HHS Public Access

Author manuscript

Dev Psychopathol. Author manuscript; available in PMC 2019 November 01.

Published in final edited form as:

Dev Psychopathol. 2019 May ; 31(2): 789–798. doi:10.1017/S0954579418000573.

Homotypic and heterotypic continuity of internalizing and externalizing symptoms from ages 3 to 12: The moderating role of diurnal cortisol

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Children who experience internalizing and externalizing symptoms in early childhood are at an increased risk for psychopathology and impaired functioning across development (Luby, Gaffrey, Tillman, April, & Belden, 2014; Mesman, Bongers, & Koot, 2001; Slemming et al., 2010). However, the course of internalizing and externalizing psychopathology can show considerable variability. Some children show homotypic continuity in their symptoms, a pattern typically referred to as stability. In contrast, other children show a pattern of heterotypic continuity, in which their presentations change or become more complex throughout development, resulting in a shift in the expression of their symptoms.

Children who show internalizing problems early in life are more likely than typical peers to exhibit anxiety and depression in adolescence and adulthood, indicating a significant degree of homotypic continuity (Roza, Hofstra, van der Ende, & Verhulst, 2003). However, some children with internalizing symptoms develop externalizing symptoms, such as conduct problems and substance abuse, demonstrating heterotypic continuity. Copeland and colleagues (2013) investigated diagnostic transitions from childhood to adolescence among over 3,000 participants drawn from multiple prospective longitudinal studies. They found that emotional disorders (i.e., depression and anxiety) in childhood predicted increased risk of both emotional and behavioral problems (e.g., oppositional defiant disorder, conduct disorder) in adolescence. Thus, they found support for both a homotypic internalizing pathway and a heterotypic pathway linking early internalizing problems to later externalizing problems.

Research has also supported homotypic pathways linking early externalizing behavior to similar problems later in life. In their longitudinal study, Copeland et al. (2013) found that behavior problems in childhood predicted behavior problems, but not emotional problems, in adolescence. However, other longitudinal studies have found support for a heterotypic pathway linking early externalizing problems to later internalizing problems. For instance, Mesman, Bongers, and Koot (2001) investigated psychopathology when children were in

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preschool to when they were 10–11 years old. They found that children with elevated externalizing symptoms in preschool were more likely to exhibit internalizing symptoms later on than those with low externalizing symptoms. Similarly, Kim-Cohen and colleagues (2003) showed that, among adults with anxiety or depression, 25 to 30% of cases were preceded by conduct disorder or oppositional defiant disorder during adolescence. These findings suggest that, like internalizing problems, externalizing problems can also follow both homotypic and heterotypic trajectories across development.

As these studies demonstrate, psychological symptoms that arise in early childhood can follow a multitude of pathways into adolescence and adulthood. These patterns have been documented in a number of studies, but we know very little about the factors that may moderate the expression of internalizing and externalizing symptoms across development (Patalay, Moulton, Goodman, & Ploubidis, 2017). Identifying such factors may allow us to more accurately predict how early childhood psychopathology will manifest over time and help better target intervention efforts to treat children's symptoms before they fully develop.

HPA Axis Functioning and Psychopathology

Stress system functioning may contribute to the developmental course of psychopathology in children. The HPA axis is involved in mounting a stress response when an individual is under threat. This system also serves important regulatory functions under non-stressed conditions: it contributes to body temperature regulation, metabolism, and immune system functioning (Tsigos & Chrousos, 2002). The hormone cortisol is an end product of the HPA axis and can be measured non-invasively via saliva. Cortisol shows a distinct diurnal pattern, with high levels upon waking, a peak approximately 30 minutes after waking, and a gradual decrease across the day, reaching a nadir in the evening (Bailey & Heitkemper, 1991; Gunnar & Donzella, 2002). HPA axis functioning can have important impacts on the neural networks underlying children's executive functioning and self-regulation (Blair, 2010). This system is also highly responsive to a child's environment. Children who experience early adversity often show dysregulated HPA axis functioning. Studies have shown that disrupted caregiving, maltreatment, and poverty contribute to a blunted diurnal cortisol pattern among children, with relatively low morning cortisol levels and relatively high evening cortisol levels (Alink, Cicchetti, Kim, & Rogosch, 2012; Bernard, Butzin-Dozier, Rittenhouse, & Dozier, 2010; Bruce, Fisher, Pears, & Levine, 2009; Dozier et al., 2006; Fisher, Gunnar, Dozier, Bruce, & Pears, 2006; Koss, Hostinar, Donzella, & Gunnar, 2014; Kuhlman, Geiss, Vargas, & Lopez-Duran, 2015; Zalewski, Lengua, Kiff, & Fisher, 2012). In some instances, early adversity is also associated with elevated cortisol. For example, children exposed to family instability and maternal depression or anxiety have been shown to have higher diurnal cortisol levels compared to low-risk peers (Goldstein et al., 2017; Koss & Gunnar, 2017; Liu et al., 2016). This demonstrates cortisol's relevance to children's self-regulation and its responsiveness to the environmental demands placed on children.

