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An In-Laboratory Stressor Reveals Unique Genetic Variation in Child Cortisol Output

Laurel Raffington[1], Margherita Malanchini[1, 2], Andrew D. Grotzinger[1], James W. Madole[1], Laura E. Engelhardt[1], Aditi Sabhlok[1], Cherry Youn[1], Megan W. Patterson[1], K. Paige Harden[1], and Elliot M. Tucker-Drob[1]

[1] Department of Psychology, University of Texas at Austin
[2] Department of Biological and Experimental Psychology, Queen Mary University of London

Dysregulation of biological stress response, as measured by cortisol output, has been a primary candidate mechanism for how social experiences become biologically embedded. Cortisol is the primary output of the hypothalamic pituitary adrenal (HPA) axis. Cortisol levels vary systematically across the day and change in response to both sudden, acute stress experiences as well as prolonged exposure to environmental stress. Using data from 8- to 15-year-old twins in the Texas Twin Project, we investigate the extent to which genetic influences are shared across different measures of cortisol output: chronic cortisol accumulations in hair (n = 1,104), diurnal variation in salivary output (n = 488), and salivary response to a standardized, acute in-laboratory stressor (n = 537). Multivariate twin models indicate that genetic factors regulating cortisol response to the in-laboratory stressor are separable from those regulating baseline cortisol levels, naturally occurring diurnal variation in cortisol, and hair cortisol levels. These findings illustrate that novel environments can reveal unique genetic variation, reordering people in terms of their observed phenotype rather than only magnifying or mitigating preexisting differences.

Keywords: children, cortisol, gene–environment interplay, stress, Trier Social Stress Task

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Genetic effects vary across time and context (Tucker-Drob et al., 2013), but although there is broad consensus that gene-by-environment interactions (G × E) exist (Dobzhansky, 1955; Gottesman, 1963; Griffiths & Tabery, 2008), several different forms of G × E are possible. Changing the environment might (a) reduce the effect of genetic influences (e.g., Barcellos et al., 2018; Raine, 2002); (b) amplify preexisting genetic influences (Briley & Tucker-Drob, 2013); or (c) reveal unique (i.e., innovative) genetic variation, such that the relative ordering of phenotypes in novel environments is unpredictable from preexisting individual differences (Gottlieb, 2007; Gupta & Lewontin, 1982). In this study, we consider these competing models of G × E in relation to human cortisol output: If we make people's environments more stressful, how does that environmental change affect genetic influences on cortisol levels?

Historically, research in nonhuman animals, where direct manipulation of the environment is possible, has allowed for the most direct

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Laurel Raffington https://orcid.org/0000-0002-0144-5605
Margherita Malanchini https://orcid.org/0000-0002-7257-6119
James W. Madole https://orcid.org/0000-0002-2301-0004
Laura E. Engelhardt https://orcid.org/0000-0001-7254-5702
Aditi Sabhlok https://orcid.org/0000-0001-6604-1698
Cherry Youn https://orcid.org/0000-0001-5445-6802
Megan W. Patterson https://orcid.org/0000-0002-8299-2706
K. Paige Harden https://orcid.org/0000-0002-1557-6737
Elliot M. Tucker-Drob https://orcid.org/0000-0001-5599-6237
Andrew D. Grotzinger is now at the Department of Psychology and Neuroscience, University of Colorado Boulder.
K. Paige Harden and Elliot M. Tucker-Drob jointly supervised this work.

Because of the potential for deductive identification and the sensitive nature of information collected, data from the Texas Twin Project are not shared with individuals outside of the research team. Code will be shared by the first author on request. This study was not preregistered.

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Correspondence concerning this article should be addressed to Laurel Raffington, who is now at Max Planck Institute for Human Development, Lentzeallee 94, 14195 Berlin, Germany. Email: laurel.raffington@austin.utexas.edu

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empirical tests of how genetic effects vary across environments. Indeed, a few animal studies of G × E (Cooper & Zubek, 1958; Freund et al., 2013; Gupta & Lewontin, 1982) have become canonical examples for theoretical work in behavioral genetics (Gottlieb, 2007; Scarr & McCartney, 1983; Tucker-Drob & Briley, 2018). Human studies of G × E, however, have most commonly examined differences between people in their naturally occurring environments. This variation in environmental context might itself be correlated with genotype (and other aspects of the environment), and this gene–environment correlation (rGE) complicates researchers' ability to make causal inferences about environmental effects (Rathouz et al., 2008; Schmitz & Conley, 2017). Additionally, by observing different people who experience different environments, researchers can estimate whether the magnitude of genetic contributions differs across environments but not whether the same or different genetic factors contribute to a phenotype in multiple environments (Tucker-Drob & Briley, 2014). Answering the latter question is critical to knowing the extent to which preexisting individual differences predict people's phenotypic expression in a novel environment, or whether the novel environments might reorder people with respect to their observed phenotype.

To determine the extent to which the same genetic factors contribute to variation in a phenotype across different environments, behavioral genetic studies can repeatedly measure individuals across an exogenously manipulated environmental change, permitting more rigorous evaluation of competing theoretical conceptions of G × E interaction. Whenever a researcher manipulates the environment, there remains the possibility that people will systematically differ in their subjective appraisal of that environment, and that individual differences in appraisal will vary genetically, introducing (uncontrollable) rGE into the study design (Plomin et al., 1977). Nevertheless, exogenous manipulations of the environment permit stronger inferences about G × E effects than purely correlational studies. Despite their strengths, genetically informative studies that involve exogenous manipulations of the environment remain remarkably rare (e.g., Burt et al., 2019; Kuo et al., 2019).

Here, we apply this study design to cortisol secretion in twins. Cortisol is the primary output of the hypothalamus-pituitary-adrenal (HPA) axis and is widely used as a biomarker of stress response in psychological and behavioral research (Koss & Gunnar, 2018). Cortisol responses have also been hypothesized to be a proxy for genetic sensitivity to environments (Roisman et al., 2012). Variation in cortisol measured at a single point in time is heritable (Rietschel et al., 2017; Tucker-Drob et al., 2017), but, of course, cortisol levels are dynamic in relation to environmental change, even over relatively short timescales. For example, exogenously-manipulated stress increases salivary cortisol output within minutes (Hellhammer, 2011). Similarly, salivary cortisol increases drastically on awakening (cortisol awakening response) and decreases over the rest of the day (diurnal slope; Miller et al., 2016). A few studies have examined the contribution of genetic variation to the magnitude of cortisol reaction and the magnitude of diurnal change (Federenko et al., 2004; Ouellet-Morin et al., 2016; Sawyers et al., 2021; Steptoe et al., 2009; Van Hulle et al., 2012). For instance, Sawyers et al. (2021) report heritability estimates between 12% and 45% for various measures of cortisol reactivity to the TSST, but did not examine genetic sharing between cortisol reactivity during the TSST naturally occurring cortisol diurnal rhythm. Thus, it remains unknown whether the heritable contribution to cortisol response to an acute stressor simply reflects a magnification of standing genetic contributions to everyday variation in cortisol or whether there are novel contributions of genetic factors not evident prior to stressor onset. Our main focus in this paper is to address this outstanding question.

We report on data from 488 to 1,104 individuals from a population-based sample of grade school monozygotic and dizygotic twins, who contributed measures of (a) hair cortisol, (b) salivary cortisol over the course of several days at home, (c) salivary cortisol over the course of an in-laboratory psychological stressor, the Trier Social Stress test (TSST). Data collection for this cohort is ongoing; we reported results from phenotypic analyses of cortisol data from a prior data freeze in (Malanchini et al., 2021). Those analyses found that children's hair cortisol levels ($r = -.16$, $p < .01$), diurnal awakening levels ($r = -.08$, $p > .05$), cortisol awakening responses ($r = .06$, $p > .05$), and diurnal slope ($r = -.14$, $p > .05$) showed limited phenotypic correspondence with cortisol responsiveness to acute stress. Although these phenotypic results are consistent with our hypothesis that a novel stressful environment might reveal unique genetic variation in HPA axis output, phenotypic correlations do not provide direct insight into with the patterning of genetic correlations. Although genetic and environmental pathways may act through shared biological, social, or developmental pathways evident at the phenotypic level, they may also operate through divergent pathways that are obscured at phenotypic levels of analysis (Cheverud, 1988). In this article, we therefore directly address the question of genetic and environmental sharing across multimodal cortisol measurement via multivariate biometric modeling.

