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Moderate Within-Person Variability in Cortisol is related to Executive Function in Early Childhood

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Abstract

Lab-based experimental studies with humans and in animal models demonstrate that the relation between glucocorticoid (GC) levels and performance on measures of higher-order cognitive ability such as executive function (EF) is best described by an inverted U-shape curve. Moderate levels of GCs (cortisol/corticosterone) are associated with comparatively better performance relative to GC levels that are particularly high or low. Although findings from experimental studies are definitive and have high internal validity, the external validity of this association as an aspect of children's development is unknown. Here we analyze data from the Family Life Project (N=1292), a prospective longitudinal sample of children and families in predominantly low-income and rural communities followed longitudinally from infancy through age 60 months. Consistent with the prior experimental literature, we found evidence of an inverted-U relation. For children with relatively low cortisol levels, on average, between the ages 7, 15, 24, and 48 months, those illustrating *moderate* fluctuations in their cortisol levels over this span tended to show subsequently better EF performance at 60 months, than did children with either highly stable *or* highly variable temporal profiles. This curvilinear function did not extend to children whose cortisol levels were high, on average. These children tended to show lower EF performance, irrespective the stability of their cortisol levels over time.

Keywords

cortisol; executive functions; early childhood; development

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A well-established research literature indicates associations between specific aspects of cognition, particularly learning and memory, and acute changes in levels of stress-related neurochemicals (Holmes & Wellman, 2009; Roozendaal, McEwen, & Chattarji, 2009). Generally speaking, changes in stress-related neurotransmitters, neuropeptides, and hormones are understood to flip the brain from a top-down to a bottom-up mode of response. Rather than a linear relation, however, studies indicate that the association between stress and neural activity is quadratic, specifically that of an inverted U-shaped curve (Arnsten, 2009). Evidence from experimental studies, including pharmacological manipulations and stress induction protocols with animal models (Arnsten & Li, 2005; Vijayraghavan et al., 2007; Yuen et al., 2009) as well as (to a more limited extent) with humans (Mattay, Goldberg, Fera, Hariri, Tessitore, Egan, & Weinberger, 2003; Lupien, Gillin, & Hauger, 1999; Qin et al., 2012) indicates that moderate, time-limited increase in catecholamines, norepinephrine and dopamine, and in the glucocorticoid hormone cortisol is associated with enhanced performance on measures of what can be considered reflective, effortful, goal-directed aspects of cognitive ability, such as working memory and executive function. As catecholamines and glucocorticoids rise beyond a moderate level, however, they reduce neural activity associated with reflective cognition and increase activity associated with habitual, reactive, and highly automatized aspects of learning and memory such as implicit and probabilistic learning and episodic memory (Arnsten, 2015; de Kloet, Oitzl, & Joëls, 1999; Lupien & McEwen, 1997; Schwabe & Wolf, 2013).

Effects of acute changes in stress-related hormones on the brain and cognition, which for the most part have been analyzed in cross-sectional studies, are related to but distinct from long-term effects of chronic elevations of stress hormones early in life on later health and wellbeing. Chronic elevations have been shown to alter neural plasticity, leading to morphological changes in the brain such as reductions in apical dendrite length in pyramidal neurons of medial PFC, reduced hippocampal volume and increased risk for the development of psychopathology (Radley et al., 2004; McEwen & Gianaros, 2011). Notably, however, experimental longitudinal studies of acute as opposed to chronic stress exposure in animal models suggest some longer-term benefits associated with intermittent time-limited increases in stress-related neurochemicals. In both rats and monkeys, intermittent stress induced by brief periods of isolation early in life is associated with enhanced regulation of the stress response as indicated by levels of cortisol (corticosterone) and also with benefits to cognitive development including performance on measures of working memory and inhibitory control (Parker, Buckmaster, Schatzberg, & Lyons, 2004; Parker, Buckmaster, Justus, Schatzberg, & Lyons, 2007; Tang, Akers, Reeb, Romeo, & McEwen, 2006). In one set of studies, squirrel monkeys randomized to one hour of isolation per week for 10 weeks between postnatal week 17 and 27 were later shown to have lower adrenocorticotrophic hormone and cortisol at rest and following a stressor, better behavior regulation in response to novelty, and a higher level of executive inhibitory control relative to a low stress control condition (Parker et al., 2004, 2005). These effects were observed whether monkeys were isolated alone or with the mother and were also observed in a manipulation to simulate high versus low foraging demand (Parker, Buckmaster, Sundlass, Schatzberg, & Lyons, 2006). Similarly, in Long-Evans rats, an innovative handling procedure over the first 21 postnatal days which exposed the pups to a novel environment but did not change other aspects of

postnatal experience such as maternal care, was associated with enhanced corticosterone reactivity to novelty and with increased spatial working memory and social behavior in adulthood (Tang et al., 2006).

