Behaviour Research and Therapy 57 (2014) 29–37

Contents lists available at ScienceDirect

Behaviour Research and Therapy

journal homepage: www.elsevier.com/locate/brat

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

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A R T I C L E I N F O

Article history:
Received 5 November 2013
Received in revised form
16 March 2014
Accepted 25 March 2014
Available online 3 April 2014

Keywords:
Pavlovian fear-conditioning
Instrumental conditioning
Generalization
Fear-potentiated startle
Behavioral-avoidance
Anxiety disorders

A B S T R A C T

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

☆ This work was supported by R00-MH080130 from the National Institute of Mental Health.

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http://dx.doi.org/10.1016/j.brat.2014.03.009
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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.

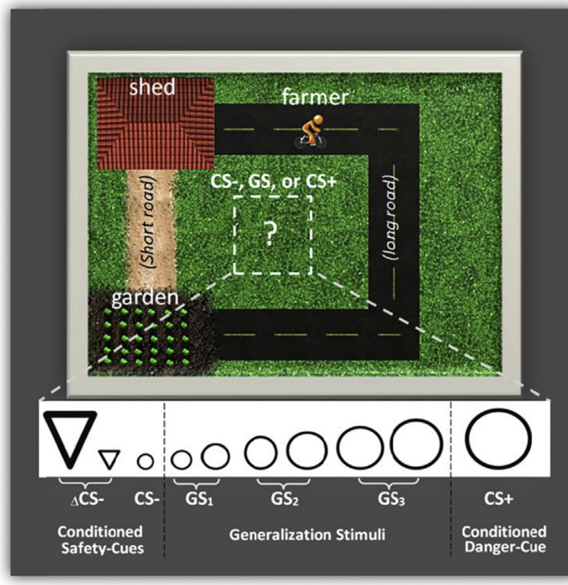

Fig. 1. Picture of the virtual-farmer computer paradigm displaying the short and long roads connecting the tool shed to the garden. Also pictured are the conditioned and generalization stimuli presented in the center of the screen during the task. Half of subjects were presented the stimulus set as displayed 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 electrodes was maintained below 20 Kilohms. The EMG signal was sampled at 1000 Hz and amplifier band width was set to 30–500 Hz. Startle was probed by a 50-ms duration, 102 dB (A) burst of white-noise with a near instantaneous rise-time presented binaurally through headphones.

Pavlovian-instrumental generalization paradigm

Pavlovian and instrumental components of the applied conditioned generalization paradigm occurred in the context of a “virtual farmer” computer game (see Fig. 1). The game includes a virtual farmer cycling back and forth between a tool shed and garden first to plant and then to harvest crops. As can be seen in Fig. 1, two different roads connect the shed to the garden: 1) a short dirt road, and 2) a long paved road. Different costs and benefits are associated with each road. Traveling the short dirt road is perilous (contingently associated with electric shock) but allows the farmer quick travel from shed to garden, and assures a successful harvest. Conversely, traveling the long paved road is always safe (never associated with shock) but often prevents the farmer from arriving at the garden to harvest before “wild birds” consume the crop. While the farmer invariably travels the short road during Pavlovian trials, the participant is given the option to avoid any chance of shock by choosing the long road on instrumental-avoidance trials.

Conditioned, generalization, and unconditioned stimuli

Shock delivery, while traveling the short path during both Pavlovian and instrumental-avoidance trials, depends on the size and form of the shape presented in the center of the screen. These shapes constitute the conditioned and generalization stimuli to which startle responses and self-reported risk of shock are recorded. Specifically, such stimuli consist of circles and triangles of different sizes (see Fig. 1). Circular stimuli include eight rings of gradually increasing size with extremes serving as conditioned-danger (CS+) and conditioned-safety cues (CS−). The six rings of intermediary size are generalization stimuli (GSs), and create a continuum-of-similarity between CS+ and CS−. As was done by Lissek et al. (2008), responses to every two GS sizes are averaged yielding 3 classes of GSs (GS_1, GS_2, GS_3). This was done to prevent an unrealistically long experiment while still maintaining a gradual continuum of size across circles. For half of participants, ring sizes from smallest to largest were: CS−, GS_1, GS_2, GS_3, and CS+. For the second half of participants this was reversed (i.e., CS+ is smallest, GS_3 is second smallest, etc.). Thus, regardless of such counterbalancing, GS_3 is most similar to CS+, GS_2 is next most similar, and GS_1 is least similar to CS+ for all subjects. Triangles serve as “non-circular” conditioned safety cues () and are included to assess the degree to which fear generalizes to all things circular (but not triangular). Triangular stimuli included one large and one small triangle to control for effects of size on responses to the triangle. Because no effects of triangle size are found, responses to the large and small triangles are collapsed. An additional trial type, referred to as no shape (NS) trials, are not accompanied by the presentation of a shape but are identical to other trial types on all other parameters (duration, time-course of startle probes and risk ratings). The unconditioned stimulus (US) is an electric shock delivered to the non-dominant wrist (3–5 mA, 100–200 ms) that was rated by participants as ‘highly uncomfortable but not painful’.

Trial structure

Fig. 2 presents sample Pavlovian and instrumental trials across acquisition and generalization sequences.

