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Authors

Bendezú, Jason José
Howland, Mariann
Thai, Michelle
et al.

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Adolescent cortisol and DHEA responses to stress as prospective predictors of emotional and behavioral difficulties: A person-centered approach

Jason José Bendezú[a], **Mariann Howland**[a,b], **Michelle Thai**[b], **Kristine Marceau**[c], **Elizabeth A. Shirtcliff**[d], **Paul D. Hastings**[e], **Carolyn Zahn-Waxler**[f], **Bonnie Klimes-Dougan**[b]

[a]The Institute of Child Development, University of Minnesota

[b]Department of Psychology, University of Minnesota

[c]Department of Human Development and Family Studies, Purdue University

[d]Department of Psychology, Iowa State University

[e]Department of Psychology, University of California – Davis

[f]The Center for Healthy Minds, University of Wisconsin - Madison

Abstract

Background.—Well-orchestrated cortisol and DHEA stress responsivity is thought to support efficacious stressor management (i.e., coping) and reduce risk for psychopathology during adolescence. Evidence of these relations, however, is lacking empirically. This longitudinal investigation had three aims: 1) to identify within-adolescent profiles of joint cortisol-DHEA responsivity, 2) examine profiles as prospective predictors of adolescents' later emotional and behavioral difficulties, and 3) examine whether distraction coping helped buffer such prospective risk in each profile.

Method.—At Time 1, boys (n=110) and girls (n=105) between 11 and 16 years of age with varied levels of risk for psychopathology completed a lab-based socio-evaluative stressor and questionnaires (e.g., coping, internalizing and externalizing problems). Emotional and behavioral adjustment was assessed again at Time 2 (2 years later).

Results.—Multi-trajectory modeling of adolescents' cortisol and DHEA within the context of the stressor revealed three groups: Normative (n=107; 49.8%), Hyperresponsive (n=64; 29.8%), Hyporesponsive (n=44; 20.5%). Relative to Normative, Hyperresponsive and Hyporesponsive adolescents were more and less advanced in pubertal status, respectively. Hyperresponsive adolescents, but not Hyporesponsive, reported greater emotional and behavioral problems at Time 2, relative to Normative adolescents. Links between distraction coping and Time 2 adjustment varied across the groups. Specifically, distraction coping was associated with fewer Time 2 emotional and behavioral problems for Normative adolescents. However, the converse was true

Corresponding author. Jason José Bendezú, Institute of Child Development, 206A ChDev, 51 E River Parkway, Minneapolis, MN 55455, (786) 390-8400, bende369@umn.edu.

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for Hyporesponsive adolescents, with distraction associated with greater Time 2 emotional and behavioral problems. Distraction was not associated with Time 2 emotional and behavioral problems for Hyperresponsive adolescents (i.e., elevated levels irrespective of distraction coping utilization).

Conclusion.—Our results strengthen inference about the role neuroendocrine coordination plays in risk for psychopathology. Findings also help to clarify inconsistent distraction coping–psychopathology linkages, illustrating different patterns of cortisol-DHEA responsivity that support as well as thwart the use of this potentially efficacious strategy.

Keywords

cortisol; DHEA; coping; internalizing; externalizing; adolescence

1. Introduction

Coping is critical to healthy adolescent development and has the potential to buffer against the development of psychopathology (Compas et al., 2017). However, little is known about multi-hormone stress response function that supports adolescent coping to this end (cf. Wemm et al., 2010). Prevailing theory points to well-organized hypothalamic-pituitary-adrenal (HPA) axis function vis-à-vis coordinated cortisol and dehydroepiandrosterone (DHEA) activity as critical to executive processes (e.g., attentional control, working memory; Byrne et al., 2017; Shields et al., 2016) that support sophisticated ways of managing stressors (Compas, 2009). However, whether well-coordinated cortisol–DHEA activity, specifically, supports such potentially efficacious coping (i.e., skills capable of buffering risk for psychopathology) is not yet known. Such research may help to clarify inconsistent buffering effects of specific strategies (e.g., distraction) on the emergence of psychopathology (Compas et al. 2017). Multi-hormone HPA responsivity and its interface with coping may be particularly important to examine during adolescence, as this period is characterized by HPA reorganization (Spear, 2009), development of executive capacities that carry complex coping (Zimmer-Gembeck & Skinner, 2016), and elevated rates of stress-related psychopathology (Zahn-Waxler et al., 2008). This person-centered study examined cortisol–DHEA responsivity patterns, longitudinal links to emotional and behavioral problems, and distraction coping-based individual differences therein in adolescents at varied risk for psychopathology.

1.1 Underlying Pathways and Risk for Psychopathology

When faced with a stressor, well-orchestrated HPA function marshals biological resources needed to effectively take action (Shirtcliff et al., 2014). Cortisol and DHEA are hormonal end products of HPA activation whose countervailing effects in the face of challenge support efficacious stressor management (Kamin & Kertes, 2017). DHEA opposes the effects of cortisol (i.e., modulates cortisol's physiologic potency; Pinto et al., 2015), permitting cortisol-mediated glucose mobilization to enervate neurobiological circuits and systems necessary for coping at a level commensurate with that required of the stressor. By antagonizing the effects of cortisol, DHEA supports HPA-mediated communication with higher-order brain regions (e.g., prefrontal cortex; Shansky & Lipps, 2013) and, thus,

recruitment of executive processes (e.g., attentional deployment, working memory) for coping skill utilization (Compas, 2009). Thus, well-coordinated cortisol–DHEA responsivity may reflect stressor-proportional neuroendocrine activity capable of supporting executive processes that undergird efficacious coping.

Conversely, poorly-coordinated cortisol–DHEA responsivity may reflect stressor disproportional arousal that interferes with efficacious coping and signals risk for psychopathology (Chen et al., 2015). When unopposed by DHEA, cortisol responses may be resultantly in excess of that warranted by a stressor and contribute to the emergence of symptomatic functioning (Cicchetti et al., 2015; Goodyer et al., 2001). Poorly modulated cortisol activity (e.g., hypercortisolemia) is known to have neurotoxic effects on higher-order brain regions (e.g., prelimbic and infralimbic medial prefrontal cortex; Shansky & Lipps, 2013). Thus, disproportional cortisol elevations may contribute to such risk by noxiously affecting neurobiological substrates that support coping and, thus, constrain efficacious strategy use.

Distraction is one potentially efficacious strategy that may be either supported or constrained by adolescent cortisol–DHEA responsivity. Distraction involves limiting the tendency to dwell on a stressor by purposefully shifting and effortfully refocusing attention towards productive (e.g., concentrating on work) or soothing (e.g., an enjoyed hobby) activities (Compas, 2009). Efficacious distraction capitalizes on cognitive processes (e.g., attentional control, working memory) that are enervated by well-coordinated HPA activity (Byrne et al., 2017; Shields et al., 2016). Thus, adolescents with cortisol–DHEA responsivity reflective of executive resource supportive (e.g., proportional) HPA function may be well-poised to reap the benefits of distraction while those with patterns reflective of executive resource challenging (e.g., excessive, inadequate) HPA function may be ill-equipped to do so.

