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Research paper

Cortisol reactivity to stress predicts behavioral responsivity to reward moderation by sex, depression, and anhedonia

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ABSTRACT

Depression is associated with blunted reactivity to acute stress, as well as blunted responsivity to rewards. However, the extent to which responses to stress are associated with responses to reward in individuals meeting criteria for a depressive disorder is unknown. The goal of this study was to examine the relation of responses to stress and reward, and to determine if this relation is moderated by depression diagnosis, anhedonia, and sex. Participants included 114 adults (68 depressed, 46 non-depressed; 75% women) recruited from the community. Stress reactivity was operationalized as the total salivary cortisol output to the Trier Social Stress Test (TSST; Kirschbaum et al., 1993). Response bias to monetary reward was assessed following the TSST recovery period with a probabilistic reward task (PRT; Pizzagalli et al., 2005). In men only, total cortisol output during the TSST was more strongly positively associated with response bias to reward across the three blocks of the PRT. In addition, among depressed participants with high levels of anhedonia, higher cortisol output during the TSST was significantly associated with higher overall response bias to reward. We suggest that in men, the stress and reward systems may both respond quickly, and resolve rapidly, in the face of acute stress. Further, in depression, our findings suggest that anhedonia may represent a specific phenotype in which the stress and reward systems are particularly tuned together.

1. Introduction

Unipolar depressive disorders affect over 300 million people globally and are the leading worldwide cause of disability (World Health Organization, 2017). Progress in understanding the etiology and pathophysiology of depression has increased in recent years by focusing on the roles of two domains of functioning that can be measured objectively and that have clear neurobiological substrates: reactivity to stress and responsivity to reward. A large body of literature has documented differences in these domains between those with and without depression (Bogdan et al., 2013; Burke et al., 2005). Additionally, there is growing evidence from the preclinical literature that the neuromodulators of the stress and reward systems are related and influence one another (Luyten and Fonagy, 2018). However, empirical examination in humans of the extent to which responses to stress relate to responses to reward is lacking (Pizzagalli, 2014). This is an important question. If individual differences in stress reactivity correlate significantly with variability in reward responsivity, this might point to shared (direct or indirect) neurobiological substrates that could be targeted by novel treatments. Literature bearing on each of these domains is reviewed below.

Reward responsivity has been examined experimentally with signal detection tasks that use a differential reinforcement schedule with monetary reward to objectively measure how participants modulate their behavior as a function of reward (Pizzagalli et al., 2005). In these tasks, individuals with depression are significantly less likely to develop a response bias to the rewarded stimulus, and are less likely to learn from reward across blocks of trials, relative to non-depressed individuals (Pechtel et al., 2013; Pizzagalli et al., 2009; Vrieze et al., 2013). Further,

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such blunted responses to reward prospectively predict the onset of depression and, more specifically, symptoms of anhedonia, defined as a loss of pleasure or interest in previously rewarding stimuli (Bress et al., 2013; Vrieze et al., 2013).

Stress reactivity in depression has been examined in terms of the release of the stress hormone cortisol in response to laboratory stress challenge paradigms. In particular, challenges with a social-evaluative component, such as the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), have shown the greatest predictive validity in depression (Dickerson and Kemeny, 2004). Meta-analytic evidence has shown that individuals with depression show a significantly lower (blunted) pattern of cortisol reactivity to the TSST relative to non-depressed individuals (Zorn et al., 2017). However, there is also strong meta-analytic evidence for sex differences. In non-psychiatric samples, women show significantly lower peak cortisol than men (Liu et al., 2017). Further, women with a diagnosis of depression evidence significantly lower cortisol reactivity to the TSST than non-depressed women, whereas, in contrast, depressed men evidence significantly higher cortisol reactivity to the TSST than non-depressed men (Zorn et al., 2017; see also Mazurka et al., 2018). Reduced output of cortisol in response to acute stress is believed to result from resistance (i.e., desensitization) of glucocorticoid receptors through a number of inter-related mechanisms that promote chronic release of cortisol (Burke et al., 2005; Harkness et al., 2011). Therefore, the above sex differences in cortisol reactivity to stress have been interpreted to suggest that men may be better able than women to quickly mobilize energy in the face of stress, thus affording protection from the harmful desensitizing effects of chronically elevated cortisol (Papadimitrou and Priftis, 2009).

A very small number of studies have also found a different pattern in the *relation* between responses to stress and responses to reward in men versus women. In two studies of healthy men, higher levels of chronic cortisol release (i.e., hair cortisol) and greater cortisol reactivity to the TSST were significantly associated with a greater difference in effort expended to consume reward versus non-rewarding sexual cues (i.e, erotic photos of women versus men; Chumbley et al., 2014), as well as stronger nucleus accumbens activation in response to masked sexual cues (Oei et al., 2014). Similarly, in a study of non-depressed adults, Lighthall et al. (2012) found that in men, higher cortisol reactivity following a cold pressor task predicted greater activation in the dorsal striatum during a subsequent reward-related decision-making task. In contrast, among women in this study, cortisol reactivity was not associated with activation in the dorsal striatum. However, in a subsequent study of non-depressed women, while Berghorst et al. (2013) found no difference between those randomly assigned to a stress (threat of shock) versus no stress condition on sensitivity to reward, women who were high responders to stress (i.e., who showed cortisol hyper-reactivity), evidenced *decreased* sensitivity to reward. These results, taken together, suggest that in men, greater release of cortisol in response to stress is associated with *heightened* reward-oriented behavior. In contrast, responses to stress and responses to reward do not appear to be correlated, or may even be negative related, in women. However, the extent to which this sex difference extends to depression, or anhedonia more specifically, is currently unknown.

