Review

Biological Psychiatry

Fear Generalization and Anxiety: Behavioral and Neural Mechanisms

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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

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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

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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+.

However, overgeneralization was not identified in a study of noncomorbid GAD patients, as assessed by gradients of FPS or shock expectancy (31); in a study of women with GAD, as assessed by gradients of pupillary responses and shock expectancy (32); or in a sample of high trait anxious undergraduates as assessed by gradients of SCR, FPS, and shock expectancy (33). The inconsistency in findings in patients may be due to whether GAD was comorbid with depression or other anxieties (31). Highlighting these inconsistencies is important before drawing strong conclusions regarding whether overgeneralization is a pathogenic marker of clinical anxiety. Critically, to date, studies of fear generalization in clinical populations are limited overall. In particular, although it is assumed that patients with PTSD would exhibit broad generalization gradients based on the symptom profile (34), systematic studies of fear generalization in PTSD are extremely limited (16).

Historically, stimulus generalization has been regarded to some extent as a byproduct of conditioned learning (2), the degree of which may be determined by the strength of the US (35). In this way, some amount of generalization is expected following a strong learning experience and is unlikely to be diagnostic of clinical anxiety. However, broad overgeneralization can be maladaptive, especially in the domain of defensive learning where overreacting to harmless stimuli that only vaguely resemble a learned threat can interfere with daily life. Laboratory demonstrations of behavioral generalization in different anxiety disorders lend some support to the idea that overgeneralization could be a pathogenic marker that cuts across anxiety disorder categories (30). Overgeneralization may also maintain pathologic behaviors by contributing to avoidance of cues or situations that are indirectly associated with a feared outcome, thus bypassing the chance to experience safety and disconfirm negative expectations (36).

The idea that overgeneralization is a pathogenic marker of clinical anxiety complements the emerging consensus that failures in extinction learning, and especially failures in extinction retention, are phenotypic of different anxiety disorder categories (37). This is especially important in light of the increasing focus on objective behavioral and neurobiological transdiagnostic measures in mental health research, which has culminated in the National Institute of Mental Health Research Domain Criteria initiative (38). In this framework, overgeneralization could provide a novel marker for dysregulated emotional circuitry and may be a target for interventions.

Finally, it is important to consider that, in the Pavlovian tradition, generalization is typically quantified as fear expression to simple cues that approximate a learned threat along a unimodal dimension, like shapes, colors, or tones. However, real world situations rarely involve simple unimodal stimuli and instead involve complex objects and situations that can be represented across a variety of dimensions. It therefore remains a theoretical and empirical challenge to target generalization that involves objects or situations that are only tangentially related to a known source of fear or trauma. One approach to capture the complexity of human fear generalization is to incorporate theoretical knowledge from other psychological disciplines that examine generalization of human knowledge, including Bayesian models of inferential reasoning, categorization, and the organization of conceptual knowledge (24).

PERCEPTUAL MECHANISMS AND SIMILARITY

Perceptual similarity is the most accessible factor to investigate in stimulus generalization research, as the degree of similarity can be quantified as distance between points along a continuum. This largely explains why most studies test generalization along simple sensory dimensions and why this approach has been adapted to most fear generalization studies in humans. Thus far, fear generalization has been tested between stimuli that vary in color (39), size (28), shape (40,41), facial identity (42–44), emotional expression (45), or tone pitch (6,46–49). The benefit of testing along a perceptual continuum is that it allows for a quantification of responses as a function of the distance between points along a psychophysical space, whether the space is a physical measure of stimulus difference (e.g., increments along a spectral range) or an invariant psychological space mapped for each individual subject (15). See Supplement 1 for a description of additional factors, beyond perceptual similarity, that influence fear generalization.

Continuous sensory dimensions also afford the chance to test effects of fear conditioning on perceptual thresholds for difficult to distinguish stimuli before and after learning. Although Guttman and Kalish (14) showed that generalization can be more than failure to perceptually discriminate, it is possible that emotional experiences induce plasticity that prevents future discrimination between highly similar stimuli. From a survival perspective, a loss of fine discrimination of a learned threat could promote fast defensive reactions to related stimuli that may portend the same danger.

