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LOW SALIVARY CORTISOL LEVELS ARE ASSOCIATED WITH EXTERNALIZING BUT NOT INTERNALIZING BEHAVIOR PROBLEMS: A LATENT STATE TRAIT MODEL IN NORMALLY DEVELOPING YOUTH

A Thesis in

Biobehavioral Health

By

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Submitted in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

August 2003

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ABSTRACT

Research relating salivary cortisol levels with internalizing and externalizing behavior problems in youth has yielded inconsistent results. The high day-to-day variation in adrenocortical activity may require an analytical strategy that separates variance in cortisol levels attributable to "stable trait-like" versus "state- or situationally-specific" sources. Early morning saliva samples were obtained from 654 low risk youth (M age = 13.5 yrs; range 6-16 yrs in year 1) on two successive days one year apart. Latent state trait modeling revealed that 70% of the variance in cortisol levels could be attributed to state-like sources, and 28% to trait-like sources. For boys only, higher levels of externalizing problem behaviors were consistently associated with lower cortisol attributable to trait-like sources across all three years of behavioral assessment. The inverse association between individual differences in children's cortisol and externalizing problem behavior is reported in studies of at-risk and clinical groups. The present findings confirm the relationship spans both normative and atypical child development, and supports speculations that boys with low cortisol may be at risk for externalizing behavior problems.

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ABBREVIATIONS

ACTH: Adrenocorticotropic Hormone

ADHD: Attention Deficit Hyperactive Disorder

BAS: Behavioral Activation System

BIS: Behavioral Inhibition System

CBCL: Child Behavior Checklist

CD: Conduct Disorder

CDI: Children's Depression Inventory

CESD: Center for Epidemiological Studies Depression Scale

CFI: Comparative Fit Index

CRH: Corticotropin-Releasing Hormone

CV %: Coefficient of variation (%)

DBD: Disruptive Behavior Disorder

DF: Degrees of Freedom

DHEA: Dehydroepiandrosterone

ERP: Event Related Potential

FI: Factor Invariance

HPA: Hypothalamic-Pituitary-Adrenal

LST: Latent State Trait

M: Mean

MTMM: Multi-Trait Multi-Method

NFI: Normed Fit Index

NNFI: Non-Normed Fit Index

OCD: Obsessive Compulsive Disorder

ODD: Opposition Defiant Disorder

PTSD: Post Traumatic Stress Disorder

R: Standardized Beta Weights

RMSEA: Root Mean Square Error of Approximation

SD: Standard Deviation

ug/dL: micrograms per deciliter

YSR: Youth Self Report

SEM: Structural Equation Modeling

PREFACE

The purpose of this study is to rigorously evaluate components of variance in salivary cortisol, to assess associations between adrenocortical activity and internalizing and externalizing behavior, and, in doing so, should help forward biosocial models that posit interactive effects between adrenocortical activity and behavior. The study of the behavioral correlates of adrenocortical activity has been hindered by the large portion of apparently "unsystematic" variance in salivary cortisol that is due to the confluence of situation-specific events, the interaction of the person with their environment and intrinsic individual differences in adrenocortical activity. Some studies imply that a small portion of the variance in adrenocortical activity may be cross-situationally consistent. This study will apply latent state trait (LST) modeling techniques to estimate the components of variance in cortisol levels attributable to "state" versus "trait" and will assess whether trait cortisol is associated with internalizing and externalizing behavior in low risk youth.

The activity of the hypothalamic pituitary adrenal (HPA) axis varies considerably in response to the day to day challenges that individuals face. Adam (2003) reveals that higher levels of positive social emotions and reports of working hard, engagement in activity, and productivity are associated with lower cortisol levels, whereas negative emotions are associated with higher cortisol levels in adults at work, home and in public places. Similar results are reported for adolescents (Adam, 2002). Smyth and colleagues (1998) report wide variation in cortisol levels measured six times a day for two days; much of that variation was due to recent or anticipated stressors, negative and positive

affect. These studies demonstrate that adrenocortical activity varies as a function of day to day fluctuations in situational demands. Is it possible that situation-specific and person-environment interactions impact a single measure of cortisol so much so that intrinsic individual differences in salivary cortisol are obscured? An answer to this question seems critical for studies on individual differences in HPA axis activity.

If individual differences in cortisol levels and associations between cortisol levels and behavior are tested using variance collapsed across trait-like and situation-specific (i.e., state) influences, the ability to detect a significantly behavioral association may be compromised. Kirschbaum and colleagues (1990) report that 60 – 70% of the variance in salivary cortisol levels in adults is due to situation-specific factors and Preville and colleagues (1996) reveal that the variance in salivary cortisol levels in older adults is completely derived from situation-specific factors. Studies on individual differences in cortisol and its relation to behavior problems may be complicated because the majority of variance in cortisol levels is changing dramatically as individuals experience the events of the day. As illustrated by Kirschbaum and colleagues (1990), only 30 – 40% of the total variance in salivary cortisol is consistent across time and has the potential to be associated with stable behavior profiles. The expected effect size of hormone-behavior correlations is not likely to be greater than 0.30 (Granger & Kivlighan, in press). Thus, the chances of detecting a significant cortisol-behavior association may be minimized by traditional statistical methods that collapse across state and trait influences on salivary cortisol (Eid, Notz, Steyer, & Schwenkmezger, 1994). Separating state and trait sources of variance in cortisol may improve the likelihood that an association between cortisol

and behavior will be observed (Steyer & Schmitt, 1990; Steyer, Schwenkmezger, & Auer, 1990).

The relationship between cortisol and internalizing and externalizing behavior problems is important to understand because these behaviors are salient in the lives of children and adolescents and present challenges for normal, at risk and clinical populations. In particular, physiological arousal appears to play a role in the development of behavior problems. Low physiological arousal may convey risk to children and adolescents for externalizing behavior problems whereas high adrenocortical activity conveys resilience against further developments of externalizing behavior problems (McBurnett et al., 1991; Raine, Venables, & Williams, 1995). Conversely, high physiological arousal may convey risk for the development of internalizing behavior problems (Zahn-Waxler, Klimes-Dougan, & Slattery, 2000), particularly for girls (Zahn-Waxler, Race, & Duggal, in press). Thus, understanding relationships between cortisol and internalizing and externalizing behaviors has the potential to contribute to our understanding of when adrenocortical activity conveys risk or resilience.

Cortisol-behavior relationships were approached from a new perspective. Stable interindividual differences in behavioral characteristics that define intraindividual differences in normative developmental trajectories were not assumed to be associated with situationally-specific variability in HPA axis activity, nor were these behaviors assumed to be associated with cortisol levels measured at any specific point in time. Instead, these key trait-like behaviors were hypothesized to be associated with stable or consistent "trait-like" variation in the activity of the HPA axis. This approach estimates individual differences in stable trait-like component of the variation of HPA axis activity.

This method should further research on adrenocortical activity by providing a tool that assesses trait cortisol and potentially allows detection of more consistent hormone-behavior associations in youth.

The following five research questions are asked in this paper: Will variance in adrenocortical activity primarily be due to situation-specific influences? Will there be significant variance in salivary cortisol that is attributable to a trait-like component? Will state and trait cortisol levels be inversely associated with externalizing behavior problems, but positively associated with internalizing behavior problems? Will there be gender differences in the variance in state or trait cortisol levels, with more state and trait variance in males compared to females? Will the association between trait cortisol and externalizing behavior be stronger in boys compared to girls, but will girls have a stronger association between trait cortisol and internalizing behavior problems? Answers to these questions may slightly increase our ability to infer causality as the number of studies which reveal consistent effects increase. Making inferential statements about hormone-behavior relationships based solely on this study is premature, but this study should help refine understanding of the biosocial model.

The first chapter of this dissertation describes the basic mechanism of the HPA axis for background material, then a body of literature that relates adrenocortical reactivity to situation-specific factors and person-situation interactions is briefly reviewed to demonstrate that the HPA axis is largely responsive to situational factors. Situation-specific factors and person-situation interactions are not the only influences on adrenocortical activity, however, so the next section reviews individual differences in the development of the HPA axis (e.g., child maltreatment and parental psychopathology) to

demonstrate that intrinsic individual differences are conceptually associated with adrenocortical activity. The purpose of this section is to suggest that the HPA axis is heavily influenced by situation-specific factors, but nonetheless individual differences in adrenocortical activity should underlie these transient changes in HPA axis activity. The second chapter describes the nature of internalizing and externalizing behavior problems; focuses on potential mechanisms that relate behavior problems with adrenocortical activity; then reviews the literature that relates cortisol with internalizing and externalizing behavior problems in clinical, at risk and low risk normally developing youth. The purpose of this chapter is to justify why biological underpinnings of behavior problems are anticipated. The premise of this study is that the inconsistencies in the literature on cortisol-behavior problems are due to the dramatic day to day variations in the HPA axis that is due to situation-specific factors; when this state variance is partialled from trait-like variance in adrenocortical activity, more consistent hormone-behavior associations potentially may be observed. The third chapter justifies the second research question on gender differences in adrenocortical activity. Conceptual justification for why gender differences in adrenocortical activity is provided, followed by a review of the literature that demonstrates gender differences in HPA axis activity in adults. Rationale for why similar patterns are expected in adolescents is then provided. The main conclusion is that gender is an individual difference factor that may have a large impact on HPA axis activity, and hormone-behavior associations and should not be ignored by researchers interested in salivary cortisol. This leads into the fourth chapter which describes methods for estimating trait constructs. Advantages and disadvantages of five different methods are presented. The main conclusion is that latent state trait models are

a natural analytical strategy for examining trait cortisol-behavior associations. The fifth chapter briefly goes over the hypotheses. The sixth and seventh chapters provide methods and results details. The eighth chapter discusses potential mechanisms behind the cortisol- behavior problem relationships, the meaning of gender differences, and the utility of LST modeling. The premise of the discussion is that separating situation-specific from stable trait-like variance in salivary cortisol may help to clarify the consistency of behavioral associations in the next generation of studies.

CHAPTER 1

INFLUENTIAL THEORETICAL PERSPECTIVES

This chapter provides a brief overview of theoretical perspectives that have shaped the nature of this study's research questions and design. The first perspective forwards a biosocial model which can be advanced through three stages of development. Through these stages, a more complete understanding of how biological and contextual forces interact will be met. The second perspective uses developmental science as a framework. This theory primarily advances a person-environment focus by emphasizing time and timing, multiple levels of analysis and context. Developmental science uses holistic interactionism and person-oriented perspectives to frame research questions. The importance of these theoretical perspectives is interpreted with respect to the current study's design.

ADVANCING A BIOSOCIAL MODEL THROUGH THREE STAGES OF DEVELOPMENT

Exploration of this study's research questions should contribute to biosocial models of children's social behavior. As outlined by Granger and Kivlighan (in press), biological functions, such as HPA axis activity, set the stage for behavioral adaptation to environmental challenge (i.e., the fight-or-flight response). Environmental challenge, in turn, induces behavioral change that reciprocally affects biological processes. This sets up an interconnected network between behavior-biological processes and contextual forces. The challenge for researchers interested in biosocial models is to discover which

behaviors, biological processes and social contexts are salient for children's development, when these reciprocal processes occur, and whether or not they can be changed (Gottlieb & Halpern, 2002; Magnusson et al., 1996). Raine (2002) proposes that the biosocial model can be advanced through a series of three stages. The first step is to document relationships between biological processes and behaviors. Many research groups have successfully done so (see review by Gunnar & Donzella, 2002), but there still are inconsistencies in this literature due to operationalization of salivary cortisol (i.e., levels, reactivity, diurnal rhythms) and variability in social contexts (i.e., laboratory stressors, naturalistic settings, home collection, Granger & Shirtcliff, in press). Adam (2003) argues that naturalistic settings are more valuable than laboratory stressors because they allow for greater expression of gene-environment correlations, in which the individual's natural tendencies are expressed through their ability to choose environments that suit their temperament or mood, and potentially stronger cortisol-behavior associations. Conversely, individual differences in adrenocortical activity are more easily interpreted given the similarity in contextual influences of a laboratory stressor (e.g., Kirschbaum, Pirke, & Hellhammer, 1993; but see Klimes-Dougan, Hastings, Granger, Usher, & Zahn-Waxler, 2001). The challenge for this stage of the biosocial model is to resolve how biobehavioral relations are influenced by the social context.

The second stage of the biosocial model is to document interaction effects between biology, behavior and the social context (Raine, 2002). This will permit systematic exploration of the impact of the social context so questions can be asked about how the context promotes or attenuates hormone-behavior relationships (Granger & Kivlighan, in press). For example, Booth and colleagues (2003) found that low

testosterone was a risk factor for depression and high testosterone was a risk factor for risky behavior, but only when relationships with parents were poor. Having a good relationship with one's parents is a component of the social context that seems to protect girls and boys from expressing testosterone-related problem behaviors. While these types of interaction effects are powerful examples of the moderating force of parent-child relationships, mid-level theories that allow models to be accepted, rejected and refined are needed to advance our understanding of biosocial models (Gottlieb & Halpern, 2002; Granger & Shirtcliff, in press).

This sets up Raine's (2002) third stage in which biosocial models are refined and developed. A deeper understanding of mechanisms underlying interaction effects will allow meaningful deductions about biobehavioral processes in child development to be made (Granger & Kivlighan, in press). We are currently at the cutting edge of stage two. Before we can advance, inconsistencies in cortisol-behavior relationships need to be adequately resolved. The purpose of the current study is to address the inconsistencies in cortisol-behavior relationships by systematically considering the importance of consistency and stability in salivary cortisol. The influence of context on adrenocortical activity is indirectly addressed through statistical methods that separate out situation-specific influences on HPA axis activity from the stable portion of variance in salivary cortisol.

DEVELOPMENTAL SCIENCE, HOLISTIC INTERACTIONISM AND PERSON-ORIENTED PERSPECTIVES

In addition to the biosocial model forwarded by Raine (2002), three other

conceptual frameworks have guided the nature of the study's core ideas: developmental science, holistic interactionism and the person-oriented perspective. Developmental science is a discipline that seeks to promote the integration of ideas from many other fields, including social, psychological and biobehavioral disciplines to study intraindividual change (Cairns, Elder, & Costello, 1996). The goal of the holistic interactionist and the person-oriented model is to integrate multiple levels of the individual by understanding the whole person. The work of Cairns (Cairns, Bergman, & Kagan, 1998; Cairns et al., 1996; Cairns, Gariepy, & Hood, 1990; Cairns, 1986; Cairns & Cairns, 1994; Magnusson & Cairns, 1996), Magnusson (Magnusson, 1996; Magnusson, 1999; Magnusson & Cairns, 1996; Magnusson et al., 1996; Magnusson & Stattin, 1998). and Bergman (Bergman, 1996; Bergman & Magnusson, 1997; Wangby, Bergman, & Magnusson, 1999) used holistic interactionism and the person-oriented approach as a framework from which to develop the discipline of developmental science. These fields are unified by the same theoretical perspective: holistic interactionism. This model considers the individual a part of a dynamic person-environment system (Magnusson & Stattin, 1998). This perspective emphasizes: 1) time and timing, 2) multiple levels of analysis, and 3) context (Cairns et al., 1996). At each of these levels, biosocial research is important for understanding how the individual develops.

Time and timing are emphasized in developmental science in order to understand development (Magnusson & Cairns, 1996). The holistic interactionism perspective postulates that the development of the individual should unfold. This lies in contrast to studying development through a series of cross-sectional studies which assume that the state of an individual at one age will naturally develop into the older, different individual.

Thus, this perspective stresses the need for longitudinal research designs and methods that model change to understand the development of the social, cognitive and biological individual (Collins & Sayer, 2001). The changing individual is complex, but this should not be statistically controlled, but rather methodologically explored and theoretically interpreted (Cairns et al., 1996). This perspective informed the current study's consideration of time and timing. Hormone-behavior relationships were modeled during a salient developmental time period and low risk youth were longitudinally followed for three years. Statistical models aimed at understanding consistency and stability in a changing biological system were used to methodologically explore biosocial models.

The second emphasis of developmental science is on multiple levels of analysis (Cairns et al., 1996). Reductionism defines the individual as the sum of the parts; this presupposes that each system does not interact with the other systems. Similar to the biosocial model, the holistic interactionism model assumes that the components of the individual interact with each other (Magnusson, 1999), and considers it futile to understand one component of a system while ignoring how that component operates in the individual who operates in a larger social, cultural and societal milieu (Cairns et al., 1990). For example, biological processes are central to developmental science in further understanding of the development of the individual, but biological processes are not separated from other aspects of the individual. Studying how hormones change over time and throughout development in a social context is the next challenge for the developmental scientist. By considering multiple levels, a larger, more complex but conceptually meaningful understanding of how hormones operate in the individual as a whole person begins to emerge (Magnusson & Cairns, 1996). This aspect of

developmental science was approached in the current study by first considering how a biological system (i.e., the HPA axis) can impact and be impacted by a behavioral process (i.e., internalizing and externalizing behavior problems). Further, the HPA axis was considered to be influenced on many other changing social, psychological and cognitive processes. This was approached by separating out these influences (i.e., state) from consistent individual differences in adrenocortical activity (i.e., trait).

The third emphasis of developmental science is on context. The person-oriented approach stresses that the individual is a purposeful part of a dynamic person-environment system who reciprocally affects and is affected by the environment (Magnusson, 1999). Within the person, the different systems are dynamic: interacting with each other in meaningful ways to help the individual develop into an integrated person. Outside of the person, similar principles apply. The person shapes and changes their environment, and is shaped and changed in turn. Social, cultural, and physical characteristics of the environment are different aspects of context which each may interact with multiple levels of the individual (Magnusson & Stattin, 1998). Biological processes are one level of the individual which are influenced by the context of the individual. In the current study, these contextual factors were considered salient influences on individual differences in adrenocortical activity and were theorized to be important influences on trait cortisol. Potential contextual factors that may influence adrenocortical activity were reviewed on page 11 and individual differences in internalizing and externalizing behavior problems were considered important influences on individual differences in adrenocortical activity in the reviews on pages 22 and 32, respectively. In sum, developmental science, person-oriented approaches, holistic

interactionist perspectives and the biosocial model contributed to the underlying theoretical theme. Multiple levels of analysis, a salient developmental time period, consideration of interactive processes and an individual difference perspective on biosocial processes formulated the conceptual core for a biosocial model of adrenocortical activity and behavior problems in low risk youth.

CHAPTER 2

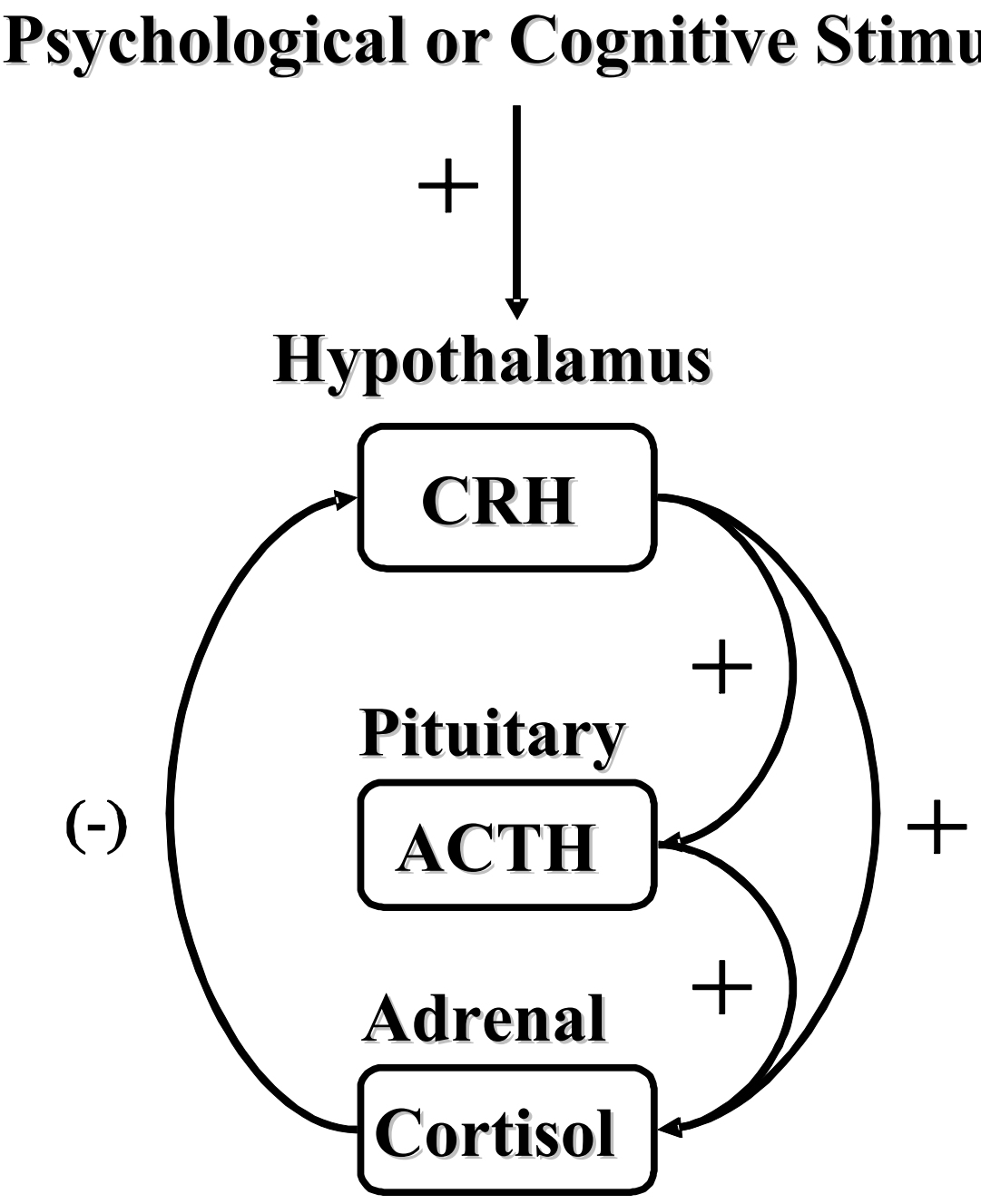
SITUATIONAL, INDIVIDUAL, AND PERSON-SITUATION INTERACTIONS WITH ADRENOCORTICAL ACTIVITY

The purpose of this chapter is to describe the mechanisms behind adrenocortical activation focusing on specific factors that influence cortisol's release. Situation-specific alterations in adrenocortical activity are described by reviewing studies that reveal cortisol reactivity to social challenge. Next, moderators of situation-specific alterations in adrenocortical activity are reviewed. These influences on adrenocortical activity – situation-specific and person-situation interactions – are referred to as 'state' cortisol because both of these factors refer to the specific state of the HPA axis activity at the time of measurement. This review justifies the first hypothesis: state cortisol will comprise the largest proportion of the total variance in salivary cortisol. Factors associated with individual differences in adrenocortical activity are then reviewed to demonstrate that individual differences in stable contextual factors may contribute to individual differences in 'basal' or 'trait' cortisol levels. This justifies the second hypothesis: some component of the total variance in salivary cortisol will be derived from trait cortisol.

Cortisol is a hormone that is released during times of stress. When an individual perceives an event as stressful (Selye, 1976), a cascade of hormonal signals is sent through the HPA axis (see Figure 1, Sapolsky, Krey, & McEwen, 1986). The HPA axis is a complex set of interconnected chemical interactions between the brain and adrenal glands (McEwen & Schmeck, 1994). In response to stress, the limbic system is activated,

causing the hypothalamus to release corticotropin- releasing hormone (CRH) which travels through a small, limited blood supply to the anterior pituitary. The pituitary then releases adrenocorticotropic hormone (ACTH) into the bloodstream. Upon receipt of this signal by ACTH receptors in the adrenal cortex, the production and release of glucocorticoids, such as cortisol, and mineralocorticoids, such as aldosterone, are activated (Nelson, 2000; Selye, 1976). Cortisol is the primary product of HPA axis activation. It does not directly measure the neuro-psychological impact of stress, but instead reflects a measure of peripheral physiological activation in response to stress. Frequent sampling of cortisol during stress shows that cortisol peaks ten to twenty minutes after a stressor (Young & Nolen-Hoeksema, 2001) although there are individual differences in adrenocortical reactivity (Seeman, Singer, Wilkinson, & McEwen, 2001).

Figure 1: Schematic representation of the hypothalamic pituitary adrenal axis. NOTE: Psychological stimuli signal a cascade of hormonal events. The hypothalamus releases corticotropin-releasing hormone into the portal system causing the release of adrenocorticotropic hormone from the anterior pituitary. Adrenocorticotropic hormone then causes the release of cortisol from the adrenal cortex into the general blood supply. Through a negative feedback mechanism, cortisol causes the release of corticotropin-releasing hormone to diminish. The + refers to positive feed forward and feedback loops and (-) refers to a negative feedback loop.



