corticotropin-releasing hormone (CRH) system and the locus coeruleus–norepinephrine (LC-NE) system. The coactivation of the these two systems, along with their linkages to limbic structures, such as the amygdala and anterior cingulate, as well as the mesolimbic dopaminergic system and the medial prefrontal cortex, produce the coordinated biobehavioral changes associated with the stress response in mammalian species.

The CRH system actually comprises two distinguishable subsystems, one centered in the paraventricular nucleus (PVN) of the hypothalamus and involved in the homeostatic regulation of the hypothalamic–pituitary–adrenocortical (HPA) axis, and the other involved in the corticolimbic circuitry of the amygdala and its connections. Within the former subsystem, CRH is released into the portal blood supply of the pituitary in a pulsatile (and, under normative conditions, circadian) fashion by neurons in the PVN and serves, along with synergistic effects of arginine vasopressin (AVP), as the primary secretagogue for expression of pro-opiomelanocortin (POMC) polypeptide by the anterior pituitary. In the second subsystem, CRH cell bodies are more widely represented in loosely related, extrahypothalamic locations, including the amygdala, the substantia innominata, the bed nucleus of the stria terminalis, and in the prefrontal, insular, and cingulate regions of the cortex (Gold & Chrousos, 2002; Owens & Nemeroff, 1991). Two or more types of CRH receptors have been elucidated, with species variation in the expression of specific receptor types. CRH_1 receptors are found in the anterior pituitary and other brain regions and are involved in generating fear-related behavior, and CRH_2 receptors, found mostly in the periphery, may play a counterregulatory role in anxiogenesis. POMC is cleaved into its component proteins, corticotropin (ACTH) and β-endorphin (Smith et al., 1998), and ACTH is transported in plasma to the zona fasciculata of the adrenal cortex, triggering secretion of cortisol, the principal human glucocorticoid regulating blood pressure, glucose metabolism, and immune competence. Glucocorticoids also inhibit those neuroendocrine axes promoting growth and reproduction (Gold, Goodwin, & Chrousos, 1988).

The intracellular actions of cortisol are mediated through binding to a widely distributed cytoplasmic receptor, translocation to the nucleus of the target cell, and subsequent direct effects on gene transcription and inhibition of other, proregulatory transcription factors such as c-jun/c-fos, and NF-kB (van der Saag, Caldenhoven, & van de Stolpe, 1996). Although such actions acutely facilitate essential biological responses to stress and threat, chronic glucocorticoid secretion is associated with a variety of pathogenic processes and disease states, including major depression, insulin resistance and diabetes, hypertension and atherosclerosis, bone loss, and disorders related to diminished immune functions (Gold & Chrousos, 1999; McEwen, 1998). The hippocampus, a brain region closely involved in memory and learning, is particularly susceptible to the effects of glucocorticoids, showing decreased dendritic branching and neuronal loss in the CA3 area, as well as changes in synaptic terminal structure and inhibition of neuron regeneration (Bremner & Vermetten, 2001; Sapolsky, 1996). Under more normative circumstances, circulating cortisol therefore adaptively regulates the activation level of the HPA axis through a process of feedback inhibition at the hypothalamus, the pituitary, and extrahypothalamic centers such as the hippocampus and frontal cortex (Dallman, Akana, Cascio, Darlington, Jacobson, & Levin, 1987).

The LC-NE system comprises the noradrenergic cells of the medulla and dorsal pons and their projections to the amygdala, hippocampus, mesolimbic dopamine system, and the medial prefrontal cortex (Aston–Jones,

Rajkowski, Kubiak, Valentino, & Shipley, 1996). LC activation of hypothalamic centers also contributes to activation and regulation of the autonomic nervous system (ANS), initiating the so-called fight or flight responses to challenge. The ANS, comprising sympathetic, parasympathetic, and enteric branches, modulates physiologic arousal and recovery in the periphery and produces the familiar biological concomitants of severely stressful encounters, including heart rate and respiratory rate acceleration, sweat production, dry mouth, and, if sufficiently severe, loss of urinary or fecal continence. These biological responses are mediated both by direct autonomic innervation of target organs by postganglionic neurons and by secretion of epinephrine and norepinephrine by the adrenal medulla. Immune regulatory effects of the catecholamines, as well as those of CRH and the glucocorticoids, appear due to differential effects on T-helper-1/T-helper-2 cells and type 1/type 2 cytokine production (Habib, Gold, & Chrousos, 2001). Through such direct effects on immune cells, experiences of severe or prolonged stress may influence susceptibility to a variety of infectious, autoimmune/inflammatory, or neoplastic diseases (Elenkov & Chrousos, 1999). NE from the LC may also contribute to vulnerability to stress-related symptoms by facilitating emotional memory retention in the hippocampus and striatum (Introini–Collison, Dalmaz, & McGaugh, 1996).

Although anatomically distinct, the neural functioning of the CRH and LC-NE systems is highly integrated and cross-regulatory. CRH-expressing neurons in the central nucleus of the amygdala, for example, project directly to the LC, escalating the firing rate of LC neurons, enhancing NE release within the ascending noradrenergic system, and producing many of the fear-related behaviors associated with stressful experience (Meaney, 2001; Valentino, Curtis, Page, Pavcovich, & Florin–Lechner, 1998). These CRH-mediated pathways from the amygdala to the LC may also serve as the neural substrate for many of the symptoms of anxiety disorders, such as increased acoustic startle responses, vigilance, symptoms of avoidance, and recurrent emotional memories. Reciprocally, activation of NE secreting neurons in the LC has been shown to increase CRH production in the PVN (Habib et al., 2001). This cross-regulatory process is only one of several ways in which the LC-NE and CRH are functionally interactive (Gold & Chrousos, 2002; Viau, 2002), and together constitute a primary integrative pathway by which psychologically and emotionally relevant environmental signals are transmuted into the behavioral, autonomic, and immunologic manifestations of human pathology (Cacioppo, Berntson, Malarkey, Kiecolt–Glaser, Sheridan, Poehlmann, Burleson, Ernst, Hawkley, & Glaser, 1998; Heilig, Koob, Ekman, & Britton, 1994; McEwen & Stellar, 1993). Dysregulated activation has been implicated, as well, in the genesis and presentation of the major neuropsychiatric disorders (Bloom & Kupfer, 1995), and the experimental administration of neurohormonal products from the CRH and LC-NE systems produces many of the physiological and behavioral symptoms that characterize affective and anxiety disorders (Dunn & Berridge, 1990; Heilig et al., 1994).

Both stress response systems, as well as their central and peripheral components, appear early in phylogeny and have been extensively conserved in the evolutionary history of vertebrate and mammalian species. Steroid hormones are derived from cholesterol and occur widely in both animal and plant species, exhibiting chemical activities reminiscent even of the mammalian glucocorticoids (Bentley, 1998). Different forms of C_{18}, C_{19}, and C_{21} adrenal corticosteroids appear in all the major vertebrate groups, with both cortisol and corticosterone found in primitive, cartilaginous fish and aldosterone and corticosterone identified in the higher fish, amphibians, and reptiles. The glucocorticoid receptors of mammalian species are thought to have evolved from a 500 million year old ancestral gene, such as that coding for the single steroid receptor expressed in teleost fish. Such fish corticosteroid receptors exhibit a 97% homology in their DNA binding region to the amino acid sequence of the human glucocorticoid receptor. Even pituitary hormones similar to those found in the vertebrate HPA axis are present in some invertebrates, including mollusks and insects.

Catecholamine hormones of the LC-NE and ANS have a similarly long phylogeny. They are present in many invertebrates, such as the chordate *Amphioxus* arrow worm, and even in some ciliated protozoans, where they function metabolically in a manner remarkably similar to their roles in higher animal species. Like steroid receptors, catecholamine receptors are also represented in primitive species and have transmembrane domains that have been highly conserved. The complexity of the ANS appears to have increased phylogenetically with that of the CNS, attaining approximately similar levels of organization and complexity within the amniote classes of reptiles, birds, and mammals.

Taken together, these observations from the human and infrahuman neurosciences suggest the following interim observations. First, homeostatic systems protecting survival and stability under conditions of stress are phylogenetically ancient, showing both genetic expression and comparable biological functions in animal species from invertebrates to primates. Second, the CRH and LC-NE systems subserve a complex, highly interactive repertoire of central and peripheral stress responses, which mobilize neurobiological and behavioral resources in defense of the organism's integrity and well being. Third, although these neurobiological responses are protective and essential in acutely stressful conditions, they can become themselves pathogenic when persistently activated under circumstances of chronic or overwhelming stress and adversity.

Genes, Environments, and Reactive Phenotypes

Reactivity has been defined (Matthews, 1986) as "the deviation of a physiological response parameter from a comparison or control value that results from an individual's response to a discrete, environmental stimulus." Broad individual variation in reactivity to psychological stressors has been documented in human adults (Cacioppo et al., 1998), human children (Alkon, Goldstein, Smider, Essex, Kupfer, & Boyce, 2003; Allen & Matthews, 1997), and both young and mature laboratory animals (Meaney, 2001; Suomi, 1987a). Although the origins of such individual differences in reactivity, which is the central focus of the present papers, remain incompletely understood, there is wide acknowledgement that both the genome and early experience account for some share of the variance in phenotypic stress responses.

Within *rodent and other subprimate mammalian models* of reactivity developed by Meaney and colleagues (Liu & Meaney, 1997; Meaney, 2001) and others (Reis & Golanov, 1997), there is evidence that individual differences are determined by strain-related genetic variations, by aspects of early maternal–infant experience, and by interactions among gene expression and experiential factors. On the one hand, clear biobehavioral differences exist between strains of mice and rats on dimensions such as behavioral and adrenocortical reactivity to stressors. BALBc mice, for example, are inherently more fearful and show more vigorous glucocorticoid responses to stressors than do C57 mice (Zaharia, Kulczycki, Shanks, Meaney, & Anisman, 1996), and comparable differences exist between Fisher 344 and Long–Evans rats (Dhabhar, McEwen, & Spencer, 1993). Such biobehavioral differences in strains are likely due, at least in part, to heritable variation in the alleles that regulate stress responsive biological systems in these animals.

On the other hand, Meaney and others have shown that perturbations in early experience resulting in changed maternal–infant behavior can also have profound regulatory effects on the calibration of biological systems, including the CRH system and HPA axis (Hofer, 1994; Meaney, 2001; Plotsky & Meaney, 1993). An experimental procedure known as "handling," in which rodent pups are separated from their mothers for 3–15 min each day over the first several weeks of life, results in permanent downregulatory changes in the CRH system at the level of the PVN and central nucleus of the amygdala and, as a consequence, produces a decreased exposure to the adrenocortical and autonomic effects of stressful events. Such downregulatory effects have been shown to result from increased glucocorticoid receptor expression following changes in mothering behavior, that is, the intensity of licking and grooming and other characteristic maternal behaviors, upon the pups' return to the nest. Further, handling can override the genetic propen-

sities shared with a fearful, highly reactive mother by inducing maternal behaviors that produce long term underarousal in the infants' adrenocortical and autonomic response systems (Champagne & Meaney, 2001). It remains unclear at present whether the regulatory effects of these maternal behaviors are constrained to a "critical," early period of development or are capable of recalibrating response systems later in infancy or beyond.

When early maternal–infant separations are more prolonged, however, in a regimen involving true deprivation of maternal care for as long as 180 min, the effect on biological stress response systems is exactly opposite that of handling (Meaney, 2001). Separated rodent pups develop chronically upregulated CRH activity in the HPA axis, the amygdala, bed nucleus of the stria terminalis, and the LC, as well as behavioral changes consistent with fearfulness and inhibition under conditions of novelty (Sanchez, Ladd, & Plotsky, 2001). There is also evidence for effects of prenatal stress-induced maternal glucocorticoids on fetal, and later infant, physiology and development. Maternal glucocorticoid exposures are associated, for example, with elevations of CRH (Cratty, Ward, Johnson, Azzaro, & Birkle, 1995) and CRH receptors (Ward, Johnson, Salm, & Birkle, 2000) in the amygdala of offspring, and with downregulation of 11β-hydroxysteroid dehydrogenase, the placental enzyme that inactivates fetal steroidal effects (Benediktsson, Lindsay, Noble, Seckl, & Edwards, 1993). Both down- and upregulatory alterations in CRH system regulation (those produced by handling and by maternal separation, respectively) can have detrimental effects on disease and survival, depending upon the kinds of exposures that the animals later sustain. Handled animals have been shown to be more susceptible, for example, to immune-mediated disorders, such as experimental allergic encephalomyelitis (Laban, Dimitrijevic, von Hoersten, Markovic, & Jankovic, 1995), while those experiencing extended maternal separations have shown increased vulnerability to stress-related hippocampal damage and deficits in learning or memory (Issa, Rowe, Gauthier, & Meaney, 1990; Sapolsky, 1996). These studies suggest both heritable and experiential influences on the expression of stress reactivity in rodent models and reveal influences that are bivalently regulatory in their effects on psychobiological response parameters.

Studies of *nonhuman primates* have similarly contributed important evidence to an understanding of constitutional and contextual determinants of stress reactivity. Suomi and colleagues (Byrne & Suomi, 2002; Champoux & Suomi, 1994; Suomi, 1987b), for example, have increasingly documented the influence of heritable genetic factors on the neurobiological systems that underpin temperamental differences in behavior. One study comparing neurobiological differences between Indian origin and Chinese hybrid rhesus monkeys found significantly lower cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid levels (a metabolite of serotonin) in Chinese hybrid monkeys beginning at 6 months of age, suggesting "strain" differences in the magnitude of central serotonergic activity (Champoux et al., 1997). Serotonergic neurons are implicated in the neural circuitry of the stress response and in brain structures involved in the processing of emotional information (Rolls, 1999). Another study by Lyons, Yang, Sawyer–Glover, Moseley, and Schatzberg (2001) showed that stress-related hippocampal atrophy is partially heritable, raising questions regarding an attribution of hippocampal volume variation to purely experiential factors. Further, primate studies by Higley and others have demonstrated heritable variation in central serotonergic drive, which is in turn related to aspects of behavioral reactivity (Higley & Linnoila, 1997), and have identified both genetic and environmental contributions to differences in serotonin and dopamine metabolites in the cerebrospinal fluid of young macaques (Higley, Thompson, Champoux, Goldman, Hasert, Kraemer, Scanlan, Suomi, & Linnoila, 1993).

Although the above research suggests at least partial genetic regulation of stress response systems, studies of nonhuman primates have also revealed a capacity for early, stress-engendering disruptions of social experience to produce long-term changes in neurobiological reactivity (Sanchez et al., 2001).

