

The Function of Conditioned Fear in Reward Propensity:  
Evidence for Interrelated Approach-Avoid Systems

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**Abstract**

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Psychology

Processes related to approach and avoidance behavior have largely been investigated independently. Thus, the understanding of how reward and fear systems work together is underdeveloped. This is problematic because threat and reward are often juxtaposed in real-life. Effective navigation of one's environment requires balance between approach and avoidance. To better characterize the interplay between systems, we examined the effect of conditioned fear on reward propensity. We hypothesized that those in a fear-relevant condition will show attenuated reward propensity compared to those in a fear-irrelevant condition and that higher anhedonia and lower salivary estradiol will predict lower reward propensity, with those in a fear-relevant condition with higher anhedonia and lower salivary estradiol showing lower reward propensity than those in a fear-irrelevant condition.

Ninety-nine female participants underwent a fear conditioning paradigm and were subsequently randomized to fear-relevant or fear-irrelevant conditions of an adapted probabilistic reward task involving a differential reinforcement schedule. The key dependent variable was reward bias, operationalized as systematic preference for the response paired with the more frequent reward. A moderation effect of anhedonia, depression, anxiety, and salivary estradiol was examined.

There was a significant Group x Time interaction,  $F(2, 192) = 3.42, p = .03$ , such that those in the fear-relevant condition showed significantly higher response bias scores ( $M = .24, SD = .24$ ) as compared to those in the fear-irrelevant condition ( $M = .12, SD = .17$ );  $d = 0.39$ . In other words, conditioned distress increased the development of a bias towards identifying the ambiguous stimulus as the stimulus more frequently associated with reward. Anhedonia moderated this effect, such that higher anhedonia predicted higher response bias in the fear-relevant group but not in the fear-irrelevant group during middle learning ( $\beta = .26, t(95) = 2.52, p = .01$ ) and late learning ( $\beta = .23, t(95) = 2.10, p = .04$ ).

This study helps characterize integral mechanisms related to avoidance and approach, suggesting that conditioned fear influences reward functioning. Increased reward propensity in the presence of cues signaling low to moderate threat may promote goal-motivated behavior in order to increase the likelihood of successfully avoiding an aversive outcome. Further, there may be stronger effects of conditioned fear on reward responding in individuals with higher anhedonia, either because they develop higher levels of distress via fear conditioning or because they are more vulnerable to dysregulation to approach-avoid balance. More precise understanding of the functional relationship between fear and reward will yield avenues for effectively incorporating reward-related treatment components and targets into interventions for pathological avoidance.

## The Function of Conditioned Fear in Reward Propensity: Evidence for Interrelated Approach-Avoid Systems

Avoidance and approach behavior in humans have largely been investigated independently. Avoidance has been primarily studied in the context of an isolated fear-eliciting stimulus (e.g., Augustson & Dougher, 1997; Boyle, Roche, Dymond, & Hermans, 2015; Delgado, Jou, LeDoux, & Phelps, 2009; Dymond, Schlund, Roche, De Houwer, & Freegard, 2012) and approach in relationship to simple incentives (Forbes et al., 2010; Pizzagalli, Jahn, & O'Shea, 2005; Richards, Plate, & Ernst, 2013). Thus, the understanding of how reward and fear systems work together is underdeveloped. This is problematic because threat and reward are often juxtaposed in real life. Additionally, excessive avoidance is a primary feature of pathological anxiety (Barlow, 2001; Craske et al., 2009) and impaired approach behavior is prevalent in depression (APA, 2013; Pizzagalli, 2014). Given high rates of co-occurrence between anxiety and depression (Hankin, Spiro, Miller, & Kazis, 1999; Kessler, DuPont, Berglund, & Wittchen, 1999; Shore, Collmer, & Tatum, 1989), how approach and avoid systems work together has particular relevance for theoretical accounts of these disorders. Pathological avoidance and approach may be indicative of impairment across systems, with a shift towards favoring avoidance over approach, despite the sacrifice of potential rewards (Stein & Paulus, 2009; Trew, 2011).

Effective navigation of one's environment requires that fear and reward systems work in synchrony so that encounters with actual threat are minimized while still enabling, and, to some degree, prioritizing obtainment of reward (Lang & Bradley, 2013; Mobbs & Kim, 2015; Stein & Paulus, 2009). One must not only assess risk and severity of threat but also evaluate incentives and learn behaviors necessary for the acquisition of reward (Kirlic, Young, & Aupperle, 2017).

Indeed, simultaneous threat and reward is a common feature of rodent avoidance models (e.g., Choi & Kim, 2010; Kumar, Bhat, & Kumar, 2013; Millan & Brocco, 2003) and, rather than isolated structures in the brain, there is significant consistency and interaction across neural regions in approach and avoidance (Aupperle & Paulus, 2010; Baxter & Murray, 2002; Choi & Kim, 2010; Choi, Padmala, Spechler, & Pessoa, 2014; Delgado et al., 2009; O'Doherty, 2004). Thus, human avoidance models that incorporate both fear and reward are more ecologically valid and have greater translational utility.

