Mnemonic Discrimination Under Stress and Its Clinical Relevance for Anxiety

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Abstract
Mnemonic discrimination, the ability to differentiate highly similar old and new entities, is a novel mechanism of interest in anxiety disorders. However, little research has been conducted with individuals experiencing severe anxiety. Mnemonic discrimination was assessed in adults with a wide range of anxiety severity. State affect was manipulated to test whether the relationship between anxiety and mnemonic discrimination is more informative under threatening versus neutral conditions. Relative to control conditions, mnemonic discrimination worsened following a psychological (social evaluative) stressor in Study 1 but not a physical (aversive sounds) stressor in Study 2. There were no main effects of performance in predicting anxiety. In Study 1, there was an interaction such that only poor performance following the stressor was associated with severe anxiety. Results suggest that mnemonic discrimination is sensitive to affective context and that mnemonic discrimination under states of psychological distress may be particularly relevant in the study of anxiety.

Keywords
pattern separation, mnemonic discrimination, worry, anxiety, stress

Anxiety disorders pose a serious public health concern because up to a third of the population will meet diagnostic thresholds during their lifetime and many more will suffer from subclinical symptoms that lower quality of life, functioning, health, and productivity (Haller, Cramer, Lauche, Gass, & Dobos, 2014; Olatunji, Cisler, & Tolin, 2007; Wittchen, 2002). A central feature of anxiety disorders is experiencing benign or ambiguous situations, thoughts, physical sensations, or stimuli as threatening. Individuals with generalized anxiety disorder (GAD) perseverate on catastrophic possibilities in response to uncertainty, individuals with social anxiety disorder (SAD) may automatically pair attending a party with inevitable social defeat, and individuals with panic disorder can interpret a quickened pulse as a sign of an imminent heart attack. Learning theories describe how such fear responses become instantiated through associative learning and paradoxically strengthened through emotion-driven behaviors such as avoidance or overpreparation (e.g., Mineka & Zinbarg, 2006). Threat-related attention and interpretation biases, which are transdiagnostic phenomena of clinical anxiety, increase the frequency and intensity of emotional distress in response to perceived stressors and thus exacerbate learning effects (McNally & Reese, 2008). Research that can identify specific, mechanism-focused targets for feasible prevention and early intervention may help to address these problems.

A key component of such etiological and maintenance models is generalization of fear learning. Generalization broadly refers to the use of past learning to make sense of new experiences. This occurs when novel stimuli or situations evoke comparisons to similar representations already stored in memory. This system of cued comparisons is essential for predicting whether a new context...
will bring reward or punishment and deciphering ambiguous or noisy scenarios (Mattson, 2014). Generalizing across time or context is an adaptive and important function. In the case of fear learning, safety and survival depend on it; for instance, nearly stepping into oncoming traffic or touching a hot stove can prevent a person from repeating these behaviors on any busy street or in any kitchen subsequently. Generalization allows for such critical judgments to be made effectively and efficiently. But, whereas some amount of generalization is critical, clinical levels of anxiety may reflect overgeneralization (Liszek, 2012; Liszek et al., 2010, 2014). These individuals may fearfully avoid safe stimuli that resemble threatening ones in form, concept, or content (Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2015). For instance, being afraid to cross any street (busy or not) or entering any kitchen would be impairing. Overgeneralization can also occur in the absence of physical danger; for example, high anxiety in anticipation of submitting college applications could generalize to high anxiety in anticipation of any deadline, large or small. Notably, generalization tends to be greater when the targets of memory or learning are negative in valence than neutral or positive (Schechtman, Laufer, & Paz, 2010). Fear responses and subsequent avoidance behaviors reinforce problematic associations because exposure to harmless stimuli is limited and thus the formation of new representations and extinction learning are as well (Foa & Kozak, 1986).

These insights have led to extensive research devoted to understanding behavioral and neural mechanisms of overgeneralization across anxiety disorders (Dunsmoor & Paz, 2015; Dymond et al., 2015). Poor mnemonic discrimination is a theoretically compelling candidate mechanism that has the potential to connect findings from basic neuroscience and functional magnetic resonance imaging (fMRI) research to behavioral and clinical outcomes, including the development of a range of anxiety disorders (Balderston et al., 2015; Kheirbek, Klemenhagen, Sahay, & Hen, 2012). Mnemonic discrimination captures one’s ability to differentiate a new entity from a past one that is highly similar. Beyond general recognition memory, this relies on encoding episodic memories with sufficient detail such that even minimal differences in subsequent encounters register as distinct (Yassa & Stark, 2011). Difficulty resolving interference from a stored memory leads people to struggle with mnemonic discrimination. In other words, if a previously encoded representation overlaps with a new one, it becomes difficult to inhibit retrieval of the prior representation and perceive the latter as distinct. Adequate mnemonic discrimination should promote greater memory flexibility, or a balance between memory specificity and generalization. Overgeneralization may partly arise from imprecise mnemonic representations because fear responses are often elicited as a result of perceived perceptual (or other) similarities between stimuli, even those unrelated to the initial aversive event itself.

Behavioral neuroscientists have discovered apparent neural correlates of mnemonic discrimination. Mnemonic discrimination appears to reflect the ongoing trade-off between hippocampal pattern separation, the computational process of encoding new stimulus inputs in distinct ways, and pattern completion, the process of retrieving memories from partial cues (Besnard & Sahay, 2015; Rolls, 2013). In cases of high pattern separation, stimuli are represented sparsely within the dentate gyrus of the hippocampus, making it more likely that their signature is unique (Yassa & Stark, 2011). In cases of low pattern separation, stimuli are instead represented with broad arrays of neural activation. With insufficient pattern separation during encoding, stimuli can increasingly overlap in their neural representations, hence producing memory interference. This makes it more difficult to differentiate between similar entities during retrieval. Excessive pattern completion can occur as a new stimulus is interpreted as very similar or even identical to a past stimulus. In contrast, sufficient pattern separation enables the formation of distinctive episodic memories and should promote the consequential ability to differentiate novel entities from highly similar, previously encoded ones (Kheirbek & Hen, 2014; Sahay et al., 2011).

Interactions between the hippocampus and other regions appear critical as well. Early research implicates connectivity between the dorsolateral prefrontal cortex (dlPFC) and hippocampus as central to resolving memory interference, namely, mnemonic discrimination. Poor mnemonic discrimination may result from difficulty engaging the dlPFC for cognitive control (Balderston, Hsiung, Ernst, & Grillon, 2017). High pattern separation may lower the threshold for the degree of cognitive control needed in these scenarios, whereas low pattern separation may require a higher degree of control. Additionally, episodic memory appears modulated by the amygdala (Leal, Tighe, Jones, & Yassa, 2014; McGaugh, 2004). The amygdala may acutely influence pattern separation when discrimination is based on reward value (Gilbert & Kesner, 2002) and when stimuli evoke emotion because the amygdala influences specificity in hippocampal encoding (McGaugh, 2004; Yassa et al., 2011). More emotional stimuli may therefore further bias people toward pattern completion and low discrimination.