The findings of intermittent stress protocols provide support for the hypothesis that acute time-limited increases in stress-related neurochemicals early in life promote the ability to flexibly regulate physiological state in ways that are conducive to executive function abilities and to the effortful regulation of emotion and attention. With repeated activation followed by return to baseline, the stress response is understood to become less prolonged and pronounced, i.e., more effectively regulated (McEwen, 2006). Such a pattern of accommodation to repeated “hits”, or activation, would represent an allostatic adaptation of the stress response to experience.

Findings from experimental studies demonstrating an association between moderate time-limited increases in stress-related neurochemicals and executive cognitive abilities have high internal validity. Few studies, however, have examined the external validity of this association in ecologically valid contexts. The experimental studies suggest that increased variability in cortisol measured longitudinally around a moderate or low average level will be associated with greater executive cognitive control, particularly as this ability is emerging in early childhood. It is currently unknown, however, whether such variability over time scales spanning months to years will also be associated with higher executive function. A small number of naturalistic studies with children suggest that moderate elevations in cortisol are positively associated with performance on measures of higher order cognitive abilities such as executive function (Blair, Granger, & Razza, 2005; Davis, Gunnar, & Bruce, 2002; Suor, Sturge-Apple, Davies, Cicchetti, & Manning 2015). To date, however, no dataset has been available to longitudinally examine whether within-person variability in cortisol levels from infancy through early childhood is associated with greater top down cognitive control as indicated by measures of executive function. Here, we analyze data from the Family Life Project, a prospective longitudinal study of children and families followed from birth in predominantly low-income and rural communities in the US. In prior analyses with this dataset we have shown that typically occurring experiences in children’s lives are associated with variation in cortisol. One such experience is the quality of parenting which children receive. In one prior analysis we found that within-parent change in parenting sensitivity, assessed in a semi-structured interaction at 7, 15, and 24 months was associated with within-child change in cortisol over this time period (Berry, Blair, Willoughby, & Granger, & the FLP Investigators, 2017). In similar analyses we have also shown that variation in cortisol over approximately one hour in response to emotion induction procedures at child ages 7, 15, and 24 months is also associated with parenting sensitivity and with child emotionality and temperament (Blair, Granger, Kivlighan, Mills-Koonce, Willoughby, Greenberg, Hibel, Fortunato, & the FLP Investigators, 2008). Further, we have shown that variation in cortisol levels among children in the sample is associated with characteristics of the home environment (Berry, Blair, Granger & the FLP Investigators, 2016; Blair, Raver, Granger, Mills-Koonce, Hibel, & the FLP Investigators, 2011b) as well as the quality of care that children receive.

Building on these prior analyses, we now examine within-child and between-child variability in cortisol in early childhood, from age 7 months to age 48 months to test the longitudinal hypothesis that moderately higher within-person variability in cortisol in early childhood, as opposed to consistently high or consistently low levels of cortisol, will be associated with better performance on a measure of executive function ability at child age 60 months, prior to entry into kindergarten. Specifically, we expected that for children who maintained characteristically low levels of cortisol across infancy and the toddler period, moderate levels of *within*-child variation in cortisol over this period would be predictive of higher executive function ability. However, we expected this ‘beneficial’ relation between cortisol variability and executive functioning to be far less pronounced for children with characteristically high average cortisol level over this period. We expected that these associations between cortisol and executive function would be observed when controlling for a number of covariates that might explain any observed association between variability in cortisol and executive function.

Method

The Family Life Project (FLP) was designed to study families living in two of the four major geographical areas of high child rural poverty (Dill, 2001). Complex sampling procedures were used to recruit a representative sample of 1,292 families at the time of the target child’s birth, with oversampling of low-income families and families of African American ethnicity. Further details on the Family Life Project sampling plan and recruitment procedures are available in Vernon-Feagans, Cox, and the Family Life Project Investigators (2013). Seventy percent of families had an average income of less than 200% of the poverty line. Additionally, forty percent of mothers had a high school education (12 years of schooling) or less, while only sixteen percent had at least 4 years of post-secondary education. A little more than half of the sample is White (57%) with the remainder of African American descent.

