A Move Towards Studying Both Pavlovian & Instrumental Contributions to Conditioning Abnormalities in the Anxiety Disorders

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Brian Gregory van Meurs

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Dedication

This thesis is dedicated to the two amazing girls in my life, Katie and Anneke. Katie, I wouldn't have been able to do this without you. You are a rock solid support and keep pushing me to succeed all the time. Anneke, your adorable smiley faces, and even your adorable grumpy faces, make me the happiest person in the world. Love you both so much.

Abstract

Fear-conditioning experiments in clinical anxiety have focused almost exclusively on passive- emotional, *Pavlovian conditioning*, rather than active-behavioral, i*nstrumental conditioning*. Paradigms capable of eliciting both Pavlovian and instrumental conditioning are thus needed to experimentally study the maladaptive behavioral consequences of Pavlovian abnormalities. One such abnormality is overgeneralization of conditioned fear, a core feature of anxiety pathology. Such generalization can be assessed by studying generalization gradients and until now has only been examined using *Pavlovian* conditioning. The current study validates a novel paradigm which applies a validated *Pavlovian* generalization experiment in the context of a 'virtual farmer' computer game in which 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 shock, serving as the conditioned danger cue (CS+). 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 (*instrumental conditioning*) at the cost of poorer performance. Fear-potentiated startle (FPS), skin conductance responses (SCR) and online risk ratings were obtained and each displayed the expected *Pavlovian* generalization gradient. Instrumental avoidance responses also form a generalization gradient and are strongly associated with Pavlovian indices of generalization (FPS and risk ratings but not SCR). Additionally, FPS at acquisition was a significant predictor of subsequent avoidance

behavior. This novel experimental tool will be useful in describing and testing individual differences associated with clinical anxiety.

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Introduction

Central to etiological accounts of clinical anxiety is conditioned fear (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). This gap is currently being filled by systematic lab-based studies of human generalization gradients in health and disorder (e.g., Greenberg et al., 2013; Dunsmoor et al., 2012; Dunsmoor et al., 2013 Lissek et al., 2008; Lissek et al., 2010; Lissek, 2012; Lissek & Grillon, 2012). To date, results from this literature demonstrate overgeneralization of conditioned fear in panic disorder (Lissek et al., 2010), generalized

anxiety disorder (Lissek, 2012), 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 he is 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 he encounters while driving in his neighborhood. Such Pavlovian, generalized fear leads to instrumental generalized avoidance, whereby the individual behaviorally withdraws from these "safe" roadside objects by avoiding all driving, and, in so doing, compromises his functioning in important personal and professional realms.

As illustrated by this example, much of the pathogenic power of conditioning abnormalities in anxiety disorders (e.g., overgeneralization) may 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.

Avoidance is a behavioral consequence of fear and anxiety that due to its prominence in presentation of clinical anxiety is a logical behavioral response to measure and observe by experimental psychopathologists. Mowrer's two-stage learning theory of fear and avoidance highlights the importance of both the initial classical fear conditioning experience as well as subsequent behavioral avoidance in the development and maintenance of anxiety (Mowrer, 1939). According to Mowrer, acquisition of classical fear-conditioning to the CS motivates avoidance of the CS, and avoidance prevents extinction by denying individuals the opportunity to experience the CS without the US. Avoidance is therefore thought to contribute to the maintenance of clinical anxiety. This idea is expressed in current etiological models of anxiety which posit that the avoidance of threat maintains fear (Barlow, 2002) and is embodied in the inclusion of avoidance behavior in the diagnostic criteria for most of the anxiety disorders (American Psychiatric Association, 2000).

Mowrer's two-stage learning theory does have difficulties explaining some findings in both laboratory and clinical research however. Most importantly, avoidance responses that only serve to prevent the US from occurring and do not have any effect on the presentation of the CS are not predicted by the theory, but are observed (Rachman, Craske, Tallman, & Solyom, 1986). Also, according to the theory, continued anxiety in the presence of the CS must be maintained to maintain the avoidance response, however once the avoidance response is learned and is performed, anxiety in the presence of the CS decreases, yet avoidance persists (Herrnstein, 1969; Rachman, 1977).

In order to address these limitations, an expectancy based account of avoidance learning was presented by Seligman and Johnson (1973). In this account, subjects learn

the outcome of making an avoidance response and not making an avoidance response, and then make a decision whether or not to avoid based on a comparison between the expected outcomes. Lovibond et al. (2008, 2013) followed this up with an expectancy based account of both instrumental, and Pavlovian conditioning. In this model, Pavlovian conditioning generates a state of expectancy or anticipation of shock, which triggers autonomic arousal. This in turn leads to performance of an instrumental response based on a comparison of the anticipated consequences (Lovibond et al., 2008). However, despite the importance given to cognitive decision making between anticipated consequences in their model, the only decision made by participants was to perform a response and avoid a US, or not perform the response, which may not require much cognitive processing.

There is evidence that there is a strong correlation between self-reported shock expectancy and skin conductance in the experiments presented by Lovibond et al. and they argue that expectancy of shock, or threat/safe appraisal, regulates anxiety. However, the expectancy theory does not account for the finding that across species, unpredictable stimuli elicit greater anxiety than predictable events (Grillon et al, 2004). This is a problem for the expectancy theory and may be why Seligman and Johnson (1973) avoided placing Pavlovian conditioning in an expectancy framework. The expectancy account also requires that participants have explicit knowledge of these contingencies and can clearly verbalize the relationship between stimuli (e.g., “blue predicts shock”) to learn the Pavlovian contingencies. However there is evidence that overt reasoning is preceded by nonconscious biasing processes (Bechara et. al, 1997). In fact there is much

evidence to suggest that contrary to cognition based on expectancy modulating anxiety, it is in fact anxiety that alters cognition and the decision making process, or some combination of both. This paradigm may offer a platform on which to address these theoretical issues, by allowing for concurrent study of cognitive, behavioral, and psychophysiological processes.

The current study represents the first effort to validate a psychophysiological (fear-potentiated startle [FPS]) 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; Lissek et al., 2010) in the context of a 'virtual farmer' computer game in which 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 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). 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. One central aim of the current study is to test the degree to which psychophysiological measures of Pavlovian generalization are associated with this type of maladaptive instrumental-avoidance response. A secondary aim is to identify the degree to which psychophysiological

measures of Pavlovian fear acquisition to a CS+ predict subsequent levels of behavioral avoidance during CS+ presentations. This latter aim is part of an effort to elucidate the antecedent mechanisms of behavioral avoidance—a fundamental yet understudied symptom of clinical anxiety. An additional aim of this study is to examine if expectancy theory accounts for the observed results.