Recently, this hypothesis was tested in humans, showing that auditory fear conditioning impairs the ability to finely discriminate tones that are near the CS+ frequency (47,48) (Figure 1). This finding accords with studies in rodents showing enhanced representational coding (tonotopic reorganization) for the CS+ frequency in auditory cortex (A1) after fear conditioning (50). Fear conditioning can also have effects on classification of stimuli that span categorical boundaries, leading ambiguous colors to be labeled as more clearly opposite the color of an unreinforced CS− color (39) and faces morphed between neutral and fearful expressions to be labeled as fearful with greater frequency after conditioning (51). It remains to be demonstrated that early perceptual mechanisms play a direct role in anxiety disorders (6,47,48) and whether the amygdala itself underlies the generalized responses and/or interactions between the amygdala and cortical regions (52–54).

NEUROBEHAVIORAL MECHANISMS OF FEAR LEARNING AND GENERALIZATION

Neural models derived from nonhuman animals (55,56) and extended to humans using functional magnetic resonance imaging (fMRI) (57) provide a developing picture of how classical fear conditioning is acquired, expressed, generalized, extinguished, and recovered following extinction. Neuroanatomical models of fear conditioning continue to evolve and have been covered in a number of detailed reviews (55,58,59). To briefly summarize, these models center on the role of the amygdala as a site of CS–US convergence and initiation of the

