

Shorter communication

Generalization of conditioned fear-potentiated startle in humans: Experimental validation and clinical relevance

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Abstract

Though generalization of conditioned fear has been implicated as a central feature of pathological anxiety, surprisingly little is known about the psychobiology of this learning phenomenon in humans. Whereas animal work has frequently applied methods to examine generalization gradients to study the gradual weakening of the conditioned-fear response as the test stimulus increasingly differs from the conditioned stimulus (CS), to our knowledge no psychobiological studies of such gradients have been conducted in humans over the last 40 years. The current effort validates an updated generalization paradigm incorporating more recent methods for the objective measurement of anxiety (fear-potentiated startle). The paradigm employs 10, quasi-randomly presented, rings of gradually increasing size with extremes serving as CS+ and CS-. The eight rings of intermediary size serve as generalization stimuli (GSs) and create a continuum-of-similarity from CS+ to CS-. Both startle data and online self-report ratings demonstrate continuous decreases in generalization as the presented stimulus becomes less similar to the CS+. The current paradigm represents an updated and efficacious tool with which to study fear generalization—a central, yet understudied conditioning-correlate of pathologic anxiety.

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Introduction

Classical fear-conditioning, the cross-species learning process by which a neutral conditioned stimulus (CS) comes to evoke fear following its repeated pairing with an aversive unconditioned stimulus (US), has long been implicated in the development of pathologic anxiety (for a review, see Mineka & Zinbarg, 2006). A recent meta-analysis of lab-based, fear-conditioning studies in the anxiety disorders implicates heightened anxious reactivity to conditioned stimuli (CSs) signaling safety as an important conditioning correlate of clinical anxiety (Lissek et al., 2005). A closer look at this literature reveals that studies of posttraumatic stress disorder

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(PTSD) contribute prominently to this pattern. Whereas healthy individuals display anxious reactivity to CSs paired (CS+: danger cue) but not unpaired (CS–: safety cue) with the aversive US, PTSD patients tend to display fear responses to both CS+ and CS–. Given that CS+ and CS– employed by this literature share many stimulus properties (e.g., size, shape, duration), such findings implicate an enhanced tendency among PTSD patients to generalize conditioned fear from danger cues to safety cues with overlapping features. In the context of PTSD, such generalization of fear represents an experimental analog of the pathologic generalization process by which fear during a traumatic event transfers to safe conditions that ‘resemble’ the distressing event (American Psychiatric Association, 2000).

Though such generalization of conditioned fear is a promising marker of pathological anxiety responses, very little is known about the psychophysiology, pharmacology, neurobiology, and genetics of this learning phenomenon in humans. Indeed, systematic tests of generalization of conditioned responses developed and tested in animals (for reviews, see Honig & Urciuoli, 1981; Kalish, 1969; Mackintosh, 1974) have sparsely been applied to study generalization of conditioned fear in humans over the years (Bass & Hull, 1934; Grant & Schiller, 1953; Hovland, 1937; Kopp, Schlimm, & Hermann, 2005; Mednick, M.T., 1957; Mednick, S.A., 1957; Mednick & Wild, 1962; Vervliet, Vansteenwegen, Baeyens, Hermans, & Eelen, 2005; Vervliet, Vansteenwegen, & Eelen, 2004).¹ These systematic tests of generalization in animals assess conditioned fear responses to both CS+ and generalization stimuli (GS) parametrically varying in similarity to the CS+, and document generalization gradients, or slopes, with the highest level of fear responding to the CS+ and gradually decreasing levels of fear generalization to GSs of decreasing similarity to the CS+ (e.g., Armony, Servan-Schreiber, Romanski, Cohen, & LeDoux, 1997). The steepness of this gradient indexes generalization, with steeper downward gradients indicating less generalization.

