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### Publication Date

2001-04-01

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Associations Between Physiological Reactivity and Children's Behavior: A Review and  
Empirical Demonstration of the Advantages of a Multi-System Approach

by

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B.A. (University of California Berkeley) 1994

M.S. (University of Stirling) 1996

Thesis submitted in partial satisfaction of the requirements for the degree of

Master of Science

in

Health and Medical Sciences

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, BERKELEY

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Spring 2001

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Spring 2001



## Acknowledgements

The thesis work reported here would not have been possible without the assistance of a diverse and wonderful group of people. First, I would like to thank the members of my thesis committee, Tom Boyce, Jodi Quas, and Bob Levenson. I was incredibly fortunate that Tom invited me to work in his lab; his wisdom and encouragement were instrumental to my completing this project. I am deeply grateful to have been given the opportunity to work with such a bright group as the group at the Child Study Center who shared their support and interest with me. I hope the future will provide the opportunity to continue this collaboration. In particular, I would like to thank Jodi Quas, who is not only a goddess, but whose dedication in helping me to conceptualize and carry out this project was heroic. Additionally, Abbey Alkon and Lauren Goldstein made a crucial contribution in collecting the data on which this project was based and graciously provided their assistance as this project unfolded. Finally, I am thankful for the assistance that Bob Levenson provided, and most importantly that he asked me questions that nobody else had.

The research upon which the empirical work reported is based was supported by grants from the MacArthur Foundation Research Network on Psychopathology and Development and the National Institute of Mental Health (R01-MH44340). Additional technical support came from the Endocrine Laboratory at the University of Minnesota, with the cooperation of Dr. Megan Gunnar and associates.

Finally, I would like to recognize the warmth and support from the entire JMP community, especially the staff, faculty, and my classmates, that has made this experience so rewarding.

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## Comments on the Impact of Mental Illnesses

*In modern life infections have diminished and nervous strains have increased ...The medical profession has not recognized in a practical way the recent shift in the etiology of disease.*

- Walter B. Cannon, Physiologist, Harvard Medical School  
(Cannon, 1936 pp. 1453-1455)

*The burdens of mental illnesses, such as depression, alcohol dependence and schizophrenia, have been seriously underestimated by traditional approaches that take account of only deaths and not disability.*

- Summary, The Global Burden of Disease project (Murray & Lopez, 1996 p. 3)

*Mental illness ... suddenly bulks very large indeed... [Mental problems] are as relevant in poor countries as they are in rich ones, and all predictions are that there will be a dramatic increase in mental problems in the coming years.*

- Dr. Gro Harlem Brundtland, Director-General, World Health Organization (Brundtland, 2000 p. 411)



## Background

A recent landmark study sponsored by the World Health Organization and Harvard University found that 5 of the top 10 leading causes of disability worldwide are psychiatric disorders (Murray & Lopez, 1996). Already substantial, the overall global burden of such conditions is projected to increase by nearly 50% over the next two decades (Murray & Lopez, 1996). There are at least 6 reasons why the burden of psychiatric conditions is so great, despite their relatively low mortality rates: they are prevalent worldwide; the onset is early in life; they often represent chronic conditions; they typically go untreated; they are extremely debilitating; and they predispose to risk-behaviors for other types of disease. Of the many strategies to reduce this burden, early intervention is promising because it addresses the early onset and the undertreatment of psychiatric conditions. However, more research is needed on early identification of children at risk in order to facilitate the implementation of targeted interventions (Kessler, 2000).

## Prevalence of Psychiatric Disorders

Epidemiological studies in the last decade have begun to uncover the staggering prevalence of psychiatric disorders in both developed and developing countries. Every month, it is estimated that more than one-sixth of Americans are affected by an anxiety, mood, or substance use disorder (WHO International Consortium in Psychiatric Epidemiology [WHO ICPE], 2000). The lifetime prevalence of these disorders in the United States is estimated to be 48.6%, a figure consistent with previous studies (WHO ICPE, 2000; see also Howard, Cornille, Lyons, & Vessey, 1996). Alarming, the World Health Organization suggests that the lifetime prevalence is increasing, as younger

cohorts evidence higher rates than older cohorts in all countries studied (WHO ICPE, 2000). Children are among those affected as well. Although fewer reliable statistics are available, published estimates are that prevalence among children is similar, with between one-fifth and three-fifths of children in the community having a diagnosable mental disorder (Costello et al., 1996; Giaconia, Reinherz, Silverman, & Pakiz, 1994; Shaffer, Fisher, Dulcan, & Davies, 1996).

#### Onset of Psychiatric Disorders

The median age of onset for anxiety disorders in six countries studied was under 15 years of age, with one-fifth of the cases being evident before age 10 (WHO ICPE, 2000). However, psychopathology is much less crystallized in children than adults, so precursors may be evident much earlier, especially for some classifications of disorders. For example, one study found that simple phobias had a peak risk period for onset of ages 2 through 5 years with a second peak at ages 10 and 11 (Giaconia et al., 1994). Earlier onset of psychiatric disorders (before 14 years of age) is also associated with an increased likelihood of having more than one disorder (Giaconia et al., 1994).

#### Chronicity of Psychiatric Disorders

Children with such disorders as major depression are at substantial risk of having continued psychopathology in adulthood (e.g., Bardone, Moffitt, Caspi, Dickson, & Silva, 1996; Rao, Ryan, Birmaher, & Dahl, 1995). Epidemiological evidence of disease chronicity comes from surveys showing a high ratio of 1-year to lifetime prevalence rates of mental disorders, indicating that most people with a disorder any time in their lives were bothered by symptoms within the preceding year (WHO ICPE, 2000). In addition to high rates of psychopathology, children with mental disorders may evidence serious

deficits in adjustment and accumulate negative outcomes across multiple domains of psychosocial functioning (Bardone et al., 1996). Compounding these problems, cases with early onset may be more severe or persistent than later-onset cases (Giaconia et al., 1994; WHO ICPE, 2000).

#### Lack of Mental Health Treatment

Despite effective treatments and a wide range of treatment modalities, patients with psychiatric disorders access treatment at much lower rates than other medical patients. Delays of 10 years or more from the onset of symptoms to the first service contact are common (WHO ICPE, 2000). Over 70% of adults with an active psychiatric disorder received no services in a 1-year period and only 13% received any services from mental health professionals (Regier, Narrow, Rae, & Manderscheid, 1993).

#### Disability Associated with Psychiatric Disorders

Psychiatric disorders make up a disproportionate share of the global disease burden because they are exceedingly debilitating. Acute psychosis and dementia were ranked among the most disabling of all diseases with unipolar major depression ranked equivalent to blindness and paraplegia (Murray & Lopez, 1996). In the United States, the Medical Outcomes Study found that the functional impairment associated with depression is comparable to or greater than impairment from such chronic medical conditions as diabetes, hypertension, or current arthritis or respiratory or gastrointestinal problems (Wells et al., 1989).

#### Risk Behaviors Associated with Psychiatric Disorders

Major health risk behaviors such as tobacco, alcohol, marijuana, and other drug use; domestic violence; and unsafe sexual practices are all common sequelae to childhood

mental disorders (Bardone et al., 1996; Bardone et al., 1998). Similarly, comorbidity between mental disorders and substance abuse is substantial (WHO ICPE, 2000). Girls with conduct disorder are likely to become women with substance abuse problems, multiple sex partners, and victims of domestic violence (Bardone et al., 1996; Bardone et al., 1998). Both conduct disorder and depression in adolescent girls have also been associated with multiple drug use, poor educational attainment, early pregnancy and childbearing and increased medical problems (Bardone et al., 1996; Bardone et al., 1998).

### The Present Study

The primary goal of the present study was to identify early biological indicators of psychopathology, a goal consistent with the aim of identifying children at risk so that early interventions can be facilitated. It has been suggested that identification of high-risk children is essential because the interventions necessary to prevent the progression of psychopathology are complex (Kessler, 2000). By augmenting current efforts to identify children based on early behavioral phenotypes, the current study was conducted to explore another mode of identification that may help target children most likely to benefit from intervention. Such interventions are important in reducing the long-term morbidity associated with mental illness.

An additional goal of the present study was to contribute to the stress physiology literature by enhancing understanding of the regulation of stress-response systems in children. Although the physiological effects of stress-response systems in the body have been known for much of the last century, their regulation is less understood. Furthermore, despite growing evidence that alterations in neuroendocrine responses to stress occur and are associated with behavior problems, few studies have considered the

possibility of interactions between physiological systems when predicting behavior problems. Ultimately, characterization of the physiological underpinnings of psychiatric disorders will reduce the stigma associated with psychiatric disorders, currently an enormous barrier to treatment. Therefore, the research reported here is intended to address several of the many issues underlying the immense global burden of psychiatric disorders. Before the study is described, an initial literature review is presented. The review focuses on the functions of the sympathetic-adrenal-medullary system and the hypothalamic-pituitary-adrenal axis in the stress response, their coordination, and their independent associations with behavior problems in children, and highlights directions for future research. The second paper consists of an empirical study conducted to determine whether studying the concurrent activation of these systems in response to stress would aid in early identification or yield new insights about the regulation of these systems in children with and without behavior problems.

**Associations Between Physiological Reactivity and Children's Behavior:  
Advantages of a Multi-System Approach**

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Abstract

The past decade has seen a notable increase in interest in the study of physiological correlates of behavior problems in childhood. A review of the literature demonstrates that disruptions in both sympathetic and adrenocortical regulation appear to be common among children with internalizing and externalizing behavior problems. The associations between such neuroendocrine alterations and behavior are discussed and their implications for the fields of stress physiology, neuroendocrinology, and developmental psychopathology are outlined. It is proposed that substantial advances can be made by investigating patterns of physiological responses among multiple, concurrent systems rather than individual response systems. Directions for future research are suggested.

Keywords: physiological reactivity; children; behavior problems.

### Overview

Over the past century, psychiatric diseases have ascended in importance as causes of morbidity and mortality in developed nations. Yet only in the past few years has the significance of psychiatric problems in developing countries been recognized. The Global Burden of Disease project, a collaborative effort sponsored by the World Health Organization and Harvard School of Public Health, for example, recently acknowledged the growing importance of psychiatric disorders as causes of morbidity and mortality by stating "in the developing regions where four-fifths of the planet's people live, noncommunicable diseases such as depression and heart disease are fast replacing the traditional enemies, such as infectious diseases and malnutrition, as the leading causes of disability and premature death" (Murray & Lopez, 1996, p. 1). Psychiatric disorders exert an enormous toll in both human and economic terms. As an example, they are among the most debilitating of all illnesses, globally estimated to account for 28% of all years of life lost to disability in 1990 (Murray & Lopez, 1996). The loss of life and functioning associated with psychiatric conditions worldwide is projected to increase by almost half by the year 2020, a greater proportionate increase than for cardiovascular disease (Murray & Lopez, 1996). Of great importance, therefore, is the need to identify causes and correlates of psychiatric disorders; such information is imperative to future intervention. One of the most consistent and powerful predictors of psychiatric disorders is psychosocial stress.

