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Stress System Development from Age 4.5 to 6: Family Environment Predictors and Adjustment Implications of HPA Activity Stability versus Change

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Abstract

This study addressed early calibration of stress systems by testing links between adversity exposure, developmental stability of hypothalamic-pituitary-adrenal (HPA) axis activity, and behavior problems in a sample of adopted children. Families (*n*=200) were assessed when the child was 9mos, 18mos, 27mos, 4.5yrs, and 6yrs to collect adversity information—parent psychopathology, stress, financial need, and home chaos. Morning and evening cortisol samples at the final 2 assessments indexed child HPA activity, and parent-reported internalizing and externalizing at the final assessment represented child behavior outcomes. Increases in cumulative adversity from 4.5–6 related to higher child morning cortisol, whereas age 6 cumulative adversity related to lower, unstable child evening cortisol. Examination of specific adversity dimensions revealed associations between (1) increasing home chaos and stable morning cortisol, which in turn related to internalizing problems; and (2) high parental stress and psychopathology and lower, unstable evening cortisol, which in turn related to externalizing problems.

Keywords

Hypothalamic-Pituitary-Adrenal Axis; Cortisol; Longitudinal; Stability; Adversity; Childhood; Adopted Children

Adverse experiences in childhood—defined as negative environmental influences that may range from moderate psychosocial and/or economic hardship to more severe forms of

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maltreatment—have been shown to lead to long-term mental and physical health problems (e.g., Danese & McEwen, 2011; Widom, Czaja, Bentley, & Johnson, 2012; Felitti et al., 1998), at least in part through modulation of stress response systems including the hypothalamic-pituitary-adrenal (HPA) axis (Fisher, Kim, Bruce, & Pears, 2011; Hunter, Minnis, & Wilson, 2011). Despite ample evidence for links among childhood adversity, stress system activity, and poor behavioral adjustment, existing research is limited in two critical areas: (1) A preponderance of cross-sectional and retrospective research cannot fully clarify unfolding risk processes—i.e., how adversity exposure affects stress system stability vs. change over time, and what this means for behavior; and (2) Behavioral research involving biological families (where parents supply both their children's genes and their proximal environment) cannot distinguish effects of adversity exposure from shared genetic effects on child functioning. Further information on both of these fronts is needed to understand and change health risk trajectories. The present study was designed to address these limitations by investigating longitudinal associations between early childhood adversity exposure, HPA activity, and behavioral problems in a sample of children adopted at birth.

Links among Childhood Adversity, HPA Function, and Behavioral Adjustment

The HPA system is designed to both register effects of environmental adversity and modulate the impacts of such adversity. Responsive to both psychological and physical stressors, the HPA axis influences mental and somatic processes involved in preparing for and surviving threat conditions via cortisol output from the adrenal gland (e.g., Dallman & Hellhammer, 2011; Sapolsky, Romero, & Munck, 2000). Normative HPA activation follows a diurnal rhythm with a peak in the morning approximately 30 minutes after awakening, followed by a decline to the lowest levels preceding sleep. Whereas the morning peak is thought to represent preparation for the stress of the day and is more genetically influenced, evening levels appear to register reactivity to experiences of the day and show less genetic influence (Bartels, van den Berg, Sluyter, Boomsma, & de Geus, 2003; Corbett, Schupp, Levine, & Mendoza, 2009; Van den Bergh & Van Calster, 2009). Life stress—particularly during sensitive periods of prenatal development-infancy and early childhood—is known to negatively impact cognitive and emotional self-regulation via changes in HPA activity and related neurotransmitter systems acting on the brain (e.g., Bremner & Vermetten, 2001; Green et al., 2011; Murgatroyd & Spengler, 2011). Although dysregulation of HPA diurnal activity and/or acute reactivity[1] has been consistently implicated in paths to behavioral disorder (see Gunnar & Vazquez, 2006), there is still ambiguity regarding conditions under which higher versus lower activity signals risk for maladaptive behavior.

On the one hand, a substantial body of research suggests elevated cortisol—particularly in the morning—relates to both early childhood adversity and behavioral problems during the preschool period and beyond. Child exposure to negative life events and perceived low-quality parental care have been related to high morning cortisol levels (Cutuli, Wiik, Herbers, Gunnar, & Masten, 2010; Engert, Efanov, Dedovic, Dagher, & Pruessner, 2011; Gustaffson et al., 2010). In turn, high morning cortisol has been characterized as a trait vulnerability marker for depression, related to parental depression history and both concurrently and prospectively to child/adolescent depression (Dougherty, Klein, Olino, Dyson, & Rose, 2009; Halligan, Herbert, Goodyer, & Murray, 2004; Goodyer, Herbert,

[1]Although the focus in this study is diurnal (basal) activity of the HPA system, the separability of daily cortisol levels—particularly in the afternoon and evening—from reactivity to acute stressors encountered during the day is questionable. Therefore, while the majority of background research cited involves diurnal cortisol levels, some of the relevant previous studies involve cortisol measures (described as "reactivity" or "response") during and after acute stress exposure.

Tamplin, & Altham, 2000). Among maltreated children specifically, internalizing problems have also been related to hypercortisolism (Cicchetti & Rogosch, 2001). Elevated cortisol is thought to prime the brain for threat and anxiety-like reactions, both through direct effects on corticoid receptors and indirect effects on other neurotransmitters (Bremner & Vermetten, 2001). This means that children with high cortisol may have a lower threshold for stress-related arousal, leading them to withdraw from potentially stressful situations and to show more internalizing characteristics (e.g., Scerbo & Kolko, 1994; Schmidt et al., 1997). In sum, there is evidence for a set of linkages from early exposure to stressful family conditions to high morning cortisol to internalizing difficulties. At the same time, existing research on genetically-related families leaves open the question of whether these associations simply reflect shared genetic influence on parental characteristics and child cortisol levels, and not effects of stress exposure per se.

