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Perspective

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Understanding clinical fear and anxiety through the lens of human fear conditioning

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Abstract

Fear is an adaptive emotion that mobilizes defensive resources upon confrontation with danger. However, fear becomes maladaptive and can give rise to the development of clinical anxiety when it exceeds the degree of threat, generalizes broadly across stimuli and contexts, persists after the danger is gone or promotes excessive avoidance behaviour. Pavlovian fear conditioning has been the prime research instrument that has led to substantial progress in understanding the multi-faceted psychological and neurobiological mechanisms of fear in past decades. In this Perspective, we suggest that fruitful use of Pavlovian fear conditioning as a laboratory model of clinical anxiety requires moving beyond the study of fear acquisition to associated fear conditioning phenomena: fear extinction, generalization of conditioned fear and fearful avoidance. Understanding individual differences in each of these phenomena, not only in isolation but also in how they interact, will further strengthen the external validity of the fear conditioning model as a tool with which to study maladaptive fear as it manifests in clinical anxiety.

Sections

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Introduction

Following the experience of a serious car crash at an intersection last month, an individual might feel apprehensive in traffic, get sweaty palms and a racing heart as soon as they even think of getting behind the wheel, and exhibit extra caution when approaching an intersection. This is fear and anxiety in action, mobilizing an evolutionarily conserved defensive machinery to prepare for the possible occurrence (or reoccurrence) of danger.

Fear and anxiety are closely related, phylogenetically adaptive emotions, experienced in response to a near and imminent threat or a more distant and future threat, respectively[1,2]. They are characterized by activity in a number of loosely correlated response systems[3–5] that include subjective phenomenological experience (a feeling of dread or apprehension), overt behaviour (aimed at increasing the physical or psychological distance to the threat or decreasing its impending impact, through immobilization or active escape or avoidance) and peripheral and central nervous activation (physiological arousal and muscle tension). Collectively, this activity prepares an individual to cope with threat in a way that is adapted to its perceived imminence[6,7].

However, the same systemic defensive activation that is adaptive and sometimes critical for survival is also centrally implicated in clinical conditions such as anxiety, post-traumatic stress disorder (PTSD) and obsessive–compulsive disorder[3,8]. In these cases, the activation is typically more sustained and out of proportion to the actual threat, which gives rise to chronic feelings of apprehension, pervasive avoidance behaviour that interferes with day-to-day functioning, and tonic physiological arousal that leads to accumulated biological wear and tear (allostatic load). Given the enormous individual and societal burden imposed by those conditions[9–11], a clear insight into the mechanisms that govern acute and chronic defensive activation is important for developing targeted and successful interventions[12].

Pavlovian fear conditioning has been a prime translational instrument for understanding the multi-faceted psychological and neurobiological mechanisms of fear and anxiety[13,14]. In Pavlovian fear conditioning[15] (Fig. 1), presentation of an initially neutral stimulus such as a geometric figure or a tone (conditioned stimulus) is followed by an intrinsically aversive or painful stimulus such as electrical stimulation (unconditioned stimulus). With sufficient repetitions of this pairing, the formerly neutral stimulus starts eliciting responses that can be linked to fear (conditioned fear responses). These responses include: high self-reported anxiety, tension or threat-expectancy; enhanced skin conductance responses (which reflect activity of the sympathetic nervous system and are linked to the defensive fight-or-flight reaction); and attempts to escape from or freeze in response to the stimulus[15,16].

Over the past two decades, Pavlovian fear conditioning research has produced a wealth of insight into general mechanisms and principles of threat learning and emotional memory formation and maintenance[17–19]. Pavlovian fear conditioning has also gained considerable popularity in translational research[20,21], owing to a number of unique strengths of the Pavlovian fear conditioning paradigm. First, because the experimental procedure has been thoroughly studied, it can be used to examine the mechanisms of behavioural plasticity that promote and counter fearful responding with a level of precision and control that cannot readily be achieved when studying real-life fears and anxieties. Second, Pavlovian fear conditioning builds on a rich empirical, methodological and theoretical tradition established by over a century of associative learning research, yielding a strong conceptual backbone[14]. Third, Pavlovian fear conditioning paradigms can be applied in highly similar ways across

