Running head: STRESS AND THE DEVELOPMENT OF SELF-REGULATION

Stress and the Development of Self-Regulation in the Context of Poverty

Clancy Blair

Department of Applied Psychology

New York University

239 Greene Street, East Building, 500

New York, NY 10003

212-998-5853

clancy.blair@nyu.edu

Abstract

This paper considers the effects of psychosocial stress on child development and describes mechanisms through which early stress as an aspect of poverty is understood to affect the functioning of neural networks that underlie executive functions (EFs) and self-regulation. Effects of stressful experience on glucocorticoid and catecholamine levels that influence neural activity in areas of the brain associated with EFs, primarily as studied in animal models, is examined. Strengths and limitations of this research, its relevance to understanding stress reactivity from the perspective of biological sensitivity to context, and its implications for the study of risk and resilience processes and early intervention to prevent developmental delays are considered.

Stress and the Development of Self-Regulation in the Context of Poverty

Stress is a central construct in the study of psychosocial adversity. It is prominent among the several mediating mechanisms through which risk for poor physical and mental health increases in inverse relation to SES (Adler, Boyce, Chesney, Cohen, Folkman, Kahn, & Syme, 1994). Persistently elevated levels of physiological reactivity to stress have been linked with adverse physical and mental health outcomes across the lifespan (McEwen, 2000) and a number of studies have definitively linked income poverty and low SES to children's health and development (McLeod & Shanahan, 1993; McLoyd, 1998). Until recently, however, in depth examination of stress as an aspect of the link between poverty and child development has been lacking (Evans, 2003).

There are many ways in which low SES environments affect child health and development. Stress within the context of poverty is only one of them. Stress is of strong interest for children's development, however, in that alterations to stress response systems resulting from the early rearing environment may have specific effects on aspects of brain development and function that promote or impede the development of reflective and goal-directed self-regulation of behavior. Much of the research linking early environment with alterations to the stress response and with brain development has been conducted using animal models and the purpose of this paper is to briefly review some of this research and consider its implications for child development. As such, at the outset it is important to note that it is only by considering the context in which stress reactivity occurs that implications for child development can be appreciated. High reactivity to stress on its own does not confer risk and may even enhance development in supportive contexts (Boyce & Ellis, 2005). In high risk environments, however, higher reactivity is likely to occur without support for the regulation of reactivity and to lead to poor developmental outcomes.

As well, it is also important to note here that the characterization of a stress response that promotes reflective self-regulation as beneficial (i.e., does not result in chronic overactivation leading to illness or to delays in the development of cognitive abilities and behaviors that are valued within socially constructed environments such as the school classroom or the workplace) is not synonymous with its characterization as adaptive. In unpredictable environments in which resources are scarce or social conflict is high, more reactive and less reflective patterns of cognition and behavior are likely to be adaptive and to result in short term benefits if not longer term health and self-regulation benefits.

Animal models of early experience. Animal models have demonstrated that chronic stress in the prenatal and/or very early neonatal periods (demonstrated through manipulations that directly increase the physiological response to stress) leads to increased stress reactivity and to poor regulation of stress reactivity in the hypothalamic-pituitary-adrenal (HPA) axis component of the stress response system (Francis, Diorio, Liu, & Meaney, 1999; Huizink, Mulder, & Buitelaar, 2004; Liu et al., 1997; Ladd, Huot, Thrivikraman, Nemeroff, Meaney, & Plotsky, 2000). This research has demonstrated that high levels early in life of the end product of HPA axis activity (corticosterone in rodents, cortisol in humans) influences the development of brain structures and neural circuitry in areas of the brain that are in combination important for initiating and regulating the HPA response to stress and also for cognitive abilities referred to as executive functions (EFs) that are important for learning and memory and the effortful regulation of behavior (Liu., Diorio, Day, Francis, & Meaney, 2000; Meaney & Szyf, 2005; Sanchez, Ladd & Plotsky, 2001; Weinstock, 2001).

Several studies (Braun, Lange, Metzger, & Poeggel, 1999; Kinnunen, Keonig, & Bilbe, 2003; Lemaire, Koehl, Le Moal, & Abrous, 2000; Liu, Diorio, Day, Frances, & Meaney, 2000) have demonstrated that chronic early stress alters neural functioning and connectivity within and

between limbic structures, notably the amygdala and hippocampus, associated with emotion, rapid contextually and temporally bound responses to stimulation, and the initiation and termination of the stress response, and areas of PFC, particularly ventral medial and orbital PFC, important for regulating the stress response, regulating emotion, and for coordinating thought and action in the control of behavior through EFs (Barbas, 2000; Barbas & Zikopoulos, 2007; Holmes & Wellman, 2009). The relation of corticolimbic neural circuitry to the self-regulation of behavior associated with EFs has also been shown in a number of studies with animal models. In these models, targeted disruptions of PFC corticolimbic connectivity through lesion, transient inactivation, and pharmacological manipulation as well as stress induction procedures result in performance decrements on tasks requiring EFs (Cerqueira, Mailliet, Almeida, Jay, & Sousa, 2007; Collins, Roberts, Dias, Everitt, & Robbins, 1998; Floresco, Seamans, & Phillips, 1997; Goldstein, Rasmusson, Bunney, & Roth, 1996; Seamans, Floresco, & Phillips, 1998) and elevated levels of reactive and inflexible behavior, as seen in fear conditioning (Champagne et al., 2008).