1.2 Methodological and Developmental Considerations

Though these initial findings show the potential of considering multi-hormone activity, this literature could be advanced in several ways. Methodologically, studies have modeled the preferential production of cortisol to DHEA with variable-centered modalities (e.g., cortisol/DHEA ratio; Sollberger & Ehlert, 2015), which are limited in their ability to illustrate qualitatively diverse within-person patterns of multi-hormone function. Person-centered methods may be useful in this regard (Quas et al., 2014). Still further, although theory implicates net glucocorticoid *response* function in normative as well as atypical adolescent development (Chen et al., 2015; Shirtcliff et al., 2014), studies often use *basal* indices (e.g., pre-stressor levels, daily averages) to quantify cortisol–DHEA relative activity. Person-centered methods that model both basal arousal and reactivity across cortisol and DHEA may extend the knowledge base.

By also attending to adolescent developmental factors, person-centered, multi-hormone studies of efficacious coping may help to clarify inconsistent buffering effects of specific skills (e.g., distraction) on psychosocial outcomes in the extant literature (Compas et al., 2017). One postulation regarding this inconsistency that has received little empirical attention is that the association between certain strategies and psychopathology changes across the adolescent transition. Pubertal development, one hallmark feature of this

transition, may be a critical factor in this regard. That is, puberty is associated with increases in neuroendocrine reactivity (Byrne et al., 2017; Gunnar et al., 2009) that support the effectiveness of coping skill utilization in the face of stressors (Zimmer-Gembeck & Skinner, 2016). Thus, it is possible that distraction may be one such coping skill that works differently (e.g., buffer against, have no effect, or exacerbate psychopathology) for different adolescents with different puberty-associated cortisol–DHEA response function. Person-centered, multi-hormone studies examining adolescents at various stages of pubertal development may inform interventions by pointing to sensitive periods of neuroendocrine reorganization that might be more or less amenable to learning specific skills.

1.3 The Current Study

The current study had the following exploratory aims. **Aim 1:** To identify subgroups of adolescents with similar cortisol–DHEA stress responsivity (i.e., joint cortisol and DHEA response trajectories) in the context of a laboratory-based socio-evaluative stressor. **Aim 2:** To examine descriptive developmental features including child sex, age, and pubertal status as correlates of subgroup membership. **Aim 3:** To examine prospective risk for emotional and behavioral difficulties two years later as a function of subgroup membership and examine whether the nature of distraction coping to emotional and behavioral difficulty longitudinal linkages varied across the identified subgroups.

2. Method

2.1 Participants

Data were obtained from adolescent boys (N=110) and girls (N=105) between the ages of 11 and 16 (M_{age}=13.76 years, SD=1.54) who participated in the Adolescent Emotion Study (for thorough sampling and recruitment details, Klimes-Dougan et al., 2001), a longitudinal examination of emotion and its contributions to the development of psychopathology. Flyers and newspaper advertisements were distributed throughout the Washington, DC metropolitan area. Adolescent participants were oversampled for internalizing and externalizing psychopathology. The final sample exhibited approximately equal proportions of youth with internalizing, externalizing, and comorbid internalizing and externalizing difficulties. Approximately 1/3 of adolescents exhibited total problems that were within normal limits (T scores < 60), 1/3 had sub-clinical total problems (T scores between 60 and 63), and 1/3 presented with clinically elevated total problems (T scores > 63). Most adolescents self-identified as White, 70.2%, followed by Black, 16.3%, mixed-ethnicity, 8.8%, Asian, 2.8%, and Hispanic, 1.9%. For annual household income, 5.6% of families earned less than $20,000, 11.2% earned between $20,000 and $40,000, 18.1% earned between $40,000 and $60,000, 18.7% earned between $60,000 and $80,000, 16.4% earned between $80,000 and $100,000, and 29.9% earned more than $100,000.

2.2 Procedure

Interested families completed a telephone-based screener consisting of an abbreviated version of the Child Behavior Checklist (A-CBCL, Achenbach, 1991). At Time 1, eligible participants were scheduled for an initial in-home visit. Following consent and assent, study staff administered a series of self-report questionnaires to adolescents (e.g., coping,

adjustment). The procedures discussed here are based primarily on the lab visit that took place 2-3 weeks after the home visit. During the several hour lab-based visit, adolescents participated in clinical interviews, self-report questionnaires, and other procedures including the Social Performance Paradigm (SPP; Klimes-Dougan et al., 2001). During the SPP, adolescents were instructed to hold a conversation (3 min) with a female staff member (i.e., confederate) and prepare (1 min) and deliver a speech (3 min) in front of two staff members (i.e., confederates). For the conversation portion, confederates were trained to appear "shy" and interact with the adolescent in an affable but curt fashion (e.g., no initiating discussion, brief answers only). For the speech portion, confederates were trained to provide minimal feedback (e.g., neutral affect, taking notes out of view, rarely nodding). Adolescents provided three saliva samples: immediately prior to the SPP (T1), 20 min post SPP (T2), 40 min post SPP (T3). Adolescents were asked to refrain from eating, drinking, or smoking 30 min prior to sampling and staff monitored for these behaviors during the visit. To reduce diurnal variation effects, SPP start time and saliva collection immediately prior to the SPP were scheduled to take place for all adolescents at 11:16 am (SD = 27 min). Families returned to the lab two years later (Time 2) where youth (N=177) attended a several hour visit that included completion of questionnaires by study staff. Of those returning, 173 youths (M_{age}=16.00 years, SD=1.93, 52% male) provided sufficient hormone data at Time 1 for inclusion in the sample. There was no evidence of selective attrition based on adolescent sex, age, pubertal status, or Time 1 total problems.

2.3 Measures

2.3.1 Salivary sample collection.—

Saliva samples were collected via passive drool (Davis et al., 2002). Specifically, adolescents rinsed their mouth with bottled water (10 sec), chewed Trident sugarless gum to stimulate saliva flow (60 sec), and expectorated (~ 5 ml) into test tubes. Adolescents did not eat in the 30 minutes prior to each saliva sample. Samples were stored at −25° C in a freezer, transported on dry ice to the Biomarker Core Lab at Penn State University (Biobehavioral Health Department), and stored at −86° C until assayed. Assay information is described in detail elsewhere (Klimes-Dougan et al., 2001).

2.3.2 Cortisol determination.—

Salivary cortisol levels (μg/dL) were determined using a commercial expanded-range high-sensitivity enzyme immunosorbent assay kit (Salimetrics, PA). Cortisol extraction was run in duplicate on 50 μl sample test volumes, with testing repeated for duplicate test volumes varying more than 5% error. Duplicates were averaged for analysis. The intra- and inter-assay coefficients of variation were 4.13% and 8.89%, respectively.

2.3.3 DHEA determination.—

Salivary DHEA levels (pg/dL) were determined using a highly sensitive enzyme immunoassay (Salimetrics, PA). The test uses 50 μl of saliva and has a minimum detection limit of 10 pg/mL. Samples were tested in duplicate, and duplicates that varied by more than 7% were repeat tested. Duplicates were then averaged. The intra- and inter-assay coefficients of variation were less than 5% and less than 15%, respectively.