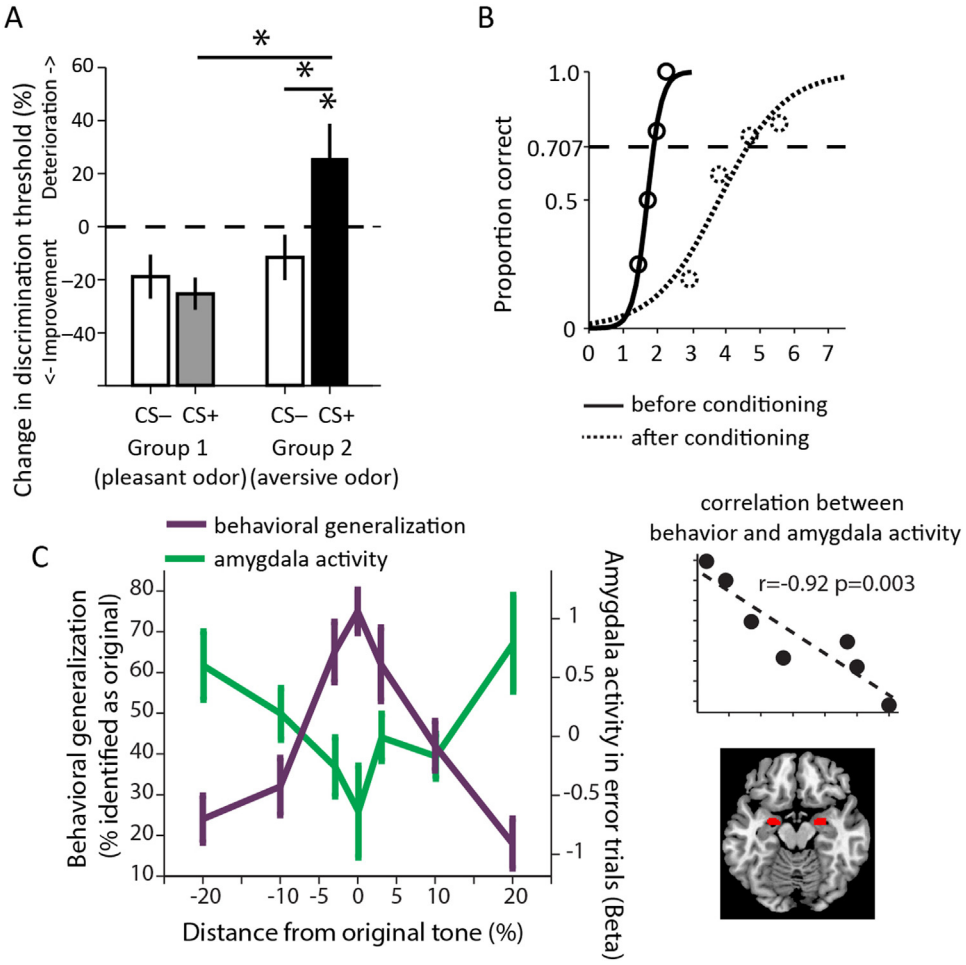

Figure 1. Aversive conditioning alters perceptual thresholds to induce overgeneralization. **(A)** Conditioning using a tone paired with an aversive outcome affects auditory discrimination thresholds in humans (47). Group 1 underwent conditioning with a tone (CS+) paired with a pleasant odor, whereas group 2 underwent conditioning with a tone paired with an aversive odor. Another tone was unpaired with odor (CS−) to serve as a within-subjects control. The ability to discriminate tone frequencies around the CS+ tone deteriorated in group 2 (aversive conditioning), whereas discrimination thresholds improved for all other tones. **(B)** Psychometric curves from a representative subject from group 2 shows stimulus discrimination (proportion of correct answers) as a function of frequency difference (Δf/f%, where f is the CS+ frequency) before (solid line) and after (dashed line) aversive conditioning. **(C)** Monetary loss associated with a specific tone increases perceptual auditory thresholds in humans (48). Changes in perceptual thresholds affected future decisions involving tones that varied in pitch from the original tone; subjects incorrectly identified other tones as the original loss-conditioned tone, incurring a monetary loss for each incorrect response. Behavioral generalization (incorrectly identifying a tone as the original loss-conditioned tone), shown here as the purple line, correlated with activity in the amygdala, shown here as the green line. The top right panel shows the correlation between these two lines, and the bottom right panel shows the amygdala anatomical region of interest. *$p < .01$.

threat-elicited conditioned response. The medial prefrontal cortex is implicated broadly in the inhibition or regulation of the CR (60), and the hippocampus plays a critical role in the modulation of fear expression (61). Regions in the hippocampal complex are also important for pattern separation, as described below, which is relevant for discriminating between present experiences and memories of threat.

Neurophysiological research on how fear is generalized has received far less attention, but research in this domain is gaining interest. Early neurophysiological studies in cats showed that ablation of the auditory cortex before conditioning resulted in broad stimulus generalization to acoustic stimuli but left frequency discrimination intact (62). In a similar way, lesions to the occipital and inferotemporal cortex in monkeys also led to broad stimulus generalization across dimensions of visual stimuli, while leaving most perceptual capacities intact (63). These early findings were important for distinguishing between generalization and discrimination processes, as they revealed that ablation to particular loci resulted in broad behavioral generalization but did not grossly interfere with the ability to perceptually discriminate between sensory stimuli.

Today, most neurobiological studies of fear generalization center on the role of the amygdala in rodents and employ acoustic stimuli. Although A1 lesions do not abolish fear conditioning to tone CSs (64), it has been argued that the cortical pathway to the amygdala is important for discriminating between auditory stimuli (50). Receptive fields of neurons in auditory cortex show sharp tuning curves, whereas neurons in the auditory thalamus are broadly tuned to respond to a wide range of frequencies (65). Exogenous increases in the transcription factor cyclic adenosine monophosphate response element-binding protein in the auditory thalamus increase generalization to other tones (66), consistent with findings that broadly tuned neurons in the auditory thalamus become more receptive to other tones following fear conditioning (67). However, Armony *et al.* (68) showed that lesions to the auditory cortex did not result in auditory fear overgeneralization, suggesting that the pathway between the auditory thalamus and the amygdala is sufficient to discriminate between simple auditory stimuli. On the other hand, lesions to the auditory cortex can reverse overgeneralization following fear conditioning (69), and circuits within the auditory cortex participate in discriminatory fear conditioning (70).

The precise role of the amygdala in fear generalization is an evolving picture. For example, it was shown that a delicate balance within subregions of the central nucleus (CE) of the amygdala regulates fear generalization (71): neuronal activations in the medial subdivision of the CE (the primary output pathway for initiating fear behaviors) are tonically inhibited by the lateral subdivision of the CE, and changes in tonic activity can tip the balance from expression of fear to the CS+ only to generalization and expression of fear to the CS− as well. This adds to previous findings showing a role for other subnuclei of the amygdala (72), as well as the closely associated bed nucleus of the stria terminalis (73), in fear generalization. A recent study has implicated the lateral nucleus (LA) as well, demonstrating that transitions in the response of LA neurons tilt the balance of activity toward a greater proportion of generalizing neurons (i.e., neurons that respond to both CS+ and CS−) over cue-specific neurons (74).

Studies by Weinberger (50) have shown evidence of plasticity in A1 following auditory fear conditioning, leading to retuning of A1 neurons toward the CS+ frequency, gradients of neural firing that peak at the CS+ frequency, and enhanced areas of representation for the CS+ frequency. Fear conditioning induced plasticity in A1 occurs through cholinergic projections from the nucleus basalis, and pairing a tone with nucleus basalis stimulation alone results in representational plasticity in A1. Interestingly, nucleus basalis stimulation results in behavioral generalization gradients, providing evidence that the cholinergic system may be involved in fear generalization to cues that physically approximate the CS+ (75).