Relations among early experience, PFC corticolimbic connectivity, and EFs demonstrated in animal models are important for child development research in that EFs describe information processing abilities that allow for actively maintaining and processing task relevant information in working memory, for flexibly sustaining and shifting attention between distinct but related aspects of a given task, and for inhibiting extraneous information and automatic responding associated with prepotent stimuli (Diamond, 2002; Zelazo, Muller, Frye, & Marcovitch, 2003). In humans, EFs have been related to multiple aspects of developing social and cognitive competence (Blair & Razza, 2007; Carlson & Moses, 2001; Hughes & Ensor, 2007) and impairments in EFs are a salient aspect of cognitive deficits in a number of developmental disorders and psychopathologies in children (Pennington & Ozonoff, 1996; Zelazo & Muller, 2002).

Early stress, brain development, and cognition. One of the implications of research on environmental influences on PFC corticolimbic circuitry and EFs is that early experience acts to program or sensitize stress response systems to meet an expected environment (Boyce & Ellis, 2005). In supportive and resource rich environments, stress response systems and PFC corticolimbic connectivity are understood to be biased toward effortful processing of information and reflective self-regulation associated with EFs. In low resource, unpredictable environments stress responding and corticolimbic connectivity are biased toward reactive rather than reflective self-regulation.

This biasing effect is due to the fact that glucocorticoid levels associated with the HPA response to stress and also catecholamine levels (epinephrine, dopamine) associated with the sympathetic-adrenal-medullary response to stress modulate neural activity in PFC networks that support EFs. In both human and animal studies, glucocorticoid and catecholamine levels demonstrate an inverted U shaped relation with EFs. Very high or very low levels of glucocorticoids and catecholamines are associated with low levels of performance on EF tasks while moderate increases are associated with higher level of EFs (Arnsten & Li, 2005; Lupien, Gillin, & Hauger, 1999; Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007).

This inverted U relation between stress levels and EFs is a manifestation at the neural level of the relation between arousal and performance first described by Yerkes and Dodson (1908). In the Yerkes-Dodson principle, arousal at moderate levels increases performance on complex tasks but at very high or very low levels impairs performance. In this relation between arousal and performance, however, the inverted U is specific to complex tasks. Although not widely recognized, Yerkes and Dodson in their original and subsequent publications demonstrated that arousal is positively and linearly related to performance on simple tasks and behaviors such as attention focusing and reactivity (Diamond, Campbell, Park, Halonen, & Zoladz, 2007). As such,

in keeping with the biological sensitivity to context model, high levels of stimulation early in life, whether positive or negative, are thought to increase physiological reactivity and to prime or sensitize stress response systems for adaptation and survival within an expected context (Ellis, Essex, & Boyce, 2005). In supportive contexts, this stimulation results in physiological reactivity that is conducive to self-regulation, while in unsupportive contexts, this stimulation leads to physiological reactivity that is conducive to high behavioral reactivity and low self-regulation.

The inverted U relation between glucocorticoid and catecholamine levels and complex tasks requiring EFs is a function of variation in the types of neural receptors present in PFC neural circuitry and the relative sensitivity or affinity of these receptors for glucocorticoids and catecholamines. For example, of the two types of glucocorticoid receptors in the brain, glucocorticoid (GR) and mineralocorticoid (MR), GR bind (take up) cortisol with less affinity than do MR and therefore remain largely unoccupied at low levels of stress arousal. However, with increasing stress and moderate cortisol increase, GR occupation increases, supporting synaptic long-term potentiation (LTP). Increases in cortisol with stress arousal beyond a moderate level, indicating increasingly high GR occupation, however, are associated with synaptic long-term depression (LTD) rather than LTP (de Kloet, Oitzl, & Joels, 1999; Erickson, Drevets, & Schulkin, 2003).

Similar relations are observed between catecholamine levels and neural activity. Moderate increases in norepinephrine (NE), a primary neuromodulator associated with the sympathetic-adrenal system, result in increased occupation of a specific type of adrenoceptor, alpha-2A adrenoceptors, which have a high affinity for NE and are predominantly located in PFC and associated with EF (Ramos & Arnsten, 2007). At increases beyond a moderate level, however, alpha-2A receptors become saturated and adrenoceptors with a lower affinity for NE become active. These receptors are predominantly located in subcortical and posterior brain regions

associated with reflexive and reactive responses to stimulation. In this way, levels of NE act to influence the neural response to stimulation, promoting neural activity in PFC associated with reflective and reasoned responses to stimulation at moderate levels of arousal, while at high levels, NE reduces neural activity in PFC and increases neural activity in brain areas associated with reactive, automatized responses to stimulation (Arnsten, 2000).

Stress in the context of poverty. In humans, primarily in research with adults, chronically stressful environments result in sustained demands on stress response systems that are ultimately pathogenic in a variety of disease states, a phenomenon referred to as allostatic load (McEwen, 2000; McEwen & Wingfield, 2003). Although it is not yet established whether chronically stressful environments early in life affect the development of stress response systems in children to the extent seen in animal models, increased allostatic load has been documented in response to chronic environmental stressors in children living in poverty and similarly related to health outcomes (Evans & Kim, 2007). There is also evidence that chronic and severe early stress results in atypically low levels in stress response systems in children that also increase risk for physical and mental health problems (Gunnar & Quevedo, 2008).

