The cortisol reactivity threshold model: Direction of trait rumination and cortisol reactivity association varies with stressor severity

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Abstract:

Various internalizing risk factors predict, in separate studies, both augmented and reduced cortisol responding to lab-induced stress. Stressor severity appears key: We tested whether heightened trait-like internalizing risk (here, trait rumination) predicts heightened cortisol reactivity under modest objective stress, but conversely predicts reduced reactivity under more robust objective stress. Thus, we hypothesized that trait rumination would interact with a curvilinear (quadratic) function of stress severity to predict cortisol reactivity. Evidence comes from 85 currently non-depressed emerging adults who completed either a non-stressful control protocol (n = 29), an intermediate difficulty Trier Social Stress Test (TSST; n = 26), or a robustly stressful negative evaluative TSST (n = 30). Latent growth curve models evaluated relationships between trait rumination and linear and quadratic effects of stressor severity on the change in cortisol and negative affect over time. Among other findings, a significant Trait Rumination x Quadratic Stress Severity interaction effect for cortisol's Quadratic Trend of Time (i.e., reactivity, B = .125, p = .017) supported the hypothesis. Rumination predicted greater cortisol reactivity to intermediate stress (rp = .400, p = .043), but blunted reactivity to more robust negative evaluative stress (rp = −0.379, p = 0.039). Contrasting hypotheses, negative affective reactivity increased independently of rumination as stressor severity increased (B = .453, p = 0.044). The direction of the relationship between an internalizing risk factor (trait rumination) and cortisol reactivity varies as a function of stressor severity. We propose the Cortisol Reactivity Threshold Model, which may help reconcile several divergent reactivity literatures and has implications for internalizing psychopathology, particularly depression.

Keywords: stress | cortisol | rumination | cortisol reactivity threshold model | depression

Article:

1. Introduction

Dysregulation in hypothalamic-pituitary-adrenal (HPA) axis stress responding is associated with risk for and concurrent experience of internalizing psychopathology—depression (Doane et al., 2013, Halligan et al., 2007, Vrshek-Schallhorn et al., 2013) and anxiety disorders (Adam et al., 2014). However, research examining how numerous trait-like internalizing psychopathology risk factors (such as trait rumination, neuroticism, and low extraversion) predict lab-based reactivity in cortisol provides diverging results. Some results indicate that trait-like risk factors predict greater cortisol reactivity to lab-based stress (Wirtz et al., 2007, Zoccola et al., 2010), while others indicate these same risk factors predict relatively blunted cortisol reactivity (Bibbey et al., 2013, Oswald et al., 2006; Vrshek-Schallhorn et al., under review; Zoccola et al., 2008).1 Similarly, a genetic predictor of cortisol reactivity suspected of being a risk factor for depression was linked first with heightened cortisol responding in two studies (Brummett et al., 2014, Brummett et al., 2012), but later with blunted responding across three samples (Avery and Vrshek-Schallhorn, 2016, Way et al., 2016). The present study examines a novel model that may help reconcile divergent findings and offer novel predictions about HPA functioning in internalizing psychopathology—predominantly depression.

1.1. The cortisol reactivity threshold model

Examination of some studies' methods suggests a striking pattern: In those yielding positive risk-reactivity associations, manipulations appear milder (e.g., reading a statement instead of giving a speech; Brummett et al., 2012) compared to those yielding negative associations (e.g., receiving negative evaluative non-verbal feedback instead of neutral feedback; Avery and Vrshek-Schallhorn, 2016). This suggests a model in which (a) individuals systematically differ in the level of objective stressor severity that provokes their peak cortisol reactivity, (b) internalizing risk contributes to this individual difference, and (c) the relationship between internalizing risk factors and cortisol reactivity will vary nonlinearly as objective stressor severity increases, such that (d) internalizing risk predicts relatively greater reactivity to modest threats, but (e) relatively less reactivity to robust threats. In addition to observations about the potential role of stressor severity, this model relies on evidence that cortisol functions in part as a resource-mobilizing hormone (for a review, see Sapolsky et al., 2000), and that internalizing risk is associated with biased perception of threat (e.g., Conway et al., 2016). Such biases might lead to mobilizing resources more readily under modest threat, but also to giving up more readily when threats are more robust (i.e., anhedonic stress responding; Pizzagalli, 2014).

In an initial conceptualization, informed by Yerkes-Dodson theory (for a review, see Teigen, 1994, Yerkes and Dodson, 1908), risk predicts achieving peak cortisol responses at a lower threshold of objective stressor severity but declining in reactivity as stressor severity increases (Fig. 1a, the "inverted-U variant"). A slightly different pattern would yield similar observations. In the "inflexibility variant" (Fig. 1b), higher risk individuals reach peak reactivity at a lower severity threshold, but have a flatter slope of reactivity change between moderate and robust stressors than their lower risk counterparts.

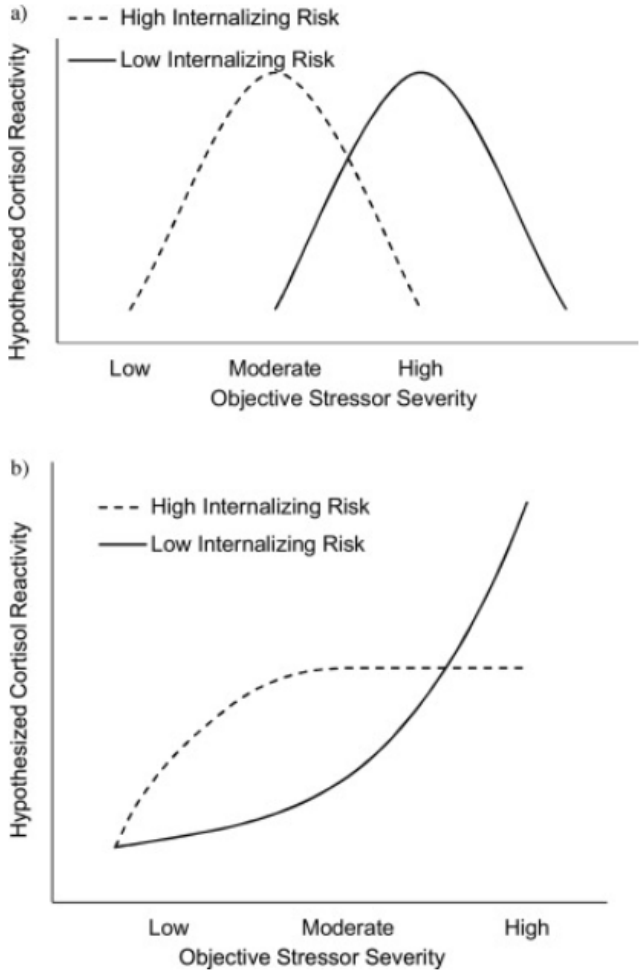

Fig. 1. Hypothesized relationship between internalizing risk factors and cortisol reactivity as a function of stressor severity level. Dashed line represents elevated internalizing risk; solid line represents relatively low internalizing risk. (a) The inverted-U curve variant. (b) The inflexibility variant.

