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Effortful Control and Context Interact in Shaping Neuroendocrine Stress Responses during Childhood

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Abstract

Trait and contextual factors can shape individual and group differences in hypothalamic-pituitary-adrenal (HPA) response to stress; but the ways in which these factors may interact with each other to modulate stress activity has rarely been examined. Here, we investigated whether the association between a temperamental self-regulatory trait – Effortful Control (EC) – and HPA axis stress response is moderated by type of laboratory stress in sixty-five children (35 boys). EC was measured at age 3 and 6 using age-appropriate laboratory batteries as well as mother reports. HPA axis responses were measured at age 7 by randomly assigning children to one of two laboratory stress tasks (frustration vs. fear). Results indicated that EC interacted with stress context in predicting cortisol response. Specifically, lower EC was associated with greater cortisol response (steeper reactivity slopes) in the context of a frustration stressor but this was reversed in a fear context where lower EC was associated with flatter, more gradual activation. It is likely that different components of EC, such as emotion regulation and attention, differentially interact with the stress context. These types of effects and interactions need to be more thoroughly understood in order to meaningfully interpret cortisol reactivity data and better characterize the role of the HPA axis in human psychopathology.

Keywords

HPA; salivary cortisol; stress; effortful control; temperament; fear; frustration; children

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Efforts to understand biological mechanisms of stress regulation have focused extensively on hypothalamic-pituitary-adrenal (HPA) axis responses to a variety of laboratory stress tasks (Biondi and Picardi, 1999; Dickerson and Kemeny, 2004; Kirschbaum et al., 1993). However, individual differences in developmentally shaped temperamental traits can also shape HPA axis functioning. Effortful Control (EC) is one such dimension of temperament that has received significant attention (see Gunnar et al., 2003; Lisonbee et al., 2010), with a documented role in facilitating the development of emotion-related self-regulation during the early developmental years (Rothbart and Rueda, 2005), and evidence of influence on HPA axis activity (Donzella et al., 2000). The HPA axis, however, is also sensitive to contextual aspects of the experimental paradigms in which it has been studied (Abelson et al., 2007; Gunnar et al., 2009; Lopez-Duran et al., 2009a). It is highly likely that task effects on cortisol responses are shaped by how individuals interpret, experience, or react to laboratory challenges, so it is also likely that temperamental trait differences in self-regulation (like EC) interact with contextual factors to shape results, and such interactions may have contributed to the many inconsistencies seen in the HPA literature. However, temperamental traits and contextual factors have rarely been studied together in HPA axis research, so we know very little about how they may interact.

Effortful Control (EC) is a self-regulatory aspect of temperament that encapsulates a variety of cognitive skills implicated in a wide range of self-regulatory outcomes (Kochanska et al., 2000). Its components include abilities to inhibit dominant responses and activate subdominant ones, to guide attention focusing, and to voluntarily regulate behavior (Rothbart, 1989, 2007; Rothbart et al., 2003). It critically shapes an individual's ability to cope with stress by regulating emotions, thoughts and actions (Derryberry et al., 2003; Eisenberg et al., 1993; Rueda and Rothbart, 2009), and is thus a crucial self-regulatory skill that develops throughout childhood and lays foundation for subsequent stress coping ability (and perhaps subsequent stress system reactivity).

Some studies have linked lower EC with greater cortisol levels or reactivity. However, other studies have shown the opposite. Preschoolers lower in EC show greater cortisol levels across the day while in childcare settings compared to when at home, with the younger children (lowest in EC) showing an actual rise in cortisol, reversing the expected diurnal decline (Dettling et al., 1999). The authors speculated that children with more immature regulatory abilities were reacting to specific aspects of the childcare context, such as frequent (potentially negative) peer interactions, which stimulated this rise across the day. Similarly, children who showed higher typical cortisol levels across the day in other peer group settings were shown to be lower in EC (attentional and inhibitory control, specifically; Gunnar et al., 1997). Children characterized by teachers as lower in EC also show elevated cortisol in response to the acute stress of a competitive game (Donzella et al., 2000). However, lower EC was linked to lower cortisol reactivity in response to an executive functioning test in children attending Head Start (Blair et al., 2005) and an emotion-eliciting non-sharing task that was preceded by laboratory executive functioning tasks (Spinrad et al., 2009). Inconsistencies here could be due to differences in sample characteristics or due to task or context differences, or an interaction between the two. Children attending Head Start come from low-income backgrounds and are at risk for aggressive and externalizing problems, which have been associated with blunted cortisol reactivity (Snoek et al., 2004;

Van Goozen et al., 2000). However, externalizing problems are also associated with problems in self-regulation or EC (Olson et al., 2005) and these characteristics could interact with task demands or contexts in shaping cortisol responses. There is in fact growing evidence that task and context matter in neuroendocrine studies (Abelson et al., 2007; Lopez-Duran et al., 2009a). In their seminal review on stressor paradigms in developmental studies, Gunnar et al. (2009) highlight the importance of context in HPA research. While they concluded that availability of coping resources and threat to the social self are key determinants of the HPA response, they also suggest that individual differences, including temperamental factors, can shape patterns of HPA reactivity. Inconsistencies described above could be due to task differences as well as temperament differences between samples. Studies linking lower EC to lower cortisol responses used executive functioning challenges, while studies linking lower EC to higher cortisol used social conflict challenges that occur in interpersonal interactions and likely involve frustration experiences. HPA responses in these types of studies may be shaped by individual differences in self-regulatory temperamental traits like EC interacting with paradigm-specific aspects of the stress tasks used.