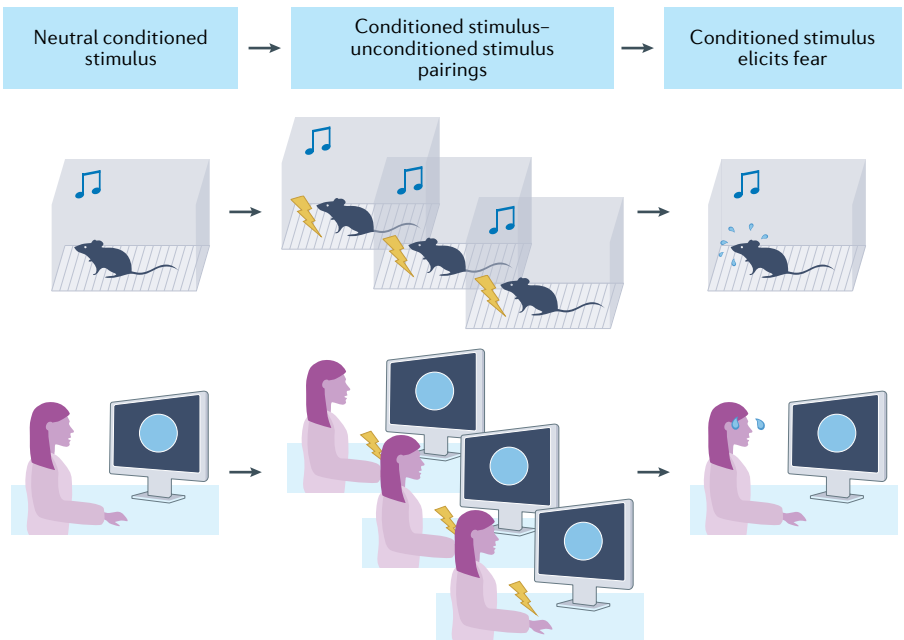

Fig. 1 | Pavlovian fear conditioning. In a Pavlovian fear conditioning procedure, an initially neutral conditioned stimulus (for example, a tone or a coloured circle presented on a computer screen) is paired with an inherently aversive stimulus (for example, electrical stimulation). After repeated pairings, the conditioned stimulus will come to elicit defensive responses even in the absence of the unconditioned stimulus. In rodents, this response is typically measured through freezing, suppression of lever-pressing or startle potentiation. In human fear conditioning, trials on which a conditioned stimulus (threat cue) is paired with the aversive unconditioned stimulus are typically interleaved with trials where a different conditioned stimulus (safety cue) is never followed by the unconditioned stimulus. Typical measurements in humans include skin conductance, startle potentiation, verbal reports and behavioural responses.

species (such as rodents and humans; see Fig. 1) and groups (such as healthy individuals and people diagnosed with anxiety-related disorders)[20]. Thus, researchers can compare and cross-validate psychological and biological mechanisms that govern the acquisition of conditioned fear responses between model organisms and evaluate how aspects of fear learning might differ between anxious and non-anxious individuals. Finally, Pavlovian fear conditioning protocols can be used to measure a range of behavioural, physiological and, in humans, experiential dimensions of fear (such as freezing, startle potentiation and verbal ratings, respectively).

In this Perspective, we first review the evidence that supports the use of Pavlovian fear conditioning as a laboratory model for clinical anxiety by considering the criteria of its construct, face and predictive validity. Next, we weigh the evidence for diagnostic and prospective validity from research on individual differences in fear conditioning. We then identify three aspects of Pavlovian fear conditioning beyond fear acquisition that might be particularly suited to capturing clinically relevant individual differences: extinction, generalization and avoidance. Building on the existing literature, we go on to discuss how future research on interactions between processes of extinction, generalization and avoidance and individual differences therein can bolster further insight into the role of Pavlovian fear learning processes in clinical anxiety.

Throughout the article we refer to conditioned fear responses. We use the term 'fear' not only to denote the conscious conceptualization of one's own state as 'being afraid', but also to cover all subjective, physiological and behavioural responses to impending danger. Although a distinction is sometimes made between 'fear' and 'threat' to contrast conscious and non-conscious responses to danger[22], here we use 'fear' as a shorthand for the broad collection of reactions that together constitute the emotional episode of fear[23].

Fear conditioning and clinical anxiety

Associative learning allows humans and non-human animals to identify signals of threat in their environment and mobilize defensive resources for survival[13]. After a car crash, associating the specific intersection where the crash happened (conditioned stimulus) with the accident (unconditioned stimulus) enables appropriately cautious reactions when approaching a similar intersection again[24]. It is difficult to imagine how this could be achieved without an ability to associate threatening experiences with preceding cues[25]. Thus, associative learning is central to the dynamics of fear.

Associations are also central to maladaptive fears. Many individuals with clinical anxiety fear benign cues and situations (conditioned stimuli) because they are associated with threatening outcomes (unconditioned stimuli). For example, being bullied as a child can lead to an association between social situations (conditioned stimulus) and threat (unconditioned stimulus), and culminate in a diagnosis of social anxiety disorder during adulthood[25]. To be clear, not every individual suffering from an anxiety disorder recalls a relevant conditioning experience, and conversely, not every individual who experiences trauma goes on to develop PTSD[26,27]. There are clearly multiple pathways besides direct conditioning experiences by which associative learning can lead to clinical anxiety[28]. Other pathways include vicarious learning[29], in which associations are learned by viewing another person going through a traumatic experience (for example, a child watching another child being bullied), and verbal learning[30], in which associations are learned when information about potential danger is communicated (for example, a child hearing about another child being bullied).