2. The current study

The primary goal of the current study was to examine the relation between cortisol reactivity to the TSST and response bias during a probabilistic reward task (PRT), and to determine whether this relation was moderated by sex and depression status. Consistent with the findings reviewed above, we hypothesized that, among men, but not women, higher cortisol reactivity to the TSST would be significantly associated with higher response bias on the PRT. Further, consistent with the meta-analytic evidence that sex differences in the stress response are heightened in depression (Mazurka et al., 2018; Zorn et al., 2017), we hypothesized that the above hypothesized sex difference in the relation between cortisol reactivity to the TSST and response bias on the PRT would be significantly stronger in the depressed group relative to the non-depressed group.

A secondary goal of this study was to examine, within the depressed group, whether the relation between cortisol reactivity to the TSST and response bias on the PRT would emerge more strongly in those with higher versus lower levels of anhedonia. Anhedonia is a core symptom of depression (American Psychological Association, 2013) that is reported by approximately 70% of depressed patients (Buchwald and Rudick-Davis, 1993). In preclinical research, exposure, and heightened glucocorticoid reactivity, to stress predicts behavioral signs of anhedonia (Antoniuk et al., 2019). Further, it has been theorized that neuroendocrine stress systems may more strongly impinge on reward circuits in depressed individuals who evidence an anhedonic phenotype than in those with low levels of anhedonia (Corral-Frias et al., 2015; Stanton et al., 2019). Therefore, we hypothesized that, within the depressed group, cortisol reactivity and response bias would be more strongly positively associated in those with higher versus lower levels of anhedonia.

3. Methods

3.1. Participants

Participants included 114 adults (68 depressed, 46 non-depressed) recruited through community advertisements (Table 1). The investigation was carried out in accordance with the latest version of the Declaration of Helsinki, and was approved by the Health Sciences Research Ethics Board at Queen's University. All participants provided written, informed consent. Participants in the depressed group all met DSM-IV-TR (APA, 2000) criteria for a current depressive disorder (major depressive disorder [MDD; $n = 63$], depressive disorder not otherwise specified [DNOS; $n = 3$], or dysthymia [$n = 2$]). Excluding participants with DNOS and dysthymia did not alter the pattern of findings reported below, so they were included in all analyses. Exclusion criteria were: lifetime bipolar disorder, psychotic disorder, alcohol or substance dependence, or medical disorder that could cause depression. Participants in the non-depressed group had no lifetime psychiatric diagnoses. Habitual smokers, those with a neuroendocrine disorder, and women who were pregnant were also excluded (Rohleder and Kirschbaum, 2006).

A total of 440 participants took part in an initial telephone screen. Of these, 83 declined participation, 135 were not eligible, and 3 were eligible but dropped out before their first appointment. Of the remaining 219, 13 met one or more exclusionary criteria based on the full diagnostic interview and 32 had remitted from their depressive episode by the time of the first appointment. Additionally, 46 participants were excluded because their reward task data failed to pass quality control and 14 participants were excluded because their cortisol data contained extreme outliers, which may be indicative of sample contamination (Kivlighan et al., 2004), leaving a final sample of 114. There were no significant demographic differences between individuals who were included versus excluded (all $ps > .10$).

3.2. Measures

Depression Diagnosis and Symptoms. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV; First et al., 2002) was administered to determine psychiatric diagnoses. At this time, we also assessed demographic variables, psychotropic and hormonal medication history, and body mass index. The 10-item clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) was administered to assess the severity of depression symptoms. Items were rated on a 7-point scale, with higher scores indicating higher severity. Anhedonia was assessed with the 14-item Snaith Hamilton Pleasure Scale – Clinician Version (SHAPS-C; Ameli et al., 2014), which

Table 1
Demographic and clinical characteristics stratified by depression group.

	Non-Depressed (n = 46)	Depressed (n = 68)	χ^2 or t
Sex: Female *n* (%)	35 (76)	51 (75)	0.02
Age *M* (*SD*)	30.52 (14.94)	31.69 (13.81)	0.43
Ethnicity *n* (%)			0.15
White	36 (78)	52 (77)	
Asian	8 (17)	9 (13)	
Other	3 (7)	4 (6)	
Marital status *n* (%)			2.52
Never married	33 (72)	46 (68)	
Married/domestic partnership	8 (17)	12 (18)	
Divorced/separated/ widowed	5 (11)	10 (15)	
Years of Education *M* (*SD*)	16.91 (2.47)	16.60 (2.34)	0.82
Body Mass Index (BMI) *M* (*SD*)	23.74 (6.10)	26.65 (9.99)	1.72
Oral contraceptives (women only): Yes *n* (%)	18 (51)	21 (41)	0.68
MADRS score *M* (*SD*)	1.17 (1.61)	27.74 (7.20)	24.58***
SHAPS-C score *M* (*SD*)	26.67 (1.74)	33.82 (6.76)	7.01***
Area Under the Curve (AUCi nmol/L) *M* (*SD*)	45.20 (24.89)	33.45 (21.05)	2.51*
Area Under the Curve (AUCi nmol/L) Range	10.85 – 135.69	3.50 – 93.57	
Total Response Bias on the PRT	0.16 (0.15)	0.13 (0.14)	1.09
M (*SD*)	0.08 (0.19)	0.08 (0.15)	0.13
Block 1 Response Bias *M* (*SD*)	0.20 (0.22)	0.15 (0.17)	1.44
Block 2 Response Bias *M* (*SD*)	0.21 (0.21)	0.16 (0.20)	1.17
Block 3 Response Bias *M* (*SD*)			
Total Response Bias on the PRT Range	-0.25 – 0.42	-0.18 – 0.42	
Age at first depression onset *M* (*SD*)		19.26 (10.19)	
Total number of depressive episodes *M* (*SD*)		3.10 (2.81)	
Psychotropic medication: Yes *n* (%)		41 (60.3)	
Comorbidity: Yes *n* (%)		44 (65)[1]	
Anxiety Disorder NOS		1 (1)	
Eating Disorder NOS		2 (3)	
Generalized Anxiety		14 (21)	
Disorder		2 (3)	
Obsessive Compulsive		14 (21)	
Disorder		9 (13)	
Panic Disorder		21 (31)	
Post-Traumatic Stress Disorder		3 (4)	
Social Anxiety Disorder			
Specific Phobia			