It is worth considering that many recent neurophysiological investigations define generalization as defensive behaviors to an unpaired CS−, while formal tests using graded sensory stimuli are rarely conducted (but see studies of receptive field analysis by Weinberger *et al.* (50)). Recent studies have begun to address this point (6,47), showing that the amygdala underlies the graded response (the generalization curve) (48) (Figure 1). A recent study identified precise changes in the architecture of the primate amygdala tuning curves that might explain broad behavioral generalization (76). Nevertheless, more studies are required to understand the roles of tonic activity and changes in tuning curves in the final shape of behavioral generalization.

Studies of fear generalization across contexts focus on the role of the hippocampus. The hippocampus is implicated in forming contextual representations (77,78), and connections between the hippocampus and the LA are important for associating a CS with a particular context and for learning to fear the context itself. While lesions to the amygdala impair or abolish fear conditioning altogether, lesions to the hippocampus impair context conditioning selectively (79). The hippocampus may be important for generalization that involves events encoded as complex multimodal representations. This enables fear to generalize across different situations or settings that activate the memory of the original context and event, despite possible variations in perceptual features or discrete elements from one context to the next (61). Notably, context conditioning generalizes to different environments, though the amount of generalization may be a function of similarity to the original context, familiarity with the generalization context, or time elapsed since initial learning (80–82).

The hippocampal complex may also play a role in discriminating threat from safety through pattern separation processes. The dentate gyrus, a region in the hippocampal complex, is important for creating new memory representations to minimize the overlap between previous memories (83). Pattern separation is considered a hallmark of episodic memory that allows us to differentiate among numerous experiences that overlap in detail. This ability allows us to separate similar events from different days, for example, remembering where we parked our car at work today versus yesterday. Kheirbek *et al.* (84) proposed that dysfunction in the dentate gyrus could be a contributing factor to the inability to discriminate threat from safety in PTSD. This pattern-separation deficit model of PTSD suggests that partial information related to a traumatic experience would be sufficient to initiate the entire memory of the event, leading to a failure to discriminate between the present experience and the emotional experience that may share overlapping details. Importantly, the hippocampal complex is part of key neurocircuitry consistently implicated as being impaired in PTSD (7). As suggested by Kheirbek *et al.* (84), the dentate gyrus provides a clear target for intervention in PTSD; by increasing neurogenesis in the dentate gyrus, pattern separation processes may be rescued, increasing the ability for PTSD patients to discriminate between a harmless present situation and the memory of a traumatic experience. Interestingly, increased pattern separation may be one way in which antidepressants affect anxiety, as some antidepressants have been shown to increase neurogenesis in the rat dentate gyrus (85).

HUMAN NEUROIMAGING OF FEAR GENERALIZATION

Human neuroimaging research on fear generalization is only now starting to gather attention, but an early picture is beginning to develop that implicates the neurocircuitry involved at initial learning as supporting fear generalization (Figure 2). For instance, Dunsmoor *et al.* (86) first identified a number of regions involved in fear acquisition, including the insula, thalamus, cingulate cortex, and striatum, and then probed activity in these regions in a subsequent generalization test. Each region showed a profile of generalization to cues that resembled a learned threat but were of greater emotional intensity than the CS+ itself. Activity in the amygdala was correlated with the behavioral expression of fear generalization, as indexed by SCR. In contrast, activity in the ventromedial prefrontal cortex (vmPFC)—a region traditionally implicated in regulating fear expression—showed increased activity to a face that more closely resembled the CS−. A similar pattern of results was also identified by Lissek *et al.* (87) using a neutral sensory dimension of increasing ring sizes, as described above. They found decreasing gradients of fMRI activity in the insula and dorsomedial prefrontal cortex, with the greatest response to the CS+ and decreasing activity as a function of similarity to the CS+. In addition, they reported a reverse gradient in the vmPFC and hippocampus, with the greatest response to the learned safety cue, CS−, and decreasing activity as similarity to the CS− diminished.