Procedures

Families were visited in their homes at child ages 7, 15, 24, and 48 months and the primary caregiver (the mother in almost all instances) answered questions about demographics, e.g., child race, sex, maternal education and household size and income. In addition to a number of other procedures, saliva samples were collected from children to assess levels of cortisol prior to the administration of emotion induction tasks at 7, 15, and 24 months. At child age 48mos, saliva was collected prior to the administration of a battery of cognitive tasks. The emotion induction tasks at 7, 15, and 24 months are standard tasks used to elicit fear and frustration responses from children (Goldsmith & Rothbart, 1996). The first saliva sample at each time point (7, 15, 24, and 48mos) was collected at approximately M=13:30h (SD=3:00h). Therefore, the majority of saliva samples at each time point were collected between 10:30h and 16:30h. Some samples, however, were collected as early as 8:00h or as late as 20:00h. Families tended to be seen at approximately the same time of day at each home visit for data collection ($r \sim .21$, $p < .0001$), however, there was considerable variability in time of day of data collection for each family across the four time points. Calculation of a ‘time-of-day’ difference scores indicated that approximately half of the sample was seen

within 1–2 hours of the time of day of the prior visit, however, some families were seen as much as five hours earlier or later than the time of day of the prior visit (between- and within-child variability in saliva collection time were controlled in all models). Data collectors were in the home one-hour on average prior to collecting the first saliva sample. Unstimulated whole saliva was collected by using either cotton or hydrocellulose absorbent material and expressing the sample into 2-ml cryogenic storage vials using a needleless syringe (cotton) or by centrifugation (hydrocellulose). Two prior studies indicated no differences in cortisol concentrations associated with the two collection techniques (Granger et al., 2007; Harmon, Hibel, Rumyantseva, & Granger, 2007). After collection, samples were immediately placed on ice, transported to interviewer's homes, and then stored frozen (-20°C).

At child age 60 months, families were again visited in the home and children were administered a battery of executive function tasks among other procedures.

Measures

Cortisol—All samples were assayed for salivary cortisol using a highly sensitive enzyme immunoassay (Salimetrics, State College, PA). The test used 25 ml of saliva, had a range of sensitivity from 0.007 to 3.0 mg/dl, and average intra- and interassay coefficients of variation less than 10% and 15%, respectively. All samples were assayed in duplicate and the average of the duplicates was used in all analyses. Natural log transformations were applied to the cortisol values to correct for positive skew.

Executive functions—The battery included three inhibitory control tasks, two working memory tasks, and one attention shifting task. The working memory tasks included a span-like task and a self-ordered pointing task. The attention shifting task was an item selection task modeled on the Dimensional Change Card Sort task (Jacques & Zelazo, 2001). The inhibitory control tasks included a Simon-like spatial conflict task, a Stroop-like silly sounds task, and a farm animal go no-go task.

In the working memory span task children see the outline of a house with an animal and a colored dot inside it. Children are prompted to name the animal and the color of the dot. Then they are shown a blank house and asked to report the animal they had seen in the previous house. In order to perform correctly, children must hold two pieces of information in mind (i.e., the animal and the color) but only activate the animal name while suppressing the color information. Trials increase in difficulty by adding more houses to each page, with each house containing different animals and colors.

In the self-ordered pointing task, children are presented with pages with the same items dispersed across different locations. Children are instructed to touch a new picture on each page that she has not previously touched so that each picture “gets a turn”. The way in which pictures are arranged on the page is randomly changed each time the child turns the page. Difficulty increases as more items, up to six, are added to the pages.

In the spatial conflict task, children are instructed to touch a response location that is either congruent or incongruent with the direction that a stimulus arrow is pointing. Task difficulty

increases across trial blocks. For the first eight items, the arrow is presented centrally, for items 9–22 the arrow is presented on the left or right upper corner of the page and all items are congruent (left-pointing arrows are on the left, right-pointing arrows are on the right). Items 23–35 present a mix of congruent and incongruent trials.

