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Special Article

Associations Between Physiological Reactivity and Children's Behavior: Advantages of a Multisystem Approach

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ABSTRACT. The past decade has seen a notable increase in interest in and research concerning the physiological correlates of behavior problems in childhood. The present article reviews what this growing body of research has revealed. The main tenet is 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. *J Dev Behav Pediatr 23:102–113, 2002.* Index terms: *physiological reactivity, children, behavior problems.*

OVERVIEW

Psychiatric disorders exert an enormous toll in both human and economic terms. They are among the most debilitating of all illnesses, with major depression currently the world's leading cause of disability.[1] Over the next two decades, the loss of life and functioning associated with psychiatric conditions as a whole is projected to increase at a substantially higher rate than that associated with other major causes of morbidity and mortality, such as cardiovascular disease.[2] Of great importance, therefore, is the need to identify causes and correlates of psychiatric disorders; such information is imperative to future intervention.

Unlike many chronic diseases, the onset of psychiatric disorders is often early in life,[3,4] providing an opportunity for the development of interventions targeting children who are potentially the most vulnerable to psychiatric problems. Further, even before psychiatric disorders have crystallized, behavior problems are evident as precursors, making the identification of behavior problems in young children a possible means of early identification of individuals at risk for the development of psychiatric disorders. Despite the ability to identify behavior problems in early childhood, such behavioral phenotypes are only moderately predictive of later psychopathology.[5] To determine more effectively which children are and are not at risk for psychiatric disorders, other indicators of early risk must also be identified. Physiological reactivity to stress reactivity is another such indicator.

Physiological responses to stress in childhood (and throughout adulthood) are products of both individual (e.g., genetic, biological, and psychological) and environmental (e.g., intensity of stressful exposure) variables. By studying how individual children react physiologically to stressors and challenges, insight into children's more general ability to regulate their arousal could be determined. As outlined below, differences in arousal regulation probably account for some of the noted differences in susceptibility to the adverse effects of stress.[6]

Recently, research has revealed that alterations in both the sympathetic-adrenal-medullary (SAM) and hypothalamic-pituitary-adrenal (HPA) systems, two major physiological stress response systems, are predictive of behavior problems in children and adolescents.[7–21] However, interactions

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between these systems have not yet been explored. Yet, there are theoretical reasons to expect that how the two systems interact, as well as how they each function independently, may contribute to the emergence of behavior problems during childhood. Because the interactions have not been the focus of previous empirical investigations, the present paper aims first to highlight the importance of this approach for advancing understanding of physiological correlates of behavior problems and second to provide a foundation from which future studies can be designed. Specifically, an overview of the biological response to stress, including the independent actions of the SAM and HPA systems and the concurrent actions of these systems, is first provided. Second, associations between the activities of these systems and behavior problems in children are discussed, within which the rationale for using a multisystem approach to advancing understanding of physiological correlates of children's behavior problems is reviewed. Third, important directions for future research are outlined. The primary working hypothesis is that physiological systems should not be viewed independently, but rather the overall profiles and interactions between systems must be taken into consideration to understand fully their associations with children's behavior problems. Of note, the present report is limited in its focus on the two main physiological systems involved in the stress response and their interaction. However, to develop a truly comprehensive understanding of the physiological correlates of children's behavior problems, it will ultimately be necessary to expand such a view to include interactions among additional physiological and psychosocial systems, including parasympathetic activity, temperament, behavioral reactivity, and coping, among others.

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, that these alterations can be long-lived, and disease can result from the long-lived changes.[22] The term "allostasis" has been introduced to describe the achievement of stability after activation of physiological systems; allostasis allows an individual to adapt to alterations in both internal and external environments.[23] Rather than proposing a fixed arousal set point for physiological parameters, as implied by homeostatic models, allostasis incorporates the notion of constant fine-tuning of multiple physiological systems to meet minute-to-minute changes in the demands of the environment and an individual's needs. This general flexibility of response patterns is an essential feature of complex systems and has been described as the "loose coupling" of biological systems.[24] When an individual is subjected to arousing stimuli for prolonged periods, accommodation to the chronic physiological activation places a demand on the organism, which is termed "allostatic load."[25,26] Alterations in the responses of the sympathetic-adrenal-medullary (SAM) and hypothalamic-pituitary-adrenal (HPA) systems represent manifestations of allostatic load that have been studied in children.[5,8,19,27]

In the short-term, allostatic changes serve vital functions by allowing individuals to react to environmental demands. Over time, however, allostatic load may accumulate and increase individuals' susceptibility to disease. In particular, the catabolic activities of stress-response systems are costly in terms of energy expenditure and, in excess, are physically damaging.[25] Insofar as stress response systems are activated 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, the costs associated with activation are acceptable. Yet stress-response systems that were adapted in an environment in which stressors were catastrophic but infrequent are now activated routinely, chronically, and possibly inappropriately.[28] Frequent, excessive activation can lead to dysregulation of the systems, a form of allostatic load, which, over time, contributes to the pathogenesis of disease, including psychiatric disorders and behavioral precursors to the disorders.[22,25,28]

Despite the potential for disease and disorders to result from chronic stress, individuals differ in their physiological responses to environmental challenges, their corresponding allostatic load, and their subsequent susceptibility to health and behavior problems. Variability in physiological responses may derive from individual differences either in resting physiological arousal or in arousal attributable to an environmental stimulus, termed "reactivity."[29–31] Reactivity has been operationalized most simply as the difference between baseline arousal and stress-induced arousal, although researchers have recently proposed that more complex patterns of reactivity can be identified.[19,32] These patterns capture aspects of the magnitude of the physiological response, the variability of response, the recovery from the response, and the tendency to adapt to stimuli over time, and are believed to reflect stable, underlying differences in individuals' overall ability to respond adaptively after exposure to stress and challenge.[19,32] Accordingly, individual differences in physiological reactivity may account for some of the noted variability in associations between stress and susceptibility to health and behavior problems.