In line with growing recognition of the need for integrated research on fear and reward in humans, there has been a recent surge in work focused on avoidance behavior in the context of incentives (See Kirlic, Young, & Aupperle, 2017, for a review). Experimental investigations so far have mostly involved approach-avoid conflict decision paradigms, in which the same behavior is associated with both threat and reward and a decision is required to either approach or avoid. Across approach-avoid conflict analogues, including a gamified computer task (Rattel et al., 2016) and several probability-based choice tasks (Aupperle, Sullivan, Melrose, Paulus, and Stein, 2011; Bublatzky, Alpers, & Pittig, 2017; Pittig, Brand, Pawlikowski, & Alpers, 2014; Pittig, Schulz, Craske, & Alpers, 2014; Schlund et al., 2016; Talmi, Dayan, Kiebel, Frith, & Dolan, 2009; Sheynin, Beck, Servatius, & Myers, 2014; Sheynin et al., 2016; Sierra-Mercado et al., 2015), avoidant choices are more likely when approach is associated with feared stimuli and less likely when there are higher costs of avoidance (e.g., potential rewards lost). Thus, converging evidence shows avoidance as a function of both threat and reward when it comes to decisions involving opposing potential positive and negative consequences. Further, when higher likelihood of reward choices were associated with a fear-relevant stimulus, avoidant decisions were more pronounced in individuals with higher trait anxiety (Pittig, Schulz, et al., 2014).

Dimensions of reward-related psychopathology, however, have been generally neglected in approach-avoid conflict studies thus far, overlooking the potential impact that factors such as depression and anhedonia have on avoidant decision making.

Decisions related to probability-based delivery of threat and/or reward involve risk propensity, or the tendency to make risky decisions (Buelow & Suhr, 2009; Buelow & Suhr, 2013; Gonzalez & Wu, 1999; Tversky & Kahneman, 1992). The role of individual difference variables like risk propensity may confound the impact of avoid and approach drives in conflict decision paradigms. Indeed, risk-based decision-making may not map on to overt behavioral avoidance and approach. How people appraise, learn about, and experience rewards over time, not just how they make decisions in moments of conflict, have relevance for avoidance behavior. For example, valuing a high grade, being able to learn about behaviors that lead to achieving a high grade, and experiencing pleasure when receiving a high grade, all may contribute to a person attending, rather than avoiding, class to take an exam. Given that avoidance and approach are dynamic in the real world (Mobbs & Kim, 2015; Stein & Paulus, 2009), fear effects on reward functioning have potential downstream implications for avoidance. However, transaction across fear and reward systems in these other integral processes, such as reward appraisal and contingency learning, have not been given much attention. The effect of co-occurring fear on reward functioning needs to be characterized. Further, reward-based psychopathology such as depression and anhedonia, in addition to fear-related psychopathology, need to be considered as potentially influencing this relationship.

Given its putative role in approach and acquisition of reward (e.g., Pizzagalli et al., 2014; Steele, Kumar, & Ebmeier, 2007; Forbes et al., 2006), reward propensity, or the ability to modulate behavior as a function of reward, may be particularly important when it comes to

avoidance. The probabilistic reward task (PRT) has been proposed as an objective way of characterizing reward propensity (Pizzagalli, Jahn & Shea, 2005). Patients with depression and higher anhedonia are consistently characterized by reduced reward propensity on the PRT, as compared to other samples (Pizzagalli, Iosifescu, et al., 2008; Webb et al., 2016; Boger et al., 2014). Further, a dopamine agonist impaired reward propensity on the PRT (Pizzagalli, Evins, et al., 2008). In the one study integrating fear into the PRT, a threat-of-shock stress induction decreased reward propensity and self-report anhedonia predicted greater decreases (Bogdan & Pizzagalli, 2006). The effect of conditioned fear, in which a previously neutral stimulus comes to elicit a conditional fear response through repeated association with an aversive stimulus, may also influence reward propensity. However, the effect of conditioned fear on reward propensity has not been studied. Conditioned fear has been shown, however, to increase avoidance in approach-avoid conflict decisions (Pittig et al., 2014b; Rattel et al., 2016). Pavlovian fear conditioning is considered a pathogenic mechanism of clinical anxiety and therefore may have particular relevance for models of pathological avoidance and approach behavior (Lissek et al., 2005).

Gonadal hormones, specifically estradiol, are also implicated in fear and reward-related responding and psychopathology (Creutz & Kritzer, 2004; Dreher et al., 2007; Glover, Jovanovic, & Norrholm, 2015; Maeng & Milad, 2015; Schiller, O'Hara, Rubinow, & Johnson, 2013). Women are twice as likely to experience major depression (MDD) and also twice as likely to experience an anxiety or stressor-related disorder (e.g., Breslau et al., 1998; Kessler et al., 1993; Kessler et al., 1995; McLean & Anderson, 2009; McLean, Asnaani, Litz, & Hofmann, 2011). Across human and rodent approach-avoid conflict decision studies, females exhibit greater avoidance behavior (Basso et al., 2011; Carobrez & Bertoglio, 2005; Aupperle et al.,

2011; Sheynin et al., 2014, 2016). Estradiol receptors are densely present along neural structures involved in fear and reward, including the amygdala and the striatum. In rodents, estradiol injection was associated with extinction of avoidance behavior (Rivas-Arancibia & Vazquez-Pereyra, 1994) and increased reward behavior (Jackson, Robinson, Becker, 2006; Lynch, Roth, Mickelberg, & Carroll, 2001). In humans, lower estradiol level, compared to higher estradiol level, was associated with both impaired fear extinction (Glover et al., 2013; Graham & Milad, 2013) and lower reward-related neural activity (Dreher et al., 2007). Thus, estradiol may influence individual differences in approach-avoid responding but, to our knowledge, has not been studied in humans in the context of simultaneous fear and reward.

