Hypothalamic–Pituitary–Adrenal Axis Dysregulation in Dysphoric Children and Adolescents: Cortisol Reactivity to Psychosocial Stress from Preschool Through Middle Adolescence

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Background: Most depressed adults exhibit dysregulation of the hypothalamic–pituitary–adrenal axis, including cortisol hyperreactivity to psychosocial challenge. In contrast, remarkably little is known about hypothalamic–pituitary–adrenal axis activity in response to psychosocial challenge among at-risk children and adolescents. This study examined cortisol response to psychosocial challenge in nondepressed, at-risk, dysphoric and nondysphoric control youth across different developmentally salient age groups (preschool, third-, sixth-, and ninth-graders).

Methods: Two samples of youth (Study 1—preschoolers; Study 2—third-, sixth-, and ninth-graders) without a history of clinical depression were administered developmentally appropriate psychosocial challenges. Of these nondepressed children, we examined youth at high-risk (n = 60) and low-risk (n = 223) status, as defined by elevated but subthreshold dysphoric symptoms according to multiple informants. Cortisol levels were assessed before and after a psychosocial stressor.

Results: Nondysphoric control youth at all ages displayed the expected cortisol rise to challenge followed by return to baseline. However, prepubertal, at-risk, dysphoric children—specifically preschoolers and third-graders—exhibited cortisol hyporeactivity to challenge, whereas postpubertal dysphoric adolescents (ninth-graders) displayed hyperreactivity to the stressor. Additional analyses revealed that this switch from cortisol hyporeactivity to hyperreactivity among at-risk, dysphoric youth occurred as a function of pubertal development.

Conclusions: Findings suggest a developmental switch in cortisol response for at-risk, dysphoric youth from preschool through adolescence and have implications for a developmental pathophysiological understanding of how at-risk youth across the lifespan might develop depressive disorder.

Key Words: Children, cortisol, depression, stress

Major depressive disorder (MDD) is a prevalent, costly psychiatric disorder; a serious public health concern; and leading cause of disability worldwide (1). Since Carlson and Cantwell (2) “unmasked” masked depression, young children (ages 3–6) have been shown to meet diagnostic criteria for MDD (3). Rates of depression then increase from childhood into adolescence (4,5). Most individuals experience first MDD onset during adolescence, and subsequently many adults experience recurrent episodes (6). Developing effective interventions, especially for those most at risk, is a clear priority. It is important to identify risk factors and pathophysiological processes contributing to depression. Because many mechanisms might be in place before first MDD onset, examining physiological mechanisms before MDD onset might be particularly fruitful.

Disregulation of the hypothalamic–pituitary–adrenal axis (HPA) is a robust biomarker for depression among many adults (7–9), who show cortisol hyperreactivity in response to a psychosocial stressor (e.g., Trier Social Stress Test) (10). Psychosocial challenge paradigms have the advantage of testing endogenous activity of the whole HPA system (7) and might better mimic effects of stress exposure, which predicts depression onset and maintenance.

Surprisingly little research has investigated whether cortisol levels are significantly different between dysphoric and control youth in response to psychosocial laboratory stressors. Indeed, only three studies used a psychosocial laboratory challenge to investigate cortisol levels in depressed versus control youth (11). With the same sample of preschoolers, Luby et al. (3,12) demonstrated cortisol reactivity differences across an extensive laboratory challenge between depressed and nondepressed preschoolers with what seem to be lower prechallenge levels in depressed preschoolers. Rao et al. (13) showed cortisol hyperreactivity in depressed adolescents compared with healthy control subjects, as is typical in adult work.

The primary aim of this study was to examine cortisol reactivity to developmentally appropriate psychosocial challenges in youth, across a wide age range, who had never been depressed but were at high-risk for depression by virtue of elevated dysphoria. Dysphoric (i.e., subthreshold for MDD but not clinically depressed) youth are at particular risk for developing later MDD (14). By studying at-risk youth who have never experienced depression across different developmental periods, this study can advance knowledge about potential pathophysiological processes contributing to MDD onset without concern about confounds of current or prior MDD.