Pavlovian trials at acquisition and generalization

The duration of all Pavlovian trials are 10.4 s, and begin with the onset of a CS ($_{\Delta}$CS−, CS−, CS+), GS (GS_1, GS_2, GS_3) or NS in the center of the screen, coincident with the farmer beginning to travel the short road between the shed and garden. Subjects have no control over the virtual farmer and simply watch as the farmer travels the short road. The farmer’s trip, as well as CS and GS presentations, last the full duration of the trial. Startle probes are administered 2.5 or 3.5 s post-trial-onset (18–22 s inter-probe interval [IPI]), and shock USs are administered on 50% of CS+ trials, but no other trial types, at 4 or 9 s post-trial-onset. In tandem with shock delivery to subjects, the virtual farmer is graphically shown receiving a “virtual shock”. Additionally, on the 50% of CS+ not paired with “actual shock”, the farmer continues to be graphically shown to receive virtual shocks, at 4 or 9 s post-CS+ onset, in order to further reinforce the CS+/US association while limiting subjects’ habituation to the US.

Instrumental-avoidance trials at generalization

Trials begin with the presentation of a CS, GS, or NS, after which subjects are instructed to choose between sending the farmer down the short road (button 1) or the long road (button 2) using a handheld response box (see Fig. 2c). The resulting trip down the short or long road is 8 s in duration during which no startle probes are presented. In order to maintain equal travel times across short and long roads, the farmer appeared to move more quickly down the long path. Decisions to travel the short path result in a successful harvest at the end of all trials, but on CS+ trials this decision is always followed by both actual and virtual shocks administered at 4 s post-choice. For all trial types, decisions to avoid the short path, by taking the long path, are not accompanied by shock (even on CS+ trials), but always result in a 75% likelihood of an unsuccessful harvest. If subjects fail to decide within the allotted 5 s, they are forced to take the short path and forfeit the crops. Additionally, response times exceeding 2.5 standard deviations from a given subject’s mean were considered outliers and discarded (Ratcliff, 1993). Of note, the motivation to take the short path during CS+ trials was simply the intrinsic reward of performing well on the experimental task, as well as a small graphic that included sparkles for a successful harvest.

Experimental phases

The paradigm consists of three phases: (1) *pre-acquisition*, including 4 NS, 4 $_{\Delta}$CS−,4 CS−, and 4 CS+ trials in the Pavlovian format, with all CS+ presented in the absence of shock; (2) *acquisition*, including 8 NS, 8 $_{\Delta}$CS−, 8 CS−, and 8 CS+ Pavlovian trials, with 4 CS+ paired with actual shocks and all 8 CS+ paired with virtual shocks to the farmer; and (3) *generalization*, consisting of alternating Pavlovian and instrumental trials, with 6 Pavlovian and 6 instrumental trials of each stimulus type (NS, $_{\Delta}$CS−, CS−, GS_1, GS_2, GS_3, CS+). During generalization, 3 of 6 Pavlovian CS+ are paired with actual shocks, and 6 of 6 are paired with virtual shocks to prevent extinction of the conditioned response while limiting US habituation. During instrumental-avoidance trials, participants could receive anywhere from 0 to 6 shocks depending on their avoidance decisions. For each of six CS+ trials, decisions not to avoid, by taking the short path, resulted in an actual and virtual shock. No actual or virtual shock was given on CS+ trials for which subjects chose to avoid shock by taking the long road.

For all three study phases, trials are arranged in quasi-random order such that no more than two stimuli of the same class occur consecutively. An additional constraint placed on the ordering of the generalization sequence is the arrangement of trials into six