2.3.4 Pubertal status.—Adolescents reported on pubertal development using Tanner criterion (Marshall & Tanner, 1970; Morris & Udry, 1980). Girls responded to a set of pictures depicting breast development and growth of pubic hair while boys responded to a set of pictures depicting pubic hair and genital development. Adolescents indicated which picture most closely reflected their own physical development. Each picture represented one of the five Tanner stages, ranging from Stage 1 (i.e., puberty has not begun) to 5 (i.e., pubertal development has completed). As in prior studies using this dataset (Natsuaki et al., 2009), the two items for each sex were aggregated to compute a sex-specific pubertal status score that was used in all analyses.

2.3.5 Medication use.—Caregivers reported current medication use. As in prior studies using this dataset (Natsuaki et al., 2009), medications were categorized into seven codes: 1) pain relief and antacids, 2) antibiotics and nonsteroidal cold, allergy, and asthma medications, 3) oral steroids, 4) nonoral steroids, 5) psychotropics, 6) hormones, 7) others. A global medication use variable was created by summing across the seven types of medication, with higher scores reflecting a greater number of different types of salivary biomarker-impacting medications.

2.3.6 Distraction coping.—The Response Styles Questionnaire (RSQ) was used to measure typical ways of coping with depressed mood (Nolen-Hoeksema et al., 1991). The 22-item Ruminative Response scale (RRS) and the 13-item Distracting Responses scale (DRS) assess rumination and distraction skills for managing depressotypic thoughts and feelings. Items were rated on a 4-point scale ranging from 1 (“almost never”) to 4 (“almost always”). Both the RRS and DRS have strong evidence of validity (Nolen-Hoeksema et al., 1990), respectively showing high internal consistency (Cronbach’s α = .80–.89). Distraction involves limiting tendencies to dwell on stressors and response styles research holds that rumination may cancel out the potential benefits of distraction (Abela et al., 2007). To account for this possibility, the DRS factor score was converted to a ratio score by dividing the DRS factor score by the sum of DRS and RRS factor scores (Roelefs et al., 2009; Wilkinson et al., 2013). This ratio score has also been recommended for use when investigating at-risk versus community samples (e.g., Hilt et al., 2010).

2.3.7 Emotional and behavioral difficulties.—Estimates of psychopathology were based on adolescents’ completions of the Youth Self-Report (YSR; Achenbach, 1991). At the Time 1 and Time 2 lab visits, youth completed these well-validated, standardized measures that involved rating 118 items based on how well the item described their behavior (0 = not true, 1 = somewhat or sometimes true, 2 = very often or often true). Given the novelty of our approach, we examined a more robust index of adjustment (i.e., Total Problems score). Internalizing and Externalizing Problem scores were also explored in post-hoc analyses. Raw scores were used to maximize variation across the sample and to allow for adequate statistical control of child sex effects as YSR T-scores are standardized across sex.

2.4 Overview of Analyses

2.4.1 Data preparation.—Adolescents missing all data values for either (n=2) or both (n=2) cortisol and DHEA were excluded from analyses. Adolescents missing single data values for both cortisol or DHEA (n=1) were also excluded. The final sample (N=215) had complete cortisol data and the following single missing DHEA values: T1 (n=2), T2 (n=3), T3 (n=2). A $\log_{10}$ transformation (with 5-point constant for cortisol) helped normalize skewed hormone data.

2.4.2 Aim 1: As outlined elsewhere (Bendezu & Wadsworth, 2018), multitrajectory modeling (MTM; Nagin et al., 2018) was used to achieve our first aim. Specifically, subgroups of adolescents were identified based on the extent to which they exhibited similar within-person patterns of cortisol and DHEA response trajectories (e.g., intercept, reactivity patterns). For example, a hypothetical subgroup might be composed of children exhibiting both a cortisol trajectory characterized by a moderate cortisol intercept and quadratic increasing cortisol reactivity while also simultaneously exhibiting a DHEA trajectory characterized by a low DHEA intercept and linear increasing DHEA reactivity. The PROC TRAJ procedure (SAS 9.4; Jones et al., 2001) with the MULTGROUPS option was employed. Little's (1988) MCAR test for all study variables was nonsignificant, X^2 (157)=151.28, p>.250, supporting our use of Full-Information-Maximum likelihood (FIML) in PROC TRAJ. To specify the best fitting model, quadratic functions for cortisol and DHEA were modeled at each step of model specification (e.g., one-group solution, two-group solution). Non-significant quadratic functions for cortisol and DHEA were eliminated at each step. The log Bayes factor approximation [$2\log_e(B_{10})$] was utilized at each step as a fit index (e.g., [$2\log_e(B_{10})$] > 10 supports superior fit of more complex model; Jones et al., 2001). Given our sample size, we limited model specification to three groups as per Nagin (2005). Following specification, we evaluated MTM adequacy (i.e., if MTM accurately identified distinct subgroups) via average posterior probability ($AvePP_j$> 0.70), odds of correct classification (OCC_j> 5.00), and the ratio of the probability of subgroup assignment to the proportion of adolescents assigned to subgroups ([$Prob_j/Prop_j$]≈1) (Nagin, 2005).

Following adequacy evaluation, a series of Wald tests were used to distinguish and label the identified groups. These tests distinguished whether basal (i.e., intercept) or reactivity (i.e., polynomial estimates) aspects of cortisol and DHEA trajectories were comparatively "higher" or "lower" (e.g., baseline) or "more pronounced" or "less pronounced" (e.g., change patterns) across subgroups. To help connect our person-centered findings with extant variable-centered literature, we computed baseline (T1) and reactivity (to capture the repeated measures aspect of the data; Area Under the Curve–Increase; Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003) cortisol/DHEA ratios and examined subgroup differences therein. Ratios were computed following recommendations outlined in Sollberger and Ehlert (2015). Specifically, the log-transformation of the baseline cortisol/DHEA ratio was used and computed as: $\log_{10}(Cortisol_{baseline}/DHEA_{baseline}) = \log_{10}(Cortisol_{baseline}) - \log_{10}(DHEA_{baseline})$. Additionally, the log-transformation of the reactivity cortisol/DHEA ratio was used and computed as: $\log_{10}(Cortisol_{AUC_I}/DHEA_{AUC_I}) = \log_{10}(Cortisol_{AUC_I}) - \log_{10}(DHEA_{AUC_I})$. Log transformed ratios were chosen to improve

the distribution and symmetry of the ratio, which ensure that further parametric tests are appropriate. Constants were added to AUCi values prior to transformation to handle negative values.

2.4.3 Aim 2: Multinomial logistic regression with listwise deletion to handle missing correlate data (2.4%) was used to achieve our second aim. Child sex, age, pubertal status, and medication use were examined as correlates of subgroup membership. All correlates were entered together in a single step.

2.4.4 Aim 3.—Multiple linear regression with listwise deletion to handle missing predictor data (3.2%) was used to achieve our third aim. First, Time 2 total problems were examined as outcomes of subgroup membership. Second, Time 1 distraction coping was examined as a predictor of Time 2 total problems. Third, Time 1 distraction (grand-mean centered) was examined as moderator of subgroup membership to Time 2 total problems outcome linkages, testing whether the nature of distraction coping to Time 2 total problems linkages varied across groups (e.g., positive, negative, nonsignificant). Child sex, age, pubertal status, medication use, and Time 1 total problems were controlled in outcome analyses.