Unlike many chronic diseases, the onset of psychiatric disorders is often early in life (Giaconia, Reinherz, Silverman, & Pakiz, 1994; WHO International Consortium in Psychiatric Epidemiology, 2000), providing an opportunity for the development of



interventions targeting children who are potentially the most vulnerable to psychiatric problems. Traditionally, efforts aimed at identifying children at risk have focused on behavioral profiles that may be associated with later psychopathology, yet such early behavioral phenotypes are only moderately predictive of later psychopathology (e.g., Kagan, 1994). Therefore, in order to identify children at risk more effectively, other indicators of early risk must be identified; and examining psychobiologic responses to stressors may be a particularly useful approach because these responses are products of both individual (e.g., genetic, biological, psychological) and environmental variables (e.g., intensity of stressful exposure). Thus, they may provide insight into individual differences in the meaning of stressful events among children, potentially accounting for some of the noted differences in susceptibility to the adverse effects of stress (Jemerin & Boyce, 1990). Consequently, the study of psychobiological reactivity represents a promising direction that may aid in identifying children at high risk for psychopathology.

Recently, studies have identified some alterations in both the sympathetic-adrenal-medullary (SAM) and hypothalamic-pituitary-adrenal (HPA) systems, two major physiological stress response systems, that are predictive of behavior problems in children and adolescents. However, possible interactions between these systems have not yet been explored, despite there being theoretical reasons to expect such interactions may reveal greater insight into the role that physiological stress systems play in the emergence of psychopathology. The purpose of the present paper is to explore how the sympathetic and adrenocortical axes are related to behavior problems in children, the implications of such associations, and directions for future research. First, an overview of the biological response to stress is provided including the independent actions of the SAM and HPA

systems and the concurrent actions of these systems; second, empirical studies investigating associations between these systems and children's behavior are described; and third, directions for future research are outlined.

### The Biology of the Stress Response

For much of the past century, it has been recognized that biological alterations occur in the face of exposure to stress, such alterations can be long-lived, and disease can result from such physiological changes (Cannon, 1936). The term "allostasis" has been introduced to describe the achievement of stability through change that allows adaptation to alterations in both internal and external environments through activation of physiological systems (Sterling & Eyer, 1988). Rather than proposing a fixed setpoint for physiological parameters as implied by the homeostatic model, allostasis incorporates the constant fine-tuning of multiple physiological systems controlled by neural and neuroendocrine circuits to meet minute-to-minute changes in the needs of an organism. This flexibility in response patterns is an essential feature of complex systems and has been described as the "loose coupling" of biological systems (Glassman, 1973). When an organism is subjected to arousing stimuli for prolonged periods, accommodation to these demands exacts a physiological burden, termed "allostatic load" (McEwen, 1998; McEwen & Stellar, 1993). Specifically, allostatic load refers to:

the strain on the body produced by repeated ups and downs of physiological response as well as by the elevated activity of physiologic systems under challenge, and the changes in metabolism and the impact of wear and tear on a number of organs and tissues [that] can predispose the organism to disease (McEwen & Stellar, 1993, p. 2094).

McEwen (1998) has described four response patterns that lead to allostatic load. First, exposure to multiple stressors over time can result in recurrent activation of the stress-response, thus creating allostatic load. Second, allostatic load accumulates when individuals fail to adapt to repetitive stressors. In this case, rather than having stress responses that attenuate after repeated exposures, every time the individual encounters the stressor, the magnitude of the stress response is as great as the first time. A third response pattern leading to allostatic load involves a failure of recovery, which is manifest as persistent or chronic activation after exposure to a single stressor rather than a relatively quick return to resting function. Finally, insufficiency of the stress-response resulting in compensatory hyperactivity of other mediators can also contribute to allostatic load (McEwen, 1998).

Because activation of stress-response systems is both costly in terms of energy expenditure and potentially damaging in excess, any of the aforementioned maladaptive responses can increase the physiological burden faced by the individual and, over time, such maladaptive responses to environmental stressors can negatively impact health (McEwen, 1998). From the perspective of conserving energy, the catabolic activities of stress-response systems are inefficient. Energy is required to break down macromolecules, which then must be replaced, a process that also requires energy. An analogy that has been proposed is that of repeatedly depositing and withdrawing money from a savings account and being charged a fee for every transaction (Sapolsky, 1994). Overactivation of stress-response systems can be directly harmful to an organism as well. For example, although both clotting and scarring are necessary processes to heal wounds, both of these actions are undesirable in excess, being the pathophysiological processes

responsible for deep venous thrombosis and liver cirrhosis, respectively. Such costs associated with activation of stress response systems are acceptable when activation of these systems occurs only occasionally and in the face of life-threatening stressors, as was characteristic during the period when evolutionary forces shaped the organization of these systems. For the majority of the history of *Homo sapiens* as a species, the predominant stressors were physical or physiological in nature (Sapolsky, 1994). Humans are adapted to respond to stressors such as starvation, injury, and the physical challenges associated with hunting prey and escaping predation. Yet these stressors no longer predominate in modern society. Current stressors are frequently psychological, economic, and interpersonal. Stress-response systems distinguish little between these stressors; systems will become activated regardless of whether the stressor is a snake attack or a bounced check. Stress-response systems that were adapted in an environment where stressors were catastrophic, but perhaps infrequent, are now activated routinely, chronically, and possibly inappropriately (Sapolsky, 1994). Such excessive activation of stress-response systems can lead to dysregulation of these systems and contribute to the pathogenesis of disease, including psychiatric disorders (Cannon, 1936; McEwen, 1998; Sapolsky, 1994).

Despite the potential for disease and disorders to result from chronic stress, however, individuals differ in their responses and susceptibility to negative consequences. Variability in physiological response to stress may derive from individual differences in baseline arousal, reactivity to stressors, recovery from arousal, or other parameters of stress responses. Before exploring how differences in patterns of activation may be associated with behavior, it is important first to summarize what is

known about the roles of the sympathetic and adrenocortical systems in the stress response and their coordination.

### Sympathetic-Adrenal-Medullary System

Walter Cannon (Cannon, 1914; 1929/1953), an early investigator in the field of stress physiology, first described the role of the sympathetic-adrenal-medullary (SAM) system in the stress response. Sympathetic activation throughout the body is responsible for a host of effects commonly referred to as the "fight or flight" response. These actions include enhancing cardiovascular tone, respiratory rate, blood flow to skeletal muscles, and elevating blood glucose while diminishing vegetative functions such as digestion (Cannon, 1914; 1929/1953). Preganglionic sympathetic fibers synapse primarily in the paravertebral ganglia where they connect with numerous postsynaptic fibers that innervate the visceral organs, thus forming the anatomic substrate for signal divergence. This arrangement allows a virtually instantaneous but short-lived signal to be carried to target organs throughout the body, permitting the fast, diffuse actions characteristic of this system (Cannon, 1914; 1929/1953). In addition, through the sympathetic innervation of chromaffin cells in the adrenal medulla, stored catecholamines (primarily epinephrine, or adrenaline, but also norepinephrine, or noradrenaline) are released directly into the bloodstream, capable of acting as hormones. Acting through membrane-bound second messenger systems, these hormones extend the duration of sympathetic effects through rapid but still relatively short-lived changes at the cellular level (Cannon, 1914; 1929/1953; 1939). The sympathetic nervous system is controlled centrally by noradrenergic neurons in the locus coeruleus. In addition to descending pathways, this nucleus projects widely throughout the cortex.

Whether or not sympathetic activation occurs in response to a stimulus depends in part on the type of stressor and in part on the individual. Several studies have found that in lab tasks designed to require high effort, both males and females showed increases in sympathetic activation (Frankenhaeuser, Lundberg, & Forsman, 1980; Lundberg & Frankenhaeuser, 1980; Peters et al., 1998). Elevated sympathetic reactivity thus may be most likely to occur among "overachievers" who tackle every challenge with maximal effort. Such increased reactivity and attendant risk for cardiovascular disease is seen among individuals with a Type A personality profile (see Jemerin & Boyce, 1990), a profile characterized by competitive striving, hostility, and time urgency. Henry (1992) has described SAM activation as a "defense reaction," that is, an active, effortful response to challenges that are manageable or controllable. Characteristics of both the situation and the individual can influence whether such a defense reaction is mounted when an individual is confronted with a challenge.

#### Hypothalamic-Pituitary-Adrenal Axis

Within a few decades of Cannon's discoveries, another pioneer in stress research, Hans Selye identified the role of the hypothalamic-pituitary-adrenal (HPA) axis in the stress response (Selye, 1950). In contrast to the quick-acting catecholamine products of the SAM system, the primary effectors of the HPA axis, glucocorticoids (GCs), are steroid hormones. They have a relatively slower onset and longer duration of action, since GCs must be synthesized *de novo* on demand and act through effects on gene transcription and resulting protein synthesis. The anterior pituitary hormone, adrenocorticotrophic hormone (ACTH), stimulates release of cortisol, the primary

glucocorticoid in humans. Release of ACTH is stimulated by corticotrophin releasing hormone (CRH) from the hypothalamus and other factors.

As with sympathetic activation, situational and psychological factors predict whether or not adrenocortical activation occurs in response to a challenge. HPA axis activation is especially likely to occur in situations that are uncontrollable (Frankenhaeuser et al., 1980; Lundberg & Frankenhaeuser, 1980; Peters et al., 1998). Individuals who tend to perceive challenges as unpredictable or threatening or feel they lack the resources to manage threats may, thus be most likely to show elevated adrenocortical responses to challenge (Gunnar, Tout, de Haan, Pierce, & Stansbury, 1997; Henry, 1997; Kirschbaum & Hellhammer, 1994). Likewise, adrenocortical activation may be more likely when there is high ego-involvement or the outcome is especially important (Gunnar et al., 1997; Kirschbaum & Hellhammer, 1994). Persistent feelings of lack of control and overwhelming threat, as occurs in unipolar major depression, for example, are also associated with heightened adrenocortical activity. In contrast to the "defense reaction", Henry (1992) has described adrenocortical activation as a "defeat reaction", a passive response pattern characterized by emotional distress, behavioral withdrawal or avoidance, and loss of control. Overall, then, adrenocortical activation appears to occur when individuals become emotionally distressed when confronted with situations judged to be overwhelming or unmanageable.

A few researchers have studied SAM and HPA activity concurrently to characterize when these systems become jointly activated, although to-date, the predictors of SAM and HPA activation have only been studied in adults. In one such study, university students participated in a series of laboratory tasks that varied in their

challenge or stressfulness. Self-reports of subjective responses and urinary catecholamines and cortisol from each task were then subjected to factor analysis, with two factors emerging. The first factor, termed "distress" was comprised of boredom, impatience, irritation, a lack of interest, and low norepinephrine. The second factor, "effort" was comprised of heightened mental concentration and tenseness, high epinephrine, low norepinephrine and low cortisol. In particular, a dissociation between sympathetic and adrenocortical function was noted between a task experienced as effortful alone and a task experienced as both effortful and distressing, such that participants demonstrated high SAM but low HPA activation in the former task but SAM and HPA coactivation in the latter task (Lundberg & Frankenhaeuser, 1980). Whether or not these response patterns reflect problem-focused versus emotion-focused coping strategies has not been studied, but is clearly a possibility (Step toe, 1991). Therefore, despite both of these systems being described as stress-response systems, results of a few studies in adults suggest that activation of the sympathetic versus adrenocortical systems occurs in response to somewhat distinct situational and psychological demands. Such differential activation allows for the possibility that these systems could become dissociated when one system is preferentially activated. In theory, there may be a prototypical stress response that has evolved to meet the demands common to physical stressors and is characterized by a given pattern of SAM and HPA activation. Deviations from this pattern may occur when an individual confronts a psychological (as opposed to physical) stressor and conditions favor greater activation in one system than the other. Likewise, altered neuroendocrine response patterns may occur when individuals are subject to situations that increase allostatic load, for example, chronic or repeated stress.



