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Cortisol's diurnal rhythm indexes the neurobiological impact of child adversity in adolescence

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ABSTRACT

Adverse early life experiences, such as child maltreatment, shapes hypothalamic-pituitary-adrenal (HPA) activity. The impact of social context is often probed through laboratory stress reactivity, yet child maltreatment is a severe form of chronic stress that recalibrates even stable or relatively inflexible stress systems such as cortisol's diurnal rhythm. This study was designed to determine how different social contexts, which place divergent demands on children, shape cortisol's diurnal rhythm. Participants include 120 adolescents (9–14 years), including 42 youth with substantiated child physical abuse. Up to 32 saliva samples were obtained in the laboratory, on days youth stayed home, and on school days. A 3-level hierarchical linear model examined cortisol within each day and extracted the diurnal rhythm at level 1; across days at level 2; and between-individual differences in cortisol and its rhythm at level 3. While cortisol's diurnal rhythm was flattened when youth were in the novel laboratory context, the impact of maltreatment was observed within the home context such that maltreated children had persistently flattened diurnal rhythms. The effect of maltreatment overlapped with current chronic interpersonal family stress. Results are consistent with the idea that maltreatment exerts a robust, detrimental impact on the HPA axis and are interpreted in the context of less flexibility and rhythmicity. The HPA axis adapts by encoding signifiers of relevant harsh or unpredictable environments, and the extreme stress of physical abuse in the family setting may be one of these environments which calibrates the developing child's stress responsive system, even throughout a developmental stage in which the family takes on diminishing importance.

1. Introduction

Maltreated children are at elevated risk for the development of mental, emotional, and physical health problems (Gruhn & Bruce, 2020; Smith & Pollak, 2020). Current thinking about the root causes of these problems has focused on the idea that children adapt to their early environments, even if those environments are aberrant or detrimental in some ways (Korte et al., 2005; Pollak, 2008; Smith & Pollak, 2021). Yet, there are high long-term costs for such adaptation (Korte et al., 2005; Pollak, 2008; Smith & Pollak, 2021). Trade-offs between immediate adaptation and long-term functioning are reflected in the development of the hypothalamic-pituitary-adrenal (HPA) axis, a critical component of the stress responsive system (Lupien et al., 2006; Engel, Melissa, & Gunnar, 2020). The HPA axis is calibrated by children's early experience (Giudice et al., 2011), exerting persistent effects throughout the body (Sapolsky, Romero, & Munck 2000, 2000). The present investigation examined diurnal cortisol over 5 days and across 3 social contexts to evaluate the extent to which early stress exposure calibrated the HPA

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axis (Hosseini-Kamkar, Lowe, & Morton, 2021). We also tested whether maltreatment effects (Tarullo & Gunnar, 2006; Alink et al., 2012) overlapped with specific components of stress exposure across potentially salient domains (e.g., school, peer, family) with different time-courses (e.g., episodic, recent chronic, lifetime) captured by life stress interviews (Slavich et al., 2020).

Social relationships actively shape HPA axis development (Gunnar & Donzella, 2002), yet social relationships may not always confer support (Dickerson, Mycek, & Zaldivar, 2008). Aversive relationships fail to provide the developing child with necessary support and can contribute additional sources of stress or negative evaluative threat (Dickerson, Gruenewald, & Kemeny, 2004). Child maltreatment, especially physical abuse, embodies this form of severe stressor (Cicchetti & Rogosch, 2001; Sousa et al., 2018; Kaiser et al., 2018; Smith & Pollak, 2021; Miu et al., 2022) to such an extent that it can impact structural and functional alterations in brain regions such as prefrontal cortex, amygdala, and hippocampus (Hanson et al., 2010; Kennedy et al., 2021; Herzberg & Gunnar, 2020). These limbic and paralimbic brain regions are implicated in the kinds of emotion- and social-information processing problems noted in individuals with histories of maltreatment (Phan, Luan, Wager, Taylor, & Liberzon, 2002). HPA functioning is initiated and coordinated in the limbic system, in part by the action of corticotrophin releasing hormone in hypothalamic- and extra-hypothalamic nuclei (Rosen & Schulkin, 1998). Bidirectional communication of peripheral cortisol with limbic activity helps an individual establish physiological set-points that calibrate according to environmental demands (Shirtcliff, Dahl, & Pollak, 2009). We focus on HPA functioning as one peripheral mechanism for how experiences like maltreatment can "get under the skin".

HPA functioning can indicate an individual's ability to regulate their stress physiology, but regulation is multifaceted. To guide our hypotheses, we broadly view stress regulation through two components (Siever & Davis., 1985): rhythmicity and flexibility (Skinner, Shirtcliff, Haggerty, Coe, & Catalano, 2011). Rhythmicity encourages changes to be regular and consistent, meeting predictable demands of the upcoming day, and can be captured by measuring cortisol throughout the day. Following an awakening response (Boehringer et al., 2015), diurnal cortisol is characterized by a steep decline by mid-morning and gradual decline thereafter until it reaches lowest values near bedtime (Adam et al., 2017). Morning cortisol reflects strong genetic influences and is largely under the control of hypothalamic and pituitary hormones; afternoon/evening levels are increasingly influenced by environmental factors (Van Hulle, Shirtcliff, Lemery-Chalfant, & Goldsmith, 2012). High morning cortisol helps individuals prepare for the day, whereas low evening cortisol permits immune and tissue repair. Flexibility enhances an individual's ability to respond to the environment to ultimately maintain stability. Flexibility is the change in cortisol levels above and below the diurnal rhythm in response to the environment. As such, flexibility would support the release of a situation-appropriate increase in cortisol to meet the demands of a challenging situation, and then encourage a return to baseline levels following the termination of the challenge. As its name suggests, flexibility is not standard across all environments, but modulates cortisol levels to appropriately respond to context. Examining cortisol's diurnal rhythm across several days allowed us to capture rhythmicity as well as flexibility in that rhythm across days and context. We focus on the diurnal rhythm across days because extant studies show that the diurnal rhythm reflects persistent effects of chronic stress and predicts psychopathology beyond absolute cortisol levels (Ruttle et al., 2011; Charles, Mogle, Piazza, Karlamangla, & Almeida, 2020). The diurnal rhythm appears to index the confluence of intrinsic, biological forces with extrinsic, environmental forces working together within an individual on a daily cycle.