There are at least two reasons why it is appealing to propose poor mnemonic discrimination as a risk or maintenance factor for anxiety disorders (Kheirbek et al., 2012). First, this follows evidence of structural and functional hippocampal deficits in those with severe
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anxiety (DeCarolis & Eisch, 2010) and dysregulation in the amygdala among individuals with or at risk for anxiety disorders (Fitzgerald et al., 2017), and fMRI research suggests some shared neurocircuitry between fear learning and pattern separation, with emphasis similarly placed on the hippocampus and amygdala (Dunsmoor & Paz, 2015; Dymond et al., 2015). Second, it fits with the conceptualization of clinical anxiety as disordered or overgeneralized fear learning (Lissek et al., 2010, 2014). When a new deadline sparks uncontrollable worry, sweating results in a panic attack, or the sound of a car backfiring triggers a flashback, it may be due to memory interference. In other words, anxious individuals may struggle to dissociate new sounds, sensations, or situations from similar ones previously encoded as threatening (Scharfman & Myers, 2016). Memory interference could serve as a diathesis for overgeneralizing fear learning. A person who subjectively experiences a past threatening context and a current safe context as similar should be especially likely to interpret the latter as threatening and respond fearfully.

Despite exciting findings in rodent models showing that degrading or enhancing hippocampal pattern separation weakens or strengthens discriminative fear learning, respectively (Bekinschtein, Oomen, Saksida, & Bussey, 2011; Kheirbek et al., 2012), and early evidence in humans without psychopathology that mnemonic discrimination is associated with generalization of shock expectancy in conditioning paradigms (Lange et al., 2017), there remains a lack of clinical research in humans. Most prior studies explicitly have excluded individuals with anxiety disorders and related psychopathology and symptoms (e.g., Balderston et al., 2015; Lange et al., 2017). Given that mnemonic discrimination appears related to anxiety, it is surprising that there have been few studies exploring mnemonic discrimination in individuals with clinical symptoms or even examining the association between mnemonic discrimination and anxiety. Research on individuals varying widely in levels of anxiety is essential for testing the robustness of the connection between anxiety and mnemonic discrimination. The first aim of this project is to test for these connections. Participants in the present studies therefore range from reporting low to severe levels of chronic, uncontrollable worry, a hallmark symptom of generalized anxiety disorder and significantly elevated in anxiety disorders more broadly (Brown, Antony, & Barlow, 1992; Hearn, Donovan, Spence, March, & Holmes, 2017; Starcevic et al., 2007).

Theoretically, highly anxious participants should exhibit worse mnemonic discrimination than less anxious or nonanxious peers. Investigating these basic associations is an important first step in identifying mnemonic discrimination as a mechanism of illness in anxiety disorders potentially suitable as a novel target for treatment. A positive signal in this foundational work would justify and inform future research to further elucidate these processes, their biological correlates, and their malleability.

Furthermore, mnemonic discrimination typically has been evaluated in neutral laboratory conditions (i.e., in which an affect state is not induced). Although this design is necessary for foundational, controlled research, it has limitations that could prevent researchers from identifying real relationships between mnemonic discrimination and anxiety. For example, in daily life, people often encounter familiar and novel stimuli in negative affective states, and persistent or frequent feelings of unease, uncertainty, or apprehension are common to anxiety disorders. Mnemonic discrimination in neutral conditions may fail to reliably delineate clinical and control populations or necessarily relate to risk. And, mnemonic discrimination in states of stress might instead be the more relevant index. Related cognitive research suggests that decline in cognitive control in stressful conditions is a better predictor of emotional health than control under neutral conditions (Quinn & Joormann, 2015; Yoon, LeMoult, Hamedani, & McCabe, 2017). Furthermore, extensive research has been conducted regarding the influence of affective state on episodic memory. Most relevant to the present study, it appears that whereas acute stress or arousal can enhance encoding (McGaugh, 2002, 2004), it can also temporarily worsen retrieval, working memory, or learning (Raio, Brignoni-Perez, Goldman, & Phelps, 2014; Roozendaal, McEwen, & Chattarji, 2009). It is unsurprising, then, that previous studies have found that mnemonic discrimination is not a stable, trait-like individual difference variable. This form of episodic memory is sensitive to states of arousal induced with emotionally arousing images (Segal, Stark, Kattan, Stark, & Yassa, 2012) or threat of shock (Balderston et al., 2015). It is thus important to understand how mnemonic discrimination might function under stressful conditions as well.

Accordingly, the second aim of this project is to examine the effects of stress on mnemonic discrimination and how subsequent changes in performance might relate to clinical anxiety. In Study 1, we used a psychological stressor to induce situational anxiety, and in Study 2, we used a physical stressor, an unpredictable aversive auditory stimulus. We hypothesized that participants would demonstrate worse mnemonic discrimination under acute stress than under neutral conditions (Balderston et al., 2015). Furthermore, we expected that performance in the stressful condition would differentiate among individuals with and without severe anxiety more than would performance in the neutral condition. We predicted that the weakest mnemonic discrimination
scores in such conditions would belong to those scoring highest on indices of pathological anxiety.

Mnemonic discrimination could be a novel endophenotype for anxiety disorders and a measurable link between neurobiological observations and clinical phenomena such as overgeneralization of fear or memory (Kheirbek et al., 2012; Yassa et al., 2011). At this point, however, limited pattern separation research has been done in humans and even less with individuals experiencing severe levels of anxiety. Thus, it remains to be established that poor mnemonic discrimination is a marker of clinical risk. Furthermore, our understanding of the processes through which mnemonic discriminations and psychopathology are interrelated remains incomplete. In the present study, we begin addressing these open questions by examining whether clinically significant anxiety is associated with worse mnemonic discrimination and whether this relationship is particularly strong or informative under conditions of acute distress.

**Methods**

**Study 1**

**Participants.** Sixty-five adults (39 women, mean age = 32.65 years, SD = 8.35, age range = 18–50 years) enrolled in the study. Of these participants, 60% were White, 16.92% were African American or Black, 15.38% were Asian or Asian American, 1.54% were Native American, and 4.62% reported being multiracial. The majority of participants (92.31%) identified as not Hispanic or Latino. Eligible participants had no history of head injury, cognitive impairment, neurologic disorder, mania, or psychosis and were not taking any psychiatric medications. To ensure representation of individuals with high levels of worry, we aimed to recruit participants such that at least one third of the sample had high scores on the Penn State Worry Questionnaire (PSWQ ≥ 55; Meyer, Miller, Metzger, & Borkovec, 1990). High scores reflect chronic, excessive, uncontrollable worry and indicate high vulnerability for or likelihood of being diagnosed with generalized anxiety disorder as well as other anxiety disorders, including social anxiety disorder and panic disorder (Behar, Alcaine, Zuellig, & Borkovec, 2003; Brown et al., 1992; Startup & Erickson, 2008). Thus, this measure provides one continuous index of anxiety severity, at the high end of which participants are experiencing clinical levels of dysfunction. Ultimately, 24 participants (36.92%) in Study 1 exceeded this threshold.

**Procedure.** Participation involved two lab visits one week apart. Participants, whom we recruited from the community, completed self-report questionnaires and the Mnemonic Similarity Task (MST) twice, once at rest and once under stress. The stressor condition—including two social-evaluative stressors—was designed to serve as an experimental analog of real-life stressors and explore the sensitivity or stability of mnemonic discrimination performance. Different versions of the task (i.e., different stimulus sets) were used in each condition. Although there is little, if any, evidence of practice effects for this task when different stimulus sets are used (Stark, Stevenson, Wu, Rutledge, & Stark, 2015), the order of conditions and stimulus sets were counterbalanced to control for this possibility. This study employed a mixed-effects design in which level of chronic, excessive worry was a between-subjects factor and condition (stressor or control) was a within-subjects factor. All procedures were approved by Harvard University’s Committee on the Use of Human Subjects.