Given the relation of EFs to the development of cognitive and social competence in children, the effect of early stress on PFC corticolimbic connectivity and functioning seen in animal models suggests one pathway through which risk for delayed cognitive development and susceptibility to learning disorders and psychopathology is increased in children in poverty (Graham, Heim, Goodman, Miller, & Nemeroff, 1999). As noted above, research in animal models suggests that one mechanism of this effect of poverty on child development is through structural effects of early stress on brain development in key areas important for EFs and stress regulation. Encouragingly, however, research with adult animals as well as humans suggests the reversibility to some extent of short-term stress on PFC neural circuitry and EFs (Liston, McEwen,

& Casey, 2009; Radley et al., 2005). Furthermore, as described in detail below, animal models suggest that early intervention alters the behavioral and cognitive if not necessarily the neural consequences of early stress on development.

In addition to possible structural effects of early stress on the brain, it is also important to recognize the general relation between individual differences in stress reactivity and context. High reactive children in supportive environments are more likely to produce glucocorticoid and catecholamine levels that are well regulated and therefore conducive to synaptic LTP in PFC and to the development of EFs and self-regulation abilities. In contrast, high reactive children in less supportive rearing circumstances are more likely to exhibit high glucocorticoid and catecholamine levels that are not well regulated and therefore not conducive to LTP and to EF and self-regulation. Although children in both contexts are stress reactive, those in more supportive contexts are more likely to exhibit efficient regulation of stress reactivity as high quality early care and higher levels of social support are known to be associated with faster glucocorticoid (Dickerson & Kemeny, 2004) and presumably catecholamine recovery. With slower recovery in less supportive contexts, glucocorticoid and catecholamine receptor occupation is more likely to reach a point at which stress acts to take PFC "offline" and to result in reflexive and reactive responses to stimulation associated with subcortical and posterior brain systems rather than reflective and reasoned responses associated with PFC (Arnsten & Li, 2005).

This general relation between reactivity and the quality of early experience has been noted in the developmental psychology literature as differential susceptibility to rearing influence (Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2007). In an increasing number of studies examining the differential susceptibility model, infants and young children characterized by high levels of behavioral reactivity and negative emotionality are particularly likely to exhibit optimal

development in high quality environments but unfavorable outcomes in low quality environments (Blair, 2002; Belsky, Hsieh, & Crnic, 1998; van den Boom, 1994).

As well, a number of studies have indicated that very high or very low levels of stress reactivity and difficulty with the up or down regulation of stress reactivity are associated with problems with EFs and self-regulation. In research on the stress response there has been an appropriate focus on the deleterious consequences of atypically high or low stress levels, as indicated by cortisol, on development (Gunnar & Donzella, 2002; Gunnar, Tout, de Haan, Pierce, & Stansbury, 1997). In similar keeping with the inverted U relation between stress levels and EFs, studies of typically developing children, both in low-income and in middle-income homes, indicate that moderately higher levels of cortisol are associated with better performance on measures of EFs and self-regulation (Blair, Granger, & Razza, 2005; Davis, Bruce, & Gunnar, 2002). Although similar relations likely exist between catecholamine levels and EFs in children, no studies to date have demonstrated these relations due to the difficulty of noninvasively assessing catecholamine levels. However, recent work with a surrogate marker of sympathetic activation present in saliva, the protein alpha amylase, shows promise (Granger, Kivlighan, El-Sheik, Gordis, & Stroud, 2007).

Stress and development: Caregiving as a mechanism. Although animal models designed to examine the effects of early stress on development make use of a variety of types of stressors, of strong interest to child development researchers has been the examination of early rearing stress associated with naturally occurring variation in maternal behavior in the rat. Building on a research tradition that spans much of the 20th century, research in behavioral neuroscience has demonstrated that extended maternal separation and low level of maternal competence in rats are associated with problems with stress regulation and adverse cognitive and behavioral outcomes in offspring (Meaney, 2001). In contrast, brief maternal separation/handling of rat pups increases

levels of maternal behaviors, notably licking and grooming upon reunion that promote gene expression associated with the density of GR receptors in the hippocampus, the development of an efficient HPA stress response system, and advantageous cognitive and social developmental outcomes in typical, adequate resource environments (Caldji, Diorio, & Meaney, 2000; Liu et al., 2000; Liu et al., 1997; Weaver et al., 2004).

Although early rearing environments for children differ in many ways from those of rats, the caregiving environment for children facing socioeconomic disadvantage is more likely than typical home environments to be disorganized and lacking in appropriate stimulation and support, thereby creating conditions that are stressful for children (Evans, 2004; McLoyd, 1998; Repetti, Taylor, & Seeman, 2002). Low quality early caregiving is highly likely to serve as a primary source of stress for children or as a mediator of environmental stressors with stressful social and physical conditions of the home leading to stress on parents and to low quality early care.