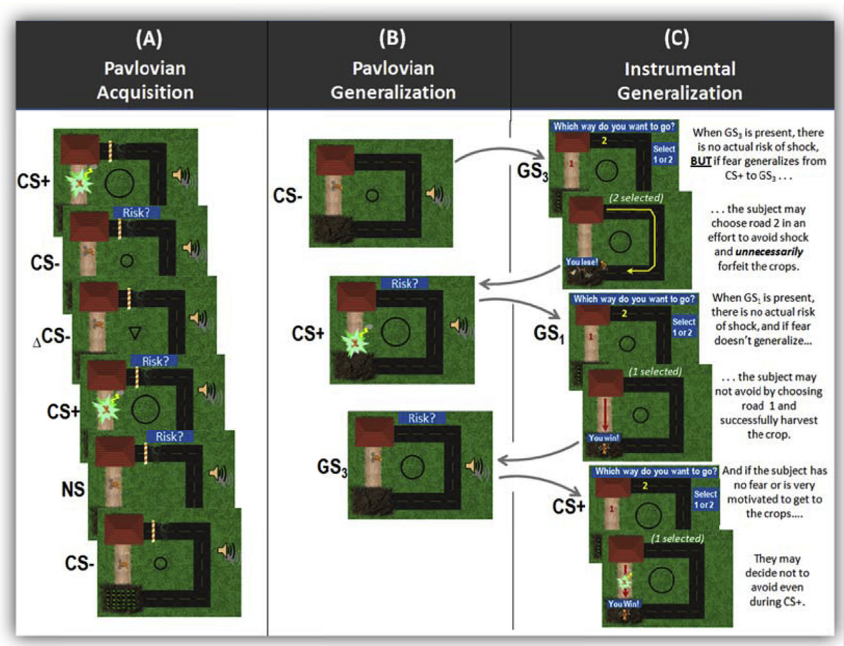

Fig. 2. Examples of acquisition and generalization trials with the largest ring serving as CS+. (A) Pavlovian acquisition trials start with presentation of one of four stimulus types (CS+, CS−, $_\Delta$CS−, and no shape [NS]) coincident with the farmer beginning to travel the short path between shed and garden (the long path is blocked). While traveling the short path, startle probes (represented by audio speakers) are delivered at 2.5 or 3.5 s post-trial-onset on all trials. For half of these trials, risk for shock is assessed at 6.5 s post-trial-onset. Actual shock is given together with virtual shock (graphic of farmer being shocked) on 50% of CS+ trials at 4 or 9 s post-trial-onset. The remaining 50% of CS+ trials are reinforced with virtual shock alone. Of note, when both risk ratings and actual shocks occurred on a given CS+ trial, actual shocks are always administered at 9 s post-trial-onset. Following acquisition, the generalization sequence begins, during which Pavlovian and instrumental trials alternate. (B) Pavlovian generalization trials begin with presentation of 1 of 7 stimulus types (CS+, GS_3, GS_2, GS_1, CS−, $_\Delta$CS−, and NA) followed by the farmer automatically traveling the short path. Startle probes at 2.5 or 3.5 s post-trial-onset are delivered on all trials and risk ratings at 6.5 s post-trial-onset are assessed on 50% of trials. Shock reinforcement (actual and virtual) occurs in the identical manner described above for acquisition trials. (C) Instrumental generalization trials begin with presentation of 1 of 7 stimuli (CS+, GS_3, GS_2, GS_1, CS−, $_\Delta$CS−, and NS) coincident with the question "Which way would you like to go"? Using a handheld button box, participants select "1" for the short, but contingently dangerous road, and "2" for the long, safe road that will likely result in an unsuccessful harvest. On CS+ trials, selecting "1" sends the farmer down the short path with actual and virtual shocks administered at 4 s post-choice. Selecting "2" allows the subject to eliminate any chance of shock and thus constitutes an instrumental avoidance response.

blocks of 14 trials (2 NS, 2 $_\Delta$CS−, 2 CS−, 2 GS_1, 2 GS_2, 2 GS_3, and 2 CS+) to ensure an even distribution of trial types throughout.

Self-report ratings

Online risk-ratings

During half of all Pavlovian trials, the question "Level of risk?" appeared at the top of the screen at 6.5 s post-trial-onset (3–4 s after the startle probe) and cued participants to use a response box to rate their perceived level of risk for shock on a 3-point Likert scale, where 1 = "no risk", 2 = "moderate risk", and 3 = "high risk". When both risk ratings and actual shocks occurred on a given CS+ trial, shocks were administered at 9 s post-trial-onset. Behavioral ratings of risk were assessed quasi-randomly with no more than three consecutive trials prompting risk ratings. Participants were instructed to answer as quickly as possible with their index finger. Risk ratings and corresponding response latencies were recorded with Presentation software (Neurobehavioral Systems), and reaction times exceeding 2.5 standard deviations above the average were considered outliers and discarded (Ratcliff, 1993).

Retrospective ratings

After acquisition and generalization phases, participants rated the level of anxiety they experienced during the experiment, generally, and to the CS+, $_\Delta$CS−, CS−, and NS trials, specifically, using an 11 point Likert scale (0 = no anxiety, 10 = extreme anxiety).

Standardized questionnaires

Participants completed the Spielberger State and Trait Anxiety Inventory (STAI: Spielberger et al., 1983), the Beck Depression Inventory (BDI: Beck et al., 1996), and the Multidimensional Experiential Avoidance Questionnaire (MEAQ: Gámez, Chmielewski, Kotov, Ruggero, & Watson, 2011). The MEAQ has 6 subscales: 1) Behavioral Avoidance—active avoidance behaviors; 2) Distress Aversion—the aversiveness of distressing states; 3) Procrastination—the tendency to delay tasks; 4) Distraction and Suppression—switching tasks or cognitive sets in an effort to avoid negative feelings; 5) Repression and Denial—Turning off emotions or remaining unaware of emotional responses; and 6) Distress Endurance—perseverance in the face of adversity.

Procedure

Following informed consent, standardized questionnaires were filled out and EMG and shock electrodes were attached. Next a shock-workup procedure was completed during which sample shocks were rated by participants, and levels of shock were adjusted to find a shock level that was highly uncomfortable but not painful for each subject. Prior to the acquisition phase, participants were told they might learn to predict the shock if they attend to the shapes in the center of the screen, but were not informed of the CS+/US contingency. Next, headphones were placed and a habituation sequence consisting of nine startle probes (IPI = 18–25 s) was run while the background image of the two roads, the shed, and the garden was displayed. The three phases of the experiment were then completed with a 10 min break separating acquisition and generalization, during which participants completed retrospective ratings. Prior to the start of the generalization phase, subjects were given additional instructions concerning the avoidance portion of the task. Specifically, subjects were told that what they learned during acquisition about the relation between shapes and shocks still applied. Additionally, participants were informed they would now be able to choose the road traveled by the farmer on some trials, and the costs and benefits associated with each road were explained. Finally, subjects practiced using the button box to send the farmer down the long and short road. Next, five habituation startle probes were delivered (IPI = 18–25 s), the generalization phase was run, and retrospective ratings were again completed.