Note. MADRS = Montgomery-Asberg Rating Scale; SHAPS-C = Snaith-Hamilton Pleasure Scale – Clinician Version; NOS = Not otherwise specified; PRT = Probabilistic Reward Task.
* $p < .05$; ** $p < .01$; *** $p < .001$
[1] The frequencies do not add up to the total because some participants had more than one comorbid diagnosis.

measures consummatory anhedonia (e.g., "I would enjoy being with my family or close friends"). This scale has excellent reliability and validity in both clinical and research populations (Franken et al., 2007). Dimensional scoring was used (possible range 14-56), where higher scores indicate higher anhedonia. Clinical interviews were conducted by senior graduate students in clinical psychology who were trained to gold-standard reliability status by the senior author (see Grove et al., 1981).

3.3. Salivary hormone and stress challenge test

Trier Social Stress Task (TSST). The TSST (Fig. 1) began with an initial saliva sample (Sample A), followed by a 30 min rest period, and then a second sample (Sample B). The participant was then led to a room where a committee of two people was sitting behind a table. Participants learned that they would have to deliver a speech for a job application to the committee, which would be videotaped. Participants then returned to the first room and were given 10 minutes to prepare, after which a third sample was collected (Sample C). Participants then gave the five-minute speech, after which they were asked to serially subtract the number 13 from 1022 as quickly as possible. If a mistake was made the participant was told to start over. The committee also prompted the participant to maintain eye contact and calculate more quickly. Following the arithmetic test, the participant was led back into the preparation room to provide a fourth sample (Sample D). The participant then relaxed quietly, with neutral reading material available, for 60 minutes to allow for hormone recovery (Samples E-H).

Saliva collection. Samples were collected by passive drool (Shirtcliff et al., 2001) between 2:00-4:30pm to avoid post-awakening increases in hormones (Groschl et al., 2003) in 5 ml polypropylene vials (PGC Scientifics Corporation, MD). We asked participants to avoid teeth brushing, vigorous exercise, smoking, caffeine, and eating or drinking other than water for 2 hours before the study (Kivlighan et al., 2004). Samples were immediately placed in -20 ℃ secure frozen storage for assay.

Sample preparation and cortisol quantitation. Saliva samples were thawed in a 20 ℃ water bath, centrifuged for 20 minutes at 2,000 xG, and 1 mL was transferred to a Hamilton Microlab Starlet workstation where 75 μL of supernatant of each sample/calibrator/quality control (QC) had proteins precipitated (75 μL $ZnSO_4$ $7H_2O$ Methanol/H_2O solution; 90/10 v/v). The precipitating solution was spiked with deuterated bioidentical internal standards. The cortisol-d4 (CDN Isotopes Inc, Pointe-Claire QC) internal standard was used for cortisol quantitation (Wynne-Edwards et al., 2013). The method is linear over a 10 calibrator range from 0.1 ng/ml through 100 ng/ml cortisol (all $r^2 > 0.995$ for the linear (with 1/x weighting to improve precision at low concentrations) fit of untransformed data). An in-house cortisol quality control at 0.5 ng/ml was included in each of 11 runs (samples for an individual were sequential within the same run) and yielded a mean concentration of 0.506 ± 0.052 ng/ml (accuracy 101.3%) with an inter-run CV of 7.32%. In human serum, this method is correlated to our APCI-positive method (cortisol $r = 0.963$; Wynne-Edwards et al., 2013), that is also in use for cortisol quantitation in human saliva (Drogos et al., 2019). No salivary cortisol concentrations fell below the limit of quantitation (LOQ) established for this method based on the threshold of <20% CV.

Cortisol parameter. The current study assessed cortisol reactivity to stress using Area Under the Curve with respect to increase over participants' individual baseline (AUCi). AUCi represents the total cortisol secreted during the TSST relative to baseline and is calculated as the sum of the area of the trapezoids bounded by the participants' baseline and framed by the cortisol concentration in each of the subsequent saliva samples. Overall, higher AUCi values are indicative of greater cortisol output relative to baseline. Because AUCi takes individuals' baseline into account it is the best marker of overall reactivity to the stressor (Pruessner et al., 2003).