3. Results

Results are organized by study aim. Descriptives and correlations for cortisol, DHEA, and child-level factors are presented in Table 1. Independent samples *t*-tests revealed that cortisol and DHEA values for children who were and were not taking medication did not differ (all $p>.15$). Over the course of the SPP, cortisol levels were positively correlated ($r=.31–.73$) as were DHEA levels ($r=.80–.90$). Of the nine cortisol – DHEA bivariate associations, seven were significant and positive in direction ($r=.20–.38$). Girls tended to exhibit higher DHEA levels and were more advanced with respect to pubertal status. Adolescent age and pubertal status were positively associated with DHEA levels and post-SPP cortisol levels. The Normative ($M=0.55$, $SD=.08$), Hyporesponsive ($M=0.54$, $SD=.09$), and Hyperresponsive ($M=0.53$, $SD=.09$) subgroups did not significantly differ on distraction coping, $F(2,198)=1.120$, $p=.328$.

3.1 Aim 1.

Multitrajectory modeling (MTM) parameter estimates and adequacy indices are displayed in Table 2. MTM results supported a three-group solution (Figure 1): two- and one-group solution comparison [$2\log_e(B_{10}) \approx 308.62$], three- and two-group solution comparison [$2\log_e(B_{10}) \approx 151.20$]. MTM adequacy indices suggested the final model fit the data well.

The Normative group was largest ($n=107$) and displayed trajectories characterized by moderate cortisol[1] and DHEA baseline levels and moderate cortisol (i.e., quadratic slope; 8.3% increase in cortisol levels from T1 to T2, 30% decrease from T2 to T3) and DHEA

[1]Baseline cortisol levels were not significantly different across groups. Thus, the term “moderate,” when used to describe baseline cortisol levels for each group, reflects levels commensurate with those observed at the sample average as opposed to those in relation to “non-moderate” (i.e., higher, lower) levels

(i.e., linear slope; 7% increase in DHEA levels from T1 to T3) reactivity. Because it was largest and potentially reflected well-coordinated multi-hormone function (Kamin & Kertes, 2017), the Normative group was used as reference in trajectory distinction analyses. The Hyperresponsive group was second largest (n=64) and displayed trajectories characterized by moderate cortisol and high DHEA baseline levels and more pronounced cortisol (i.e., quadratic slope; 88.4% increase in cortisol levels from T1 to T2, 30% decrease in cortisol levels from T2 to T3) and DHEA (i.e., quadratic slope; 22.2% increase in DHEA levels from T1 to T2, 3% decrease in DHEA levels from T2 to T3) reactivity. The Hyporesponsive group was smallest (n=42) and displayed trajectories characterized by moderate cortisol and low DHEA baseline levels and non-reactive cortisol (i.e., linear slope; 50% decrease in cortisol levels from T1 to T3) and DHEA (i.e., non-significant linear change; 0% increase/decrease in DHEA levels from T1 to T3) patterning.

Connecting our person-centered findings to the variable-centered literature, the relationship between subgroup membership and baseline cortisol/DHEA ratio was significant, $F(2,210)=9.559$, $p<.001$. Relative to Normative, adolescents in the Hyporesponsive group had significantly *higher* baseline cortisol/DHEA ratios, $M_{diff}=0.173$, $SE=0.072$, $p=.018$, while adolescents in the Hyperresponsive group had significantly *lower* baseline cortisol/DHEA ratios, $M_{diff}=-0.217$, $SE=0.081$, $p=.008$. However, the converse was true when differences in reactivity cortisol/DHEA ratio were examined. The relationship between subgroup membership and reactivity cortisol/DHEA ratio was similarly significant, $F(2,210)=7.386$, $p<.001$. However, relative to Normative, adolescents in the Hyperresponsive group had significantly *higher* reactivity cortisol/DHEA ratios, $M_{diff}=0.139$, $SE=0.038$, $p<.001$. No differences in reactivity cortisol/DHEA ratio emerged for adolescents in the Hyporesponsive subgroup relative to Normative, $M_{diff}=-0.050$, $SE=0.034$, $p=.14$.

3.2 Aim 2.

Multinomial logistic regression parameter estimates are presented in Table 3[2,3]. The model predicting subgroup membership was significant, $X^2(6)=57.950$, $p<.001$, Nagelkerke $R^2=.273$. The Normative subgroup was used as reference in all subgroup membership correlate analyses. Pubertal status was significantly associated with MTM subgroup membership, $X^2(2)=25.621$, $p<.001$. Specifically, the multinomial log odds of membership in the Hyporesponsive group (relative to Normative) decreased with more mature pubertal status, $B=-0.302$, $SE=0.115$, $p=.009$. Additionally, the multinomial log odds of membership in the Hyperresponsive group (relative to Normative) increased with more mature pubertal status, $B=0.463$, $SE=0.143$, $p<.001$. No other significant correlate associations emerged (all $p>.16$)

[2]As in other studies using this dataset, medication use was not associated with hormone data (e.g., Natsuaki et al., 2009), as well as subgroup membership or Time 2 total problems. Thus, medication use was removed from analyses in the interest of model parsimony

[3]An additional Time 1 MTM was conducted using only adolescents with Time 2 data (n=173). Similar subgroups emerged: Normative (n=88, 50.9%), Hyperresponsive (n=49, 28.3%), Hyporesponsive (n=36, 20.8%). The overall pattern of correlate and outcome findings was also similar to that obtained with the full sample (n=215) and did not alter conclusions

3.3 Aim 3.

Multiple linear regression parameter estimates are presented in Table 4. The main effects model predicting Time 2 total problems was significant, $F(6)=12.451$, $p<.001$, $R^2=.313$. The Normative group was similarly used as reference in all outcome analyses. Adolescents in the Hyperresponsive group (relative to Normative) reported greater total problems at Time 2, $B=5.706$, $SE=2.852$, $p=.047$. Membership in the Hyporesponsive group (relative to Normative) did not significantly predict total problems at Time 2, $B=-0.424$, $SE=3.245$, $p>.25$. Time 1 total problems predicted total problems at Time 2, $B=0.464$, $SE=0.058$, $p<.001$. No other significant main effects emerged (all $p>.25$).

The main effects model including distraction as a predictor of Time 2 total problems was also significant, $F(6)=9.740$, $p<.001$, $R^2=.307$. A similar pattern of associations emerged for our covariates of interest and subgroups predicting Time 2 total problems. However, distraction coping was not a significant predictor of Time 2 total problems, $B=-9.714$, $SE=16.131$, $p>.25$.

The interaction effects model predicting Time 2 total problems was significant, $F(9)=8.706$, $p<.001$, $R^2=.340$ (Figure 2). A significant subgroup by distraction coping interaction predicting Time 2 total problems emerged. For adolescents in the Normative subgroup, $B=-51.151$, $SE=23.342$, $p=.030$, distraction coping was negatively associated with total problems at Time 2. However, for adolescents in the Hyporesponsive subgroup, $B=98.105$, $SE=35.926$, $p=.007$, distraction coping was positively associated with total problems at Time 2. No significant distraction coping to Time 2 total problems effects emerged for the Hyperresponsive subgroup, $B=49.185$, $SE=33.762$, $p=.15$.

