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SUFFOLK UNIVERSITY

THE ADDITIVE EFFECT OF SOCIAL ANXIETY DISORDER ON LEARNING IN
VETERANS WITH UNIPOLAR DEPRESSION

A DISSERTATION SUBMITTED TO
THE FACULTY OF THE COLLEGE OF ARTS AND SCIENCES
IN CANDIDACY FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

DEPARTMENT OF PSYCHOLOGY

BY

AMANDA J. KHAN

BOSTON, MASSACHUSETTS

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ABSTRACT

Differential patterns of punishment and reward responsivity are found in social anxiety disorder (SAD), which is highly comorbid with major depressive disorder (MDD). Individuals with either SAD or MDD react and respond differently to receipt of punishing and rewarding stimuli compared to healthy controls, suggesting a shared diathesis. Little is known, however, about punishment and reward responsivity in comorbid SAD and MDD compared to MDD-alone. In a sample of 80 veterans with unipolar depression, mixed model repeated measures analyses of variances (ANOVA) were conducted to explore the additive effect of co-occurring SAD and MDD on response bias (RB) in punishment and reward learning. For the punishment task, the SAD group demonstrated greater bias away from the more frequently punished stimuli and slower reaction times (RT). However, the interactions between Block and Group for RB and RT were not significant. For the reward task, no statistically significant main effects or interactions emerged, suggesting a unique effect of comorbid SAD on punishment responsivity in a depressed sample. Implications for etiology, maintenance, and treatment of comorbid SAD and MDD are reviewed as well as future directions for exploring this presentation.

Introduction

Social Anxiety Disorder (SAD) and Major Depressive Disorder (MDD) frequently co-occur, and together are associated with significant impairments (Belzer & Schneier, 2004; Moussavi et al., 2007; Stein & Stein, 2008; Zimmerman, Chelminski, & McDermut, 2002). Individuals with SAD or MDD react and respond differently to unpleasant (punishing) and pleasant (rewarding) stimuli compared to healthy controls. However, little is known about reward and punishment responding in comorbid SAD and MDD. The current study compared punishment and reward responding, as well as learning behaviors, in individuals with comorbid SAD and MDD to individuals with MDD-alone.

Clinical Disorders

SAD is characterized by an underlying motivation to avoid perceived social threat and danger leading to avoidance behaviors including escape and withdrawal from social situations (APA, 2013; Liebowitz, 1987). With a prevalence of 12%, SAD is the fourth most common psychological disorder in the United States (US; Kessler, Chiu, Demler, Merikangas, & Walters, 2005). It is well known that anxiety disorders are highly comorbid with depression. Perhaps less well-known, SAD is second only to Generalized Anxiety Disorder (GAD) in current comorbidity rate with MDD and dysthymia above all other anxiety, mood, impulse control, and substance disorders (Kessler, Chiu, Demler, Merikangas, & Walters, 2005).

MDD is marked by both increases in negative affect and decreases in positive affect (Brown, Chorpita, & Barlow, 1998). Depression consists of a complex variety of symptoms from mood changes to cognitive impairment (APA, 2013). Notably, anhedonia, the lack of reactivity and/or motivation to pursue pleasurable stimuli, is a

hallmark feature of depression that has been proposed as a potential endophenotype of this disease (APA, 2013).

Comorbidity

Comorbidity refers to the statistical association of two distinct diseases in the same individual at a rate higher than expected by chance (Lipton & Silberstein, 1994). Comorbidity extends beyond simple co-occurrence and may indicate that a condition is directly or indirectly causally involved with another. It may also indicate the existence of shared mechanisms that independently promote both diseases in an individual (Bonavita & De Simone, 2008). The statistical association may be unidirectional or bidirectional, indicative of a shared mechanism. The shared mechanism(s) can be predetermined (i.e. genetic) or acquired (environmental). These possibilities will be explored in more detail in the context of etiological models below.

Lifetime comorbidity rates between SAD and MDD range from 15% to 33% (Belzer & Shneier; 2004; Zimmerman, Chelminski, & McDermut, 2002). Comorbid SAD and MDD (SAD+MDD) has been associated with earlier onset of MDD, more frequent and longer depressive episodes, and increased risk for suicide attempts (Dalrymple & Zimmerman, 2007; Nelson et al., 2000; Stein et al., 2001). Given the level of impairment associated with comorbid depression among individuals with SAD, it is important to further our understanding of the interrelationship of these two conditions.

SAD and MDD share a number of overlapping features including low positive affect (reduced hope, reward responsivity), high levels of self-focused attention, self-critical cognitions and rumination, withdrawal or isolation and loneliness, and increased negative affect (see review: Dalrymple, 2012; Trew & Alden, 2009). As a consequence of

these characteristics, individuals with SAD or MDD often experience low self-esteem and avoid interpersonal situations. These overlapping features could be explained by simple criterion contamination in our diagnostic criteria (Spinhoven, Elzinga, van Hemert, de Rooij, & Penninx, 2014). Alternatively, these overlapping features may suggest shared mechanisms or pathways underlying both disorders.

Previous research has amassed strong evidence to suggest that SAD and MDD are comorbid rather than simply co-occurring. For example, SAD precedes MDD in approximately 70-85% of comorbid cases (Belzer & Schneier, 2004), suggesting SAD may increase vulnerability for the onset of MDD (Aune & Stiles, 2009; Grant et al., 2005; Keenan et al., 2009; Starr & Davila, 2013). One study found that behavioral avoidance, a symptom of both disorders, partially mediated the relationship between SAD and MDD (Moitra, Herbert, & Forman, 2008). The authors hypothesized that behavioral avoidance in SAD may lead to loneliness and loss of social support, thus enhancing a vulnerability to depression. However, the exact mechanisms underlying this shared phenomenology remain unclear.

Etiological Models of SAD and MDD Comorbidity

Several studies have examined the possible biological contributions to this comorbidity. Twin and family studies have revealed a shared genetic vulnerability to both diagnoses and those with first-degree relatives with SAD have higher rates of MDD, consistent with the finding that SAD precedes MDD in approximately 70-85% of comorbid cases (Belzer & Schneier, 2004; Fyer, Mannuzza, Chapman, Liebowitz, & Klein, 1993; Nelson et al., 2000). A common shared substrate through serotonergic pathways in the amygdala and brainstem has also been proposed as a possible biological

mechanism explaining the comorbidity of SAD and MDD (Pohl, Wolkow, & Clary, 1998).

Several psychological etiological models have also been proposed to explain the comorbidity between SAD and MDD. Three models will be reviewed below in order to: 1) provide a theoretical framework for understanding the etiology of comorbid SAD and MDD, and 2) examine the importance of examining punishment and reward responding, as well as learning behaviors, in the context of these models. In general, these models have considered three factors: temperament or personality, biology, and/or environmental influences on learning. Temperament or personality also includes the mood-based personality factor, affect. Affect is the experience and expression of feeling or emotion and is generally categorized into one of two types of valence: negative and positive. Negative affect refers to the extent to which an individual subjectively experiences unpleasant emotions (e.g., sadness, fear, and anger). Positive affect refers to the extent an individual subjectively experiences pleasant emotions (e.g., joy, interest, and alertness). Notably, negative and positive affect refer to both state (transient) and trait (stable; Watson, Clark, & Carey, 1988) processes. In general, the models reviewed below focus on negative and positive affect as trait constructs.

Clark and Watson (1991) proposed the tripartite structure of anxiety and depression. This model proposed that negative affect is present in both anxiety and depression, whereas physiological hyperarousal is unique to anxiety and an absence of positive affect is unique to depression. Subsequent evidence has shown underlying biological and psychological vulnerabilities that contribute to negative affect (Barlow, Chorpita, & Turovsky, 1996). However, research using factor analyses to test this theory

among those with anxiety and mood disorders has revealed that only SAD and MDD exhibit *both* increased negative affect and diminished positive affect (Brown, Chorpita, & Barlow, 1998). Unlike other anxiety disorders, Brown et al. (1998) found that SAD and MDD were the only mood and anxiety disorders associated with a lack of positive affect, and without significant differences in factor loadings between the two. These findings led to several additional studies that provide confirmatory evidence for the role of reduced positive affect in social anxiety (for review: Kashdan, 2007). For example, Kashdan (2004) found individuals with social interaction anxiety had similar self-reported hedonic deficits (e.g., positive experiences, curiosity) to depressed individuals. Taken together, the aforementioned research strongly suggests that, SAD and MDD are both marked by low positive affect and elevated negative affect. Given the association between affect and behavior it is also possible that individuals with SAD and MDD may demonstrate uniquely shared behavioral responses as a consequence of this affective pattern (Lang & Bradley, 2013). These potential behavioral responses will be discussed below.

Another etiological model that may be applied to explain SAD and MDD comorbidity is Reinforcement Sensitivity Theory (RST; Gray & McNaughton, 2000). RST is a biologically-based personality model that identifies three brain mechanisms that are proposed to underlie behavior (Gray, 1971; Gray, 1981). These mechanisms include the Fight-Flight-Freeze system (FFFS), Behavioral Inhibition System (BIS), and Behavioral Activation System (BAS). Only the BIS and BAS will be reviewed in this paper because of the relevance to theories reviewed below. BIS and BAS will be used to refer to the system, whereas Behavioral Inhibition (BI) and Activation (BA) will refer to the temperament or personality trait involved in the system.

Behavioral Inhibition (BI) is a temperamental style that guides behaviors in punishing, non-rewarding or novel situations. Given the potential threat in these situations, BI involves the tendency to avoid or withdraw from situations and increase attention, or vigilance, to the environment (Gray, 1971; Gray, 1981). In contrast, Behavioral Activation (BA) is sensitive to reward cues and guides behaviors in rewarding situations. Thus, BA involves the tendency to approach situations, driving reward-seeking behavior and feelings of elation. RST posits that although individuals are predisposed to certain levels of BI and BA by genetic and biological factors, these can be modified by learning through environmental experiences. Both BI and BA levels are associated with psychopathology (Johnson, Turner, & Iwata, 2003; Pickering & Gray, 1999).

Elevated BI is considered to be a risk factor for the development of anxiety disorders, particularly SAD (Beidel & Turner, 2007). Research has demonstrated that the relationship between BI and SAD is stronger than the relationship between BI and any other anxiety disorder (Biederman et al. 2001; Chronis-Tuscano et al. 2009; McDermott et al., 2009). Elevated BI is also a risk factor for, and related to, depression generally (Caspi et al., 1996, Gladstone & Parker, 2006; Kasch, Rottenberg, Arnow, & Gotlib, 2002; Muris et al., 2003; Sportel et al., 2011) and anhedonic depression specifically (Kasch et al., 2002; Meyer et al., 1999, Hundt et al., 2007). Interestingly, in both prospective and retrospective analyses, SAD fully mediated the relationship between BI and MDD (Beesdo et al., 2007; Gladstone & Parker, 2006), suggesting a pathway to comorbidity by which elevated BI contributes to SAD, which in turn increases avoidance and subsequently contributes to the development of MDD. Taken together, these findings

suggest that BI is a biologically-based temperamental construct underlying both SAD and MDD. Thus, it may be that individuals with comorbid SAD and MDD demonstrate greater hypervigilance to threatening stimuli and avoidance of punishment than those with SAD or MDD alone.

An additional etiological model explaining comorbid SAD and MDD was developed in developmental psychology. Developmental frameworks merge both development and clinical psychology by examining pathology, risk factors, and resilience over the life span. The Cumulative Interpersonal Risk (CIR; Epkins & Heckler, 2011) theory identifies both core (biological) and specific (interpersonal) risk factors in the development of both SAD and/or MDD. CIR posits that the cumulative risk, or the effect of having multiple sources of risk and their interactions, explains the development of comorbid SAD and MDD. To test their theory, Epkins and Heckler (2011) reviewed the extant literature to identify core factors (including temperament, genetics, and parent psychopathology), and specific interpersonal factors (including parent-child attachment, social skills deficits, parenting, peer acceptance and rejection, friendships, loneliness, and peer victimization) associated with SAD and MDD. In this review they distinguished between risk factors, or variables shown to increase the likelihood of developing SAD and MDD, and correlates, or variables simply associated with the presentation of SAD and MDD.

Epkins and Heckler (2011) found that SAD and MDD share 16 correlates and eight risk factors. Two findings were particularly notable because of their relevance to the current study. First, there was an interpersonal theme among the shared correlates and risk factors, suggesting the importance of interpersonal variables functioning in both

SAD and MDD. Second, there was evidence for elevated BI as both a shared risk factor and shared correlate, supporting the RST model of MDD-SAD comorbidity. Importantly, the model emphasized that these risk factors and correlates add up and interact with each other to increase the likelihood of developing SAD and MDD.

In sum, there are several etiological models explaining the comorbidity of SAD and MDD. Across these models, certain temperament factors are consistently implicated in each disorder and comorbid SAD and MDD. More specifically, these models suggest decreased positive affect, increased negative affect, and elevated behavioral inhibition are transdiagnostic factors contributing to both disorders, perhaps reflecting a shared diathesis. It is possible that these transdiagnostic factors may also lead to impairments in the way individuals with both disorders react and respond to and subsequently learn from the environment.

Implications of Etiological Models for Understanding Reactivity and Responsivity to Reward and Punishment

Temperament reflects a person's predisposition to react and respond a certain way (Rothbart, Ahadi, & Evans 2000). Thus, aberrant levels of positive and negative affect and BI likely reflect atypical reactivity and responsivity to certain types of environmental stimuli. Reactivity refers to the autonomic arousal and subjective emotional experience that occur following exposure to a stimulus (Lang, 1978; 2014). Said differently, it is how we feel and how our body reacts in response to something. ***Reactivity*** is often involuntary; for example, increased heart rate upon seeing a snake or feeling sad when a loved one dies. ***Responsivity***, or responsiveness, refers to the behavioral response(s) that occur following exposure to a stimulus (Merriam-Webster; Robinson, Moeller, &

Fetterman, 2010). In other words, it is what we do or how we choose to respond to something. Responsivity is often voluntary; for example, picking up money spotted on the street or using feedback to fix a dissertation. Notably, reactivity influences responsivity; how reactive a person is often influences how they behave (Carver and White, 1994). For example, greater unpleasantness and autonomic arousal from receiving negative feedback would likely increase the likelihood of avoiding a situation that might elicit negative feedback. Similarly, decreased pleasure from social interactions would likely reduce the likelihood of approaching a social event.

