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Cognitive disengagement and biological stress responses in early adolescence

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ABSTRACT

Individual differences in biological responses to stress increase risk for the onset and exacerbation of health and psychiatric conditions. Biases in cognitive disengagement are hypothesized to underlie these individual differences in biological responses to stress. However, no studies have examined which cognitive disengagement bias has the strongest relation with biological responses to stress, and no studies have examined this relation during early adolescence, despite evidence that this is a critical developmental window in which patterns of cognition and biological responses to stress influence trajectories of health throughout life. The current study is the first to test whether difficulty disengaging attention versus working memory from valenced stimuli is associated with biological responses to stress in early adolescence. Youth between 11 and 13 years of age completed two computer-based tasks to assess biases in attention and working memory disengagement to valenced stimuli, and then completed a standardized psychosocial stressor. Consistent with expectations, attention and working memory disengagement biases were associated with stress responses of both the neuroendocrine and autonomic nervous systems, but bias valence and cognitive system influenced the directionality of results. These findings inform our understanding of cognitive mechanisms that influence biological stress reactivity.

1. Introduction

The early adolescent period represents a critical window in which to understand biological responses to stress (Dorn et al., 2019). Indeed, individual differences in biological responsivity during early adolescence are associated with wellbeing across the lifespan. The early adolescent period is also marked by rapid development and plasticity across neural and physiological systems, following which patterns of biological responsivity to stress become more embedded and resistant to change (e.g., Ganzel et al., 2013). Thus, identifying mechanisms underlying individual differences in biological responses to stress during early adolescence offers a valuable opportunity to influence long-term trajectories of health and wellbeing.

The hypothalamic-pituitary-adrenal axis (HPA axis) and the sympathetic nervous system (SNS) represent two major stress response systems in the human body. The HPA axis is composed of the hypothalamus, pituitary gland, and adrenal glands, the interactions of which trigger a number of biological events culminating in the synthesis and subsequent secretion of cortisol, a corticosteroid that is considered to be an index of the HPA axis (Smith and Vale, 2006). In contrast to the relatively slow-acting HPA axis, the fast-acting sympathetic nervous system (SNS) is responsible for preparing an organism to respond quickly to stress and/or threat. This system is frequently indexed by alpha-amylase, a digestive enzyme synthesized and stored in the acinar cells of the salivary glands, whose release has been directly tied to sympathetic nerve stimulation (Ali and Pruessner, 2012).

A moderate stress response, as measured by the HPA axis or the SNS, supports functioning across the adolescent period when individuals face increased responsibilities in numerous domains (Gunnar et al., 2009). Indeed, moderate biological responses to stress help prepare an individual to respond to stress (Lucassen et al., 2014). However, dysregulated biological responses to stress predict the emergence and exacerbation of various forms of psychopathology, maladaptive behaviors, and adverse physical health across adolescence and into adulthood (Nederhof et al., 2015; Ruttle et al., 2013). Further, dysregulated biological stress-response patterns have pronounced effects on the structure and function of various brain regions (Joëls, 2011). Despite the importance of understanding mechanisms underlying dysregulated biological responses to stress in youth, the vast majority of work has been in samples of adults. Given that patterns of biological stress responsivity differ significantly between youth and adults (e.g., Gunnar and Vazquez, 2015), the specific mechanisms responsible for individual differences in

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stress responsivity during adolescence are poorly understood. Thus, this represents an important area of investigation.

Theoretical models suggest that individual differences in cognition may underlie individual differences in biological responses to stress (De Raedt and Koster, 2010; LeMoult, 2020). Specifically, biases in cognitive disengagement – the ability to disengage from valenced information that has captured attention or entered working memory – is a critical candidate mechanism influencing maladaptive biological stress responsivity. Cognitive disengagement biases may prolong biological stress responses due to their perseverative nature. Indeed, as argued by the perseverative cognition hypothesis, perseverative processing of negative information prolongs stress-related affective and physiological activation (Brosschot et al., 2006). For example, researchers have documented that rumination, a perseverative cognitive style related to cognitive disengagement biases (Joormann and Gotlib, 2008), impairs recovery of both the neuroendocrine and autonomic nervous systems (Key et al., 2008; LeMoult and Joormann, 2014). Also consistent with the perseverative cognition hypothesis, attentional and working memory disengagement biases are associated with prolonged HPA axis and SNS recovery in adults (Bardeen and Daniel, 2017; Jopling et al., 2020; LeMoult et al., 2020). However, to date, most of this research has been conducted in adults, and data in youth are lacking.

We also do not understand which aspects of cognitive disengagement biases influence biological responses to stress. This gap in the literature is surprising given calls for research arguing that, to best understand the precise mechanisms underlying biological responses to stress, we must refine and disentangle the relative contribution of candidate mechanisms (such as biases across multiple cognitive systems; LeMoult, 2020). Yet studies investigating biological responses to stress focus on either attentional or working memory disengagement biases. Though these cognitive processes are related, both behavioral and biological evidence indicates that dissociable mechanisms are involved in attention and working memory. There is also reason to believe that attentional and memory-based processes might be both qualitatively and functionally distinct. For instance, attention and working memory function on different timescales, whereby attentional processes influence which items will occupy the limited space in working memory. For this reason, attention is considered to be a "gatekeeper" for information entering working memory (Awh et al., 2006). Moreover, distinct brain regions are involved in attention and working memory (Awh and Jonides, 2001), further underscoring the importance of better understanding which cognitive disengagement biases are associated with biological responses to stress.