Research on early deprivation, beginning with the seminal work of Harlow and colleagues at the University of Wisconsin Primate Laboratory (Harlow, Harlow, & Suomi, 1971), has demonstrated the centrality of maternal–infant relationships in the emergence of species normative behavior, and the capacity for isolate- or peer-rearing conditions to disrupt behavioral and psychobiological regulatory functions in several Old and New World primate species. Accompanied by behavioral changes such as protest vocalizations, autistic-like stereotypies, nonnutritive sucking, and self-mutilation, maternal separations produce predictable changes in peripheral and central neural circuitry. Among these are alterations in functional immune competence (Lubach, Coe, & Ershler, 1995), upregulation of autonomic responses to physical stressors (Martin, Sackett, Gunderson, & Goodlin–Jones, 1988), increased CRH expression in CSF (Coplan, Andrews, Rosenblum, Owens, Friedman, Gorman, & Nemeroff, 1996), and dysregulatory changes in HPA axis reactivity (Shannon, Champoux, & Suomi, 1998). As comprehensively reviewed by Sanchez et al. (2001), dysregulatory changes in the CRH system have reliably been found following exposures of infant monkeys to isolated or deprived early rearing conditions, but the character and direction of such changes remain indeterminate in the existing literature. Although some groups have shown consistent elevations in cortisol expression under conditions designed to undermine maternal attentiveness (Champoux, Hwang, Lang, & Levine, 2001; Lyons, Wang, Lindley, Levine, Kalin, & Schatzberg, 1999), others have detected no differences in HPA responses to stressors among isolation reared rhesus infants (Meyer & Bowman, 1972). In one study by Boyce, Champoux, Suomi, and Gunnar (1995), peer rearing of infant macaques appeared associated with blunted, *down*regulatory changes in the circadian periodicity of cortisol secretion. Further, the work of Sapolsky (1990; Sapolsky & Share, 1994) among wild olive baboons has revealed associations between dominance status and adrenocortical activation, suggesting either that experiences related to social adeptness and dominant hierarchical status tended to lower cortisol levels or that constitutionally less reactive individuals occupied higher status positions. Comparable to observations within rodent models of stress reactivity, studies of nonhuman primates offer further evidence for both genetic and contextual influences on the calibration of stress response systems.

Finally, a growing number of studies in *human children and adults* have similarly revealed both genomic and environmental origins for the individual differences observed in biological reactivity (Heim & Nemeroff, 1999). In parallel to genetic evidence from nonhuman primates, studies of children and their parents (Matthews, Manuck, Stoney, Rakaczky, McCann, Saab, Woodall, Block, Visintainer, & Engebretson, 1988), adults in preidentified genetic pedigrees (Cheng, Carmelli, Hunt, & Williams, 1997), as well as mono- and dizygotic twins (Bartels, de Geus, Kirschbaum, Sluyter, & Boomsma, 2003; Busjahn, Faulhaber, Viken, Rose, & Luft, 1996; Turner & Hewitt, 1992) have all affirmed a moderate heritability of reactivity phenotypes. A parental history of hypertension has frequently been shown to be predictive of autonomically mediated blood pressure reactivity in both children (e.g., Lemne, 1998) and young adults (e.g., Adler & Ditto, 1998). Elevated cortisol levels have also been identified in the nondepressed, first-degree relatives of patients with major depression, suggesting that hypercortisolism might be appropriately viewed as a trait measure of a heritable diathesis to affective disorders (Holsboer, Lauer, Schreiber, & Krieg, 1995).

In addition, the research programs of a number of investigators have produced findings supporting experiential, contextual contributions to the emergence of high reactivity. A number of studies in human children suggest, for example, that disruptions in early attachment relationships are associated with regulatory influences on and disturbances in stress–responsive biological systems (Hertsgaard, Gunnar, Erickson, & Nachmias, 1995; Meyer, Chrousos, & Gold, 2001; Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996; Willemsen–Swinkels, Bakermans–Kranenburg, Buitelaar, van, & van Engeland, 2000). Further, a prospective, longitudinal study by Es-

sex, Klein, Cho, and Kalin (2002) demonstrated that, parallel to the findings of animal research, early exposures to stressors such as maternal depression can sensitize children's CRH systems to subsequent adversities, resulting in the development of mental health symptoms. In a singular study of healthy women by Heim, Newport, Heit, Graham, Wilcox, Bonsall, Miller, and Nemeroff (2000), participants with a history of abusive experiences in childhood had dramatically increased levels of pituitary (ACTH) and autonomic reactivity to a standardized laboratory stress protocol. Abused women with current major depression exhibited sixfold greater ACTH responses than age-matched controls and were the only group to show significantly elevated cortisol responses, as well. De Bellis, Baum, Birmaher, Keshavan, Eccard, Boring, Jenkins, and Ryan (1999) similarly found increased 24-hr urinary excretion of cortisol and norepinephrine among children with abuse-related posttraumatic stress disorder (PTSD) symptoms, in comparison to healthy controls, and Perry (1994) reported diminished adrenergic receptors on platelets and increased heart rates in a group of severely abused children. A series of studies by Yehuda and coworkers (Yehuda, 2002; Yehuda, Halligan, & Bierer, 2001; Yehuda, Halligan, & Grossman, 2001) has further documented the psychobiological sequelae of early abusive experiences. Sexual abuse was associated with elevated 24-hr urinary cortisol excretion (Yehuda et al., 2001), increased density of lymphocyte glucocorticoid receptors, and enhanced suppression of plasma cortisol responses to dexamethasone (Stein, Yehuda, Koverola, & Hanna, 1997), each reflecting disturbances in the regulation of the HPA axis. In an interesting parallel to the observations in nonhuman primates mentioned above, Yehuda et al. (2001) also reported that emotional abuse and PTSD were associated with *diminished*, rather than elevated, 24-hr urinary cortisol levels. In studies of broader societal influences on the development of stress responses, Lupien, King, Meaney, and McEwen (2000) found that lower socioeconomic status was associated with higher salivary cortisol levels in children as young as 6 years of age, and Fernald and Grantham–McGregor (1998) observed higher salivary cortisol levels and greater cardiovascular reactivity among growth-stunted children growing up in impoverished neighborhoods in Jamaica.

Taken together, rodent, nonhuman primate, and human research all point to a common conclusion: that both genetic and environmental factors contribute to the calibration of biological stress response systems over the course of early development. These studies further suggest that, while stable individual differences in stress reactivity emerge with maturation, there is pronounced early plasticity in the neurobiological systems that subserve such reactivity (Davidson, Jackson, & Kalin, 2000). Stress reactivity, like many developmentally acquired phenotypic features, appears to become "canalized" over time, revealing progressively greater resistance to change and diminishing plasticity (Turkheimer & Gottesman, 1991; Waddington, 1966). Within the setting of human development, however, little is understood of the developmental time course over which such canalization occurs. Some of the papers reviewed provide evidence for a central developmental role of primary attachment relationships and maternal behavior in shaping, constraining, and regulating psychobiological responses to experiences of future challenge and adversity. Such findings suggest, although with considerable imprecision, that social contextual effects over the first 3–5 years of life may have particular potency in the calibration of stress responsive biological systems.

Stress Reactivity and Health

The CRH and LC-NE systems together constitute a primary integrative pathway by which psychologically and emotionally relevant environmental signals are transmuted into the behavioral, autonomic, and immunologic manifestations of human pathology (Cacioppo et al., 1998; Heilig et al., 1994; McEwen & Stellar, 1993). Dysregulated activation has been implicated, as well, in the genesis and presentation of the major neuropsychiatric disorders (Bloom & Kupfer, 1995), and the experimental administration of neurohormonal products from the CRH and LC-NE systems produces many of the physiological and behavioral symp-

toms that characterize affective and anxiety disorders (Dunn & Berridge, 1990; Heilig et al., 1994). In epidemiologic and observational studies of humans, individual differences in adrenocortical and autonomic reactivity have been associated with a variety of mental and physical disorders, including internalizing and externalizing psychopathology (Boyce, Quas, Alkon, Smider, Essex, & Kupfer, 2001; Kagan, 1994; Raine, Venables, & Mednick, 1997), psychological and physical symptoms (Boyce, Chesney, Alkon–Leonard, Tschann, Adams, Chesterman, Cohen, Kaiser, Folkman, & Wara, 1995; Gannon, Banks, Shelton, & Luchetta, 1989), risk for atherosclerotic heart disease (Lynch, Everson, Kaplan, Salonen, & Salonen, 1998), injuries (Boyce, 1996), and risk-taking behavior (Liang, Jemerin, Tschann, Irwin, Wara, & Boyce, 1995). As reviewed by Cacioppo, Berntson, Sheridan, and McClintock (2000), assessments of stress reactivity to challenge, in a variety of physiological modalities, enhances significantly the clinical predictions of health outcomes that are possible on the basis of resting or static measures alone.

The conventional understanding of stress reactivity is that it represents a pathogenic biobehavioral atavism: a vestige of physiological responsivity to prehistoric environments that is no longer adaptive within the intensity and challenges of modern life and, consequently, increases risk for the development of various morbidities. This view has been convincingly articulated by a generation of investigators, including René Dubos, the pioneering 20th century human biologist, and Randolph Nesse, an eminent evolutionary psychiatrist at the University of Michigan's Institute for Social Research:

> Another illustration of the fact that modern man retains essential traits of his evolutionary past is the persistence in him of hormonal and metabolic responses which were developed to meet threatening situations during his animal ancestry, but which no longer fit the needs of life in civilized societies . . . what was once an advantage is increasingly becoming a handicap under the conditions of modern human life. (Dubos, 1965, p. 29)

> Despite the amount of stress we experience, however, our ancestors almost certainly experienced more. With no police, no food reserves, no medicine, no laws, rampant infections, and prevalent predators, danger could come at any time . . . Perhaps in that environment, where stressors were more often physical, the stress response was more useful than it is now. Today, we mainly face social and mental threats, so the actions of the HPA system may yield net costs. This is plausible and supports the many efforts to reduce stress and to find drugs that block the stress response. (Nesse & Young, 2000, p. 83)

A full rendition of this widely endorsed account comprises the following twin premises: (a) because stress responses evolved in ancestral environments characterized by frequent, severe threats to survival, a unitary system of physiological arousal emerged, which readies the organism for confrontation or retreat, often in a manner disproportionate to the actual hazards encountered; and (b) prolonged activation or acute overactivation of such pathways ultimately undermines the health of organisms by impairing, rather than activating, the function of target organs. Although the essential, protective aspects of these neurobiological responses to adversity are broadly acknowledged, it has become an article of faith that overreactivity promotes the genesis of disease. Compelling and intuitive as the two premises have appeared, both are now challenged by evidence suggesting that stress reactivity is not a unitary physiological process, because adversity often results in down- rather than upregulatory changes in component neural circuits, and that high reactivity exerts bidirectional, rather than univalent, influences on health. It is to this evidence and these findings that the discussion now turns.

Anomalous findings on stress reactivity and health

The *first premise*, that stress reactivity constitutes a unitary, unidirectional set of biological responses to threat, has been contested by a collection of observations and new hypotheses suggesting that the components of the stress response system often act in opposition to, rather than in alliance with, each other. More than 40 years ago, Lacey (1959) criti-

cized the concept of uniform arousal, arguing that, even within the ANS, different neural components pursue different profiles of response. His observations were followed by those of other investigators such as Ekman, Levenson, and Friesen (1983), who maintained that no general state of "arousal" exists, and that specific emotional experiences are linked to specific constellations of ANS and central neural activity. In 1984, Munck, Guyre, and Holbrook advanced a new and then counterintuitive proposal. They hypothesized that glucocorticoids and the HPA axis, rather than constituting the hormonal sine qua non of stress-induced arousal, as had been widely believed since the inception of stress research, function instead as a buffering or counterregulatory influence, essentially "braking" the duration or intensity of an otherwise overly exuberant physiological response. It may thus be the more slowly activated HPA axis that is responsible for the termination or tempering of the immediate, autonomically mediated fight or flight state, by the glucocorticoids' physiological opposition to the effects of adrenergic arousal. Such a view would resolve, they argued, the paradoxical observation that diseases with known associations to psychological stressors, such as rheumatoid arthritis or inflammatory bowel disease, can actually be treated with glucocorticoids. Such sequences of paired, counterregulatory processes are common in biological systems, such as the neuronal action potential and the clotting cascade, in which the same stimuli that activate initial responses (e.g., the opening of sodium channel gates or the cleaving of fibrinogen into fibrin) also activate a delayed suppressor (e.g., the closing of sodium channels or the activation of plasminogen to plasmin to lyse clots), which is required to restore a homeostatic state.

Munck's proposal is, in fact, consistent with a number of empirical observations that have been reported since. Most recently, for example, Bauer (2002) found, in a cross-sectional study, that the absolute levels of activation in either the sympathetic or adrenocortical system were less predictive of serious behavior problems in 4- to 8-year-old children than was the lack of concordance between the systems. Children with symmetrical activation or no activation at all had the fewest behavior problems, whereas children with activation asymmetries had the most, suggesting that dissociations between the sympathetic and adrenocortical arousal under conditions of challenge put children at risk for early psychopathology, a conclusion commensurate with Munck's hypothesis. Similarly, a review paper by Yehuda, McFarlane, and Shalev (1998) concluded that, among adult patients following an acutely stressful event, the combination of low cortisol levels and high heart rates, indicating a disjunction between adrenocortical and sympathetic responses, was most predictive of later PTSD symptoms. The findings of both groups are also consistent with more recent observations that catecholamines and glucocorticoids interact in a variety of complex ways, involving conjoint (but sometimes counterregulatory) effects on such functions as lymphoproliferative responses, appetite, and memory (e.g., Sapolsky, Romero, & Munck, 2000).

Another collection of findings, recently summarized by Gunnar and Vazquez (2001) and Heim, Ehlert, and Hellhammer (2000), also challenges the first premise with evidence of paradoxical *suppression* of HPA activation under conditions of stress. Such "hypocortisolism," that is, lower basal cortisol levels, less HPA reactivity, or a flattening of the circadian cortisol cycle among higher risk samples, has been noted in both animal and human research, by multiple investigators, and in a variety of research settings. In the previously noted study by Boyce, Champoux, et al. (1995), for example, peer rearing of infant macaques was associated with blunted, downregulatory changes in the circadian periodicity of cortisol secretion. Similarly, although Gunnar, Morison, Chisholm, and Schuder (2001) found persistent elevations in salivary cortisol levels among children adopted *out* of Romanian orphanages, Carlson and Earls (1997) found low morning cortisol levels and an absence of the normal circadian decline in cortisol among children continuing to live *inside of* Romanian institutions. Infants with colic (White, Gunnar, Larson, Donzella, & Barr, 2000), children with psychosocial dwarfism (Vazquez, Watson, & Lopez, 2000), and chil-

dren living near the epicenter of a major earthquake (Goenjian, Yehuda, Pynoos, Steinberg, Tashjian, Yang, Najarian, & Fairbanks, 1996) have all shown lower morning cortisol levels and a flattening of the normal circadian cycle, relative to control children without such conditions or experiences. Children characterized as shy or introverted similarly showed diminished cortisol reactivity to normative stressors such as the beginning of a new school year (Davis, Donzella, Krueger, & Gunnar, 1999; de Haan, Gunnar, Tout, Hart, & Stansbury, 1998). These findings with regard to the HPA system are notably similar to those of two other studies in which stressful life events were found inversely related to cardiovascular (rather than adrenocortical) reactivity in children or youth (Chesterman, Boyce, & Winkleby, 1989; Musante, Treiber, Kapuku, Moore, Davis, & Strong, 2000). In an interesting parallel to such observations in children, Heim, Ehrlert, et al. (2000) reviewed evidence for associations between hypocortisolism and stress-related disorders in adults and similarly concluded that low cortisol patterns are sometimes associated with experiences of stress or adversity or with stress-related disorders. Yehuda et al. (2001) reported, for example, that among adult children of Holocaust survivors those with a self-reported history of childhood trauma showed diminished, rather than elevated, 24-hr urinary cortisol levels, relative to a comparison group with no history of trauma.