There is evidence that participants' first cortisol sample (Sample A) may be artificially inflated due to the stress of entry into an unfamiliar laboratory environment (Goodman et al., 2017; Lazarus, 1993) and, thus, may not accurately represent their biologically relevant baseline. In the current sample, modelling of all eight cortisol samples indicated that, on average, Sample C was the lowest and reflected the anticipated decline in participant cortisol levels after acclimation to the laboratory environment (see Fig. 1). Therefore, Sample C was used as the "baseline" sample when calculating AUCi values. Specifically, AUCi in the current study was bounded by Samples C-H. Likely due to our focus on a biologically relevant baseline, mean AUCi values in the current study did not fall below zero.

Probabilistic Reward task (PRT; Pizzagalli et al., 2005). In the PRT, participants were presented with cartoon face stimuli on a

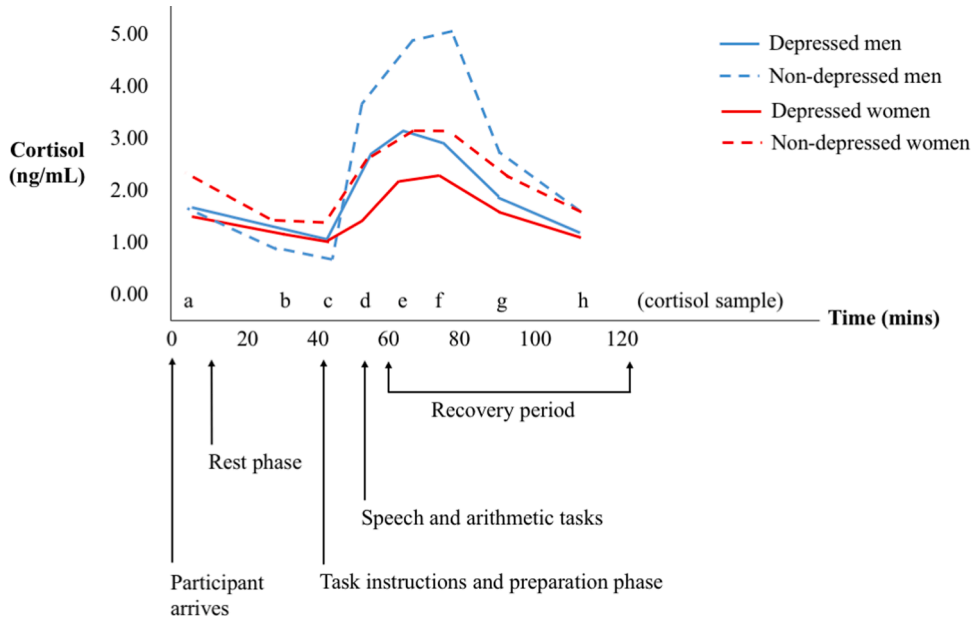

Fig. 1. *Cortisol Collection Timeline for the Trier Social Stress Task (TSST) and Cortisol Values from Sample A to Sample H Stratified by Depression Status and Sex Note.* Untransformed cortisol values are presented for ease of interpretation.

computer screen, and they indicated by key press whether the mouth on the face was short (11.5mm) or long (13mm). Stimuli were presented for 100ms in three blocks of 100 trials. To elicit a response bias, correct identification of the long mouth ("rich stimulus") was rewarded ("Correct! You won 20 Cents") three times more frequently than correct identification of the short mouth ("lean stimulus"). In each block, only 40 correct trials (30 rich, 10 lean) were rewarded to ensure that participants were exposed to similar reinforcement schedules across blocks. Therefore, participants had to integrate reinforcement history over time to optimize their responses. Participants were informed that their goal was to win as much money as possible. They were told that not all correct responses would receive reward feedback, but they were not informed that one stimulus would be disproportionately rewarded.

Response Bias was calculated as: Log b = ½ log $((Rich_{correct}+0.5)*(Lean_{incorrect}+0.5)/(Rich_{incorrect}+0.5)*(Lean_{correct}+0.5))$. High response bias indicates high rates of correct identification (hits) for the rich stimulus, and high miss rates for the lean stimulus. We examined Response Bias at each of the three blocks. For quality control purposes, trials with reaction times less than 150 ms or longer than 2500 ms were excluded. Next, trials with reaction times (following natural log transformation) falling outside the mean +/– 3 SD were considered as additional outliers and excluded. Rates of exclusion did not differ between depressed and non-depressed groups, $\chi^2(1) = 0.47$, $p = .49$.

3.4. Procedure

All participants engaged in two 2-hour sessions separated by one week: Session 1 consisted of consent procedures, the diagnostic interview, and questionnaires. In Session 2, participants completed the TSST and, following the 60-minute recovery period, the PRT. Both sessions also included additional measures not of relevance to the current report. Participants received $56.05 compensation for their time, which included the amount won during the PRT. Participants already in treatment were referred back to their treatment provider. Those in the depressed group who were not already receiving services were provided with a list of mental health resources.

4. Results

4.1. Preliminary analyses

Missing values for cortisol and reward parameters were addressed using the SPSS (IBM, 2017) multiple imputation macro, assuming data missing at random. Pooled estimates not provided by SPSS were derived by hand using Rubin's rule (Rubin, 1987; van Ginkel, 2020). The depressed group had significantly higher MADRS scores and SHAPS-C scores than the non-depressed group, but groups did not differ on any other demographic variable (Table 1).