On the other hand, studies in at-risk, predominantly low SES samples have demonstrated relations between childhood adversity and low cortisol. Foster children who experienced extreme conditions of physical abuse or neglect have shown suppressed cortisol responses and diurnal rhythms (Bruce, Fisher, Pears, & Levine, 2009; Fisher et al., 2011). Even among non-maltreated children, adversity—including exposure to stressed and/or depressed parents, as well as family financial strain and instability—has been related to low cortisol levels in some studies (Bush, Obradovic, Adler, & Boyce, 2011; Fernald, Burke, & Gunnar, 2008). This pattern has been suggested to reflect HPA axis downregulation following excessive stress system activation, which comes with its own costs (Fries, Hesse, Hellhammer, & Hellhammer, 2005).

Although the evidence is less consistent than that for hypercortisolism and internalizing, hypocortisolism has been associated with externalizing problems (e.g., Laurent et al., 2012; Shirtcliff, Granger, Booth, & Johnson, 2005; Smider et al., 2002). A meta-analysis confirmed inverse relations between basal cortisol levels and externalizing in both clinical and non-clinical samples and both boys and girls, particularly during school ages (Alink et al., 2008). In contrast to the effects of high cortisol outlined above, low cortisol levels are thought to allow more approach-related behavior, which may include aggression, by increasing the threshold for stress-related arousal and disinhibiting testosterone activity (e.g., Raine, 2002; Viau, 2002). As suggested by a study of children exposed to high levels of interparental conflict (Davies, Sturge-Apple, Cicchetti, & Cummings, 2007), children who encounter high levels of stress may habituate with reduced HPA activation, which in turn makes them relatively insensitive to potential threat and more likely to engage in acting-out or externalizing behaviors. Thus, an alternate set of linkages may exist among early family adversity, low cortisol, and externalizing difficulties. Again, conclusions about how and when adversity shapes child HPA function are limited by the lack of genetically-informed designs that can distinguish stress exposure from shared genetic effects from parent to child, as well as the paucity of prospective longitudinal research in this area.

HPA Axis Modulation in Early Childhood

Early childhood, which spans ages 2–6, presents a particularly important time window for studying adversity effects on HPA function. In particular, the period during which children typically begin school (age 4–6) straddles the early developmental range during which stress effects are most marked and the time when the HPA system has matured enough to exhibit a diurnal rhythm (Essex et al., 2011; Gunnar & Donzella, 2002). This is also a critical time in that it presents new psychosocial challenges related to the school transition, and a child's ability to meet these challenges with adequate behavioral self-regulation is tested. As such, it is no accident that early signs of both internalizing and externalizing difficulties related to HPA axis dysregulation are often detected during the preschool-kindergarten period (e.g.,

Dougherty et al., 2009; Smider et al., 2002). Research on children during the first year of school has demonstrated a normative increase in daily cortisol levels followed by a decline over the course of the year (Gunnar, Tout, de Haan, Pierce, & Stansbury, 1997). In addition, individual differences related to child adjustment and adversity have been identified; inhibited or anxious children evidence sustained cortisol elevations, and more marked effects of family adversity have been shown to emerge over the course of the school year (Bush et al., 2011; Russ et al., 2012; Tarullo, Milner, & Gunnar, 2011). This is a dynamic time during which shifts in physiological and behavioral function could be decisive for later outcomes, and research focusing on such shifts is needed.

A few studies have addressed childhood adversity or HPA function over time, yielding conflicting evidence for factors driving higher versus lower cortisol. Duration of time in poverty and unstable family environments have each been related to high child cortisol (Blair et al., 2011; Evans & Kim, 2007). Longitudinal investigations of HPA activity have shown both increasing and decreasing cortisol predicted by family financial need (Blair et al., 2011; Chen, Cohen, & Miller, 2010). These studies have typically only assessed one part of the equation—i.e., adversity or cortisol—at several times, making it difficult to examine dynamic interplay among the two. Furthermore, the two studies addressing cortisol over time examined change in absolute levels, but not within-person stability versus change in cortisol output, a potentially critical adaptation marker according to newer theoretical conceptualizations of stress system development (Del Giudice, Ellis, & Shirtcliff, 2011). Although preliminary evidence for longitudinal associations between child adversity exposure and both hyper- and hypocortisol profiles exists, more comprehensive research assessing both constructs over time, guided by a coherent theoretical model, is needed to advance research in this area.

The adaptive calibration model (ACM) proposed by Del Giudice and colleagues (2011) lays out a set of predictions for how early adverse conditions should shape stress response systems, and ultimately adaptation. As a filter for social threat information, HPA activity—both diurnal levels and acute responsiveness—should modulate to best prepare the child to survive in his/her particular family environment, shifting upward or downward (within certain genetically defined limits) as risk conditions change. Whereas moderately stressful conditions should lead to lowered HPA activity—a “buffered” phenotype less responsive to daily stressors—an unpredictably threatening environment should lead to elevated HPA activity—a “vigilant” phenotype prepared to respond to ambiguous stressors. More severe, chronically stressful conditions such as those represented by abuse or neglect, should lead to an unresponsive “unemotional” phenotype. Although these adaptations make sense in the context of the challenges children face, they are acknowledged to come with costs: internalizing (depression, anxiety) difficulties for the vigilant type, and externalizing difficulties and ultimately antisocial tendencies for the unemotional type. Complementing previously described theories of how stress shapes behavior via neurobiology, this model provides a framework with which to understand the impact of childhood adversity exposure not only on HPA activity levels, but also on (in)stability over time. Concrete evidence for these predictions awaits empirical testing in longitudinal samples with varying risk characteristics.