Indeed, several teams of researchers have found that differences in children's cardiovascular reactivity, a form of allostatic load, is predictive of variability in their susceptibility to physical illness. For example, Boyce et al[33] proposed that cardiovascular reactivity moderates the association between stress and illness by increasing vulnerability to illness in the face of stressful exposure among children who show exaggerated, intense cardiovascular responses to stress and challenge. Johnston-Brooks and colleagues[27] found evidence that cardiovascular reactivity mediates rather than moderates the association between stressful exposure and illness in children. Although these studies have focused on physical health as dependent measures, their results highlight the potential for interactions between physiological systems, environmental stress, and subsequent health. They also reveal that such interactions may well be evident in early and middle childhood, a time when mental disorders may not be solidified and interventions may be most effective.

Before exploring in depth how differences in patterns of physiological reactivity to stress are associated with behavior problems, it is important to summarize what is known about the roles of the sympathetic and adrenocortical systems in the stress response and the coordination of the systems.

Sympathetic-Adrenal-Medullary System

Walter Cannon,[34,35] an early investigator in the field of stress physiology, first described the role of the 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.[34,35] Preganglionic sympathetic fibers from the locus ceruleus synapse primarily in the paravertebral ganglia with numerous postsynaptic fibers that innervate the visceral organs, thus forming the anatomic substrate for signal divergence. This arrangement allows for a virtually instantaneous but short-lived signal to be carried to target organs throughout the body, permitting the fast, diffuse responses characteristic of the system.[34,35] 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. These hormones extend the duration of sympathetic effects through rapid but again relatively short-lived changes at the cellular level.[34–36]

Henry[37] has described SAM activation as the physiological component of a ''defense reaction,'' that is, an active, effortful response to challenges that are manageable or controllable. This view of SAM activation is supported by research showing that characteristics of both the situation (e.g., controllable stressors[38–40]) and the individual (e.g., the tendency to exert high effort to obtain control, known as Type A personality [6,41]) influence whether such a defense reaction is mounted when confronted with a challenge. Further, children as young as 3 years old identified as demonstrating Type A responses to challenges (competitiveness, aggression, and impatience) show elevated systolic blood pressure responses to stress.[41,42] Therefore, even in early childhood, SAM activation in response to challenges may be more likely to occur in certain situations and among certain children.

Hypothalamic-Pituitary-Adrenal Axis

Within a few decades of Cannon's discoveries, another pioneer in stress research, Hans Selye, identified the role of the HPA axis in the stress response.[43] 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 because GCs must be synthesized de novo on demand and act through effects on gene transcription and resulting protein synthesis. When an individual is confronted with a stressor, the hypothalamus releases corticotropin-releasing hormone (CRH), which, along with other factors, stimulates the release of adrenocorticotropic hormone (ACTH), the anterior pituitary hormone, which then signals the adrenal cortex to release cortisol, the primary GC in humans. Whereas cortisol is released within 10 to 30 minutes after a stressor, its effects on target tissues may not be manifest for over an hour.[44,45]

In contrast to the aforementioned ''defense reaction'' of the SAM system, Henry[37] described adrenocortical activation as the physiological component of a ''defeat reaction,'' a passive response pattern characterized by emotional distress, behavioral withdrawal or avoidance, and loss of control. Several studies have revealed, in support of Henry's view, that HPA axis activation is especially likely to occur among adults in situations that are uncontrollable[38–40] and among children when there is high ego involvement or the outcome is especially important.[13,44] For example, among clinic-referred children, those with high HPA reactivity are more likely than those with low reactivity to perceive themselves as having little personal control in life.[11] Thus, individuals who tend to perceive challenges as unpredictable or threatening or feel that they lack the resources to manage threats may be most likely to show elevated adrenocortical responses to challenge.[13,44,46] Accordingly, activation of the adrenocortical system in response to challenges may be associated with specific situational and psychological demands that are distinct from the demands associated with SAM activation.

Coordination of Sympathetic-Adrenal-Medullary and Hypothalamic-Pituitary-Adrenal Activity in the Stress Response

Although both systems were described over a half-century ago, the precise roles of the SAM and HPA systems in stress responses, including their coordination, remain topics of theoretical debate and empirical investigation. It has long been assumed that the SAM and HPA systems work in alliance in generating the physiological changes associated with the stress response. For example, the actions of catecholamines and GCs increase circulating glucose levels. GCs are also known to sensitize the myocardium to the effects of circulating catecholamines.[45] However, given that the SAM and HPA systems are activated in response to different situational demands and are differentially activated depending on individuals' perceptions of events, the systems' responses could become dissociated. Such a dissociation between systems may not pose a problem for an individual if the SAM and HPA systems serve the same function, that is, to protect an individual when confronted with challenge. Conversely, as discussed in more detail in the next section, a dissociation between the systems may be much more problematic if the systems perform complementary functions in the stress response. In this case, a dissociation of neuroendocrine response systems may reflect allostatic load that builds over time when an individual is exposed to chronic or repeated stress. Allostatic load may manifest as dysregulated patterns of stress response across systems rather than alterations in individual system activity. Therefore, examining the associations between concurrent actions across systems and behavior will allow a more thorough understanding of the physiological correlates of behavior problems than examining activity in single systems.