1.2. Influence of explicit negative evaluation on cortisol reactivity

A related question is whether explicitly negative evaluative stress inductions result in greater cortisol reactivity than those without explicit negative evaluation. Studies without explicit negative evaluation have been described by some as neutral, and by others as provoking (implicit) negative evaluation due to ambiguity. For example, standard TSST judges are, "trained to communicate with the subject in an unresponsive neutral manner…[without] any facial or verbal feedback," behaviors that are not intended to, "resemble harassment or evoke anger in participants," (Kudielka et al., 2007). Others characterize such methods as negative evaluative because of the potential for participants to infer negative evaluation, e.g., "confederates provided negative, non-verbal feedback by maintaining stoic expressions and eye contact," (Zoccola and Dickerson, 2015). Thus, although a number of studies report using negative evaluation, typically this characterizes ambiguous, neutral responses, rather than explicit negative evaluation. Critically, methods in which confederates are explicitly instructed to display non-verbal negative evaluative behavior (e.g., Taylor et al., 2010) primarily emerged after a rigorous meta-analysis showed that

uncontrollability and social evaluation uniquely contribute to reactivity (Dickerson and Kemeny, 2004). No test yet compares cortisol reactivity between ambiguous, neutral manipulations and explicitly negative evaluative ones.

1.3. Negative affect under stress

Diathesis-stress models predict that trait-like internalizing risk factors will interact with objective stress to predict augmented or prolonged negative affect (e.g., Monroe and Simons, 1991, Nolen-Hoeksema et al., 2008). Evidence includes that trait rumination interacted with self-reported negative events to predict greater negative affect in an experience sampling study (Moberly and Watkins, 2008). Similarly, neuroticism interacted with interview-assessed stressful events to predict depression onset, consistent with both heightened and prolonged negative affect (Kendler et al., 2004), and engagement in rumination mediated self-reported stressful events' effect on increased internalizing symptoms (Michl et al., 2013). These findings suggest that internalizing risk factors may amplify the effect of increasingly stressful experiences on negative affect, thus differing from the curvilinear pattern anticipated for cortisol.

1.4. The present study

The present study examined non-depressed emerging adults and employed latent growth curve modeling to test how one transdiagnostic internalizing risk factor, trait rumination (dwelling on the causes or consequences of depressed mood; Treynor et al., 2003), predicts cortisol and negative affect reactivity to three levels of lab-induced stress: a non-stressful control, an intermediate severity-level TSST, and a negative evaluative TSST. We selected trait rumination to extend our previous work in which there was an association of trait rumination with blunted cortisol reactivity in a negative evaluative TSST compared to a non-stressful control (Vrshek-Schallhorn et al., under review).

We tested six hypotheses—five pertaining to cortisol and one pertaining to negative affect. We predicted that the relationship between trait rumination and cortisol reactivity would vary as a nonlinear function of stressor severity, an interaction between rumination and quadratic stressor severity (Hypothesis 1), such that trait rumination would predict greater cortisol reactivity to an intermediate stressor (Hypothesis 2), but would inversely predict reactivity in a more robust stressor (Hypothesis 3). We did not hypothesize an association in the non-stressful control. We predicted that increasing stressor severity would predict on-average greater cortisol reactivity (Hypothesis 4; Dickerson and Kemeny, 2004) and that an explicitly negative evaluative TSST would yield greater cortisol reactivity than a neutral/ambiguous intermediate TSST (Hypothesis 5). Finally, the literature suggests that greater trait rumination may predict increasingly pronounced negative affect reactivity as stress severity increases, an interaction of linear (not quadratic) stressor severity and trait rumination (Hypothesis 6).

2. Methods

2.1. Participants

In a larger study, emerging adults age 18–30 were recruited at a midsize Southern U.S. public university. This developmental stage was appropriate due to its importance for depression's

emergence (Rohde et al., 2013). We excluded those who endorsed chronic health conditions (e.g., asthma) or use of hormonal contraception, nicotine, corticosteroids, or psychoactive medications (e.g., antidepressants). Several exclusions pertained to cognitive tests not presented: head trauma history, uncorrected hearing/visual deficits, learning disabilities, and colorblindness. Participants earned either course credit or $30 for study completion, and all received a $5 cognitive task performance incentive.

Only currently non-depressed participants were included in analyses because depression predicts blunted cortisol reactivity (Burke et al., 2005). Prior to the TSST, if the interviewer administering a diagnostic screening interview preliminarily diagnosed a current major depressive episode, the participant was assigned to the control condition, but was excluded from these analyses (n = 10). If a past major depressive episode was diagnosed, the participant was permitted to continue in the originally scheduled condition. Of the 104 consented participants, nine additional participants withdrew: 6 asked to discontinue the TSST (1 intermediate, 5 negative evaluative), 2 had scheduling difficulties, and 1 experienced an unrelated physical illness. Analyses thus utilize 85 participants (43 females, age 18–28, Mage = 19.61, SD = 1.80; 29 control, 26 intermediate, 30 negative evaluative) who were Black/African-American (n = 32, 37.6%); White (n = 28, 32.9%); Asian/Pacific Islander (n = 11, 12.9%); biracial (n = 6, 7.1%), Hispanic/Latino (n = 3, 3.5%); or another race or ethnicity (n = 5, 5.9%).

2.2. Materials

2.2.1. Negative affect

The Positive and Negative Affect Schedule (PANAS; Watson and Clark, 1999) assessed momentary negative affect using 10 items rated on a 5-point Likert scale (1, very slightly or not at all to 5, extremely). Internal consistency in this sample was $\alpha = 0.70$ for negative affect at baseline.

