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Maladaptive behavioral consequences of conditioned fear-generalization: A pronounced, yet sparsely studied, feature of anxiety pathology☆

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ABSTRACT

Fear-conditioning experiments in the anxiety disorders focus almost exclusively on passive-emotional, *Pavlovian conditioning*, rather than active-behavioral, *instrumental conditioning*. Paradigms eliciting both types of conditioning are needed to study maladaptive, instrumental behaviors resulting from Pavlovian abnormalities found in clinical anxiety. One such Pavlovian abnormality is generalization of fear from a conditioned danger-cue (CS+) to resembling stimuli. Though lab-based findings repeatedly link overgeneralized Pavlovian-fear to clinical anxiety, no study assesses the degree to which Pavlovian overgeneralization corresponds with maladaptive, overgeneralized instrumental-avoidance. The current effort fills this gap by validating a novel fear-potentiated startle paradigm including Pavlovian and instrumental components. The paradigm is embedded in a computer game during which shapes appear on the screen. One shape paired with electric-shock serves as CS+, and other resembling shapes, presented in the absence of shock, serve as generalization stimuli (GSs). During the game, participants choose whether to behaviorally avoid shock at the cost of poorer performance. Avoidance during CS+ is considered adaptive because shock is a real possibility. By contrast, avoidance during GSs is considered maladaptive because shock is not a realistic prospect and thus unnecessarily compromises performance. Results indicate significant Pavlovian-instrumental relations, with greater generalization of Pavlovian fear associated with overgeneralization of maladaptive instrumental-avoidance.

Central to etiological accounts of clinical anxiety is conditioned fear (e.g., Bouton, Mineka, & Barlow, 2001; Lissek et al., 2005; Mineka & Zinbarg, 2006), the associative learning process whereby a neutral conditioned stimulus (CS) acquires the capacity to elicit fear-related emotion and behavior following repeated pairings with an aversive unconditioned stimulus (US). Conditioned fear has long been known to transfer, or generalize, to stimuli resembling the original CS (Pavlov, 1927). Evidence linking pathologic anxiety to conditioned generalization dates back to Watson and Rayner (1920) who famously demonstrated generalization of conditioned fear to all things fury in a toddler ('Little Albert') following acquisition of fear-conditioning to a white rat. Here, the pathogenic influence of generalization can be seen as the proliferation of anxiety cues in the individual's environment that then serve to increase the frequency and duration of anxious states and behavioral avoidance.

Since 'Little Albert', fear generalization has been adopted as a core feature of anxiety pathology by clinical practitioners and theorists (e.g., Foa, Steketee, & Rothbaum, 1989; Mineka & Zinbarg, 1996), but has received limited testing in humans with systematic methods developed in animals. Such methods assess *generalization gradients*, or continuous downward slopes in conditioned responding as the presented stimulus gradually becomes less perceptually similar to the CS (Pavlov, 1927). With this method, the strength of generalization is indexed by the steepness of the generalization gradient, with less steep gradients reflecting stronger generalization. The gap in human fear-generalization work is currently being filled by systematic lab-based studies of human generalization gradients in health and disorder (e.g., Dunsmoor & LaBar, 2013; Dunsmoor, White, & LaBar, 2011; Greenberg, Carlson, Cha, Hajcak, & Mujica-Parodi, 2013; Lissek, 2012; Lissek et al., 2008, 2010, 2013, in press; Lissek & Grillon, 2012). To date, results from this literature demonstrate overgeneralization of Pavlovian conditioned fear in panic disorder (Lissek et al., 2010), generalized

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anxiety disorder (Lissek et al., in press), and preliminarily in PTSD (Lissek & Grillon, 2012), as indicated by less steep generalization gradients among those with versus without an anxiety disorder.

A remaining question of central clinical importance relates to the degree to which conditioned overgeneralization in anxiety patients results in maladaptive behavior that may serve to impair day-to-day functioning among those diagnosed with clinical anxiety. To illustrate maladaptive behavioral consequences of Pavlovian generalization, consider a combat soldier in Iraq who acquires Pavlovian fear-conditioning to a roadside object (CS) used to encase an improvised explosive device (US), or IED, by which they are injured. After returning to civilian life, the veteran's Pavlovian fear to the IED encasement generalizes to benign roadside objects such as trash cans, fire hydrants, or other roadside debris they encounter while driving in their neighborhood. Such Pavlovian generalized-fear leads to instrumental generalized avoidance, whereby the individual behaviorally withdraws from these "safe" roadside objects by discontinuing all driving, and, in so doing, compromises their functioning in important personal and professional realms.

As illustrated by this example, the pathogenic power of conditioning abnormalities in anxiety disorders (e.g., overgeneralization) may, in no small part, lie in the maladaptive behavior it motivates. Fear-conditioning experiments in clinical anxiety, however, have focused almost exclusively on passive-emotional, *Pavlovian conditioning*, rather than active-behavioral, *instrumental conditioning* (Lissek et al., 2005). Paradigms capable of eliciting both Pavlovian and instrumental conditioning are thus needed to experimentally study the maladaptive behavioral consequences of Pavlovian abnormalities such as overgeneralization.

