Generalized Anxiety Disorder Is Associated With Overgeneralization of Classically Conditioned Fear

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Background: Meta-analytic results of fear-conditioning studies in the anxiety disorders implicate generalization of conditioned fear to stimuli resembling the conditioned danger cue as one of the more robust conditioning markers of anxiety pathology. Due to the absence of conditioning studies assessing generalization in generalized anxiety disorder (GAD), results of this meta-analysis do not reveal whether such generalization abnormalities also apply to GAD. The current study fills this gap by behaviorally and psychophysiologically assessing levels of conditioned fear generalization across adults with and without GAD.

Methods: Twenty-two patients with a DSM-IV-Text Revision diagnosis of GAD and 26 healthy comparison subjects were recruited and tested. The employed generalization paradigm consisted of quasi-randomly presented rings of gradually increasing size, with extreme sizes serving as conditioned danger cues (CS+) and conditioned safety cues. The rings of intermediary size served as generalization stimuli, creating a continuum of similarity between CS+ and conditioned safety cues across which to assess response slopes, referred to as generalization gradients. Primary outcome variables included slopes for fear-potentiated startle (electromyography) and self-reported risk ratings.

Results: Behavioral and psychophysiological findings demonstrated overgeneralization of conditioned fear among patients with GAD. Specifically, generalization gradients were abnormally shallow among GAD patients, reflecting less degradation of the conditioned fear response as the presented stimulus differentiated from the CS+.

Conclusions: Overgeneralization of conditioned fear to safe encounters resembling feared situations may contribute importantly to the psychopathology of GAD by proliferating anxiety cues in the individual's environment that are then capable of evoking and maintaining anxiety and worry associated with GAD.

Central to many etiological accounts of anxiety disorders is classical fear conditioning (1): the evolutionarily conserved learning process through which a neutral conditioned stimulus (CS) acquires the capacity to elicit fear following its co-occurrence with an aversive unconditioned stimulus (2). Because the neural substrates of fear conditioning have been mapped in lower mammals (3,4), conditioning-based research in anxiety patients represents a particularly valuable approach to generating neurobiological insight on clinical anxiety. A first step in this line of work is to link specific conditioning abnormalities to anxiety disorders.

Meta-analytic results implicate overgeneralization of conditioned fear as one of the most robust conditioning abnormalities in the anxiety disorders (5). In overgeneralization, fear responses appropriate to a danger cue (CS+) are inappropriately evoked by perceptually similar conditioned safety cues (CS−). Due to the absence of conditioning studies testing overgeneralization in generalized anxiety disorder (GAD) at the time of this meta-analysis, results do not reveal whether such abnormalities in conditioned generalization also apply to GAD. Additionally, the one lab-based study of fear generalization in GAD patients conducted after this meta-analysis found no behavioral or autonomic (pupillary response) evidence of overgeneralization in GAD patients (6). Substantial research and clinical findings linking GAD to overgeneralization, however, warrant further testing of this relation. Empirical evidence derives from the well-established link between GAD and both heightened intolerance of uncertainty (7) and increased tendencies to interpret ambiguous stimuli as threatening (8–10). Stimuli resembling the CS+, referred to as generalization stimuli (GS), constitute degraded versions of the original conditioned danger cue and, as such, represent a more ambiguous and uncertain source of threat. It thus follows that individuals with GAD may be both more stressed by the threat uncertainty of GS and more prone to interpret GS as threatening, resulting in heightened anxious reactivity to GS. Additionally, the clinical phenomenology of GAD seems consistent with a tendency toward overgeneralization. For example, a GAD patient with an anxiogenic preoccupation of a family member's risk for cancer not only may become worried when confronted by encounters directly related to cancer (e.g., news of a relative with a malignancy, meeting a child with cancer) but also may generalize this fear to stimulus events with only moderate relatedness to cancer (e.g., noticing the health section of the newspaper open on the counter, seeing a medical doctor on a TV show). This type of fear generalization is thought to proliferate anxiety cues in the individual's environment (11) and, in so doing, may increase the persistence of anxiety and worry associated with GAD. Importantly, because of extensive animal research on conditioned fear and its generalization, confirming overgeneralization in GAD patients may aid in

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bridging the gap between basic and GAD-relevant clinical science by implicating neural substrates of conditioned generalization found by animal work in the pathophysiology of GAD.

