Fear Generalization and Anxiety: Behavioral and Neural Mechanisms

Joseph E. Dunsmoor and Rony Paz

ABSTRACT

Fear can be an adaptive emotion that helps defend against potential danger. Classical conditioning models elegantly describe how animals learn which stimuli in the environment signal danger, but understanding how this learning is generalized to other stimuli that resemble aspects of a learned threat remains a challenge. Critically, the overgeneralization of fear to harmless stimuli or situations is a burden to daily life and characteristic of posttraumatic stress disorder and other anxiety disorders. Here, we review emerging evidence on behavioral and neural mechanisms of generalization of emotional learning with the goal of encouraging further research on generalization in anxiety disorders. We begin by placing research on fear generalization in a rich historical context of stimulus generalization dating back to Pavlov, which lays the foundation for theoretical and experimental approaches used today. We then transition to contemporary behavioral and neurobiological research on generalization of emotional learning in humans and nonhuman animals and discuss the factors that promote generalization on the one hand from discrimination on the other hand.

Keywords: Amygdala, Anxiety, Aversive-conditioning, Discrimination, Fear, Similarity, Specificity

http://dx.doi.org/10.1016/j.biopsych.2015.04.010

Because natural stimuli rarely occur in the exact same form from one encounter to the next, the ability to generalize learning across stimuli and across situations is essential. It can be equally as important to discriminate between different stimuli and events and therefore limit generalization (specificity) to avoid inappropriate behavioral responses. Generalization and specificity therefore help ensure survival in an ever-changing environment by applying learning only when appropriate: not too much or too little. This delicate balance between generalization and specificity is a crucial factor of any animal that has to learn from examples and a hallmark of primate evolution. How humans and other species achieve this balance has been an overriding concern in psychological science for nearly a century (1,2), as well as in machine learning (3). One domain of learning and behavior where this balance is especially important is fear learning, wherein stimuli that predict an aversive event acquire the capacity to elicit defensive responses. In such scenarios, other stimuli that are not involved in the initial learning process and that resemble the original conditioned stimulus to a mild degree might also elicit a defensive response. This phenomenon is referred to as stimulus generalization or, more specifically, fear generalization. Here, when the stimulus predicts aversive outcomes, it makes sense to have a wider generalization and respond to stimuli that are even less similar to the original one. This is because a miss—incorrectly identifying the dangerous stimulus as a safe one—is more costly than a false alarm—incorrectly identifying a safe stimulus as the conditioned one (4–6). Simply put, better safe than sorry.

Although generalization of emotional and especially fear learning is an adaptive process from a survival- or fitness-related perspective, broad generalization can present a burden to daily life. This overgeneralization can occur in the form of wide generalization for harmless stimuli that bear a vague similarity or prior association with a learned threat, as in anxiety disorder categories, or in people suffering from trauma and stressor-related disorders (i.e., posttraumatic stress disorder [PTSD]) (7–9).

In this review, we discuss emerging research on generalization of emotional learning with a focus on fear generalization. We provide a brief historical account of stimulus generalization research from animal learning models and discuss how the principles of classical conditioning and stimulus generalization have been successfully applied to better understand and investigate disorders of fear and anxiety in humans. These principles frame contemporary empirical research on fear generalization in humans. We then review behavioral and neurobiological research on fear generalization in humans and nonhuman animals and discuss factors that mediate generalization on the one hand from discrimination on the other hand. Rather than focus on the differences in methodologies and paradigms of extant fear generalization research (e.g., the nature of the conditioned and unconditioned stimuli and dependent measures of conditioning), the purpose of this review is to provide a conceptual overview of fear generalization studies to understand the clinical implications of this research [but see (10)].

STIMULUS GENERALIZATION

Classical conditioning techniques have proved to be a highly effective tool to investigate generalization of learning across

Biological Psychiatry September 1, 2015; 78:336–343 www.sobp.org/journal ISSN: 0006-3223

species. The earliest demonstrations from Pavlov's laboratory revealed generalization of conditioned learning using sensory stimuli that approximated a conditioned stimulus (CS) (e.g., a tone of a 1000 Hz) paired with an unconditioned stimulus (US) (e.g., food). In these experiments, it was observed that the conditioned response (CR) (e.g., salivation) was not specific to the CS and could be evoked by other stimuli that were never directly paired with food, such as tones of different frequencies. Intriguingly, CRs plotted as a function of the stimulus along a sensory continuum (e.g., different stimulus frequencies) revealed a decremented gradient that peaked at the CS and diminished as similarity between the CS and the unreinforced stimuli decreased (1). The factors that shape stimulus generalization gradients became a predominant concern in conditioning research and was the topic of much theoretical debate throughout the 20th century (2,11–13).