1.1. The current study

To address these gaps, the present study was designed to investigate which cognitive disengagement biases were associated with individual differences in biological responses to stress in a sample of early adolescent youth. Toward this goal, we examined whether attentional and/or working-memory disengagement biases predicted (1) HPA axis responses to stress, (2) SNS responses to stress, and (3) HPA-SNS dissociation. This study is the first to concurrently measure attentional and working memory disengagement biases, and to consider the relative contribution of these biases to individual differences in biological responses to stress. Early adolescents were invited into the laboratory to complete measures of attentional and working memory disengagement. Participants then completed a standardized psychosocial stressor. We assessed biological responses to stress via markers of both the HPA axis (i.e., cortisol) and SNS (i.e., salivary alpha-amylase; sAA) in order to take a multisystem approach. Simultaneous measurement of multiple biological systems provides more meaningful information than measurement of either system alone given their interconnected nature (Buss et al., 2018). We also calculated the ratio of total sAA over total cortisol produced (area under the curve with respect to ground [AUCg] of sAA divided by the AUCg of cortisol; henceforth referred to as amylase over cortisol [AOCg]), an indicator of stress system dysregulation. Higher AOCg indicates the predominance of sAA release over variations in cortisol, and thus, represents maladaptive asymmetry between the physiological and endocrinological systems (Andrews et al., 2013). Higher AOCg is associated with indices of chronic stress and depression in adults, as well as with both health and behavioral problems in youth (Ali and Pruessner, 2012; Allwood et al., 2011).

Overall, based on previous theoretical (Brosschot et al., 2006) and empirical work (e.g. Key et al., 2008; LeMoult and Joormann, 2014), we expected that disengagement biases would be most strongly associated with levels of sC and sAA at baseline and with trajectories of biological recovery from stress, rather than with trajectories of reactivity to stress. Specifically, given previous work showing that constructs related to negative cognitive disengagement biases prolong biological responses to stress (e.g., Joormann and Tanovic, 2015; Shull et al., 2016), we hypothesized that greater attentional biases for dysphoric stimuli and greater working-memory biases for negative stimuli (broadly defined) would be associated with a pattern of stress response marked by higher levels of sC and sAA at baseline, a blunted slope of recovery, and greater total output of sC and sAA across the stressor. Given previous work showing that training a positive disengagement bias can abbreviate biological responses to stress (Jopling et al., 2020), we expected an opposite pattern of response for positive disengagement biases, in which greater positive disengagement biases would be associated with lower levels of sC and sAA at baseline, a steeper recovery slope, and overall less output of both sC and sAA across the TSST-C. As threatening disengagement biases remain understudied in the context of biological stress responsivity, no specific a priori hypotheses were made regarding the impact of attentional disengagement biases for threating stimuli on biological responses to stress. Similarly, we made no specific hypotheses regarding associations between disengagement biases and the AOCg ratio, which is a novel ratio that is relatively understudied in youth.

2. Method

2.1. Participants

Early adolescents between 11 and 13 years of age were eligible to participate in this study if they were fluent in English. Participants were excluded if parent or child reported that the child had a history of serious head trauma, medical conditions known to affect the autonomic nervous system (ANS) or neuroendocrine system, current substance use disorder, or if they were currently using corticosteroids, depot neuroleptics, or oral or inhaled steroids. These exclusion criteria were used given evidence that each can alter biological responsivity to stress (Bay et al., 2009; Granger et al., 2009). Participants were also not eligible for participation if they endorsed a significant learning or psychiatric problem likely to interfere with completing the extensive laboratory protocol (e.g., mania, psychosis, autism spectrum disorder). We recruited participants from the Vancouver metropolitan area. Efforts were made to recruit participants from diverse neighborhoods. For example, we partnered with school boards in both high and low-income areas, used both online and paper advertisements that were distributed in communities across the Vancouver area, and offered compensation for transportation to the university so that transportation costs were not a barrier to participation. The final sample included 78 early adolescent youth between 11.88 and 13.90 years of age ($M = 12.93$, $SD = 0.36$). 55% of adolescents reported being assigned male at birth and all participants were cisgender with the exception of one participant, who identified as non-binary. The majority (60%) of our sample identified as European-Canadian, 19% identified as Chinese, 4% identified as Latinx, 4% identified as South Asian, 3% identified as Canadian Indigenous, 3% identified as Japanese-Canadian, 3% identified as Korean-Canadian, 1% identified as Chinese-Japanese, 1% identified as Chinese-Korean, 1% identified as South Asian-Latinx, and 1% identified as West Asian. Participant characteristics are presented in Table 1 and are generally representative of the Vancouver

Table 1
Participant Characteristics.

Variable	
Age, *M(SD)*	12.93 (0.36)
Sex (% Male)	55%
Gender, *%*	
Male	55%
Female	44%
Non-binary	1%
Pubertal Stage, *M(SD)*	2.68 (1.07)
Current or past DSM-5 diagnosis, *%*	9%
Household Income	
$20,000–$40,000	4.2%
$40,000–$60,000	5.6%
$60,000–$80,000	6.9%
$80,000–$100,000	12.5%
$100,000–$120,000	15.3%
$120,000–$140,000	9.7%
$140,000–$160,000	13.9%
$160,000–$180,000	6.9%
$180,000–$200,000	6.9%
+$200,000	18.1%
Racial Identity	
European-Canadian	60%
Chinese	19%
Latinx	4%
South Asian	4%
Canadian Indigenous	3%
Japanese-Canadian	3%
Korean-Canadian	3%
Other[a]	4%

Note: SD = Standard deviation.
[a] Other racial identities included Chinese-Japanese, Chinese-Korean, South Asian-Latinx, and West Asian.

metropolitan area (Statistics Canada, 2017).

2.2. Measures

2.2.1. Cognitive disengagement – attention

2.2.1.1. Design. Attentional disengagement was measured using an affective Posner paradigm (Koster et al., 2005). Each trial began with two white frames presented side-by-side on a black background with a fixation cross between them for 500 ms. Participants were then presented with a picture of an emotional stimulus (a cue), which appeared either in the right or the left frame for 1000 ms. Immediately after the presentation of the emotional stimulus, the cue disappeared and a probe letter ("E" or "F") appeared either in the location previously occupied by the cue (valid cue trial) or on the other side of the screen (invalid cue trial). Participants were asked to indicate whether an "E" or an "F" appeared by pressing the corresponding computer key as quickly and as accurately as possible. Participants were then presented with a black screen for 700 ms, following which the subsequent trial began. Cue valences and trial types (valid and invalid) were randomized within each block. Error trials and trials with outlier reaction times (RTs; $<$ 150 m or $>$1000 ms) were excluded from analyses, consistent with previous research. This resulted in the loss of 7.11% of trials. In the present study, split-half reliability coefficients on critical trial RTs ranged from 0.78 to 0.89. Given the aims of the study, we focused exclusively on trials used to calculate the attentional disengagement bias (ADB) using the formula proposed by Koster et al. (2005). Specifically, attentional disengagement was calculated separately for each cue valence as the difference between RTs to invalid valenced cues and RTs to invalid neutral cues. Therefore, a total of 3 variables were calculated: ADB for dysphoric stimuli, for threatening stimuli, and for positive stimuli. Higher positive scores indicate slower disengagement of attention from the valenced cue, meaning that more time was required for the participant to shift attention away from emotional material than from neutral material.