That anxiety symptoms might result at least in part from associative learning processes, just like the acquisition of fear responses in Pavlovian conditioning[31], supports the use of Pavlovian fear conditioning to model maladaptive fear[32]. This satisfies the criterion of construct validity, which means that the theory behind the model is linked to the theory of the disorder, such that the model can be used to recreate the etiological conditions that lead to the disorder[33].

Pavlovian fear conditioning also passes several other criteria for external validity, that is, the extent to which the results of the model can be meaningfully applied to the disorder of interest[34]. The criterion of face validity refers to the similarity between behaviour in the model and symptoms of the disorder[35]. Pavlovian fear conditioning induces increased arousal (as measured through skin conductance or subjective self-report) and a motivation to avoid (as reflected in a facilitation of avoidance-compatible actions and an impediment of approach-compatible actions[36]). These conditioned responses mimic the high levels of fearful distress and avoidance that characterize anxiety disorders[37], thereby providing face validity. However, whereas Pavlovian fear conditioning research typically relies on physiological measures of arousal and behavioural measures of avoidance, clinical research and judgement of clinical status is often limited to self-report of distress or avoidance. This disconnect might somewhat obscure face validity.

Face validity might also be hampered to some extent by the typical use in Pavlovian fear conditioning of arbitrary conditioned stimuli like geometrical shapes rather than personally relevant stimuli like human faces or biologically prepared stimuli such as snakes or spiders. The latter might be more readily translatable to conditions like social anxiety disorder or phobia. Moreover, some research suggests that fear learning might develop differently for biologically prepared conditioned stimuli than for neutral conditioned stimuli (or differently for some evolutionarily prepared combinations of conditioned stimuli and unconditioned stimuli than for others)[38]. In particular, preparedness might give rise to a faster acquisition of conditioned fear, a lesser involvement of conscious contingency knowledge in the development of conditioned fear, and a higher persistence of conditioned fear in the face of disconfirmation[39–42]. However, the evidence is inconsistent and the notion of prepared fear learning has been contested[43,44].

The criterion of predictive validity is supported when interventions that attenuate the disorder also influence behaviour in the model[35]. Conditioned fear responses in the laboratory decrease acutely when participants are administered anxiolytics (benzodiazepines)[45], much as anxiety symptoms are acutely reduced by anxiolytics[46]. In addition, more sustained decreases in conditioned fear responses are observed following repeated exposure to the conditioned stimulus without the unconditioned stimulus (extinction)[47,48], in much the same way as exposure treatment leads to sustained reductions in anxiety symptoms[49]. These findings provide evidence for predictive validity.

In sum, although no single laboratory model will ever capture the complex phenomenology of clinical anxiety[50], Pavlovian fear conditioning meets criteria for construct validity, face validity and predictive validity.

Individual differences in fear conditioning

If Pavlovian fear conditioning taps into anxiety-relevant processes, as suggested by the evidence reviewed above, one should expect anxious participants to behave more fearfully than non-anxious participants in Pavlovian conditioning situations (that is, to develop a conditioned fear response more quickly or exhibit more intense conditioned fear responses), just as they do in real-life circumstances (diagnostic validity).

In the same vein, if Pavlovian fear conditioning picks up on associative learning processes that are involved in the development of clinical anxiety, one would expect that at-risk individuals would show different patterns of responding in a Pavlovian conditioning procedure than others would, and that this propensity to acquire conditioned fear would prospectively predict anxiety disorder later in life (prospective validity) (see Box 1 for a discussion of how acquisition of conditioned fear relates to individual traits that might put an individual at risk for the development of clinical anxiety). Below, we discuss how well evidence supports those assumptions.

Diagnostic validity

Regarding diagnostic validity, a meta-analysis of studies published before 2014 concluded that individuals diagnosed with an anxiety disorder typically acquire fear to a neutral cue paired with an unconditioned threat stimulus at a similar rate and to a similar extent to controls, and they also show stronger conditioned fear when responding to this conditioned threat cue than to a conditioned safety cue that is paired with the absence of the unconditioned threat stimulus[51]. This similarity in fear learning propensity between individuals with clinical anxiety and non-anxious controls might seem to contradict the diagnostic validity of the Pavlovian fear conditioning paradigm. However, the meta-analysis also indicated that the differential fear learning of individuals diagnosed with an anxiety disorder is less robust than that of controls. In particular, individuals with clinical anxiety show stronger fear responses to the conditioned safety cue in a differential fear conditioning procedure than do controls. These results suggest that, although present, differential learning of threat (versus safety) cues might be impaired in (some) individuals with an anxiety disorder, resulting in fear responding to cues for which such responding is not adaptive.

