



## Pilot for novel context generalization paradigm

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### ABSTRACT

**Background and objectives:** Following an aversive experience, fears often generalize across contexts. Contextual fear generalization is modeled in a laboratory paradigm in which one context (CTX+) is paired with an aversive unconditional stimulus (US), while the other context (CTX-) is not. The current study sought to validate a novel paradigm assessing contextual fear generalization, and to determine the extent to which stress and anxiety symptoms enhanced contextual fear generalization.

**Methods:** Fifty-nine participants were randomized to a stress induction or control arithmetic test, followed by a differential context fear conditioning paradigm. One to three days later, participants completed a generalization gradient test with CTX+, CTX-, and four generalization contexts.

**Results:** We found successful contextual fear conditioning on measures of US expectancy, self-report fear and valence, and startle reflex, and linear generalization across the contextual gradient on expectancies and self-report measures. Acute stress induction impaired learning of the US-CTX+ association during context fear acquisition. Anxiety significantly predicted greater contextual fear generalization as measured by US expectancy.

**Limitations:** Our study provides pilot data introducing a novel fear conditioning paradigm to assess contextual generalization of fear. There is a need for further replication to validate its utility.

**Conclusions:** Findings suggest that individuals high in anxiety show greater contextual fear generalization as measured by US expectancy. Results are discussed in terms of potential mechanisms that contribute to pervasive anxiety.

### 1. Introduction

Pavlovian fear learning, or the process through which a neutral stimulus comes to evoke fear due to its association with an aversive outcome, is thought to be central to the genesis, maintenance, and treatment of anxiety and traumatic-stress disorders (Vervliet & Raes, 2012). Anxious individuals have demonstrated deviant processes in fear learning, including reduced encoding of safety cues, impaired retention of extinction learning, and heightened fear reactivity to both threatening and safe stimuli (Vervliet, Craske, & Hermans, 2013). Most recently, Pavlovian generalization, or the process through which conditional emotional responding generalizes to stimuli related to the original threatening stimulus (i.e., conditional stimulus or CS), has emerged as a defining feature of anxiety and traumatic-stress disorders (e.g., Jovanovic, Kazama, Bachevalier, & Davis, 2012; Lissek et al., 2005, 2012). When conditional fear is not restricted to appropriate cues, it may become excessive and maladaptive, leading to fear and avoidance of a wide range of stimuli and contexts.

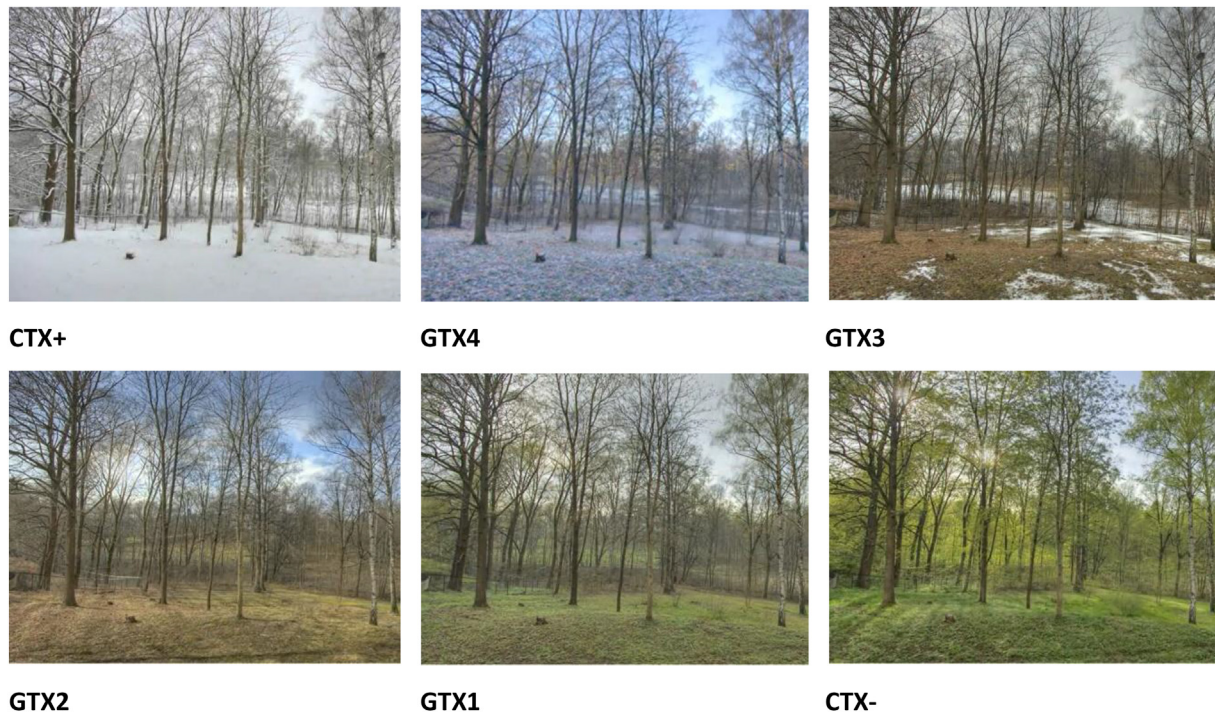
A series of studies by Lissek and colleagues elucidated the nature of conditional fear generalization and its relation to anxiety (Lissek et al.,

2008a, 2010, 2014). They found that, relative to non-anxious participants, those with panic disorder (Lissek et al., 2010) and generalized anxiety disorder (Lissek et al., 2014) generalized fear of the CS+ to perceptually similar stimuli to a greater extent than their non-anxious counterparts.