Cortisol influences an organism through permissive, suppressive, stimulatory and preparative actions on a wide variety of organ systems (Sapolsky, Romero, & Munck, 2000). Cortisol's primary role in the body deals with glucose metabolism (Dabbs & Hopper, 1990), but it also is involved with maintaining fat and carbohydrate metabolism, glucose production from protein, down-regulation of inflammatory responses, vascular responsiveness and immune system function (Nelson, 2000). The HPA cascade operates through both feed-forward and negative feedback mechanisms. Cortisol suppresses CRH and ACTH levels (Posener, Schildkraut, Williams, & Schatzberg, 1997), which returns cortisol levels to normal when a stressful event is over. Cortisol levels return to near-baseline levels forty to sixty minutes after a stressor (Seeman et al., 2001; Young & Nolen-Hoeksema, 2001). However, many subjects do not show any discernable reactivity or recovery in cortisol levels, suggestive of wide individual differences in appraisal, coping mechanisms and HPA axis profiles (Negrao, Deuster, Gold, Singh, & Chrousos, 2000; Seeman et al., 2001). If cortisol levels fail to return to baseline before the individual experiences another event that activates the HPA axis, a variety of deleterious consequences result (Sapolsky, 1998). Chronic exposure to cortisol has a negative impact on a wide variety of systems and functions, including the nervous system (e.g., Ohl, Michaelis, Vollmann-Honsdorf, Kirschbaum, & Fuchs, 2000; Packan & Sapolsky, 1990; Sapolsky & Plotsky, 1990; Sapolsky, Uno, Rebert, & Finch, 1990; Yehuda, 1999), cardiovascular system (e.g., Roy, Kirschbaum, & Steptoe, 2001; Roy, Steptoe, & Kirschbaum, 1998), metabolism and insulin function (see Sapolsky et al., 2000), gastrointestinal function (see Sapolsky, 1998), reproduction (see Sapolsky, 1985), immune function (e.g., Blalock & Smith, 1985), growth (see Sapolsky, 1997), learning

and memory (e.g., Sapolsky, 1996), mood (e.g., Dahl et al., 1991; Dorn, Susman, & Petersen, 1993; Susman et al., 1999) and behavior profiles (e.g., Granger, Serbin et al., 1998; Granger, Weisz, McCracken, Ikeda, & Douglas, 1996; Klimes-Dougan et al., 2001; Scerbo & Kolko, 1994).

Situation specific alterations in adrenocortical activity: Cortisol reactivity to social challenge

Children are often exposed to situations and experiences that may briefly alter adrenocortical function. Many of these situations are psychological or cognitive stressors that require immediate attention and physiological resources. However, these situations are often transient. Cortisol levels are thought to return to baseline levels 40 to 60 minutes after the social challenge ends (Seeman et al., 2001; Young & Nolen-Hoeksema, 2001). At any given time point, adrenocortical reactivity to recent or anticipated stressors or challenges may be more or less activated by the busy and frequently changing social circumstances of the lives of children and adolescents (Adam, 2002). These factors are presumed to influence state cortisol more than trait cortisol because many situational influences on HPA axis functioning are not steady (Granger & Shirtcliff, in press). This is the basic definition of state cortisol. A single measure of salivary cortisol is thought to be influenced by factors that are specific to the events and experiences evident at the time of measurement. For the purpose of this paper, state cortisol is the summation of situation specific variance in salivary cortisol which is not consistent across time. It consists of both situational and person-situation interaction factors. In this section, it is demonstrated that the HPA axis is responsive to a wide variety of transient social

contexts and to suggest that a single measure of salivary cortisol is largely impacted by these changing social circumstances.

Situation-specific alterations in HPA axis activity have often been assessed through adrenocortical reactivity to stressful or challenging tasks. Physiological arousal may be adaptive if it helps the individual mount an appropriate response to challenge, or it may be maladaptive if that response is too little or too great (Gunnar & Vazquez, 2001; Heim, Ehlert, & Hellhammer, 2000; Raine, 2002). Studies using laboratory or naturalistic stressors reveal that there are considerable individual differences in adrenocortical reactivity to a wide range of environmental challenges. Klimes-Dougan and colleagues (2001) demonstrated immediate and delayed cortisol reactivity to a Trier-like (Kirschbaum et al., 1993) social performance task in which adolescents were asked to give a speech in front of a small audience. Studies by Granger and colleagues demonstrate cortisol reactivity to a conflict-oriented discussion with a parent (e.g., Granger, Dennig, Weisz, Rudolph, & Ikeda, 1998; Granger, Serbin et al., 1998; Granger, Weisz, & Kauneckis, 1994; Granger et al., 1996). Several studies also demonstrate changes in cortisol levels in response to interactions with unfamiliar and familiar peers (e.g., Granger, Stansbury, & Henker, 1994; Gunnar, Tout, de Haan, Pierce, & Stansbury, 1997; Legendre & Trudel, 1996; Schmidt et al., 1999; Stansbury & Harris, 2000). Cortisol levels also appear to rise across the day in childcare settings, but demonstrate the characteristic diurnal decline at home (Dettling, Gunnar, & Donzella, 1999; Tout, de Haan, Campbell, & Gunnar, 1998). This may be evident in a large majority of children; Watamura, Sebanc and Gunnar (2002) found that cortisol levels increased across the day in 91% of children in childcare, but the majority (75%) of children's cortisol levels

dropped at home. In contrast, cortisol levels when children enter school or begin a new school year are not consistently elevated. Studies from Gunnar's laboratory report no differences between home and school cortisol levels and reactivity or between cortisol levels on the first compared to the fifth day of school in children (Davis, Donzella, Krueger, & Gunnar, 1999; de Haan, Gunnar, Tout, Hart, & Stansbury, 1998), and also report that first graders displayed a steeper decline in cortisol levels across the first day of school (Bruce, Davis, & Gunnar, 2002). Conversely, Boyce and colleagues (1995) found that cortisol levels were elevated after kindergarten entry. Finally, cortisol levels were higher on test days in second graders compared to non-test school days (Tennes & Kreye, 1985; Tennes, Kreye, Avitable, & Wells, 1986). These studies collectively demonstrate that adrenocortical activity is responsive to social challenges. The impact of these situations is transient, so it should contribute to situation-specific variance rather than trait-like variance in salivary cortisol. Importantly, these studies demonstrate adrenocortical reactivity to a wide range of social challenges, suggesting that the HPA axis is highly responsive to moderate changes in the social context. It is hypotehsized that situation-specific variance in HPA axis activity comprises the largest component of the total variance in cortisol levels in children (Adam, 2002), as is the case with adults (Adam, 2003; Kirschbaum et al., 1990; Preville et al., 1996).

Moderators of situation-specific alterations in adrenocortical activity: Person-situation interactions

Studies in adults suggest that psychological moderators of the link between cortisol and stress are central to understanding the HPA axis (Sapolsky, 1998).

Perceptions of control (e.g., Pruessner, Hellhammer, & Kirschbaum, 1999), predictability (e.g., Smyth et al., 1998), mood (e.g., Adam, 2003), social support (e.g., Kirschbaum, Klauer, Filipp, & Hellhammer, 1995), novelty (e.g., Gerra et al., 2001), and confidence (e.g., Young & Nolen-Hoeksema, 2001) are all consistent moderators of the association between cortisol, stress, and behavior. Studies in children are not as consistent as those with adults, but collectively they suggest that there are important emotional, temperamental and social moderators of adrenocortical activity in youth. This literature is important because it demonstrates that short-term alterations in HPA axis activity do not affect each individual the same. Rather, individual differences in cortisol reactivity profiles have been associated with psychological, social and cognitive profiles. The literature that demonstrates person-situation interactions in HPA axis reactivity is a bridge between studies that demonstrate situational influences (reviewed above) and studies that demonstrate person-specific influences on the development of the HPA axis activity (reviewed below).

Individual differences in appraisal, mood and emotion may moderate the HPA response to social challenge. For example, cortisol levels upon awakening are higher when subjects report more worrying, experiences with social stress and lack of social recognition (Wust, Federenko, Hellhammer, & Kirschbaum, 2000). Increased cortisol reactivity to challenge has also been linked with higher reports of embarrassment and shame (Lewis & Ramsay, 2002), more surgency (Bruce et al., 2002; Davis et al., 1999; Donzella, Gunnar, Krueger, & Alwin, 2000) and both more (Donzella et al., 2000) and less effortful control (Bruce et al., 2002). Children with tense and angry affect have also been shown to demonstrate elevated cortisol reactivity to a win/lose challenge (Donzella

et al., 2000), low reactivity in a novel school setting (Davis et al., 1999), but high cortisol reactivity in a familiar school setting (Gunnar et al., 1997), and larger increases in cortisol from morning to afternoon at childcare (Dettling, Parker, Lane, Sebanc, & Gunnar, 2000). These studies show that individual differences in emotions may moderate adrenocortical reactivity to challenge.

Individual differences in temperamental factors (e.g., shyness or behavioral inhibition) also may moderate HPA axis reactivity. Pioneering work by Kagan and colleagues (1987) establish a theoretical model in which behaviorally inhibited children are at risk for chronically heightened physiological arousal states. Several studies in moderately and extremely shy children provide support for this model. Sanchez-Martin and colleagues (2001) found that social isolation during freeplay interaction in preschoolers was associated with low cortisol in some children, but high cortisol in others. This effect was particularly pronounced for females. Smider and colleagues (2002) revealed that high cortisol levels in preschool were associated with high levels of social wariness when youngsters transitioned to kindergarten. High adrenocortical activity was associated with shyness in extremely behaviorally inhibited children (Kagan et al., 1987); in two year olds after they transitioned to preschool (de Haan et al., 1998); and in preschool-aged boys in daycare (Dettling et al., 1999). Nevertheless, a growing literature reports findings that contradict Kagan's (1987) theoretical model. Low adrenocortical reactivity in elementary school-aged children (Davis et al., 1999) and steeper declines in cortisol across the day have also been associated with shyness (Bruce et al., 2002). Finally, cortisol levels were low in novel and high in familiar settings in solitary children (Gunnar et al., 1997). These studies demonstrate that the association

between cortisol reactivity and shyness may not be straightforward because person-situation interactions moderate physiological relationships with temperament. Shy or socially inhibited children may be particularly prone to physiological arousal in social settings when situational demands overwhelm their resources for dealing with challenge (Kagan et al., 1987). On the other hand, compared to less inhibited children, outgoing children may be exposed to a greater number of physiologically arousing situations when they seek out social inter-changes (Gunnar, 1993; Stansbury & Harris, 2000), and may be more likely to experience social rejection and concomitant heightened physiological arousal when they approach others too quickly (Stroud, Salavey, & Epel, 2002).

Individual differences in social factors (e.g., social affiliation, social competence) may also moderate adrenocortical activity and reactivity to challenge. As the literature above suggests, outgoing children may have heightened HPA axis activity because they often seek out social situations (Gunnar, Bruce, & Donzella, 2000). For example, high cortisol is positively related to child initiated social interaction, social competence, popularity (Tennes & Kreye, 1985), and social affiliative behavior at school in second-graders (Tennes et al., 1986). High cortisol reactivity during novel situations followed by less extreme reactivity when the situation is familiar is positively associated with outgoing behavior in socially competent, well-liked preschoolers (Gunnar et al., 1997). Stansbury and Harris (2000) revealed heightened cortisol reactivity to meeting new peers in socially competent children who behaved in a socially inhibited manner as well as children who reported low social competence but behaved in a socially outgoing manner suggesting relationships between cortisol and social competence may be dependent on social contextual factors (e.g., familiar and novel settings). Nevertheless,

Granger and colleagues (1996) report that consistently high adrenocortical reactivity to a parent-child conflict task at intake and follow-up was associated with deflated social competence over a 6- month period in clinic-referred children and adolescents. This study is the only report (to my knowledge) that has examined social competence and cortisol in adolescents. It is possible that developmental changes in adrenocortical activity may take place as children transition from preschool and kindergarten (Gunnar et al., 1997; Stansbury & Harris, 2000) through middle and high school (Granger et al., 1996).

These studies suggest that person-situation interactions may influence the activity of the HPA axis. Cortisol is reactive to a wide variety of situational factors, but these changes in HPA axis activity do not occur uniformly in all individuals. Individual differences in emotional, temperamental and social moderators may operate differently from one situation to another (e.g., de Haan et al., 1998) or from one appraisal style to another (e.g., Stansbury & Harris, 2000). Nevertheless, individual differences in adrenocortical reactivity to stress are not the endpoint of this endocrine system.

Individual differences in adrenocortical activation: The context of the family environment

The HPA axis is malleable in young children, but as youngsters consistently react (or fail to react) to social challenges, or are chronically exposed to particular types of stress, the HPA axis is thought to become entrenched in a psychopathological state (see review by Gunnar et al., 2000). In response to chronic stress, children at risk may consistently fail to respond to contextual change that would be physiologically arousing

to low risk normally developing children, or their physiological response to changing social contexts may consistently be over-active. Consistent reactivity profiles contribute to individual differences in adrenocortical activity (i.e., trait-like variance) if chronic arousal alters the development of the HPA axis. Support for the assertion that there may be consistent alterations in the development of the HPA axis come from time-lagged studies on individual differences in adrenocortical activity and children's behavior problems. Longitudinal relationships between cortisol and behavior support the idea that there is trait-like variance in the HPA axis and this component of the HPA axis is associated with behavior problems (e.g., Granger et al., 1996; Susman, Dorn, Inoff-Germain, Nottelman, & Chrousos, 1997). The portion of the variance in salivary cortisol that is consistent or stable across time should operate like a trait factor. The purpose of this section is to justify why person-specific factors are expected to impact a single measure of salivary cortisol. While reviewing child maltreatment and parental psychopathology as sources of individual differences does not clearly connect to a study on low risk normally developing youth, this literature is important because it suggests that individual differences in adrenocortical activity are not just due to genetic influences (Bartels, Van den Berg, Sluyter, Boomsma, & de Geus, 2002; Wust et al., 2000), but may be derived from biosocial factors as well. In keeping with a developmental science perspective, it also illustrates the importance of considering the social context as an important feature of the person-environment focus and points to the need to consider when situational factors are changing or stable.

Compared to normal children, maltreated children have higher afternoon (Hart, Gunnar, & Cicchetti, 1996) and daytime cortisol levels (Carrion et al., 2002). Adult

women with a history of childhood abuse evidenced higher cortisol reactivity to challenge compared to normal or depressed women (Heim et al., 2002). Similarly, HPA axis activity is hyperactive in foster children (Fisher, Gunnar, Chamberlain, & Reid, 2000) and Romanian orphans (Gunnar, Morison, Chisholm, & Schuder, 2001; Schuder, 2002). Yet, others have found lower cortisol in sexually abused girls (King, Mandansky, King, Fletcher, & Brewer, 2001). Maltreated children also exhibited less cortisol reactivity to challenge and failed to mount a HPA response during days marked by high classroom conflict (Hart, Gunnar, & Cicchetti, 1995). It is somewhat disconcerting that the effect of child maltreatment on adrenocortical activity is inconclusive. It seems that such a powerful social disruption as maltreatment should alter HPA axis functioning in a clear and consistent fashion. Nevertheless, the model proposed by Gunnar, Bruce and Donzella (2000) provides no clear prediction for the direction of alterations in HPA axis activity from maltreatment, and Cicchetti and Rogosch (2001a; 2001b) propose that the cortisol profile of maltreated youth depends on the nature of the abuse and the youth's psychopathology profile.

Parental PTSD has been associated with low cortisol levels in offspring (Yehuda et al., 2000; Yehuda, Halligan, & Bierer, 2002). This may be because parents with post-traumatic stress disorder (PTSD) are at risk of maltreating their children. Offspring report more emotional abuse, trauma and neglect as a function of their parents' PTSD symptoms (Yehuda, Hallig, & Grossman, 2001). Children of depressed mothers have higher cortisol levels and larger reactivity to challenge compared to normal controls (Ashman, Dawson, Panagiotides, Yamada, & Wilkinson, 2002). Children's cortisol levels before a parent-child interaction challenge were inversely associated with mother's

childhood levels of socially withdrawn behavior, current psychosocial problems, and family aggression, anger and conflict. After the task, cortisol levels were inversely associated with maternal aggression and rigid rules in childhood (Granger, Serbin et al., 1998). Sons of fathers with a substance abuse history have consistently lower cortisol levels (Dawes et al., 1999; Moss, Vanyukov, & Martin, 1995; Vanyukov et al., 1993) and less reactivity to stress compared to control boys (Dawes et al., 1999; Moss, Vanyukov, Yao, & Kirillova, 1999; Moss et al., 1995). These studies are consistent with the model proposed by Gunnar, Bruce and Donzella (2000) because they demonstrate developmental alterations in adrenocortical activity in children whose parents have psychological or substance abuse disorders.

These studies demonstrate that family environment has an important impact on the developing HPA axis of children and adolescents. Family stress may result in either hyper- and hypo-arousal of the HPA axis. The mechanism that causes an individual to demonstrate hypo- or hyperarousal one or the other is not readily apparent. Individual differences in psychological (e.g., psychosocial stress, Heim et al., 2002), social (e.g., social competence, shyness, acting out behavior, Hart et al., 1995) or other (e.g., drug use, developmental timing, Lupien, King, Meaney, & McEwen, 2001; Moss et al., 1999) characteristics may contribute to the development of risk or resilience against alterations in HPA functioning in children and adolescents. Importantly, these studies demonstrate individual differences in adrenocortical activity. These individual differences may partially be genetic in origin (Bartels et al., 2002), but Yehuda and colleagues (2001) reveal that family stress and conflict is the mediating factor for parental psychopathology-HPA axis relationships and Wust and colleagues (2000) reveal person-

situation interactions that explain variance in adrenocortical activity beyond genetic contributions. Gunnar, Bruce and Donzella (2000) theorize that normally developing children have a wide range of possible physiological responses to social contexts, but the HPA axis may develop along a deleterious pathway given chronic exposure to damaging social contexts. Thus, individual differences in stable trait-like variance in salivary cortisol may underlie variability in HPA axis functioning.

Summary and conclusions regarding sources of influence on adrenocortical activity

This review demonstrates the importance of considering situational influences on adrenocortical activity, person-situation interactions derived from individual differences in emotional, temperamental and social factors, and individual differences in HPA axis functioning. The two former influences on the HPA axis are likely to comprise a large component of variance in situation-specific (i.e., state) cortisol levels. The first hypothesis is that situation specific variance will comprise the largest proportion of the total variance in salivary cortisol. The latter influence on the HPA axis suggests that person-specific factors are important moderators of the long-term development of the HPA axis. Thus, some component of variance in HPA activity must be due to person-specific factors (i.e., trait cortisol). The second hypothesis focuses on these intrinsic individual differences in adrenocortical hypothesis and states that some component of the total variance in salivary cortisol will be due to trait cortisol.

CHAPTER 3

INTERNALIZING AND EXTERNALIZING BEHAVIOR PROBLEMS: DEFINITION, PREVALENCE AND EVIDENCE FOR BIOSOCIAL RELATIONSHIPS

This chapter describes the nature and prevalence of internalizing and externalizing behavior problems. The premise of the first section is that studies that examine behavior problem symptoms in low risk normally developing youth are important (see review by Cicchetti & Cannon, 1999). The next section describes internalizing behavior problems in more detail, provides information about the nature and prevalence of depression and anxiety disorders, and explores the literature that connects cortisol levels and reactivity with internalizing behavior. The last section describes externalizing behavior problems in similar detail, and then summarizes the literature that relates cortisol with externalizing behavior problems. The purpose of this chapter is to justify why an association between cortisol and behavior problems is expected in low risk youth. This chapter provides justification for the third and fourth hypotheses: trait cortisol will be positively associated with internalizing behavior problems but inversely associated with externalizing behavior problems. An accumulating body of literature that reveals relationships between adrenocortical activity and comorbid internalizing and externalizing behavior problems is reviewed to justify the fifth hypothesis: Children with high internalizing and externalizing behavior problems will have high trait cortisol levels. A small body of literature which reveals time-lagged cortisol-behavior relationships is emphasized throughout these sections in order to justify the sixth hypothesis: cortisol-behavior relationships will be relatively stable from one year to the next.

Psychiatrists view behavior problems as a disease or disorder, and, in turn, operationalize it as either present or absent (Mash & Terdal, 1988a). However, individual differences within a normal range of behavior can also be informative for research on psychopathology under the assumption that these behaviors operate on a continuum and have similar developmental antecedents and consequences (Cicchetti & Cannon, 1999). Normally developing youth display a restricted frequency and intensity of behavior problems that do not require the attention of mental health professionals (Kovacs & Devlin, 1998), but nevertheless may have implications for individual, family and societal health (Moffitt, Caspi, Harrington, & Milne, 2002), and may present a large societal health problem because the high frequency of subclinical symptoms impacts the lives of many individuals (Hunt & Emslie, 2001). Components of behavior problems often reflect behaviors that occur in the normal range of symptoms. For example, Barrios and Hartmann (1988) found that as many as 90% of children have fears and anxieties, and 43% of children aged 2 to 14 years display moderate levels of fears. Similarly, Kazdin (1988) reports that many symptoms of depression appear readily in normally developing youth, such as crying, mood disturbance, poor appetite and excessive sadness. Mild forms of externalizing behavior may be normative (McMahon & Forehand, 1988), particularly in adolescence (Dishion, 2000; Moffitt & Caspi, 2001). Overactivity, poor regulation of impulses, noncompliance and difficulty controlling anger or aggression are common complaints of the parents of adolescents (Campbell, Shaw, & Gilliom, 2000). Behavior that stays within the normal range can lead to poor outcomes (e.g., crime and convictions, poor social skills, low educational attainment, unemployment, mental health problems, Loeber & Farrington, 2000; Moffitt et al., 2002), but the social outcomes of

children with clinical behavior problems is much worse (Moffitt et al., 2002). It is possible that internalizing and externalizing behavior represents a continuum between relatively normative behaviors to problems in the clinical range. Further, in a sample size as large as that of the current study (654 youth) it is possible that a considerable number of children have subclinical or clinical range behavior problems. Based on Angold, Costello and Erkanli (1999), clinical range anxiety problems should be evident in 44 children and 20 children should be clinically depressed; approximately 47 children should have conduct or oppositional defiant disorder and 21 children should have ADHD in the clinical range. Examining behaviors in the normal range is of merit in its own right, for these children may experience developmental 'snares' or difficulties (Moffitt, 1993a), and is also of merit for clinical studies if behaviors exhibited in low risk youth reflect a mild form of more extreme behavior problems (Cicchetti & Cannon, 1999) and may reflect clinical level behavior problems in a small, though significant, subset of low risk youth (Angold et al., 1999). Thus, examining adrenocortical activity in low risk children has implications for normally developing youth and potentially may inform biosocial studies on mechanisms that contribute to the development of clinical behavior problems in at risk youth.

THE NATURE OF INTERNALIZING BEHAVIOR PROBLEMS

The following section describes the nature of internalizing behavior problems, focusing on the types of behaviors evident in low risk normally developing youth. The prevalence and stability of internalizing behavior problems is presented. While internalizing behavior is comprised of several different types of problems, this review

focuses on anxiety and depressive symptoms because these components of internalizing behavior problems are well understood (e.g., Zahn-Waxler et al., 2000), adrenocortical activity has often been related to depression and less frequently anxiety, and the measure of internalizing behavior in the current study taps into depressive symptomatology. Next, biosocial models of adrenocortical activity and internalizing behavior are explored. This section justifies why a relationship between cortisol and internalizing behavior is anticipated. A large, complex body of literature that relates HPA axis activity with internalizing behavior is presented to justify the hypothesis that adrenocortical activity will be associated with internalizing behavior problems. The literature is organized by studies that examine clinically depressed children, at-risk groups and normally developing children with internalizing symptoms. It is clear that studies across these three populations yield mixed findings. The current study will advance this literature because there are few studies of low risk normally developing adolescents.

Definition of internalizing behavior problems

The term *internalizing behavior problems* has been used to describe a broad series of symptoms that relate to disturbances in intropunitive emotions and moods such as guilt, fear and worry (Zahn-Waxler et al., 2000), and often has been operationalized using measures of depressive and anxiety symptoms in children and adolescents using the child behavior checklist (CBCL) and youth self report (YSR, Achenbach, 1991a; Achenbach, 1991b) or as psychiatric symptoms of anxiety (e.g., generalized anxiety, specific phobia, separation anxiety, social phobia, obsessive compulsive, agoraphobia and panic disorder and depression (i.e., dysthymia and major depressive disorder) using the Diagnostic

Interview Schedule for Children (Fisher et al., 1993; Schwab-Stone et al., 1993; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000; Shaffer, Fisher, Piacentini, Schwab-Stone, & Wicks, 1989; Shaffer et al., 1993). Symptoms of depression include feeling down, fatigue or loss of energy, feelings of worthlessness, inappropriate guilt and loss of interest in pleasurable things. Anxiety symptoms include feelings of fear, terror, or panic, physical reactions of respiration, dizziness and breathlessness, and behavioral responses of avoidance (Mash & Terdal, 1988b).