Neither AUCi nor response bias at each block were significantly related to age, ethnicity, socioeconomic or marital status, oral contraceptive use (among women), or, within the depressed group, number of previous episodes, age at first onset, psychotropic medication treatment, MADRS score, or the presence/absence of a comorbid diagnosis (all *ps* > .10). We note specifically that neither anti-depressant medication use nor oral contraceptive use emerged as significant covariates or changed the pattern of findings in follow-up analyses within the depressed group or women, respectively. Therefore, the uncontrolled models are presented below for ease of interpretability.

4.2. Group differences on AUCi and response bias

The depressed group had significantly lower (i.e., more blunted) AUCi relative to the non-depressed group, but groups did not differ on response bias across blocks (see Table 1). Women had significantly lower AUCi than men, *Ms* = 36.72, 48.85; *SEs* = 2.29, 4.74; $t(112) = 2.53$, $p = 0.01$, but there was no evidence for a significant difference between women and men in response bias at block 1, $t(112) = 0.47$, $p = .64$, block 2, $t(112) = 0.28$, $p = .78$, or block 3, $t(112) = -0.38$, $p = .71$ (see Supplemental Figure 1). Further, within the full sample, the relation between AUCi and response bias was not significant at block 1, $r(112) = -.03$, $p = .75$ or block 2 $r(112) = .04$, $p = .65$, of the PRT. However, greater AUCi was associated at a trend with greater response bias at block 3, $r(112) = .17$, $p = .07$.

4.3. Moderation model of the relation between AUCi and response bias over blocks

A 3 (block) x 2 (depression group) x 2 (sex) mixed-model analysis of variance (ANOVA) was conducted with response bias at each block as the within-subject variable, depression group and sex as between-subject factors, and AUCi as a between-subject covariate. Preliminary model-building revealed that depression group did not significantly moderate the effect of AUCi or the interaction of AUCi and sex (all *ps* > .39). Therefore, for the sake of parsimony and ease of interpretation, we present the results of the final model with AUCi and sex as the between-subject moderators and depression group included as a main effect covariate only.

The within-subject contrasts revealed a significant linear effect of block, $F(1, 108) = 10.36$, $p = .002$, $\eta_p^2 = .09$, which was qualified by a significant quadratic effect, $F(1, 108) = 4.17$, $p = .004$, $\eta_p^2 = .04$. As shown in Fig. 2, participants evidenced the expected increase in response bias, indicating that, in the full sample, participants learned from reward over the course of the task and this learning was steepest at the start of the task. This effect was qualified by a significant 2-way interaction between AUCi and block, also in the linear trend, $F(1, 108) = 5.27$, $p = .02$, $\eta_p^2 = .05$, such that, as noted above in the univariate analyses, the relation between AUCi and response bias became significantly more positive across blocks. Finally, the 3-way interaction between block, AUCi, and sex was significant in the linear trend, $F(1, 108) = 3.34$, $p = .07$, $\eta_p^2 = .03$. Follow-up analyses stratified by sex indicated that the linear increase in the relation between AUCi and response bias over blocks was statistically significant for men, $F(1, 25) = 5.35$, $p = .03$, $\eta_p^2 = .18$, but did not even approach significance for women, $F(1, 83) = 0.62$, $p = .62$, $\eta_p^2 = .003$ (see Fig. 2).

4.4. Moderation by anhedonia in the depressed group

An additional moderated regression model was conducted within the depressed group to examine the moderating role of anhedonia on the relation between AUCi and response bias while controlling for overall depression severity. Continuous variables were centered within the moderation model. This analysis focused exclusively on the depressed group due to the restricted range of anhedonia scores within the non-depressed participants (SHAPS-C range = 20-28). Further, due to concerns regarding low power in this subgroup analysis, we focused on the "Total Response Bias" across trials as the dependent variable. Total Response Bias is defined in the literature on the PRT as an individual's average response bias across all blocks (Pizzagalli et al., 2005).

Preliminary univariate analyses revealed that, within the depressed group, SHAPS-C socres were not significantly correlated with AUCi, $r(66) = -.05$, $p = .71$, or response bias, $r(66) = -.15$, $p = .21$. Further, within the depressed group, men and women did not differ significantly on AUCi, $t(66) = -1.33$, $p = 0.19$, response bias, $t(66) = -0.10$, $p = 0.92$, or SHAPS-C scores, $t(66) = -0.23$, $p = 0.84$.

Step 1 of the model, including the main effects of sex, AUCi, and SHAPS scores, was not significant (see Table 2). However, the parameter estimate for the 2-way interaction of AUCi and anhedonia on Step 2 was significant. The Johnson-Neyman technique (Johnson and Neyman 1936), was used to follow-up this significant interaction. The Johnson-Neyman technique is superior to the simple slopes or pick-a-point technique in following up an interaction with a continuous moderator (Hayes and Matthes, 2009). Specifically, instead of testing for significance at artificial fixed values of the moderator, the Johnson-Neyman technique solves for values of the moderator at which the effect of the independent variable on the dependent variable becomes significant. That is, this technique identifies "regions of significance" in the moderator for its effect on the relation between the independent and dependent variable. In the current model, the region of significance was determined as SHAPS-C scores greater than or equal to 39 (21.57% of the sample). Specifically, in this region, higher total cortisol output in the TSST (i.e., greater AUCi values) was significantly associated with higher response bias on the PRT (all *ps* < .05). In contrast, the relation between AUCi and response bias was not significant for anhedonia scores less than 39 (78.43% of the sample; all *ps* > .17; see Fig. 3).[1]