We hypothesized that normal children would exhibit an increase in cortisol levels in response to a psychosocial stressor (i.e., reactivity) and then would return to baseline (i.e., recovery). Dysphoric children were hypothesized to exhibit dysregulated HPA axis activity. We recruited children of different ages, including preschoolers, third-, sixth-, and ninth-graders—given the wide age ranges of prior research (3,12,13)—to systematically examine whether developmental level affected cortisol levels.
Methods and Materials

Study 1

Participants were 81 preschoolers (53% female; mean age = 4.2 years) recruited as part of a larger project from community child care centers. Preschoolers were excluded from this sub-sample if they had a diagnosed pervasive developmental disability (e.g., autism), were taking medications for asthma or allergy, or were currently ill.

Assessment of Depression Risk. Mothers completed the Child Behavior Checklist (CBCL) (CBCL/1½–5) (17) and a background health questionnaire on their child to screen for current illness and medication use. Lead teachers from the child’s classroom also completed the teacher report form of the CBCL.

Cortisol Collection and Stress Tasks. Preschoolers participated in a 20-min semi-structured interaction with their primary caregiver designed to elicit a mild stress-reaction during a 1-hour home visit. Children were asked to not eat or drink for 20 min before the visit. The interaction was adapted from the National Institute of Child Health and Human Development Early Child Care Research Network three boxes task (18). During the interaction, the dyad was instructed to play with four different sets of materials for 5 min each in the following order: a set of books as a warm-up activity, two hand puppets to elicit child-directed play, a scary robot to elicit fear, and a box with an attractive toy that was difficult to open to elicit frustration.

Three saliva samples were collected in 20-min intervals: at baseline before the challenge (immediately after arriving at the home); at the end of the psychosocial challenge, reflecting possible initial cortisol reactivity; and after quiet play time/rest, reflecting possible recovery. Importantly, individuals vary in the timing of both their initial response to a challenge and to the length of time it takes to recover after mounting a physiological response to a stressor; therefore these labels of “reactivity” and “recovery” are simply convenient labels of expected average responses. Saliva samples were obtained via synthetic salivette collection devices without the use of stimulants (Sarstedt, Nuem- brecht, Germany). Saliva was extracted by centrifuging for 4 min at 2500 rpm. Vials and salivettes were frozen at −20°C until data collection was complete. Samples were sent to the Biochemical Laboratory, Psychobiology, University of Trier, Germany to be assayed. All samples were assayed in duplicate. Cortisol levels were determined by employing a competitive solid-phase, time-resolved fluorescence immunoassay with fluorometric end point detection (DELFIA; Wallac, Gaithersburg, Maryland) (19). The mean intra-assay coefficients of variation for blind controls of real saliva of high and low concentration were 6.6%–8.5%. For duplicates of the samples used in this study and in Study 2, the interassay coefficients of variation was 6.5%.

Study 2

Children and adolescents in third, sixth, and ninth grades were recruited through public schools. Interested parents called the laboratory and responded to a brief phone screen that established that both the parent and the child were fluent in English and the child did not carry an autism spectrum or psychotic disorder diagnosis and had an IQ >70. At the laboratory, parents gave consent, and children gave assent. A total of 246 youth in third, sixth, or ninth grades participated, and 205 did not have a current or past diagnosis of depression. These never-depressed youth comprised the sample that was the primary focus of Study 2. Third-graders were 52% female; mean age = 8.7 years; sixth-graders were 62% female, mean age = 11.7 years; and ninth-graders were 58% female, mean age = 14.3 years.