Unfortunately, the few human studies applying this method are not adequate for present purposes. Specifically, the early work from Bass and Hull (1934) and Hovland (1937) employs methods that diverge considerably from current experimental practice. Additionally, studies by Martha and Sarnoff Mednick (Mednick, M.T., 1957; Mednick & Wild, 1962) employ words associatively linked to the CS+ as GSs and thus do not form an interval scale of generalization. Furthermore, the paradigm by Kopp et al. (2005) has not been psychophysiologicaly validated and used animal-fear relevant stimuli that are largely unrelated to anxiety disorders other than specific phobia. Finally, whereas conditioned fear-generalization studies by Vervliet et al. (2004, 2005) elegantly demonstrate the persistence of conditioned responding following extinction to GSs, such studies do not take as their focus the generalization of fear-acquisition to stimuli approximating the CS+. The difference between studies by the Vervliet group and the current effort can be viewed in terms of a fear *inhibition* versus *excitation* focus, with the former studying inhibition of fear to a CS+ following extinction to a CS+ approximate, and the current effort assessing the transfer of fear excitation to CS+ approximates.

In addition to the above, existing human paradigms applying psychophysiological techniques measure generalization with skin conductance responses (SCR), and it is yet to be demonstrated whether such generalization can be captured by fear-potentiated startle (FPS: the reliable enhancement of the startle reflex when an organism is in a state of fear (Davis & Astrachan, 1978)). Measuring conditioned fear and its generalization with FPS may be advantageous over SCR for a few important reasons. Whereas SCR is highly sensitive to attentional processes (e.g., Filion, Dawson, Schell, & Hazlett, 1991) and reflects increases in general sympathetic arousal, attentional effects on FPS—though present—may well be smaller than emotional effects (e.g., Bocker, Baas, Kenemans, & Verbaten, 2004) and FPS is more valence specific (for a review, see Lang, Bradley, & Cuthbert, 1998). Additionally, the construct validity of FPS as a measure of fear is supported by the central role played by amygdala-based “fear circuits” in the potentiation of startle in both rodents (e.g., Hitchcock & Davis, 1986) and humans (e.g., Pissioti et al., 2003). Because of these advantages, FPS is increasingly used to measure psychophysiological correlates of pathologic anxiety and to test the anxiolytic properties of pharmaceutical compounds (for a review, see Grillon, *in press*). Given the strong

¹There is small literature from the 1950s and 1960s testing the influence of anxiety states and traits on fear-irrelevant generalization tasks such as reaction times to target stimuli and stimuli parametrically varying in similarity to the target stimulus (e.g., Mednick, M.T., 1957; Mednick, S.A., 1957; Rosenbaum, 1953). Because such generalization tasks do not assess the degree to which conditioned fear is transferred from the CS+ to approximations of the CS+, this literature is not considered relevant to the current paper.

relevance of conditioned fear generalization to anxiety disorders (e.g., Foa, Steketee, & Rothbaum, 1989; Grillon & Morgan, 1999; Keane, Zimmering, & Caddell, 1985; Lissek et al., 2005; Mineka, 1992), conditioned startle-potentiated paradigms capable of eliciting continuous gradients of fear generalization may be a particularly powerful translational tool. The current study tests a novel conditioned startle-potentiation paradigm designed for this purpose in 20 healthy participants.

Methods

Participants

Twenty healthy participants (50% female) with a mean age of 26.10 (SD = 8.16), and average State and Trait Anxiety Inventory scores (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) of 26.30 (SD = 7.02) and 29.41 (SD = 6.38), were recruited from the community and reimbursed for their time. Prior to testing, participants gave written informed consent that had been approved by the NIMH-IRB. Inclusion criteria included: (1) no past or current Axis-I psychiatric disorder as per Structured Clinical Interview for DSM-IV, (SCID-I/NP: First, Gibbon, Spitzer, & Williams, 2001), (2) no major medical condition that interfered with the objectives of the study, (3) no current use of medications altering central nervous system function, and (4) no current use of illicit drugs as per urine test.