In the attention shifting task, children are first presented with two items on a page that are similar in size, shape, or color. The experimenter points out the way in which the two objects are similar and then presents the child with a second page which has the same two items to which a third item is added. The third item is similar to one of the two original items along a second dimension that is different from the similarity of the first two items. The experimenter asks the child to identify the way in which the new item is similar to one of the two previously presented items.

In the Stroop-like task, children are instructed to make the sound of a dog when they see a picture of a cat and to make the sound of a cat when they see a picture of a dog.

In the farm animal go no-Go task, children respond by clicking a button in response to sequentially presented farm animals (one per page) except when the animal is a pig. The standard order of consecutive go trials between no-go trials is one-go, three-go, three-go, five-go, one-go, one-go, and three-go.

Each task was presented in an open spiral bound flipbook with pages that measured 8" × 14". For each task, research assistants established that the child knew colors and numbers and administered training trials and up to three practice trials if needed. If children failed to demonstrate an understanding of the goals of the task following the practice trials, the examiner discontinued that task. Full details regarding the administration rules, psychometric properties, and scoring approach for each of these tasks have been presented elsewhere (Willoughby, Blair, Wirth, Greenberg & the FLP Investigators, 2012).

Item response theory was used to generate expected a posteriori (EAP) scores for each task and these scores were equated over time using a calibration sample. For details about the generation of the EAP scores and information about the longitudinal measurement invariance of these scores see Willoughby, Wirth, Blair, and the Family Life Project Investigators (2012). EAP scores were averaged to form a composite measure of EF ability. As is typical of EF measures (Willoughby, Holochwest, Blanton, & Blair, 2014), the reliability coefficient for the composite was relatively low, $\alpha = 0.50$. As discussed in the online supplementary material (S1), sensitivity analyses indicated that the results were consistent regardless of whether the EF tasks were composited or modeled as discrete tasks.

Data Analytic Plan—To test the extent to which moderate levels of variability in cortisol across early childhood (7 – 48 months age) were associated with more effective executive functioning skills at school transition (60 months), we fitted a taxonomy of multiple regression models using the robust full-information maximum likelihood estimator available in Mplus 5.21 (Muthen & Muthen, 2009). Specifically, we first tested whether children's mean level of basal cortisol over the period 7, 15, 24, and 48 months of age, as well as within-person cortisol variability around this mean was uniquely predictive of EF abilities at

child age 60 months, after adjusting for our vector of control covariates (see Supplementary Materials S2 for details on the control covariates). To test whether these relations were non-linear, we subsequently added quadratic terms to the model. Finally, to address whether the quadratic relation between within-child cortisol variation and EF was particularly pronounced for those with lower *mean* cortisol across the age range examined, we tested the three-way interaction between the cortisol variation quadratic term and mean cortisol level (with its constituent two-way interactions). We fitted model constraints to probe substantively meaningful simple slopes. Satorra-Bentler (S-B) (Satorra & Bentler, 2001) adjusted likelihood ratio tests were used to compare nested models.

Given that higher-order interactions can reflect the potential influence of aberrant points of high-leverage and/or high influence, we conducted a series of sensitivity analyses (descriptive and inferential) to test this possibility (e.g., robust regression; quantile regression). As the results were virtually identical, we limit our discussion of these somewhat lesser known treatments to the Supplementary Material S3.

Results

Preliminary Analyses

As displayed in the zero-order correlations in Table 1, there was initial evidence of a modest negative correlation between children's mean cortisol levels between the ages of 7 and 48 months and their subsequent executive function ability at 60 months ($r = -.15, p < .001$). Mean cortisol was also modestly correlated (in the expected direction) with several of the control covariates. In contrast, within-child variation in cortisol over this period was orthogonal to executive functioning at child age 60 months and most of the control covariates. As would be expected, however, children with higher mean levels of cortisol had higher variability in cortisol ($r = .36, p < .001$). There was, however, ample coverage of individuals throughout this bivariate distribution.

The scatterplots presented in Figures 1a and 1b display the observed and estimated bivariate relations between within-child cortisol variation (7–months) and executive functioning (60 months), conditional on low (grand mean – 1 SD) and high (grand mean + 1 SD) *mean* levels of cortisol, respectively. As shown in Figure 1a, there was evidence of a non-linear relation between within-child cortisol variation and executive functioning, when this variation occurred around *low mean* cortisol levels, defined as –1 SD. Specifically, the relation was well represented by a quadratic function—descriptively, the shape of an inverted-U. The fitted zero-order quadratic relation accounted for nearly 11% of the variation in child executive function abilities at 60 months. Notably, as suggested by the scatterplot displayed in Figure 1b, this association became considerably more linear, positive, and weak for those with high mean cortisol levels.