The current study represents the first effort to validate a psychophysiological (fear-potentiated startle) paradigm designed to assess the relation between Pavlovian generalization and maladaptive choice behavior. This paradigm applies a validated Pavlovian generalization experiment (Lissek et al., 2008, 2010) in the context of a 'virtual farmer' computer game. In this game, the participant is a farmer whose task it is to successfully plant and harvest crops. While playing the game, shapes are superimposed on the screen with one such shape, paired with electric shock, serving as the conditioned danger-cue (CS+). Other presented shapes, referred to as generalization stimuli (GS), parametrically vary in similarity to the CS+, but are never paired with shock. While playing the game, participants are given the opportunity to avoid shock at the cost of poorer performance (i.e., reduced likelihood of a successful harvest). Participants are thus placed in an *approach-avoidance conflict* in which 'approach' oriented motivation to win the game, is in conflict with 'avoidance' oriented motivation to evade electric shocks. Importantly, avoidance responses during CS+ presentations are considered adaptive, even though performance is compromised, because shock is a real possibility. By contrast, avoiding during GS presentations is considered maladaptive because shock is not a realistic possibility and avoiding thus unnecessarily compromises performance on the task. The central aim of the current study is to test the degree to which subjective ratings and psychophysiological measures of Pavlovian generalization are associated with this type of maladaptive instrumental-avoidance response.

Once validated, this paradigm would serve as a lab-based tool with which to: 1) test group differences in maladaptive behavioral consequences of Pavlovian generalization across those with and without an anxiety disorder, 2) assess the degree to which maladaptive avoidance can be reduced in anxiety patients via psychosocial and pharmacologic interventions, and 3) interrogate neurobiological mechanisms through which Pavlovian generalization transfers to instrumental avoidance, and identify potential aberrancies in such mechanisms associated with anxiety pathology.

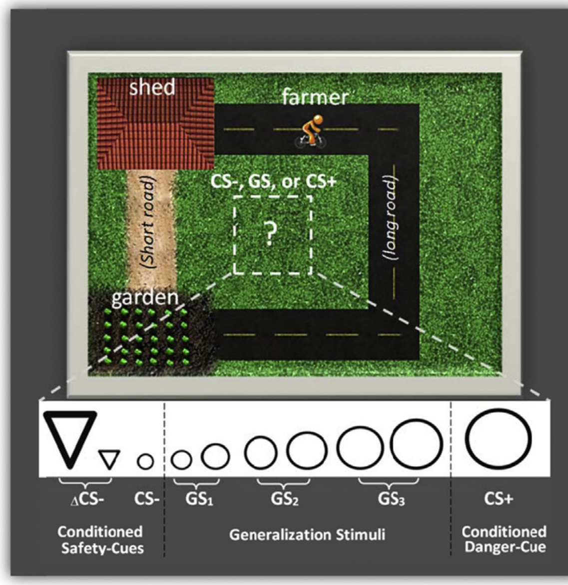

Fig. 1. Picture of the virtual-farmer computer paradigm displaying the short and long roads connecting the tool shed to the garden. Also pictured are the conditioned and generalization stimuli presented in the center of the screen during the task. Half of subjects were presented the stimulus set as displayed above, with the largest and smallest ring serving as CS+ and CS−, respectively. For the second half of subjects this was reversed with the largest and smallest rings serving as CS− and CS+, respectively. The diameters of rings from smallest to largest was .8″, .96″, 1.12″, 1.28″, 1.44″, 1.60″, 1.76″, 1.92″ (size increases were established in 20% increments). Width and height are .8″ for the small triangle, and 1.92″ for the large triangle. CS− = conditioned safety cue; GS = generalization stimulus; CS+ = conditioned danger cue; $_{\Delta}$CS− = triangular CS−; GS_1, GS_2, GS_3 = generalization stimulus classes 1–3.

Method

Participants

Fifty healthy participants were recruited from the University of Minnesota research experience program and received course credit for their time. Prior to testing, participants gave written informed consent that had been approved by the University IRB. Inclusion criteria included: (1) no past or current Axis-I psychiatric disorder, (2) no major medical condition that interfered with the objectives of the study, and (3) no current use of medications altering central nervous system function. Startle data for two participants were lost due to apparatus malfunction, and 4 participants had no discernible startle leaving a total of 44 participants (57% female) with a mean age of 19.45 (SD = 1.96), mean Spielberger State and Trait Anxiety Inventory (STAI: Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) trait scores of 34.18 (SD = 6.04) and state scores of 35.00 (SD = 8.54), and mean Beck Depression Inventory (Beck, Steer, & Brown, 1996) scores of 3.55 (SD = 3.64).

Physiological apparatus

Stimulation and recording were controlled by a commercial system (Contact Precision Instruments). Startle-blink EMG was recorded with two 6-mm tin cup electrodes filled with a standard electrolyte (SignaGel, www.biomedical.com[CG04]) placed under the right eye. More specifically, one EMG electrode was placed below the lower eyelid in line with the pupil in forward gaze, and the second electrode was placed approximately 2 cm lateral to the first. Additionally, a 9-mm disk electrode was placed on the anterior forearm and served as a ground. Impedance levels for EMG