### Coordination of SAM and HPA Activity in the Stress Response

Although described over a half-century ago, the precise role of each of these systems and their coordination remains a topic of intense study and debate. Despite recent evidence suggesting that the SAM and HPA systems are activated in response to somewhat different types of stressors, it has long been assumed that the SAM and HPA systems worked in alliance in generating the physiological changes associated with the stress response. For example, the actions of catecholamines and GCs increase circulating glucose levels. Glucocorticoids are also known to sensitize the myocardium to the effects of circulating catecholamines (see Sapolsky, Romero, & Munck, 2000).

Although it is well established that SAM activity mediates the initial response to stress, in the last two decades, a different perspective has emerged as to the role of GCs in the stress response. Munck and colleagues (Munck, Guyre, & Holbrook, 1984) first suggested that GCs are important in suppressing the initial stress response, largely mediated by catecholamines. This type of association is not unknown in biological systems, with examples including the action potential and the clotting cascade. In both cases, the same stimuli that activate the initial response (opening sodium channel activation gates, cleavage of fibrinogen into fibrin) also activate a delayed suppressor (closing of the sodium channel inactivation gates, activation of plasminogen to plasmin to lyse clots) necessary to restore the system to its resting state. From this perspective, Munck and colleagues argued that the role of the HPA axis is to protect the organism from damage that could be incurred if the body's normal responses to stress go unchecked and the body does not return promptly to its resting state. Thus, not only can external stressors perturb the balance of physiological activity, but the body's own activities can

provide internal threats to this balance, a concept recognized early on by Cannon (1939). If the SAM system is capable of generating such a threat, this would suggest that an adaptive response would require concurrent activation of the SAM and HPA systems in the stress response and that activation asymmetries would be maladaptive, a prediction yet to be tested empirically in adults or children.

Elaborating on Munck et al.'s (1984) thesis, Sapolsky and colleagues (e.g., Sapolsky et al., 2000) outlined four roles that GCs fulfill in the stress response. The authors describe actions as preparative, permissive, stimulatory, or suppressive. Preparative actions assist an organism in preparing for subsequent stressors. Permissive effects, due to pre-stress circulating GCs, augment the body's initial (i.e., catecholamine-mediated) response to stress. Stimulatory actions, attributable to stress-induced increases in GCs, are not manifest for at least an hour after the onset of a stressor. Like permissive effects, they enhance the stress response, albeit at a slightly longer delay. Like SAM activity, all three of these actions, therefore, help to augment the stress response. The fourth potential role, however, involves the stress-induced high levels of GCs acting to restrain the stress response and prevent additional disruptions caused by an excessive initial response. Acting in this manner, GCs may exert effects that oppose the sympathetically-mediated changes occurring early in the stress response. In the domains of cardiovascular function, fluid homeostasis, metabolism, and immune function, GCs appear to perform all four of these functions in various combinations in ways that are specific to the target in question (Sapolsky et al., 2000). Therefore, as opposed to having a single role as activator or suppressor, the actions of GCs appear to be situation and organ-specific. Because the joint activation of stress-response systems has not been

studied in relation to behavioral outcomes, it remains unknown which of the above roles may be fulfilled by GCs and how such actions are associated with or influence behavior.

Understanding the neural substrates that contribute to activation of both or one or the other of the SAM and HPA systems may ultimately aid in clarifying the purpose of the diverse, complex actions of these systems in coping with stressors. Centrally, there are mutual influences of each of the SAM and HPA systems on the other. Specifically, hypothalamic CRH neurons and noradrenergic neurons have shared inputs. Both systems are activated by serotonergic and cholinergic systems and inhibited by GCs, gamma amino butyric acid (GABA), ACTH, and opioid peptides (see Stratakis & Chrousos, 1995). That these systems have shared inputs suggests that they can become activated in response to similar stimuli. Additionally, there are reciprocal neural connections between CRH and catecholaminergic neurons (see Stratakis & Chrousos, 1995), thus providing an anatomic substrate for coordination of their activities and potential functional interactions between these systems. The existence of neural connections between these systems implies that central coordination is important in orchestrating an effective response to a given stressor. Interactions between these systems in the periphery may reflect this underlying neural structure; therefore investigation of peripheral biological changes in response to stress may suggest whether efficient central coordination is occurring. Pathological processes that disrupt central regulation of the stress response may be important etiologic agents in both stress-related medical diseases and psychiatric disorders.

Despite the central coordination of the SAM and HPA axes and the fact that both systems become activated in response to stress, there are surprisingly few significant

relations between the activity of these systems in the periphery. For example, van Goozen et al. (1998) found no significant association between cortisol responsiveness and heart rate or systolic blood pressure responsiveness among boys. Likewise, Henry et al. (1992) found that in nondepressed former alcoholic men, 24-hr urinary MHPG (a catecholamine metabolite) was unrelated to resting plasma ACTH or cortisol. On the surface, studies of peripheral activation may conclude that these systems are not well coordinated. However, given the evidence for emotion-specific physiological processes in both children and adults (e.g., Eisenberg et al., 1988; Ekman, Levenson, & Friesen, 1983; see review in Davidson et al., 1994), it could be argued that peripheral activation is well coordinated but specific to demands associated with given emotions or situations. Low overall correlations between peripheral responses may obscure regularities that are highly attuned to unique characteristics of given situations. Furthermore, characteristic patterns of peripheral responses may occur among subgroups of individuals, yet be obscured in heterogeneous samples. Therefore, gaining a better understanding of the patterns of activation and their behavioral correlates may shed new insight into why peripheral correlations are typically low. Likewise, whether the SAM and HPA axes operate in alliance or in opposition with respect to behavior has not been studied in either adults or children. Therefore, examination of this piece of fundamental stress physiology represents an important, but heretofore neglected area that has implications for the organization of stress response systems.

Several investigators have attempted to account for the findings that SAM and HPA activation do not necessarily occur in response to the same stimuli (e.g., Henry, 1997; Lovallo, Pincomb, Brackett, & Wilson, 1990). One model contends that there are

innate individual differences in sympathetic reactivity and that, among those with high sympathetic reactivity, differences in the motivational components of stressor (aversive versus appetitive) determine whether the HPA axis is activated (Lovallo et al., 1990). Several studies provide support for this hypothesis. For instance, cortisol responses to aversive laboratory stressors occur only among men with high heart rate reactivity (Lovallo et al., 1990; Sgoutas-Emch et al., 1994). Additionally, among women, cortisol increases following exposure to a stressor correlated with sympathetic reactivity but not heart rate or parasympathetic reactivity (Cacioppo et al., 1995; Uchino, Cacioppo, Malarkey, & Glaser, 1995). These findings suggest that adrenocortical activation would not be elevated without an elevation in sympathetic activity, thereby implying that a pattern of high adrenocortical but low sympathetic reactivity is unlikely to occur. A second model contends that norepinephrine secretion increases to meet challenges. However, when uncertainty about control prevails, anxiety sets in and epinephrine and cortisol rise (Henry, 1997). This latter model may be somewhat more flexible than the former in accounting for different patterns of activation as a function of stimulus intensity. In particular, at high stimulus intensity, declining sympathetic function may accompany increasing adrenocortical activation, suggesting that high HPA with low SAM activation could occur in addition to other neuroendocrine patterns (e.g., concurrent low or high activation, high SAM and low HPA activation). Although the aforementioned ideas remain intriguing possibilities that have implications for the roles of these stress-response systems, there remains little empirical data assessing joint functioning of the SAM and HPA axes. However, these models provide testable predictions about when certain patterns of SAM and HPA activation should occur,

predictions whose outcomes could guide future research efforts aimed at understanding the mechanisms underlying the role of stress-response systems in psychiatric problems and designing intervention strategies to reduce the negative consequences of stress.

### Physiological Correlates of Behavior Problems in Children

Although much remains to be elucidated with respect to the functions of the SAM and HPA axes, over the past decade, researchers have begun to examine behavioral correlates of activation of these systems in children. A few studies are longitudinal in design; most are cross-sectional or case-control studies. Consequently, little is known about the causal factors that underlie associations between peripheral physiological measures and behavior. Among children, two broad categories of behavior have been studied: externalizing and internalizing behaviors. Externalizing symptoms include behaviors problems such as physical and verbal aggression, vandalism, lying, and cheating. Internalizing symptoms include behavior problems such as avoidance, social withdrawal, and worrying, and feelings of inferiority, sadness, and fear. Although the two general types are typically treated as orthogonal, particularly in studies of physiological correlates of such problems, some studies have found that these symptoms are moderately related in young children (e.g., Essex et al., submitted; Keiley, Bates, Dodge, & Pettit, 2000).

### Physiological Correlates of Externalizing Symptoms

Although researchers have examined physiological correlates of externalizing problems, results have been mixed, especially with regard to associations with HPA axis activity. Low sympathetic activation has been linked to externalizing, aggressive, or disruptive behaviors in children (Boyce et al., in press; Dobkin, Tremblay, & Treiber,

1998; Raine, Venables, & Williams, 1990; van Goozen et al., 1998). In particular, boys with oppositional-defiant disorder have lower resting heart rates than comparison boys (van Goozen et al., 1998). Likewise, in a prospective study of adolescents, heart rate reactivity and electrodermal arousal were lower among those boys who were convicted of a crime within the following nine years compared to those who had no convictions during that time (Raine et al., 1990). Low autonomic reactivity has also been found in nonclinical samples among children high in externalizing behaviors compared to children low in externalizing behaviors (Boyce et al., in press). Finally, Dobkin et al. (1998) found that adolescents low in systolic blood pressure reactivity were twice as likely to score high on a measure of risk-taking than boys higher in blood pressure reactivity. Together, these studies suggest that low levels of autonomic arousal, particularly in the sympathetic branch while resting or during times of potential stress, appear to be associated with increased externalizing behavior problems.

A similar behavior profile has been found in association with low adrenocortical activation. Compared to children with higher cortisol, lower cortisol levels are associated with hostility toward teachers and severity of conduct disorder (Tennes & Kreye, 1985; Vanyukov et al., 1993). Similarly, when compared to children without psychiatric disorders, children with oppositional-defiant disorder or conduct disorder have lower cortisol levels, as do boys with a paternal history of either conduct disorder or antisocial personality disorder (Pajer, Gardner, Rubin, Perel, & Neal, 2001; van Goozen et al., 1998; Vanyukov et al., 1993). Likewise, cortisol reactivity and externalizing behaviors are negatively related in boys (Tout, de Haan, Campbell, & Gunnar, 1998). The association between externalizing behaviors and reduced cortisol responsivity to stressors

may be especially prominent among boys with low levels of anxiety (van Goozen et al., 1998). Importantly, however, a few studies have reported no association between cortisol and antisocial behavior (e.g., Kruesi, Schmidt, Donnelly, Hibbs, & Hamburger, 1989), and thus, although further research is needed to determine when and in whom externalizing behaviors are associated with low adrenocortical activity, it appears that underactivity in this system, like the SAM system, may be associated with externalizing behaviors. Based on these findings, one might expect that children who evidence low reactivity in both the sympathetic and adrenocortical systems would have the most externalizing behavior problems. To date, however, a paucity of empirical research exists concerning concurrent SAM and HPA activity and externalizing symptoms in children.