Remaining Questions

One of the issues that must be resolved in this work is the relative importance of previous versus concurrent adversity exposure for HPA activity levels and stability. The studies discussed above provide substantial evidence for both *prospective* and *concurrent effects of adversity* on cortisol levels, though the direction of such effects (i.e., higher vs. lower cortisol) has been inconsistent. Thus far, no studies to our knowledge have addressed

prediction of intra-individual *cortisol stability* (i.e., maintenance of higher or lower diurnal levels, relative to peers) during early childhood, which may represent an important complement to the adaptive information provided by *cortisol levels*. Another factor to consider is the *absolute degree of adversity* versus *changes over time*; prior research has generally shown effects of adversity severity at either one time or across a range of times, but less attention has been paid to the possibility that variations in adversity (unexplained deviations from a mean level or systematic change across time) may matter. Considering the tenets of adaptive calibration, one might expect earlier and concurrent *degree* of adversity to predict lower child cortisol levels, whereas *changes* in adversity (earlier and/or concurrent variability) would predict higher cortisol levels and instability. However, no studies have yet been designed to systematically compare these classes of effects, and little is known about any of these effects on child cortisol stability.

Another issue requiring further clarification is the type of adversity driving stress adaptation. On the one hand, research has demonstrated effects of *cumulative adversity*—defined here as the sum of diverse sources of adversity at a given time, rather than of adversity exposure over time—on child stress systems and behavioral adjustment. For example, Gustafsson and colleagues (2010) found an association between the total number of children's adverse experiences—including socioeconomic disadvantage, negative life events, and potentially traumatic life events—and their daily cortisol levels. Similarly, Fisher and colleagues (2011) showed that the sum of children's adverse experiences—including parental substance use, chronic poverty, low social status, primary caretaker changes, sexual or physical abuse, and community violence—predicted their behavioral dysregulation trajectories. On the other hand, studies have shown differential effects of *specific forms of adversity*. In particular, structural hardships posed by low SES may relate differently to children's HPA function than do more intimate psychosocial hardships (i.e., negative or unstable family environments, negative life events), with the latter more often tied to hypercortisolism (Blair et al., 2011; Bush et al., 2011; Cutuli et al., 2010). At the same time, these two factors are often related, in that financial strain can restrict parents' ability to relate positively to one another and to their children (see Stover et al., 2012), and further exploration is needed to assess common versus distinct effect. In any case, it will be important to investigate adversity at both cumulative and specific component levels of analysis to determine which targets should be a focus for prevention efforts.

Finally, existing research leaves unanswered questions about the centrality of *rearing parent influences*, as opposed to *prenatal and genetic influences*, in child HPA function and behavioral regulation. Because birth parents provide all three of these influences in genetically-related families, it is difficult to discern whether the associations described above truly reflect effects of adversity exposure during postnatal development, effects of ongoing adversity starting in the womb, or shared genetic effects driving both parent and child cortisol and behaviors. By separating birth and rearing parent influences, as in an adoption design, and controlling for the former, researchers can be more confident that adversity measured during early childhood represents a decisive shaper of child adaptation.

The Current Study

The current investigation was conceived to test adaptive calibration predictions in a sample of adopted children and their parents. In particular, we wished to examine relations between family adversity—i.e., exposure to parents' stress, relationship instability, psychiatric symptoms, financial need, and home chaos—and both levels and stability of children's morning and evening cortisol from age 4.5 to 6. In addition, we wanted to characterize what these profiles meant for behavioral adaptation by testing relations between child cortisol levels/stability and internalizing and externalizing problems.

In an effort to better understand dynamic relations between adversity and cortisol over time, we considered both prospective and concurrent predictive models that tapped (a) the degree of childhood adversity exposure (mean levels from 9 months–4.5 years; levels at age 6, controlling for 9-month levels) and (b) longitudinal changes in adversity exposure (systematic growth and unexplained deviations from the mean from 9 months–4.5 years; acute change from 4.5–6 years). We were also interested in both the effect of a cumulative measure of adversity and effects of specific adversity dimensions, which offer a more precise picture of factors influencing child stress. Finally, we wished to rule out birth parent effects on both child cortisol (prenatal adversity, birth mother cortisol levels) and behavioral problems in order to establish specific rearing parent effects.

Based on previous research outlined above and the ACM, we proposed the following hypotheses: (1) The degree of both earlier (9-month–4.5-year) and concurrent (6-year) adversity exposure would predict lower child cortisol levels, which would in turn relate to externalizing problems; (2) Changes in adversity exposure (deviations from the mean and growth from 9 months–4.5 years; increases from 4.5 years–6 years) would predict higher child cortisol levels and instability, particularly in the morning, which would in turn relate to internalizing problems; (3) These effects would be apparent for cumulative adversity, as well as for specific dimensions; and (4) These effects would hold even when controlling for prenatal adversity exposure, birth mother cortisol, and birth mother internalizing/externalizing problems.

Method

Participants

Participants were drawn from Cohort I of the Early Growth and Development Study, a longitudinal study of adopted children and their birth and adoptive parents. Recruitment of Cohort I participants occurred between 2003 and 2006, beginning with the recruitment of adoption agencies (N = 33 agencies in 10 states located in the Northwest, Mid-Atlantic, and Southwest regions of the United States). The participating agencies reflected the full range of adoption agencies operating in the United States: public, private, religious, secular, those favoring open adoptions, and those favoring closed adoptions. Agency staff identified participants who completed an adoption plan through their agency and met the following eligibility criteria: (a) the adoption placement was domestic, (b) the infant was placed within 3 months postpartum (M = 7.11 days postpartum, SD = 13.28; median = 2 days), (c) the infant was placed with a nonrelative adoptive family, (d) birth and adoptive parents were able to read or understand English at the eighth-grade level, and (e) the infant had no known major medical conditions such as extreme prematurity or extensive medical surgeries. Of the families who met eligibility criteria, 68% (n = 361) agreed to participate. The participants were representative of the adoptive parent population that completed adoption plans at the participating agencies during the same time period (Leve et al., in press).