5. Discussion

In the current study, we provided a novel examination of the relation between cortisol reactivity to stress and response bias to reward in a sample of men and women with and without a current diagnosis of depression. Our findings indicate that, first, in men only, total cortisol output during the TSST and reponse bias on the PRT became more strongly positively associated over the three blocks of the reward task. That is, greater AUCi was associated with greater reward *learning* over the course of the PRT in men, but not in women. Second, our secondary analyses tentatively suggest that in the depressed group with high levels of anhedonia only, greater cortisol output in the TSST was associated with a higher response bias on the PRT.

The results of our primary model are consistent with previous studies showing that greater release of cortisol in the face of stress is associated with heightened reward-related behavior and neural activity in men, but not in women (Chumbley et al., 2014; Lighthall et al., 2012; Oie et al., 2014; Wang et al., 2007). These findings, taken together, suggest that there are sex differences in the degree to which stress-induced changes in HPA axis activation affect subsequent reward-related behaviors. In rodent models, which typically focus exclusively on male animals, glucocorticoids potentiate behavioral responses to rewards and underlie stress-related increases in reward behaviors, such as drug taking (Lamontagne et al., 2018). Interpreted in this context, the current results suggest that, in men, those who mount a greater glucocorticoid response to stress may also be those most sensitive to, and most motivated to approach, subsequent rewards.

In contrast, among women, there was no evidence of a significant relation between cortisol release in the TSST and response bias on the PRT. This relation did not even approach significance in the women ($p = .62$) and, thus, this null result is unlikely to be simply a consequence of low power. Further, our results are consistent with those of Lighthall et al. (2012) who also failed to find a significant relation between cortisol reactivity to a cold pressor task and subsequent activation in reward-related areas of the brain in women. Nevertheless, future studies with larger samples are required to confirm the current findings. Consistent with meta-analytic findings (Liu et al., 2017), the women in our sample showed significantly lower (blunted) cortisol release to the TSST than men. Liu et al. (2017) argue that observations of blunted cortisol reactivity to stress in women may simply be a function of greater initial reactivity to the laboratory environment relative to men (i.e., higher baseline cortisol). In the current study, we employed a 30-minute acclimation period to bring all participants to their biologically relevant baseline, thus strengthening confidence that our observed sex difference represents a true difference in terms of cortisol output to the TSST. And, indeed, men and women did not differ significantly in terms of their sample C cortisol concentration ($t[112] = 0.65$, $p = .52$; see Fig. 1). Therefore, a speculative interpretation of the current sex difference is that women may not be mounting a strong enough glucocorticoid response to stress needed to activate the reward pathways that motivate reward-related behavior.

Taken together, the current pattern of findings may help in understanding higher rates of addictive and other negative reward-related

[1] When we re-ran the above model replacing SHAPS-C scores with overall depression severity (MADRS score) as the moderator, neither the main effect of MADRS score, nor its interaction with sex or AUCi were significant in predicting response bias, suggesting that our results above are specific to symptoms of anhedonia.

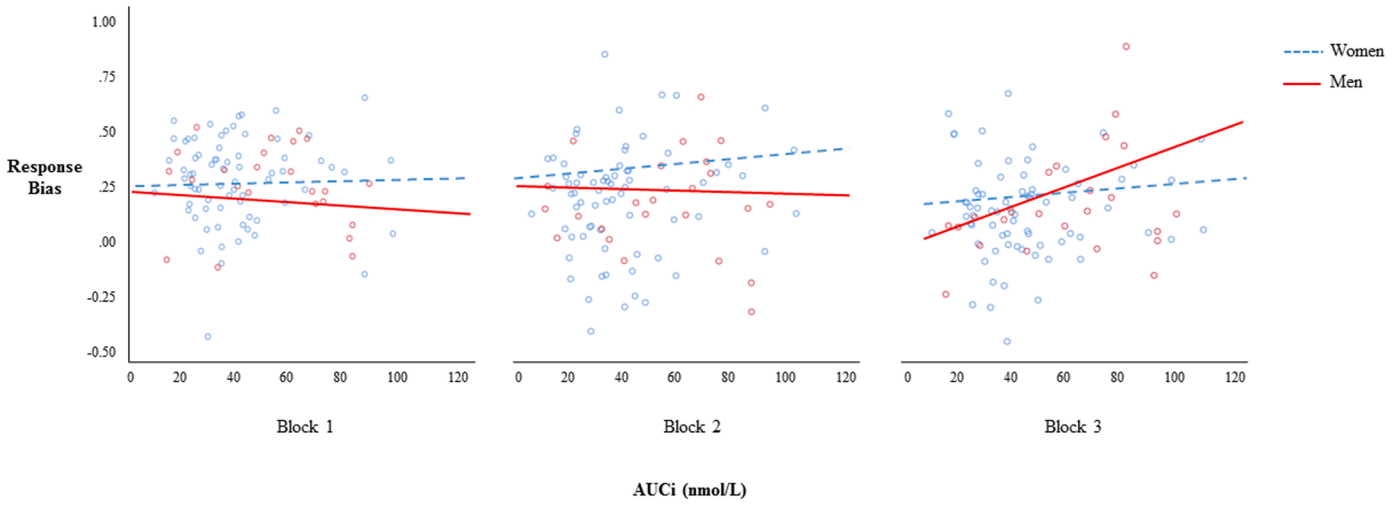

Fig. 2. The Relation Between AUCi and Response Bias Across PRT Blocks Stratified by Sex