Diurnal cortisol is highly stable within individuals across days and years, yet it is highly influenced by contextual forces, especially if these stressors consistently accumulate throughout the day (Skinner et al., 2011). This may be how children's maltreatment experience gets "under the skin" to contribute to a loss of flexibility and rhythmicity. Several reports indicate that maltreated youth in a summer-camp have a flattened diurnal rhythm, though whether cortisol is chronically low or high may depend on characteristics of the child (Cicchetti, Rogosch, Gunnar, & Toth, 2010; Cicchetti, Rogosch, & Oshri, 2011; Rogosch, Dackis, & Cicchetti, 2011; VanZomeren et al., 2020; Handley et al., 2022). Others show school-related stress impacts diurnal cortisol (Bai et al., 2017; Behnsen, Buil, Koot, Huizink, & van Lier, 2018). At home, flattened diurnal rhythms may persist only if the child remains within that same context (Bernard, Butzin-Dozier, Rittenhouse, & Dozier, 2010). Other components of HPA functioning beyond the diurnal rhythm also appear altered in maltreated children and adolescents. Maltreated youth have found both heightened or attenuated responses to acute laboratory stressors depending on the child characteristics (MacMillan et al., 2009; Harkness et al., 2011; Ouellet-Morin et al., 2011; Doom, Cicchetti, & Rogosch, 2014; Bernard, Frost, Bennett, & Lindhiem, 2017); maltreated youth may display either elevated or blunted morning cortisol depending on the severity and type of abuse or characteristics of the child (Harkness et al., 2011; Alink et al., 2012). This heterogeneity of findings persists and even magnifies when the impact of retrospective child maltreatment is examined in adulthood (Robson et al., 2021; Demakakos & Steptoe, 2022). Individuals with a history of child maltreatment may exhibit dysregulated diurnal rhythms (Gonzalez, Jenkins, Steiner, & Fleming, 2009; Nicolson, Davis, Kruszewski, & Zautra, 2010; Kessler et al., 2021), basal cortisol levels (Shea et al., 2007; Marques-Feixa et al., 2021) and altered responses to acute laboratory challenges depending on the vulnerabilities of the individual, type of abuse, and context (Carpenter, Shattuck, Tyrka, Geracioti, & Price, 2009, 2011; Tyrka et al., 2009; Doom et al., 2014; Shirtcliff, Hanson, Phan, Ruttle, & Pollak, 2021).

The present study specifically considers whether these effects of maltreatment are robust across social contexts which may modulate HPA functioning through different underlying mechanisms. We examine the diurnal rhythm in the laboratory as a highly novel context (Klimes-Dougan et al., 2001), and a school context which is socially salient (Boyce et al., 1995). The home context is familiar but, for maltreated youth, may confer additional stress exposure (Rogosch et al., 2011; Shonkoff, 2010). We also assessed a wide range of demographic and developmental factors that might influence HPA functioning in relation to maltreatment status. Youth life stress interviews assessed a wide range of stress exposure to determine whether, even in the absence of substantiated maltreatment, HPA functioning was calibrated by stress exposure. The study targeted early adolescents because this is a developmental stage during which the consequences of early environmental forces appear to be activated through hormonal mechanisms and long-term vulnerabilities may become exacerbated or persistent (DePasquale et al., 2019; King et al., 2017). Based on prior findings (Bernard et al., 2010; Cicchetti et al., 2010, 2011; Handley et al., 2022), we hypothesize maltreated youth will display less cortisol rhythmicity as indexed by a flattened diurnal rhythm in comparison to non-maltreated youth. Second, based on theoretical considerations (Giudice et al., 2011) and drawing from the cortisol response literature (MacMillan et al., 2009; Ouellet-Morin et al., 2011; Bernard et al., 2017), we hypothesized that maltreated youth would display less cortisol flexibility as demonstrated by less change as a function of context. Third, we expected that youth exposed to high levels of chronic life stress/ adversity would demonstrate flattened cortisol patterns (diurnal rhythms and deviations from the rhythm), regardless of abuse status. Finally, we took an exploratory approach to examining differences in cortisol as a function of maltreatment versus life stress and the influence of domain of life stress.

2. Method

2.1. Participants

One hundred and twenty adolescents ranging in age from 9 to 15 years participated in this study (Table 1). Youth whose parents scored above 15 on the Physical Abuse subscale of the Conflict Tactics Scale (CTS; described below) *and/or* had substantiated case(s) of physical abuse on record with the County Department of Human Services (n = 42) were recruited. Youth were classified as nonabused (n = 78) if their CTS scores were 15 or below and there was no Child Protective Services (CPS) history. Youth with signs of fetal alcohol exposure or fetal alcohol syndrome were excluded by a medical geneticist who reviewed participants' facial photographs for (1) distance between the endocanthion and exocanthion landmarks, (2) philtrum smoothness, and (3) upper lip thinness (Astley et al., 2002).