#### Physiological Correlates of Internalizing Symptoms

In contrast to externalizing behaviors, internalizing behaviors have been associated with high sympathetic and adrenocortical activation in children, although again, relatively few studies of concurrent activation in both systems and internalizing behaviors have been conducted. Among adolescent boys, anxiety was positively associated with systolic blood pressure reactivity (Dobkin et al., 1998). Compared to uninhibited children, inhibited children show greater sympathetic activation, indexed by greater pupillary dilation in response to cognitive challenges at age 5.5 years and greater postural reflex tachycardia at age 7.5 years (Kagan, Reznick, & Snidman, 1988). In children 6 to 7 years of age with high levels of internalizing behaviors, high autonomic reactivity was evidenced only in the parasympathetic arm of the autonomic nervous



system, suggesting its actions may be important in this group of children (Boyce et al., in press).

Several studies, although not all, have similarly suggested that exaggerated adrenocortical activity is associated with internalizing behaviors. For instance, at 5.5 years of age, inhibited children were found to have higher morning cortisol levels than uninhibited children (Kagan et al., 1988). Likewise, socially wary 4-year olds had higher morning cortisol levels than less wary children (Schmidt, Fox, Rubin, & Sternberg, 1997). The association between cortisol and inhibition appears to persist over time: for instance, infants classified as behaviorally inhibited at 14 months had somewhat higher cortisol levels at 4 years than infants classified as uninhibited (Schmidt et al., 1997). Compared to boys low in anxiety, among highly anxious boys, cortisol increases during stress (van Goozen et al., 1998). Yet some studies reveal a positive association between cortisol reactivity and social competence suggesting the association between cortisol and behavior may be more complex (Gunnar et al., 1997; Hart, Gunnar, & Cicchetti, 1995). However, consistent with other studies, during periods of social stability, high cortisol reactivity was noted among children who were less outgoing and observed to partake in more solitary and negative behaviors (Gunnar et al., 1997). Thus, associations between cortisol and social competence may occur only in certain social contexts. Contextual factors may provide important cues to individuals about the nature of a potential threat. Alternately, perceptions of a stressor or challenge may vary in different contexts when different resources are available to an individual who then has different perceptions of her or his competence. Through mechanisms such as these, social context appears important in interpreting associations between physiology and behavior. This is likely

true for externalizing behaviors as well as internalizing behaviors, although the effects of context on associations between externalizing behaviors and physiology have not been examined. Notwithstanding the effects of context, given the findings of elevated sympathetic and adrenocortical activity in children with internalizing problems, one might predict that children highly reactive along both axes have the most internalizing problems, again an untested prediction.

Whereas a number of studies have investigated associations between behavior problems and either sympathetic or adrenocortical activity in children, virtually none has investigated the concurrent activity of these two systems in predicting behavior problems. In the few studies that have measured activity in both systems, they are generally treated independently such that potentially important interactions between the physiological systems have not been explored (e.g., Kagan et al., 1988; van Goozen, Matthys, Cohen-Kettenis, Buitelaar, & van Engeland, 2000). Therefore, it remains unknown how the concurrent activity in these two systems is associated with risk for behavior problems in children or whether risk for behavior problems is better predicted by the levels of activity in each system independently or by patterns of activation across both systems.

#### Joint Activation and Psychopathology

A small number of studies has examined associations between joint activation of the SAM and HPA systems and psychopathology in adults. In these studies, altered patterns of neuroendocrine responses have been found, thus suggesting dysregulation of the SAM and HPA systems, possibly as a result of stressful experience. Specifically, an elevated ratio of norepinephrine to cortisol occurs in women with premenstrual dysphoric disorder, veterans with post-traumatic stress disorder, and men with alexithymia (Girdler

et al., 1998; Henry et al., 1992; Mason, Giller, Kosten, & Harkness, 1988). This profile of neuroendocrine response is consistent with the observation that cortisol responses adapt more rapidly than catecholamine responses when chronically stimulated (Rose, 1980). Administration of the glucocorticoid agonist, dexamethasone inhibits HPA responses but not SAM responses to stress (Malarkey, Lipkus, & Cacioppo, 1995), thus raising the possibility that GC feedback inhibition of CRH may be important in generating this neuroendocrine profile. Although more research is needed to determine the prevalence of such neuroendocrine dysregulation in both adults and children who manifest different types of psychopathology, these studies suggest that certain neuroendocrine profiles may emerge in response to chronic stressful experience and can be identified as components of behavioral syndromes.

#### Directions for Future Research

Interest in the study of psychobiological correlates of behavior problems in children has expanded considerably in recent years. Although some studies have taken a multi-system approach to investigating physiological variables, none has taken an interactive approach. That is, each physiological variable has been treated as an independent predictor without consideration of the biological context in which it occurs. However, by their nature, physiological systems interact. Therefore, the use of single physiological variables in assessing risk for behavior problems is bound to be of limited utility, and assessments of multiple physiological systems in children at high and low risk for behavior problems is in need of investigation.

At present, it is unknown whether peripheral physiological measures somehow cause alterations in behavior, whether they represent the outcomes of disordered

behavior, or whether both are outcomes of central processes that have gone awry. Therefore, investigation of the continuity or change in physiological reactivity across development and in response to environmental changes would be worthwhile. While developmental changes have not been a primary focus of this paper, given that physiological processes are known to change with age, the study of developmental trends in physiological reactivity is warranted. For example, circulating GCs may have opposing effects on brain development at different points in development (see McEwen, 1999). Developmental changes are particularly important in light of evidence that early exposure to stress can have effects on neuroendocrine function that last a lifetime and may be behaviorally transmitted to future generations (for a review, see McEwen, 1999). Accordingly, how the SAM and HPA systems mature over childhood and reciprocally influence and are affected by stress reactivity is an area ripe for investigation.

Although peripheral physiological processes can feed back and have effects on neural processes, both behavior and peripheral physiology can be viewed as products as well, and the central mechanisms that underlie both of these products are poorly defined. In particular, although a moderate amount of knowledge has accumulated about central pathways mediating the stress response via the SAM and HPA axes, little is known about how centers controlling affect or behavior influence these pathways. With the advent of rapid functional brain imaging techniques, direct investigation of central activity in response to stress and among children with and without behavior problems is warranted.

### Conclusions

Mounting evidence demonstrates that alterations in sympathetic and adrenocortical function occur in children with behavior problems. Although research is

needed to address the direction of causality of these changes, it is probable that these alterations represent physiological manifestations of central dysregulation that underlie and possibly contribute to behavior problems. By focusing on patterns of neuroendocrine response rather than single peripheral correlates, advances can be made in understanding how regulation or dysregulation of the stress response relates to children's behavior. From a theoretical perspective, this knowledge will contribute to understanding of the roles of different physiological systems in the stress response. Of equal significance, from a clinical viewpoint, insight into physiological correlates of behavior problems and potentially subsequent psychopathology may add considerably to the predictive capacity of early behavior phenotypes in identifying children at increased risk for psychiatric disorders. Such identification is a necessary component of targeted interventions that hold the promise to reduce the considerable morbidity associated with untreated psychiatric problems.

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**Concurrent Sympathetic and Adrenocortical Activity as Predictors of Behavior in  
Middle Childhood**

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The research upon which this paper is based was supported by grants from the MacArthur Foundation Research Network on Psychopathology and Development and the National Institute of Mental Health (R01-MH44340). Saliva samples were assayed by the Endocrine Laboratory, University of Minnesota, with the cooperation of Dr. Megan Gunnar and associates.

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### Abstract

Studies of the associations between psychobiological risk factors and behavioral outcomes in children have most often relied upon single or serial measures of physiological systems. The present study, however, explores concurrent activation in two psychobiological response systems -- the sympathetic-adrenal-medullary and the hypothalamic-pituitary-adrenal axis in predicting internalizing, externalizing, and ADHD symptoms in children 4 to 8 years of age. Goals were (1) to assess whether distinct neuroendocrine profiles were associated with risk for behavior problems, and (2) to examine whether patterns of concurrent sympathetic and adrenocortical activation differed among children at high and low risk for behavior problems. Cardiovascular indicators of autonomic reactivity were recorded while 118 children completed a series of challenging and standardized laboratory tasks. Salivary cortisol was measured before and after tasks. Results indicated that interactions between the activity of these systems are more strongly related to behavioral outcomes than absolute levels of single system activation, that patterns of activation differ according to risk status, and that children at risk for different types of behavior problems share similar neuroendocrine profiles. Findings have implications for understanding the regulation of sympathetic and adrenocortical systems in children and for future studies of psychobiological risk factors for developmental psychopathology.

Keywords: sympathetic nervous system; hypothalamic-pituitary-adrenocortical axis; children; behavior problems; developmental psychopathology.

### Background

Dysregulation of stress response systems can lead to long-term medical and psychiatric disorders, a problem exacerbated by the mismatch between modern lifestyles and those predominant over the millennia in which evolutionary forces shaped the human stress response (Cannon, 1936; McEwen, 1998; Sapolsky, 1994). When activation of stress response systems is inordinate and potentially inappropriate, a physiological burden termed "allostatic load" may be exacted; because allostatic load may build over an individual's lifetime, some diseases related to stress may become most evident later in life (McEwen, 1998; McEwen & Stellar, 1993). As a consequence, children have often been overlooked in the study of physiological responses to stress, a deficit that is particularly troubling given recent evidence suggesting that exposure to stress prenatally and early in postnatal life can have lasting effects on the body's capacity to respond effectively (e.g., Meaney et al., 1996; Weinstock, 1997; see also McEwen, 1999). Identification of children at risk for early psychopathology represents an important early intervention strategy, but the use of children's behavior as the only indicator of early risk is insufficient for identifying those likely to have long-term problems. As a complementary approach, the study of psychobiological factors associated with risk for psychopathology is a promising direction (e.g., Johnston-Brooks, Lewis, Evans, & Whalen, 1998).

The present study examines the role of children's physiological response to stress as a predictor of early psychopathology. Focussing on both the sympathetic-adrenal-medullary (SAM) and the hypothalamic-pituitary-adrenal (HPA) axes, two major neuroendocrine systems involved in the stress response, the study attempts to identify peripheral indicators of central dysregulation that may occur in children with behavior



problems. Although several studies have measured activity in one or the other system, few have examined the response of both systems concurrently in relation to behavior problems in children. Thus, goals were twofold: to assess whether children grouped according to neuroendocrine profiles were distinguishable on behavioral outcomes and to examine whether children with and without behavior problems differed in patterns of activation within these two systems. Such differences in patterns of concurrent reactivity in the periphery, if present, would begin to elucidate the complex central mechanisms that may underlie the stress response because alterations in the periphery may reflect changes in the brain.

Although described over a half-century ago, the precise roles of each of these systems and their coordination remain a topic of intense study and debate. It has long been assumed that the sympathetic-adrenal-medullary and HPA systems work in concert in generating the physiological changes associated with the stress response. For example, the actions of both catecholamines and glucocorticoids increase circulating glucose levels, glucocorticoids sensitize the myocardium to the effects of circulating catecholamines, and both inhibit reproductive physiology and behavior (see Sapolsky, Romero, & Munck, 2000).