Different stress tasks make different emotional and cognitive demands, such that individual or group differences in self-regulatory skills and capacities could produce different HPA responses in different contexts. For example, a frustration-eliciting task might engage emotion regulation processes, and poor emotion regulation (low EC) in such a situation may exacerbate the stress response to the challenge. Notably, lower levels of EC have been linked to higher levels of anger/frustration (Kochanska and Knaack, 2003). Thus, previously reported high cortisol reactivity in low EC children facing a social frustration challenge might result from an interaction of individual differences in self-regulation (EC) and context (frustration). In contrast, lower EC may actually result in blunted cortisol response in executive functioning tasks as well as in contexts that require attentional control in order to identify and focus on the task-presented threat. For example, children with Attention-Deficit/Hyperactivity Disorder (ADHD; hyperactivity/impulsivity subgroup) – a disorder related to lower levels of EC (Martel and Nigg, 2006) – tended to show lower cortisol levels in a fear context (dental examination; Blomqvist et al., 2007), likely due to children's inability to attend to fear-related stimuli (Blomqvist et al., 2005). Although averting attention from fear-eliciting stimuli would be a successful strategy of emotion regulation, some level of attention might be necessary to initially identify fear/threat-related stimuli. Attentional focusing on cues that indicate an imminent threat (e.g., upcoming dental examination) might be particularly challenging for poor EC children in a naturalistic setting with high potential for distraction – resulting in blunted reactivity. Lower EC has been associated with reduced attention and executive function (Rothbart and Rueda, 2005) as well as with reduced fearfulness in children (Kochanska and Knaack, 2003). Furthermore, selective attention to emotional stimuli has been positively associated with stress-induced cortisol levels (Epel et al., 2000; Van Honk et al., 2000). We therefore hypothesized that lower levels of EC might be associated with reduced HPA axis response in executive function tasks or tasks that require executive function skills (e.g., attention) in order to identify and respond to the stress cues (as in most fear paradigms). Smaller HPA responses may thus be seen in children with lower EC in tasks where individual differences in attention are “in play,” but larger HPA responses may be seen with lower EC when attention

to the salient cues is more fully captured by the task and capacity for emotion regulation comes into play.

The current study investigated whether the impact of EC (collected at age 3 and 6) on the stress response (measured at age 7) is moderated by the type of stressor – a frustration versus a fear task. We hypothesized that lower levels of EC would be associated with enhanced HPA stress responses to frustration (indicated by steeper reactivity slope parameters and elevated peak levels), but that in a fear inducing task lower levels of EC would be associated with reduced HPA responses.

Methods

Participants

Participants included sixty-five children (35 boys), recruited from an NIMH-funded longitudinal study of typically developing children and children considered at risk for school-age conduct problems due to high levels of early externalizing problems (for recruitment procedures and sample characteristics of the original study see Choe et al., 2013; Olson et al., 2005). Children participating in the original, community-based study ($N = 241$) were recruited in early childhood (age 3), with oversampling of toddlers in the medium to high range of the Externalizing Problems scale ($T > 60$; 44%) and full representation of symptom severity on the Child Behavior Checklist/2–3 (Achenbach, 1992). At the time of recruitment for this study (age 7), the sample was more representative of the local community with only 10% scoring in the high range on the externalizing problem scale, likely because preschool externalizing behaviors that are of parental concern often reflect normal and age-appropriate behavior during a transitional developmental period (Campbell, 1995).

For the current study, we contacted all eligible families (those who had agreed to be contacted for future studies and who still lived in the area; $N = 203$) by phone or postal mail and invited them to participate in a *separate add-on study* examining HPA axis response in children. Children with mental retardation, any pervasive developmental disorder (including Autistic Disorder, Asperger's Disorder, and Pervasive Developmental Disorder NOS), major systemic medical condition (e.g., diabetes, cancer, endocrine disorders), or medications that are associated with changes in neuroendocrine functioning (e.g. asthma medication) were excluded from the study. Only one child was excluded due to Autistic Disorder. Seventy-eight families were scheduled to complete the laboratory procedure. The Institutional Review Board at the University of Michigan approved the study, and participants completed written and oral informed consent. Five participants did not complete all necessary questionnaires or tasks and another 8 were not exposed to one of the stress tasks (validity check condition), yielding a final sample of sixty-five children. Families in the current sample did not differ from those in the original sample in terms of sex ($p = .688$), age, (Age 3: $p = .133$; Age 6: $p = .287$), parents' marital status ($p = .191$), family income level ($p = .927$), socioeconomic status (SES; based on education and occupation; $p = .802$), or mother reported behavior problems (Achenbach, 1992, 2001), such as externalizing behavior problems (Age 3 current: $M = 11.76$; $SD = 6.90$ vs. original: $M = 11.52$; $SD = 7.31$; $p = .813$; Age 6 current: $M = 7.13$; $SD = 7.07$ vs. original: $M = 6.65$; $SD = 5.95$; $p = .590$) or

internalizing behavior problems (Age 3 current: $M = 6.97$; $SD = 5.28$ vs. original: $M = 6.54$; $SD = 4.79$; $p = .531$; Age 6 current: $M = 3.63$; $SD = 4.10$ vs. original: $M = 3.74$; $SD = 4.03$; $p = .857$). The ethnic distribution of the current sample was mostly Caucasian (94%), with 1.6% African American, 3.1% Hispanic American, and 1.5% Asian American. The median annual family income was \$70,000–80,000, ranging from \$15,000 to over \$100,000.

Study Design

Participants were assessed at three time points. Laboratory and mother-rated effortful control was assessed at time 1 when children were about 3-years-old ($M_{age} = 3.4$ years, $SD = 0.2$) as well as at time 2 when they were almost 6 ($M_{age} = 5.8$ years, $SD = 0.3$). Between 1–2 years later (age 7; $M = 7.48$ years, $SD = 0.7$), participants visited the laboratory and were randomly assigned to take part in one of two standardized protocols (frustration vs. fear condition) to measure neuroendocrine stress responses.