2.2.2. Trait rumination

The Ruminative Response Scale (RRS; Nolen-Hoeksema and Morrow, 1991) questionnaire measures ruminative tendencies while feeling down. Responses on 22-items range from 1 (almost never) to 4 (always) and are reported as individuals' item means to facilitate interpretation. Internal consistency was $\alpha = 0.93$ in this sample.

2.2.3. Manipulation checks

Post-TSST, participants completed items about perceived evaluation. Individuals who reported feeling evaluated (to any extent) were then asked to what extent the evaluation was positive or negative, and to what extent they felt challenged.

2.2.4. Salivary cortisol

Participants provided saliva samples via passive drool through a straw into a sterile cryogenic vial 5 times. Samples were stored at −80 °C following testing completion and were later shipped to Trier, Germany, for duplicate assay by time-resolved fluorescent-detection immunoassay (DELFIA; Dressendörfer et al., 1992). Our a priori plan was to use all sampling times except the

one immediately after the TSST preparation period, 5 minutes after baseline, which we believed too soon to observe an increase in cortisol. Intra-assay variation ranged from 4.0%–6.7%; interassay variation ranged from 7.1%–9.0%.

2.2.5. Socioeconomic status (SES)

The Hollingshead Index was used to estimate the SES of each participant's family of origin (Hollingshead, 1975)

2.2.6. Diagnostic screening interview

Participants completed the current and past major depressive episode sections of the Structured Clinical Interview for DSM-IV Disorders, Non-Patient Edition (SCID-I/NP; First et al., 2001). All interviewers had at least a bachelor's degree and completed extensive training including readings, face-to-face didactics with the PI, practice rating sample tapes, administration practice with peers, rating internally developed gold-standard diagnostic tapes to criterion on both diagnosis and clinical significance, and passing a face-to-face mock interview administration and scoring with the PI (SVS). Interviewers presented all cases at supervision meetings with the PI.

2.3. Procedure

Condition assignment was quasi-random. Participants were blind to the condition planned for their scheduled session, and the study coordinator who facilitated scheduling by email did not know the participants when scheduling. All TSST protocols began between 1 and 4 P.M. to help control for diurnal cortisol variation. The control and challenge conditions occurred over visits on two consecutive days as part of a larger study; the intermediate condition specifically addressed only the research questions presented here and was completed in a single visit, omitting a time-consuming objective life stress interview.

Participants completed the SCID-I/NP depression sections and questionnaires (including health questions about caffeine use, exercise, and allergies), and were present for at least 20 min of low-intensity tasks before the TSST protocol began. Participants provided saliva samples included in the present analyses immediately prior to the TSST, +20 min (following the TSST), +45 min (following cognitive tasks), and +65 min (following debriefing). Participants completed the PANAS at 4 time points corresponding to the cortisol collection times analyzed here. Experimenters debriefed participants after the third PANAS measurement; participants then affirmed consent.

2.3.1. Modified TSST versions

Participants completed one of three modified versions of the TSST (Kirschbaum et al., 1993), using previously reported control and negative evaluative protocols (Way and Taylor, 2010) and an intermediate condition developed to have stressful features in between these two extremes, which closely approximates a traditional TSST (for differences between conditions, see Table 1). Across all conditions, participants completed three 5-min tasks: (a) preparing a speech on a condition-specific topic, (b) delivering this speech, and (c) counting backward aloud by 13′s from 2017, beginning again when they made errors. All judge panels were balanced on gender (1 male,

1 female), and in most instances on minority status (1 minority, 1 white). Participants were told they would be video-recorded during the TSST, although they were not recorded. Participants were asked not to eat for 30 min prior to arriving and to abstain from caffeine, tobacco, alcohol/drugs, and exercising for one hour prior to arriving.

Table 1. Key Differentiating Elements of Three TSST Conditions.

	Control	**Intermediate**	**Negative Evaluative**
Information presented about level of evaluation	Participants explicitly told they would not be evaluated	Participants not told whether or not they would be evaluated	Participants told their performance would be evaluated by trained raters and public speaking experts
Speech Topic	Non-evaluative: "tips people can use to live a healthy lifestyle…"	Mildly evaluative: "the kinds of things you would do if you were chosen for a student leadership position and why you think these actions are important…"	Explicitly evaluative: "explain why you think you are the best person for your peers to elect to a student leadership position…"
Audience and Tone	1 Experimenter out of line of sight, appears busy in background. Remains polite and pleasant	2 Confederates behave politely, pleasantly, attentively with a non-evaluative (neutral) tone	2 Confederates speak sternly and appear bored and dissatisfied with participant's performance
Examples of Experimenter or Confederate Behavior	Experimenter organizes papers to appear busy as though minimally attending to the participant	Confederate sham behaviors: briefly glance at stopwatch, make neat notes, interlace fingers	Confederate negative evaluative behaviors: Subtle grimace and rub bridge of nose, make conspicuous X on papers, sigh of fatigue, exchange dissatisfied glance with other judge
Eye Contact During Speech and Math Tasks	No eye contact	Includes eye contact	Includes eye contact

2.3.2. Data reduction

Cortisol and negative affect data were examined for outliers (>3 standard deviations above the mean) across combined conditions for baseline, but within condition and timepoint after baseline. Minimal cortisol and negative affect outliers were winsorized to 3 standard deviations (Tukey, 1977). Resulting values of cortisol were natural log-transformed to further address skew, consistent with conventions. In addition, we calculated Area Under the Curve with respect to Increase (AUCI) for cortisol (Pruessner et al., 2003a) from untransformed, winsorized values, for use in post-hoc analyses in which a single dependent variable facilitated analyses. Although originally articulated for use with cortisol reactivity, we also calculated AUCI for negative affect for consistency across outcomes. Final AUCI values showed no outliers and approximated a normal distribution.