Using these definitions to interpret the etiological models reviewed above, the decreased positive affect found in MDD and SAD may suggest decreased reactivity to positively valenced or rewarding stimuli in these groups. Increased negative affect may imply increased reactivity to aversive or punishing stimuli. It is possible that the altered reactivity to rewarding and punishing stimuli proposed by the tripartite model could also affect responsivity to these types of stimuli (i.e., increased avoidance of negative stimuli and decreased approach behavior towards positive stimuli). This interpretation is consistent with RST theory, which suggests individuals with high levels of BI are hypervigilant of and more likely to avoid punishing stimuli. Thus, all three transdiagnostic factors (NA, PA, and BI) may support greater punishment responsivity and diminished reward responsivity in individuals with MDD and SAD. Since these factors may be compounded in comorbid SAD and MDD, these effects on responsivity could be more pronounced in this comorbid group. This altered responsivity may influence subsequent learning, whereby individuals with comorbid SAD and MDD show enhanced punishment-based learning and reduced reward-based learning.

Learning

Learning is the acquisition of knowledge or skills through experience (Fine & Jacobs, 2002; Merriam-Webster; Wright & Fitzgerald, 2001). Skinner's operant conditioning is one of the hallmark theories of learning. In operant conditioning, reinforcement or punishment are provided in order to elicit a certain behavioral change or response (Skinner, 1938). Reinforcement functions to increase behavior, whereas punishment functions to decrease behavior (Rescorla & Wagner, 1972; Schacter, Gilbert, & Wegner, 2011). Operant conditioning is further classified as positive or negative. Positive reinforcement involves the addition of a rewarding stimulus (e.g., winning money, praise) whereas negative reinforcement involves the removal of an aversive stimulus (e.g., loud noise, day off of work). Positive punishment involves adding an aversive stimulus (e.g., yelling, detention) and negative punishment involves removing something pleasing (e.g., removal of TV privileges, losing money). By definition then, a rewarding stimulus is something pleasant that increases behavior and a punishing stimulus is something unpleasant or aversive that decreases behavior.

Learning through operant conditioning has been well studied using various methodologies. One particular technique has been the use of probabilistic reinforcement tasks, which are grounded in signal detection theory (SDT; Macmillan & Creelman, 1991; McCarthy, 1991; Pizzagalli et al., 2005). SDT aims to understand decision-making when uncertainty is present. In other words, what leads an individual to make a decision when posed with the question of whether ambiguous stimulus A or B was present? For example, when presented with one of two virtually identical cartoon faces with two differing yet indiscriminate mouth lengths, how does a person determine if it was face A

instead of face B? To answer this question, SDT provides a mathematical formulation that considers several variables.

Decisions made when confronted with ambiguity can be driven by both the ability to distinguish stimuli and a general tendency to respond a certain way. In order to determine which explanation is applicable, it is important to measure these separately (Stanislaw & Todorov, 1999). There are three primary outcome variables generally derived from signal detection based tasks: reaction time, discriminability, and response bias (Liverant et al., 2014; Pizzagalli et al., 2005, 2008; Santesso et al., 2008). Reaction time (RT) is how long it takes for the participant to respond with a decision (stimulus A or B). Longer reaction times typically suggest more information processing. Discriminability, sometimes referred to as accuracy or sensitivity, refers to the ability to differentiate between the presented stimuli. In contrast, bias is the tendency to respond a certain way irrespective of what is accurate. Therefore, in order to tease apart the reasons why a person makes a certain decision, it is to our advantage and necessary to use tasks that differentiate between accuracy and bias.

Response bias (RB) in this context refers to the preference a respondent might express for the less frequently punished or more frequently rewarded stimulus. For example, participants who are more reactive to punishment will likely demonstrate a response bias by failing to correctly identify a stimulus if it has been frequently associated with punishment. Change in RB across Blocks reflects the degree to which behavior is moderated by feedback/conditioning history. Thus, punishment and reward learning can be operationalized in SDT tasks as the *change* in RB across a series of stimulus presentations (Pizzagalli et al., 2005; Santesso et al., 2008). Punishment

learning is therefore defined as the modulation of behaviors based on punishment history. Reward learning is defined as the modulation of behaviors based on reward history. The current study manipulated punishment and reinforcement schedule (i.e., frequency of receipt of punishments and rewards) to examine punishment and reward responsivity and learning in comorbid SAD and MDD compared to each disorder alone.

Reinforcement and punishment schedules typically fall into two categories: continuous or intermittent. Continuous schedules involve delivering reinforcement or punishment every single time a desired behavior or response occurs. Intermittent schedules involve delivering reinforcement or punishment after some, but not all responses. The current study used an intermittent schedule, which is more resistant to extinction, ecologically valid, and encourages continued behavior more than a predictable continuous schedule.

In probabilistic learning tasks that use intermittent schedule, trials that provide feedback are based on an asymmetrical reinforcer/punisher ratio. An asymmetrical ratio is the relative number of reinforcers/punishers for a given correct/incorrect response compared to another correct/incorrect response. For example, incorrect answers for stimulus A may be punished more often than incorrect responses for stimulus B. Asymmetrical feedback (punishment, reward) frequency leads to trial-by-trial bias adjustments that yield stable response estimates (Friedman, Carterette, Nakatani, & Ahumada, 1968; Johnstone & Alsop, 2000; McCarthy & Davidson, 1979). An asymmetrical reinforcer/punisher ratio is thus required to produce a response bias. When completing tasks of this type, healthy participants reliably develop a response bias or *preference* for the stimulus that is less frequently punished (Santesso et al., 2008) or more

frequently reinforced (Pizzagalli, Jahn, & O'Shea, 2005). The current study utilized a probabilistic SDT task to examine compare RB and learning during punishment and reward tasks between individuals with MDD and SAD+MDD.

Punishment Learning

Social Anxiety Disorder. Research on responsivity to punishment and punishment learning in SAD is limited. However, because learning is influenced by multiple behavioral and cognitive processes, including attention, working memory, interpretation, encoding/storage, and retrieval of information (Ellis, 1973), research examining these constructs in those diagnosed with SAD can be helpful in informing specific hypotheses about the potential nature of alterations in punishment responsivity and learning in SAD.

The DSM characterizes SAD as a fear of and hypersensitivity to negative evaluation. This fear is “out of proportion to the actual threat of the social situation” and is driven by expectations or anticipations of potential future harm (Beck, Emery, & Greenberg, 1985; DSM-V, 2014, p. 203). In SAD, social situations are perceived as threatening because there is a possibility of aversive or punishing social outcomes (i.e. humiliation, rejection). For example, a person with SAD may avoid a party because there is a possibility (threat) of rejection (social punishment). Interestingly, studies using self-report measures demonstrate that individuals with SAD report heightened reactivity and responsivity to both social and non-social (e.g., losing money) punishment (see Herbert, Rheingold, & Brandsma, 2010; Hofmann & Bitran, 2007). A recent study found self-reported heightened reactivity and responsivity to all punishment predicted SAD symptom severity above and beyond self-reported maladaptive behavior patterns and

parental attachment (Kimbrel, Cobb, Mitchell, Hundt, & Nelson-Gray, 2008). These findings suggest that there may be different patterns of reactivity and responding to both social and non-social punishment in SAD.

Experimental studies of SAD have demonstrated behavioral responses indicating sensitivity to threat in attention, interpretation, and memory. Briefly, individuals with SAD show greater attention (i.e., longer looking periods) and slower response times towards aversive/threatening social and non-social stimuli (Gamble & Rapee, 2010; Hope, Rapee, Heimberg, & Dombeck, 1990; Mattia, Heimberg, & Hope, 1993; Musa, Lepine, Clark, Mansell, & Ehlers, 2003). Individuals with SAD are also more likely to interpret neutral or ambiguous stimuli, both social and non-social, as aversive or threatening (Amir, Beard, & Przeworski, 2005; Eysenck, Mogg, May, Richards, & Mathews, 1991; Foa, Franklin, Perry, & Herbert, 1996; Richards, Reynolds, & French, 1993; Stopa & Clark, 2000; Winton, Clark, & Edelmann, 1995). Furthermore, individuals with SAD interpret even mildly aversive social stimuli as more catastrophic and costly (Foa et al., 1996; Stopa & Clark, 2000). Socially anxious individuals also memorize aversive social stimuli faster and with less practice, selectively recall negative information, and are better at implicitly remembering negative social stimuli (Amir, Bower, Briks, & Freshman, 2003; Amir, Foa, & Coles, 2000; Foa, Gilboa-Schechtman, Amir, & Freshman, 2000; O'Banion & Arkowitz, 1997). Collectively, these studies indicate aversive social stimuli may be more salient in individuals with SAD compared to healthy individuals. They also provide some evidence for increased attention to aversive non-social stimuli. This attentional bias could potentially facilitate the acquisition of punishment-based learning in this group.

To date, there have been two studies that have directly examined punishment using operant conditioning paradigms among individuals with SAD (Abraham & Hermann, 2015; DeVido et al., 2009). This is an important area of study as it can help us understand how individuals with SAD modify their behavior in response to punishment, providing an experimental analog for expected behavioral change in response to punishment in daily life. Abraham and Hermann (2015) used different reward versus punishment contingencies to examine whether individuals with and without social anxiety learned better from reward or punishment. Participants were presented with a task designed to have them learn which of two neutral human faces was associated with more positive feedback. There were three pairs (A/B, C/D, E/F) of neutral faces in total and feedback was provided on an asymmetrical reinforce/punisher ratio. In other words, unbeknownst to participants, each pair of neutral faces (stimulus) was associated with differing probabilities for receiving a social reward (happy face) or social punishment (angry face). Hence, each stimulus was associated with both positive reinforcement and positive punishment (i.e., affective faces). For example, one pair of faces, A/B, was 80/20; this meant that selecting face A resulted in reward 80% of the time and punishment 20% of the time whereas selecting face B resulted in reward 20% of the time and punishment 80% of the time. This pairing should be easier to discriminate than one with a more subtle contingency, such as 60/40. Participants were presented with these contingencies in a “learning phase” and were then tested to determine their learning in response to reward versus punishment in a “test phase.” In other words, in the test phase, no reinforcement or punishment was provided; instead, the authors assessed whether individuals were more likely to select one face in a pair (e.g., A or B, C or D, E or F). If

participants selected a face within a pair more frequently in the test phase, this suggested that they had learned the contingency (i.e. Face A is the more rewarded face and thus the correct response). Therefore, learning, in this study, was indexed by the participant's accuracy, not their response bias.

In the learning phase, socially anxious participants were more accurate (i.e. higher discriminability) at learning contingencies for ambiguous stimuli (i.e. 60/40 pair) than non-socially anxious participants. This between group difference was not found for the two other pairs of faces that had more distinguishable contingencies. In the test phase, although the groups did not differ in how much they chose the most positive reinforced stimulus, they did differ in how much they avoided the most punished stimulus. More specifically, socially anxious individuals avoided the most punished stimulus (80% of trials) significantly more than those without social anxiety. The authors concluded highly socially anxious individuals are more accurate at learning contingencies under ambiguous situations and demonstrate enhanced avoidance of punished stimuli. These findings give some initial support to the hypothesis of increased socially-based punishment learning in SAD and further support the possibility of increased salience of social reward and punishment.

There are several notable limitations of this study that should be mentioned. First, the study did not use a clinical sample and thus the true effect of SAD on learning and any possible additional effect of comorbidity could not be examined. Furthermore, the study used a mixed incentive paradigm, which reflects the participant's responsiveness to punishment relative to reward. Specifically, each stimulus was both punished *and* rewarded therefore participants' response was based on the degree of punishment given

the possible degree of reward and vice versa. Therefore, the specific impact of punishment on responsivity was undetectable since it was conflated with the impact of reward.

One study has examined the effects of non-social punishment in those with SAD. DeVido and colleagues (2009) compared individuals with GAD, SAD, and healthy controls using a computerized non-social learning task that involved positive reinforcement and punishment. Specifically, the task assigned different point values to different stimuli and measured whether the participants accurately chose the stimuli associated with winning the *most* or losing the *least* points. In other words, the primary dependent variable was accuracy in choosing the superior object over the more inferior object. Therefore, error rates (i.e., inaccuracy) were examined and defined as instances when the inferior object was chosen instead of the superior object.

The stimuli used were images of different objects (house, cup, duck, pineapple, necklace, etc.). In the task, objects were randomly assigned a value that varied by participant (i.e., shoe is -900, duck is 700). One pair of objects was presented at a time. There were three conditions: reward only, punishment only, and mixed reward and punishment. Similar to the current study design, reward was both point gains (e.g., 100, 300, etc.) and feedback (“You have WON 100 points”). Likewise, punishment was both point deduction (e.g., -100, -300, etc.) and feedback (“You have LOST 100 points”). In the reward condition, both objects in a pair were associated with reward, albeit different values (e.g. shoe is 100, fork is 300). In the punishment condition, both objects in a pair were associated with punishment, albeit different values (e.g., house -100, raccoon -900).

In the reward and punishment condition, one object was associated with reward (door 700) and the other was associated with punishment (fork -500).

DeVido and colleagues (2009) found that the GAD group made significantly more errors across all conditions than SAD and control groups. Examining only the clinical participants, the authors also reported those with GAD and comorbid SAD made more errors than those with SAD alone. Notably, no interaction effects were found for the different reward and punishment conditions. One possible interpretation of these findings germane to the current study is that, in contrast to the findings from Abraham and Hermann (2015), there is no difference between SAD and healthy controls in their ability to accurately select a more rewarded or punished stimulus.

However, there are several methodological features that may limit the implications of these findings. First, the authors used points instead of actual money as a reinforcer/punisher, raising questions about the salience of the reward and punishment feedback. Second, half of the GAD comparison group also met criteria for comorbid SAD, leaving only 9 participants with GAD alone. Given this small sample size, it is unclear whether the study was appropriately powered to examine comorbidity and SAD. Finally, the exclusion criteria of the study potentially limits its generalizability. Participants who met criteria for any co-occurring anxiety disorder (except SAD & GAD) were excluded from the study and despite the high rates of comorbidity among anxiety and depression, only one participant in the study met criteria for comorbid MDD. Participants were also excluded if they were on psychiatric medications.

Building on the findings and limitations of the two previous studies examining punishment responsivity in SAD reviewed above, the proposed study investigated

responsivity to, and learning from, receipt of punishment alone, allowing us to isolate the unique impact of punishment in these domains. Furthermore, unlike the tasks used in the studies conducted by Hermann and Abraham (2015) and Devido et al. (2009), the task in the current study differentiates stimulus (accuracy) from tendency to respond a certain way (bias). As previously mentioned, separating accuracy from bias is critical to assess the unique factors that contribute to, or inhibit, learning. The current study also advances the current literature by using non-social punishment to explore the presence of generalized changes in punishment-based responsivity and learning. In addition, the current study has greater external validity through use of a relatively large clinical sample and inclusion of participants on psychiatric medication. Lastly, this study is the first to investigate the effect of SAD in conjunction with MDD on punishment learning, which is important given the common co-occurrence of these two disorders.