Disruptions in the daily pattern of cortisol are also associated with a range of emotional and behavioral problems in children (Shirtcliff & Essex, 2008). A blunted cortisol slope, characterized by lower than typical morning levels and higher than typical evening levels, is associated with externalizing psychopathology in children and adolescents (Alink et al.,

2008; Hawes, Brennan, & Dadds, 2009). There is also prospective evidence to suggest that a blunted pattern of cortisol may be a risk factor for the later development of externalizing problems (Fairchild, Goozen, Stollery, & Brown, 2008; Kohrt et al., 2015; McBurnett, Lahey, Rathouz, & Loeber, 2000; Popma, Doreleijers, & Jansen, 2007; Salis, Bernard, Black, Dougherty, & Klein, 2016). For example, Salis and colleagues (2016) demonstrated that a blunted cortisol slope at age 6 predicted an increase in externalizing problems from age 6 to age 9. There is less evidence investigating cortisol slope in relation to internalizing problems, but research has shown that internalizing symptoms and risk for internalizing psychopathology are generally associated with increased morning cortisol, a greater cortisol awakening response, and a high daily output of cortisol (Ellenbogen, Hodgins, Linnen, & Ostiguy, 2011; LeMoult, Ordaz, Kircanski, Singh, & Gotlib, 2015; Lok et al., 2012; Lopez-Duran, Kovacs, & George, 2009). Although there are some findings linking internalizing symptoms with a blunted cortisol slope (Doane, Mineka, Zinbarg, & Craske, 2013; Van Den Bergh & Van Calster, 2009), much of the research generally indicates a pattern of high morning cortisol as a risk factor for internalizing symptoms (Koss & Gunnar, 2017; Lopez-Duran et al., 2009).

As HPA axis functioning is involved in children's adaptation and self-regulation, it may play a role in how early internalizing and externalizing symptoms are expressed over time (Blair, 2010). However, no studies to date have investigated how cortisol patterns interact with early psychopathology to predict symptoms later in development.

The Current Study

Longitudinal patterns of psychopathology have been well characterized in the literature, but little work has sought to clarify the factors that contribute to heterotypic or homotypic continuity. Identifying these factors is critical in delineating and understanding the course of psychopathology. Given that diurnal cortisol has been shown to predict later internalizing and externalizing problems, it may modulate the expression of psychopathology over time. In the current study, we tested whether diurnal cortisol patterns moderated the course of internalizing and externalizing symptoms (i.e., patterns of homotypic or heterotypic continuity) from preschool to early adolescence. Given the previous research, we hypothesized that a blunted cortisol slope will be associated with homotypic continuity of externalizing symptoms and heterotypic continuity from early internalizing symptoms to later externalizing symptoms. In addition, we hypothesized that a relatively steep cortisol slope will be associated with homotypic continuity of internalizing symptoms and heterotypic continuity from age 3 externalizing symptoms to age 12 internalizing symptoms.

Method

Participants

Participants included 554 children (54% male) and parents. They were primarily non-Hispanic white (86%) and the majority had at least one parent with a college degree (66%).

Procedure

The current study drew on data from a longitudinal project examining the development of psychopathology in children (Olino, Klein, Dyson, Rose, & Durbin, 2010). Families with three-year-old children (M = 3.55, SD = 0.26) were recruited through commercial mailing lists. As described elsewhere (Olino et al., 2010), the demographic characteristics of the sample were similar to those of the community from which it was recruited. 554 families completed questionnaires assessing child internalizing and externalizing symptoms when children were about three years old. The majority of respondents were mothers (n= 549, 99%), but father report was used when mother report was not available (n=5, 1%). Of these 554, 387 families went on to participate in the saliva data collection when children were approximately nine years old (M = 9.29, SD = 0.42). Three years later, when children were 12 years old (M = 12.75, SD = 0.50), 406 parents again reported on their child's psychological functioning. 332 families completed all of the three study components. There were no differences in child sex, race, parental education, age 3 internalizing symptoms, or age 3 externalizing symptoms between those who completed all three study components and those who did not. Full information maximum likelihood was used in analyses to account for missing data. Thus, the analytic sample includes 554 participants.

Measures

Cortisol.—When children were 9 years old, they collected saliva samples three times per day over three consecutive days. Parents were asked to assist their children in taking saliva samples right after they woke up in the morning, 30 minutes after waking up, and 30 minutes before going to bed. The waking and bedtime samples were used in this analysis to capture diurnal slope (i.e., the wake-up level to the evening nadir in cortisol). Children were asked to passively drool into a polypropylene tube using a straw, then label each tube with the date and time. Parents instructed children not to eat or drink for 30 minutes before each sample. After three days, samples were either mailed back to the lab or retrieved by research assistants. Samples were stored at −20°C before being sent to Trier, Germany for cortisol assay. Samples were assayed in duplicate using a time-resolved immunoassay with fluorometric detection (DELFIA).