Method

Participants

Participants were members of the Texas Twin Project, an ongoing longitudinal, population-based study of twins living near Austin recruited from public school rosters. Although all children were recruited from a single metropolitan area, inequalities in children's social contexts were stark (annual family income median = 121,500 USD, SD = 660,281, range = 1,000–10,000,000; years of parental education median = 18, SD = 2.37, range = 4–22 years). The Gini index of the income distribution in this sample was .35. This estimate is very similar to the Gini coefficient for the United States as a whole in 2016 (.39). For a comprehensive description of socioeconomic measures and their phenotypic associations with multimodal cortisol secretion, please see Malanchini et al. (2021). Twin pairs identified as being best described as White (62.11%), Latinx (13.88%), Latinx-White (8.59%), African American (3.52%), Asian (4.40%), or other (multi-)racial/ethnic categories (7.50%).

Twin pairs included in the current analyses had at least one measure of cortisol, no hormone-disrupting disorder (n = 12) and had not taken steroid-based medication regularly in the past 6 months (n = 19; total exclusion n = 27). The final sample (N = 1,104 unique individuals, 53% female) consisted of 150 monozygotic and 304 dizygotic twin pairs from 454 families (see zygosity classification). Participants ranged in age from 8 to 15 years (M = 11.01, SD = 1.81). Sample size varied depending on the cortisol collection modality (see Table 1).

The University of Texas at Austin Institutional Review board granted ethical approval (project title: "Genes and Development Study," IRB protocol number 2014-11-0021). Informed consent to

Table 1
Descriptive Statistics for Raw Cortisol Values

Sample	*n*	*M*	*SD*
Stress cortisol 1	535	5.61	47.25
Stress cortisol 2	519	6.45	39.38
Stress cortisol 3	519	4.40	17.16
Stress cortisol 4	518	3.52	16.22
Diurnal cortisol 1, day 1	550	7.70	17.30
Diurnal cortisol 2, day 1	504	13.25	83.19
Diurnal cortisol 3, day 1	500	0.96	5.21
Diurnal cortisol 1, day 2	566	7.27	11.23
Diurnal cortisol 2, day 2	521	9.67	7.27
Diurnal cortisol 3, day 2	525	0.79	2.06
Diurnal cortisol 1, day 3	574	6.94	7.20
Diurnal cortisol 2, day 3	526	9.57	8.19
Diurnal cortisol 3, day 3	502	0.67	1.50
Diurnal cortisol 1, day 4	566	6.78	5.14
Diurnal cortisol 2, day 4	506	8.95	8.04
Diurnal cortisol 3, day 4	559	1.34	4.70
Diurnal cortisol 1, day 5 (optional overflow day)	126	7.67	9.09
Diurnal cortisol 2, day 5	96	30.88	217.28
Diurnal cortisol 3, day 5	110	1.5	4.09
Hair cortisol	1,338	11.09	68.61

Note. Descriptive statistics for raw cortisol values after exclusions and before cortisol residualization for year of assay and log transformation. Salivary cortisol concentrations are measured in nmol/L and hair cortisol concentrations in pg/ml. Diurnal and hair cortisol descriptive statistics include repeat participants.

participate in the study was obtained from all participants and their parent or legal guardian.

Because of the potential for deductive identification, and the sensitive nature of information collected, data from the Texas Twin Project are not shared with individuals outside of the research team without prior approval from study investigators. Code will be shared by the first author on request. This study was not preregistered.

Measures

Cortisol Reactions to Acute Stress

Cortisol reactions to stress were measured using the Trier Social Stress test for children (Buske-Kirschbaum et al., 1997). Participants were instructed to refrain from eating 1 hr before their lab visit. Twin pairs came to the lab together, but each child completed the TSST–C separately. Approximately 30 min after their arrival at the lab, participants were instructed to prepare a short story to be presented in front of two judges. After a 5-min preparation period, they then presented the story (5 min) and were asked to calculate mental arithmetic problems orally in front of the judges (5 min). Four salivary samples indexed cortisol reactions: (a) shortly on arrival to the lab and at least 30 minutes before the TSST-C, (b) 20 minutes after the start of the TSST-C, (c) 20 minutes after the completion of sample 2, and (d) 20 minutes after the completion of sample 3. Five hundred thirty-seven unique participants contributed at least one measure of cortisol secretion in reaction to the TSST-C (Table S1 in the online supplemental materials). Salivary samples were collected as passive drool extracted into 2-ml plastic vials. Research assistants recorded the exact time at which each sample was collected. All samples were frozen at the same time (maximum of 2.5 hr from the collection of the first sample) at −80°C prior to being shipped on dry ice to Dr. Clemens Kirschbaum's lab in Germany for assay using liquid chromatography tandem mass spectrometry (LC-MS/MS). The inter- and intraassay coefficients of variation have been established as less than 10% cortisol in other samples (Gao et al., 2013). All samples from the same participant at one data collection wave were tested in the same batch. Salivary cortisol values were residualized for batch (assay year; three batches) and log-transformed. No further outlier removal was performed.

Diurnal Cortisol Secretion

Saliva collection kits were provided for four consecutive days with an additional fifth kit in case of sampling problems. The completion rate was 94%, and 22% of participants also completing the optional overflow fifth day. Samples were taken at home three times a day: immediately on waking, 30 min after waking, and right before bedtime. Four hundred eighty-eight unique participants contributed at least one measure of diurnal cortisol secretion. Several participants contributed diurnal data over multiple collection waves, resulting in 574 unique sets of sampling days (see Table 1). Participants were asked to refrain from eating, drinking, or brushing their teeth for the 30 min preceding each sample, and they were provided with diaries where they could record their daily activities and experiences regarding the data collection. Participants were instructed to place each vial in their home freezer immediately after sampling. Saliva samples were returned to the lab the day after saliva collection was completed using a provided pre–paid envelope. Samples were frozen −80°C in the lab prior to being shipped on dry ice to Dr. Clemens Kirschbaum's laboratory.

Minor deviations in sampling timing can have dramatic effects on cortisol values, especially in the morning (Stalder et al., 2016). Thus, each sampling vial had to be removed from a bottle equipped with an electronic date- and time-tracking cap (MEMs Track Cap; Aardex, Denver, CO), and participants recorded the date and time of collection on an adhesive label attached to each vial after sampling. MEMs cap times were unavailable for 13.73% of returned samples, primarily owing to product failure or because participants had opened the MEMs container to remove samples 1 and 2 simultaneously. For those with MEMs data available, the median deviation of MEMs-recorded time from that reported by participants ranged from 2–4 minutes across all samples and days (M = 6.50, SD = 9.24). Participant- or parent-reported sampling times were used for the current quality control procedures and following analyses; if those were missing, the MEMs cap times were used.

Individual samples were excluded when they deviated severely from normative diurnal secretory patterns, indicating a failure to provide saliva at the correct sampling times or an abnormal sleep–wake schedule. Sample 1 was excluded when the interval between reported wake and sample 1 exceeded 20 minutes, because this is considered not indicative of waking levels but rather of the cortisol awakening response (n ranging from 0 samples on day 3 to 8 for day 2). Sample 2 was excluded when the time interval between sample 1 and 2 exceeded 60 minutes (daily n ranged from 2 to 7 across the 5 days of data collection). Sample 2 was also excluded when it was lower than concentrations for the evening sample on the same day (n excluded day 1 = 30, n excluded day 2 = 29, n excluded day 3 = 23, n excluded day 4 = 32, n excluded day 5 = 4). Last, sample 3 was excluded when its concentrations were higher than the next day's waking concentrations (n excluded day 1–2 = 35, n excluded day 2–3 = 29, n excluded day 3–4 = 37).