Major Depressive Disorder. A large body of research indicates that MDD is associated with biased processing of negative information and hyperreactivity (i.e., increased autonomic arousal and subjective emotional experience) to punishment (see reviews: Bylsma, Morris, & Rottenberg, 2007; Eshel & Rosier, 2010). However, findings regarding responsivity, or the behavioral response, to punishment in MDD are mixed. Specifically, some studies have demonstrated hyperresponsivity to punishment (Beats et al., 1996; Beevers et al., 2013; Elliott et al., 1996; Murphy et al., 2003; Taylor Tavares et al., 2007) among those with MDD, others have found hyporesponsivity to punishment (Elliott et al., 1997; Holmes & Pizzagalli, 2007; Steele, Kumar, & Ebmeier, 2007), while others have reported no difference in responsivity to punishment among those diagnosed with MDD compared to controls (Henriques, Glowacki, & Davidson, 1994; Henriques &

Davidson, 2000; Must et al., 2006; Robinson et al., 2012; Santesso et al., 2008; Shah, O'Carroll, Rogers, Moffoot, & Ebmeier, 1999). These responsivity findings are reviewed in detail below (see Table 1 below).

Several studies have reported increased responsivity to punishment in depressed individuals (Beats et al., 1996; Beevers et al., 2013; Elliott et al., 1996; Murphy et al., 2003; Taylor Tavares et al., 2007). However, none of these studies examined responsivity to punishment using SDT tasks. Instead, most of these studies used various neuropsychological and gambling tasks to assess responsivity to punishment (e.g., Beats et al., 1996; Elliott et al., 1996; Murphy et al., 2003; Taylor Tavares et al., 2007). Unfortunately, there are several drawbacks to using neuropsychological tests in this context. First, and most importantly, neuropsychological assessments by nature are designed to characterize cognitive domains (executive functioning, memory, etc.) and, therefore, are not validated to specifically assess punishment responsivity and learning unlike SDT tasks, which have been designed with the sole purpose of assessment of responsivity and learning (e.g., Pizzagalli et al., 2005, 2008, 2009; see Stanislaw & Todorov, 1999). Any alternate conclusions drawn from neuropsychological performance beyond abnormalities in cognitive domains is likely speculative at best. Another limitation of using neuropsychological tests is that they only yield information about the accuracy of a particular response, such as total accuracy (number of correct responses), error rates (number of incorrect responses), maintenance failure rates (number of errors following learning of a contingency), and perseverance rates (number of errors after the contingency changes). Thus, these neuropsychological studies cannot disentangle accuracy from bias (i.e., a key index of punishment learning). Therefore, findings from

these neuropsychological studies are difficult to interpret as they may reflect decreased executive functioning abilities (planning, organization, set-shifting, etc.; see review: Synder, 2013) among those diagnosed with MDD rather than specific deficits in

Table 1. *Punishment Responsivity in Depression*

<u>Study</u>	<u>Sample</u>	<u>Task</u>	<u>Finding</u>	<u>Comorbidity & Medication</u>
Beats et al., 1996	Clinical	Neuropsychological	Hyperresponsivity	U/A
Elliot et al., 1996	Clinical	Neuropsychological	Hyperresponsivity	Comorbidity N/A; included medication
Murphy et al., 2003	Clinical	Neuropsychological	Hyperresponsivity	Comorbidity N/A; included medication
Taylor Tavares et al., 2007	Clinical	Neuropsychological	Hyperresponsivity	Excluded both
Elliot et al., 1997	Clinical	Neuropsychological	Hyporesponsivity	Included both
Holmes & Pizzagalli, 2007	Non-clinical	Neuropsychological	Hyporesponsivity	U/A
Steele, Kumar, & Ebmeier, 2007	Clinical	Neuropsychological	Hyporesponsivity	Excluded comorbidity; included medication
Herzallah et al., 2013	Clinical	Category Learning	Hyporesponsivity	Included both
Henriques, Glowacki, & Davison, 1994	Non-clinical	SDT	No difference	U/A

Henriques & Davidson, 2000	Clinical	SDT	No difference	Excluded both
Must et al., 2006	Clinical	Neuropsychological	No difference	Included both
Robinson et al., 2012	Clinical	Reversal Learning	No difference	Included
				comorbidity;
				excluded
				medication
Santesso et al., 2008	Clinical	SDT	No difference	Comorbidity U/A; excluded medication
Shah et al., 1999	Clinical	Neuropsychological	No difference	Included both

Note. SDT = Signal Detection Task. U/A = Information was not available.

punishment responsivity and learning. Another major problem in this literature is the absence of a shared definition of hyperresponsivity across studies. Some researchers interpret errors (i.e., inaccuracy) after receipt of punishment as an indication of hyperresponsivity to punishment while others interpret this result as evidence of hyporesponsivity (Elliott et al., 1997; Holmes & Pizzagalli, 2007; Steele, Kumar, & Ebmeier, 2007).

One study, which used a learning, rather than a traditional neuropsychological, task demonstrated punishment hyporesponsivity in a sample of individuals diagnosed with MDD. Herzellah and colleagues (2013) compared controls to medicated (SSRI) individuals with MDD and medication naïve individuals with MDD on a computerized category-learning task. Participants viewed ambiguous images and were instructed to learn which stimulus predicted rainy or sunny weather. Similar to the current study, correct classification was rewarded with an increase in points and positive feedback and

incorrect classification was punished with a loss of points and negative feedback; conditioning was provided on an intermittent schedule. Participants with an MDD diagnosis who were being treated with SSRIs were significantly less accurate in their responses, which lead the authors to conclude that this group less responsive to punishment than the un-medicated depressed individuals and controls. However, because this study relied on accuracy (ability to distinguish between stimuli) as an outcome measure and did not measure bias (tendency to respond based on conditioning), it is unclear as to whether the current findings indicate blunted punishment responsivity in depressed individuals using SSRIs. Further, although the authors did not exclude participants with comorbid anxiety, they failed to provide any information on the number of participants with a comorbid anxiety disorder and they did not examine the impact of comorbidity on learning.

Using a SDT task similar to the one used in the current study, Henriques and colleagues (1994) compared dysphoric and non-dysphoric individuals to assess responses to punishment. The authors found no differences between the two groups in response bias during neutral or punishment. However, neither comorbidity nor psychiatric medication usage was assessed in this study. These findings were replicated comparing clinically depressed individuals to healthy controls in a later study (Henriques & Davidson, 2000). Using the same probabilistic punishment learning task as the current study, Santesso and colleagues (2008) compared individuals with remitted MDD to controls. The authors examined both performance on the punishment task and electrophysiological responses during the task. Electrophysical response was conceptualized as an index physiological sensitivity to punishment (i.e., reactivity). Group differences in reactivity were found

such that individuals with remitted MDD exhibited elevated physiological reactivity (i.e., electroencephalogram (EEG)) compared to controls. The authors posited this increase was indicative of hypersensitivity to punishment. However, they failed to find group differences in any behavioral index in the SDT (discriminability, response bias, reaction time). In other words, the ability to differentiate between stimuli, tendency to avoid punishment, and ability to learn associations was similar for individuals previously depressed and never depressed, respectively. Notably, the authors did not report comorbid diagnoses in the sample, and participants were excluded for psychiatric medication use.

In sum, it remains unclear whether there are differences in punishment responsivity and learning in MDD. Different participant characteristics (e.g., MDD, MDD on SSRIs, dysphoria) and tasks across studies have yielded mixed findings. It also is possible that these inconsistent results may be due to failure to assess and control for psychiatric medication status, comorbidity, and severity and duration of depression in these studies. The current study aimed to clarify the existing findings by using a signal detection task specifically designed to assess accuracy as well as bias to punishment in a large representative sample of depressed veterans. As previously reviewed, the separation of bias from accuracy is critical to assess the effect of changes in response based on receipt of punishment irrespective of accuracy with a given task. Moreover, the current investigation aimed to isolate the effect of comorbid SAD on punishment learning in MDD.

Post-Traumatic Stress Disorder. The current study used a sample of Veteran participants. Lifetime prevalence rate of PTSD in Veterans in the US ranges from 6-31%

(Richardson, Frueh, Acierno, 2010). Current comorbidity rates of PTSD and MDD across military and civilian samples is approximately 50% (Rytwinski, Scur, Feeny, & Youngstrom, 2013), and Veterans meeting criteria for PTSD are significantly more likely to meet criteria for SAD (15%-72%; Orsillo et al., 1996). It is, thus, germane to briefly review the literature on punishment learning in PTSD.

Two studies have examined punishment learning in PTSD (Sawyer et al., 2016; Dretsch, Thiel, Athy, Born, & Prue-Owens, 2013). Using the same punishment task as the current study, Sawyer and colleagues (2016) compared Veterans with and without PTSD. The authors found increased response bias away from the more frequently punished stimuli in PTSD versus controls. In contrast, control participants showed a decreased responsivity to punishment, suggesting it may be adaptive to persist with accurate responding in the face of intermittent punishment. Notably, individuals in the PTSD group with comorbid depression and on psychiatric medications were not excluded from this study, and the potential impact of these factors on punishment learning was not examined. Thus, it is impossible to determine whether the results were influenced by PTSD status, co-occurring depression, or psychiatric medications.

Dretsch, Thiel, Athy, Born, and Prue-Owens (2013) used the Iowa Gambling Task, a monetary decision-making task, to examine reward and punishment learning among active duty soldiers with PTSD compared to controls. Soldiers with PTSD demonstrated elevated responsivity to immediate punishment (monetary loss) and decreased responsivity to delayed reward. In contrast, Myers and colleagues (2012) found no differences in punishment learning between Veterans with severe PTSD symptoms and few to no PTSD symptoms using a probabilistic classification task. Together, these

preliminary findings may suggest increased responsivity to punishment in PTSD, but further exploration is still needed to confirm this. Details on how PTSD comorbidity was handled are reviewed in the methods section.

Summary of Punishment Learning. Responsivity to punishment and the ability to learn, or modify behaviors, based on receipt of punishment is an important aspect of life. For example, a student may learn that studying is important after receiving a bad grade on an exam. As important as learning from punishment is, it is also important to persist with adaptive responding in the face of intermittent or unpredictable punishment. As humans, we receive punishment on a daily basis in various forms (e.g., criticism, rejection, and loss). Yet, we continue to engage in adaptive behaviors and approach our goals despite the possibility of punishment. This is consistent with the findings from Sawyer and colleagues (2016). If the ability to continue to respond adaptively in the face of punishment is impaired, we may end up living a life that is limited and unfulfilling.

One population particularly vulnerable to this outcome is individuals with comorbid SAD and MDD. Both SAD and MDD are associated with decreased positive affect and increased negative affect and BI. All three of these factors encourage avoidant responses to aversive stimuli or punishment. In comorbid SAD and MDD, these factors may be compounded and present as enhanced avoidance to punishment, perhaps generalizing beyond just social stimuli. However, no study has examined punishment responsivity and/or learning in this comorbid group. Much of the research into this and related topics has been done with these disorders individually.

Studies consistently find that individuals with SAD demonstrate attentional biases towards punishing social and non-social stimuli and propensities to interpret stimuli as

aversive and remember aversive stimuli. This heightened salience likely facilitates improved learning of punishing stimuli, possibly even for non-social stimuli. There is some initial evidence of increased punishment learning in social anxiety and increased avoidance of punishment compared to controls (Abraham & Hermann, 2015). However, whether this pattern extends to non-social stimuli is still unclear.

In MDD, there are generally mixed findings of punishment responsivity and learning across different types of methodologies, dependent variables, and samples (e.g., clinical vs. non-clinical, comorbidity, medication). However, the studies that have used tasks that measure response bias and have found no differences in punishment responsivity and learning in MDD compared to controls. In other words, individuals with depression are not more avoidant of punishment than those without depression. Although replication is needed to confirm these findings, it may be that depressed individuals demonstrate adaptive responding via continued approach behaviors in the face of punishment. However, if avoidant responsivity to punishment and enhanced punishment learning generalizes to non-social stimuli in SAD, it is possible that individuals with comorbid SAD and MDD may represent a subset of individuals with MDD who may be marked by alterations in punishment learning.

Reward Learning

Social Anxiety Disorder. Research with SAD suggests that individuals with this disorder may be marked by fear of *positive* as well as negative social evaluation (Weeks, Heimberg, Rodebaugh, & Norton, 2008). This growing body of literature has concentrated mainly on studies that demonstrate cognitive and attentional biases to positive or rewarding social stimuli (see review: Kashdan, 2007). For example, socially

anxious individuals are slower to recognize positive facial expressions (Silvia, Allan, Beauchamps, Maschauer, & Workman, 2006), exhibit attention bias away from positive social stimuli (Taylor, Bomyea, & Amir, 2010), and ignore positive audience member cues (Perowne & Mansell, 2002; Velijaca & Rapee, 1998). Individuals with social anxiety also fail to expect positive outcomes even when primed with positive social cues (Garner, Mogg & Bradley, 2006) and interpret positive social outcomes in an anxiety-provoking manner (Alden, Taylor, Mellings, & Laposa, 2008). These findings suggest aberrant processing of positive, rewarding, social stimuli among individuals with this disorder. However, there is still little research examining how individuals with SAD respond to reward, both social and non-social.

Research in social anxiety has used diaries to examine both the quantity and frequency of daily rewarding experiences and the extent to which experiences are rated as rewarding (Kashdan, Julian, Merritt, & Uswatte, 2006; Kashdan & Steger, 2006; Vittengl & Holt, 1998). Findings from these studies show individuals with social anxiety report significantly fewer rewarding social and non-social life experiences. More importantly, findings from these diary studies also revealed individuals with social anxiety report obtaining less pleasure from the positive experiences they do have. This blunted responsivity to rewarding everyday-life experiences is consistent with the previously mentioned theoretical models suggesting SAD is associated with decreased positive affect (Barlow, Chorpita, Brown, 1998).