Of the three days of waking samples, 91% of participants provided all three samples, 5.2% of participants provided two samples, and 0.3% of participants provided one sample. Of three days of bedtime samples, 86.0% provided all three samples, 8.8% provided two samples, and 1.6% provided one sample. In total, there were 1,097 morning and 1,073 evening samples for 387 participants. We define sample compliance as morning samples taken within 15 minutes of wake-up time and evening samples taken within an hour of bedtime. Using these criteria, 85.8 % of participants were compliant with all morning samples, 10% were compliant with 2 morning samples, 2.4% were compliant with 1 sample, and 1.8% were not compliant with any morning samples. For evening samples, 90.7% of participants were compliant with all samples, 6.1% were compliant with 2 samples, 1.6% were compliant with one sample, and 1.6% were compliant with no samples. Two cortisol samples were removed because they were physiologically improbable. Thirteen samples were excluded due to medication use. In addition, any waking sample that was taken more than 15 minutes after waking time, as determined by self-report, was excluded. This resulted

in a total of 102 waking samples being excluded across the three study days. Any evening sample that was taken more than an hour before self-reported bed time was excluded, resulting in 44 excluded samples. Finally, outlying cortisol values (n=3) were winsorized to three standard deviations above the mean. In the final analysis, 346 children provided at least one saliva sample. Intra-assay coefficients of variation (CVs) were between 4.0% and 6.7%, and inter-assay CVs ranged from 7.1% to 9.0%.

Child internalizing and externalizing symptoms.—Mothers reported on children's psychological symptoms using the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2000). Mothers reported on the CBCL 1 ½ - 5 when children were three years old and the CBCL 6–18 when children were 12 years old. On each questionnaire, parents evaluate the severity of internalizing and externalizing symptoms using a scale from 0 (never true) to 3 (very true or often true). Coefficient alphas for the internalizing scale were .84 (36 items) and .87 (32 items) at ages 3 and 12, respectively. Coefficient alphas for the externalizing scale were .91 (24 items) and .88 (33 items) at ages 3 and 12, respectively.

Data Analysis

Data were analyzed using Mplus version 7 (Muthén & Muthén, 2013). We utilized a latent change model to estimate cortisol slope, following procedures used in previous studies (Bernard, Peloso, Laurenceau, Zhang, & Dozier, 2015; Kertes, Gunnar, Madsen, & Long, 2008). We created latent factors for wake-up and evening cortisol using the daily values as indicators. Then, cortisol slope was modeled as a latent difference score between evening and morning samples (i.e., Bedtime – Wake-up). In this model, more negative values indicate a steeper slope across the day, whereas more positive values indicate a blunted slope.

Studies have shown that the latent change models allow for more reliable estimates of change compared to simple difference scores (Burt & Obradovi, 2012; King et al., 2006; McArdle, 2009). By creating latent factors out of individual cortisol indicators, we parse out observed scores from error variance, which allows the change score to account for measurement error and produce less biased estimates (Burt & Obradovi, 2012). The model was estimated using full information maximum likelihood (FIML) estimation with standard errors approximated by first-order derivatives. FIML utilizes all available information to estimate parameters in models with missing data (Enders & Bandalos, 2001). This method has been shown to be a reliable way to account for missing data in latent variable interaction models (Cham, Reshetnyak, Rosenfeld, & Breitbart, 2017).

The main question of this project surrounds the continuity of psychopathology over time, and whether cortisol alters the strength or direction of the relationship between age 3 and age 12 symptoms. Thus, we ran moderation models testing the interactive effects of cortisol and preschool psychopathology on adolescent psychopathology. We ran a series of multiple regressions with the interaction between preschool psychopathology (using observed variables) and age 9 cortisol slope (using latent change scores) predicting internalizing and externalizing symptoms at age 12. There were four models in total: (1) internalizing homotypic pathway; (2) internalizing heterotypic pathway; (3) externalizing homotypic

pathway; and (4) externalizing heterotypic pathway. In order to account for the co-occurrence of psychological symptoms, all models controlled for concurrent internalizing or externalizing problems at ages 3 and 12 (see Figure 1 for a conceptual diagram of the latent difference model using the internalizing homotypic pathway as an example). Finally, to account for cortisol sample timing, we included the difference between each sample time and wake time as statistical covariates in each model. Additional analyses using CBCL subscales are presented in Appendix A[1].

Results

Descriptive statistics and bivariate correlations of the observed study variables are presented in Table 1. Morning cortisol had a mean of 7.86 nmol/l (SD = 3.38) and evening cortisol had a mean of 0.86 nmol/l (SD = 0.92). The majority of children were in the normative range on the CBCL at both ages: 9.9% and 11.4% of children were in the clinical or borderline clinical range for age 3 internalizing and externalizing symptoms, respectively; 10.1% and 9.3% were in the clinical or borderline clinical range for age 12 internalizing and externalizing symptoms, respectively. Age 3 and age 12 internalizing and externalizing symptoms were significantly intercorrelated. Notably, neither age 3 nor age 12 internalizing and externalizing symptoms were correlated with observed age 9 cortisol slope. Associations of demographic characteristics, including child sex, parental education, race, and pubertal status at ages 9 and 12 (Petersen, Crockett, Richards, & Boxer, 1988) with study variables were examined to consider the inclusion of additional covariates. Parental education was negatively correlated with age 3 internalizing symptoms, so it was included as a covariate in all models.