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.

Methods

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).

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. 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. The left palmar skin conductance was recorded from the ring and middle finger of the left hand.

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 Figure 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 Figure 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 Figure 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 and colleagues (2008), responses to every two GS sizes are averaged yielding 3 classes of

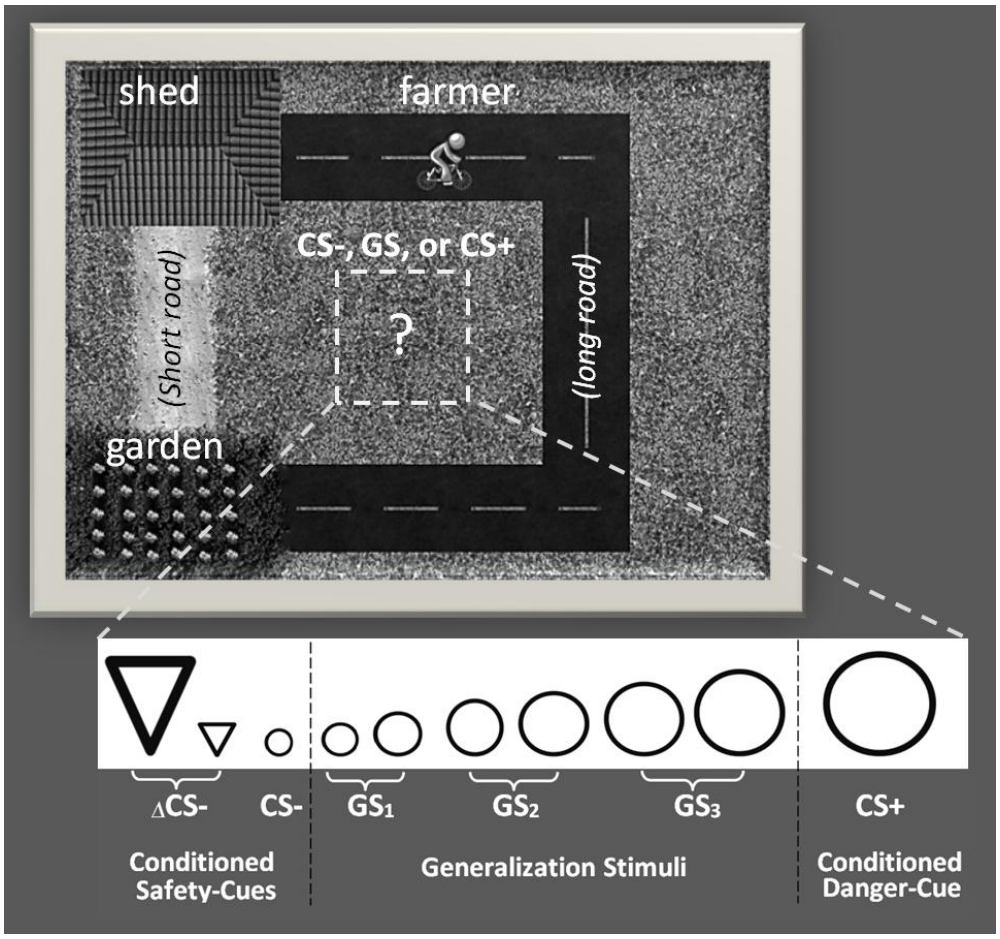


Figure 1. Virtual farmer paradigm and conditioning and generalization stimuli. Replication of image presented to subjects showing shed, garden, the short dangerous road, the long safe road, and a picture of the avatar travelling on the long safe road after a decision to avoid the short dangerous road has been made. Also showing where the stimuli were presented in relation to the other elements. The shape and size of the stimuli are pictured below. The diameter of the small ring is .8" and each ring is 20% larger than the smallest ring (i.e., .96", 1.12", 1.28", 1.44", 1.60", 1.76", 1.92"). Width and height are .8" for the small triangle and 1.92" for the large triangle. CS- = conditioned safety cue; etc.

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. Triangles serve as "non-circular" conditioned safety cues ($_{\Delta}$CS-) and are included to assess the degree to

which fear generalizes to all things circular (but not triangular). 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. 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

Pavlovian trials. The duration of Pavlovian trials was 10.4 s, and began 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 had no control over the virtual farmer and simply watched as the farmer traveled the short road. The farmer's trip, as well as CS and GS presentations, lasted the full duration of the trial. Startle probes were administered 2.5 or 3.5 s post-trial onset (18-22 s inter-probe interval [IPI]), and shock USs were 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 was graphically shown receiving a "virtual shock" (see Figure 2). Additionally, on the 50% of CS+ not paired with "actual shock", the farmer continued

to be graphically shown receiving 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.