Adding to an emerging empirical base examining integrated fear and reward processes, the present study investigated reward propensity in a conditioned fear-relevant reward task. Unlike research thus far focusing on approach-avoid conflict decision making, we examined the influence of conditioned anxiety on another construct: reward propensity. Reward propensity was captured objectively, using the PRT, which has been consistently linked to reward system neurobiology and psychopathology. Participants were randomized to one of two conditions of an adapted version of the PRT, one of which used a previously conditioned fear-stimulus (fear-relevant condition) while in the other condition the stimulus used was a similar but neutral stimulus (fear-irrelevant condition). We also examined whether related psychopathology, specifically anhedonia, trait anxiety, and depression, and circulating salivary estradiol level moderated the relationship between conditioned fear and reward propensity.

Given evidence that conditioned anxiety and threat-of-shock are related to less advantageous reward-related decisions and lower reward propensity (Pittig et al., 2014b; Bogdan & Pizzagalli, 2006), it was hypothesized that participants in the conditioned fear-relevant

condition would show attenuated reward propensity compared to those in the conditioned fear-irrelevant condition. Second, because higher anhedonia, anxiety, depression, and lower estradiol have each been associated with either decreased reward-responding, increased fear-responding, or both (e.g., Dreher et al., 2007; Duits et al., 2015; Glover, Jovanovic, & Norrholm, 2015; Pittig et al. 2014b; Pizzagalli et al., 2008a), it was hypothesized that individuals with higher anhedonia and lower salivary estradiol would show lower reward propensity, and this would be moderated by fear-relevant condition with participants in the conditioned fear-relevant condition with higher anhedonia and lower estradiol showing lower reward propensity than those in the conditioned fear-irrelevant condition with lower anhedonia and higher estradiol.

## **Method**

### **Participants**

Participants were 99 female undergraduate students at a large urban university. Participants were recruited through their introductory psychology class, in which they were offered extra credit in exchange for signing up to participate in research studies. Females who were between the ages of 18 and 45 years were eligible to enroll in the study. Participants ranged from 18-29 years of age. Thirty-nine percent of participants were Caucasian, 56% were Asian, 4% were African American, and 1% were Native Hawaiian or other Pacific Islander. See Table 1.

### **Measures**

**Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995).** The SHAPS is a 14-item self-administered instrument that measures level of anhedonia. Items are rated on a 4-point Likert scale (1 = *definitely agree*, 4 = *strongly disagree*). The four response categories are recoded into dichotomous categories (0 = *agree*, 1 = *disagree*). Total scores result from the sum

of the 14 items so that scores range from 0 to 14. A higher total SHAPS score indicates higher levels of present anhedonia. The SHAPS has demonstrated good internal consistency ( $\alpha = .91$ ) and convergent validity with other measures of mood, such as the Inventory of Depressive Symptomatology (IDS-C;  $r = .56$ ; Snaith et al., 1995), Hamilton Rating Scale for Depression ( $r = .49$ ; Snaith et al., 1995), and Quick Inventory of Depressive Symptomatology QIDS-C ( $r = .55$ ; Snaith et al., 1995). Further, group differences in SHAPS total score are found for those who score 0 or 1 vs. 2 or 3 on the pleasure/enjoyment item of the IDS-C (Snaith et al., 1995).

**Quick Inventory of Depressive Symptomatology Self-Report Version (QIDS-SR;** Rush et al., 2003). The QIDS-SR is a 16-item self-report measure that assesses symptoms and severity of depression. All items are rated on a 4-point scale with anchors that vary in accordance with the content of the question (e.g., 0 = *I do not feel sad*, 3 = *I feel sad nearly all of the time*). QIDS-SR total score is calculated by adding scores obtained for the highest score on any one of the four sleep items, the highest score obtained for any one of the four weight items, and the highest score on the two psychomotor questions to the total score of the remaining items. Total scores range from 0-27. The QIDS-SR has high internal consistency ( $\alpha = .86$ ) and good convergent validity with the 30-item Inventory of Depressive Symptomatology Self-Report IDS-SR ( $r = .96$ ) and the 24-item clinician-rated Hamilton Rating Scale for Depression ( $r = .84$ ; Rush et al., 2003).

**State-Trait Anxiety Inventory (STAI;** Spielberger, Gorsuch, & Lushen, 1983). The STAI is a 40-item self-administered measure of anxiety. The scale includes both a state anxiety (STAI-S) and trait anxiety (STAI-T) scale. Items are rated on a four-point Likert scale (1 = *not at all*, 4 = *very much so*). Total scores are calculated by summing the twenty items for the STAI-S and STAI-T separately with total scores ranging from 20-80, with higher scores indicating

greater anxiety. The STAI-T has demonstrated good test-retest reliability ( $r = .73-.87$ ; Spielberger et al., 1983) and good convergent validity with other measures of trait anxiety ( $r = .52-.80$ ; Spielberger et al. 1983).