Assessment of Effortful Control

EC was assessed at ages 3 and 6 using age-appropriate laboratory behavioral batteries and mother-reports. Kochanska's toddler-age behavioral battery (Kochanska et al., 1996) was administered at time 1 to assess individual differences in children's EC via six tasks ($\alpha = 0.70$) that tap into Rothbart's general construct of effortful control (1989). Briefly, the child's ability to suppress and initiate activity in response to a signal was measured with the *Tower* task. Delaying was assessed with the *Delay* task, the *Tongue* task, and the *Lab Gift* task. The child's ability to slow down motor activity was assessed with the *Turtle and Rabbit* task. The *Whisper* task assessed the child's ability to lower his/her voice. Detailed descriptions of individual tasks, coding procedures, and psychometric properties are available elsewhere (Olson et al., 2005). Kochanska's early school-age behavioral battery was administered at time 2 (Kochanska et al., 1997). The ability to suppress or initiate a movement according to changing instructions was measured with the *Simon Says* task and the *Green-Red Signs* task. Cognitive reflectivity was assessed with Wright's (1971) *Kansas Reflectivity/Impulsivity Scale for Preschoolers*. The ability to slow down motor activity was assessed with the *Walk-a-Line-Slowly* task and two drawing trials (*Circle* and *Star*). The *Shapes* task is a version of the Stroop paradigm and measured effortful attention (Rothbart and Bates, 1998). Information regarding these individual tasks ($\alpha = .59$) are also described in detail elsewhere (Choe et al., 2013). Briefly summarized, these behavioral batteries are internally consistent, correspond meaningfully with mothers' ratings of effortful control, and reflect longitudinal stability (Kochanska et al., 1997; Kochanska et al., 1996). As recommended (Kochanska et al., 1997; Kochanska et al., 1996; Murray and Kochanska, 2002), a total score of laboratory effortful control was computed for each time point by summing standardized individual subtest scores.

Effortful control at age 3 and 6 was also assessed by mother-report using an abbreviated version of Rothbart's Child Behavior Questionnaire (CBQ; Ahadi et al., 1993). CBQ scales for attentional focusing and inhibitory control were used to measure mother-rated effortful control at each time point by averaging children's standardized scores on these two most theoretically and empirically relevant components of EC (Muris and Ollendick, 2005; Posner and Rothbart, 2000; Rothbart and Bates, 1998). Attentional focusing ($\alpha_s = .83-.85$;

Choe et al., 2013) assessed the ability to concentrate on tasks (e.g., “When drawing or coloring a book, shows strong concentration”). Inhibitory control ($\alpha s = .82-.85$; Choe et al., 2013) measured the ability to suppress dominant responses according to demands (e.g., “Can wait before entering into new activities if s/he is asked to”).

Both laboratory behavioral assessment and mother ratings of EC are thought to reflect the same underlying construct and can be meaningfully aggregated and interpreted in a unified theoretical framework. We therefore averaged them to create a single index of EC at each age. We should note however, that we also conducted analyses with the laboratory and mother-reports separately and the results were consistent with those described below.

Missing data for effortful control at age 3 was low (one child each for the laboratory battery and mother-rated EC). At age 6, nine children did not complete the laboratory EC battery (14%) and two children missed mother-reports of EC (3%). Children missing effortful control data at age 6 were compared by t-tests to those with complete data and no differences were found in sex, age, parents’ marital status, family income level, socioeconomic status, mother reports of externalizing and internalizing behavior problems (all $ps > .20$), or EC measures at age 3 (mother-rated EC, laboratory EC, or composite EC index; all $ps > .10$). This suggests that children with missing data did not systematically differ in any of the main study measures from remaining children.

Experimental Procedures and Stress Conditions (Age 7)

Participants were randomly assigned to a frustration ($n = 32$) or fear ($n = 33$) stress task. After a 30-minute baseline play session, an undergraduate research assistant (RA) escorted the child to a different room and conducted the 3-minute stress task. After the stress protocol, children watched two 30-minute movies during which cortisol collection continued. The laboratory visit lasted approximately 90 minutes and began between 1500h and 1630h. Time of the laboratory procedure (1500h vs. 1630h) did not influence cortisol levels as previously reported with this sample (see Lopez-Duran et al., 2009a). Detailed description of the experimental procedures are provided elsewhere (Lopez-Duran et al., 2009a).

Thirty-two children were exposed to a **frustration condition** (Calkins, 1997). A Toys-R-Us gift certificate was placed inside a clear plastic box. Each child was told that he or she would receive the prize if able to open the box with his or her hands inside tennis socks. The RA modeled the task and made standardized challenging verbalizations such as, “This is so easy even a baby can do it.” Before leaving the room the RA discreetly switched boxes and gave the child an identical box that was glued shut. The child was given one minute to open the box before the RA returned. Upon returning, the RA explained that the box was probably broken and the child received the prize.

Thirty-three children were exposed to a **fear condition** protocol (Calkins et al., 2008). Each child was taken into an unfamiliar semi-dark room, slowly and quietly led by the RA to an empty fish tank partially showing a snake. The RA’s standardized verbalizations during this task included “I have something that I want to show you. It’s inside that tank. Let’s be quiet so it doesn’t wake up.” The child was instructed to stay away while the RA removed a

blanket that covered the top. The RA then asked the child to approach the tank and abruptly took the rubber snake out while simultaneously indicating that the snake was not real. The child also received a prize.

After the stress task (post stress phase), each participant was escorted to a different classroom equipped with chairs and a TV/VCR. The RA then played two 30-minute episodes of the children's series "Wallace and Gromit" from Aardman Animations. The episodes were "A Grand Day Out" and "A Close Shave." The videos were selected because they were entertaining enough to keep the child's attention for extended periods of time but lacked significant emotionally arousing content (for methodological validation of these procedures with this sample, see Lopez-Duran et al., 2009a).