Data analysis

Startle EMG was rectified and then smoothed (20-ms moving window average). The onset latency window for the blink reflex was 20–100-ms and the peak magnitude was determined within a window of time extending from the response onset to 120 ms. Additionally, the average baseline EMG level for the 50 ms immediately preceding delivery of the startle stimulus was subtracted from the peak magnitude. EMG magnitudes across all phases of the study were standardized together using within subject *T*-score conversions to normalize data and reduce the influence of between subjects' variability unrelated to psychological processes. Because similar results were obtained with the raw and *T*-scored data, only the results of *T*-scored data are presented. Startle and behavioral indices of acquisition were separately averaged for each stimulus type and analyzed with separate 3-level (Stimulus type: $_{\Delta}$CS−, CS−, CS+) repeated measures analysis of variance (ANOVA). Startle and behavioral indices of generalization were separately averaged for each stimulus type and analyzed with separate 5-level (Trial type: CS−, GS_1, GS_2, GS_3 and CS+) repeated measures ANOVAs. Because past studies from our group have identified linear versus quadratic generalization slopes in anxiety patients versus healthy controls (e.g., Lissek et al., 2010), linear and quadratic trends in generalization slopes were tested for future reference to patient data collected with this virtual-farmer paradigm. When necessary, analyses were followed by paired samples *t*-tests. Alpha was set at .05 for all statistical tests and effect sizes were estimated with measures of omega squared (ω^2) and Cohen's *d* for all repeated measures ANOVAs and *t*-tests, respectively.

Results

Descriptive statistics for startle and subjective responses across pre-acquisition and Pavlovian acquisition are displayed in Table 1.

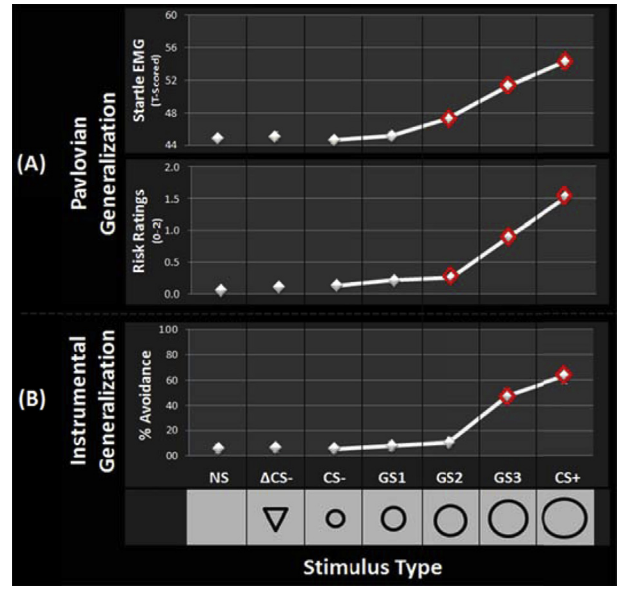

Fig. 3. (A) Pavlovian generalization-gradients for standardized startle-EMG magnitudes and online risk ratings (0 = no risk, 1 = some risk, 2 = high risk) across the conditioned danger cue (CS+) generalization-stimulus classes 3, 2, and 1 (GS_3, GS_2, GS_1), the circular conditioned safety cue (CS−), the triangular CS− ($_{\Delta}$CS−), and no-shape (NS) conditions. (B) Instrumental generalization gradients reflecting percent of trials during which avoidance responses were displayed across CS+, GS_3, GS_2, GS_1, CS−, $_{\Delta}$CS−, and NS conditions. Data points outlined in red mark stimulus classes for which startle is potentiated relative to the CS− (at the Hochberg-adjusted *p* value). Startle EMG was standardized using within-subject *T* score transformations ($[(EMG_{single\ trial} - EMG_{mean}]/SD)*10]+50$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Pre-acquisition

Prior to conditioning, there was no effect of trial-type on startle ($p = .87$), online ratings of shock risk ($p = .49$), or reaction times for risk ratings ($p = .34$).

Pavlovian acquisition

Startle EMG

A main effect of trial-type was found, $F(2, 86) = 38.48$, $p < .001$, $\omega^2 = .46$, and reflected startle potentiation to CS+ relative to both CS−, $t(43) = 6.19$, $p < .001$, $d = 1.27$, and $_{\Delta}$CS−, $t(43) = 7.56$, $p < .001$, $d = 1.48$. Additionally, there was a trend toward greater startle EMG to CS− compared to $_{\Delta}$CS−, $t(43) = 1.85$, $p = .07$, $d = .32$.

Online risk ratings and reaction times

A main effect of trial-type was found for risk ratings, $F(2, 86) = 224.93$, $p < .001$, $\omega^2 = .83$, with higher ratings to CS+

Table 1
Means (standard deviations) and paired samples *t*-tests for standardized startle, online risk-ratings, reaction times, and retrospectively reported anxiety for each stimulus-type during pre-acquisition and acquisition.