To test these theorized relations inferentially, we fitted a taxonomy of multiple regression models. Preliminary models (Table 2; M1) indicated a statistically marginal negative main-effect relation between mean cortisol level and EF, after adjusting for the control covariates ($B = -.06, p = .05$). No linear (M1; $B = .05, p = .30$) or quadratic (M2; $B = -.04, p = .61$) main-effect relations were evident between within-child cortisol variation and EF. However,

there was a statistically significant 3-way interaction (i.e., $\text{cortSD} \times \text{cortSD} \times \text{Mean cort}$), such that the quadratic relation of within-person cortisol variation with executive function was moderated by children's average cortisol levels between 7 and 48 months of age (M2: $B = .18$, $p = .04$). Specifically, as hypothesized and as suggested by the descriptive data, the interaction indicated that the quadratic relation was strongest when children's average cortisol levels in early childhood were low, with the magnitude of this non-linear association becoming increasingly less pronounced for children with higher mean cortisol levels between the ages of 7 and 48 months.

As displayed in Figure 2, the conditional quadratic was reflected in an inverted-U function, such that moderate levels of within-child variation in cortisol between 7 and 48 months were predictive of better performance on the measure of executive function at 60 months, for children with lower *mean* cortisol levels (green line) over this period (e.g., grand mean – 1 SD). For these children, tests of model constraints indicated that the quadratic effect was statistically significant ($B_{\text{lo_mean_cort}} = -.25$; $p = .01$). The initially positive instantaneous linear effect at the low end of the cortisol variation distribution decayed at rate of $-.36$ (i.e., $-.18 \times 2$), reaching its vertex at a level that was just above the grand mean (i.e., vertex = $.69$; grand mean = $.65$). Beyond this peak of the curve the relation “flipped;” higher levels of within-child variability in cortisol were associated with increasingly lower executive function ability.

To put this in context, children who maintained low mean levels of cortisol, yet experienced moderate variability in their cortisol levels around this low mean had significantly higher executive functioning abilities prior to kindergarten entry compared with their otherwise statistically identical peers who showed very little (e.g., 5th percentile) or substantial amounts (e.g., 95th percentile) of variability in their cortisol levels over time ($B_{\text{mean_vs_lo}} = .07$ & $B_{\text{mean_vs_hi}} = .11$; Wald $\chi^2 = 6.356$, $df = 2$, $p = .04$). These estimates correspond to approximately .14 SD and .22 SD differences, respectively.

Notably, the quadratic relation between cortisol variability and executive functioning became increasingly less pronounced for children with higher mean cortisol levels between 7 and 48 months of age. For example, although the quadratic effect remained statistically significant for children with average cortisol levels (black line) that were at the grand mean (Table 2, M2; $B = -.15$, $p = .04$), this non-linearity was comparatively less pronounced. Indeed, model constraints indicated that for children with high levels of mean cortisol over time (blue line) there was no quadratic effect (Figure 2, blue slope; $B_{\text{hi_mean_cort}} = -.06$; $p = .43$). That is, when average cortisol levels are high and chronic (i.e., little variability) between 7 and 48 months of age, these children tend to perform the worst on the measure of executive function at age 60 months. In addition, there was some indication that high variability (i.e., more substantial time-to-time variation in cortisol) around a high mean level, indicating less chronicity, was associated with somewhat better performance on the measure of executive function. Notably, when this simple slope was constrained to be linear, it did not reach levels of statistical significance. Subsequent probes indicated that the positive linear relation between variability in cortisol and executive functioning only became statistically significant at very high mean cortisol levels (e.g., grand mean + 2 SD). This provides some indication that greater variability—i.e., *less chronicity*—in very high levels of cortisol across early

childhood is associated with comparatively better executive function performance prior to school entry. Notably, however, this interpretation warrants some caution given the limited representation of individuals in this tail of the multivariate distribution.

The final model (M2) accounted for 22% of the variation in EF; approximately 7% of this explained variation was uniquely accounted for by individual differences in children's cortisol profiles between 7 and 48 months. These findings were robust to a non-trivial series of sensitivity analyses (see Supplementary material S3 for detailed descriptions).