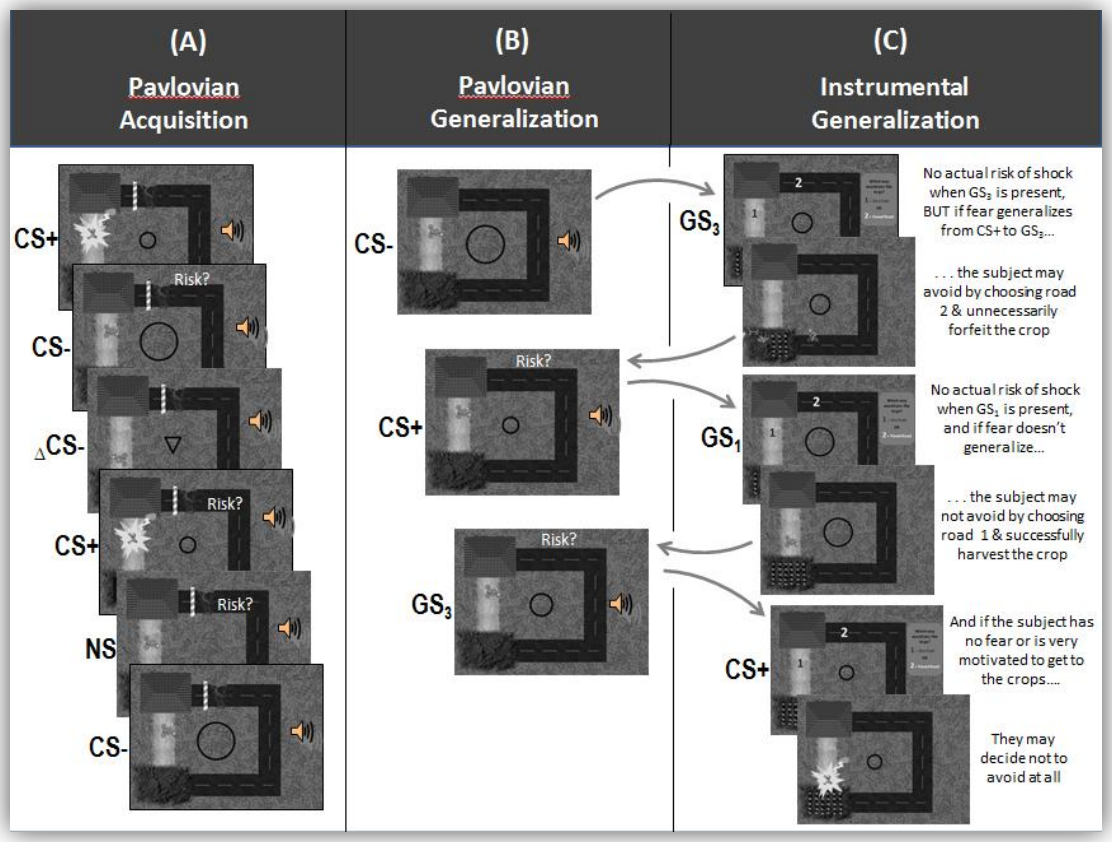


Figure *2*. Visual description of acquisition and generalization sequences. Startle probes (indicated by speaker) are administered on every Pavlovian trial with half of those trials also cuing for a risk rating (indicated by "Risk?" On top of screen). During generalization, trials switched back and forth from Pavlovian to Instrumental trials.

Instrumental-avoidance trials. Trials began with the presentation of a CS, GS, or NS, after which subjects were instructed to choose between sending the farmer down the short road (button 1) or the long road (button 2) using a hand held response box (see Figure 2c). The resulting trip down the short or long road was 8 s in duration during which no startle probes were presented. Decisions to travel the short path resulted 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, were not accompanied by shock (even on CS+ trials), but always resulted in a 75% likelihood of an unsuccessful harvest. If subjects failed to decide within the allotted 5 s, they were forced to take the short path and forfeit the crops. 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 consisted 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+ were paired with actual shocks, and 6 of 6 are paired with virtual shocks to prevent extinction of the conditioned response while limiting US habituation. The frequency of shock reinforcement during instrumental-avoidance trials varied depending on participants' decisions, with one additional shock for each short-road-choice on CS+ trials.

For all three study phases, trials were 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

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.

Behavioral 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 seconds post-trial-onset (3-4s 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 0= "no risk", 1= "moderate risk", and 2="high risk". 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.

Retrospective ratings. After acquisition and generalization phases, participants rated the level of anxiety they experienced during CS+, $_{\Delta}$CS-, CS-, and NS trials using an 11 point Likert scale (0=no anxiety, 10=extreme anxiety). Additionally, participants answered questions about their emotions and decision making during the task.

Standardized Questionnaires

Participants completed the Spielberger State and Trait Anxiety Inventory (STAI: Spielberger et al., 1983) and the Multidimensional Experiential Avoidance Questionnaire (MEAQ: Gámez et al., 2011). The MEAQ has 6 subscales; behavioral avoidance which measures active avoidance behaviors, distress aversion which measures how aversive

individuals find distressing states, procrastination which measures putting things off, distraction & suppression which measures doing something else to avoid negative feelings, repression & denial which measures "turning off" emotions or not realizing emotional responses cognitively, and distress endurance which is persevering in the face of adversity.

Procedure

Following informed consent, standardized questionnaires were filled out, EMG and shock electrodes were attached, and a shock workup procedure was completed. 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=18-25s) 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 minute 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 they would now be able to choose the road traveled by the farmer on some trials, and were reminded of the costs and benefits associated with each road. Additionally, subjects practiced using the button box to send the farmer down the long and short road. Next, five habituation startle probes were delivered (IPI=18-25s), 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 120ms. Additionally, the average baseline EMG level for the 50ms 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. SCRs were required to have an onset within a 1–5 s latency window of the start of the trial. SCRs were computed using the average of the square root for each trial. Startle and behavioral indices of acquisition were each analyzed with separate 3 level (Stimulus type: $_{\Delta}$CS-, CS-, CS+,) repeated measures analysis of variance (ANOVA). Startle and behavioral indices of generalization were each analyzed with separate 5 level (Trial type: CS-, GS_1, GS_2, GS_3 and CS+) repeated measures ANOVAs. When necessary, analyses were followed by paired samples t-tests. Alpha was set at .05 for all statistical tests. A regression analysis using avoidance behavior as the dependent variable was conducted at each stimulus level using forward selection of variables.

Results

Because no effects between the small and the large $_{\Delta}$CS- were found, regardless of the size of the CS+, data for the two $_{\Delta}$CS- sizes were collapsed into a single category for all analyses.

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

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, $F(2, 86)=38.477$, $p<.001$, and reflected startle potentiation to CS+ relative to both CS-, $t(43)=6.191$, $p<.001$, and $_{\Delta}$CS-, $t(43)=7.56$, $p<.001$. Additionally, a trend toward greater startle EMG to CS- compared to $_{\Delta}$CS-, $t(43)=1.847$, p=.072.

SCR. A main effect of trial-type was found, $F(2, 84)=12.767$, $p<.001$, and reflected skin conductance response potentiation to CS+ relative to both CS-, $t(43)=3.383$, p=.001, and $_{\Delta}$CS-, $t(43)=4.480$, p=.001.

Online risk ratings and reaction times. A main effect of trial-type was found for risk ratings, $F(2, 86)=224.931$, $p<.001$, with higher ratings to CS+ compared to CS- $t(43)=15.23$, $p<.001$, and $_{\Delta}$CS- $t(43)=17.40$, $p<.001$. There was no difference between ratings of risk for CS- compared to $_{\Delta}$CS-, $t(43)=.606$, p=.547. Additionally, a main effect

of response times was found across stimuli, $F(2,76)=3.758$, $p=.025$, with faster responses to CS+ versus CS- $t(39)=2.334$, $p=.025$ and $_{\Delta}$CS- $t(40)=2.472$, $p=.018$.

Retrospective anxiety ratings. A main effect of trial-type was found, $F(3,129)=117.00$, $p<.001$, with CS+ rated as more anxiety provoking than CS-, $t(43)=13.11$, $p<.001$, and $_{\Delta}$CS-, $t(43)=12.46$, $p<.001$). There was no difference between retrospective anxiety ratings for CS- compared to $_{\Delta}$CS-, $t(43)=.150$, $p=.882$.