In the last two decades, however, it has been suggested that the roles of these systems may be more distinctive and complex. Munck and colleagues (Munck, Guyre, & Holbrook, 1984) first suggested that catecholamines and glucocorticoids may have opposing effects, with catecholamines mediating the initial stress response and glucocorticoids suppressing these effects. This type of complementarity is not unknown in biological systems. For example, in both the action potential and the clotting cascade,

the same stimuli that activate the initial response (opening sodium channel activation gates or cleavage of fibrinogen into fibrin) also activate a delayed suppressor (closing of the sodium channel inactivation gates or activation of plasminogen to plasmin to lyse clots) necessary to restore the system to its resting state. From this perspective, the SAM and HPA axes would be serving complementary functions, both needed to restore homeostasis, first threatened by the stressor, then threatened if the body's response continued unrestrained. This would suggest that an adaptive response would require concurrent activation of the SAM and HPA systems in the stress response and that activation asymmetries would be maladaptive, a prediction yet to be tested empirically in children.

#### Physiological Predictors of Externalizing Behaviors

Researchers have yet to investigate associations between concurrent sympathetic and adrenocortical activity and behavior problems. When these systems have been studied independently, associations between either SAM or HPA activity and behavior problems in children have been found, although the results have varied as to whether high or low activation is associated with adverse outcomes. For instance, several studies suggest that low levels of sympathetic or adrenocortical activation are linked to externalizing, aggressive, or extroverted behaviors in children (Boyce et al., in press; Dobkin, Tremblay, & Treiber, 1998; Pajer, Gardner, Rubin, Perel, & Neal, 2001; Raine, Venables, & Williams, 1990; Tennes & Kreye, 1985; Tennes, Kreye, Avitable, & Wells, 1986; van Goozen et al., 1998; Vanyukov et al., 1993). Low autonomic reactivity (typically the difference between post-stress and pre-stress values of a parameter) has also been found among boys with oppositional-defiant disorder, adolescent offenders, and

nonclinical children high in externalizing behaviors (Boyce et al., in press; van Goozen et al., 1998; Raine et al., 1990). Likewise, adolescent boys who exhibit low systolic blood pressure reactivity are more likely to be rated by teachers as disruptive than boys who are high in reactivity (Dobkin et al., 1998). Similarly, within the HPA system, low cortisol levels are associated with aggression toward peers, hostility toward teachers, conduct disorder symptoms, and oppositional-defiant disorder (Pajer et al., 2001; Tennes & Kreye, 1985; Tennes et al., 1986; van Goozen et al., 1998; Vanyukov et al., 1993). In contrast, some studies have reported no association between cortisol and antisocial behavior (Kruesi, Schmidt, Donnelly, Hibbs, & Hamburger, 1989; McBurnett et al., 1991). In other cases, increased, rather than decreased, cortisol secretion has been found among children exhibiting dominant or outgoing behavior (Gunnar, Tout, de Haan, Pierce, & Stansbury, 1997). Studies have not considered specific physiological predictors of attention deficit hyperactivity disorder (ADHD) symptoms, yet externalizing and ADHD symptoms share common features suggesting they may share physiological correlates as well.

These conflicting findings suggest that other variables may be important moderators of the association between cortisol and behavior. Contextual factors have been implicated (Gunnar et al., 1997), but it is equally plausible that other physiological systems may play an important role. The current study expands on past research by including concurrent measures of activity within two physiological systems. Given that low levels of activation in each system independently has been linked to increased risk for externalizing behaviors, it might be expected that low levels of activity in both systems would be associated with the greatest risk for externalizing behaviors. On the

other hand, if, as Munck proposed, these systems oppose one another, activation asymmetries may be expected to be associated with externalizing behavior problems.

### Physiological Predictors of Internalizing Behaviors

In contrast to externalizing behaviors, internalizing behaviors have been more consistently associated with high sympathetic or high adrenocortical activation in children (often referred to as high physiological reactivity), although again, concurrent activation has not been investigated. Compared to uninhibited children, inhibited children show greater sympathetic activation, indexed by postural reflex tachycardia and pupillary dilation, and increased morning cortisol levels (Kagan, Reznick, & Snidman, 1988). Likewise, socially wary 4-year olds have higher cortisol than less wary children (Schmidt, Fox, Rubin, & Sternberg, 1997). The association between cortisol and inhibition appears to persist over time: for instance, infants classified as behaviorally inhibited at 14 months have higher cortisol levels at 4 years than infants classified as uninhibited (Schmidt et al., 1997).

It should be noted, however, that context may play a role not only in which children exhibit high cortisol levels, but also in associations between cortisol and behavior problems. Conflicting results have been reported, with some studies revealing a positive association between cortisol reactivity and surgent or socially competent behavior (Gunnar et al., 1997; Hart, Gunnar, & Cicchetti, 1995). Nevertheless, during periods of social stability, high cortisol reactivity is noted among children who are less outgoing and observed to partake in more solitary and negative behaviors (Gunnar et al., 1997). As with externalizing behavior, these findings suggest that other factors are important in the associations between adrenocortical activity and internalizing behavior.

Given that high reactivity in both the SAM and HPA systems has been associated with internalizing behaviors, if these systems contribute independently to risk, it would be hypothesized that the greatest risk for internalizing symptoms would be among children with high activity in both systems.

Whereas several studies have investigated associations between behavior problems and either sympathetic or adrenocortical activity in children, few studies to date have investigated the concurrent activity of these two systems in predicting behavior problems. In those that have, the two systems are generally treated independently, and potentially important interactions have not been explored (e.g., van Goozen, Matthys, Cohen-Kettenis, Buitelaar, & van Engeland, 2000). Therefore, it remains unknown how concurrent activity in these two systems is associated with risk for behavior problems in children. By studying both systems simultaneously, it will be possible to ascertain whether risk for behavior problems is better predicted by the levels of activity in each system independently or by patterns of activation across both. Advancing understanding in this area will help to refine what is known about the physiological profiles associated with early psychopathology and provide insights into the more fundamental question of how regulation or dysregulation of these systems in the stress response may relate to behavior problems in children.

#### The Present Study

The purpose of this study was to explore how the SAM and HPA axes operate jointly to predict behavioral outcomes in childhood. Children took part in a series of standardized, challenging and mildly stressful tasks, during which measures of SAM and

HPA activity were obtained. Children's physiological reactivity was then correlated with externalizing, ADHD, and internalizing symptomatology.

### Hypotheses

Based on past research, it was hypothesized that the physiological profiles associated with externalizing behaviors would differ from the profiles associated with internalizing behaviors. However, the profiles themselves depend upon whether the SAM and HPA systems are thought to act in alliance or in opposition; therefore the predictions of these different models were tested. Two opposing hypotheses were tested with regard to interactions between the SAM and HPA systems. The traditional view is that these systems operate in alliance during the stress response and would predict that the SAM and HPA systems contribute independently to risk. Thus, children with high activity in both the sympathetic and adrenocortical systems would be expected to have the most internalizing but the fewest externalizing behavior problems (i.e., additive risk). Conversely, children with low activity would be expected to have the most externalizing but the fewest internalizing behavior problems. In contrast, the view advanced by Munck and colleagues, an interactive model, would predict that coactivation or coinhibition of the SAM and HPA axes would be associated with a more adaptive outcome, in this case, fewer behavior problems, than unopposed activation of just one system. Therefore, this model predicts the most behavior problems in children with activation asymmetries (high SAM and low HPA activity or low SAM and high HPA activity) whereas the former model predicts the most behavior problems in children with concurrent high or low activation (internalizing or externalizing problems, respectively). Because the relative contributions to risk of SAM and HPA activity are not known, no specific prediction was

made regarding whether one or the other system would be a stronger predictor of behavior problems.

## Method

### Participants

Participants consisted of a convenience sample of 118 children (61 boys and 57 girls) between the ages of 4 and 8 years ( $M = 6.4$ ,  $SD = 1.4$ ) recruited from the Berkeley community from press releases, childcare centers, and community organizations. All sessions were conducted between 1995 and 1998. There were approximately equal numbers of boys and girls in each of five age groups (4, 5, 6, 7, or 8 years). Children were from a variety of ethnic backgrounds and from predominantly middle- to upper-income families (Table 1).

Children were excluded from analyses if they were missing either physiological or questionnaire data (e.g., equipment malfunction, failure to return questionnaires). Children who were missing data did not differ from those included in all analyses in age  $t = -0.22$ , 116  $df$ , NS, gender  $\chi^2 = 0.80$ , 1  $df$ , NS, or physical characteristics (e.g., height, weight),  $t$ s ranged from  $-0.83$  to  $1.00$ , 73-116  $dfs$ , NS. Likewise, children with missing data were not disproportionately from a particular ethnic background or from a family with high or low income.

### Procedure

Interested parents were contacted by telephone and the study was described. Appointments were then scheduled for families who wished to take part at the University of California, Berkeley. To control for diurnal cycles in basal cortisol levels, all sessions took place in the afternoon or early evening. When families arrived at the Center, the

study was described in detail to parents, their informed consent was obtained, and the child participant's assent was secured. This study was approved by the Committee for the Protection of Human Subjects at the University of California, Berkeley.

An initial saliva sample was then immediately collected from the child. After collection, saliva samples were frozen at  $-20^{\circ}\text{C}$ . They were then packed on dry ice and shipped in batches to the University of Minnesota where they were assayed for cortisol using an Amersham International Amerlex cortisol RIA kit, an assay that is both sensitive and specific for cortisol. Salivary cortisol is a noninvasive measure commonly used to ascertain both basal and stress-induced activity of the HPA axis. Cortisol in the saliva reflects the unbound, or active, fragment of plasma cortisol and typically increases within 10 to 30 minutes following the onset of a stressor (Kirschbaum & Hellhammer, 1994).

Next, physical characteristics of the child were measured including height; weight; face height (vertex to chin); face width (bizygomatic width); and tympanic membrane temperatures. Body mass index (BMI) was calculated as weight (kg) divided by height<sup>2</sup> (m<sup>2</sup>). Similarly, craniofacial ratio (CFR) was calculated as bizygomatic width (cm) divided by face height (cm) (Arcus & Kagan, 1995).

After measurements were taken, spot electrodes were attached to the child to obtain cardiographic data. Electrocardiographic (ECG) information was obtained through disposable electrodes placed on the right clavicle, right lower abdomen, left rib, and grounded on the left lower abdomen. Impedance data were recorded from inner electrodes placed at the suprasternal notch and xiphoid process while a 4-mA AC current at 100kHz was passed through two outer electrodes placed on the fourth cervical and ninth thoracic vertebra. ECG, basal thoracic impedance ( $Z_0$ ), and the first derivative of



the impedance signal ( $dZ/dt$ ) were recorded continuously while the child participated in a series of tasks with a trained research assistant. The tasks, ranging from 1-3 minutes in length, were designed to be ecologically valid challenges for children in middle childhood and have been shown in past research to elicit mild stress responses in preschool-age children (Alkon et al., submitted; Boyce, Alkon, Tschann, & Chesney, 1995). Analog data were monitored during the protocol (described below) and were digitized and saved in one-minute epochs that were then inspected and cleaned prior to analysis.

Pre-ejection period (PEP) was used as an index of sympathetic innervation of the myocardium. Unlike heart rate, PEP is not influenced by parasympathetic activity and therefore represents an index of cardiovascular sympathetic activation that is independent of parasympathetic activation (Cacioppo, Uchino, & Berntson, 1994). PEP corresponds to the period of isovolumetric contraction during the cardiac cycle. Epochs were ensemble-averaged and pre-ejection period was quantified as the time (msec) between the ECG Q wave (ventricular depolarization) and the B-point of the  $dZ/dt$  wave (the onset of left ventricular ejection). Because sympathetic activation results in a more rapid phase of isovolumetric contraction, lower PEP corresponds to higher sympathetic activation.