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Table 2
Latent Growth ACE Model of Cortisol Reactions to Stress

Measure	Estimate	*SE*	*p*
Level 1: Within-person			
Sample-specific disturbances			
A	0.025	0.315	.937
C	0.062	0.090	.489
E	0.201	0.022	<.001
Level 2: Between-person variance decomposition			
Prestress intercept			
A	0.512	0.093	<.001
C	0.188	0.156	.228
E	0.637	0.072	<.001
Prestress intercept ⇒ Stress response			
A	0.080	0.379	.833
C	−0.801	0.205	<.001
E	−1.028	0.170	<.001
Prestress intercept ⇒ Stress recovery			
A	−0.194	0.129	.133
C	0.390	0.094	<.001
E	0.040	0.061	.513
Stress response unique of prestress intercept			
A	1.028	0.314	.001
C	0.000	0.009	.996
E	1.351	0.106	<.001
Stress response unique of prestress intercept ⇒ Stress recovery			
A	−0.154	0.113	.173
C	0.000	0.005	.996
E	−0.412	0.051	<.001
Stress recovery unique of prestress intercept and stress response			
A	0.000	0.000	.349
C	0.000	0.000	.076
E	0.567	0.040	<.001
Covariates			
Age ⇒ Pre-TSST intercept	0.153	0.039	<.001
Age ⇒ Stress response	−0.030	0.096	.752
Age ⇒ Stress recovery	−0.102	0.040	.010
Sex ⇒ Pre-TSST intercept	0.041	0.079	.603
Sex ⇒ Stress response	−0.574	0.208	.006
Sex ⇒ Stress recovery	0.132	0.081	.102
Age × Sex ⇒ Pre-TSST intercept	−0.054	0.062	.381
Age × Sex ⇒ Stress response	−0.177	0.184	.336
Age × Sex ⇒ Stress recovery	0.111	0.072	.121
Prestress time ⇒ Pre-TSST intercept	−0.079	0.040	.048
Prestress time ⇒ Stress response	0.259	0.101	.010
Prestress time ⇒ Stress recovery	−0.072	0.041	.081
Conditional means			
Prestress intercept	0.769	0.048	<.001
Stress response	0.878	0.113	<.001
Stress recovery	−0.660	0.044	<.001
Model fit indices: −2log Likelihood = −3,609.866, AIC = 7,309.732			

Note. All estimates are unstandardized. Units are in raw concentrations residualized for batch year and log-transformed. Cholesky path; Pre-stress time = time between waking and start of TSST-C. Age and pre-stress time were standardized; sex was effect coded.

Salivary cortisol values were residualized for factors known to affect cortisol measurement, including assay batch (together with stress cortisol; three batches), nonsteroid medication use on the day of sampling, self-reported dairy consumption on that day (which can cross-react with anticortisol antibodies and cause false results, https://salimetrics.com/analyte/salivary-cortisol/), and waking time. Residualized cortisol values were log-transformed. No further outlier removal was performed.

Hair Cortisol

One thousand seventy-eight participants contributed at least one measure of hair cortisol. Several participants contributed multiple samples of this ongoing longitudinal study, resulting in 1,338 hair cortisol samples. Participants were instructed to refrain from using leave-in hair products, such as hair gel, on the day of the lab visit. Samples were stored in a dry location and shipped to Dr. Clemens

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Table 3
Latent Growth ACE Model of Diurnal Secretion

Measures	Estimate	*SE*	*p*
Level 1: Within-person			
Day 2 ⇒ Cortisol values	0.047	0.026	.068
Day 3 ⇒ Cortisol values	0.010	0.037	.779
Day 4 ⇒ Cortisol values	0.046	0.040	.247
Day 5 ⇒ Cortisol values	0.063	0.045	.166
Quadratic term ⇒ Cortisol values	0.009	0.002	<.001
Sample-specific disturbances			
A	0.271	0.029	<.001
C	0.000	0.000	.425
E	0.471	0.023	<.001
Level 2: Between-person variance decomposition			
Waking intercept			
A	0.311	0.103	.002
C	0.467	0.077	<.001
E	0.269	0.042	<.001
Waking intercept ⇒ Awakening response			
A	−0.423	0.281	.133
C	−0.137	0.222	.537
E	−0.384	0.122	.002
Waking intercept ⇒ Diurnal slope			
A	−0.009	0.013	.461
C	0.000	0.008	.995
E	0.001	0.006	.903
Awakening response unique of waking intercept			
A	0.431	0.189	.022
C	0.336	0.288	.242
E	0.364	0.081	<.001
Awakening response unique of waking intercept ⇒ Diurnal slope			
A	0.002	0.013	.849
C	−0.002	0.019	.923
E	0.004	0.005	.505
Diurnal slope unique of waking intercept and awakening response			
A	0.028	0.010	.008
C	0.035	0.007	<.001
E	0.019	0.006	.001
Covariates			
Age ⇒ Waking intercept	−0.046	0.035	.197
Age ⇒ Awakening response	−0.003	0.055	.957
Age ⇒ Diurnal slope	0.001	0.003	.747
Sex ⇒ Waking intercept	−0.088	0.041	.031
Sex ⇒ Awakening response	−0.165	0.086	.056
Sex ⇒ Diurnal slope	0.002	0.005	.645
Age × Sex ⇒ Waking intercept	0.001	0.003	.747
Age × Sex ⇒ Awakening response	−0.083	0.067	.214
Age × Sex ⇒ Diurnal slope	−0.003	0.006	.577
Conditional means			
Waking intercept	1.623	0.047	<.001
Awakening response	0.779	0.056	<.001
Diurnal slope	−0.343	0.021	<.001
Model fit Indices: −2log likelihood = −10,999.257, AIC = 22,084.515			

Note. All estimates are unstandardized. Units are in raw concentrations residualized for batch year and log-transformed; ⇒ Cholesky path. Age was standardized; sex was effect-coded.

Kirschbaum's lab for steroid measurement. Research assistants collected a hair sample approximately 3 mm wide and 3 cm long from the posterior vertex of the scalp; this served as a marker for average cortisol secretion over the most recent three-month period. Technical details on the extraction procedure are provided elsewhere (Gao et al., 2013). Internal consistency estimates for cortisol analyzed using liquid chromatography tandem mass spectrometry (LC-MS/MS) have been reported above .96 (Stalder et al., 2012). In a subsample of 27 participants, reliability for cortisol samples analyzed in duplicate was estimated at .89 (Grotzinger et al., 2018). The lower limit of sensitivity for hair cortisol was .1 pg/ml (Gao et al., 2013). Hair cortisol values were residualized for assay batch (separately from salivary cortisol; six batches) and log-transformed. No further outlier removal was performed.

Zygosity

Opposite-sex twin pairs were classified as dizygotic. Same-sex twin pair zygosity was assessed using responses to ratings about

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the twins' physical similarities (e.g., facial appearance). The ratings were completed by parents and two research assistants. Parents additionally rated how often the twins are mistaken for one another. These ratings were entered into a latent class analysis that was used to obtain zygosity classifications. In the present study, latent class analysis accurately determined zygosity >97% of the time in 713 genotyped individuals.

Analyses

Phenotypic Stress Reaction and Diurnal Cortisol Models

Following the modeling approach of Malanchini et al. (2021), we applied multilevel piecewise latent growth models to characterize the change in salivary cortisol within people over time and between people. Level 1 represented within-person variation in the cortisol trajectory, and Level 2 denoted between-person variation after controlling for the effect of intraindividual variability. Time was scaled in hours (such that, e.g., the mean diurnal slope can be interpreted as a rate of change in transformed cortisol residuals per hour).

