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Impaired discriminative fear conditioning during later training trials differentiates generalized anxiety disorder, but not panic disorder, from healthy control participants

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ABSTRACT

Background: Fear conditioning is implicated as a central psychopathological mechanism of anxiety disorders. People with anxiety disorders typically demonstrate reduced affective discrimination between conditioned danger and safety cues. Here, affective discrimination refers to the ability to selectively display fear to dangerous but not safe situations. Though both generalized anxiety disorder (GAD) and panic disorder (PD) are linked to impaired affective discrimination, the clinical phenomenology of these disorders suggests that people with GAD versus PD might be less able to overcome such deficits. It is unclear how this potential difference would manifest during lab-based conditioning.

Methods: We used a classical fear conditioning paradigm over two discrimination training sessions to examine whether those with GAD, but not PD, would display persistent discrimination deficits. Sixty-seven participants (21 GAD, 19 PD, 27 Healthy Controls) completed a task in which conditioned fear was measured psychophysiologically (fear-potentiated startle), behaviorally, and via self-report.

Results: Although similar levels of impaired discrimination were found for both GAD and PD groups during initial training, such impairments tended to persist across a subsequent training session only for patients with GAD when compared with Controls.

Conclusion: Our results provide a foundation for additional research of discrimination deficits in specific anxiety disorders, with an ultimate goal of improved customization of psychological treatments.

1. Introduction

Classical fear conditioning is the associative learning process through which a neutral stimulus comes to elicit fear after being paired with an inherently aversive stimulus (Pavlov, 1927). This cross-species process of fear learning has been behaviorally and neurobiologically characterized [1–4] and is widely viewed as an important pathogenic mechanism in the anxiety disorders [5–8]. Indeed, meta-analyses of fear conditioning studies in the anxiety disorders have identified impaired affective discrimination between learned danger-cues (CS+) and learned safety-cues (CS−) as a robust conditioning correlate of clinical anxiety [7,9]. Here, affective discrimination refers to the ability to selectively display fear to dangerous but not safe situations, and impaired affective discrimination in anxiety patients is characterized by heightened fear responding to both learned cues of danger and safety. Though lab-based findings implicate impairments in affective discrimination across anxiety disorders broadly, there is reason to believe some anxiety disorders might evidence more profound deficits in this area than others. The current paper explores this possibility by comparing affective discrimination of learned danger from safety signals across individuals with generalized anxiety disorder (GAD) and panic disorder (PD).

Both of these disorders are associated with discrimination learning impairments. For example, a person with GAD who has concerns about colon health might associate the gastroenterologist's office with danger due to receiving negative health updates in that context. The same person might also always receive benign health updates in a dermatologist's office, but walking into *either* office evokes health related anxiety. Similarly, a person with PD who acquires fear responding to a subway on which a panic attack occurred might in the future display fear to both the subway, now a conditioned danger-cue (i.e., CS+), and other modes of routinely-used transportation that have never been aversively reinforced by panic (e.g., a bus), reflecting a failure to affectively discriminate between stimulus-events to which conditioned

Abbreviations: CS+, conditioned danger cue; CS−, conditioned safety cue; EMG, electromyography; US, unconditioned stimulus.

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fear has and has not been acquired. Of note, this example illustrates PD-related discrimination deficits with exteroceptive rather than interoceptive stimuli [8] given the focus of the current paper on exteroceptive conditioning.

The above examples of discrimination learning deficits in GAD and PD represent difficulty with differential affective responding to danger and safety information. That said, studies of the clinical phenomenology of these disorders suggest key differences, with GAD (versus PD) associated with more persistent and difficult to reverse deficits in affective discrimination of danger from safety [11–27]. Below, we describe extant evidence for this GAD-PD difference separately for each disorder.

1.1. GAD and affective discrimination deficits

Persistent worry about a variety of life areas and difficulty controlling this worry is the cardinal feature of GAD [10] and distinguishes it from PD and other anxiety disorders, which have more circumscribed domains of concern [8]. This chronic and pervasive form of worry is potentially driven by tendencies to broadly distrust or neglect available safety information and to continue worrying in safe situations [11,12], leading to persistent defensive responding across stimulus events whether they indicate danger or safety. Worry then becomes a chronic (and maladaptive) coping strategy for those with GAD [13–15].

Impaired affective discrimination in GAD is also consistent with the Emotional Contrast Avoidance Model of worry in GAD [16], premised on the notion that staying in a negative state via worry serves a function for those with GAD by preventing large affective shifts if negative stimuli are encountered, as the person is already in a negative state. According to the model, people with GAD prefer to be in a negative state because they find contrasts between negative and positive states more aversive than the negative state itself [16–18]. This suggests that there is a lack of motivation for people with GAD to affectively discriminate between danger and safety cues, as the affective shift from safety to threat is aversive enough that they prefer to continuously stay on guard for threat.