Although it is well established that SAM activity mediates the initial response to stress, a somewhat different perspective has emerged more recently regarding the role of the HPA system in the stress response. Munck and colleagues[47] suggest that GCs are important in suppressing, rather than augmenting, the initial SAM-activated stress response. Such reciprocal associations are well known in biological systems, with examples including the action potential and the clotting cascade. In both examples, the same stimuli that activate the initial response (e.g., opening sodium channel activation gates, cleavage of fibrinogen into fibrin) also activate a delayed suppressor (e.g., closing of the sodium channel inactivation gates, activation of plasminogen to plasmin to lyse clots) necessary to restore the system to its resting state. Munck et al specifically argue that the role of the HPA axis is to protect the organism from damage that would result if the body's normal responses to stress went unchecked and the body did not return promptly to a resting state. Thus, not only can external stressors perturb the balance of physiological activity, but the body's own responses can provide internal threats to this balance, a concept recognized early on by Cannon.[36] Sapolsky and colleagues[45] recently elaborated on Munck's hypothesis and summarized research indicating that GCs act both to augment and suppress sympathetically mediated changes in cardiovascular function, metabolism, fluid homeostasis, and immune function, providing support for the notion that optimum functioning after exposure to challenge requires coordinated activity within these systems.

Coordination of activities of the SAM and HPA systems occurs in the brain. Both physiological and anatomic substrates for this coordination have been identified that allow functional interactions between these systems. For one, hypothalamic CRH neurons and noradrenergic neurons have shared inputs and both systems are activated and inhibited by the same transmitters,[48] indicating that they can become coactivated. In addition, reciprocal neural connections between CRH and catecholaminergic neurons[48] allow each system to modulate the activity of the other. Given that the two systems' functioning is guided by the same underlying central coordination, dissociated activity in the periphery may indicate inefficient or poor central coordination, a possibility discussed in further detail shortly. Pathological processes that disrupt central regulation of the stress response may be important etiologic agents in both stress-related medical and psychiatric disorders and their precursors, including behavior problems in children.

Although both the SAM and HPA axes are activated in response to stress, and their actions are coordinated centrally, there are surprisingly few significant relations between the activity of these systems in the periphery. For example, van Goozen et al[17] found no significant association between heart rate (HR) or systolic blood pressure responsiveness and cortisol responsiveness among boys. On the surface, results such as this seem to indicate that these systems are not well coordinated. However, given the evidence for emotion-specific physiological processes in both children and adults,[49–51] activation may be well coordinated, but the expression of the activation may be specific to the demands associated with given emotions or situations. Additionally, subgroups of individuals may have different patterns of peripheral responses that are obscured in heterogeneous samples. For instance, children with behavior problems may evidence patterns of SAM and HPA arousal that are distinct from children without behavior problems, a possibility that has not been, but could be, tested empirically. In such a situation, the overall correlation between SAM and HPA activity in a mixed sample would be low, and the regularity of the associations between the systems would not be apparent without closer inspection. Therefore, gaining a better understanding of the patterns of activation and their behavioral correlates may shed new insight into why correlations among peripheral responses are typically low even when the same central mechanisms underlie responses.

In summary, the SAM and HPA systems are anatomically and physiologically connected in the central nervous system, although much remains to be determined about the nature of the systems' coordination at the physiological response level as well as the behavioral consequences of this coordination or its disruption. From a theoretical standpoint, understanding how the coordination of stress-response systems is related to children's behavior may provide insight into how physiological regulation of affect changes with development and how disruption of physiological processes may contribute to behavior problems in childhood. Clinically, insight into coordination of physiological systems may allow for more specific identification of response profiles that influence vulnerability to behavior problems. Next, research concerning associations between SAM and HPA activity and behavior problems in children will be reviewed, the advantages of adopting a multisystem approach will be highlighted, and directions for future research will be discussed.

PHYSIOLOGICAL CORRELATES OF BEHAVIOR PROBLEMS IN CHILDREN

Theoretical Models of Physiology-Behavior Associations

Kagan's[5] theoretical model concerning physiological correlates of behavior problems has served as a guiding principle for much of the research on physiology-behavior associations in childhood. He argues that certain children have an inborn tendency toward overarousal of the central nervous system (particularly of the hypothalamic and limbic circuits, including the amygdala),[5] possibly based on a lower activation threshold. Such children, he contends, are excessively fearful and compensate for their limbic hyperactivity through their overt behaviors, such as withdrawal and avoidance. These children show an inhibited temperament and are more susceptible to internalizing behavior disorders than children who do not tend toward overarousal. In contrast to overaroused, inhibited children, some children are born with an exceptionally high threshold for limbic activation. They appear underaroused and inappropriately lack fear. Such children are more likely to be hyperactive, intrusive, or aggressive and more likely to manifest externalizing behaviors than the children prone to overarousal.

Kagan's model is both unique and important in specifying specific, predictable patterns of physiological responses in children with behavior problems and has been supported