The current study tests for overgeneralization in GAD patients with a previously validated, conditioned fear-generalization paradigm assessing fear-potentiated startle (electromyography [EMG]) and behavioral responses to both conditioned danger cues (CS+) and generalization stimuli parametrically varying in similarity to the CS+ (12,13). This paradigm affords assessment of downward slopes in conditioned responding as the presented stimulus differentiates from CS+, known as generalization gradients (2). The strength of generalization is captured by the steepness of gradients, with less steep downward slopes indicative of greater generalization. In both intact animals and healthy humans, generalization gradients form steep, quadratic slopes with highest levels of fear conditioning to CS+, precipitous declines in responding to the closest two or three approximations of the CS+, and a leveling off of responses to the remaining generalization stimuli (12,14–16). By contrast, responses to CS+ and GS in patients with GAD are predicted to deviate from this pattern, with less quadratic and more gradual generalization gradients reflecting heightened levels of generalization.

Previous applications of this paradigm demonstrate overgeneralization of fear conditioning reflected by abnormally gradual generalization gradients in patients with panic disorder (13) and posttraumatic stress disorder (PTSD) (11). Such data are beginning to paint a picture of overgeneralization as a broad vulnerability marker cutting across traditional anxiety disorder categories. An additional aim of this study is to further assess the reach of overgeneralization by testing whether it extends to patients with GAD.

Methods and Materials

Participants

Participants included 22 patients with a diagnosis of GAD and 26 healthy comparison subjects matched for gender and age. For all patients, GAD symptoms constituted the primary source of current discomfort and dysfunction. Table 1 displays sample characteristics for each group. Diagnostic and consenting procedures, as well as inclusion-exclusion criteria for each group, are included in Supplement 1.

Conditioned Generalization Paradigm

The paradigm used in this study was identical to the one we described in detail elsewhere (12), in which 10 rings of gradually increasing size (Figure 1) presented on a computer monitor served as conditioned and generalization stimuli. The largest and smallest rings served as the conditioned danger cue (CS+) and conditioned safety cue (CS−), the former paired and the latter unpaired with an aversive unconditioned stimulus. The eight intermediately sized rings served as generalization stimuli (GS) that formed a continuum of size between the CS+ and CS−. As can be seen in Figure 1, the eight GS were collapsed into four classes of GS (GS$_1$, GS$_2$, GS$_3$, GS$_4$). All conditioned and generalization stimuli were presented for 8 seconds on a computer monitor. The unconditioned stimulus was a 100-millisecond electric shock delivered to the left wrist (3–5 mA) that was rated by participants as "highly uncomfortable but not painful."

This paradigm consisted of three phases: habituation (startle habituation to nine startle probes), preacquisition, acquisition (presentation of CS− and CS+ only, with CS+ reinforced in 75% of trials), and generalization (presentation of the CS−, CS+, and the eight GS, with CS+ reinforced in 50% of trials). The trial types and frequencies for each phase are listed in Table 2. During each phase, half of the trials were followed by acoustic startle probes (40 msec, 102 dBA) that occurred 4 or 5 seconds after onset of the conditioned or generalization stimulus. A balanced number of startle probes were presented during intertrial intervals.

During trials without startle probes, behavioral ratings (perceived risk for shock) and associated response times were collected. Specifically, the question "Level of risk?" appeared above the stimulus 1 to 2 seconds after trial onset, which cued participants to rate their perceived likelihood of receiving a shock on a 3-point scale (1 = no risk, 2 = moderate risk, and 3 = high risk). Further details on risk ratings and self-report measures, as well as the startle EMG apparatus and EMG data processing, can be found in Supplement 1.

Table 1. Demographics and Clinical Characteristics Across Patient and Control Samples

Variable	GAD Patients (n = 22)		Healthy Control Subjects (n = 26)		Significance[a]
	Mean	SD	Mean	SD	
Age (years)	32.91	8.66	29.27	10.43	$p = .20$
STAI-State	47.00	8.44	26.32	6.99	$p < .0001$
STAI-Trait	52.54	6.76	29.94	6.59	$p < .0001$
BDI	10.68	6.39	2.33	2.37	$p < .0001$
	n	%	n	%	Significance[a]
Male Gender	5	23%	8	31%	$p = .54$
Comorbidities					
Social anxiety disorder	10	45%	0	0%	–
Specific phobia	1	5%	0	0%	–
Past MDD	2	9%	0	0%	
Ethnicity					
African American	4	18%	3	12%	–
Caucasian	16	73%	18	69%	–
Hispanic	1	5%	2	8%	–
Asian Pacific	0	0%	3	12%	–
Other	0	0%	0	0%	–