Cortisol Sampling and Analysis

Saliva cortisol samples (17 samples per participant) were densely obtained during the experiment, to allow detailed tracking of slopes, slope changes, and timing as well as magnitude of peaks. The initial saliva sample was collected at the beginning of the baseline period, 30-minutes prior to the stress task. Additional baseline samples were collected at 20, 10, and 5 minutes prior to the stress task. Immediately following the stress task, an initial post-stress saliva sample was collected (time 0). Additional samples were collected 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 and 60 minutes after the initiation of the stress condition. To obtain saliva samples, the child was given the option of either chewing on a cotton dental roll or spitting directly into a salivette tube. Most of the participants chose the latter, which shortened the collection time from 30–45 seconds to under 10 seconds. We experienced no difficulties with saliva production, and no agents were used to facilitate it (sugar crystals, gum, etc.). A research assistant ensured that all samples were collected. No child refused any samples. All samples were stored within 4 h of collection at -20°C until assayed and were centrifuged for 15 min prior to assay. Samples were assayed in duplicate and averaged, using a commercial radioimmunoassay kit (Salimetrics). Duplicates varying more than 15% were re-assayed. The inter-assay and intra-assay coefficients of variability were 7.6% and 6.2%, respectively.

Statistical Analysis

To test if EC and stress context (frustration vs. fear) interact in predicting cortisol reactivity slopes (speed of acceleration) and peak values (magnitude of response), we used a growth curve modeling framework via SAS PROC MIXED. However, due to significant individual and stress-modality variability in peak timings in these tasks (see Lopez-Duran et al., 2009a; also see Figure 1), we used a modified landmark registration approach so that the modeling of reactivity slopes and peak levels could be compared across stress modalities (see Lopez-Duran et al., in press; Ramsay and Li, 1998). Specifically, we anchored individual peaks upon a common peak time by aligning the individual growth curves on the horizontal (time) axis so that individual peaks fall on the same time point, and the horizontal axis reflects *minutes before peak*. This approach allows us to model the impact of predictors (i.e. EC, Stress Context, and the EC-by-Stress Context interaction) on reactivity slopes towards peak, as well as true peaks (common intercept), while controlling for baseline levels. We did not log transform cortisol values given that the frequent and dense sampling procedure and the

use of a mixed modeling framework (aggregating over all 17 samples in “long” format) yielded a normally distributed cortisol variable (Skewness = .57; Kurtosis = .05). Since our analyses were based on multivariate random effects models, we used a modification of Cohen’s f^2 as a measure of effect size based on the recommendations described in Selya et al. (2012). Cohen’s f^2 effect sizes were only reported for significant predictors of primary analyses of interest. Effect size estimates for pairwise comparisons were determined by calculating Cohen’s d .

Results

The fear and frustration tasks both elicited robust cortisol responses, with no differences in peak levels achieved, although peaks occurred later in the frustration task (see Figure 1; for more information on individual differences in cortisol responses also see Lopez-Duran et al., 2009a). The peaks occurred on average 25 minutes after the stressor in the fear task and were significantly higher than baseline levels, $t(32) = 6.28$, $p < .001$, Cohen’s $d = 1.16$. In the frustration task, peaks occurred on average 55 minutes after the stressor and were also significantly elevated above baseline levels, $t(31) = 4.39$, $p < .001$, Cohen’s $d = 0.80$. Individually selected cortisol peak levels achieved in the two tasks did not differ from each other, $t(63) = 0.81$, $p = .419$, $M = 0.113$; $SD = 0.023$ for fear and $M = 0.108$; $SD = 0.023$ for frustration.

Correlations among EC measures, across time (age 3 and 6) and across measurement type (behavioral and mother rating), are presented in Table 1. The overall pattern suggests reasonable coherence between the two types of measurement and reasonable stability over time. The composite EC index was significantly correlated across the two ages, $r(62) = 0.59$, $p < .0001$.

Modeling Cortisol Stress Responses

We first examined unconditional linear and quadratic growth curve models of poststress cortisol using peak values as the final intercept. All of our models included baseline cortisol levels as a control variable. The quadratic model was the best fit to the data (linear model AIC = -3445.5 vs. quadratic model AIC = -3640.4) indicating an acceleration of the response as it approaches peak (time $b = 0.002708$, $t(554) = 20.49$, $p < .0001$; time² $b = 0.000040$, $t(554) = 15.44$, $p < .0001$). Adding child gender to this quadratic model (AIC = -3637.8) revealed no effect of gender on slopes (gender x time $b = -0.00040$, $t(552) = -1.51$, $p = .131$; gender x time² $b = -0.000003$, $t(552) = -0.54$, $p > .20$) or peak levels (gender $b = -0.00770$, $t(60) = -1.50$, $p = .138$). Nevertheless, given previously reported gender differences in EC (girls showing greater EC; Ahadi et al., 1993; Kochanska et al., 2000), and gender differences at age 3 in the current sample (females had higher EC compared to males, $t(63) = -2.12$, $p = .04$, Cohen’s $d = .53$), child gender was added as a control variable to all subsequent models, although results did not change whether or not gender was included as a covariate.

Direct Effects of EC and Stress Context on Cortisol Responses

In an initial conditional model we examined the *direct effects* of EC (at age 3 and 6) and stress context on the reactivity slope parameters and cortisol peak values (intercept). The EC-by-Stress Context interaction effects are of primary interest, but direct effects from the non-interaction model will be briefly summarized. Lower levels of EC were associated with steeper reactivity slopes (faster activation), significantly for EC at age 3, and marginally for EC at age 6 (linear slope). EC had no effect on the magnitude of cortisol peak values. Children in the fear context showed steeper reactivity slopes (faster non-linear activation), but stress context (frustration versus fear) did not differentially impact peak levels in these models, paralleling the significant but equivalent cortisol levels reached for both tasks in direct comparisons (reported above). Parameter estimates and statistics for these direct effect models are presented in Tables 2 and 3.