**Self-report measures.** All participants completed a battery of questionnaires, including demographics (e.g., gender, race), a trait measure of pathological worry (PSWQ), and exploratory measures of additional, related clinical constructs, including somatic anxiety, general stress, and depressed mood (Depression Anxiety Stress Scales [DASS]; Lovibond & Lovibond, 1995).

The PSWQ is a widely used, 16-item self-report measure of pathological worry and general anxiety (Meyer et al., 1990). The PSWQ measures the frequency, severity, and negative consequences of chronic anxiety. The PSWQ has high internal consistency, test–retest reliability, and construct validity and performs well in discriminating among individuals meeting all, some, or no criteria of GAD (Behar et al., 2003; Meyer et al., 1990; Startup et al., 2003; Startup & Erickson, 2008). Higher PSWQ scores indicate more severe anxiety.

The DASS is a 21-item self-report measure assessing three clinical constructs that are distinct though not mutually exclusive from pathological worry: depression symptoms, physical anxiety symptoms, and stress. Examples of anxiety items include sweating, racing heart, situational anxiety, and panic. Example stress items include irritability, tension, and startle. Example depression items include sadness, hopelessness, and psychomotor retardation. In all cases, higher scores indicate more severe symptoms or pathology. This measure has good internal consistency and concurrent validity. Subscales correlate strongly with Diagnostic and Statistical Manual of Mental Disorders (DSM–IV; American Psychiatric Association, 1994) diagnosis (e.g., individuals with major depressive disorder score high on the depression subscale, individuals with panic disorder score high on the anxiety subscale, and control groups score low across subscales; Antony, Bieling, Cox, Enns, & Swinson, 1998).

**Computer task.** After completing the battery of self-report measures, participants then completed the MST, a
behavioral measure of mnemonic discrimination. The MST is a well-validated behavioral proxy to tax hippocampal pattern separation and is sensitive to age- and disease-related changes therein (Stark, Yassa, Lacy, & Stark, 2013). The MST includes an encoding phase (Phase 1) and a retrieval phase (Phase 2). During the encoding phase (5 min), participants saw a series of 128 everyday objects (e.g., glasses, sock) and were instructed to label each object as belonging indoors or outdoors. During the retrieval phase (8 min), participants saw a second series of 192 objects. Sixty-four were repeated from Phase 1 (targets), 64 were novel (foils), and 64 were similar but not identical to stimuli from Phase 1 (lures). Participants labeled each item as old, new, or similar and were given examples before beginning. Images were shown for 2 s with an interstimulus interval of 0.5 s. The main index, a mnemonic discrimination score—that is, the lure discrimination index (LDI)—is derived from the ratio of similar judgments made correctly to those made incorrectly on foils. The foils control for any bias to use the similar rating when participants are uncertain. Low LDI scores indicate poor performance. Additionally, a traditional index of recognition memory can be calculated by subtracting the rate of incorrectly labeling targets from the rate of correctly identifying targets. Subjects were not informed prior to the first MST that it would include a retrieval phase. Because subjects completed the task multiple times, they may have employed different strategies during the second administration than the first. As noted above, the order of conditions was counterbalanced to limit possible order effects.

**Experimental manipulation.** Before each phase of the MST, participants underwent experimental manipulations according to their random assignment for that visit. This design followed prior findings that stress during the entire MST most reliably weakens performance (Balderston et al., 2015) because the goal was to look for a signal of stress-induced declines better predicts anxiety.

**Stressor condition.** Before the encoding phase (Phase 1) of the MST, participants completed the first part of a modified Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993), one of the most commonly used and reliable tasks for experimentally inducing acute stress in the study of numerous emotional disorders (Allen et al., 2017). They prepared and delivered a 5-min speech while believing they were being videotaped (we installed on the wall a nonfunctioning prop camera) and judged by two experimenters, who provided no feedback. Participants were told to imagine that they had been invited to interview for a new job and were to speak about why they would be a good colleague. Participants were allowed 3 min to prepare but were not allowed to use any notes during the speech. Before the retrieval phase (Phase 2) of the MST, participants completed the second part of the modified TSST, which involved a challenging serial subtraction task for 5 min while again being videotaped and observed by two experimenters. Participants were not allowed to use pen or paper and received no feedback other than being told they had to start over after making an error. After each stressor, participants were told that they would continue to be taped and evaluated during the subsequent computer task.

**Control condition.** Before each phase of the MST, participants completed a parallel control task for the TSST. Before the encoding phase (Phase 1), they read aloud a neutral passage. Participants were allowed 3 min to browse a few options before selecting one for the 5-min speaking portion. Before the retrieval phase (Phase 2), participants completed a simple addition task aloud (counting by twos). Participants were not judged, nor was there a video camera present in either phase. In previous experiments, this placebo TSST rarely provoked stress in participants, although it shares all other components, including general procedure and duration, and thus can help to control for cognitive and physical load associated with the stressor (Frisch, Häusser, & Mojzisch, 2015; Het, Rohleder, Schoofs, Kirschbaum, & Wolf, 2009).

**Stress response.** To quantify subjective stress responses to the experimental conditions (stressor vs. control), we used the arousal and valence items from the Self-Assessment Manikin (SAM; Lang, Greenwald, Bradley, & Hamm, 1993). Participants selected visual icons that best corresponded to their state level of emotional arousal and valence, respectively. To quantify objective stress response to the experimental conditions, we also measured autonomic reactivity to the manipulations. The primary psychophysiological outcome measure was skin conductance level (SCL), and secondary measures included heart rate (HR) and respiratory sinus arrhythmia (RSA). SCL reflects sympathetic activity within the autonomic nervous system. Increases in SCL signify increased sympathetic reactivity (Watts, 1975) and often accompany emotional states marked by high arousal, such as anxiety during an experimental stressor (Ax, 1953). HR estimates provide a general index of physiological reactivity, being influenced by both sympathetic and parasympathetic nervous systems, and RSA provides an indicator of parasympathetic nervous system reactivity and control (Berntson, Quigley, Norman, & Lozano, 2017). Note that we use RSA to refer to high-frequency heart-rate variability. However, RSA values were derived not from respiration data but by using the AcqKnowledge RSA-spectral analysis tool, which performs analyses on electrocardiographic (ECG)
waveforms. Higher resting RSA and RSA suppression under stress signify robust emotion regulation and less emotional reactivity (Porges, 2007; Porges, Doussard-Roosevelt, & Maiti, 1994). Task-related increases in RSA reflect efforts at emotional coping (Butler, Wilhelm, & Gross, 2006; Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012). Details of the psychophysiological acquisition methods are included later in the Recording Psychophysiology section. We expected increases in subjective arousal, SCL, HR, and RSA and more negative valence ratings during the stressor condition relative to the control condition.

**Statistical analysis.**

**Self-report measures.** Demographic and clinical characteristics of the sample are described in terms of counts and proportions for categorical variables and means and standard deviations for continuous variables. One-way analyses of variance (ANOVA) were used to explore differences in worry status (PSWQ score) by sex, race, ethnicity, and education, and pairwise correlations were used to explore differences by age, DASS-Depression, DASS-Anxiety, DASS-Stress, baseline valence, and baseline arousal.

**Manipulation check.** To confirm that the stressor condition induced a state of anxiety or distress relative to the control condition, we conducted linear mixed models with valence and arousal ratings as the criterion variables and time, condition, and their interaction as predictors. Subjects were included as random effects. Because unique stressors (or placebo tasks) were administered prior to each phase of the MST, the following time points were included: baseline, start of encoding phase (Phase 1), between phases, start of retrieval phase (Phase 2), and end of study. We conducted follow-up post hoc multiple comparisons among means with Tukey adjustment. We also examined differences in the average HR, and RSA between the two conditions to gauge physiological stress response.