The sample included male (57%) and female (43%) children with a range of racial backgrounds (57.6% White, 11.1% Black/African American, 9.4% Latino, 20.8% multiracial, .3% American Indian/Alaskan Native, .6% unknown or not reported). Adoptive parents were predominantly White (over 90% of adoptive mothers/fathers) and middle class and involved in a stable marital or marriage-like relationship (M = 18.5 years, SD = 5.2 at first assessment).[2] The current analyses are based on the subset (n = 200) of the total sample for which family adversity data from 9 months to 6 years, as well as child age 6 problem

[2]A small proportion (7.8%) of adoptive families in this sample included same-sex or divorced parents. There were no differences in reported results when models included vs. excluded these families.

behavior data, were available. A comparison of cases included versus not included revealed nonsignificant differences on all other study variables.

Procedure and Measures

Parent and child data for this study were collected through in-person interviews, home-based questionnaires, and web-based assessments, as well as saliva samples (for cortisol). Descriptive information for questionnaire measures used in this study is presented in Table 1. Further details on each measure and timing of assessments are given below. Unless otherwise noted, adversity indices were measured in adoptive parents, and the term "parent" refers to adoptive rather than birth parents. Measures from the 9-month, 18-month, 27-month, 4.5-year, and 6-year assessments were used to measure family adversity; saliva samples at age 4.5 and 6 were used to measure cortisol; and age 6 data were used to measure child behavior outcomes.

Adversity Indices

Parent depressive and anxiety symptoms—Adoptive mothers and fathers completed a 20-item version of the Beck Depression Inventory (Beck & Steer, 1993a) at all assessments (the suicidal ideation item from the original 21-item scale was dropped to minimize situations requiring clinical follow-up). Alphas were acceptable (a = .71–.87). Mothers and fathers also completed an anxiety measure—the full 21-item Beck Anxiety Inventory (Beck & Steer, 1993b) at the 9-month and 4.5-year assessments (α = .73–.82), and the 20-item state subscale of the Spielberger State Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushere, 1970) at the 6-year assessment (α = .92). Total symptom scores were standardized, and mean Z-scores across adoptive parents and depression/anxiety scales were computed to index parental internalizing symptoms at each wave (mean *r* across parents = . 10 for anxiety, .12 for depressive symptoms; mean *r* within parents across anxiety and depressive symptoms = .60 for mothers, .63 for fathers). Despite modest cross-parent correlations suggesting symptoms were not consistent across caregivers, the mean score was considered a useful index of total exposure to parent psychopathology.

Parent negative life events—Both adoptive parents reported on stressful life events using a standard 34-item checklist (Dohrenwend, Krasnoff, Askenasy, & Dohrenwend, 1978) at all except the 18-month assessment (α = .44–.65; these modest alphas are typical for life events checklists, in which items are not necessarily expected to correlate). The mean across parents' standardized total scores was computed for each wave (mean *r* across parents = .45).

Parent (low) social support—Adoptive parents were asked about satisfaction with available support in the areas of (1) intimate relationships, (2) friendships, and (3) neighborhood or community (Crnic, Greenberg, Ragozin, Robinson, & Basham, 1983) at all except the 18-month assessment (α= .71–.85). The mean across parents' standardized support satisfaction scores was calculated for each wave (mean *r* across parents = .23).

Parent marital instability—An abbreviated version of the Marital Instability Index (Booth & Edwards, 1983) containing the 5 items the scale authors found most predictive of instability was administered to adoptive parents at all assessments (α = .78–.88). Summed scores were computed, and the mean across parents' standardized scores for each wave was used in analyses (mean *r* across parents = .60).

Financial need—Adoptive parents indicated the degree to which the family had insufficient money to cover material needs (i.e., for housing, clothing, etc.) using a 6-item subscale of a larger demographics questionnaire (Conger et al., 1992) at all assessments (α

= .89–.92). Summed scores were computed, and the mean across parents' standardized scores for each wave was used in analyses (mean *r* across parents = .42).

Home chaos—Both adoptive parents reported on relative chaos versus order in the home at the 4.5-year and 6-year assessments using a modified 6-item version (see Johnson, Martin, Brooks-Gunn, & Petrill, 2008) of the Confusion, Hubbub, and Order Scale (Matheny, Wachs, Ludwig, & Philips, 1995; α = .52–.64). The mean across parents' standardized total chaos scores was calculated for each of these waves (mean *r* across parents = .48).

Cumulative adversity index—A composite adversity score was calculated for each family at each assessment wave. The family was assigned a 0 if they fell in the bottom 75% and a 1 if they fell in the top 25% for each of the risk factors listed above (with the exception of social support, for which the bottom 25% indicated risk). A mean of these indicators for each wave was computed to represent cumulative adversity (see NICHD Early Child Care Research Network, 2004 and Trentacosta et al., 2008 for background and justification for this approach).

Child Cortisol

Child morning and evening saliva samples were collected with the help of adoptive parents across 3 consecutive days as part of both the 4.5-year and 6-year assessments (*M* morning time = 7:36 a.m., *SD* = 42 mins at 4.5 years; *M* = 7:33 a.m., *SD* = 43 mins at 6 years; *M* evening time = 8:12 p.m., *SD* = 53 mins at 4.5 years; *M* = 8:10 p.m., *SD* = 46 mins at 6 years). Parents were instructed to collect the samples within 30 minutes after the child awoke in the morning (wake time range 5:00–10:15 a.m.) but before breakfast, and when the child was in bed for the night (sleep time range 6:35 p.m.–12:30 a.m.). On average, morning saliva samples were collected 19 minutes after waking (*SD* = 16 mins; range 0 – 111 mins) and evening samples 12 hours, 57 minutes after waking (*SD* = 42 mins; range 11 hrs, 10 mins – 14 hrs, 28 mins). Associations among sample timing, adversity, and cortisol were tested to determine whether adversity-related differences in collection times could impact results. The only significant association (*r* = .16 for age 6 cumulative adversity and day 2 evening sample time since waking) was small in size, and sample time did not relate to the cortisol value, making it unlikely that timing differences influenced adversity-cortisol effects.