Several studies have demonstrated that economic adversity is associated with disruptions in parenting behaviors and that psychological distress in parents is linked to poor child cognitive and behavioral outcomes in children (Brody & Flor, 1998; Jackson, Brooks-Gunn, Huang, & Glassman, 2000). However, the extent to which the experience of psychologically distressed parenting in poverty is stressful for children, and if so, whether problems with the regulation of the stress response in children in poverty is linked to poor developmental outcomes, is not well known. Studies have indicated contexts which are more prevalent in low-income homes in which infants and young children are likely to exhibit problems with stress regulation, such as nonoptimal attachment relationships with primary caregivers (de Haan, Gunnar, Tout, Hart, & Stansbury, 1998; Gunnar, Brodersen, Nachmias, Buss, & Rigatuso, 1996) and maternal unavailability (Bugental, Martorell, & Barraza, 2003; Haley & Stansbury, 2003). And high quality caregiving in numerous studies has been shown to moderate the effects of poverty on child

development outcomes (e.g., Ramey & Campbell, 1991; Wyman et al., 1999). The extent to which high quality caregiving may have moderated effects of stress, however, is not clear. As noted above, research on the stress response in adolescent children in poverty has indicated increased allostatic load associated with cumulative risk in the home, including physical (crowding, noise) and psychosocial (violence, family turmoil) risk factors. Importantly, the relation between cumulative risk and allostatic load in this study was present only when combined with low levels of maternal responsiveness (Evans, Kim, Ting, Tesher, & Shannis, 2007). Similarly, in a large predominantly low-income sample followed longitudinally, baseline cortisol was low and cortisol reactivity and regulation high in response to a moderate stressor in infants at age 7 months whose mothers were high in sensitivity. Furthermore, when followed up at age 15 months, overall cortisol levels, both at baseline and in response to stress, were reduced for children of mothers high in sensitivity (Blair et al., 2008). Consistent with an emphasis on the role of early caregiving in animal models of stress (Meaney & Szyf, 2005), and on the relation between stress reactivity and context (Ellis, Essex, & Boyce, 2005), these studies suggest that relations between stress reactivity and later developmental outcomes are determined by early caregiving.

Stress and development: Implications for early intervention. Given evidence relating early rearing adversity to atypical stress responding and poor cognitive and social developmental outcomes in animal models, it is notable that these models of early stress also indicate that environmental enrichment can offset disadvantage associated with early stress exposure. For example, Francis, Diorio, Plotsky, and Meaney (2002) demonstrated reversal of the effect of early stress associated with maternal separation during the neonatal period on the HPA response to stress, as indicated by corticosterone levels, and on learning and memory among rats receiving environmental enrichment. Effects on corticosterone and behavior, however, could not be attributed to expected changes at the neural level in terms of primary processes that influence

stress reactivity, namely GR mRNA expression in the dentate gyrus of the hippocampus and corticotrophin releasing factor mRNA expression in the paraventricular nucleus of the hypothalamus. Similarly, Bredy, Humpartzoomian, Cain, and Meaney (2003) demonstrated that the effects of low maternal caregiving competence on hippocampally dependent learning and memory could be reversed at the behavioral level through environmental enrichment but that the physiological function of the hippocampus was not altered in expected ways. These findings of Francis et al. (2002) and Bredy et al. (2003) indicate that the effects of enrichment as seen at the behavioral level are not necessarily mirrored in expected changes at the biological level (Fernandez-Teruel, Gimenez-Llort, Escorihuela, Gil, Aguilar, Steimer, & Tobena, 2002). Rats experiencing prenatal or postnatal stress followed by enrichment continue to some extent to look at the neural level like rats experiencing low early caregiving competence without enrichment. Consistent with the adaptive nature of the stress response, however, the findings of Francis et al. (2002) and Bredy et al. (2003) suggest a functional reversal of the effects of early stress in which environmental enrichment leads to compensatory neurobiological changes, perhaps associated with changes in frontal cortex, that alter the phenotypic expression of high reactivity.

Neurobiological evidence from animal models suggests that early education and care interventions for children in poverty may work in part by preventing or limiting the influence of problems with stress reactivity and regulation that detrimentally impact self-regulation abilities such as EFs. In the evaluation of model early intervention programs there is an increasing recognition of the importance of a focus on self-regulation, on personality and social competence factors associated with self-control and on aspects of cognition that are distinct from general intelligence (Heckman, 2006, 2007). In what is termed human capability formation, early inputs (parenting quality, effective preschool and early elementary education) are seen to influence cognitive and personality factors that promote the capacity of the individual to benefit from later

opportunities. Findings from the early intervention literature provide a wealth of evidence in favor of the efficacy of improving life outcomes in children in families at high economic and psychosocial risk (Bryant & Maxwell, 1997). The provision of competent caregiving in early compensatory care and education would be expected, in theory, to have effects on developing self-regulation in children experiencing high levels of disrupted caregiving that are in part mediated through PFC corticolimbic functioning. Most, though not all, intervention studies have either targeted parenting behaviors directly (Barnard, 1997; Olds, 2002) or, as in the case of center-based care, have provided a type of care that is characterized by high levels of caregiver sensitivity and careful structuring of experience (Gross, Spiker, & Haynes, 1997). In general, the literature on parenting and infant and child stress in the context of low SES suggests that one way in which early intervention has enhanced child developmental outcomes is through reducing the exposure of infants and children in treated groups to a type of care that is stressful in the context of adversity.