2.3.3. Analytic plan

Limited missing data (<2% across the dataset; 0% of cortisol values) were addressed with a multiple imputation procedure as recommended (Preacher, 2010). Models used 340 observations of cortisol and negative affect respectively (four measurements from 85 individuals). For analyses of cortisol and negative affect repeated measures, we employed Mplus 7.11 (Muthén and Muthén, 2012) to examine latent growth curve models, a type of confirmatory factor analysis modeling change in repeated measures of a dependent variable over time (Preacher, 2010, Preacher et al., 2008). Latent growth curve models first partial out the starting level (intercept), linear growth upward or downward (linear time trend), and curvilinear reactivity upward then downward (quadratic time trend). These models then permit prediction of each of these three aspects with independent variables, providing results analogous to standard linear regression. In secondary models, depression history and variables related to reactivity were covaried (predicting intercept, linear, and quadratic change) to ensure robust results: gender (Kirschbaum et al., 1992), SES (Hackman et al., 2012), regular caffeine use (Lovallo et al., 2006), regular exercise (Klaperski et al., 2014), and allergies (Buske-Kirschbaum et al., 2010). Growth curve models used maximum likelihood with robust standard errors (MLR) computed using a sandwich estimator (Yuan and Bentler, 2000). Model fit was evaluated with the Comparative Fit Index (CFI; where values >.95 indicate good fit), the Root Mean Squared Error of Approximation (RMSEA; where values <0.06 indicate good fit and those <0.08 indicate adequate fit), and the Standardized Root Mean Square Residual (SRMR; where values <0.08 indicate adequate fit) (Hu and Bentler, 1998). Initial models included correlated residuals for repeated measures; minimal, theoretically-consistent adjustments to models were made in response to output modification indices to achieve sufficient fit, and are described in 3.2 and 3.3 below, in keeping with best practices (Preacher, 2010).

To model the hypothesized curvilinear effect of stressor severity, we first coded stress condition linearly (0 controls, 1 intermediate, 2 negative evaluative), then squared this uncentered variable to obtain a Quadratic Stress variable (0 controls, 1 intermediate, 4 negative evaluative). We grand mean centered trait rumination, but not stressor severity or its quadratic function, for interaction term calculation; growth curve models grand mean centered natural log transformed cortisol levels. To parse significant interactions, we planned post-hoc tests of trait rumination's effect in each condition using partial correlations of rumination with AUCI reactivity with the same covariates as in the latent growth curve models. This plan addressed a concern that latent growth models would not be appropriate for these smaller groups. All analyses other than growth curve models were conducted in IBM SPSS 22.

3. Results

3.1. Group equivalence

Conditionsdid not differ on sex or minority status (both $\chi2(2) \leq 0.755$, $ps \geq 0.685$), major depressive episode history ($\chi2(2) = 0.292$, $p = 0.864$), age or rumination ($Fs \leq 2.734$, $ps \geq 0.071$). Conditions differed on SES ($F(2,82) = 4.103$, $p = 0.020$) and baseline cortisol ($F(2,82) = 3.786$, $p = 0.027$). Tukey HSDs showed that the intermediate condition had higher SES (Mean difference [MD] = 9.29, SE = 3.35, $p = 0.020$) and LN-transformed baseline cortisol (MD = 0.343, SE = 0.12, $p = 0.020$) than the negative evaluative condition. We covaried SES in secondary models; modeling

group differences in the intercept partials this out of other growth curve effects. No other pairwise comparisons showed differences.

3.2. Manipulations checks

Responses to four questionnaire items administered following the TSST were compared using one-way ANOVAs with polynomial (linear and quadratic) contrasts for stressor severity. The expected linear association between stressor severity and perceived general evaluation emerged ($F(1,82) = 8.780$, $p = 0.004$), but an unexpected quadratic association emerged ($F(1,82) = 7.959$, $p = 0.006$), where intermediate participants felt more evaluated than control or negative evaluative participants (Table 2). This may be because intermediate participants were not told whether they were evaluated (Table 1), leading to ambiguity. Participants who indicated feeling evaluated also reported on perceived positive or negative evaluation, and the extent to which they felt challenged. The expected significant linear association emerged for stressor severity and perceived negative evaluation ($F(1,76) = 22.467$, $p < 0.001$); non-significant linear associations for perceived positive evaluation ($F(1,76) = 3.814$, $p = 0.054$) and feeling challenged ($F(1,76) = 3.120$, $p = 0.081$) characterized the expected changes across increasing. To test which forms of evaluation might correspond best with momentary subjective experiences, we predicted negative affect reactivity (as AUCI) using perceived general, positive, and negative evaluation. Perceived negative evaluation was significantly associated with negative affect reactivity ($b = 7.792$, $SE(b) = 2.846$, $t = 2.738$, $p = 0.008$) over and above the other two forms, which did not significantly predict negative affect reactivity (ps .536–.789). Overall, results suggest sufficient effectiveness of the manipulations, in particular for perceived negative evaluation, which also appeared to best correspond with momentary negative affect.

Table 2. Group Demographics and Means.

	Control	Intermediate	Negative Evaluative
Gender	16 M, 13 F	13 M, 13 F	14 M, 16 F
Minority Status (%)	62.06%	73.08%	66.67%
History of major depressive episode	17.24% (n = 5)	23.07% (n = 6)	20.00% (n = 6)
Age	19.28 (1.31)	20.23 (2.34)	19.40 (1.59)
Hollingshead SES	46.97 (12.67)	49.67 (11.86)	40.38 (13.12)
Trait Rumination Item Mean	1.80 (0.58)	2.14 (0.56)	1.93 (0.48)
Baseline Negative Affect Item Mean	1.33 (0.44)	1.25 (0.27)	1.27 (0.30)
Baseline Cortisol (nmol/L) a	4.62 (2.24)	5.47 (2.89)	3.79 (1.66)
Felt Evaluated in General	2.38 (0.86)	3.27 (0.72)	3.03 (0.93)
Felt Positively Evaluated	2.12 (0.88)	1.96 (0.77)	1.71 (0.60)
Felt Negatively Evaluated	1.80 (0.76)	2.50 (0.81)	2.86 (0.85)
Felt Challenged	2.80 (0.74)	3.00 (0.85)	3.18 (0.72)
Cortisol AUCI	−29.11 (113.02)	4.39 (106.07)	126.74 (194.64)
Negative Affect AUCI	−0.31 (16.12)	11.39 (14.76)	8.75 (19.57)

Note: SES = Socioeconomic Status. M = Male, F = Female. Means (standard deviations) of demographic variables, manipulation checks, and dependent variables by group. Negative values for AUCIs reflect overall decline from baseline across subsequent points.

a = Analyses conducted with natural log transformed values, but raw values are reported here.