Study parents were trained in sample collection procedures in person, which involved saturating salivettes before placing them in prelabeled plastic vials. Samples were then mailed to the primary study site, at which point they were frozen and stored on site until all samples for all participants had been collected and could be mailed jointly to the analysis laboratory. Samples were stored at −5° F (−20° C) until assay using a competitive solid phase time-resolved fluorescence immunoassay (DELFIA; see Dressendörfer, Kirschbaum, Rohde, Stahl, & Strasburger, 1992) with interassay coefficients of variation (CV) 7.1%–9.0%. Samples were assayed in duplicate, and mean scores were used in analyses (*M* morning cortisol = .626 μg/dl, *SD* = .22 at 4.5 years; *M* = .501, *SD* = .19 at 6 years; *M* evening cortisol = .077 μg/dl, *SD* = .14 at 4.5 years; *M* = .081, *SD* = .13 at 6 years; *M* intraassay coefficient of variation = 6%, *SD* = 1.9 at 4.5 years; *M* = 7%, *SD* = 2.4 at 6 years). These levels are somewhat higher than those reported as normative (i.e., .30–.35 μg/dl post-waking; .05–.06 μg/dl pre-bedtime) in children of this age (see McCarthy et al., 2009; Russ et al., 2012). Cortisol scores were related to one another across days for both morning (mean *r* = .18 at 4.5 years, .23 at 6 years) and evening (mean *r* = .48 at 4.5 years, .38 at 6 years) samples, but morning and evening cortisol scores within days were unrelated (mean *r* = .02 at 4.5 years, −.04 at 6 years).

Parents recorded the exact time of saliva collection and other information that could affect cortisol measurement, such as illness, medication use, and sleep time, in a collection diary. Standard data screening procedures (e.g., identifying and eliminating extreme outlying values, checks for implausible/contradictory time recording) were used. Such screening resulted in the deletion of 1-8 cortisol values (.5%–3.7% of the total) from each sampling period due to extreme values (> 2 μg/dl), reported sampling time before reported wake time or after sleep time, or inconsistency of 30 mins or more between reported sampling time and time recorded on the saliva vial. Morning and evening cortisol values from the age 6 assessment were entered as the primary HPA activity outcome, with corresponding morning or evening values from the age 4.5 assessment entered as a covariate to test HPA axis stability (see below).

Child Problem Behavior Outcomes

Adoptive parents reported on child problem behaviors using the Child Behavior Checklist (Achenbach & Rescorla, 2000). T-scores for the broadband Internalizing and Externalizing scales at the final (6-year) assessment were selected as outcome measures (α= .85–.92). The mean across parents' reports for these scales was used in analyses (*r* across parents = .41 for internalizing, .54 for externalizing problems).

Birth Mother Control Variables

Birth mothers completed self-report questionnaires on previous (pregnancy-related) and current experiences at 3 months postpartum, and they contributed saliva samples at 48 months. The measures of interest for the current study include the following:

Prenatal adversity—Birth mothers reported on a number of prenatal and obstetric factors that could have adversely impacted their child's development using a pregnancy history calendar (adapted version of the life history calendar, Caspi et al., 1996) and a pregnancy screener. These included questions about use of alcohol, cigarettes, and illegal drugs during pregnancy, physical health problems, pregnancy complications, and perinatal events such as low birth weight. Responses were scored based on validated risk indices (e.g., McNeil et al., 1994; Kotelchuck, 1994; Williams & Ross, 2007) to derive a weighted total score.

Internalizing and externalizing symptoms—Birth mothers reported on current depressive and anxiety symptoms using the same version of the Beck Depression and Anxiety Inventories as those administered to adoptive parents (α= .91–.92). They also reported on commission of delinquent behaviors using the Elliott Social Behavior Questionnaire (Elliott & Huizinga, 1983; α = .75 for index offenses scale, α = .84 for minor offenses scale). The mean of standardized anxiety and depression scale scores represented birth mother internalizing, and the mean of standardized index and minor offense scales (log-transformed to correct for positive skew) represented birth mother externalizing.

Cortisol—Birth mothers' morning and evening cortisol levels were assayed from saliva samples collected across 3 days using the same procedures as described above for the children.

Analytic Strategy

This study aimed to clarify links from childhood adversity exposure to cortisol stability from age 4.5–6, and from cortisol stability to behavior problems at age 6. Multilevel modeling using Hierarchical Linear Modeling (HLM; Raudenbush & Bryk, 2002) was used to account for the dependent data structure in this study. This approach separates variance into within-child (i.e., repeated measures of cortisol; Level 1) and between-child (i.e., different levels of

child adversity exposure and problem behaviors; Level 2) components. Besides yielding more accurate standard errors for testing effects at each level, HLM has the benefit of allowing missing data at Level 1 while using Full Information Maximum Likelihood Estimation to arrive at model parameters. Thus, children missing partial cortisol data (n = 48–55 for each sample) were still included, but weighted less heavily, in analyses.

The Level 1 model included child cortisol (morning or evening) scores measured at age 4.5 as a within-child predictor of matched morning or evening scores at age 6. This provided a test of each child's HPA axis stability from age 4.5–6. The stability coefficient was allowed to vary across children, as was the intercept (representing predicted age 6 cortisol level).