Conclusion. Although evidence from animal models is compelling due to its specificity and high level of control, the extent to which neural and physiological mechanisms relating stress, early caregiving, and developmental outcomes might be at work in human populations remains open to question. The breadth and diversity of influences on human development is far greater than that examined in nonhuman animal models (Gottlieb & Lickliter, 2004). Furthermore, there are numerous influences on neural plasticity in addition to early care, such as increased activity in enriched environments (Panksepp, Burgdorf, Turner & Gordon, 2002; van Praag, Kempermann, & Gage, 2000), as well as individual differences in genetic background that are relevant to relations between the stress response and early environment.

Individual differences in genetic background figure largely in relations between stress and development. Increasing numbers of studies in human populations indicate that single nucleotide polymorphisms associated with glucocorticoid and catecholamine activity in PFC corticolimbic

circuitry are related to variation in EF and perhaps to some extent, susceptibility to early stress effects on cognition (Hariri, Drabant, & Weinberger, 2006; Pezawas et al., 2005; Tan et al., 2007). Examples of gene-environment interaction in the study of stress and development (Caspi et al., 2003) have also made clear that research incorporating information on genetic background can lead to a more specific understanding of the mechanisms through which the stress response and early care are likely to influence development and for whom effects will be largest. Of greatest relevance, however, is evidence of epigenetic modifications of DNA expression through early experience. Remarkably, it has been shown that the maternal licking and grooming behavior in the rat that is so essential to the development of the HPA stress response system produces its effect through molecular mechanisms that alter the epigenetic state of the gene that codes for GR receptor density in the hippocampus (Meaney & Szyf, 2005; Weaver, 2007; Weaver et al., 2004). And of further profound epigenetic interest is evidence indicating that levels of glucocorticoids have widespread influences on gene expression in a variety of gene classes (Datson, Morsink, Meijer, & de Kloet, 2008).

Emerging evidence of epigenetic modification of genes associated with the stress response, self-regulation, and physical and mental health is consistent with a probabilistic-epigenetic model in which context plays a powerful role in human development (Gottlieb, 1992. 1998). Consideration of PFC corticolimbic functioning in terms of probabilistic-epigenesis and developmental models such as the differential susceptibility model and the biological sensitivity to context model helps to illuminate the complexity of relations between nature and nurture in development. As outlined in the biological sensitivity model, both very high and very low quality of early experience can be expected to lead to high stress reactivity. In high quality care, this reactivity is more likely to promote aspects of cognition and behavior important for reflective self-regulation while in low quality care to promote reactive responses to stimulation. In terms of

probabilistic-epigenesis, it is necessary to think developmentally when considering early experience and to consider how stress reactivity in children may or may not lead to specific outcomes. Determinist developmental programming hypotheses through which early life experiences are thought to inexorably lead to later life outcomes are inconsistent with fundamental principles known to characterize development (Cairns, Elder, & Costello, 1996). As such, evidence relating rearing experience to self-regulation in animal models provides neurobiological evidence of one way in which environmental adversity associated with poverty and, conversely, early compensatory education and care, may affect developing competence in human populations. Chronic early rearing stress affects the activity of stress response systems with consequences for the regulation of cognition and behavior. As a result, early life stress, which is more frequent in the context of poverty, would attenuate developing self-regulation in children characterized by high reactivity and begin to shape developmental trajectories toward non-optimal outcomes. Conversely, early compensatory education and care interventions to promote learning and increase the regulation of reactivity through various activities with caring and supportive others in a predictable, stimulating environment would be expected to promote competencies such as EF and self-control that are important contributors to ongoing success in life.

Acknowledgements

This work was supported in part by National Institute of Child Health and Human Development Grants R03 HD39750, P01 HD39667, and R01 HD 51502.

References

Adler, N.E., Boyce, T., Chesney, M.A., Cohen, S., Folkman, S., Kahn, R.L., & Syme, S.L. (1994). Socioeconomic status and health: The challenge of the gradient. *American Psychologist, 49,* 15-24.

Arnsten, A.F. (2000). Through the looking glass: differential noradenergic modulation of prefrontal cortical function. *Neural Plasticity, 7,* 133-146.

Arnsten, A.F. & Li, B.M. (2005). Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. *Biological Psychiatry, 57,* 1377-1384.

Barbas, H. (2000). Complementary roles of prefrontal cortical regions in cognition, memory, and emotion in primates. *Advances in Neurology, 84,* 87-110.

Barbas, H. & Zikopoulos, B. (2007). The prefrontal cortex and flexible behavior. *The Neuroscientist, 13*, 532-545.

Barnard, K. (1997). Influencing parent-child interactions for children at risk. In M. Guralnick (Ed.) *The effectiveness of early intervention* (pp. 249-268). Baltimore MD: Brookes.

Belsky, J., Bakermans-Kranenburg, M., & van Ijzendoorn, M. (2007). For better and for worse: Differential susceptibility to environmental influences. *Current Directions in Psychological Science, 16,* 300-304.

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

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.

Blair, C., Granger, D.A., Kivlighan, K.T., Mills-Koonce, R., Willoughby, M., Greenberg, M.T., Hibel, L., Fortunato, C & the Family Life Project Investigators (2008). Maternal and child contributions to cortisol response to emotional arousal in young children from low-income, rural communities. *Developmental Psychology, 44,* 1095-1109.

Blair, C., Granger, D., & Razza, R.P. (2005). Cortisol reactivity is positively related to executive function in preschool children attending Head Start. *Child Development, 76,* 554-567.