Assessment of Depression and Diagnostic Interviews. Mothers and youth were interviewed separately with the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) (20). Of the total sample of 246, 7 youth met criteria for current MDD (2.8%) and 34 for prior MDD (13.8%); none met criteria for any bipolar or psychotic disorder. Diagnostic interviewers, who were advanced graduate students in clinical psychology, completed an intensive training program for administering the K-SADS interview and for assigning DSM-IV diagnoses. The training program consisted of attending a minimum of 40 hours of didactic instruction, listening to audiotaped interviews, and conducting practice interviews. The first author (BLH) held weekly supervision sessions for the interviewers and reviewed interviewers’ notes and tapes to confirm the presence or absence of a diagnosis. An independent, trained rater—with numerous years of experience conducting diagnostic interviews and who was blind to parent or child diagnostic status—randomly evaluated 20% of the K-SADS interviews, to assess interrater reliability. Reliability was good (κ = .87), and presence/absence of current MDD in youth was confirmed.

Also during the laboratory visit, both parent and child completed the Children’s Depression Inventory (CDI-C for Child and CDI-P for parent informant) (21). The CDI is a self-report measure of general dysphoria with good reliability and validity for children ages 8–17 years (21,22), although it does not enable depression diagnosis and most accurately assesses dysphoria and broad negative affect (22).

Pubertal Development. All youth were administered the Pubertal Development Scale (PDS) (23), which includes five questions about physical development, scored from 1 (no) to 4 (development complete). Reliability and validity of the PDS is high (23,24), including evidence that PDS scores are strongly associated with physical examination for pubertal development (24). We followed standard PDS scoring to create prepubertal and postpubertal groups separately for girls and boys.

Cortisol Collection and Stress Tasks. Most third, sixth, and ninth grade participants (n = 129; 52%) completed questionnaires and K-SADS interview during the first 60 min. The other youth (n = 117; 48%) completed K-SADS interview after the stress challenge and collection of cortisol samples. Timing of K-SADS did not affect any results. After 1 hour in the laboratory, youth participated in an approximately 15–20-min psychosocial challenge. This included a 5–10-min parent–child discussion concerning a recent fight or argument. Then, youth auditioned for a “reality TV show” by giving a speech directly into a video camera; youth were instructed that judges would evaluate their performance. Because there is no current consensus on stress/challenge paradigms that elicit cortisol reactivity across different ages (25), we selected this laboratory challenge task because it was likely to be developmentally appropriate across third-, sixth-, and ninth-graders, and it involved the essential elements (e.g., threat of social rejection and social evaluation and anticipatory and processive stress) known

to activate a cortisol response across the lifespan (26). For 45 min after the challenge, youth quietly completed additional questionnaires. Youth were debriefed at the end of the laboratory visit. On average, most of the first cortisol samples were collected at 5:00 PM (range 4:00 PM–6:30 PM). Cortisol collection intervals, assay procedures, and coefficients of variation were identical to that of Study 1.

Results

Study 1

As indicated in Table 1, of the 81 preschool participants, 18 (22.2%) had combined parent- and teacher-reported anxious/depressed scores from the internalizing dimension of the CBCL that fell within the clinical range (t scores > 70). Of these, 8 were boys and 10 were girls. The χ² revealed no gender difference in dysphoric group (p = .51). Still, given the small sample, the main analysis was conducted both controlling and not controlling for gender. Cortisol values were not normally distributed and exhibited negative skew for all three time points, so log e transformations were used for analyses. There was considerable variation in scheduled time of home visits (mean = 15:48; range = 8:15 to 20:15). A one-way analysis of variance (ANOVA) revealed no differences between dysphoric groups in sampling time [F(1,79) = .27, p = .61]. Still, to be conservative all analyses were also recomputed controlling for time of first saliva sample. To examine potential effects of sleep on cortisol, values, one-half of the preschoolers (36 nondysphoric, 5 dysphoric) were fitted with actigraphy watches. Average time of first saliva sample from nearest awakening time (i.e., morning wake up or afternoon nap) was 3:51 hours (range = .90–6.80 hours) for the nondysphoric group and 3:05 hours (range = 2:05–3:63 hours) for the dysphoric group.