However, there is a limited amount of experimental research examining reward responsivity in SAD. Moreover, the research that has been conducted has utilized varied methodology. Interestingly, findings from experimental and self-report questionnaires

appear inconsistent with diary card findings. To date, there have been two studies using experimental tasks (Abraham & Hermann, 2015; DeVido et al., 2009) and three self-report studies (Kimbrel, Cobb, Mitchell, Hundt, & Nelson-Gray, 2008; Kimbrel, Mitchell, & Nelson-Gray, 2010; Ly & Gomez, 2014) examining reward responsivity. As previously mentioned, Abraham and Hermann (2015) used neutral faces with differing probabilistic accuracy contingencies and positive social reinforcement (i.e., happy face) to compare high and low socially anxious individuals. The investigators reported no significant differences between high and low socially anxious individuals in their choice of the most positively reinforced social stimulus. DeVido and colleagues (2009) compared individuals with SAD to GAD and controls using a non-social task that involved positive reinforcement (i.e. point gains). The authors found no group differences in reward-based responsivity and learning. Despite the limitations of these studies reported earlier, these findings could indicate normal responsivity to non-social reward in SAD.

Self-report research examining responsivity to reward in general (i.e. both social and non-social) has yielded similar findings. Using a self-report measure, the Sensitivity to Punishment, Sensitivity to Reward Questionnaire (SPSRQ), sensitivity to reward was not associated with social anxiety (Kimbrel et al., 2008; Kimbrel et al., 2010). Similarly, Ly and Gomez (2014) found that self-reported sensitivity to reward did not predict social anxiety. Notably, none of these three studies used a clinical sample or assessed for comorbidity in general, depression in particular, or psychiatric medication status. Further, the measure used in all three studies includes operationally defines sensitivity with a range of questions that tap into both reactivity and responsivity using both social and

non-social rewards without yielding specific sub-scores, thus caution should be taken when interpreting the meaning of these results. Nonetheless, these initial self-report findings, consistent with the limited experimental findings in this domain, might suggest that suggest responsivity to non-social reward in SAD is not significantly different from that of healthy individuals.

In sum, there is strong evidence of aberrant attention, interpretation, and memory for positive, or rewarding social stimuli in SAD. For example, individuals with SAD tend to turn away from positive stimuli and interpret it negatively. Individuals with SAD may also exhibit decreased responsivity to reward as evidenced by self-report diary cards. However, laboratory experiments and self-report questionnaires have yet to reveal similar results. These conflicting results may be due to the use of non-clinical samples and varying methodologies. The current study expands on these preliminary findings and addresses several of their limitations including using a clinical sample, examining the impact of MDD comorbidity, and using an experimental task that objectively assesses reward responsivity and learning. Findings from the current study will help to better characterize and clarify how individuals with SAD and MDD (versus MDD-alone) respond to rewards and how individuals with these disorders modulate their behavior over time in response to receipt of reward.

Major Depressive Disorder. Individuals with MDD have consistently shown reduced responsivity to rewards or pleasurable stimuli (see review: Eshel & Roiser, 2010). This blunted responsiveness has been proposed as representing a deficit in approach-related or appetitive systems (Bylsma, Morris, & Rottenberg, 2008; Henriques & Davidson, 1991). These systems are hypothesized to aid in both regulating behavior in

anticipation of and in response to pleasant stimuli and generating positive affect as a part of this process (Davidson, 1998; Depue & Iacono, 1989; Fowles, 1987). Deficits in these systems have been linked to anhedonia, a symptom, but also a possible phenotype, of depression. Anhedonia has been studied in response to two types of reward processing, anticipatory and consummatory (Gard, Gard, Kring, & John, 2006; Gard, Kring, Gard, Horan, & Green, 2007; Klein, 1984). Anhedonic anticipatory reward processing refers to a lack of pleasure experienced in the expectation of a normally pleasurable activity. Anticipatory reward processing has been found to be linked to motivational processes that encourage goal-directed behaviors intended to attain desired rewards (Carver, 2001). Anhedonic consummatory reward processing refers to a lack of pleasure experienced during or in response to a pleasurable stimulus (“in the moment”). Research exploring anhedonia in individuals with depressive symptoms has found deficits in anticipatory, but not consummatory pleasure (Berlin, Givry-Steiner, Lecrubier, & Puech, 1998; Fawcett, Clark, Scheftner, & Gibbons, 1983; Germans & Kring, 2000). Typically, when an individual experiences reward (stimuli associated with pleasure), this association is stored and motivates future goal-directed behavior.

Interest in understanding the potential decreased reward responsivity associated with depression has generated a growing body of reward learning research. Henriques, Glowacki, and Davidson (1994) were among the first to utilize a signal detection task to examine learning in depression. The study examined reward and punishment learning differences in dysphoric and non-dysphoric undergraduate females. The authors used a verbal recognition task with three conditions: neutral, reward, and punishment. In the reward condition, correct identification of a target word was rewarded monetarily and

verbally (“Correct response”). In the punishment condition, an incorrect identification of a target word was punished monetarily and verbally (“Incorrect Response”). In the neutral condition, participants received only verbal feedback. Participants also completed a distractor task in between reward and punishment conditions to increase the difficulty of the verbal recognition task. Dysphoric participants demonstrated a smaller change in response bias during the reward condition compared to non-dysphoric individuals. There were no other group differences across conditions or outcome variables. These findings were replicated by Henriques and Davidson (2000) in a clinically depressed sample. The authors posited these deficits in approach-related behavior were representative of anhedonia. Although this latter study used a clinical sample, anxiety disorder comorbidity and current psychopharmacological treatment were exclusionary criteria for the study. Thus, questions remain about the external validity and specificity of these findings.

Pizzagalli and colleagues (2005, 2008, 2009) used the same signal detection task as the current study to explore responsiveness to reward in depressed individuals. Pizzagalli et al. (2005) found individuals with high BDI scores (> 16) did not develop response bias as compared to individuals with lower levels of depression ($BDI < 16$). This finding was replicated later in a sample of individuals with MDD (2008) and those with bipolar disorder who were in a euthymic state (2009). Blunted reward responsiveness was significantly associated with self-reported anhedonia across all three studies. In fact, in the 2008 study, blunted reward learning predicted anhedonia symptoms one-month later, further supporting the clinical correlates of impaired reward learning. Interestingly, using trial-by-trial probability analysis, the authors also found individuals with MDD were responsive to single rewards, but were impaired at

integrating reinforcement history over time (Pizzagalli et al., 2008). These findings are consistent with research showing deficits in anticipatory, but not consummatory reward processing. In other words, depressed individuals may actually respond with approach-behavior towards single rewards, but are impaired at learning behavior-reward associations over time, which in turn decreases approach-behavior. Notably, exclusion criteria in the 2008 study included absence of any psychotropic medication for 4 weeks – 6 months depending on specific drug classification. Additionally, although comorbid anxiety disorder was not excluded, only 30% of the participants met criteria for an anxiety disorder, which varied across five types of anxiety disorders. Thus, the effects of specific types of comorbid anxiety disorders on reward learning in depression were unable to be examined.

Notably, Liverant and colleagues (2014) used the same SDT task as the current study as well to compare depressed smokers and nonsmokers. The authors found that when depressed smokers were allowed to smoke to satiation, they demonstrated greater bias towards the more frequently rewarded stimuli than did depressed non-smokers. These findings are consistent with research suggesting nicotine increases dopaminergic surges, which facilitate reward responsivity (Picciotto, 1998; Pidoplichko, DeBiasi, Williams, & Dani, 1997; Shoaib, 1998).

Subsequent research has replicated these findings and broadened our understanding of the presence and role of impaired reward learning in depression. For example, blunted reward responsiveness has been found in both subsyndromal (Liu et al., 2011) and remitted MDD (Pechtel, Dutra, Goetz, Pizzagalli, 2013), suggesting it may be phenotypic. If impaired reward learning is a trait-like characteristic that is present outside

of active mood disorder episodes, it may be a characteristic that if targeted could reduce the likelihood of developing or relapsing into depression. In fact, research has shown that reward learning predicts treatment outcome among individuals with MDD above and beyond baseline depression severity. Individuals with more substantially impaired reward learning were seven times more likely to still meet diagnostic criteria for MDD at the end of treatment than those without this deficit (Vrieze et al., 2013). These findings collectively provide strong evidence of impaired reward learning in individuals with depression. However, it remains unclear whether the commonly comorbid condition of SAD may further alter reward learning among individuals with depression, which may have important implications for the treatment of this comorbid group.

Post-Traumatic Stress Disorder. PTSD shares a number of symptoms with MDD (Franklin & Zimmerman, 2001). In addition to problems with sleep and concentration, PTSD and MDD are both marked by the experience of anhedonia. In fact, a newly proposed and tested 7-factor hybrid model of PTSD includes anhedonia as a unique, latent factor (Armour et al., 2015; Seligowski & Orcutt, 2016). Given the presence of anhedonia in PTSD, researchers have begun to examine the role of reward responsivity and learning in this group (Elman et al., 2009; Hopper et al., 2008; Myers et al., 2012; Sailer et al., 2008).

While it is beyond the scope of the current paper to review these studies in detail, it is worth noting that these studies use a range of gambling tasks to assess various reward processing components (anticipation, expectation, reactivity, satisfaction, responsivity). For example, Hopper et al. (2008) used a task that did not require any choices or reward-seeking behavior, but instead assessed expectancy of, and satisfaction following, reward.

The authors found PTSD participants reported lower reward expectancy and lower satisfaction compared to those without the disorder, suggesting the presence of both anticipatory and consummatory anhedonic reward processing deficits. Sailer et al. (2008) did not find differential reward responsivity between those with PTSD and controls. They did, however, find individuals with PTSD showed decreased brain activation in the nucleus accumbens and medial prefrontal cortex in response to reward, but not punishment. Elman et al. (2009) examined brain activity and found decreased striatal activation in response to reward versus punishment in PTSD participants compared to controls. Interestingly, using a probabilistic task, a recent study by Myers et al. (2012) found Veterans with severe PTSD symptoms demonstrated enhanced performance on a reward task compared to those with few to no PTSD symptoms. Notably, the authors did not control for smoking, which may have influenced reward responsivity. Therefore, although anhedonia is a clinical feature of PTSD, the extent to which reward responsivity and learning are impaired in this group is unclear.

Notably, Kashdan, Julian, Merritt, and Uswatte (2006) used a combat Veteran sample to compare the daily positive experiences (i.e., diary cards) of individuals with SAD with and without comorbid PTSD. The authors found social anxiety accounted for significant incremental variance in positive experiences even after controlling for PTSD and trait negative affect, and was uniquely negatively related to percentage of pleasant days. Furthermore, the authors failed to find evidence that comorbid PTSD and SAD resulted in even greater diminished positive functioning (i.e., affect, experiences, etc.) than those with SAD alone. These findings suggest that SAD may have effects on reward responsivity above and beyond PTSD and, thus, differences in reward learning may be

present and detectable in Veteran samples with expectedly high rates of comorbid SAD, PTSD, and depression.

Summary of Reward Learning. Responsivity to reward and the ability to learn, or modify behavior, following receipt of reward is an important aspect of life. Reactivity and responsivity to rewards motivate us to engage in goal directed behaviors. For example, a teenager learns that studying hard pays off when they receive an A on a test. If the grade elicits positive emotion and the teenager associates the behavior of studying with receipt of the grade reward, then they will be more likely to study hard in preparation for the next test. If reward responsivity and learning are impaired, however, the teenager will not learn to associate his/her behavior with receipt of rewards and will not continue the adaptive behavior of studying for an exam. Over time, this failure to learn contingencies between behavior and rewards can have detrimental effects.

Although no study has yet examined reward responsivity and/or learning in comorbid SAD and MDD, some research has been done in these individual populations. In general, studies examining attention, interpretation, and memory in SAD report biases away from rewarding social stimuli. However, experimental tasks using social stimuli to examine reward responsivity report individuals with social anxiety do not respond or learn differently than non-socially anxious individuals. This is consistent with findings from experimental tasks and self-report questionnaires assessing reactivity to non-social stimuli. Of note, these experimental studies have examined accuracy as indicator of reward responsivity and used tasks that could not differentiate between accuracy and bias. Therefore, these findings are difficult to interpret.

In contrast, there is substantial evidence that individuals with MDD demonstrate decreased reward responsivity and learning. Specifically, depressed individuals consistently develop smaller response biases to rewards than controls. These biases have also correlated with self-reported anhedonia, which suggests that self-reported pleasure from everyday life experiences is related to propensity to modulate behaviors in response to rewards. Given the lack of findings in SAD, individuals with comorbid SAD and MDD may not be different in their reward responsivity as compared to individuals with MDD alone. Overall, better characterization of the impact of SAD on reward learning among individuals with depression may inform treatment strategies in this comorbid group.

Outliers

Individuals are classified as an outlier on the Signal Detection Task if there is sufficient (see Methods below) behavioral evidence suggesting the participant (1) answered too quickly or never responded, (2) was accurate less than 60% of the time, despite relatively unchallenging nature of the task, and (3) did not complete the task. Outlier rates for reward learning range anywhere from 1% to 12% in healthy controls (Pizzagalli et al., 2008; Pizzagalli, Jahn, & O'Shea, 2005; Tripp & Aslop, 1999) and 30-35% in clinical populations with more severe psychopathology (Ahnallen et al., 2012; Liverant et al., 2014; Pizzagalli, Iosifescu, et al., 2008; Sawyer et al., 2016). This uniformly higher outlier rate in samples with more severe clinical conditions may not simply reflect a failure to comply with the task. Instead, outlier status on the SDT may reflect, behavioral avoidance; avoidance of a task that involves both ambiguity and punishment. This behavioral avoidance could represent an underlying mechanism such as

distress intolerance and/or behavioral inhibition. In fact, several studies have examined these mechanisms in the context of task completion and will be reviewed.

Distress tolerance (DT) has been conceptualized as a person's ability to engage and continue towards a goal in spite of having activated negative emotions (Bornovalova, Gratz, Daughters, Hunt, & Lejuez, 2012; Brown, Lejuez, Kahler, & Strong, 2002; Roemer et al., 2009). DT has been operationalized in laboratory setting as behavioral persistence during challenging tasks (Ellis, Vanderlind, & Beevers, 2012; Lejeuz, Kalher, & Brown, 2003). Decreased persistence during frustrating tasks has been found in participants with a broad array of clinical disorders typically associated with reduced distress tolerance (Brown et al., 2002; Ellis et al., 2010, 2012; Feldner, Leen-Feldner, Zvolensky, & Lejuez, 2006; Williams, Vik, & Wong, 2015). These studies collectively suggest lower distress tolerance is related to task completion.