**Main analyses.** Two LDI scores from the MST falling more than 2.5 standard deviations below the mean were excluded prior to analysis. No scores exceeded 2.5 standard deviations above the mean. We tested whether the LDI scores were significantly worse in the stressor condition than in the control condition as predicted by fitting a linear model with LDI score as the criterion, condition as the main (fixed) predictor, and subject as a random effect. We ran an additional analysis including age as a moderator, given known age-related declines in pattern separation and downstream mnemonic discrimination performance and the sample’s relatively wide age range (18–50), and explored how performance differed by age (Stark et al., 2013, 2015). Prior work has shown that MST performance among adults under 40 years old significantly differs from those over 40 (Stark et al., 2013). We expected to find a similar pattern in the present sample. As basic processes underlying performance could differ in older participants, older individuals may be differentially affected by the stressor as well. We then examined the relationship between LDI and pathological worry (PSWQ score). We first explored the main effect of LDI on PSWQ score, followed by the interaction between LDI and condition using multiple regressions. To address the possibility that results were due to order effects, general memory function, or differences in response to the stressor, we also controlled for MST order, simple recognition memory ability, changes in self-reported anxiety (a composite of valence and arousal ratings), and mean SCL, HR, and RSA.

Sample sizes were suitable for detecting at least medium effect sizes per an a priori power analysis (F test, repeated measures, within-between interaction) with \( \alpha > .05 \), power = .95, and Cohen’s \( f \) effect size = .25.

**Study 2**

The goal of Study 2 was to conceptually replicate and extend the hypotheses tested in Study 1. Specifically, we tested whether a physical (auditory) stressor would produce the same effects on mnemonic discrimination as a social stressor did in Study 1.

**Participants.** One hundred twenty-eight individuals (77 female, mean age = 23.38 years, \( SD = 4.85 \), age range = 18–40 years) completed the study. An additional 5 individuals enrolled in the study, but they were excluded because of technical issues (\( n = 1 \)) or inability to comprehend or follow the protocol (\( n = 4 \)). Within the final sample, 43.75% identified as White, 20.31% as African American or Black, 21.09% as Asian or Asian American, 0.78% as Native American or American Indian, 9.38% as multiracial, and 3.91% as other or unreported. The majority of participants were not Hispanic or Latino (82.81%). Allowable age range was restricted to 18 to 40 years. All other eligibility criteria and recruitment strategies were repeated from Study 1. Sixty participants (46.51%) in Study 2 exceeded the threshold for high anxiety on the PSWQ.

**Procedure.** A similar procedure to Study 1 was used in Study 2. Participants completed the same self-report questionnaires and mnemonic discrimination task (MST). The task was completed twice, once at rest and once under stress (i.e., unpredictable loud noises), during one study visit. Different versions of the task (i.e., different stimulus sets) were used in each condition. Stimulus set and order of conditions were counterbalanced across
participants. To avoid any potential carryover effects, we had participants take a 10-min break between the two tasks, during which they watched an emotionally neutral nature video. In addition to modifying the type of stressor used, we also were able to conduct a psychiatric diagnostic interview with each participant. These two modifications are detailed below. All procedures were approved by Harvard University’s Committee on the Use of Human Subjects.

**Diagnostic interview.** Select modules of the Structured Clinical Interview for DSM–5 (SCID; First, Williams, Karg, & Spitzer, 2015) were administered by an advanced doctoral student to assess for anxiety and related pathology. Anxiety disorders, posttraumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and major depressive disorder (MDD) were assessed. The SCID is a semi-structured interview used to assess the diagnostic criteria for DSM–5 (American Psychiatric Association, 2013) disorders. The SCID has shown adequate interrater reliability (First et al., 2015).

**Experimental manipulation.** During each phase of the MST, participants underwent experimental manipulations according to their random assignment for that visit.

**Stressor condition.** Threat of unpredictable aversive noises was used as the experimental stressor. Participants were told that they would hear a loud noise periodically during the MST. Brief and harmless 0.5-s sounds (recording of a fork on a chalkboard; 80 db) were delivered through over-the-ear headphones during randomly selected interstimulus intervals of the MST (12 during encoding phase and 16 during retrieval phase). The timing was unpredictable to induce anxiety. A similar approach, though with mild shocks, has induced the intended stress response and lowered MST performance (Balderston et al., 2015).

**Control condition.** In the control condition, participants also wore the headphones but were informed that the only sounds they would hear during the task were instructions to begin.

**Statistical analysis.**

**Baseline measures.** Demographic and clinical characteristics of the sample are presented as counts and proportions (categorical variables) or means and standard deviations (continuous variables). Potential differences in severity of chronic worry (i.e., PSWQ score) by sex, race, ethnicity, and education were tested with ANOVA and differences by age, DASS-Depression, DASS-Anxiety, DASS-Stress, baseline valence, and baseline arousal with pairwise correlations.

**Manipulation check.** Similar to Study 1, linear models were conducted to confirm that the physical stressor induced more state anxiety than the control condition. Valence and arousal ratings were included as criterion variables, and time or context was the predictor. Subjects were included as random effects. As the stressor (or control environment) was implemented continuously during both MST phases and the two MSTs were administered on the same day, the following time points were included: baseline (prior to the MST instructions), end of first MST, end of recovery period, and end of second MST. For analysis, time points were ordered as follows: baseline, control MST, recovery period, and stressor MST. However, the order of conditions was counterbalanced across participants. Follow-up post hoc multiple comparison of means with Tukey adjustment were employed. We also examined differences in mean SCL, HR, and RSA between the two conditions to gauge physiological stress response.

**Main analyses.** One LDI score, which was more than 2.5 standard deviations below the mean, was excluded prior to analysis. No score fell 2.5 standard deviations above the mean. Initial linear models used condition as the main dichotomous predictor, LDI score as the criterion, and subject as a random effect. Subsequent analyses controlled for age and recognition memory. Second, we included pathological worry (PSWQ score) as the criterion and examined main and interaction effects of LDI score and condition. In the event of positive results, we also would control for MST order, simple recognition memory ability, changes in self-reported anxiety (a composite of valence and arousal ratings), and mean SCL, HR, and RSA.

**Psychophysiology recording**

Electrodermal activity (EDA) and ECG data were collected continuously with Biopac MP160 hardware (Biopac Systems, Inc., Goleta, CA) at a 2000 Hz sampling rate. Equipment was connected to a separate computer running AcqKnowledge 5.0 software. Event markers implemented through AcqKnowledge via the STP100C computer interface denoted the beginning and end of each period of interest (e.g., start of MST). Participants were asked to remove jewelry (e.g., watches, rings) and limit movement to minimize artifacts. EDA was captured via two reusable electrodes (TSD203 transducer; Biopac Systems, Inc.) placed on the second and third fingers (contact area = 6 mm diameter; isotonic, 0.05 M NaCl, electrode paste) of the nondominant hand. Participants washed their hands with oil-free soap prior to setup. The Biopac GSR100C module, connected to the transducer, was set with a low-pass filter of 1.0 Hz, and high-pass filters were set to DC. ECG was...
captured via disposable foam chest electrodes (1% in. diameter; three-lead placement). Before placing the electrodes, the experimenter cleaned the participant’s skin with an electrode skin prep pad to remove excess oil and enhance adhesion and skin contact. The Biopac ECG100C module used a band-pass filter of 35 Hz and high-pass filter of 0.5 Hz.