More recent research largely aligns with these findings and often reports comparable fear acquisition in individuals with an anxiety disorder and in control groups, as measured by skin conductance responses, startle potentiation, fear or arousal ratings, and/or ratings of shock expectancy in the presence of the threat cue[52–65]. Other studies confirmed that individuals with an anxiety disorder indeed exhibit differential acquisition of fear to threat and safety cues, but to a lesser

Box 1

Fear conditioning and anxiety-related traits

Differences in fear conditioning have been linked to individual traits and dispositions (such as trait anxiety, neuroticism or intolerance of uncertainty) that signal vulnerability to the development of anxiety disorders in the future[152]. In line with dimensional views of psychopathology, studying anxiety-relevant personality traits and dispositional factors in non-clinical populations can therefore be valuable for elucidating the role of Pavlovian fear conditioning in clinical anxiety in parallel with research in clinical samples[153,154].

Fear acquisition

Trait anxiety has been investigated most intensively in relation to Pavlovian fear conditioning compared with other traits and dispositional factors (for reviews and meta-analyses on relations between fear conditioning and personality traits including but not limited to trait anxiety, see refs. [118,152,155]). A substantial number of studies have reported no association between trait anxiety and fear acquisition measured by self-report ratings[135,156–172] and psychophysiological measures[159–165,167,170,173–178]. Other studies found that trait anxiety modulates fear acquisition. For example, high-trait-anxious individuals show faster acquisition of eyeblink conditioning[179], higher differential self-reported anxiety[157], higher fear ratings across conditioned stimulus types[180], or higher distress or fear ratings to conditioned safety cues[173,175] compared with those low in trait anxiety. High-trait-anxious individuals also show reduced contingency awareness during fear learning compared with low-trait-anxious individuals[175,181,182]. In line with this finding, some studies reported reduced differential skin conductance responses[169,183] and reduced differential startle responses[173,180] between conditioned threat and safety cues during fear learning in individuals with high trait anxiety compared with low-trait-anxious individuals. At the same time, high-trait-anxious individuals who were contingency-aware showed stronger startle responses to a threat context than low-trait-anxious individuals[157], and compared with low-trait-anxious women, high-trait-anxious women exhibited superior detection of the contingencies between conditioned threat stimuli and the unconditioned stimulus in a challenging conditioning procedure involving many different conditioned threat and safety cues[178]. In sum, the literature concerning the relationship between trait anxiety and fear acquisition is inconsistent and sometimes contradictory.

Extinction, generalization and avoidance

Meta-analyses have found that trait anxiety, intolerance of uncertainty and neuroticism are related to slower extinction[184] and overgeneralization[155] in non-clinical samples. However, the effects sometimes depend on the specific trait questionnaire and the type of fear reaction considered (for example, slowed extinction of skin conductance responses was found for individuals who scored high on intolerance of uncertainty but not trait anxiety[184]). No meta-analysis is available for avoidance, but several studies have found increased avoidance in individuals that score higher on trait anxiety[149], intolerance of uncertainty[185] or neuroticism[186]. Together, the available evidence suggests that impaired extinction, excessive avoidance and overgeneralization might not be unique to patients with anxiety but are also present in individuals with sub-clinical levels of anxiety, which is in line with the hypothesized role of these behaviours in the development of anxiety disorders. Future research should further test whether extinction, avoidance and generalization are stable traits (by examining test–retest reliability) and whether individual differences in these traits predict the development of anxiety disorders in at-risk individuals. Finally, mega-analyses that pool individual data across many studies are needed to pinpoint the exact contribution of distinct anxiety-related personality characteristics to the modulation of extinction, avoidance and generalization.

extent than do non-anxious control participants, owing to heightened fear responses to the safety cue in those with an anxiety disorder[66–69]. Despite the evidence confirming the results of the meta-analysis discussed above[51], a few studies found lower skin conductance responses to the threat cue in individuals with PTSD and obsessive–compulsive disorder than in controls[70,71]. Although those observations might be consistent with a deficit in differentiating threat from safety cues, they deviate from the conclusion of the meta-analysis that there are differences in differential responding but generally not in threat cue responding between individuals with and without anxiety disorder. Conversely, a meta-analysis of seven studies in youth with clinical anxiety suggested comparable differential fear acquisition to threat versus safety cues as in controls, but stronger verbal and physiological fear responses to both threat and safety cues[72], which indicates that both adaptive and non-adaptive fear responding might sometimes be amplified in individuals with an anxiety disorder.