3.4 Post-hoc analyses.

To understand whether our outcome findings could be attributed to heterogeneity in cortisol alone, group-based trajectory modeling (GBTM; Nagin, 2005) was used to identify subgroups on the basis of shared cortisol trajectories only. Three subgroups emerged: Normative ($n=127$, 59.1%), Hyperresponsive ($n=55$, 25.6%), Hyporesponsive ($n=33$, 15.3%). GBTM intercept and reactivity parameter estimates and results of trajectory distinction analyses were similar to those obtained with MTM: Normative (moderate baseline levels, moderate quadratic reactivity), Hyperresponsive (elevated baseline levels, more pronounced quadratic reactivity), Hyporesponsive (moderate baseline levels, less pronounced linear declining reactivity). However, study correlates were not significantly associated with GBTM subgroup membership (all $p>.12$). Also, no significant GBTM main effects (all $p>.25$) or distraction coping interactive effects (all $p>.25$) predicting Time 2 total problems emerged.

To ascertain whether our total problem outcomes could be attributed to specific emotional and behavioral difficulty classifications, we explored internalizing and externalizing independently as outcomes. Subgroup membership did not significantly predict Time 2 internalizing problems (all $p>.22$) or externalizing problems (all $p>.064$) when each were examined independently. Thus, our significant total problem outcome results perhaps reflect a severity effect (e.g., Essex et al., 2006), such that joint cortisol-DHEA stress

responsivity as a risk factor predicts overall symptom severity regardless of symptom type. Similar distraction coping moderation results emerged predicting Time 2 internalizing, Normative, B=−22.078, SE=9.811, p=.026; Hyporesponsive, B=40.669, SE=14.975, p=.007; Hyperresponsive, B=16.980, SE=13.692, p=.22, but not Time 2 externalizing (all p>.091).

To understand whether our outcome findings could be explained by variable-centered multi-hormone methods, we explored baseline and reactivity cortisol/DHEA ratios as predictors of Time 2 total problems. These variable-centered models included the same covariates as in our person-centered models. No significant correlate effects (all p>.25), baseline and reactivity cortisol/DHEA ratio main effects (all p>.11), or distraction coping interactive effects emerged (all p>.11).

4. Discussion

The current study identified unique within-person patterns of neuroendocrine stress response function that demonstrated theoretically meaningful associations with the development of psychopathology and clinically informative coping-based individual differences therein. Multitrajectory modeling (MTM; Nagin et al., 2018) of cortisol and dehydroepiandrosterone (DHEA) in the context of a lab-based, socio-evaluative stressor revealed three subgroups. Most adolescents (labeled “Normative”) exhibited moderate cortisol-DHEA response trajectories with longitudinal links to healthy functioning that align with functionalist views of well-orchestrated HPA multi-hormone coordination (Wemm et al., 2010; Marceau et al., 2015). A smaller subgroup of adolescents (labeled “Hyporesponsive”) exhibited trajectories that deviated from Normative response patterns in developmentally typical ways (Kamin & Kertes, 2017). Relative to Normative, Hyporesponsive adolescents exhibited more attenuated (i.e., non-reactive) cortisol-DHEA response trajectories, but were understandably also relatively less advanced in their pubertal status (Gunnar et al., 2009). Another subgroup (labeled “Hyperresponsive”) exhibited response trajectories that deviated from Normative in ways that signaled risk (Chen et al., 2015). Relative to Normative, Hyperresponsive adolescents exhibited more exaggerated cortisol-DHEA response trajectories, consistent with the observation that they were also more advanced in pubertal status. However, closer inspection of Hyperresponsive trajectories revealed a greater preferential production of cortisol to DHEA (Sollberger & Ehlert, 2015), consistent with the finding that adolescent in this group were more likely to experience emotional and behavioral problems two years later (Goodyer et al., 2001). Lastly, distraction coping to emotional and behavioral problem longitudinal linkages varied across the groups, highlighting ways in which cortisol-DHEA stress function either supports (e.g., Normative) or thwarts (e.g., Hyporesponsive, Hyperresponsive) the efficacious use of this complex skill. As we discuss, identification of these subgroups and their unique constellation of developmental factors and prospective risk supports the notion that adolescence is a developmental period characterized by substantive heterogeneity with respect to neuroendocrine reorganization, with implications for person-specific tailoring of prevention and intervention efforts targeting the emergence of psychopathology.

Adolescents in the Normative group exhibited cortisol–DHEA stress response patterns that (relative to Hyperresponsive) negatively predicted emotional and behavioral

problems at follow-up and supported distraction-driven buffering of prospective risk for psychopathology. For these adolescents, joint moderate increases in cortisol and DHEA in the context of a stressor may reflect countervailing HPA multi-hormone activation that mobilizes physiologic resources at a level commensurate with stressor demands and skills needed to efficaciously address them. Still further, distraction coping predicted fewer emotional and behavioral problems at follow-up for these adolescents specifically, but not for the sample as a whole. These coping findings are consistent with the notion that stressor-proportional HPA activity may be a requisite consideration when attempting to understand the potential benefits afforded to adolescents by the use of complex coping skills in service of navigating difficult thoughts and feelings that arise in their daily lives. Indeed, as distraction coping has been inconsistently linked to psychopathology (Compas et al., 2017), our findings extend to this literature the suggestion that these protective effects may become evident for adolescents with healthy multi-hormone HPA stress response function.

Relative to Normative, Hyporesponsive adolescents were more likely to be less advanced in pubertal status. Thus, one possibility may be that the non-reactive cortisol–DHEA response patterns exhibited by Hyporesponsive adolescents reflect neuroendocrine coordination during early as opposed to later puberty. Significant baseline cortisol/DHEA ratio differences observed between Normative and Hyporesponsive adolescents are consonant with this claim. Specifically, lower baseline DHEA levels and moderate baseline cortisol levels are characteristic of the developmental changes in enzymatic activity during the adolescent transition (i.e., decline in 3βHSD production; Rainey & Nakamura, 2008), shifts posited to precipitate a rise in basal DHEA but not cortisol levels as children grow from early into late puberty (Goto et al., 2006). Hyporesponsive adolescents' neuroendocrine non-reactivity to psychosocial challenge (i.e., linear declining cortisol levels, non-significant linear change in DHEA levels) is also consistent with evidence of attenuated hormone release patterns typically observed during early puberty (Gunnar et al., 2009; Shirtcliff et al., 2007). Indeed, a lack of cortisol reactivity to stressors during developmental periods characterized by low DHEA levels (e.g., prepubescence) promotes stress adaptation, protecting children's developing brains and bodies against the potential neurotoxic effects of cortisol overexposure that might otherwise confer risk for the development of psychopathology later on (Kamin & Kertes, 2017). Taken together, our findings suggest that Hyporesponsive trajectories may reflect normative developmental differences (i.e., early puberty) in multi-hormone HPA function.