Clinical translational neuroimaging has started to identify regions implicated in fear generalization in anxiety disorders. Greenberg *et al.* (32) found that healthy women showed

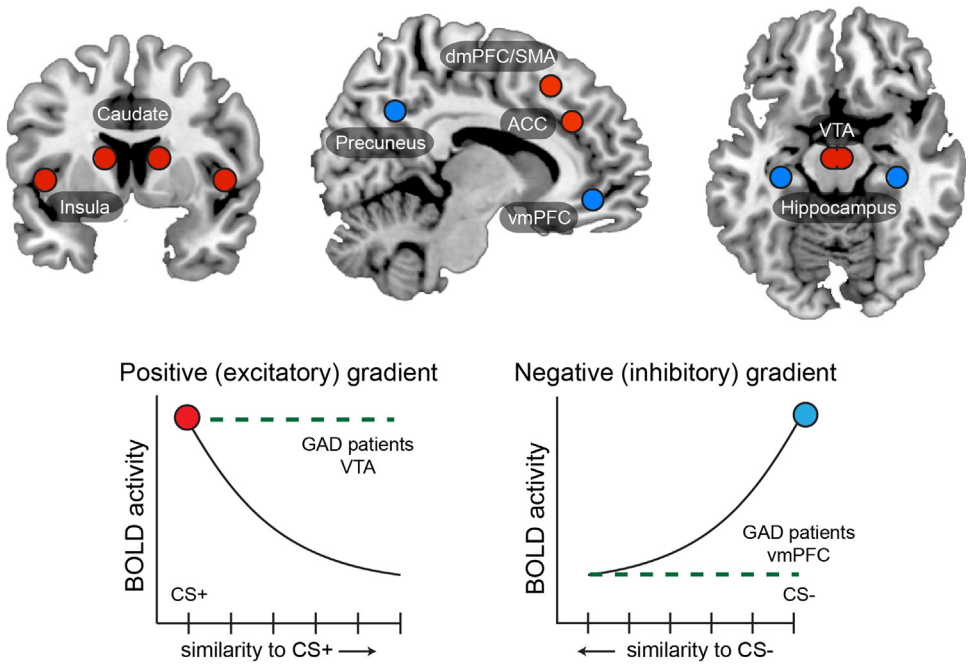

Figure 2. Functional magnetic resonance imaging of fear generalization gradients. Extant neuroimaging studies exploring fear generalization in healthy adults have reported gradients of blood oxygen level-dependent (BOLD) activity in regions traditionally implicated in differential fear conditioning between paired (CS+) and control (CS−) stimuli (86,87,90). Studies have so far revealed positive gradients that peak at or near the CS+ and negative gradients that peak at or near the CS−. Activity declines as perceptual similarity to the CS+ and CS−, respectively, diminishes (black line). Patients with generalized anxiety disorder (GAD) (green dashed line) have shown flat gradients of BOLD activity in the ventral tegmental area (VTA) (89) and ventromedial prefrontal cortex (vmPFC) (32,88). Functional magnetic resonance imaging studies have so far examined generalization using gradients of morphed faces, size, and shape. ACC, anterior cingulate cortex; dmPFC, dorsomedial prefrontal cortex; SMA, supplementary motor area.

enhanced activity in the vmPFC to generalized stimuli that were dissimilar from the learned threat CS+ (a reverse gradient), while GAD patients showed a flat response slope across the dimension. As the vmPFC is generally implicated in the control of conditioned fear, this failure to recruit the vmPFC by safe stimuli may be associated with deficiencies in fear generalization [see also (88)]. In line with prior fMRI studies in healthy adults, Greenberg *et al.* (32) identified excitatory gradients of fMRI activity in the insula, cingulate, and caudate that peaked at the CS+ and diminished as a function of perceptual similarity, though these excitatory gradients were not different between GAD and control subjects in these regions. A flat excitatory gradient of fMRI activity was observed in midbrain regions corresponding to the ventral tegmental area in women with GAD, suggesting that the mesocorticolimbic dopaminergic system may contribute to overgeneralization in anxiety (89).

CONCLUSIONS AND FUTURE DIRECTIONS

After nearly a century of research on classical conditioning, this basic paradigm continues to afford critical insight into the nature of learning and memory across species. As attention returns to models of stimulus generalization to examine fear conditioning, there is exciting potential for new insights that will shed new light on disorders of fear and anxiety characterized by broad generalization and failure to discriminate threat from safety. More research is needed to understand the neural mechanisms associated with fear generalization in humans and other species. Progresses in neuroimaging, cellular and molecular approaches, and pharmacologic manipulations that have advanced our neurophysiological understanding of fear learning and memory should be applied to investigate generalization processes directly. Such techniques will provide detail into the neural circuits contributing to overgeneralization and could reveal targets for pharmacologic intervention. Future research should also work toward establishing innovative and effective behavioral techniques to promote the generalization of extinction in primates, as these advances will inform translational models for the treatment of clinical disorders marked by excessive fear and anxiety.

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