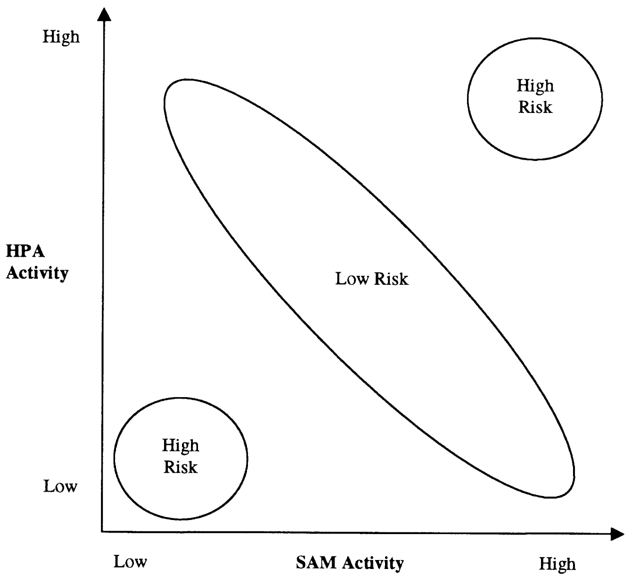

FIGURE 1. Predicted risk for behavior problems based on physiological profile: additive model. This figure represents the predictions about risk for behavior problems that would be expected if sympathetic-adrenal-medullary (SAM) and hypothalamic-pituitary-adrenal (HPA) activity contribute independently, or additively, to risk. In this model, there is an optimal medium level of arousal achievable by concurrent mid-level arousal in both systems or high activity in one system and low activity in the other. Children with excessive or inadequate overall arousal are at greatest risk for behavior problems.

by a number of empirical studies. However, a major limitation is that such a unidimensional model does not account for comorbid behavior problems, which are common, especially in early and middle childhood.[11,19,52] Indeed, research generally has not adequately dealt with comorbidity when investigating physiological correlates of behavior problems. On the one hand, if physiological variables are associated with behavior problems generally rather than there being separate physiological correlates of internalizing and externalizing behaviors (as argued by Kagan), it is possible that, among children globally classified as "at risk" according to their physiological profile, environmental characteristics determine whether problems will be expressed as externalizing, internalizing, or a combination of symptoms. On the other hand, comorbid behavior problems may be associated with a unique pattern of physiological responsivity to stress, a pattern substantively different from that associated with either internalizing or externalizing problems in isolation. Neither of these possibilities fits with a unidimensional model of arousal and risk for behavior problems.

Because the joint activation of stress-response systems has not been studied in relation to behavioral outcomes, it remains unknown how these systems may interact in their influence on behavior and whether the hypothalamic-pituitary-adrenal (HPA) axis serves primarily to augment or suppress sympathetic influences on behavior. Classic theories and empirical research concerning arousal and performance (e.g., memory, attention) indicate that their relation may be nonlinear (e.g., an inverted "U" such that when arousal is inadequate or excessive, performance suffers).[53–56] This concept has been informally exported to the literature on arousal and behavior problems, with Kagan's model[5] incorporating the commonly held belief that there is an optimal medium level of arousal associated with the least risk of behavior problems. Drawing on this model, if glucocorticoids (GCs) are believed to act primarily to augment sympathetically mediated effects, overall arousal could be conceptualized as the sum of activation of both systems. It would follow that children at the highest risk for behavior problems would have either concurrently low activity in both systems or high activity in both systems. Children at the least risk for behavior problems would display a medium level of overall arousal, which could be achieved either by high activation in one system and low activation in the other or by medium levels of arousal in both systems concurrently. The pictorial representation of such a hypothesis is displayed in Figure 1.

There are, however, several reasons to believe that such a model is inadequate in explaining the association between physiology and behavior. First, as previously outlined, there is increasing evidence to indicate that the sympathetic-adrenal-medullary (SAM) and HPA systems are not redundant in their actions and their actions are often in opposition. Second, this view cannot account for the substantial comorbidity among different types of behavior problems. The hypothesis advanced by Munck and colleagues[45,47] that the HPA axis functions to suppress SAM responses to stress leads to a second theoretical possibility,

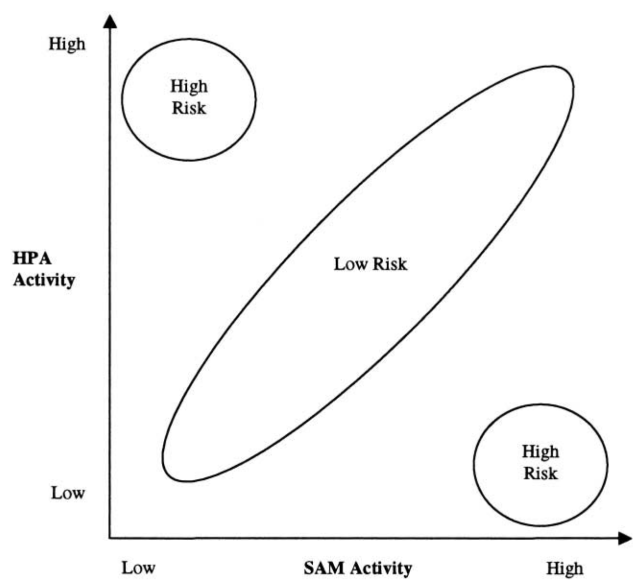

FIGURE 2. Predicted risk for behavior problems based on physiological profile: interactive model. This figure represents the predictions about risk for behavior problems that would be expected if sympathetic-adrenal-medullary (SAM) and hypothalamic-pituitary-adrenal (HPA) activity interact to predict risk. In this model, the children whose SAM and HPA activity are balanced are at the lowest risk for behavior problems, whereas children with activation asymmetries are at increased risk for behavior problems. Such behavior problems may be expressed as externalizing, internalizing, or combined behavioral phenotypes.

specifically, that the SAM and HPA systems are complementary in their actions and influences on behavior. Accordingly, optimal functioning is possible when SAM and HPA activity are balanced. Concurrent activation or deactivation of the SAM and HPA systems would be the most adaptive (associated with few behavior problems) and activation asymmetries would be maladaptive (associated with increased behavior problems). Figure 2 illustrates the predictions of this model. To date, these competing hypotheses have not been tested empirically in adults or children, although such investigation would significantly advance knowledge of how stress response systems are coordinated and the influence of such coordination or dysregulation on children's behavior problems.

