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Acquisition of CS-US contingencies during Pavlovian fear conditioning and extinction in social anxiety disorder and posttraumatic stress disorder

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ABSTRACT

Background: Fear-based disorders, like social anxiety disorder (SAD) and posttraumatic stress disorder (PTSD), are characterized by an exaggerated fear response and avoidance to trigger cues, suggesting a transdiagnostic mechanism of psychopathology. Current theories suggest that abnormalities in conditioned fear is a primary contributor to the pathophysiology of these disorders. The primary goal of this study was to compare acquisition of conditioned stimulus (CS) and aversive unconditioned stimulus (US) contingencies during fear learning and extinction in individuals with SAD and PTSD.

Methods: In a standard Pavlovian fear conditioning-extinction paradigm we measured subjective US expectancy ratings to different CSs in patients with SAD (n=16) compared to patients with PTSD (n=13) and healthy controls (n=15)

Results: Both patient groups (SAD, PTSD) acquired differential conditioning between a CS that predicted US (CS+) and a CS that never predicted the US (CS-), however, both groups reported an increased expectancy that the US would occur following the CS-. Additionally, the PTSD group overestimated that the US would occur in general. Neither patient group showed evidence of successful extinction of the CS+-US contingency nor differentiated their expectation of US occurrence between the CS+ and CS- during extinction learning.

Limitations: Group sample sizes were small and we did not include a trauma-exposed group without PTSD

Conclusions: Both SAD and PTSD generalize expectations of an aversive outcome across CSs, even when a CS never signals an aversive outcome and PTSD may tend to over-expect threat. Fear learning and extinction abnormalities may be a core feature underlying shared symptoms across fear-based disorders.

1. Introduction

Experiences involving threat result in strong fear learning, allowing rapid detection of associations between cues in the environment and prediction of imminent threat. Importantly, ever-changing environments require that an individual flexibly re-adjust learned fear such that it would appropriately track the ongoing change in circumstances (e.g., stimulus might cease to signal danger; Schiller and Delgado, 2010). Current theories of anxiety and posttraumatic stress disorder (PTSD) suggest that abnormalities in conditioned fear are a primary contributor to the pathophysiology of these disorders (Briscione et al., 2014; Duits et al., 2015; Lissek et al., 2005). Maladaptive cognitions play a crucial role in the development and maintenance of anxiety and fear responses and while some cognitions may be disorder-specific there are commonalities in cognition across disorders, such as future-oriented perceptions of danger or threat (Hofmann, 2008; Newby et al., 2015; Norton and Paulus, 2015).

In the laboratory, these associative learning processes can be

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modeled using Pavlovian fear conditioning and extinction models in which fear is first linked to a previously innocuous cue (conditioned stimulus; CS) and is then decreased by presenting the CS alone (producing extinction). To date, findings from patient studies suggest that fear acquisition and/or extinction abnormalities may be a core feature underlying shared symptoms across fear-based disorders (Milad et al., 2005). For instance, patients with PTSD show deficits in the ability to discriminate between a CS that was paired with an aversive outcome (CS+; danger cue) and a CS that was never paired with an aversive outcome (CS-; safety cue), as well as, a general inability to acquire safety signals, and/or increased fear conditioning (Blechert et al., 2007; Grillon and Morgan, 1999; Jovanovic et al., 2010, 2009; Norrholm and Jovanovic, 2011; Norrholm et al., 2011; Orr et al., 2000; Peri et al., 2000).

While the vast majority of research efforts have focused on fear extinction in patients with PTSD there are emerging studies that have examined fear conditioning and extinction in other fear-based disorders and consistently demonstrate evidence of impaired fear extinction (Duits et al., 2015). For example, patients with panic disorder exhibit larger physiological responses during extinction training and rate the extinguished CS as more unpleasant than healthy controls (Michael et al., 2007). Enhanced fear learning has been reported in patients with spider phobia (Schweckendiek et al., 2011) and extinction retention deficits have been reported in patients with obsessive-compulsive disorder (Milad et al., 2013). Two behavioral studies in patients with social anxiety disorder (SAD) have shown increased conditioned fear responses, suggesting increased fear conditionability (Lissek et al., 2008) and increased tendency to not only associate threat to safety cues, but an inability to extinguish conditioned fear responses (Hermann et al., 2002). Together, these studies suggest that fear acquisition and/or extinction abnormalities may be a core feature underlying shared symptoms across fear-based disorders as well as their high degree of comorbidity (Goldstein et al., 2016). However, in the aforementioned fear extinction studies, the experiments conducted in patients with SAD, both used neutral facial expressions as the CS, which may have confounded the overall results.