Table 1. Demographic and Clinical Characteristics of Never-Depressed Dysphoric and Nondysphoric Children and Adolescents

<table>
<thead>
<tr>
<th>Age (n = 81)</th>
<th>Dysphoric Group (n = 16)</th>
<th>Nondysphoric Control Group (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>44.7 (.70)</td>
<td>4.13 (.72)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>63% girls</td>
<td>51% girls</td>
</tr>
<tr>
<td>CBCL-P, T</td>
<td>P: 4.83 (2.37)/T: 7.25 (2.92)</td>
<td>P: 1.72 (1.48)/T: 1.63 (1.93)³</td>
</tr>
<tr>
<td>3rd-Graders (n = 66)</td>
<td>(n = 12)</td>
<td>(n = 54)</td>
</tr>
<tr>
<td>Age</td>
<td>8.43 (.64)</td>
<td>8.75 (.49)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>57% girls</td>
<td>53% girls</td>
</tr>
<tr>
<td>CDI-C, P</td>
<td>15.91 (4.37)</td>
<td>4.34 (2.89)</td>
</tr>
<tr>
<td>6th-Graders (n = 70)</td>
<td>(n = 15)</td>
<td>(n = 55)</td>
</tr>
<tr>
<td>Age</td>
<td>11.41 (.67)</td>
<td>11.73 (.52)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>64% girls</td>
<td>53% girls</td>
</tr>
<tr>
<td>CDI-C, P</td>
<td>14.4 (3.12)</td>
<td>4.46 (3.08)³</td>
</tr>
<tr>
<td>9th-Graders (n = 69)</td>
<td>(n = 17)</td>
<td>(n = 52)</td>
</tr>
<tr>
<td>Age</td>
<td>14.50 (1.04)</td>
<td>14.30 (.54)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>62.5% girls</td>
<td>60.5% girls</td>
</tr>
<tr>
<td>CDI-C, P</td>
<td>15.19 (5.95)</td>
<td>4.86 (3.06)³</td>
</tr>
</tbody>
</table>

CBCL, Child Behavior Checklist; CDI, Child Depression Inventory; C, Child report; P, Parent report; T, Teacher report. ³p < .05.

Figure 1. Mean (± SEM) cortisol response to psychosocial challenge among preschoolers in Study 1 as a function of at-risk, dysphoric group and control, nondysphoric group.

To examine the primary hypothesis, we employed a 2 (dysphoric group) × 3 (cortisol time point: baseline, reactivity, recovery) repeated measures ANOVA. The time × dysphoric group interaction was significant [F(2,73) = 3.72, p = .03], and results were unchanged controlling for gender and sampling time [F(2,71) = 3.63, p = .03]. Dysphoric preschoolers demonstrated hypoactivity to the challenge, as illustrated in Figure 1, with significantly lower cortisol 20 min into the challenge but cortisol similar to nondysphoric preschoolers at baseline and recovery. Our first sample should be a true baseline sample, because it reflects cortisol before the arrival of the research team to the home. However, to verify that dysphoric and nondysphoric children did not differ at baseline, we also compared their average baseline cortisol, available from the larger study from which these data were drawn. For each child we selected their closest baseline sample matched for the type of day (weekend vs. weekday) and time (morning vs. afternoon) they completed their home visit. The nondysphoric (mean = .13) and dysphoric groups (mean = .13) did not differ on this true baseline cortisol measure (p = .95).

To determine whether children among the dysphoric group with greater dysphoria might be driving our results, we also compared cortisol patterns between the nine dysphoric children with the lower CBCL scores (mean = 15.8, range = 14–17) and the nine dysphoric children with the higher CBCL scores (mean = 24.7, range = 20–38). Both groups displayed an overall flat patterning of cortisol across the interaction. Therefore, although the more dysphoric preschoolers might have especially low cortisol, both groups of dysphoric preschoolers were hyporesponsive to the challenge.