Methodological Issues in the Study of Physiology and Behavior

Over the past two decades, a large body of literature employing a wide range of methodological approaches has emerged examining behavioral correlates of activation of the SAM and HPA systems in children. Although a methodological critique of the extant literature is not a focus of this paper, a brief review of several salient issues will illustrate the diversity of approaches that have been used. 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 or the developmental trajectories of such associations across childhood. Prospective research will be essential in this regard.

Methods for assessing SAM activation have been varied, including cardiovascular measures such as heart rate (HR), blood pressure (BP), and pre-ejection period. Whereas the former two parameters reflect the combined activity of the sympathetic and parasympathetic nervous systems, among other influences, the latter measure is a relatively pure index of sympathetic influence on the heart.[57] In studies of children's reactivity to stressors, cardiovascular measures have the advantage of detecting SAM activation almost instantaneously. In adults, serum and urinary catecholamines have also been measured, although urinary catecholamines and metabolites are limited by their lack of sensitivity to rapid changes in SAM activation.

HPA axis activation in children has been assessed using urinary cortisol (both 2-h and 24-h), serum cortisol, adrenocorticotropic hormone (ACTH), and, more recently, salivary cortisol. Again, urinary measures are limited in sensitivity to changes in response to environmental stimuli but may be adequate for reflecting cumulative activation over longer periods of time. Salivary measurements are easily obtained, especially in child samples, and are believed to change within 10 to 30 minutes after the onset of a stressor.[44] Cortisol measurements are further complicated by the known diurnal variation in cortisol secretion, making it important to take measurements at consistent times. Both resting (baseline) physiological measures and measures of reactivity in response to known and unknown stimuli have been used.

Behavioral variables have similarly been subject to a variety of assessment methods. Among children, two broad categories of behavior have been studied: externalizing and internalizing. Externalizing symptoms include behavior 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. Both types of behavior problems have been measured in clinical and nonclinical samples of children, according to self-, parent-, and teacher-reports, observational methods, and even court records.[7,9,16,19] In most studies of physiological correlates of behavior problems, internalizing and externalizing symptoms have been treated as orthogonal or only one has been examined.[7–11,13,14,16–18,20,21] Yet several studies indicate that these symptoms are positively related in young children.[11,19,52]

The following review is not designed to be a comprehensive presentation of all former research concerning behavior problems and physiological responses in children; rather, the studies were selected to represent the diverse approaches, samples, and measures that have been used to study physiological reactivity in childhood. Notwithstanding methodological variability across studies and limitations of individual studies, some consistencies are evident and will be important to take into account when designing future research.

Physiological Correlates of Externalizing Symptoms

Across a variety of studies, using different types of samples, measures, and procedures, low sympathetic activation has been linked to externalizing, aggressive, or disruptive behaviors in children.[9,15,17,19] Low adrenocortical activation has also been associated with increased levels of externalizing behaviors.[7,10,16,17,21] To illustrate the wide range of methodological approaches that have been used, a few examples are discussed in more detail. First, studies assessing physiological responses among primarily clinical samples (and case-control samples) are described, followed by studies among nonclinical samples, for instance, children with high levels of externalizing symptoms.

Van Goozen and colleagues[17] compared HR, systolic and diastolic blood pressure (SBP and DBP), and salivary cortisol at rest and during a 75-minute competitive stressor. Participants included 42 boys aged 8 to 11 years, 21 of whom were diagnosed with oppositional defiant disorder (ODD) or conduct disorder (CD). The remaining 21 were not diagnosed with any disorder. The researchers expected that the ODD/CD group would show lower levels of all physiological variables at rest but higher HR and SBP during stress than controls. Results partially supported the predictions. The ODD/CD group had lower baseline and higher stress-induced HR and lower baseline cortisol than the controls, but no differences were found between the groups in stress-induced cortisol levels or SBP and DBP. Although cortisol levels may provide insight into HPA functioning, HR and BP are peripheral physiological responses that are affected by sympathetic and parasympathetic activation, making it unclear as to what specifically may be contributing to the evident differences between the two groups in resting and stress-induced HR. Analyses of systems underlying changes in HR may provide greater insight into whether boys with externalizing symptoms are under- or over-aroused.

Associations between low baseline cortisol and antisocial behavior have also been found in girls. Pajer et al[21] compared morning resting cortisol in 47 15- to 17-year-old girls with CD to 37 similar-age girls without CD. Even after controlling for potential confounds, such as oral contraceptives, psychotropic medications, and post-traumatic stress disorder, the girls with CD had lower resting serum cortisol levels than the girls without CD. As noted by the researchers, however, possible group differences in bedtime or waking patterns were not considered, which could have influenced the diurnal pattern of cortisol secretion. Nonetheless, these findings are consistent with the aforementioned results indicating that low HPA activation is related to some types of externalizing disorders.

In a third study, Kruesi et al[58] compared cortisol secretion between 19 boys with ODD, CD, or attention deficit hyperactivity disorder (ADHD) and 19 controls (boys aged 7−16 yr). No significant differences in cortisol levels were found between the two groups.[58] However, 24-hour urinary cortisol levels were collected. Because such measures are cumulative, they may be less sensitive to variations throughout the day, which may distinguish groups of children, than are event-specific serum or salivary measurements. These measurement differences could lead to discrepant findings across studies.