Prevalence of internalizing problems in the general population

Internalizing behavior symptoms are common in children and adolescents. For example, anxiety symptoms are present in 90% of children, 43% of children report at least seven specific fears, and the average child reports feeling three or four specific fears and anxieties (Barrios & Hartmann, 1988). Depressive symptoms, such as feelings of sadness, are expressed by a large majority of children (Kazdin, 1988). Relatively few children in the general population, however, express these behaviors in the clinical range. Across 21 general population studies, anxiety disorders were prevalent in 6.65% and depressive disorders were prevalent in 3.07 % of children (Angold et al., 1999). Prevalence rates vary greatly from one population to the next. Rates of anxiety disorders vary from 5.7 to 17.7 % and prevalence of depressive disorders varies from 2.0 to 8.0 % in children ages 4 to 18 years (Lyon & Morgan-Judge, 2000; Zahn-Waxler et al., 2000). The incidence of internalizing disorders varies by age. The age of onset of anxiety disorders is very early, and the nature of the disorder changes with age (Barrios & Hartmann, 1988). In middle childhood and adolescence, anxiety disorders were prevalent

in 7.5%, 10.7%, and 19.7% of 11, 15, and 18 year olds, while depressive disorders were prevalent in 1.8%, 4.2% and 18% of 11, 15, and 18 year olds from the general population, respectively (Kovacs & Devlin, 1998). Finally, there is an interaction between age and gender. Throughout childhood, boys and girls have similar prevalence rates of anxiety and depression, but adolescent females are more than twice as likely than are adolescent males to develop internalizing problems (Mash & Terdal, 1988a; Wilhelm, Roy, Mitchell, Brownhill, & Oarker, 2002; Zahn-Waxler et al., 2000). One cause of the gender difference in depression may be that boys and girls experience depressive symptoms differently, with boys expressing depression through anger and aggression and girls expressing more typical types of behaviors associated with depression (Klein & Corwin, 2002).

Stability of internalizing behavior problems from childhood to adulthood

Depression and anxiety appears largely stable from middle childhood to adulthood (Kazdin, 1988; Zahn-Waxler et al., 2000). Girls with depression or anxiety problems at age 11 were 6.2 times more likely to have an internalizing disorder at age 15 than were girls without depression or anxiety (McGee, Feehan, Williams, & Anderson, 1992). However, Angold and colleagues (1999) make the observation that stability may be difficult to estimate because behavior problems manifest themselves differently across diverse ages while still under the rubric of the same disease (see also Zahn-Waxler et al., 2000) and Kazdin (1988) observes that specific symptoms of anxiety and depression are not developmentally stable. For example, suicidal ideation is rare in childhood, but is more common in adolescence (Kazdin, 1988). Separation anxiety is common in

childhood but rare in adolescents, but the reverse is true for generalized anxiety, social phobia and panic disorder (Angold et al., 1999; Barrios & Hartmann, 1988). Importantly, internalizing behaviors appear stable in the normal range of behavior problems. Normal children with 'deviant' depression scores were 10 times more likely to have similar depression scores six years later (Kovacs & Devlin, 1998). Normal adolescents who experience depressive symptoms also are much more likely to continue reporting depressive symptoms five years later (Rao, Hammen, & Daley, 1999). Normally developing first graders with anxiety scores in the top third of their class were twice as likely as their peers to be in the top third tertile on anxiety problems in the fifth grade (Ialongo, Edelsohn, Werthamer-Larsson, Crockett, & Kellam, 1995). It is important for the present study that depressive and anxiety symptoms are stable and consistent across time because it suggests that, at least at some level, internalizing symptoms operate like a trait. Expecting trait cortisol to be related to trait-like behavior problems, then, seems credible.

A biosocial model for cortisol-internalizing relationships: Theoretical links and experimental evidence

As Raine (2002) notes, the establishment of biosocial associations between adrenocortical activity and behavior problems represents the first step in a long process. The mechanisms underlying physiological correlates of behavior problems must be explained before their meaning can be derived for physical and mental health. The search for these mechanisms, however, should not automatically focus on discovery of the biological determinants of behavior. Indeed, consistent with the multidimensional

nature of developmental psychopathology (Cicchetti & Walker, 2001; Dawson, Ashman, & Carver, 2000; Susman, 1997), our understanding of how social, cognitive, emotional, and temperamental factors shape individual differences in biological processes holds the key to extending our knowledge to new limits. Biosocial models of internalizing behavior problems posit that hyperarousal of the HPA axis is a risk factor for internalizing problems because these individuals have a heightened physiological response to stress, experience chronic stress that taxes the developing stress systems, or have a lowered threshold of activity in areas of the brain responsive to stressful stimuli. Gray (1994) postulates that three interdependent brain systems that govern behavior – the fight or flight system, the behavioral activation (BAS) or reward system and the punishment or behavioral inhibition system (BIS) – act to regulate internalizing-related emotions. Anxiety and depression result when the BIS is overactivated and children over-interpret stimuli as punishment cues (Beauchaine, 2001; McBurnett et al., 1991). Gunnar, Bruce and Donzella (2000) postulate a diathesis-stress model in which the HPA axis in children is malleable and responsive to the particular nature of the environment. As the individual develops, the HPA respond in a habitual manner to a wide variety of stimuli until hypo- or hyper- arousal is evidenced consistently across situations. Studies in adults consistently associate hyperarousal of cortisol with depression (Sapolsky, 1998). Studies in children and adolescents, however, reveal that depression and anxiety are often associated with hyperarousal of the HPA axis, although depression may have a different relationship with adrenocortical activity than anxiety (Zahn-Waxler et al., 2000).

Several studies link major depression in childhood with high cortisol levels. Children who are clinically depressed, compared to normal control groups, have been

found to have higher morning cortisol (Goodyer, Herbert, Moor, & Altham, 1991; Goodyer, Herbert, Tamplin, & Altham, 2000b) especially when comorbid with obsessive compulsive disorder (OCD, Goodyer, Park, & Herbert, 2001); display higher evening cortisol (Goodyer et al., 1991; Goodyer et al., 1996; Herbert et al., 1996); higher cortisol across the day except in the morning (Foreman & Goodyer, 1988); and higher cortisol after sleep onset (Rao et al., 1996).

In children at risk for behavior problems, similar relationships between adrenocortical activity and internalizing behavior emerge. HPA axis activity was positively associated with internalizing behavior problems in clinically referred children (Scerbo & Kolko, 1994). Cortisol levels and reactivity were higher in children of depressed mothers with many internalizing symptoms (Ashman et al., 2002). Maltreated children with clinical levels of internalizing problems had significant elevations in cortisol levels compared to maltreated or nonmaltreated children (Cicchetti & Rogosch, 2001b).

Most importantly, relationships between internalizing symptoms and cortisol are found in normally developing children and adolescents. In two year olds, internalizing behaviors were associated with higher cortisol levels at home (de Haan et al., 1998). In four to five year olds, cortisol levels predicted more internalizing behavior one and a half years later (Smider et al., 2002). Finally, teenagers with the highest levels of anxiety symptoms had higher cortisol levels than did healthy subjects (Colomina, Canals, Carbajo, & Domingo, 1997). These findings in clinical, at risk and in normal children demonstrate that cortisol levels are related to internalizing behavior within the normal and deviant range of depressive or anxiety problems. Exploring cortisol-internalizing

behavior relationships in low risk normally developing youth may reflect biosocial relationships that are operating in normal and at risk youth.

Childhood depression is also related to increased cortisol reactivity to pharmacological and social challenge. Compared to normal controls, many depressed children fail to suppress cortisol following dexamethasone administration (Doherty et al., 1986; Foreman & Goodyer, 1998). Adolescents whose cortisol levels increased in response to social challenge had more symptoms of depression a year later compared to those whose cortisol levels decreased or stayed the same (Susman et al., 1997). Clinic-referred youngsters whose cortisol levels increased in response to social conflict displayed more internalizing behavior problems six months later compared to youth who did not show an adrenocortical response (Granger et al., 1996). Children at risk also show abherent cortisol responses to challenge. Klimes-Dougan and colleagues (2001) found that at-risk youth whose cortisol levels decreased in response to a conflict discussion had high attention and internalizing problems, but youth whose cortisol levels increased in response to the task were elevated in internalizing and externalizing problems. For a social performance task, children whose cortisol levels responded to the task had elevated internalizing symptoms. Finally, a small literature also reveals that, in a group of normal preschoolers, symptoms of internalizing behavior positively predicted subsequent cortisol reactivity in response to playgroup activity (Granger, Stansbury et al., 1994). These studies suggest that HPA axis reactivity to challenge is positively related to internalizing symptoms in clinical, at-risk and normally developing children and adolescents. Combined with the observation that high cortisol levels are related to internalizing behavior problems, these findings suggest that individual differences in

cortisol levels as well as situation-specific variations in cortisol reactivity are related to depression and anxiety. It is of note that a handful of these studies document longitudinal or time-lagged relationships between adrenocortical activity and internalizing behavior (e.g., Granger et al., 1996; Susman et al., 1997). This is important because it suggests that situational factors evident when cortisol was measured are not responsible for cortisol-internalizing relationships. These associations presumably tap into the consistent portion of the variance in salivary cortisol. These findings support the hypothesis that some portion of the variance in salivary cortisol is consistent across time and that this component of the total variance is associated with behavior problems. It is possible that when the trait portion of the variance in salivary cortisol is explicitly modeled, the consistency of cortisol-internalizing behavior relationships will be great.

Although the studies above demonstrate high cortisol levels and reactivity in children with depression or depressive symptoms, a handful of studies relate low cortisol levels and reactivity to depressive symptoms. Depressed adolescents were found to have lower cortisol after sleep onset (De Bellis, Dahl, Perel, & Birmaher, 1996). Children with depressive symptoms also showed diminished cortisol responses to physical challenge, but not psychological challenge, compared to normal children (Jansen et al., 1999). Children at risk for behavior problems with internalizing symptoms had lower cortisol levels before a challenging task than children with fewer symptoms (Granger, Serbin et al., 1998). Finally, internalizing symptoms were associated with lower cortisol levels and an unexpected increase in cortisol across the day in normally developing preschool boys (Tout et al., 1998). The findings from these studies contract studies which show high adrenocortical activity in children with internalizing problems. It is

interesting that this small body of literature also includes populations ranging from clinical to normally developing children because it suggests that the range of internalizing behavior problems in normally developing versus clinical samples does not distinguish studies which find hyper- or hypo-arousal of the HPA axis.

Several researchers have failed to reveal a difference in cortisol levels or reactivity between depressed and normal control subjects when the sample size was limited (N = 24, Kutcher, Malkin, Silverberg, & Marton, 1991; N = 19, Targum, Clarkson, Magac-Harris, Marshall, & Skwerer, 1990). Nevertheless, studies with larger sample sizes also fail to reveal a biobehavioral association. No differences in cortisol levels across the day and night were found between depressed and normal control subjects (Dahl et al., 1989; Puig-Antich et al., 1989) and no differences in morning or afternoon cortisol levels between depressed and normal control subjects were found (Goodyer, Herbert, Tamplin, & Altham, 2000a). Cortisol reactivity in response to a social challenge was not different in anxious compared to normal subjects (Gerra et al., 2000). Goodyer, Herbert and Altham (1998) do not report a direct association of internalizing behavior with cortisol, but instead found that the ratio of cortisol to dehydroepiandrosterone (DHEA) was associated with depression. This finding suggests that the neuroendocrine profile of depressed or anxious adolescents may differ from normal control subjects in a complex manner and more than one hormone may be necessary to reveal HPA axis- internalizing behavior relationships. The ability to detect an association between cortisol levels and internalizing problems may be compromised because either internalizing behavior problems are manifest as alterations in the normal diurnal pattern of cortisol secretion rather than levels (e.g., Goodyer et al., 1991; Goodyer

et al., 1996), the association may be moderated by other hormone products of the hypothalamic-pituitary-adrenal axis such as DHEA (e.g., Goodyer et al., 1998), or day-to-day change in emotions and situation specific influences causes variability in HPA axis activity (e.g., Adam, 2003; Smyth et al., 1998) that obscures the stable hormone-behavior relationship.

Conclusions about the consistency of cortisol-internalizing behavior relationships in clinical, at-risk and normally developing youth

In summary, several studies report no association between adrenocortical activity and internalizing behavior problems, many find a positive relationship, but several report a negative association between cortisol and depression or anxiety. Studies with small and adequate sample sizes yield equally mixed findings, suggesting that power issues are not at the heart of these diverse findings. Similarly, neither gender nor time of sample collection clearly distinguishes studies that find positive from negative results. Studies of clinical, at-risk and normally developing youth are nearly equally represented across all three patterns. Factors that differ across populations are not likely to be mediators of the cortisol-depression association. It is the premise of the current study that the inconsistencies in the cortisol-internalizing literature may be partially due to situation-specific influences that are present to varying degrees across studies. Thus, the third hypothesis is that 'trait' cortisol will be positively associated with internalizing behavior problems. Several studies which demonstrate time-lagged relationships between cortisol and internalizing behavior support this interpretation because it is likely that longitudinal relationships with behavior problems tap into the consistent portion of variance in the

HPA axis. Consistent with Granger and colleagues (1996) and Susman and colleagues (1997), the sixth hypothesis is that time-lagged positive associations between trait-cortisol and internalizing behavior problems will be evident.

THE NATURE OF EXTERNALIZING BEHAVIOR PROBLEMS

The following section describes the nature of externalizing behavior problems, focusing on the type and intensity of behaviors that are evident in low risk youth. The prevalence and stability of externalizing behavior problems is then presented. Biosocial models of adrenocortical activity and externalizing behavior are then explored to justify why cortisol- externalizing relationships are anticipated. A review of the literature that relates the HPA axis with externalizing behavior ranging from clinical to normally developing samples is then presented. Finally, a brief discussion of the importance of examining comorbid behavior problems is presented to justify our exploration of the interaction between internalizing and externalizing behavior problems. The purpose of this section is to provide a rationale for why studying HPA axis activity in relation to externalizing behavior problems in low risk youth is worthwhile.

Definition of externalizing behavior problems

Externalizing behavior disorders are a broadly defined category that refers to a continuum of behavior problems described as disinhibited, undercontrolled, undersocialized and aggressive (Kovacs & Devlin, 1998). Externalizing behavior includes a pattern of persistent and repeated violations of social rules and the rights of

others (American Psychiatric Association, 1994), such as aggression toward people and animals, destruction of property, deceitfulness and theft, and an emotional profile that includes impulsivity, hostility, and a lack of empathy. The Diagnostic Interview Schedule for Children (Fisher et al., 1993; Schwab-Stone et al., 1993; Shaffer et al., 2000; Shaffer et al., 1989; Shaffer et al., 1993) operationalizes externalizing behavior problems using conduct disorder (CD), oppositional defiant disorder (ODD) and attention deficit hyperactive disorder (ADHD). Externalizing behavior is operationalized using the CBCL and YSR as aggression, attention and delinquency problems (Achenbach, 1991a, 1991b). In the current study, externalizing behavior is defined using a measure of 'risky behavior' which taps into behaviors that are likely to be expressed within the normal range of externalizing behaviors (e.g., thrill seeking behavior, lying, stealing, defiance, Eccles & Barber, 1990) in an attempt to represent individual differences in externalizing behavior problems on a continuum in a sample of low risk youth.

Prevalence of externalizing problems in the general population

Lewisohn and colleagues (1993) report prevalence of externalizing disorders at 1.81% in 14 – 18 year olds, but others report prevalence at 9.1%, 11.9% and 5.5% in 11, 15, and 18 year olds (Kovacs & Devlin, 1998). National surveys report that 6 – 9% of children below age 13 have engaged in serious delinquent acts (Kovacs & Devlin, 1998). Across 21 general population studies, ADHD occurs in 3.19 % and CD/ ODD occurs in 7.18% of children on average (Angold et al., 1999). The age of onset of externalizing behavior is the center of much discussion, with differences in risk factors (e.g., parental, social, temperamental, and neurobiological factors, Moffitt & Caspi, 2001) and lifetime

trajectories (e.g., severity and persistance of crime, Moffitt et al., 2002) expected for youth who begin engaging in problem behavior in childhood versus adolescence (Campbell et al., 2000; but see Dishion, 2000; Dishion & Owen, 2002; Moffitt et al., 2002).

Stability of externalizing behavior problems from childhood to adulthood

The stability of externalizing behaviors across settings and time is extremely high (Achenbach, McConaughy, & Howell, 1987), and expression of externalizing behaviors is likely to increase across the adolescent years. As externalizing behavior expression goes from mild to moderate (e.g., risky or truant behavior) to severe (e.g., delinquent and criminal acts), the likelihood that externalizing behaviors will desist decreases and the cost to the general public increases (Moffitt & Caspi, 2001; Moffitt et al., 2002). A big challenge for research on externalizing behavior is predicting when normative behaviors (e.g., stubborn, defiant behavior) will escalate to truancy (e.g., running away, bullying and annoying others, stealing and lying), to child delinquency (e.g., physical fighting, gang fighting, vandalism and firesetting), to serious and violent juvenile offending (e.g., rape, attack, autotheft, burglary, fraud, Loeber & Farrington, 2000). One quarter to one half of children who engage in disruptive acts go on to engage in more delinquent acts; one-third to two-thirds of children who engage in delinquent acts escalate to serious delinquency; and 40 – 60% of seriously delinquent youth become chronic lifetime offenders (Loeber & Farrington, 2000). Antisocial behavior in adolescence persists into early adulthood for life-course persistent and adolescent limited antisocial males (Moffitt et al., 2002). Males with life-course persistent antisocial behavior account for 53% of

violent offenses though they comprise 10% of the total population; 'adolescent- limited' delinquents account for 29% of violent offenses, 45% of drug offenses, 34% of rule offenses and 54% of property offenses though they comprise only 26% of the total population. Extreme and mild forms of externalizing behavior appear stable once they emerge in childhood or adolescence (Moffitt et al., 2002). Ninety percent of adults with antisocial personality disorder met criteria for CD in childhood (Loeber, Burke, & Lahey, 2002). Externalizing behaviors are more common and more stable for males compared to females. Sex differences in externalizing behavior emerge as early as two years old, with males engaging in externalizing behavior 1.5 (Moffitt & Caspi, 2001) to three times (Loeber & Farrington, 2000) as much as females. The finding that externalizing behavior is stable is important because it suggests that these types of behaviors may operate somewhat like a stable, trait-like factor and may be related to trait cortisol.

A biosocial model for cortisol-externalizing relationships: Theoretical links and experimental evidence

Exploring biosocial models of externalizing behaviors is particularly important for predicting the long term prognosis of children with externalizing behavior problems because individuals with a biological predisposition for externalizing behavior appear most resistant to treatment (Beyers, Loeber, Wikstrom, & Stouthamer-Loeber, 2001). Gunnar and Vazquez (2001) and Heim and colleagues (2000) suggest that hypoarousal of the HPA axis in individuals with externalizing problems may be indicative of underarousal, overregulation, or increased thresholds for stress (Kruesi, Schmidt, Donnelly, Hibbs, & Hamburger, 1989). Gray's (1994) motivational theory may

contribute to our understanding of biological explanations for externalizing behavior problems. Externalizing behavior, such as extraversion, aggression and impulsivity, are thought to be associated with heightened behavioral activation system (BAS) activity (Beauchaine, 2001). Conversely, the consequences of an underactive behavioral inhibition system (BIS) may be sensation seeking and aggression when the individual experiences insensitivity to reward and in response seeks rewarding stimuli too often (Beauchaine, 2001). Individuals with low cortisol levels may display a lack of fear and anxiety across situations in which a mild stress response is warranted. Fearlessness might predispose individuals towards externalizing behavior because the execution of such behavior requires a low state of arousal (Raine, 2002). Conversely, individuals with low adrenocortical activity may have an increased threshold for stress, and consequently seek types of stimulation that successfully induces a physiological response. Individuals with low HPA axis activity may find externalizing behavior arousing whereas those with higher cortisol levels mount a response to more benign stimulation (Raine, 2002).

Studies generally find an inverse association between externalizing behavior problems and markers of arousal, including heart rate (Raine, Venables, & Mednick, 1997; Van Goozen et al., 1998), galvanic skin response (el-Sheikh, Ballard, & Cummings, 1994), vagal tone (Beauchaine, 2001), and serotonin (Clarke, Murphy, & Constantino, 1999). A consistent inverse association between adrenocortical activity and externalizing behaviors in studies of children and adolescents emerges despite variation in the frequency and intensity of externalizing behavior problems, ranging from diagnoses of disruptive behavior disorders (DBD, e.g., Scerbo & Kolko, 1994) to anger,

aggression and impulsivity (e.g. McBurnett, Lahey, Rathouz, & Loeber, 2000; Moss et al., 1995; Tennes & Kreye, 1985).

Clinic referred disruptive children with attention problems had low cortisol levels (Scerbo & Kolko, 1994). Low cortisol levels were associated with persistent and early onset aggression in school aged boys with DBD (McBurnett et al., 2000). Children comorbid with ADHD and ODD had lower cortisol levels compared to controls (Kariyawasam, Zaw, & Handley, 2002). Adolescent girls with CD had significantly lower morning cortisol levels compared to normal control girls (Pajer, Gardner, Rubin, Perel, & Neal, 2001). Cortisol reactivity may also be attenuated in children with externalizing disorders. Children with DBD showed reduced reactivity to a frustration provocation task compared to normal controls (Van Goozen, Matthys, Cohen-Kettenis, Buitelaar, & Van Engeland, 2000). Cortisol levels were lower and reactivity to a frustration provocation task was diminished in ODD boys with externalizing symptoms compared to normal controls, although heightened reactivity was found for boys with comorbid anxiety problems (Van Goozen et al., 1998). Children with ADHD who maintained their diagnosis across one year had a blunted response to a stressor compared to children whose ADHD symptoms subsided (King, Barkley, & Barrett, 1998).

The association between low HPA axis activity and behavior problem symptoms also extends to populations at risk for developing externalizing behavior problems. CD symptoms were inversely associated with cortisol levels in sons of substance abusing fathers (Vanyukov et al., 1993). Low HPA axis reactivity to an event-related potential (ERP) challenge was found in boys with a family history of substance abuse disorder compared to normal controls, and hyporeactivity was related to the magnitude of

aggressive and impulsive symptoms (Moss et al., 1995). Pajer and colleagues (2001) found that behavioral disinhibition was associated with lower cortisol levels in daughters, and there was a trend for sons, of substance abusing fathers. Externalizing symptoms were inversely associated with cortisol levels in children of risky mothers, but this association was explained by poor parent child relationships (Granger, Serbin et al., 1998). Finally, Klimes-Dougan and colleagues (2001) reported that at risk adolescents whose cortisol levels decreased in response to parent-child conflict had more attention problems.

The association between adrenocortical activity and externalizing behavior symptoms may also be evident in low risk youth. Cicchetti and Rogosch (2001b) found that externalizing behavior problems were associated with low morning and average cortisol levels in control boys, but not in maltreated children. Flinn and England (1995) report low cortisol levels in normally developing boys with subclinical levels of antisocial behavior. Boys with lower cortisol levels displayed more externalizing behavior problems in a large group of low risk normally developing kindergarteners (Smider et al., 2002). In normal second graders, cortisol levels were negatively associated with hostile and aggressive behavior towards the teacher (Tennes & Kreye, 1985). In normally developing preschoolers, cortisol reactivity to playgroup activity was negatively associated with concurrent and subsequent aggressive and disruptive externalizing behavior problems (Granger, Stansbury et al., 1994). These studies suggest that there is a consistent relationship between reduced HPA axis activity in children with externalizing behavior disorders and symptoms in clinical, at risk and normally developing populations and across different ways of operationalizing externalizing

behavior problems, suggesting that the relationship between adrenocortical activity and externalizing behavior is fairly robust and may have broad implications for studies on child development.

Nevertheless, several studies fail to find this association and a handful of studies reach opposite conclusions. Targum and colleagues (1990) did not find differences between cortisol levels and reactivity to dexamethasone challenge between 11 patients with CD and 8 normal control youth. Kruesi and colleagues (1989) found that urinary cortisol did not differ between 19 boys with DBD and 19 control boys. High cortisol levels in response to starting school was associated with assertive, angry and aggressive behavior in preschoolers (de Haan et al., 1998). Cortisol reactivity has been positively associated with externalizing behavior problems in 57 adolescent males and females (Susman et al., 1997). It is of note that in this study cortisol reactivity was associated with behavior problems measured one year later. This longitudinal relationship supports the idea that some component of the HPA axis is stable and consistent, and that this component may be associated with externalizing behavior problems. Preschoolers who scored lower on measures of attentional and inhibitory control showed increases in cortisol reactivity from group formation to a familiar group setting (Gunnar et al., 1997) and externalizing behavior was positively associated with cortisol reactivity in preschool aged boys (Tout et al., 1998). It appears that the large majority of studies report an inverse relationship between adrenocortical activity and externalizing behavior, but a handful of studies do not find this relationship. Nevertheless, the fourth hypothesis of the current study is that low trait cortisol will be associated with externalizing behavior

problems and the sixth hypothesis is that time-lagged relationships between trait cortisol and externalizing behavior problems will be evident.

Comorbidity between internalizing and externalizing behavior problems: Clarifying links with adrenocortical activity

Understanding comorbidity may contribute to developmental psychopathology by differentiating clusters of symptoms, pointing to important risk factors for multiple disorders, and determining causal pathways from one disorder to another (Angold et al., 1999). Comorbidity between two childhood disorders occurs more frequently than would be expected given the rate of occurrence of individual disorders in the general population (Caron & Rutter, 1991). For example, across 21 general population studies, 33% of depressed adolescents were comorbid for CD compared to 5.9% of depressed adolescents without CD. Thus, depressed adolescents are 6.6 times more likely to have CD than non-depressed adolescents (95% CI 4.4 to 11.0, Angold et al., 1999). There is some suggestion that comorbidity also occurs within the normal range of symptoms. Factor structure for Achenbach's (1991a; 1991b) broad band internalizing and externalizing scales are known to be moderately correlated with each other in clinical and general population studies (McConaughy & Achenbach, 1994). Angold (1999) proposes that comorbidity between CD and depression is an important phenomena to examine because it is not a statistical artifact derived from referral bias or rater expectancies or a marker for severity of an undifferentiated mass of symptoms with arbitrary cutoffs. Rather, examining comorbidity between CD and depression may indicate whether one disorder is a manifestation of the other; for example, anger and aggression may be manifestations of

depression in males that is misclassified as externalizing problems (Klein & Corwin, 2002). Examining comorbidity may also indicate when the two disorders share common etiological risk factors (i.e., child maltreatment, Cicchetti & Lynch, 1995) and when biological factors convey risk or resilience.