In summary, the often tacit, but largely conventional, impression that stress reactivity represents a singular, unitary biological response to adversity is weakened by two categories of new evidence. First, recent findings suggest that components of the stress response system may act in a coordinated but counterregulatory manner, as proposed by Munck and colleagues (1989), some operating to dampen, rather than magnify, the physiological effects of others. Second, traumatic events and severe stressors may be associated, in both children and adults, with a downregulated HPA axis, a diminution in circadian cortisol secretion, and a reduction in cardiovascular reactivity.

The *second premise*, that exaggerated or persistent reactivity is univalently associated with stress-related morbidities, has also been questioned in a growing number of studies revealing that high reactivity phenotypes under specific environmental conditions may be associated with protective, rather than harmful, effects and generate normative or improved health outcomes. Such bivalent effects of stress reactivity on human and primate morbidities have thematically characterized a series of studies reported by Boyce and colleagues over the past decade. Examining cardiovascular and immunologic reactivity in two cohorts of 3- to 5-year-old children, for example, significant interactions (see, e.g., Figure 1A) were detected with environmental stressors in the prediction of respiratory illness incidence over the ensuing several month periods (Boyce, Chesney, et al., 1995). Specifically, the noted interactions suggested bidirectional effects of reactivity on illness incidence: highly reactive children in high-stress families or childcare centers sustained significantly higher rates of respiratory illness than their low reactive peers, but equally reactive children in low-stress settings were the healthiest of all children in the samples. By contrast, the respiratory illness incidence of low reactivity children was unresponsive to environmental stress levels, showing approximately the same, midlevel illness rates in both low- and high-stress conditions. Similarly significant interactions were found for injury incidence (Boyce, 1996).

Although prospective in design, both of these studies were observational in nature and lacked experimental data on the incidence of illnesses or injuries among the same group of highly reactive children in both low- and high-stress conditions. In a subsequent study of semifree-ranging rhesus macaques, however, such quasiexperimental conditions were satisfied (Boyce, O'Neill–Wagner, Price, Haines, & Suomi, 1998). The troop of macaques, which had been previously assessed for their degree of biobehavioral reactivity to novel or challenging stimuli, lived in a 5-acre wooded habitat in rural Maryland, on the grounds of the National Institutes of Health Primate Center. In 1993, the troop encountered a 6-month period of protective confinement to a small, 1000-square foot building, during a construction

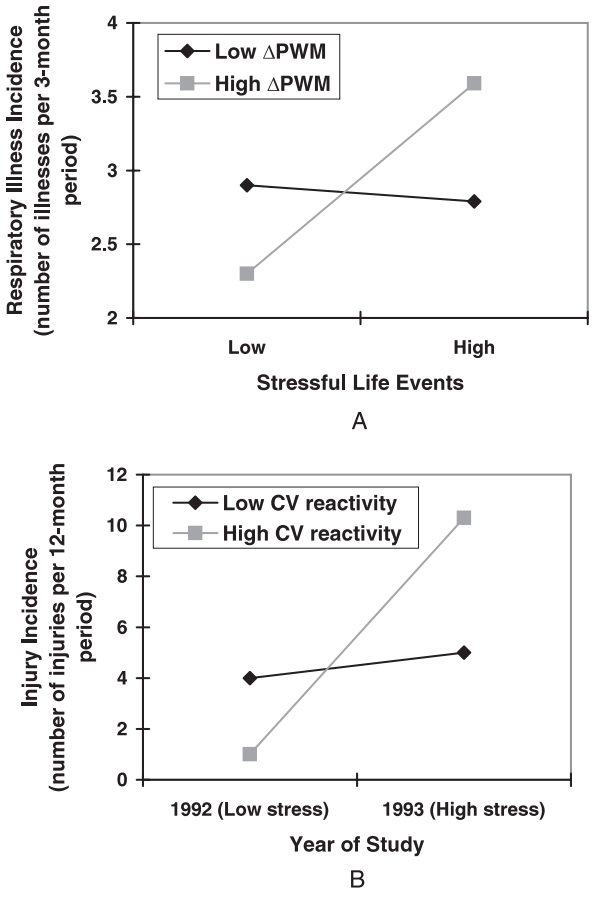

Figure 1. The interactions among laboratory-based stress reactivity and environmental stressors in predicting health outcomes. (A) Immune reactivity (changes in pokeweed nitrogen response) × family stressful events and respiratory illness incidence in kindergartners ($N = 99$; adapted from Boyce, Chesney, et al., 1995). (B) Biobehavioral reactivity × confinement stress and injury incidence in a troop of semi-free-ranging rhesus monkeys ($N = 36$; adapted from Boyce et al., 1998).

project on the habitat grounds. The confinement proved highly stressful, however, and the incidence of violent injuries increased fivefold during the 6-month period. Blinded ascertainment of medically attended injury rates from veterinary records produced evidence for a significant interaction between reactivity status and confinement stress, which is plotted in Figure 1B. As with the prior studies of children, low reactivity individuals showed little effect of the confinement, while those with high reactivity showed dramatically higher rates of violent injuries in the high-stress situation but lower rates in the preceding, low-stress condition.

These findings documenting Reactivity × Context interactions in the prediction of biomedical outcomes have been supplemented by recent observations from the same group of investigators and several others on associations among stressors, reactivity and *psychological* symptoms in children and young adults. There is reason to believe that the influence of biological reactivity on mental health outcomes may be even more profound than those observed for biomedical disorders. Worthman, Angold, and Costello (1998), utilizing data from the Great Smoky Mountains Study, found associations in Appalachian children between high adrenocortical reactivity and future diagnoses of anxiety disorders and between low reactivity and diagnoses of conduct disorder. In other work examining cross-sectional data from the Wisconsin Study of Families

and Work, main effects of autonomic reactivity on risk for both internalizing and externalizing spectrum psychopathology in middle childhood have been reported (Boyce et al., 2001). Children with high levels of parasympathetic reactivity to laboratory stressors were significantly more likely to fall into the top 20% on mother and teacher reports of internalizing symptoms, while those with low reactivity in both sympathetic and parasympathetic branches of the ANS were significantly more likely to display high rates of externalizing behavior problems (see also Scarpa & Raine, 1997). A third paper by Gannon et al. (1989), reporting on a cross-sectional study of college students, found that participants with laboratory evidence of exaggerated autonomic reactivity showed higher rates of physical symptoms and depression under stressful circumstances, but lower than average rates under low or minimally stressful conditions. Finally, a recent randomized experimental study by Quas, Bauer, and Boyce (2004) again showed an interaction effect between autonomic reactivity and social context, with highly reactive children showing significantly better memory for a previous, standardized stressful event in a supportive social environment and poorer memory under conditions of low support, relative to a low reactivity comparison group. Although not all research examining Reactivity $\times$ Context interactions have replicated these findings (see, e.g., Musante et al., 2000), a sufficiently substantial number of studies have produced homologous results to suggest a robust phenomenon worthy of further and more explicit analysis.

Recent findings from a variety of investigators and settings thus call into question the second of the premises that circumscribe the prevailing conceptualization of stress reactivity. Rather than acting as a unidirectional risk factor for poor health outcomes, as the second premise would assert, high-stress reactivity has been shown repeatedly to operate in a *bivalent* manner, most often escalating the risk of maladaptive outcomes in high-stress contexts, but diminishing such risk and acting protectively under supportive, low-stress conditions. Such evidence signifies the need for a reconceptualization of high reactivity phenotypes and suggests that highly reactive individuals may be more accurately described as biologically sensitive to the health-eroding or health-sustaining effects of particular social and physical contexts. *BSC* is therefore advanced here as a means of denoting and characterizing this bidirectional influence of high-stress reactivity on psychiatric and biomedical health endpoints. As argued above, stress reactivity is a nonunitary, multifaceted complex of central and peripheral neural responses. The present thesis, however, is that heightened reactivity in each stress response system is reflective of a more elemental biological predisposition to context responsiveness. In the remainder of this paper, we therefore refer to BSC as a phenotypic property of individuals, which has both constitutional and experiential origins, and is indexed by heightened reactivity in one or more of the stress response systems.

BSC: The Dandelion and the Orchid

Such evidence for bivalent, context-dependent health effects of highly reactive phenotypes suggests that reactivity may reflect not simply overarousal of neurobiological pathways, but rather *sensitivity to both harmful and protective contextual effects*. Highly reactive children appear to experience either the best or the worst of psychiatric and biomedical outcomes, within the populations from which they are drawn. Under conditions of adversity, such children sustain higher rates of disease, disorder, and injuries than their more normatively reactive peers from the same environments. On the other hand, equally reactive children in low-stress, protective social environments experience substantially lower rates of health problems than their low reactive peers. These results suggest that the highly reactive biological profiles found in this subset of children reveal a unique sensitivity or "permeability" to the influence of environmental conditions (Boyce, Chesney, et al., 1995).

A Swedish idiomatic expression, *maskrosbarn* (dandelion child), refers to the capacity of some children, not unlike those with *low* reactive phenotypes, to survive and even thrive in whatever circumstances they encounter, in much the same way that dandelions seem to

prosper irrespective of soil, sun, drought, or rain. Observations of such children have generated, for example, an extensive developmental literature on the phenomenon of resilience, the capacity for positive adaptation despite experiences of significant adversity (Luthar, Doernberger, & Zigler, 1993; Masten, 2001). A contrasting Swedish neologism, *orkidebarn* (orchid child), might better describe the context-sensitive individual, whose survival and flourishing is intimately tied, like that of the orchid, to the nurturant or neglectful character of the ambient environment. In conditions of neglect, the orchid promptly declines, while in conditions of support and nurture, it is a flower of unusual delicacy and beauty.

This metaphorical invocation of children with contrasting environmental sensitivities is reminiscent of Belsky's (1997, 2000) theory of individual differences in susceptibility to rearing influence. Belsky has proposed that some individuals have traits and developmental trajectories that are more fixed by their genetic endowment, while others are more plastic and susceptible to rearing influence. Employing an evolutionary framework, he suggests that parents have been selected to "hedge their bets" against an uncertain future by producing both types of offspring: more fixed types capable of achieving higher reproductive success in the particular ecological niche that matches their genotype, and more plastic types capable of fitting and thriving in a wider range of niches, depending upon rearing conditions encountered during ontogeny. The latter, more malleable individuals are hypothesized to monitor features of early childhood environments and to adjust biobehavioral development accordingly. As summarized by Belsky (2000, 2005), it is infants who are high in negative emotional reactivity who appear most susceptible to early rearing influences.

Although Belsky and the theoretical framework presented here both equate heightened reactivity with susceptibility to environmental influence, and both theories posit that reactivity moderates relations between the quality of early family environments and salient developmental outcomes, the theories differ in their definitions of reactivity and their conceptualizations of its origins and consequences. First, the current theory defines BSC as heightened reactivity in one or more of the neurobiological stress response systems, whereas Belsky operationalizes reactivity at the behavioral level. Comparisons between biological and behavioral reactivity have yielded inconsistent results (Kagan, 1994; Quas, Hong, Alkon, & Boyce, 2000), and are in need of further clarification and study. Second, the current theory specifies a conditional adaptation model of the developmental origins of BSC, emphasizing gene–environment interactions. Belsky, by contrast, focuses on heritable variation in susceptibility to rearing influence and does not specify environmental antecedents of this variation. Third, the current theory conceptualizes highly reactive phenotypes as *orchidebarnen*, which are pointedly not adaptable to a broad range of rearing milieus, but tend to do especially well in conditions of high social resources and support. Belsky, by contrast, conceptualizes emotionally reactive infants as more developmentally malleable and capable of entraining biobehavioral development to fit a relatively wide range of niches.

A substantial body of other work provides a broad but reasonably consistent picture of behavioral predispositions found among context-sensitive, biologically reactive orchidebarnen. The research of Kagan and colleagues, for example, has documented the tendency for behaviorally inhibited, shy children to share particular psychobiological features reflecting exaggerated activation of both peripheral and central stress response circuitries (Kagan, 1994, 1997; Snidman, Kagan, Riordan, & Shannon, 1995). In cohorts of infants and children followed by Kagan and others, those displaying shy or fearful behaviors in social or novel situations were significantly more likely to have low heart periods (and thus high heart rates), diminished heart period variability, and greater pupillary dilatation, reflecting sympathetic activation and parasympathetic withdrawal, as well as higher baseline and reactive salivary cortisol levels, indicating heightened adrenocortical activation (Kagan, Reznick, & Snidman, 1987, 1988; Reznick, Kagan, Snidman, Gersten, Baak, & Rosenberg, 1986). Other studies (Calkins, Fox, & Marshall, 1996; Fox, Rubin, Calkins, Marshall,

Coplan, Porges, Long, & Stewart, 1995; Schmidt, Fox, Schulkin, & Gold, 1999) have similarly revealed associations between behavioral inhibition and high, stable heart rates, elevated measures of cortisol secretion, and increased acoustic startle responses. In addition, in a series of studies by Fox and colleagues (Fox, 1991; Fox et al., 1995; Fox, Henderson, Rubin, Calkins, & Schmidt, 2001), a pattern of asymmetrical, right frontal EEG activation was described among shy children, possibly signaling individual differences in prefrontal regulation of amygdalar and limbic fear circuitry (Davidson & Irwin, 1999).

Further, associations noted between behavioral inhibition and biological reactivity have not been limited to human children; the research of Suomi and colleagues at the NIH Laboratory of Comparative Ethology has produced systematic evidence of upregulated adrenocortical and autonomic responses to challenge among the fearful, inhibited subsets of several primate species (Byrne & Suomi, 2002; Suomi, 1997). Although associations between temperamental differences in inhibition and aspects of central and peripheral stress reactivity have been frequently documented, negative results have also been reported (Asendorpf & Meier, 1993; Calkins & Fox, 1992), and there have been suggestions that other developmental factors, such as mother–child attachment, could play moderating roles in such relations. Stevenson–Hinde and Marshall (1999), for example, found the predicted association between low inhibition and high vagal (or parasympathetic) tone only among securely attached children, and Nachmias et al. (1996) reported adrenocortical reactivity in novel coping conditions only for toddlers with both behavioral inhibition and insecure attachment. As reviewed by Fox and Card (1999) and Carter (1998), studies examining attachment, mother–child behavior, and psychophysiological processes have met with varying and sometimes contradictory results. Given the known neuroendocrine correlates of social bonding behavior in lower mammals, however, such relations remain a promising and understudied area of investigation. More generally, the findings noted above indicate associations of moderate magnitude between BSC and behavioral inhibition and suggest the possibility that the character of parent–child relationships could constrain or modify the emergence of high reactivity–high inhibition phenotypes.