EC-by-Stress Context Interaction Effects on Cortisol Responses

We then conducted a second conditional model that added the *interactions* between EC indices (EC_{age3} and EC_{age6}) and Stress Context predicting reactivity slopes towards peak (speed of acceleration) and magnitude of salivary cortisol peak levels. EC_{age3} and Stress Context significantly interacted in shaping reactivity slopes ($EC_{age3} \times \text{Stress Context} \times \text{time}$ $F_{1, 548} = 19.20$; $EC_{age3} \times \text{Stress Context} \times \text{time}^2$ $F_{1, 548} = 14.24$; Cohen's $f^2 = .03$) and marginally interacted in predicting cortisol peak levels ($EC_{age3} \times \text{Stress Context}$ $F_{1, 57} = 3.43$; see Table 2). Specifically, in the frustration context (see Figure 2, panel A; Table 2 Frustration only model), as EC at age 3 decreases, children displayed steeper reactivity slopes ($EC_{age3} \times \text{time}$ $b = -0.000730$, $t(385) = -4.08$, $p < .001$; $EC_{age3} \times \text{time}^2$ $b = -0.000010$, $t(385) = -4.63$, $p < .001$; Cohen's $f^2 = .06$) and marginally elevated cortisol peak values (EC_{age3} $b = -0.008240$, $t(27) = -1.99$, $p = .057$). However, in the fear context (see Figure 2, panel B; Table 2 Fear only model), a decrease in EC was linked to flatter reactivity slopes ($EC_{age3} \times \text{time}$ $b = 0.001056$, $t(163) = 2.36$, $p = .019$; $EC_{age3} \times \text{time}^2$ $b = 0.000033$, $t(163) = 2.15$, $p = .033$; Cohen's $f^2 = .02$), with no impact on the magnitude of the peak values ($p > .20$).

EC_{age6} and Stress Context interacted in shaping reactivity slopes ($EC_{age6} \times \text{Stress Context} \times \text{time}$ $F_{1, 532} = 14.91$; $EC_{age6} \times \text{Stress Context} \times \text{time}^2$ $F_{1, 532} = 19.33$; Cohen's $f^2 = .04$), but did not interact in predicting cortisol peak levels ($EC_{age6} \times \text{Stress Context}$ $F_{1, 56} = 1.48$; see Table 3). In the frustration context (see Figure 2, panel C; Table 3 Frustration only model), as EC at age 6 decreases, children showed steeper acceleration to peak ($EC_{age6} \times \text{time}$ $b = -0.000540$, $t(369) = -2.70$, $p = .007$; $EC_{age6} \times \text{time}^2$ $b = -0.000009$, $t(369) = -2.75$, $p = .006$; Cohen's $f^2 = .02$) and marginally elevated cortisol peak values (EC_{age6} $b = -0.007660$, $t(26) = -1.78$, $p = .087$). However, in the fear context (see Figure 2, panel D; Table 3 Fear only model), a decrease in EC_{age6} was linked to flatter reactivity slopes ($EC_{age6} \times \text{time}$ $b = 0.001189$, $t(163) = 2.37$, $p = .019$; $EC_{age6} \times \text{time}^2$ $b = 0.000050$, $t(163) = 2.88$, $p = .004$; Cohen's $f^2 = .06$), with no impact on cortisol peak values ($p > .20$).

Discussion

In this study, we investigated how temperamental trait differences in self-regulation (Effortful Control, EC) and type of laboratory stress (frustration versus fear context) interact in shaping neuroendocrine stress responses. We found that the impact of EC (measured at age 3 and 6) on children's stress responses at age 7 varied as a function of stress context. Specifically, lower levels of effortful control were associated with higher endocrine responses in the frustration context, but this was reversed in the fear context. This highlights the role of EC as a differential modulator of the stress response in specific stress contexts. It likely helps explain some inconsistencies in the literature on EC and the HPA axis, since different studies used different types of stress tasks. It suggests that task type needs more attention in these studies, and that other studies of HPA axis function need to measure salient temperamental traits, like EC. It also suggests that variation in HPA responses to laboratory challenges may reflect variability in higher levels of the brain than processes within the HPA axis itself.

Our findings linking lower levels of EC (measured at age 3 and age 6) to greater endocrine response to a frustration task are consistent with previous studies linking lower EC to greater cortisol reactivity in response to other frustrating tasks (i.e., a competitive game; Donzella et al., 2000) and in group settings (Dettling et al., 1999; Gunnar et al., 1997). This enhanced HPA response in children with lower EC may result from poor emotion regulatory processes that are uniquely tapped by these types of challenges. Indeed, EC reflects voluntary control of emotion-related self-regulation (Eisenberg and Spinrad, 2004) and lower levels of EC skills have been linked to poor emotion regulation and higher levels of anger/frustration in both laboratory settings (Kochanska and Knaack, 2003) and in parent and teacher reports (Olson et al., 2005; Zhou et al., 2004). Poor emotion regulation processes, as reflected in low frustration tolerance and heightened anger have, in turn, been linked with enhanced HPA axis activity (Stansbury and Gunnar, 1994). The salience of post-task, self-regulatory factors to HPA responses in the frustration task is perhaps consistent with the later peak level in this task (compared to the fear task), since self-regulatory processes likely come into play after task completion. Children with lower EC who fail an easy task with a self-evaluative component (derogatory comment "This is so easy even a baby can do it") may not be equipped with adequate self-regulatory capacities to manage the resulting anger/frustration and negative self-referent emotions following the frustration experience. This may have exacerbated their neuroendocrine stress responses to this challenge, resulting in steeper reactivity slopes (faster activation) and a trend for higher peak levels occurring relatively late.