Comorbid anxiety or internalizing problems often appear to play a moderating role in the cortisol-externalizing relationship (Raine et al., 1995). For example, low cortisol levels appear to place children at risk for ODD or CD (McBurnett et al., 2000), but children with CD and comorbid anxiety problems have high cortisol levels (McBurnett et al., 1991). Similarly, Van Goozen and colleagues (1998) found that cortisol reactivity to a frustration provocation task was heightened in boys with ODD who also had high anxiety problems compared to normal controls. Klimes-Dougan and colleagues (2001) reported that adolescents at risk for emotional problems whose cortisol levels increased in response to parent-child conflict had high levels of both internalizing and externalizing problems and this cortisol elevation persisted 40-min after the task in boys with elevated disruptive behavior symptoms. Thus, the observation that high cortisol levels are associated with externalizing behavior problems when these children were comorbid for internalizing problems may indicate that comorbid internalizing problems protects children from escalating externalizing behavior problems (see Zahn-Waxler, 2000 for a review). It is possible that low risk children with high levels of internalizing and externalizing problems in the present study may have high cortisol, but children with externalizing problems only may have low cortisol levels. The fifth hypothesis is that children with high internalizing and externalizing behavior problems will have high trait cortisol levels.

CHAPTER 4

GENDER DIFFERENCES IN HPA AXIS ACTIVITY: RELATIONSHIPS BETWEEN ADRENOCORTICAL ACTIVITY AND SOCIAL BEHAVIOR

The purpose of this chapter is to justify why gender differences in HPA axis activity are anticipated in adolescents. First, a growing body of literature is presented which documents gender differences in reactivity to social challenge. These findings are interpreted in terms of a recent theoretical model that posits that the neuroendocrine underpinnings of the stress response differ in males and females (Taylor et al., 2000). The evidence for this theoretical model has largely been tested in animals and a handful of studies have been conducted in adults (e.g., Kirschbaum, Wust, & Hellhammer, 1992), so the next section explores conceptual reasons for why gender differences in HPA axis activity in adolescents are anticipated. The premise of this chapter is that gender is potentially an important individual difference factor in adrenocortical activity that should be explored further in studies of cortisol and problem behavior. This idea sets the stage for the seventh hypothesis: males will have more 'state' and 'trait' cortisol compared to females because they are likely to have larger cortisol responses to stress compared to females. A small literature that demonstrates gender differences in cortisol-behavior relationships is then reviewed. This literature reveals that internalizing behavior problems may be particularly salient for girls while externalizing behavior problems may be salient for boys. Based on the nature of internalizing behavior problems, the eighth hypothesis is that trait cortisol will be related to internalizing behaviors more for girls

than boys. The ninth hypothesis is that externalizing behaviors will be inversely related to trait cortisol more for boys than girls.

Exploring gender as an important individual difference factor in adrenocortical activity has the potential to unmask subtle gender differences in the nature of the HPA axis. Gender differences in cortisol levels are not consistently found (e.g., Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Shirtcliff & Granger, 2001), leading several research groups to disregard separate examination of cortisol-behavior associations by gender (e.g., Gunnar et al., 1997; Tennes et al., 1986). Gender differences in cortisol reactivity, however, are reported in adults (see review by Kiecolt-Glaser & Newton, 2001), such that men are usually more physiologically aroused by stress and challenge (e.g., win/loss, achievement, conflict, social performance) than women (e.g., Kirschbaum et al., 1999; Kirschbaum et al., 1993) [1]. This presents the possibility that the HPA axis is activated by different types of stressors in males and females. Kirschbaum and colleagues (1992) demonstrate subtle gender differences in adrenocortical reactivity to challenge in both adolescents and adults. In response to public speaking and mental arithmetic, men showed greater cortisol increases above baseline levels compared to women. Men, but not women, also showed elevations in cortisol levels in anticipation of the task without actually having to perform the tasks, suggesting that, compared to women, the HPA axis in men may be activated for longer periods of time in anticipation and response to challenge. In response to physical

[1] The biggest exception to this gender difference is that women appear to be more physiologically aroused in response to marital discord and relationship dissatisfaction compared to men (see reviews by Kiecolt-Glaser et al., 1996; Kiecolt-Glaser & Newton, 2001). Similarly, Stroud and colleagues (2002) found that females showed greater reactivity to social rejection tasks while males showed greater cortisol reactivity to achievement oriented tasks.

challenge (e.g., CRH administration or physical exercise), however, men and women showed similar HPA responses to challenge. From these data, Kirschbaum and colleagues (1992) concluded that women were less responsive to stress compared to men because of cognitive or emotive, but not physiological, origins. Kirschbaum and colleagues (1995) later demonstrated gender differences in emotional moderators of adrenocortical reactivity to challenge. They showed that women were less reactive to stressful laboratory tasks when given social support by a stranger and more reactive to stress when given social support by their partners. Conversely, men were less reactive only when given support from their partners. Finally, Seeman and colleagues (2001) suggest that gender differences in HPA axis activity may vary by age. They showed that college-aged males showed greater reactivity to challenge than young females, but older females (i.e., post-menopausal women) showed greater reactivity to challenge than age-matched males. They speculate that the cause of the gender difference may be estrogen-mediated. Whether gender differences in adrenocortical activity would also vary by age in childhood and adolescence, another time of life when the hormonal milieu of males and females changes dramatically, has yet to be examined. It is of interest because gender differences in behavior problems emerge in adolescence (Zahn-Waxler et al., 2000). It is possible that developmental changes in adrenocortical activity contribute to gender differences in problem behavior profiles (Walker, Walder, & Reynolds, 2001). These studies demonstrate that, though gender differences in cortisol levels may not be evident, males and females may respond differently to social challenge, and moderators of adrenocortical responses to stress may operate differently in males and females. If males respond more to challenge than do females, more variance in salivary cortisol may

be derived from situation-specific factors (e.g., recent or anticipated stress, Smyth et al., 1998) in males compared to females. Thus, state cortisol may be a larger component of the total variance in salivary cortisol for males than for females.

THE "*TEND AND BEFRIEND* HYPOTHESIS:" A CONCEPTUAL FRAMEWORK TO GUIDE PREDICTIONS ABOUT GENDER DIFFERENCES IN ADRENOCORTICAL ACTIVITY

Gender differences in physiological responses to stress have recently been placed within a theoretical framework that attempts to explain why the stress response is different in males and females. Taylor and colleagues (2000) propose that males and females have different biobehavioral responses to stress in large part because they evolved with different factors influencing their survival. Men respond to stress through the *fight or flight* response proposed by Cannon and developed by Selye (1976). In response to stress, the sympathetic nervous system and the HPA axis activate organ systems that will help the person mobilize resources to fight or flee from the source of danger. Sapolsky's (1990; 1998) classic example of the *fight or flight* mechanism illustrates how the body's physiological systems are primed to help a zebra run away from an immediate threat, like a lion enjoying the thrill of the hunt. Sapolsky challenges the adaptability of the fight or flight response for modern day chronic stressors which are not life threatening but activate the same biological systems. Taylor and colleagues (2000) challenge the adaptability of the fight or flight response for females because this response may have endangered females and their young offspring. Pregnant females would endanger themselves if they tried to waddle away from a threat, and females with

young children would leave their young offspring unprotected if they fought with an adversary. Instead, the female response to stress often takes the form of the *tend and befriend* response in which females tend to offspring and affiliate within social groups, generally other females who help protect offspring by banding together in sisterly solidarity (Taylor et al., 2000; Taylor, Dickerson, & Klein, 2002). Both the *fight or flight* and the *tend and befriend* response can be used by men and women, but the neuroendocrine system in men favors the *fight or flight* and the neuroendocrine system in women favors the *tend and befriend* response (Geary & Flinn, 2002; Taylor, Lewis et al., 2002). In men, the interaction of testosterone and vasopressin with the HPA axis heightens and reduces the *fight or flight* response; in women, estrogen, oxytocin and endogenous opioids all act to increase the likelihood that women respond to stress in an affiliative manner (Taylor et al., 2000; Taylor, Lewis et al., 2002) [2]. Thus, the adrenocortical response to stress is downregulated in females relative to males (Taylor, Dickerson et al., 2002).

This review leads to several tentative conclusions. First, HPA axis activity may operate differently in males and females and moderators of HPA axis reactivity to stress may be different in males and females. Second, if the stress response differs between men and women as a function of adrenocortical interactions with other hormonal mechanisms such as oxytocin, vasopressin and endogenous opioids, the nature of gender differences in adrenocortical activity may be complex. Third, gender differences in adrenocortical activity may change as the HPA axis develops. Given that estrogen,

[2] This theory is not challenged by the findings of Kirschbaum and colleagues (1995) because females in the study received social support from a male stranger or boyfriend. Taylor and colleagues' (2000) predictions are relatively specific to social support provided by females.

which moderates adrenocortical activity, operates differently in adolescent females than in older females, it may be difficult to predict how the *tend and befriend* theory would apply to children and adolescents. This topic is addressed in the next section.

Speculations and Implications for Gender Differences in Adrenocortical Activity in Adolescents

The impact that gender differences in HPA axis reactivity has on state and trait cortisol in adolescents may take one of three forms. First, it may be the case that gender differences emerge in adulthood but are not evident in childhood and adolescence. For example, Shirtcliff and Granger (2001) did not find gender differences in cortisol levels, variance or stability in youth ages 6 – 16 years. This suggests that researchers who have not examined potential gender differences in adrenocortical activity may not have been in error. This would also lead to the prediction that state and trait variance in salivary cortisol is similar in males and females. Second, if male adolescents express more reactivity to stress than female adolescents, as is the case with adults, adrenocortical reactivity to challenge may be heightened in young males. If so, then cortisol levels should change more dramatically in males, and more of the variance in salivary cortisol levels should be situation-specific (i.e., state) in males. It is unclear how this might impact trait-like variance in salivary cortisol because gender differences in state cortisol do not necessarily cause gender differences in trait cortisol. Nevertheless, it is important to examine gender differences in trait cortisol because this will contribute to our understanding of the consistency and clarity of studies on the HPA axis in boys and girls. Third, it may be the case that gender differences in cortisol levels and variance are

negligible, but moderators of adrenocortical activity operate differently in males and females. Gender differences in the nature of children's behavior problems may render the relationship between behavior problems and the HPA axis to be more or less salient for boys and girls. Gender differences in adrenocortical activity in adolescents are difficult to predict. Nevertheless, the seventh hypothesis is that the variance in state and trait cortisol is hypothesized to be larger in males compared to females.

Gender differences in cortisol-internalizing behavior links: Internalizing behavior may be more salient for girls than boys

Given the prediction that males will have more trait cortisol than females, it would follow that males should show stronger behavioral associations with adrenocortical activity. Nevertheless, the relationship between cortisol and internalizing behavior may also be stronger for females compared to males. Given that depression is more common in females (Zahn-Waxler et al., 2000; Zahn-Waxler et al., in press), the range and severity of internalizing problems may be wider in girls and the biological relationship between depression and cortisol may be stronger for girls compared to boys. It may be the case that, though the HPA axis in males has a larger trait component than females, this trait component is associated with factors other than internalizing behavior for boys. For example, individual differences in cortisol levels may be influenced more by externalizing than by internalizing behavior in males. The eighth hypothesis is that trait cortisol-internalizing relationships will be stronger in females compared to males.

Gender differences in cortisol-externalizing behavior links: Adrenocortical activity and externalizing behavior is more salient for boys

Externalizing behavior disorders are more common in males than females (Loeber & Farrington, 2000; Moffitt & Caspi, 2001). Many researchers have found cortisol-externalizing associations in boys only (McBurnett et al., 1991; McBurnett et al., 2000; Moss et al., 1995; Van Goozen et al., 1998; Vanyukov et al., 1993; Virkkunen, 1985), although Pajer and colleagues (2001) found low cortisol levels in girls with conduct disorder as well. Other researchers have included both male and female subjects (de Haan et al., 1998; Granger, Serbin et al., 1998; Granger, Stansbury et al., 1994; Gunnar et al., 1997; Tennes & Kreye, 1985; Tennes et al., 1986; Van Goozen et al., 2000) but did not explicitly examine potential gender differences in hormone behavior associations. Finally, Smider and colleagues (2002) and Cicchetti and Rogosch (2001b) found that cortisol was inversely related with externalizing behavior problems in boys only, but interestingly Pajer and colleagues (2001) found that the inverse association between cortisol levels and behavioral disinhibition was significant in girls but displayed a trend in boys. It is possible that males will show stronger cortisol-externalizing behavior relationships compared to girls because the range and severity of externalizing behavior problems is wider in boys compared to girls (Loeber & Farrington, 2000), and neurobiological risk factors appear to influence the trajectory of behavior problems in males much more than females (Moffitt & Caspi, 2001). Given the prediction that males will have more state and trait variance compared to females, there may potentially be more variance in trait cortisol that can be explained by behavior problems in boys. It

may be that the HPA axis in males has a larger trait component than females, and behavior problems in males may be a particularly salient factor that is associated with adrenocortical activity. From both a biological and a behavioral standpoint, cortisol-externalizing behavior relationships should be stronger in boys compared to girls. The ninth hypothesis is that low trait cortisol levels will be associated with more externalizing behavior problems, and this relationship will be stronger for boys than girls.

CHAPTER 5

STATISTICAL MODELING OF TRAITS AND THE USE OF LST MODELING FOR SALIVARY CORTISOL

The purpose of this chapter is to justify why latent state trait modeling is a useful tool, particularly for evaluating individual differences in salivary cortisol. First, a discussion of the characterization of a trait and perspectives on the utility of the trait-state distinction will be provided. Five different methods that examine traits will be presented. The first method uses aggregation to assess the consistent dimension of a person's trait construct and the second method utilizes a twin design to estimate heritable traits. The last three methods use structural equation modeling (SEM) to separate error from the true score. Multitrait-multimethod, factorial invariance, and latent state trait modeling are three statistical tools that examine consistency in behavioral or biological measures. The components of the LST model are presented in more detail, focusing specifically on the factors that influence variance in salivary cortisol. The premise of this section is that the conceptual match between the components of variance in salivary cortisol and the latent variables in the LST model is best compared to other similar alternatives. LST modeling is an ideal tool to decompose salivary cortisol into distinct latent state and trait constructs.

TRAITS AND MEASUREMENT PARADIGMS: DEFINITION AND ASSUMPTIONS

The concept of a trait refers to "an enduring characteristic of the individual which is manifested in a consistent way of behaving in a wide variety of situations" (Krech &

Crutchfield, 1958) and commonly refers to a person's personality or temperament characteristics. Traits are more widely understood as attributes of the person that are stable, constant, or at least evidence a shallow growth function (Smith, 1999) and whose characteristics can be traced back at least to adolescence or early adulthood (Johnson, Cohen, Skodol, Hamagami, & Brook, 2000). Statistically, traits refer to "the consistency of interindividual differences in intraindividual change" (Kenny & Zautra, 2001a). Steyer and Schmitt (1990) propose three prerequisites before a construct can be considered a trait. First, variation in the construct across individuals must exist or else a trait would have no discriminative value. Second, a trait is not directly observable but is rather a conceptual tool to describe an individual's tendencies (e.g., behavioral, temperamental, physiological). Third, if a trait is an enduring characteristic of the individual, it follows that it should show stability across time. Thus, it appears that a trait is a consistent, stable yet abstract characteristic of the individual that differs from one person to the next.

The utility of the trait definition has received some scientific scrutiny. The major criticism of trait research is that an individual's attributes are largely influenced by situational factors. If these influences are too large, the prerequisite that a trait is consistent and stable becomes questionable. Some argue that the influence of the situation is so great that trait approaches should be abandoned (Wright & Mischel, 1987), but others propose that traits can be assessed as long as they are measured across more than a single setting and properly aggregated (Epstein & O'Brien, 1985). Steyer and colleagues (1999) contend that traits are measurable and are of use for behavioral scientists when situation-specific effects are considered important sources of variance.

That is, when both situation- and person- specific factors are incorporated as an integral part of models, a more parsimonious model is maintained. This is a central tenet of the state-trait distinction and is integral to the utility of trait cortisol. Chapter 1 describes a wide variety of situations that activate the HPA axis, and studies of adrenocortical activity in naturalistic settings reveal that the lion's share of the variance is due to recent or anticipated stress, momentary moods and emotions (Adam, 2003; Kirschbaum et al., 1990; Preville et al., 1996; Smyth et al., 1998). While situational influences on salivary cortisol measures at any one time point may overwhelm the stable and consistent component of salivary cortisol, underlying this variability may be a stable trait that can be rendered explicit using appropriate modeling strategies.

The utility of statistical modeling to address the state-trait distinction rests on several premises (Steyer et al., 1999). First, it is presumed that measurement does not take place in a vacuum. The state that the individual is in at the time of measurement influences their responses. This was illustrated by Steyer and colleagues (1990) who showed that measures designed to assess trait anxiety were still greatly influenced by subjects' anxiety levels are the time of measurement. Thus, even when the purpose is to measure a stable component of the individual, situational factors may influence the outcome. The second premise is that individual and situational differences are confounded to an unknown extent at any given time point. Any measure will potentially be influenced to varying degrees by both state and trait factors, but we do not know the extent to which this confound attenuates the size of the hormone-behavior correlation (Eid et al., 1994). The third premise is that the situation does not have to be measured or observed to be accounted for as long as there is more than one occasions of measurement

(Nesselroade, 1988; Steyer et al., 1999). Steyer and Schmitt (1990) demonstrate this mathematically using classical psychometric test theory. Further, relevant psychological conditions can be systematically evaluated through correlates and predictors of individual differences in the trait once the conceptualization of the trait is constructed (Eid & Diener, 1999; Steyer et al., 1999). From these premises, it follows that traits can be estimated when the same factor has been measured repeatedly within the same occasion of measurement and on different occasions. Different methods for conceptualizing a trait measure have been used. These are reviewed below.

Five techniques for modeling traits: Advantages and disadvantages for determining trait salivary cortisol

Five major techniques have been used to model a trait construct: aggregation, heritability, multitrait-multimethod (MTMM), factor invariance (FI) and latent state trait (LST) models. Each of these addresses the stable, consistent portion of a construct in different ways. The latter three methods use SEM, so a brief discussion on the manifest and latent variables in SEM is provided. The advantages and disadvantages of each method for assessing salivary cortisol are discussed in turn.

Aggregation: The average gradually assesses traits

The first method, aggregation, has often been used to represent trait HPA axis activity. Benefits of aggregation include simple interpretation and calculation. Aggregation reduces measurement error and situation specificity but does so gradually

(Steyer & Schmitt, 1990). Thus, many measures may be needed before aggregation assesses the trait component of a measure. As Van Goozen et al (1998) and Smider et al (2002) discuss, and Moss et al (1995) demonstrate, including multiple measures of cortisol yields more consistent and interpretable hormone-behavior associations than a single measure. However, given that much of the variance in cortisol is due to context-specific factors, a prohibitive number of cortisol measures may be needed before a stable trait emerges. Gunnar and colleagues (1997) report using over a dozen measures to estimate median cortisol levels (range 5 – 23 samples per child). Further, aggregation improves estimates, but does not allow for separation of state-like influences from the trait factor.

Heritability: Genetic traits for salivary cortisol

The second method for determining consistent traits is heritability estimates which estimate the size of the trait when studies include genetically-related individuals. This method rests on the premise that individual differences in a construct result from either genetic or environmental influences. In the twin design, heritability estimates are a function of the difference in the size of the correlation between monozygotic twins, who share all of their genes, and dizygotic twins who share on average half of their genes. Heritability then defines a trait as the portion of the variance in a factor that is consistent across individuals. Heritability estimates of cortisol vary greatly, from 0 to 84%, although the simultaneous heritability estimate across five studies was estimated to be between 37 and 59% of the total variance in cortisol (Bartels et al., 2002). However, Bartels and colleagues (2002) illustrates that these heritability estimates of cortisol are

not reliable because the sample sizes used to estimate heritability are well below the level needed for generating stable estimates. For example, assuming a generous correlation in cortisol levels between monozygotic twins of 0.60, detection of a heritability component of 55% of the variance would require over 200 subjects, and a more modest heritability component of 35% would require nearly 450 subjects. The studies that have examined heritability thus far have used sample sizes, ranging from seven to 146 (M = 70); further, studies with relatively large sample sizes failed to find significant heritability estimates (e.g., Froehlich, Zink, Li, & Christian, 2000; Maxwell, Boyle, Grieg, & Buchanan, 1969). Using heritability as an indicator of trait factors has been criticized for assuming that all traits are of genetic origin (Kenny & Zautra, 2001a). It appears that heritability is an appropriate method for estimating the consistent portion of the variance in cortisol across large groups of genetically related individuals, but when the individual is the unit of analysis, or when generalizing to non-twins is of interest, other methods may be more appropriate.

Latent Constructs: Using structural equation modeling to assess traits

The final three methods for determining consistency use latent constructs. Latent constructs are unidimensional concepts that cannot be measured with a single item but together conceptually form the central meaning of a construct free from random and systematic measurement errors (Bollen, 1989). Put more simply, latent constructs are the sum or average of a number of manifest variables (the observed or measured items) that together represent an unobserved construct. The latent variable represents a 'true score' because it is free of measurement error at the item and construct level (Steyer, 2002).

Given that measurement error contributes to biased estimates of coefficients and attenuates the size of correlations, latent constructs represent an attractive alternative to analyses involving manifest variables (Eid et al., 1994; Kenny & Zautra, 2001b). Latent constructs are easily modeled and interpreted within a structural equation format using readily available software packages (Byrne, 2001). Three methods of determining consistency using latent constructs within a SEM format include MTMM, FI and LST modeling.

Multitrait- multimethod modeling: Examining consistency across time and informant

This is a statistical model that examines individual differences in consistency by using method factors. Method factors are latent constructs that are composed of variance specific to a type of measure or item response (Bollen, 1989). The purpose of MTMM modeling is to examine the consistent portion of an individual's true score by partialling out the effects of response bias caused by informant or methodological tool (Graham & Collins, 1991). MTMM modeling partials out the response bias caused by informant by creating a method factor with loadings on items reported by the same informant; similarly, the response bias caused by the measurement tool is factored out by creating a method factor with loadings on items from the same scale. The true score of the individual is free of unsystematic measurement error and systematic error caused by informant or method (Nesselroade & Featherman, 1997). MTMM methods, while extremely useful, are not appropriate for determining the consistency in cortisol across time because cortisol levels are derived from the same informant using the same

measurement tool (i.e. radioimmunoassay). For cortisol, examination of the consistency across time, not informant or method, is desirable.

Factor invariance procedures: Testing for a trait factor to derive trait cortisol

FI procedures provide a statistical test for invariance of measures across time or groups (Hofer, 1999; Meredith, 1993; Meredith & Horn, 2001). FI is a set of nested procedures that explicitly test the assumption often made using aggregation techniques: that the items in the factor are the same across or within individuals. First, weak FI places equality constraints on the regression weights from the manifest items to the latent construct. This tests the assumption that the factor pattern matrix is the same across time or groups. If weak FI is not met, the latent construct is not the same at the measurement level, and assessments between individuals or measurements across time are limited to qualitative comparisons. Strong FI tests for invariant mean intercepts across groups or times so that all mean differences in the variable can be expressed at the latent factor level. However, FI procedures developed specifically for LST models do not make this assumption (Dumenci & Windle, 1998). Finally, strict FI places equality constraints on the unique variances. Strict FI tests the assumption that the random error variance affecting each manifest construct is similar and random. When these three levels of FI constraints are in place, it can be assumed that the only differences across groups or time are at the latent variable level and are not caused by measurement design issues (Hofer, 1999). FI procedures are extremely useful for testing whether the measurement of a construct changes with time, but the limitation of FI procedures is that a latent construct that represents consistency is not obtained by this procedure. However, the combination

of FI procedures with another modeling strategy may be an optimal analytical strategy. The assumptions of stability and consistency across time can be tested using FI procedures in order to create a construct representing a trait factor using a SEM strategy. Also, FI procedures can test for invariance across multiple groups. Using FI procedures in combination with LST modeling is a favorable strategy because LST modeling creates a second order latent construct to represent trait cortisol and FI procedures ensure that trait construct is the same across time and groups.

Latent State Trait Modeling: Second order latent factor assessments of trait cortisol

The fifth method of determining consistency uses latent state trait modeling. When the same construct is measured across time and the consistent portion of that construct is of interest, LST modeling can be used to separate the situation-specific variance from the trait factor. The model represents a hierarchy of different components of the manifest variable (Bollen & Lennox, 1991; Eid et al., 1994). The manifest variable is the item that is actually measured in behavioral studies. The manifest variable theoretically is a function of some constant, a state variable and some underlying consistency across time (Steyer et al., 1999). At the first level, each manifest variable is separated into two factors representing measurement or unique error and a latent variable that is composed of person, person-environment interactions and situation-specific effects. When two or more manifest variables are measured, this latent construct can be further differentiated into a second order latent construct that separates the person-specific variance from the situation-specific variance. The meaning of the latent trait

factor is the portion of total variance that is consistent across time; that is, the portion of the variance that is person-specific. The meaning of the latent state factor is the portion of the total variance that is situation-specific or a part of the person-situation interaction (Kirschbaum et al., 1990). This conceptualization is abstract because the situational factors that influence state cortisol are unmeasured.