2.2.1.2. Stimuli. Consistent with previous versions of the affective Posner task, a stimulus set of 32 faces expressing dysphoric, threatening, positive, and neutral affectivity from the NimStim Face Stimulus Set was used (Tottenham et al., 2009). An equal number of male and female faces were selected. Further information about the final stimulus set can be found in the online supplement.

2.2.2. Cognitive disengagement – working memory

2.2.2.1. Design. Difficulty disengaging from material that has entered working memory was measured using the affective Sternberg task (Joormann and Gotlib, 2008). Each of the 96 trials consisted of a learning display, a cue display, and a probe-recognition display. During the learning display, participants simultaneously viewed two lists of three words: the words in one list were presented in red, and the words in the other list were presented in blue. On critical trials, words of one list included three negative words and the words of the other list included three positive words. Critical trials were interspersed with control trials, which included a mixture of positive and negative words in each list to ensure that participants could not use list valence as a cue when responding to the probes. Word lists were shown for 6000 ms, following which participants were shown a red or blue frame (cue display) for a duration of 2000 ms, indicating which of the two lists would be relevant for the remainder of the trial; this prompted participants to remove the other (irrelevant) set of words from working memory. Finally, during the probe-recognition display, a probe word appeared in the frame and participants were given 3000 ms to answer as quickly and as accurately as possible whether the probe word was from the relevant set or not. This probe word could be a word from the relevant list (relevant probe trial), the previously seen irrelevant list (intrusion probe trial), a new positive word (new positive probe trial), or a new negative word (new negative probe trial). Consistent with previous research, analyses were restricted to trials in which participants made correct responses (i.e., accurate trials) and in which RTs were $<$3000 ms. This resulted in the loss of 8.89% of trials. Split-half reliability coefficients on critical trial RTs ranged from.75 to.90. Following the recommendations set forth by Joormann and Gotlib (2008), participants' ability to update the contents of working memory was modeled separately for positive and negative stimuli as decision latencies to intrusion probes minus the decision latencies to new probes of the same valence as the relevant list. Therefore, two variables were calculated: working memory disengagement bias (WMDB) for positive stimuli, and WMDB for negative stimuli (broadly defined). Higher scores indicate increased interference from irrelevant words that had been seen previously. In other words, higher scores indicate that an individual took longer to indicate that participants had more difficulty disengaging from words of that valence.

2.2.2.2. Stimuli. The affective Sternberg task uses stimuli from the Affective Norms of English Words list. As intended, positive and negative word lists did not differ either in word length or arousal, *ps* $\geq$ 0.120. Further information about the final word list can be found in the online supplement.

2.2.3. Acute laboratory stressor

To examine the biological stress response, participants completed the *Trier Social Stress Test for Children* (Buske-Kirschbaum et al., 1997), a standardized paradigm that reliably induces subjective stress and both a salivary cortisol and alpha-amylase (sAA) response (Dickerson and Kemeny, 2004; Nater et al., 2007). Following best-practice guidelines, all participants completed the TSST-C in the afternoon to control for diurnal variations in cortisol and sAA (Nater et al., 2007). To capture baseline levels of cortisol and sAA, participants watched a 15-minute calming nature video prior to the stressor. Biological responses to stress were captured via saliva samples taken after this baseline period

(S1; 5 min prior to stressor onset), after the prep period (S2; immediately prior to stressor onset), after the 10-minute stressor (S3; 10 min following stressor onset), and at 3 time points throughout the recovery period (S4-S6; from 20 to 40 min following stressor onset [i.e., 10–30 min following stressor offset]). To ensure the effectiveness of the stress task, self-reported positive and negative affect was also assessed at these 6 time points across the TSST-C.

2.2.4. Cortisol and alpha-amylase

Saliva samples were stored at −20 °C until analyses were carried out in the endocrinological laboratory of the Technische Universität Dresden. Cortisol concentrations were measured using chemiluminescence immunoassay with high sensitivity (IBL International, Hamburg, Germany). Alpha-amylase concentrations were measured by an enzyme kinetic method using a Genesis RSP8/150 liquid handling system (Tecan, Crailsheim, Germany). The intra and interassay coefficients for both cortisol and sAA were below 8%. Further information regarding the methodology of cortisol and alpha-amylase assay can be found in the online supplement. As both cortisol and sAA values across the TSST-C were positively skewed, cortisol and sAA values were transformed prior to analyses by natural log transformation following current practices (e.g., Chen et al., 2020).

2.2.5. Covariates

To assess variables known to affect responses of both the HPA axis and SNS, participants completed a brief questionnaire assessing demographic and health-related variables including age, sex assigned at birth, race, household income, current use of both psychotropic and non-psychotropic medication, and past and current non-pharmacological psychological interventions. To assess pubertal stage, participants completed the self-report Tanner Staging questionnaire (Marshall and Tanner, 1968). We averaged Tanner scores for each participant to compute an index of average stage of pubertal development, a methodology that is consistent with prior research (Dorn et al., 2006). To assess levels of current symptoms of depression and anxiety, participants completed the 10-item version of the Children's Depression Inventory (CDI; Kovacs, 1992) and the Multidimensional Anxiety Scale for Children (March et al., 1997). Current and past psychopathology was assessed via the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS-PL DSM-5; Kaufman et al., 2016). Finally, we calculated the number of minutes between midnight and the first saliva sample.