Data were analyzed with AcqKnowledge 5.0. SCL in microsiemens was calculated from EDA data. We derived HR (beats per minute; BPM) and RSA from the ECG data. SCL data were right-skewed. We therefore conducted analyses on log-transformed (normalized) SCL data. ECG data were analyzed in 30-s epochs after we visually identified and removed artifacts (e.g., irregular beats, movement). Epochs requiring more than 10% of the data segment to be edited or removed were excluded (<1% of epochs excluded). Average RSA estimates across epochs were computed in Acqknowledge via spectral analysis by using fast Fourier transformations. Average HR was also computed. RSA and HR analyses for 25% of participants, selected at random, were repeated by a second rater. Interrater reliability was high for both RSA (Study 1: \( r = .98, p < .0001 \); Study 2: \( r > .99, p < .001 \)) and HR (Study 1: \( r = .99, p < .0001 \); Study 2: \( r > .99, p < .001 \)). We calculated mean SCL, RSA, and HR values for analysis.

**Results**

Table 1 provides summaries of demographic and clinical characteristics of the two samples. In Study 1, at baseline, there was no relationship between PSWQ score and age, sex, race, ethnicity, or education level (ps > .05). In Study 2, there was also no relationship between PSWQ score and age, race, ethnicity, or education level (ps > .05). However, there were differences in PSWQ scores by sex in Study 2, \( F(2, 125) = 14.43, p < .001 \). Follow-up t tests employing a Benjamini-Hochberg adjustment for multiple comparisons revealed that PSWQ scores were significantly higher among participants identifying as female (\( M = 56.34, SD = 13.47 \)) than among those identifying as male (\( M = 43.55, SD = 13.83 \)), \( p < .001 \), or as other (\( M = 35.00, SD = 22.63 \)), \( p = .048 \). Scores for participants identifying as male and other did not differ, \( p = .39 \). As expected, PSWQ scores were significantly associated with clinical diagnosis (data only available in Study 2). Notably, participants meeting criteria for GAD (\( M = 63.93, SD = 7.43 \)) reported substantially higher scores than those not meeting criteria for GAD (\( M = 44.39, SD = 13.67 \)), \( t(125.79) = 10.47, p < .0001 \). The PSWQ and all DASS scales (Depression, Anxiety, Stress) were significantly correlated in both samples. Baseline correlations among clinical measures appear in Table 2.

**Manipulation check**

Because the stressor conditions were intended to induce state anxiety and the control conditions were not, we expected participants to report higher arousal scores and lower (i.e., more negative) valence scores in the stressor conditions than the control conditions. We also predicted that participants would experience elevated mean SCL in the stressor conditions relative to the control conditions.

**Study 1.** The effects of psychological stressor and the time by condition interactions were significant for both valence, \( F(4, 537) = 6.94, p < .0001 \), and arousal, \( F(4, 536) = 8.55, p < .0001 \). Most importantly, as revealed in post hoc comparisons, whereas valence ratings did not differ by condition prior to the manipulation at Time 1 (baseline, \( p > .99 \)) or after the manipulation had ended at Time 5 (end of study, \( p > .99 \)), they were consistently lower in the stressor condition than control condition at Time 2 (mean difference = –1.01, \( p < .01 \)), Time 3 (mean difference = –0.69, \( p < .01 \)), and Time 4 (mean difference = –0.99, \( p < .01 \)). Similarly, arousal ratings did not differ by condition at Time 1 (\( p > .99 \)) or Time 5 (\( p = .24 \)) but did differ by condition at Time 2 (mean difference = 1.53, \( p < .001 \)), Time 3 (mean difference = 0.85, \( p = .003 \)), and Time 4 (mean difference = 1.41, \( p < .001 \)). Figure 1 shows valence and arousal ratings as a function of time and condition. We conclude that as intended, participants experienced more subjective anxiety (negative valence and higher arousal) while under stress (i.e., Times 2–4) than while in the control condition. Ratings did not diverge prior to the initiation of either manipulation (Time 1) or after the stressor or placebo was removed (Time 5).

Mean SCL data provided similar results to self-report ratings. There was a main effect of time such that SCL was elevated during both manipulation periods and both phases of the MST relative to baseline, \( F(4, 519) = 38.99, p < .001 \). There was also a main effect of condition such that mean SCL was elevated during the stressor visit relative to the control visit, \( F(1, 522) = 21.77, p < .001 \). Finally, there was a time by condition interaction such that increases in SCL from baseline were greater in the stressor condition compared with the control condition, \( F(4, 514) = 2.83, p = .02 \). Post hoc comparisons revealed no group (i.e., condition) differences at baseline (mean difference = .003, \( p = 1.0 \)) but significant group differences during the manipulations (speaking aloud mean difference = .24, \( p = .003 \); counting aloud mean difference = .24, \( p = .004 \)) and differences in the same direction during the MST (encoding phase mean difference = .13, \( p = .14 \); retrieval phase mean difference = .15, \( p = .08 \)). Visit number was controlled for in these analyses because SCL tended to be
elevated during the first visit. Additionally, there were main effects of time, $F(4, 534) = 4.74, p = .0009$, and condition, $F(1, 557) = 26.71, p < .0001$ for RSA. Relative to baseline, RSA tended to increase during the manipulations, and MSTs and values tended to be higher in the stressor condition. The time by condition interaction was not statistically significant, $F(4, 529) = 1.19, p = .31$. There was a main effect of time on HR, $F(4, 534) = 29.70, p < .0001$, and a trend for condition, $F(1, 537) = 3.34, p = .068$. The time by condition interaction was

Table 1. Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Measure</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$ (%)</td>
<td>$n$ (%)</td>
</tr>
<tr>
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</tr>
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<tr>
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<tr>
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<td>11 (8.59)</td>
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<tr>
<td>PTSD</td>
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<td>5 (3.91)</td>
</tr>
</tbody>
</table>

Measure | $M \pm SD$ | Range  | Measure | $M \pm SD$ | Range  |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Age</td>
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<td>18–50</td>
<td>Age</td>
<td>23.38 ± 4.85</td>
<td>18–40</td>
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<tr>
<td>PSWQ</td>
<td>47.28 ± 17.27</td>
<td>17–77</td>
<td>PSWQ</td>
<td>51.11 ± 15.09</td>
<td>16–76</td>
</tr>
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<td>DASS-Depression</td>
<td>8.66 ± 9.38</td>
<td>0–40</td>
<td>DASS-Depression</td>
<td>7.50 ± 8.31</td>
<td>0–34</td>
</tr>
<tr>
<td>DASS-Anxiety</td>
<td>6.19 ± 8.21</td>
<td>0–30</td>
<td>DASS-Anxiety</td>
<td>6.45 ± 6.59</td>
<td>0–28</td>
</tr>
<tr>
<td>DASS-Stress</td>
<td>12.34 ± 10.37</td>
<td>0–40</td>
<td>DASS-Stress</td>
<td>10.83 ± 8.61</td>
<td>0–38</td>
</tr>
<tr>
<td>Valence</td>
<td>6.08 ± 1.57</td>
<td>1–9</td>
<td>Valence</td>
<td>5.86 ± 1.01</td>
<td>3–9</td>
</tr>
<tr>
<td>Arousal</td>
<td>3.22 ±1.92</td>
<td>1–9</td>
<td>Arousal</td>
<td>2.95 ± 1.46</td>
<td>1–7</td>
</tr>
</tbody>
</table>

Note: PSWQ = Penn State Worry Questionnaire; DASS = Depression Anxiety Stress Scales (Depression, Anxiety, and Stress subscales); GAD = Generalized Anxiety Disorder; SAD = Social Anxiety Disorder; MDD = Major Depressive Disorder; OCD = Obsessive Compulsive Disorder; PTSD = posttraumatic stress disorder.
statistically significant, F(4, 529) = 7.70, p < .0001. Overall, psychophysiological data largely supported participants experiencing greater autonomic arousal or reactivity during the stressor condition relative to the control condition as expected. A summary of psychophysiological measurements is included in Table S1 in the Supplemental Material available online.