Finally, although not technically a clinically-diagnosed sample, Raine and colleagues[9] investigated physiological reactivity in British adolescents in relation to criminal convictions 10 years later. HR, skin conductance, and electroencephalogram (EEG) data at rest were collected for 101 schoolboys aged 14 to 16 years. At follow-up, 17 of the 101 men had criminal convictions (one of these convictions was before the physiological testing). Comparisons between the physiological response profiles from adolescence between the men with and without criminal conviction records revealed that the men with a history of criminal convictions had lower HR as well as diminished electrodermal and EEG arousal as adolescents than the men without convictions. Although none of the measures in this study is a direct measure of either SAM or HPA activity, these results show concurrent alterations across more than one system in boys later convicted of criminal activity.

Several studies have tested associations between physiological parameters and externalizing symptoms in nonclinical samples of children. Boyce and colleagues[19] investigated physiological reactivity and behavior problems in 122 6- to 7-year-old children who were selected because they were categorized in the upper quartile of internalizing or externalizing behavior problems during a prior assessment period. The children completed a protocol composed of mild stressors during which the children's HR, mean arterial pressure, respiratory sinus arrhythmia (RSA, a measure of parasympathetic activity) and pre-ejection period (PEP) were recorded. Children with high levels of externalizing symptoms had diminished sympathetic arousal (indexed by PEP) compared with children with low levels of externalizing symptoms. This study extends findings based on clinical samples to a nonclinical sample, but the children were not randomly selected; rather, they were explicitly selected on the basis of having high or low levels of symptoms. It is therefore not clear whether the results would generalize and predict behavior problems in a normative or unselected sample of children. The findings are nonetheless noteworthy because they show significant associations between underarousal and externalizing problems in a nonclinical sample.

Other researchers have examined associations between physiological response profiles in children and specific behaviors often linked to externalizing symptomatology, rather than the general behavior problem categories per se. Tennes and Kreye,[7] for instance, examined associations between 2-hour urinary cortisol secretion and both teacher-reported and observer-coded classroom behavior in 70 second graders. No significant relations were uncovered between teacher-rated behaviors and children's morning cortisol levels, although observer-rated peer contact, preoccupation with school, and hostility toward teachers were associated with cortisol levels. Lower cortisol levels were associated with less peer contact, less preoccupation with school, and higher levels of hostility toward teachers. That hostility toward authority figures was associated with diminished cortisol levels is consistent with the notion that underarousal and externalizing symptoms are linked.

Somewhat different results were obtained by Tout et al[16] in a study of cortisol responses in preschool-aged children. Teachers rated 75 children's behavior, and children were observed during play times at preschool. Morning saliva samples were collected periodically over the course of a month, and median morning cortisol and morning cortisol reactivity (defined as the difference between third quartile and median cortisol, reflecting a tendency to have frequent high morning cortisol levels) were computed. Median cortisol was not predicted by three composite behavior indices derived from observer and teacher ratings (i.e., anxious/internalizing, angry/externalizing, and competent social behaviors). However, classroom behavior did predict cortisol reactivity such that angry and aggressive behaviors were associated with increased cortisol reactivity, a finding that contrasts with Tennes and Kreye's findings of an association between hostility and low cortisol levels.[7]

In summary, the studies described here reflect the diversity of approaches used to study associations between physiological variables and externalizing behavior problems in clinical and nonclinical groups as well as behaviors often associated with such problems (e.g., angry or aggressive acts among children). Children ranging in age from the preschool years to adolescence have been included in different samples. Together, results converge in indicating that low levels of SAM and HPA arousal, while resting or during times of potential stress, are associated with externalizing problems. Based on these findings, one might expect children who evidence low reactivity in both the SAM and HPA systems concurrently to have the highest levels of externalizing behavior problems (Fig. 1). However, as discussed in the previous sections, it may be that unbalanced activity in the SAM and HPA systems is associated with greater risk than concurrent low activity (Fig. 2). To date, however, a paucity of empirical research exists concerning concurrent SAM and HPA activity and externalizing symptoms in children. Examining concurrent activity in multiple systems and possible interactions between systems will help clarify when and in whom externalizing behaviors are associated with low arousal.

Physiological Correlates of Internalizing Symptoms

In contrast with externalizing behaviors, internalizing behaviors have been associated with high sympathetic and adrenocortical activation in children,[8,11–15,17,20] although again, relatively few studies of concurrent activation have been conducted. Selected examples, discussed below, illustrate the diversity of approaches that have been used. As in the previous section, studies including case-control groups are described, followed by studies including primarily nonclinical or nondiagnosed samples.

Goodyer and colleagues[20] examined morning and evening cortisol secretion among 47 clinically depressed 8- to 16-year-old children followed over 72 weeks. Saliva samples were collected at 8 a.m. and 8 p.m. for two consecutive days at study entry and again 36 weeks and 72 weeks later. Children whose symptoms had not remitted after the 72-week period were classified as chronically depressed, and those whose symptoms had subsided were classified as recovered. With age statistically controlled, children with chronic depression had higher evening cortisol levels at all three time-points than children who recovered from their depression. Adverse life events over the course of follow-up were also related to elevated evening cortisol at study entry and to chronicity of depression. The authors speculate that cortisol hypersecretion may affect cognitive processes that influence risk for adverse events and, ultimately, the course of major depression, although other interpretations are possible. Unfortunately, the study did not include children without a history of depression, inhibiting the authors from determining how depressed and recovered children's cortisol levels compare with those of their nondepressed peers.