2.3. Procedure

Data were collected in a multi-session procedure. Participants first came to the lab to complete the K-SADS-PL, assessments of pubertal stage and current symptoms of depression and anxiety, and a general health screening questionnaire. Eligible participants were then invited to return to the lab within two weeks for a second session, which took place in the afternoon to control for diurnal variations in cortisol and sAA (Nater et al., 2007). During the second session, participants completed the Posner and Sternberg tasks, followed by the TSST-C. Both computer tasks were completed on an ASUS 20-inch color computer monitor with a refresh rate of 60 Hz, and the order in which these two tasks were completed was counterbalanced across participants. Because cognitive biases can remain latent before they are triggered by a negative mood state (Teasdale, 1988), participants watched one of three randomly assigned 6-minute negative movie clips before completed each cognitive task. Participants completed self-reported ratings of positive and negative affect before and after each movie clip to confirm they induced a more negative, and less positive, mood state.

2.4. Statistical analyses

2.4.1. Manipulation check

A repeated-measures analysis of variance (ANOVA) was conducted to confirm that the mood induction conducted in the context of the cognitive tasks successfully induced the expected negative affective response. Similarly, to ensure the effectiveness of the TSST-C in inducing an affective and biological stress response, repeated-measures ANOVAs were conducted on positive affect, negative affect, cortisol, and sAA across the stressor.

2.4.2. Main analyses

Given that the present study involves nested levels of analysis (i.e., time nested within participants), a hierarchical linear modeling (HLM) approach was used to examine associations between biological responses to stress and biases in cognitive disengagement (Raudenbush and Bryk, 2002). Specifically, to examine the relative contribution of ADBs and WMDBs to biological responses to stress, models were conducted examining the association between biological responses to stress at Level 1 and both ADBs and WMDBs at Level 2. This approach is ideal for the present analyses as it permits the examination of unevenly spaced measurement occasions by modeling repeated measurements of both cortisol and sAA within persons as a function of time. HLM is also well suited to instances of multiple comparisons as it utilizes a partial pooling approach, which yields more valid and unbiased estimates than other approaches by building multiplicity into models from the start. Linear, quadratic, and piecewise models were evaluated for both cortisol and sAA, and we selected the model that best fit the data based on Akaike's Information Criteria (AIC) values, deviance statistics, and visual inspection of the data. For piecewise models, reactivity and recovery slopes were determined separately for cortisol and sAA given evidence that sAA peaks prior to cortisol (see online supplement for additional details). Prior to including disengagement biases at Level 2, variables known to influence HPA axis and SNS responses to stress were tested as potential covariates: age, sex assigned at birth, race, household income, pubertal stage, current use of both psychotropic and non-psychotropic medication, past or current non-pharmacological psychological interventions, symptoms of depression and anxiety, presence of a DSM-5 diagnosis, and minutes between midnight and the first saliva sample. Based on best-practice recommendations, only significant covariates were retained in the final model in order to maximize power and model parsimony. Using HLM 7.03, models were fit using full information maximum likelihood for the calculation of deviance and AIC and restricted maximum likelihood for the estimation of model parameters. To achieve adequate power using HLM, it has been recommended that sample sizes at Level 2 should be greater than 50 (Maas and Hox, 2005). In the present study, coefficients, variance components, and standard errors were based on a sample size of 78 at Level 2, and we used robust standard errors for all HLM analyses to reduce bias, following recommendations put forth by Raudenbush and Bryk (2002). HLM equations are presented in the online supplement.

In order to examine the relative contribution of disengagement biases to the overall production of cortisol and sAA across the stressor, we also calculated AUCg for both cortisol and sAA using trapezoidal integration (Pruessner et al., 2003). Moreover, following recommendations set forth by Ali and Pruessner (2012), we calculated the ratio of total sAA over total cortisol produced by dividing the AUCg of sAA by the AUCg of cortisol to yield amylase over cortisol (AOCg). Ali and Pruessner found that this ratio is an indicator of stress system dysregulation and strongly correlates with indices of chronic stress, social stress, depression, and anxiety. Linear regression analyses were then conducted to examine the relation between biases in cognitive disengagement and the AUCg of cortisol, the AUCg of sAA, and AOCg. The same variables were tested as potential covariates and were included in the regression analyses if significant.

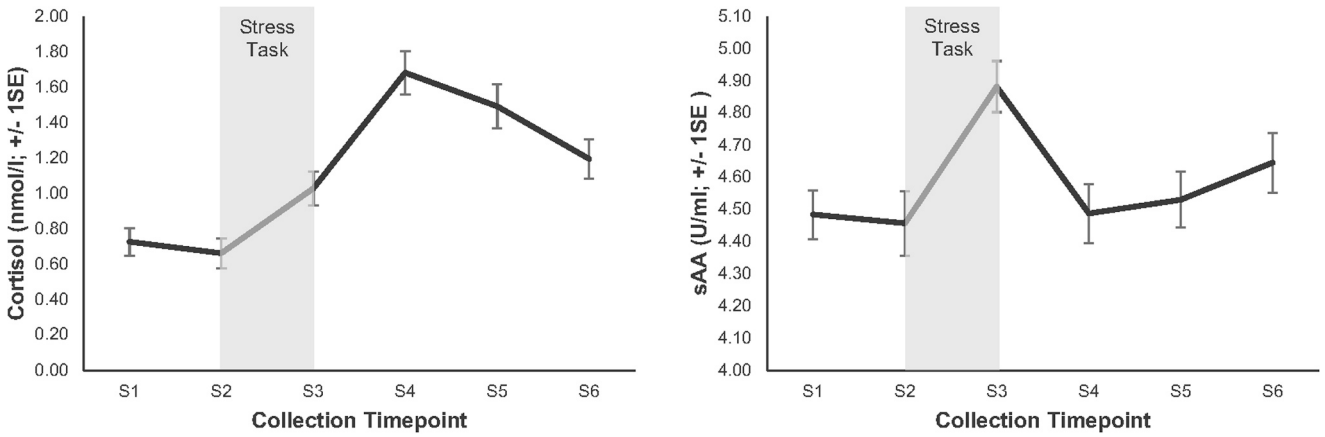

Fig. 1. Pattern of cortisol and sAA responses to the psychosocial stressor.