Another literature closely related to the construct of context sensitivity, whether by analogy or, more directly, by its status as a potential neurobiological substrate, is a body of work addressing neurosensory "gating." Operationalized as attenuations in either the component amplitudes within auditory event-related potentials or in the capacity for prepulse inhibition,[1] sensory gating is a complex, multifaceted neural function thought to protect higher cortical centers from being flooded with incoming sensory stimuli (Boutros, Torello, Barker, Tueting, Wu, & Nasrallah, 1995), and is thus one candidate modality by which "BSC" might be instantiated in the brain circuitry that could plausibly subserve such sensitivity. Deficits in gating the P50 wave component following paired auditory signals have been found among patients with PTSD (Neylan et al., 1999) and schizophrenia (Braff & Geyer, 1990), and in their first-degree relatives (Waldo, Myles–Worsley, Madison, Byerley, & Freedman, 1995), and similar deficits in prepulse inhibition have been identified among boys with comorbid Tourette syndrome and attention-deficit/hyperactivity disorder (Castellanos, Fine, Kaysen, Marsh, Rapoport, & Hallett, 1996). A variety of brain regions have been implicated in the filtering of incoming sensory information, including the temporal cortex (Boutros et al., 1995), prefrontal cortex (Shimamura, 2000) and thalamus (McCormick & Bal, 1994). Potential linkages between sensory gating deficits and dysregulation in stress response systems are found in observations that glucocorticoids (Stevens, Bullock, & Collins, 2001) and catecholamines (Adler, Pang, Gerhardt, & Rose, 1988) are capable of disrupting gating functions, that impairments in gating are found among clinical populations with stress-related disorders (Neylan et al., 1999), and that laboratory protocols used for the induction of car-

1. Prepulse inhibition is the inhibition of an acoustic startle response by a weaker stimulus presented just before the auditory probe.

diovascular reactivity, such as the cold pressor test, also diminish auditory gating (Johnson & Adler, 1993). BSC, evoked and measured as autonomic or adrenocortical reactivity to challenges in laboratory paradigms, thus appears to have analogous expressions in neural pathways involved in sensory gating.

Personality and BSC

Individual differences relevant to BSC have also received considerable attention from personality researchers interested in the neurobiological bases of personality. Of particular relevance is the personality construct of *reactivity* (Strelau, 1983), which indexes relatively stable individual differences in the intensity (or magnitude) of response to stimulation. Higher reactivity indicates less gating of internal information stemming from external events, and more reactive individuals are therefore susceptible to relatively weak environmental signals, have comparatively low optimal levels of arousal, and are less able than others to endure strong stimulation for prolonged periods of time (Kohn, 1991; Strelau, 1983). Variation in reactivity is, moreover, a common, underlying element of many biologically oriented personality traits. Specifically, high "reactivity" individuals, "introverts," "augmenters," and "sensation avoiders" all tend to avoid situations and activities that involve strong stimulation and arousal, whereas low "reactivity" individuals, "extraverts," "reducers," and "sensation seekers" are all predisposed to pursue such situations and activities (Strelau & Eysenck, 1987). For example, individuals on the reactive end of these personality traits tend to seek out quieter study rooms in libraries (Campbell & Hawley, 1982) and reside in less stimulating suburban neighborhoods (Strelau, 1983); set volume levels lower when listening to music (Davis, Cowles, & Kohn, 1984; Kohn, Hunt, Cowles, & Davis, 1986) or performing a learning task (Geen, 1984); choose hobbies and professions that involve relatively low levels of stimulation (Strelau, 1983; Zuckerman, 1984); and display lower tolerance for pain and discomfort (Kohn, 1991).

Paralleling BSC, a central feature of Strelau's concept of reactivity is susceptibility to environmental influence. Compared with lower reactivity individuals, those with higher reactivity profiles are more adversely affected by environmental stressors and distractions when performing learning and decision-making tasks (Eliasz, 1987; Klonowicz, 1987; Strelau, 1983) and appear more susceptible to social pressure in conformity experiments (Eliasz, 1987). Moreover, unless intense or prolonged stimuli are used, highly reactive people tend to develop conditioned responses more easily and quickly than do their peers with less reactive profiles (Strelau, 1983).

Aron and Aron (1997, p. 362) provide an important further elucidation of the reactivity construct in their discussion of sensory-processing sensitivity and suggest that "there is an underlying differentiating characteristic regarding how some individuals process stimuli, involving a greater sensory-processing sensitivity, reflectivity, and arousability." Anticipated by early investigators noting exceptional sensitivities in young children (Bergman & Escalona, 1949), Aron and Aron posit that individuals high in sensory-processing sensitivity tend to be more attentive, discriminating, and reflective, especially as the complexity of incoming stimuli increases. Linked to both conscientiousness and low impulsivity, sensory-processing sensitivity may function as a "pause and check" system that results in temporary inhibition of activity (Aron & Aron, 1997) and increases susceptibility to environmental influence. This increased susceptibility has been suggested by a series of retrospective studies showing that, for at least men, sensory-processing sensitivity moderates the relation between the quality of early family environments and childhood adjustment (Aron & Aron, 1997).

Complementing these retrospective studies, a number of prospective studies have now documented a similar moderating role for context sensitivity (as indexed by negative emotional reactivity in infants) in associations between family environment and child behavioral outcomes (reviewed in Belsky, 2000, 2005). Specifically, links between quality of parenting and indices of child adjustment have been found to be reliably stronger among emotionally reactive infants. For example, Kochan-

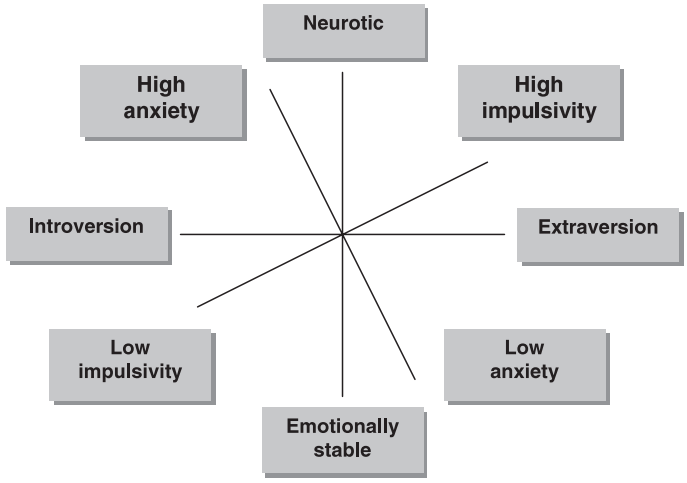

Figure 2. The relation between Eysenck's dimensions of extraversion and neuroticism and Gray's dimensions of impulsivity and anxiety.

ska (1993, 1997) has found much larger effects of maternal discipline (e.g., reliance on gentle guidance vs. forceful control) on development of self-control among infants and toddlers who are high in fearfulness and negative emotionality than among those who are low on these traits (see also Feldman, Greenbaum, & Yirmiya, 1999). Similar moderating effects of infant negative emotionality have also been documented in the relations between quality of parenting and the development of both externalizing and internalizing behavior problems (Belsky, Hsieh, & Crnic, 1998; Blair, 2002; Deater–Decker & Dodge, 1997). Belsky (1997, 2005) has argued convincingly that these interactions provide evidence of greater susceptibility to rearing influence among temperamentally reactive children.

High susceptibility to environmental influence implies that the personality development of reactive children will be especially context dependent, and the multidimensional systems of personality advanced by Eysenck (e.g., 1967; Eysenck & Eysenck, 1985) and Gray (e.g., 1982, 1990) provide a framework for conceptualizing this context dependency (see Figure 2). Eysenck specifies introversion versus extraversion and neuroticism versus emotional stability as major dimensions of personality and locates them at right angles to each other in two-dimensional space. Gray, by contrast, specifies anxiety and impulsivity as major dimensions of personality. Although Gray also locates these dimensions at right angles from each other, he rotates them approximately 30 (conceptual) degrees away from Eysenck's introversion and neuroticism dimensions (see Figure 2). Thus, in Gray's system, individuals who are both neurotic and somewhat introverted are regarded as most anxious, whereas individuals who are both introverted and fairly emotionally stable are viewed as least impulsive. Given that introversion is associated with greater biological reactivity to moderate levels of stimulation (Bullock & Gilliland, 1993; Taub, 1998), and should thus reflect sensitivity to context, the process through which temperamental differences in introversion in children (often labeled shyness or inhibition) develop into stable individual differences in personality should be especially sensitive to the quality of family environments. Under conditions of family stress, characterized by harsh, insensitive, and/or inconsistent parenting, the position of relatively shy, inhibited children (high introversion in Figure 2) may be developmentally rotated to the right toward high anxiety; conversely, under conditions of family support characterized by sensitive and responsive parenting, the position of such children may be developmentally rotated to the left toward low impulsivity (see Figure 2).

This theoretical position is supported by cluster analyses conducted by Aron and Aron (1997) on individuals high in sensory-processing sensitivity. In analysis of three diverse samples, two distinct clusters of highly sensitive people consistently emerged. One group had more troubled childhoods and scored relatively high on measures of social introversion and fearfulness/anxiety. The other group was more similar in childhood adjustment and personality to those who were not highly sensitive. Aron and Aron, who conceptualize sensory-processing sensitivity as a basic dimension of temperament, suggest that the developmental implications of this dimension depend on environmental factors. Based on their interviews with prototypically high sensitivity people, Aron and Aron (1997, p. 363) conclude: "Sensitive individuals from home environments that support their temperament seem quite successful in their lives and adept at making their sensitivity an asset while avoiding shyness or over-self-consciousness."

An Evolutionary–Developmental Theory of BSC

The framework constructed above provides the theoretical groundwork for an alternative explanatory account of the ontogeny and functions of BSC, within an evolutionary model. As reviewed above, there are enduring individual differences in BSC; such differences emerge from the coaction of genetic and environmental influences; different BSC phenotypes yield different costs and benefits in different childhood environments; and individual differences in BSC are hypothesized to constitute variations in susceptibility to environmental influence.

What are the evolutionary origins of such individual differences in BSC? One possibility is that this variation is simply random (i.e., evolutionary noise), much as differences between people in the length of their toes is random, owing to selection-irrelevant genetic variation, the random effects of sexual recombination, and nonadaptive phenotypic plasticity in response to experience. Such variation could still be heritable, and somewhat predictable in response to environmental factors, but would not be the product of natural selection and would have had little bearing on fitness in ancestral environments.

Another possibility is that variation in BSC is adaptively patterned. If this were the case, then different levels of BSC should produce mean differences in survival and reproductive outcomes when all individuals are constrained to a single environment, but similar survival and reproductive outcomes when different BSC phenotypes are allowed to covary with salient features of the environment (i.e., when individuals with different reactivity profiles can employ strategies and inhabit niches that are matched to those profiles; see Mealey, 2001). As cited above, a quasiexperimental study of the effects of stress reactivity under varying environmental conditions in rhesus monkeys suggested that individual differences in stress reactivity may meet these criteria. Specifically, during a 6-month confinement period, when behavioral strategies available to troop members were severely curtailed, highly reactive monkeys suffered dramatically higher rates of violent injuries than did their less reactive peers (Figure 1B). In the free-ranging wooded habitat, however, where a wide range of behavioral strategies could be employed, including escape from conflict, highly reactive monkeys suffered comparatively low rates of violent injury.

The claim advanced here is that variation in stress reactivity has been produced and maintained by natural selection, because differences in BSC reliably produced different fitness outcomes in different childhood environments encountered over evolutionary history. This functional model, which conceptualizes individual differences in BSC as underlying variation in susceptibility to features of the social environment, both positive and negative, can be described by the following three interrelated propositions:

1. As suggested by both the human and animal literature, individuals who experience traumatic, *high-stress environments* in early childhood tend to develop exaggerated stress reactivity profiles. High-stress reactivity in this context may function to increase the overall capacity and readiness of individuals to deal with the very real

dangers in their environment, even when such a strategy results in chronic overarousal and associated sequelae. Gunnar (1994) has suggested, for example, that higher levels of both sympathetic and parasympathetic reactivity in inhibited children cause lower thresholds for anticipating threat in new, unfamiliar situations and support greater vigilance and wariness.

2. In addition to increasing awareness of and sensitivity to threat, the stress response systems may also enable children to experience and absorb more fully the beneficial, protective features of supportive, predictable environments. Reactive, sensitive children have been found, for example, to be more reflective and perhaps more conscious of self and environment (Aron & Aron, 1997; Kagan, Snidman, Zentner, & Peterson, 1999; Lewis & Ramsay, 1997; Patterson & Newman, 1993). Biologically reactive phenotypes should thus also enable children to flourish under stable and nurturant *low-stress environments* and ecological conditions, where they may particularly benefit from high levels of parental investment.
3. The third, complementary assertion is that *low* reactive phenotypes may have also been favored by natural selection, because they enabled children to cope more effectively within the highly prevalent, *moderate stress environments* encompassing the broad, normative range of familial and ecological stressors. Low biological stress reactivity may have served a protective function for children in these environments, by way of increased gating of the emotional signals from chronic stressors, which allowed greater resilience under difficult conditions. These benefits of low reactivity, however, should be specific to conditions of chronic, moderate level stress and threat, and could pose liabilities under developmental conditions characterized by either very high or very low stress (where heavy gating could interfere with responsiveness to the environment).

Thus, phenotypic variation in biological stress reactivity may be adaptively patterned; that is, it may increase the capacity and tendency of different individuals to respond adaptively to specific types of early childhood environments.

This post hoc explanation of observed phenotypic variation in stress reactivity, however, does not meet minimum standards of evolutionary epistemology (Ketelaar & Ellis, 2000). As Lakatos (1970, 1978) has shown, it is relatively easy to construct new explanations or to tinker with old ones to accommodate what is already known. Indeed, there are few empirical findings in psychology and medicine that, after the fact, could not be claimed by multiple theories as falling within their explanatory purview. A good evolutionary explanation must therefore not only account for known facts, but also "stick its neck out" by predicting experimental results that are not known in advance (Ellis & Ketelaar, 2000; Ketelaar & Ellis, 2000). In the final sections of this paper, we present an evolutionary theory of the developmental origins of BSC in children, which is based on the concept of "conditional adaptation," and which generates a novel hypothesis about environmental sources of variation in stress reactivity. This hypothesis is then explored empirically in the second paper of this sequence.

The concept of conditional adaptation

Over the last 2 decades, theory and research in evolutionary biology has begun to acknowledge that, in most species, single "best" strategies for survival and reproduction are unlikely to evolve (Gangestad & Simpson, 2000; Gross, 1996). This is because the best strategy varies as a function of the physical, economic, and social parameters of one's environment (Crawford & Anderson, 1989), and thus a strategy that promotes success in some environmental contexts may lead to failure in others. Selection pressures therefore tend to favor adaptive *phenotypic plasticity*, the capacity of a single genotype to produce a range of phenotypes (manifested in morphology, physiology, and/or behavior) in response to particular ecological conditions that recurrently influenced fitness during a species' evolutionary history (Belsky, Steinberg, & Draper, 1991; Chisholm, 1999; Hrdy, 1999).

Importantly, the development of alternative phenotypes is a nonrandom process; that is, it is the outcome of a structured transaction between genes and environment that was shaped by natural selection to increase the capacity and tendency of individuals to track their developmental environments and adjust their phenotypes accordingly.