BDI, Beck Depression Inventory; GAD, generalized anxiety disorder; MDD, major depressive disorder; STAI, Spielberger State/Trait Anxiety Inventory.
[a]Two-tailed *p* values reflecting the significance of group differences derived from independent samples *t* tests for all variables except gender, which was assessed using the chi-square statistic.
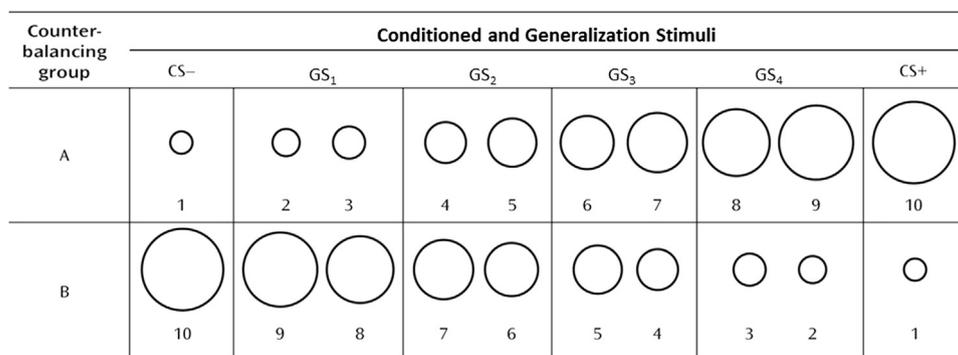
Figure 1. Conditioning and generalization stimuli (GS) for counterbalancing groups A and B. For half of participants, the largest ring was the conditioned stimulus paired with shock (CS+) and the smallest was the conditioned stimulus unpaired with shock (CS−) (group A), and for the other half this is reversed (group B). The numbers 1 to 10 at the bottom of the rings label the stimuli from smallest (1) to largest (10). As was done by Lissek *et al.* (12)—to avoid an unduly large number of trials while maintaining a gradual continuum of size across rings—each of two intermediaries are collapsed into a single class of stimulus leaving four classes of GS. For both counterbalancing groups A and B, these classes of GS are numbered such that class GS_4 consists 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 GS_3 through GS_1 consist of rings progressively increasing in similarity to the CS−. The diameter for the smallest ring (ring #1) was 2.00 inches 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, and 4.70 inches. GS_1, GS_2, GS_3, GS_4 = generalization stimulus classes 1–4.

Data Analysis

For acquisition, startle and behavioral data were analyzed with a 2 (stimulus type: CS−, CS+) × 2 (group: GAD patients, healthy comparison subjects) repeated measures analysis of variance. Startle and behavioral data at generalization were analyzed with a 6 (stimulus type: CS−, GS_1, GS_2, GS_3, GS_4, CS+) × 2 (group: GAD patients, healthy comparison subjects) repeated measures analysis of variance. Analyses of variance were computed using Wilks' lambda and were followed, when necessary, by either trend analyses, paired-samples *t* tests, or independent-samples *t* tests. Quadratic trend analyses were particularly important for testing the shape of generalization gradients, with the a priori hypothesis that gradients of patients, but not healthy comparison subjects, would depart from the quadratic function found in healthy humans and intact animals (12,14). Alpha was set at .05 for all statistical tests.

Results

Preacquisition

Neither main effects of stimulus type nor stimulus type × group interactions were significant for behavioral risk ratings and startle EMG (all *p*s < .47).

Table 2. Trial Types and Frequencies During Preacquisition, Acquisition, and Generalization Phases of the Study

						CS+		
Phase	CS−	GS_1	GS_2	GS_3	GS_4	Yes US	No US	ITI
Preacquisition	6					0	6	6
Acquisition	12					9	3	12
Generalization	12	12	12	12	12	6	6	12

During the generalization test, the CS+ continued to be reinforced with shock to avoid extinction of the conditioned response during the generalization sequence.

CS+, conditioned danger cue; CS−, conditioned safety cue; GS_1, GS_2, GS_3, and GS_4, generalization stimulus classes 1, 2, 3, and 4; ITI, intertrial intervals; US, unconditioned stimulus.

Acquisition

Startle EMG. A main effect of stimulus type was found, $F_{1,46}$ = 46.09, *p* < .0001, and resulted from significant potentiation of startle to CS+ versus CS− in both GAD (mean CS+ = 57.38 [SD = 6.51], mean CS− = 52.22 [SD = 4.97]; t_{21} = 3.74, *p* = .001) and healthy groups (mean CS+ = 56.05 [SD = 4.99], mean CS− = 49.15 [SD = 3.51]; t_{25} = 6.04, *p* < .0001). The group × stimulus type interaction was not significant (*p* = .33).