Stimulus	Pre-acquisition			Acquisition			
	Startle (*T*-score)	Risk ratings[a]	Reaction times (ms)	Startle (*T*-score)	Risk ratings	Reaction times (ms)	Anxiety ratings[b]
NS	50.80(5.46)	0.17(.30)	1702(536)	50.40(3.03)	0.20(.30)	1441(326)	1.27(2.02)
$_{\Delta}$CS−	53.45(5.44)	0.14(.29)	1372(645)	50.13(3.44)	0.18(.30)	1229(409)	1.55(2.11)
CS−	53.01(5.21)	0.11(.30)	1382(474)	51.17(3.02)	0.21(.29)	1241(247)	1.59(1.93)
CS+	53.21(6.13)	0.17(.32)	1497(578)	56.01(4.43)*	1.49(.44)*	1124(284)	7.09(2.95)*

NS = no shape; $_{\Delta}$CS− = triangular shaped CS−; CS− = conditioned safety-cue; CS+ = conditioned danger-cue. *Significantly different from all other stimuli at $p < .001$.
[a] Online ratings on a 3-point scale, where 0 = no risk, 1 = some risk, and 2 = a lot of risk.
[b] Retrospective ratings on a 11-point scale, where 0 = no anxiety and 10 = extreme anxiety.

compared to CS−, $t(43) = 15.23$, $p < .001$, $d = 3.48$, and $_{\Delta}$CS−, $t(43) = 17.40$, $p < .001$, $d = 3.52$. There was no difference between ratings of risk for CS− compared to $_{\Delta}$CS−, $t(43) = .61$, $p = .55$, $d = .10$. Additionally, a main effect of response times was found across stimuli, $F(2,76) = 3.76$, $p = .025$, $\omega^2 = .07$, with faster responses to CS+ versus CS−, $t(39) = 2.33$, $p = .025$, $d = .43$, and $_{\Delta}$CS− $t(40) = 2.47$, $p = .018$, $d = .30$, and no difference between response times to CS− versus $_{\Delta}$CS− ($p = .46$).

Retrospective anxiety ratings

A main effect of trial-type was found, $F(2,86) = 130.89$, $p < .001$, $\omega^2 = .75$, with CS+ rated as more anxiety provoking than CS−, $t(43) = 13.11$, $p < .001$, $d = 4.00$, and $_{\Delta}$CS−, $t(43) = 12.46$, $p < .001$, $d = 2.16$. There was no difference between retrospective anxiety ratings for CS− compared to $_{\Delta}$CS−, $t(43) = .15$, $p = .88$, $d = .02$.

Pavlovian generalization

Startle EMG

Robust enhancement of startle during CS+ relative to CS− persisted during generalization, $t(43) = 9.44$, $p < .001$, $d = 2.09$. Importantly, a main effect of trial-type was found, $F(4,172) = 42.57$, $p < .001$, $\omega^2 = .48$, and, as can be seen in Fig. 3A, was driven by continuous generalization gradients. Specifically, significant decreases in startle were found from CS+ to GS_3 to GS_2 to GS_1 to CS− (linear decrease: $F(1,43) = 89.54$, $p < .001$, $\omega^2 = .663$; quadratic decrease: $F(1,43) = 10.89$, $p = .002$, $\omega^2 = .18$). Follow up analyses comparing each GS-type to CS− revealed significant startle potentiation to GS_3, $t(43) = 7.31$, $p < .001$, $d = 1.47$, and GS_2, $t(43) = 3.60$, $p = .001$, $d = .72$, but not GS_1 $t(43) = .96$, $p = .34$, $d = .17$. Thus, subjects in the current study generalized startle potentiation from CS+ to two degrees of CS+ differentiation (GS_3, GS_2).

Risk ratings and reaction times

Risk rating differences between CS+ and CS− also persisted throughout generalization $t(43) = 16.56$, $p < .001$, $d = 3.47$. A main effect of trial-type, $F(4,172) = 147.80$, $p < .001$, $\omega^2 = .768$, was found for levels of perceived risk. Similar to startle results, risk ratings evidenced gradients of generalization consisting of both linear, $F(1,43) = 276.45$, $p < .001$, $\omega^2 = .86$, and quadratic, $F(1,43) = 112.00$, $p < .001$, $\omega^2 = .69$, decreases in perceived risk from CS+ down the continuum-of-size to CS− (see Fig. 3A). Relative to CS−, risk ratings were enhanced to CS+, $t(43) = 16.56$, $p < .001$, $d = 3.47$, GS_3, $t(43) = 10.52$, $p < .001$, $d = 1.98$, GS_2, $t(43) = 3.02$, $p = .004$, $d = .46$, and, at the level of a non-significant trend, GS_1, $t(43) = 1.86$, $p = .07$, $d = .30$. There was no main effect of trial-type on reaction times during generalization ($p = .14$, $\omega^2 = .02$).

Instrumental generalization

Behavioral avoidance

Generalization gradients were also present in instrumental avoidance decisions (see Fig. 3B). The main effect of trial-type, $F(4,172) = 65.64$, $p < .001$, $\omega^2 = .59$, consisted of linear, $F(1,43) = 89.58$, $p < .001$, $\omega^2 = .66$, and quadratic, $F(1,43) = 32.09$, $p < .001$, $\omega^2 = .43$, decreases in avoidance from CS+ to GS_3 to GS_2 to GS_1 to CS−. Relative to CS−, avoidance behavior was increased to CS+, $t(43) = 9.69$, $p < .001$, $d = 1.90$, and GS_3, $t(43) = 7.86$, $p < .001$, $d = 1.42$, but not GS_2 ($p = .16$, $d = .19$), or GS_1, ($p = .23$, $d = .10$). Thus avoidance behavior can be said to have generalized to only one degree of differentiation from the CS+.