Phenotypic plasticity is necessarily a constrained process. Although it would seem advantageous for individuals to respond to environmental changes quickly, appropriately, and flexibly throughout their lives, high levels of responsiveness are not always either possible or desirable. Instead, for many phenotypic characteristics, individuals have been selected to register particular features of their childhood environments as a basis for entraining relevant developmental pathways early in life. There are several reasons to expect early entrainment. First, many complex adaptations are "built" during development and cannot be easily rebuilt when environments fluctuate. For example, the neural and hormonal pathways underlying the stress response systems are set down and calibrated during the early years of development, when the plasticity of neural circuits and structures is at its zenith (Davidson et al., 2000). Second, prolonged practice and attention is required for the successful execution of many behavioral strategies (Draper & Harpending, 1982). For example, individuals who pursue an early and stable life strategy of predatory social interactions (i.e., primary sociopathy) are generally better at executing social deception than individuals who contingently adopt this life strategy at a later age (i.e., secondary sociopathy; see Mealey, 1995). Third, extreme malleability of personality in response to environmental circumstances is not plausible, because different personality systems compete and interfere with each other. For example, high levels of the Big Five Factor Agreeableness, which underlies variation in the extent to which individuals seek out and enjoy intimate, committed relationships (MacDonald, 1995), would surely interfere with sociopathy. Indeed, the social emotions characteristic of individuals high in Agreeableness (e.g., love, compassion, empathy) are essentially absent in sociopaths (Mealey, 1995).

Although the developmental pathways underlying many phenotypic characteristics are likely to be entrained early in life, a capacity for responding to immediate contingencies is also important. As Richard Alexander notes: "It would be the worst of all strategies to enter the competition and cooperativeness of social life, in which others are prepared to alter their responses, with only pre-programmed behaviors" (cited in Mealey, 2000, p. 59). Selection should therefore favor a hierarchy of mechanisms for tracking and responding to environmental information (Slobodkin & Rapoport, 1974; but see also Chisholm, 1999). At the top of this hierarchy are psychological mechanisms underlying general and social intelligence. These mechanisms enable quick and flexible responses to changing opportunities and threats in the immediate environment. Lower in the hierarchy are anatomical, physiological, endocrine, and developmental mechanisms, which track slower and more pervasive changes in the environment. These mechanisms often take the form of *conditional adaptations*: that is, evolved mechanisms that detect and respond to specific features of childhood environments, features that have proven reliable over evolutionary time in predicting the nature of the social and physical world into which children will mature, and entrain developmental pathways that reliably matched those features during a species' natural selective history. Conditional adaptations, which reflect systematic gene–environment interactions, underpin development of contingent survival and reproductive strategies and thus enable individuals to function competently in a variety of different environments.

Illustrations of conditional adaptation

There are myriad examples of conditional adaptation found in the natural world. Although the best examples are found in plants, insects, and fish, there are good mammalian examples, as well, and emerging evidence in humans.

Environmentally triggered polymorphism in caterpillars. The caterpillar *Nemoria arizonaria* develops almost completely different morphologies depending upon its diet in the first 3 days of life (Greene, 1989, 1996). These

caterpillars inhabit oak woodlands in the American Southwest and produce both spring and summer broods. Although the two broods have the same appearance when they first hatch, the spring brood feeds on oak catkins and develops the appearance of the oak's drooping flowers, whereas the summer brood feeds on oak leaves and develops the appearance of twigs. The flower morphology enables the spring brood to blend into the environment while feeding on the ubiquitous spring catkins. Likewise, the twig morph provides camouflage for the leaf-eating summer brood. If either the spring or summer broods are experimentally fed out-of-season food, they develop the corresponding out-of-season morphology and become highly vulnerable to predation. These caterpillars have therefore evolved physiological mechanisms that register features of diet in the first 3 days of life and activate alternative developmental pathways, which function to match the organism's morphology to its feeding ecology (see Greene, 1989, 1996).

Weaning effects on play behavior in kittens. Nursing cats on restricted diets wean their offspring early. Kittens respond to early weaning by engaging in significantly more *object* play, but not more *social* play, compared to normal controls (Bateson, Mendl, & Feaver, 1990). Although early weaning does not affect overall levels of play, it does change the quality of play toward a more object-oriented form. During the cat's natural selective history, early weaning would have been reliably associated with environments where food was scarce, maternal nurturance was limited, and young cats were required to hunt for themselves at a relatively early age. Object play is especially important in the development of hunting skills in cats, and high rates of object play prepare kittens to hunt at an earlier age. Bateson et al. (1990, p. 524) conclude "It seems likely that, by responding to cues from the mother, the individual animal is able to move along a developmental route that is appropriate to the conditions it will encounter in later life." Thus, kittens appear to have evolved mechanisms for registering information about maternal feeding as a basis for upregulating the development of motivational systems involved in object play.

Paternal investment and development of female reproductive strategies. Draper and Harpending (1982, 1988) together with Belsky et al. (1991) have proposed a conditional adaptation theory of adolescent sexual development. Drawing on the concept of sensitive-period learning, the theory posits that the physiological and motivational systems underlying variation in timing of girls' sexual development are especially sensitive to the father's role in the family in approximately the first 5 years of life. Specifically, experiences associated with early father absence and father–daughter distance are hypothesized to entrain the development of reproductive strategies that are matched to the social niche into which the daughter was born, a niche in which male parental investment is relatively unreliable and unimportant. Girls in this context are predicted to develop in a manner that speeds rates of pubertal maturation, accelerates onset of sexual activity, and orients the individual toward relatively unstable pair bonds. Conversely, experiences associated with early father presence and father–daughter closeness are hypothesized to entrain the opposite pattern of sexual development. Either way, the girl "chooses" a developmental trajectory that, in the adult social environment into which she was born, was likely to have promoted reproductive success during human evolutionary history.

There is now a substantial body of empirical data that are consistent with this theory. Specifically, studies in the United States (Doughty & Rodgers, 2000; Ellis & Garber, 2000; Ellis, McFadyen–Ketchum, Dodge, Pettit, & Bates, 1999), Canada (Surbey), New Zealand (Moffitt, Caspi, Belsky, & Silva, 1992), and Australia (Jones, Leeton, McLeod, & Wood, 1972) have all found that girls from homes where the fathers are absent tend to experience earlier pubertal development than girls from homes where the fathers are present. In addition, Ellis et al. (1999) presented longitudinal data showing that girls who had more *distant* relationships with their fathers during the first 5 years of life experienced earlier

pubertal development, and in studies in the United States and New Zealand, early onset of father absence has been found to have a dramatic effect on rates of early sexual activity and teenage pregnancy (Ellis, Bates, Dodge, Fergusson, Horwood, Pettit, & Woodward, 2003). It is important to acknowledge that the apparent effects of father absence and other experiences within families on developmental endpoints, such as pubertal timing, could also be a consequence of genetic influences on both. Comings, Muhleman, Johnson, and MacMurray (2002), for example, have shown that a variant of the X-linked androgen receptor gene is associated both with paternal divorce and father absence in males and with early menarche and early sexual activity in females. Taken together, the cited findings support the plausibility of both experiential and genetic accounts for associations between father absence and the development of precocious reproductive strategies (reviewed in Ellis, 2004).

A conditional adaptation theory of BSC development

The present theory posits that natural selection has favored developmental mechanisms (conditional adaptations) that function to adjust levels of BSC to match familial and ecological conditions encountered early in life. Just as the timing of girls' sexual development may be sensitive to paternal investment, individual differences in BSC may track specific features of childhood environments. Specifically, humans may have evolved developmental mechanisms that detect and internally encode information about levels of supportiveness versus stressfulness in early childhood environments, as a basis for calibrating the activation thresholds and response magnitudes within stress response systems to match those environments.

Based on the claim that individual differences in stress reactivity constitute variation in susceptibility to features of the social environment, both positive and negative, the current theory postulates a U-shaped, curvilinear relationship between levels of supportiveness versus stressfulness in early childhood environments and the development of BSC (see Figure 3). The right side of Figure 3 depicts expected reactivity levels for individuals who experience very high levels of stress in early childhood. Consistent with the experimental animal and epidemiologic human research summarized above, these individuals are hypothesized to develop heightened reactivity profiles. We do not, however, expect reactivity to decline monotonically with decreasing childhood stress. The left side of Figure 3 shows predicted reactivity levels for individuals whose early childhoods are characterized by intensive, stable caregiving and family support. These individuals are also hypothesized to develop exaggerated reactivity profiles, which function in this context to garner the health and survival benefits of highly supportive rearing environments. Finally, the middle of Figure 3 reflects the anticipated, relatively muted reactivity profiles of individuals whose early childhood experiences are characterized by moderate levels of ongoing stress and threat. These individuals, occupying the broad, normative range of species-typical contextual stressors, are hypothesized to develop comparatively low reactivity profiles as a way of gating or filtering highly prevalent, moderate level stressors.[2,3] For the present purposes of sim-

2. Note that we are *not* claiming that moderate level stressors result in extremely low reactivity or biological *insensitivity* to context. Rather, "low reactivity" here refers to low to moderate levels of biological response, relative to the high reactivity individuals we predict would be disproportionately represented in very low and very high stress environments. Our evolutionary–developmental theory of BSC is thus agnostic with regard to the contextual origins of the extremely low reactivity individuals examined, for example, in the work of Raine et al. (1997).
3. Of possible but uncertain interest is the commonality between the hypothesized quadratic association between early adversities and BSC and the historical observations of an inverted U-shaped relation between arousal and performance (Yerkes & Dodson, 1908). Although the former hypothesis addresses the experiential *origins* of biological reactivity, the latter observation describes its *consequences* within cognitive functioning. The Yerkes–Dodson association has been contested in recent years (Neiss, 1988), and the construct of "arousal" may be only distantly allied to reactivity or BSC. Nonetheless, future theoretical and/or empirical work might benefit from a deeper examination of how the two phenomena may be linked or related.

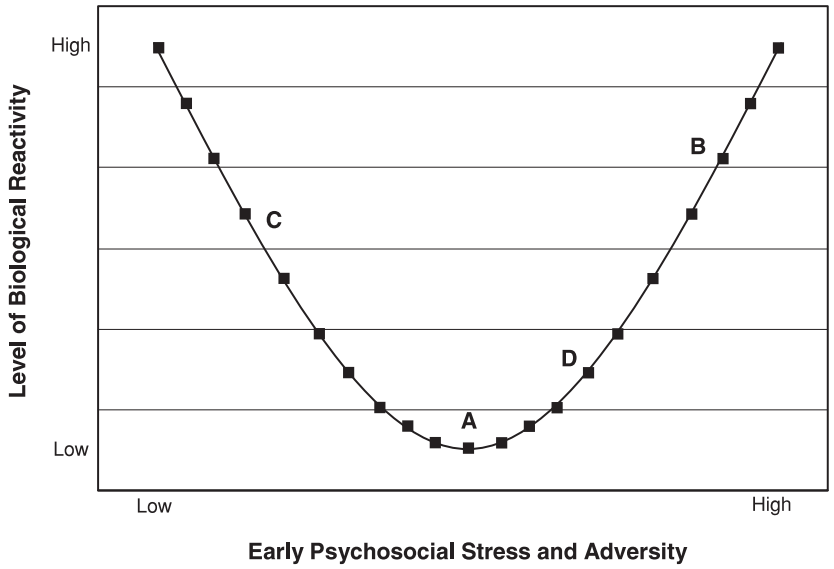

Figure 3. The hyopthesized curvilinear relation of biologic reactivity to early stress and adversity. Comparisons of subjects at points A and B would result in a conclusion that early adversity is associated with greater stress reactivity. Conversely, comparisons at points C and D would generate the inference that early adversity produces diminished reactivity.

plicity and tractability, we further suggest that this curvilinear, quadratic association with early adversity will hold for reactivity in *both* the LC-NE and CRH systems, acknowledging that far greater complexity in the interplay and balancing of the two stress response systems will likely surface as these relations are explored.

Although the U-shaped curve depicted in Figure 3 specifies environmental sources of variation in BSC, genetic sources of variation and gene–environment interactions are also important and need to be addressed in a comprehensive theory of BSC. Children who are genetically disposed toward high reactivity, for example, may alter levels of stress and support in their home environments in ways that further increase BSC. Children may also differ in the location of reaction norms underlying the spectrum of variation in BSC. A reaction norm is a genetically inherited constraint that specifies the range of phenotypes that will be produced by a genotype in different environmental contexts (Schlichting & Pigliucci, 1998). Given equivalent life experiences, children with reaction norms that are located on the upper end of the BSC spectrum should be more likely to develop highly reactive phenotypes than children with reaction norms on the lower end of the spectrum, and vice versa. In addition, children may differ in the breadth of reaction norms. That is, genotypes can be expected to differ in the extent to which they are capable of producing a range of different BSC phenotypes (cf. Belsky, 2005), even given comparable ontogenetic histories. The current evolutionary–development model should be more successful in accounting for the development of individual differences in BSC among children with wider reaction norms. Finally, consistent with the principle of "equifinality" (von Bertalanffy, 1968), we expect that the effects of different BSC phenotypes on child health and adjustment will be equivalent, regardless of whether a child develops a given phenotype primarily as a result of a narrow reaction norm or as a result of particular childhood experiences operating within a relatively broad reaction norm.

Developmental mechanisms for adjusting BSC in response to early childhood experiences may have resulted from a long and recurrent evolutionary history in which (a)

different children confronted substantially different rearing environments; (b) highly reactive children experienced better survival and reproductive outcomes, on average, in both intensely stressful and highly supportive rearing environments; and (c) less reactive children experienced generally better survival and reproductive outcomes in developmental settings characterized by moderate levels of stress and threat. Such an account would reconcile important contradictions, reviewed above, in the existing literature on the origins and consequences of stress reactivity in children. Investigators comparing individuals from points A and B in Figure 3, for example, would conclude, as have Yehuda (2002), De Bellis et al. (1999), and many others, that experiences of family and environmental stress are associated with upregulatory calibrations in biological reactivity systems. On the other hand, studies comparing individuals from points C and D would find, as have those reviewed by Gunnar and Vazquez (2001) and Heim, Ehrlert, et al. (2000), that early stressors are rather associated with downregulatory changes in salient biological responses. The current theory, which posits two oppositionally distinctive ontogenies for BSC, explains both of these up- and downregulatory effects.

Conclusion

Our principal aim in the present paper has been to articulate the precepts and rationale for a new claim about the nature of relations between early life experience and stress reactivity, a claim that we further explore empirically in the companion paper, which follows. The logic of the argument we have sought to present can be summarized in the following way. Biological reactivity to psychological stressors consists of an elaborated, highly coordinated, but phylogenetically primitive set of neural and peripheral neuroendocrine responses, designed to ready the organism for external challenges and threats to survival. Standard explanations of such responses' role in the pathogenesis of human disorders suggest that prolonged or exaggerated reactivity, such as that seen in highly reactive biobehavioral phenotypes, exerts deleterious and impairing effects on a broad range of target organs, including structures within the brain, leading to decrements in health, cognition, and functional capacities. Often overlooked in such accounts is a body of anomalous observations, revealing oppositional, counterregulatory processes within the stress response circuitry itself and, even more compellingly, bivalent effects of reactivity on biomedical and psychiatric outcomes. Highly reactive children sustain disproportionate rates of morbidity when raised in adverse environments but unusually low rates when raised in low-stress, highly supportive settings.