Level 1 Model—Age 6 cortisol = β_0 + β_1 (age 4.5 cortisol) + error

Between-child predictors were added at Level 2 to address primary study questions. The first set of models included family adversity measures as predictors of cortisol levels at age 6 and stability from age 4.5–6. Degree of adversity was tested as both a prospective predictor (an intercept[3] representing the mean level from 9 months–4.5 years) and a concurrent predictor (observed level at 6 years, controlling for 9-month level). Changes in adversity were also tested as prospective predictors (deviation from the 9-month–4.5-year intercept, linear growth from 9 months–4.5 years) and as a concurrent predictor (difference score from 4.5–6 years). These models were designed to clarify paths from adversity exposure to child HPA activity profiles. Examples of the concurrent predictive models are given below:

Level 2 Model A—Relating concurrent adversity to child cortisol

$\beta_0, \beta_1 = \gamma_0 + \gamma_1$ (9-month family adversity) + γ_2 (6-year family adversity) + error

Level 2 Model B—Relating age 4.5–6 change in adversity to child cortisol

$\beta_0, \beta_1 = \gamma_0 + \gamma_1$ (6-year family adversity – 4.5-year family adversity) + error

Finally, a model testing child problem behaviors at age 6 as predictors of cortisol levels and stability was examined. This model was designed to clarify the adjustment implications of child HPA activity profiles.

Level 2 Model C—Relating concurrent child problem behaviors to child cortisol

$\beta_0, \beta_1 = \gamma_0 + \gamma_1$ (6-year internalizing) + γ_2 (6-year externalizing) + error

Results

Controls

Birth mother control measures—prenatal adversity (for adversity exposure models), internalizing and externalizing symptoms (for the child problem behavior model), and cortisol (all models)—were tested in the models reported below. Other variables that could impact child cortisol were also examined; these included child age and sex, sleep and wake times, illness, steroid medication use, and sample collection time. None of these variables was found to alter the effects reported below (i.e., estimated coefficient including the control

[3]Separate HLM models were run with adversity as the outcome measure to derive estimates of mean levels and residual variability (intercept-only model) and growth (intercept and linear slope model) from the 9-month to the 4.5-year assessment.

fell within the 95% confidence interval of the estimate without the control). Therefore, the more parsimonious models including hypothesized predictors only are reported.

Cortisol Stability and Variability

Initial models of morning and evening cortisol levels at age 6, predicted by levels at age 4.5, were fit to determine sample-wide cortisol stability and variability across children. Significant effects of age 4.5 cortisol confirmed a normative pattern of cortisol stability for both morning ($b = .69$, $p < .001$) and evening ($b = 1.26$, $p < .001$) levels. At the same time, significant between-child variability in these associations—$\chi^2(180) = 651.14$, $p < .001$ for morning; $\chi^2(182) = 2061.70$, $p < .001$ for evening—suggested greater or lesser stability for different children that could be explained by adding Level 2 predictors. All models reported below offered a significant improvement in fit over the baseline model containing no predictors, as measured by change in the deviance statistic.

Prospective Effects of Adversity on Child Cortisol

All effects of previous adversity—both degree (mean adversity from 9 months–4.5 years) and variability (residual variability and growth from 9 months–4.5 years)—were found to be nonsignificant. Additionally, effects of prenatal adversity and of prenatal × postnatal adversity were tested and found nonsignificant. These models are not discussed further.

Concurrent Effects of Adversity on Child Cortisol

Cumulative adversity—Family adversity at the 6-year assessment, controlling for the earliest recorded postnatal adversity (9-month assessment), predicted child evening cortisol levels at age 6 and stability from age 4.5 to 6 (Table 2, right panel). Higher levels of adversity were associated with lower concurrent evening cortisol and less stability over time. Change in total family adversity from age 4.5 to 6 predicted child morning cortisol levels at age 6 (Table 2, left panel). In particular, increasing adversity from age 4.5 to 6 was associated with higher morning cortisol levels at age 6.

Specific adversity dimensions—To better understand the source and nature of family adversity effects identified above, specific adversity measures were tested as predictors of child morning and evening cortisol. Parental depressive and anxiety symptoms, negative life events, and marital instability at age 6 (controlling for levels at 9 months) all related to lower and/or less stable child evening cortisol (Table 3, right panel). A model including all adversity dimensions simultaneously demonstrated that only marital instability contributed significant unique variability. Increasing home chaos from age 4.5 to 6 related to more stable (and marginally higher) child morning cortisol (Table 3, left panel), and this remained a significant predictor when all adversity dimensions were tested simultaneously.

Child Cortisol and Problem Behaviors

To put the above effects in a child adjustment context, child cortisol levels and stability were tested in relation to parent-reported child problem behaviors at age 6. Child externalizing was associated with lower, less stable evening cortisol, whereas internalizing was associated with more stable morning cortisol (Table 4).

Summary

The above models provided partial support for study hypotheses. The degree of concurrent (but not previous) adversity exposure predicted lower child evening cortisol, whereas variation in concurrent (but not previous) adversity predicted higher child morning cortisol. Contrary to hypotheses, concurrent change in adversity also predicted more stable child morning cortisol, and higher concurrent adversity predicted less stable child evening

cortisol. In line with predictions, lower child evening cortisol related to externalizing problems, and more stable child morning cortisol additionally related to internalizing problems. Finally, these effects applied to both cumulative adversity and specific adversity dimensions, and they held even when controlling for birth mother influences.

Discussion

This study demonstrated effects of concurrent family adversity on children's levels of HPA activation and stability across 18 months, offering preliminary support for calibration of the stress system during early childhood. Because adversity measures came from adoptive parents (and accounting for birth parent risk measures failed to change these effects) this research confirms that exposure to family adversity, and not simply shared genetic influences, can drive effects on child HPA function. The present findings further support distinctions between factors influencing morning versus evening cortisol, and internalizing versus externalizing problems. Implications for stress system development and future research in this area are discussed below.