3. Results

3.1. Manipulation check

A two-way Time by Valence (positive, negative) repeated measures ANOVA indicated that the mood induction successfully induced the expected significant increase in negative mood as well as a significant decrease in positive mood, main effects $Fs \geq 11.46$, $ps \leq 0.001$, partial η^2s ≥ 0.162. Repeated measures ANOVAs conducted on positive and negative affect across the psychosocial stressor indicated that the TSST-C successfully induced the expected significant increase in negative mood and the expected significant decrease in positive mood, $Fs \geq 8.71$, $ps \leq 0.002$, partial η^2s ≥ 0.135. Similarly, there was a significant main effect of time for both cortisol, $F(5, 66) = 25.90$, $p < .001$, partial $\eta^2 = .662$, and sAA across the TSST-C, $F(4, 66) = 15.27$, $p < .001$, partial $\eta^2 = .481$, indicating that the TSST-C induced the expected biological stress response. Cortisol and sAA responses to stress are presented in Fig. 1.

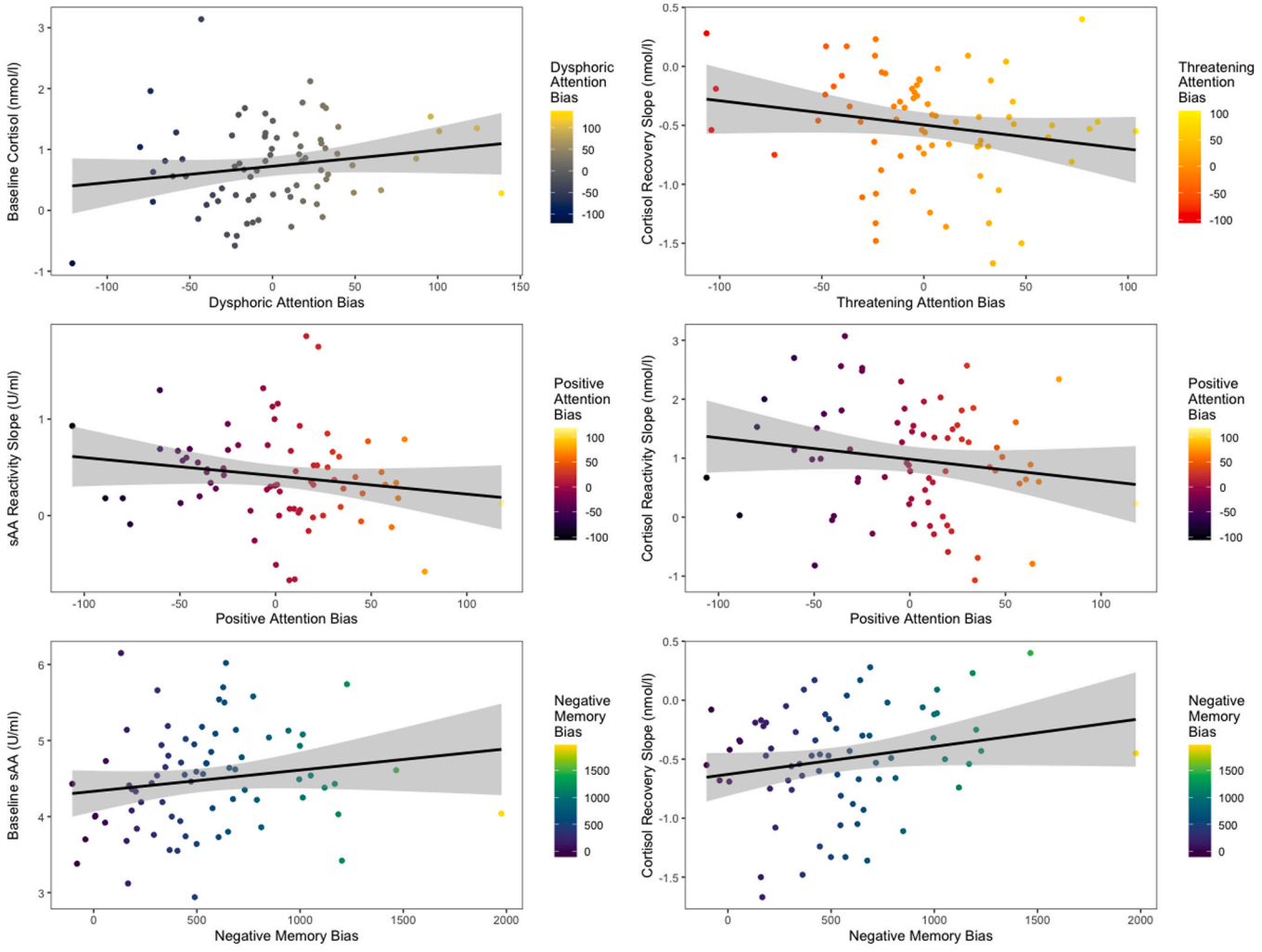

Fig. 2. Associations between cognitive disengagement biases and biological responses to stress.

3.2. Salivary cortisol

Based on visual inspection of the data, deviance statistics, and AIC values, a piecewise linear growth model best fit the cortisol data, which estimated the slope of cortisol across baseline, reactivity, and recovery phases of the stressor (see online supplement for additional details). Of the covariates tested (see Section 2.2.5), greater distance in time between midnight and the first saliva sample predicted higher levels of cortisol at baseline, $B = 0.004$, $t(50) = 5.14$, $p < .001$, and higher pubertal stage predicted a steeper slope of cortisol reactivity, $B = 0.01$, $t(50) = 2.18$, $p = .034$. Thus, these variables were included as covariates in the corresponding Level 2 equation.

ADBs and WMDBs were then included at Level 2. Findings indicated that greater ADB for dysphoric stimuli was associated with higher levels of cortisol at baseline, $B = 0.01$, $t(60) = 2.04$, $p = .046$. Greater ADB for positive stimuli was associated with less cortisol reactivity in response to the stressor, $B = -0.0002$, $t(60) = -2.53$, $p = .014$. Finally, greater ADB for threatening stimuli was associated with a faster slope of cortisol recovery from the stressor, $B = -0.0002$, $t(61) = -2.38$, $p = .020$, while greater WMDB for negative stimuli (broadly defined) was associated with a prolonged slope of cortisol recovery from stress, $B = 0.00001$, $t(61) = 2.14$, $p = .037$. Associations between cognitive disengagement biases and cortisol responses to stress are presented in Fig. 2.