Risk Ratings. A main effect of stimulus type, $F_{1,46}$ = 250.22, *p* < .0001, was driven by increased risk ratings to the CS+ versus CS− in both GAD, t_{21} = 6.62, *p* <.0001, and healthy groups, t_{25} = 21.46, *p* < .0001. Additionally, a group × stimulus type interaction was found $F_{1,46}$ = 18.70, *p* < .0001. As can be seen in Figure 2, this interaction resulted from greater levels of reported risk among GAD patients versus healthy comparison subjects to CS− (*p* < .0001) and intertrial interval (*p* = .001) but equal levels across groups to CS+ (*p* = .41).

Response Times. A main effect of stimulus type was found, $F_{1,46}$ = 8.88, *p* = .004, and reflected quicker response times to CS+ than CS−. No stimulus type × group interaction was found (*p* = .38).

Retrospective Anxiety. Conditioning to the danger cue was also apparent in self-reported anxiety as evidenced by a main effect of stimulus type, $F_{1,46}$ = 115.32, *p* < .0001, driven by greater reported anxiety to CS+ versus CS− in both GAD (*p* = .001) and control groups (*p* < .0001). Furthermore, the group × stimulus type interaction was significant, $F_{1,46}$ = 12.90, *p* = .001, and reflected greater anxiety in GAD patients versus control subjects to CS− (*p* < .0001) but not CS+ (*p* = .37).

Generalization Test

Startle EMG. Generalization of fear conditioning was evidenced by main effects of stimulus type in both patients, $F_{5,17}$ = 4.12, *p* = .012, and healthy comparison subjects, $F_{5,21}$ = 9.43, *p* < .0001, which derived from graded decreases in startle magnitude as the presented stimulus diverged from CS+ (Figure 3A). The shape of this declining slope differed across groups, as reflected by a significant group × stimulus type interaction, $F_{5,42}$ = 2.35, *p* < .05, attributable to between-group differences in the quadratic component of their respective slopes (group × stimulus type quadratic trend: $F_{1,46}$ = 4.13, *p* < .05).
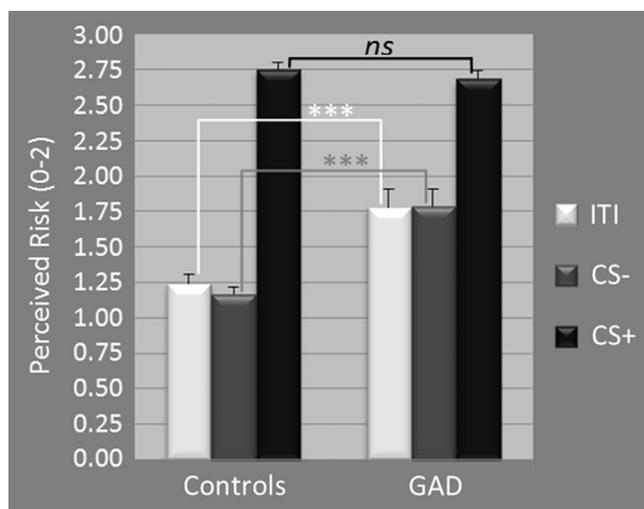
Figure 2. Acquisition results across groups for self-reported risk of shock, where 0 = no risk, 1 = some risk, and 2 = high risk. CS+, conditioned stimulus paired with shock; CS−, conditioned stimulus unpaired with shock; GAD, generalized anxiety disorder; ITI, intertrial interval; ns, nonsignificant. ***$p <$ .001.

Follow-up tests on the group $\times$ stimulus type quadratic interaction revealed a significant quadratic component in the generalization gradient of comparison subjects, $F_{1,25} = 19.69$, $p = .0002$, but not GAD patients, $F_{1,21} = .91$, $p >$ .35.

Group differences in quadratic components are visualized in Figure 3A for GAD and healthy groups separately. The dotted lines represent hypothetical linear declines in startle potentiation from CS+ to CS−, which illustrate the presence and absence of a quadratic deviation from linearity among healthy control subjects and patients. Whereas healthy control subjects display a marked departure from linearity, characterized by a steep quadratic decline in fear conditioning as the presented stimulus differentiates from CS+, the absence of a quadratic function in GAD patients is evidenced by substantially less deviation from linearity, indicating a more gradual decline in fear conditioning as stimuli move down the continuum of similarity.