Study 2

We used the CDI (child and parent ratings) to form groups of at-risk, dysphoric children and nondysphoric healthy control subjects. As indicated in Table 1, 44 of the 205 (21.4%) never-clinically depressed youth from third, sixth, and ninth grades had CDI scores in the at-risk, dysphoric range (21). Across ages, the nondysphoric and dysphoric groups did not differ on any demographic variable. Overall, 49% of the mothers reported a prior history of clinical depression, as ascertained via the Structured Clinical Interview for DSM-IV (SCID) (27).
Stress Reactivity, Depression Level, and Age Group. Cortisol values were not normally distributed and exhibited negative skew for all three time points, so in transformations were used for analyses, and Greenhouse-Geisser corrections were reported where sphericity was evident. There was a main effect of gender on cortisol levels \(F(1,204) = 4.19, p = .04\) (boys mean = .068, SE = .004; girls mean = .058, SE = .003) but no significant gender effect across time \(F(1,62, 325.21) = .02, p = .96\). Moreover, gender did not moderate any of the findings reported next. Likewise, there was no main effect of mothers’ history of depression on cortisol levels \(F\) was significant for third-graders \(p = .01\) or across time \(F(1,61,380.91) = .01, p = .98\), and maternal depression history did not moderate any findings.

To examine the primary hypotheses, we employed a 3 (age group) \(\times\) 2 (dysphoric group) \(\times\) 3 (cortisol time point) repeated measures ANOVA. The 3-way interaction was significant \(F(3,21,314.94) = 3.21, p = .02\). Planned follow-up analyses to decompose the 3-way interaction involved repeated measures ANOVAs for 2 (dysphoric group) \(\times\) 3 (cortisol time point) within each age group. This 2 \(\times\) 3 repeated measures ANOVA was significant for the third-graders \(F(1,88,139.53) = 3.83, p = .02\), was not significant for sixth-graders \(F(1,38,114.53) = .97, p = .36\), and was significant for ninth-graders \(F(1,61,380.91) = .04, p = .96\). Figure 2 shows that the overall stress response was quadratic, with increases from baseline to reactivity followed by decreases from reactivity to recovery. This quadratic component was significant for third-graders \(F(1,65) = 7.32, p = .008\), was not significant for sixth-graders \(F(1,69) = .61, p = .43\), and was significant for ninth-graders \(F(1,68) = 7.66, p = .007\).

As illustrated in Figure 2, dysphoric third-graders exhibited cortisol hyporeactivity to the stress challenge, whereas the healthy control youth displayed the expected quadratic cortisol response. The sixth grade dysphoric youth displayed a trend toward hyporeactivity, although the dysphoric group’s pattern did not significantly differ from the control subjects who exhibited the expected quadratic pattern. Finally, and in contrast to the younger children, the ninth grade dysphoric group exhibited significantly greater cortisol hyperreactivity in response to the psychosocial stressor compared with the healthy control youth, who displayed the expected quadratic cortisol response. Neither temperament (28) nor recent stressors (29) showed this pattern, suggesting that significant results for at-risk, dysphoric youth cannot be explained by temperament or recent stress (Supplement 1).

Given these results suggesting a developmental switch from cortisol hyporeactivity in third grade to hyperreactivity in ninth grade for the at-risk, dysphoric youth and the nonsignificant pattern in sixth-graders, we explored whether pubertal development (prepubertal vs. postpubertal as defined by PDS) rather than grade operated as a more appropriate developmental marker affecting cortisol response to psychological stress in at-risk, dysphoric youth compared with control youth. The 2 (pubertal group) \(\times\) 2 (dysphoric group) \(\times\) 3 (cortisol time point) repeated measures ANOVA was significant \(F(1,79,275.27) = 4.73, p = .01\). The 2 (dysphoric group) \(\times\) 3 (cortisol time point) for prepubertal youth approached significance \(F(1,92,144.12) = 2.75, p = .07\), and this 2 \(\times\) 3 ANOVA was significant for the postpubertal youth \(F(1,58, 123.49) = 4.02, p = .03\). The quadratic component was significant for prepubertal \(F(1,101) = 6.21, p = .01\) and postpubertal youth \(F(1,102) = 5.81, p = .01\).