Table 1

	Pre-Acquisition			Acquisition			
Stimulus	*Startle*	*Risk Rating*	*Reaction Time*	*Startle*	*Risk Rating*	*Reaction Time*	*Retrospective Anxiety Rating*[a]
NS	50.80(5.46)	1.17(.30)	1702(536)	50.40(3.03)	1.20(.30)	1441(326)	1.27(2.02)
$_{\Delta}$CS-	53.45(5.44)	1.14(.29)	1372(645)	50.13(3.44)	1.18(.30)	1229(409)	1.55(2.11)
CS-	53.01(5.21)	1.11(.30)	1382(474)	51.17(3.02)	1.21(.29)	1241(247)	1.59(1.93)
CS+	53.21(6.13)	1.17(.32)	1497(578)	56.01(4.43)*	2.49(.44)*	1124(284)	7.09(2.95)*

[a] Subjective ratings reported on a 10-point scale where 1 = not at all and 10 = extremely.
*Significantly different from all other stimuli at p<.001

Pavlovian Generalization

Startle EMG. Robust enhancement of startle during CS+ relative to CS- persisted during generalization, $t(43)=9.44$, $p<.001$. Importantly, a main effect of trial-type was found, $F(4,172)=42.568$, $p<.001$, and, as can be seen in Figure 3, 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: $F(1,43)=89.54$, $p<.001$;

quadratic decrease: $F(1,43)=10.889$, $p=.002$). Follow up analyses comparing each GS-type to CS- revealed significant startle potentiation to GS_3, $t(43)=7.31$, $p<.001$, and GS_2, $t(43)=3.60$, $p=.001$, but not GS_1 $t(43)=.96$, $p=.34$. Thus, subjects in the current study generalized startle potentiation from CS+ to two degrees of CS+ differentiation (GS_3, GS_2).

SCR. Increases in skin conductance response during CS+ relative to CS- persisted during generalization, $t(40)=3.544$, $p=.001$. A main effect of trial-type was found, $F(4,152)=6.580$, $p<.001$, and, as can be seen in Figure 3, was also 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: $F(1,38)=11.385$, $p=.002$; quadratic decrease: $F(1,38)=4.152$, $p<.05$). Follow up analyses comparing each GS-type to CS- revealed significant skin conductance potentiation to GS_3, $t(40)=2.957$, $p<.01$, but not to GS_2, $t(40)=1.86$, $p=.07$ or GS_1 $t(38)=.296$, $p=.769$. Thus, subjects in the current study generalized skin conductance potentiation from CS+ to one degree of CS+ differentiation (GS_3).

Risk ratings and reaction times. Risk rating differences between CS+ and CS- also persisted throughout generalization $t(43)=16.560$, $p<.001$. A main effect of trial-type, $F(4,172)=147.80$, $p<.001$, was found for levels of perceived risk. Similar to startle results, risk ratings evidenced gradients of generalization consisting of both linear, $F(1,43)=276.45$, $p<.001$, and quadratic, $F(1,43)=112.00$, $p<.001$, decreases in perceived risk from CS+ down the continuum-of-size to CS- (see Figure 4). As with startle data, risk ratings were enhanced to CS+, $t(43)=16.56$,$p<.001$, GS_3, $t(43)=10.52$, $p<.001$, and

GS_2, $t(43)=3.02$, $p=.004$, but not GS_1, $t(43)=1.86$, $p=.07$, when compared with CS-. Generalization of risk perception for controls in the current paradigm can thus be said to extend to GS_3 and GS_2, but not GS_1. There was no main effect of trial-type on reaction times during generalization, $F(4,148)=1.791$, $p=.143$.

Instrumental Generalization

Behavioral Avoidance. Generalization gradients were also present in instrumental avoidance decisions. The main effect of trial-type, $F(4,172)=65.64$, $p<.001$, consisted of linear, $F(1,43)=89.58$, $p<.001$, and quadratic, $F(1,43)=32.09$, $p<.001$, 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+, $t(43)=9.69$, $p<.001$, and GS_3, $t(43)=7.86$, $p<.001$, but not GS_2 **(**$p=.16$**)**, or GS_1, **(**$p=.23$**)**. 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, $F(4,164)=451.579$, $p<.001$. Follow up paired sample *t*-tests revealed longer decision times for CS+, $t(43)=3.409$, $p=.001$, GS_3, $t(42)=4.871$, $p<.001$, and GS_2, $t(42)=3.161$, $p=.003$, but not to GS_1, $t(43)=1.348$, $p=.185$, when compared with CS-. An additional follow up comparing CS+ and GS_3 revealed that reaction times to GS_3 were significantly longer than to CS+ $t(43)=2.395$, $p=.021$.