Blair, C. & Razza, R.P. (2007). Relating effortful control, executive function, and false-belief understanding to emerging math and literacy ability in kindergarten. *Child Development, 78,* 647-663.

Boyce, W.T. & Ellis, B.J. (2005). Biological sensitivity to context: I. An evolutionary–developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology, 17,* 271-301.

Braun, K., Lange, E., Metzger, M., & Poeggel, G. (1999). Maternal separation followed by early social deprivation affects the development of monoaminergic fiber systems in the medial prefrontal cortex of Octodon Degus. *Neuroscience, 95,* 309-318.

Bredy, T.W., Humpartzoomian, R.A., Cain, D.P. & Meaney, M.J. (2003). Partial reversal of the effect of maternal care on cognitive function through environmental enrichment. *Neuroscience, 118,* 571-576.

Brody, G.H. & Flor, D.L. (1998). Maternal resources, parenting practices, and child competence in rural, single-parent African American families. *Child Development, 69,* 803-816.

Bryant, D., & Maxwell, K. (1997). The effectiveness of early intervention for disadvantaged children, in M. Guralnick (Ed.), *The effectiveness of early intervention* (pp. 23-46). Brookes: Baltimore MD.

Bugental, D.B., Martorell, G.A. & Barraza, V. (2003). The hormonal costs of subtle forms of infant maltreatment. *Hormones and Behavior, 43,* 237-244.

Cairns, R.B., Elder, G.H., & Costello, E.J. (1996). *Developmental science.* New York: Cambridge University Press.

Caldji, C., Diorio, J., & Meaney, M.J. (2000). Variations in maternal care in infancy regulate the development of stress reactivity. *Biological Psychiatry, 48,* 1164-1174.

Carlson, S.M. & Moses, L.J. (2001). Individual differences in inhibitory control and children's theory of mind. *Child Development, 72,* 1032-1053.

Caspi, A., Sugden, K., Moffitt, T., Taylor, A., Craig, I., Harrington, H., et al. (2003, July). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science, 301,* 386–389.

Cerqueira, J.J., Mailliet, F., Almeida, O.F., Jay, T.M., & Sousa, N., (2007). The prefrontal cortex as a key target of the maladaptive response to stress. *Journal of Neuroscience, 27,* 2781–2787.

Champagne, D.L., Bagot, R.C., van Hasselt, F., Ramakers, G., Meaney, M.J., de Kloet, E.R., Joëls M., & Krugers, H. (2008). Maternal care and hippocampal plasticity: Evidence for experience-dependent structural plasticity, altered synaptic functioning, and differential responsiveness to glucocorticoids and stress. *Journal of Neuroscience, 28,* 6037-6045.

Collins, P., Roberts, A.C., Dias, R., Everitt, B.J. & Robbins, T.W. (1998). Perseveration and strategy in a novel spatial self-ordered sequencing task for nonhuman primates: Effects for excitotoxic lesions and dopamine depletions of the prefrontal cortex. *Journal of Cognitive Neuroscience, 10,* 332-354.

Davis, E.P., Bruce, J., & Gunnar, M.R. (2002). The anterior attention network: Associations with temperament and neuroendocrine activity in 6-year-old children. *Developmental Psychobiology, 40,* 43-56.

Datson, N., Morsink, M., Meijer, O., & de Kloet, R. (2008). Central corticosteroid actions: Search for gene targets. *European Journal of Pharmacology, 583,* 272-289.

de Haan, M., Gunnar, M., Tout, K., Hart, J. & Stansbury, K. (1998). Familiar and novel contexts yield different associations between cortisol and behavior among 2-year-old children. *Developmental Psychobiology, 33,* 93-101.

de Kloet, E.R., Oitzl, M.,S., & Joels, M. (1999). Stress and cognition: Are corticosteroids good or bad guys? *Trends in Neurosciences, 22,* 422-426.

Diamond, A. (2002). Normal development of the prefrontal cortex from birth to young adulthood: Cognitive functions, anatomy, and biochemistry. In Stuss & Knight (Eds.), *Principles of frontal lobe function* (pp. 466-503). Oxford: UK.

Diamond, D.M., Campbell, A.M., Park, C.R., Halonen, J., & Zoladz, P.R. (2007). The temporal dynamics model of emotional memory processing: a synthesis on the neurobiological basis of stress-induced amnesia, flashbulb and traumatic memories, and the Yerkes-Dodson law. *Neural Plasticity.*

Dickerson, S.S. & Kemeny, M.E. (2004). Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychological Bulletin, 130,* 355-391.

Ellis, B.J., Essex, M.J. & Boyce, W.T. & (2005). Biological sensitivity to context: II. Empirical explorations of an evolutionary–developmental theory. *Development and Psychopathology, 17,* 303-328.

Erickson, K., Drevets, W., & Schulkin, J. (2003). Glucocorticoid regulation of diverse cognitive functions in normal and pathological emotional states. *Neuroscience and Biobehavioral Reviews, 27,* 233-246.

Evans, G.W. (2003). A multimethodological analysis of cumulative risk and allostatic load among rural children. *Developmental Psychology, 39,* 924-933.

Evans, G.W. (2004). The environment of childhood poverty. *American Psychologist, 59,* 77-92

Evans, G.W. & Kim, P. (2007). Childhood poverty and health: cumulative risk exposure and stress dysregulation. *Psychological Science, 18,* 953-957.