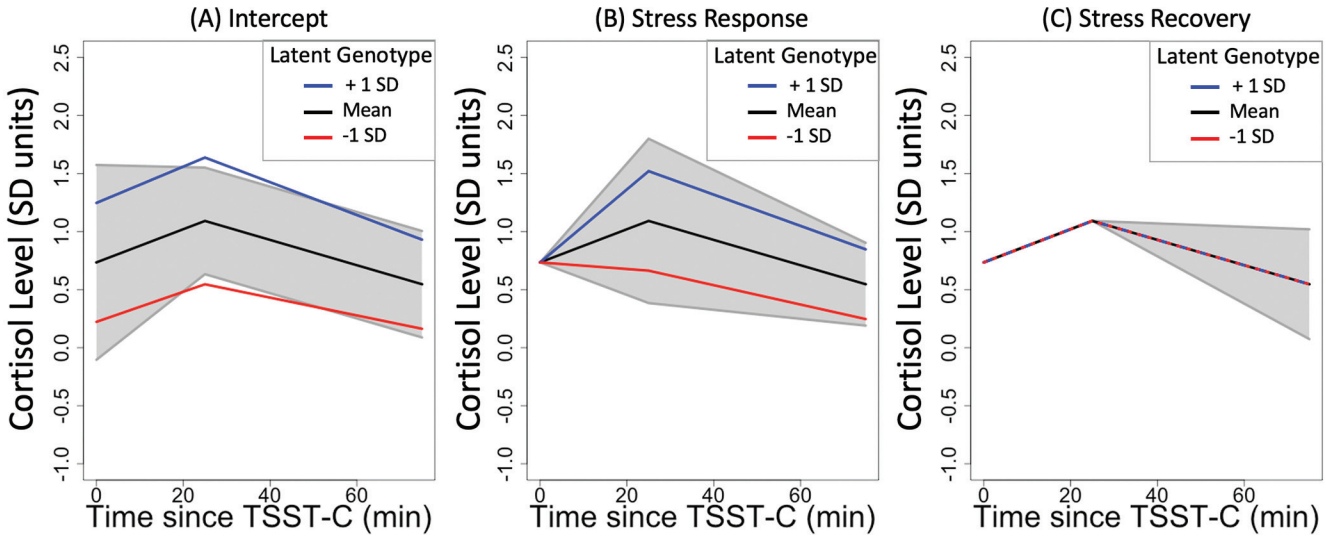
At Level 1, we specified three latent factors to characterize cortisol levels surrounding the acute stressor: (a) a latent intercept that reflects prestress baseline cortisol levels, (b) a latent response slope capturing the rise in cortisol following stress, and (c) a latent recovery slope representing the decline in cortisol following the response. (In referring to these components as latent factors, we adopt the terminology of latent growth curve modeling, which is statistically equivalent to methods commonly referred to as random coefficient modeling, mixed effects model, and multilevel modeling. In the terminology of these latter modeling traditions, what we refer to as "latent factors" are often referred to as "random effects" or "random coefficients"; Bauer, 2003; Ferrer et al., 2004.) The model estimated the rise in cortisol response prior to a specified turning point and an independent recovery slope following the turning point, which was found to be optimal 25 minutes from the start of the TSST-C in the present sample (Malanchini et al., 2021). Each latent factor constituted a random effect and was consequently allowed to vary at Level 2. Thus, variance of the latent factors represented between-person differences in intercept and slopes.

We applied this same two-level latent growth modeling approach to data on diurnal cortisol secretion. At Level 1, we specified three latent factors: (a) an intercept that reflects cortisol levels at awakening, (b) a latent response slope capturing the cortisol awakening response, and (c) a latent diurnal slope representing the decline in cortisol from morning to evening. The turning point was found to be optimal 32 minutes after awakening in analyses of cortisol data from a prior data freeze that has largely overlapping data with the current paper (Malanchini et al., 2021). Level 1 additionally included a quadratic term (time since turning point squared) to account for nonlinearity in the diurnal slope (Miller et al., 2016) and days of sampling (e.g., first day, second day) as dummy coded covariates to account for day-to-day variation. Our previous phenotypic analyses showed there was substantial variability in the latent cortisol constructs at the intra- and interindividual levels. See Malanchini et al. (2021) for more information on phenotypic cortisol models.

Additionally, the model of cortisol secretion in response to stress was combined with the diurnal secretion model by specifying a shared intercept that reflected awakening cortisol levels, resulting in five latent factors: (a) a shared intercept that reflected awakening

Figure 1

Patterns of Individual Differences in Cortisol Reactions to Stress Accounted for by Genetic Variability



Note. The blue (dark gray), black, and red (gray) lines represent expected trajectories for individuals who were higher (1 *SD* above the mean log-transformed cortisol value), average, and lower (1 *SD* above the mean), respectively, on genetic dispositions (the additive genetic "A" factor) for prestressor cortisol levels and its downstream genetic effects on stress response and recovery (A), stress responses unique of the intercept and its downstream genetic effects on stress recovery (B), and stress recovery unique of the intercept and stress response (C). These expected means by genotype are superimposed on the full ± 1 *SD* phenotypic range of variation indicated by the gray shading in the respective variance components. See Table 2 for parameter estimates. Raw cortisol levels were residualized for assay batch and log-transformed. See the online article for the color version of this figure.

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cortisol levels, (b) cortisol awakening response, (c) diurnal slope, (d) response to stress, and (e) recovery following stress.

Twin Model Specification

Behavior genetic models were fit to the data to determine variance attributable to additive genetic influences (A), shared environmental influences (C), and nonshared environmental influences unique to each twin (E). The ACE factors were standardized. Multivariate Cholesky decompositions were conducted to examine the extent to which genetic variance overlapped between measures. These were converted to total genetic correlations (total rA; Loehlin, 1996). Twin models were run as multigroup models for monozygotic pairs, dizygotic same-sex pairs, and dizygotic opposite-sex pairs. All models included age (standardized), sex (effect coded as female = −.5 and male = .5), and age-by-sex interaction effects predicting latent cortisol indices. All models were fit with FIML as implemented in Mplus 8.2 (Muthén & Muthén, 2017). To account for nesting of multiple waves of data within individuals and multiple twin pairs within families, a sandwich correction was applied to the standard errors in all analyses. Significance of parameter estimates was determined at $\alpha < .05$.

Derivation of Cortisol Trajectories From Variance Decompositions

We used a common mathematical approach to calculate regression parameters from variance decompositions, just as one can to estimate simple slopes after observing an interaction effect in an ANOVA (Fox, 2015; West et al., 1996). See also Tucker-Drob (2012) for the same approach applied to latent environmental factors and Briley and Tucker-Drob (2013) for longitudinal heritability modeling.

Y is modeled as a function of a mean, m, and latent additive genetic (A), shared environmental (C), and nonshared environmental (E) variance components that are weighted by regression coefficients (a, c, e):

$$Y = m + \ a \times A + c \times C + e \times E. \tag{1}$$

We assume that the latent A, C, and E factors are normally distributed (N), each with a mean of zero and standard deviation of one:

$$A \sim N(0,1), C \sim N(0,1), E \sim N(0,1). \tag{2}$$

Under this model, the expected value of Y for any unobserved set of scores on A, C, and E can be easily derived by substituting the Z score on each of the respective variance components into Equation 1. For example, for latent genotypes that are Z standard deviations from the mean of A, holding environmental factors constant and their mean, the expected value of Y is:

$$Y_{A+Z} = m + a \times (Z) + c \times (0) + e \times (0). \tag{3}$$

When Y is itself a latent growth curve intercept or slope, the expectation for Y can be further substituted into the multilevel model to produce an expected trajectory over the course of the day or exposure to the stressor. Different values for Z (e.g., −1, 0, 1) can be used to produce expected trajectories for different unobserved scores on each latent genetic factor. We have plotted simple slopes for individuals at 1 *SD* above and below the mean specifically to provide a visual representation that is commensurate with standard practices for computing effect sizes (Aiken & West, 1991). Of course, the plotted values are chosen for illustration purposes. For polygenic traits, the distributions of genotypes are continuous, such that more or less extreme values could have been chosen. A property of latent variables is that they cannot directly be observed for individual people. Thus, observed data cannot be plotted alongside growth curve expectations.

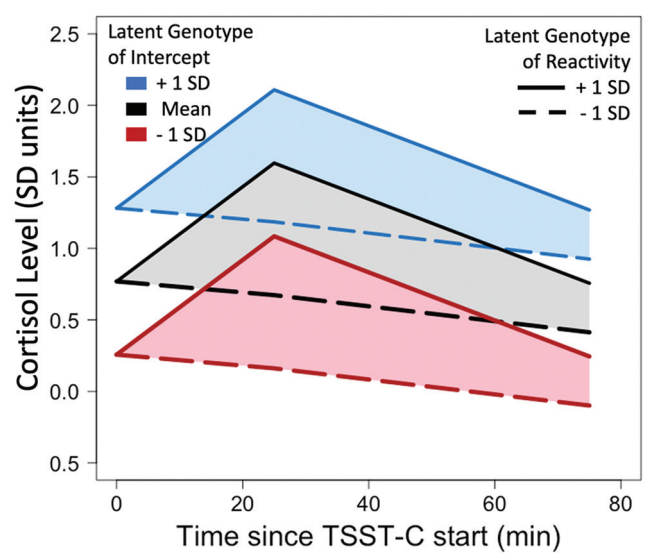
Results

Is There Genetic Variation in Cortisol Reactions to Stress?

In the model of cortisol secretion in response to stress, we estimated significant latent genetic effects on variation in the prestressor cortisol intercept (i.e., cortisol levels prior to stress), distinct variation in response to in-laboratory stress (i.e., unique of prestressor intercept; unstandardized estimate = 1.028, p = .001), but no distinct variation in recovery following stress (unique of the prestressor intercept and stress response; see Table 2 for single modality Cholesky decomposition parameter estimates and Table 3 for single modality total ACE variance estimates).