3.3. Does rumination interact with stressor severity non-Linearly to predict cortisol reactivity?

The best fitting model was a random intercept model with correlated linear and quadratic curves for time (i.e., growth and reactivity were related) and as initially specified, correlated residuals (Fig. 2). To achieve fit, based on modification indices, we permitted further correlation between the first, third, and final cortisol samples, which is consistent with an expectation that in reactivity data, these samples ought to be similar to each other. Final model fit was adequate, RMSEA = .067, CFI = .984, SRMR = 0.048.

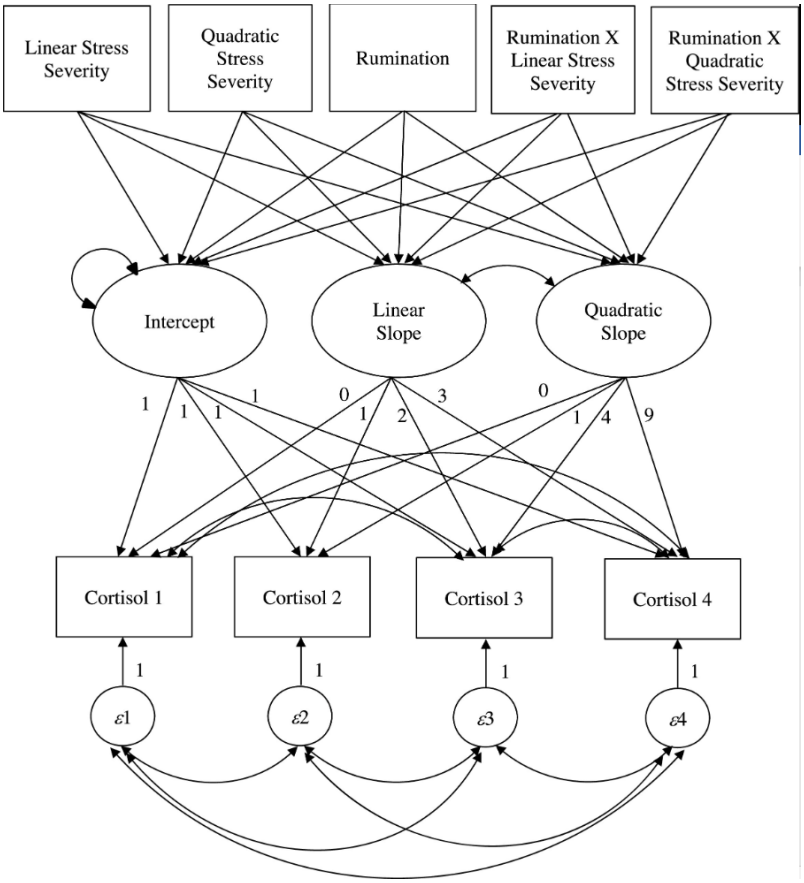

Fig. 2. Final path model for latent growth curve model of cortisol repeated measures. Ovals represent latent variables; rectangles represent observed variables. Final random intercept model included correlated error residuals, correlation between linear and quadratic growth terms, and limited correlations between repeated measures of cortisol based on model modification indices.

Full model results for cortisol appear in Table 3A; significant results are summarized here with p-values. First, intercept values (baseline) were significantly predicted by a Quadratic Stress effect (p = .008) and a Rumination x Quadratic Stress (p = .048). This was consistent with evidence from group equivalence tests indicating that Intermediate participants had the highest initial cortisol levels, and indicated that the relationship between rumination and baseline cortisol levels varied across the conditions (rs of −.15, −.34, and .33, respectively, ps > .05). Remaining growth curve effects emerge despite accounting for this pattern.

Table 3. Growth Curve Models for Cortisol and Negative Affect.

A. LN-Cortisol	**Beta**	***SE(B)***	***t***	***p***
Intercept (Starting Level)				
Linear Stress	0.541	0.242	2.235	0.025*
Quadratic Stress	−0.311	0.117	−2.659	0.008*
Rumination	−0.114	0.124	−0.923	0.356
Rumination x Linear Stress	−0.592	0.397	−1.494	0.135
Rumination x Quadratic Stress	0.387	0.195	1.981	0.048*
Linear Slope (Growth)				
Linear Stress	−0.145	0.261	−0.558	0.577
Quadratic Stress	0.23	0.129	1.783	0.075
Rumination	−0.142	0.162	−0.876	0.381
Rumination x Linear Stress	0.849	0.39	2.177	0.029*
Rumination x Quadratic Stress	−0.551	0.202	−2.724	0.006*
Quadratic Slope (Reactivity)				
Linear Stress	0.078	0.073	1.072	0.284
Quadratic Stress	−0.075	0.036	−2.112	0.035*
Rumination	0.042	0.043	0.962	0.336
Rumination x Linear Stress	−0.202	0.105	−1.925	0.054
Rumination x Quadratic Stress	0.125	0.052	2.38	0.017*
B. Negative Affect	**Beta**	**SE(B)**	**t**	**p**
Intercept (Starting Level)				
Linear Stress	−0.21	0.156	−1.343	0.179
Quadratic Stress	0.073	0.069	1.059	0.289
Rumination	0.200	0.141	1.423	0.155
Rumination x Linear Stress	−0.317	0.264	−1.199	0.231
Rumination x Quadratic Stress	0.114	0.124	0.920	0.358
Linear Slope (Growth)				
Linear Stress	0.453	0.225	2.017	0.044*
Quadratic Stress	−0.177	0.103	−1.714	0.086
Rumination	−0.175	0.159	−1.101	0.271
Rumination x Linear Stress	−0.340	0.383	−0.889	0.374
Rumination x Quadratic Stress	0.218	0.182	1.200	0.230
Quadratic Slope (Reactivity)				
Linear Stress	−0.125	0.068	−1.838	0.066
Quadratic Stress	0.048	0.032	1.492	0.136
Rumination	0.050	0.042	1.185	0.236
Rumination x Linear Stress	0.132	0.115	1.148	0.251
Rumination x Quadratic Stress	−0.080	0.055	−1.448	0.148

* = p-values < .05.

Second, linear growth was predicted by a Rumination x Linear Stress effect ($p = .029$, the strength of the correlation between rumination and cortisol growth increases with severity), but also by a Rumination x Quadratic Stress effect ($p = .006$, the strength of the correlation between rumination and cortisol growth decreases after it increases, which parallels Hypothesis 1).