**Study 2.** We compared self-reported valence and arousal ratings across contexts (baseline, post control condition, recovery between conditions, post stressor condition) to confirm that participants experienced the threat of unpredictable aversive sounds as stressful relative to the other portions of the study that were not intended to be anxiety inducing. There were significant effects for time on valence, F(3, 371) = 18.83, p < .0001, and arousal, F(3, 371) = 24.70, p < .0001. Follow-up comparisons revealed that as expected, valence declined (i.e., was more negative) from baseline (M = 5.87, SD = 1.00, p < .001) to the stressor condition (M = 5.22, SD = 1.50) and was lower following the stressor MST than following the control MST (M = 5.55, SD = 1.16, p = .002) and following the recovery period (M = 5.73, SD = 1.28, p < .001). Participants also felt more negatively following the control condition than at baseline, p = .003. No other pairwise comparisons differed significantly, ps > .05. Valence and arousal ratings across time points are presented in Figure 1. Results support the conclusions that participants experienced more subjective anxiety (negative valence and higher arousal) under threat of unpredictable aversive sounds than during the rest of the study period.

Furthermore, significant differences in psychophysiological responses to the stressor and control conditions emerged. Participants experienced higher mean SCL under threat of unpredictable sounds (M = 1.53, SD = .52) than under no threat (M = 1.43, SD = .57, t(122) = -3.54, p = .001. RSA was also higher in the stressor condition (M = 6.48, SD = 1.09) than control condition (M = 6.28, SD = 1.01), t(121) = -3.66, p = .0004. HR, however, was lower in the stressor condition (M = 71.43, SD = 9.90) than control condition (M = 72.84, SD = 10.22), t(116) = 5.16, p < .0001. Results are largely consistent with the self-report measures and with participants experiencing heightened stress during the intended manipulation. Table S1 in the Supplemental Material includes a summary of psychophysiological measurements.

**Effects of acute stress on performance**

**Study 1.** When we examined the entire sample, there was no relationship between condition (social-evaluative stressor vs. control) and LDI score, F(1, 54) = 2.30, p = .14 (control mean = 29.88, SD = 20.31; stressor mean = 27.02, SD = 20.71). However, when age was included as a moderator, a significant condition by age interaction effect emerged, F(1, 53) = 4.23, p = 0.045, b = 0.45. Simple

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**Table 2.** Correlations Between Baseline Measures of Clinical Symptoms and State Affect

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 DASS-depression</td>
<td>.73**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 DASS-anxiety</td>
<td>.73**</td>
<td>.80**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 DASS-stress</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 PSWQ</td>
<td>.58**</td>
<td>.54**</td>
<td>.75**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Arousal</td>
<td>.25</td>
<td>.25</td>
<td>.26</td>
<td>.16</td>
<td></td>
</tr>
<tr>
<td>6 Valence</td>
<td>-.44**</td>
<td>-.34*</td>
<td>-.37*</td>
<td>-.53**</td>
<td>-.26*</td>
</tr>
</tbody>
</table>

| Study 2  |           |           |           |           |           |
| 1 DASS-depression | .61**     |           |           |           |           |
| 2 DASS-anxiety    | .60**     | .77**     |           |           |           |
| 3 DASS-stress     |           |           |           |           |           |
| 4 PSWQ        | .47**     | .53**     | .68**     |           |           |
| 5 Arousal      | .19       | .31**     | .39**     | .33**     |           |
| 6 Valence      | -.42**    | -.32**    | -.39**    | -.40**    | -.25*     |

Note: The p values were adjusted for multiple comparisons using Benjamini-Hochberg procedure. DASS = Depression Anxiety Stress Scales; PSWQ = Penn State Worry Questionnaire. Arousal and valence ratings from the Self-Assessment Manikin.

*p < .1. **p < .05. ***p < .01.
Fig. 1. Valence and arousal ratings as a function of time and condition. Valence: lower values indicate more negativity. Arousal: higher values indicate more arousal. Time: 1 = baseline, 2 = start of encoding phase, 3 = between phases, 4 = start of retrieval phase, 5 = end of study.
slopes tests showed that performance was worse under stress than in the control conditions when age was held at 20 ($p = .01$) or 30 ($p = .04$) but that there were no differences when age was 40 or 50, $ps > .05$. When we examined only participants under 40 ($n = 52$), the majority of the sample, there was a significant relationship between condition and LDI score, $F(1, 42) = 9.96$, $p = .003$, $b = −5.93$, marginal $R^2 = .02$, conditional $R^2 = .81$ (control $M = 32.44$, $SD = 19.69$, stressor $M = 26.29$, $SD = 19.77$). This difference held after including age and recognition memory, $F(1, 39) = 8.98$, $p = .005$, $b = −5.94$. Among participants age 40 or older ($n = 13$), the effect was not significant, $F(1, 11) = 3.53$, $p = .09$, $b = 8.26$ (control $M = 20.25$, $SD = 20.48$; stressor $M = 29.88$, $SD = 24.80$). Results were similar partialing age and recognition memory, $F(1, 9) = 3.12$, $p = .11$, $b = 3.45$. To test whether older participants simply responded differently to the stressor or control conditions emotionally, we repeated the manipulation checks but added age as a moderator. There was no time by condition by age interaction for valence, $F(4, 528) = .16$, $p = .96$; arousal, $F(4, 528) = 1.15$, $p = .33$; mean SCL, $F(4, 505) = .19$, $p = .94$; HR, $F(4, 521) = .90$, $p = .46$; or RSA, $F(4, 520) = .08$, $p = .99$. Given the small number of participants above 40, it is difficult to ascertain whether this age effect would replicate or whether these individuals were outliers in their resilience against the stressor. Above results remained unchanged controlling for MST order. MST performance metrics are summarized in Table S2 in the Supplemental Material.

**Study 2.** There was a marginal difference in MST performance (LDI score) by condition, $F(1, 119) = 2.88$, $p = .09$, $b = −2.75$, marginal $R^2 = .005$, conditional $R^2 = .59$, conditional $R^2 = .59$. Participants performed better in the control condition ($M = 30.99$, $SD = 20.05$) than in the stressor condition ($M = 28.17$, $SD = 19.40$); however, this difference was not statistically significant. Results were unchanged, including age, recognition memory, and MST order, $F(1, 117) = 2.87$, $p = .09$, $b = −2.26$. See Table S2 in the Supplemental Material for a summary of MST performance.