For Hyporesponsive adolescents, distraction was associated with greater emotional and behavioral difficulties at follow-up, a finding best understood from the development of coping framework (Zimmer-Gembeck & Skinner, 2016). Perhaps our identified Hyporesponsive cortisol-DHEA trajectories and coping moderated links to psychopathological functioning point to the shortcomings of sophisticated coping skill engagement for adolescents less advanced in their development. These limitations are informative, given that adolescents earlier on in their development are just beginning to rely less on parents to support coping, develop neuroendocrine response function capable of supporting more autonomous stressor management, as well as cultivate cognitive capacities requisite for more complex forms of coping (Gunnar et al., 2009; Zimmer-Gembeck & Skinner, 2016). In the absence of more mature HPA axis function and executive resource

mobilization that would support effortful cognitive control (Shields et al., 2016), one postulation may be that distraction "backfires" for adolescents who may be developmentally less able to purposefully shift and refocus their attention (Compas, 2009). For these adolescents, distraction attempts may be less sophisticated and effortful, thus functioning more like rudimentary avoidance or involuntary disengagement, each of which have demonstrated links to negative emotionality and symptomatology (Compas et al., 2017). If so, Hyporesponsive distraction efforts may evince short-term benefits in the form of unfocused distress alleviation but over time contribute to inadvertent refocusing on difficult thoughts and feelings (Wegner & Wenzlaff, 2000), guilt related to self-regulation failure (Kelly & Kahn, 1994), and related disturbances (Wolgast & Lundh, 2017).

Adolescents in the Hyperresponsive subgroup exhibited cortisol–DHEA stress response patterns that, relative to Normative, were associated with more advanced pubertal status and greater emotional and behavioral difficulties at follow-up. Relative to those in the Normative subgroup, Hyperresponsive adolescents exhibited significantly higher baseline DHEA levels alongside similarly moderate baseline cortisol levels, a pattern consistent with proposed basal DHEA level increases and basal cortisol level maintenance with advancing puberty (Goto et al., 2006; Rainey & Nakamura, 2008). With respect to joint hormone function, Hyperresponsive adolescents exhibited more pronounced cortisol-DHEA responses and higher reactivity cortisol/DHEA ratios (i.e., more disproportional increases in cortisol to that of DHEA). A higher preferential production of cortisol to DHEA has been linked to adolescent internalizing and related psychopathology (Cicchetti et al., 2015, Goodyer et al., 2001), supporting the claim that poorly modulated (i.e., unopposed by DHEA) cortisol activity may exert neurotoxic influence on neurobiological circuits involved in mental and behavioral function and, thus, the emergence of psychopathology (Shansky & Lipps, 2013). However, as this literature has focused on *basal* indices, our study is the first to illustrate a pattern of joint cortisol-DHEA *response* dysregulation (e.g., proportionally more pronounced cortisol response to that of DHEA) with longitudinal linkages to maladjustment. In sum, the Hyperresponsive profile may reflect both normative developmental processes (i.e., basal levels) as well as pathological alterations (i.e., reactivity) to neuroendocrine functioning, highlighting the potential importance of prioritizing puberty when examining HPA and coping related adjustment during the adolescent period.

For adolescents in the Hyperresponsive profile, distraction coping was not significantly related to emotional and behavioral outcomes. Specifically, these adolescents' emotional and behavioral problems at Time 2 remained elevated irrespective of their distraction coping utilization at Time 1. If unopposed by DHEA, cortisol can have toxic effects on higher-order brain regions (e.g., hippocampus, prelimbic and infralimbic medial prefrontal cortex; Shansky & Lipps, 2013) that support efficient and efficacious coping (Compas et al., 2017). Thus, one possibility may be that distraction coping utilization failed to buffer against the emergence of psychopathology for Hyperresponsive adolescents due to cortisol overexposure in the face of stress, resulting stress-impaired core executive functions (e.g., attentional control, working memory; Shields et al., 2016), and related constraints on efficacious use of sophisticated coping skills. Further research is needed to determine whether variation in neurobiological (Byrne et al., 2017) or executive functioning (Evans

et al., 2016) might help explain nonsignificant distraction coping to psychopathological adjustment findings for adolescents in the Hyperresponsive subgroup.

4.1 Strengths and Implications

Our identification of within-person patterns of cortisol-DHEA response function offers a more nuanced depiction of adolescent net glucocorticoid activity, strengthening inference about the role multi-hormone coordination may play in the development of psychopathology and implications for the tailoring of prevention and intervention efforts for at-risk adolescents. Different patterns of joint HPA hormone responsivity were longitudinally linked to salutary as well as deleterious mental health outcomes, findings which did not hold for cortisol alone despite having identified similar response patterns (e.g., Normative, Hyperresponsive). Still further, these findings did not emerge with our variable-centered approach (e.g., baseline and reactivity cortisol/DHEA ratios). Thus, our results highlight the potential utility and added value of person-centered modeling of multi-hormone activity for elucidating pathways towards and away from maladjustment (Chen et al., 2015; Kamin & Kertes, 2017; Marceau et al., 2015).

Our findings suggest that there may be no universally “good” or “bad” ways of coping (Wadsworth, 2015), but rather skills that may be a better and poorer fit for different children (i.e., *regulatory fit*; Bendezú et al., 2016). To this postulation, we extend evidence that this might also hold for children with different multi-hormone response function at different stages of pubertal maturation. One potential avenue for future research may be to examine whether developmentally sensitive and neuroendocrine informed modifications improve the efficacy of coping skill-based prevention and intervention efforts. Distraction may be a skill just beyond the reach of prepubescent youth with limited arousal function and neophyte skill at recruiting executive resources in service of autonomous coping. Prevention efforts for Hyporesponsive adolescents might instead focus on improving emotion identification (e.g., worry, anger) and expression skills (e.g., calmly letting someone know about their distress levels), as these adolescents may still rely primarily on support-seeking (e.g., parents) to meet their coping needs (Zimmer-Gembeck & Skinner, 2016). For Hyperresponsive adolescents, pathological alterations in stress reactivity may limit ability to access this developmentally appropriate skill and utilize it to navigate difficult thoughts and feelings. Training in mindfulness (i.e., directed attention to the present moment, openness to and acceptance of experience) may improve capacity to redirect attention and stay focused so that distraction attempts might be more fruitful (e.g., productive, soothing). Such training may also help these adolescents both identify and limit engagement in unproductive thought processes (e.g., dwelling on the stressor, rumination) that also emerge during this period (Wagner et al., 2015).