Third, quadratic growth (reactivity) was predicted by a main effect of Quadratic Stress ($p = .035$, reactivity increases exponentially with increasing stress, consistent with Hypothesis 4). A Rumination x Quadratic Stress interaction, $p = .017$, also predicted quadratic growth, supporting Hypothesis 1 that the relationship between rumination and cortisol reactivity varies nonlinearly as severity increases. In a model with covariates added including SES (see 2.3.3), results for Hypothesis 1, Rumination x Quadratic Stress predicting reactivity remained significant, $B = 0.137$, $SE(B) = 0.050$, $t = 2.742$, $p = 0.006$ (full results available from the first author on request).2

To parse these results, we examined rumination predicting cortisol AUCI within experimental condition using partial correlations, after regressing out the influence of covariates (Fig. 3). Controls showed no rumination-cortisol AUCI relationship ($rp = -.111$, $p = .566$), the intermediate condition showed a positive rumination-cortisol AUCI relationship ($rp = .400$, $p=.043$; Hypothesis 2), and the negative evaluative condition showed a negative rumination-AUCI relationship ($rp = -.379$, $p = .039$; Hypothesis 3).

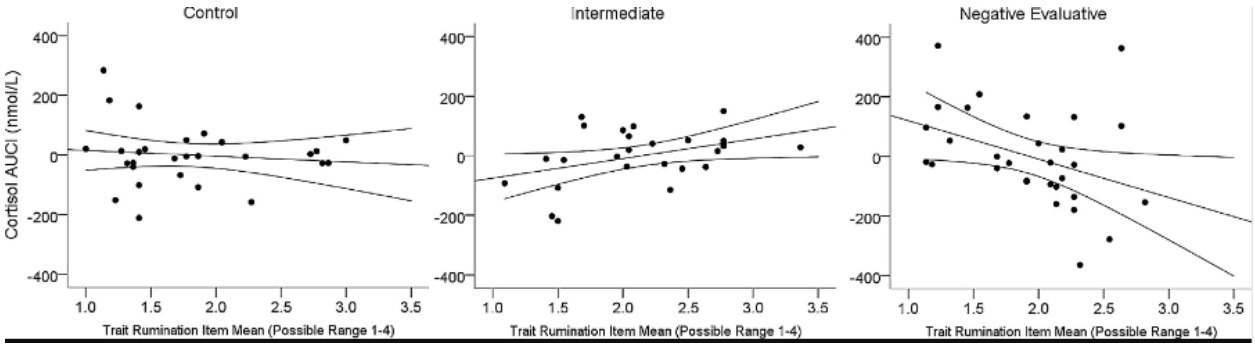

Fig. 3. Scatterplots depict trait rumination item mean scores and cortisol area under the curve with respect to increase (AUCI) in nmol/L by experimental condition. Center lines depict the best fitting correlation; outer curves depict 95% confidence intervals. Covariates used in secondary models to ensure robustness (history of major depressive episode, gender, socioeconomic status, allergies, caffeine use, and frequent exercise) were partialed out.

3.3.1. Does cortisol reactivity increase between the intermediate and explicitly negative evaluative conditions?

A one-way ANOVA revealed that the negative evaluative condition had greater cortisol AUCI (i.e., cortisol reactivity) than did the intermediate condition, $F(1,54) = 7.921$, $p = .007$ (Hypothesis 5; Table 2).

3.4. Relationship of stress severity with negative affect

The final model for negative affect was a random intercept model, but one that required uncorrelated residuals, in contrast to our initial specification, perhaps due to greater stability within person over time. Consistent with this, based on modification indices, we added correlations between several of the repeated measures of negative affect (measure 1 with 2 only, and 2 with 3

and 4), suggesting that the growth curve model adequately but not fully captured similarities. Final model fit was excellent, RMSEA = .000, CFI = 1.00, SRMR = 0.054.

The sole significant effect, a main effect of Linear Stress predicting linear growth ($p = .044$; Table 3B), indicated that negative affect growth increased with greater stress severity only. Hypothesis 6 that negative affect reactivity would grow at greater rates with increasing trait rumination (Rumination x Linear Stress predicting quadratic slope, $p = .251$) was not supported. A model with covariates added (see 2.3.3) revealed the same pattern of findings, including the main effect of Linear Stress predicting negative affect linear growth ($p = 0.042$; full model available from the first author on request).

4. Discussion

We present the first evidence that the direction of the relationship between a transdiagnostic internalizing psychopathology risk factor—trait rumination—and cortisol reactivity depends upon lab-based stressor severity in a curvilinear fashion (Hypothesis 1) in currently non-depressed emerging adults. Supporting hypotheses, under moderate stressor severity of the intermediate condition, trait rumination was positively associated with cortisol reactivity (Hypothesis 2), but under higher stressor severity of the negative evaluative condition, trait rumination was negatively associated with reactivity (Hypothesis 3). These findings suggest an explanatory framework for previous divergent cortisol reactivity results showing that internalizing risk factors predict either augmented (Wirtz et al., 2007, Zoccola et al., 2010) or blunted reactivity (Bibbey et al., 2013, Oswald et al., 2006; Vrshek-Schallhorn et al., under review; Zoccola et al., 2008).

Results have at least two implications for conceptualizing cortisol reactivity. First, not only the sample average level of cortisol reactivity varies across different severities of experimental stress (Hypothesis 4, i.e., reactivity increased with increasing stress severity), but also who produces peak cortisol reactivity at each severity. Thus, heightened reactivity cannot necessarily be equated across studies. The field should develop best practices for describing the severity of stress manipulations, particularly the extent of negative social evaluation. Second, an explicitly negative evaluative manipulation provokes greater cortisol reactivity on average than does a neutral intermediate difficulty manipulation (Hypothesis 5). What we describe as neutral or intermediate here has been referred to as (implicitly) negative evaluative in prior work, and understandably so, as ambiguous feedback could appear negative; however, in future work it will be critical to distinguish between these manipulations.