**PTSD Scale-Self-Report for DSM-5 (PSS-SR5;** Foa & McLean, 2015). The PSS-SR-5 is a 24-item self-report measure used to assess prior trauma exposure and subsequent PTSD symptoms. Participants are asked to rate the frequency and intensity of their symptoms on a 5-point Likert scale (0 = *not at all*, 4 = *6 or more times/severe*). Total scores range from 0 – 80. An earlier version of this measure has shown good diagnostic test-retest reliability ( $r = .83$ , Foa, Cashman, Jaycox, & Perry, 1997) and was found to be highly correlated with PTSD interview measures ( $r = .78$ , Powers, Gillihan, Rosenfield, Jerud, & Foa, 2012).

**Reproductive Status and Hormones Questionnaire** (Freeman, Walker, Laughren, Miller, & Fava, 2013). This questionnaire asks basic questions about a number of reproductive and hormonal variables. Specifically, participants are asked to indicate if they are currently using hormonal contraceptives (yes/no) and, if so, to indicate the form (e.g., oral contraceptive pills, NuvaRing, contraceptive patch, DepoProvera injections, intrauterine device) and type. Participants also indicate pregnancy status, regularity/frequency of menstrual cycle, and most recent menstrual cycle.

### **Saliva Estradiol**

Salivary samples were collected using Salimetrics, LLC passive drool collection method. Salivary specimens were stored in a  $-20^{\circ}$  freezer after collection and later shipped on dry ice for analysis (University of Dresden, Germany). Hormone levels were assessed using Salimetrics luminescence immunoassay. Salivary analysis of estradiol provides a non-invasive, reliable assessment of menstrual cycle phase (Gandara, Leresche, & Mancl, 2007; Gröschl, 2008).

## **Conditioned Fear and Reward Propensity Paradigms**

**Fear conditioning task.** Using a differential fear conditioning paradigm (Garcia & Zoellner, 2017; Lau et al., 2008), an aversive brief, scream (unconditioned stimulus; US) was paired with a conditioned stimulus (CS+) but not the conditioned safety stimulus (CS-). Two photographs of neutral facial expressions from the NimStim Set of Facial Expression (Tottenham et al., 2009) served as the CS+ and CS-, the former paired and the latter unpaired with the US. The US was a loud scream, 1s and 95dB, delivered through headphones and paired with a fearful face on the computer screen (US). There were two trial phases: preacquisition and acquisition. In the preacquisition phase, six CS+ and six CS- stimuli were presented on the screen for 2s each followed by a 1.9s inter-trial interval (ITI) in order to familiarize participants with the CS+ and CS-. In the acquisition phase, twelve CS-, and twelve CS+ stimuli were presented in randomized order for 2s, with 24 1900ms ITIs. The stimuli serving as the CS+ and CS- were counterbalanced. In 75% of trials, the CS+ co-terminated with the US. A 75% contingency ratio was used given that partial reinforcement prevents extinction to the unconditioned stimulus.

**Reward learning task.** The reward task was adapted from an existing signal detection paradigm (Probabilistic Reward Task; Pizzagalli et al., 2005). At the beginning of each trial, one of the stimuli (CS+ for fear-relevant condition; CS- for fear-irrelevant condition) was presented in the center of the computer for 500ms. The stimulus was followed by either a neutral or a fearful expression made by the same face for 100ms. Each trial was terminated by either the “z” key or the “/” key, identifying whether a neutral or fearful face was presented, which was difficult to differentiate given similarity between the faces and the speed at which the face is flashed on the screen. Correct identification of one stimulus (“rich” stimulus) was rewarded three times more frequently than the other stimulus (“lean” stimulus), an asymmetrical reinforcer ratio

shown to produce a response bias. For each block, 40 correct trials were followed by reward feedback, “Correct! You won 5 cents!” while all other trials are followed by a blank screen. Which stimulus served as the “rich” and “lean” stimulus was counterbalanced: for half of the participants, correct identification of the neutral face was associated with three times more positive feedback (30 of 40) than correct identification of the fearful face (10 of 40). Overall, there were 300 trials, divided into 3 blocks of 100 trials. For the other half of participants, the contingencies were reversed. For the entire task, half of the participants earned \$5.80 and the other half \$6.20, which was counterbalanced. Throughout the task, the loud scream that was heard in the fear conditioning task was presented on 15% of trials, at random, in order to maintain distress to the key stimuli during the task (Lissek et al., 2008; Lissek et al., 2014). Performance was assessed by two variables: discriminability and response bias. Discriminability measured ability to differentiate between the two stimuli, and response bias assessed the general tendency to define an ambiguous stimulus as the stimulus more frequently associated with reward. These variables were calculated as follows:

$$\text{Response bias: } \log b = \frac{1}{2} \log \left( \frac{Rich_{correct} * Lean_{incorrect}}{Rich_{incorrect} * Lean_{correct}} \right)$$

$$\text{Discriminability: } \log b = \frac{1}{2} \log \left( \frac{Rich_{correct} * Lean_{correct}}{Rich_{incorrect} * Lean_{incorrect}} \right)$$

Excluded trials were trial reaction time (RT) shorter than 150 ms or greater than 2500 ms, and participants were excluded if, on any blocks 1-3, 20% or greater trials were excluded for RT or the ratio of valid rich trials to valid lean trials rewarded was less than 2:1 (Boger et al., 2014; Janes et al., 2015; Lawn et al., 2016; Pizzagalli et al., 2005; Pizzagalli et al., 2008). For the analyses, 15.97% of participants were excluded (fear-relevant condition:  $n = 12$ ; fear-irrelevant condition:  $n = 7$ ) and, of 300 total trials, the average number of trials excluded per participants

was 5.88 ( $SD = 4.28$ ).

