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Impaired discriminative fear-conditioning resulting from elevated fear responding to learned safety cues among individuals with panic disorder☆

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ABSTRACT

Classical fear-conditioning is central to many etiologic accounts of panic disorder (PD), but few lab-based conditioning studies in PD have been conducted. One conditioning perspective proposes associative-learning deficits characterized by deficient safety learning among PD patients. The current study of PD assesses acquisition and retention of discriminative aversive conditioning using a fear-potentiated startle paradigm. This paradigm was chosen for its specific capacity to independently assess safety- and danger learning in the service of characterizing putative anomalies in each type of learning among those with PD. Though no group difference in fear-potentiated startle was found at retention, acquisition results demonstrate impaired discriminative learning among PD patients as indexed by measures of conditioned startle-potentiation to learned safety and danger cues. Importantly, this discrimination deficit was driven by enhanced startle-potentiation to the learned safety cue rather than aberrant reactivity to the danger cue. Consistent with this finding, PD patients relative to healthy individuals reported higher expectancies of dangerous outcomes in the presence of the safety cue, but equal danger expectancies during exposure to the danger cue. Such results link PD to impaired discrimination learning, reflecting elevated fear responding to learned safety cues.

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Introduction

Classical fear-conditioning is the associative-learning process by which a neutral conditioned stimulus (CS) comes to evoke fear following its repeated pairing with an aversive unconditioned stimulus (US). Though fear-conditioning has long been implicated in the etiology of panic disorder (PD: Bouton, Mineka, & Barlow, 2001; Eysenck & Rachman, 1965; Goldstein & Chambless, 1978; Wolpe & Rowan, 1988), few lab-based studies characterize fear-conditioning correlates of PD, and such studies provide mixed results (Del-Ben et al., 2001; Michael, Blechert, Vriends, Margraf, & Wilhelm, 2007). Current learning models predict elevated classically conditioned fear among panic patients, through which benign situations (CSs) occurring coincident with panic attacks acquire the capacity to trigger future attacks when re-encountered (e.g., Bouton et al., 2001; Wolpe & Rowan, 1988). A second model, by contrast, predicts impaired conditioning in the form of associative-learning deficits (Grillon, 2002; Grillon, Lissek, McDowell, Levenson, & Pine, 2007). From this perspective, successful fear-conditioning leads CS events to warn individuals of a looming aversive US. Associative-learning deficits deprive PD patients of such warnings which, in turn, render panic attacks un-signaled and unpredictable. This unpredictability impairs the patient's ability to perceive safety in the absence of CSs, leading to the sustained anxious anticipation of future panic attacks seen in the disorder (American Psychiatric Association, 2000; Klein & Gorman, 1987).

A quantitative review of conditioning studies in the anxiety disorders supports this latter learning-deficit framework of PD (Lissek et al., 2005). Results from this meta-analysis implicate deficient discrimination learning in clinical anxiety. Whereas healthy individuals display anxious reactivity to CSs paired (CS+: danger cue) but not unpaired (CS−: safety cue) with the aversive US, anxiety patients tend to display fear responses to both CS+ and CS−. Thus, proposed conditioning deficits in PD may take the form of poor discrimination learning driven by elevated responding to the CS−. The primary purpose of the current study was to test this model by assessing fear-learning abnormalities in PD. Unlike prior conditioning studies, however, the current study devotes special attention to the discrimination learning process. Because

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discriminative fear-conditioning is the combined effect of danger learning to the CS+ and safety learning to the CS−, it was important that our applied method provide separate indices of each. The human conditioned startle-potentiation paradigm (Grillon, Ameli, Woods, Merikangas, & Davis, 1991) is ideal for this purpose because the magnitude of startle probed during inter-trial-intervals (ITI) serves as a baseline with which to assess contributions of danger (CS+ minus ITI) and safety (CS− minus ITI) learning to discriminative conditioning. The current study represents the first application of a conditioned fear-potentiated startle paradigm to assess putative anomalies in discriminative fear learning among panic patients.

An additional question of interest was the degree to which acquisition of conditioned fear is retained over time. Because the psychopathology of panic disorder unfolds over time, the chronometry of conditioning effects may be of central importance. For example, a public bus in which an individual experiences a panic attack may become a cue for future attacks via classical conditioning. The central factor determining the contribution of this conditioning experience toward the course of the disorder may be the degree to which the *bus-panic* association is retained in memory, which then has direct bearing on whether re-exposure to buses at some later point will trigger further attacks. To date, retention of conditioned fear in the anxiety disorders has received little attention. This is likely due to the wide interest in testing extinction processes in clinical anxiety and the methodological obstacles preventing assessment of both extinction and retention in a single study. Specifically, if acquisition is directly followed by extinction, retention of conditioned responding over time cannot be assessed because the conditioned response has undergone extinction. Additionally, if acquisition and extinction are separated by a time interval for assessment of retention, extinction rates will be confounded by the strength of retention. Because of this difficulty assessing both learning processes, together with the paucity of retention data in the anxiety disorders, the current study tests the relation between panic disorder and retention of conditioned fear rather than extinction.