2.2. Procedures

All procedures were approved by the Institutional Review Board. After the set schedule was fully explained, parents and youth provided informed consent and assent, respectively. Beginning at 9 am on the lab day, youth completed several laboratory activities which may be stressful (e.g., laboratory arrival (Klimes-Dougan et al., 2001), physical exam (Shirtcliff et al., 2009), MRI (Eatough, Shirtcliff, Hanson, & Pollak, 2009); after lunch, youth completed non-stressful interviews and questionnaires. Saliva sampling on the laboratory day provided extensive training opportunities on self-administered saliva collection for youth and parents. Participants were sent home with saliva collection materials for 2 subsequent home days and 2 school days, resulting in a total of 5 days of saliva collection and up to 32 samples per youth.

2.3. Measures

2.3.1. Salivary cortisol

Each youth provided up to 32 saliva samples via passive drool, which were assayed for cortisol using a well-validated enzyme immunoassay and subsequently winsorized to within three standard deviations of the mean and natural-log transformed to normalize the distribution. Youth completed a daily diary with each saliva sample. Saliva was immediately frozen at − 80°C in the lab and collected (1) upon arrival (M= 9:28 AM, SD=21 min), (2) after the puberty assessment (M=10:20 AM, SD=16 min), (3) before the MRI (M=11:04 AM, SD=36 min), (4) after the MRI (M=12:14 PM, SD=43 min), (5) after lunch (M=1:37 PM, SD=47 min), (6) after the interviews (M=3:30 PM, SD=36 min), (7) before dinner (M=5:35 PM, SD=37 min), and (8) at bedtime (M=9:06 PM, SD=67 min). Samples 6 through 8 were collected at home after the child's lab session was completed. Collection procedures for home and school days were identical to lab-day procedures with the exception that instructions were to (a) immediately freeze samples in home freezers; (b) record times of collection with additional verification of compliance by an electronic time-cap; and (c) ship the samples frozen with freezer-brix overnight to the laboratory. Self-administered sample collection times largely paralleled laboratory-times: (1) upon awakening (M=7:41 AM, SD=61 min), (2) mid-morning at least an hour after breakfast (M=9:38 AM, SD=24 min), (3) before lunch (M=11:38 AM, SD=26 min), (4) mid-afternoon (or after school on school-days) (M=3:37 PM, SD=40 min), (5) before dinner (M=5:34 PM, SD=40 min) and (6) before bedtime (M=9:23 PM, SD=64 min). On school-days, the mid-morning and before-lunch sample were collected at school and stored frozen with freezer-brix until transport to home freezers.

2.3.2. Puberty

We examined pubertal status and timing as it can modify the impact of maltreatment on HPA functioning (Quevedo, Johnson, Loman, LaFavor, & Gunnar, 2012; DePasquale, Herzberg, & Gunnar, 2021). Following a picture-based interview about puberty, youth self-reported Tanner staging (Shirtcliff et al., 2009). Next, experienced pediatric nurse practitioners conducted physical examinations. Assessments for girls involved palpation for breast development stage and visual examination of pubic hair. An orchidometer was used to measure testicular size in boys, along with visual inspection of pubic hair. Interobserver reliability with nurse practitioners (n = 10) was good, k = 0.88. The Pubertal Development Scale (Petersen, Crockett, Richards, & Boxer, 1988) was converted to the Tanner metrics following published protocols (Shirtcliff et al., 2009) which consider adrenal- and gonadal- origins of secondary sexual characteristics as well as timing of the PDS items. Scores on the three puberty measures (Self- and Nurse-reported Tanner stage, Pubertal Development Scale) were averaged, and then residualized for age to derive pubertal timing scores.

2.3.3. Socioeconomic status

The Four Factor Index of Social Status (de Belmont Hollingshead & de, 1975) assessed family socioeconomic status.

2.3.4. Child abuse

All parents completed the Conflict Tactics Subscale (CTS; Straus, Murray, Hamby, Boney-Mccoy, & Sugarman, 1998; Straus, Hamby, Finkelhor, Moore, & Runyan, 1996), which measures the extent to which they carried out specific acts of physical aggression toward the youth. A Physical Abuse summary score was calculated by summing scores on three subscales: Minor Physical Assault (e.g., shook him/her); Physical Assault-Maltreatment (e.g., hit him/her with a fist or kicked him/her hard); and Severe Physical Maltreatment (e.g., beat him/her up, that is you hit him/her over and over as hard as you could). Two variables were created from this information. First, a dichotomous variable indicating presence or absence of physical abuse was created. Youth were assigned to the physical abuse (PA) group if the physical abuse CTS summary score was above 15 or if there was a Child Protective Services (CPS) history substantiating abuse (n = 42). Youth were classified as non-abused (n = 78) if their CTS scores were below 15 and there was no CPS history. Second, the continuous summary score of the CTS was examined as an indication of Severity of Child Abuse to better understand whether severity of abuse was driving the group effects.

2.3.5. Episodic, chronic, and lifetime stress

To assess stress exposure, parents and youth separately completed the semi-structured Youth Life Stress Interview (YLSI; Rudolph, Karen, & Megan, 2007). Three types of stress exposure for the child were assessed: (1) past-year episodic stress, (2) past-year chronic stress, and (3) lifetime adversity. Standardized probes were used to elicit objective information about stressful events and experiences across several life domains (see Table 1). A team of 3–6 independent coders then rated the interviews following the interview and based on predetermined anchors for stress ratings on a scale of 1–5, where 2 is typical stress level and 5 is life-changing extreme stress; the exception is that lifetime adversity was a ranking of 1–10 where 1 is no lifetime adversity and 10 is repeated, severe, stress exposure. A consensus was determined within the group of coders for each event. Furthermore, stress exposure is conceptualized as belonging to one of five domains: (1) mother-child relationship, (2) parents' marital relationship, (3) peer relationships, (4) academic performance, and (5) school behavior. The three "duration of stress" variables and the five "domain of stress" variables were examined independently in models. High reliability for the YLSI has been achieved (Rudolph et al., 2007; Rudolph & Hammen, 1999). Youth and parents were interviewed separately, and responses were integrated within the coding session. These stress indices were modestly correlated with abuse severity (average r = .23, ps ranging.196 to <.0001, all R<.42) suggesting that multicollinearity was not an issue.