Internalizing symptoms at age 3

Homotypic model: internalizing at age 3 predicting internalizing at age 12.— Age 3 internalizing symptoms and age 9 cortisol slope were negatively associated with age 12 internalizing symptoms. However, these main effects were qualified by a significant interaction between age 3 internalizing symptoms and age 9 cortisol slope in predicting age 12 internalizing symptoms (B = −0.36, p <.001, see Table 2), suggesting that cortisol slope moderated the continuity of internalizing symptoms over time. This interaction yielded an R^2 value of 0.1029, meaning it explained 10.29% of the variance in age 12 internalizing problems. To probe the interaction, simple slopes were tested. For children with a relatively steep cortisol slope (defined as 1.5 standard deviations below the mean), higher internalizing symptoms at age 3 predicted higher age 12 internalizing symptoms (B = 0.57, p <.001, see Figure 2). However, for children with a blunted slope (defined as 1.5 standard deviations above the mean), greater internalizing problems at age 3 did not predict internalizing

[1]Analyses using other cortisol indicators (including waking alone, evening alone and the cortisol awakening response). There were no significant interactions for the internalizing homotypic and externalizing heterotypic models. In the externalizing homotypic model, both low morning cortisol (B= −.22, p<.05) and high evening cortisol (B=.25, p<.05) predicted higher externalizing symptoms at age 12 in the presence of high externalizing symptoms at age 3. Similarly, in the internalizing heterotypic model, low morning cortisol (B= −.14, p<.05) and high evening cortisol (B=.21, p<.05) predicted higher externalizing symptoms at age 12 in the presence of high internalizing symptoms at age 3. There were no significant interactions involving the cortisol awakening response. Thus, the effects are driven entirely by diurnal cortisol rhythm and are not replicated using another cortisol indicator.

problems at age 12 (B = −0.39, p >.05). This model supports a pattern of homotypic continuity for early internalizing symptoms in the presence of a steep cortisol slope.

Heterotypic model: internalizing at age 3 predicting externalizing at age 12.— There were main effects of age 3 internalizing symptoms and age 9 cortisol slope on age 12 externalizing symptoms. However, they were qualified by an interaction between cortisol slope and age 3 internalizing symptoms in predicting externalizing symptoms at age 12 (B =. 42, p <.001, see Table 2). This interaction explained 6.68% of the variance in age 12 externalizing problems. Simple slopes analyses showed that, among children with a blunted cortisol slope, higher internalizing symptoms at age 3 predicted higher externalizing symptoms at age 12 (B = 0.53, p <.01, see Figure 2). Among children with a relatively steep cortisol slope, higher internalizing symptoms at age 3 predicted *lower* externalizing problems at age 12 (B = −.60, p <.01). These results support a pattern of heterotypic continuity for early internalizing symptoms in the presence of a blunted cortisol slope, as well as significantly less heterotypic continuity than expected in the presence of steep cortisol slope.

Externalizing symptoms at age 3

Homotypic model: externalizing at age 3 predicting externalizing at age 12.— There were main effects of age 3 externalizing symptoms and age 9 cortisol slope on age 12 externalizing symptoms. However, these effects were qualified by a significant interaction between age 3 externalizing symptoms and cortisol slope in predicting externalizing symptoms at age 12 (B = 0.48, p <.001, see Table 3). This interaction explained 4.41% of the variance in age 12 externalizing problems. Simple slopes analysis showed that for children with a blunted cortisol slope, higher externalizing problems at age 3 predicted higher externalizing problems at age 12 (B = 0.90, p <.001, see Figure 3). For children with a steep cortisol slope, there was no effect of early externalizing problems on age 12 externalizing problems (B = −0.41, p >.05). Overall, these results support a pattern of homotypic continuity for externalizing symptoms in the presence of a blunted cortisol slope.

Heterotypic model: externalizing at age 3 predicting internalizing at age 12.— Age 3 externalizing symptoms and age 9 cortisol slope were negatively associated with later internalizing problems. These effects were qualified by a significant interaction between age 3 externalizing symptoms and age 9 cortisol slope in predicting age 12 internalizing problems (B = −0.38, p <.001, see Table 3). This interaction explained 5.51% of the variance in age 12 internalizing problems. For children with a relatively steep slope, higher externalizing problems at age 3 predicted higher internalizing problems at age 12 (B = 0.49, p <.05, see Figure 3). For children with a blunted slope, higher externalizing symptoms at age 3 predicted *lower* internalizing problems at age 12 (B = −0.53, p <.05). This model supports a pattern of heterotypic continuity for early externalizing symptoms for children with a steep cortisol slope, as well as a lower chance of heterotypic continuity for children with a blunted cortisol slope.