Importantly, individuals with MDD and co-occurring anxiety disorders demonstrate even lower distress tolerance than those with MDD-alone (Bernstein, Marshall, Zvolensky, 2011). Most relevant to the current study's Veteran sample, PTSD has been more strongly linked to distress intolerance (DI) compared to other anxiety disorders. DI, particularly for negative emotional states, is significantly associated with PTSD symptom severity (Marshall-Berenz, Vujanovic, Bonn-Miller, Bernstein, & Zvolensky, 2010; Vujanovic et al., 2011; Zvolensky, Berstein, & Vujanovic, 2011). If during the current study, the punishment received elicited distress or negative emotions, Veterans with MDD and co-occurring PTSD (54% of sample) may demonstrate less tolerance to the distress associated with completing the SDT tasks. If this is the case,

those with comorbid PTSD and depression may be more likely to be classified as outliers than those with MDD-alone.

As previously reviewed, BI guides behaviors in punishing, non-rewarding or novel situations. Often, BI involves the tendency to avoid or withdraw from situations and increased attention, or vigilance, to the environment (Gray, 1971; Gray, 1981). Sheynin and colleagues (2013) used a SDT and operant conditioning, similar to the method used in the current study, to compare the performance of individuals high and low in BI. The task assessed whether individuals would develop a tendency to acquire avoidance behaviors more frequently than other responses. In this study, participants were provided with an additional response choice on each trial. Instead of classifying the stimulus as belonging to one of two categories (A, B), they could opt-out of responding, avoiding the chance to be punished or rewarded. Individuals with high self-reported BI opted-out more frequently than those with low scores. Interestingly, opting-out increased over time (i.e. was not a pre-existing tendency), which suggests this behavior was negatively reinforcing. These findings may suggest that BI drives avoidant behaviors during laboratory learning tasks. Therefore, individuals with elevated BI scores may be more likely to meet outlier status during the punishment task used in this study than those with lower scores.

Aims and Hypotheses

The current study investigated whether individuals with comorbid SAD and MDD respond to, and learn from, punishment and reward differently than individuals with MDD-alone. Notably, as SAD and MDD are both associated with increased negative and decreased positive affect, it is important to examine both punishment and reward

responsivity and learning to more fully characterize the presence and nature of learning impairments in these comorbid disorders. The current study also examined whether potential alterations in punishment learning exist in SAD when using non-social stimuli. In an attempt to clarify conflicting findings in the literature, this study employed two separate signal detection tasks specifically designed to measure punishment and reward responsivity and learning. Use of these specific tasks allowed us to measure bias separately from accuracy to elucidate changes in responsivity distinct from the discriminability of the task stimuli.

Hypothesis 1. Given the initial evidence suggesting hyperresponsivity to punishment in SAD, individuals with co-occurring social anxiety disorder (SAD+MDD) will show greater RB during the punishment task compared to the MDD-alone group, but there will be no between-group differences in RB during the reward task (controlling for smoking status).

Hypothesis 2. Individuals with co-occurring social anxiety disorder (SAD+MDD) will show greater punishment learning as defined by significantly larger increases in RB from Block 1 to Block 2 during the punishment task compared to the MDD-alone group, but there will be no between-group differences in change in RB during reward task (controlling for smoking status).

Hypothesis 3. An exploratory analysis will be conducted to examine the influence of co-occurring PTSD and BI as potential predictors of outlier status on the punishment task.

Method

Participants

Eighty veterans were recruited from a large VA Healthcare System in the Northeastern

United States. Consistent with other veteran samples, the majority of the sample was White (78.85) and male (87.5%), and the average age was 51.2 years ($SD = 11.19$; see Table 2 for full demographics). Age ranged from 25 to 80 years old, and years of education ranged from 10 to 18. The majority of the sample (65.0%) reported taking an antidepressant medication at the time of enrollment (Selective Serotonin Reuptake Inhibitor (SSRI): $N = 31$, Serotonin Norepinephrine Reuptake Inhibitor (SNRI): $N = 6$, Norepinephrine Dopamine Reuptake Inhibitor (NDRI): $N = 16$, tricyclics: $N = 4$, tetracyclics: $N = 13$).

Inclusion and Exclusion Criteria. The primary inclusion criterion was a current diagnosis of unipolar depression, which included a diagnosis of either MDD or dysthymia (93.8% met criteria for MDD and 11.3% met for dysthymia). Apart from the diagnostic criteria, additional inclusion criteria included a minimum age of 18 and the ability to read and write English. Individuals were excluded from the study if they had a history of bipolar disorder, current psychotic-spectrum diagnosis, current suicidal or homicidal intent and/or psychiatric hospitalization within last two months, and/or symptoms that interfered with study participation (see review of differences between groups below in Results).

Table 2. *Demographic and Psychiatric Characteristics of Sample*

	<u>Whole Sample</u>		<u>SAD+MDD</u>		<u>MDD-alone</u>		
	<u>N = 80</u>		<u>N = 29</u>		<u>N = 51</u>		
<u>Characteristic</u>	<u>Mean</u>	<u>N(%)</u>	<u>Mean(SD)</u>	<u>N(%)</u>	<u>Mean(SD)</u>	<u>N(%)</u>	<u>t, χ^2</u>
	<u>(SD)</u>						
Age (years)	51.17		49.31		52.24		1.12
	(11.19)		(11.29)		(11.10)		
Education	13.71		13.24		13.98		1.72
(years)	(1.87)		(1.62)		(1.96)		
Sex							0.19
Male		70 (87.5%)		26 (89.7%)		44 (86.3%)	
Female		10 (12.5%)		3 (10.3%)		7 (13.7%)	
Race							2.44
Hispanic		3 (3.8%)		1 (3.4%)		2 (3.9%)	

White	63 (78.8%)	24 (82.8%)	39 (76.5%)	
Black	10 (12.5%)	4 (13.8%)	6 (11.8%)	
Asian	2 (2.5%)	0 (0%)	2 (3.9%)	
Other	2 (2.5%)	0 (0%)	2 (3.9%)	
Marital Status				4.26
Never	23 (28.7%)	10 (34.5%)	13 (25.5%)	
Married				
Married	15 (18.8%)	3 (10.3%)	12 (23.5%)	
Divorced	28 (35.0%)	10 (34.5%)	18 (35.3%)	
Separated	9 (11.3%)	5 (17.2%)	4 (7.8%)	
Widowed	5 (6.3%)	1 (3.4%)	4 (7.8%)	
MDD	75 (93.8%)	27 (93.1%)	48 (94.1%)	0.03
Dysthymia	9 (11.3%)	4 (13.8%)	5 (9.8%)	0.30
SAD	27 (33.8%)			

Note. All diagnoses listed are current. MDD = Major Depressive Disorder; SAD = Social Anxiety Disorder.

Measures

Biochemical Verification.

Breathalyzer. A breathalyzer was used to rule out alcohol use on the day of the experiment and ensure alcohol free status for the study visit. This electronic device offered a noninvasive means of estimating an individual's blood alcohol concentration (BAC) based on an analysis of the alcohol level on his breath (Ralevski et al., 2006). A breathalyzer reading of ≤ 0.005 g/l was required to establish alcohol free status for the study visit and allow for participation. The Alcomate Prestige AL6000 (AK Solutions, Palisades Park, NJ) was used to measure blood alcohol level.

Smokerlyzer. The EC50 Micro 4 Smokerlyzer (Bedfont Scientific, LTD) was used to measure carbon monoxide (CO) in expired rapid lung-breath. CO concentration was assessed in parts per million (ppm). This procedure was employed to verify self-reported smoking status (Liverant et al., 2014). Self-reported smoking status (yes/no), not smokerlyzer results, was used as a control variable for the reward task analyses.

Diagnostic Assessment.

The Structured Clinical Interview for DSM-IV Axis I Disorders – Clinician

Version (SCID-CV; First, Spitzer, Gibbon, & Williams, 1997) was used to determine current and lifetime Axis I diagnoses. Interviews were conducted by a trained doctoral level psychologist. The SCID was used to: (a) determine inclusion criteria (b) assess current Axis I diagnoses; specifically, to determine the presence or absence of SAD and MDD. Inter-rater reliability is not available as all of the diagnostic interviews were conducted by Dr. Liverant.

Self-Report Measures.

Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996). The BDI is a 21-item scale that is a widely used measure of depression. Each item is rated on a 4-point Likert scale, ranging from 0-3. Total scores on this measure range from 0-63, with higher scores indexing more severe depressive symptoms. The BDI-II has demonstrated excellent internal consistency, validity, and test-retest reliability (Beck, Steer, Ball, & Ranjeri, 1996; Dozois, Dobson, & Ahnberg, 1998).

Beck Anxiety Inventory-II (BAI-II; Beck, Epstein, Brown, & Steer, 1988). The BAI is a 21-item scale that is a widely used measure of anxiety. Each item is rated on a 4-point Likert scale, ranging from 0-3. Total scores on this measure range from 0-63, with higher scores indexing more severe anxiety symptoms. Analyses indicate good reliability and validity (e.g., $\alpha = .92$). The BAI was used to characterize the level of anxiety in the study sample.

Behavioral Inhibition System/Behavioral Activation System (BIS/BAS; Carver & White, 1994). The BIS/BAS is a 20-item scale designed to assess the reported sensitivity of approach and avoidance motivational systems. The BIS subscale has seven items and is thought to be an index of sensitivity to punishment. The BIS scale measures the tendency for respondents to experience negative affect and behavioral inhibition

when cues for punishment or threat are present. The BAS subscale has 13 items and is theorized to be an index of sensitivity to signals of reward and a general tendency toward approach motivation. The BAS dimension has three measures: Reward Responsiveness (5 items), Drive (4 items) and Fun Seeking (4 items). Each item of the BIS/BAS is rated on a four-point Likert-scale, where 1 indicates “very false for me” and 4 indicates “very true for me.” Higher scores indicate higher sensitivities. The BIS/BAS has good convergent, discriminant, and concurrent validity (Campbell-Sills, Liverant, & Brown, 2004; Carver & White, 1994; Ly & Gomez, 2014).

Mood and Anxiety Symptom Questionnaire (MASQ; Watson, Weber, et al., 1995). The MASQ Anhedonic Depression (AD) subscale was used to assess anhedonia. The 22 items on this subscale index loss of interest and reduced positive affect. Each item is rated on a Likert scale from 1 to 5. Scores from the MASQ AD subscale range from 22-110, with higher scores indicating greater levels of anhedonia. The MASQ AD subscale has demonstrated good reliability and validity (e.g., Watson, Clark, et al., 1995). The MASQ AD was used to characterize the sample.

Posttraumatic Stress Disorder Check-List-C (PCL-C; Blanchard, Jones-Alexander, Buckley, & Forneris, 1996; Weathers, Litz, Herman, Huska, & Keane, 1993). The PCL-C is a 17-item scale that assesses the 17 DSM-IV symptoms of PTSD in a general civilian population. PTSD related items are not linked to a specific event; the questions refer to “a stressful experience in the past.” Participants rate items on a 5-point Likert scale (1 = not at all; 5 = extremely). Total score ranges from 17 -85, with higher scores indicating greater PTSD symptom severity. There are four subscales: re-experiencing (5 items, “*Repeated, disturbing dreams of a stressful experience from the*

past?”), avoidance (3 items, “*Avoid activities or situations because they remind ou of a stressful experience from the past?*”), numbing (4 items, “*Feeling distant or cut off from other people?*”), and hyperarousal (5 items, “*Being ‘super alert’ or watchful on guard?*”). The 17 items across the four subscales correspond to the diagnostic criteria for PTSD in the DSM-IV (Blanchard et al., 1996; see Wilkins, Lang, & Norman, 2011). The PCL has demonstrated good test-retest reliability and construct validity (Weathers, Litz, Herman, Huska, & Keane, 1993). The PCL-C has also been well validated in a sample of male veterans, similar to the current study (Keen, Kutter, Niles, & Krinsley, 2008). The PCL was used as a dimensional indicator of PTSD-symptoms to examine differences between punishment outliers and non-outliers. .

Smoking Behavior Questionnaire (SBQ). The SBQ is a scale developed for use in the current study. The measure consists of a combination of yes/no and open-ended questions assessing current smoking behaviors (e.g., average number of cigarettes smoked per day, duration of smoking behavior). As previously mentioned, nicotine affects dopaminergic pathways and reward learning. However, nicotine has not been previously implicated in punishment responsivity or learning. Therefore, the current study controlled for smoking status (yes/no) in analyses with the reward, but not punishment task.

Computerized Task Assessing Learning

Punishment Learning. The current study used a previously validated signal detection task designed to assess modulation of behavior as a function of punishment and reinforcement history (i.e. punishment and reward learning, Bogdan and Pizzagalli, 2006; Pizzagalli et al., 2005, 2008; Santesso et al., 2008). Participants started the computerized

task with \$10 and were informed the aim of the task was to lose as little money as possible. Participants were informed they would keep their winnings from the task. They were unaware that one of the stimuli would be disproportionately punished.

Stimuli were presented using E-Prime software (version 1.1; Psychology Software Toole, Pittsburgh, Pennsylvania) on a 17" PC monitor. The task consists of two blocks of 100 trials. Stimuli for the task involved one of 10 possible different patterns of colored squares and circles set within a black square (see Figure B); stimuli were either: 10 squares and 7 circles or 7 squares and 10 circles. Participants are asked to identify which array was presented (i.e. more circles or more squares) via pressing a button on the keyboard. Each trial follows an identical sequence: (a) presentation of a fixation point (500 ms); (b) appearance of a shape array, circles and squares (350 ms); (c) blank screen until a response is made.

Participants were not informed that an asymmetrical punishment ratio (3:1 rich/lean) was used for punishment of incorrect identifications. Incorrect identifications of the rich stimulus were associated with three times more punishment feedback ($n = 15$) than the lean stimulus ($n = 5$). A controlled punishment procedure was implemented according to prior procedures (Johnstone & Alsop, 2000; McCarthy & Davison, 1979). Therefore, twenty incorrect trials per 100-trial block were followed by punishment feedback ("Incorrect! You lost 10 cents") in a pseudo-randomized sequence to ensure each subject was exposed to the same punishment ratio.

Reward Learning. A slightly modified version of the punishment paradigm was used to assess reward learning. Prior to beginning, participants were informed that the goal of the task was to win as much as possible. The reward paradigm utilized different

stimuli, different feedback, and a similar asymmetrical ratio for reinforcement of correct responses. Stimuli for the task involved two cartoon faces without either a short or long mouth (see Figure A). Participants were asked to identify which mouth was presented (i.e. short or long) via pressing a button on the keyboard. All other components of this paradigm were the same as the punishment task. More specifically, each trial followed an identical series: (a) appearance of a fixation cross (500 ms); (b) appearance of a mouthless cartoon face (350 ms); (c) appearance of a short mouth (11.5mm) or a long mouth (13mm) for 100 ms; and (d) reappearance of the mouthless cartoon face, which stayed on the screen until participants responded. Participants were not aware that an asymmetrical reinforcer ratio (3:1 rich/lean) was used to reward correct responses. Specifically, correct identification of the rich stimulus was paired with three times more *reward* feedback (“Correct! You won 5 cents”) than the lean stimulus (30 vs 10 reward feedback).