Our results seem to contradict the notion that biological under-reactivity, including cortisol response to stress, is associated with the development of antisocial and externalizing behaviors/disorders (Raine, 1996; Snoek et al., 2004; Van Goozen et al., 2000). This apparent conflict may be explained by the possibility that our laboratory stress task purely tapped frustration experiences without eliciting aggression, though it is also plausible that the externalizing-under-reactivity link is a function of clinical severity since it is seen in studies using clinical populations (Snoek et al., 2004; Stansbury and Gunnar, 1994; Van Goozen et al., 2007; Van Goozen et al., 2000) as opposed to studies with healthy

populations and community samples (Gerra et al., 1997; Lopez-Duran et al., 2009b; Scarpa et al., 2000). It is possible that amount of exposure to adverse early childhood experiences, which can contribute to HPA underactivity (Carpenter et al., 2009) and to development of psychiatric disorders, may be what differentiates the two populations. Future studies investigating the EC-by-stress context interaction in children with externalizing behaviors are warranted.

In contrast to the frustration task, lower levels of EC at age 3 and 6 predicted flatter reactivity slopes in the fear task but did not predict peak magnitude, suggesting that EC impacted the rate of cortisol activation but not the ultimate peak achieved. Although lower EC has been linked to lower laboratory observed fearfulness (Kochanska and Knaack, 2003), little is known about the effect of EC on the cortisol response to fear-eliciting tasks. One study demonstrated a trend towards blunted cortisol levels in a fear-eliciting situation (dental examination) in a high hyperactivity/impulsivity subgroup of children with ADHD (Blomqvist et al., 2007) – a disorder associated with low EC and marked inattention (Martel and Nigg, 2006). This effect may have been due to inattention to the fear-eliciting stimuli of the procedure. Our fear task likely activated the HPA axis through a combination of novelty-induced stress reactivity and increasing anticipation of a potential threat. Children walked into a novel, dark room, and the research assistant's comments – "I have something that I want to show you. Let's be quiet so it doesn't wake up" – indicated that something dangerous and uncontrollable might happen. This arousal of a threat-expectancy might have initiated HPA responding more quickly in this task than the frustration task, contributing to its shorter peak latency. However, children with lower levels of EC may have been less attentive to the assistant's comments (Rothbart and Rueda, 2005) and may have been reacting more diversely to a wider range of less specific cues, perhaps related to the novelty of the experience more generally (Hennessy et al., 1995). They ultimately reacted to a similar extent (in terms of peak magnitude), but perhaps did so in a less cue-entrained fashion, producing a more gradual slope to their peaks.

Alternatively, if children with higher EC displayed heightened fearfulness (which unfortunately was not measured), this could also potentially explain the observed stress response pattern in the fear context. High inhibitory control, which contributes to high EC, may emerge from early fearful inhibition (Aksan and Kochanska, 2004) and lead to heightened expression of fearfulness (Kochanska and Knaack, 2003). Heightened fearfulness might then contribute to faster and steeper cortisol slopes in high EC children in response to the fearful situation. However, fearfulness itself is not linked to HPA axis responses in adults (Curtis et al., 1978). Further work is needed to more precisely dissect the role of attention, novelty, or fear itself in shaping HPA responding and the ways in which individual variation in temperamental trait characteristics like EC may contribute to differential responding in different experimental and environmental stress contexts. If laboratory tasks vary in the degree to which they capture attention, and low attentional control can reduce responses to an experimental cue in the presence of distractors, but can contribute to heightened or prolonged responses when no distractors are present due to diminished regulatory capacity, we will clearly not be able to bring coherence to the existing literature unless these types of interactions are understood and regularly measured in our studies.

Strengths and Limitations

Our study has some important strengths and some limitations. It utilized a fully randomized experimental protocol that allowed us to directly compare two different stress tasks, both of which produced reliable HPA axis activation. It also utilized multi-modal measures of EC (laboratory and mother reports) collected at two different ages and well-before the stress procedures, allowing us to directly test the impact of EC on variability in stress-related activation. Our dense cortisol sampling procedure also ensured accurate capture of the dynamics of individual differences in cortisol responses (Lopez-Duran et al., 2009a). Limitations include a small sample size that did not allow us to conduct separate analyses by gender, although child gender was utilized as a covariate in all analyses. The study was a late add-on to a large original project, resulting in a relatively low participation rate and introducing the possibility of selection bias and non-representativeness of the larger population. However, the subsample did not differ from the original sample on any key variables (e.g., age, sex, SES, behavior problems). We did not assess concurrent EC at the time of the stress task – so it is possible that EC changed from age 6 to age 7. However, the finding that EC was relatively stable from age 3 to 6 is consistent with previous evidence that EC is longitudinally stable and represents a robust dimension in children (Ahadi et al., 1993; Kochanska and Knaack, 2003; Kochanska et al., 1997; Kochanska et al., 1996). We did not assess time from waking or napping. It is possible that children who are low and high in effortful control awake at different times, which could confound our results. However, all subjects were run in the afternoon and variation in time across the window used had no effect on cortisol levels. Various subcomponents of EC, such as emotion regulation and attentional control, might be critical elements in shaping HPA responses in different contexts; and our laboratory tasks did not allow us to differentiate EC subcomponents. Future research should focus on additional, more specific measures of, for example, executive attention. Marker tasks used in functional imaging studies could be helpful in efforts to target discrete components of EC (Rothbart and Rueda, 2005). Additional biological measures, such as salivary alpha-amylase, would also be helpful in validating the observed interaction between EC and stress context in predicting neuroendocrine stress responses. Furthermore, we conducted analyses on cortisol peak levels despite a non-significant interaction in the omnibus test, in order to most directly test our hypotheses. There is ongoing debate about this issue, with many supporting the need to test initial specific hypotheses (a priori comparisons) even in the absence of significant omnibus tests (see Kirk, 1995; Quinn and Keough, 2002; Ruxton and Beauchamp, 2008; Sokal and Rohlf, 1995).