Additional evidence for overgeneralization in GAD patients lies in response slopes from CS+ to GS₄. Whereas conditioned fear drops precipitously from CS+ to GS₄ in healthy comparison subjects, GAD patients display approximately equal levels to CS+ and GS₄, suggesting complete generalization of conditioned fear from CS+ to its first approximation. This group difference in startle responding was confirmed by a significant 2 (group: GAD, control subjects) $\times$ 2 (stimulus: CS+, GS₄) interaction, $F_{1,46} = 3.83$, $p <$ .05, with significant declines from CS+ to GS₄ in control subjects ($p = .009$) but not patients ($p = .96$).

Risk Ratings. Main effects of stimulus type where found in both patient and comparison groups ($ps <$ .0001) and resulted from downward generalization gradients in perceived risk as the presented stimulus differentiated from CS+ (Figure 3B). Additionally, a significant group $\times$ stimulus type quadratic trend emerged, $F_{1,46} = 9.90$, $p = .003$, indicating group differences in the quadratic component of generalization gradients. Figure 3B includes dotted lines demarcating linear declines in risk ratings from CS+ to CS− with which to visualize group differences in quadratic departures from linearity. As can be seen, such departures are more substantial in healthy comparison subjects versus individuals with GAD—a group difference responsible for the resulting group $\times$ stimulus type quadratic trend.

As was the case for startle data, group differences in generalization of risk ratings were most apparent when looking at response slopes from CS+ to GS₄. Specifically, perceived risk of shock generalized more strongly from CS+ to GS₄ in GAD patients relative to healthy comparison subjects as evidenced by a significant 2 (group: GAD, control subjects) $\times$ 2 (stimulus: CS+, GS₄) interaction, $F_{1,46} = 10.76$, $p = .002$.

Response Times. There was a main effect of stimulus type, $F_{5,42} = 4.40$, $p = .003$, with significant quadratic components found for both healthy comparison subjects, $F_{1,25} = 11.64$, $p = .002$, and GAD patients, $F_{1,21} = 4.45$, $p <$ .05. As can be seen in Figure 3C, these quadratic components take the form of inverted U-shaped curves reflecting slower risk ratings for GS with ambiguous signal value and faster ratings for stimuli communicating more certain threat or safety information (i.e., CS+ and CS−). This pattern of results implicates reaction time as an index of threat uncertainty, with longer reaction times reflecting more uncertainty.

Group differences in reaction times across stimuli were evidenced by a group $\times$ stimulus type interaction, $F_{5,42} = 4.07$, $p = .005$. This interaction was driven by significantly faster responses to GS₄ in patients relative to comparison subjects ($p <$ .02), as group differences between all other stimulus classes were nonsignificant, and reaction times to GS₄ versus CS+ were significantly longer for healthy comparison subjects ($p = .004$) but not patients ($p = .30$), resulting in a significant 2 (group: GAD, control subjects) $\times$ 2 (stimulus: CS+, GS₄) interaction, $F_{1,46} = 4.21$, $p <$ .05. That response times for GS₄ were not significantly different from CS+ among GAD patients suggests that patients were equally certain of risk for shock whether presented with the closest approximation of the danger cue or the danger cue itself.

Retrospective Anxiety. Self-reported levels of anxiety, following the generalization test, revealed greater anxiety to the CS+ versus CS− in both GAD patients and healthy comparison subjects (both $ps <$ .0001). Additionally, self-reported anxiety was higher in patients versus control subjects to CS− ($p = .002$) but not CS+ ($p = .53$).

Testing Effects of Social Anxiety Disorder in GAD Patients. Because 10 of 22 GAD patients were diagnosed with comorbid social anxiety disorder (SAD), the influence of comorbid SAD on generalization results in GAD patients was examined with two sets of subanalyses. In the first set, differences between GAD patients with and without comorbid SAD on behavioral and psychophysiological indices of generalization were tested using group (two levels: GAD-alone, GAD + SAD) $\times$ stimulus type (six levels: CS−, GS₁, GS₂, GS₃, GS₄, CS+) interactions. Such analyses found no group $\times$ stimulus type interactions for startle data or behavioral risk ratings (all $ps >$ .30), suggesting that comorbid SAD did not alter results in GAD patients. Because these null effects may have resulted from underpowered sample sizes, such effects should be interpreted with caution.