Evans, G.W., Kim, P., Ting, A., Tesher, H. & Shannis, D. (2007). Cumulative risk, maternal responsiveness, and allostatic load among young adolescents. *Developmental Psychology, 43,* 341-31.

Fernandez-Teruel, A., Gimenez-Llort, L., Escorihuela, R.M., Gil, L., Aguilar, R., Steimer, T. & Tobena, A. (2002). Early-life handling stimulation and environmental enrichment: Are some of their effects mediated by similar neural mechanisms? *Pharmacology, Biochemistry, and Behavior, 73,* 233-245.

Floresco, S.B., Seamans, J.K., & Phillips, A.G. (1997). Selective roles for hippocampal, prefrontal cortical, and ventral striatal circuits in radial-arm maze tasks with or without a delay. *Journal of Neuroscience, 17,* 1880-1890.

Francis, D., Diorio, J., Liu, D., & Meaney, M.J. (1999). Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science, 286,* 1155-1158.

Francis, D.D., Diorio, J., Plotsky, P.M., & Meaney, M.J. (2002). Environmental enrichment reverses the effects of maternal separation on stress reactivity. *Journal of Neuroscience, 22,* 7840-7843.

Goldstein, L.E., Rasmusson, A.M., Bunney, B.S. & Roth, R.H. (1996). Role of the amygdala in the coordination of behavioral, neuroendocrine, and prefrontal cortical monoamine responses to psychological stress in the rat. *Journal of Neuroscience, 16,* 4787-4798.

Gottlieb, G. (1992). *Individual development and evolution: The genesis of novel behavior*. New York: Oxford University Press.

Gottlieb. G. (1998). Normally occurring environmental and behavioral influences on gene activity: From central dogma to probabilistic epigenesis. *Psychological Review, 105,* 792-802.

Gottlieb, G. & Lickliter, R. (2004). The various roles of animal models in understanding human development. *Social Development, 14,* 311-325.

Graham, Y.P., Heim, C., Goodman, S.H., Miller, A.H., & Nemeroff, C.B. (1999). The effects of neonatal stress on brain development: Implications for psychopathology. *Development and Psychopathology, 11,* 545-565.

Gross, R., Spiker, D., & Haynes, C. (1997). *Helping low birth weight, premature babies: The Infant Health and Development Program.* Stanford, CA: Stanford University Press.

Gunnar, M.R., Brodersen, L., Nachmias, M., Buss, K. & Rigatuso, J. (1996). Dampening of adrenocortical responses during infancy: Normative changes and individual differences. *Child Development, 67,* 877-889.

Gunnar, M.R. & Donzella, B. (2002). Social regulation of the cortisol levels in early human development. *Psychoneuroendocrinology, 27,* 199-220.

Gunnar, M.R., Tout, K., de Haan, M., Pierce, S. & Stansbury, K. (1997). Temperament, social competence, and adrenocortical activity in preschoolers. *Developmental Psychobiology, 31,* 65-85.

Gunnar, M.R. & Quevedo, K.M. (2008). Early care experiences and HPA axis regulation in children: A mechanism for later trauma vulnerability. *Progress in Brain Research, 167,* 137-147.

Haley, D.W. & Stansbury, K. (2003). Infant stress and parent responsiveness: regulation of physiology and behavior during still-face and reunion. *Child Development, 74,* 1534-1546.

Hariri, A.R., Drabant, E.M., & Weinberger, D.R. (2006). Imaging genetics: Perspectives from studies of genetically driven variation in serotonin function and corticolimbic affective processing. *Biological Psychiatry, 59,* 888-897.

Heckman, J. (2006). Skill formation and the economics of investing in disadvantaged children. *Science, 312,* 1900-1902.

Heckman, J. (2007). The economics, technology, and neuroscience of human capability formation. *Proceedings of the National Academy of Sciences, USA, 104,* 13250-13255.

Holmes, A. & Wellman, C.L. (2009). Stress-induced prefrontal reorganization and executive dysfunction in rodents. *Neuroscience and Biobehavioral Reviews*.

Huizink, A.C., Mulder, E.J., & Buitelaar, J.K. (2004). Prenatal stress and risk for psychopathology: Specific effects or induction of general susceptibility. *Psychological Bulletin, 130,* 115-142.

Jackson, A.P., Brooks-Gunn, J., Huang, C. & Glassman, M. (2000). Single mothers in low-wage jobs: Financial strain, parenting, and preschoolers' outcomes. *Child Development, 71,* 1409-1423.

Kinnunen, A.K., Keonig, J.I., & Bilbe, G. (2003). Repeated variable prenatal stress alters pre- and postsynaptic gene expression in the rat frontal pole. *Journal of Neurochemistry, 86,* 736-748.

Ladd, C., Huot, R., Thrivikraman, K.V., Nemeroff, C.B., Meaney, M.J., & Plotsky, P.M. (2000). Long-term behavioral and neuroendocrine adaptations to adverse early experience. *Progress in Brain Research, 122,* 81-103.

Lemaire, V., Koehl, M., Le Moal, M. & Abrous, D.N. (2000). Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. *Proceedings of the National Academy of Sciences, USA, 97,* 11032-11037.

Liston, C., McEwen, B.S. & Casey, B.J. (2009). Psychosocial stress reversibly disrupts prefrontal processing and attentional control. *Proceedings of the National Academy of Sciences, USA, 106,* 912-917.