It is also important to bear in mind that both low and high levels of EC can have adaptive and maladaptive outcomes (Kochanska and Knaack, 2003; Rothbart and Ahadi, 1994; Rothbart and Bates, 1998). Similarly, low and high cortisol reactivity can be either adaptive or maladaptive in nature, depending upon context. Flatter cortisol reactivity to fear situations in children with lower EC may be adaptive in some contexts. This study cannot determine whether low/high levels of EC or cortisol reactivity are adaptive or maladaptive, but rather sought to investigate the complex interactions between EC, stress context, and HPA axis activity. We think those interactions have relevance to psychopathology, but it is unlikely that low/high EC or low/high cortisol reactivity are, by themselves, indicators of pathology.

Lastly, our findings are correlational despite the longitudinal nature of the study, so causal direction of the links between developmentally measured EC and later HPA axis responsivity cannot be determined. There is evidence that early life stress and associated frequent activation of stress are linked to impairments in executive functions (e.g., Hostinar et al., 2012); and early life stress is also linked to later HPA axis regulation (Heim et al., 2008; Tyrka et al., 2008). In adulthood, cognitive function can exert top-down control of stress-endocrine activity (Abelson et al., 2008), and stress hormones can also shape cognitive function (Blair and Ursache, 2011). These may be inextricably intertwined phenomena. Future studies would benefit from longitudinal tracking of both stress responses and effortful control functioning. Our findings support the longitudinal stability of this relationship over time.

Conclusions and Implications

Our data suggest that variations in the HPA axis response to laboratory stressors are shaped by an interaction between important developmental self-regulatory traits related to emotion regulation and executive control and often neglected aspects of task specifics or experimental paradigms. We speculate that such EC-by-context interactions may involve many brain regions and their connections to and interactions with the hypothalamus, including the anterior cingulate cortex (ACC), amygdala, and hippocampus (Herman et al., 2005). For example, EC is associated with activity in the ACC – a limbic brain region in the medial prefrontal cortex that has been linked to EC components such as emotion regulation and attention processes (Bush et al., 2000; Posner et al., 2007), as well as neuroendocrine stress modulation (Herman et al., 2005). However, the effect of the ACC as well as other limbic areas on the hypothalamus are stressor-specific (Herman et al., 2005). Pruessner and colleagues (2008) argued that social-evaluative stress, which likely involves frustration experience, and fear-related stress (see, for example, Davidson, 2002) *differentially* activate a network of limbic structures. The hippocampus is involved in context-regulation of affective and neuroendocrine responding (Davidson et al., 2000; Herman et al., 2005) and might be a key player in modulating these processes and shaping hypothalamic output. Overall, the underlying neural network allows adapting behavior to particular cues that demand different responses depending on self-regulatory skills and varying environmental contexts. Our result, showing links between a self-regulatory temperamental trait measured at age 3–6 and context-sensitive cortisol reactivity at age 7 is consistent with the idea that the HPA axis is part of a system for long-term programming for adaptive responding to future expectable environments, which might have significant implications for its role in human psychopathology.

The HPA axis has been associated with a variety of psychiatric disorders (Abelson et al., 2007; Burke et al., 2005; Simeon et al., 2007). Given its role as an integrator of genetic and early environmental information (Gotlib et al., 2008; Heim et al., 2008; Korosi and Baram, 2008), it likely marks a predisposing etiologic agent that is not disorder specific, but contributes to general vulnerability to psychopathology (Abelson et al., 2007). The field of stress studies must shift its focus from disorders to critical dimensions of behavior and to predispositions within behavioral dimensions (e.g., temperamental traits). Fuller understanding of human psychopathology will require knowledge about how behavioral

predispositions develop over time, their neural underpinnings, how they are intertwined with neuroendocrine stress activity, and how they interact with contextual factors in shaping stress responses in experimental studies and in the real world.

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Highlights

- Effortful control (EC) and context interact to shape HPA response in 65 children.
- Lower EC is associated with steeper cortisol reactivity in a frustration context.
- However, lower EC in a fear context is associated with more gradual HPA activation.
- Different components of EC may differentially interact with the stress context.
- Our results have implications for the interpretation of cortisol reactivity data.

Figure 1.

Mean ($\pm$ SE) salivary cortisol values (μ g/dl) in response to each stress task (fear vs. frustration). Children showed significant increases in cortisol levels in response to both stress tasks, though peaks occurred later in the frustration task.

Figure 2.

Salivary cortisol as a function of minutes to peak and effortful control (EC) at age 3 (top panels A and B) and age 6 (bottom panels C and D) in different stress contexts: frustration (left panels A and C) vs. fear (right panels B and D). To facilitate visual representation, low and high groups of EC were created, representing ± 2 SD above the mean. The graphs suggest that EC and stress context interact in shaping cortisol response to stress. In response to frustration (left panels), children with low EC at age 3 and 6 displayed steeper reactivity slopes and slightly elevated cortisol peak values. However, in response to fear (right panels), low EC at age 3 and 6 was linked to flatter cortisol slopes (slower, more gradual reactivity), with no impact of EC on peak levels.

Table 1

Mean (M), standard deviation (SD), sample size (N), and correlations between effortful control (EC:) measures.