Granger and colleagues[11] examined associations between cortisol reactivity to a laboratory-based interaction task and behavior symptoms among clinic-referred 7- to 17-year-old children with internalizing or externalizing symptoms or a combination of both types of symptoms. Saliva samples were collected before and after the interaction task, and behavior problems were assessed by parent- and child-report. Findings revealed that children with high cortisol reactivity (the top quartile of residualized cortisol difference scores comparing children's pre- and post-task cortisol levels) displayed more internalizing problems including social withdrawal and anxiety than did children with low cortisol reactivity (the bottom quartile). When children's continuous cortisol reactivity scores were examined, they were predictive of a composite measure of overcontrolled behaviors, which included several components of internalizing symptoms (e.g., social withdrawal, anxiety, depression, and somatic complaints). It should be noted that the children were tested throughout the day and variables that could influence HPA activity, such as stage of development or menstrual cycle, oral contraceptive use, and psychiatric diagnosis, were not controlled in the analyses. Nonetheless, the participants were drawn from an unselected clinic population, and a large number of children had concurrent internalizing and externalizing problems. Thus, these results may be potentially more generalizable to behavior problems as they occur naturally than results of other studies using more restricted samples and diagnoses.

A longitudinal study conducted by Kagan and colleagues[8] confirms some of the aforementioned findings concerning cortisol and internalizing symptoms among nonclinical children, specifically those with temperamental characteristics resembling internalizing behaviors. Two cohorts of children were followed from 21 and 31 months of age through 7.5 years. Based on children's behavior during novel laboratory tasks at the study intake, children in the upper and lower 15% of the sample were classified as either inhibited (shy, quiet) or uninhibited (talkative, outgoing), respectively. Of relevance to the current discussion, when a continuous measure of inhibition was examined, rather than the dichotomous inhibited versus noninhibited groups, morning home salivary cortisol levels were positively associated with inhibition. When the groups were compared, inhibited children showed greater sympathetic reactivity over time than uninhibited children. Specifically, across all follow-ups, the inhibited and uninhibited children had the highest and lowest HR, respectively, of the sample. Similarly, the inhibited children were more likely to show HR accelerations when engaged in challenging tasks than uninhibited children. At 5.5 years, inhibited children evidenced greater pupillary dilation during cognitive testing than uninhibited children; at 7.5 years, inhibited children had greater reflex tachycardia to postural change than uninhibited children, both indicative of greater sympathetic activation.

Insofar as behavioral inhibition in young children is related to and increases risks for internalizing behavior problems,[5] these findings, when considered in conjunction with research on clinical populations of children, indicate that heightened physiological reactivity, particularly adrenocortical activation, is predictive of or at least associated with internalizing behavior problems in early and middle childhood. The findings of elevated SAM and HPA activity in children with internalizing problems might lead one to predict that children highly reactive along both axes have the most internalizing problems (Fig. 1), again an untested prediction. Particularly in light of evidence that associations between HPA reactivity and behavior are not constant across social settings, described next briefly, an important next step will be to determine when increased HPA reactivity may or may not be associated with internalizing behavior problems. In this respect, evaluating the biological context (i.e., other physiological variables that may influence cortisol-behavior associations) will be of significant value.

As a final note with regard to physiological variables (primarily HPA activity) and temperamental characteristics in infants and young children, results of several studies are beginning to indicate that the associations between cortisol reactivity and behavioral tendencies are influenced by the social context in which both are measured.[12,13] For instance, when first in an unfamiliar social environment (e.g., a new kindergarten or preschool), children who are socially competent and outgoing show elevated salivary cortisol. However, once children are familiar with their social environment (e.g., several months after the new school year), children who are withdrawn or inhibited evidence higher levels of salivary cortisol than socially competent children.[12,13] Although a thorough discussion of this noteworthy advancement is not possible in this paper, it is important to recognize that physiology is only one of many domains that interact to affect behavior. Once a basic understanding of physiological systems' interactions and relations to behavior problems is gleaned, it will be necessary to expand this understanding by considering the impact of psychological and environmental influences and their interactions with stress-response systems.

Joint Activation and Psychopathology

Whereas a number of studies have investigated associations between behavior problems and either SAM or HPA activity in children, few studies have investigated the concurrent activity of these two systems in predicting behavior problems. In those that have measured activity in both systems, the systems are generally treated independently, and potentially important interactions between the physiological systems have not been explored.[8,18] Therefore, it remains unknown how concurrent activity in the two systems is associated with risk for behavior problems in children (Figs. 1 and 2) 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. Such investigations would contribute to the understanding of the coordination of stress response systems in children. Additionally, as knowledge of associations between physiology and behavior is refined, more accurate identification of children at risk will be possible.

A few studies have examined associations between joint activation of the SAM and HPA systems and psychopathology in adults.[59–61] In general, findings indicate that among individuals with psychiatric symptoms or disorders, altered patterns of neuroendocrine responses are evident, indicating dysregulation of the SAM and HPA systems. Researchers have speculated that this dysregulation may be due to prior chronic stressful experiences. Specifically, an elevated ratio of norepinephrine to cortisol is evident in women with premenstrual dysphoric disorder, veterans with post-traumatic stress disorder, and men with alexithymia.[59–61] To date, studies of patterns of neuroendocrine response have yet to be conducted in children, although it is important to know if children exposed to chronic stress manifest similar alterations in neuroendocrine function.

DIRECTIONS FOR FUTURE RESEARCH

Interest in the study of physiological correlates of behavior problems in children has expanded considerably in recent years. Although some studies have taken a multisystem approach to investigating physiological variables, none has taken an interactive approach. Instead, each physiological variable has been treated as an independent predictor without consideration of the biological context in which it occurs. By their nature, however, physiological systems interact, and the assessment of multiple physiological systems in children at high and low risk for behavior problems is in need of investigation. As a first step, investigators who collect data on multiple systems can easily incorporate an interactive approach into existing studies. Many investigators already have data that can be tested for such interactions between physiological systems. Further, investigators of planned studies of physiology and behavior should consider collecting data on more than one physiological system. These relatively straightforward modifications and analyses would permit more refined examination of physiological correlates of behavior.