Avoidance decision-times

There was a main effect of trial-type for decision times, $F(4,164) = 14.84$, $p < .001$, $\omega^2 = .25$. As can be seen in Fig. 4, decision times were longest for CS+ and GS_3, and gradually decreased from GS_3 to GS_2, $t(41) = 2.74$, $p = .009$, $d = .41$, and from GS_2 to GS_1, $t(42) = 4.46$, $p < .001$, $d = .58$, with equally fast reaction times to GS_1 and CS− ($p = .19$, $d = .15$). This pattern of results suggests longest decision times for stimuli evoking the strongest conflict between motivations to avoid and not avoid, and progressively shorter decision times for stimuli eliciting less motivational conflict. Specifically, CS+ and GS_3 stimulate the highest motivation to avoid which then competes with motivations not to avoid (driven by a desire to perform well on the task). Resolving the conflict elicited by CS+ and GS_3 requires time and delays decisions. By contrast, GS_2, GS_1, and CS− elicit progressively less avoidance motivation, and thus motivation not to avoid increasingly predominates, resulting in reduced response conflict and reduced decision times.

Testing the relation between Pavlovian and instrumental generalization

Central to the goals of the current paper are assessments of the degree to which increases in Pavlovian generalization are associated with increases in instrumental generalization. For such tests, Pavlovian generalization to each of three GSs was operationalized separately as the degree to which startle was potentiated to the respective GS (GS_3, GS_2, GS_1) versus the CS−. Additionally, instrumental generalization to each GS was indexed separately as the degree to which participants avoided the respective GS (GS_3, GS_2, GS_1) relative to CS−. Next, these indices of Pavlovian and instrumental generalization were correlated for each of three GSs separately. As shown in Fig. 5A and B, measures of Pavlovian and instrumental generalization were highly correlated for GS_3 ($r = .49$, $p = .001$) and GS_2 ($r = .39$, $p = .008$). Such findings indicate that greater Pavlovian generalization of fear to GS_3 and GS_2 is associated with greater generalized avoidance during GS_3 and GS_2, respectively. Importantly, shocks were never paired with GS_3 and GS_2, and generalized avoidance during these GSs unnecessarily compromised performance on the harvesting task. As such, increases in fear generalization to GS_3 and GS_2 can be said to have been accompanied by increasing levels of maladaptive behavior.

Unlike results for GS_3 and GS_2, there was no Pavlovian-instrumental correlation for GS_1, $r = .16$, $p = .30$ (see Fig. 4C). This was likely due to uniformly low levels of avoidance evoked by GS_1 (35 of 44 subjects never avoided to GS_1) resulting in little variability

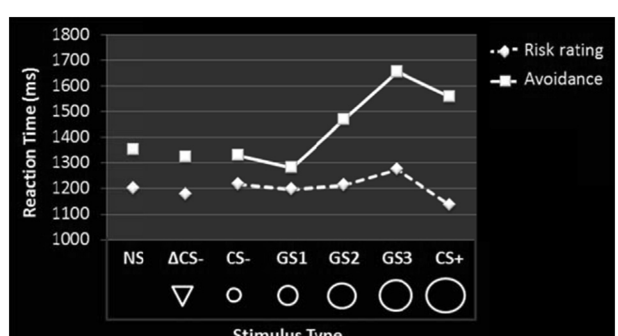

Fig. 4. Reaction times for risk ratings and avoidance decisions during the generalization phase. NS = no shape; CS− = conditioned safety cue; $_{\Delta}$CS− = triangular shaped CS−; GS_1, GS_2, GS_3 = generalization stimulus classes 1–3; CS+ = conditioned danger cue.

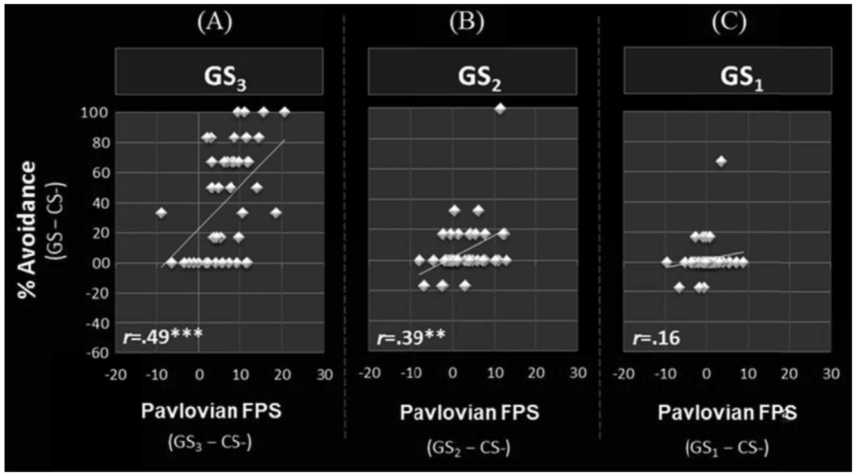

Fig. 5. Relations between Pavlovian fear-potentiated startle (FPS) and percent avoidance for (A) generalization stimulus class 3 (GS_3), (B) generalization stimulus class 2 (GS_2), and (C) generalization stimulus class 1 (GS_1). FPS and avoidance are expressed as difference scores between a given GS and the conditioned safety-cue (CS−). $^{*}p \le .05$, $^{**}p \le .01$, $^{***}p \le .001$.

in avoidance with which to account for variance in startle potentiation to GS_1 (vs. CS−).