	1	2	3	4	5	6	7	8	9	10	M	SD	N
1 Time 1 (Age 3) EC index	1										-0.002	0.83	65
2 Laboratory EC	0.82**	1									-0.03	0.56	64
3 Mother-rated EC	0.82**	0.32**	1								-0.01	1.83	64
4 Attentional focusing	0.75**	0.34**	0.88**	1							4.72	0.87	64
5 Inhibitory control	0.63**	0.20	0.82**	0.45**	1						4.56	0.71	64
6 Time 2 (Age 6) EC index	0.59**	0.27**	0.72**	0.65**	0.58**	1					-0.04	0.82	64
7 Laboratory EC	0.20	0.04	0.29*	0.29*	0.20	0.79**	1				-0.03	0.43	56
8 Mother-rated EC	0.68**	0.32*	0.83**	0.73**	0.67**	0.81**	0.20	1			-0.06	1.72	63
9 Attentional focusing	0.60**	0.34**	0.69**	0.76**	0.37**	0.69**	0.20	0.84**	1		4.92	0.83	63
10 Inhibitory control	0.55**	0.19	0.71**	0.49**	0.76**	0.68**	0.16	0.84**	0.42**	1	4.86	0.92	63

*
 $p < .05$,**
 $p < .01$

Adjusted modeling of effortful control at age 3 (EC_{age3}) and stress context (frustration vs. fear) predicting salivary cortisol reactivity slopes and peak values.

Table 2

Model	Predictor variable	Estimates			Type 3 effects	
		<i>b</i>	<i>SE</i>	<i>t</i>	<i>F</i>	
Direct effect	EC_{age3} effect on linear slope	-0.000320	0.000161	-1.98*	3.90*	
	EC_{age3} effect on quadratic slope	-0.000008	0.000003	-2.52*	6.33*	
	EC_{age3} effect on peak	-0.003640	0.003307	-1.10	1.21	
	Stress Context effect on linear slope	0.000370	0.000313	1.18	1.40	
	Stress Context effect on quadratic slope	0.000017	0.000008	2.05*	4.22*	
	Stress Context (frustration = 0) effect on peak	-0.000510	0.005333	-0.10	0.01	
Interaction	EC_{age3} effect on linear slope	-0.000730	0.000200	-3.67**	0.93	
	EC_{age3} effect on quadratic slope	-0.000010	0.000003	-4.09**	3.18†	
	EC_{age3} effect on peak	-0.007650	0.004444	-1.72†	0.25	
	Stress Context effect on linear slope	0.000227	0.000308	0.74	0.54	
	Stress Context effect on quadratic slope	0.000013	0.000008	1.52	2.32	
	Stress Context (frustration = 0) effect on peak	-0.001290	0.005270	-0.24	0.06	
	EC_{age3} X Stress Context effect on linear slope	0.001883	0.000430	4.38**	19.20**	
	EC_{age3} X Stress Context effect on quadratic slope	0.000051	0.000014	3.77**	14.24**	
	EC_{age3} X Stress Context effect on peak	0.012020	0.006490	1.85†	3.43†	
Frustration only	EC_{age3} effect on linear slope	-0.000730	0.000179	-4.08**	16.68**	
	EC_{age3} effect on quadratic slope	-0.000010	0.000003	-4.63**	21.40**	
	EC_{age3} effect on peak	-0.008240	0.004152	-1.99†	3.94†	
Fear only	EC_{age3} effect on linear slope	0.001056	0.000448	2.36*	5.55*	
	EC_{age3} effect on quadratic slope	0.000033	0.000015	2.15*	4.61*	
	EC_{age3} effect on peak	0.003856	0.005281	0.73	0.53	

† $p < .10$;

$10' > d'$
**
 $p < .05$
*

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Adjusted modeling of effortful control at age 6 (EC_{age6}) and stress context (frustration vs. fear) predicting salivary cortisol reactivity slopes and peak values.

Table 3

Model	Predictor variable	Estimates			Type 3 effects	
		<i>b</i>	<i>SE</i>	<i>t</i>	<i>F</i>	
Direct effect	EC_{age6} effect on linear slope	-0.000320	0.000180	-1.79 [†]	3.21 [†]	
	EC_{age6} effect on quadratic slope	-0.000005	0.000004	-1.46	2.13	
	EC_{age6} effect on peak	-0.004470	0.003478	-1.29	1.65	
	Stress Context effect on linear slope	0.000494	0.000323	1.53	2.35	
	Stress Context effect on quadratic slope	0.000019	0.000009	2.19*	4.82*	
	Stress Context (frustration = 0) effect on peak	0.001000	0.005455	0.18	0.03	
Interaction	EC_{age6} effect on linear slope	-0.000550	0.000220	-2.47*	2.53	
	EC_{age6} effect on quadratic slope	-0.000009	0.000004	-2.49*	10.04**	
	EC_{age6} effect on peak	-0.006500	0.004696	-1.38	0.43	
	Stress Context effect on linear slope	0.000499	0.000318	1.57	2.46	
	Stress Context effect on quadratic slope	0.000018	0.000008	2.17*	4.69*	
	Stress Context (frustration = 0) effect on peak	0.001125	0.005437	0.21	0.04	
	EC_{age6} X Stress Context effect on linear slope	0.001853	0.000480	3.86**	14.91**	
	EC_{age6} X Stress Context effect on quadratic slope	0.000067	0.000015	4.40**	19.33**	
	EC_{age6} X Stress Context effect on peak	0.008431	0.006941	1.21	1.48	
Frustration only	EC_{age6} effect on linear slope	-0.000540	0.000200	-2.70**	7.29**	
	EC_{age6} effect on quadratic slope	-0.000009	0.000003	-2.75**	7.55**	
	EC_{age6} effect on peak	-0.007660	0.004310	-1.78 [†]	3.16 [†]	
Fear only	EC_{age6} effect on linear slope	0.001189	0.000501	2.37*	5.64*	
	EC_{age6} effect on quadratic slope	0.000050	0.000017	2.88**	8.30**	
	EC_{age6} effect on peak	0.001235	0.005609	0.22	0.05	

[†] $p < .10$;

$10' > d'$
**
 $p < .05$
*

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