Discussion

Results from this prospective longitudinal analysis provide unique evidence in support of the ecological validity of the association between longitudinal variability in stress-related neurochemicals in early childhood, here indicated by cortisol, and the development of higher-order aspects of cognitive ability such as executive function. Findings indicate that for children with low *average* resting levels of cortisol between 7 and 48 months of age, moderate fluctuation in cortisol over this time period was associated with comparatively better performance on a battery executive function tasks at 60 months relative to very little *or* substantial amounts of variability in cortisol over this period. In contrast, this curvilinear relation was not evident for children with high average levels of cortisol. Notably, when children's average cortisol level was high and chronic (i.e., little within-child variability), children tended to show the worst performance on the battery of executive function tasks.

As noted in the introduction, findings from experimental studies using pharmacological agents and intermittent stress protocols have high internal validity and definitively demonstrate associations between acute elevations in levels of stress-related neurochemicals and cognition (Arnsten, 2009; Parker et al., 2006). The novel contribution of this analysis is the demonstration of a prospective longitudinal association between within-person variability in levels of salivary cortisol in infancy and early childhood and executive functioning prior to school entry. Our expectation for this effect was based on the large literature indicating widespread effects of stress-related changes in neurochemicals on brain function (Joëls & Baram, 2009; McEwen, Gray, & Nasca, 2015). Acute increases in glucocorticoids and catecholamines potentiate synaptic activity and increase neural firing in areas of PFC associated with top down cognitive control of behavior (Timmermans, Xiong, Hoogenraad, & Krugers, 2013). Generally speaking, this effect is driven the affinity of neural receptors for these neurochemicals. At moderate levels of increase in norepinephrine, high affinity alpha-2 adrenergic receptors are occupied and increase the firing rate of neurons that are important for retaining information in working memory (Arnsten, 2009). Similarly, at moderate levels of glucocorticoid increase, high affinity mineralocorticoid receptors as well as low affinity glucocorticoid receptors are active at the cell membrane and potentiate glutamatergic transmission in PFC pyramidal neurons important for working memory (de Kloet, 2014; Joëls et al., 2008; Yuen et al., 2009).

Our expectation for an association between moderate variability in cortisol and executive cognition was further based on the findings of intermittent stress protocols with nonhuman primates that experimentally induce variation in cortisol levels over several weeks. Findings

from these experiments indicate broad effects of the manipulation on measures of the regulation of physiology, behavior, and cognition (Parker & Mastripietri, 2011). Our analysis detected an association between variability in cortisol and executive function ability across a much longer timeframe, specifically four time points of measurement over four years. In the absence of more intensive assessment of cortisol, we assume that variability in cortisol occurring over essentially annual intervals is a marker for variability occurring over more frequent timescales and as such indicative of the acute, flexible regulation of the stress response associated with more effective executive cognitive function. Of course, this remains an assumption to be tested directly.

Notably, our findings are generally consistent with but extend in a meaningful way the only other study of which we are aware to have examined longitudinal relations between cortisol and cognitive ability in early childhood. Specifically, a prior analysis by Suor and collaborators (2015) using growth mixture modeling identified groups characterized by sustained low, moderate, and high mean levels of cortisol at ages 2, 3 and 4 years. This analysis found that the mean age 4 IQ of the group characterized by consistently moderate mean level of cortisol was substantially and significantly higher than that of the consistently low and consistently high cortisol groups. As with our analysis, poorest cognitive ability in that prior analysis was observed among the group characterized by consistently high mean cortisol from age 2 to age 4 years. Our findings build on and extend these prior findings by attending to variability in cortisol. Specifically, in the prior analysis, the low and moderate cortisol trajectories are similar to one another and both are clearly differentiated from the high cortisol trajectory. Our analysis indicates that modeling variability in cortisol provides valuable additional information with which to differentiate low and moderately elevated groups. That is, low level of cortisol in the absence of variability in our analysis, as in the analysis of Suor et al. (2015), is associated with lower level of executive function relative to low average level with moderate variability. The same is true at the mean (i.e., moderate) level of cortisol in our analysis. Again, however, our analysis strongly suggests the need to account for variability when examining relations between mean levels of cortisol over time and cognitive development.