Pavlovian-instrumental correlations with the same structure were computed using risk ratings, rather than startle magnitudes, to operationalize Pavlovian generalization. Such analyses yielded strong correlations between Pavlovian risk-ratings and instrumental avoidance for GS_3 ($r = .467$, $p = .001$), GS_2 ($r = .563$, $p < .001$), and GS_1 ($r = .533$, $p < .001$).

Shape of generalization gradients

For each subject, the shape of Pavlovian and instrumental generalization gradients was assessed separately by calculating the degree to which each gradient departed from linearity using the equation: *Linear departure = (average of GS_1, GS_2, GS_3) − (average of CS+, CS−)*. Here, the second expression *(average of CS+, CS−)* reflects the theoretical, linear midpoint of the gradient, and *(average of GS_1, GS_2, GS_3)* reflects the average response to GSs which could fall above the linear midpoint (positive departure), on the linear midpoint (zero departure), or below the linear midpoint (negative departure). This equation thus provides a single number reflecting the steepness of generalization gradients (Pavlovian or instrumental), with positive versus negative values reflecting shallow convex gradients versus steep concave gradients. This single number also indicates the strength of generalization with positive, zero, and negative values reflecting large, medium, and small levels of generalization, respectively. To assess the degree to which the shape of Pavlovian gradients matched that of instrumental gradients, Pavlovian and instrumental linear departures were correlated across subjects. Results reveal significant positive correlations between the shape of Pavlovian and instrumental gradients whether indexing the shape of Pavlovian gradients with startle, $r = .32$, $p = .04$, or risk ratings, $r = .522$, $p < .001$. Such results indicate that stronger, less steep gradients of Pavlovian generalization were accompanied by stronger, less steep gradients of instrumental generalization.

Individual differences in instrumental avoidance

Trait effects

Two subscales of the MEAQ were found correlated with measures of instrumental avoidance. Specifically, the Distress Endurance subscale was negatively correlated with rates of maladaptive avoidance to GSs ($r = -.35$, $p = .02$) and overall avoidance ($r = -.38$, $p = .01$). Similarly, the Distraction and Suppression subscale was related to both maladaptive avoidance to GSs ($r = -.39$, $p = .009$) and overall avoidance ($r = -.47$, $p = .001$). Such results suggest that resilience in the face of stress (Distress Endurance) and coping styles characterized by diversion from, and suppression of, negative emotion (Distraction and Suppression) buffer individuals from avoidance behavior. Additionally, an inverse correlation at the level of a trend was found between BDI scores and overall rates of avoidance ($r = -.28$, $p = .068$). This result may reflect the link between *learned helplessness* and depression, whereby depressed individuals abandon attempts to neutralize, or escape, the source of stress. All other measures of psychological traits were found unrelated to levels of avoidance. These null effects may be due to a restriction of range in anxiety scores in this healthy, college-student population.

State effects

Though scores on STAI-State prior to study start were unrelated to rates of avoidance, levels of state anxiety 'generally' experienced during the experiment were positively associated with both rates of maladaptive avoidance to GSs ($r = .46$, $p = .002$) and overall avoidance ($r = .52$, $p < .001$). Such results suggest that individuals more anxiously reactive to a given stressor display higher rates of maladaptive (and adaptive) behavioral avoidance when exposed to cues of that stressor.

Discussion

Current findings validate a novel experimental paradigm for assessing maladaptive behavioral correlates of Pavlovian generalization of conditioned fear. The applied 'virtual farmer' paradigm elicited both Pavlovian and instrumental generalization gradients with strongest fear-related responses (startle potentiation, perceived risk, behavioral avoidance) to the CS+, and curve-linear decreases in responding as presented stimuli differentiated from CS+. Central to the primary aim of the study, Pavlovian and instrumental generalization were strongly related, with increases in Pavlovian generalization associated with greater behavioral avoidance of GSs. Because GSs were in fact benign, by virtue of never being paired with shock, avoidance of GSs unnecessarily compromised performance on the virtual-farmer task and thus reflected maladaptive behavior. The current study provides the first lab-based tool with which to probe the neurobiology, psychopharmacology, genetics, and therapeutic responsiveness of the maladaptive behavioral consequences of Pavlovian generalization.

Findings substantiating the link between Pavlovian and instrumental generalization

Current evidence for the relation between Pavlovian and instrumental generalization derive from two sources. The first includes correlational findings indicating stronger levels of generalized instrumental avoidance to GS_3 and GS_2 with increasing levels of Pavlovian generalization to GS_3 and GS_2, respectively. This was true whether indexing Pavlovian generalization with fear-potentiated startle or online ratings of perceived risk for shock. The second source arises from analyses comparing the overall shape of Pavlovian versus instrumental generalization-gradients. Here, shape was quantified on a subject-by-subject basis as the degree to which gradients deviate from linearity. Positive deviations from linearity reflect shallow, *convex* slopes indicative of stronger generalization, whereas negative deviations reflect steeper, concave slopes indicative of weaker generalization. As predicted, results demonstrate more shallow, convex slopes of instrumental generalization among subjects displaying more shallow, convex gradients of Pavlovian generalization. That is, gradient shapes reflective of stronger Pavlovian generalization were accompanied by gradient shapes reflective of stronger generalized avoidance. The same Pavlovian-instrumental correspondence in gradient shape was found whether indexing Pavlovian generalization with fear-potentiated startle or online ratings of risk for shock.