In the mid 20th century, investigations of generalization gradients turned to operant (or instrumental) techniques. In a landmark study by Guttman and Kalish (14), pigeons trained to peck to a specific color for food showed decremented gradients of pecking responses that peaked at the CS and decreased in an orderly fashion to unreinforced test stimuli along the color spectrum. Importantly, pigeons possess the vision necessary to discriminate between colors, which allowed Guttman and Kalish (14) to address a theoretical concern of whether generalization is merely a failure in perceptual discrimination (11). Pigeons exhibited orderly bell-shaped generalization gradients that tracked the underlying wavelength dimension and did not abruptly drop off at perceptual color boundaries, thus convincingly demonstrating that stimulus generalization is not simply a perceptual discrimination failure. In other words, generalization can be an active process in which behavior is expressed despite the capacity to detect perceptual differences from what was learned (15).

Contemporary research on fear conditioning and generalization in humans focuses predominately on sympathetic autonomic arousal, as measured by increases in the skin conductance response (SCR), or potentiation of the startle eyeblink response during periods of anticipatory anxiety (fear-potentiated startle [FPS]). In this way, fear generalization can be operationally defined as the extent to which the CR, initially elicited by the CS, is also elicited by other stimuli that have not before predicted the US. Thus, generalization occurs as a result of original learning and is subject to factors that influence associative learning processes. Fear generalization as described in this review can therefore be distinguished from nonassociative effects, such as sensitization or habituation (16). Fear generalization tests are valuable for quantifying the effect of different experimental manipulations and between-group differences (e.g., people with anxiety versus healthy control subjects) to assess the breadth of fear responses following discriminative fear conditioning.

FEAR LEARNING AND GENERALIZATION IN ANXIETY DISORDERS

Classical fear conditioning has proved an exceptional model to conceptualize the etiology and maintenance of pathological anxiety and is a useful experimental tool for investigating abnormal emotional learning and regulation in anxiety disorders. The earliest laboratory studies of fear conditioning showed that learned fear responses [e.g., Little Albert's fear of rats (17)] provide an analog to behavioral reactions stemming from real-world emotional experiences. The monumental shift away from stimulus-response models toward cognitive-oriented models of conditioning in the late 20th century has benefited our understanding of fear disorders even further (18). For example, contemporary learning models account for the fact that, through language and observation, fears can be acquired to stimuli that have never been paired with an aversive outcome [i.e., vicarious conditioning (19)]. Applying cognitive processes to fear conditioning adds flexibility to models of stimulus generalization as well. For instance, higher order associative learning processes like acquired equivalence (20), sensory preconditioning (21), second-order conditioning (22), and category-based induction (23) can lead to the transfer of fear behaviors despite minimal or no physical similarity between cues (24).

Overgeneralization of fear behaviors is common in many mental health disorders, including specific phobia, obsessive-compulsive disorder, panic disorder, generalized anxiety disorder, and PTSD (10). For example, a person with a fear of spiders may react defensively to all crawling bugs (phobias), the presence of various contamination cues can trigger anxiety (obsessive-compulsive disorder), a panic attack in an elevator leads to fear of having a panic attack in other enclosed spaces (panic disorder), reminders of death cause excessive worrying about one's own health and safety (generalized anxiety disorder [GAD]), or myriad cues related to a trauma trigger an intense physiological response (PTSD). Clinical fears and anxieties also generalize readily across contexts (25). For example, a fear of spiders is not confined to a location where spiders have been encountered but extends to contexts where spiders might be encountered (e.g., forests).

Fear conditioning in the anxiety disorders is often characterized by similarly high levels of autonomic arousal to a CS paired with the US (referred to as CS+) as an unpaired safety signal (referred to as CS−), indicating a failure in discrimination or overgeneralization (26,27). Recent investigations have adopted the stimulus generalization test approach, which involves initial discrimination learning between the CS+ and CS− followed by a formal test of generalization to unreinforced stimuli that vary parametrically in physical properties from the CS+. For example, Lissek *et al.* (28) developed a task using a perceptual dimension of increasing ring size to characterize broad generalization gradients of FPS in panic disorder (29) and GAD (30) relative to healthy control subjects. Initially, subjects learned to discriminate between a CS+ and CS− at distal ends of a size continuum (the largest or smallest ring, counterbalanced), followed by a generalization test including the CS+, CS−, and unpaired test stimuli of intermediate sizes. Healthy subjects showed a steep response slope of FPS with the greatest response to the CS+, some amount of generalization to the ring that most closely approximated the CS+ in size, and a drop in responses to other rings that were dissimilar to the CS+ (or, correspondingly, more similar to the CS−). In contrast, anxiety patients showed a shallow response slope, with strong responses to both the CS+ and other unreinforced stimuli that were clearly dissimilar from the CS+.