Such bidirectional, environment-dependent health effects suggest that *BSC* is the core, defining feature of highly reactive phenotypes. These observations call into question the presumably unitary pathogenic effects of high reactivity and suggest that its protective effects within specific developmental ecologies might explain the conservation of such phenotypic variation within evolutionary history. Furthermore, conditional adaptations, in which a single genotype supports a range of environmentally contingent phenotypic expressions, enable entrainment of biological and behavioral development to adaptively match early (and predicted future) social environments. Given past evidence that early trauma can evoke upregulatory changes in stress reactivity and new evidence that high reactivity can be protective in highly supportive settings, we postulate a curvilinear, U-shaped relation, shown in Figure 3, between levels of early adversity and the magnitude of biological response dispositions. Specifically, we hypothesize that (a) exposure to acutely stressful childhood environments upregulates BSC, increasing the capacity and tendency of individuals to detect and respond to environmental dangers and threats; (b) exposure to exceptionally supportive childhood environments also upregulates BSC, increasing susceptibility to the social and developmental benefits of such environments; and (c) typical of the large majority of children, exposure to childhood environments that are extreme in neither direction downregulates BSC, buffering individuals against the chronic stressors encountered in a

world that is neither highly threatening nor universally safe.

Because evolutionary "stories" of the kind advanced here are especially vulnerable to the perils of post hoc explanation, it is essential that the current evolutionary–developmental theory of the origins and functions of stress reactivity be put eventually to rigorous tests of its predictive strength. In the paper that follows, we offer a provisional, "promissory note" on such a requirement, by presenting exploratory analyses from two studies, in geographically and culturally distinctive settings, that produce empirical derivations of the same hypothesis first advanced here on conceptual grounds. Such convergence of theoretical and empirical reasoning, we would argue, portends well for the validity of the evolutionary–developmental hypothesis. In the presentation of its conceptual and analytical origins, it is our hope that new knowledge concerning the causes and consequences of children's responsivity to stress will be uncovered, and that richer, more protective environments will be fostered in which highly sensitive children can develop and thrive.

References

Adler, L. E., Pang, K., Gerhardt, G., & Rose, G. M. (1988). Modulation of the gating of auditory evoked potentials by norepinephrine: Pharmacological evidence obtained using a selective neurotoxin. *Biological Psychiatry*, *24*, 179–190.

Adler, P. S., & Ditto, B. (1998). Psychophysiological effects of interviews about emotional events on offspring of hypertensives and normotensives. *International Journal of Psychophysiology*, *28*, 263–271.

Alkon, A., Goldstein, L. H., Smider, N., Essex, M., Kupfer, D., & Boyce, W. T. (2003). Developmental and contextual influences on autonomic reactivity in young children. *Developmental Psychobiology*, *42*, 64–78.

Allen, M. T., & Matthews, K. A. (1997). Hemodynamic responses to laboratory stressors in children and adolescents: The influences of age, race, and gender. *Psychophysiology*, *34*, 329–339. [erratum p. 730]

Aron, E. N., & Aron, A. (1997). Sensory-processing sensitivity and its relation to introversion and emotionality. *Journal of Personality and Social Psychology*, *73*, 345–368.

Asendorpf, J. B., & Meier, G. H. (1993). Personality effects on children's speech in everyday life: Sociability-mediated exposure and shyness-mediated reactivity to social situations. *Journal of Personality and Social Psychology*, *64*, 1072–1083.

Aston–Jones, G., Rajkowski, J., Kubiak, P., Valentino, R. J., & Shipley, M. T. (1996). Role of the locus coeruleus in emotional activation. *Progress in Brain Research*, *107*, 379–402.

Bartels, M., de Geus, E. J., Kirschbaum, C., Sluyter, F., & Boomsma, D. I. (2003). Heritability of daytime cortisol levels in children. *Behavior Genetics*, *33*, 421–433.

Bateson, P. P. G., Mendl, M., & Feaver, J. (1990). Play in the domestic cat is enhanced by rationing of the mother during lactation. *Animal Behaviour*, *40*, 514–525.

Bauer, A. S. (2002). *Concurrent sympathetic and adrenocortical activity as correlates of behavior in middle childhood*. Unpublished master's thesis, University of California, Berkeley.

Belsky, J. (1997). Variation in susceptibility to environmental influence: An evolutionary argument. *Psychological Inquiry*, *8*, 182–186.

Belsky, J. (2000). Conditional and alternative reproductive strategies: Individual differences in susceptiblity to rearing experiences. In J. L. Rodgers, D. C. Rowe & W. B. Miller (Eds.), *Genetic influences on human fertility and sexuality: Theoretical and empirical contributions from the biological and behavioral sciences* (pp. 127–145). Boston: Kluwer Academic.

Belsky, J. (2005). Differential susceptibility to rearing influence: An evolutionary hypothesis and some evidence. In B. J. Ellis & D. F. Bjorklund (Eds.), *Origins of the social mind: Evolutionary psychology and child development* (pp. 139–163). New York: Guilford Press.

Belsky, J., Hsieh, K., & Crnic, K. (1998). Mothering, fathering, and infant negativity as antecedents of boys' externalizing problems and inhibition at age 3: Differential susceptibility to rearing influence? *Development and Psychopathology*, *10*, 301–319.

Belsky, J., Steinberg, L., & Draper, P. (1991). Childhood experience, interpersonal development, and reproductive strategy: An evolutionary theory of socialization. *Child Development*, *62*, 647–670.

Benediktsson, R., Lindsay, R. S., Noble, J., Seckl, J. R., & Edwards, C. R. (1993). Glucocorticoid exposure in utero: New model for adult hypertension. *Lancet*, *341*(8841), 339–341.

Bentley, P. J. (1998). *Comparative vertebrate endocrinology*. Cambridge: Cambridge University Press.

Bergman, P., & Escalona, S. K. (1949). Unusual sensitivities in very young children. *Pschoanalytic Studies of the Child*, *4*, 333–352.

Bernard, C. (1878). *Les phenomenes de la vie*. Paris: Baillière.

Blair, C. (2002). Early intervention for low birth weight preterm infants: The role of negative emotionality in the specification of effects. *Development and Psychopathology*, *14*, 311–332.

Bloom, F. E., & Kupfer, D. J. (1995). *Psychopharmacology* (4th ed.). New York: Raven Press.

Boutros, N. N., Torello, M. W., Barker, B. A., Tueting, P. A., Wu, S. C., & Nasrallah, H. A. (1995). The P50 evoked potential component and mismatch detection in normal volunteers: Implications for the study of sensory gating. *Psychiatry Research*, *57*, 83–88.

Boyce, W. T. (1996). Biobehavioral reactivity and injuries in children and adolescents. In M. H. Bornstein & J. Genevro (Eds.), *Child development and behavioral pediatrics: Toward understanding children and health*. Mahwah, NJ: Erlbaum.

Boyce, W. T., Champoux, M., Suomi, S. J., & Gunnar, M. R. (1995). Salivary cortisol in nursery-reared rhesus monkeys: Reactivity to peer interactions and altered circadian activity. *Developmental Psychobiology, 28*, 257–267.

Boyce, W. T., Chesney, M., Alkon–Leonard, A., Tschann, J., Adams, S., Chesterman, B., Cohen, F., Kaiser, P., Folkman, S., & Wara, D. (1995). Psychobiologic reactivity to stress and childhood respiratory illnesses: Results of two prospective studies. *Psychosomatic Medicine, 57*, 411–422.

Boyce, W. T., O'Neill–Wagner, P., Price, C. S., Haines, M., & Suomi, S. J. (1998). Crowding stress and violent injuries among behaviorally inhibited rhesus macaques. *Health Psychology, 17*, 285–289.

Boyce, W. T., Quas, J., Alkon, A., Smider, N., Essex, M., & Kupfer, D. J. (2001). Autonomic reactivity and psychopathology in middle childhood. *British Journal of Psychiatry, 179*, 144–150.

Braff, D. L., & Geyer, M. A. (1990). Sensorimotor gating and schizophrenia. Human and animal model studies. *Archives of General Psychiatry, 47*, 181–188.

Bremner, J. D., & Vermetten, E. (2001). Stress and development: Behavioral and biological consequences. *Development and Psychopathology, 13*, 473–489.

Bullock, W. A., & Gilliland, K. (1993). Eysenck's arousal theory of introversion–extraversion: A converging measures investigation. *Journal of Personality and Social Psychology, 64*, 113–123.

Busjahn, A., Faulhaber, H. D., Viken, R. J., Rose, R. J., & Luft, F. C. (1996). Genetic influences on blood pressure with the cold-pressor test: A twin study. *Journal of Hypertension, 14*(10), 1195–1199.

Byrne, G., & Suomi, S. J. (2002). Cortisol reactivity and its relation to homecage behavior and personality ratings in tufted capuchin (*Cebus apella*) juveniles from birth to six years of age. *Psychoneuroendocrinology, 27*(1–2), 139–154.

Cacioppo, J. T., Berntson, G. G., Malarkey, W. B., Kiecolt–Glaser, J. K., Sheridan, J. F., Poehlmann, K. M., Burleson, M. H., Ernst, J. M., Hawkley, L. C., & Glaser, R. (1998). Autonomic, neuroendocrine, and immune responses to psychological stress: The reactivity hypothesis. *Annals of the New York Academy of Sciences, 840*, 664–673.

Cacioppo, J. T., Berntson, G. G., Sheridan, J. F., & McClintock, M. K. (2000). Multilevel integrative analyses of human behavior: Social neuroscience and the complementing nature of social and biological approaches. *Psychological Bulletin, 126*, 829–843.

Calkins, S. D., & Fox, N. A. (1992). The relations among infant temperament, security of attachment, and behavioral inhibition at twenty-four months. *Child Development, 63*, 1456–1472.

Calkins, S. D., Fox, N. A., & Marshall, T. R. (1996). Behavioral and physiological antecedents of inhibited and uninhibited behavior. *Child Development, 67*, 523–540.

Campbell, J. B., & Hawley, C. W. (1982). Study habits and Eysenck's theory of extraversion–introversion. *Journal of Research in Personality, 16*, 139–146.

Cannon, W. B. (1929). *Bodily changes in pain, hunger, fear and rage*. New York: Appleton.

Carlson, M., & Earls, F. (1997). Psychological and neuroendocrinological sequelae of early social deprivation in institutionalized children in Romania. *Annals of the New York Academy of Sciences, 807*, 419–428.

Carter, C. S. (1998). Neuroendocrine perspectives on social attachment and love. *Psychoneuroendocrinology, 23*, 779–818.

Castellanos, F. X., Fine, E. J., Kaysen, D., Marsh, W. L., Rapoport, J. L., & Hallett, M. (1996). Sensorimotor gating in boys with Tourette's syndrome and ADHD: Preliminary results. *Biological Psychiatry, 39*, 33–41.

Champagne, F., & Meaney, M. J. (2001). Like mother, like daughter: Evidence for non-genomic transmission of parental behavior and stress responsivity. *Progress in Brain Research, 133*, 287–302.

Champoux, M., Higley, J. D., & Suomi, S. J. (1997). Behavioral and physiological characteristics of Indian and Chinese–Indian hybrid rhesus macaque infants. *Developmental Psychobiology, 31*, 49–63.

Champoux, M., Hwang, L., Lang, O., & Levine, S. (2001). Feeding demand conditions and plasma cortisol in socially-housed squirrel monkey mother–infant dyads. *Psychoneuroendocrinology, 26*, 461–477.

Champoux, M., & Suomi, S. J. (1994). Behavioral and adrenocortical responses of rhesus macaque mothers to infant separation in an unfamiliar environment. *Primates, 35*, 191–202.

Cheng, L. S., Carmelli, D., Hunt, S. C., & Williams, R. R. (1997). Segregation analysis of cardiovascular reactivity to laboratory stressors. *Genetic Epidemiology, 14*, 35–49.

Chesterman, E., Boyce, W. T., & Winkleby, M. A. (1989). *Psychosocial predictors of maternal and infant health: A "sense of permanence" as a mediating variable (Abstract)*. Paper presented at the Society of Behavioral Medicine Annual Meeting, San Francisco.

Chisholm, J. S. (1999). *Death, hope and sex: Steps to an evolutionary ecology of mind and morality*. New York: Cambridge University Press.

Chrousos, G. P. (1998). Stressors, stress, and neuroendocrine integration of the adaptive response. The 1997 Hans Selye Memorial Lecture. *Annals of the New York Academy of Sciences, 851*, 311–335.

Comings, D. E., Muhleman, D., Johnson, J. P., & MacMurray, J. P. (2002). Parent–daughter transmission of the androgen receptor gene as an explanation of the effect of father absence on age of menarche. *Child Development, 73*, 1046–1051.

Coplan, J. D., Andrews, M. W., Rosenblum, L. A., Owens, M. J., Friedman, S., Gorman, J. M., & Nemeroff, C. B. (1996). Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult nonhuman primates exposed to early-life stressors: Implications for the pathophysiology of mood and anxiety disorders. *Proceedings of the National Academy of Sciences of the United States of America, 93*, 1619–1623.

Cratty, M. S., Ward, H. E., Johnson, E. A., Azzaro, A. J., & Birkle, D. L. (1995). Prenatal stress increases corticotropin-releasing factor (CRF) content and release in rat amygdala minces. *Brain Research, 675*, 297–302.

Crawford, C. B., & Anderson, J. L. (1989). Sociobiology: An environmentalist discipline? *American Psychologist, 44*, 1449–1459.

Dallman, M. F., Akana, S. F., Cascio, C. S., Darlington, D. N., Jacobson, L., & Levin, N. (1987). Regulation of ACTH secretion: Variations on a theme of B. *Recent Progress in Hormone Research, 43*, 113–173.

Davidson, R. J., & Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. *Trends in Cognitive Sciences, 3*, 11–21.

Davidson, R. J., Jackson, D. C., & Kalin, N. H. (2000). Emotion, plasticity, context, and regulation: Perspectives from affective neuroscience. *Psychological Bulletin, 126,* 890–909.

Davis, C., Cowles, M., & Kohn, P. (1984). Behavioural and physiological aspects of the augmenting-reducing dimension. *Personality and Individual Differences, 5,* 683–691.

Davis, E., Donzella, B., Krueger, W. K., & Gunnar, M. R. (1999). The start of a new school year: Individual differences in salivary cortisol response in relation to child temperament. *Developmental Psychobiology, 35,* 188–196.

Deater–Deckard, K., & Dodge, K. (1997). Spare the rod, spoil the authors: Emerging themes in research on parenting. *Psychological Inquiry, 8,* 230–235.

De Bellis, M. D., Baum, A. S., Birmaher, B., Keshavan, M. S., Eccard, C. H., Boring, A. M., Jenkins, F. J., & Ryan, N. D. (1999). A.E. Bennett Research Award. Developmental traumatology. Part I: Biological stress systems. *Biological Psychiatry, 45,* 1259–1270.

de Haan, M., Gunnar, M. R., Tout, K., Hart, J., & Stansbury, K. (1998). Familiar and novel contexts yield different associations between cortisol and behavior among 2-year-olds. *Developmental Psychobiology, 31,* 93–101.