Hypothesized effects of concurrent adversity exposure were supported in this study, whereas prospective effects of earlier (both prenatal and postnatal) adversity were not. This does not imply that previous experience does not play an important role in shaping HPA function, but that stability of the HPA system is likely to be more closely aligned with what the child currently experiences than with what came before. It may be that moderating effects of prenatal adversity found in previous infant studies (i.e., Laurent, Ablow, & Measelle, 2011; Sandman, Davis, & Glynn, 2012) could not be replicated because of the longer time lag and/or the difference between pre- and postnatal adversity measures in the current study. The retrospective nature of the prenatal adversity measure in this study may also have diluted its effect. Whereas earlier experiences should shape cortisol levels at the start of an observation period, it makes sense that changes during that period (here, from age 4.5 to 6) and the ultimate level of adversity at the end should determine the course of HPA activity during that time frame. Unfortunately, the current study was limited to just two longitudinal intervals for assessments of cortisol and concurrent adversity; a longer assessment window including more numerous matched measures of adversity and HPA activity would allow researchers to better evaluate the coupling of the two processes over time. Still, the present findings provide a critical first step in delineating how different aspects of adversity exposure contribute to children's diurnal HPA activity.

An acute rise in home stress appeared to stabilize high child morning cortisol, whereas the degree of stressful family circumstances in early childhood (relative to conditions during infancy) related to lower child evening cortisol. While direct comparison with ACM phenotypes must be approached with caution, given longitudinal and behavioral measurement restrictions in this study, these trajectories are at least partially congruent with ACM proposals; sudden or unpredictable increases in stress might be expected to lead to consistently higher activation via the "vigilant" phenotype, and sustained or gradually escalating stress conditions to variable lower activation via the "buffered" phenotype. Consistent with the ACM and with neurobiological findings for stress-related arousal, the former trajectory was associated with internalizing problems, suggesting excessive sensitization to negative or threat-related social cues as home chaos increased. The fact that the latter trajectory also came with negative outcomes (i.e., externalizing problems) calls into question the idea that lower HPA activity comes without some of the costs associated with the "unemotional" phenotype. Although this type is thought to arise only under extremely adverse conditions (or when genetic load is high), there may be a gradation from relatively subtle HPA hypoactivation and externalizing arising under moderate stress (as seen in the current sample) to more severe versions of these qualities under extreme stress.

(i.e., the “unemotional” phenotype proposed by the ACM). Indeed, previous research in a normative sample has demonstrated relations between HPA axis habituation to family stressors and child externalizing (Davies et al., 2007), suggesting that even relatively modest increases in child arousal thresholds may carry psychosocial costs. These ideas should be further explored in samples experiencing a range of environmental risk, from the moderate adversity observed here to more extreme forms of maltreatment.

Consistent with previous research, effects were found for both cumulative adversity as a broad influence on HPA hyper- and hypoactivity, and for specific dimensions of childhood adversity relating to each pattern. As in a previous study, psychosocial stressors rather than socioeconomic hardship predicted child cortisol (Cutuli et al., 2010). Although the SES measure used in this study likely tapped subjective financial worry rather than actual poverty, the fact that it did not exert significant effects supports a distinction between economic and more intimate interpersonal stressors in children’s lives. Home chaos related to elevated cortisol, similar to previous findings for an effect of family instability on sustained hypercortisolism across early childhood (Blair et al., 2011). By contrast, parent-specific difficulties (especially marital instability) showed inverse relations with cortisol, echoing prior work linking parent-focused adversity measures to lower child cortisol (Bush et al., 2011). It is possible that factors more immediately impacting the child’s daily experience of stability versus instability serve to raise cortisol levels, whereas parental factors indirectly impacting the child through parenting spillover more often lead to suppression. Clearly, more information is needed on mediating processes such as child perceptions of the environment and family interactions, as well as on the specificity of these influences. However, the present results validate examining both cumulative adversity and specific components in order to understand stress dysregulation.

Divergent correlates of morning and evening cortisol suggest these should be examined and interpreted separately to understand child risk for behavioral dysregulation. Consistent with previous research (e.g., Dougherty et al., 2009), morning cortisol levels constituted a risk marker for internalizing problems. Heightened stress exposure may consolidate inherited depression/anxiety risk, whereas lower stress conditions destabilize this risk indicator, allowing a more variable approach to the day. Although we are not aware of prior work specifically linking evening cortisol and externalizing problems, it is quite plausible that the lowered cortisol previously noted in externalizing disorders would be evident at the end of the day. Although low evening cortisol can be a positive sign of recovery from the day’s events, it may also signal unresponsiveness to social contingencies, and there is evidence that children’s HPA activation to school-related social stimulation relates to social competence (Gunnar et al., 1997). In the case of evening cortisol, instability was a negative (problem-related) indicator, perhaps reflecting HPA axis downward modulation in response to high levels of stress. Because children in this study tended to have higher than normal cortisol levels, we cannot say that adversity-exposed children showed “hypocortisolism” in an absolute sense. However, cortisol downregulation relative to their peers was associated with heightened externalizing in this sample, suggestive of a maladaptive cascade that could continue in later development. Again, these findings are preliminary and should be followed up with further investigation of upstream influences and downstream effects of cortisol levels measured at different points in the diurnal rhythm.