In sum, the bulk of the evidence suggests that individuals with and without anxiety disorder mostly exhibit a similar propensity to acquire conditioned fear, but the ability to differentiate a conditioned threat cue from a stimulus that signals the absence of threat might be compromised in individuals with clinical anxiety. We note that this latter finding is somewhat incidental because a safety cue was originally included in human fear conditioning studies as a control stimulus to rule out non-associative explanations for conditioned fear responses. Consequently, smaller differences in fear acquisition between threat and safety cues might stem from a reduced propensity for safety learning or increased generalization of acquired fear from the threat cue to the safety cue.

Prospective validity

In contrast to the rather extensive literature comparing fear acquisition in individuals with and without anxiety disorder, the number of prospective studies (that is, studies examining whether the propensity to acquire conditioned fear predicts the development of anxiety symptoms) is limited.

Some studies have found positive evidence for prospective validity. For instance, in first-year university students, ratings of conditioned threat expectancy during fear acquisition predicted anxiety symptoms 6 months later[73]. However, other studies did not confirm the prospective value of fear acquisition differences. For example, ratings of conditioned threat expectancy in soldiers leaving for Afghanistan did not predict PTSD symptoms 3–4 months later[74]. Moreover, startle responses to conditioned threat and safety cues were not predictive of PTSD symptom development in 8–16-year-old children growing up in disadvantaged circumstances (although startle responding to conditioned threat cues was predictive of anxiety symptoms)[75], and differential skin conductance responding for conditioned threat versus safety cues did not predict the development of PTSD symptoms in the first 3 months following a hurricane in 4–7-year-old children[76].

A few studies found mixed results, such that some measurements of fear acquisition were predictive, whereas others were not. For instance, in firefighters, differential facial muscle responding as measured through corrugator electromyography was predictive of PTSD symptoms 2 years later, whereas skin conductance responses were not[77]. In police and firefighter trainees, there was a positive relationship between heart rate in response to the threat cue and psychophysiological reactivity to trauma-related imagery (but not PTSD symptoms) 1 year after a traumatic event, whereas corrugator electromyography and skin conductance responses had no predictive value[78]. Finally, a study in an undergraduate sample found a relationship between self-reported anxiety for the threat cue and COVID-19-related anxiety early in the COVID-19 pandemic, but no predictive value of anxiety for the safety cue, nor of shock expectancies for either threat or safety cues[79].

In sum, evidence for the prospective validity of fear acquisition is mixed. Some studies find no predictive value for acquisition responses, whereas others do. In yet other studies, one particular measure of fear acquisition is predictive, whereas others are not, with limited consistency across studies.

Beyond initial fear acquisition

The preceding section paints a mixed picture of the diagnostic and prospective validity of fear conditioning as a model of clinical anxiety. Perhaps it should not be surprising that Pavlovian fear acquisition is not optimally suited for detecting individual differences. After all, Pavlovian fear acquisition often constitutes a 'strong' situation[80] that by virtue of its lack of ambiguity exerts a strong normative influence on behaviour. In Pavlovian fear acquisition, a cue repeatedly and consistently precedes an aversive event and consequently unambiguously indicates threat. Indeed, this is what makes fear conditioning such a powerful tool with which to investigate the universal principles of associative learning. The conditioned stimulus is a reliable signal of a clear and present danger (the aversive unconditioned stimulus). Under these conditions it is entirely sensible to react fearfully to this signal. Meaningful individual differences might be overshadowed by this complete certainty of threat. More room for relevant individual differences is afforded by a so-called 'weak' situation, that is, a situation that owing to its ambiguity exerts less normative influence on behaviour, thereby increasing the variance in responding that originates from the characteristics of the individual[81,82]. This proposition also lines up with the observation that, to the extent that differences in fear acquisition are found between individuals with and without anxiety disorder, they are more often centred on differential responding to threat versus safety cues than on responding to the threat cue itself.

Returning to the car crash example, it is normal and even normative to experience stress in the aftermath of an accident, and to feel afraid the next time the intersection where the accident happened is approached. This is the strong situation. The situation becomes considerably more ambiguous when other intersections that might or might not resemble the intersection of the accident are encountered (are these dangerous too?), when one has gained new, safe experiences of the accident intersection (is it still dangerous?), or when one could take a long detour to avoid driving past the intersection altogether (to avoid or not to avoid?). Clinical case reports suggest that a propensity for fear to spread to situations that were not directly involved in threatening experiences[83], a tendency for fear to persist despite corrective experiences[84,85], and an excessive urge to avoid situations that elicit fear[86,87] are all part of the phenomenology of anxiety-related disorders. These three ambiguities are captured by the behavioural principles of generalization, extinction and avoidance (Table 1), and can be probed in the laboratory via extensions to the fear conditioning procedure (Fig. 2). These aspects of fear conditioning might have better diagnostic and prospective validity than fear acquisition because they represent situations that might be particularly prone to the expression of relevant individual differences and they mimic core characteristics of clinical anxiety (see Box 1 for a discussion of how these phenomena might be linked to anxiety-relevant traits and dispositions). Below, we discuss each of these aspects of fear conditioning and their relationship to anxiety disorders in clinical populations.