Dhabhar, F. S., McEwen, B. S., & Spencer, R. L. (1993). Stress response, adrenal steroid receptor levels and corticosteroid-binding globulin levels—A comparison between Sprague–Dawley, Fischer 344 and Lewis rats. *Brain Research, 616*(1–2), 89–98.

Doughty, D., & Rodgers, J. L. (2000). Behavior genetic modeling of menarche in U.S. females. In J. L. Rodgers, D. C. Rowe, & W. B. Miller (Eds.), *Genetic influences on human fertility and sexuality: Theoretical and empirical contributions from the biological and behavioral sciences*. Boston: Kluwer Academic.

Draper, P., & Harpending, H. (1982). Father absence and reproductive strategy: An evolutionary perspective. *Journal of Anthropological Research, 38,* 255–273.

Draper, P., & Harpending, H. (1988). A sociobiological perspective on the development of human reproductive strategies. In K. B. MacDonald (Ed.), *Sociobiological perspectives on human development* (pp. 340–372). New York: Springer–Verlag.

Dubos, R. J. (1965). *Man adapting*. New Haven, CT: Yale University Press.

Dunn, A. J., & Berridge, C. W. (1990). Physiological and behavioral responses to corticotropin-releasing factor administration: Is CRF a mediator of anxiety or stress responses? *Brain Research Reviews, 15,* 71–100.

Ekman, P., Levenson, R. W., & Friesen, W. V. (1983). Autonomic nervous system activity distinguishes among emotions. *Science, 221*(4616), 1208–1210.

Elenkov, I. J., & Chrousos, G. P. (1999). Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. *Trends in Endocrinology and Metabolism, 10,* 359–368.

Eliasz, A. (1987). Temperament-contingent cognitive orientation toward various aspects of reality. In J. Strelau & J. H. Eysenck (Eds.), *Personality dimensions and arousal. Perspectives on individual differences* (pp. 197–212). New York: Plenum Press.

Ellis, B. J. (2004). Timing of pubertal maturation in girls: An integrated life history approach. *Psychological Bulletin, 130,* 920–958.

Ellis, B. J., Bates, J. E., Dodge, K. A., Fergusson, D., Horwood, J., Pettit, G. S., & Woodward, L. (2003). Does early father absence place daughters at special risk for early sexual activity and teenage pregnancy? *Child Development, 74,* 801–821.

Ellis, B. J., & Garber, J. (2000). Psychosocial antecedents of variation in girls' pubertal timing: Maternal depression, stepfather presence, and marital and family stress. *Child Development, 71,* 485–501.

Ellis, B. J., & Ketelaar, T. (2000). On the natural selection of alternative models: Evaluation of explanations in evolutionary psychology. *Psychological Inquiry, 11,* 56–68.

Ellis, B. J., McFadyen–Ketchum, S., Dodge, K. A., Pettit, G. S., & Bates, J. E. (1999). Quality of early family relationships and individual differences in the timing of pubertal maturation in girls: A longitudinal test of an evolutionary model. *Journal of Personality & Social Psychology, 77,* 387–401.

Essex, M. J., Klein, M. H., Cho, E., & Kalin, N. H. (2002). Maternal stress beginning in infancy may sensitize children to later stress exposure: Effects on cortisol and behavior. *Biological Psychiatry, 52,* 776–784.

Eysenck, H. J. (1967). *The biological basis of personality*. Springfield, IL: Charles C. Thomas.

Eysenck, H. J., & Eysenck, M. W. (1985). *Personality and individual differences: A natural science approach.* New York: Plenum Press.

Feldman, R., Greenbaum, C., & Yirmiya, N. (1999). Mother–infant affect synchrony as an antecedent of the emergence of self-control. *Developmental Psychology, 35,* 223–231.

Fernald, L. C., & Grantham–McGregor, S. M. (1998). Stress response in school-age children who have been growth retarded since early childhood. *American Journal of Clinical Nutrition, 68,* 691–698.

Fox, N. A. (1991). If it's not left, it's right: Electroencephalograph asymmetry and the development of emotion. *American Psychologist, 46,* 863–872.

Fox, N. A., & Card, J. A. (1999). Psychophysiological measures in the study of attachment. In J. Cassidy & P. R. Shaver (Eds.), *Handbook of attachment: Theory, research, and clinical applications* (pp. 226–245). New York: Guilford Press.

Fox, N. A., Henderson, H. A., Rubin, K. H., Calkins, S. D., & Schmidt, L. A. (2001). Continuity and discontinuity of behavioral inhibition and exuberance: Psychophysiological and behavioral influences across the first four years of life. *Child Development, 72,* 1–21.

Fox, N. A., Rubin, K. H., Calkins, S. D., Marshall, T. R., Coplan, R. J., Porges, S. W., Long, J. M., & Stewart, S. (1995). Frontal activation asymmetry and social competence at four years of age. *Child Development, 66,* 1770–1784.

Gangestad, S. W., & Simpson, J. A. (2000). The evolution of human mating: Trade-offs and strategic pluralism. *Behavioral and Brain Sciences, 23,* 573–644.

Gannon, L., Banks, J., Shelton, D., & Luchetta, T. (1989). The mediating effects of psychophysiological reactivity and recovery on the relationship between environmental stress and illness. *Journal of Psychosomatic Medicine, 33,* 167–175.

Geen, R. (1984). Preferred stimulation levels in introverts and extraverts: Effects on arousal and performance. *Journal of Personality and Social Psychology, 46,* 1303–1312.

Goenjian, A. K., Yehuda, R., Pynoos, R. S., Steinberg, A. M., Tashjian, M., Yang, R. K., Najarian, L. M., & Fairbanks, L. A. (1996). Basal cortisol, dexamethasone suppression of cortisol, and MHPG in adoles-

cents after the 1988 earthquake in Armenia. *American Journal of Psychiatry, 153*, 929–934.
Gold, P. W., & Chrousos, G. P. (1999). The endocrinology of melancholic and atypical depression: Relation to neurocircuitry and somatic consequences. *Proceedings of the Association of American Physicians, 111*, 22–34.
Gold, P. W., & Chrousos, G. P. (2002). Organization of the stress system and its dysregulation in melancholic and atypical depression: High vs low CRH/NE states. *Molecular Psychiatry, 7*, 254–275.
Gold, P. W., Goodwin, F. K., & Chrousos, G. P. (1988). Clinical and biochemical manifestations of depression. Relation to the neurobiology of stress (1). *New England Journal of Medicine, 319*, 348–353.
Gray, J. A. (1982). *The neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system*. New York: Clarendon/Oxford University Press.
Gray, J. A. (1990). Brain systems that mediate both emotion and cognition. *Cognition and Emotion, 4*, 269–288.
Greene, E. (1989). A diet-induced developmental polymorphism in a caterpillar. *Science, 243*, 643–646.
Greene, E. (1996). Effect of light quality and larval diet on morph induction in the polymorphic caterpillar Nemoria arizonaria (Lepidoptera: Geometridae). *Biological Journal of the Linnean Society, 58*, 277–285.
Gross, M. R. (1996). Alternative reproductive strategies and tactics: Diversity within sexes. *Trends in Ecology & Evolution, 11*, 92–98.
Gunnar, M. R. (1994). Psychoendocrine studies of temperament and stress in early childhood: Expanding current models. In J. E. Bates & T. D. Wachs (Eds.), *Temperament: Individual differences at the interface of biology and behavior* (pp. 175–198). Washington, DC: American Psychological Association.
Gunnar, M. R., Morison, S. J., Chisholm, K., & Schuder, M. (2001). Salivary cortisol levels in children adopted from Romanian orphanages. *Development and Psychopathology, 13*, 611–628.
Gunnar, M. R., & Vazquez, D. M. (2001). Low cortisol and a flattening of expected daytime rhythm: Potential indices of risk in human development. *Development and Psychopathology, 13*, 515–538.
Habib, K. E., Gold, P. W., & Chrousos, G. P. (2001). Neuroendocrinology of stress. *Neuroendocrinology, 30*, 695–728.
Harlow, H. F., Harlow, M. K., & Suomi, S. J. (1971). From thought to therapy: Lessons from a primate laboratory. *American Scientist, 59*, 538–549.
Heilig, M., Koob, G. F., Ekman, R., & Britton, K. T. (1994). Corticotropin-releasing factor and neuropeptide Y: Role in emotional integration. *Trends in Neurosciences, 17*, 80–85.
Heim, C., Ehlert, U., & Hellhammer, D. H. (2000). The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology, 25*, 1–35.
Heim, C., & Nemeroff, C. B. (1999). The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. *Biological Psychiatry, 46*, 1509–1522.
Heim, C., Newport, D. J., Heit, S., Graham, Y. P., Wilcox, M., Bonsall, R., Miller, A. H., & Nemeroff, C. B. (2000). Pituitary–adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *Journal of the American Medical Association, 284*, 592–597.
Hertsgaard, L., Gunnar, M. R., Erickson, M. F., & Nachmias, M. (1995). Adrenocortical responses to the strange situation in infants with disorganized/disoriented attachment relationships. *Child Development, 66*, 1100–1106.
Higley, J. D., & Linnoila, M. (1997). Low central nervous system serotonergic activity is traitlike and correlates with impulsive behavior. A nonhuman primate model investigating genetic and environmental influences on neurotransmission. *Annals of the New York Academy of Sciences, 836*, 39–56.
Higley, J. D., Thompson, W. W., Champoux, M., Goldman, D., Hasert, M. F., Kraemer, G. W., Scanlan, J. M., Suomi, S. J., & Linnoila, M. (1993). Paternal and maternal genetic and environmental contributions to cerebrospinal fluid monoamine metabolites in rhesus monkeys (*Macaca mulatta*). *Archives of General Psychiatry, 50*, 615–623.
Hofer, M. A. (1994). Early relationships as regulators of infant physiology and behavior. *Acta Paediatrica Supplement, 397*, 9–18.
Holsboer, F., Lauer, C. J., Schreiber, W., & Krieg, J. C. (1995). Altered hypothalamic–pituitary–adrenocortical regulation in healthy subjects at high familial risk for affective disorders. *Neuroendocrinology, 62*, 340–347.
Hrdy, S. B. (1999). *Mother nature: Maternal instincts and how they shape the human species*. New York: Ballantine Books.
Introini–Collison, I. B., Dalmaz, C., & McGaugh, J. L. (1996). Amygdala beta-noradrenergic influences on memory storage involve cholinergic activation. *Neurobiology, Learning and Memory, 65*, 57–64.
Issa, A. M., Rowe, W., Gauthier, S., & Meaney, M. J. (1990). Hypothalamic–pituitary–adrenal activity in aged, cognitively impaired and cognitively unimpaired rats. *Journal of Neuroscience, 10*, 3247–3254.
Johnson, M. R., & Adler, L. E. (1993). Transient impairment in P50 auditory sensory gating induced by a cold-pressor test. *Biological Psychiatry, 33*, 380–387.
Jones, B., Leeton, J., McLeod, I., & Wood, C. (1972). Factors influencing the age of menarche in a lower socioeconomic group in Melbourne. *Medical Journal of Australia, 2*, 533–535.
Kagan, J. (1994). *Galen's prophecy*. New York: Basic Books.
Kagan, J. (1997). Conceptualizing psychopathology: The importance of developmental profiles. *Development and Psychopathology, 9*, 1–14.
Kagan, J., Reznick, J. S., & Snidman, N. (1987). The physiology and psychology of behavioral inhibition in young children. *Child Development, 58*, 1459–1473.
Kagan, J., Reznick, J. S., & Snidman, N. (1988). Biological bases of childhood shyness. *Science, 240*, 167–171.
Kagan, J., Snidman, N., Zentner, M., & Peterson, E. (1999). Infant temperament and anxious symptoms in school age children. *Development and Psychopathology, 11*, 209–224.
Ketelaar, T., & Ellis, B. J. (2000). Are evolutionary explainations unfalsifiable? Evolutionary psychology and the Lakatosian philosophy of science. *Psychological Inquiry, 11*, 1–21.
Klonowicz, T. (1987). Reactivity and the control of arousal. In J. Strelau & J. H. Eysenck (Eds.), *Personality dimensions and arousal. Perspectives on individual differences* (pp. 183–196). New York: Plenum Press.
Kochanska, G. (1993). Toward a synthesis of parental socialization and child temperament in early development of conscience. *Child Development, 64*, 325–347.

Kochanska, G. (1997). Multiple pathways to conscience for children with different temperaments: From toddlerhood to age 5. *Developmental Psychology, 33*, 228–240.

Kohn, P. M. (1991). Reactivity and anxiety in the laboratory and beyond. In J. Strelau & A. Angleitner (Eds.), *Explorations in temperament: International perspectives on theory and measurement*. London: Plenum Press.

Kohn, P. M., Hunt, R. W., Cowles, M. P., & Davis, C. A. (1986). Factor structure and construct validity of the Vando Reducer–Augmenter Scale. *Personality and Individual Differences, 7*, 57–64.

Laban, O., Dimitrijevic, M., von Hoersten, S., Markovic, B. M., & Jankovic, B. D. (1995). Experimental allergic encephalomyelitis in adult DA rats subjected to neonatal handling or gentling. *Brain Research, 676*, 133–140.

Lacey, J. I. (1959). Psychophysiological approaches to the evaluation of psychotherapeutic process and outcome. In E. A. Rubinstein & M. B. Parloff (Eds.), *Research in psychotherapy* (pp. 161–196). Washington, DC: American Psychological Association.

Lakatos, I. (1970). Falsificationism and the methodology of scientific research programmes. In I. Lakatos & A. Musgrave (Eds.), *Criticism and the growth of knowledge* (pp. 91–196). Cambridge: Cambridge University Press.

Lakatos, I. (1978). *The Methodology of scientific research programmes: Philosophical papers* (Vol. 1). Cambridge: Cambridge University Press.

Lemne, C. E. (1998). Increased blood pressure reactivity in children of borderline hypertensive fathers. *Journal of Hypertension, 16*, 1243–1248.

Lewis, M., & Ramsay, D. S. (1997). Stress reactivity and self-recognition. *Child Development, 68*, 621–629.

Liang, S. W., Jemerin, J. J., Tschann, J. M., Irwin, C. E., Wara, D. W., & Boyce, W. T. (1995). Life events, cardiovascular reactivity, and risk behavior in adolescent boys. *Pediatrics, 96*, 1101–1105.

Linnoila, M., Virkkunen, M., George, T., Eckardt, M., Higley, J. D., Nielsen, D., Goldman, D. (1994). Serotonin, violent behavior and alcohol. *Experientia Supplement, 71*, 155–163.

Liu, D., & Meaney M. J. (1997). Maternal care, hippocampal glucocorticoid receptors, and hypothalamic–pituitary–adrenal responses to stress. *Science, 277*, 1659–1662.

Lubach, G. R., Coe, C. L., & Ershler, W. B. (1995). Effects of early rearing environment on immune responses of infant rhesus monkeys. *Brain Behavior and Immunity, 9*, 31–46.

Lupien, S. J., King, S., Meaney, M. J., & McEwen, B. S. (2000). Child's stress hormone levels correlate with mother's socioeconomic status and depressive state. *Biological Psychiatry, 48*, 976–980.

Luthar, S. S., Doernberger, C. H., & Zigler, E. (1993). Resilience is not a unidimensional construct: Insights from a prospective study of inner-city adolescents. *Development and Psychopathology, 5*, 703–717.