Liu, D., Diorio, J., Day, J.C., Francis, D.D., & Meaney, M.J. (2000). Maternal care, hippocampal neurogenesis, and cognitive development in rats. *Nature Neuroscience, 3,* 799-806.

Liu, D., Diorio, J., Tannenbaum, B., Caldji, C., Francis, D., Freedman, A., Sharma, S., Pearson, D., Plotsky, P. & Meaney, M. (1997). Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. *Science, 277,* 1659-1662.

Lupien, S.J., Gillin, C.J., & Hauger, R.L. (1999). Working memory is more sensitive than declarative memory to the acute effects of corticosteroids: A dose-response study in humans. *Behavioral Neuroscience, 113,* 420-430.

Magnusson, D. & Cairns, R.B. (1996). Toward a unified framework. In R. Cairns, G. Elder, & J Costello (Eds.), *Developmental science* (pp. 7-30). New York: Cambridge.

McEwen, B.S. (2000). The neurobiology of stress: From serendipity to clinical relevance. *Brain Research, 886,* 172-189.

McLeod, J.D. & Shanahan, M.J. (1993). Poverty, parenting, and child development. *American Sociological Review, 58,* 351-366.

McLoyd, V. (1998). Socioeconomic disadvantage and child development. *American Psychologist, 53,* 185-204.

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.

Meaney, M.J. & Szyf, M. (2005). Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome. *Dialogues in Clinical Neuroscience, 7,* 103-123.

Olds, D.L. (2002). Prenatal and infancy home visiting by nurses: from randomized trials to community replication. *Prevention Science, 3,* 153-172.

Panksepp, J., Burgdorf, J., Turner, C. & Gordon, N. (2003). Modeling ADHD-type arousal with unilateral frontal cortex damage in rats and beneficial effects of play therapy. *Brain and Cognition, 52,* 97-105.

Pennington, B.F. & Ozonoff, S. (1996). Executive functions and developmental psychopathology. *Journal of Child Psychology and Psychiatry, 37,* 51-87.

Pezawas, L., Meyer-Lindenberg, A., Drabant, E.M., Verchinski, B.A., Munoz, K.E., Kolachana, B.S., Egan, M.F., Mattay, V.S., Hariri, A.R., & Weinberger, D.R. (2005). 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nature Neuroscience, 8,* 828-8. 34

Radley, J.J., Rocher, A.B., Janssen, W.G., Hof, P.R., McEwen, B.S., & Morrison, J.H., (2005). Reversibility of apical dendritic retraction in the rat medial prefrontal cortex following repeated stress. *Experimental Neurology, 196,* 199–203

Ramey, C. T., & Campbell, F. A. (1991). Poverty, early childhood education, and academic competence: The Abecedarian experiment. In A. Huston (Ed.), *Children in poverty* (pp. 190-221) New York: Cambridge University Press.

Ramos, B.P. & Arnsten, A.F. (2007). Adrenergic pharmacology and cognition: Focus on the prefrontal cortex. *Pharmacology and Therapeutics, 113,* 523-536.

Repetti, R.L., Taylor, S.E., & Seeman, T.E. (2002). Risky families: family social environments and physical health of offspring. *Psychological Bulletin, 128,* 330-366.

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

Seamans, J.K., Floresco, S.B., & Philips, A.G. (1998). D1 receptor modulation of hippocampal-prefrontal cortical circuits integrating spatial memory with executive functions in the rat. *Journal of Neuroscience, 18,* 1613-1621.

Tan, H.Y., Chen, Q., Goldberg, T.E., Mattay, V.S., Meyer-Lindenberg, A., Weinberger, D.R., & Callicott, J.H. (2007). Catechol-O-methyltransferase Val158Met modulation of prefrontal-parietal-striatal brain systems during arithmetic and temporal transformations in working memory. *Journal of Neuroscience, 27,* 13393-13401.

van Praag, H., Kempermann, G. & Gage, F.H. (2000). Neural consequences of environmental enrichment. *Nature Reviews: Neuroscience, 1,* 191-198.

Vijayraghavan, S., Wang, M., Birnbaum, S.G., Williams, G.V., & Arnsten, A.F. (2007). Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. *Nature Neuroscience, 10,* 376-384.

Weaver, I.C. (2007). Epigenetic programming by maternal behavior and pharmacological intervention: Nature vs. nurture – let's call the whole thing off. *Epigenetics, 2,* 22-28.

Weaver, I.C., Cervoni, N., Champagne, F.A., D'Alessio, A.C., Sharma, S., Seckl, J.R., Dymov, S., Szyf, M., & Meaney, M.J. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience, 7*, 847-854.

Weinstock, M. (2001). Alterations induced by gestational stress in brain morphology and behavior of the offspring. *Progress in Neurobiology, 65*, 427-451.

Wyman, P.A., Cowen, E.L., Work, W.C., Hoyt-Meyers, L., Magnus, K.B., & Fagen, D.B. (1999). Caregiving and developmental factors differentiating young at-risk urban children showing resilient versus stress-affected outcomes: A replication and extension. *Child Development, 70*, 645-659.

Zelazo, P.D., Muller, U., Frye, D., & Marcovitch, S. (2003). The development of executive function in early childhood. *Monographs of the Society for Research on Child Development, 68*(3), vii–137.