Generalized Anxiety Disorder is Associated with Overgeneralization of Classically Conditioned-Fear

Supplemental Information

Supplemental Methods

Participants

Diagnostic and consenting procedures. Generalized anxiety disorder (GAD) diagnoses were determined by the Structured Clinical Interview for DSM-IV-TR, Patient Edition (SCID) (1), administered by an experienced psychiatric research nurse. All patients were also independently assessed by a senior psychiatrist (D.S.P.) to confirm the SCID diagnosis. At study outset, participants received a description of the experimental procedures and gave written informed consent, as approved by the National Institute of Mental Health institutional review board.

Inclusion/exclusion criteria. All participants had normal or corrected-to-normal vision and hearing and no history of a major neurological condition. Diagnostic exclusion criteria for both groups included: current major depressive disorder; alcohol or substance abuse or dependence (other than nicotine) within 6 months of study start; current or past history of bipolar disorder, psychosis, or delusional disorders; use of psychopharmacological medication or other drugs that alter central nervous system function within 2 weeks of testing, or use of fluoxetine within 6 weeks of testing; current use of illicit drugs, as determined by the SCID and confirmed with a urine test; pregnancy; or medical conditions or treatment for conditions that would interfere with the objectives of the study as determined by a staff physician. Additional exclusion criteria for healthy comparisons included any current or past axis I psychopathology as assessed by the SCID.

Behavioral Measures

For online risk ratings, participants were instructed to respond based on their 'gut feeling' of risk and to respond as quickly as possible with their dominant hand using a computer keyboard. Additionally self-reported levels of anxiety evoked by CS+ and CS- were collected using 10-point Likert scales (1 = none, 5 = some, 10 = a lot) following acquisition and generalization phases. Participants also completed the Beck Depression Inventory (2), the State/Trait Anxiety Inventory (3), and a demographics questionnaire.

Startle Electromyography (EMG)

Apparatus. Stimulation and recording were controlled by a commercial system (Contact Precision Instruments, London). Startle blink was measured with EMG using two 6 mm silver-chloride electrodes positioned under the left eye (sampling rate = 1000 Hz; bandwidth = 30–500 Hz). A ground electrode was placed on the participant's non-dominant forearm. Startle probes consisted of 40 ms, 102 dBA bursts of white noise with a near instantaneous rise time presented binaurally through headphones. Startle probes were separated by 18-25 second time intervals throughout the study.

Data Analysis. Raw EMG data reflecting the startle blink was rectified and smoothed using a 20 ms moving window average. The onset latency window for the startle EMG response was 20–100 ms following onset of the startle probe. Peak EMG magnitude was determined within 20-120 ms following startle-probe onset and the average baseline EMG level 50 ms prior to probe onset was subtracted from this peak. EMG startle magnitudes were standardized using within subject *T*-scores.

Supplemental Results

Testing the Shape of Gradients Across Groups

For each subject, the shape of generalization gradients was assessed 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, GS_4] /4).* Here *[CS+, CS-] /2* reflects the theoretical, linear midpoint of the gradient, and *[GS_1, GS_2, GS_3, GS_4] /4* 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, with positive versus negative values reflecting shallow convex-gradients versus steep concave-gradients, respectively. The product of this equation also indicates the strength of generalization, with more positive versus negative values indicating stronger versus weaker generalization, respectively. Results of this analysis for standardized startle data indicate that linear departures for GAD patients (M = -.16, SD = 2.82) versus healthy controls (M = -1.60, SD = 2.47) approached significance, $t_{(46)}$ = -1.87, p = .069. Follow up contrasts revealed a significant negative departure from linearity in healthy controls, $t_{(25)}$ = -2.35, p = .028, but not GAD patients, $t_{(21)}$ = -.13, p = .898, indicating steeper-than-linear gradients in controls but not healthy subjects. In terms of behavioral (risk ratings) generalization gradients, linear departures in GAD patients (M = -.10, SD = .25) versus healthy controls (M = -.34, SD = .23) were significantly different, $t_{(48)}$ = -3.36, p = .002, indicating less negative linear departures in GAD patients reflective of stronger generalization. These results nicely complement the Group x Stimulus interaction effects reported above in that both characterize the generalization gradients of GAD patients as more linear, and less steep, than those of healthy controls.

Supplemental References

1. First MB, Spitzer RL, Gibbon M, Williams JBW (2002): *Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition. (SCID-I/P).* New York: Biometrics Research, New York State Psychiatric Institute.
2. Beck AT, Steer RA, Brown GK (1996): *Manual for the Beck Depression Inventory II.* San Antonio, TX: Psychological Corporation.
3. Spielberger CD, Gorsuch RL, Lushene R, Vagg P, Jacobs GA (1983): *Manual for the State-Trait Anxiety Inventory*. Consulting Psychologist Press, Palo Alto, CA.