Use of short versus long mouth as the rich stimulus was counterbalanced across participants. In each block, only 40 out of 100 possible correct trials (30 rich, 10 lean) were rewarded so that each subject was exposed to the same reward ratio. To achieve this goal, a controlled reinforcer procedure was implemented according to prior procedures (Johnstone and Alsop, 2000; McCarthy and Davison, 1979). Therefore, if participants responded incorrectly on a trial that was scheduled to be rewarded (based on a pseudo-randomized reinforcement sequence), the reward feedback was delayed until the next correct identification of the rich or lean stimulus.

Primary Outcome Variables for Reward and Punishment Tasks

Standard scoring procedures for the current task provide mean level data across

100-trial blocks (Macmillan & Creelman, 1991; McCarthy, 1991; Pizzagalli, Goetz, et al., 2008; Pizzagalli et al., 2009). Three primary outcome variables were derived from the signal detection task: response bias (RB), discriminability, and reaction time (RT; see Pizzagalli et al., 2005). RB, the main variable of interest, reflects the preference for the less frequently punished or the more frequently rewarded stimulus (rich; i.e., an index of reward/punishment responsiveness). RB (log b) is calculated as:

$$\log b = \frac{1}{2} \log [(Rich_{incorrect} + 0.5) * (Lean_{correct} + 0.5) / (Rich_{correct} + 0.5) * (Lean_{incorrect} + 0.5)]$$

Higher scores indicate greater bias away from the more frequently punished stimuli for the punishment task and towards the more rewarded stimuli for the reward task. A score of 0 represents no bias or a “neutral” bias, positive scores indicate a bias in the expected direction based on conditioning (i.e., punishment and reward receipt), and negative scores represent a bias in the opposite direction of conditioning. The range of possible log(RB) scores is $-\infty$ to $+\infty$. Norms for RB using this task have yet to be established. As previously discussed, change in RB across blocks (ΔRB) has been identified as a primary index of conditioned learning (punishment and reward) during the task. Importantly, a large body of research has shown that unequal frequency of reward/punishment following correct/incorrect identification of stimulus A and B produces a systematic preference for the response paired with the more frequent reward/punishment (Macmillan & Creelman, 1991; McCarthy, 1991).

Discriminability (log d) is an index of participants’ ability to differentiate between the two different mouth stimuli/shapes (i.e., a measure of task difficulty), and is calculated as follows:

$$\log d = \frac{1}{2} \log [(Lean_{correct} + 0.5) * Rich_{correct} + 0.5) / (Lean_{incorrect} + 0.5) * Rich_{incorrect} + 0.5)]$$

A score of 0 indicates an inability to distinguish between stimuli and higher scores indicate greater ability to determine which stimulus was presented. The range of possible d scores is $-\infty$ to $+\infty$.

RT is the time elapsed in milliseconds from the reappearance of the mouthless face/shapes and the participant's button press response. Larger RT indicates a slower response time. RT was used for all trials (i.e., not just correct trials). Data screening procedures are reviewed in the results section.

Procedures

Interested individuals were interviewed over the phone to determine if they met inclusion or exclusion criteria. Participants were provided a description of the study and engaged in a brief phone assessment to determine eligibility. The two-part nature of the study was explained. During the telephone screen, participants were advised not to consume any alcoholic beverages in the 24-hour period prior to the scheduled appointment. It was explained that a Breathalyzer test of alcohol level would be performed on the day of the visit, and any participants with a BAC reading above 0.06 would not be eligible for the study.

All participants were provided written informed consent prior to study participation. The visit was divided into two parts that occurred sequentially as listed here: (a) informed consent, breathalyzer and smokerlyzer screens, structured clinical interview, and (b) psychological measures and experimental paradigm (punishment and reward counterbalanced across participants). If the participant did not meet inclusion/exclusion criteria based on the SCID or breathalyzer, the study was terminated

and they were compensated for their time. The structured clinical interview took approximately two hours.

Compensation

Participants were reimbursed for their time with \$90 cash when they completed the entire study. Participants who did not meet the inclusion and exclusion criteria based on the clinical interview were reimbursed at a rate of \$5 per hour.

Data Analysis

To test hypothesis 1, two 2 (*Block*: 1, 2) x 2 (*Group*: SAD+MDD, MDD-alone) mixed model repeated measures repeated measures analyses of variance ANOVA were conducted for each task (punishment, reward) using SPSS statistical software version 19.0 (SPSS Inc., Chicago, IL, USA). Block was the within-subjects variable. For this analysis, punishment and reward learning was operationalized as change in RB from block 1 to 2 ($\Delta RB = RB \text{ Block } 2 - RB \text{ Block } 1$). Comorbid SAD status was the between-subjects variable in the analyses. Hypothesis 2 was evaluated by examining the significance of the Block x SAD status interaction. This process was repeated for the both tasks. For only the reward task, smoking status (not smoking satiation status) was entered as a covariate (thus an analysis of covariance was conducted) to control for the effects of nicotine on reward responsivity and learning.

An additional aim of this study was to examine predictors of punishment outlier status. As previously mentioned, traditional person-level outlier standards for the current learning tasks include: < 80% of valid trials within a block, < 10 rich punishment/block, > 30% outlier trials for any block, < 60% accuracy for each block; RB scores ± 3 SD from the sample mean. I conducted a series of independent samples t-tests and Chi

Square analyses to determine if there were significant differences between punishment outliers and non-outliers (dummy coded, 0 = not outlier, 1 = outlier). More specifically, I investigated whether co-occurring PTSD status (chi-square) and Behavioral Inhibition (BI) score (t-test), separately, differed based on punishment outlier status.

Supplementary Data Analysis

In addition to the analyses listed above, several supplementary exploratory analyses were performed. First, to explore the impact of comorbid PTSD in the sample of Veterans, the current study performed the same primary analyses listed above for the punishment task using comorbid PTSD instead of comorbid SAD. Second, given the research implicating BI in comorbid SAD and MDD, the current study examined the effects of BI as a possible transdiagnostic factor that may influence punishment learning. Specifically, a linear regression was performed in order to determine if BI, as measured by continuous BIS score on the BIS/BAS, predicts punishment response bias. In this analysis, BIS score was the independent variable and punishment task response bias was the dependent variable.

Results

Demographics

A series of independent samples t-tests were performed to assess differences on demographic, comorbid diagnoses, and baseline variables between the two groups (see Tables 2 and 3 for full demographics). There was a significant difference in comorbid PTSD between comorbid SAD and MDD-alone groups ($\chi^2 (1, N = 80) = 5.50, p = .02$). Specifically, 49% ($N = 25$) of individuals without comorbid SAD had comorbid PTSD and 76% ($N = 22$) of individuals with comorbid SAD also had comorbid PTSD. Also as would be expected, behavioral inhibition (BI) was significantly different between

comorbid SAD and MDD and MDD-alone groups ($t(77) = -2.16, p = .03$). Comorbid SAD and MDD reported greater BI ($M = 23.07, SD = 3.57$) than the MDD-alone group ($M = 21.24, SD = 3.67$). No other demographic, diagnostic, or baseline variables were significantly different between the two groups.

Additionally, as would be expected in a sample of this clinical severity, scores on all psychological assessments tended to be elevated towards the upper range of possible scores, consistent with prior studies using clinical samples. For example, anhedonia scores (MASQ; maximum score of 110) in the current sample ($M = 87.14, SD = 9.98$) were similar to those previously reported in clinically depressed samples ($M = 91.00, SD = 7.60$; e.g., Pizzagalli et al., 2015). Additionally, behavioral activation (BAS) and PTSD symptom (PCL) scores in the current sample were consistent with those previously reported in clinical and Veteran samples, respectively (e.g., Campbell-Sills, Liverant, & Brown, 2004; Keen, Kutter, Niles, & Krinsley, 2008). Notably, behavioral inhibition scores (BIS) were elevated in the current sample ($M = 21.91, SD = 3.72$) compared to previously reported outpatient clinical samples ($M = 16.98, SD = 2.94$; Campbell-Sills, Liverant, & Brown, 2004).

Table 3. *Self-reported Symptom Severity Scales for Sample*

	<u>Whole Sample</u>		<u>SAD+MDD</u>	<u>MDD-alone</u>	
	<u>N = 80</u>		<u>N = 29</u>	<u>N = 51</u>	
<u>Characteristic</u>	<u>Mean(SD)</u>	<u>Min-Max</u>	<u>Mean(SD)</u>	<u>Mean(SD)</u>	<u>Statistic (t, χ^2)</u>
BDI-II	30.04 (9.43)	11-51	32.14 (8.22)	28.84 (9.94)	-1.51
MASQ	87.14 (9.98)	59-106	88.00 (8.91)	86.64 (10.60)	-0.58
BAI	19.00 (12.24)	1-63	20.71 (13.24)	17.91 (11.59)	-0.95
PCL-T	53.28 (12.02)	17-78	56.31 (11.34)	51.40 (12.17)	-1.78
PCL-R	14.66 (4.52)	5-24	15.52 (4.35)	14.16 (4.58)	-1.29
PCL-A	9.10 (2.54)	3-15	9.59 (2.59)	8.81 (2.50)	-1.30
PCL-N	13.80 (3.64)	4-20	14.35 (3.28)	13.49 (3.83)	-1.01

PCL-Anh	10.84 (2.80)	3-15	11.31 (2.51)	10.57 (2.94)	-1.14
PCL-H	16.24 (4.40)	5-25	16.86 (4.50)	15.88 (4.34)	-0.96
BIS	21.91 (3.72)	9-28	23.07 (3.57)	21.24 (3.67)	-2.17*
BAS	35.36 (7.66)	16-52	33.86 (7.48)	36.28 (7.70)	1.34

Note. * = Significant difference between the two groups, $p < .05$. BDI-II score = Beck Depression Inventory-II total score. BAI = Beck Anxiety Inventory total score; MASQ = Mood and Anxiety Symptoms Questionnaire anhedonia score; PCL-T through H = PTSD Checklist total score, re-experiencing, avoidance, numbing, numbing-anhedonia, and hyperarousal subscale scores. BIS Total = Behavioral Inhibition System subscale score from BIS/BAS. BAS Total = Behavioral Activation System subscale score from BIS/BAS.

Punishment and reward task data were checked for outliers based on previously established procedures (Pizzagalli, Jahn, & O'Shea, 2005). RTs < 150 ms or > 2500 ms were used to identify outlier trials within each block. Outliers of the entire task (i.e., person-level) were defined based on if a participant met any the following criteria: < 80% of valid trials within a block, < 10 rich punishment/block, > 30% outlier trials for any block, < 60% accuracy for each block; RB scores > 3 SD from the sample mean. There were 36 (45.0%) outliers for the punishment task and 23 (28.7%) outliers for the reward task. All outlier data were excluded from analyses with task outcomes. There were no significant differences in punishment outlier status based on demographic variables (i.e., race/ethnicity, gender, marital status, military branch, education level, or diagnosis including comorbid SAD and PTSD).

Primary Analyses

Punishment Learning in SAD+MDD vs. MDD. Consistent with hypotheses, for the punishment task, findings indicated there were main effects of Block ($F(1, 40) = 5.95$, $p = .02$) and comorbid SAD on response bias (RB; $F(1, 40) = 8.50$, $p = .00$, $\eta^2 = .20$; see

Figure C)¹. Within subjects effects indicated that across the entire sample, RB significantly increased from Block 1 ($M = -0.02$, $SE = 0.03$) to 2 ($M = 0.06$, $SE = 0.04$). Individuals with comorbid SAD demonstrated greater RB ($M = 0.10$, $SE = 0.44$) than those without comorbid SAD ($M = -0.06$, $SE = 0.03$) averaged across both Blocks, indicating Veterans with comorbid SAD preferred the less frequently punished stimulus relative to Veterans without SAD. However, in contrast to hypotheses, the interaction between Block and comorbid SAD diagnosis was not statistically significant.

For Discriminability, there were no main effects for Block or comorbid SAD diagnosis, indicating that Discriminability did not significantly change from Block 1 to 2 and there were no mean between-group differences across the task. In addition, the interaction between Block and comorbid SAD was not significant.

For reaction time (RT), there were main effects of Block ($F(1, 40) = 12.71$, $p = .00$) and comorbid SAD ($F(1, 40) = 4.45$, $p = .04$, $\eta^2 = .10$; see Figure D). Within subjects effects indicated that RT significantly decreased across the entire sample from Block 1 ($M = 971.82$, $SE = 34.90$) to 2 ($M = 907.60$, $SE = 31.94$). Individuals with comorbid SAD had slower RT ($M = 1007.68$, $SE = 50.70$) than those without comorbid SAD ($M = 871.74$, $SE = 39.77$) across both Blocks. The interaction between Block and comorbid SAD was not significant.

Reward Learning in SAD+MDD vs. MDD. Consistent with hypotheses, for the reward task, there was no main effect of smoking status, or comorbid SAD on RB. The main effect of Block was also not significant, suggesting the task did not produce reward

¹ Given baseline differences in BIS and comorbid PTSD between the two groups, repeated measures ANCOVAs on the punishment task were also performed controlling for BIS and PTSD. There was still a main effect of comorbid SAD on RB ($F(1, 37) = 8.26$, $p = .01$, $\eta^2 = 0.19$) and RT ($F(1, 37) = 5.21$, $p = .03$, $\eta^2 = 0.12$).

learning across blocks. The interaction between Block and comorbid SAD and the interaction between Block and smoking status were both not significant. Notably, the interaction between RB and smoking status approached significance ($F(1, 53) = 3.73, p = .059$).

Additionally, there was no main effect of smoking or comorbid SAD on Discriminability. However, there was an expected main effect of Block on Discriminability ($F(1, 53) = 3.87, p = .05$). Within subjects effects indicated that Discriminability significantly increased from Block 1 ($M = .50, SE = .03$) to 2 ($M = .58, SE = .04$), while controlling for smoking status. The interaction between Block and comorbid SAD and the interaction between Block and smoking status were both not significant. There were also no main effects of Block, smoking status, or comorbid SAD on RT.