Further support for impaired affective discrimination in GAD derives from studies on exposure therapy [19–22]. Exposure therapy is an empirically-validated intervention [23] that relies on repeatedly exposing patients to feared stimuli in the absence of negative outcomes. The repeated nature of exposures leads to habituation of fear responses, and the absence of negative outcomes evokes an extinction-like process whereby patients learn to expect no aversive consequences from exposures to the feared stimulus [24]. The result of extinction, as supported by experimental work on extinction, is the inhibition of aversive associations to the feared stimulus and the development of a competing association between the feared stimulus and safety [5,25]. Prior research shows that traditional exposure is typically not effective for those with GAD when compared with other anxiety disorders [20–22]. Those with GAD, more than individuals with other anxiety disorders, respond anxiously to their feared stimuli both before exposure therapy (when such stimuli were perceived as danger cues) and after therapy when such stimuli acquired safety value [20,21]. Additionally, people with GAD demonstrate poorer maintenance of long-term gains from cognitive-behavioral treatment packages featuring exposure techniques [22], suggesting discrimination deficits are more persistent in GAD than other anxiety disorders. Such effects reflect an impaired ability to affectively discriminate between phobic stimuli presented before versus after safety value was imparted by way of exposure therapy. Although it is possible that exposure has the desired effect in those with GAD (creating a safety association with a feared stimulus), there might not be a corresponding reduction in anxiety due to those with GAD not necessarily viewing safety as positive/non-negative.

1.2. PD and affective discrimination deficits

People with PD also demonstrate some insensitivity to safety [26,27]. However, in contrast to the broad worry of GAD, the worry and anxiety experienced in PD are circumscribed to stimulus-events resembling those paired with panic attacks and do not typically extend broadly to other benign situations [10]. Additionally, and again in contrast to those with GAD, people with PD endorse experiencing anxiety reductions in identified safe situations such as being at home or when carrying a comforting item on their person when leaving the house [28, 29]. The differential capacity for anxiety reduction in the presence of safety across PD and GAD has been attributed to the fact that safety signals for those with PD are typically more concrete, easily located, and less ambiguous (e.g., being completely inside one's home) than safety signals for people with GAD [12].

Further, lab-based findings indicate that those with PD show deficits in affective discrimination between learned danger and safety during earlier parts of training, but display a more intact ability to discriminate during the latter part of training [26]. This suggests that although those with PD might demonstrate initially poor affective discrimination between danger and safety, they are able to learn to discriminate with additional training trials. This is supported by prior treatment research, which has shown use of exposure techniques during psychological treatment to be efficacious for PD [30,31] and that treatment gains are typically maintained over time [22].

Taken together, it is clear that impaired affective discrimination contributes to GAD and PD pathologies, but clinical observation, experimental findings, and treatment efficacy results suggest people with GAD have greater and more persistent affective discrimination deficits. In the current study, we tested this idea using a lab-based discriminative fear conditioning paradigm. We hypothesized that those with GAD and PD would both show initial impaired affective discrimination of CS+ from CS−, but that such impairment would persist with additional training trials only among those with GAD.

2. Materials and methods

2.1. Participants

In the current study, our sample consists of combined data from previously published studies by our group [32,33]. Specifically, participants included 67 medication-free adults (42 women) and consisted of 21 participants with a current and primary DSM-IV-TR [34] diagnosis of GAD, 19 with a current and primary diagnosis of PD, and 27 with no DSM pathology who served as healthy comparisons. Three participants with a primary diagnosis of PD also received a secondary GAD diagnosis; there were no participants in the GAD group with comorbid PD. See Table 1 for additional participant characteristics.

We obtained DSM diagnoses using the Structured Clinical Interview for the DSM-IV-TR, Patient Edition (SCID) [35] which was administered by a trained psychiatric nurse or staff psychiatrist. A senior psychiatrist independently assessed and confirmed all SCID diagnoses. In addition to the SCID, all participants completed the state and trait versions of the Spielberger State-Trait Anxiety Inventory (STAI) [36] and the Beck Depression Inventory (BDI) [37] to dimensionally assess anxiety and depression symptoms, respectively.

Participants in either the GAD or PD group were excluded if they had a history of alcohol or substance abuse or dependence (other than nicotine) within 6 months of study start. They were also excluded if they had current major depressive disorder, or a current or past diagnosis of bipolar disorder, psychosis, or delusional disorders. Exclusion criteria specific to healthy comparisons included a current or past Axis I diagnosis (determined by SCID). Additional exclusion criteria for all participants included: use of psychopharmacological medication or other drugs that alter central nervous system function within 2 weeks of testing; use of fluoxetine within 6 weeks of testing; current use of illicit drugs (determined by the SCID and confirmed with urine testing); current pregnancy; or medical conditions/treatment for medical conditions (as determined by staff physicians) that would interfere with study