These three components of latent genetic variation, superimposed atop the comparable components of phenotypic variation,

Figure 2
Reaction Ranges in Cortisol Responses to Stress Reorder Individual Differences in Cortisol Output



Note. The first cortisol value at 0 minutes is the prestress intercept. The blue (dark gray), black, and red (gray) lines represent expected trajectories for individuals who were higher (1 *SD* above the mean log-transformed cortisol value), average, and lower (1 *SD* below the mean) on latent genetic dispositions for the prestress intercept, respectively. The trajectories diverge into solid and dashed lines as genotypes for higher (1 *SD* above the mean) and lower (1 *SD* above the mean) stress responses were innovative. The shaded areas depict the range of reactivity of different genotypes. Raw cortisol levels were residualized for assay batch and log-transformed. See the online article for the color version of this figure.

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are illustrated in Figure 1. The blue, black, and red lines represent expected phenotypic trajectories for individuals who were, respectively,1 *SD* above the mean, at the mean, and 1 *SD* below the mean on genetic dispositions (the "A" factor) for the following variance components: prestressor cortisol levels (Panel A), stress responses (Panel B), and stress recovery (Panel C). The trajectories represent the expected mean cortisol trajectories, stratified by level of genetic disposition on each variance component, allowing for effects to magnify or diminish over time, as indicated by the dependencies among the components. These expected means by (unobserved) genotype are superimposed on the full ± 1 *SD* phenotypic range of variation in the respective variance components.

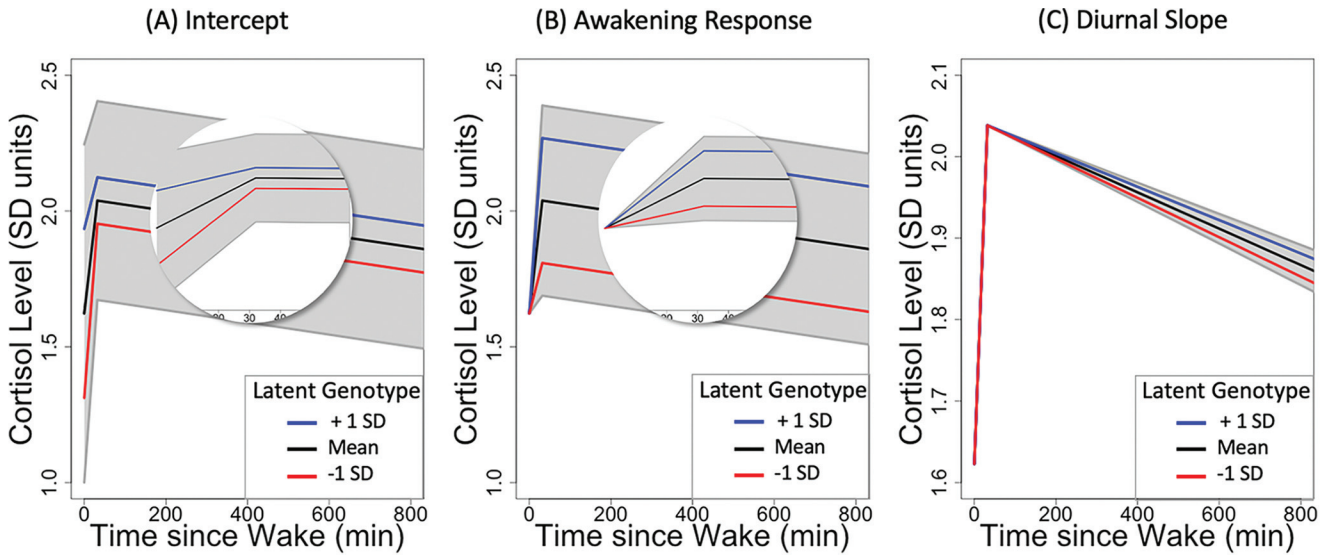
Panel A of Figure 1 illustrates genetic differences in baseline cortisol levels prior to stress exposure and how such differences progress over the course of the stressor protocol. There were differences in baseline cortisol levels that were strongly heritable and persisted across the laboratory assessment. Baseline genetic differences in cortisol levels were not related to genetic differences in stress response, and therefore no slope differences were observed between genotypes over the first ∼20 minutes. In contrast, baseline genetic differences were negatively associated with cortisol recovery, as indicated by the subtle narrowing of cortisol differences associated with genotypes over the last ∼40 minutes.

Panel B of Figure 1 illustrates the magnitude of genetic effects on the cortisol response to stress that were independent of genetic effects on baseline levels. Individuals with similar genotypes for elevated prestress baseline levels subsequently diverged phenotypically in response to a stressful environment, as largely independent genotypes for stress response magnitude were revealed.

Panel C of Figure 1 illustrates the lack of genetic effects on the cortisol stress recovery independent of genetic effects on baseline levels and response to stress. The stress recovery did not reveal unique genetic variation relative to baseline and stress reactions.

This is further depicted in Figure 2, which combines Panels A and B of Figure 1, such that the blue, black, and red lines represent expected phenotypic trajectories for individuals who were higher (1 *SD* above the mean; 84th percentile), average (50% percentile), and lower (1 *SD* below the mean, 16th percentile), respectively, on genetic dispositions for the prestress intercept. Because the genetic factor underlying stress response was unique of that underlying baseline variation, we depict the genotypes for higher (1 *SD* above the mean; 84th percentile) and lower (1 *SD* below the mean; 16th percentile) stress responses with solid and dashed lines, respectively, allowing the trajectories to originate at the expected values for either higher, average, or lower genotypes on the baseline genetic factor. It can be seen that genetic variation in stress response reorders individual differences during the stressor exposure: An individual with a genetic disposition for an average prestress intercept can subsequently have higher cortisol levels than an individual with a genetic disposition for a higher prestress intercept, because the former has a genetic disposition for higher stress responses, whereas the latter has a genetic disposition for lower stress responses (i.e., maximum gray shaded area relative to minimum blue shaded area).

Figure 3
Patterns of Individual Differences in Diurnal Cortisol Secretion Accounted for by Genetic Variability



Note. The blue (dark gray), black, and red (gray) lines represent expected trajectories for individuals who were higher (1 *SD* above the mean), average, and lower (1 *SD* above the mean log-transformed cortisol value), respectively, on genetic dispositions for awakening cortisol intercept and its downstream genetic effects on awakening responses and diurnal slopes (A), awakening response unique of the intercept and its downstream genetic effects on the diurnal slope (B), and the diurnal slope unique of the intercept and awakening response (C). These expected means by genotype are superimposed on the full ± 1 *SD* phenotypic range of variation indicated by the gray shading in the respective variance components. See full text for further interpretation. Circles are zoomed in on the first hour after awakening. Y-axis scaling for C differs to aid visibility of diurnal slope effects. Raw cortisol levels were residualized for assay batch and log-transformed. See Table 3 for parameter estimates. See the online article for the color version of this figure.

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Is There Latent Genetic Variation in Cortisol Change Over the Course of the Day?

In the model of diurnal cortisol secretion, we observed significant genetic effects on variation in the cortisol intercept at awakening, distinct variation in cortisol awakening response (unique of intercept), and distinct variation in diurnal slope (unique of intercept and awakening response; see Table 3 for single modality Cholesky decomposition parameter estimates and Table 2 for single modality total ACE variance estimates). Specifically, we estimate a genetic component of the cortisol awakening response that is unique of the waking intercept (unstandardized estimate = .431, p = .022) and a genetic component of the cortisol diurnal slope that is unique of both the waking intercept and the awakening response (unstandardized estimate = .028, p = .008).

The three components of genetic variation, superimposed atop the corresponding ranges of phenotypic variation, are illustrated in Figure 3. The blue, black, and red lines represent expected phenotypic trajectories for individuals who were, respectively, 1 *SD* above the mean, at the mean, and 1 *SD* below the mean on genetic dispositions for the following variance components: cortisol intercept at awakening (Panel A), cortisol awakening response (Panel B), and diurnal slope (Panel C). The trajectories represent the expected mean cortisol trajectories stratified by level of genetic disposition on each component of variance, allowing for effects to magnify or diminish over time, as indicated by the dependencies among the components. These expected means by latent genotype are superimposed on the full ± 1 *SD* phenotypic range of variation in the respective variance components.