Figure 3 shows that nondysphoric, control youth, regardless of pubertal status, exhibited the expected quadratic cortisol response. Of interest, at-risk, dysphoric prepubertal youth displayed hyporeactivity (cortisol levels decreased from baseline to reactivity and recovery), and at-risk postpubertal youth exhibited hyperreactivity from baseline to reactivity and then return to baseline at recovery.

Finally, we examined whether youth with current MDD \((n = 7)\) exhibited cortisol hyperreactivity to the psychological stressor, as would be expected, given research with adults and limited work with depressed adolescents (15). The 2 (pubertal group) \(\times\) 2 (currently depressed group) \(\times\) 3 (cortisol time point) repeated measures ANOVA was significant \(F(1,76,326.7) = 9.22, p < .001\). As shown in Figure 4, prepubertal youth with current depression exhibited significantly greater cortisol before the challenge compared with nondepressed youth but no difference in reactivity or recovery. In contrast, the postpubertal currently depressed youth revealed the expected cortisol hyperreactivity compared with nondepressed youth. Last, parallel analyses with remitted depressed youth showed no significant effect in the 2 (pubertal group) \(\times\) 2 (remitted depressed group) \(\times\) 3 (cortisol time point) ANOVA \(F(1,78,318.73) = .19, p = .80\). This is

![Figure 2](www.sobp.org/journal)
consistent with work with adult populations showing normalization in cortisol reactivity after MDD remittance.

**Discussion**

This study investigated cortisol response to a psychosocial stressor in never-depressed youth, who are at risk for depression on the basis of subthreshold dysphoria, from preschool through middle adolescence. Results showed that nondysphoric youth, from preschool through adolescence, exhibited the expected quadratic cortisol response to psychosocial challenge. For these control youth, cortisol levels increased 20 min after the challenge (i.e., reactivity) and then returned to baseline 40 min later (i.e., recovery). This mild response is appropriate for the challenges posed and provides youth with an extra boost of energy to face the challenge without extended exposure to elevated steroid hormones. In contrast, the at-risk dysphoric groups displayed HPA axis dysregulation, and the particular form of dysregulation depended on developmental level. Younger dysphoric children (i.e., preschoolers and third-graders) exhibited cortisol hyporeactivity, whereas the dysphoric adolescents (ninth-graders) displayed cortisol hyperreactivity. This developmental switch from blunted cortisol response to hyperreactivity to challenge was explained by pubertal stage, such that prepubertal at-risk children exhibited hyporeactivity, and the postpubertal at-risk youth displayed hyperreactivity to challenge. The findings advance knowledge of the biological response of youth to stressful challenges and how this response differs across development between at-risk dysphoric and nondysphoric youth.

These results are consistent with and extend the limited prior research studying cortisol response to challenge with currently clinically depressed (13) or healthy youth (15,16). Our results, with never-depressed but at-risk dysphoric ninth-graders exhibiting cortisol hyperreactivity expand on the one prior study (13) with currently depressed versus control adolescents. Additionally, the small group of currently clinically depressed postpubertal youth exhibited cortisol hyperreactivity, replicating this research. Of interest and new are the findings with currently depressed prepubertal youth. These children exhibited higher baseline cortisol before challenge and then no reactivity to the stressor. Because there were few currently depressed youth, these findings should be interpreted cautiously and require replication. Last, we found that the group of dysphoric preschoolers exhibited cortisol hyporeactivity, a finding possibly consistent with the work of Luby et al. (3,12) with different tasks and timing with clinically depressed preschoolers.