Table 1
Demographic, Developmental and Life Stress Measures between the Physically Abused and Nonabused Control Youth. For continuous measures, columns present the Mean (and Standard Deviations) and p-values from t-tests. For categorical measures, columns present the N, %s, and p-values from chi-square tests (reference group is in parentheses).

Demographic and Developmental Measures	Physically Abused		Nonabused		Group Difference (*p*-value)	Impact on Cortisol's Slope (coefficient and p value)	
Gender (Female)	N = 18	42.9%	N = 38	48.7%	.54	-0.002	0.47
Race (White)	N = 8	19.0%	N = 51	65.4%	.0001	-0.001	0.62
Race (Black)	N = 24	57.1%	N = 16	20.5%	.0001	0.002	0.46
Race (All others)	N = 10	23.8%	N = 11	14.1%	.182	-0.01	0.36
Socioeconomic Status	29.00	(8.97)	46.40	(14.12)	.0001	0.000	0.82
Lowest SES Group (0-19)	N = 2	2.6%	N = 5	11.9%	.0001	-0.0007	0.79
Age	11.5	(1.74)	11.2	(1.71)	.30	0.002	0.054
Tanner Stage	2.76	(1.12)	2.68	(1.27)	.72	-0.000	0.93
Pubertal Timing	.26	(1.40)	.56	(1.15)	.19	-0.004	0.002
Life Stress Measures							
Academic	2.96	(1.02)	2.22	(1.17)	.001	0.000	0.89
Behavioral	2.67	(1.03)	1.83	(.90)	.0001	-0.002	0.26
Peer	3.0	(.82)	2.47	(.93)	.003	-0.000	0.67
Other-Sex Platonic	2.21	(.76)	2.05	(.71)	.25	-0.000	0.99
Other-Sex Romantic	2.18	(.47)	2.03	(.43)	.075	-0.000	0.94
Parent-Child	3.23	(.87)	2.40	(.87)	.0001	0.003	0.096
Parental	3.39	(.92)	2.82	(1.04)	.003	0.003	0.095
Past-Year Composite	2.81	(.44)	2.26	(.56)	.0001	0.002	0.51
Lifetime Stress	6.57	(1.91)	3.28	(2.07)	.0001	-0.000	0.85
Episodic Stress	9.09	(4.21)	7.50	(4.45)	.06	0.0001	0.58

2.4. Analytic strategy

Hierarchical Linear Modeling (HLM; Raudenbush, Bryk, & Congdon, 2004) was used to run analyses. A three-level hierarchical linear model with cortisol levels as outcome accounted for inherent nesting of samples within a day (level 1, N = 2971 cortisol measures), days within an individual (level 2, N = 484 days across individuals), and between individual (level 3, N = 120 individuals) sources of variation. This strategy optimally distinguishes trait-like stable cortisol from time-varying components, and distinguishes a diurnal rhythm based on time-since-waking (TSW). The Level 1 base-model included three Time Since Waking variables (TSW; linear slope [variant], quadratic slope [variant], cubic slope [fixed]). As their names suggest, they are centered on time of waking and provide a measure of how much time has passed since the participant woke. These variables will allow us to test hypotheses involving rhythmicity. Clocktime (fixed) reflects the effect of samples taken later in the day with negative values representing times of day before noon and positive values indicating times of day after noon. As expected, Clocktime was highly correlated with TSW ($r = .977$, $p < .001$), therefore TSW and its functions were residualized out of clocktime to provide a measure of cortisol samples taken later in the day, beyond the effect of the diurnal slope. The resulting variable was still correlated with TSW ($r = .21$, $p < .05$) but not to a degree that multicollinearity presents an issue. Sample-at-school (fixed) is a dichotomous variable that identifies samples taken while the participant was in the school building. Sample-at-lab (fixed) is a dichotomous variable that identifies samples taken while the participant was in the laboratory. Fixed variables (i.e., cubic TSW, clocktime, sample-at-school, sample-at-lab) were included to better model the shape of the diurnal rhythm across days and explore if cortisol differed when examined as a function of cortisol samples while in the building of lab/ school versus examining the day as a whole (i.e., samples gather on a school day but samples that were also taken at home before and after school were also considered) but were not further explored. At Level 2, the dichotomous variables that separated the different contexts were included in the model: SCHOOLDAY and LABDAY. The remaining cortisol samples (HOMECORT) reflect cortisol levels on home days. Given that there were two days of collection on home days and two days of collection on school days, effects are collapsed across both days. Given that school and the laboratory are generally considered to be more stressful environments than the home environment, demonstrating slight elevations in cortisol would be considered adaptive and a sign of flexibility whereas no change across the contexts may signify lack of flexibility. At Level 3, between-individual predictors were included, although to promote clarity, these effects are not illustrated in the model below. See Table 2 for a depiction of this model. First, the PA group variable was included to examine between-individual effects of the experience of physical abuse on intercept, TSW, and TSWSQ variables across all contexts; non-significant effects were removed in a stepwise manner for a more parsimonious model. We then included demographic variables, PA Severity, and type of life stress (i.e., episodic, chronic, lifetime) one after another to see if they could account for any observed effects of PA group. An exploratory examination of the domain of life stress followed. Interactions of between-level variables (i.e., PA* life stress) were not pursued due to sample size limitations.