Details of the reactivity protocol are as follows. The child was first read a 3-minute story that was chosen to be neutral and calming to young children. The child then participated in a sequence of 5 tasks designed to be mildly challenging. A range of behavioral tasks was employed, allowing for measurement of physiological reactivity across situations (Krantz & Manuck, 1984). The first task was a social interview adapted from the Gesell School Readiness Screening Test (Carlson, 1985). A research assistant

asked the child a series of questions about the child, her or his family, and school. The second task, a cognitive challenge from the Kaufman Assessment Battery for Children (Kaufman & Kaufman, 1983), required the child to repeat digits read by the research assistant. For the third task, the research assistant asked the child to identify drops of two unknown substances placed sequentially on the anterior tongue (both were lemon juice) (Kagan & Snidman, 1991). This was followed by a brief one-minute rest period during which the child sat quietly. For the fourth and fifth tasks, the child watched two video clips previously demonstrated to elicit fear (a young boy frightened by a thunderstorm) and sadness (a girl whose pet bird had died) in children (Eisenberg et al., 1988). Finally, after watching the videos, children were read another calming, neutral story. A second saliva sample was collected after the story. Together, the two stories were included to obtain resting cardiovascular data, and the tasks were included to obtain cardiovascular data under conditions of mild stress.

While the child participated in the tasks, the parent completed a demographic questionnaire concerning the child's age and gender, parents' occupations, education levels, and family income, and the MacArthur Health and Behavior Questionnaire (HBQ). The HBQ is a standardized questionnaire that assesses various domains of physical health, emotional and behavioral problems, and social and school adaptation in 4- to 8-year old children. This report concerns three of the subscales of the HBQ: externalizing, ADHD, and internalizing symptoms. Items that created these subscales consisted of descriptions of behavior to which the parent indicated whether the behavior was "never or not true", "sometimes true", or "often or very true" of their child. The validity and reliability of the HBQ have been established in several recent studies (e.g.,

Essex et al., submitted), which together reveal that HBQ subscales show strong convergence with clinical status and other measures of early psychopathology and have strong test-retest reliabilities over the course of a year (Essex et al., submitted). Scores on the subscales have successfully distinguished children with high and low risk for different types of behavior problems.

### Data Processing

Cardiovascular data. Three types of scores were calculated to reflect different dimensions of cardiovascular reactivity. Resting scores were represented by the average PEP during the two story epochs. Intensity scores were represented by the average PEP during tasks (social interview, number recall, taste task, and video clips). Because resting and intensity scores were highly correlated,  $r = .99$ ,  $p < .001$ , resting scores were not considered further. Difference scores, which have often been used to index reactivity (Cacioppo et al., 1994), were calculated as the intensity minus resting scores.

Salivary cortisol. Each saliva sample was assayed twice for cortisol. The average values were computed and entered as the mean for each collection time. To parallel the dimensions of cardiovascular reactivity, three scores were computed to reflect cortisol activity. Baseline scores were defined as the mean of the time 1 cortisol levels. Intensity corresponded to mean cortisol level at time 2. As with PEP, because baseline and intensity scores were strongly correlated,  $r = .78$ ,  $p < .001$ , baseline scores were not considered further. Difference scores were calculated as cortisol intensity minus baseline.

Physiological groups. A goal of this study was to determine whether the concurrent distributions of sympathetic and adrenocortical reactivity suggest rationally

distinguishable groups of children who differ in terms of behavior problems. Because of this, attempts were made to identify PEP and cortisol groups. To elucidate how best to group children according to their SAM and HPA activity, frequency distributions were examined and cluster analyses conducted. Children were successfully classified into groups based on cortisol intensity scores. The cut-point between high and low cortisol groups identified by cluster analysis corresponded to the 80<sup>th</sup> percentile, 0.28  $\mu\text{g/dl}$ . Examination of the positively-skewed frequency distribution showed that this point also corresponded to a visually logical point that divided the upper tail from the remainder of the sample<sup>1</sup>. PEP intensity was distributed normally and no logically distinguishable groups emerged. Thus, children were not grouped according to sympathetic reactivity; but rather the continuous scores were used in all analyses.

High and low cortisol groups did not differ significantly on age, height, weight, BMI, face length, face width, or CFR,  $t_s$  ranged from -1.24 to 0.84,  $d_f s = 68 - 109$ , NS. Cortisol groups also were comparable in terms of average sympathetic intensity and difference,  $t_s \leq 1.61$ ,  $d_f = 106$ , NS.

Behavior groups. It has been proposed that children extreme in their behavioral phenotype may be distinctive in a number of dimensions from children with more moderate behavior (Kagan, Snidman, Arcus, & Reznick, 1994). Thus, for analyses comparing the patterns of physiological activation among children at high and low risk for behavior problems, children were grouped into quartiles based upon HBQ scores,

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<sup>1</sup> Cortisol group assignment was confirmed after controlling for time of saliva sampling (which, as discussed subsequently, was related to cortisol levels). Cortisol intensity was regressed on time of second saliva sample and the top 22 children were assigned to the high cortisol group. Five children missing data on time of saliva sample (all originally in the low cortisol group) were excluded. Of the 22 children originally assigned to the high cortisol group, 18 remained in the high cortisol group when classified by

with the upper quartile defined as high-risk and the remaining three quartiles defined as low-risk. Such a categorical (as opposed to continuous) representation of problem behavior has been used successfully in several prior studies (Boyce et al., in press).

### Results

First, preliminary analyses were conducted to examine the relations of children's age, gender, physical characteristics, ethnicity, and family income to their physiological profiles and behavioral outcomes. Second, bivariate associations among physiological variables and among HBQ variables were computed. Third, associations between behavior problems and sympathetic activity were examined among children in the two cortisol groups. And fourth, analyses were conducted to identify whether patterns of physiological activation could be distinguished between children at high versus low risk for behavior problems.

#### Preliminary Analyses

Five (age in years: 4 to 8) by 2 (gender) analyses of variance (ANOVAs) were conducted with cortisol and PEP intensity followed by the 3 HBQ scales (externalizing, ADHD, and internalizing) entered as separate dependent measures. A significant main effect of age emerged for PEP intensity  $F(4,103) = 5.72, p < .001$ , older children showing diminished sympathetic reactivity. However, when height was entered as a covariate (because of its strong association with age,  $r = .88$ ), the main effect of age was no longer significant. No other significant effects emerged for the physiological variables. Likewise, no significant effects of age or gender emerged for the HBQ scales.

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adjusted cortisol intensity scores. Patterns of results were the same irrespective of which method was used to assign children to cortisol groups.

Next, because some studies have suggested that physiological variables are related to physical characteristics through developmental mechanisms (Arcus & Kagan, 1995; Barker, 1997), children's height, weight, face length, face width, and CFR were compared to the physiological and HBQ variables. Contrary to past research (Arcus & Kagan, 1995), higher cortisol intensity scores were associated with larger face width,  $r = .27$  and greater CFR,  $r = .26$ ,  $ps < .05$ . These correlations remained when time of day of cortisol sampling, age, gender, height, weight, BMI, and ethnicity were considered. Lower sympathetic reactivity was positively related to children's height,  $r = .51$ ,  $p < 0.05$ , which remained unchanged when age, BMI and weight were controlled statistically.

One-way ANOVA was conducted with ethnicity as the independent variable (coded into 5 groups: White,  $n = 59$ ; African-American,  $n = 13$ ; Asian-American,  $n = 12$ ; Latino,  $n = 6$ ; or Other/mixed,  $n = 24$ ) and the physiological and HBQ variables as separate dependent measures. No significant effects were uncovered. Family income was not significantly related to the physiological variables and HBQ scales,  $r_s$  ranged from  $-.10$  to  $.07$ ,  $dfs = 105-109$ , NS.

Finally, because cortisol secretion follows a circadian cycle, correlations were conducted to investigate whether cortisol levels varied depending on the times of day the cortisol samples were obtained. Time between samples was unrelated to cortisol intensity, however, time of saliva sample was related to cortisol intensity,  $r = -.36$ ,  $p < 0.001$ , such that submitting saliva samples later was associated with lower cortisol levels. Consequently, the results reported here were confirmed after covarying time of day.

### Bivariate Associations Between Physiological Variables and HBQ Variables

Pearson correlations revealed that none of the sympathetic variables were significantly related to any of the cortisol variables,  $r_s$  ranged from  $-.19$  to  $-.08$ , NS, suggesting that levels of cortisol are were largely orthogonal to sympathetic activation (Figure 1). In other words, children high in reactivity along either the sympathetic or adrenocortical axis are not necessarily reactive along other. Despite this lack of association in the entire sample, it remains possible that associations between SAM and HPA activity may exist among subgroups of children. In contrast to the physiological variables, the HBQ scales were moderately intercorrelated,  $r_s$  ranged from  $.45$  to  $.55$ ,  $n = 107$ ,  $p_s < .001$ .

### Prediction of Behavior Problems with Physiological Variables

Three regression analyses were conducted, one each with externalizing, ADHD, and internalizing symptoms entered as a separate dependent measure. Because children were successfully classified into cortisol intensity groups, the intensity scores were used as the independent measures. That is, the independent variables included the cortisol extreme group classification (a dichotomous variable) and PEP intensity (entered as a continuous variable). Possible interactions between these systems were of particular interest, thus the interaction between the two scores was also entered. The overall model for externalizing symptoms was significant,  $F(3,93) = 3.93$ ,  $p < .05$ , and accounted for 11% of the variance. The cortisol group by PEP intensity interaction,  $B = .30$ ,  $p < .01$ , emerged as a significant predictor. As can be seen in Figure 2, children in the high cortisol group who had higher sympathetic reactivity displayed the fewest externalizing symptoms, followed by children in the low cortisol group who had low levels of

sympathetic activation. The most externalizing symptoms were evident among children with high levels of activation along one system and low levels of activation along the other, that is, activation asymmetries.

The model predicting ADHD symptoms was not statistically significant,  $F(3,93) = 1.58, p > .10$ . However, for internalizing symptoms, the model approached significance,  $F(3,93) = 2.26, p < .10$ ; and the cortisol group by PEP intensity interaction emerged as a significant predictor of internalizing symptoms,  $p \leq .05$ . The pattern was similar to the significant interaction predicting externalizing symptoms, such that children with high cortisol but low sympathetic reactivity tended towards the most internalizing symptoms, followed by children in the low cortisol group with high sympathetic reactivity (Figure 3). Children with low levels of reactivity in both systems had the fewest internalizing behavior problems.

Entering age, gender, height, BMI, or time of day as covariates into the regression models did not alter the pattern of results. Additionally, given the pattern shown in Figures 2 and 3, these data are not consistent with an additive model of physiological risk factors.

#### Physiological Predictors of High Risk for Behavior Problems

Two types of analyses were conducted to explore physiological patterns associated with high risk for behavior problems. First, a signal detection method, a form of recursive partitioning, was used to assess whether children with and without behavior problems differed in sympathetic or adrenocortical activation when all scores were considered concurrently. Second, children with and without behavior problems were



compared to determine whether they differed in patterns of concurrent SAM and HPA activity as suggested by the regression analyses.