**Relationship between anxiety and performance**

**Study 1.** We then tested whether MST performance could predict the severity of PSWQ scores and more specifically, whether this predictive capacity would differ by condition. Considering the entire sample, we found no main effect of LDI score, $F(1, 54) = .05$, $p = .83$, or condition by LDI interaction, $F(1, 52), p = .11$. However, among participants under 40 years of age, the hypothesized pattern emerged. There was no main effect of LDI on PSWQ score, $F(1, 42) = .26$, $p = .62$, but the interaction between LDI and condition was significant, $F(1, 40) = 5.80$, $p = .02$, $b = −0.10$, marginal $R^2 = .004$, conditional $R^2 = .96$. This interaction is visualized in Figure 2. In the control condition, there appears to be a slight positive, if any, relationship between LDI and PSWQ score. In the stressor condition, performance and level of chronic, excessive worry are inversely related. Simple slopes analyses revealed that this difference by condition is driven by low LDI data points. Specifically, whereas effects were not significant at the mean (LDI = 29.43; $b = 0.95$, $p = .26$) or one standard deviation above the mean (LDI = 49.29; $b = −1.08$, $p = .35$), the effect was significant at one standard deviation below the mean (LDI = 9.56; $b = 2.97$, $p = .02$). Low LDI scores predicted high PSWQ scores significantly more in the stressor condition than in the control condition. The interaction holds even after we adjusted for age, recognition memory, MST order, change in anxiety, and mean SCL, HR, and RSA, $F(1, 11) = 6.02$, $p = .03$. Among participants 40 years old or above, however, there was no main effect of LDI, $F(1, 11) = 1.00$, $p = .34$, or interaction with condition, $F(1, 9) = .15$, $p = .71$.

**Study 2.** Analyses revealed no main effect of MST performance on the severity of PSWQ scores, $F(1, 234) = .47$, $p = .49$. Additionally, there was no LDI by condition interaction, $F(1, 230) = .00$, $p = .99$. Because there were initial gender differences in PSWQ scores, we repeated analyses controlling for gender. There remained no main effect of LDI score, $F(1, 232) = .56$, $p = .45$, or interaction effect, $F(1, 228) = .08$, $p = .78$.

**Fig. 2.** Condition moderates the relationship between mnemonic discrimination and level of pathological worry (Study 1). PSWQ = Penn State Worry Questionnaire; LDI = lure discrimination index, as measured in the Mnemonic Similarity Task (MST); higher LDI scores indicate better mnemonic discrimination performance.
Discussion

The goal of this study was to explore whether anxiety is associated with worse mnemonic discrimination and whether this relationship is particularly strong or informative under conditions of acute distress. Results support early evidence that affective state, specifically anxiety, influences mnemonic discrimination (Balderston et al., 2015; Segal et al., 2012). Study 1 extended prior work by utilizing a social-evaluative stressor, akin to anxiety-inducing circumstances that could be encountered in everyday life. When encoding and retrieval followed such stressful encounters, performance declined. However, results do not support extant hypotheses that general mnemonic discrimination performance is directly related to clinical anxiety. There did not appear to be a relationship between performance during the control condition and severity of clinical symptoms. Instead, performance during the stressor condition emerged as more discriminating. There was an inverse relationship between mnemonic discrimination and PSWQ score such that individuals struggling with memory interference under stress were most likely to also report high levels of chronic, pathological worry. Importantly, this relationship could not be explained by highly anxious participants simply experiencing greater subjective or psychophysiological responses to the manipulations or struggling with recognition memory in general. In fact, change in state anxiety following the stress induction, SCL, HR, and RSA were not correlated with PSWQ scores in this sample. Thus, poor mnemonic discrimination in general may not be the best marker or mechanism to pursue in the study of anxiety. Results of Study 1 suggest a more nuanced relationship between mnemonic discrimination and risk for developing anxiety disorders.

Poor mnemonic discrimination alone, even under threat, may be a diathesis rather than necessarily a negative prognostic factor for anxiety disorders. It is likely that poor mnemonic discrimination heightens the risk afforded by other psychological factors, such as intolerance of uncertainty, or environmental factors, such as chronic stress. Memory interference among stimuli or situations that have not been categorized (consciously or not) as threatening should not lead to overgeneralization of fear. Instead, pairing an initial fear response with or as part of an encoded memory is critical to the causal story connecting mnemonic discrimination to anxiety. For example, it is probable, then, that the combination of intolerance of uncertainty, whereby more situations are interpreted as distressing, and poor mnemonic discrimination would be risky. Individuals with both characteristics would have more opportunities for conflating similar entities and overgeneralizing fear responses across them. Similarly, poor mnemonic discrimination could exacerbate the risks associated with chronic stress or high trait anxiety. A key feature of the current paradigm was the inclusion of only two experimental conditions: neutral state during encoding and retrieval phases or anxious state during encoding and retrieval phases. Individuals with high trait anxiety or undergoing chronic stress may be most likely to both encode and retrieve memories for potentially threatening stimuli in an anxious or distressing state, akin to the current paradigm. Poor mnemonic discrimination could compound this problem of frequent state anxiety, in line with evidence that stress can promote habit, rigid, or generalized learning and memory (Schwabe & Wolf, 2013). Overall, results suggest that stress-induced impairments in mnemonic discrimination among vulnerable individuals may be particularly indicative of clinical risk.

Importantly, research using the MST typically focuses on processes occurring during encoding when pattern separation presumably occurs. However, performance can clearly be affected by both encoding and retrieval functions. In the present paradigm, stress during the task could affect encoding, retrieval, or both. Results therefore speak to mnemonic discrimination, a behavioral index, but cannot parse the roles of representation and retrieval therein. Furthermore, there is evidence that had we included incongruent phases (e.g., anxious state during encoding and neutral state during retrieval), results may differ. For example, past studies have shown that arousal during encoding phases but not during retrieval can actually facilitate better mnemonic discrimination in healthy adults (Balderston et al., 2015; Segal et al., 2012). More work is needed to examine whether arousal only during encoding would also enhance mnemonic discrimination among individuals with severe anxiety and whether adding valence as a second dimension would further affect results.

Relatedly, that mnemonic discrimination under psychological stress is a better predictor of anxiety severity than mnemonic discrimination at rest is consistent with findings from related cognitive functions. For example, although performance on executive control tasks is associated with psychopathology, stress-induced declines in performance may be a better predictor of developing or worsening symptoms (Quinn & Joormann, 2015). Indeed, as Eysenck’s attentional control theory emphasizes, high anxiety does not invariably impair performance on cognitive tasks because anxious individuals may redouble their efforts. Yet impairments emerge when additional resources are recruited for a secondary task (Eysenck & Derakshan, 2011). When focusing on single tasks in a quiet, neutral laboratory environment, anxious or at-risk individuals may
perform on par with healthy participants on cognitive tasks. In other conditions (e.g., complex, chaotic, stressful, or dual-task environments), anxious or at-risk individuals may struggle to adapt. Thus, impairments in cognitive function may not manifest as functional deficits in typical circumstances, akin to the control condition. In stressful or challenging circumstances, however, we could expect to see downstream consequences (Tanti & Belzung, 2013). Our findings suggest that although difficulties with mnemonic discrimination at rest may still afford some risk, a better clinical marker of risk or impairment may be the extent of declines in discrimination when a person needs that ability most (i.e., under stress). If adequate mnemonic discrimination is necessary to prevent the overgeneralization of fear, then mnemonic discrimination under relevant conditions is most important. What those conditions are and how individual differences may come into play remain open questions, evinced by our inconsistent findings—namely, that a psychosocial stressor and unpredictable physical shocks (Balderston et al., 2015) induced the expected declines in mnemonic discrimination but unpredictable aversive sounds did not.