Table 2
Depiction of the overall model across three hierarchical levels of analysis simultaneously modeled.

Level 1 [within-individual, within-day]	$p_0 + p_{1TSW} + p_{2TSW\text{-}SQ} + p_{3TSW\text{-}CUBIC} + p_{4CLOCKTIME} + p_{5SAMPLE\text{-}AT\text{-}SCHOOL} + p_{6SAMPLE\text{-}AT\text{-}LAB} + e$
Level 2 [day-level, within-individual]	$p_{0jk} = \beta_{00} + \beta_{01labday} + \beta_{02schoolday} + R_0$
	$p_{1jkTSW} = \beta_{10} + \beta_{11labday} + \beta_{12schoolday} + R_1$
	$p_{2jkTSWSQ} = \beta_{20} + \beta_{21labday} + \beta_{22schoolday} + R_2$
	$p_{3jkTSWCUBIC} = \beta_{30}$ [fixed]
	$p_{4jkCLOCKTIME} = \beta_{40}$ [fixed]
	$p_{5jkSAMPLE\text{-}AT\text{-}SCHOOL} = \beta_{50}$ [fixed]
	$p_{6jkSAMPLE\text{-}AT\text{-}LAB} = \beta_{60}$ [fixed]
Level 3 [between-individuals]	$\beta_{00kHOMECORT\ intercept} = \gamma_{000} + u_{00k}$
	$\beta_{01kLABDAY\ intercept} = \gamma_{010} + u_{01k}$
	$\beta_{02kSCHOOLDAY\ intercept} = \gamma_{020} + u_{02k}$
	$\beta_{10kHOMECORT\ slope} = \gamma_{100} + u_{10k}$
	$\beta_{11kLABDAY\ slope} = \gamma_{110} + u_{11k}$
	$\beta_{12kSCHOOLDAY\ slope} = \gamma_{120} + u_{12k}$
	$\beta_{20kHOMECORT\ slopesq} = \gamma_{200} + u_{20k}$
	$\beta_{21kLABDAY\ slopesq} = \gamma_{210} + u_{21k}$
	$\beta_{22kSCHOOLDAY\ slopesq} = \gamma_{220} + u_{22k}$
	$\beta_{30kTSWCUBIC} = \gamma_{300}$ [fixed]
	$\beta_{40kCLOCKTIME} = \gamma_{400}$ [fixed]
	$\beta_{50kSAMPLE\text{-}AT\text{-}LAB} = \gamma_{500}$ [fixed]
	$\beta_{60kSAMPLE\text{-}AT\text{-}SCHOOL} = \gamma_{600}$ [fixed]

Note: A significant between-individuals effect on the LABDAY level suggests that levels were different than the remaining cortisol levels which, given SCHOOLDAY is in the model, reflects cortisol levels on the home days.

3. Results

3.1. Cortisol's diurnal rhythm

Across the day, cortisol levels in youth declined and the decline was steeper in the morning than afternoon (linear $\beta = -.16$, $p < .001$; $\beta = .017$ for quadratic, $\beta = -.000$ for cubic, $ps < .001$; average decline was $-.04$). There was also a small Clocktime effect such that, beyond time-since-waking, samples collected later in the day returned lower cortisol values ($\beta = -.029$, $p < .001$) (Shirtcliff et al., 2012). For cortisol intercept levels, 39% of the total variance was due to between-individual differences, 26% was due to day-to-day differences, and the remaining 35% of the variance was due to momentary fluctuations in cortisol, $ps < .001$. The diurnal slope also had substantial variance across days and between individuals, with 24% due to day-to-day differences in the diurnal-slope and 76% of the variance being stable across days, $ps < .001$.

3.2. Effect of social contexts on diurnal cortisol

Next, we examined whether cortisol was systematically different at Level 1 depending on the context of sample collection (i.e., "sample-at-lab" and "sample-at-school"). Compared to samples that were not collected while the participant was in the lab or at school, cortisol was higher when the participant was physically in the lab ($\beta = 0.097$, $p < .001$) and lower when they were at the school building ($\beta = -.05$, $p < .05$). To examine the possibility that the school or lab context influenced cortisol beyond these momentary effects (e.g., by altering the entire day's diurnal rhythm), variables for "lab-day" and "school-day" were introduced at the day-specific level (Level 2). HPA functioning across the entire school-day was not substantially different from home-days in terms of morning level or linear or quadratic slope ($\beta = .07$, $p < 0.10$, $\beta = -.02$, $p < 0.10$, $\beta = .00$, $p < .10$, respectively). Whereas samples collected across the entire lab-day had significantly lower morning levels ($\beta = -.345$, $p < .001$) and flatter diurnal rhythms (linear slope $\beta = .051$, $p < .001$, quadratic slope $\beta = -.00$, $p < .05$) than home days. After adding these variables in to the model, Level 1 variables "sample-at-lab" and "sample-at-school" retained significance. See Fig. 1.

Upon examining these associations for each group (i.e., physical abuse and control), there was no significant difference between cortisol collected in the home context and the other two contexts for participants who experienced physical abuse (lab level $\beta = -.10$, $p > 0.05$; lab linear slope $\beta = .01$, $p > 0.05$; school level $\beta = .06$, $p > 0.05$; school linear slope $\beta = .00$, $p > 0.05$) or control participants (lab level $\beta = .02$, $p > 0.05$; lab linear slope $\beta = .00$, $p > 0.05$; school level $\beta = .07$, $p > 0.05$; school linear slope $\beta = -.01$, $p > 0.05$).