## **Procedure**

Participants underwent study procedures in groups of two to eight in a computer lab, equipped with 18-inch color monitors and Windows XP software. Participants sat individually and were given their own pair of headphones. The computer lab had a total of thirteen computers and participants were placed so that they could only see their own screen and there was at least one seat between them and another participant. All stimuli were presented at a viewing distance of 18 in., approximately. The study was described as examining how individuals make associations and react to various faces. Participants then provided informed consent. Next, they completed self-report questionnaires (SHAPS, STAI, QIDS-SR, PSS-SR, Reproductive Status and Hormones Questionnaire). Participants then provided a passive drool sample. Following procedures recommended by Salimetrics, LLC, participants were told to allow saliva to pool in their mouth, and then, with their head tilted forward, to gently force saliva through a saliva collection aid into a cryovial. Next, participants completed the fear conditioning task. Then, participants were randomized to the fear-relevant or fear-irrelevant condition of the PRT. Participants were given verbal instructions and told that the aim of the task is to win as much money as possible in the form of a gift card. Upon completion of the PRT, participants were given a gift card for the amount earned in the PRT, were compensated for course credit, and were given a debriefing form.

## **Results**

Baseline means and standard deviations can be seen in Table 1, representative of a primarily psychiatrically healthy sample. As expected, prior to the manipulation, there were no

differences between the fear-relevant and fear-irrelevant PRT conditions on age, ethnicity, or any measure of psychopathology.

**Overall Effect of Fear Manipulation in Reward Propensity Task.** To examine differences across conditions in discrimination of the stimuli and also to examine our primary hypothesis that individuals in the fear-relevant condition would show an attenuated response bias on the PRT compared to those in the fear-irrelevant condition, two repeated measures analysis of variance (ANOVAs), with between-subjects variables of condition (fear-relevant, fear-irrelevant) and within-subjects variables of block (1, 2, 3) were performed.

**Discriminability.** For discriminability, as expected, a repeated measures ANOVA revealed a main effect of block,  $F(2, 194) = 81.94, p < .001$ , with participants showing lower discrimination in block 1 ( $M = 0.54; SD = 0.44$ ) than in both block 2 ( $M = 0.90; SD = 0.58; d = 0.68$ ) and block 3 ( $M = 1.04; SD = 0.60; d = 0.94$ ) and lower discrimination in block 2 than in block 3 ( $d = 0.24$ ), indicating that participants got better at discriminating between the two stimuli as they progressed through the task. The condition X block interaction effect for discrimination was not significant, indicating that participants in the fear-relevant and fear-irrelevant groups did not differ in their ability to discriminate between the two stimuli throughout the task.

**Response bias.** Overall, participants developed a response bias towards the more frequently rewarded stimulus as they progressed through the early blocks of the task,  $F(2, 192) = 3.95, p = .02$ . Participants showed an increased response bias from block 1 ( $M = 0.12; SD = 0.19$ ) to block 2 ( $M = 0.18; SD = 0.23; d = 0.32$ ). See Figure 1. The condition x block interaction was significant,  $F(2, 192) = 3.42, p = .03$ , such that, in middle learning (block 2) those in the fear-relevant condition showed significantly higher response bias scores ( $M = 0.24, SD = 0.24$ ) as

compared to those in the fear-irrelevant condition ( $M = 0.14$ ,  $SD = 0.22$ ,  $d = 0.39$ ). In early learning (block 1), however, response bias scores in the fear-relevant ( $M = 0.11$ ,  $SD = 0.22$ ) and fear-irrelevant conditions ( $M = 0.12$ ,  $SD = 0.17$ ) did not differ. Similarly, response bias scores in late learning (block 3) in the fear-relevant condition ( $M = 0.13$ ,  $SD = 0.24$ ) and fear irrelevant condition ( $M = 0.17$ ,  $SD = 0.22$ ) were not significantly different.

### **Moderating Effects of Anhedonia, Depression, and Anxiety**

To examine whether anhedonia (SHAPS), depression (QIDS), or anxiety (STAI-T), moderated the relationship between conditioned fear and reward propensity, separate regression analyses were conducted to examine anhedonia, anxiety, and depression as predictors of response bias as well as interaction effects of condition (fear-relevant and fear-irrelevant) x anhedonia (SHAPS), condition x depression (QIDS) and condition x trait-anxiety (STAI-T). Dependent variables were response bias in early learning (block 1), middle learning (block 2), and late learning (block 3).

**Anhedonia.** There was no significant main effect of anhedonia as a predictor of response bias in blocks 1, 2, or 3. In block 1, the main effect of condition and the group x anhedonia interaction effect was not significant. In block 2, however, there was a significant main effect of condition ( $\beta = .21$ ,  $t(95) = 2.14$ ,  $p = .03$ ), which was modified by a condition x anhedonia interaction, such that higher anhedonia predicted higher response bias in the fear-relevant condition ( $\beta = .26$ ,  $t(95) = 2.52$ ,  $p = .01$ ) but not in the fear-irrelevant condition. In block 3, the main effect of condition was not significant but there was a significant condition x anhedonia interaction, such that higher anhedonia predicted higher response bias in the fear-relevant condition ( $\beta = .23$ ,  $t(95) = 2.10$ ,  $p = .04$ ) but not in the fear-irrelevant condition. See Figure 2.