4.1. The cortisol reactivity threshold model

We propose the Cortisol Reactivity Threshold Model to characterize this pattern of cortisol findings. Two model variants are possible: an "inverted U-curve variant" speculates that elevated risk individuals' reactivity actively declines from their peak level under a modest stressor to a relatively blunted level under a more robust stressor, and an "inflexibility variant" speculates that elevated risk individuals' reactivity remains largely static between modest and robust stressors. In both variants, those with greater internalizing risk have relatively higher cortisol reactivity levels than their peers at lower stressor severity levels, while at higher stressor severity levels show reactivity surpassed by their lower risk counterparts. Although it is not appropriate to draw conclusions about within-subjects effects across stressor severity using the present between-

subjects design, the changing relationship of trait rumination to cortisol reactivity as a function of stressor severity is consistent with the model.

Although we initially hypothesized that results would conform to the inverted-U variant before we identified the possibility of an inflexibility variant, the present study was not designed or powered to differentiate between the two models. Future research should test between the two models because they have different implications. The inverted U-variant suggests active inhibition of cortisol release under robust stress in elevated risk individuals, whereas the inflexibility variant suggests that allostatic wear and tear processes (e.g., McEwen, 2003) have damaged elevated risk individuals' ability to generate an arguably adaptive robust cortisol response to robust stress.

We are not the first to speculate about a curvilinear relationship. Bauer and colleagues invoked the Yerkes-Dodson model of arousal level and performance, but concluded it required high-risk individuals to have simultaneous HPA and sympathetic-adrenal-medullary activation or deactivation (Bauer et al., 2002). Way and colleagues noted the possible role of stressor severity to explain recent divergent genetic findings (Way et al., 2016). Further, these results in some ways parallel findings for depression symptoms predicting both augmented and blunted cardiovascular activity as difficulty of a task increased, framed in terms of motivational intensity theory (Silvia et al., 2016).

4.2. Implications of negative affect findings

Only a main effect of stressor severity, not the hypothesized moderation by trait rumination, was observed for negative affect: As severity increased, growth in negative affect increased. Results therefore do not support that trait rumination amplifies momentary negative affect in a diathesis-stress manner in response to controlled stressors, as has been found for naturalistic self-reported daily hassles (Moberly and Watkins, 2008). However, negative affect may help differentiate whether relatively low cortisol reactivity reflects an unperturbed response or a problematic blunted response in other studies.

4.3. Relationship to prior research and theory

The Cortisol Reactivity Threshold Model may help explain divergent findings regarding early adversity, which has been associated with both HPA hyper-reactivity (Heim et al., 2002, Rao et al., 2008) and hypo-reactivity to lab-induced stress (Carpenter et al., 2011, Ouellet-Morin et al., 2011). Several studies showed that moderators influence responding consistent with a reactivity threshold model. Compared to those without marked early adversity, individuals with early adversity and low lifetime distress exhibited heightened cortisol reactivity, while individuals with early adversity and recurrent lifetime distress showed blunted reactivity (Goldman-Mellor et al., 2012). Similarly, current depression severity moderated the impact of early maltreatment on reactivity, with mildly depressed maltreated individuals exhibiting the highest cortisol reactivity to the stressor, and moderately/severely depressed maltreated individuals showing blunted reactivity (Harkness et al., 2011). Although we cannot test this hypothesis here, the present model suggests that the recurrently distressed individuals and the more severely depressed individuals in these two samples demonstrated more "left-shifted" inverted U-curves (Fig. 1a) than their less severely distressed or depressed but maltreated counterparts.

The present model may also be consistent with Bauer and colleagues' model suggesting that asymmetry between HPA and sympathetic-adrenal-medullary (SAM) axis stress responding

predicts psychopathology (Bauer et al., 2002). This model posits that the HPA and SAM are distinct, yet complimentary stress responsive systems, and that "optimal functioning" occurs when both react in parallel. For example, maltreated youth exhibited no relationship between cortisol and alpha-amylase levels under stress (indicative of asymmetry), while non-maltreated youth exhibited a significant and positive relationship between the two markers (Gordis et al., 2008). HPA and SAM asymmetry may be maladaptive because at-risk individuals experiencing a robust stressor show blunted cortisol reactivity, while simultaneously possibly experiencing robust sympathetic reactivity.

4.4. Implications for pathways to depression

Three implications for internalizing psychopathology etiology, namely depression etiology, are evident from the reactivity threshold model and supporting data. First, data provide further support that trait rumination predicts HPA functioning in a stress-sensitive fashion, and should receive attention in diathesis-stress models (Michl et al., 2013) examining physiological responding. This model suggests that high internalizing risk individuals might show relatively greater HPA activation to minor naturalistic stressors. Paradoxically, if cortisol as a resource-mobilizing hormone leads to greater behavioral activation after minor stressors, these individuals may be at reduced risk for depression or show fewer symptoms after minor stressors. By contrast, following major stressful life events, they may mount insufficient cortisol and behavioral responses. The model further suggests that these at-risk individuals likely experience more frequent HPA reactivity in daily life, in which minor threats are more common than major ones (e.g., Vrshek-Schallhorn et al., 2015), potentially leading to heightened allostatic load and HPA-axis alterations (McEwen, 2003).

Second, others have observed that the relationship between lab-based cortisol reactivity and prospective depression risk is inconsistent (e.g., Colich et al., 2015); the present results suggest that lab-based stressor severity influences which type of response, relatively augmented or blunted, is associated with greater prospective depression risk. One prior explanation for divergent prospective prediction is that puberty onset results in the association switching directions: in pre-pubescent individuals, blunted reactivity is associated with greater prospective risk, while in post-pubescent individuals heightened reactivity is riskier (Colich et al., 2015). The present model augments this view, suggesting that this pattern may emerge because pre-pubescent individuals experience the stressor task as more severe. Additionally, within individuals of the same developmental stage, the reactivity threshold model predicts that augmented cortisol reactivity to modest stressors but blunted cortisol reactivity to robust stressors will prospectively predict depression.

