Overgeneralization of Conditioned Fear in the Anxiety Disorders

Putative Memorial Mechanisms

Shmuel Lissek and Christian Grillon

National Institute of Mental Health, Mood and Anxiety Disorders Program, Bethesda, MD, USA

According to many conditioning accounts of clinical anxiety, the central pathogen can be found in aberrant acquisition or extinction of learned fear to neutral stimuli (i.e., conditioned stimuli [CS]) paired with an aversive unconditioned stimulus (US). While overresponding to the CS is an important candidate source of anxiety pathology, both clinical observation and mounting experimental data implicate generalization of fear to stimuli resembling the CS as an equally promising candidate (e.g., Grillon & Morgan, 1999; Lissek et al., 2005; Lissek et al., 2010; Mineka & Zinbarg, 1996). Important to the current issue on "Trauma and Memory," generalization of fear to stimuli resembling those present during a traumatic event is a core feature of the posttraumatic stress response (American Psychiatric Association, 2000) and is likely influenced by conditioning-dependent modifications to the neural representation of the CS stored in memory. The current paper (1) summarizes the connection between conditioned-fear generalization and pathologic anxiety including a recent empirical example demonstrating the link and (2) explores memorial substrates of conditioned generalization and the ways they are related to overgeneralization of the kind seen in anxiety pathology.

Conditioned Generalization and Clinical Anxiety

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. Since then, fear generalization has been adopted as a core feature of anxiety pathology by clinical practitioners and theorists (e.g., Mineka & Zinbarg, 1996) but has received little empirical attention. Indeed, few analyses of conditioning data in clinical anxiety have looked specifically at the generalization process (Grillon & Morgan, 1999; Kopp, Schlimm, & Hermann, 2005; Lissek et al., 2005; Lissek et al., 2009), and systematic psychobiological assessments of conditioned generalization with the aim of understanding anxiety pathology have been conducted only very recently (Lissek et al., 2008; Lissek et al., 2010). The weight of the data from this small experimental literature implicates overgeneralization of conditioned fear as a robust marker of clinical anxiety generally, and posttraumatic stress disorder (PTSD) and panic disorder (PD) specifically. While the US in PTSD (trauma) is distinct from that in PD (panic attack), both USs are thought to confer anxiogenic valence to CSs occurring coincident with the US and, by way of generalization, to stimuli resembling the CS (e.g., Bouton, Mineka, & Barlow, 2001; Foa, Steketee, & Olasov-Rothbaum, 1989). This latter generalization process results in the proliferation of trauma/panic cues in the individual's environment that then serve to sustain anxiety related to the disorder.

Figure 1 displays the results of a recent study using rings of varying sizes as conditioned and generalization stimuli to demonstrate overgeneralization in panic patients (Lissek et al., 2010). In this study, anxious reactivity was assessed to a conditioned danger cue (CS+); a conditioned safety cue (CS−); and four generalization stimuli (GS_1, GS_2, GS_3, and GS_4) forming a continuum-of-similarity between the CS+ and CS−. The central finding is represented by data-points highlighted in green, reflecting classes of stimuli eliciting anxious arousal relative to the CS−. Whereas healthy controls displayed anxious reactivity to the CS+ that generalized to GSs with only one degree of differentiation from the CS+ (i.e., GS_4), panic patients displayed anxiety responses to the CS+ that generalized to GSs with up to three degrees of differentiation (GS_4, GS_3, and GS_2). This finding clinically validates the paradigm as a tool with which to explore neural and psychological substrates of overgeneralization, including the putative contribution of memorial mechanisms to which our attention will now turn.

Memorial Substrates of Conditioned Generalization

During mammalian fear-conditioning, the amygdala activates the nucleus basalis of Meynert (Kapp, Whalen, Supple, & Pascoe, 1992) which then projects to the visual, auditory,

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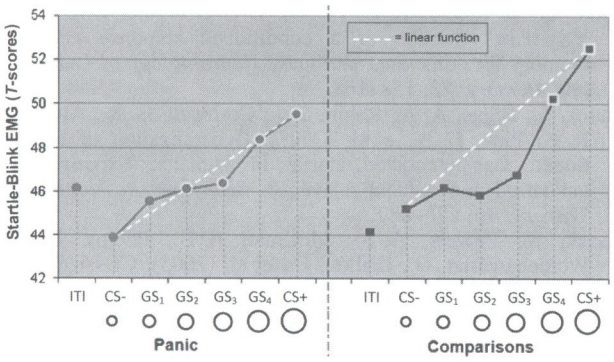