Predicting Punishment Outliers

In contrast to hypotheses, Chi-square and independent samples t-tests analyses revealed that neither PTSD diagnosis nor BI significantly predicted punishment outlier status, respectively. However, to further probe whether PTSD was related to punishment outlier status, an independent samples t-test was performed to see if there were significant differences between outliers and non-outliers on the PCL subscales. Findings showed only the hyperarousal subscale significantly differed based on punishment outlier status ($t(76) = -2.67, p = .01$). More specifically, punishment outliers endorsed greater hyperarousal ($M = 17.47, SD = 4.29$) than non-outliers ($M = 14.93, SD = 4.12$). A follow-up independent samples t-test was performed to examine the items on the subscale further. For the hyperarousal subscale, punishment outliers reported significantly greater

irritability or angry outbursts ($t(76) = -2.55, p = .01, M = 3.25, SD = 1.20$) than non-outliers ($M = 2.52, SD = 1.29$), greater feelings of being super-alert, watchful, or on guard ($t(76) = -2.75, p = .01, M = 3.39, SD = 1.40$) than non-outliers ($M = 2.60, SD = 1.15$), and feeling jumpy or easily startling significantly more ($t(76) = -2.00, p = .05, M = 3.22, SD = 1.38$) than non-outliers ($M = 2.62, SD = 1.29$). The two remaining hyperarousal items (sleep and concentration difficulties) did not significantly differ between outliers and non-outliers.

Supplementary Analyses

Punishment Learning in PTSD+MDD vs. MDD. For the punishment task, there was a main effect of Block on RB ($F(1, 40) = 7.58, p = .01$), but no main effect of comorbid PTSD and the interaction between Block and comorbid PTSD was not significant. Similar to the findings with comorbid SAD, within subjects effects indicated that RB significantly increased from Block 1 ($M = -0.04, SE = 0.03$) to 2 ($M = 0.04, SE = 0.04$). For Discriminability, there were no main effects of Block or comorbid PTSD and the interaction between Block and comorbid PTSD was not significant. Within subjects effects indicated that Discriminability did not significantly change from Block 1 to 2. For RT, there was a main effect of Block ($F(1, 40) = 14.14, p < .01$), but no main effect of comorbid PTSD and the interaction between Block and comorbid PTSD was not significant. Within subjects effects indicated that RT significantly decreased from Block 1 ($M = 955.65, SE = 35.30$) to 2 ($M = 891.14, SE = 32.89$).

Behavioral Inhibition Predicting Punishment RB. Four separate linear regressions (RB for Block 1, 2, Total, ΔRB) were conducted to determine if BIS (as a

continuous independent variable) predicted punishment RB. The effect of BI did not approach statistical significance for all regression analyses.

Discussion

This is one of the first studies to examine punishment and reward learning differences between individuals with comorbid SAD and MDD versus MDD-alone using non-social stimuli. Although sensitivity to punishment has long been studied in SAD (e.g., see Hofmann & Bitran, 2007), most studies have examined responsivity using social related punishment stimuli. Furthermore, despite the high comorbidity rate between SAD and MDD, no studies have examined punishment responsivity in a comorbid sample. Thus, the current findings may have important clinical implications for understanding the etiology, maintenance, and treatment of this comorbid presentation.

Punishment Findings

Consistent with hypotheses, the comorbid SAD and MDD group demonstrated greater response bias (RB) than the MDD-alone group across the punishment task. These findings suggest individuals with comorbid SAD and MDD demonstrate a greater bias away from non-social punishment overall than individuals with MDD-alone. However, contrary to hypotheses, there was no significant interaction for punishment RB, suggesting that the trajectory of learning across the two 100-trial Blocks did not differ between groups. Instead, there were elevations in behavioral response to punishment during the first Block of the task in the comorbid versus MDD-alone group that then remained elevated in the second Block. These findings may suggest the presence of baseline differences indicative of hyper-responsivity to punishment in this comorbid group as opposed to differences in change in behavior over time (i.e., learning). However, this finding also may be consistent with some animal research, which shows that not all

conditioned behaviors demonstrate a gradual acquisition of learning, and rather, some conditioned behaviors emerge when a threshold is crossed (which may occur early on) and persist thereafter (i.e., similar to a ceiling effect; Morris & Bouton, 2006). Thus, it may be that for this particular comorbid clinical presentation, conditioned avoidance away from punishment emerges early on. Notably, the current study used mean-level analysis, which precludes our ability to determine if the elevated responsivity in the comorbid group was present at the beginning of the Block or acquired trial-by-trial over the course of the first Block.

Together, these results may have significant clinical implications. The current findings suggest that individuals with comorbid SAD and MDD may have increased avoidance in response to non-social punishment relative to individuals with MDD-alone. This is broadly consistent with learning theories that support stimulus generalizability related to avoidant responding and suggests that social avoidance may generalize to other types of punishing stimuli (Bouton, 2007; Craske, Hermans, & Vansteenwegen, 2006; Hull, 1943; Lissek, 2012; Pavlov, 1927). In line with theoretical models examining the comorbidity of SAD and MDD (Clark & Watson, 1991; Epkins & Heckler, 2011; Gray & McNaughton, 2000), this increased responsivity to non-social punishment could result from the cumulative impact of shared transdiagnostic factors present in both disorders (e.g., increased behavioral inhibition) in the comorbid SAD/MDD versus MDD-alone population. Importantly, when controlling for baseline differences in BIS, the main effect of group on punishment RB remained significant, suggesting these results were likely not driven simply by increased BIS in the comorbid group. However, other transdiagnostic

factors (e.g., increased negative affect, decreased positive affect) were not examined in the current study design and, thus, could be contributing to the current findings.

Irrespective of the precise understanding of the etiology of the observed greater avoidant responsivity to punishment in the comorbid group, this finding may suggest a meaningful and novel treatment target for individuals with comorbid SAD and MDD. Research suggests individuals receiving cognitive-behavioral therapy (CBT) for comorbid SAD and MDD have poorer treatment outcomes as compared with individuals MDD and a different comorbid anxiety disorder, SAD with a comorbid anxiety disorder, as well as MDD or SAD-alone (Campbell-Sills et al., 2012; Chambless, Tran, & Glass, 1997; Ledley et al., 2005; LeMoult, Rowa, Antony, Chudzik, & McCabe, 2014; Marom, Gilboa-Schechtman, Aderka, Weizman, & Hermesh, 2009; O'Neil & Kendall, 2012). The greater behavioral responsivity to non-social punishment demonstrated in this study may suggest that individuals with comorbid SAD and MDD avoid a wider array of situations/stimuli in their daily lives in order to avoid punishment in general (i.e., not just for fear of negative social evaluation or consequences). For example, an individual with comorbid SAD and MDD may avoid taking a job promotion, taking a test in school, or starting a new hobby for fear of failing, doing poorly, or loss. This more generalized punishment avoidance behavior could contribute to greater overall withdrawal behavior and functional impairment, increased loneliness, low self-esteem, and reduced efficacy that are characteristic of both of disorders (Dalrymple, 2012; Trew & Alden, 2009), as well as treatment resistance in this comorbid group.

At present, there is no specific treatment for comorbid SAD and MDD although CBT is recommended as a first-line treatment for both disorders (Belzer & Schneier,

2004). In a survey of CBT expert clinicians, almost 75% reported they usually treat comorbid anxiety disorders and depression sequentially based on which disorder is determined to be primary (Collimore & Rector, 2014). Thus, it is important to consider the current findings in the context of both CBT for SAD and for MDD. Currently, CBT for SAD involves exposure to social situations and incorporates exposure to socially punishing experiences (e.g., disapproving facial expressions, negative feedback, rejection) to facilitate extinction or new learning (Heimberg & Becker, 2002; Hofmann, 2004; Hope, Heimberg, Juster, & Turk, 2000). Results from the current study may suggest a need to include exposure to punishment using non-social stimuli as well, while encouraging continued approach behavior more broadly for individuals with comorbid SAD and MDD. CBT and Behavioral Activation (BA) for MDD also include exposure-like activities, through re-engagement in personally meaningful activities and goals (Martell, Dimidjian, & Herman-Dunn, 2010). Findings suggest that CBT treatments for comorbid SAD and MDD may be enhanced by inclusion of a broader array of exposure targets related to non-social, potentially punishing stimuli (e.g., monetary loss, doing poorly on a task). However, future research is needed to determine the efficacy of this treatment approach.

There was also a significant difference between the comorbid SAD and MDD group versus MDD-alone group on RT for the punishment task. In the current study, RT referred to the amount of time it took for a participant to respond starting from when the stimulus appeared to when they pressed the button with a selection. As expected and consistent with existing signal detection literature (e.g., Pizzagalli et al., 2005), both groups demonstrated decreases in (i.e., quicker) RTs from the first to the second Block,

suggesting both groups responded faster with more practice. The comorbid group demonstrated overall slower RT across both Blocks compared to the MDD-alone group. Therefore, the comorbid group was slower to respond with a decision about which stimulus was presented than the MDD-alone group. Notably, the groups did not significantly differ in discriminability, suggesting that speed was not being traded for accuracy. The interaction between Block and Group was not significant, although follow-up analyses revealed the comorbid group was only significantly slower in the second Block compared to the MDD-alone group.

According to signal detection theory (SDT), RT is thought to be a composite measure that reflects the duration of a set of mental processes (see Jastrow, 1890; Luce, 1986; Sternberg, 1998; Welford, 1980). These mental processes include components both from psychological theory (e.g., approach-avoidance motivation) and information processing theory (e.g., attention, discriminability/identification, encoding). During signal detection tasks, the participant gathers evidence for possible choices and makes a decision once the evidence reaches a threshold (Hancock, Masalonis, & Parasuraman, 2000). A potential interpretation of the current findings is that slower RT in the comorbid group may reflect a difficulty with decision-making (i.e., information processing), perhaps out of fear for receipt of punishment (i.e., psychological). Notably, the current study did not examine trial-by-trial differences, thus interpretations are limited.

Research on RT in SAD and MDD is limited and no studies have utilized non-social stimuli or punishment in their tasks. Despite this, there is some evidence that individuals with SAD demonstrate longer RTs when naming socially threatening stimuli (e.g., Mattia, Heimberg, & Hope, 1993). Individuals with MDD have

also demonstrated this lag for depressive threatening stimuli (Gotlib & Cane, 1987; Gotlib & McCann, 1984), although other studies have not found this effect (Mogg, Bradley, Williams, & Mathews, 1993). Only one study to date (Grant & Beck, 2006) has examined RT in individuals with both social anxiety and dysphoria/depression. Using the Emotional Stroop task, the authors reported there were no significant differences in time to name threatening words between the dysphoric-alone and comorbid socially anxious and dysphoric groups. However, the study used a non-clinical sample, limiting the generalizability of this finding to clinical comorbid samples. Future research is needed to better understand the role of RT in the context of operant conditioning in the etiology and maintenance of comorbid SAD and MDD.

Together, the current findings demonstrate that individuals with comorbid SAD and MDD demonstrate greater response bias and reaction time compared to MDD-alone. That these effects were not found for the reward task suggests a unique effect of non-social punishment (as opposed to more general learning processes) on behavioral responses in this comorbid presentation. This interpretation may suggest that individuals with SAD and MDD may demonstrate greater behavioral avoidance in tasks in which they might be apprehensive about receiving punishment. For example, greater avoidance both in selection (RB) and time to respond with a selection (RT) may have important real world implications such as delays or avoidance in important daily tasks such as paying bills or going to the doctor. However, future research examining RB and RT with non-social punishment in SAD-alone and healthy controls is needed to clarify the specific impact of SAD comorbidity on these patterns.

Reward Findings

As described above, the reward task in the current study was used as a control for the punishment task. Consistent with hypotheses, there were differential effects of punishment compared to reward in comorbid SAD and MDD versus MDD-alone. Specifically, unlike the punishment task, there were no significant differences between the comorbid SAD and MDD and MDD-alone groups on any variable across the reward task. These findings suggest that the reward responsivity deficit in depression (e.g., Pizzagalli et al., 2005, 2008, 2009) is not worsened by comorbid SAD. Furthermore, the results are consistent with laboratory (Abraham & Hermann, 2015; DeVido et al., 2009) and self-report findings (Kimbrel et al., 2008; Ly & Gomez, 2014) that reward responsivity is not impaired in SAD. However, future research is needed to examine reward responsivity in SAD-alone versus comorbid SAD and MDD. In sum, the findings provide evidence for the unique effect of SAD in the domain of punishment learning.

Notably, as would be expected, discriminability significantly improved across Blocks in the reward task. However, this was not the case in the punishment task. This discrepancy may suggest that distinguishing between stimuli on the reward task was easier than on the punishment task. This interpretation is also consistent with the lower rate of outliers on the reward task compared to the punishment task.

Punishment Outliers

In SDT tasks, there are several reasons why participants become outliers including poor accuracy, inability to distinguish stimuli, and avoidant responses (e.g., people who stop responding and just press the same key). Given the elevated rate of outliers on the punishment task (i.e., approximately 50% in this study) versus outlier rates

with similar reward-based learning tasks in psychiatric samples (25-30%; Ahnallen et al., 2012; Liverant et al., 2014; Pizzagalli, Goetz, Ostacher, Iosifescu, & Perlis, 2008), I also investigated potential predictors of outlier status. Contrary to hypotheses, BI did not significantly predict punishment outlier status. This finding suggests that greater self-reported tendency to avoid or withdraw from and increase attention or vigilance to punishing stimuli may not influence the likelihood of completing tasks involving punishment. Notably, the entire sample was composed of individuals with clinical depression and multiple psychiatric comorbidities. Thus, BIS scores were likely elevated in most participants, and restricted range in BIS severity in the sample may have influenced findings with BI, inhibiting our ability to find significant associations. The average BIS score ($M = 21.91$; $SD = 3.72$) was higher than those reported in other outpatient clinical samples ($M = 16.98$; $SD = 2.94$; e.g., Campbell-Sills, Liverant, & Brown, 2004) further supporting this interpretation.