**Anxiety.** Level of trait anxiety was not a significant predictor of response bias in any block. Additionally, the condition x trait anxiety interaction effect was not significant for response bias in block 1, block 2, or block 3.

**Depression.** Similar to above, there was no main effect for level of depression as a predictor of response bias across the three blocks and the condition x depression interaction did not significantly predict response bias in blocks 1, 2, or 3.

### **Salivary Estradiol**

Finally, the relationship among salivary estradiol and response bias was explored across blocks. Higher salivary estradiol was modestly associated with lower response bias only in block 1 ( $r = -.21, p = .04$ ). See Table 2. Estradiol did not moderate the relationship between condition and response bias.

## **Discussion**

Conditioned fear enhanced, rather than reduced, reward propensity. After exposure to the differential reinforcement schedule, those in the fear-relevant reward task were more likely than those in the fear-irrelevant reward task to identify the ambiguous stimulus as the more frequently rewarded stimulus. In other words, participants were more sensitive to the reward contingency and more likely to modify their behavior as a function of reward in the presence of a conditioned stimulus. This effect emerged after initial exposure to the differential reinforcement schedule, in which one stimulus choice was rewarded at a higher rate than the other, and remained throughout the task, but was strongest in the middle phase of the task. The impact of conditioned fear was most pronounced for those endorsing a higher level of anhedonia. Individuals with higher anhedonia showed higher reward propensity as compared to those with lower anhedonia but only when completing the fear-relevant reward task. Thus, transaction across fear and reward domains

is further demonstrated in that anhedonia, a dimension of reward-related psychopathology, augmented the impact of conditioned fear on reward propensity. Taken together, in line with accumulating evidence suggesting synergism across fear and reward systems in approach-avoid conflict decision making, our work demonstrates this synergism in non-conflict situations.

Our findings suggest that, under certain conditions, distress may be helpful to motivate reward-directed approach behavior. Across species, anxiety has been found to have non-linear effects on performance, with low to moderate levels of anxiety facilitating performance and high levels of anxiety impairing performance (Eysenck, Derakshan, Santos, & Calvo, 2007; Kofman et al., 2006; Sung et al., 2016; Yerkes & Dodson, 1908). Given that the current sample primarily consisted of psychiatrically healthy participants, it is likely that most of the participants experienced no more than mild to moderate levels of distress in response to the CS+. Distress at this low intensity may enhance sensitivity to the differential reinforcement schedule and increase behavioral adjustment as a function of reward. Heightened vigilance associated with anxiety has been suggested to contribute to the facilitatory effects of anxiety on performance (Eysenk et al., 2007; Mogg & Bradley, 1998). Importantly, however, those in the conditioned fear-relevant and conditioned fear-irrelevant reward task conditions did not differ in their ability to correctly categorize the stimuli throughout the task. Thus, distress did not have global effects on PRT performance. The observed facilitation effect is therefore likely not capturing a general attentional or perceptual enhancement effect; instead, it reflects a domain specific effect of conditioned fear on reward propensity.

Heightened attention towards threat is a relatively robust phenomenon in clinical and non-clinical individuals experiencing anxiety (Cisler & Kostler, 2010; Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van Ijzendoorn, 2007). However, orienting towards

stimuli indicating potential reward is also integral to survival, and arousal is found to be similarly enhanced in the presence of reward-related cues (Bradley & Lang, 2007; Lang & Bradley, 2010; Lang & Bradley, 2013). Thus, unlike high threat situations when the approach system is thought to be actively inhibited, in low or moderate situations involving simultaneous reward and threat, the approach system is proposed to co-activate (Bradley, 2000; Cacioppo & Bernston, 1994). Heightened reward sensitivity may actually serve to promote successful avoidance of an aversive outcome, such as when a student studies extensively to achieve good marks and, at the same time, avoids failure (Bradley, 2000; Eysenck & Calvo, 1992; Struthers, Perry, & Menec, 2000). Thus, in the present study, increased reward propensity in the threat-relevant condition may represent adaptive up-regulation of the approach system in the context of low-consequence or low-likelihood threat. On the other hand, pathological avoidance may be related to a deficit in this reward up-regulation, which otherwise serves to buffer against avoidance and facilitate successful approach.

Unlike approach-avoid conflict paradigms, our study examined reward propensity in the presence of an ongoing threat (CS+). Importantly, conditioned anxiety was elicited but the task did not require a decision between approach and avoid. Thus, our findings relate to how people under distress learn about and acquire rewards over time. This may, in part, explain why our findings differ from direct approach-avoid conflict findings which showed that approach choices were decreased when associated with a threat (Pittig, Brand, et al., 2014; Pittig, Schulz et al., 2014; Bublatzky et al., 2017). Additionally, individual differences, such as a tendency to make risky decisions, may contribute substantially to conflict decision making but not to reward propensity (Buelow & Suhr, 2009; Buelow & Suhr, 2013; Gonzalez & Wu, 1999; Tversky & Kahneman, 1992). In terms of the one other threat-related PRT study, key differences in threat

manipulations could account for discrepant findings (Bogdan & Pizzagalli, 2006). Indeed, in Bogdan and Pizzagalli (2006), threat-shock delivery was perceived by participants as contingent on personal performance, potentially resulting in greater interference in reward-related approach learning and responding. The tipping point where distress switches from facilitating to attenuating reward functioning and contextual and threat-related factors that influence this relationship warrant further study.