The second set of subanalyses tested whether generalization effects in the GAD-alone patients were similar to those found in the total GAD group. Again, statistics from this subanalysis are likely underpowered due to small sample size, and results should be interpreted cautiously. After excluding the 10 GAD patients with comorbid SAD, the group $\times$ stimulus interaction for startle EMG was reduced to a nonsignificant trend, $F_{5,32} = 1.91$, $p = .117$. Nevertheless, the pattern of results in the GAD-alone subjects remained the same as those for the total GAD group with generalization gradients characterized by linear, $F_{1,11} = 14.54$, $p = .003$, but not quadratic components, $F_{1,11} = .52$, $p = .49$. Additionally, GAD-alone subjects, versus healthy control subjects, continued to display less steep declines in startle responding
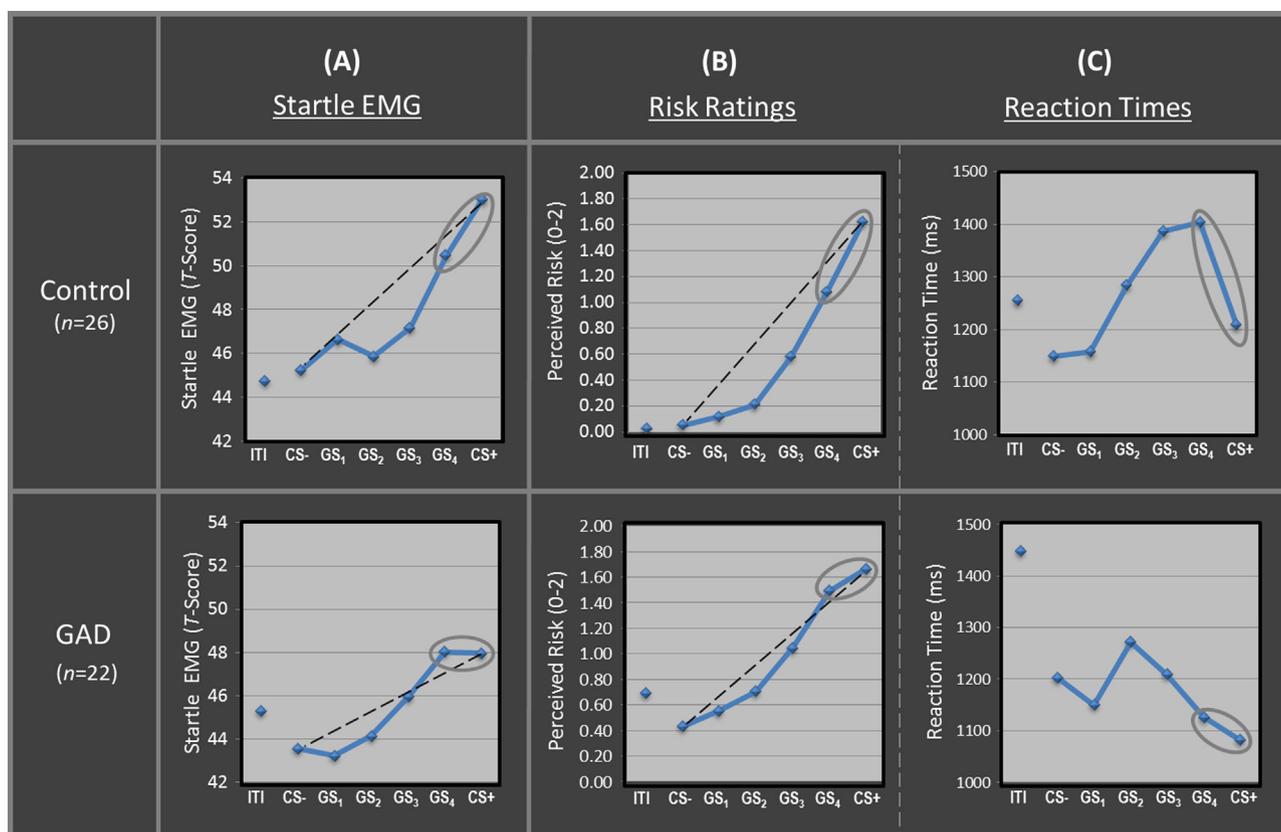
Figure 3. Generalization results across groups and dependent variables including **(A)** standardized startle electromyography (EMG), **(B)** behavioral risk ratings (0 = no risk, 1 = some risk, 2 = high risk), and **(C)** reaction times. Levels of responding for all indices are displayed across conditioned danger cues (CS+) and conditioned safety cues (CS−), as well as four classes of generalization stimuli (GS$_1$, GS$_2$, GS$_3$, GS$_4$), forming a continuum of similarity between CS+ and CS−. Black dotted lines reflect linear decreases in responding from CS+ to CS− with which to visualize the deviation of gradients from linearity. Gray ellipses around the rightmost data points highlight more shallow response slopes from CS+ to GS$_4$ in patients versus control subjects across all indices. GAD, generalized anxiety disorder; ITI, intertrial interval.