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, bio-medical.com[CG04]) placed under the left eye. The EMG signal was sampled at 1000 Hz and amplifier band width was set to 30–500 Hz. Startle was elicited by a 40-ms duration, 102 dB(A) burst of white-noise with a near instantaneous rise-time presented binaurally through headphones.

Conditioned, unconditioned, and GSs

Ten rings of continuously increasing size (see Fig. 1) served as conditioned stimuli (CS+, CS–) and generalization stimuli (GSs). The dimensions and size increments for employed rings are described in Fig. 1. For half of participants the smallest ring was the CS+ and the largest was the CS–; for the other half this was reversed. The eight intermediately sized rings served as GSs and formed a continuum-of-size between the CS+ and CS–. All CSs and GSs were presented for 8 s on a computer monitor at a viewing distance of approximately 46 cm. The US was a 100-ms electric shock delivered to the left wrist (3–5 mA) that was rated by participants as being ‘highly uncomfortable but not painful’.

Behavioral ratings

During half of the of CS+ and CS– trials at pre-acquisition and acquisition, as well as during half of CS+, CS–, and GS trials during generalization, the question “Level of risk?” appeared on the computer monitor above the presented stimulus at 1- or 2-s post trial-onset and cued participants to rate their perceived level of risk for shock. Similar to other studies assessing subjective risk (e.g., Foster et al., 2002; Jackson, Hobfoll, Jackson, & Lavin, 2001), participants completed risk ratings using a three-point Likert scale, where 1 = “no risk”, 2 = “moderate risk”, and 3 = “high risk”. Participants were instructed to answer based on their ‘gut feeling’ of risk and to respond as quickly as possible using their index finger to depress buttons 1, 2, or 3 on a computer keyboard. 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). These behavioral ratings and response times were elicited on odd trials and startle responses were probed on even trials. This separation of behavioral and startle responses was applied due to concerns that behavioral ratings would alter startle magnitudes via attentional