Third, this model contributes to a new perspective on the cortisol awakening response (CAR), the robust increase in cortisol levels occurring upon awakening (Fries et al., 2009). Heightened CARs have been linked with prospective depressive episode onsets (Adam et al., 2010, Vrshek-Schallhorn et al., 2013), and individuals under stress appear to show larger awakening responses (Chida and Steptoe, 2009). By contrast, blunted CARs have been associated with current depression (Huber et al., 2006, Stetler and Miller, 2005), though with exceptions (Pruessner et al., 2003b). If the CAR in part represents reactivity to expectations for the day (Wetherell et al., 2015), and adaptively increases energy for the upcoming day (i.e., the "boost" hypothesis, Adam et al., 2006), it might be that at-risk individuals are actively engaged in an effortful struggle but currently depressed individuals have succumbed to unmotivated despair and have withdrawn from effortful

struggle. Thus, an augmented CAR during heightened risk may parallels relationships observed for modest lab-based stressors, while blunted CAR during current depression may parallel to relationships observed for robust lab-based stressors. Such an interpretation is consistent with emerging evidence of an inverted U-curve association between depression symptoms and the CAR, where both the lowest and highest levels of depression symptoms were associated with lower CAR, while moderate levels of symptoms were associated with augmented CAR (Veen et al., 2011, Wardenaar et al., 2011).

4.5. Implications for understanding active depression

This model helps conceptualize current depression dimensionally and generates several predictions about cortisol reactivity in current depression. Parsimony suggests that active depression represents an intensified manifestation of the model phenomena associated with heightened internalizing risk. Previously, blunted cortisol reactivity in depression (Burke et al., 2005) was interpreted as evidence that depression was a categorical condition—rather than part of a dimension. In this view, a marked change would be necessary for individuals to shift from elevated cortisol reactivity, for example as observed in mildly symptomatic adolescents with prior maltreatment described by Harkness et al. (2011), to blunted cortisol reactivity observed in more severely symptomatic adolescents in the same sample. The present model instead suggests a smaller change can account for a shift from maximal to blunted reactivity, consistent with an underlying dimensional process. We speculate that the mechanisms underlying these processes include alterations in cortisol receptor sensitivity (Jarcho et al., 2013) and cognitive factors, including enhanced perception of threat, known to predict reactivity (Juster et al., 2012).

At least three predictions for current depression emanate from the model. First, individuals with active depression are predicted to have reactivity threshold curves that are more left-shifted than those at elevated risk in Fig. 1a. Thus, individuals with current depression would be likely to display blunted reactivity to even a modest lab-based stressor, consistent with meta-analytic evidence that depressed individuals show blunted responding (Burke et al., 2005). Both model variants also suggest that depressed individuals show relatively augmented cortisol levels under very low threat, perhaps even basal conditions. A meta-analysis of children and adolescents supported higher basal cortisol in depression (Lopez-Duran et al., 2009), and a meta-analysis in adults produced significant evidence of heightened morning and evening basal cortisol, however results were problematic due to high heterogeneity (Knorr et al., 2010). Second, the model predicts that the reactivity curve would shift somewhat rightward in Fig. 1a in recovery from a depressive episode, similar to individuals at heightened risk. Cortisol reactivity to modest severity stress should increase within-person in recovery versus active depression, and reactivity to robust stress should remain blunted, although perhaps to a less extreme degree during recovery. Third, the concept of a continuum suggests that, within individuals with current depression, risk factors such as personality traits, prior maltreatment, and symptom severity may predict the degree of blunting in cortisol reactivity to modest lab stressors. For example, meta-analytic evidence indicated that, among studies conducted in the afternoon when blunting is more detectable, depression severity was associated with more extreme blunting (Burke et al., 2005).

4.6. Future directions

Next steps in evaluating this reactivity threshold model include replication in a larger sample, in particular one designed to clarify whether the inverted U-curve variant or the inflexibility variant is more accurate. Future work will ideally examine multiple stress response systems to evaluate whether the patterns reported here are unique to cortisol. Additionally, elucidating the psychological and biological mechanisms involved in blunting under considerable objective stress is vital to understanding the pathways by which cortisol relates to depression risk. Given excess cortisol secretion's deleterious effects (Sapolsky, 1999), it may be adaptive for at-risk individuals to generate attenuated responses to very stressful circumstances, conserving metabolic resources and avoiding harmful effects of excessive secretion. Further, the pattern observed here mimics aspects of the inverted U-curve observed in other areas of neuroscience, raising a remote possibility of common underlying pathways. For example, dopamine relates to performance in an inverted U-curve (Cools and D'Esposito, 2011), and animal studies suggest that mesolimbic dopamine signaling and associated behavioral activation increases with controllable (i.e., mild) acute stressors, but is blunted to uncontrollable (more severe) acute stressors (Pizzagalli, 2014). In addition, the cognitive and affective mechanisms influencing the cortisol reactivity threshold will be critical. There is evidence that cortisol is at least in part activated downstream of primary threat perception (Juster et al., 2012); further research may also implicate motivation or behavioral activation.

4.7. Limitations

The present report has several limitations. First, using only four samples of salivary cortisol (as opposed to sampling every 10 min, for example) does not permit a fine-grained characterization of the cortisol trajectory. Second, we examined stressor severity level between- not within-person, which is common in this literature due to concerns about stressor habituation. Thus, we emphasize that results are cross-sectional and between groups (rather than within-person with respect to condition) and provide no evidence of how reactivity might change over time as individuals' symptomatology or circumstances change, or how a given individual's reactivity varies across conditions. Third, the hierarchy of stress severity (control < intermediate < negative evaluative) is partially novel, and evidence for the hierarchy's validity was adequate but not without issues. A significant effect for perceived negative evaluation, plus descriptive patterns for other variables (perceived positive evaluation, perceived challenge) were consistent with the intended stressor severity hierarchy. To avoid the unexpected elevation pattern in perceived global evaluation among intermediate participants, however, future investigations might choose to state explicitly to participants that they are not being evaluated, or perhaps to use only one confederate.

Fourth, we only used clinical interviews to evaluate participants on current and past depression, and did not assess full psychiatric histories; we cannot conclusively rule out that unobserved diagnoses might account for results obtained for trait rumination. Finally, we permitted differences in the protocol across conditions (one longer session for the intermediate condition versus two shorter sessions for control and negative evaluative conditions), and we observed group differences in baseline cortisol and SES that we addressed in models. Thus, although the current model is consistent with the totality of prior evidence and provides a significant conceptual advancement, we urge replication.

5. Conclusions

Using three levels of severity of a lab-induced stressor, we provide the first evidence that the direction of the relationship between depression risk and cortisol reactivity varies as a function of stressor severity. The Cortisol Reactivity Threshold Model provides a new lens through which to interpret a divergent reactivity literature.

Disclosures and Conflicts of Interest

The authors report no conflicts of interest.

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