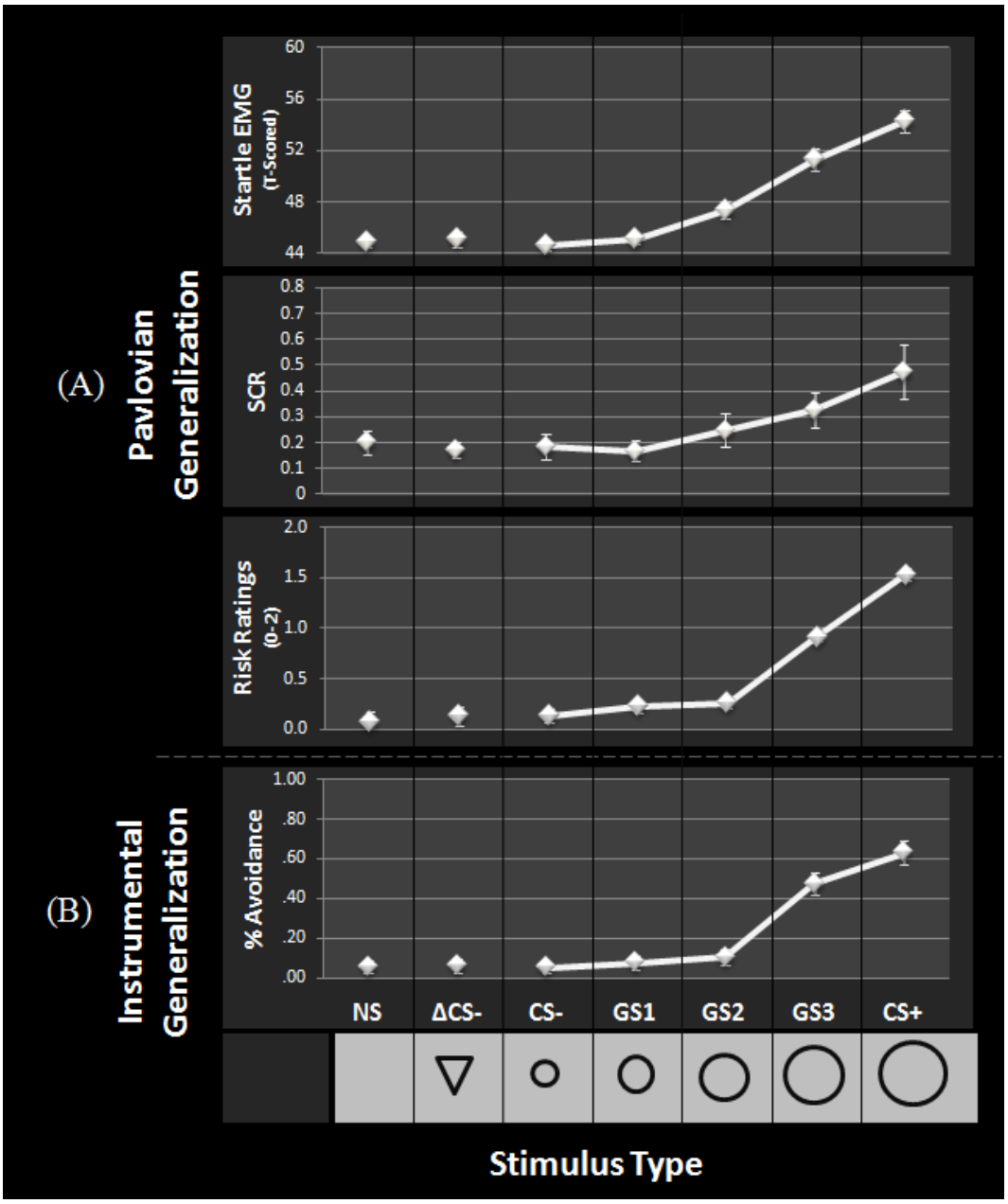
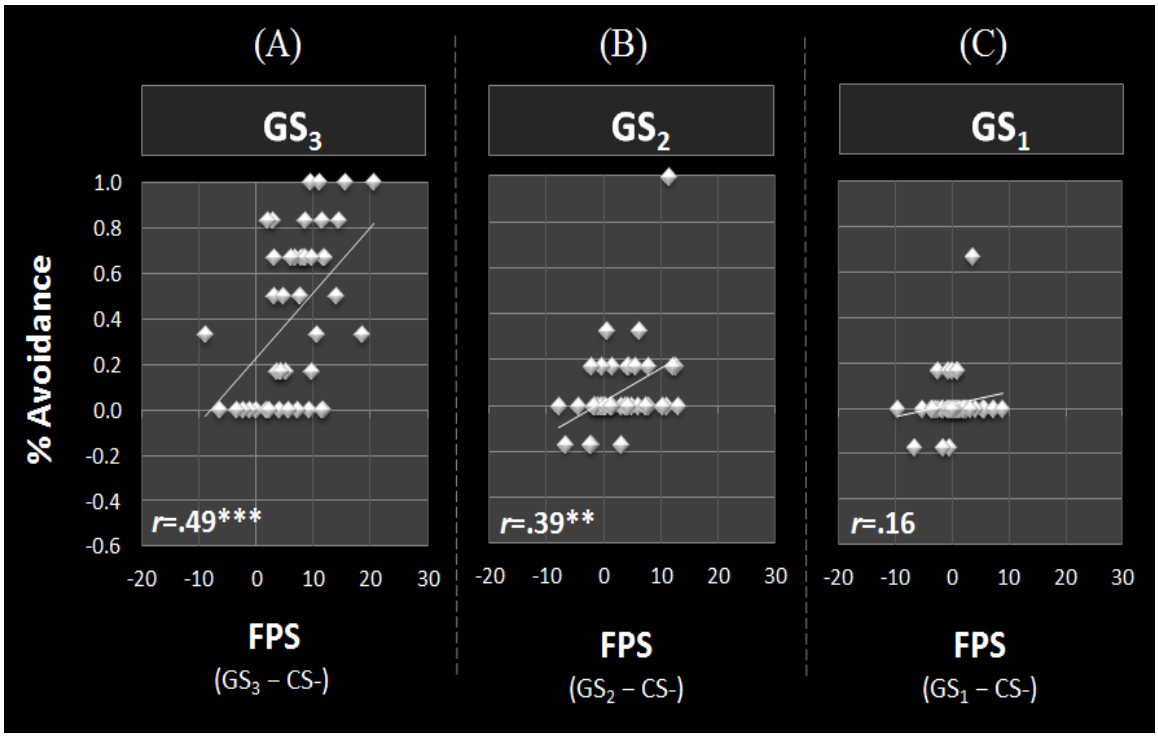


Figure 3. (A). Top row: Startle EMG generalization gradient. Results for standardized (*T*-scored) startle EMG across conditioned and generalization stimuli. Bottom row: Risk rating generalization gradient. Risk ratings (0=no risk, 1=some risk, 2=high risk) across conditioned and generalization stimuli. (B). Avoidance generalization gradient. Rates of avoidance, as proportion of trials where the long road was taken to overall decisions made, across conditioned and generalization stimuli. NS = no stimuli; CS- = conditioned safety cue; $_{\Delta}$CS- = triangular shaped conditioned safety cue; GS_1=generalization stimuli class 1; GS_2 = generalization stimuli class 2; GS_3 = generalization stimuli class 3; CS+=conditioned danger cue.

Testing the Relation Between Pavlovian and Instrumental Generalization

For such tests, Pavlovian generalization was operationalized as the degree to which startle was potentiated to each GS (GS_3, GS_2, GS_1) above and beyond the CS-. Additionally, instrumental generalization was indexed as the degree to which participants avoided each GS relative to CS-. Next, these indices of Pavlovian and instrumental generalization were correlated for each of three GSs separately. As shown in Figure 4A and 4B, 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 Figure 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 in avoidance with which to account for variance in startle potentiation to GS_1 (vs. CS-).