Signal Detection Analyses. The signal detection method identified dichotomous division values on selected predictors that discriminated children at risk (i.e., in the upper quartile for each type of behavior problem) and not at risk (all other children) with the greatest possible efficiency. This method employed a quality receiver operating characteristic (QROC) approach to maximizing the selected variables' sensitivity and specificity in discriminating among groups. In the analyses conducted, age, gender, and the intensity and difference scores for both PEP and cortisol, along with their respective ranges of values and interval cutpoints, were entered into an algorithm to identify which variables and cutpoints best predicted risk. Although age and gender were unrelated to HBQ scales in this sample, they were included in these analyses because some prior research has suggested these variables may relate to physiological reactivity or behavior in childhood (Alkon et al., submitted; Boyce et al., 1995; Murphy, Stoney, Alpert, & Walker, 1995). After selecting the first optimally efficient variable and cutpoint, the algorithm then identified additional variables and cutpoints within each subgroup until the subgroups contained too few participants or no other significantly discriminating variable emerged.

None of the physiological variables emerged as a significant predictor of risk for externalizing behavior problems. However, for ADHD symptoms, the greatest proportions of high-risk children were evident among those with low cortisol reactivity (44%) and children with high cortisol reactivity but low sympathetic activation (27%).

None of the children who were highly active along both the sympathetic and adrenocortical systems were in the high-risk group.

The algorithm derived for internalizing symptoms was consistent with the algorithm for ADHD symptoms. Again, among younger children, higher risk was associated with low cortisol level (57%) and high cortisol level but lower sympathetic reactivity (43%). The lowest proportion of at-risk children (13%) was found among younger children with high activity along both sympathetic and adrenocortical axes. Children over 7.8 years of age were at higher risk for internalizing problems than younger children, but there were too few children older than 7.8 to conduct subsequent analyses to identify physiological predictors.

Concurrent SAM and HPA Activity Among High- and Low-Risk Children. As described earlier, in the entire sample, there were no linear associations between any dimensions of PEP and cortisol activation. However, regression analyses were conducted to explore whether PEP and cortisol associations were evident at different levels of risk for behavior problems. To parallel the signal detection analyses, the association between PEP intensity and cortisol intensity was examined among high risk children (highest quartile on externalizing, ADHD, or internalizing symptoms) and low risk children (lower 3 quartiles).

Regression analyses were conducted predicting sympathetic activation (negative PEP intensity) with cortisol intensity (a continuous variable), behavior risk group (a dichotomous variable), and the cortisol by behavior group interaction. The overall models were significant when externalizing or internalizing risk group were used as predictors,  $F_s(3,93) = 2.75$  and  $2.91$ , respectively,  $p_s < .05$ . The model utilizing ADHD

risk groups approached significance,  $F(3,93) = 2.34, p < .10$ . For the regressions with both the externalizing and internalizing dichotomous groups entered, the interaction between cortisol intensity and risk group was significant, indicating that the relationship between cortisol and sympathetic activation varied depending on whether children were at low or high risk for behavior problems,  $t_s = -2.34$  and  $-2.43, p_s < .05$ , respectively. The interactions in both cases revealed positive associations between cortisol and sympathetic activation among children at low risk for behavior problems, whereas an inverse association among children at high risk (see Figure 4).

Figure 4 is a representation of how the magnitude and direction of association between sympathetic and cortisol activity varied among children at differing levels of risk for externalizing symptoms. The “not at risk” group was further divided into quartiles for illustrative purposes. As can be seen, coactivation decreased among children in higher externalizing risk groups, and that children with the most externalizing behaviors (i.e., the upper quartile) are characterized by reciprocal activation. Parallel graphs for ADHD and internalizing behavior quartiles were generally similar to Figure 4, suggesting again that the progressive decline in coactivation with increasing risk is evident across a range of behavior problems.

### Discussion

The present study aimed to identify neuroendocrine profiles associated with increased risk for behavior problems in middle childhood. Results from regression and signal detection analyses revealed that the absolute levels of activation in either the sympathetic or adrenocortical system were less predictive of behavior problems in middle childhood than was the degree of concordance between systems. Children with

coactivation or coinhibition had the fewest behavior problems, whereas children with activation asymmetries had the most behavior problems. Furthermore, the degree of coactivation decreased in a dose-response pattern with increasing behavior problems.

The same general trends found for externalizing symptoms were evident for ADHD and internalizing symptoms, although findings were strongest for externalizing behaviors. Externalizing behaviors may be more common than internalizing behaviors during middle childhood. Also, parents may be more aware of externalizing than internalizing behaviors. For example, acting out may be more easily identified than fearfulness.

These findings suggest that dissociations of the sympathetic and adrenocortical axes occur under conditions of challenge among children at risk for early psychopathology. This conclusion is commensurate with Munck's hypothesis (Munck et al., 1984) that the HPA axis serves to protect against sympathetically mediated responses to stress. In other words, if activation asymmetries are present, either the initial response to stress is too great or the suppression of the initial response is too great, either of which can be maladaptive. The present study's findings are also consistent with observations that catecholamines and cortisol have opposing effects on such functions such as immune activation, appetite, and memory (see Sapolsky et al., 2000). In all of these cases, a balance of activity promotes optimal functioning.

If sympathetic and adrenocortical systems act in opposition to restore homeostasis when threatened, this would suggest that both a minimum level of activation as well as the proper balance between SAM and HPA activation are necessary for adaptive responses to environmental challenge. Thus, although the absolute level of activation

may vary between individuals and in response to different types of challenges, maintaining a balance between sympathetic and adrenocortical activation may be essential for adaptive function in all organisms. Coordinated activity in the periphery, whether at low or high absolute levels, suggests effective central coordination. Peripheral activation asymmetries, conversely, may be a marker for central dysregulation of the stress response and perhaps broader irregularities in central processing, including disruption of such functions as concentration, attention, and affective processing that manifest as behavior problems. As understanding of peripheral physiological responses to stress improves, it will be valuable to study associated psychological responses that mediate the relations between stress and psychopathology as well as central correlates that may directly contribute to both behavior and peripheral physiology. Likewise, in this study, SAM and HPA activation were each measured with only one indicator (PEP and cortisol); therefore, in the future it will be important to assess other indicators of SAM and HPA activation to determine how multiple measures within each physiological system may contribute to greater understanding of their joint regulation.

The interpretation that the peripheral activation asymmetries observed in children at risk for behavior problems mark central abnormalities is consistent with the observation that activation asymmetries of either type (high SAM-low HPA or low SAM-high HPA) were associated with the same behavior vulnerabilities. If activation asymmetries represent peripheral markers for generalized central dysregulation that could cause disordered behavior, the nature of peripheral asymmetries may be less revealing than their presence until more is known about the underlying central mechanisms regulating physiological response.

Overall, the physiological profiles associated with different behavior outcomes were quite similar. It is possible that more robust behavior-specific profiles would emerge in samples of children with more extreme behavior problems (e.g., clinical samples) or older children, for example, if externalizing and internalizing behavior problems diverge over the course of development. Both in the present study and previous research with the HBQ, significant associations were found between externalizing, ADHD, and internalizing behaviors (Essex et al., submitted), a finding consistent with research using other parent-report measures of behavior problems (Keiley, Bates, Dodge, & Pettit, 2000). The relatively common co-occurrence of these behavior problems in children at this age explains, at least in part, why similar patterns of physiological predictors of risk emerged and suggests a common underlying diathesis.

In particular, the physiological patterns associated with high risk for behavior problems may represent responses to shared psychosocial stressors associated with behavior problems, such as peer rejection and academic problems (DeRosier, Kupersmidt, & Patterson, 1994; Keiley et al., 2000). The social consequences of behavior problems themselves are likely to act as significant, chronic stressors in children's lives that may result in dysregulation of stress-response systems, an interpretation consistent with the observation that adults with post-traumatic stress disorder evidence dysregulation of neuroendocrine responses to stress (Henry et al., 1992; Liberzon, Abelson, Flagel, Raz, & Young, 1999). Longitudinal studies of physiology and behavior across childhood are necessary to address issues related to directionality. Likewise, it will be important to assess whether neuroendocrine profiles

are stable within children or whether they appear to vary over the course of development or in response to environmental changes.

Although this study represents one of the first empirical investigations of the SAM and HPA systems as concurrent predictors of behavior problems, limitations to the generalizability of the findings also need to be mentioned. First, in the study of physiological systems, the mechanisms responsible for average values in a given system often differ from the mechanisms responsible for extreme values (Kagan et al., 1994). As an example, although blood pressure in normal ranges may be a function of genetic factors, fluid balance, hormonal status, and dietary influences, and other factors, extreme hypotension may occur as a component of anaphylactic reactions or after toxin ingestion. Conversely, extreme hypertension may occur in association with adrenal medullary neoplasms. Therefore, children who are at the extremes of either physiological reactivity or behavior problems may reveal processes that are qualitatively different from processes that underlie the more moderate levels typical of this nonclinical sample. Second, although dimensional measures were used to collect the data in this study, assuming the presence of a single underlying distribution may be misleading. To begin to understand how multiple physiological systems are related to behavior problems, various analytic strategies were used that treated both physiological and behavioral data as continuous or categorical. A strength of such an approach is that a coherent picture emerged and was confirmed through these various methods. Nevertheless, it is necessary to assess whether the patterns found here generalize to children with more severe behavior problems.

Third, the patterns of coactivation and reciprocal activation were identified on a group level and represent responses of different children to the same group of tasks. It is

possible that if individual children were exposed to a wider variety of stimuli (both in terms of type and intensity), different patterns of concurrent activation may emerge. Cacioppo and colleagues (Cacioppo et al., 1992) have discussed how opposite patterns of association between physiological and behavioral variables have emerged from studies using different methodological strategies. Therefore, the next step would be to examine concurrent sympathetic and adrenocortical activation within children across a variety of stimulus conditions.

In conclusion, the present study provides evidence that patterns of sympathetic and adrenocortical responses under conditions of challenge vary depending on children's risk for behavior problem. Greater coactivation occurred among children at low risk for behavior problems, and activation asymmetries existed among children at high risk for behavior problems. Because sympathetic and adrenocortical measures are peripheral measures of centrally regulated systems, these findings can be interpreted as suggesting central dysregulation may underlie behavior problems in early to middle childhood. More generally, these results demonstrate that examining activation symmetries and asymmetries represents a promising approach to identifying psychobiological risk factors, whether in children or adults. When coupled with identification of behavioral phenotypes in childhood, better prediction of long-term risk for psychopathology may be possible.