Next, we examined whether disengagement biases were associated with the AUCg of cortisol. Of the covariates tested, greater distance in time between midnight and the first saliva sample was significantly associated with greater AUCg of cortisol, $\beta = 0.527$, $t(58) = 4.63$, $p < .001$. As such, this variable was included in the linear regression analysis in which the AUCg of cortisol was regressed on each of the disengagement bias scores. The AUCg of cortisol was not predicted by either ADBs or WMDBs, $\beta s \leq 0.160$, $ps \geq 0.162$. All results for salivary cortisol can be found in Table 2.

3.3. Salivary alpha-amylase

Based on visual inspection of the data, deviance statistics, and AIC values, a piecewise linear growth model was also the best fit for the sAA data. Prior to including disengagement biases at Level 2, the aforementioned variables were tested as potential covariates. None of the potential covariates were associated with sAA at baseline, or with the slope of sAA reactivity or recovery, $ps \geq 0.125$.

Including ADBs and WMDBs at Level 2, we found that greater working memory bias for negative stimuli was associated with greater sAA output at baseline at a trend level, $B = 0.0004$, $t(68) = 1.92$, $p = .059$. In addition, greater attention bias for positive stimuli was associated with less sAA reactivity to the stressor, $B = -0.0002$, $t(68) = -2.49$, $p = .015$. Associations between cognitive disengagement biases and sAA responses to stress are presented in Fig. 2.

We then examined whether disengagement biases predicted the AUCg of sAA. Of the covariates tested, greater distance in time between midnight and the first saliva sample was associated with greater AUCg of sAA, $\beta = 0.303$, $t(58) = 2.24$, $p = .030$. This variable was included in the linear regression in which the AUCg of sAA was regressed on each of the disengagement bias scores. Findings indicated that greater WMDB for negative stimuli (broadly defined) was associated with greater sAA output across the stressor, $\beta = 0.246$, $t(70) = 2.12$, $p = .038$. All findings for sAA can be found in Table 3.

3.4. Ratio of alpha-amylase over cortisol

A linear regression analysis was conducted in which AOCg was regressed on each of the disengagement bias scores. Of the covariates tested, the use of non-psychotropic medication was associated with lower AOCg, $\beta = -0.36$, $t(58) = -2.71$, $p = .009$. Thus, this variable was included in the linear regression including disengagement biases.

Table 2
Predicting Cortisol Response to Stress.

Baseline	Coeff (*B*)	SE	*t*	*p*
Attention - Dysphoric	.005	.003	2.04	**.046**
Attention - Threatening	−0.003	.003	−1.16	.252
Attention - Positive	−0.002	.003	−0.79	.434
Memory - Negative	−0.0001	.0002	−0.29	.774
Memory – Positive	−0.00003	.0001	−0.24	.811
Stress Reactivity				
Attention - Dysphoric	−0.00002	.0001	-0.25	.801
Attention - Threatening	.0002	.0001	1.81	.075
Attention - Positive	−0.0002	.0001	−2.53	**.014**
Memory - Negative	−0.000002	.000009	−0.17	.864
Memory – Positive	.00001	.00001	1.52	.133
Stress Recovery				
Attention - Dysphoric	.0001	.0001	0.91	.369
Attention - Threatening	−0.0002	.0001	−2.38	**.020**
Attention - Positive	.00004	.0001	0.48	.632
Memory - Negative	.00001	.00001	2.14	**.037**
Memory – Positive	.000003	.000003	1.08	.284
	Coeff (β)	SE	*t*	*p*
Cortisol AOCg				
Attention - Dysphoric	.043	.160	0.29	.777
Attention - Threatening	.160	.152	1.24	.221
Attention - Positive	−0.200	.179	−1.30	.198
Memory – Negative	.029	.014	0.26	.796
Memory – Positive	.157	.009	1.42	.162

Note: Coeff = regression coefficient; SE = standard error.
Significant p-values are presented in bold.

Table 3
Predicting Alpha-Amylase Response to Stress.

Baseline	Coeff (*B*)	SE	*t*	*p*
Attention - Dysphoric	.001	.003	0.34	.739
Attention - Threatening	−0.004	.003	−1.34	.185
–	−0.0002	.003	−0.06	.952
Memory-Neg	.0004	.0002	1.92	.059
Memory-Pos	.0002	.0001	1.65	.103
Stress Reactivity				
Attention - Dysphoric	.0001	.00004	1.25	.215
Attention - Threatening	.0001	.0001	0.81	.418
Attention - Positive	−0.0002	.0001	−2.49	**.015**
Memory-Neg	−0.00001	.00001	−0.65	.515
Memory-Pos	.00001	.00001	1.02	.312
Stress Recovery				
Attention - Dysphoric	−0.00004	.0001	−0.69	.495
Attention - Threatening	−0.0001	.0001	−1.06	.292
Attention - Positive	.0001	.0001	1.62	.110
Memory-Neg	.000001	.00001	0.13	.896
Memory-Pos	.00001	.000004	−1.32	.191
	Coeff (β)	SE	*t*	*p*
Alpha-Amylase AOCg				
Attention - Dysphoric	.049	.159	0.31	.755
Attention - Threatening	−0.050	.151	−0.37	.711
Attention - Positive	−0.089	.178	−0.55	.582
Memory – Negative	.246	.246	2.12	**.038**
Memory – Positive	.198	.009	1.71	.092

Note: Coeff = regression coefficient; SE = standard error.
Significant *p*-values are presented in bold.

Table 4
Predicting AOCg.