In sum, the current effort was aimed at characterizing putative abnormalities in discrimination learning among PD patients, with predictions of elevated anxiety to conditioned safety cues (CS−) and enhanced retention of learning among PD patients relative to healthy controls.

Method

Participants

Twenty-four patients with a current DSM-IV-TR diagnosis of panic disorder (PD) (25% male; $M_{age} = 32.13$, $SD_{age} = 9.74$) and 24 healthy controls (21% male; $M_{age} = 36.67$, $SD_{age} = 11.43$) constituted study groups that differed on neither gender ($p = .73$) nor age ($p = .18$). PD diagnoses were determined by the Structured Clinical Interview for DSM-IV-TR, Patient-Edition (SCID-I/P: First, Spitzer, Gibbon, & Williams, 2002) administered by one of four staff psychologists (inter-rater Kappa of .76). Furthermore, all patients were independently assessed by a senior psychiatrist (coauthor D.S.P.) to confirm SCID diagnosis. Finally, the Panic Disorder Severity Scale (PDSS: Shear et al., 1997) was completed by PD patients to provide a continuous measure of symptom severity. Diagnostic exclusion criteria for PD patients included: 1) current major depressive disorder or suicidal ideation; 2) history of alcohol or substance abuse or dependence (other than nicotine) within 6 months of study start; 3) and current or past history of bipolar depression, psychosis, or delusional disorders. Of the 24 patients, three met criteria for PD with agoraphobia. Additionally, psychiatric comorbidities among patients included social anxiety disorder ($n = 6$), generalized anxiety disorder ($n = 1$), past major depression ($n = 4$), past PTSD ($n = 2$), and past substance abuse ($n = 2$).

Healthy comparisons were required to be free of any current or past Axis I psychopathology as per SCID interview. Additionally, exclusion criteria applied to all participants included: 1) use of psychopharmacologic medication or other drugs altering CNS function within two weeks of testing, or use of fluoxetine within six weeks of testing; 2) current use of illicit drugs as per SCID and confirmed with a urine test; 3) pregnancy, for female participants; and 3) medical conditions or treatment for conditions that interfered with the objectives of the study as determined by a staff physician during a physical exam. At study outset, experimental procedures were described in detail and participants gave written informed consent approved by the NIMH Human Investigation Review Board.

Physiological apparatus

Stimulation and recording were controlled by a commercial system (Contact Precision Instruments, London, Great Britain). Startle-blink EMG was recorded with two 6-mm tin-cup-electrodes placed under the right eye. Additionally, amplifier band width was set to 30–500 Hz and digital data was sampled at 1000 Hz. Startle was elicited by a 40-ms duration, 102 dB(A) burst of white-noise with a near instantaneous rise time presented binaurally through headphones.

Stimuli

Conditioned stimuli were neutral images from the International Affective Picture System (IAPS: Lang, Öhman, & Vaitl, 1988) of a bowl (image #7006: valence = 4.88, arousal = 2.33, dominance = 6.18) and a mug (image #7035: valence = 4.98, arousal = 2.66, dominance = 6.39). For half of participants the bowl and mug served as the CS+ and CS−, respectively, and for the other half this was reversed. The unconditioned stimulus was electric shock (100 ms, 3–5 μA) produced by a constant current stimulator and administered to the right wrist.

Conditioning paradigm

A classical, discriminative conditioned startle-potentiation paradigm was employed and included pre-acquisition and acquisition phases, followed one week later, by a retention test. During pre-acquisition, acquisition, and retention components, 8-s duration CS+ and CS− were intermixed with inter-trial-interval (ITI) assessments and were presented in a quasi-random order where no more than two trials of the same type (i.e., CS+, CS−, ITI) occurred consecutively. Pre-acquisition consisted of 6 CS+, 6 CS−, and 6 ITI startle-trials occurring in the absence of any electric-shock delivery. Acquisition included 10 CS+, 10 CS−, and 10 ITI startle-trials with all CS+ presentations co-terminating with shock delivery (100% reinforcement schedule). Finally, retention consisted of 6 CS+, 6 CS−, and 6 ITI startle-trials presented in the absence of electric shock. During pre-acquisition, acquisition and retention, startle probes were delivered 4–5 s following onset of each CS and during the ITI period separating CS presentations, and an inter-probe interval of 18–25 s was maintained throughout. Startle elicited during ITI provided a baseline measure of startle with which to compare startle magnitudes during CS+ and CS− presentations.

Procedure

Following informed consent and placement of electrodes, a shock workup procedure was completed to establish a level of shock that was "highly annoying but not painful". Next, nine startle probes (inter-probe interval of 18–25 s) were delivered to habituate the