Individuals in the fear-relevant reward task with higher anhedonia showed higher reward propensity. This finding is of considerable relevance to theories of anxiety and depression, suggesting that vulnerability in one system may be buffered or exacerbated by disruption in the other. Consistent with evidence that anxiety disorders tend to precede depression (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Hankin et al., 2016; Merikangas et al., 2003; Wittchen, Kessler, Pfister, Hofler, & Lieb, 2000), it is possible that distress activates an existing vulnerability to reward-system dysregulation or subclinical deficits, marked by higher levels of anhedonia. Alternatively, anhedonia may moderate susceptibility to fear acquisition, potentiating the intensity of conditioned fear acquired. Thus, participants with higher anhedonia may have acquired greater conditioned fear and, in turn, experienced higher levels of distress in the fear-relevant reward task, as compared to those with lower anhedonia and those in the fear-irrelevant condition. Thus, anhedonia, like trait anxiety (Duits et al., 2015; Hettema, Neale, & Kendler, 2001; Pittig, Schulz, et al., 2014; Zinbarg & Mohlman, 1998) and neuroticism (Khan, Jacobson, Gardner, Prescott, & Kendler, 2005; Kotov, Gamez, Schmidt, & Watson, 2010), may serve as a marker for potentiated anxious responding or increased acquisition of fear. Notably, a direct effect of anhedonia, anxiety, or depression on reward propensity was not found, which differs from findings in clinical samples (Pizzagalli, Iosifescu, et al., 2008; Webb et al., 2016; Boger et

al., 2014). However, very few participants in the current sample endorsed clinical levels of anhedonia, depression, or anxiety.

Lower estradiol was related to higher reward propensity but only in the early learning phase, when participants were first being introduced to the reward contingency. Given that lower estradiol has been previously associated with increased fear responding (Rivas-Arancibia & Vazquez-Pereyra, 1994; Jackson, Robinson, Becker, 2006; Lynch, Roth, Mickelberg, & Carroll, 2001; Glover et al., 2013), lower estradiol in our sample may be related to a slight increase in distress and related increased enhancement of reward propensity. Still, the effect found was not strong and did not carry into the middle and late phase of the PRT. Given that there appears to be an interactive effect of gonadal hormone levels during the menstrual cycle (Soni, Curran, & Kamboj, 2013), the association between gonadal hormone levels and approach-avoid responding may be more robust if estradiol-to-progesterone ratio were taken into account.

The current study was limited in several ways. The sample consisted of generally psychiatrically healthy undergraduates, limiting the ability to generalize responding to individuals with fear and reward impaired psychopathology, although the sample did report a range of anhedonia, trait anxiety, and psychopathology. Self-report and physiological (e.g., skin conductance) indices of state anxiety were not collected during fear conditioning or during the PRT. However, we used a well-established fear-conditioning task with evidence across self-report and physiological indices suggesting that the task successfully elicits conditioned distress (Garcia & Zoellner, 2017; Lau et al., 2008). Future research should compare responding in male and female participants, given findings indicating differential responding across sex in approach-avoid conflict situations (Aupperle et al., 2011). Due to feasibility, menstrual cycle phase was not standardized across participants and included participants using hormonal contraceptives,

which are associated with lower circulating levels of estradiol and progesterone (Graham & Milad, 2013; Merz et al., 2012) but may have different effects on fear and reward processes than naturally fluctuating estradiol directly related to menstrual cycle phase. Calculating menstrual cycle phase is an intensive process and including women across the menstrual cycle allowed the examination of estradiol levels as a predictor. Further, the broader inclusion of women using hormonal contraceptives increased generalizability of the findings, given high rates of female hormonal contraceptive use (Jones, Mosher, & Daniels, 2012).

Our work suggests we need to start conceptualizing avoidance in broader terms, not solely as a fear-based process. Recent approach-avoid conflict studies suggest that both fear and reward systems impact the decision to avoid. Our findings extend this work to non-conflict situations, showing that conditioned anxiety can increase reward propensity. An ecologically valid, comprehensive conceptualization of avoidance accounts for the push-pull of fear and reward. Understanding how reward processes are disrupted by anxiety will help us better understand why maladaptive avoidance develops. More precise understanding of the functional relationship between fear and reward will yield avenues for effectively incorporating reward-related treatment components and targets into interventions for pathological avoidance.

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Table 1  
*Demographics and Baseline Psychopathology*

Variable	<i>M</i>	<i>SD</i>	Range
Age (years):	19.45	1.6	18-29
Gender (% female)	100%		
Race			
Asian	55.9%		
Black or African American	4.3%		
Native Hawaiian or Other Pacific Islander	1.1%		
White	38.7%		
Criterion A Exposure (PS-SR-5, %)	35.35%		
PTSD Severity (PS-SR-5, <i>n</i> = 39)	6.62	8.12	0-25
Anhedonia (SHAPS)	1.1	1.76	0-7
Depression (QIDS-SR)	5.91	3.9	0-19
Trait Anxiety (STAI-T)	40.95	10.59	24-67
State Anxiety (STAI-S)	36.71	9.46	22-26
Estradiol Level	4.36	2.63	1.07-16.96
Hormonal Contraceptive (%)	26.3%		

*Note.* PS-SR-5 = PTSD Scale-Self-Report for DSM-5; SHAPS = Snaith-Hamilton Pleasure Scale; QIDS-SR = Quick Inventory of Depressive Symptomatology Self-Report Version; STAI-T = State-Trait Anxiety Inventory-Trait; STAI-S = State-Trait Anxiety Inventory-State.