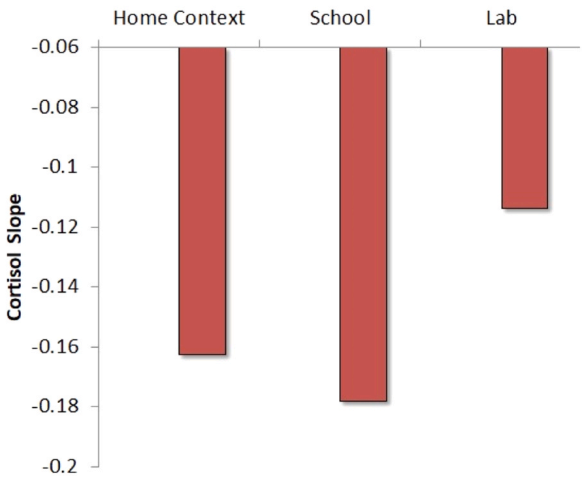

Fig. 1. Cortisol's diurnal-slope (illustrated with predicted HLM estimates) was significantly flatter on the day that youth came to the laboratory. Standard errors are not presented as these are predicted HLM scores.

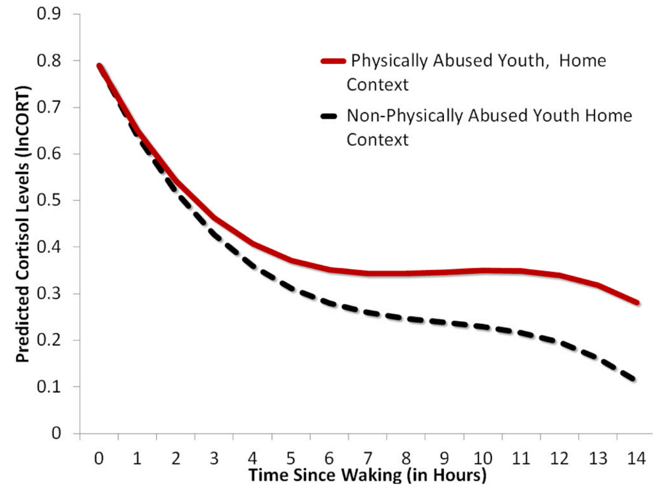

Fig. 2. The diurnal rhythm showed the expected nonlinear declining pattern (illustrated with predicted HLM estimates); this decline across the day was flatter in maltreated youth.

3.3. Effect of physical abuse on diurnal cortisol

We next included the dichotomous variable PA group status as a Level 3 (between-individual) predictor of HPA functioning. Non-significant level-3 predictor variables were removed from the model. It should be noted that this includes removal of the non-significant effect of PA on the intercept and, as such, the PA x TSW interaction (and all subsequent findings involving this term) may be biased. Compared to non-abused youth, physically abused youth demonstrated flatter diurnal slopes at home (see Table 3), suggesting that physical abuse specifically alters the amount of decline in diurnal rhythms while in the home context. See Fig. 2. The effect of PA was non-significant in the school and laboratory contexts (ps>.51), suggesting the same general pattern was evident for the laboratory and the school contexts.

3.4. Can the effect of physical abuse be explained by control variables or severity of abuse?

We next determined whether the PA group effect on cortisol's diurnal rhythm persisted after accounting for control variables such as demographics and developmental status (see Table 1 for a list of these variables). Socioeconomic status, socioeconomic group, race, menstrual cycle day count, medications, or BMI did not significantly influence cortisol or its linear slope, ps> 0.05. Older youth had slightly steeper slopes (linear slope $\beta = .00$, $p = 0.054$) and more pubertally advanced youth had steeper diurnal slopes (linear slope $\beta = -.004$, $p = .002$), however, the effect of PA group on the diurnal slope persisted after accounting for age and pubertal development (PA group linear slope $\beta = .01$, $p = .021$; $\beta = .01$, $p = .020$, respectively). Furthermore, after accounting serially for each demographic and developmental metric, the PA group effect on cortisol's diurnal rhythm remained significant (*ps* < .05).

Next, we included Severity of Child Abuse in the model to examine whether the PA group effect could be accounted for by severity of abuse. Although youth with the most severe physical abuse demonstrated flatter diurnal-slopes in the home context than other abused youth (linear slope $\beta = .00$, $p = .012$), the PA group effect persisted (linear slope $\beta = .01$ $p = .021$), suggesting that physically abused youth in general demonstrated flattened rhythms compared to non-abused youth.

Table 3
Effect of abuse group status by context on cortisol.

	df	*B*	*S.E.*	*t-ratio*	*p-value*
Morning Level					
Intercept	117	0.791	0.038	20.897	< 0.001
LABDAY	117	-0.341	0.063	-5.437	< 0.001
SCHOOLDAY	117	0.073	0.037	1.944	0.054
Slope					
Intercept	116	-0.168	0.014	-11.652	< 0.001
Intercept*PA	116	0.009	0.004	2.337	0.021
LABDAY	428	0.050	0.013	3.804	< 0.001
SCHOOLDAY	428	-0.015	0.009	-1.751	0.080
Quadratic Slope					
Intercept	117	0.018	0.002	9.056	< 0.001
LABDAY	428	-0.002	0.001	-1.992	0.047
SCHOOLDAY	428	0.001	0.001	1.742	0.082
Cubic Slope	117	-0.001	0.000	-7.999	< 0.001
Location School	2599	-0.062	0.029	-2.110	0.035
Location Lab	2599	0.245	0.037	6.705	< 0.001
CLOCKTIME	2599	-0.029	0.011	-2.779	0.006

Note: df = *degrees of freedom; B* = unstandardized beta coefficient; *S.E.* = standard error
Note: Intercept reflects cortisol levels on HOMEDAY.