*p≤.05, **p≤.01, ***p≤.001

Figure 4. Pavlovian to instrumental transfer. (A) Correlation between classically conditioned fear-potentiated startle, as indexed by difference score between standardized startle magnitude for GS_3 and CS-, and later behavioral avoidance proportion difference score for $GS_3$and CS-. (B) (A) Correlation between classically conditioned fear-potentiated startle, as indexed by difference score between standardized startle magnitude for GS_2 and CS-, and later behavioral avoidance proportion difference score for $GS_2$and CS-. (C) (A) Correlation between classically conditioned fear-potentiated startle, as indexed by difference score between standardized startle magnitude for GS_1 and CS-, and later behavioral avoidance proportion difference score for GS_1 and CS-. NS = no stimuli; CS- = conditioned safety cue; $_{\Delta}$CS- = triangular shaped conditioned safety cue; GS_1=generalization stimuli class 1; GS_2 = generalization stimuli class 2; GS_3 = generalization stimuli class 3; CS+=conditioned danger cue.

Whereas startle potentiation was significantly correlated with avoidance responses, there was no significant relationship between SCR and avoidance: GS_3 (r=.133, p=.407), GS_2 (r=-.284, p=.072), GS_1 (r=.028, p=.867). Risk ratings however were very strongly correlated with avoidance responses: GS_3 (r=.467, p=.001), GS_2 (r=.563, p<.001), GS_1 (r=.533, p<.001).

One other variable that may have been influencing decision making was intrinsic motivation to complete the farming task the most efficiently. Therefore the question "in general how important was winning" which was assessed on an 11-point scale during the retrospective questionnaire at the end of the study was included with the FPS, SCR and risk rating data in a regression analysis with avoidance behavior as the dependent variable.

For GS_3 the significant variables in the model using forward selection were the importance of winning question (β=-.401, t=-3.001,p=.005) and FPS (β=.345, t=2.589,p=.013). This model accounted for 34.5% of the variance in avoidance at GS_3 and indicates that avoidance behavior did decrease as winning was more important, but also that fear potentiated startle is accounting for variance not accounted for by the desire to win. For GS_2 the significant variables in the model using forward selection were risk ratings (β=.527, t=4.272, p<.001) and FPS (β=.296, t=2.403, p=.021). This model accounted for 44.1% of the variance in avoidance at GS_2 and indicates that avoidance behavior increased as cognitive expectancy of shock increased, and again fear potentiated startle is accounting for additional variance not accounted for by this expectancy. Only the risk rating variable was significant for the GS_1 regression model and is therefore best summarized by the simple correlational statistics above.

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 = ([CS+, CS-]/2) – ([GS_1, GS_2, GS_3]/3).* Here *[CS+, CS-]/2* reflects the theoretical, linear

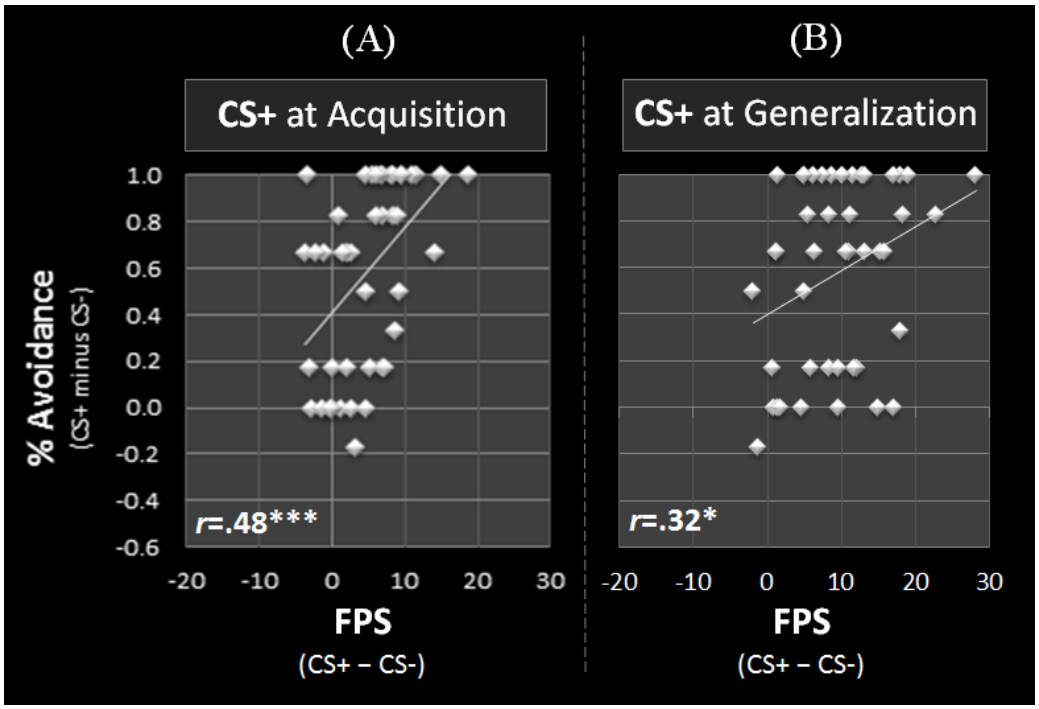
midpoint of the gradient, and $[GS_1, GS_2, GS_3] /3$ reflects the average response to GSs which could fall above the linear midpoint (positive departure), on the linear midpoint (zero departure), or below the linear midpoint (negative departure). This equation thus provides a single number reflecting 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 a significant positive correlation, r=.330, p=.033, indicating that stronger, less steep gradients of Pavlovian generalization were accompanied by stronger, less steep gradients of instrumental generalization. Again, whereas this was true for assessments of Pavlovian generalization with FPS, when using SCR there was no relationship (r=-.027, p=.876), and the relationship was even stronger between risk ratings and avoidance (r=.522, p<.001).

Pavlovian and Instrumental Conditioning to the CS+

Pavlovian antecedents of instrumental avoidance. The predictive power of Pavlovian conditioning on instrumental avoidance was assessed by associating levels of conditioned fear-potentiated startle during the acquisition phase of the experiment with levels of avoidance displayed during the subsequent generalization phase. Conditioned fear-potentiated startle to the CS+ versus CS- at acquisition strongly predicted later instrumental avoidance to the CS+ versus CS-, r=.476, p=.001 (see Figure 5A). Such

findings implicate Pavlovian conditioned fear as an important precursor of behavioral avoidance.

The positive relation between Pavlovian and instrumental conditioning persisted during the generalization phase, with conditioned fear-potentiated startle to the CS+ (vs. CS-) significantly correlated with levels of instrumental avoidance to the CS+ (vs. CS-), r=.32, p=.03 (see Figure 5B).