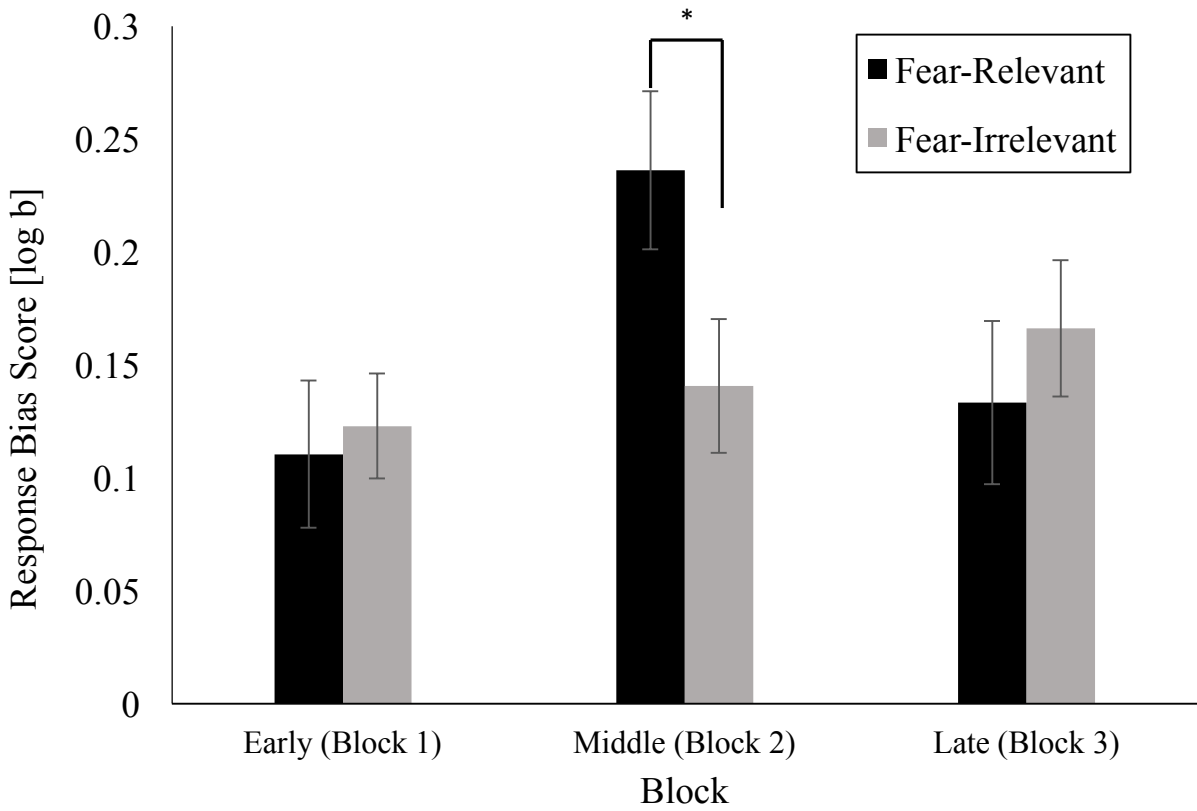
Table 2

*Association Between Response Bias, Psychopathology, and Menstrual Cycle Variables*

Variable	1.	2.	3.	4.	5.	6.	7.	8.
1. Response Bias 1	--							
2. Response Bias 2	.22*	--						
3. Response Bias 3	.19*	.51**	--					
4. Anhedonia (SHAPS)	.04	-.01	-.01	--				
5. Depression (QIDS)	.05	.11	.08	.09	--			
6. Trait Anxiety (STAI-T)	.03	.06	.07	.19	.63**	--		
7. Hormonal Contraception (0 = No; 1 = Yes)	-.18	-.05	-.08	-.14	-.02	-.10	--	
8. Salivary Estradiol	-.21*	-.16	.03	-.01	.03	-.001	.14	--

*Note.* Hormonal contraception from self-report and includes current use of oral contraceptive pills, NuvaRing, contraceptive patch, DepoProvera injections, intrauterine device. Salivary estradiol measures via passive drool. Response Bias 1 = Response bias from block 1 of the Probabilistic Reward Task; Response Bias 2 = Response bias from block 2 of the Probabilistic Reward Task; Response Bias 3 = Response bias from block 3 of the Probabilistic Reward Task; SHAPS = Snaith-Hamilton Pleasure Scale; QIDS-SR = Quick Inventory of Depressive Symptomatology Self-Report Version; STAI-T = State-Trait Anxiety Inventory-Trait. \* $p > .05$ . \*\* $p < .01$ .

**Figure 1.** Mean response bias scores in blocks 1, 2, and 3 for participants in the fear-relevant and fear-irrelevant conditions. Error bars represent standard error. \* $p < .05$ .



**Figure 2.** Mean response bias scores in block 1, 2, and 3 for participants in the fear-relevant and fear-irrelevant conditions with low ( $M-1SD$ ) anhedonia and high ( $M+1SD$ ) anhedonia.