Discussion

In this study, we examined whether patterns of diurnal cortisol moderated associations between internalizing and externalizing symptoms from early childhood to early adolescence. Despite the frequency of heterotypic continuity between internalizing and externalizing disorders, little research has identified predictors of this kind of heterotypic continuity (Patalay et al., 2017). Overall, results suggest that internalizing problems show homotypic continuity in the presence of a steep cortisol slope and heterotypic continuity (i.e., early internalizing problems predicting later externalizing problems) in the context of a blunted cortisol slope. In addition, children who have early internalizing symptoms and a steep cortisol slope show fewer externalizing symptoms at age 12. Externalizing symptoms show homotypic continuity in the presence of a blunted cortisol slope and heterotypic continuity (i.e., early externalizing problems predicting later internalizing problems) in the presence of a steep cortisol slope. Children with high age 3 externalizing symptoms and a blunted cortisol slope also show fewer internalizing problems at age 12.

These results align with some previous work examining cortisol patterns and psychopathology in youth. In particular, past research has shown that a blunted cortisol slope prospectively predicts externalizing problems in children (Kohrt et al., 2015; Salis et al., 2016). In the present study, we found that a blunted slope interacted with age 3 internalizing and externalizing symptoms to predict higher externalizing symptoms at age 12. Blunted slope also predicted decreased age 12 internalizing problems in the presence of early externalizing problems. By contrast, children who had a steep cortisol slope or low symptom levels at age 3 did not show increased externalizing problems at age 12.

Many studies have investigated the relationship between various cortisol indices (e.g., morning cortisol, cortisol awakening response, total cortisol output) and internalizing problems, but few have utilized diurnal slope as a metric for cortisol regulation. The current study demonstrated a link between a relatively steep diurnal slope and internalizing problems in the presence of early internalizing and externalizing symptoms. This study also showed that a relatively steep slope predicted fewer externalizing problems at age 12 when combined with high internalizing problems at age 3. This aligns with previous work showing that high morning cortisol predicts the onset of internalizing psychopathology (Harris et al., 2000; Goodyer et al., 2000). However, this contrasts with some previous work demonstrating a link between blunted cortisol slope and the onset of internalizing problems (Doane et al., 2013; Van Den Bergh & Van Calster, 2009). This may be because other studies did not account for the interaction between cortisol and early symptoms when predicting the onset of anxiety and depression or control for prior or co-occurring externalizing problems.

Our results suggest that stress system regulation plays a role in moderating homotypic and heterotypic patterns of psychopathology from preschool to early adolescence. Children's physiological regulation may play a role in the development and course of their psychological symptoms over time. Children with a blunted diurnal rhythm may have a general dampening of the HPA axis, or hypocortisolism, which puts them at risk for externalizing psychopathology (Kohrt et al., 2015; Koss, Mliner, Donzella, & Gunnar, 2016; van Goozen et al., 1998). In contrast, a cortisol slope that is steeper than normal may be

reflective of a system that is more primed to react to stressful experiences, which may put children at higher risk for internalizing problems (Koss & Gunnar, 2017; Lopez-Duran et al., 2009). However, given that this study examined diurnal cortisol regulation and not reactivity, we are limited in our ability to draw conclusions about psychopathology and the acute stress responsivity functions of the HPA axis. In general, the mechanisms linking cortisol regulation and psychopathology are not well understood and warrant further research.

Notably, cortisol slope was not correlated with internalizing or externalizing symptoms at either time point, indicating that there are no direct effects in either direction (i.e., early childhood symptoms directly predicting middle childhood cortisol or middle childhood cortisol directly predicting symptoms in early adolescence). Thus, at least in this sample, cortisol was independent of early symptoms, but appeared to shape the patterns of symptoms from early childhood to early adolescence. Interestingly, early internalizing and externalizing symptoms interacted with cortisol in similar ways to predict later psychopathology; that is, steep slope predicted internalizing problems and blunted slope predicted externalizing problems in the presence of early symptoms, regardless of the *type* of early symptom. In addition, a blunted slope predicted lower internalizing problems and a steep slope predicted lower externalizing problems in the presence of high age 3 externalizing and internalizing problems, respectively. This suggests that much of the variance in early symptomatology may reflect a general vulnerability to psychopathology (Lahey, Krueger, Rathouz, Waldman, & Zald, 2017), as opposed to liabilities to specific disorders. Stress system regulation may then serve as a more specific risk factor that modulates the development of internalizing or externalizing symptoms over time (Beauchaine & McNulty, 2013).