Taken together, our findings are consistent with recent work with healthy youth showing that HPA axis activity increases with age, particularly after the pubertal transition (15,16). Our findings, both with currently clinically depressed and nondepressed at-risk youth, suggest that there is a developmental shift in the pattern of HPA axis activity with increases in cortisol among adolescents compared with children, and this normative HPA axis increase among healthy youth might be exacerbated among at-risk, dysphoric as well as currently depressed individuals.

Surprisingly little research has investigated HPA axis activity throughout different developmental periods, especially in childhood and adolescence (26). The adolescent brain and HPA axis response might be more reactive to stress and associated glucocorticoid exposure. In animals, adolescent rats exhibit elevated release of adrenocorticotropic hormone and glucocorticoids after repeated stress exposure (30). In humans, potentiated basal and stress-induced HPA axis activity starts around midpuberty (15,16). These developmental shifts in heightened HPA axis activity from childhood into adolescence might be related to the
substantial increase in sex hormones during puberty as sex steroids affect HPA axis activity (31).

These normative changes in HPA axis activity during the pubertal transition might be important for understanding the surge in depression observed from adolescence into young adulthood (4,5). The developmental shift in cortisol response might inform a developmental pathophysiological perspective on how at-risk individuals at different salient age periods might become depressed. Hyperreactivity to psychosocial challenge in dysphoric adolescents is also observed in depressed adults (9). These patterns are consistent with strong continuity from adolescent-onset depression into adulthood. However, less continuity is observed between child-onset and adult depression (6), and the processes contributing to child-onset depression differ from adolescent and adult-onset depression (32). The adolescent transition comes with a host of changes, including desire for greater autonomy from parents and a dramatic increase in stressor exposure (33). Individuals begin to experience substantial increases in stress starting in adolescence, when most people first become depressed (33). At-risk, postpubertal adolescents, who display cortisol hyperreactivity to stressful challenges, might be at particular susceptibility to develop depression as they experience more stressors throughout adolescence and have a disregulated biological stress response system that is less capable of adaptively coping with increasing stress. We speculate that at-risk prepubertal children who exhibit cortisol hyporeactivity to challenge might be more susceptible to depression, because they have a less responsive stress system and, as a result, have more difficulty increasing energy to meet challenges and sufficiently cope with stress. Alternatively, young children with early depressive symptoms might be experiencing chronic stress that they are unable to change or escape and are exhibiting HPA-axis suppression because of early chronic exposure. Future research would benefit from longitudinal research examining whether the developmental switch in cortisol reactivity occurring with puberty, as found in the current cross-sectional study, can be observed to change in individuals as they progress through pubertal development as well as accumulating stress exposure over time.

Study strengths include developmentally appropriate psychosocial challenges to test for cortisol reactivity from early childhood through adolescence. Also, studying at-risk, dysphoric youth, who were never depressed, ensures that results are not confounded by depression history. Additional research is needed to examine whether disturbed HPA axis function predicts development of MDD. Moreover, investigating developmentally equivalent, time-limited laboratory stressors that elicit cortisol response across different ages would help to further understand developmental pathophysiology of depression. Our relatively mild challenges sufficiently elicited cortisol responses as well as other ethical tasks used in prior research (e.g., serial subtraction, social competence interview [34], public-speaking task [13]). However, the tasks and procedures differed between Studies 1 and 2, precluding analyses across the two studies. Future research would benefit from greater number of cortisol samplings both before and after challenge. Most studies investigating HPA axis function index cortisol reactivity at approximately 20 min after stressor, as we did. Meta-analytic findings show this is an average time for cortisol reactivity (35), although individual variability in cortisol response over time is likely (36).

Overall, findings highlight developmental factors in understanding the dynamic relation between direction of HPA axis dysregulation and risk to depression over the lifespan. Such knowledge holds promise to inform intervention efforts to reduce occurrence and recurrence of depression among high-risk individuals.

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