Table 2
Regression coefficients for relation of anhedonia, sex, and AUCi to overall response bias within the depressed group

Predictor	R^2	ΔR^2	B	SE	*t*	$CI_{95}B$
Step 1	0.025	0.025				
MADRS			0.003	0.003	1.26	-0.002, 0.01
Anhedonia			-0.005	0.003	-1.67	-0.002, -0.002
Sex			0.006	0.04	0.16	-0.07, 0.08
AUCi			0.001	0.001	0.15	-0.001, 0.01
Step 2	0.12	0.098^{+}				
Anhedonia x Sex			0.004	0.007	0.56	-0.01, 0.02
Anhedonia x AUCi			0.001	0.001	2.26*	0.0, 0.001
Sex x AUCi			0.001	0.002	0.68	-0.002, 0.01
Step 3	0.12	<0.001				
Anhedonia x Sex x AUCi			0.001	0.001	0.16	-0.001, 0.001

Note. MADRS = Montgomery-Asberg Depression Rating Scale; AUCi = Area under the curve with respect to increase
$^{+}$ $p = 0.09$; * $p < 0.5$.

behaviors in men than women, in general (Becker, 2017), as well as increases in rates of such maladaptive behaviors during periods of stress (Thege et al., 2017). On the other hand, if heightened reactivity to stress can also motivate adaptive reward-related behaviors, such as the pursuit of social support and positive distractions, greater tuning together of the stress and reward systems may also help to account for the *lower* rates of depressive disorders in men relative to women (Salk et al., 2017). In this context, the current results are consistent with those showing benefits of heightened cortisol release in other areas of cognition, such as negative memory bias (Abercrombie et al., 2017). Future research is needed to understand the specific mechanisms that account for the sex differences observed here, as well as the implications of sex differences in the relation between stress reactivity and reward responsivity for sex differences in reward- and stress-related psychopathology.

The above sex difference in the relation between cortisol response to stress and response bias on the PRT was not further moderated by depression. Again, the interaction effects including depression did not even approach significance in our preliminary model-building (all *ps* > .39). Therefore, while replication is needed, one possible interpretation of these null results is that individual differences in the tuning together of the stress and reward systems are driven more strongly by stable biological determinants, and psychosocial correlates, of sex than by proximal state changes in affect or symptoms.

An alternative possibility is that depression, in general, may be too heterogeneous a phenotype and that moderation may instead emerge when focused on the subset of depressed individuals whose presentation is most strongly associated with alterations in the stress and reward systems – anhedonia. Due to the expected restricted range on our measure of anhedonia, we could not examine moderation by SHAPS scores in our full sample. However, our secondary analysis within our depressed group provides tentative preliminary support for the above speculation. Specifically, in the depressed group with higher levels of anhedonia, across sex, greater cortisol release over the course of the TSST was associated with a higher response bias on the PRT. This follow-up analysis was based on a subset of the full sample and, thus, should be interpreted with caution. Nevertheless, it should be noted that this effect was not simply driven by the men in our sample, and the same pattern of findings emerged in the women only.[2] Further, it appears to be specific to anhedonia as this moderation relation emerged even when controlling for severity of overall depression symptoms and did not emerge when severity of overall symptoms was modelled instead of anhedonia. In preclinical research, exposure, and heightened glucocorticoid reactivity, to stress predicts behavioral signs of anhedonia (Antoniuk et al., 2019). Further, in humans, particularly traumatic stress exposure predicts an anhedonic presentation in both depression and post-traumatic stress disorder (Feeny et al., 2000; Harkness and Monroe, 2002). It has been theorized that anhedonia may represent a depressive phenotype in which the stress and reward systems are particularly "tuned" together. The implication from existing theoretical and emerging empirical evidence is that the association between responses to stress and reward and anhedonia may be shaped by a history of heightened lifetime stress exposure (Stanton et al., 2019). However, other mechanisms are possible (e.g., genetic vulnerability), and this remains an important open question for research.

Finally, contrary to previous findings, we did not find evidence for differences in response bias between our depressed and non-depressed groups, nor did we find evidence for a relation of response bias to anhedonia scores within our depressed group. One potential reason for these null findings is that, in the current study, the PRT was administered directly following the TSST. Given the potential effect of this stress exposure on dampening reward processing, the design of the current study may have obscured individual differences on this task. It should be noted, however, that replication of the relation of depression or anhedonia to response bias was not the goal of the current investigation. Further, previous studies that used a similar design to ours also did not find evidence of group differences (in their case, either sex or condition

[2] Full results available by request.