The LST model is both simple and complex at the same time (Kenny & Zautra, 2001b): the concept of a trait is easily understood; the interpretation of the trait construct is straightforward (Steyer & Schmitt, 1990); there are fewer parameters to disentangle; and the interpretation of the trait-behavior correlation is parsimonious. The trait factor represents only person-specific factors, so the interpretation of a correlation is not cluttered by the possibility that the cause of the correlation is due to measurement error or situational effects. In some ways, behavioral correlates of a latent trait are as simple as a partial correlation, but the complexity is that it partials out an unmeasured variable (situation-specific effects, Gottlieb, 2002). The model is also complex: the statistical modeling of a trait is intricate; it is difficult to understand a second order latent construct; and a tangible score for 'trait' cortisol is not obtained. This creates problems for individuals who question the external validity of a construct that is not concrete (Rogosch, 2003). Nevertheless, the benefits of simple conceptual meaning may outweigh the statistical complexity.

There are three key assumptions underlying LST modeling. The first is the stationarity assumption which asserts that the variance explained by the state factor is the same across each time of measurement (Kenny & Zautra, 2001b). This is easily tested using FI procedures (Hofer, 1999) or some similar alternative (Dumenci & Windle,

1998). The second assumption is that the sources of variance in the manifest variable – trait, state and error – are not correlated with each other at the same time or across time. This assumption is often relaxed in practice (Dumenci & Windle, 1998; Steyer & Schmitt, 1990; Steyer et al., 1990). The third assumption is that the state variable follows first order autoregressive structure (Kenny & Zautra, 2001a, 2001b).

An additional caveat is that the interpretation of a trait is limited by situational influences that vary across time (Nesselroade & Featherman, 1997). This refers to the fact that an individual's trait score is not independent of situational effects, but rather is independent of situational effects evident at the time of measurement (i.e., the relativism problem, Steyer et al., 1999). The trait coefficient may change when additional situational variation is introduced by including measures taken in a different setting or across a larger time span (Kenny & Zautra, 2001a, 2001b). This does not necessarily pose a problem for LST models, but instead presents an opportunity for systematic evaluation of steady situational influences that may explain trait hormone-behavior associations.

USING THE LATENT STATE TRAIT MODEL FOR TRAIT CORTISOL: THE MATCH BETWEEN COMPONENTS OF THE MODEL AND VARIANCE IN SALIVARY CORTISOL

Several aspects of the nature of the HPA axis make LST modeling of salivary cortisol appear ideal. As noted by Kirschbaum and colleagues (1990), there are three sources of variance in cortisol levels in addition to diurnal variation: internal person factors (i.e., trait), external situational and/or person-situational interaction (i.e., state),

and the reliability of the biochemical assays used to measure cortisol (i.e., measurement error). LST modeling allows us to systematically consider these sources of variance on salivary cortisol, to evaluate trait cortisol-behavior relationships distinct from situational influences on cortisol, and to do so across multiple groups.

Measurement error in the laboratory is usually dealt with by measuring each sample in duplicate, then using the average of the duplicates as an estimate of salivary cortisol. In LST modeling, the disagreement between the duplicates is modeled so that the latent construct is free of the measurement error in salivary cortisol. Very little variance in salivary cortisol is expected to be due to measurement error. Cortisol levels vary greatly across situations and across time (e.g., Susman, 1997; Susman, Nottelmann, Dorn, Inoff-Germain, & Chrousos, 1988), so much of the variance in cortisol should be related to situation-specific factors. The majority of the variance in salivary cortisol is expected to be due to the latent state variable. Finally, cortisol levels have some predictive value suggesting that some stable trait-like component of cortisol must underlie the day-to-day fluctuations in cortisol levels. Therefore, a significant portion of the variance in salivary cortisol is hypothesized to be attributable to trait cortisol.

Support for these hypotheses come from Kirschbaum and colleagues (1990) and Preville and colleagues (1996) who used LST modeling to discover state and trait influences on morning salivary cortisol. In a sample of 48 college students, 75% of the variance in salivary cortisol was due to situation-specific factors and 21% was due to the latent trait and in 54 new mothers, 60% was due to state and 33% of the total variance was due to the trait factor (Kirschbaum et al., 1990). Similarly, in a sample of 46 healthy older adults, 70 to 80% of the total variance was due to situation-specific factors and the

trait construct was not significant (Previlleet al., 1996). These studies are limited, however, because they used small samples to estimate state and trait factors, questionable saliva collection methods, and did not examine behavioral correlates of the trait factor to determine whether trait cortisol is externally valid.

Summary and conclusion

This study employs a LST model in a large sample of low risk normally developing youth and relates trait cortisol with internalizing and externalizing behavior in males and females. LST modeling was selected because the latent constructs derived are a good match with the conceptual sources of variance of salivary cortisol. The latter two components of the study, whether trait cortisol is associated with behavior and whether it is the same across gender, has not been assessed before (to my knowledge) but the LST model can easily be extended to examine behavioral correlates of a trait (Eid et al., 1994; Schmitt, in press; Steyer et al., 1990) in addition to a multiple group strategy (Steyer et al., 1999) across populations (i.e., boys and girls, Li et al., 2001; Ridgon, Schumacker, & Wothke, 1998).

CHAPTER 6

HYPOTHESES AND PREDICTIONS

1. The first hypothesis is that situation specific variance, that is, state cortisol, will comprise the largest proportion of the total variance in children's salivary cortisol. This prediction is supported by the literature reviewed that demonstrates considerable variation in cortisol in response to situational events as well as person-situation interactions (e.g., Kirschbaum et al., 1990). This hypothesis is confirmatory because a large literature suggests that adrenocortical activity is derived from situational events and studies that use LST modeling for salivary cortisol support this hypothesis (see Gunnar et al., 2000 for a review).

2. Chapter 2 also reviewed several studies which found individual differences in salivary cortisol which should be expressed as trait cortisol (Kirschbaum et al., 1990). The second hypothesis is that some component of the total variance in salivary cortisol will be due to trait cortisol. This hypothesis is relatively confirmatory because a large literature documents individual differences in salivary cortisol (see Gunnar et al., 2000 for a review).

3. The number of studies which link high cortisol levels and reactivity with internalizing behavior is greater than studies which find low adrenocortical activity-internalizing relationships (see chapter 3). Thus, the third hypothesis is that trait cortisol levels will be positively associated with internalizing behavior problems. This hypothesis is relatively confirmatory even though the literature that documents relationships between cortisol and internalizing behavior is mixed.

There are many studies to draw from which show high cortisol levels are associated with internalizing behavior problems. The purpose of the present study is primarily to extend this literature to low risk normally developing adolescents.

4. The clear majority of studies relate low cortisol levels with externalizing behavior problems (see chapter 3). Confirming this finding in normally developing youth will further the biosocial model by providing clear evidence for the first stage of the biosocial model, that is, documenting relationships between biology and behavior. The fourth hypothesis is that trait cortisol levels will be inversely associated with externalizing behavior problems in adolescents. This hypothesis is confirmatory.

5. Raine and colleagues (1995) propose that low physiological arousal is associated with escalations in 'pure' externalizing disorders, but that high physiological arousal associated with comorbid internalizing behavior problems protect children from further developing externalizing behavior disorders. This suggests that associations between adrenocortical activity and comorbidity may convey resilience to clinical populations. This hypothesis extends this finding to low risk normally developing youth. The fifth hypothesis is that children with high internalizing and externalizing behavior problems will have high trait cortisol levels. This hypothesis is relatively exploratory. Only three studies have reported interactions between internalizing and externalizing behavior problems and these relationships were not hypothesized *a priori*. It is also possible that 'comorbidity' within a low risk sample has different physiological underpinnings.

6. To determine the robustness of the cortisol-behavior relationship, time-lagged relationships between cortisol and behavior problems are explored. The sixth hypothesis is that cortisol-behavior relationships will not be different from one year to the next because these behaviors are relatively stable and the measure of trait cortisol is also stable across time. Based on the strength of the third and fourth hypotheses, this hypothesis is confirmatory because on the strength of the trait cortisol construct.

7. Following the adult literature explored in the fourth chapter, the seventh hypothesis is that males will have more state and trait derived variance in salivary cortisol compared to females because they are likely to have larger cortisol responses to stress compared to females. This hypothesis is primarily exploratory because studies that have examined LST modeling of salivary cortisol have not examined gender differences (Kirschbaum et al., 1990; Preville et al., 1996), the literature that guides the prediction about state cortisol is based on adult populations, and there is no literature to draw from to guide predictions about gender differences in trait cortisol.

8. Gender may be an important individual difference factor that moderates cortisol-behavior relationships (Kirschbaum et al., 1992). Given that internalizing behaviors are more salient constructs for adolescent girls (Zahn-Waxler, 2000; Zahn-Waxler et al., in press), the eighth hypothesis is that trait cortisol will be related to internalizing behaviors more for girls than boys. This hypothesis is primarily exploratory because few studies have examined gender differences in cortisol-internalizing relationships.

9. Externalizing behavior problems, variability in HPA axis activity, and neurobiological risk factors for externalizing behavior problems are more salient for boys than girls (Moffitt & Caspi, 2001). Thus, the ninth hypothesis is that trait cortisol will be related to externalizing behaviors more strongly for boys than girls. This hypothesis is confirmatory because there is theoretical and empirical evidence that cortisol-externalizing behavior relationships are evident in boys more than in girls.

The current study was designed to address these hypotheses, to resolve the apparent inconsistencies in cortisol-behavior relationships, to confirm or explore several hypotheses, and potentially advance biosocial theories of child development.

CHAPTER 7

METHODS: SALIVARY CORTISOL AND BEHAVIOR PROBLEMS IN A LARGE SAMPLE OF LOW RISK NORMALLY DEVELOPING YOUTH

SAMPLE

Data for this study came from the Pennsylvania State University Family Relations Project, a study of 400 families, 203 of which had two pre-teen children and 197 of which had two adolescent children (see also Booth et al., 2003). The families were selected so that the gender composition of the offspring dyad was balanced with approximately equal numbers of male-male pairs, female-female pairs, male-female pairs where the male was older, and female-male pairs where the female was older. Families were recruited through 13 local school districts from students enrolled in either the fourth and fifth or the ninth and tenth grades. The participants were not screened or selected for internalizing or externalizing behavior problems. It is possible that a subset have subclinical or clinical levels of problem behavior. Examination of the distributions of behavior problems reveals normally distributed scores (though slightly positively skewed) suggesting that these behavior problems lie on a continuum from low risk to potentially clinical level problem behavior.

Families participating in the study were middle and working class and resided in rural areas, towns and small cities. Median income for these predominantly dual earner families was $35,000 for fathers and $17,200 for mothers. Average educational attainment was 14.6 years. Ninety seven percent of the participants were of European-

American origin. The remaining three percent were Asian and Latino. Mean age for offspring was 13.5 years (range from 6 to 16 years in year 1 of the study). Parents had been married for an average of 17.5 years. Families were given a $100 honorarium and an additional $25 if they chose to provide saliva samples.

PROCEDURES

Youth were interviewed in 1997, 1998, and 1999. Separate home interviews were conducted with both first- and second-born offspring. During these interviews family members reported on their family relationship experiences and individual well being. A saliva sample was collected during the interview then participants were instructed on how to collect, store, and mail the morning saliva samples. A member of the household (usually the mother) was responsible for overseeing the morning saliva collections for the entire family. Behavioral data was collected across three years while saliva collection took place in years 2 and 3 of data collection.

MEASURES

Salivary cortisol: Sample collection, immunoassay and reliability

Saliva was collected from each child upon arising on two consecutive days in year 2 and then again according to the same schedule one year later for a total of four samples for each child. Children who had a fever (2.5%) or problematic samples (i.e., discolored) were asked to provide saliva at a later date. Participants were instructed to provide saliva before brushing teeth or eating the morning meal on each of the four mornings. Following Dabbs (1991), subjects were instructed to chew Trident original flavor-sugarless gum to stimulate saliva flow, and salivate 10-15 mLs of saliva into a 20 mL

scintillation vial over 15-20 minutes. At the time of sample collection, children reported whether they had used tobacco (5.5%) or anabolic steroids (0.15%), taken allergy (7%) or pain medication (15%), whether uplifts (28%) or hassles (15%) happened recently, and when they had last eaten or exercised. Girls reported whether they had begun menstruating (88%), and, if so, the number of days since their last menstrual period began and whether they were taking oral contraceptives (4%). We obtained complete saliva samples from 654 youth. A comparison of demographic characteristics of families whose children provided morning samples and those who did not revealed no systematic differences. There was sufficient variation in the actual time of the morning samples (M = 7:56 AM, SD = 2:48) that time of day was included as a covariate in all analyses at the state cortisol level. How much this differs from the normal time of awakening and the amount of time that has passed since awakening still may influence cortisol levels. The impact of these factors on a single measure of cortisol are conceptually a component of state, not trait, cortisol. Thus, the impact of fluctuations in the diurnal rhythm should not influence trait cortisol-behavior associations. We examined whether menstrual cycle status, day count, or oral contraceptive use influenced the model parameters. In year 2, 123 girls indicated that they had begun menstruating and 4 girls reported oral contraceptive use. In year 3, 125 girls indicated that they had begun menstruating[3] and 8 girls reported oral contraceptive use. When these measures were included in the model, there was no relationship between cortisol and menstrual cycle status, ps > 0.48, day

[3] For this measure, 247 girls had missing data suggesting that a large number of participants refused to answer this question. The reliability of this measure is questionable.

count, ps > 0.07, or oral contraceptive use, ps > 0.27. Thus, these measures are not included in the final analysis.

Samples and controls (see below) were assayed for cortisol using a modification of a serum-based coated tube radioimmunoassay for use with saliva (Diagnostic Products Corporation, Santa Monica CA). The test used 200 ul of saliva, had a lower limit of sensitivity of .03 ug/dL (micrograms per deciliter) and upper limit of 2.0 ug/dL. The intra-assay coefficient of variation (CV) for cortisol was 7.60 %, with a correlation between duplicates of 0.993, $\underline{p} < 0.0001$. The inter-assay CVs, estimated across 128 separate runs (occurring over the course of 2 years) for the high (1.91 ug/dL), mid (0.86 ug/dL) and low (0.14 ug/dL) external controls, were 4.98%, 5.08%, and 10.42 %. All samples were tested in duplicate and duplicate tests values that varied by more than 5% error were subject to repeat testing. The unit of measurement for cortisol is ug/dL. Cortisol levels were normally distributed (M skew = 0.70, range 0.45 to 0.88).

Internalizing behavior: Children's Depression Inventory and the Center for Epidemiological Studies Depression Scale

We represented internalizing behavior problems for younger children (age 6 to 13 in year 1) using an age-appropriate 26 item adaptation of Kovacs (1980) Children's Depression Inventory (CDI). Items include "I am sad all the time", "Nothing will ever work out for me", "I do everything wrong", "Nothing is fun at all", "I am bad all the time", "I am sure that terrible things will happen to me", "I hate myself", "All bad things are my fault", "I feel like crying every day", "Things bother me all the time", "I do not want to be with people at all", "I cannot make up my mind about things", "I look ugly",

"I have to push myself all the time to do my schoolwork", "I have trouble sleeping every night", "I am tired all the time", "Most days I do not feel like eating", "I worry about aches and pains all the time", "I feel alone all the time", "I never have fun at school", "I do not have any friends", "I do very badly in subjects I used to be good in", "I can never be as good as other kids", "nobody really loves me", "I never do what I am told", "I get into fights all the time." The scales had alpha coefficients of 0.78, 0.88, 0.78 for boys and 0.76, 0.78, and 0.76 for girls in years 1, 2, and 3, respectively.

Adolescents (age 10 to 16 in year 1) were administered a 12- item adaptation of the Center for Epidemiological Studies Depression Scale (CESD, Devins & Orme, 1985). Items include "I had trouble keeping my mind on what I was doing", "I felt depressed", "I felt that everything was an effort", "I felt hopeful", "I thought my life had been a failure", "I felt fearful", "I was happy", "I talked less than usual", "I felt lonely", "people were unfriendly", "I felt sad", "I could not 'get going'." The scales had alpha coefficients of 0.73, 0.78, and 0.81 for boys and 0.78, 0.83, and 0.86 for girls in years 1, 2, and 3, respectively. These measures were chosen because they capture a range of depressive symptoms likely to be expressed by low risk normally developing children. Scales were subject to log transformation to correct for a mild skew. No obvious outliers were detected. Given that the CDI and CESD scales administered were modified, it is not possible to determine how many children in the sample had clinical or subclinical level internalizing behavior problems based on published clinical cutoff criteria (Devins & Orme, 1985; Kovacs, 1983). It is likely, given the prevalence of depression in this age group, that a small proportion of children in this sample have clinical level depression.

Following Angold and colleagues (1999), approximately 20 subjects would be expected to have a current diagnosis or history of depression.

Externalizing behavior: Eccles and Barber's (1990) Risky Behavior Scale

To measure externalizing behavior problems (see also Booth et al., 2003) items from the Risky Behavior Scale developed by Eccles and Barber (1990) were selected because they represent the range and type of externalizing behavior expected in a low risk normally developing sample. Established clinical cutoffs are not available for this scale, but based on prevalence rates from general population studies reported by Angold and colleagues (1999), approximately 47 children in this age group would be expected to have conduct or oppositional defiant disorder. Youth were asked to report on the frequency of 18 activities during the past year using a 4-point scale: never, once, sometimes, more than 10 times. A principal components factor analysis of the items revealed a factor with 11 items, all of which had loadings exceeding 0.5. The 11-item scale had alpha coefficients of 0.82, 0.83, and 0.82 for boys and 0.77, 0.84, 0.84 for girls in years 1, 2, and 3, respectively. Items include "skip a day of school", "do something dangerous just for the thrill", "contact with the police for something you did or they thought you did", "damage public or private property", "stay out all night without parents' permission", "get suspended from school", "take something from a store without paying for it", "get sent to principal's office for misbehavior", "disobey parents on an important issue", "lie to parents about something important", and "get into a fist fight". This scale was not administered to younger siblings of fourth and fifth graders (age 6 – 10 in year 1) because many items were not age appropriate (N=388 in year 1, 586 in

years 2 and 3). The scales were subject to log transformation to correct for a mild skew (M skew = 1.38; after transformation M skew = 0.71). No obvious outliers were evident.

Choices for measures of development: Age and pubertal status

Most studies have focused on children ranging in age from 6 to 12 years (Cicchetti & Rogosch, 2001b; Smider et al., 2002; Tennes & Kreye, 1985; Tennes et al., 1986). Walker and colleagues (2001) argue that middle childhood and adolescence may yield important clues about hormone-behavior relationships because behavior problems and gender differences in the expression of behavior problems often emerge during this time frame (see also Zahn-Waxler et al., 2000). This developmental period is also characterized by maturational change in the activity of the HPA axis (i.e., adrenarche, McClintock & Herdt, 1996; Parker, 1991) and integrative processes between the HPA and hypothalamic-pituitary-gonadal (HPG) axes (Susman et al., 1988). We specifically focus on cortisol-behavior associations in 6 to 16 year olds because adrenal activation begun after adrenarche (ages 6 to 13 years) and the HPA axis's changing relationship to HPG axis activity before and during puberty may potentiate the development of behavior problems (Viau, 2002). The relationship between the maturation of the HPA axis and the emergence of behavior problems is likely to occur within the normal range of behavior problems, illustrating the utility of examining behavior problems in low risk normally developing adolescents (Susman et al., 1988).

During middle childhood and adolescence, development is usually measured with chronological age or pubertal status. Researchers typically do not include both because they are highly inter-correlated. Indeed, in our sample, they were correlated 0.80 for girls

and 0.83 for boys. We considered the merits of age and pubertal phase and chose age for two reasons. The majority of studies focused on hormones have denoted development with chronological age, and the Petersen, Crockett, Richards and Boxer (1988) pubertal status index had less variability at the two ends of the scale in our sample. This measure of puberty focuses on the appearance of secondary sexual characteristics that emerge in middle puberty, but our sample includes youth from early through late puberty. For boys, items include "Would you say that your growth in height has not yet begun to spurt?"; "How about the growth of body hair (underarm and pubic hair)? Would you say that your body hair has not yet started growing?"; "Have you noticed any skin changes, especially pimples?"; "Have you noticed a deepening of your voice?"; "Have you begun to grow hair on your face?" For girls, items include "Would you say that your growth I height has not yet begun to spurt?"; "How about the growth of body hair (underarm and pubic hair)? Would you say that your body hair has not yet started growing?"; "Have you noticed any skin changes, especially pimples?"; "Have your breasts begun to grow?"; "Have you begun to menstruate?" Developmental differences across middle childhood and late adolescence are not captured well by this measure of puberty because there are floor effects in pubertal development in middle childhood (especially for boys) and ceiling effects in middle adolescence (especially for girls). While it is true that chronological age is only a marker of development (Wohlwill, 1973), for the current study's purposes, it is the most useful marker available.

Analytical strategy: Latent state trait modeling of salivary cortisol, factor invariance procedures and a multiple group strategy for age and comorbidity

The analytical strategy was designed to address each of the study's nine hypotheses. A LST strategy was used to examine the association between cortisol and behavior problems[4] (see Figure 2). The analyses first examined whether decomposing salivary cortisol into measurement error, state- and trait-related variance was viable. The basic LST model tested the hypotheses that (1) state cortisol will comprise the largest proportion of the total variance in salivary cortisol, and (2) some component of the total variance in salivary cortisol will be due to trait cortisol. The basic LST model was also used to assess (7) the hypothesis that state and trait derived variance in cortisol will be larger in males compared to females. Bidirectional relationships of trait or state cortisol with behavior problems were then modeled controlling for the effects of age. Including internalizing then externalizing behavior problems, respectively, into the model allowed

[4] Because it is a possibility that maturational processes are a component of trait cortisol, we also examined a LST change model in which the change in cortisol from year 2 to year 3 was derived as a second order latent factor following Steyer and colleagues (Steyer, Eid, & Schwenkmezger, 1997; Steyer, Partchev, & Shanahan, 2000). The fit of the change model was good, $\chi 2(116) = 187.09$, NFI = 0.983, NNFI = 0.994, CFI = 0.994, RMSEA = 0.028. The change in cortisol from year 2 to year 3 was significant in both boys, 0.015, $\underline{t} = 3.73$, $\underline{p} < 0.001$, and girls, 0.022, $\underline{t} = 3.72$, $\underline{p} < 0.001$. Cortisol levels rose from year 2 to year 3 in boys and girls (see Table 3). For both boys and girls, the rise in cortisol across one year was not associated with externalizing behavior problems in any year, $\underline{p}s > 0.43$, and did not change the cortisol -externalizing behavior problems association for boys, $\underline{p}s < 0.005$. Internalizing behavior problems was associated with the rise in cortisol levels across the year in two of the twelve models, all other $\underline{p}s > 0.119$. Boys who completed the CDI (age 6 to 13 in year 1) with more internalizing problems in year 1 had lower cortisol levels, $\beta = -0.210$, $\underline{p} < 0.05$, and a faster rise in cortisol levels across the year, $\beta = 0.279$, $\underline{p} < 0.05$, compared to boys with fewer problems. Girls who completed the CDI with more internalizing problems in year 3 had a faster rise in cortisol levels across the year, $\beta = 0.375$, $\underline{p} < 0.005$.

assessment of the hypotheses that (3) trait cortisol levels will be positively associated with internalizing behavior and (4) inversely associated with externalizing behavior problems. Concurrent and time-lagged associations between cortisol and behavior problems were modeled separately for three years of behavioral data. (6) The hypothesis that there will be time-lagged cortisol-behavior relationships was examined by relating behavior problems measured in year 1 with trait cortisol measured in years 2 and 3 of assessment. Sampling time of day was controlled in all analyses. (5) The hypothesis that children with comorbid internalizing and externalizing behavior problems will have high trait cortisol levels was examined by testing for an interaction between internalizing and externalizing behavior problems. Other potential control measures -- including hassles, uplifts, recent exercise or eating, smoking, steroid, allergy and pain medication and oral contraceptive use, menstrual cycle status and day count -- did not significantly influence the cortisol-behavior relationship, so they were not included in the final analysis [5]. Boys' and girls' models were analyzed separately using a multiple group strategy (Li et al., 2001; Ridgon et al., 1998) to assess the hypotheses that (8) girls will have stronger inverse cortisol-internalizing relationships and (9) boys will have stronger positive trait cortisol-externalizing relationships.

Our sample size varied across analyses because the Eccles and Barber (1990) scale was not administered to very young children, internalizing behavior was assessed using two scales (CDI and CESD, see table 1), and not all subjects provided saliva

[5] Two children from each family participated in this study which potentially can produce unnaturally large estimates because each participant is not independent of the others. To test for this "clustering effect" (Johnson & Elliot, 1998), we removed one sibling and reran the analyses. This did not change the model parameters or behavioral associations, so in all analyses we treated each child in the sample as the unit of analysis.

samples across all four time points. A total of 389 girls and 401 boys provided behavioral or biological data. Of these, 298 girls and 326 boys provided complete saliva samples which were later assayed for cortisol. For the internalizing models, a total of 157 girls and 160 boys had complete CDI and cortisol data and 141 girls and 165 boys had complete CESD and cortisol data. For the externalizing models, a total of 141 girls and 165 boys had complete behavioral and biological data in year 1 and 222 girls and 299 boys had complete behavioral and biological data in years 2 and 3.