The majority of research in humans has examined gradients of fear generalization using brief, punctate conditional stimuli, and has largely ignored generalization across more complex contextual stimuli (e.g., Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2015; Lissek et al., 2008b, 2008a). Contextual fear learning, in which a context rather than a discrete cue predicts an aversive event, may play a prominent role in fear maintenance and serves as an externally valid analogue for clinical anxiety (Lissek, 2012). For example, deficits in using contextual information to modulate behavioral responses to threat are thought to be central to the pathology of many anxiety disorders and posttraumatic stress disorder (PTSD) (Lissek & Grillon, 2012), such as impediments to using contextual information to properly restrict trauma-related cues to relevant environments (Acheson, Gresack, & Risbrough, 2012; Cohen, Liberzon, & Richter-Levin, 2009; Liberzon & Sripada, 2008).

Contextual fear learning typically involves a context in which USs

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**Fig. 1.** Contextual stimuli presented during fear acquisition (CTX+, CTX-) and generalization test (CTX+, GTX4, GTX3, GTX2, GTX1, CTX-). CTX + assignment was counterbalanced between subjects to be the summertime or wintertime context.

are presented (CTX+) compared to a context in which no US is presented (CTX-). Studies have found that individuals with panic disorder and with PTSD show increased fear responding to the context containing threat relative to non-anxious participants (Grillon et al., 2008, 2009). Generalization of contextual fear is tested by evaluating subsequent fear of a novel context that includes features of both the CTX+ and CTX- (e.g., Andreatta, Leombruni, Glotzbach-Schoon, Pauli, & Mühlberger, 2015; Mühlberger et al., 2014). Generalization of contextual fear has been observed using measures of self-report, but has not been observed on physiological measures (Andreatta et al., 2015). A key limitation is the lack of testing of a gradient of contexts between threatening and safe contexts; to date, gradients of conditional fear generalization have been limited to cue conditioning (Lissek et al., 2014). Furthermore, prior studies have explored generalization of contextual fear in high versus low anxiety groups (Andreatta et al., 2015) rather than as a function of anxiety as a continuous measure. Given the clinical relevance of contextual fear generalization to anxiety disorders and PTSD, one aim of the current study was to evaluate generalization of contextual fear learning as a function of anxiety.

Furthermore, stress is thought to enhance maladaptive fear generalization. Animal research suggests that rats exposed to acute stress show enhanced conditioned freezing in a contextual fear conditioning task (Cordero, Venero, Kruyt, & Sandi, 2003). Additionally, stress hormones injected into the hippocampus in mice impair ability to restrict fear responses to the correct predictive contextual cues (Kaouane et al., 2012). It is hypothesized that cortisol impairs contextual dependency of memories in humans as well, given that acutely elevated cortisol levels suppress hippocampal activity, which is important for encoding emotional and contextual memories (Henckens, Hermans, Pu, Joels, & Fernandez, 2009; Lovallo, Robinson, Glahn, & Fox, 2010). In accord, oral administration of cortisol impairs contextualization of fear, leading to increased generalization as measured by startle reflex in human samples (van Ast, Vervliet, & Kindt, 2012). The association between acute stress and generalization of fear has predominantly been studied via induced stress through artificial means (e.g., cortisol administration). The current study sought to explore this relationship in

the context of a natural stressor, using a paradigm that allowed for a more sensitive measure of contextual fear generalization to assess individual and group differences.

The current investigation aimed to (1) test a novel paradigm assessing contextual generalization of conditional fear, (2) determine the extent to which acute stress enhances contextual generalization, and (3) investigate whether anxiety modulates contextual fear generalization. The primary hypotheses were that participants would show generalization of fear across the gradient of contextual stimuli, increasing from contexts without US presentation to contexts with US presentation; acute stress would increase contextual generalization of fear relative to control; and that anxiety would be positively associated with enhanced contextual generalization, operationalized as greater fear of generalization contexts more proximate to the context in which the US was presented (Lissek, 2012, 2014; Vervliet et al., 2013).

## 2. Materials and methods

### 2.1. Participants

Participants were 59 undergraduates from the University of California, Los Angeles (UCLA), who participated for course credit. Eight participants were excluded from analyses for discontinued participation after acquisition ( $N = 4$ ) and technical difficulties ( $N = 4$ ). Participants were 67% female and 27.45% White/Caucasian, 37.25% Asian or East Indian, 7.84% Black or African American, 7.84% Hispanic/Latino, and 19.61% other or multi-racial. Mean age was 20.76 years ( $SD = 2.24$ ). The study was approved by UCLA's Institutional Review Board. All participants provided informed consent prior to the study and were debriefed after study completion.

### 2.2. Materials & apparatus

On Acquisition Day, participants completed an arithmetic task (stress induction or control version) followed by a differential context fear conditioning paradigm, programed in E-Prime Build 2.0.

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