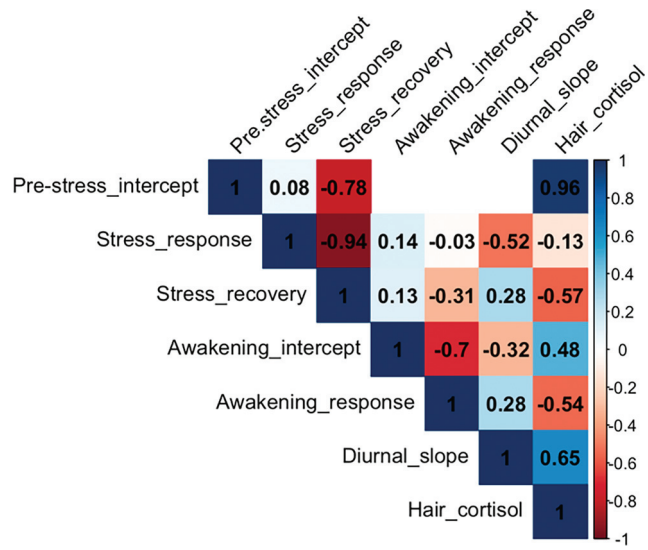
Panel A of Figure 3 illustrates genotype differences in baseline cortisol levels at awakening and how such differences progress over the course of the day. There were differences in baseline cortisol levels at awakening that were strongly heritable. Baseline genetic differences at awakening were negatively associated with the awakening response, as indicated by the cortisol differences associated with genotypes over the first ∼60 minutes of the day. Individuals with genetic dispositions for higher awakening levels subsequently showed lower awakening responses (blue line) than individuals with genetic dispositions for lower awakening levels (red line). Therefore, following the cortisol awaking response, genotypes related to substantially higher levels at awakening were associated with only slightly higher subsequent cortisol levels throughout the day.

Panel B of Figure 3 illustrates the genetic effects on the cortisol response to awakening that were independent of genetic effects on baseline awakening levels. Individuals with similar genotypes for elevated awakening levels subsequently diverged phenotypically in response to awakening, as largely unique genotypes for awakening magnitude were revealed. Individuals with genetic dispositions for higher awakening responses subsequently showed higher cortisol levels (blue line) than individuals with genetic dispositions for lower awakening responses (red line). Thus, genotypes for higher cortisol levels at awakening cannot be used to infer subsequent cortisol levels across the day, because distinct genotypes are revealed in response to awakening.

Panel C of Figure 3 illustrates the genetic effects on the diurnal slope that were independent of genetic effects on baseline awakening levels and awakening responses. Genetic differences in baseline cortisol levels and awakening responses were not related to genetic differences in the diurnal slope, and therefore no slope differences were observed between genotypes after ∼30 minutes in panel A and B.

Figure 4

Total Latent Genetic Correlations Between Cortisol Reactions to Stress, Diurnal Secretion, and Hair Cortisol



Note. Genetic correlations between latent factors were computed on the basis of 5 separate models: (1) acute stress reaction only, (2) diurnal secretion only, (3) combined model of acute stress reaction and diurnal secretion, (4) acute stress reaction with hair cortisol, and (5) diurnal secretion with hair cortisol. There were no correlations of the prestress intercept with diurnal secretion (white cubes), because the combined model includes only one intercept (the prestress intercept is determined from the diurnal trajectory and timing of stressor within the day). See the online article for the color version of this figure.

Are Cortisol Reactions to Stress and the Day Regulated by the Same Latent Genetic Variation?

In the combined model of cortisol reactions to stress and the day, we identify a genetic component of TSST response that is unique of waking intercept, awakening response, and diurnal slope (unstandardized estimate = 1.311, $p < .001$; in this joint model, the prestress intercept is not directly modeled as it is subsumed by the diurnal rhythm). The total latent genetic correlation between the diurnal slope and the cortisol response to stress (total rA = −.516, SE = .319, p = .106) or the recovery following stress (total rA = .280, SE = .284, p = .324) were modest-to-moderate. The magnitude of these genetic correlations is depicted in Figure 4.

The latent genetic correlation between the cortisol awakening response with cortisol response to stress (total rA = −.030, SE = .277, p = .912) or recovery following stress (total rA = −.313, SE = .245, p = .202) was negligible-to-modest. Critically, a significant genetic effect on the cortisol response to stress unique of awakening intercept, awakening response, and diurnal slope was still found (see Table 4). Therefore, the genetic variation involved in reactions to stress and the day were largely uncorrelated.

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Table 4
Combined Model of the Cortisol Reactions to Stress and Diurnal Secretion

Measure	Estimate	*SE*	*p*	Measure	Estimate	*SE*	*p*
Level 1: Within-person							
Day 2 ⇒ Cortisol values	0.095	0.025	<.001				
Day 3 ⇒ Cortisol values	0.057	0.035	.102				
Day 4 ⇒ Cortisol values	0.094	0.035	.007				
Day 5 ⇒ Cortisol values	0.119	0.046	.010				
Quadratic term ⇒ Cortisol values	0.013	0.001	<.001				
Sample-specific disturbances							
A	0.288	0.022	<.001				
C	0.000	0.000	.747				
E	0.449	0.020	<.001				
Level 2: Between-person diurnal secretion							
Cholesky variance decomposition				Single modality model			
Waking intercept				Waking intercept			
A	0.292	0.097	.003	A	0.292	0.097	.003
C	0.480	0.071	<.001	C	0.480	0.071	<.001
E	0.281	0.041	<.001	E	0.281	0.041	<.001
Waking intercept ⇒ Awakening response							
A	−0.333	0.273	.224				
C	−0.279	0.180	.122				
E	−0.374	0.119	.002				
Waking intercept ⇒ Diurnal slope							
A	−0.007	0.013	.586				
C	0.002	0.009	.853				
E	−0.002	0.005	.777				
Awakening response unique of waking intercept				Awakening response			
A	0.485	0.159	.002	A	0.588	0.216	.007
C	0.384	0.180	.033	C	0.474	0.222	.033
E	0.389	0.071	<.001	E	0.540	0.101	<.001
Awakening response unique of waking intercept ⇒ Diurnal slope							
A	0.001	0.012	.919				
C	−0.009	0.016	.566				
E	−0.002	0.006	.676				
Diurnal slope unique of waking intercept and awakening response				Diurnal slope			
A	0.029	0.008	.001	A	0.029	0.008	<.001
C	0.039	0.007	<.001	C	0.040	0.007	<.001
E	0.023	0.004	<.001	E	0.023	0.004	<.001
Level 2: Between-person stress reaction							
Cholesky variance decomposition				Single modality model			
Waking intercept ⇒ Stress response							
A	0.176	0.470	.708				
C	−0.298	0.217	.170				
E	0.253	0.242	.295				
Waking intercept ⇒ Stress recovery							
A	0.042	0.151	.781				
C	−0.173	0.107	.105				
E	0.046	0.078	.558				
Awakening response unique of waking intercept ⇒ Stress response							
A	0.074	0.432	.865				
C	0.122	0.287	.671				
E	−0.040	0.241	.869				
Awakening response unique of waking intercept ⇒ Stress recovery							
A	−0.088	0.114	.441				
C	−0.064	0.178	.718				
E	−0.032	0.066	.632				
Diurnal slope unique of waking intercept and awakening response ⇒ Stress							
A	−0.655	0.393	.095				
C	0.103	0.214	.630				
E	−0.002	0.200	.992				

(*table continues*)

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Table 4 (*continued*)