A further relevant point is that for children with high average cortisol in early childhood, the association between variability and executive function was linear. The association between cortisol variability and executive function, however, only became significant when variability was very high (+2SD). This finding would seem to indicate that even for children with very high mean level of cortisol, less chronicity (i.e., greater variability around a high mean level) is associated with some cognitive benefit. There are, however, relatively few individuals in this extreme tail of the distribution. For most children with high average cortisol in early childhood, risk is increased for future difficulty in school and for emerging psychopathology (Tarullo & Gunnar, 2006). Future analyses with this longitudinal dataset could focus on this elevated group and address questions concerning the chronicity versus timing of stressful events from infancy through early childhood.

Conclusion

Associations among chronic early life stress and poor physical and mental health outcomes are well established both in humans and animal models (Holmes & Wellman, 2009; Miller, Chen, & Parker, 2011). When stress, defined as implied threat to the organism, is chronic, physiological and behavioral systems adjust or adapt in ways that maximize reactive responses to threat. These physiological adaptations, as indexed by increases in stress hormone levels and inflammatory markers, are understood to promote vigilance. Yet, in so doing they lead to behaviors and physiological and psychological states that degrade the integrity of organ systems and neural circuitry, with adverse consequences for physical and mental health (McEwen & Gianaros, 2011). This is presumed to particularly be the case when stress is occurring early in life, such as that associated with disruptions in early caregiving (Loman & Gunnar, 2010; McLaughlin et al., 2015).

Although the effect of chronic psychosocial stress on stress response physiology and developmental outcomes is well established, much less is known about moderate elevations in stress-related neurochemicals and child development. In theory, there are multiple aspects of experience that could potentially contribute to moderate variability in cortisol. As noted in the introduction, one that we have examined previously in this dataset is parenting behavior. In that prior analysis, within-parent increases in parenting sensitivity, assessed in a semi-structured interaction at 7, 15, and 24 months were associated with within-child decreases in cortisol over this time period but only for children of parents whose average sensitivity from 7 to 24 months was low (Berry et al., 2017). When parents who were initially low in sensitivity increased in their sensitivity over time, there was a concomitant decrease in child cortisol level. For parents initially high in sensitivity, increases in sensitivity were associated with increases in child cortisol. This analysis suggests that variability in parenting sensitivity within a typical range is associated with variability in cortisol.

Another aspect of children's experience likely associated with variability in cortisol is novelty exposure. A strong experimental literature in animal models indicates that novelty exposure, whether through handling procedures, environmental enrichment, or intermittent stress induction is a potent influence on the activity of the HPA axis and on cognitive and social competence (Parker et al., 2004; Tang et al., 2006). In the absence of experimental control, we cannot definitively test a novelty exposure mechanism. We have shown in a prior analysis, however, that for children from highly chaotic homes, more time out of that home environment in childcare is associated with decreased cortisol at 15 and 24 months of age (Berry et al., 2016). As with our analysis of change in parenting sensitivity, this analysis indicates a relevant aspect of children's early experience that impacts variation in cortisol.

Limitations

Although our study has notable strengths, such as its sample size and sample characteristics, it is limited in certain respects. In particular, results were observed with resting state cortisol obtained from saliva at essentially annual intervals. Although we used identical data collection protocols at each time point, were in the home for at least one hour prior to the first saliva collection, and adjusted our estimates for an extensive array of potential confounds—including between- and within-child variability in saliva collection times and

maternal sensitivity—it remains possible that unobserved confounds could have biased our estimates. Furthermore, cortisol from saliva is only one peripheral marker of the stress response. Our analysis suggests that it is a reasonably good indicator of a host of stress-related processes that are occurring centrally but we have no way of verifying this in our dataset. In addition, the sample is predominantly low-income and living in specific regions of the United States characterized by high poverty. As such, the range of both independent and dependent variables is restricted and resulting estimates of effect sizes may be underestimates. Notably, the purely descriptive functional forms evident in the raw data, as well as the robustness of our estimates to varying analytic strategies strengthen confidence in our findings. As such, our analysis provides a relatively clear look at variability in cortisol in early childhood in relation to a key aspect of cognitive development in children.