It should be noted that environmental moderators of cortisol activity may play a role in the effects demonstrated in this study. For instance, factors such as parenting, child maltreatment, socioeconomic status, and maternal depression have been shown to influence diurnal cortisol activity and psychopathology in children (Cicchetti & Rogosch, 2001; Dozier et al., 2006; Gunnar & Vazquez, 2001; LeMoult et al., 2015; Zalewski et al., 2012). It could be that these environmental predictors influence internalizing and externalizing symptoms through their effects on stress system regulation (Bernard, Zwerling, & Dozier, 2015; Koss & Gunnar, 2017; Koss et al., 2016). Alternatively, cortisol could serve a moderating role in this relationship, such that aberrant stress system activity places youth at higher risk for psychological symptoms in the presence of some forms of adversity (Badanes, Watamura, & Hankin, 2011; Halligan, Herbert, Goodyer, & Murray, 2007; Rudolph, Troop-Gordon, & Granger, 2011). Given the close relationship between HPA axis functioning and environment, cortisol itself may also be an index of environmental stress, rather than a moderator or mediator of this relationship. Generally, stress system regulation, environmental factors, and psychopathology demonstrate complex relationships that should be explored in future research on the continuity of emotional and behavioral problems over time.

This study had several strengths, including a fairly large, community-based sample and a longitudinal design. However, there were also some limitations that should be considered when interpreting the results of this study. During cortisol data collection, we relied on

parent self-report for the timing of saliva samples. In the future, the use of electronic monitoring devices (e.g., actigraphy and smart caps) would allow for a more objective measure of participant noncompliance in sample timing. In addition, while a community sample allows for greater generalization, it may not be as readily applicable to children with clinical levels of internalizing or externalizing problems. Indeed, few children in the current sample showed clinical or borderline clinical levels of internalizing or externalizing problems according to the CBCL. Thus, future work should attempt to replicate these findings in a clinical sample. Future work should also investigate these effects in a more ethnically and socioeconomically diverse sample, given the research demonstrating the effects of ethnic minority status, poverty, and early adversity on psychopathology and stress system regulation (DeSantis et al., 2007; Evans & Kim, 2013; Koss et al., 2014). In this study, we focused on shifts among broad classifications of symptom expression (i.e., internalizing symptoms to externalizing symptoms and vice versa). Future studies should examine factors that influence heterotypic continuity within these broad dimensions. In addition, by covarying externalizing symptoms in analyses of internalizing symptoms, and vice versa, we focused on relatively “pure” expressions of each dimension. As many youth have concurrent internalizing and externalizing symptoms, it would be useful to extend our work to examine determinants of “uncomplicated” versus comorbid symptom patterns.

This study focused on diurnal cortisol slope as a marker of stress system regulation. There are several systems involved in stress responsivity and daily regulation, including the Sympathetic Nervous System (SNS). The SNS has links with HPA axis functioning and psychological adjustment in children (El-Sheikh, Erath, Buckhalt, Granger, & Mize, 2008; Hastings et al., 2011; Schumacher, Kirschbaum, Fydrich, & Ströhle, 2013). Sex hormones may also interact with cortisol to predict psychopathology (Tackett et al., 2015; Turan, Tackett, Lechtrek, & Browning, 2015). In order to more fully understand the links between physiological stress systems and psychopathology, it is imperative that future researchers account for the role of multiple systems, and their interaction, in children’s behavioral and emotional adjustment (Bauer, Quas, & Boyce, 2002; Koss & Gunnar, 2017). In addition, due to the design of the larger project, we examined cortisol at a single time point and psychopathology at two time points in this study. Future research should assess both cortisol and psychopathology at more time points to explore these effects across developmental periods and to examine within-person change over time. In addition, as most children were in middle or junior high school at the age 12 assessment, and had different teachers for each class, this study does not include teacher report of children’s internalizing and externalizing symptoms. This limits our ability to draw conclusions about children’s behavior within the school environment. Finally, it is unclear if these relationships will persist into later adolescence and adulthood. Future studies should explore the interactions among cortisol and psychopathology in predicting psychological functioning beyond childhood and early adolescence. Overall, however, the results of this study shed light on the factors that influence homotypic and heterotypic continuity in psychological symptoms from early childhood to early adolescence, and point to the utility of examining cortisol to predict trajectories of early childhood psychopathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by National Institute of Mental Health grant R01 MH069942 (Klein) and National Science Foundation Graduate Research Fellowship 1315232 (Frost).

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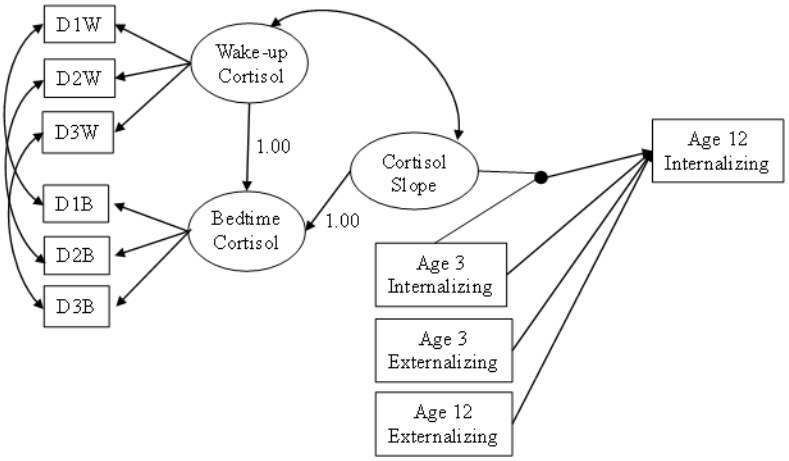

Figure 1.