Measure	Estimate	*SE*	*p*	Measure	Estimate	*SE*	*p*
Diurnal slope unique of waking intercept and awakening response ⇒ Stress recovery							
A	0.256	0.112	.023				
C	0.015	0.102	.885				
E	−0.062	0.077	.415				
Stress response unique of waking intercept, awakening response, and diurnal slope				Stress response			
A	1.119	0.340	.001	A	1.311	0.193	<.001
C	−0.135	0.232	.561	C	0.362	0.234	.122
E	1.159	0.163	<.001	E	1.188	0.182	<.001
Stress response unique of waking intercept, awakening response, and diurnal slope ⇒ Stress recovery							
A	−0.184	0.084	.028				
C	0.18	0.192	.347				
E	−0.166	0.056	.003				
Stress recovery unique of waking intercept, awakening response, diurnal slope, and stress response				Stress recovery			
A	0.000	0.000	.172	A	0.330	0.099	.001
C	0.000	0.000	.721	C	0.258	0.120	.031
E	0.000	0.000	.555	E	0.187	0.058	.001
Covariates							
Age ⇒ Waking intercept	−0.039	0.038	.300				
Age ⇒ Awakening response	0.040	0.055	.468				
Age ⇒ Diurnal slope	0.000	0.003	.974				
Age ⇒ Stress response	0.239	0.102	.019				
Age ⇒ Stress recovery	−0.060	0.045	.179				
Sex ⇒ Waking intercept	−0.083	0.045	.062				
Sex ⇒ Awakening response	0.056	0.096	.559				
Sex ⇒ Diurnal slope	−0.001	0.006	.874				
Sex ⇒ Stress response	0.210	0.208	.313				
Sex ⇒ Stress recovery	0.115	0.085	.179				
Age × Sex ⇒ Waking intercept	−0.062	0.044	.161				
Age × Sex ⇒ Awakening response	−0.013	0.092	.890				
Age × Sex ⇒ Diurnal slope	0.005	0.006	.386				
Age × Sex ⇒ Stress response	0.048	0.196	.807				
Age × Sex ⇒ Stress recovery	0.070	0.076	.356				
Stress time ⇒ Awake intercept	0.039	0.020	.057				
Stress time ⇒ Stress response	0.971	0.107	<.001				
Stress time ⇒ Stress recovery	−0.076	0.043	.079				
Conditional means							
Waking intercept	1.575	0.047	<.001				
Awakening response	0.705	0.061	<.001				
Diurnal slope	−0.386	0.019	<.001				
Stress response	0.412	0.118	<.001				
Stress recovery	−0.591	0.051	<.001				
Model fit indices: −2log likelihood = −15,412.505, AIC = 30,995.009							

Note. All estimates are unstandardized. Total ACE Variance = total A, C, or E variance in each outcome accounted for by all respective components of variance. Stress time = time between waking and start of TSST-C. ⇒ Cholesky path. Age was standardized, sex was effect-coded. Units are in raw concentrations residualized for batch year and log-transformed. Single modality models only model one mode of cortisol output (i.e., acute stressor or diurnal) at a time.

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Are Cortisol Reactions to Stress and the Day Regulated by the Same Latent Genetic Variance as Hair Cortisol Levels?

In the combined model of cortisol reactions to stress and hair cortisol, the latent genetic correlation of hair cortisol levels with the cortisol prestress intercept was high (total *r*A = .965, *SE* = .189, $p < .001$, Figure 4). In contrast, genetic correlations of hair cortisol with the response to stress (total *r*A = −.133, *SE* = .760, *p* = .861) and recovery following stress (total *r*A = −.566, *SE* = .795, *p* = .477) were negligible-to-moderate and not reliably different from zero. In our Cholesky models, the genetic effects on intercept, stress response, and recovery unique of hair cortisol and each other were not reliably different from zero (see Table 5). This may be attributable to our attempts to divide variation into too fine grain components of variation, particularly given the relatively low heritability estimate for hair cortisol.

In the combined model of cortisol reactions to the day and hair cortisol, genetic correlations of hair cortisol levels with the cortisol intercept at awakening (total *r*A = .485, *SE* = .398, *p* = .223), cortisol awakening response (total *r*A = −.544, *SE* = .478, *p* = .255), or

Table 5
Latent Growth ACE Model of Cortisol Stress Response Combined With Hair Cortisol

Measure	Estimate	*SE*	*p*
Level 1: Within-person			
Sample-specific disturbances			
A	0.024	0.326	.942
C	0.062	0.089	.481
E	0.201	0.022	<.001
Level 2: Between-person variance decomposition			
Hair cortisol			
A	0.203	0.179	.257
C	0.731	0.100	<.001
E	0.770	0.052	<.001
Hair cortisol ⇒ Prestress intercept			
A	0.447	0.261	.087
C	0.130	0.15	.387
E	0.048	0.071	.493
Prestress intercept unique of hair cortisol			
A	−0.122	0.315	.698
C	0.220	0.307	.474
E	0.645	0.087	<.001
Hair cortisol ⇒ Stress response			
A	−0.143	0.824	.862
C	−0.272	0.215	.206
E	−0.011	0.122	.927
Prestress intercept unique of hair cortisol ⇒ Stress response			
A	−1.067	0.27	<.001
C	−0.592	0.702	.399
E	−1.023	0.167	<.001
Stress response unique of prestress intercept and hair cortisol			
A	0.000	0.000	.964
C	−0.394	0.998	.693
E	1.343	0.105	<.001
Hair cortisol ⇒ Stress recovery			
A	−0.154	0.232	.508
C	0.139	0.081	.085
E	0.014	0.041	.728
Prestress intercept unique of hair cortisol ⇒ Stress recovery			
A	0.224	0.16	.160
C	0.245	0.576	.670
E	0.034	0.069	.623
Stress response unique of prestress intercept and hair cortisol ⇒ Stress recovery			
A	0.000	0.000	.908
C	0.249	0.618	.687
E	−0.411	0.051	<.001
Stress recovery unique of pre-stress intercept, stress response, and hair cortisol			
A	0.000	0.000	.411
C	0.000	0.000	.076
E	0.567	0.041	<.001
Covariates			
Age ⇒ Hair	−0.059	0.051	.242
Age ⇒ Pre-TSST intercept	0.147	0.039	<.001
Age ⇒ Stress response	−0.025	0.095	.789
Age ⇒ Stress recovery	−0.104	0.040	.009
Sex ⇒ Hair	0.332	0.092	<.001
Sex ⇒ Pre-TSST intercept	0.052	0.075	.486
Sex ⇒ Stress response	−0.595	0.207	.004
Sex ⇒ Stress recovery	0.141	0.081	.081
Age × Sex ⇒ Hair	0.02	0.098	.839
Age × Sex ⇒ Pre-TSST intercept	−0.069	0.062	.266
Age × Sex ⇒ Stress response	−0.148	0.18	.411

(*table continues*)

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Table 5 (*continued*)

Measure	Estimate	*SE*	*p*
Age × Sex ⇒ Stress recovery	0.100	0.071	.157
Prestress time ⇒ Pre-TSST intercept	−0.085	0.037	.022
Prestress time ⇒ Stress response	0.264	0.101	.009
Prestress time ⇒ Stress recovery	−0.073	0.041	.075
Conditional means			
Prestress intercept	0.766	0.047	<.001
Stress response	0.883	0.112	<.001
Stress recovery	−0.662	0.044	<.001
Hair	0.095	0.053	.075
Model fit indices: −2log likelihood = −4,453.334, AIC = 9,028.668			

Note. All estimates are unstandardized. Units are in raw concentrations residualized for batch year and log-transformed. ⇒ Cholesky path; Prestress time = time between waking to start of TSST–C. Age and stress time were standardized; sex was effect-coded.

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diurnal slope (total *r*A = .647, *SE* = .388, *p* = .096) were modest-to-moderate and not reliably different from zero. Notably, a genetic effect of the awakening intercept unique of hair cortisol was still found to be reliably different from zero, but that was not true for the awakening response (unique of hair cortisol and awakening intercept) or diurnal slope (unique of hair cortisol, awakening intercept, and awakening response; Table 6). Even though the Cholesky results involving hair cortisol are somewhat less precise, the strong evidence for differentiation of TSST and diurnal rhythm components reported in the models that did not include hair cortisol, precludes the possibility that hair cortisol can fully index genetic variation in all components. Results involving hair do indicate that, as an aggregate marker of cortisol accumulation over several months, it gives some (imperfect) insight into the cumulative effects of diurnal variation and acute stress on cortisol levels over time.

Discussion

We present results from a comprehensive behavioral genetic study of cortisol response. Results indicated that genetic variation was associated with dynamic patterns of cortisol secretion, both in response to a standardized in-laboratory stressor and across the day. Counter to the view that environmental effects either compete with genetic effects or merely serve to magnify standing genetic influences on biopsychosocial phenotypes, cortisol responses to acute stress were regulated by distinct genetic variation that was not apparent prior to stressor onset or in hair cortisol levels. Moreover, genetic variation in cortisol changes in response to acute stress was genetically discernable from variation in cortisol changes across the day, indicating that genetic variation in these components cannot simply be conceptualized as a general disposition to cortisol change. Finally, although hair cortisol was genetically correlated with multiple aspects of cortisol variation, hair cortisol was not a full proxy for all the genetic variation in the complex system of processes indexed by repeated sampling over time and context.