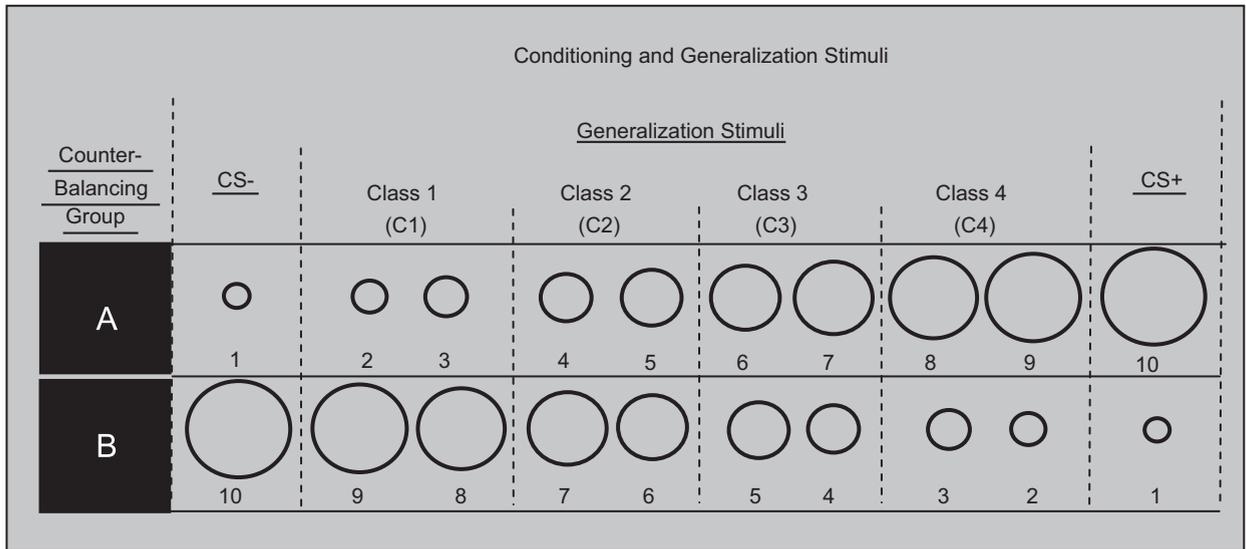


Fig. 1. Conditioning and generalization stimuli for counterbalancing groups A and B. Half of participants were assigned to counterbalancing group A and half to B. The numbers 1–10 at the bottom of the rings label the stimuli from smallest (1) to largest (10) but did not appear when the rings were presented to participants. For both counterbalancing groups A and B, Class 4 consisted of the two rings closest in size to the CS+ and Classes 3–1 gradually decreased in similarity to the CS+. Prior to data analysis, startle and behavioral responses to every two neighboring intermediaries were averaged to form the mean level of responding for that class of ring (e.g., [Ring 2 + Ring 3]/2 = Class 1). This allowed for the capture of a more gradual slope of generalization—produced by eight rather than four gradations—while requiring half the number of trials per intermediary. This methodological decision was made to avoid an unrealistically long experiment (leading to undue habituation of the startle reflex and subject fatigue) while achieving a gradual continuum of similarity. The diameter for the smallest ring (Ring #1) was 2.00 in and subsequent rings increased by 15% with Ring #2 increasing 15% from Ring #1 (2.30 in), Ring #3 increasing 30% from Ring #1 (2.60 in), Ring #4 increasing 45% from #1 (2.90 in), and so on. Such size increments resulted in ring diameters, from smallest to largest, of 2.00, 2.30, 2.60, 2.90, 3.20, 3.50, 3.80, 4.10, 4.40, 4.70. CS+ = conditioned stimulus paired with shock, CS- = conditioned stimulus unpaired with shock.

demands (Lipp, Siddle, & Dall, 2000) or preparation of motor movements (Valls-Sole, Valdeoriola, Tolosa, & Nobbe, 1997).

Design

The generalization paradigm included three phases: (1) *pre-acquisition*—consisted of six CS+ (three startle, three behavioral), six CS- (three startle, three behavioral), and six inter-trial-interval (ITI) measures (three startle, three behavioral) all presented in the absence of any shock USs; (2) *acquisition*—included 12 CS+ (six startle, six behavioral), 12 CS- (six startle, six behavioral), and 12 ITI (six startle, six behavioral), with nine of 12 CS+ coterminating with shock delivery (75% reinforcement schedule), and (3) *generalization test*—included 12 CS+ (six startle, six behavioral), 12 CS- (six startle, six behavioral), and 12 ITI (six startle, six behavioral), as well as six trials from each of the eight GS sizes (three startle and three behavioral). Because every two sizes of GSs formed a single class of GS (see Fig. 1), there were 12 GSs from each class (six startle and six behavioral) providing balanced numbers of trials across GS classes, CS+, CS-, and ITI. Though all eight GSs were presented to participants, prior to analyses, responses to every two GSs were averaged resulting in four classes of responses to GSs. This decision to collapse every two intermediaries was due to concerns that treating each of eight GSs as a separate class would require an unrealistically long experiment (leading to excessive startle habituation and subject fatigue), but having only four gradients-of-size would not allow a gradual enough continuum between CS+ and CS-. Having four classes of intermediaries with two ring sizes in each class seemed a good compromise as the generalization slope was a derivative of eight gradations of CS+ similarity while each intermediary required half as many trials. As displayed in Fig. 1, classes of GSs were numbered such that Class 4 consisted of the two rings closest in size to the CS+ (rings 8

and 9 for counterbalancing group A, rings 3 and 2 for group B), and Classes 3 through 1 consisted of rings progressively increasing in similarity to the CS–. Finally, during the generalization test, 6 of 12 CS+ coterminated with shock delivery (50% reinforcement schedule) to prevent extinction of the conditioned response during the generalization sequence.