Conceptual diagram illustrating the latent difference model with the internalizing homotypic model as an example.

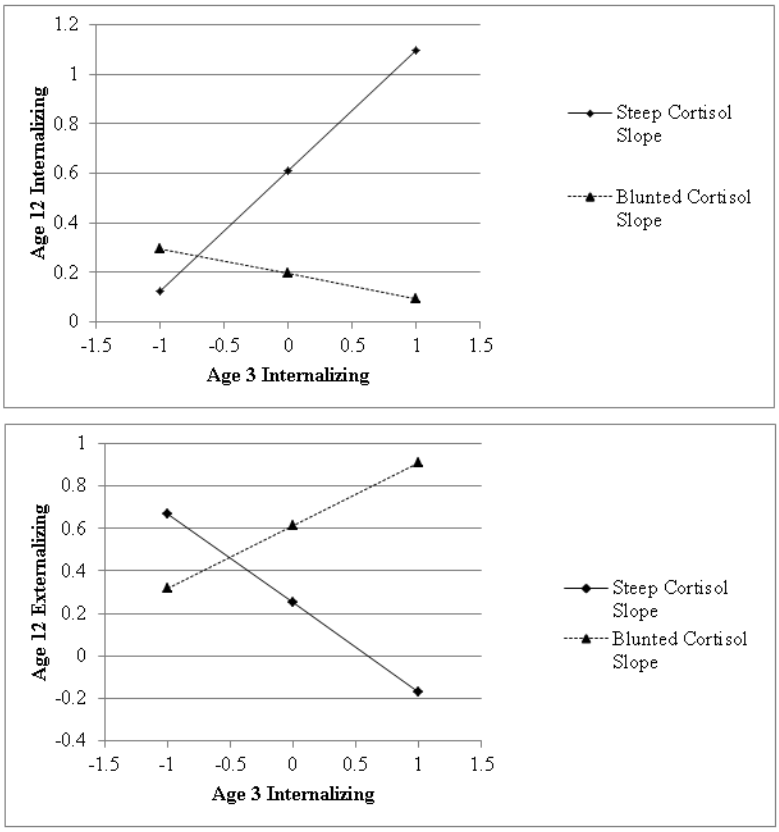

Figure 2.

Interactions between age 9 cortisol and age 3 internalizing symptoms in predicting age 12 internalizing (top) and externalizing (bottom) symptoms. Steep slope is defined as 1.5 standard deviations below the mean and blunted slope is 1.5 standard deviations above the mean.

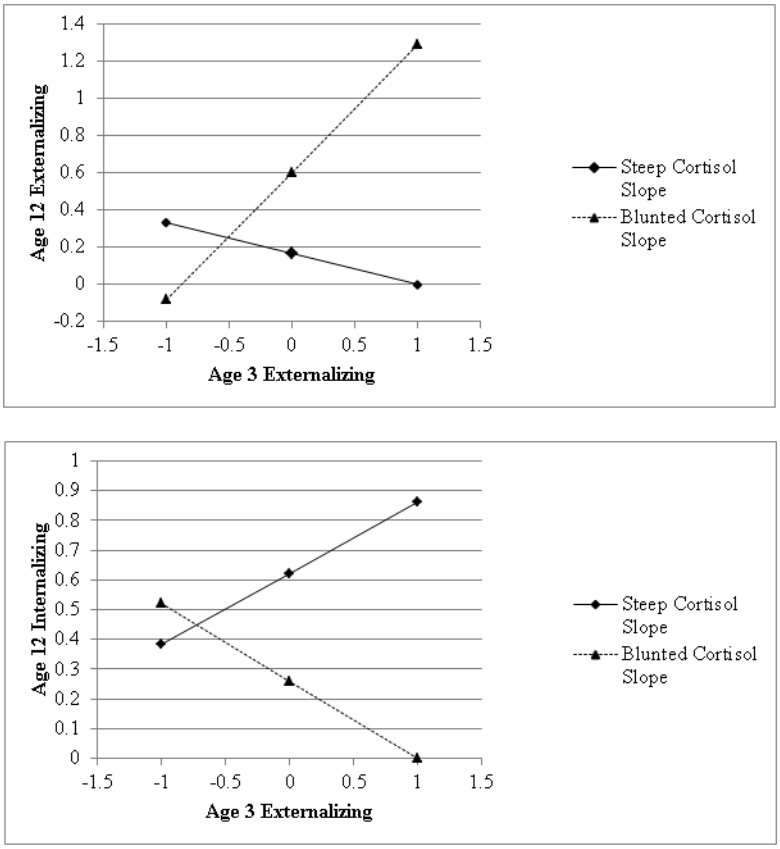

Figure 3.