Many previous studies of Gene × Environment interactions on biopsychosocial phenotypes have been limited by comparing different groups of individuals in different environmental contexts, rather than identifying individual differences in within-person change over time, and by the lack of experimental control over environmental change. The current study advances the literature by examining genetic variation in within-person change in cortisol in two contexts: (a) an exogenously imposed environmental stressor administered in a controlled laboratory condition, and (b) naturally occurring changes throughout the day. In both contexts, mean changes in cortisol secretion were associated with a substantial reordering of individuals, partly on the basis of their genotypes.

The fact that we identified genetic factors relevant to cortisol change that were independent of those relevant to baseline and chronic levels of cortisol variation indicates that it would be inappropriate to describe one genotype or another as coding for higher cortisol output. Rather, the relative ordering of people in their cortisol levels was dependent on the context. This pattern resembles classic findings on genetic reaction ranges in fruit flies (Gupta & Lewontin, 1982) and mice (Cooper & Zubek, 1958), in which relative ordering of organisms on multiple traits substantially changed across environments. Here, we provide an empirical demonstration of the same theoretical process in a human phenotype. Despite some convergence of genetic effects across environments (stress and day), unique genetic variation was revealed in response to a new stressful environment. Individual differences in stress appraisal, which are themselves partly regulated by genotype, may be part of the mechanism through which genotype moderates cortisol responses to the same external stressor. This can be considered a form of active gene–environment correlation that even an exogenously imposed environment cannot control for, in that the individual can still actively attend (or fail to attend) to aspects of the environment, and form an idiosyncratic appraisal of it (Plomin et al., 1977).

These findings have implications for molecular genomic studies aiming to integrate genetically influenced individual propensities and environmental exposures to advance our understanding of stress system functioning. They suggest that cortisol reactivity reflects genetic variability regulating responses to environmental context, as posited by diathesis stress and differential susceptibility models (Roisman et al., 2012). Our results also provide evidence that changing environments can reveal genetic variations that might remain silent in alternative situations or even reveal inverse effects of standing genetic variation. As a corollary of this observation, we can conclude that genetically associated differences observed in one group in a specific environment may not fully inform the relative ordering of genetically-associated individual differences of that group in a new environment (Gottlieb, 2007) or

Table 6
Latent Growth ACE Model of Diurnal Cortisol Secretion Combined With Hair Cortisol

Measures	Estimate	*SE*	*p*
Level 1: Within-person			
Day 2 ⇒ Cortisol values	0.047	0.025	.062
Day 3 ⇒ Cortisol values	0.010	0.035	.766
Day 4 ⇒ Cortisol values	0.046	0.037	.213
Day 5 ⇒ Cortisol values	0.063	0.045	.158
Quadratic term ⇒ Cortisol values	0.009	0.002	<.001
Sample-specific disturbances			
A	0.271	0.028	<.001
C	0.000	0.000	.431
E	0.471	0.023	<.001
Level 2: Between-person variance decomposition			
Hair Cortisol			
A	0.512	0.246	.038
C	0.711	0.154	<.001
E	0.814	0.072	<.001
Hair Cortisol ⇒ Waking intercept			
A	0.152	0.143	.287
C	−0.052	0.122	.671
E	0.019	0.036	.608
Waking intercept unique of hair cortisol			
A	0.275	0.107	.011
C	0.461	0.084	<.001
E	0.268	0.040	<.001
Hair cortisol ⇒ Awakening response			
A	−0.337	0.308	.274
C	0.226	0.191	.239
E	0.096	0.092	.300
Waking intercept unique of hair cortisol ⇒ Awakening response			
A	−0.319	0.295	.280
C	−0.103	0.244	.674
E	−0.383	0.113	.001
Awakening response unique of hair cortisol and waking intercept			
A	0.410	0.213	.055
C	0.243	0.429	.571
E	0.343	0.070	<.001
Hair cortisol ⇒ Diurnal slope			
A	0.019	0.012	.111
C	0.004	0.008	.615
E	−0.001	0.003	.766
Waking intercept unique of hair cortisol ⇒ Diurnal slope			
A	−0.020	0.013	.144
C	0.000	0.008	.992
E	0.000	0.005	.978
Awakening response unique of hair cortisol and waking intercept ⇒ Diurnal slope			
A	0.011	0.018	.538
C	−0.004	0.028	.900
E	0.004	0.005	.429
Diurnal slope unique of hair cortisol waking intercept, and awakening response			
A	0.000	0.000	.842
C	0.034	0.007	<.001
E	0.019	0.006	.001
Covariates			
Age ⇒ Hair cortisol	−0.079	0.058	.175
Age ⇒ Waking intercept	−0.047	0.033	.157
Age ⇒ Awakening response	−0.006	0.053	.915
Age ⇒ Diurnal slope	0.001	0.003	.777
Sex ⇒ Hair cortisol	0.407	0.106	<.001
Sex ⇒ Waking intercept	−0.099	0.042	.017
Sex ⇒ Awakening response	−0.157	0.089	.079

(*table continues*)

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Table 6 (*continued*)

Measures	Estimate	*SE*	*p*
Sex ⇒ Diurnal slope	−0.003	0.005	.590
Age × Sex ⇒ Hair cortisol	0.006	0.108	.958
Age × Sex ⇒ Waking intercept	0.001	0.003	.777
Age × Sex ⇒ Awakening response	0.085	0.066	.198
Age × Sex ⇒ Diurnal slope	0.002	0.005	.635
Conditional means			
Hair cortisol	−0.050	0.060	.410
Waking intercept	1.627	0.045	<.001
Awakening response	0.780	0.060	<.001
Diurnal slope	−0.342	0.021	<.001
Model fit indices: −2log likelihood = −10,868.946, AIC = 21,843.891			

Note. All estimates are unstandardized. Units are in raw concentrations residualized for batch year and log-transformed ⇒ Cholesky path. Age was standardized; sex was effect-coded.

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what differences between groups will be in a new environment (Taylor, 2006).

Our results further indicate that the genetic architecture of different modes and timescales of cortisol measurement may differ from one another, and that unique aspects of genetic architecture will be lost if genome-wise association studies (GWAS) were to naively combine such data in an attempt to increase power. Similarly, the patterns of genetic correlations among different modalities and timescales of cortisol measurement may differ, such that a GWAS meta-analysis across modalities may give downwardly biased estimates of heritability. These limitations, of course, pose major challenges to leveraging molecular genetic methods at large scale to further our understanding of genetic risk and resilience mechanisms in the face of adversity. Multivariate methods (for example, Grotzinger et al., 2019) for GWAS that are able to discern common and unique components of genetic architecture across related phenotypes at genome-wide and individual-variant levels of analysis may be useful for overcoming such limitations.

Our current focus on the genetics of cortisol diurnal rhythm and acute response should not be taken to mean that environmental variation beyond the TSST is unimportant for HPA output. The estimates of the nonshared environmental components of variation (E) reported in Tables 2–6 for cortisol levels and changes highlight the important contribution of unmeasured variation in environmental experience and/or idiosyncratic or stochastic processes in cortisol output. Importantly, our previous work in this sample (Malanchini et al., 2021) failed to document consistent associations between multiple dimensions of neighborhood, school, and family socioeconomic factors and the dimensions of cortisol accumulation, rhythm, and response studied here. This suggests that the environmental contributions to cortisol variation are unlikely to correlate strongly with commonly studied dimensions of socioeconomic stratification, contrary to some previous speculations (Lupien et al., 2001).

Cortisol secretion is a model phenotype that is well suited for the study of Gene × Environment interactions because of its posited relevance to psychological and behavioral research (Koss & Gunnar, 2018), responsiveness to change over short timescales, and heritability. Despite these strengths, our results may not generalize to other psychobiological domains. Evaluating the generalizability of our findings that show distinct genetic variation in changing environments will require further genetically informative studies that exogenously manipulate environments and characterize interactively changing reactions to them. For instance, future studies could explore genetic variation in behaviorally or neuroanatomically observed learning curves of new knowledge (e.g., an unfamiliar language) and new skills (e.g., writing with the nondominant hand). Such studies could use twin-based designs, as was applied here, or they could capitalize on molecular genetic measures (e.g., polygenic scores; Belsky & Harden, 2019).

In conclusion, this study provides empirical evidence that the genome regulates individuals' reactions to the environment that differ across environments. If environments are constantly changing, it follows that the genetic factors that are relevant to the outcomes under study may be continuously in flux.

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