	Coeff (β)	SE	*t*	*p*
Attention - Dysphoric	.206	.003	1.31	.194
Attention - Threatening	.041	.003	0.30	.767
Attention - Positive	−0.179	.004	−1.10	.275
Memory – Negative	.025	.000	0.21	.837
Memory – Positive	.331	.000	2.81	**.007**

Note: Coeff = regression coefficient; SE = standard error.
Significant *p*-values are presented in bold

Findings indicated that greater WMDB for positive stimuli was associated with greater HPA-SNS dissociation (as indicated by higher AOCg), $\beta = 0.331$, $t(70) = 2.81$, $p = .007$. All results are presented in Table 4.

4. Discussion

Individual differences in biological responses to stress during early adolescence have been associated with negative mental and physical health outcomes across the lifespan. Thus, it is critical to elucidate the factors associated with individual differences in biological responses to stress among youth. We found a complex pattern of associations between disengagement biases and stress responses of both the HPA axis and the SNS, which differed by bias valence and cognitive system (i.e., attention versus working memory). Greater ADB for dysphoric stimuli was associated with higher levels of cortisol at baseline. Greater ADB for positive stimuli was associated with a more attenuated pattern of stress reactivity for both cortisol and sAA. Moreover, greater WMDB for negative stimuli (broadly defined) was associated with an attenuated slope of cortisol recovery from stress whereas greater ADB for threatening stimuli was associated with a steeper slope of cortisol recovery. Interestingly, only WMDBs were associated with comprehensive markers of the stress response (i.e., AUCg indices and AOCg): WMDB for negative stimuli was associated with greater total sAA production across the stressor, as measured via the AUCg of sAA, while greater WMDB for positive stimuli was associated with greater HPA-SNS dissociation, as measured via the AOCg ratio. These findings were documented among a sample of youth during early adolescence, which is considered an important "window of opportunity" for understanding and impacting health and wellbeing in young adulthood and beyond (Dorn et al., 2019). This study is the first to examine associations between biases across multiple cognitive systems and biological responses to stress. We examined markers of both the HPA axis and the SNS, which allows for the examination of individual differences in both single system functioning and in the dissociation between the HPA axis and SNS. As such, we were able to comprehensively measure the stress response by considering indices of change (i.e., slopes of reactivity and recovery), overall system activity (i.e., baseline levels of cortisol and sAA) and output (i.e., AUCg of cortisol and sAA), and biological stress system asymmetry (i.e., AOCg).

ADB for dysphoric information was associated with levels of cortisol at baseline. Specifically, individuals with greater ADB for dysphoric stimuli (i.e., greater difficulty disengaging attention from dysphoric stimuli) had greater HPA activation at rest. This association is consistent with findings reported by Ursache and Blair (2015), who also found a positive association between negative cognitive biases and higher resting levels of HPA axis activity among samples of youth (Ursache and Blair, 2015). Higher levels of cortisol at rest also are associated with increased rumination, a construct related to cognitive disengagement that is characterized by difficulty disengaging cognitive resources from processing negative stimuli (McCullough et al., 2007). Broadly, however, the association of baseline levels of cortisol with cognitive disengagement biases is understudied, and previous work has focused primarily on adults. Given that basal levels of cortisol change with age (Strahler et al., 2010; Van Cauter et al., 1996), future work should continue to investigate what predicts individual differences in basal cortisol levels in youth.

We also found that greater ADB for positive stimuli (i.e., greater difficulty disengaging attention from positive stimuli) was associated with less reactivity of both the HPA axis and the SNS. Current theoretical models have focused predominantly on the influence of cognitive disengagement biases on stress recovery (Flynn and Rudolph, 2007). However, our results suggest that ADBs may begin to act on the HPA axis and SNS earlier, during individuals' initial reactivity to the stressor. Given the lack of research investigating associations between cognitive disengagement and biological reactivity to stress, this represents a promising area for future investigation. Notably, we found that ADBs, but not WMDBs, were associated with reactivity to stress. The unique influence of attention on initial stress reactivity may be due to the temporal association between attention and working memory: attention can be considered a "gatekeeper" for working memory by biasing the information that is ultimately encoded (Awh et al., 2006). This finding further supports the importance of considering both attentional and working memory processes as it highlights that biases in these two cognitive domains predict different components of the stress response.

It is also noteworthy that the association between attention and biological reactivity was found to be exclusive to disengagement from positive information. Specifically, we found that greater ADB for positive stimuli was associated with less reactivity of both the HPA axis and the SNS. While much of the literature on cognitive biases and biological responses to stress has focused on negatively valenced biases, our findings highlight the importance of measuring the way individuals' process positive information. Individual differences in the processing of positive stimuli may be particularly relevant to models of resilience to stress, as positive information processing biases may serve as a protective mechanism that is associated with an adaptive pattern of biological reactivity. Indeed, while the majority of research in the area of cognitive biases has focused on biases towards negative information, the role of positive cognitive biases is increasingly being acknowledged as relevant to trait resilience and wellbeing across the lifespan (e.g., Jopling et al., 2020). Moreover, researchers have documented that many psychiatric disorders are not associated with the positive cognitive biases that typify healthy controls. Further, there is evidence that positive and negative information is processed in distinct ways (Vaish et al., 2008). For instance, positive information is thought to have a speed advantage over negative information, and responses to positive information are more easily primed than responses to negative information (Unkelbach, Fiedler, Bayer, Stegmüller, Danner, 2008). Thus, there is important reason to continue to study positive cognitive disengagement biases.

When considering findings related to biological recovery from the stressor, it is critical that they are interpreted in light of individual differences in reactivity to the stressor given that the more an individual reacts to stress, the greater they have to recover in order to return to baseline. That being said, there is also an extensive literature documenting that variables influence biological reactivity and recovery in distinct ways. Indeed, in the present study, we found variables that predicted biological recovery from stress were distinct from those that predicted reactivity. Specifically, whereas the ADB described above predicted cortisol reactivity to stress, WMDB for negative stimuli (broadly defined) and ADB for threatening stimuli predicted cortisol recovery. Evidence of an association between greater negative WMDB and attenuated cortisol recovery from stress is consistent with evidence that constructs related to negative cognitive disengagement biases (e.g., rumination, deficits in other forms of cognitive control) prolong recovery of the HPA axis following stress (Shull et al., 2016). Indeed, difficulty disengaging from negative information in working memory has been proposed as a central mechanism underlying rumination, which is associated with prolonged activation of the HPA axis (Joormann and Tanovic, 2015). Therefore, it is reasonable that difficulty disengaging from negative information in working memory would be associated with prolonged activation of the HPA axis. We also found that greater ADB for threatening stimuli was associated with a steeper slope of cortisol recovery following stress. While this result is surprising given that the same association was not found for ADB for dysphoric stimuli, it highlights the importance of taking a nuanced approach to defining negative stimuli (see Hankin et al., 2010). Our results are consistent with evidence showing that threatening information is processed differently than other negative emotions, as demonstrated by different behavioral and neural patterns (Zhang et al., 2017). As such, future research should work to better understand the differential processing and downstream effects of diverse categories negative stimuli.