Table 1 | Fear conditioning phenomena in non-clinical individuals and clinical anxiety

	Observation in non-clinical individuals	Potential causal role in the development of anxiety disorders
Acquisition	The repeated pairing of a conditioned stimulus with an aversive event leads to the development of conditioned fear responses to the conditioned stimulus Intermixed presentations of a second conditioned stimulus that is never paired with the unconditioned stimulus lead to the development of differential responding between conditioned stimuli	Conditioned responses develop more readily or more strongly, meaning that signals for threat elicit more fear Responding does not strongly differentiate between conditioned stimuli that are paired with the presence versus absence of the unconditioned stimulus, implying a failure to learn safety signals
Extinction	Repeated presentations of the conditioned stimulus alone (that is, without the unconditioned stimulus) after fear conditioning result in a gradual reduction of conditioned fear responses	Conditioned responses remain high following repeated presentations of the conditioned stimulus alone (impaired extinction), leading to persistent fear and uncorrected expectations of aversive outcomes
Generalization	Stimuli that have a perceptual or symbolic similarity to the conditioned stimulus elicit conditioned fear responses despite never having been paired with the unconditioned stimulus themselves The magnitude of these responses decreases as generalization stimuli become less similar to the conditioned stimulus (generalization gradient)	The generalization gradient is broader, indicating that more stimuli induce fear responses. Consequently, the world is more fear-inducing This widespread nature of fear-inducing stimuli has debilitating consequences
Avoidance	Avoidance responses that prevent the occurrence of the unconditioned stimulus following the conditioned stimulus are performed if they are not associated with substantial costs	Avoidance is pervasive, even though it interferes with opportunities for rewarding experiences and valued life-goal activities This excessive avoidance prolongs anxiety by preventing new experiences that could indicate that feared situations are, in fact, safe

Extinction

One important characteristic of anxiety disorders is that they persist in the face of manifest safety. The unrealistic fears of individuals with an anxiety disorder need never come true; yet they seem unable to learn that their threat associations are unfounded and that the world is safer than expected[88]. This mechanistic deficit in safety learning is confirmed in extinction studies that add trials where the conditioned stimulus is presented alone after standard Pavlovian fear conditioning (Fig. 2a). The expectation that the conditioned stimulus signals danger should diminish when the conditioned stimulus is no longer followed by the unconditioned stimulus, and the conditioned fear response should decrease[89]. However, according to a meta-analysis[51], individuals diagnosed with an anxiety disorder display delayed and/or reduced fear extinction compared to non-anxious control participants. The results of subsequent studies are consistent with this conclusion[68,90]. However, other studies did not find such an extinction deficit[62,63].

Rather than evaluating the speed of extinction learning, other studies have looked at the retention of extinction learning over time, evaluating how well the diminished conditioned fear responding that results from fear extinction training is preserved on a delayed test. In a typical procedure, Pavlovian fear acquisition and subsequent extinction training might occur on the same or consecutive days; an extinction retention test during which the conditioned stimulus is repeatedly presented again would then be performed one or several days later. Studies of the retention of extinction learning over time yield a pattern similar to that provided by studies on initial extinction learning: some studies find impaired extinction retention in individuals with anxiety-related disorders[56,60,91,92], whereas other studies failed to observe behavioural evidence for extinction retention impairments in individuals with clinical anxiety[57,59,93], perhaps owing to sample size limitations.

Evidence for the role of impaired extinction in the pathogenesis of clinical anxiety also comes from prospective studies that include populations at risk of developing an anxiety disorder (for example, soldiers, firefighters and policemen). In these studies, deficits in extinction learning (such as a weaker decline in early extinction, larger differential fear responding to a conditioned threat versus a conditioned safety cue throughout extinction or impaired extinction retention) predicted the occurrence of anxiety symptoms after a traumatic event[74,77,78]. Notably, predictive effects were sometimes observed for one extinction parameter but not another (for example, present in facial electromyography but not in skin conductance responding[77], or only present for the first series of extinction trials[74]), and in at least one case researchers were unable to replicate their earlier results[94].