This analysis builds on prior analyses of the FLP dataset to demonstrate a relation between variability in cortisol and executive function prior to kindergarten entry at age 60 months. Future analyses with this and other datasets might profitably examine other aspects of cognitive ability, particularly learning and memory tasks and the capture of attention by emotional stimuli (e.g., Cahill & Alkire, 2003; Anderson, 2005). In light of the prior experimental literature, however, it is important to acknowledge that no causal claims can be made from this analysis. In theory, repeated time-limited activation and regulation of the stress response would be expected to support the effective, volitional regulation of cognition, as indicated by measures of executive function. It may be, however, that children with higher executive function abilities in early childhood are more effective at maintaining cortisol in a moderate range. In the absence of reliable and valid precursors of executive function abilities that can be measured in the infant and toddler periods we cannot definitively rule out this potential alternative explanation for our findings. Be this as it may, executive function develops throughout childhood and into early adulthood. Variability in cortisol and changes in average levels of cortisol over time are likely related in a reciprocal manner to this ongoing development not only in childhood but throughout the lifespan.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

Experimental studies indicate moderate time-limited increase in cortisol is associated with better cognitive ability

Few longitudinal studies have examined variability in cortisol in infancy and early childhood and cognitive development

Moderate variability in cortisol around a low average level is associated with higher executive function ability in children

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a.

b.

Figures 1.

Conditional scatterplots describing the zero-order relations between within-child variability in cortisol over time (7, 15, 24 and 48 months) and 60-month executive functioning, conditional on low (mean – 1 SD; figure 1a) and high (mean + 1SD; figure 1b) levels of average cortisol across this this period.

Figure 2.

Fitted relations displaying the relation between within-child variability in cortisol between 7, 15, 24, and 48 months and children's 60-month executive functioning abilities, conditional on low (grand mean - 1SD), moderate (grand mean), and high (grand mean +1) levels of average cortisol across this period ($n = 1,292$).

Note: All other variables are held constant at their respective grand means.

Table 1

Correlation matrix and descriptive statistics for core variables and key control covariates (n =1,292).

	EF 60	Mean Cort	SD CORT	Site	Income	Male	Temp.	MDI	African American
Mean Cort	-0.15***	1.00							
SD Cort	-0.01	0.36***	1.00						
Site	-0.18***	0.04	0.00	1.00					
Income	0.24***	-0.13***	0.00	-0.16***	1.00				
Male	-0.16***	0.04	-0.01	-0.08*	0.04	1.00			
Temperament	0.04	-0.05	0.00	-0.18***	0.07*	-0.02	1.00		
MDI	0.05	0.03	0.01	-0.01	0.03	0.00	-0.11***	1.00	
African American	-0.24***	0.21***	0.05*	0.49***	-0.33***	0.02	-0.12***	0.02	1.00
Mean	0.358	-0.049	-0.008	0.407	0.514	2.177	0.066	99.585	0.23
SD	0.21	0.27	0.141	0.241	0.25	3.586	1.061	63.269	0.177

* <.05.

** <.01.

<.001; Mean Cort = Average cortisol level across, 7, 15, 24, & 48 months; SD Cort = within- child standard deviation in cortisol level across, 7, 15, 24, & 48 months

Table 2

Select fitted estimates from a multiple regression model (FIML) testing the quadratic relationship between cortisol variability between 7 and 48 months and EF, conditional on overall mean cortisol levels over this period (n = 1,292).

	M1		M2	
Parameter	B	SE	B	SE
Intercept	.405 ***	.022	0.411 ***	0.022
Mean Cortisol	−0.06 *	.030	−0.098 **	0.032
Cortisol SD	0.052	.05	0.047	0.050
Mean Cortisol *			0.047	0.089
Cortisol SD				
Cortisol SD ²	−0.04	.078	−0.154 *	0.076
Cortisol SD ² *			0.183 *	0.089
Mean Cortisol				
<i>R</i> ²	.21		.22	

~<.10,

*<.05.

**<.01,

***<.001 Mean Cortisol = Average cortisol level across, 7, 15, 24, & 48 months; Cortisol SD = within-child standard deviation in cortisol level across, 7, 15, 24, & 48 months

Notes: The following control covariates were also included in the model: mean time of saliva collection within-child SD in time of saliva collection, research site, family income, mean maternal sensitivity, within-child SD in maternal sensitivity, maternal education, functional literacy, marital status, obesity, blood pressure, learning disability, anxiety, depression, emotional problems, family problems, weekly work hours, WIC receipt, SNAP(food stamps) receipt; public housing receipt, smoked during pregnancy with target child; Child sex, race, general cognitive abilities, and temperament.