Also contrary to hypotheses, comorbid PTSD did not significantly predict punishment outlier status. However, when examining self-reported PTSD symptoms as a dimensional construct in the full sample, punishment outliers had significantly higher hyperarousal scores than non-outliers. The DSM-5 defines the PTSD hyperarousal symptom cluster as including heightened startle reaction, hypervigilance, irritability or aggression, and difficulty concentrating and sleeping (APA, 2013). Item-specific analyses from the current study revealed that individuals who were punishment outliers endorsed more hyperarousal (i.e., startle reaction), hypervigilance, and irritability, but not increased concentration or sleep difficulties than non-outliers. That is, specific symptoms of hyperarousal, unrelated to concentration or fatigue, are associated with greater

difficulties completing tasks involving receipt of punishment. One possible interpretation of these findings is that greater vigilance and reactivity (i.e., arousal and irritability) to punishment may result in lower distress tolerance and, therefore, increase the likelihood of giving up or quitting a task. This interpretation is consistent with prior research demonstrating that low distress tolerance is associated with decreased persistence during frustrating tasks (e.g., Ellis, Vanderlind, & Beevers, 2012; Lejeuz, Kalher, & Brown, 2003) and a study that found hyperarousal has the strongest association to distress tolerance compared to the other PTSD symptom clusters (Vujanovic, Bonn-Miller, Potter, Marshall, & Zvolensky, 2011).

With no significant differences in punishment outlier status between the comorbid PTSD and MDD and the MDD-alone groups, the current findings may also suggest that hyperarousal is an important transdiagnostic factor associated with aberrant responses to punishment. Increased arousal has been studied beyond PTSD in the context of depression. For example, irritability in the form of anger attacks is highly prevalent in depression (Fava & Rosenbaum, 1999) and has even been proposed as a subtype of depression (Painuly, Sharan, & Mattoo, 2005). Other studies have found that hyperarousal is associated with a dampening in emotional reactivity, which is a feature of depression (Flack, Litz, Hsieh, Kaloupek, & Keane, 2000; Litz et al., 1997; Weems, Saltzman, Reiss, & Carrion, 2003). Theories suggest that prolonged hyperarousal in PTSD and depression leads to the depletion of cognitive and emotional resources (Flack et al., 2000; Litz et al., 1997). Thus, another possible interpretation of the current findings is that depressed individuals experiencing elevated levels of hyperarousal while receiving punishment may deplete their resources needed to complete the task, increasing the

likelihood of becoming an outlier. Prior studies have found hyperarousal leads to increased error rates during experimental tasks (e.g., Edinger, Means, Krystal, & 2013).

In line with this, hyperarousal may be a particularly important factor for researchers to consider when employing experimental tasks of this type, especially in comorbid samples where levels of this symptom cluster may be especially high. Importantly, few studies have actually examined predictors of outlier status (Sheynin et al., 2013) despite significantly higher rates in clinical samples (Ahnallen et al., 2012; Liverant et al., 2014; Pizzagalli, Iosifescu, et al., 2008; Sawyer et al., 2016). Future research is needed to examine the relationship between psychological variables and outlier status on experimental tasks used in clinical research, which could help articulate additional behavioral patterns that may currently be being missed.

Exploratory Findings

Exploratory analyses examining whether there were differences in learning between individuals with comorbid PTSD and MDD compared to MDD-alone revealed no significant differences on any task outcome variable (i.e., RB, RT, or discriminability) across both punishment and reward learning tasks. These findings suggest that there is a unique impact of SAD on responsivity to non-social punishment in SAD+MDD versus MDD-alone even in a Veteran sample with high levels of comorbid PTSD.

Using the same task as the current study, Sawyer and colleagues (2016) found Veterans with PTSD compared to controls without PTSD demonstrated greater punishment learning. Importantly, in this study, approximately one third of their PTSD sample had co-morbid MDD, and clinical depression was an exclusionary criterion for the control group. Thus, Sawyer et al. (2016) were unable to determine whether the

observed differences in task performance were associated with PTSD or co-occurring depression in their PTSD sample. The lack of difference in punishment learning between individuals with PTSD and MDD versus MDD alone in the current study may suggest that the observed differences in punishment learning in the Sawyer et al. study were due to depression symptoms in the PTSD group. More research with larger sample sizes is needed to statistically examine the relative contributions of PTSD and co-occurring depression to punishment learning. Furthermore, exploratory analysis revealed that behavioral inhibition did not significantly predict punishment response bias (RB). These findings suggest that behavioral inhibition alone did not significantly contribute to avoidant responsivity to punishment. However, it is possible that the restricted range in BIS scores in the current sample composed of severely clinically depressed Veterans may have influenced our ability to find significant associations.

Limitations

Although the current study adds to the literature on punishment-based learning in comorbid SAD and MDD, there are some limitations that should be noted. First, 45% of the sample was classified as an outlier on the punishment task and PTSD-related hyperarousal was significantly related to punishment outlier status, raising questions about the generalizability of study findings to the broader population of individuals with MDD and SAD. These findings may suggest that failure to validly complete the punishment task (for reasons previously reviewed) is influenced by another un-assessed variable such as distress tolerance or executive functioning (given that there were no differences in outlier status between groups). However, literature examining predictors of outlier status on tasks of this type is limited. Future research is needed to examine the

impact of other variables on outlier status to better interpret the external validity of findings.

Second, the current study did not have a healthy control or a SAD-alone group to compare against SAD+MDD and MDD-alone, thus interpretations of group differences are limited to only those between the comorbid and depressed group. It remains unclear how punishment responsivity in SAD-alone or MDD-alone differs compared to healthy controls, or how responsivity differs between comorbid SAD and MDD versus SAD-alone. Future research focusing on punishment responsivity differences between these groups will help clarify the relative effects of diagnostic status in this behavioral domain. Furthermore, compared to the punishment task, which used both non-social stimuli (shapes) and punishment (money loss), the reward task used social stimuli (cartoon face) and non-social reward (money gain). The use of social stimuli calls into question whether the reward task can be considered a control task given the possible effect of social stimuli on responsivity (e.g., Sripada, Angstadt, Liberzon, McCabe, & Luan Phan, 2013; Taylor, Bomyea, & Amir, 2010). Additionally, the current sample had minimal exclusion criteria and thus comorbid psychiatric diagnoses other than SAD and PTSD may have affected findings. Furthermore, the current sample was predominantly composed of male Veterans, thus caution should be used in interpreting results in female and non-Veteran samples.

Conclusions

Despite these limitations, this is the first study to examine response bias to non-social punishment between individuals with comorbid SAD and MDD versus MDD-alone. Findings suggest the importance of broadening the stimuli used in

exposures/behavioral activation tasks to include a broader array of potentially punishing experiences for this comorbid presentation, while encouraging continued approach behaviors. Furthermore, the current findings highlight the need for continued investigation in the role of punishment responsivity and learning in the onset and maintenance of comorbid SAD and MDD. In order to better understand this behavioral domain, future studies should examine the effects of non-social punishment responsivity in this comorbid presentation compared to both individuals with SAD-alone and healthy controls.

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APPENDIX A. LEARNING PARADIGMS

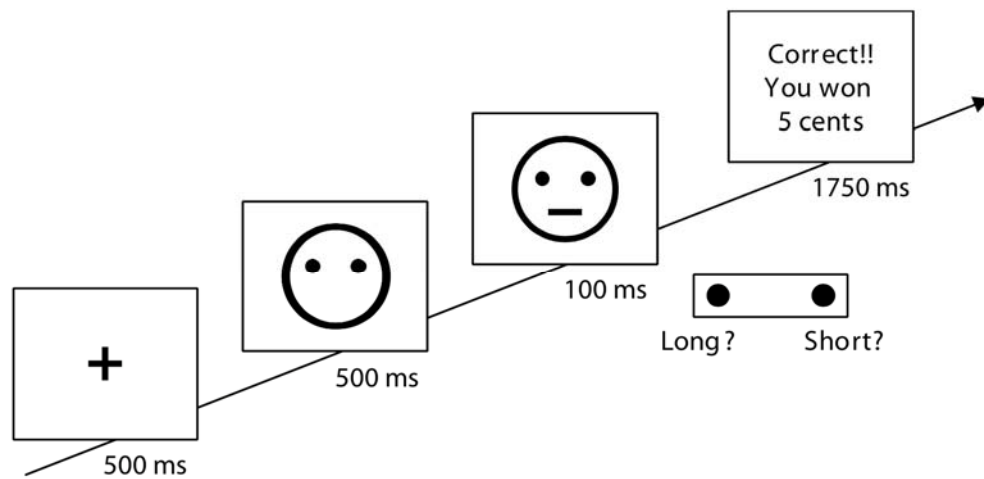


Figure 1. Reward paradigm.

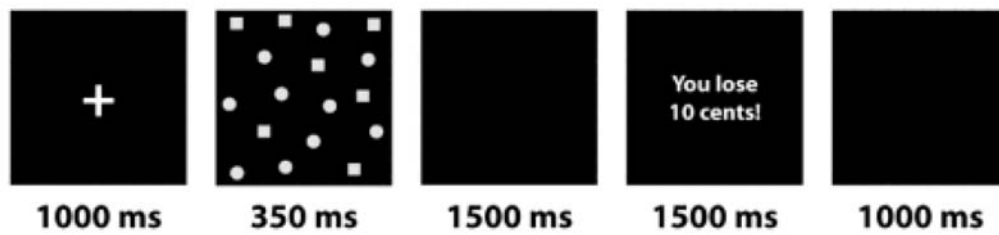


Figure 2. Punishment paradigm.

APPENDIX B. GRAPHS OF PUNISHMENT TASK RESULTS

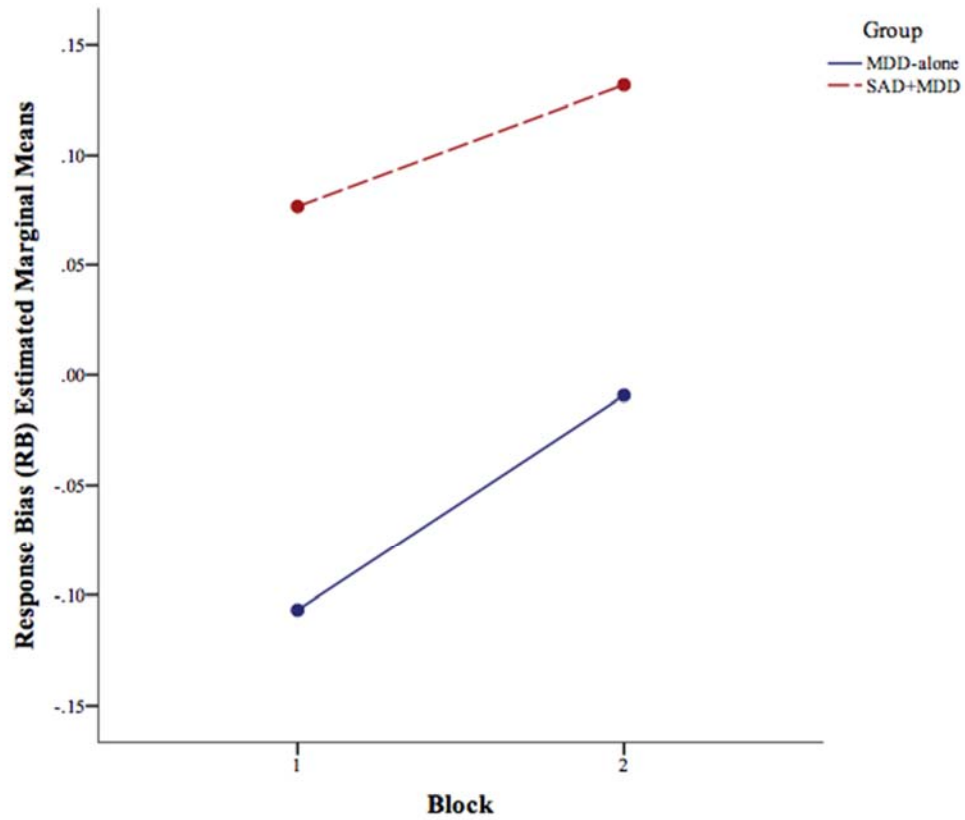


Figure 3. Punishment response bias between groups across blocks.

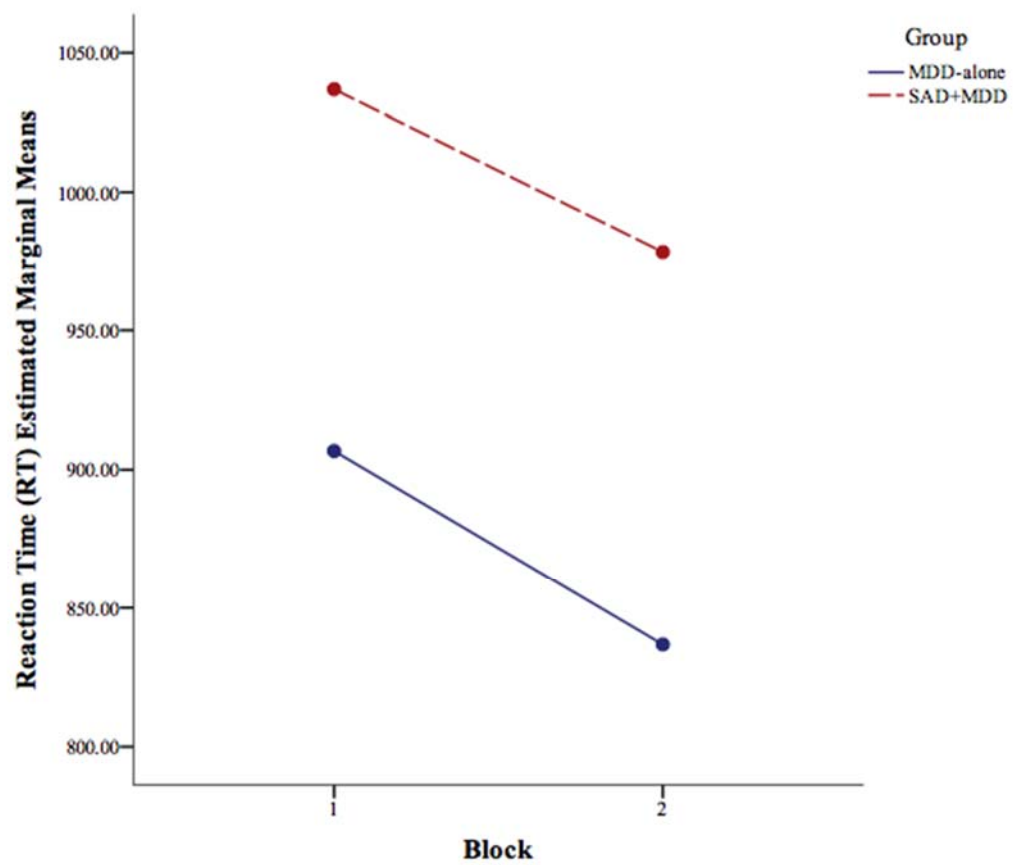


Figure 4. Punishment RT between groups across blocks.