Individuals diagnosed with clinical anxiety differ in how they respond to exposure-based treatments, the clinical analogue of fear extinction. If fear conditioning is indeed a valid model of clinical anxiety, one might expect that individual differences in fear extinction predict how individuals respond to treatment that is based on exposing individuals to the source of their anxiety (analogous to a conditioned stimulus) without harm occurring. Of the seven prospective studies that address this question (reviewed by ref. [95]), some have found support for this notion[96–100], while others have not[101,102]. Many of these studies included relatively small samples, suggesting the need for further prospective studies with larger sample sizes in order to draw solid conclusions.

In sum, the literature largely supports the implication of extinction deficits (as measured in Pavlovian fear conditioning) in clinical anxiety, but such deficits are not universally observed and their prospective value is at present unclear.

Generalization

Clinical anxiety is rarely confined to a specific stimulus or situation. In fact, it is often its widespread character that promotes fear's debilitating consequences — as the number of threatening situations increases, one's experience of fear increases[103–105]. Generalization refers to the spread of fear beyond the situation in which it was originally learned.

Following standard Pavlovian fear conditioning, fear generalization can be studied by presenting novel stimuli that share some similarity with the initially trained conditioned stimulus, either perceptually or symbolically[106,107] (Fig. 2b). In a landmark study[108], a small and a large circle, situated at the extremes of a size continuum, were

presented during the conditioning phase. One of the circles served as the threat cue and was paired with the aversive unconditioned stimulus, whereas the other served as the safety cue and was never paired with the unconditioned stimulus. Generalization was tested by measuring fear reactions to circles varying in size between the threat and safety cues. Thus, generalization of fear could be measured for stimuli on a continuum between a clear signal of danger and a clear signal of safety.

This procedure typically elicits an orderly gradient of fear, such that fear responses to the generalization stimuli ordinally increase as their size approaches that of the threat cue. The slope of the response gradient indexes the degree of generalization[109–111]. A steep slope or sharp gradient (indicated by a curvilinear trend that can be picked up by a statistical model in the form of a quadratic effect) indicates that fear responding is largely confined to stimuli that closely resemble the threat cue and readily drops off as a function of dissimilarity. A flatter slope (a linear, but not quadratic effect) points towards broader generalization and elevated fear responding to stimuli that are clearly dissimilar from the threat cue and more similar to the safety cue.

A meta-analysis of 16 conditioned fear generalization studies involving individuals with various anxiety disorders revealed a small positive effect size for the linear effect (Hedges' $g = 0.24$) and, more importantly, a stronger effect size on the quadratic effect (for the subset of nine studies for which this information was available; Hedges' $g = 0.3$)[112]. An independent meta-analysis of a subset of 11 studies confirmed the quadratic effect (as calculated by a departure-from-linearity index; Hedges' $g = 0.44$)[113]. Together, these meta-analyses confirm a broader fear gradient in individuals with an anxiety disorder relative to non-anxious controls. However, two caveats remain. First, the effect is not uniformly observed across all anxiety disorders[113] — generalization gradients have not been studied in some disorders (for example, in agoraphobia) and a broader fear gradient has not been observed consistently in other disorders[53,65]. Second, all studies are cross-sectional, which makes it impossible to know whether the broader fear gradient is a cause or consequence of clinical anxiety symptoms[112,113]. Nevertheless, one large-scale study in a broad student sample not selected on the basis of baseline anxiety found that a broader fear gradient predicted anxiety symptoms 6 months later[73].

In sum, the results reviewed here suggest that a broader generalization gradient in individuals with clinical anxiety is well established. However, more prospective studies are needed to test its causal role in the development of maladaptive fear.

Avoidance

The experience of fear can be unpleasant and exhausting. However, in anxiety disorders, daily functioning is primarily impaired by the propensity to avoid all things feared, rather than by the fearful experience itself[114]. Excessive avoidance precludes opportunities for rewarding experiences and valued life-goal activities. Moreover, avoidance