3.5. Can stress exposure type and domain explain the effect of physical abuse?

We then examined whether stress exposure across domains explained the effect of PA group on cortisol's diurnal rhythm using the Youth Life Stress Interview's multimodal conceptualization of stress. Chronic, persistent stress exposure in the past year was associated with flattened diurnal rhythms (linear slope $\beta = .005$, $p = .008$). When chronic stress and PA group were included together as predictors, the effect of chronic stress was no longer significant, $p = .40$, and the PA group effect was reduced to marginal significance (linear slope $\beta = .00$, $p = .08$), suggesting that chronic stress and physical abuse captured overlapping effects. When episodic stress (e.g., episodes in the past year) or lifetime adversity were included in the model with PA group, neither were associated with the linear diurnal slope ($p = .64$ and $p = .17$, respectively), and the PA group effect remained significant (ps<.05).

Next, we disentangled the chronic stress effect by examining the specific domains of stress exposure within the broad measure. The two domains of stress that had robust effects, both captured components of family interactions: parent-child stress and interparental stress. Parent-child stress was linked with a flattened diurnal rhythm (linear slope $\beta = .004$, $p < .01$) and when parent-child stress and PA group status were included together as predictors, the effects of parent-child stress and PA group status were both diminished ($p = .10$ and $p = .12$, respectively). Similarly, when included in the model without PA group in the model, interparental stress was associated with flattened diurnal rhythms (linear slope $\beta = .004$, $p < .01$), and when interparental stress and PA group status were included together, effects of interparental stress and PA group on HPA functioning were diminished ($p = .10$ and $p = .07$, respectively). The effects of academic, behavioral, peer, romantic, or other-sex platonic stress on diurnal rhythm were nonsignificant, ps> .29, and the PA group effect remained significant, ps< .02.

In sum, maltreated youth displayed flattened diurnal rhythms at home, and the effect of abuse overlaps with current interpersonal stress in the family. A range of chronic family stress seems key for understanding the effects of maltreatment on HPA functioning.

4. Discussion

The present investigation illustrates that diurnal cortisol patterns are influenced by context and highlights the unique impact of physical abuse according to context. Here we show that samples taken on the laboratory day were higher than samples taken on the home days whereas samples taken at school were lower than those taken at home. We demonstrated that the impact of physical abuse is particularly impactful on levels of cortisol in the home environment, persisting after demographic and developmental variables are considered. Additionally, physically abused youth demonstrated an elevated and flattened pattern of cortisol in the home context compared to physically abused youth, and this effect persisted across both of the other contexts. Furthermore, overlapping effects of abuse and persistent life stress exposure in socially based domains suggests a similar mechanism through which these experiences get under the skin to influence well-being.

Although typically held constant in diurnal cortisol research, context is an important component to explore as it is highly flexible, calibrating to social contexts to help individuals adapt to changing environmental demands. Overall, youth demonstrated the anticipated patterns of cortisol rhythmicity (i.e., high morning levels with a steep decline in the morning hours and a less steep decline later in the day) and flexibility as rhythms varied as a function of context. Cortisol levels taken while the youth were at school were lower than home days, whereas cortisol was higher and diurnal rhythms were flattened in the laboratory context and for the remainder of the day, reflecting the responsiveness of stress physiology to proximal social contexts. Although HPA responsivity is often heightened in response to peer entry (Bruce, Davis, & Gunnar, 2002; Quas, Murowchick, Bensadoun, & Boyce, 2002), the present study found that cortisol levels in the school setting were significantly lower than in the home setting (Boyce et al., 1995). This pattern suggests that HPA responsivity to context, when no longer novel or unfamiliar, quickly habituates. Conversely, the novel laboratory setting led to higher cortisol levels and flatter diurnal rhythms across the lab-day, suggesting that novelty exerts a large, likely temporary, impact on HPA functioning. Indeed, previous research suggests that novel and unpredictable contexts can influence diurnal cortisol (Gunnar et al., 2000).

When the effect of context was explored in each group, physically abused youth demonstrated a similar pattern of high, flat cortisol across all three contexts, suggesting the possibility of decreased flexibility. Moreover, although not presented in the manuscript, exploratory analyses revealed that this pattern of higher levels of cortisol in abused youth were also evident when samples were taken at school ($\beta = 0.102$, $p = 0.029$) (but not across the entire schoolday [$\beta = 0.008$, $p = 0.116$]) as compared to control youth, suggesting the presence of elevated cortisol levels across all three contexts. Elevated cortisol levels across all contexts reflects loss of flexibility, and the persistence of a state of hyperarousal, regardless of the level of threat present (Del Giudice, Ellis, & Shirtcliff, 2011). It is difficult to disentangle when HPA adjustments are adaptive versus maladaptive (Del Giudice et al., 2011) as both higher or lower activity can be advantageous depending on the context (Ruttle et al., 2011; Shirtcliff et al., 2021; Hosseini-Kamkar et al., 2021). Although higher cortisol can allow an individual to be open to their environment, when the environment is unpredictable or dangerous, high basal/ diurnal cortisol profiles may develop as a protective mechanism to promote vigilance (Del Giudice et al., 2011). Our thinking is that maltreated youth raised in stressful environments develop an elevated flattened diurnal rhythm as an adaptive response to their adverse environments (Fisher, Stoolmiller, Gunnar, & Burraston, 2007; Blaisdell, Andrea, & Fisher, 2019). However, it should be mentioned that control youth demonstrated a consistent pattern of diurnal cortisol levels across all three contexts as well, albeit a more typical pattern of diurnal cortisol decline.