Table 1

Demographic Characteristics of Participants (n = 118)

	Number of Children
<b>Gender</b>	
Boys	61
Girls	57
<b>Age in Years (boys; girls)</b>	
4	12; 14
5	14; 12
6	12; 10
7	14; 9
8	9; 12
<b>Child's Ethnicity</b>	
White / Caucasian	59 (50%)
African American	13 (11%)
Asian American	12 (10%)
Latino	6 (5%)
Other (multiracial)	24 (20%)
Missing	4 (3%)
<b>Family Income</b>	
Less than \$19,999	17 (14%)
\$20,000 - \$29,999	11 (9%)
\$30,000 - \$39,999	7 (6%)
\$40,000 - \$49,999	14 (12%)
\$50,000 - \$59,999	16 (14%)
Over \$60,000	49 (42%)
Missing	4 (3%)

Figure 1

Representative Association Between Sympathetic and Adrenocortical Measures (n = 108)

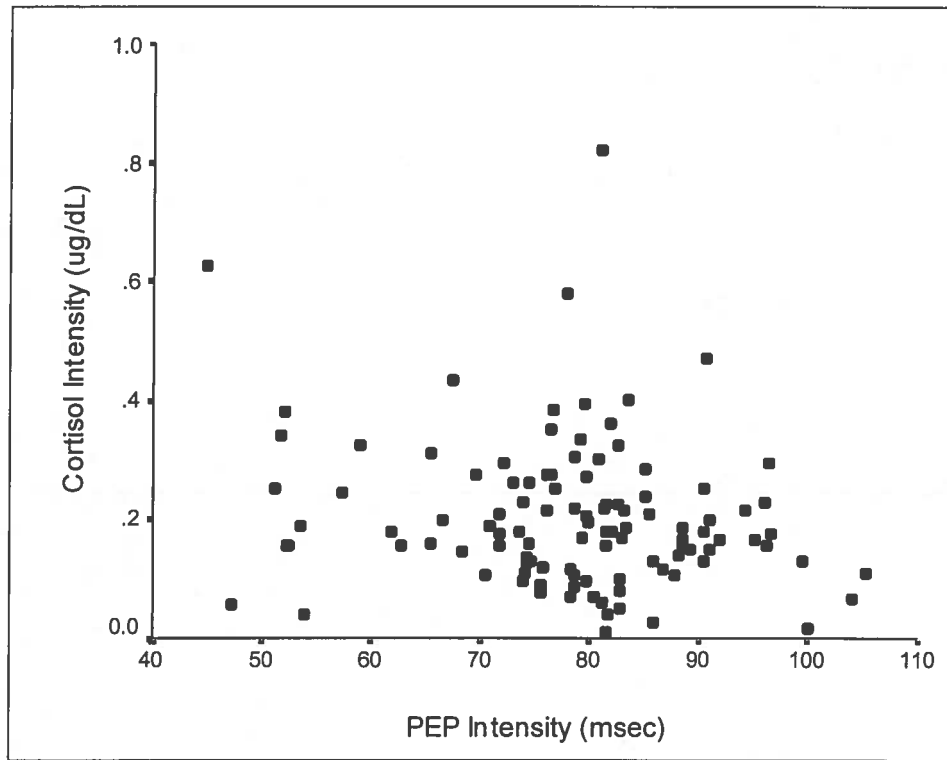


Figure 2

Externalizing Behaviors as a Function of Sympathetic Activation Among High and Low Cortisol Groups (n = 97)

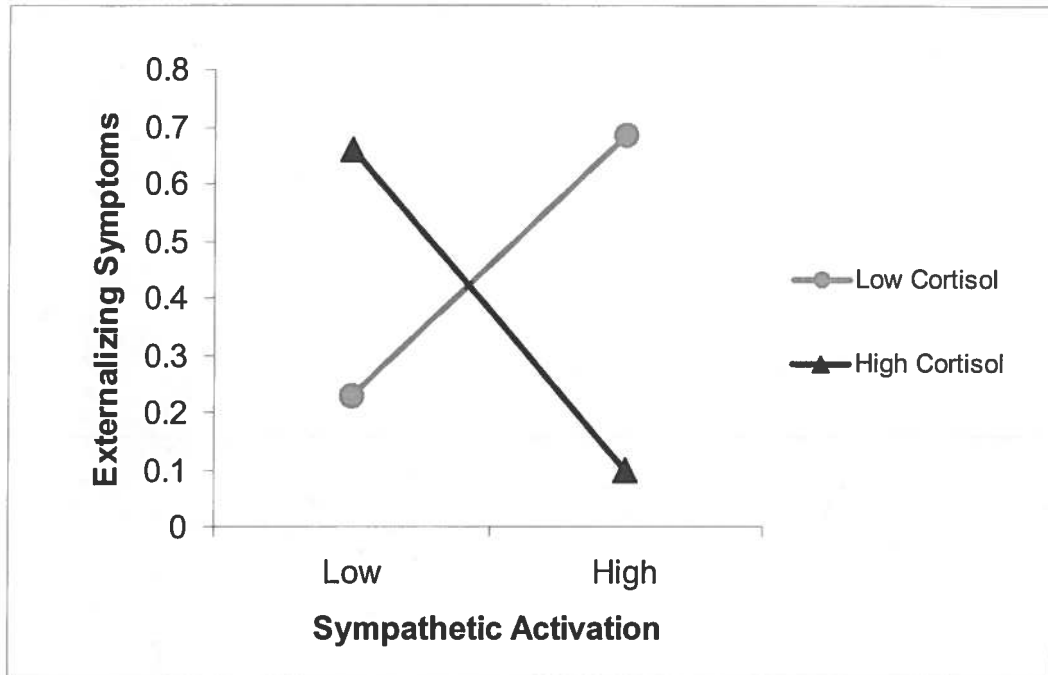


Figure 3

Internalizing Behaviors as a Function of Sympathetic Activation Among High and Low Cortisol Groups (n = 97)

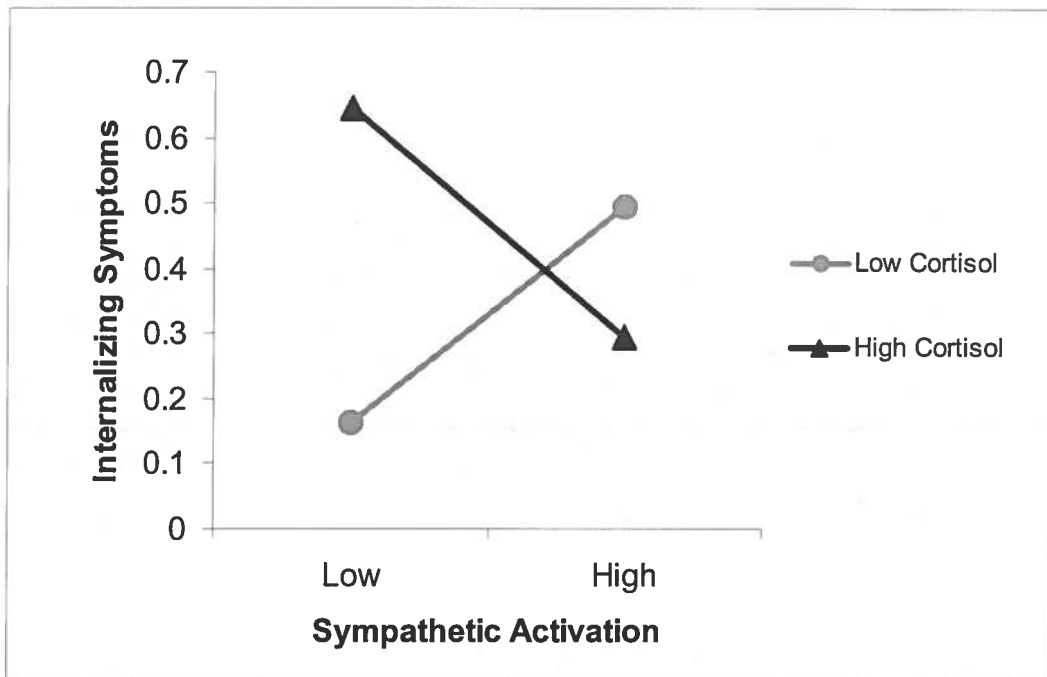
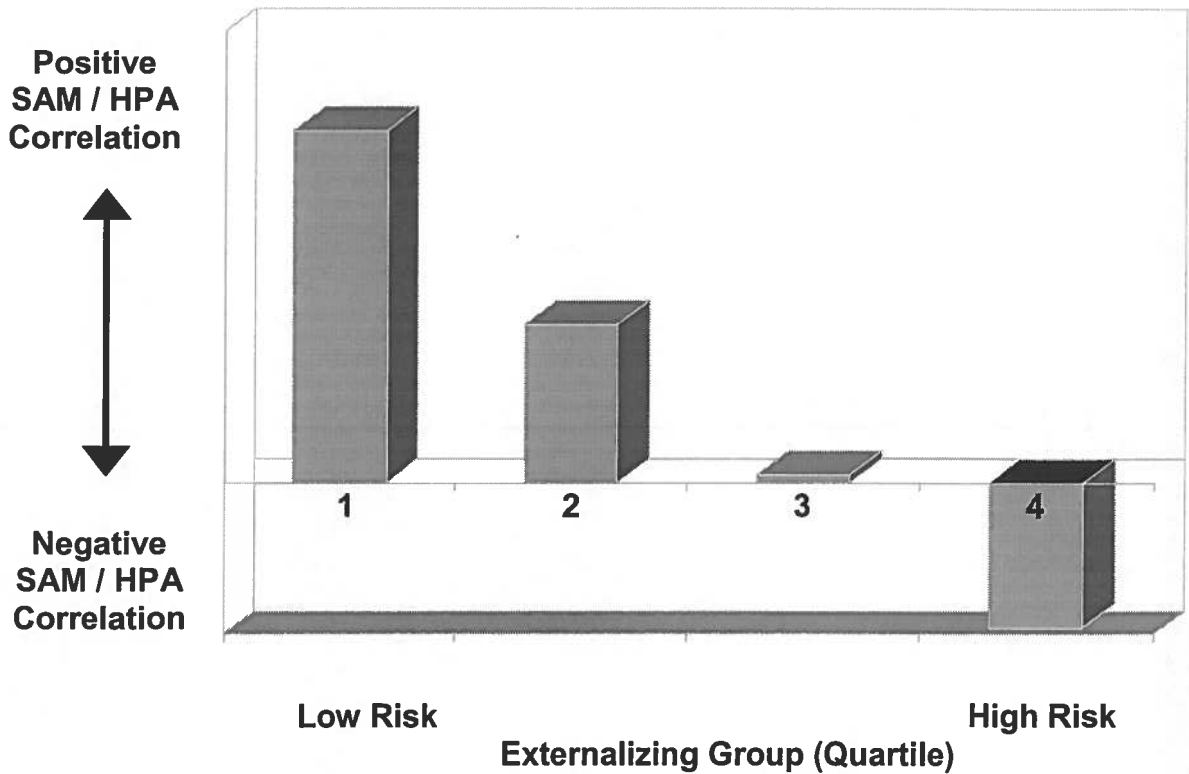


Figure 4

Degree of Sympathetic and Adrenocortical Coactivation Among Children

Classified By Externalizing Behavior Problems (n = 97)



The figure displays the value of cortisol intensity when sympathetic activation was regressed on cortisol intensity separately for each of the four quartiles of the behavior groups. A positive value indicates a positive association between sympathetic and adrenocortical function, or coactivation, and a negative value indicates an inverse association between sympathetic and adrenocortical activity, or reciprocal activation.

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## Conclusions

As outlined in the first paper, there are theoretical reasons to expect interactions between activities of the two major stress-response systems in the body. These systems become activated in response to somewhat distinct psychological and situational factors and appear to have specific behavior correlates as well. The second paper described empirical research conducted to explore the utility of taking a multi-system approach to the study of children's psychobiological responses to stress. The results of the empirical analysis clearly showed first, that such an approach is feasible and that second, important insights into the regulation of the stress-response can be gained from such an approach. Although the results of this study suggest a dissociation of physiological systems in response to stress among children with behavior problems, further research is needed to replicate and extend upon these findings. Future research aimed at identifying children at increased risk for psychopathology should consider activity and patterns of interactions along multiple physiological systems. This approach holds the promise to improve prediction of long-term risk for psychopathology, an essential intermediate goal to guide the targeted interventions that will be needed to alleviate some of the global burden associated with untreated psychiatric disorders.

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