Figure 1. Overgeneralization of conditioned fear in panic patients as indexed by *fear-potentiated startle*: the reliable, amygdala-mediated, enhancement of the startle reflex by fear states (Davis & Astrachan, 1978; Grillon et al., 1991). Data reflect average, standardized startle-blink electromyogram (EMG) magnitudes across patients and healthy comparisons during presentation of conditioned stimuli paired (CS+) and unpaired (CS−) with electric shock; classes of generalization stimuli (GS_1, GS_2, GS_3, and GS_4); and inter-trial-intervals (ITI). White dotted lines reflect linear decreases in startle from CS+ to CS− with which to visualize the deviation of generalization gradients from linearity. Such deviations reflect a Group × Stimulus quadratic trend ($p = .03$) driven by a significant quadratic component (i.e., departure from linearity) in the gradient of healthy comparisons ($p = .001$) but not panic patients ($p = .62$). The green outlined data-points signify stimulus classes for which startle is potentiated relative to the CS− (at the $p \leq .05$ level). Such results indicate greater generalization in PD as reflected by: (1) less steep declines in responding as the presented stimulus diverges from the CS+ among patients and (2) the transfer of anxious arousal to stimuli with up to three units of CS+ differentiation (GS_4, GS_3, and GS_2) in patients, as compared to one unit of differentiation (GS_4) in healthy comparisons.

and somatosensory cortices – providing acetylcholine to the representation of the CS+ in sensory cortex (Weinberger, 2007). This influx of acetylcholine has been shown to retune receptive fields in sensory cortex toward CS+ attributes, such that an increased number of sensory neurons become responsive to the CS+ (for a review, see Weinberger, 2007). Importantly, neurons that retune to the CS+ following conditioning have also been shown to retune to stimuli resembling the CS+ (Scheich, Simonis, Ohl, Thomas, & Tillein, 1992) with decreasing levels of retuning as the stimulus becomes less similar to the CS+ (Weinberger, 2007). Thus the memorial representation of the post-acquisition CS+ includes an enlarged population of cortical neurons that extends beyond those engaged by the pre-acquisition CS+ to neurons comprising the cortical representation of sensory stimuli similar to the CS+. This conditioning-induced neural overlap between the CS+ representation and its approximations increases the likelihood that post-acquisition exposure to stimuli similar to the CS+ will activate the CS+ representation, culminating in the neural and behavioral constituents of the fear response (i.e., fear generalization to the CS+ approximate).

As mentioned previously, the nucleus-basalis-mediated cholinergic influx into sensory cortex during aversive conditioning follows from fear-related amygdala excitation of the nucleus basalis (Kapp et al., 1992). Given findings of increased amygdala activity during fear-conditioning in clinical anxiety (Bremner et al., 2005), it logically follows that anxiety patients undergoing fear-conditioning may incur greater influx of acetylcholine into sensory cortex, increased neural overlap between the memorial representations of the CS+ and its approximations, and a heightened likelihood of activating the CS+ representation – and the associatively linked fear circuitry – upon exposure to stimuli resembling the CS+. Such a mechanism by which anxiety patients may develop overgeneralization of conditioned fear derives logically from animal findings but awaits empirical testing in human beings. We are currently pursuing this line of work with an fMRI version of our paradigm using retinotopic mapping annuli (rings) as CSs/GSs. Each CS/GS is represented by an annulus of distinct eccentricity (i.e., size) that provides a unique neural signature in the calcarine sulcus (Engel, Glover, & Wandell, 1997). Use of these retinotopic stimuli allows for assessment of the conditioning-induced overlap in calcarine representations of the CS+ and its approximations, as well as the contribution of this overlap toward generalization.

A second neural mechanism with promise for understanding the memorial contributions to conditioned generalization is the NMDA-dependent rise in intracellular Ca^{2+} in lateral amygdala neurons, thought essential for the formation of associative links between the CS and US (Rodrigues, Schafe, & LeDoux, 2004). Consistent with this idea, the partial NMDA agonist D-cycloserine (DCS) has been found to enhance acquisition (e.g., Monahan, Handelmann, Hood, & Cordi, 1989) and retention (e.g., Land & Riccio, 1999) of conditioned fear – a learning critically reliant on the CS-US connection. Such results support the potential efficacy of (partial) NMDA agonists, such as DCS, for reducing generalization of conditioned fear by strengthening the accuracy of the conditioning memory and thereby reducing the frequency of "generalization errors." This possibility receives support from animal findings demonstrating that DCS dose-dependently improves acquisition of conditioning and results in less generalization to stimuli resembling the CS+ (Thompson & Disterhoft, 1997). Such findings support the potential utility of DCS for reversing overgeneralization associated with clinical anxiety by increasing the strength and accuracy of the encoded conditioning memory – an effect apt for testing given the favorable neurotoxicity profile of DCS in human beings.

Concluding Thoughts

The long known connection between generalization of conditioned fear and anxiety pathology is only now becoming the focus of empirical testing. Such recent efforts have

provided a psychophysiologically validated, conditioned-generalization paradigm with which to interrogate the neural, pharmacologic, and genetic basis of this central, yet understudied conditioning marker of clinical anxiety. One promising area of interrogation, informed by conditioning findings in animals, is the way neural substrates of memory contribute to conditioned generalization. Because memory is the mechanism by which psychopathological consequences of aversive events are retained over time, it is not surprising that generalization – an associative consequence of aversive conditioning that retains post-conditioning fear-reactivity – derives in part from memorial processes.

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Dr. Shmuel Lissek

National Institute of Mental Health
Mood and Anxiety Disorders Program
15K North Drive
Bldg 15k
MSC 2670
Bethesda, MD 20892-2670
USA
Tel. +1 301 402 7219
Fax +1 301 402 6353
E-mail lisseks@intra.nimh.nih.gov