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.

Key Words: Fear conditioning, fear-potentiated startle, generalized anxiety disorder, interpretation bias, pathophysiology, stimulus generalization

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)		
	Mean	SD	Mean	SD	Significance[a]
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.