*p≤.05, **p≤.01, ***p≤.001

Figure 5. (A) Pavlovian to instrumental transfer. Correlation between classically conditioned fear-potentiated startle at acquisition, as indexed by difference score between standardized startle magnitude for CS+ and CS-, and later behavioral avoidance proportion difference score for CS+ and CS-. (B) Correlation between classically conditioned fear-potentiated startle at generalization, as indexed by difference score between standardized startle magnitude for CS+ and CS-, and behavioral avoidance proportion difference score for CS+ and CS-. CS- = conditioned safety cue; CS+=conditioned danger cue.

Again, there was no relationship between SCR at acquisition and later avoidance (r=.105, p=.503). Interestingly, while the relationship between risk ratings and avoidance during the generalization phase of the study was generally stronger than the relationship between avoidance and startle, there was not a significant relationship between acquisition risk rating and subsequent avoidance (r=.256, p=.094) suggesting that physiological responses may have more predictive power than cognitive expectancies in this task. A regression similar to the ones computed for each GS was computed for avoidance behavior to the CS+. When using FPS during generalization, SCR and risk ratings as well as the importance of winning question, only the importance of winning question was significant and the simple correlation was r=-.440, p=.003. However, when acquisition FPS was included in the model, both the winning question (β=-.455, t=-3.678, p=.001) and acquisition FPS (β=.413, t=3.337, p=.002) were significant and accounted for 42.8% of the variance in avoidance to CS+. This highlights the importance of physiological measures in predicting future behavior as well as the influence of both positive and negative motivational systems on behavioral decisions.

Questionnaires. Two subscales of the MEAQ were found to be correlated with overall avoidance proportion. More specifically, overall avoidance was negatively correlated with both the Distraction and Suppression subscale (r=-.469, p=.001) and the Distress Endurance subscale (r=-.378, p=.01). No associations were found between these subscales and avoidance of the CS+ or GSs either raw or indexed as difference scores from CS-. No significant associations were found between startle EMG for CS+ or any of the GSs indexed as difference scores from CS- and avoidance. No associations were

found between state or trait scores on the STAI and avoidance or startle EMG for the CS+ or any of the GSs indexed as difference scores from CS-. This was likely due to a restriction of range in our sample of healthy controls.

Table 2

Regression Analysis

Overall Model Fit	GS3			GS2			GS1			CS+		
	R^2	F (2,39)	p	R^2	F (2,39)	p	R^2	F(1,40)	p	R^2	F(2,38)	p
	0.345	10.264	<0.001	0.441	15.391	<0.001	0.335	20.173	<0.001	0.428	14.199	<0.001
Variable	β	t	p	β	t	p	β	t	p	β	t	p
How important was winning	-0.401	-3.007	<0.001	Not Significant			Not Significant			-0.455	-3.678	0.001
FPS during Generalization	0.345	2.589	0.013	0.296	2.403	0.021	Not Significant			Not Significant		
Risk Rating	Not Significant			0.527	4.272	<.001	0.579	4.491	<0.001	Not Significant		
SCR	Not Significant			Not Significant			Not Significant			Not Significant		
FPS at Acquisition	Not included in model			Not included in model			Not included in model			0.413	3.337	0.002

Discussion

Behavioral avoidance responses form generalization gradients where the responses are made most to the CS+ and decrease as the presented stimulus gradually becomes less perceptually similar to the CS. Pavlovian generalization gradients were also demonstrated with startle magnitudes to CS+ potentiated relative to CS- with gradually decreasing responses across the continuum-of-similarity. Similarly, skin conductance and online ratings of risk fell along a downward gradient with highest ratings to the CS+ and gradually decreasing responses across the continuum-of-similarity. These generalization gradients are consistent with the generalization gradients previously reported by this line of research, but importantly, there were some differences in the shape of the instrumental generalization gradient and the Pavlovian gradient.

The instrumental generalization gradient had a significant cubic trend which was absent in the startle and risk rating gradients. The cubic trend indicates two changes in direction of the slope of responding, which is seen in the instrumental gradient by downward curve starting after the GS_3 and then bottoming out after GS_2. This is evidence of both increased avoidance to GS_3 and decreased avoidance to GS_2 compared to a gradient that only has a linear and quadratic component. This may reflect a tendency for healthy subjects to err on the side of caution for ambiguous stimuli with a lot of threat information (GS_3) when there is a high cost (i.e. shock) associated with a miss and not avoiding a true CS+ while the cost of a false alarm(i.e. not harvesting the crops) is relatively low. This stands in contrast to the behavioral risk rating which has no response cost associated with the decision and only follows the expected curvilinear decrease.

Additionally, the dichotomous nature of avoidance decision could capture a threshold where the reward associated with success overcomes the risk, leading to a pronounced split between stimuli such as is observed between GS_2 and GS_3.

One of the most significant findings from this study was the degree to which instrumental avoidance responses were correlated the Pavlovian index of FPS. Importantly, this relationship was not found when assessed using SCR. Skin conductance which measures arousal more broadly, and may also be capturing reward based arousal, or even orienting responses which would explain why there was a trend towards a negative association between SCR and avoidance at GS_2. Perhaps the stimuli at GS_2 by virtue of being the most ambiguous, require additional attentional resource which elevates SCR, while avoidance does not also increase. This underscores the importance of using valence specific fear-potentiated startle when assessing the fear related behavior of avoidance. When assessed using the CS- as a baseline, there was a strong relationship between individuals' potentiation of startle during generalization and an increase in their avoidant responses. Moreover, the degree of potentiation to the CS+ compared to the CS- during acquisition, which preceded any avoidance responses as well as any instructions informing participants they would even be able to make avoidance responses, was predictive of the degree to which they avoided the CS+ more than the CS-. These findings highlight the relationship between the more passive Pavlovian processes and the more active instrumental responses and studying them concurrently can broaden our understanding of anxiety processes. It also brings fear potentiated startle "out-of-the-box"

of just measuring passive emotional responses, and into the realm of predicting how people will make decisions and behave.

In a recent review of decision making and anxiety, Hartley and Phelps (2012) propose that processes involved in fear learning and regulation are recruited in decision making contexts. Their review draws on a large body of evidence from neuroeconomics to support their claims. However, clearly lacking from the available literature is a direct manipulation of rewards and consequences across a range of threatening situations. Most of the "risk" in these neuroeconomic studies is risk of losing money, which is not a biologically relevant event that should induce anxiety in a manner that is comparable to anxiety manifest in PTSD or panic disorder. This paradigm enters the inclusion of real physical risk into the equation which may be more appropriate for studying clinical anxiety. Results from the regression analysis support the idea that both positive reward motivation to complete the task well and fear towards the stimulus indexed by FPS are important in the decision making process. By studying both the positive reward and negative fear motiviation systems, one can build a more complete model of decision making and examine the effects of individual differences in both systems.