Whereas overall maltreated youth displayed an elevated flattened diurnal rhythm, this pattern was even more pronounced in the extreme abuse cases, suggesting even more vigilance in this portion of the abused group. This pattern of amplified cortisol levels is predicted in the adaptive calibration model which suggests that while youth in unpredictable or dangerous environments often experience elevated levels of cortisol, those exposed to severe or traumatic environments are expected to exhibit either further augmented cortisol levels or a low, unemotional pattern of severely blunted pattern (Giudice et al., 2011). The downward shift is anticipated to occur in adolescence so it may be that the current sample was not old enough to identify such a shift. It will be important for future studies to determine whether individual difference factors other than severity (e.g., gender, health outcomes) help identify which youth show which patterns of dysregulated diurnal rhythms. Additional studies should also examine whether these adaptive patterns come with additional physiological consequences and health trade-offs (DePasquale, Donzella, & Gunnar, 2019).

Although child maltreatment is often used as a proxy for, or example of, early life stress, it has been unclear which aspect of this experience exerts toxic effects on children's biobehavioral regulation (Joos, McDonald, & Wadsworth, 2019; Kessler et al., 2021). Recent reconceptualizations suggest that a focus on types of maltreatment experiences may have less utility for understanding diverse biobehavioral outcomes than other aspects of children's environments that shape their experience, including how children perceive and understand their circumstances (Smith & Pollak, 2020). The present data are consistent with the idea that chronic, negative parent-child and interparental relationships largely explain perturbations in HPA axis functioning among maltreated youth. This finding may at face value support cumulative burden models (Bucci, Marques, Oh, & Harris, 2016; Zalewski, Lengua, Kiff, & Fisher, 2012), yet also echo growing awareness that features of the social and interpersonal context such as contingency, predictability, personal resources, and perceived safety channel biobehavioral processes towards supporting the types of outcomes that best help the child adapt to the situation in all its complexity (Smith & Pollak, 2020).

Chronic stress in other domains – academic, behavior, peer, romantic and other-sex platonic – did not account for the maltreatment effect, suggesting that the family domain is especially salient for establishing set-points for HPA functioning. This finding is surprising given that adolescence is a developmental stage during which academics, peers, and romantic relationships assume increasing salience, yet is consistent with other recent work that highlights the profound psychobiological impact of the family domain. Parents continue to impact adolescents' HPA functioning, well into a developmental stage in which parents' roles are presumably diminished (Shirtcliff, Skinner, Obasi, & Haggerty, 2017). Against the backdrop of chronic family stress, the proximal context of school and the laboratory also exerted an influence on HPA functioning.

Although the present study contributes to the literature by exploring how exposure to physical abuse impacts cortisol in a variety of contexts, sampling across different contexts is not without its challenges. First, on the day participants spent in the laboratory, they did not take their first morning sample at the same time as they did on the other four days and thus the statistical program extrapolated from the existing data to derive predicted morning values on the laboratory day. While this is a limitation, our hypotheses and findings are focused on slope effects which are much more robust to predicted morning values. Another limitation to sampling within different contexts, participants did not have direct access to freezers upon taking each sample although they were provided with freezer-brix. While freezing saliva samples upon collection is the gold standard practice, research suggests that samples stored at room temperature for a reasonable amount of time may not significantly impact the integrity of cortisol samples (Nalla, Thomsen, Knudsen & Frojaer, 2015). Additionally, the backwards elimination process involved removing the main effect of PA from the intercept, possibly biasing the PA x TSW interaction findings. Furthermore, although the concept of flexibility is more established in other physiological indicators such as cardiovascular reactivity, the notion of cortisol flexibility is in its naissance. Establishing guidelines for cortisol flexibility may be particularly daunting given the number of data points typically required to obtain a measure of flexibility would require participants to provide saliva/ blood/ urine samples multiple times per hour. The data presented in the current manuscript is unique as diurnal cortisol was sampled over multiple days in various contexts allowing for statements to be made regarding what is perceived to be flexibility. However, given the lack of established guidelines surrounding cortisol flexibility, these statements should be made and interpreted tentatively. Furthermore, the lack of significant change in cortisol across contexts may simply reflect the possibility that the contexts included in the manuscript were not stressful enough to elicit sufficient changes in cortisol or that the sampling of cortisol was not properly temporally aligned with the cortisol response. Additional thought and research should be allotted to determining exactly what constitutes cortisol flexibility, how it is measured, what measures may be able to help disentangle flexibility from reactivity (e.g., self-report, cut-offs), and how it can be practically incorporated into mainstream biophysiological research.

In sum, the present study illustrates the importance of the family domain as a regulator of stress responsiveness that persists in adolescence. These results are consistent with the idea that the HPA axis, particularly a flattened diurnal rhythm, serves as one neurobiological pathway toward the development of a myriad of physical and psychiatric problems. The HPA axis adapts by encoding signifiers of harsh or unpredictable environments that are especially relevant. The extreme stress of physical abuse in the family setting appears to calibrate the developing child's stress responsive system to be especially attuned to threat or unpredictability.

CRediT authorship contribution statement

Elizabeth Shirtcliff: Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Seth D. Pollak:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Paula L. Ruttle:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis. **Jamie L. Hanson:** Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Brandon Smith:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors did not use generative AI technologies for preparation of this work.

Declaration of Competing Interest

The authors reported no biomedical financial interests or potential conflicts of interest.

Data Availability

Data will be made available on request.

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