from CS+ to GS$_4$, $F_{1,36} = 4.09$, $p = .05$, indicating overgeneralization in GAD-alone patients. In terms of online risk ratings, after removing the 10 GAD patients with comorbid SAD, the group (two levels: GAD-alone, healthy control subjects) × stimulus type (six levels: CS−, GS$_1$, GS$_2$, GS$_3$, GS$_4$, CS+) quadratic trend was reduced to nonsignificance ($p = .18$), though a trend for less steep declines from CS+ to GS$_4$ remained in GAD-alone versus healthy control subjects, $F_{1,36} = 3.50$, $p = .07$. Thus, while the significance of group differences in generalization was generally reduced after dropping GAD patients with comorbid SAD, results continued to reflect overgeneralization in the GAD-alone group, suggesting that comorbid SAD was not responsible for the pattern of results found in the total GAD sample.

Discussion

This study represents the first behavioral and psychophysiological demonstration of laboratory-based overgeneralization of fear conditioning in generalized anxiety disorder. Whereas generalization gradients in healthy comparison subjects fell along precipitous, quadratic declines in conditioned responding as the presented stimulus diverged in similarity from the CS+, gradients among GAD patients fell along less steep and less quadratic slopes of responding, indicating stronger transfer of fear to stimuli resembling the CS+. This heightened generalization in GAD patients was found whether indexing the generalization

gradient with behavioral risk ratings or psychophysiological assessments of fear-potentiated startle. Furthermore, analyses testing effects of SAD on levels of generalization in GAD patients suggest that results in GAD patients are not driven by comorbid SAD, although such analyses were likely underpowered.

Differential Response Slopes from CS+ to GS$_4$ Across Groups

In addition to group differences in the overall shape of generalization gradients, response slopes from CS+ to the closest approximation of the CS+ (GS$_4$) among GAD patients deviated consistently from such slopes in healthy comparison subjects across behavioral and psychophysiological measures. Specifically, slopes in startle magnitudes, risk responses, and reaction times from CS+ to GS$_4$ were steep in healthy comparison subjects but nearly flat among GAD patients (see circled data points in Figure 3). Such findings indicate that those with GAD, but not without GAD, behaviorally and psychophysiologically responded to the closest approximation of the CS+ much like they responded to the conditioned danger cue itself. That is, patients with GAD displayed virtually full generalization of fear from CS+ to the first approximation. By contrast, levels of responding to GS$_4$ deviated significantly from responses to CS+ among healthy comparison subjects, indicative of less generalization. Whereas the group effects for startle data and risk ratings directly reflect greater transfer of conditioned responding to GS$_4$ among those with GAD, the group effect for reaction times suggest that GAD patients were equally certain of their risk for shock during CS+

and GS$_4$, and healthy comparison subjects were significantly less certain of their risk during GS$_4$ relative to CS+.

Relation to Past Generalization Findings in GAD

To date, the only published study testing generalization gradients in GAD patients found no abnormalities in behavioral or psychophysiological measures (6). The reason for the discrepancy with current results may result from methodological differences between the two studies. One key difference lies in the way behavioral data were collected. Though, like the current study, Greenberg et al. (6) assessed behavioral generalization by recording participants' perceived risk of shock to CS+ and GS, these ratings were collected retrospectively at the end of the experiment, when shock was no longer possible. In the current study, behavioral risk ratings were collected online when shock was a real possibility. As discussed earlier, threat ambiguity signaled by GS may elicit heightened fear in GAD patients through "what if" speculations (i.e., "I don't think shock will follow the GS, but what if it does"). If shock is not a real possibility, as was the case in the Greenberg et al. (6) study, GAD patients may be less likely to engage in this kind of anxiogenic counterfactual thinking, resulting in less overgeneralization of perceived risk. By contrast, in the current study, participant ratings occurred amidst real risks of shock, which may increase "what if" speculations in GAD patients and increase their overgeneralization of risk ratings.

Toward a Neurobiology of Conditioned Overgeneralization

Owing to the cross-species relevance of fear-conditioned generalization, neural substrates of overgeneralization, of the kind presently found in GAD, are informed by neurobiological findings in animals. Among them are results suggesting a critical role for the hippocampus, with lesions of either hippocampus (17,18) or cortical inputs to the hippocampus (i.e., postrhinal and perirhinal cortex) (19) increasing generalization of fear from CS+ to resembling safety cues (i.e., CS−) in animals. These findings suggest that hippocampal activations are necessary for successful discrimination of CS+ from GS, potentially attributable to the pattern separation function of the hippocampus (20), through which brain representations resembling, yet distinct, sensory experiences are discriminated. Thus, one important candidate neural substrate of overgeneralization in GAD may be deficits in hippocampally mediated pattern separation of GS from CS+.