Trials for all three phases of the study were arranged in quasi-random order such that no more than two stimuli of the same class occurred consecutively. An additional constraint placed on the ordering of the generalization sequence was the arrangement of trials into six blocks of 14 trials (two CS+, two CS–, two ITI, and one each of rings 2–9) to ensure an even distribution of trial types throughout the generalization run. Finally on odd CS+, CS–, GS, and ITI trials across phases, startle probes were delivered at either 4- or 5-s post-trial onset, and the inter-probe interval was maintained between 18 and 25 s throughout.

Procedure

Participants were not instructed of the CS/US contingency but were told that they might learn to predict the shock if they attend to the presented stimuli. Shock electrodes were then attached and a shock workup procedure was completed. Next, EMG electrodes and headphones were placed and a habituation sequence consisting of nine startle probes (ITI = 18–25 s) was run. The three phases of the experiment were then completed with pre-acquisition followed by acquisition and generalization test, with a 10-min break separating acquisition and generalization test. After acquisition and generalization phases, participants rated levels of anxiety and arousal evoked by CS+ and CS– using 10-point Likert scales (1 = none, 5 = some, 10 = a lot).

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 time of 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 to 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 the *T*-scored data are presented though descriptive statistics for raw startle magnitudes are available in Table 1. Acquisition of conditioning was analyzed with a 2 (CS-type: CS+, CS–) × 2 (size: CS+ = largest ring vs. CS+ = smallest ring) multivariate analysis of variance (MANOVA) with repeated measures. Additionally, generalization effects were analyzed using a 6 (trial-type: CS+, CS–, Class1, Class 2, Class 3, Class 4) × 2 (size: CS+ = largest ring vs. CS+ = smallest ring) MANOVA with repeated measures. MANOVAs were computed using Wilk's Lambda and were followed, when necessary, by paired samples *t*-tests. Alpha was set at .05 for all statistical tests and effect sizes were estimated using the unbiased estimator *d* (Hedges & Olkin, 1985).

Because CS+ size was not found to interact with dependent measures (startle EMG, reported risk, reaction times) at either pre-acquisition, acquisition, or generalization (all *ps* > .20, all *ds* < .33), such effects are not reported below. Nevertheless these null effects of CS+ size should be interpreted with caution as the small number of participants receiving the smallest (*n* = 10) or largest ring (*n* = 10) conferred poor statistical power

Table 1

Means (and standard errors of the mean) for raw startle EMG values in microvolts

Testing phase	ITI	CS–	C1	C2	C3	C4	CS+
Pre-acquisition	34.43 (8.51)	29.67 (8.28)	–	–	–	–	32.92 (8.23)
Acquisition	26.68 (6.74)	27.36 (7.51)	–	–	–	–	36.09 (7.37)
Generalization	16.64 (4.45)	16.14 (3.84)	19.80 (4.75)	18.63 (4.63)	21.94 (5.29)	26.66 (5.99)	32.80 (7.64)

Note: CS+ = conditioned stimulus paired with shock; CS– = conditioned stimulus unpaired with shock; C1, C2, C3, and C4 = generalization stimulus Classes 1, 2, 3, and 4; ITI = inter-trial-interval.

(β) to such analyses with β ranging from .10 to .48, indicating false negative rates (i.e., $1-\beta$) ranging from .52 to .90. Thus, larger sample sizes will be needed before effects of circle size on conditioning and generalization can be ruled out.

Results

Pre-acquisition

Prior to conditioning, there was no main effect of CS-type for startle magnitudes ($p = .82$, $d = .07$), online risk ratings ($p = .24$, $d = .36$), and reaction times ($p = .20$, $d = .40$).