Rather than pointing to stability or change in cortisol levels as universally adaptive, these results suggest that each can signal a helpful or harmful dynamic. Based on this study alone, it is difficult to make firm conclusions about stabilizing versus destabilizing processes; however, it is interesting to note that acute change in adversity was associated with (morning) cortisol stability, whereas current degree of adversity was associated with (evening) cortisol instability. This suggests a sort of compensatory process whereby an

unstable environment gives rise to more consistent stress system activity, and a stable or gradually changing environment to more variable stress system activity. Despite the behavioral problems associated with each pattern, this may represent a larger adaptive process that calls for further investigation across a range of stress systems and over longer time periods. Similarly, we must be careful not to automatically interpret higher or lower cortisol levels as pathological; these HPA activation profiles represent appropriate evolutionary adaptations to acute versus chronically stressful conditions that are likely to promote population survival, even as they may limit an individual's ability to flourish in more advantageous conditions.

This study was limited in several respects, pointing to areas that should be addressed in future research. While innovative in examining longitudinal measures of both adversity and cortisol, the present investigation only covered a portion of early childhood and included two cortisol assessments. A wider longitudinal lens would allow tests of developmental "switch points" proposed by the ACM at the juvenile and/or adolescent transitions; indeeed, early childhood is thought to be a time of relative quiescence in HPA function (e.g., Gunnar & Donzella, 2002; Shirtcliff et al., 2012), and some of the null effects in this study may be due to the timing of assessments. More numerous cortisol measures both over time and within days could yield a better picture of HPA axis stability and coupling with adversity. For example, further controlled measures of morning cortisol would offer insight into the cortisol awakening response (CAR), which has been related previously to both adversity and adjustment. Variability in the timing of sample collection and the lack of an explicit CAR measure may have introduced noise contributing to null effects. The adoptive sample offered an important separation of genetic risk from environmental adversity effects, but it also imposed a relatively normative range of family adversity and child behavior problems. Testing similar models in high-risk rearing families might offer greater power for detecting adversity effects. Finally, the ACM posits different phenotypes involving not only diurnal levels of HPA activity, but also acute responsivity of this and other stress systems such as the sympathetic nervous system. This study was not designed to test the ACM, and more definitive support (or refutation) of its proposals will require comprehensive measurement of behavioral phenotypes, as well assessment across physiological systems and contexts.

These limitations notwithstanding, the current study adds to our understanding of paths from early childhood adversity to compromised health. Both concurrent exposure to family stress and increasing stress were shown to predict children's daily cortisol levels and stability over time, which were in turn predictive of behavior problems. These effects were separable from genetic risk effects measured in birth parents. It is hoped that these findings will focus attention on the dynamic interplay of stress exposure and physiological regulation across development in efforts to prevent behavioral maladjustment.

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Table 1

Sample Descriptives

Variable	9 months		18 months		27 months		4.5 years		6 years		Correlations Across Assessments
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	
Family Adversity Measures											
Depressive Symptoms	3.17	2.22	3.31	2.55	3.19	2.73	4.03	3.38	4.61	3.37	.45–65
Anxiety Symptoms*	3.47	2.58	2.89	2.43	2.65	2.52	4.16	3.46	33.87	6.85	.39–68
Negative Life Events	2.36	1.49			1.89	1.22	2.41	1.80	2.62	1.84	.17–.36
Social Support	3.43	.33			3.29	.43	3.36	.38	3.34	.41	.43–.63
Marital Instability	5.59	1.42	5.71	1.73	5.98	2.15	6.31	2.66	6.31	2.34	.22–.72
Financial Need	9.37	2.89	9.05	2.83	9.07	3.04	10.18	2.95	10.21	3.24	.35–.72
Home Chaos							6.48	3.07	6.18	2.83	.71
Cumulative Adversity	.28	.18	.30	.22	.28	.20	.31	.19	.27	.20	.41–.61
Child Outcome Measures											
Internalizing Problems									45.72	8.29	
Externalizing Problems									45.24	7.77	

Note. Family adversity measures represent means across adoptive mother and father reports.

*Different anxiety measure used at age 6 assessment.

Table 2
Family Cumulative Adversity Associated with Child Cortisol

	Morning Cortisol		Evening Cortisol	
Predictor	**Coefficient**	***P***	**Coefficient**	***P***
Cortisol Level, age 6				
A. Cumulative Adversity, 6 years			−.10	.007
B. Change in Cumulative Adversity, 4.5–6 years	.09	.05		
Cortisol Stability, age 4.5–6				
A. Cumulative Adversity, 6 years			−2.71	.03
B. Change in Cumulative Adversity, 4.5–6 years	.25	.12		

Note. Letters indicate model categories as outlined in the Analytic Strategy.

Table 3

Individual Adversity Factors Associated with Child Cortisol

	Morning Cortisol		Evening Cortisol	
Predictor	**Coefficient**	***P***	**Coefficient**	***P***
Cortisol Level, age 6				
A1. Parent Internalizing Symptoms, 6 years			−.02	.05
A2. Parent Negative Life Events, 6 years			−.01	.02
A3. Parent Marital Instability, 6 years			−.02	.01
B. Change in Home Chaos, 4.5–6 years	.006	.08		
Cortisol Stability, age 4.5–6				
A1. Parent Internalizing Symptoms, 6 years			−.56	.10
A2. Parent Negative Life Events, 6 years			−.47	.04
A3. Parent Marital Instability, 6 years			−.70	.02
B. Change in Home Chaos, 4.5–6 years	.02	.03		

Note. Letters indicate model categories as outlined in the Analytic Strategy. Numbers indicate separate models within a category.

Table 4
Problem Behaviors Associated with Child Cortisol

	Morning Cortisol		Evening Cortisol	
Predictor	**Coefficient**	***P***	**Coefficient**	***P***
Cortisol Level, age 6				
C. Internalizing Problems, 6 years	.002	.14	.002	.09
C. Externalizing Problems, 6 years	−.001	.47	−.002	.04
Cortisol Stability, age 4.5–6				
C. Internalizing Problems, 6 years	.01	.02	.07	.08
C. Externalizing Problems, 6 years	−.008	.10	−.08	.04

Note. Letters indicate model category as outlined in the Analytic Strategy.