Predictions for Anxiety Patients

The tendency for anxiety patients to generalize Pavlovian conditioned fear as evidenced by less steep Pavlovian generalization gradient across the continuum of similarity from CS+ to CS- (Lissek et al., 2010, Lissek et al., 2012), supports the prediction of less steep instrumental generalization gradient slopes in those with clinical anxiety. Anxiety patients versus healthy controls display fear potentiated startle to

generalization stimuli with more degrees of perceptual differentiation from CS+ . The strong relationship between startle and instrumental responses in the current study supports the prediction of more avoidance responses in a clinically anxious population. As the instrumental generalization gradient seems to capture a threshold of the cost-benefit analysis for healthy individuals between GS_2 and GS_3 we predict that anxiety patients may show this threshold between GS_1 and GS_2. We would also expect that if the threshold shifts, response times would also shift accordingly such that the longest response times for an anxious group would be at GS_2 reflecting a greater threat uncertainty. Whereas healthy individuals took longest to respond for the CS+ and stimuli with more threat information than for those with safety information, we might also predict a total reversal in the shape of the response times with the quickest response time to the more threatening stimuli and longer latencies for those with safety information in anxiety patients. Healthy individuals may have a tendency towards approaching, and not avoiding and therefore long response times to the CS+ and GSs with high threat information may reflect overcoming this bias or at least debating the possibility of avoiding. Anxiety patients may have a strong tendency towards avoidance that would need to be overcome and therefore have the longest response times to the CS- and safer GSs because they need to overcome the bias to avoid. On the other hand they may be very to avoid the CS+ and high threat GSs as there is no conflict and they simply avoid those stimuli. Lastly, we would predict that the regression weights for decision making in anxious individuals will reflect a greater importance of fear related motivation than

reward motivation than in a healthy population, with increased strength in the β-weight for FPS in a clinically anxious population.

Emotional Theory

Many emotional theories include behavior or behavior tendencies as a distinct response system from the subjective and physiological response systems (Frijda, 1986; Lang et al., 1998). One of the biggest critiques for Pavlovian fear conditioning is that it ignores this aspect of anxiety. Assessing both instrumental and Pavlovian conditioning as well as online risk ratings in anxiety patients will help to elucidate the interaction of the subjective, physiological and behavior response systems. Additionally, it could lead to dissociation of sub-types of anxiety patients that display exaggerated responses in one or two systems, but not the other(s). These classifications will lead to more targeted treatments for distinct anxiety process.

While there have been some attempts recently to address behavior and behavior tendencies in anxiety mainly through avoidance studies, research in this field is sparse. One study assessed avoidance to three stimuli: a CS+ learned with Pavlovian conditioning, a stimulus that was associatively paired with the CS+ stimulus prior to fear acquisition (derived CS+), and a CS+ that wasn't learned, but instructed (Dymond et al., 2012). Participants made similar avoidance responses to the three different types of conditioned danger stimuli, the learned CS+, the instructed CS+ and the derived CS+ despite different mechanisms for learning. Another study on avoidance included a gradient of ambiguous stimuli and showed an increase in avoidance to stimuli resembling the CS+ in individuals high in neuroticism when given 5s to make a decision, but no

difference with the low neuroticism group when only given 1s (Lommen et al., 2010). Although these studies incorporate avoidance they lack physiological measures of fear and arousal that bring to bear the wealth of information from neurocircuitry in animals studies in both Pavlovian and instrumental fear conditioning and previous research on the physiological indices such as skin conductance and fear-potentiated startle in humans.

Lovibond's expectancy theory is based on a single cognitive learning system and does not account for our findings that FPS provides incremental information about instrumental responses above cognitive expectancy of shock and desire to win. Results from the regression analysis at GS_2 suggest that both cognitive expectancy and psychophysiology are contributing to avoidance decision making. Additionally, results from the regression analysis for CS+ demonstrate that psychophysiology from the acquisition is a better predictor of future behavior than cognitive expectancy assessed at the same time the avoidance responses are being made, after taking positive reward motivation into account. Expectancy theory would predict otherwise. This paradigm may not be directly comparable to the studies conducted by Lovibond, as the instructed response in this study is instructed (see limitations for additional information) and there are rewards for not completing the instrumental response. However, our results still suggest that we need to examine behavior more holistically than solely as a result of cognitive expectancy. It also highlights the power of this paradigm to study behavior in this way, by placing it in a more complex and closer to real life environment, while still maintaining direct control and manipulation of variables of interest.

Limitations

One of the main limitations of this study was the lack of reward for harvesting crops besides a simple congratulatory graphic. Therefore, the cost associated with avoidance, even to generalization stimuli which is maladaptive, is low as little reward is being forfeited with an avoidance decision. Given this, it is interesting that avoidance levels were as low as they were and that healthy participants were willing to take a shock on over 35% of CS+ trials. Two potential concerns that arise from this are that clinically anxious subjects may disregard information they learned from the acquisition and choose to avoid all stimuli since there is little reward for not-avoiding, or that if the reward is increased, there may not be any avoidance behavior.

One additional limitation of the study is that subjects were instructed how to respond to make an avoidance response or a non-avoidance response and did not have to learn this. It raises the question if it is appropriate to label the decisions they are making as instrumental responses as in the animal literature instrumental responses must of course be learned as animals cannot be instructed. However, we feel that this is the most appropriate designation even if they are instructed instrumental responses.

Future Directions

This study was designed as a proof-of-concept with the intention of validating an experimental paradigm for use with clinically anxious individuals which is the main future direction in this line of work. Additionally, it can be used as a tool to assess the pharmacology, genetics, and brain basis of what allows the transfer of fear from a

passive motivational value acquired during Pavlovian conditioning to an instrumental response. In one fMRI study in healthy participants, amygdala-striatal interactions were found to underlie the acquisition of avoidance responses after classical fear conditioning (Delgado et al. 2009) however this has not been expanded to assess differences in healthy individuals and those with clinical anxiety. Lastly, as previously mentioned, this line of work could help establish subtypes of anxious individuals who have different patterns of exaggerated responses across the subjective, physiological, and behavioral domains and differences in pathology or brain mechanisms associated with these subtypes.

Conclusion

Current findings validate a novel paradigm for assessing Pavlovian generalization and its relation to instrumental generalization. The paradigm is capable of eliciting instrumental avoidance responses which form a generalization gradient and are strongly associated with Pavlovian indices of generalization. Additionally, FPS at acquisition was a significant predictor of subsequent avoidance behavior. This tool will be useful in describing and testing individual differences associated with clinical anxiety.

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