Although results in Study 1 largely conformed to hypotheses, there is an important qualification: Results only held for participants under the age of 40. There was no relationship between severity of anxiety, condition, and performance in the older group. This may be attributable to low power as a result of small sample size (n = 13) in the older group. These select individuals could be outliers. Still, this surprising observation requires more research to explain. First, mnemonic discrimination declines with age. And when individuals are grouped into age blocks, there is a distinct difference in performance among adults under and over the age of 40 (Stark et al., 2013). Thus, it is possible that there were floor effects precluding detectable differences among older participants. Second, we used a performance-based stressor, the first half of which involved an imaginary job interview. Older participants may be less sensitive to this type of manipulation, for example, because they are more educated (Fiocco, Joober, & Lupien, 2007), having more experience with job interviews, or having more material to draw on for a 5-min speech. If older participants were not as distressed, it would not be surprising that performance did not decline in this group. However, there was no difference in educational attainment by age in the sample, nor was there a relationship between age and self-reported negative valence, arousal, or mean SCL at any time point, suggesting that older and younger participants were not experiencing different degrees of subjective anxiety or psychophysiological arousal. But, these measures of emotional response are nonspecific.

In other words, we are unable to differentiate between types of anxious responses, such as more somatic stress versus more cognitive responses like worry. If the stressor does facilitate better performance among older participants, it could be due to different manifestations of anxiety between age groups. For example, experimental work has demonstrated dissociable effects of these types of anxious tasks in older adults (65+ years; Beaudreau et al., 2017); such differences could extend to slightly younger adults (40–50 years) and mnemonic discrimination, a specific form of episodic memory.

Results from Study 2 diverge from Study 1, calling into question whether all types of stress can weaken mnemonic discrimination. Although data trended in the same direction, aversive auditory stimuli did not consistently or robustly induce changes in performance. Additionally, as in Study 1, we did not find a relationship between general mnemonic discrimination and symptoms of anxiety. However, in Study 2, there was also no relationship between performance during the stressor condition and any clinical measure.

It is possible that differences between Study 1 and Study 2 results reflect a false positive or a false negative, respectively. But, it is also possible that the latter null finding could be due to critical differences between Study 1 and Study 2. First, the type of stressor differed between the two studies. Psychological and physical stressors are taxing and may relate to the development of psychopathology in different ways. For example, there is evidence that psychological stress may affect memory more than physical stress (Sauro, Jorgensen, & Pedlow, 2003). It is also notable that enrollment for both studies targeted individuals with chronic, excessive, uncontrollable worry, a cognitive manifestation of anxiety. The social-evaluative stressor from Study 1 more likely induced this type of anxiety, because it is intended to evoke concerns about performance and social judgment, than the threat of unpredictable aversive sounds in Study 2. The sounds more likely induced a sense of unease, or a more somatic type of anxiety. The looming vulnerability literature, for example, shows that individuals with social phobia or GAD are more sensitive to anticipated social threats than physical ones (Riskind, Kleiman, Seifritz, & Neuhoff, 2014; Riskind, Rector, & Casssin, 2011). Thus, in the present samples, the physical stressor could have been insufficient to yield meaningful or at least detectable differences in this sample. This is evinced by the overall effects of the manipulation on mnemonic discrimination (i.e., LDI scores) as marginal and because although the two stressors in this project induced similar changes in self-reported arousal, the psychological stressor induced more negative valence ratings than the physical stressor.
Second, even among the subset of participants in Study 1 who were below 40 years of age, Study 1 participants were on average older than Study 2 participants. As pattern separation and mnemonic discrimination tend to decline with age, a more substantial stressor may be necessary to induce detectable changes in the younger sample.

Future studies utilizing varied and stronger stressors, more sensitive measures, and different clinical populations are required to tease apart these possibilities. Results emphasize the need to study emotional context as it relates to mnemonic discrimination and psychopathology. An important limitation of the present work is that the MST stimuli are neutral, everyday objects. As with other cognitive and memory tasks, it is possible that results would differ if emotional, anxiety-specific (e.g., angry or disgust faces), or idiographic stimuli were used (Garrison & Schmeichel, 2018). For example, it is conceivable that MST deficits are greater for aversive or negatively valenced stimuli. In fact, differentiation may be worse for emotional than neutral stimuli both immediately after encoding and after delay (Leal, Tighe, & Yassa, 2014). Modified MSTs including different stimuli are also necessary because generalization occurs along multiple dimensions beyond perceptual similarity and discriminability, such as fear-relevance (Dunsmoor, Mitroff, & LaBar, 2009). It is unclear the extent to which mnemonic discrimination could be involved across dimensions. Additional variations of the MST could also be informative, such as allowing unlimited response times or lengthening the time between phases. More work is also needed with larger samples and more diverse and severe clinical presentations as well as multiple methods of assessment (e.g., behavioral and neuroimaging data, varying parameters for the MST). Studies focusing on specific diagnostic categories would also be an important next step as mnemonic discrimination may be more relevant for disorders such as phobias for which worry is more situation-specific than generalized anxiety disorder, for example.

**Conclusion**

This research was intended to test whether mnemonic discrimination performance is sensitive to state anxiety and explore how this cognitive-affective factor may relate to anxiety disorders. Although there is strong theoretical basis for predicting that poor mnemonic discrimination contributes to the development and maintenance of anxiety disorders, few studies have examined this connection using experimental methods or in clinical samples.

In the present data, mnemonic discrimination does not appear to be a stable, trait-like memory function. Instead, consistent with prior work (Balderston et al., 2015; Segal et al., 2012), results suggest that mnemonic discrimination is sensitive to context. Specifically, participants exhibited worse mnemonic discrimination when encoding and retrieval occurred under conditions of heightened anxiety than under neutral conditions. Notably, this decline was more robust in the psychological threat condition than the physical threat condition. Although inexpensive, noninvasive, and informative, the MST is ultimately a proxy for underlying computational processes of pattern separation and completion, and performance on the task is likely influenced by other neurocognitive processes as well. Thus, results can suggest but not confirm differences in function within the hippocampus and associated neurocircuits under these experimental conditions. Consequently, there remains the possibility that other factors could contribute to or account for the observed behavioral results. And although future work is needed to fully discern the boundary conditions of the relationship between pattern separation, mnemonic discrimination, and state affect, for example exploring a range of emotions, results highlight the importance of considering this variable for future research.

To our knowledge, these are the first studies to experimentally examine mnemonic discrimination in individuals with clinically severe pathological worry. In so doing, we observed that limited mnemonic discrimination in socially threatening contexts but not neutral ones was related to severe levels of anxiety. As participants were only tested at one time point, results speak to associations between mnemonic discrimination, pathological worry, and other symptoms of anxiety but cannot prove direction of causality. Longitudinal research is necessary to determine whether detectable impairments in mnemonic discrimination indeed precede disorder onset, whether impairments are a consequence of pathology, or whether relationships are bidirectional.

This project examined mnemonic discrimination among individuals both high and low on the dimension of chronic, excessive worry, a common and often functionally impairing symptom of anxiety. Results corroborate prior claims that this basic ability to overcome memory interference is a relevant variable in the study of anxiety disorders (Balderston et al., 2015; Kheirbek et al., 2012) but bear the qualification that state affect is an important contextual variable to consider. This study is an important step in translating basic science in rodent models to relevant clinical outcomes in humans. This line of work provides new insight into a
particular cognitive-affective abnormality and may lead to a noninvasive, inexpensive marker of risk and potential target for prevention and early interventions for clinical anxiety.

**Action Editor**

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**Author Contributions**

E. E. Bernstein and R. J. McNally developed the study concept and design. E. E. Bernstein and E. M. Kleiman performed testing and data collection. E. E. Bernstein completed the data analysis and interpretation under the supervision of R. J. McNally. E. E. Bernstein drafted the manuscript, and E. M. Kleiman and R. J. McNally provided critical revisions. All the authors approved the final manuscript for submission.

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**Supplemental Material**

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