Missing data was handled using maximum likelihood estimation for means and intercepts. AMOS returns biased indices of practical fit based on the saturated and independence models when there is extensive missing data, so Graham's RHO program (Graham, 1999) was used to calculate accurate indices of practical fit. Maximum likelihood estimation with AMOS provides reasonable standard errors in a single analysis, the estimates of error variance are accurate and variance around the beta weights is unbiased. Maximum likelihood estimation was chosen over analyzing complete cases because analyzing complete cases is rational only when less than 5% of the data is missing. When missing data is more extensive, analyses involving complete cases may be biased (depending on the cause of missingness) and substantially reduces statistical power. Mean imputation, a common technique used with SPSS, is not appropriate because it underestimates error, produces biased variance estimates and inflates beta weights. Though there is fairly extensive missing data in both behavioral and biological measures, the missing data techniques used in the current study produces unbiased model parameters and allows all of the available data to be fully used.

Externalizing and internalizing behavior problems were initially examined in separate models, then interactions between internalizing and externalizing behavior and gender were assessed using a multiple group approach following Rigdon, Schumacker and Wothke (1998) to test for moderator effects. Following Baron and Kenny (1986), a moderator was defined as a third variable which partitions an independent variable into subgroups to determine its domain of maximal effectiveness; as such, internalizing behavior problems were divided into a bivariate categorical measure to determine whether low or high internalizing boys and girls had stronger relationships between cortisol and externalizing behavior problems. Thus, internalizing behavior problems operate as a variable that can potentially affect the direction or strength of the relationship between adrenocortical activity and externalizing behavior problems. Baron and Kenny (1986) suggest using a correlational test, in which the difference between the correlations in each group are compared, to examine interaction effects. They demonstrate that this approach may have flaws if there are differences in variance between the groups of interest. Within an SEM framework, however, unstandardized regression weights are tested for differences between the groups, providing a test for the variance and the slope of the two measures, thereby satisfying Baron and Kenny's (1986) criteria for a test of a moderator effect. Constraining the slope of the association between trait cortisol and externalizing behavior problems in low and high externalizing boys and girls, thus, provides a good test for a moderator/ interaction effect. This strategy was chosen over an indicant product approach (Li et al., 2001; Ridgon et al., 1998), which allows assessment of the interaction between two variables as a continuous measure for several reasons. First, gender is a dichotomous variable, so the multisample approach is appropriate when

one of the interacting variables is categorical (Ridgon et al., 1998). Second, the indicant product approach may require a large number of manifest measures which may lead to model convergence problems. Third, the multiple group approach does not require a larger sample size than the indicant product approach when equality constraints are imposed using factor invariance procedures (Hofer, 1999). Fourth, the multisample approach is flexible, but the indicant product approach is limited to multiplicative interactions. Thus, interactions between internalizing and externalizing behavior and gender and between age and gender were investigated using a multiple group approach (Li et al., 2001; Ridgon et al., 1998). In summary, the analytical strategy has three main parts: (1) the basic LST model was assessed separately for boys and girls to assess the variance in state and trait cortisol, (2) internalizing and externalizing behavior problems were included in the model to assess whether cortisol is associated with behavior problems, and (3) interactions between internalizing and externalizing behavior problems were analyzed by age and gender using the multiple group approach.

Factor invariance procedures: Cortisol is similar across time and in boys and girls

FI procedures provide a statistical test for invariance of measures and allow us to conclude that the constructs are comparable across time or groups (Hofer, 1999; Meredith, 1993; Meredith & Horn, 2001). FI procedures were utilized to determine whether cortisol could be considered the same across days and across one year. Weak FI (constraining the regression weights to be equal across time), strong FI (constraining the mean intercepts), and strict FI (constraining the variance estimates) caused extreme

model misspecification (see Table 2) similar to other LST models (Dumenci & Windle, 1998). Constraining the variance to be equal within each year did not cause model misspecification, so these constraints are included in the final model. We can conclude that the variance in cortisol is similar across days and years.

FI procedures were utilized to determine whether error, state and trait cortisol could be considered the same measure in boys and girls (see Table 2). Factor loadings and mean intercepts for the cortisol measures were statistically different in boys and girls, but the implication of this difference may be of little practical significance because cortisol levels and loadings are quite similar (see Table 3). Strong FI constraints are maintained in all subsequent analyses so that boys' and girls' coefficients could be compared. We repeated all analyses without strong FI constraints and confirmed that the pattern of associations was the same in the unconstrained and strong FI models.

Figure 2. Basic latent state trait model deriving state and trait estimate of salivary cortisol. Cortisol was measured in saliva samples collected on two days (samples A and B) in year two and on two days in year three (samples C and D). The duplicate assay results (Duplicate 1 and 2) of each saliva sample are the manifest variables used to derive estimates of measurement error and four latent state constructs. Time of day is controlled at the 'state' cortisol level to account for individual differences in the time that each sample was collected. Trait cortisol is derived from the four state constructs as a single second-order latent construct. Separate models are computed for boys and girls. Error terms (unlabelled arrows) are modeled at each level of the analysis to examine the percentage of unique variance at the error, state and trait level.

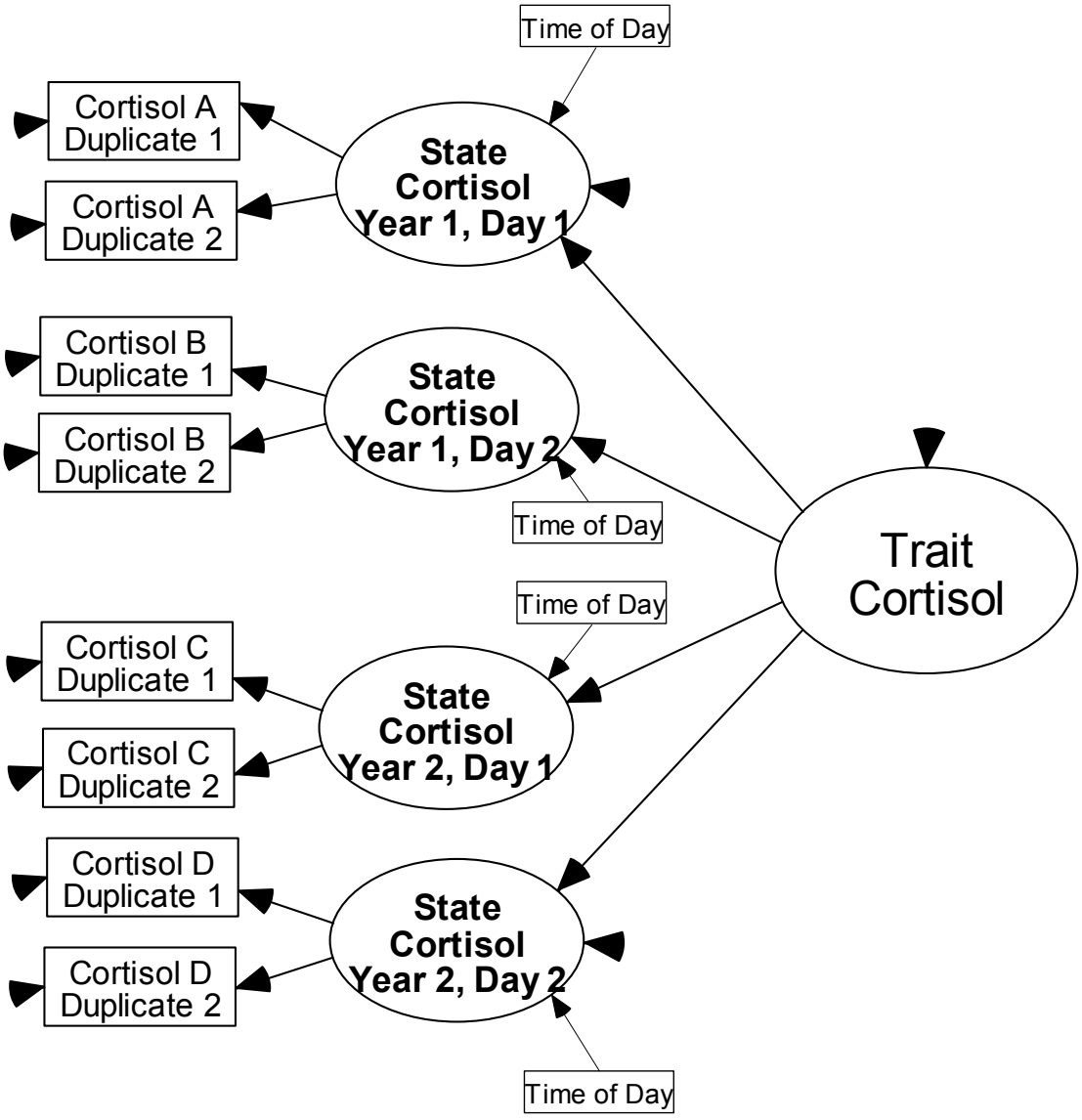


Table 1. Number of cases with complete data by externalizing and internalizing behavior problems by age in year 1. Given that there is fairly extensive missing data in the behavioral and biological measures, missing data was imputed using maximum likelihood estimation for means and intercepts to return unbiased parameter estimates.

		Age 6-9		Age 10-13		Age 14 – 16		Total
	Year	Boys	Girls	Boys	Girls	Boys	Girls	
Externalizing Behavior Problems	1	0	0	74	83	91	58	307
	2 & 3	3	5	150	160	91	58	467
Internalizing Behavior Problems								
CDI	1-3	84	76	77	81	0	0	318
CESD	1-3	0	0	74	83	91	58	306

NOTE: CDI: Children's Depression Inventory, CESD: Center for Epidemiological Studies Depression Scale, Externalizing behavior: The Risky Behavior Scale (Eccles & Barber, 1990).

Table 2. The factor loadings and mean intercepts for cortisol are not equal across time, suggesting that the variance in cortisol is similar across time. Factor loadings and mean intercepts for cortisol are statistically different by gender. Strong factor invariance constraints across gender were imposed on the final model. Constraining the association of cortisol with externalizing behavior and age to be equal in boys and girls consistently reduced the fit of the model revealing gender differences in cortisol-behavior associations.

	DF	χ^2	DF Difference	χ^2 difference
Cortisol Across Days and Years				
No Constraints	84	116.526***		
Weak FI	92	176.087***	8	59.561***
Strong FI	106	571.813***	22	455.287***
Strict FI	126	269.813***	42	152.978***
Variance across years	104	160.005***	20	43.479***
Variance within years	100	139.015***	16	22.489
Cortisol Across Boys and Girls				
No Constraints	102	149.184***		
Weak FI	108	163.338***	6	14.154*
Strong FI	116	185.783***	14	36.599***
Strict FI	120	229.421***	18	80.237***
Measurement error variance	117	192.623***	1	6.840**
State variance	118	216.845***	2	31.062***

Trait variance	117	186.051***	1	0.268
Gender Differences in Behavior Associations				
Year 1: No Constraints	160	244.538***		
Cortisol-Externalizing	161	264.317***	1	19.779***
Cortisol-Age	161	252.066***	1	7.528**
Age-Externalizing	161	248.225***	1	3.687
Year 2: No Constraints	160	242.359***		
Cortisol-Externalizing	161	250.968***	1	8.609***
Cortisol-Age	161	249.607***	1	7.248**
Age-Externalizing	161	242.399***	1	0.04
Year 3: No Constraints	160	240.096***		
Cortisol-Externalizing	161	244.380***	1	4.284*
Cortisol-Age	161	247.573***	1	7.477**
Age-Externalizing	161	240.904***	1	0.808

NOTE: *p< 0.05, **p< 0.01, ***p< 0.001, DF = degrees of freedom. Weak: Constraining regression weights. Strong: Constraining mean intercepts. Strict: Constraining unique variance estimates.

Table 3. Descriptive statistics for salivary cortisol duplicates (D1 and D2) across days and years shows that the mean cortisol levels tends to increase across one year of development though this developmental change does not appear to have implications for internalizing and externalizing behavior problems. Factor loadings for state cortisol fluctuated closely around 1 suggesting that each duplicate received nearly equal weight in the state construct. Factor loadings for trait cortisol were constrained to be 1 in year 2, but appeared somewhat reduced in year 3. Trait cortisol represents year 2 cortisol slightly more than year 3 cortisol levels.

		Boys' Cortisol				Girls' Cortisol			
		Factor Loadings		Descriptive Statistics		Factor Loadings		Descriptive Statistics	
Cortisol Construct:		Trait	State	Mean	STDEV	Trait	State	Mean	STDEV
Year 2									
Day 1	D1	1.000	1.002	0.478	0.250	1.000	0.976	0.550	0.276
	D2		1.000	0.481	0.250		1.000	0.557	0.283
Day 2	D1	1.000	0.977	0.456	0.227	1.000	0.987	0.528	0.270
	D2		1.000	0.461	0.232		1.000	0.534	0.274
Year 3									
Day 1	D1	0.737	0.977	0.514	0.251	0.651	1.005	0.560	0.291
	D2		1.000	0.524	0.257		1.000	0.562	0.289
Day 2	D1	0.793	0.987	0.495	0.257	0.840	0.973	0.577	0.285
	D2		1.000	0.502	0.261		1.000	0.586	0.293

Table 4. Chi-square goodness of fit and indices of practical fit for the basic, externalizing, and internalizing behavior models and standardized β weights between trait cortisol and behavior problems for boys and girls: The chi-square goodness of fit was significant in each model. Indices of practical fit, however, suggest that the fit of each model was good.

	DF	Chi-square goodness of fit	NFI	NNFI	CFI	RMSEA	R for boys	R for girls
A. Basic Model	116	185.783**	0.984	0.993	0.994	0.027		
B. Externalizing Problems								
Year 1	160	244.538**	0.979	0.992	0.993	0.026	-0.459**	0.122
Year 2	160	242.359**	0.979	0.992	0.993	0.025	-0.279**	0.052
Year 3	160	240.096**	0.980	0.992	0.993	0.025	-0.229**	0.007
C. CDI								
Year 1	160	241.747**	0.979	0.992	0.993	0.025	-0.144	0.029
Year 2	160	240.062**	0.979	0.992	0.993	0.025	-0.119	0.051
Year 3	160	240.219**	0.979	0.992	0.993	0.025	-0.090	-0.050
D. CESD								
Year 1	160	248.539**	0.979	0.991	0.992	0.026	-0.138	-0.065
Year 2	160	245.804**	0.979	0.992	0.993	0.025	-0.007	-0.068
Year 3	160	246.886**	0.979	0.991	0.992	0.026	-0.074	-0.051

NOTE: ** $p < 0.001$. DF = degrees of freedom, NFI = Normed Fit Index, NNFI = Non-normed Fit Index, CFI = Comparative Fit Index, RMSEA = Root Mean Square Error of Approximation. R = standardized β weights. Externalizing Problems = Risky Behavior Scale, CDI = Children's Depression Inventory. CESD = Center for Epidemiological Studies Depression Scale.

Table 5. Variance components of the basic model. Error variance comprises a very small percentage of the total variance in salivary cortisol, ranging from 1.22% to 2.00% of the total variance. Most of the variance is derived from state cortisol, ranging from 62.00% to 74.39%. Trait cortisol represents 24.39% to 36.00% of the total variance.

		Boys		Girls	
Model Component	Year	Variance	%	Variance	%
Trait	2	0.018	36.00%	0.020	28.99%
State	2	0.031	62.00%	0.048	69.57%
Error	2	0.001	2.00%	0.001	1.45%
Year 2 Total		0.050	100.00%	0.069	100.00%
Trait	3	0.018	28.13%	0.020	24.39%
State	3	0.045	70.31%	0.061	74.39%
Error	3	0.001	1.56%	0.001	1.22%
Year 3 Total		0.064	100.00%	0.082	100.00%

NOTE: Gender differences in state but not trait cortisol are possible because girls have more total variance in salivary cortisol than boys.

CHAPTER 8

RESULTS

THE FIT OF THE BASIC MODEL AND EXAMINATION OF GENDER DIFFERENCES IN STATE, TRAIT AND ERROR VARIANCE

The chi-square goodness of fit was significant in all models. However, the chi-square is known to be sensitive to sample sizes as large as that used in this study; even trivial deviations from a perfect model indicate statistically significant model misspecification (Bollen, 1989; Hu & Bentler, 1995). For this reason, indices of practical fit were used to make our main judgments about model fit including the normed fit index (NFI, Bentler & Bonett, 1980), Tucker-Lewis Index or non-normed fit index (TLI or NNFI, Tucker & Lewis, 1973), the comparative fit index (CFI, Bentler, 1990) and the root mean square error of approximation (RMSEA, Cudeck & Browne, 1992).

The indices of practical fit suggest that the basic LST model demonstrated good fit (see Table 4a). Variance estimates for measurement error were significantly larger for boys than girls; however, the practical significance of this difference seems negligible. State cortisol comprised the largest percentage of the total variance and was significantly larger for girls than boys (see Table 2). The gender difference in state cortisol is 5.83% on average. The direction of the association is counter to our prediction, and was largely due to the fact that girls had more total variance in salivary cortisol compared to boys (see Table 5). Importantly, the variance in trait cortisol estimates was significant in both boys, $t = 6.82$, $p < 0.001$, and girls, $t = 5.80$, $p < 0.001$. No gender difference in trait

cortisol was observed. Thus, the hypothesis that state cortisol would be the largest component of the total variance as well as the hypothesis that trait cortisol would comprise a significant proportion of the total variance in salivary cortisol was confirmed. However, the hypothesis that males would have more state and trait variance than females was not supported Indeed, if anything, females have more state variance than males.

Associations between trait cortisol and internalizing behavior problems are not significant

The fit of the internalizing behavior problem models for children (using the CDI) and adolescents (using the CESD) was good (see Table 4c and d). Regardless of the internalizing measure, trait cortisol was not concurrently associated with internalizing behavior problems in boys or girls. Time-lagged cortisol → internalizing and internalizing → cortisol directional associations revealed that internalizing behavior problems in year 1 negatively predicted trait cortisol for boys' ratings on the CDI, $\underline{\beta} = -0.15$, $\underline{p} < 0.05$, and displayed a trend for boys' ratings on the CESD, $\underline{\beta} = -0.12$, $\underline{p} = 0.09$. The hypotheses that trait cortisol would be positively related to internalizing behavior problems, and that this would be stronger for girls than boys were not supported. Time-lagged relationships between trait cortisol and internalizing behaivor are in the opposite direction as hypothesized.

State cortisol was not concurrently associated with internalizing behavior problems as measured by the CDI, $\underline{p}s > 0.31$, or CESD methods, $\underline{p}s > 0.26$. Concurrent trait cortisol-internalizing behavior associations were not different in younger (ages 6 to 9

in year 1) and older (ages 10 to 13 in year 1) youth who completed the CDI and younger (ages 10 to 13 in year 1) and older (ages 14 to 16 in year 1) youth who completed the CESD based on a median split of the behavioral data, χ^2diff < 1.00 for boys and χ^2diff < 2.70 for girls.

Low trait cortisol in boys is associated with high levels of externalizing behavior problems

When externalizing behavior was covaried with trait cortisol (separately for each year of behavioral assessment), the model fit was good (see Table 4b). Gender differences in cortisol-externalizing behavior associations were significant (see Table 2). Consistently across all three years of assessment, boys with more externalizing problems had lower cortisol (see Figure 3) but parallel relationships were not significant in girls. Cortisol-externalizing associations in boys were evident across all three years of behavioral assessment and, indeed, for every item of the externalizing scale. One year time-lagged cortisol → externalizing and externalizing → cortisol directional associations were of similar magnitude for boys across all models, $\underline{\beta}$s > -0.18, $\underline{p}$s < 0.006. For girls, year 1 externalizing behavior problems negatively predicted trait cortisol, $\underline{\beta}$ = -0.16, $\underline{p}$ < 0.01, but other models (girls' concurrent and time lagged, N = 8 models) were not significant. These observations support the prediction that externalizing behavior problems would be associated with low trait cortisol and that cortisol-exernalizing behavior relationships would be stronger in boys than girls [6].

[6] In order to assess whether trait cortisol yielded different relationships with behavior than measures of cortisol that are more commonly assessed, associations between minimum or average cortisol levels (based on the four AM cortisol measures) and

For both boys and girls, state cortisol was not associated with externalizing behavior problems at any time, ps > 0.17. To test for possible differences between younger and older children, concurrent trait cortisol-externalizing behavior associations were not different in younger (ages 10 to 13 in year 1) or older (ages 14 to 16 in year 1) boys and girls based on a median split of subjects with complete behavioral data. The association between externalizing behavior problems and trait cortisol is significant in both younger and older boys, χ^2age difference (1) < 1.70, and is not significant in either younger or older girls, χ^2age difference(1) < 1.40.

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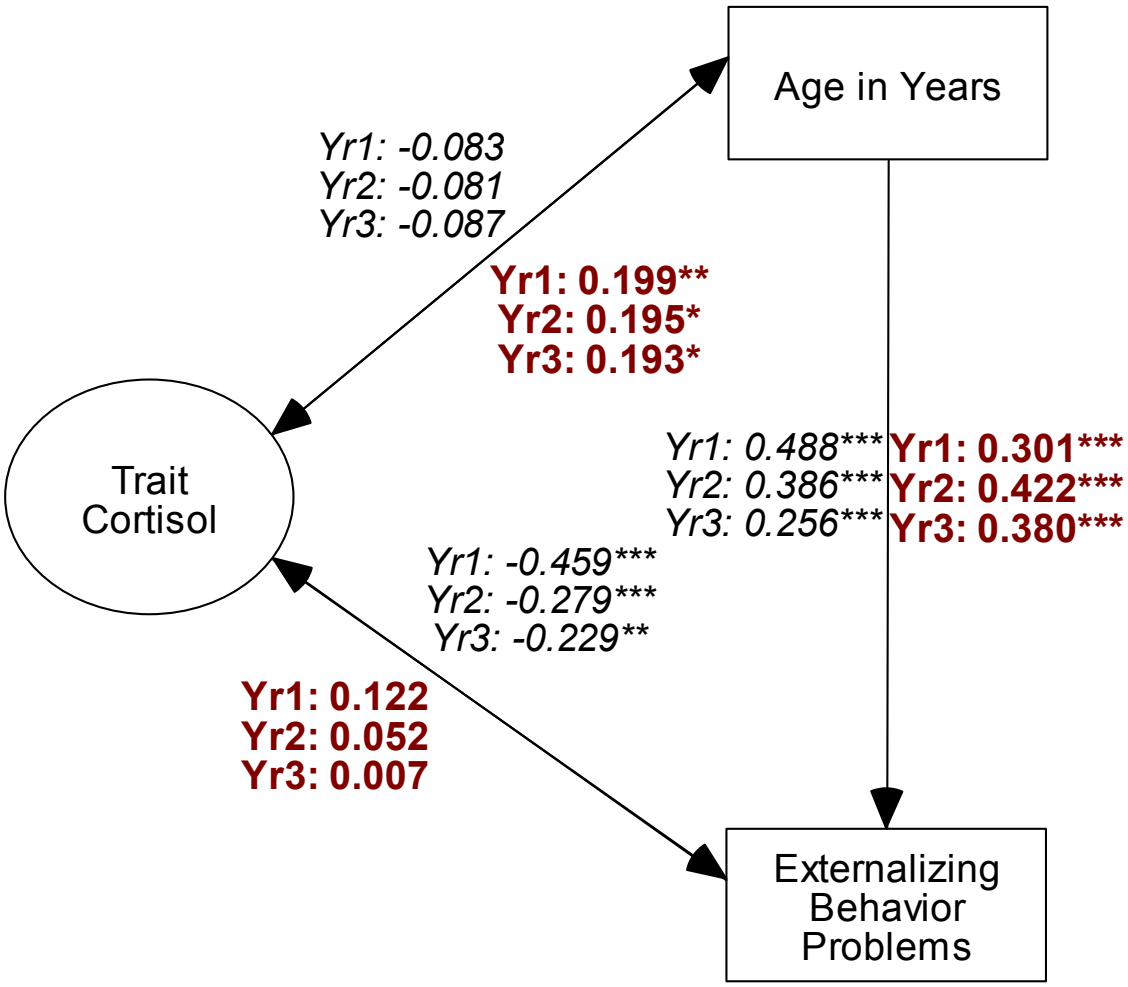
average (across three years of behavioral assessment) internalizing and externalizing behavior problems were explored using bivariate correlations. There was no association between minimum cortisol levels and internalizing behavior problems in either boys or girls (M r = 0.01 and 0.08, respectively). The association between minimum cortisol levels and externalizing behavior problems in boys is significant, but not large (r = -0.18), and there is no association in girls (M r = -0.08). Associations between average cortisol levels and internalizing behavior problems was negligible for girls (M r = 0.07) and boys (M r = 0.05). Associations between average cortisol levels and externalizing behavior problems was significant for three of the four AM cortisol measures for boys (M r = 0.16), but was not significant for girls (M r = 0.02). This suggests that the association between cortisol and externalizing behavior problems in boys is fairly attenuated when aggregated cortisol or minimum cortisol is used. By not isolating trait cortisol, the cortisol-externalizing behavior problem association is somewhat obscured by situation-specific variance.