Acquisition

During acquisition, startle was potentiated by the CS+ ($M = 52.66$, $SD = 4.18$) relative to CS– ($M = 47.35$, $SD = 3.15$), $F(1,18) = 22.69$, $p = .0002$, $d = 1.02$. Consistent with startle data, online ratings of shock risk were higher for CS+ ($M = 2.75$, $SD = .24$) compared to CS– ($M = 1.17$, $SD = .22$), $F(1,18) = 343.68$, $p < .0001$, $d = 3.98$, and CS+ relative to CS– was retrospectively rated as more anxiety provoking ($M = 8.15$, $SD = 1.69$ vs. $M = 1.85$, $SD = 1.31$; $t(19) = 14.26$, $p < .0001$, $d = 3.06$) and arousing ($M = 6.35$, $SD = 2.85$ vs. $M = 2.20$, $SD = 1.32$; $t(19) = 7.03$, $p < .0001$, $d = 1.51$). Finally, a trend for shorter reaction times to report risk to the CS+ relative to CS– was found ($p = .08$, $d = .55$).

Generalization test

Startle EMG

Robust enhancement of startle during CS+ relative to CS– persisted during the generalization sequence, $t(90) = 7.13$, $p < .0001$, $d = 1.53$ (see Fig. 2A). Additionally, a main effect of trial-type was found, $F(5,14) = 13.18$, $p < .0001$, $d = .78$, and trend analyses of this effect revealed both linear, $F(1,18) = 36.18$, $p < .0001$, $d = 1.29$, and quadratic decreases in startle, $F(1,18) = 19.45$, $p < .001$, $d = .95$, with decreasing GS similarity to the CS+ (see Fig. 2A). Such results demonstrate the efficacy of the current paradigm for eliciting continuous generalization gradients of conditioned FPS.

In order to identify the point on the continuum-of-similarity at which startle potentiation ceased to generalize, paired samples t -tests were computed with CS– as the reference condition compared against CS+,

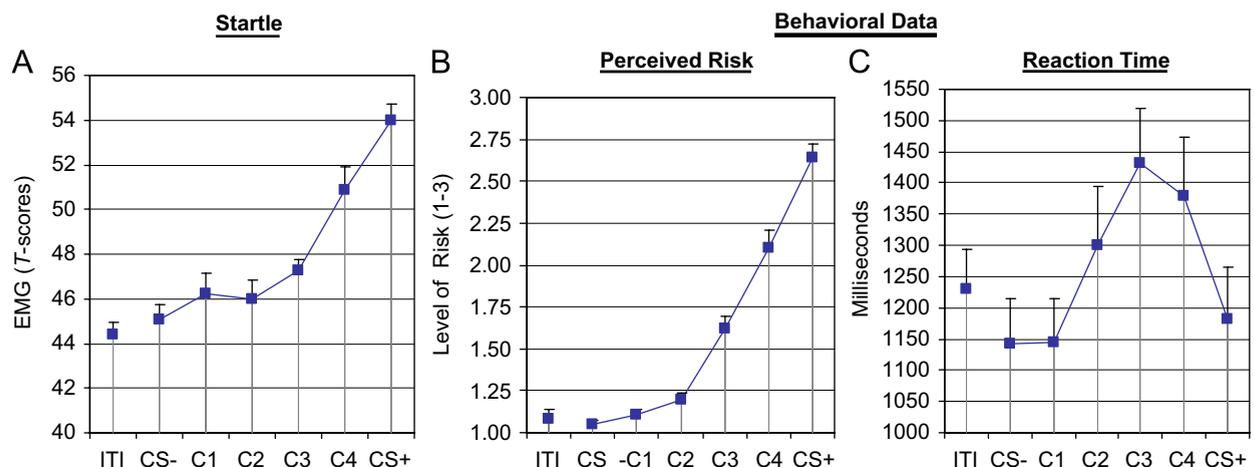


Fig. 2. Results for both psychophysiological (standardized startle EMG) and behavioral indices (risk ratings [1 = no risk, 2 = some risk, 3 = high risk], reaction times [ms]) of conditioned fear generalization. Error bars reflect the standard error of the mean. CS+ = conditioned stimulus paired with shock; CS– = conditioned stimulus unpaired with shock; C1, C2, C3, and C4 = generalization stimulus Classes 1, 2, 3, and 4; ITI = inter-trial-interval.