4.2 Limitations and Future Directions

Our investigation had several limitations. First, most adolescents in our sample were White and from well-resourced families, underscoring the need to examine the generalizability of our findings to different samples. Second, our sample size was small for a person-centered design. As such, our identification of three multi-hormone profiles with low, moderate, and high baseline levels and reactivity patterning may have been an artifact of

our having limited MTM specification to three groups as recommended. Still further, small and unequal subgroup samples sizes may have contributed to a reduction in power in our correlate and outcome analyses. Future studies with larger samples may be well-poised to identify additional unique profiles linked to risk for psychopathology. Thus, both cautious interpretation of the findings and replication with larger samples is warranted. Third, our study focused solely on adolescents' self-report and only one of many developmentally appropriate coping skills. Future research may benefit from use of multiple informants (e.g., parents) and investigation of other relevant strategies (e.g., problem solving, cognitive restructuring). Third, our characterization of multi-hormone HPA axis activity was limited to cortisol and DHEA obtained from only three saliva samples. While cortisol levels generally peak 20 min post-stressor (Kirschbaum & Hellhammer, 1994), some evidence suggests that salivary DHEA emergence may be more delayed than cortisol (Shirtcliff et al., 2007). Research including additional post-stressor samples may more fully capture cross-hormone reactivity and recovery patterns, but also support examination of intra-individual coupling of cortisol and DHEA and links to psychopathology (Marceau et al., 2015). Fourth, as described in Klimes-Dougan et al. (2001), the "shy stranger" in our socioevaluative stressor was always a female confederate (i.e., college-aged research assistant), which may have contributed to sex differences in cortisol-DHEA responsivity to the stressor. Fifth, as our study did not assess neurobiological or executive function, we can only speculate that, consistent with theory (Byrne et al., 2017; Kamin & Kertes, 2017; Shields et al., 2016), disproportional increases in cortisol to that of DHEA contributed to Hyperresponsive total problems and constrained coping efficacy vis-à-vis deleterious effects on higher-order cognitive function. Future research incorporating fMRI or neuropsychological testing methods is needed to further investigate these claims.

4.3 Conclusion

These findings offer novel insight into the nature of adolescent cortisol-DHEA stress response functioning. By attending to both developmental factors and psychopathology concurrently (Kamin & Kertes, 2017), our person-centered, multi-hormone study identified profiles reflective of both typical (e.g., Normative, Hyporesponsive) and aberrant (e.g., Hyperresponsive) neuroendocrine coordination. Importantly, identification of these profiles had implications for the efficacy of children's coping skill utilization, suggesting that multi-hormone HPA function might be a requisite consideration when disentangling for whom distraction coping might "work" or "backfire" in managing emotional and behavioral symptoms. While we await independent replication, our profiles tentatively point to person-centered means of tailoring prevention and intervention towards adolescents' unique HPA function.

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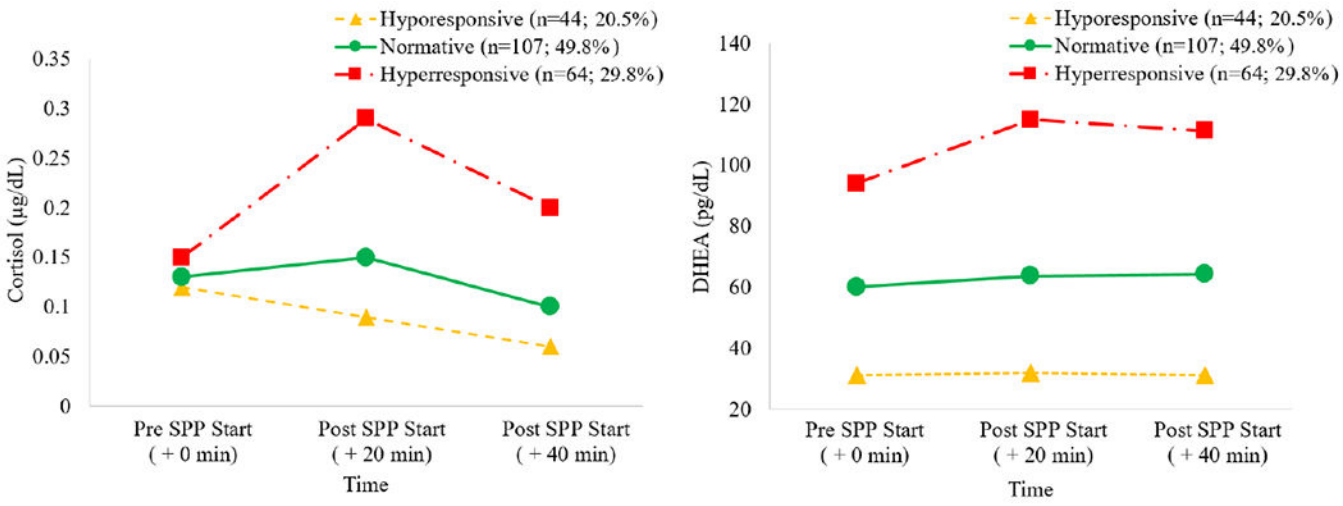

Figure 1.

Salivary cortisol and dehydroepiandrosterone (DHEA) response trajectories to Social Performance Paradigm (SPP) for the final three-group solution. Reverse log transformed values presented for visual clarity and ease of interpretation.