Figure 3. Trait cortisol is strongly associated with age and externalizing behavior problems for boys but not girls (in bold). Coefficients represent associations across the three years of behavioral assessments with years one to three from top to bottom, respectively. Similar coefficients are obtained when directional arrows between cortisol and externalizing behavior problems are modeled. *p < 0.05, **p < 0.01, ***p < 0.001.



There is no interaction between internalizing and externalizing behavior problems on trait cortisol

This analysis was limited to adolescents who completed the CESD (ages 10 to 16.5 in year 1, N = 388, see table 5) because the externalizing behavior problem scale was not administered to the youngest siblings. Interaction effects between internalizing and externalizing behavior problems on concurrent trait cortisol were tested using a multiple group approach (Li et al., 2001; Ridgon et al., 1998). Across all three years, constraining the association between trait cortisol and externalizing problems to be equal in children with low versus high levels of internalizing problems did not change the fit of the model. There was no evidence for a moderation of cortisol and externalizing behavior problems by internalizing behavior problems. Following Baron and Kenny (1986), it appears that both low and high internalizing behavior problem boys have strong inverse associations between trait cortisol and externalizing behavior problems, suggesting that there is no domain of maximal effectiveness with regard to internalizing behavior problems and the hypothesis that children with high internalizing and externalizing behavior problems would have high trait cortisol levels was not supported.

CHAPTER 9

DISCUSSION

SUMMARY OF THE MAIN FINDINGS

The findings confirm the first hypothesis that situation-specific variance comprises the largest proportion of the total variance in salivary cortisol. Appoximately 70% of variance in AM cortisol levels can be attributed to day-to-day fluctuations in adrenocortical activity. A large portion (28%) of variance in salivary cortisol remains consistent across time (day-to-day and across one year), providing support for the second hypothesis that some component of the total variance in saliary cortisol is due to trait cortisol. The third hypothesis that high trait cortisol levels would be associated with more internalizing behavior problems was not confirmed. If anything, low trait cortisol levels are related to internalizing behavior problems, but for year one only. This null result is of more than passing interest and is discussed further below. The fourth hypothesis that low trait cortisol levels would be associated with more externalizing behavior problems was confirmed. Across all three years of behavioral assessment, low trait cortisol levels were associated with higher concurrent externalizing behavior problems in boys. Implications of this finding for the biosocial model are discussed below. The fifth hypothesis that high trait cortisol levels would be associated with high internalizing and externalizing behavior problems was not confirmed. There was no interaction between internalizing and externalizing behavior problems suggesting that for both low and high internalizing boys, low trait cortisol levels are associated with

externalizing behavior problems. The sixth hypothesis that time-lagged relationships between trait cortisol and behavior problems would be evident received modest support. Externalizing and internalizing behavior problems measured in year one predicted low trait cortisol levels in boys based on saliva samples measured one to two years later. Parallel associations were not significant for girls. The seventh hypothesis that males would have more state and trait variance than females was not confirmed. Indeed, females had slightly more state variance than males and there was no gender difference in trait variance in salivary cortisol. Given that internalizing behavior was not associated with trait cortisol in either boys or girls, the findings do not support the eighth hypothesis that trait cortisol would be related to internalizing behaviors more for girls than boys. Indeed, time-lagged associations between trait cortisol and behavior problems in year 1 were significant in boys but not girls. The ninth hypothesis that trait cortisol would be related to externalizing behavior problems for boys more than girls was supported. Associations between cortisol and externalizing behavior problems were significant across three years of behavioral assessment for boys, but not girls.

Utility of the LST model for salivary cortisol for researchers interested in trait cortisol

The findings from the first two hypotheses have important implications for researchers interested in the HPA axis: A large component of the variance in morning cortisol levels is due to situation-specific factors, but there are consistent individual differences in salivary cortisol. These findings may help resolve the apparent inconsistencies in cortisol-behavior relationships. For researchers interested in

examining consistent cortisol-behavior relationships, the use of LST modeling may advance our understanding of hormone-behavior relationships. The use of this statistical tool should not replace rigorous data collection (e.g., multiple saliva measures, non-interfering sampling strategies, controlling for time of day). LST modeling requires large samples (N~100) to return stable model estimates (Bollen, 1989), but only two saliva samples for each subject were required to derive an estimate of trait cortisol (Steyer et al., 1999). As Van Goozen (1998) and Gunnar (1997) discuss, and Moss and colleagues (1995) demonstrate, including multiple measures of cortisol may yield more consistent hormone-behavior associations than a single measure. Given that approximately 70% of the variance in cortisol is due to context-specific factors, a substantial number of cortisol measures may be needed before a stable trait emerges using averaging techniques. For example, Gunnar and colleagues (1997) report using, on average, more than a dozen saliva samples per subject to estimate median cortisol levels (range 5 – 23 samples). Extensive repeated sample collection may not be feasible for studies that require large numbers of subjects to examine interaction or mediating effects or when the expected effect size is small. We suggest that collecting fewer samples per subject may be practical when sample sizes permit the use of LST modeling.

It is important to frame the LST model of trait cortisol within a broader context of studies which examine consistency in cortisol-behavior relationships. Heritability estimates in twin and family studies are conceptually related to LST modeling of trait cortisol. A recent review (Bartels et al., 2002) estimates the heritability of salivary cortisol at 60%. Shared environmental influences were negligible and unshared environmental influences comprised the remaining 40% of the variability in cortisol.

Heritability estimates across studies varied greatly, from zero to 84%, though Bartels and colleagues (2002) illustrate that the sample size of the studies used to derive these estimates were far from adequate for calculating reliable heritability estimates. Nevertheless, a genetic contribution of 60% of the total variability of cortisol appears to contradict our estimate that 30% of the variability is consistent within individuals. Bartels and colleagues (2002) argue that individual differences in cortisol arise from genetic and environmental influences, but the gene-environment interaction may also be a component of the genetic estimate (McClearn, 1993). It is possible that the gene-environment interaction accounts for approximately half of the variance in the heritability estimate of cortisol if within individual consistency is truly 30% of the total variability. It appears that studies of the gene-environment interaction may be fruitful in studies of salivary cortisol. Also, it is clear that heritability estimates of trait cortisol and trait cortisol derived from LST models are not the same construct.

Trait cortisol potentially may be interpreted as basal cortisol levels. Basal cortisol is usually derived using the average of two or more measures of cortisol taken before a challenge (e.g., Goenjian et al., 1996) although some interpret basal cortisol to be measures taken in the early morning (e.g., Klimes-Dougan et al., 2001; Lupien et al., 2001). However, the term 'basal' may not be appropriate for trait cortisol because it implies that some change from baseline is expected. LST models derived from measures taken during reactivity challenges (e.g., Preville et al., 1996) may not be appropriate because systematic growth functions (i.e., reactivity and recovery from challenge) may influence cortisol levels. Other methods may be more appropriate (e.g., growth curve models, McArdle & Bell, 2000; latent change models, Steyer, Eid, & Schwenkmezger,

1997). Trait cortisol also does not reflect the average (i.e., aggregate) of AM cortisol measures or the minimum cortisol level. Trait cortisol is conceptually similar to average or minimum cortisol levels, but separating out the situation-specific variance adds another dimension to trait cortisol. This adds to the complexity of the interpretation of trait cortisol (Gottlieb, 2002), but also allows cortisol-behavior relationships to be detected more easily.

Another difference between trait cortisol and average or basal cortisol levels is that a particular score for an individual's trait cortisol levels are not computed. Rather, trait cortisol is a latent construct which remains relatively abstract. Within the structural model (Bollen, 1989), the components of the LST model are formed at the individual level. Relationships between hormones and behavior are expressed at an individual difference level within a single model, but the final output (e.g., % variance, standardized beta weights, etc.) is reported at the group level. Thus, the LST model takes an individual difference perspective without explicitly computing a score for each individual. The LST approach can be used to forward research on individual differences in adrenocortical activity despite this apparent limitation. It appears that trait cortisol is conceptually distinct from heritable traits, basal, minimum or average cortisol levels.

Another factor which complicates the interpretation of trait cortisol is the relativism problem (Steyer et al., 1999). Trait cortisol separates out the situational influences that are specific to the points of measurement at the time samples are collected. Situational factors that are constant across all points of measurement are a component of trait instead of state cortisol. These factors appear as individual differences in salivary cortisol levels instead of person-situation interactions. The addition of another

measure of salivary cortisol into the model may potentially change trait cortisol. This is important for the interpretation of trait cortisol because it suggests that state factors can operate like traits and that a trait factor can change depending on how it is operationalized. There are three major implications for the relativism problem with respect to the conceptualization and meaning of state and trait cortisol.

First, depending on the sample collection strategy, influences on adrenocortical activity that conceptually are state factors may be operationalized as trait factors. Some of these state factors clearly contribute to individual differences in salivary cortisol. For example, social context is a situational factor that, when relatively consistent, may be operationalized as a trait. The social context varies from person to person, so individual differences in the social context will contribute to individual differences in trait cortisol. Parent-child relationships, child maltreatment, and socioeconomic status are all components of the social context which potentially may be expressed as individual differences in trait cortisol.

Second, other intraindividual processes may also affect how trait cortisol is operationalized. These factors should contribute to state cortisol if these factors vary across measurement, but if they are constant, then they will be operationalized as trait cortisol. This does not violate the definition of a trait (Krech & Crutchfield, 1958) because traits can be person-specific factors that evidence a shallow growth function (Smith, 1999). For example, the influence of age on trait cortisol may be an intraindividual difference factor which, because the influence of development on adrenocortical activity is relatively shallow, becomes a component of trait cortisol rather than state cortisol. If cortisol levels change as individuals age, then this developmental

process will be a component of state, not trait, cortisol. This may explain why state cortisol measured within the same year was correlated but was not correlated across years.

The third implication for the relativism problem builds upon the first two implications: consistency in the social context across time may influence the development of the HPA axis such that the proportion of variance attributed to state and trait cortisol changes with development. This idea was initially proposed by Gunnar and colleagues (2000) when they suggested that the HPA axis is malleable and flexible in young children, but becomes entrenched in a psychopathological state as children chronically activate or fail to activate the HPA axis. Thus, psychopathology may result when the HPA axis is consistently hyper- or hypoaroused (Gunnar & Vazquez, 2001; Heim et al., 2000). If this theoretical position proves true, there are important implications for the relativism problem. Not only can individual differences in the social context and intraindividual differences in age influence trait cortisol, but developmental differences in the influence of the social context on adrenocortical activity may change the way in which trait cortisol is operationalized.

These three caveats to the interpretation of trait cortisol have important implications for the interpretation of hormone-behavior relationships in the current study. Trait cortisol should not be interpreted as a constant, unchanging factor. Rather trait cortisol represents a construct that is stable and consistent within the occasions of measurement included in the study. This construct may indeed be different in younger children and older youth; may be different across a variety of social contexts; may vary as a function of psychopathology status; and may change differently with time as a

function of the social context (Boyce et al., 1998). Systematically evaluating the contribution of age, development, social context and psychopathology on the trait cortisol construct is an important future work that will contribute to our understanding of the factors which influence the consistency, stability and development of the HPA axis. These studies will enrich our understanding of adrenocortical activity and thereby will further our understanding of how and when adrenocortical activity has implications for children's behavior problems.

Conclusions about cortisol- internalizing behavior relationships: Consistency with studies in low risk youth

With regard to the third hypothesis, we did not reveal evidence of a concurrent association of trait cortisol with internalizing behavior problems. This null pattern is consistent with several studies that reveal internalizing behavior problems were not consistently associated with cortisol levels in low risk normally developing and clinical samples (Cicchetti & Rogosch, 2001b). Studies by Gunnar (Davis et al., 1999; de Haan et al., 1998; Gunnar et al., 1997) report cortisol-internalizing relationships in pre-school aged children, raising the possibility that the mechanisms that influence this biosocial relationship are fundamentally different before and after adrenarche. This interpretation is complex, however, because adrenocortical activity in adults is consistently related to depression (Sapolsky, 2000a, 2001). It is interesting that in individuals younger and older than our sample consistent internalizing-HPA relationships are revealed. It is possible that depression in adolescents is different from that measured in younger and older subjects. Zahn-Waxler and colleagues (2000) raise the possibility that anxiety

problems in children undergo a developmental shift during the adolescent years when problems begin to manifest themselves as depression more than anxiety. By adulthood, children that were once anxious now experience problems with depression. Angold and colleagues (1999) further this idea by suggesting that the type of internalizing behaviors that children and adolescents exhibit change across development. Thus, the development and expression of depression and anxiety may be critical during adolescence. The nature, and perhaps physiological underpinnings, of these disorders may also change dramatically during this time period (McBurnett et al., 1991; Zahn-Waxler et al., in press). It is possible that adrenocortical activity would be more closely related to anxiety rather than depression in our sample, but later in development (i.e., during adulthood) relationships between the HPA axis and depression may emerge.

Three major areas for future research emerge from this line of thinking. First, a measure of anxiety in addition to a measure of depression seems critical for studies of adrenocortical activity in adolescents. The CBCL and YSR (Achenbach, 1991a, 1991b) operationalized anxiety and depression in a singular construct in the broad band scales and the DISC (Schwab-Stone et al., 1993) includes diagnoses for both anxiety and depressive disorders. Use of measures like these which allow assessment of both anxiety and depression would be useful to test the developmental trajectories of adrenocortical relationships with internalizing disorders.

Second, it will be important to disentangle the literature on physiological correlates of internalizing behavior problems and discover when anxiety and depression are uniquely associated with adrenocortical activity. A potential mechanism that explains why adrenocortical activity should be related to internalizing disorders emphasizes

different affective states associated with anxiety (e.g., fear) and depression (e.g., sadness). This view predicts different relationships between the HPA axis and behavior based on the underlying emotional constructs. Thus, it is important that researchers interested in cortisol and internalizing behavior understand when their study has implications for depression and sadness or anxiety and fear. The literature that describes relations with 'internalizing symptoms' broadly defined may not advance our understanding of the HPA axis. The broadband internalizing scale from CBCL and YSR (Achenbach, 1991a, 1991b), which collapses across anxiety and depression, may not be appropriate for studies of adrenocortical activity in adolescents because the relevance of anxiety and depressive symptoms is distinct and potentially has different physiological underpinnings. If affective states are the underlying mechanism that links adrenocortical activity with internalizing behavior, it makes sense that we found null results when we investigated depressive symptoms. It is interesting to note that the only study to find relationships between internalizing behavior problems and adrenocortical activity in normally developing adolescents operationalized these behavior problems as anxiety (Colomina et al., 1997).

Third, longitudinal studies aimed at understanding the potential biobehavioral shift in cortisol-internalizing relationships from anxiety to depression are critical to understanding when adrenocortical activity is associated with fear and/ or sadness. Given that adolescence may be a critical period for this theoretical developmental change, follow up assessment of the current sample as they enter young adulthood may be critical for revealing eventual cortisol-depression relationships. While the current study did not reveal cortisol-depression links, nevertheless, this relationship is still an important area

for future studies to explore through longitudinal assessment of depression and anxiety problems.

Conclusions about externalizing behavior problems: Implications for the biosocial model

The finding that externalizing behavior problems is associated with trait cortisol in boys supports the fourth hypothesis and Brennan and Raine's (1997) theory that boys with more externalizing behavior problems have lower basal cortisol than boys with fewer problems and do not support the speculation that cortisol-externalizing relationships would only be evident in children at risk for behavior problems (Gunnar et al., 2000). The inverse direction of the cortisol-behavior association observed is consistent with the literature on extreme groups (e.g., McBurnett et al., 2000; Van Goozen et al., 2000; Van Goozen et al., 1998) and younger low risk normally developing children (e.g., Cicchetti & Rogosch, 2001a; Smider et al., 2002; Tennes & Kreye, 1985; Tennes et al., 1986). The findings add to the accumulating body of literature by revealing robust associations between low cortisol and externalizing behavior across concurrent and time-lagged assessments. Importantly, the pattern of relationships has now been observed in low risk normal, at-risk, and psychiatric groups.

The present study suggests that the relationship between cortisol and externalizing behavior problems is a stable phenomenon that spans both normative and atypical child development. This is important for developmental psychopathology because it helps confirm the assumption that these behaviors operate on a continuum and have similar biological antecedents and consequences (Cicchetti & Cannon, 1999). Similar biosocial

processes that contribute to extreme behavior problems may be operating in low risk normally developing youth within a more restricted range of behavior problems. It is possible that mechanisms that link low cortisol with externalizing behavior, such as fearlessness or stimulus seeking tendencies, are expressed in mild forms in low risk normally developing youth. A potential implication for this biosocial finding is that low cortisol may have predictive validity for behavior problems in boys. This has ramifications for escalating behavior problems if individual differences in low cortisol levels indicate the severity of fearlessness or stimulus seeking tendencies and, in turn, externalizing behavior problems.

The inverse association between externalizing behavior problems and trait cortisol may reflect a number of different mechanisms. Gunnar and Vazquez (2001) and Heim and colleagues (2000) have speculated about the meaning and implications of hypo-arousal of the HPA axis. They suggest that individuals with low cortisol may be underaroused, overregulated, or may have an increased threshold for stress (Kruesi et al., 1989). Emotions are a potential mechanism which explains relationships between low physiological arousal and externalizing behavior problems. Individuals with low cortisol may display a lack of fear and anxiety across situations in which a mild stress response should be warranted. Fearlessness might predispose individuals towards externalizing behavior because the execution of such behavior requires a physiological state of low arousal (Raine, 2002). Conversely, individuals who are hypo-aroused may have an increased threshold for stress, and consequently seek stimulation to induce a physiological response. Individuals with low cortisol may find externalizing behavior arousing whereas those with higher trait cortisol levels mount a physiological response to

more benign stimulation (Raine, 2002). Interestingly, in a large study of male military veterans, Gimbel and Booth (1996) reported that individuals with the lowest cortisol levels were likely to experience military combat in Vietnam. Gimbel and Booth (1996) hypothesize that men with the lowest cortisol levels were assigned to combat because of their superior stress management skills, or they sought out combat to attain a sense of control, a psychological high, and/or to receive admiration from others.

On a more biological level, lower cortisol levels in youth with externalizing behavior problems may allow for greater expression of testosterone-linked behaviors such as aggression, risky behavior, delinquency and dominance (e.g., Finkelstein et al., 1997; Mazur & Booth, 1998; Schaal, Tremblay, Soussignan, & Susman, 1996; Tremblay et al., 1998). In animal studies, corticosterone (the rodent parallel to cortisol) affects receptor affinity for testosterone such that reduced corticosterone levels increase the availability of testosterone receptor sites and glucocorticoid and androgen receptors interact particularly during times of stress (Viau, 2002). Testosterone is able to bind to its receptor more easily when corticosterone levels are low. Bilaterally adrenalectomized rats develop spontaneous aggressive behavior within 24 hours of surgery, and low doses of testosterone elicit episodes of sustained attack behavior in adrenalectomized but not non-adrenalectomized rats (Essman, 1981). Non-human primate models also support an association between low cortisol levels and increased levels of defensive and offensive aggressive behaviors and testosterone (Kalin, 1999a, 1999b). If this extends to humans, individuals with low cortisol and high testosterone may be at particularly risk for externalizing behavior problems (Virkkunen, 1985). Recent findings, however, suggest that the influence of testosterone on the expression of risk behavior in normally

developing youth is moderated by the quality of parent-child relationships (Booth et al., 2003) suggesting that biological interactions between cortisol and testosterone may be influenced by the immediate social context. This potential mechanism is important for the biosocial model because it points to the utility of examining multiple biological markers (Granger & Kivlighan, in press) and the potential moderation of a biosocial effect by another biological factor.

IMPLICATIONS FOR THE LACK OF ASSOCIATION BETWEEN ADRENOCORTICAL ACTIVITY AND COMORBID INTERNALIZING AND EXTERNALIZING BEHAVIOR PROBLEMS

There was no support for the hypothesis that an interaction between internalizing and externalizing behavior problems would be evident. Findings by several research groups indicate that adrenocortical activity and comorbidity between internalizing and externalizing behavior problems conveys a protective factor for children with externalizing behavior problems (McBurnett et al., 1991; Van Goozen et al., 1998). Boys with low cortisol levels may be at risk for externalizing behavior problems because a state of low physiological arousal is required to execute such behaviors (i.e., low fear or anxiety). A state of high fear or anxiety may protect against externalizing behaviors. Zahn-Waxler and colleagues (2000) argue that comorbid anxiety problems protects children with externalizing behavior from escalating behavior problems, but puts them at risk for developing extant anxiety problems. These theoretical and empirical findings suggest that comorbid internalizing behavior problems, broadly defined, may not protect children with externalizing behavior problems from low adrenocortical activity. Rather,

comorbid anxiety problems specifically may be a protective factor against HPA-externalizing associations. Expression of depressive symptoms does not require a state of high fear or anxiety. Children who are depressed or sad may still be able to express low fear, anxiety, adrenocortical activity and high externalizing behavior. It is possible that the fifth hypothesis was not supported because our measure of internalizing behavior tapped into depression, but comorbidity with anxiety problems conveys resilience against developing externalizing problems (McBurnett et al., 1991; Van Goozen et al., 1998). Thus, a direct association between adrenocortical activity and depression was not revealed, suggesting that sadness and depression are not directly associated with HPA axis activity in low risk normally developing adolescents. An interactive effect with externalizing behavior problems was also null, providing further support for the exploration of studies aimed at studying anxiety problems and the HPA axis rather than depression. The utility of considering emotions as moderators of cortisol-behavior problems relationships will be substantiated if anxiety problems (i.e., fear) prove to be more directly related to adrenocortical activity than depressive symptoms (i.e., sadness) in adolescents.

TIME-LAGGED RELATIONSHIPS BETWEEN TRAIT CORTISOL AND BEHAVIOR PROBLEMS SUGGEST HORMONE-BEHAVIOR ASSOCIATIONS ARE ROBUST

The nature of the study's design allowed us to explore time-lagged associations between behavior problems and cortisol. The hypothesis that cortisol-behavior relationships would be consistent from one year to the next because these behaviors are relatively stable and the measure of trait cortisol is stable across time when modeled

using LST methodology was confirmed. Externalizing and internalizing behavior problems in year one (when cortisol was not measured) negatively predicted trait cortisol based on samples collected one to two years later. This finding is noteworthy because, at face value, it suggests that behavior is driving individual differences in the activity of the HPA axis. This interpretation appears at odds with the common conception that biological predispositions contribute to the development of behavior problems. Following Granger and colleagues (1996), we suggest that the relationship between cortisol and behavior problems is likely to be reciprocal with HPA axis activity affecting behavior and behavior mutually affecting the HPA axis. This is informative for developmental biosocial models because it points to a possible mechanism for how the HPA axis can become entrenched in a psychopathological state (Gunnar et al., 2000). It is possible that low physiological arousal during challenge contributes to escalating risky behavior, and that being able to engage in risky behavior without extant anxiety further lowers adrenocortical activity. This interpretation is tentative, however, because the study's design does not allow for causal conclusions. It is possible that a third factor, such as intrinsic maturational processes, is causing changes in both cortisol and externalizing behavior. An additional behavioral assessment of this sample would be needed to test whether trait cortisol predicts externalizing behavior some years later and an experimental design would be needed to formulate causal statements.

GENDER DIFFERENCES IN ADRENOCORTICAL ACTIVITY AND CORTISOL-BEHAVIOR RELATIONSHIPS

The seventh hypothesis that males would have more variance in state and trait cortisol when compared to females was not supported. There was no gender difference in trait cortisol and females had more state variance compared to males. This hypothesis was exploratory because there was no literature on gender differences in state and trait cortisol to guide predictions and the literature that guided the gender difference prediction (based on the argument that situation-specific variance relates to adrenocortical reactivity to challenge) was based primarily on adults. Thus, it is not surprising that this hypothesis was rejected. Nonetheless, examining gender differences in adrenocortical activity is clearly important from a biological and a behavioral perspective. This finding represents a first step toward establishing a biosocial model for gender differences in HPA axis activity (Brennan & Raine, 1997; Raine, 2002; Taylor et al., 2000). The next step is to replicate this finding to confirm that female adolescents have more state variance than male adolescents. This could also be accomplished by examining reactivity to challenge in male and female adolescents. Assuming that it replicates, a theoretical perspective which accounts for this gender difference is needed. It is possible that the HPA axis is more reactive to achievement challenge for males but is more reactive to social stress and challenge for females (Smith, Gallo, Goble, Ngu, & Stark, 1998; Stroud et al., 2002). Adolescence may be a time period in which social cues and challenges are primarily able to activate the HPA axis (Zahn-Waxler, 2000). Given that females tend to value social relationships more than males (Taylor et al., 2000; Taylor, Dickerson et al., 2002), social stress, challenge and rejection may activate the HPA axis in females more than males

(Kiecolt-Glaser et al., 1996; Kiecolt-Glaser & Newton, 2001). Thus, in adolescents, state variance may comprise more of the variance for female compared to male adolescents because of the salience of social challenge for each respective gender.

The eighth hypothesis that internalizing behavior problems would be related to trait cortisol more for females than males was not confirmed because we did not find cortisol-internalizing relationships in either boys or girls. Based on the idea that anxiety, not depression, is associated with adrenocortical activity, it is possible that internalizing behavior problems, operationalized as anxiety problems, would be associated with trait cortisol for females more than males. Thus, exploration of the eighth hypothesis is important for future studies that measure anxiety problems.