C4, C3, C2, and C1. The Bonferroni-corrected criterion of significance for these tests was set at $p < .05/5 = .01$. Results indicate startle potentiation to the CS+ ($p < .0001$, $d = 1.49$), generalization of this potentiation to C4 ($p = .0004$, $d = .91$), a trend for generalization to C3 ($p = .015$, $d = .57$), and no generalization to C2 ($p = .36$, $d = .19$) or C1 ($p = .32$, $d = .22$). Thus generalization of startle potentiation for healthy controls in the current paradigm can be described as extending to C4 but not beyond C3.

Online risk ratings

Consistent with startle data, a main effect of trial-type, $F(5,14) = 52.44$, $p < .0001$, $d = 1.55$, was found. Additionally, the main effect of trial-type consisted of both linear, $F(1,18) = 211.04$, $p < .0001$, $d = 3.12$, and quadratic gradients, $F(1,18) = 42.00$, $p < .0001$, $d = 1.39$, with increasing levels of risk from CS– to C1 to C2 to C3 to C4 to CS+ (see Fig. 2B). As was done with startle data, paired samples *t*-tests were computed with CS– as the reference condition compared against CS+, C4, C3, C2, and C1. Results indicate elevated risk perception to the CS+ ($p < .00001$, $d = 3.80$) and generalization of this elevation to C4 ($p < .00001$, $d = 2.09$), C3 ($p < .00001$, $d = 1.65$), and C2 ($p = .001$, $d = .79$), but not C1 ($p = .20$, $d = .29$). Thus generalization of risk perception in the current paradigm can be described as extending to C4, C3, and C2 but not C1.

Reaction times

A main effect of trial-type, $F(5,14) = 10.38$, $p < .0001$, $d = .69$, was found and consisted of linear, $F(1,18) = 10.96$, $p = .003$, $d = .71$, quadratic, $F(1,18) = 18.72$, $p < .0004$, $d = .93$, and cubic components, $F(1,18) = 15.75$, $p = .001$, $d = .85$ (see Fig. 2C). Additionally, CS– was associated with the quickest reaction times, with responses to C1 being equally fast to CS– ($p = .96$, $d = .02$); responses to C2, C3, and C4 each significantly slower than CS– (all $ps < .005$, $ds > .97$); equally fast reaction times for CS+ relative to CS– ($p = .36$, $d = .28$); and significantly slower reaction times to C4 and C3 versus CS+ (both $ps < .008$, $ds > .90$). This pattern of results suggests that participants were more certain of their level of risk (or lack thereof) during CS+ and CS– presentations and less certain during presentations of rings in Classes 4, 3, and 2.

Retrospective ratings

CS+ relative to CS– was rated as more anxiety provoking ($M = 7.45$, $SD = 1.85$ vs. $M = 1.25$, $SD = .44$; $t(19) = 13.58$, $p < .0001$, $d = 2.92$) and arousing ($M = 6.20$, $SD = 3.05$ vs. $M = 2.00$, $SD = 1.12$; $t(19) = 6.70$, $p < .0001$, $d = 1.44$), suggesting that robust aversive conditioning persisted during the generalization sequence.

Discussion

Current findings demonstrate the sensitivity of FPS for measuring continuous gradients of conditioned fear-generalization. In particular, startle magnitudes were potentiated by CS+ relative to CS– and gradually decreased when elicited during stimuli falling on a continuum-of-similarity from CS+ to the intermediary classes of GSs (Class 4 to 3 to 2 to 1) to CS–. Similarly, online ratings of perceived risk for shock fell along a downward gradient, with highest ratings to the CS+ and continuous decreases in such ratings corresponding with a gradual decrease in similarity to the CS+. Finally, reaction times for risk ratings indicated quickest response latencies for CS+ and CS–, and significantly longer latencies for stimuli from Classes 4, 3, and 2. This final result suggests that reaction times capture the ‘threat ambiguity’ of the presented stimulus, with faster risk ratings for stimuli with unambiguous safe/threat information (CS+, CS–) and slower response times for stimuli with more uncertain signal value (Classes 2, 3, and 4).