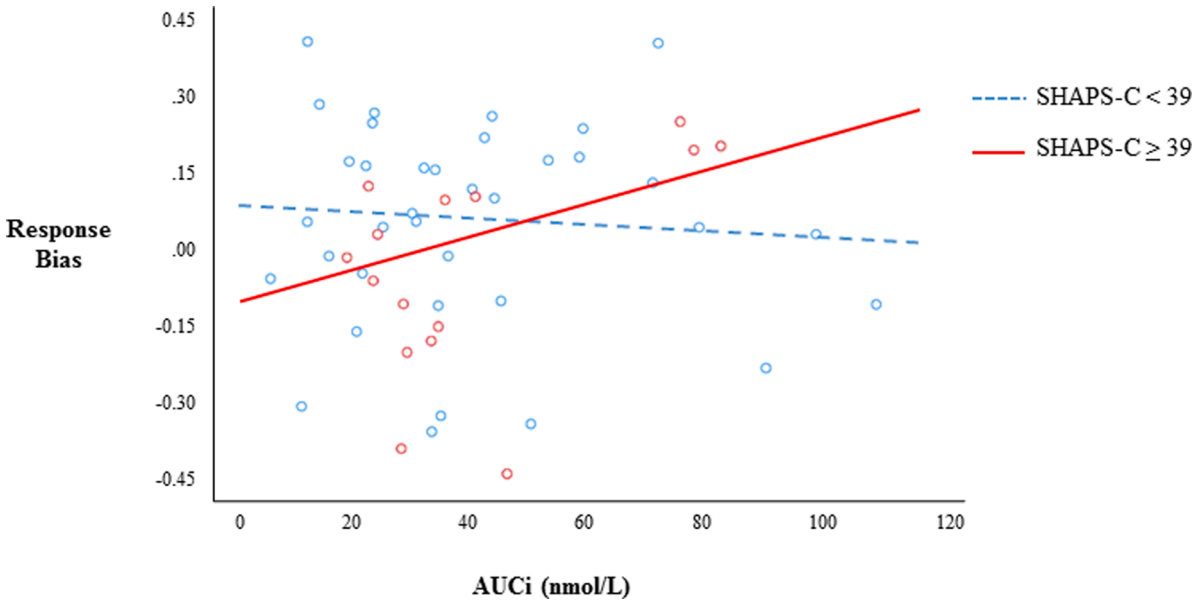

Fig. 3. Conditional Effects of AUCi on Response Bias for Johnson-Neyman Identified Regions of Significance Note. SHAPS-C = Snaith Hamilton Pleasure Scale – Clinician Version.

differences) on reward outcomes (Berghorst et al., 2013).

The current results should be interpreted in light of the following limitations. First, the sample size was small and some comparisons were under-powered. Post hoc sensitivity analyses revealed that the minimal effect size that could have been detected in the main model with a sample size of 114, 4 groups, and 3 repeated measurements was 0.21, thus our main analysis was likely sufficiently powered to detect even a small effect. However, the minimal effect size in the follow-up model examining anhedonia was 0.29. therefore, these follow-up analyses in particular should be considered preliminary until replicated in a larger sample. Second, this was a volunteer community sample and, thus, results may not generalize to patient samples. Third, our study design was cross-sectional and, thus, prospective, longitudinal studies are now required to permit conclusions regarding the causal associations between stress and reward processes, or between these processes and factors such as the age of onset or chronicity of depression.

In summary, the results of the current study suggest two primary conclusions. First, greater cortisol output in the face of stress was associated with greater reward learning over the course of the PRT in men, but not in women. These results suggest that there is sex-driven heterogeneity in the extent to which stress systems impinge upon reward-related behavior, and that this may have implications for understanding sex differences in reward-related (e.g., addiction) and threat-related (e.g., depression) psychopathology. Second, and similarly, in depressed individuals with high levels of anhedonia only, greater total release of cortisol in the face of acute stress was significantly associated with higher response bias towards rewards. These results support the primacy of anhedonia as a phenotype with both stress- and reward- related pathology. Traditional treatments for depression, including selective serotonin reuptake inhibitors (SSRIs), have shown poorer efficacy in patients with higher levels of anhedonia (McCabe et al., 2009; McMakin et al., 2013). Therefore, an important translational direction emerging from the current results is to determine whether treatments that target *both* serotonin- and norepinephrine-mediated threat processing systems, and dopamine-mediated reward processing systems, may show greater efficacy in this vulnerable group of patients.

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Supplemental Fig. 1

Response Bias on the PRT at Each Block Stratified by Depression Group and Sex

Note. SE = standard error.

CRediT authorship contribution statement

Simone Cunningham: Conceptualization, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Raegan Mazurka:** Investigation, Data curation, Writing - review & editing. **Katherine E. Wynne-Edwards:** Methodology, Writing - review & editing. **Roumen V. Milev:** Writing - review & editing. **Diego A. Pizzagalli:** Methodology, Writing - review & editing. **Sidney Kennedy:** Writing - review & editing. **Kate L. Harkness:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

Over the past three years, Dr. Diego Pizzagalli has received consulting fees from BlackThorn Therapeutics, Boehringer Ingelheim, Compass Pathway, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals as well as one honorarium from Alkermes. In addition, he has received stock options from BlackThorn Therapeutics, and research support from National Institute of Mental Health, Dana Foundation, Brain and Behavior Research Foundation, and Millennium Pharmaceuticals. Dr. Pizzagalli has a financial interest in BlackThorn Therapeutics, which has licensed the copyright to the Probabilistic Reward Task through Harvard University. Dr. Pizzagalli's interests were reviewed and are managed by McLean Hospital and Partners HealthCare in accordance with their

conflict of interest policies. No funding from these entities was used to support the current work, and all views expressed are solely those of the authors. None of the other authors have any competing interests or disclosures with regard to the work presented in this manuscript.

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