One difference between Pavlovian and instrumental gradients was the extent to which fear generalized across the continuum-of-similarity between CS+ and CS−. Specifically, when averaging across subjects, Pavlovian conditioning generalized to two degrees of CS+ differentiation (GS_3, GS_2), whereas instrumental conditioning generalized to only one (GS_3). Thus, while there was significant Pavlovian fear to GS_2, such fear was not, on average, sufficient to trigger the avoidance response. This pattern of findings suggests that lower levels of threat may activate the fear system without eliciting behavioral avoidance.

Predictions for anxiety patients

As described above, subjects with stronger Pavlovian generalization displayed higher levels of generalized instrumental-avoidance. As such, past demonstrations of Pavlovian overgeneralization in panic disorder, GAD, and preliminarily in PTSD support predictions of overgeneralized avoidance in these patient populations. More specifically, Pavlovian generalization in anxiety patients, relative to healthy controls, has been found to extend to one or two additional GSs (i.e., 1 or 2 additional degrees of CS+ differentiation: Lissek et al., 2008; Lissek & Grillon, 2012; Lissek et al., in press), and similar patient-control differences might be expected for instrumental generalization. Thus, whereas healthy controls in the current study generalized instrumental-avoidance to one degree of differentiation from CS+ (i.e., GS_3), those with an anxiety disorder may be expected to generalize avoidance to one or two additional degrees of differentiation (e.g., GS_3, GS_2, and GS_1), constituting greater maladaptation during the virtual-farmer paradigm. Underlying this enhanced generalization in anxiety patients may be lowered thresholds for threat reactivity, leading to activation of the fear circuit, and the resulting avoidance behavior, to stimuli with less threat information (or less resemblance to the CS+).

The prediction of enhanced avoidance in anxiety patients is consistent with clinical conceptualizations implicating behavioral avoidance as a cardinal feature of anxiety disorders (American Psychiatric Association, 2013). Indeed, most treatments for clinical anxiety counter avoidance by including an exposure component in which patients are directed to confront the feared situation while applying relaxation techniques (e.g., Foa & Kozak, 1986; Wolpe, 1982). One influential account of the pathogenic contribution of behavioral avoidance comes from Mowrer's two-stage learning theory (Mowrer, 1947). The first stage includes acquisition of fear to a CS+, paired with an aversive US, through Pavlovian fear-conditioning. In the second stage, this Pavlovian fear motivates instrumental escape of the CS+ and avoidance of the US, which leads to anxiety reduction (i.e., relief), and thereby reinforces and strengthens the avoidance response. Failure of Mowrer's theory to account for some experimental findings has led to newer, more cognitive conceptualizations of avoidance in which Pavlovian conditioning elicits expectancies of the US in the presence of the CS+, which then motivates avoidance (e.g., Lovibond, Suanders, Weidemann, & Mitchell, 2008). Whether motivated by anxiety-reduction (Mowrer, 1947) or US-expectancies (Lovibond et al., 2008), avoidance denies the individual opportunities to experience the CS+ in the absence of the US, and thereby prevents extinction of fear and reduction of US-expectancies to the CS+.

Past findings related to current results

Only one fear conditioning study to date assesses generalized avoidance across a continuum of perceptual similarity (Lommen, Engelhard, & van den Hout, 2010; see Dymond, Schlund, Roche, De Houwer, & Freegard, 2012 for a study on symbolic generalization of avoidance). This study documents stronger generalized avoidance, from CS+ to stimuli resembling the CS+, among participants high versus low on neuroticism. Because neuroticism is a robust risk factor for clinical anxiety (van Os & Jones, 1999), such results support the above described prediction of overgeneralized avoidance in anxiety patients. Though Lommen et al. (2010) represents an important start to this line of work, the current study adds several important features including: 1) psychophysiological measures of conditioning and generalization, 2) analysis of continuous generalization-gradients, 3) tests of the relation between Pavlovian and instrumental generalization, and 4) an avoidance response reflective of maladaptive behavior.

Fear-Potentiated Startle (FPS) as a correlate of anxiety-related decision making

Though a sizeable literature characterizes FPS as a robust psychophysiological marker of "passive" aversive motivational states, few if any experiments demonstrate the utility of FPS for studying the more "active", choice-behaviors prompted by aversive motivation. This seems to be a significant omission, given predominant views of emotion as motivators of survival-relevant action (Dickinson & Dearing, 1979; Konorski, 1967), or *action tendencies* (Frijda, Kuipers, & Schure, 1989). Current results begin to fill this gap by validating FPS as a powerful correlate of decisions to avoid. Specifically, increased FPS to GS_3 and GS_2 (GSs most similar to CS+) was associated with increased rates of decisions to avoid during GS_3 and GS_2 presentations. Indeed, levels of FPS to GS_3 and GS_2 accounted for 24% and 15% of the variance in avoidance decisions to GS_3 and GS_2, respectively. These results support the view that applications of FPS need not be restricted to passive assessments of emotion, and can be extended to studying more active decision-making and motivated behavior.

Conclusion

Current findings validate a novel paradigm for assessing Pavlovian and instrumental generalization of conditioned fear and the relations among them. Higher levels of Pavlovian generalization were associated with stronger maladaptive avoidance of benign GSs with resemblance to CS+. The current paradigm offers the field a lab-based tool with which to probe the neurobiology, pharmacology, and therapeutic responsiveness of maladaptive, generalized avoidance—a key but understudied feature of clinical anxiety.

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