The ninth hypothesis that externalizing behavior problems was associated with trait cortisol for males more than females was confirmed. Similar to other researchers who have examined gender differences in adrenocortical activity and externalizing behavior problems, we found behavioral correlates of trait cortisol in males but not females (Cicchetti & Rogosch, 2001b; Smider et al., 2002), but see (Pajer, Gardner, Rubin et al., 2001). This gender difference may have been overlooked by researchers who have almost exclusively studied males (e.g., Kruesi et al., 1989; McBurnett et al., 1991; McBurnett et al., 2000; Van Goozen et al., 1998; Vanyukov et al., 1993) or did not test gender differences (e.g., de Haan et al., 1998; Gunnar et al., 1997; Tennes & Kreye, 1985; Tennes et al., 1986). Taylor and colleagues (2000) argue that males have a fundamentally different biobehavioral response to stress than do females. Female aggression involves less sympathetic arousal, is cerebral and primarily defensive, and is likely to be moderated by social context. Following Taylor and colleagues (2000), we

suggest that externalizing behavior problems may be more strongly connected to trait-like levels of HPA activity in males than females. The nature of this gender difference is important because it shows that a similar physiological system (i.e., the HPA axis) can operate very differently in males and females and that individual differences in adrenocortical activity may mean different things for boys and girls. Consistent with the speculations of Zahn-Waxler and colleagues (2000), understanding the etiology of behavior disorders will be advanced through exploration of gender differences in cortisol-behavior relationships. This may potentially contribute to our understanding of how cortisol-externalizing relationships convey risk for escalating behavior problems for males, but resilience against behavior problems for females.

Implications of the LST model for cortisol measured across the day: Potential influence of the diurnal rhythm on state and trait cortisol

We found that early morning cortisol was a good marker for behavioral associations in youth. Gunnar and Vazquez (2001) propose that low morning cortisol may be a risk factor for psychopathology, but differences between normal and extreme groups may no longer be evident by late afternoon and early evening (Van Goozen et al., 2000). For example, non-maltreated (comparison group) boys with externalizing behavior problems displayed lower cortisol levels than other non-maltreated groups in the morning but not the afternoon (Cicchetti & Rogosch, 2001b). The percentage of variance attributable to trait sources may be different when modeling afternoon and evening cortisol levels. Adam (2002) proposes that morning cortisol may reflect basal

physiological processes while afternoon and evening cortisol levels may be influenced primarily by the events of the day. This hypothesis was forwarded by Kirschbaum and colleagues (1990), but it was not tested because the LST model did not have adequate model fit for PM cortisol. It is possible that the percentage of variance in levels due to trait would be less in the afternoon than in the morning. In all models we controlled for time of day at the state cortisol level. This controls for the fluctuation in time of waking from person to person, but does not address whether cortisol levels were higher or lower than expected at the specific time of sample collection for the individual. Some of the variance in state cortisol may be derived from the diurnal rhythm if the subject awoke on the day of sample collection earlier or later than usual and their cortisol levels were in a different point in the diurnal decline during assessment. This may be viewed as a potential strength of LST modeling when trait cortisol is of primary interest and also brings up an important issue about our ability to control for the diurnal rhythm through the use of time of day. Controlling for time of day should address variability in when subjects wake up, how much this time differs from their normal time of awakening and the amount of time that has passed since awakening before the sample was collected.

The diurnal rhythm also has important implications for the meaning of trait cortisol as a stable and consistent factor. In the current study, trait cortisol represents the stability in cortisol levels from one morning to the next, but underneath those individual differences in AM cortisol levels, cortisol levels change across the day within each individual. Changes in AM and PM cortisol levels should be a component of state cortisol because cortisol levels are not stable or consistent across time. However, if all saliva samples are measured at the same time of day, then the influence of the diurnal

rhythm on salivary cortisol is a constant. The diurnal rhythm represents individual differences in change, not levels. Thus, conceptualizing the diurnal rhythm in terms of state and trait cortisol is a misnomer because a different process is operating. The diurnal rhythm should be phrased in terms of initial level and degree of change. This demonstrates the need to understand that the conceptualization of trait cortisol is specific to the sample collection strategy. If AM cortisol levels are measured, then trait cortisol is specific to that time of day. Including samples taken in the morning and evening in the same LST model would be problematic because a change process in intraindividual differences is operating. Other types of analytical strategies would be more appropriate, such as growth curve (McArdle & Bell, 2000; McArdle & Nesselroade, 1994) or latent change models (Steyer et al., 1997; Steyer, Partchev, & Shanahan, 2000). Future studies should consider the use of LST modeling of afternoon or evening cortisol to determine if a stable, trait-like component of cortisol emerges and is associated with behavior.

Utility of the multiple hormone perspective: Operationalizing adrenocortical activity through two endocrine markers

This study has operationalized the HPA axis using a single neuroendocrine endpoint marker: salivary cortisol. However, when stimulated, the HPA axis releases a wide range of hormones into the blood stream and those products influence each other, functions within the HPA axis itself, and a variety of target tissues throughout the body (see Nelson, 2000). Like cortisol, the adrenal secretion of DHEA is under control of ACTH. During acute stress, DHEA levels increase in response to activation of the HPA axis (Hornsby, 1995; Parker, 1991). DHEA is likely to be co-released with cortisol in

response to events and psychological states typically studied in relation to cortisol secretion (e.g., Gunnar & Vazquez, 2001; Lupien et al., 2001). Unlike cortisol, numerous animal-model studies show that DHEA has anti-amnestic, neuroprotective, anxiolytic, and anti-aggressive properties (see reviews by Kroboth, Salek, Pittenger, Faban, & Frye, 1999). DHEA protects neurons against the toxic effects of corticosterone, suggesting that its potent anti-glucocorticoid actions protect hippocampal neurons from glucocorticoid-induced neurotoxicity (e.g., Baulieu & Kelly, 1990; Kimonides, Spillantini, Sofroniew, Fawcett, & Herbert, 1999).

Importantly, DHEA levels are associated with internalizing behavior problems in youth. Susman and colleagues (1996) reported a positive association between DHEA(S) and anxiety levels in boys. Several reports by Goodyer, Herbert and colleagues are noteworthy (Goodyer et al., 1998; Goodyer et al., 1996; Goodyer, Park, & Herbert, 2001; Goodyer, Park, Netherton, & Herbert, 2001). For instance, Goodyer and colleagues (2000a) prospectively studied a community sample of 246 youth (12 to 16 years) and observed that the combination of increased morning DHEA and increased negative mood and feelings predicted subsequent development of major depression. In a companion study of adolescents at high risk for psychopathology (N = 180; 12 – 16 year olds), Goodyer and colleagues (2000b) reported that subsequent onset of major depression was predicted by DHEA levels. A recent study by Granger and colleagues (2003) reveals an interesting pattern of findings between DHEA levels and reactivity and recovery from challenge and internalizing behavior problems. A composite measure of anxiety-depression using the CBCL, YSR and DISC was associated with increased reactivity and recovery from a social performance challenge in boys, and was associated with lower

levels and a rise in DHEA levels during the recovery period in girls. These effects were specific to boys and girls with high externalizing behavior problems. Interestingly, Goodyer and colleagues (1998) failed to reveal direct associations between cortisol or DHEA and internalizing behavior problems, but instead found that high cortisol/DHEA ratios in the evening predicted persistent major depression. Preliminary findings from our research group reveal that correlated rates of change between DHEA and cortisol levels in response to social challenge has important implications for internalizing behavior problems (Granger, 2002). This suggests that the coactivity of cortisol and DHEA may better represent the HPA axis than either hormone alone and that considering both hormones together may have important behavioral implications for studies on children with internalizing behavior problems.

DHEA levels are also associated with externalizing behavior problems in youth. Van Goozen, van den Ban, Matthys, Cohen-Kettenis, Thijssen and van Engeland (2000) studied a clinical sample of youth (N = 96, males and females) ages 6-12 years and reported that children with oppositional defiant disorder had higher DHEA(s) levels than normal controls. Dmitrieva, Oades, Hauffa and Eggens (2001) reported that DHEA(s) levels were 50% higher in 28 clinic-referred males with conduct disorder than 13 healthy controls. Strous and colleagues (2001) reported that levels of DHEA(S) were inversely associated with symptoms of attention deficit hyperactivity disorder in a clinic sample of 29 males aged 7-15 years. Brooks-Gunn and Warren (1989) report a linear effect of DHEA(S) for aggression in a community sample of 103 girls (ages 10-13 years). Two reports by Susman and colleagues based on the same community sample of 56 boys and 52 girls (ages 9-15 years) found DHEA levels were positively associated with

rebelliouness, an inverse correlation was observed with delinquency (Susman et al., 1987) and an inverse correlation between DHEA and externalizing behavior problems in girls was noted (Susman et al., 1996). A study by Granger and colleagues (2003) revealed that DHEA levels before a social performance challenge were inversely associated with externalizing behavior problems in girls, and rising DHEA levels during the recovery period after the social performance challenge were associated with externalizing behavior problems in boys. Associations between DHEA reactivity and recovery and internalizing behavior problems were specific to high externalizing boys and girls. Further, interactions between internalizing and externalizing behavior problems and DHEA reactivity to a parent child conflict were revealed. Within high externalizing adolescents, internalizing behavior problems were associated with low reactivity and recovery from challenge in boys and high DHEA levels in girls. Within low externalizing adolescents, internalizing behavior problems were associated with high reactivity to challenge in boys, and low DHEA levels and rising DHEA levels during the recovery period in girls. These findings suggest that DHEA levels and reactivity to challenge is important for children's behavior problems, particularly comorbid behavior problems. Studies with youth yield evidence of associations between DHEA levels and externalizing behavior problems, but these findings are difficult to interpret because the direction of the effect is not necessarily consistent across studies. Preliminary reports by Granger and Shirtcliff (2002) reveal that externalizing behavior problems and, more specifically, comorbid internalizing and externalizing behavior problems were associated with the correlated rate of change between cortisol and DHEA during social challenge. This study points to the need to consider cortisol and DHEA in tandem to provide a more

complete picture of HPA axis- externalizing behavior relationships. Answers to these research questions may help to refine our understanding of biosocial models by understanding when biological measures interact with other biomarkers to predict behavioral outcomes. These studies also illustrate the utility of considering multiple hormones to examine consistency. It is possible that operationalizing cortisol (i.e., the bad hormone) and DHEA (i.e., the good hormone) together will contribute to our understanding of how hormone levels and response to social challenge may convey risk or resilience against the development of behavior problems in youth (Granger, 2002; Sapolsky, 2000b; Shirtcliff, 2002). The balance of these adrenal hormones may help to clarify the inconsistencies in the literature (McEwen, 1998). Future studies are needed that examine multiple endocrine markers and children's behavior problems (Granger & Kivlighan, in press).

Policy Implications for children's health and development

The results of the current study may have important policy implications that may inform research aimed at preventing or treating children's behavior problems. These policy implications directly address boys' externalizing behavior problems and not adrenocortical activity in girls or internalizing behavior problems (Broidy et al., 2003). The first policy implication is that associations between HPA axis activity and behavior problems may help to identify boys who are resistant to treatment (Moffitt, 1993b; Moffitt & Caspi, 2001; Moffitt et al., 2002). Low adrenocortical activity may be a biological risk factor that, because it is relatively stable and consistent across one year of development, is difficult to change (Eddy, Dishion, & Stoolmiller, 1998; Raine et al.,

1997). A related treatment implication is that the current study demonstrates that these biosocial processes operate within the normal range of behavior problems. This suggests that children with clinical level behavior problems represent the end of a continuum rather than a distinct subpopulation or group (Pajer, Gardner, Rubin et al., 2001) and that the developmental sequelae operating in extreme groups is evident in milder forms within the general population (Cicchetti & Cannon, 1999; Moffitt & Caspi, 2001). Thus, biosocial barriers to treatment that are evident within clinical or at risk populations may also be evident within the general population (Loeber & Farrington, 2000). On a more positive note, it is possible that if emotions are the mechanism that links adrenocortical activity with externalizing behavior problems, then emotions and affective states may be one avenue toward change. First, it is necessary to identify ways to change emotions. These methods may then be used as a means of changing physiology and behavior.

The current study has implications for children's physical health as well, specifically the finding that low cortisol levels are associated with externalizing behavior problems in boys. As Heim and colleagues discuss (2000), hypoarousal is a risk factor for mental health problems, such as conduct or oppositional defiant disorder, but also accompany physical health problems including chronic fatigue syndrome, fibromyalgia, other somatoform disorders, rheumatoid arthritis, and asthma. In their seminal review, Angold and colleagues (1999) discuss the implications of comorbidity between a mental and physical health condition. They emphasize that physical health conditions are often accompanied by cognitive and emotional changes that can closely resemble mental health problems (Raison, Gumnick, & Miller, 2002). It is possible that low adrenocortical activity acts as a risk factor for mental and physical health problems, increasing the

probability of substantial comorbidity between mental and physical conditions associated with low adrenocortical activity. It is also possible that some common risk factor which increases the probability of expressing low adrenocortical activity underlies both mental and physical health problems (Heim et al., 2000). Discovering similarities in the etiology of mental and physical health problems has important implications for prevention, diagnosis and treatment of mental and physical health problems associated with low adrenocortical activity.

LIMITATIONS OF THE CURRENT STUDY

This study has many strengths, but several issues limit the interpretation of the findings. The first limitation has to do with behavioral associations with state cortisol. The finding that variance in AM cortisol levels attributable to state sources was not associated with internalizing and externalizing behavior should be interpreted with caution. It is likely that situation-specific factors (e.g., concurrent emotions, moods or stress states) are associated with state cortisol (Adam, 2003; Smyth et al., 1998). Our behavioral measures were designed to tap into trait-like behavior profiles, so it makes sense that trait-like behaviors were associated with trait cortisol. It is possible, however, that the mechanism that links cortisol with behavior problems operates like a state. That is, individuals may have behavioral and physiological tendencies toward particular states, thereby becoming more trait-like. Emotions and affective states, when chronically accessed, may begin to operate like a trait when the individual expresses those emotions across time and a wide range of situations. Similarly, Gunnar and colleagues (2000) speculate that the HPA axis becomes chronically under- or overaroused across a wide

variety of situations, becoming entrenched in a psychopathological state. Thus, physiological arousal and related emotional states can become under- or overactivated and become like traits. It will be important in future studies to examine how the relationship between emotions and adrenocortical activity in particular situations (i.e., states) becomes generalized to be like traits.

On a related note, the second limitation regards the relativism problem discussed by Steyer and colleagues (1999). Trait cortisol represents the extent to which cortisol is invariant across the occasions of measurement included in this study. The variance that is attributable to trait cortisol may change if cortisol were measured in other contexts (e.g., at school, in novel environments, in stressful situations), across a different age range, or in other populations (Kirschbaum et al., 1990). Future studies are needed to systematically examine trait cortisol across different social contexts (Boyce et al., 1998), developmental stages, and times of the day.

The third potential limitation of the study is that the sample collection strategy may not have been optimal for modeling trait cortisol. It is possible that the variance attributed to trait cortisol would change if additional samples were collected. The trait cortisol construct would be more generalizable, and the behavioral relationships observed may potentially have been even more consistent. Given that the behavioral associations were extremely consistent, however, this limitation may not have a large impact on the findings. Further, preliminary analyses revealed that trait cortisol represented approximately 30% of the total variance in salivary cortisol when measured using two samples (within each year), and Kirschbaum and colleagues (1990) report that trait cortisol comprises 20 to 30% of the total variance in salivary cortisol across two or three

measures. It appears that the consistent portion of the variance in salivary cortisol comprises approximately 30% of the total variance regardless of how many measures are included. It is likely that including additional similar measures would yield the same trait cortisol construct and associations with behavior would be similar.

This limitation is complicated by the fact that trait cortisol would represent a different concept if measured in another context. For example, including weekend and weekday mornings would change the interpretation of trait cortisol and may result in a smaller portion of variance being attributed to trait cortisol. Including measures of salivary cortisol taken across different contexts, however, seems to defeat the purpose of using the LST model to compose a conceptually clear latent construct. Systematic change processes that operate in tandem with 'random' situation-specific variance makes the interpretation of trait cortisol difficult and potentially washes away these effects. For example, Preville and colleagues (1996) did not find a trait cortisol construct across fifteen measures of salivary cortisol, but this may be because the measures were taken during a laboratory stressor. The situational influence of the laboratory stressor, which impacts each measure differently depending on the time-lag after the challenge, may have overwhelmed the consistency in salivary cortisol. Trait cortisol may have been observed if each measure was not confounded by autoregressive situational factors. Given that there was a theoretical change process at work in this study, an analytical strategy that measures reactivity to the challenge, such as a latent change (Steyer et al., 1997) or growth curve model (McArdle & Bell, 2000) may have been more appropriate (Preville et al., 1996). This demonstrates that the strength of the LST model is relatively specific

to the current study's sample collection strategy. Other analytical strategies may be more useful when the sample collection strategy involves growth or change processes.

This conceptualization leads into the fourth limitation of the study's sample collection strategy. An optimal strategy would have included multiple measures of salivary cortisol taken at even time-lagged intervals. It would be ideal to presume that there is no reason to believe that one sample is more or less similar to another based on autoregressive factors (i.e., the third assumption of the LST model, 2001a; Kenny & Zautra, 2001b). The sample collection strategy included a one year time lag which raises the possibility that developmental change influenced the trait cortisol construct. Indeed, cortisol levels rose across the year (see table 3). Modeling salivary cortisol using a latent change model (Steyer et al., 1997) revealed that this developmental process did not change associations between cortisol levels and behavior problems and was not associated with behavior. Thus, this limitation does not appear to have a great impact on the results of the study. In sum, the sample collection strategy potentially has limitations based on inclusion of only four measures of salivary cortisol, generalizability of trait cortisol across contexts, and possible developmental processes operating across one year. Collection of only four measures does not have a great impact on trait cortisol, so the use of LST modeling for four measures of salivary cortisol appears valid. The generalizability limitation primarily impacts the conceptual interpretation of the trait cortisol construct; sample collection strategies should collect in very similar situations if a 'true' trait construct is desirable or should collect across a wide variety of situations if a more generalizable construct is of interest. In either case, discussion of the utility of trait cortisol should keep theoretical contextual factors in mind. The limitation about

development and change should be dealt with analytically; if developmental processes are at work, appropriate analytical strategies should model change.

The final limitation regards the behavioral measures. Our measure of externalizing problems was administered to youth aged 10 to 16 in year 1, constraining the interpretation of the findings to adolescent boys. This measure primarily taps into conduct and delinquent behaviors so our findings should not generalize to verbal, relational or physical aggression. The findings from the different internalizing behavior scales, when different, may reflect method- or age-related differences in cortisol-behavioral associations. The two depression measures, however, largely converged in their results, suggesting minimal method- and age-related differences in cortisol-behavior relationships. Given that the HPA axis is activated in response to social stress (Kirschbaum et al., 1993) and social anxiety (Granger et al., 1996), it is possible that studies that focus specifically on the anxiety component of internalizing behavior problems, in particular trait-like anxious behavior (Gunnar, 2001), may find consistent cortisol-behavior associations in low risk normally developing populations (Colomina et al., 1997).

Future directions and conclusions

Future studies are needed to refine our understanding of cortisol-behavior associations. First, trait cortisol may comprise a larger percentage of the total variance, or stress may be experienced by extreme groups differently than low risk normally developing youth. For instance, cortisol may operate differently in maltreated compared to normal youth and may have different developmental sequelae across these groups

(Cicchetti & Rogosch, 2001a). Second, trait cortisol may be reflecting different amounts of physiological and environmental influences when assessed in the afternoon. It is possible that environmental forces impact PM trait cortisol variance more than AM cortisol because of the accumulated effects of the events of the day on adrenocortical activity (Adam, 2003). While trait cortisol is not influenced by situation-specific factors evident at the time of sample collection (Kirschbaum et al., 1990), some stable contextual or persistent situational factors such as socioeconomic status (Lupien et al., 2001), parental psychopathology (Ashman et al., 2002; Hammen, Henry, & Daley, 2000), and parental alcoholism and chronic substance abuse (Moss et al., 1995) may still influence the association between trait cortisol and behavior. Biosocial perspectives on adrenocortical activity and behavior problems in youth have been advanced by the current study, but our models need to be refined further before the meaning and interpretation of these associations is clear. A theme throughout the discussion of this study has been that emotions and affective states act as potential mediators of adrenocortical activity- behavior problem relationships. Specifically, low fear or thrill seeking behavior was theorized to be a potential mechanism that links cortisol with externalizing behavior problems. Sadness was a potential mediator of HPA-internalizing relationships, but the null results with depression suggests that fear or anxiety are more likely candidates for affective states that underlie cortisol-internalizing relationships. Future studies which explicitly examine how fear, thrill-seeking behavior and sadness potentially mediate adrenocortical-behavior relationships are needed to test whether emotions are empirical and theoretical mediators and to discover the circumstances under which these mediators operate. Examining how consistency in adrenocortical activity is

associated with trait-like behavior profiles has advanced our understanding of how emotional states can become entrenched in a psychopathological state (Gunnar et al., 2000). The next step toward refining this model is to examine children's adrenocortical responses to salient events and experiences which specifically tap into sadness, fear, anxiety and sensation seeking. Extending this research to a longitudinal study design will permit examination of consistency in emotional and physiological responses to emotion. Researchers interested in examining trait cortisol should take heed of the large amount of variance that is attributable to the situation, and consider using appropriate methodology to examine trait cortisol-behavior associations. To that end, the consistency and clarity of behavioral associations with salivary cortisol may be improved in the next generation of studies, furthering the understanding of when individual differences in HPA axis confers risk or resilience, and potentially refining biosocial models of behavior.

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Curriculum Vitae

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Education History:

- B.S. 1998 in Psychology at the University of Oregon
  Honors: Honors in Psychology; Zach Award for Undergraduate Honor's Thesis.
  Thesis: Cortisol's Role in Exam Expectation (Advisor: Daniel P. Kimble, Ph.D)
- Ph.D. August 2003 in Biobehavioral Health, minor in Statistics at Penn State University
  Thesis: Low salivary cortisol levels are associated with externalizing but not internalizing behavior problems: A latent state trait model in normally developing youth (Advisor: Douglas A. Granger, Ph.D.)

Teaching Experience:

- Graduate Teaching Assistantships for Biological Psychology, Hormones and Behavior, Human Performance, Intervention strategies, Research Applications, Drugs and Society, Gender Differences. Instructor for Lab Practicum on Salivary Biomarkers, January 20 – 22 and August 4 – 5.

Selected Awards:

- 2001 Biobehavioral Health Graduate Student Scientific Achievement Award Recipient for "Assessing Estradiol in Biobehavioral Studies Using Saliva and Blood Spots: Simple Radioimmunoassay Protocols, Reliability, and Comparative Validity".

Selected Publications:

1. Granger, D. A., Dreschel, N. A., & Shirtcliff, E. A. (in press). Developmental Psychoneuro-immunology: The Role of Cytokine Network Activation in the Epigenesis of Developmental Psychopathology. In D. Cicchetti & E. Walker (eds). Neurodevelopmental mechanisms in the genesis and epigenesis of psychopathology. Cambridge University Press: New York.
2. Granger, D. A., Dreschel, N. A., & Shirtcliff, E. A. (in press). Immunology and Developmental Psychopathology. In D. Cicchetti & D. Cohen (eds). Developmental Psychopathology. John Wiley & Sons: New York.
3. Granger, D. A., Shirtcliff, E. A., Zahn-Waxler, C., Usher, B., Klimes-Dougan, B., & Hastings, P. (in press). Adolescent internalizing and externalizing behavior problems predict individual differences in testosterone diurnal variation. Development and Psychopathology.
4. Granger, D. A. & Shirtcliff, E. A. (in press). The Biosocial Model, Hypothalamic-Pituitary-Adrenal Axis, and Behavioral Science. In B. Schneider & L. Waite (Eds.), Families Working: Time Apart, Time Together.
5. Shirtcliff, E. A., & Marrocco, R. T. (2003). Salivary cotinine levels in human tobacco smokers predict the attentional validity effect size during smoking abstinence. Psychopharmacology, 166, 11 -18.
6. Bateup, H.S., Booth, A., Shirtcliff, E., & Granger, D. A. (2002). Testosterone, cortisol and women's competition. Evolution and Human Behavior, 23, 181-192.
7. Shirtcliff, E. A., Granger, D. A., & Likos, A. (2002). Gender differences in the validity of testosterone measured in saliva by immunoassay. Hormones and Behavior, 42, 62 – 69.
8. Shirtcliff, E. A., Granger, D. A., Schwartz, E. B., & Curran, M. J., (2001). Use of salivary biomarkers in biobehavioral research: Cotton-based sample collection methods can interfere with salivary immunoassay results. Psychoneuroendocrinology, 26, 165 - 173.
9. Shirtcliff, E. A., Reavis, R., Overman, W. H., & Granger, D. A. (2001) Measurement of Gonadal Hormones in Dried Blood Spots Versus Serum: Verification of Menstrual Cycle Phase. Hormones and Behavior, 39(4), 258- 266.
10. Shirtcliff, E. A., Granger, D. A., Schwartz, E. B., Curran, M. J., Booth, A., & Overman, W. H. (2000). Assessing estradiol in biobehavioral studies using saliva and blood spots: Simple radioimmunoassay protocols, reliability, and comparative validity. Hormones and Behavior, 38, 137 – 147.