While greater WMDB for negative stimuli was associated with greater AUCg of sAA across the stress task, the AUCg of cortisol was not

associated with any disengagement biases. This highlights the importance of examining multiple biological outcomes to comprehensively understand the impact of cognitive biases on biological responses to stress (Ali and Pruessner, 2012; Bauer et al., 2002). Greater WMDB for positive stimuli (i.e., greater difficulty disengaging from positive stimuli in working memory) was also associated with greater AOCg, a relatively novel ratio considered to be a marker of stress system dysregulation. Greater AOCg ratio indicates blunted HPA axis activity accompanied by increased activity of the SNS and has been associated with chronic stress and depression (Ali and Pruessner, 2012). While the association between greater positive WMDB and greater AOCg may appear surprising given that difficulty disengaging from positive stimuli is often considered to be an adaptive bias, WMDBs are considered a form of perseverative cognition, and other forms of perseverative cognition (e.g., rumination) have been associated with a reduced ability of the ANS to inhibit sympathetic arousal (Vrshek-Schallhorn et al., 2018). Thus, although there is some tentative evidence to indicate that WMDBs, even in the context of positive stimuli, could be associated with a greater AOCg ratio, this relatively novel ratio has been understudied in youth, and thus represents an important area for future investigation.

Findings should be interpreted in light of several limitations. First, the present study used a 30-minute recovery period. Although a number of previous studies in samples of youth have demonstrated that levels of cortisol return to baseline within 30-minutes following stressor offset (Buske-Kirschbaum et al., 1997), in the current study, levels of cortisol and sAA were significantly higher at the end of the recovery period than at baseline, $ps \leq 0.028$. Thus, we suggest that future work examining cortisol recovery from stress in youth should consider using at least a 40-minute recovery period. A second limitation of the current study is that we are unable to determine the directionality of the observed association. While empirical evidence suggests that biases in cognitive disengagement could prolong biological responses to stress, there is also reason to believe that the relation is bidirectional (LeMoult, 2020). Indeed, hyperactivity of the HPA axis has been tied to atrophy of the hippocampus, a structure that is important for working memory (Lupien et al., 1998), and the prefrontal cortex, a neural structure associated with the executive control of attention (McEwen and Morrison, 2013). Therefore, it is possible that exaggerated biological responses to stress could cause broad attentional and working memory deficits. As such, future work should examine the relation between disengagement biases and biological responses to stress experimentally and/or longitudinally. Finally, it is critical that findings from the current findings are replicated. Although the final sample in the current study exceeded best-practice recommendations of sample sizes for HLM (Maas and Hox, 2005), larger samples offer numerous advantages including more closely approximating the population (Aron and Aron, 1999). Therefore, it is important that the present results are replicated in a large sample. Finally, although HLM offers multiple advantages such as the precise modeling of individual differences in trajectories of biological responses to stress, it is not well suited to traditional computations of effect size (see Snijders and Bosker, 2011). As such, unstandardized coefficients are presented for those analyses conducted in HLM. However, standardized coefficients are presented for regression analyses examining associations between cognitive biases and summary indices of biological responsivity (i.e., the AUCg of cortisol and sAA and the AOCg ratio) and are suggestive of moderate associations ($\beta s \geq 0.246$).

Despite these limitations, the implications of study findings are broad. As noted previously, methodologically, this is the first study to concurrently measure ADBs and WMDBs, and to consider the relative contribution of these biases to individual differences in biological responses to stress. Further, the present study contributes to a relatively small, but growing, literature measuring activity of the neuroendocrine system and ANS in tandem (Ali and Pruessner, 2012; Allwood et al., 2011). By measuring the activity of these two systems simultaneously, we can better understand how biological systems respond to psychosocial stress in youth.

The present findings also contribute to theoretical models of the relation between cognition and biological responses, and they advance perseverative cognition models that link repetitive thought processes with negative mental and physical health outcomes (Watkins, 2008). Specifically, the present study provides evidence for a factor that could help explain the association between perseverative cognitive processing and negative mental and physical health-related outcomes among youth – namely, individual differences in biological responses to stress. This work responds to recent calls to understand how multiple units of analysis within the Research Domain Criteria (RDoC) matrix relate to one another in youth, as research elucidating a tighter coupling between multiple units of analysis early in development has the potential to improve our understanding of the factors putting youth at risk of maladaptive trajectories across adolescence and into adulthood (Beauchaine and Hinshaw, 2020). Such work is particularly important during early adolescence, a transitional period of psychobiological development.

Findings from this study represent an important first step toward identifying possible candidate mechanisms that may underlie maladaptive biological stress responses in youth. This is critical, given the deleterious effects of chronic malfunction of both the HPA axis system and the SNS in response to stress. As discussed previously, individual differences in biological responses to stress are causally associated with the onset of both mental and physical health disorders (Gunnar and Vazquez, 2015) and have a number of important neurotoxic effects on the brain (Joëls, 2011), effects that have in turn been associated with broad cognitive deficits (Holsboer and Ising, 2010). The present findings suggest that cognitive disengagement biases might be considered in future studies testing the mechanisms underlying the development of maladaptive biological responses to stress. This could both further our understanding of the interplay between cognition and biological processes among youth and enhance our ability to develop transdiagnostic interventions to help buffer youth against the detrimental effects of life stress as they enter the transition to adolescence.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2021.105166.

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