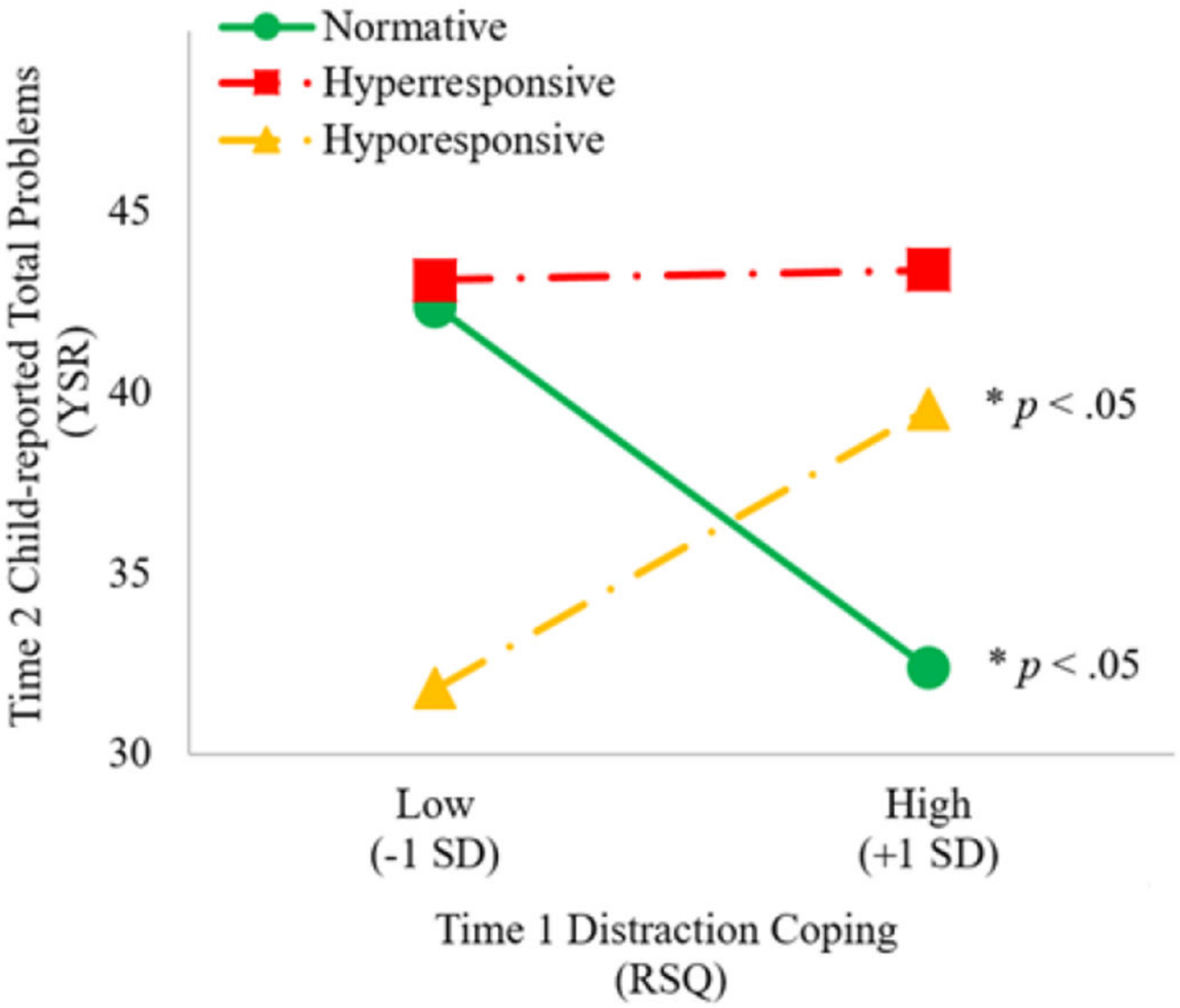

Figure 2.
Moderation effects of Time 1 distraction coping on subgroup membership to Time 2 total problems. Effects plotted at − 1 SD and + 1 SD for illustrative purposes.

Table 1

Descriptives and Bivariate Correlations for Stress Response Indices and Correlates

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
1. SC +0 min SPP	—									
2. SC +20 min SPP	.43*	—								
3. SC +40 min SPP	.31*	.73*	—							
4. DHEA +0 min SPP	.20*	.24*	.25*	—						
5. DHEA +20 min SPP	−.04	.38*	.36*	.80*	—					
6. DHEA +40 min SPP	−.05	.27*	.37*	.80*	.90*	—				
7. Child sex[a]	−.01	−.10	.01	.23*	.17*	.20*	—			
8. Child age	.02	.23*	.11	.24*	.35*	.25*	.02	—		
9. Child pubertal status	−.02	.26*	.20*	.37*	.50*	.43*	.19*	.59*	—	
10. Child medication	−.01	−.01	.01	−.06	−.03	−.04	.03	.02	.02	—
M	3.14	3.22	3.05	1.78	1.82	1.81	0.49	13.76	7.39	0.38
SD	0.48	0.46	0.45	0.21	0.22	0.22	0.50	1.54	1.99	0.66
Min	1.94	2.25	0.93	1.18	1.16	1.08	0.00	10.70	2.00	0.00
Max	4.33	4.29	4.08	2.22	2.29	2.23	1.00	17.16	10.00	3.00

Note. SC = salivary cortisol (μg/dL); DHEA = dehydroepiandrosterone (pg/dL); SPP = Social Performance Paradigm. SC and DHEA values were log-transformed (with an additional 5-point constant for SC) prior to all analyses (including descriptive and bivariate correlation statistics displayed above). Child sex coded 0 for boys and 1 for girls.

[a]Spearman's rho.

*$p < .05$.

Table 2

Parameter Estimates (Standard Errors) and Model Adequacy Indices for Final Multitrajectory Modeling Three-Group Solution

	Salivary Cortisol (SC)	Dehydroepiandrosterone (DHEA)	$AvePP_j$	OCC_j	$Prob_j$	$Prop_j$	*Ratio*
Normative (n=107)			.952	89.972	.503	.498	1.010
Intercept	3.141 * (0.045) A	1.782 * (0.012) A					
Linear	0.006 (0.005)	0.001 † (0.001) a					
Quadratic	−0.001 † (0.001) a						
Hyporesponsive (n=44)			.949	64.600	.201	.204	0.985
Intercept	3.082 * (0.062) A	1.497 * (0.013) B					
Linear	−0.008 * (0.002) −	0.001 (0.001) b					
Quadratic							
Hyperresponsive (n=64)			.935	65.412	.295	.298	0.990
Intercept	3.183 * (0.059) A	1.974 * (0.017) C					
Linear	0.026 * (0.007)	0.007 * (0.002)					
Quadratic	−0.001 * (0.001) b	−0.001 * (0.001) −					

Note. $AvePP_j$=Average posterior probability; OCC_j=Odds of correct classification; $Prob_j$=Probability of group assignment; $Prop_j$=Proportion of children assigned to each group; *Ratio*=Ratio of $Prob_j$ to $Prop_j$. Upper-case superscripts denote significant differences in intercept estimates within the same stress response index. Lower-case superscripts denote significant differences in polynomial parameter estimates within the same stress response index.

† $p = .06$.

* $p < .05$.

Table 3

Parameter Estimates from a Multinomial Logistic Regression Model Linking Correlates to Multitrajectory Modeling Subgroup Membership

Comparison Subgroup	Time 1 Correlates	Correlate X^2 (df) [a]	*B*	*SE*	Exp(*B*)	95% CI for Exp(*B*)
Hyporesponsive	Intercept		0.891	0.722		
	Child sex[b]	3.694 (2)	0.127	0.384	1.135	0.534, 2.412
	Child age	1.511 (2)	−0.100	0.165	0.904	0.655, 1.249
	Child pubertal status	25.621 (2)	−0.302*	0.115	0.740	0.590, 0.927
Hyperresponsive	Intercept		−5.726*	1.328		
	Child sex[b]		−0.615	0.348	0.541	0.273, 1.070
	Child age		0.115	0.129	1.122	0.871, 1.445
	Child pubertal status		0.463*	0.143	1.589	1.201, 2.104

Note. Beta parameter estimates reflect multinomial log-odds of comparison subgroup membership relative to Normative for each unit increase in the correlate of interest.

[a] = Predictor X^2 estimates were the same for each comparison.

[b] = Child sex coded 0 for boys and 1 for girls.

* $p < .05$.

Table 4

Parameter Estimates for a Nested Taxonomy of Multiple Linear Regressions Predicting Time 2 Total Problems

	MTM Group Main Effects		MTM Group and Distraction Main Effects		MTM Group and Distraction Interactive Effects	
Time 1 Predictors	***B***	***SE***	***B***	***SE***	***B***	***SE***
Intercept	11.929	10.888	23.946	16.863	22.324*	11.852
Child sex[b]	0.098	2.371	0.094	2.465	−0.296	2.429
Child age	0.593	0.919	0.024	0.982	−0.054	0.966
Child pubertal status	−0.207	0.837	0.111	0.890	0.081	0.875
Child total problems	0.464*	0.058	0.436*	0.066	0.397*	0.068
Multitrajectory modeling (MTM) group[a]						
Hyporesponsive	−0.424	3.245	−1.540	3.393	−1.946	3.339
Hyperresponsive	5.706*	2.852	5.387†	2.959	5.457†	2.912
Distraction coping			−9.714	16.131		
Normative × distraction coping					−51.151*	23.342
Hyporesponsive × distraction coping					98.105*	35.926
Hyperresponsive × distraction coping					49.185	33.762

[a] = Normative served as the reference group.

[b] = Child sex coded 0 for boys and 1 for girls.

† $p = .06$.

* $p < .05$.