Interactions between age 9 cortisol and age 3 externalizing symptoms in predicting age 12 externalizing (top) and internalizing (bottom) symptoms. Steep slope is defined as 1.5 standard deviations below the mean and blunted slope is 1.5 standard deviations above the mean.

Table 1.

Descriptive Statistics and Bivariate Correlations of Observed Study Variables

	1	2	3	4	5	6	7	8	9	10
1. Age 3 Internalizing	—	.57***	.33***	.31***	.00	-.02	-.01	-.13**	-.06	.01
2. Age 3 Externalizing		—	.32***	.46***	.02	-.01	.02	-.11	-.04	.04
3. Age 12 Internalizing			—	.54***	.01	.01	.01	-.05	-.01	-.01
4. Age 12 Externalizing				—	.01	-.07	.01	-.06	.01	-.00
5. Age 9 Average Cortisol Slope					—	-.01	-.07	-.08	-.01	-.08
6. Female						—	.01	-.06	.48***	.48***
7. Race (Caucasian)							—	.06	-.07	-.07
8. Parental Education[a]								—	-.08	-.08
9. Pubertal Status Age 9[b]									—	.45***
10. Pubertal Status Age 12[b]										—
M (SD)	9.19(6.37)	12.85(7.61)	3.49(4.78)	3.38(4.68)	-7.40(4.59)	.46	.87	.71	7.08(1.78)	11.02(3.16)
Range	0–38.32	0–39.27	0–26	0–27	-46.85–1.58	0–1	0–1	0–1	5–14	5–18

* $p < .05$

** $p < .01$

*** $p < .001$

[a] Parental education is dummy coded variable representing whether either parent completed college at the time of the age 3 assessment.

[b] Pubertal development is measured using the Pubertal Development Scale (Petersen et al., 1988).

Table 2.

Multiple Regressions with Age 3 Internalizing Symptoms and Age 9 Cortisol Predicting Internalizing and Externalizing Symptoms at Age 12

Effect	B		95% CI	
		SE	Lower	Upper
Model 1: Homotypic Model: Outcome = Age 12 Internalizing Symptoms				
Parental Education	0.05	0.12	-0.15	0.26
Age 3 Internalizing	-0.94**	0.32	-1.46	-0.41
Age 3 Externalizing	0.02	0.07	-0.09	0.13
Age 12 Externalizing	0.49***	0.05	0.40	0.58
Age 9 Cortisol Slope	-0.26**	0.08	-0.40	-0.12
Age 9 Slope x Age 3 Internalizing	-0.36***	0.09	-0.51	-0.21
Model 2: Heterotypic Model: Outcome = Age 12 Externalizing Symptoms				
Parental Education	-0.05	0.10	-0.27	0.11
Age 3 Internalizing	1.33***	0.23	0.95	1.71
Age 3 Externalizing	0.28***	0.06	0.17	0.38
Age 12 Internalizing	0.43***	0.04	0.37	0.50
Age 9 Cortisol Slope	0.24**	0.08	0.10	0.38
Age 9 Slope x Age 3 Internalizing	0.42***	0.07	0.30	0.54

* $p < .05$

** $p < .01$

*** $p < .001$

Note. Each model includes the difference between each sample time and wake time as statistical covariates.

Table 3.

Multiple Regressions with Age 3 Externalizing Symptoms and Age 9 Cortisol Predicting Externalizing and Internalizing Symptoms at Age 12

Effect	B	*SE*	95% CI	
			Lower	Upper
Model 3: Homotypic Model: Outcome = Age 12 Externalizing Symptoms				
Parental Education	-0.04	0.09	-0.18	0.11
Age 3 Internalizing	-0.08	0.06	-0.18	0.03
Age 3 Externalizing	2.06***	0.28	1.60	2.53
Age 12 Internalizing	0.42***	0.04	0.36	0.48
Age 9 Cortisol Slope	0.28***	0.07	0.18	0.39
Age 9 Slope x Age 3 Externalizing	0.48***	0.07	0.37	0.59
Model 4: Heterotypic Model: Outcome = Age 12 Internalizing Symptoms				
Parental Education	-0.04	0.12	-0.23	0.16
Age 3 Internalizing	0.23***	0.07	0.11	0.34
Age 3 Externalizing	-1.28***	0.32	-1.79	-0.76
Age 12 Externalizing	0.50***	0.05	0.42	0.59
Age 9 Cortisol Slope	-0.32*	0.09	-0.46	-0.18
Age 9 Slope x Age 3 Externalizing	-0.38***	0.08	-0.51	-0.25

* $p < .05$

** $p < .01$

*** $p < .001$

Note. Each model includes the difference between each sample time and wake time as statistical covariates.