The generalization gradient of conditioned startle potentiation in the current study is consistent with the curvilinear shape of such gradients found in animals: fear responding is highest to the CS+, curves downward for the first and second closest approximations of the CS+, hits floor levels of responding at the third or fourth closest approximation, and remains at floor for the remaining test stimuli (e.g., Thompson, 1962). Similarly, current results demonstrate significant transfer of FPS to the closest approximation of the CS+ (Class 4), a trend for transfer of potentiation to the second closest approximation (Class 3) and no difference in startle magnitudes among the three farthest approximations of the CS+ (CS– and Classes 1–2).

Inhibitory versus excitatory fear generalization

Current results, taken together with past findings by Vervliet et al. (2004, 2005), point to strong tendencies toward excitatory fear generalization, and to weak tendencies toward inhibitory fear generalization in healthy humans. Whereas present data demonstrate robust generalization of fear excitation to stimuli resembling the CS+, results from Vervliet and colleagues reveal that fear extinction—an inhibitory process—does not generalize from CS+ approximates to the CS+ itself. The presence and absence of generalization across excitatory and inhibitory fear processes is consistent with findings in rodents in which learned fear-excitation (acquisition) but not learned fear-inhibition (extinction) generalizes across experimental contexts (Bouton, 2004). This pattern of findings may result from the high response-cost associated with overgeneralization of inhibition learning, resulting in the miss of a “true” danger.

Predictions for anxiety patients generated from current results

Though the shape of the generalization gradient in healthy humans resembles that of animals, the elevated tendency of anxiety patients to transfer conditioned fear to a CS– with strong resemblance to the CS+ (Grillon & Morgan, 1999; Lissek et al., 2005) supports the prediction of less steep generalization gradients among those with clinical anxiety, whereby startle magnitudes would remain elevated during presentation of Classes 3, 2, and perhaps 1 before dropping to CS– levels. Additionally, given that anxious individuals are characterized by a heightened tendency to appraise ambiguous stimuli as threatening (for a review, see Richards, 2004), those with clinical anxiety relative to healthy controls would be expected to display elevated risk ratings for shock when presented with classes of rings containing ambiguous threat information (i.e., Classes 4, 3, and 2), but would display approximately equal risk ratings for rings with more certain signal-value (i.e., CS+, CS–). A final prediction derives from current reaction-time results demonstrating longer latencies to assess risk when presented with more uncertain threat information (i.e., Classes 4, 3, and 2). Whereas healthy controls in the current study displayed a marked increase in response latency to the closest approximation of the CS+ (i.e., Class 4: see Fig. 2C), indicating greater threat uncertainty to C4 versus CS+, anxiety patients would be expected to be more certain of their risk for shock during presentation of Class 4, resulting in equally fast reaction times to CS+ and Class 4. Furthermore, healthy controls showed equally fast reaction times during presentation of the closest approximation of the CS– (i.e., Class 1: see Fig. 2C), whereas patients would be expected to experience less certainty of their safety during C1, resulting in significantly longer reaction times to C1 relative to CS– among anxiety patients.

Conclusion

Though continuous generalization gradients of conditioned fear are a particularly powerful method for assessing rates of fear generalization that have been applied extensively in animal research, to our knowledge, no psychobiological studies over the past 40 years have applied this method in humans. Given the strong relevance of fear generalization to anxiety disorders such as PTSD, an updated paradigm incorporating FPS methods was warranted. Present results provide psychophysiological and behavioral validation of a conditioned FPS paradigm capable of eliciting continuous gradients of generalization. This paradigm represents a novel tool with which to study the pharmacology, genetics, and psychobiology of a central, yet understudied, symptom of pathological anxiety.

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