Lynch, J. W., Everson, S. A., Kaplan, G. A., Salonen, R., & Salonen, J. T. (1998). Does low socioeconomic status potentiate the effects of heightened cardiovascular responses to stress on the progression of carotid atherosclerosis? *American Journal of Public Health, 88*, 389–394.

Lyons, D. M., Wang, O. J., Lindley, S. E., Levine, S., Kalin, N. H., & Schatzberg, A. F. (1999). Separation induced changes in squirrel monkey hypothalamic–pituitary–adrenal physiology resemble aspects of hypercortisolism in humans. *Psychoneuroendocrinology, 24*, 131–142.

Lyons, D. M., Yang, C., Sawyer–Glover, A. M., Moseley, M. E., & Schatzberg, A. F. (2001). Early life stress and inherited variation in monkey hippocampal volumes. *Archives of General Psychiatry, 58*, 1145–1151.

MacDonald, K. (1995). Evolution, the five-factor model, and levels of personality. *Journal of Personality, 63*, 525–567.

Martin, R. E., Sackett, G. P., Gunderson, V. M., & Goodlin–Jones, B. L. (1988). Auditory evoked heart rate responses in pigtailed macaques (*Macaca nemestrina*) raised in isolation. *Developmental Psychobiology, 21*, 251–260.

Masten, A. S. (2001). Ordinary magic: Resilience processes in development. *American Psychologist, 56*, 227–238.

Matthews, K. A. (1986). Summary, conclusions and implications. In K. A. Matthews, S. M. Weiss & T. Detre (Eds.), *Handbood of stress, reactivity and cardiovascular disease*. New York: Wiley–Interscience.

Matthews, K. A., Manuck, S. B., Stoney, C. M., Rakaczky, C. J., McCann, B. S., Saab, P. G., Woodall, K. L., Block, D. R., Visintainer, P. F., & Engebretson, T. O. (1988). Familial aggregation of blood pressure and heart rate responses during behavioral stress. *Psychosomatic Medicine, 50*, 341–352.

McCormick, D. A., & Bal, T. (1994). Sensory gating mechanisms of the thalamus. *Current Opinion in Neurobiology, 4*, 550–556.

McEwen, B. S. (1998). Protective and damaging effects of stress mediators. *New England Journal of Medicine, 338*, 171–179.

McEwen, B. S., & Stellar, E. (1993). Stress and the individual. Mechanisms leading to disease. *Archives of Internal Medicine, 153*, 2093–2101.

Mealey, L. (1995). The sociobiology of sociopathy: An integrated evolutionary model. *Behavioral and Brain Sciences, 18*, 523–599.

Mealey, L. (2000). *Sex differences: Development and evolutionary strategies*. San Diego, CA: Academic Press.

Mealey, L. (2001). Kinship: The tie that binds (disciplines). In H. Holcomb (Ed.), *Conceptual challenges in evolutionary psychology*. New York: Kluwer Academic.

Meaney, M. J. (2001). Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annual Review of Neuroscience, 24*, 1161–1192.

Meyer, J. S., & Bowman, R. E. (1972). Rearing experience, stress and adrenocorticosteroids in the rhesus monkey. *Physiology & Behavior, 8*, 339–343.

Meyer, S. E., Chrousos, G. P., & Gold, P. W. (2001). Major depression and the stress system: A life span perspective. *Development and Psychopathology, 13*, 565–580.

Moffitt, T. E., Caspi, A., Belsky, J., & Silva, P. A. (1992). Childhood experience and the onset of menarche: A test of a sociobiological model. *Child Development, 63*, 47–58.

Munck, A., Guyre, P. M., & Holbrook, N. J. (1984). Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocrine Reviews, 5*, 25–43.

Musante, L., Treiber, F. A., Kapuku, G., Moore, D., Davis, H., & Strong, W. B. (2000). The effects of life

events on cardiovascular reactivity to behavioral stressors as a function of socioeconomic status, ethnicity, and sex. *Psychosomatic Medicine*, *62*, 760–767.

Nachmias, M., Gunnar, M. R., Mangelsdorf, S., Parritz, R. H., & Buss, K. (1996). Behavioral inhibition and stress reactivity: The moderating role of attachment security. *Child Development*, *67*, 508–522.

Neiss, R. (1988). Reconceptualizing arousal: Psychobiological states in motor performance. *Psychological Bulletin*, *103*, 345–366.

Nesse, R. M., & Young, E. A. (2000). Evolutionary origins and functions of the stress response. In G. Fink (Ed.), *Encyclopedia of stress* (Vol. 2, pp. 79–84). New York: Academic Press.

Neylan, T. C., Fletcher, D. J., Lenoci, M., McCallin, K., Weiss, D. S., Schoenfeld, F. B., Marmar, C. R., & Fein, G. (1999). Sensory gating in chronic posttraumatic stress disorder: Reduced auditory P50 suppression in combat veterans. *Biological Psychiatry*, *46*, 1656–1664.

Owens, M. J., & Nemeroff, C. B. (1991). Physiology and pharmacology of corticotropin-releasing factor. *Pharmacological Reviews*, *43*, 425–473.

Patterson, C. M., & Newman, J. P. (1993). Reflectivity and learning from aversive events: Toward a psychological mechanism for the syndromes of disinhibition. *Psychological Review*, *100*, 716–736.

Perry, B. (1994). Neurobiological sequelae of childhood trauma: PTSD in children. In M. Murburg (Ed.), *Catecholamine function in post-traumatic stresss disorder: Emerging concepts* (pp. 233–255). Washington, DC: American Psychiatric Press.

Plotsky, P. M., & Meaney, M. J. (1993). Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. *Molecular Brain Research*, *18*, 195–200.

Quas, J. A., Bauer, A. M., & Boyce, W. T. (2004). Physiological reactivity, social support, and memory in early childhood. *Child Development*.

Quas, J. A., Hong, M., Alkon, A., & Boyce, W. T. (2000). Dissociations between psychobiologic reactivity and emotional expression in children. *Developmental Psychobiology*, *37*, 153–175.

Raine, A., Venables, P. H., & Mednick, S. A. (1997). Low resting heart rate at age 3 years predisposes to aggression at age 11 years: Evidence from the Mauritius Child Health Project. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*, 1457–1464.

Reis, D. J., & Golanov, E. V. (1997). Autonomic and vasomotor regulation. *International Review of Neurobiology*, *41*, 121–149.

Reznick, J. S., Kagan, J., Snidman, N., Gersten, M., Baak, K., & Rosenberg, A. (1986). Inhibited and uninhibited children: A follow-up study. *Child Development*, *57*, 660–680.

Rolls, E. T. (1999). *The brain and emotion*. Oxford: Oxford University Press.

Sanchez, M. M., Ladd, C. O., & Plotsky, P. M. (2001). Early adverse experience as a developmental risk factor for later psychopathology: Evidence from rodent and primate models. *Development and Psychopathology*, *13*, 419–449.

Sapolsky, R. M. (1990). Adrenocortical function, social rank, and personality among wild baboons. *Biological Psychiatry*, *28*, 862–885.

Sapolsky, R. M. (1996). Why stress is bad for your brain. *Science*, *273*, 749–750.

Sapolsky, R. M., Romero, L. M., & Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews*, *21*, 55–89.

Sapolsky, R. M., & Share, L. J. (1994). Rank-related differences in cardiovascular function among wild baboons: Role of sensitivity to glucocorticoids. *American Journal of Primatology*, *32*, 261–275.

Scarpa, A., & Raine, A. (1997). Psychophysiology of anger and violent behavior. *Psychiatric Clinics of North America*, *20*, 375–394.

Schlichting, C. D., & Pigliucci, M. (1998). *Phenotypic evolution: A reaction norm perspective*. Sunderland, MA: Sinauer Associates.

Schmidt, L. A., Fox, N. A., Schulkin, J., & Gold, P. W. (1999). Behavioral and psychophysiological correlates of self-presentation in temperamentally shy children. *Developmental Psychobiology*, *35*, 119–135.

Selye, H. (1950). *Stress: The physiology and pathology of exposure to stress*. Montreal: Acta Medical Publishers.

Shannon, C., Champoux, M., & Suomi, S. J. (1998). Rearing condition and plasma cortisol in rhesus monkey infants. *American Journal of Primatology*, *46*, 311–321.

Shimamura, A. P. (2000). The role of the prefrontal cortex in dynamic filtering. *Psychobiology*, *28*, 207–218.

Slobodkin, L., & Rapoport, A. (1974). An optimal strategy of evolution. *Quarterly Review of Biology*, *49*, 181–200.

Smith, G. W., Aubry, J. M., Dellu, F., Contarino, A., Bilezikjian, L. M., Gold, L. H., Chen, R., Marchuk, Y., Hauser, C., Bentley, C. A., Sawchenko, P. E., Koob, G. F., Vale, W., & Lee K. F. (1998). Corticotropin releasing factor receptor 1-deficient mice display decreased anxiety, impaired stress response, and aberrant neuroendocrine development. *Neuron*, *20*, 1093–1102.

Snidman, N., Kagan, J., Riordan, L., & Shannon, D. C. (1995). Cardiac function and behavioral reactivity during infancy. *Psychophysiology*, *32*, 199–207.

Stein, M. B., Yehuda, R., Koverola, C., & Hanna, C. (1997). Enhanced dexamethasone suppression of plasma cortisol in adult women traumatized by childhood sexual abuse. *Biological Psychiatry*, *42*, 680–686.

Stevens, K. E., Bullock, A. E., & Collins, A. C. (2001). Chronic corticosterone treatment alters sensory gating in C3H mice. *Pharmacology Biochemistry and Behavior*, *69*, 359–366.

Stevenson–Hinde, J., & Marshall, P. J. (1999). Behavioral inhibition, heart period, and respiratory sinus arrhythmia: An attachment perspective. *Child Development*, *70*, 805–816.

Strelau, J. (1983). *Temperament personality activity*. New York: Academic Press.

Strelau, J., & Eysenck, H. J. (1987). *Personality dimensions and arousal*. New York: Plenum Press.

Suomi, S. J. (1987a). *Individual differences in rhesus monkey behavioral and adrenocortical responses to social challenge: Correlations with measures of heart rate variability*. Paper presented at the Heart Rate Variability and Social Behavior: Behavioral and Biological Correlates Conference, Baltimore, MD.

Suomi, S. J. (1987b). Genetic and maternal contributions to individual differences in Rhesus monkey biobehavioral development. In N. Krasnagor (Ed.), *Psychobiological aspects of behavioral development* (pp. 397–419). New York: Academic Press.

Suomi, S. J. (1997). Early determinants of behaviour: Evidence from primate studies. *British Medical Bulletin*, *53*, 170–184.

Surbey, M. K. (1990). Family composition, stress, and the timing of human menarche. In T. E. Ziegler (Ed.), *Socioendocrinology of primate reproduction. Monographs in primatology* (pp. 11–32). New York: Wiley–Liss.

Taub, J. M. (1998). Eysenck's descriptive and biological theory of personality: A review of construct validity. *International Journal of Neuroscience, 94,* 145–197.

Turkheimer, E., & Gottesman, I. I. (1991). Individual differences and the canalization of human behavior. *Developmental Psychology, 27,* 18–22.

Turner, J. R., & Hewitt, J. K. (1992). Twin studies of cardiovascular response to psychological challenge: A review and suggested future directions. *Annals of Behavioral Medicine, 14,* 12–20.

Valentino, R. J., Curtis, A. L., Page, M. E., Pavcovich, L. A., & Florin–Lechner, S. M. (1998). Activation of the locus ceruleus brain noradrenergic system during stress: Circuitry, consequences, and regulation. *Advances in Pharmacology, 42,* 781–784.

van der Saag, P. T., Caldenhoven, E., & van de Stolpe, A. (1996). Molecular mechanisms of steroid action: A novel type of cross-talk between glucocorticoids and NF-kappa B transcription factors. *European Respiratory Journal, Supplement 22,* 146s–153s.

Vazquez, D. M., Watson, S. J., & Lopez, J. F. (2000, July). *Failure to terminate stress responses in children with psychosocial dwarfism: A mechanism for growth failure*. Paper presented at the International Conference of Infant Studies, Brighton, UK.

Viau, V. (2002). Functional cross-talk between the hypothalamic–pituitary–gonadal and –adrenal axes. *Journal of Neuroendocrinology, 14,* 506–513.

von Bertalanffy, L. (1968). *General system theory: Foundations, development, applications*. New York: George Braziller.

Waddington, C. H. (1966). *Principles of development and differentiation*. New York: MacMillan.

Waldo, M., Myles–Worsley, M., Madison, A., Byerley, W., & Freedman, R. (1995). Sensory gating deficits in parents of schizophrenics. *American Journal of Medical Genetics, 60,* 506–511.

Ward, H. E., Johnson, E. A., Salm, A. K., & Birkle, D. L. (2000). Effects of prenatal stress on defensive withdrawal behavior and corticotropin releasing factor systems in rat brain. *Physiology & Behavior, 70,* 359–366.

White, B. P., Gunnar, M. R., Larson, M. C., Donzella, B., & Barr, R. G. (2000). Behavioral and physiological responsivity and patterns of sleep and daily salivary cortisol in infants with and without colic. *Child Development, 71,* 862–877.

Willemsen–Swinkels, S. H., Bakermans–Kranenburg, M. J., Buitelaar, J. K., van, I. M. H., & van Engeland, H. (2000). Insecure and disorganised attachment in children with a pervasive developmental disorder: Relationship with social interaction and heart rate. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 41,* 759–767.

Worthman, C. M., Angold, A., & Costello, E. J. (1998). *Stress, reactivity and psychiatric risk in adolescents*. Paper presented at the Biennial Meeting of the Society for Research on Adolescence, San Diego, CA, February 26–28.

Yehuda, R. (2002). Post-traumatic stress disorder. *New England Journal of Medicine, 346,* 108–114.

Yehuda, R., Halligan, S. L., & Bierer, L. M. (2001). Relationship of parental trauma exposure and PTSD to PTSD, depressive and anxiety disorders in offspring. *Journal of Psychiatric Research, 35,* 261–270.

Yehuda, R., Halligan, S. L., & Grossman, R. (2001). Childhood trauma and risk for PTSD: Relationship to intergenerational effects of trauma, parental PTSD, and cortisol excretion. *Development and Psychopathology, 13,* 733–753.

Yehuda, R., McFarlane, A. C., & Shalev, A. Y. (1998). Predicting the development of posttraumatic stress disorder from the acute response to a traumatic event. *Biological Psychiatry, 44,* 1305–1313.

Yerkes, R. M., & Dodson, J. D. (1908). The relation of strength of stimulus to rapidity of habit formation. *Journal of Comparative Neurology and Psychology, 18,* 459–482.

Zaharia, M. D., Kulczycki, J., Shanks, N., Meaney, M. J., & Anisman, H. (1996). The effects of early postnatal stimulation on Morris water-maze acquisition in adult mice: Genetic and maternal factors. *Psychopharmacology (Berlin), 128,* 227–239.

Zuckerman, M. (1984). Sensation seeking: A comparative approach to a human trait. *Behavioral and Brain Sciences, 7,* 413–471.