A further area implicated in generalization of classical conditioning in animals is the orbital prefrontal cortex (OPFC) (21). Specifically, rats with OPFC lesions generalize freezing behavior from a context paired with shock to an unpaired context, while intact animals display freezing only in the paired context. Such results suggest that OPFC activations are needed to inhibit fear to stimulus events resembling the CS+, and deficits in such activations among those with GAD may result in overgeneralization.

Contributions from the hippocampus and OPFC toward conditioned fear generalization in humans have been supported by recent functional magnetic resonance imaging evidence of generalization gradients instantiated in both anterior hippocampus and an area of the OPFC referred to as ventromedial prefrontal cortex (vmPFC) (22). Such findings support a proposed neural model of generalization in which GS presentations elicit hippocampally mediated pattern separation of GS and CS+ brain representations, leading to activation of vmPFC and culminating in inhibition of fear to GS (i.e., successful discrimination and little generalization) (23). According to this model, overgeneralization in anxiety disorders may result from both reduced hippocampally

mediated pattern separation and reduced vmPFC activation in response to GS. Specifically, anxiety patients may require greater dissimilarity between the CS+ and GS before the hippocampus initiates pattern separation and propogates activation to the fear-inhibiting vmPFC. Additionally, clinical abnormalities may lie in the vmPFC, whereby fear to the GS fails to be inhibited following normative hippocampally mediated pattern separation due to insufficient vmPFC reactivity to hippocampal inputs. This latter prediction receives support from Greenberg and colleagues (6) who found less steep increases in vmPFC activity as the presented GS differentiated from CS+ among those with versus without GAD.

Overgeneralization as a Phenomenological Constituent of GAD

A cardinal feature of GAD is excessive and persistent worry that future events will be negative and disastrous (24). Such worry is often expressed as catastrophic "what if" speculations (8), which serve to bias those with GAD toward threatening appraisals of unclear or ambiguous situations (i.e., interpretation bias) (8–10). That is, less objective threat information is required for someone with GAD, versus without GAD, to interpret a stimulus event as threatening. Stimuli resembling conditioned danger cues (i.e, GS) include degraded threat information that may be sufficient to exceed the threshold for threat detection among those with GAD but not those without GAD. In this way, overgeneralization of fear may be viewed as a special case of interpretation bias, in which safe stimuli with resemblance to feared situations are over-interpreted as threatening by those with GAD. This form of generalization-based interpretation bias may contribute to the psychopathology of GAD by transferring fear to situations resembling other anxiety-provoking situations, resulting in the undue proliferation of environmental cues capable of eliciting and maintaining anxious apprehension. Of note, the opposite direction of causality is also plausible. That is, worry and anxious states may predispose an individual with GAD to interpret ambiguous stimuli as threatening, resulting in overgeneralization. Unfortunately, the current study cannot determine the direction of causality and future longitudinal studies are needed to clarify this issue.

Overgeneralization as a Pathogenic Mechanism Cutting Across Traditional Anxiety Disorder Categories

Abnormally shallow gradients of generalization, reflecting overgeneralization of conditioned fear, have recently been documented in panic disorder (13) and preliminarily in posttraumatic stress disorder (11). Such results, together with current findings in GAD, are beginning to paint a broader picture of overgeneralization as a conditioning abnormality operating across the anxiety disorders. Indeed, the shape of shallow generalization gradients across these three anxiety groups were extremely similar, with the exception of a more marked generalization of fear to the first approximation of the CS+ among GAD versus panic or PTSD patients. A common precipitant of overgeneralization in anxiety patients may be an underlying disposition toward reduced thresholds for threat reactivity, resulting in less danger information required for a stimulus to activate the fear system. That is, generalization stimuli with degraded resemblance to conditioned danger cues may contain sufficient threat information to cross fear thresholds in those with, but not without, clinical anxiety. What may differentiate specific disorders is the type of conditioned danger cue from which fear is overgeneralized. For example, overgeneralization in PTSD, panic disorder, and GAD may be triggered by stimuli resembling trauma

cues, panic cues, and features of worrisome situations, respectively. Though overgeneralization is precipitated by different classes of danger cues, once evoked, the underlying mechanics are likely shared across disorders. Studying these shared mechanics is consistent with the National Institute oh Mental Health, Research Domain Criteria project, in which fundamental neural mechanisms of mental illness are dimensionally assessed across disorders. In the current context, shared mechanics likely draw from the neural substrates of overgeneralization described above and putatively include vmPFC hyporeactivity to GS and deficiencies in hippocampally mediated pattern separation.

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