Previous studies have reported that patients with SAD are likely to interpret neutral and other emotionally ambiguous facial expressions negatively (Cooney et al., 2006; Winton et al., 1995; Yoon and Zinbarg, 2007, 2008), making it possible that neutral faces may not be regarded as neutral stimuli that become a threat cue as a result of associative learning. The baseline difference in CS and/or the unconditioned stimulus (US) meaning in patients with SAD compared to healthy controls may obscure differences in the acquisition and extinction of conditioned fear responding to socially relevant cues. To control for this potential confound and to determine whether patients with SAD, like patients with PTSD, have deficits in general acquisition of fear-related CS-US contingencies and subsequent extinction of these contingencies we used a standard Pavlovian fear conditioning and extinction paradigm with non-social cues as the CSs (colored lights) in patients with SAD, PTSD, and healthy controls (Milad et al., 2005, 2007a). We hypothesized that patients with SAD and patients with PTSD would show deficits in extinction learning as evidence by greater US expectancy ratings during extinction learning and recall compared to healthy volunteers.

2. Materials and methods

2.1. Participants

Forty-four volunteers participated in this study (SAD=16; PTSD=13; Healthy Controls [HC]=15; see Supplemental Table 1 for sample demographics and clinical characteristics) and were recruited from the University of Michigan Anxiety Disorders Clinic, the University of Michigan campus, and surrounding Metro Detroit communities via online advertisements and flyers.

Participants with SAD or PTSD were required to have a primary diagnosis of SAD or PTSD, respectively, while participants in the HC group could not meet criteria for any current or past Axis I disorder. Psychiatric diagnoses based on the DSM-IV criteria (Association, 2000), were established via the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). Of note, all clinical assessments were conducted by Dr. Rabinak, who was trained to administer and score these assessments for research-related purposes (See Supplemental Materials and methods for additional inclusion and exlusion critiera and comorbities).

There was no significant difference in age between the HC and SAD groups [$t(29)=-1.53$, $p=.14$] nor the SAD and PTSD groups [$t(27)=-1.21$, $p=.24$], however the HC group was significantly younger than the PTSD group [$t(26)=-2.46$, $p=.03$; Supplemental Table 1], therefore age was included as a covariate in the analyses. Between-group comparisons on sex of the participants, ethnicity, and racial composition are included in the Supplemental Results.

2.2. Additional assessment measures

2.2.1. Liebowitz Social Anxiety Scale (LSAS)

The LSAS is a 24-item, clinician-administered questionnaire used to assess the range of social interactions and performance situations that patients with SAD may fear and/or avoid (Heimberg et al., 1999).

2.2.2. Social Interaction Anxiety Scale (SIAS)

The SIAS is a 20-item, self-report scale that assesses fears of more general social interaction (Mattick and Clarke, 1998).

2.2.3. Clinician-Administered PTSD Scale for DSM-IV (CAPS)

The CAPS the “gold standard” for PTSD assessment and diagnosis and is clinician-administered. Severity ratings are based on symptom frequency and intensity (Blake et al., 1995).

2.2.4. Life Stressor Checklist-Revised (LSC-R)

The LSC-R is a self-report measure designed to screen for potentially traumatic events in a person's lifetime (Wolfe and Kimerling, 1997).

2.2.5. PTSD Checklist-Civilian (PCL-C)

The PCL-C is a 17-item, self-report measure reflecting DSM-IV symptoms of PTSD. The PCL-C asks about symptoms in relation to generic “stressful experiences” and can be used in aiding diagnostic assessment of PTSD (Blanchard et al., 1996; Weathers et al., 1993).

2.2.6. Hamilton Anxiety Scale (HAM-A)

The HAM-A is a 14-item, clinician-administered questionnaire that measures severity of a patient's anxiety (Hamilton, 1959).

2.2.7. Hamilton Depression Scale (HAM-D)

The HAM-D is a 21-item, clinician-administered questionnaire used to determine a patient's level of depression (Hamilton, 1960).

2.2.8. Beck Depression Inventory (BDI-II)

The BDI-II is a 21-item, self-report questionnaire used to measure severity of depression (Beck et al., 1974; Beck and Steer, 1984; Beck et al., 1996; Beck et al., 1961).

2.2.9. State-Trait Anxiety Inventory (STAI)

The STAI is a 40-item, self-report measure of trait and state anxiety (Spielberger et al., 1983).

Between-group differences on the additional assessment measures are presented in the Supplemental Results and Supplemental Table 1. All participants gave written informed consent after explanation of the experimental protocol with research staff and were monetarily compensated for their time, as approved by the University of Michigan