Second, insight into physiological correlates of behavior would be enhanced significantly by exploring how physiological correlates of relatively "pure" behavioral types may differ from correlates in children with comorbid problems. Using a multisystem approach in such an investigation would allow researchers to examine a wider range of potential correlates and their patterns of interactions to pinpoint where similarities or differences exist. Although such research could be conducted in case-control studies with groups of children with "pure" externalizing and internalizing problems and a group with comorbidity, this question can also be addressed by cross-sectional research in an unselected sample of children in whom externalizing and internalizing problems are measured. An advantage of this last strategy is that the findings would be generalizable to a broader group of children.

Third, although developmental trends and gender differences in associations between physiology and behavior have not been a primary focus of this paper, knowledge of such associations needs to be gleaned from future research. There is evidence, for example, that circulating glucocorticoids (GCs) may have opposing effects on brain development at different points in development.[62] 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.[62] There is also evidence that, with development, boys' and girls' risk for behavior problems diverges. For instance, with age, girls tend toward internalizing symptomatology, whereas boys tend to show increased externalizing problems.[63,64] To address effects of development and gender on physiology-behavior associations, longitudinal studies in clinical and nonclinical samples of boys and girls would be desirable. However, cross-sectional research that systematically examines associations between physiology and behavior in both girls and boys of different ages would also make an important contribution.

Fourth, it will be imperative to integrate multiple biological and behavioral systems in investigations of predictors of behavior problems in childhood. As mentioned, physiological reactivity is a risk factor for illness and behavior problems in childhood. Boyce and colleagues speculate that reactive children have difficulty regulating their arousal when faced with stress. This difficulty may not only be manifested in physiological responses but may also be evident in behavioral coping strategies.[65] In fact, a growing body of research indicates that children (as well as adults) vary considerably in the strategies they employ to cope with stress and challenge and the effectiveness of those strategies (Compas et al, 2001[66] for a review). The classic and most commonly studied strategies include approach versus avoidance (or engagement vs disengagement) or problem versus emotion focused coping.[67–69] Whether children avoid or approach a particular stressor may affect their physiological responses, including how the different physiological systems coordinate their responses. Alternatively, children's overt coping behavior may be a product of their physiological arousal across multiple systems. As knowledge regarding interactions among physiological systems increases, behavioral and other coping responses must be integrated into theoretical models and investigated to understand the complex nature of risk for psychiatric disorders and their precursors.

Fifth, it remains unknown whether peripheral physiological responses somehow cause alterations in behavior, whether such responses are themselves caused by disordered behavior, or whether both physiological responses and behavior are outcomes of central processes that have gone awry. To address issues of causality, longitudinal studies would be valuable in documenting the natural history of physiology-behavior associations over time, and intervention studies would be able to show whether such associations change with treatment. For instance, it would be important to know if behavior change resulting from either behavioral or pharmacological intervention is associated with corresponding changes in physiological parameters or whether physiological variables remain as markers despite clinical improvement. Furthermore, because the brain is responsible for integration and organization of behavior and physiological responses to stress, direct investigation of central activity in response to stress and among children with and without behavior problems is warranted.

Knowledge regarding physiological correlates of behavior problems will permit better identification of children at risk and may also provide markers of treatment response. Advances such as these will facilitate the early intervention that is essential to minimize the likelihood that children with behavior problems will develop psychiatric disorders as adolescents and adults. Because untreated and undertreated psychiatric disorders exact tremendous economic, social, and human costs and there is evidence that early interventions reduce this morbidity, advancing understanding in this domain must be a priority.

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Literary Quotes

Suetonius on How Nero Became Such a Monster

Nero (37–68 AD), who was emperor of the Roman Empire from 54 to 68 AD, began his reign with signs of virtue, but it soon degenerated into numerous infamous acts of brutality. He had his wife murdered so that he could marry his mistress Poppea, but then he kicked the pregnant Poppea to death. When a fire destroyed much of Rome in 64, he blamed the Christians and had them persecuted. Because his philosopher-tutor Seneca disagreed with him, he ordered him to commit suicide.

Suetonius (75?–150?) described the lives of the first 12 Roman emperors from Augustus to Domitian (De Vita Caesarum). *One might hope that this respected author, who was also private secretary to the later emperor Hadrian, from 119 to 121, would have had sufficient information and wisdom to offer us some insights into the origins of Nero's bizarre and uncivilized behavior.*

However, Suetonius's analysis is disappointing. He concludes, "A closer study of the Domitian family history would probably suggest that Nero's vices were inherited. . . ." As evidence for this view he describes the antisocial acts of Nero's ancestors, including his father's "wholly despicable character":

Nero's horoscope at once (at his birth) occasioned many ominous predictions; and a significant comment was made by his father in reply to friendly congratulations: namely, that any child born to himself and Agrippina was bound to have a detestable nature and become a public danger.

Suetonius appears not to have considered seriously the environmental impact of such influences as these parental attitudes, his father's early death, his extended separation from his mother because of her banishment, a prolonged period of poverty, and his early education by a barber and a dancer.

As pointed out previously in these notes, although the general literature has become rich in insights about child development during the last 200 years, such understanding was very rare before that. Even one of the greatest biographers of the ancient world evidently chose to put the blame for Nero's antisocial behavior on his inheritance rather than on an interaction of his inborn traits with these deleterious environmental influences.

Suetonius: The Twelve Caesars. Baltimore, MD, Penguin Classics, 1957. Translated by Robert Graves.

Noted by William B. Carey, M.D.