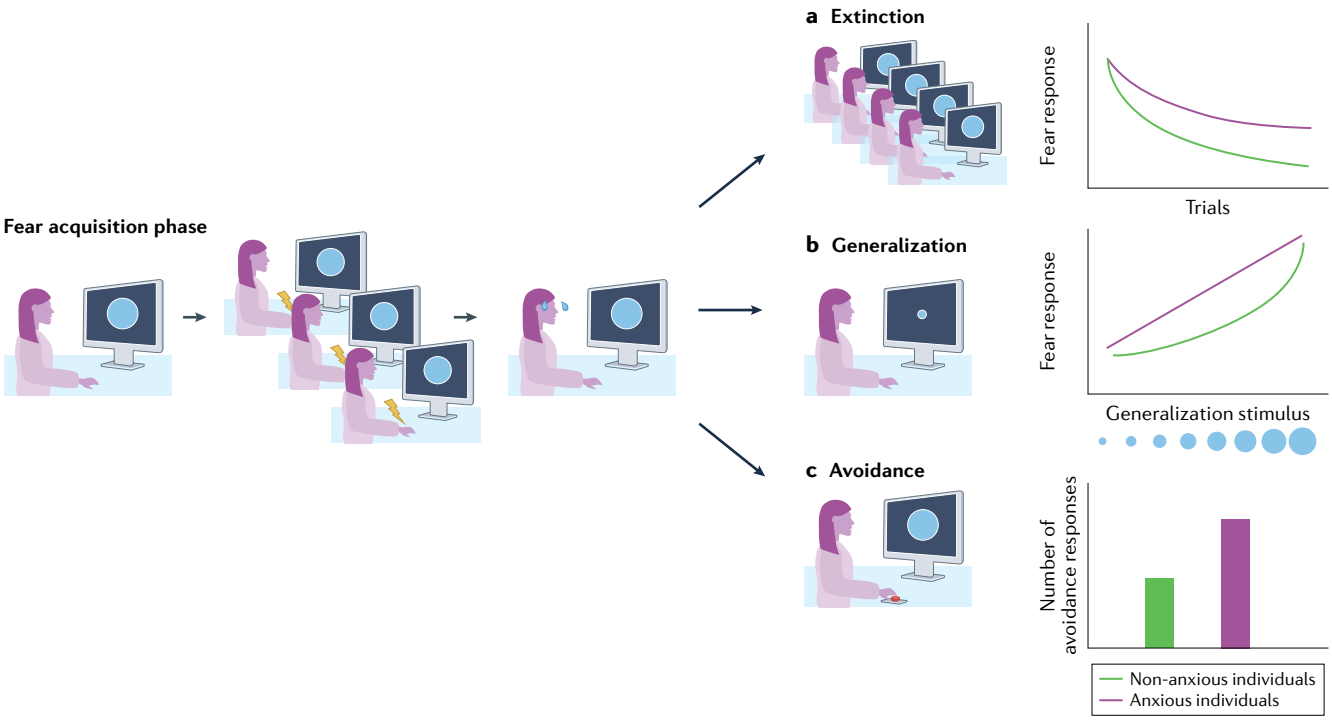

Fig. 2 | Additional fear conditioning processes. After fear acquisition via Pavlovian fear conditioning, various procedures can be used to study three key features of pathological anxiety in the laboratory. **a**, Extinction can be examined by repeatedly presenting the conditioned stimulus without the unconditioned stimulus. Evidence suggests that extinction is slower and less likely to be retained on a delayed test in individuals with clinical anxiety relative to non-anxious controls. **b**, Generalization can be investigated by presenting stimuli that vary in their perceptual or conceptual similarity to the conditioned stimulus. Evidence suggests that fear generalizes more broadly along a continuum of similarity in individuals with clinical anxiety relative to non-anxious controls. **c**, Avoidance can be studied by introducing a behavioural response that allows participants to avoid or escape the unconditioned stimulus, for example, giving participants access to a button that can prevent or stop the unconditioned stimulus. Emerging evidence suggests that imposing a cost for avoidance discourages avoidance less in individuals with clinical anxiety than in non-anxious controls.

prolongs anxiety by preventing new experiences that could indicate that feared situations are, in fact, safe[37,115–118].

Avoidance is an operant behaviour that serves to minimize exposures to an expected threat[87]. Avoidance can be added to the Pavlovian fear conditioning procedure by allowing participants to perform (active avoidance) or withhold (passive avoidance) a designated response, and by making the delivery of the unconditioned stimulus conditional upon the participant's response[119] (Fig. 2c). A cost can be added to the response (loss of points or money) to mimic the conflict between avoidance and competing positive outcomes or other life goals in clinical anxiety[120–124]. Few studies have investigated avoidance behaviour in individuals with anxiety disorders using Pavlovian fear conditioning, but the available evidence points to more frequent and more persistent avoidance performance in such individuals compared with non-anxious control participants[125,126]. Only one study has examined the prospective validity of avoidance conditioning. In that study of more than 500 firefighters, performance on a computerized avoidance conditioning task was not associated with PTSD symptoms cross-sectionally, nor did it predict the development of PTSD symptoms 2 years later[127]. In sum, more research is needed to elucidate how conditioned avoidance relates to clinical anxiety.

An integrated perspective

Delineating the extent to which individuals with an anxiety disorder and at-risk individuals exhibit enhanced acquisition, impaired extinction, overgeneralization and/or excessive avoidance helps to gauge the diagnostic and prospective validity of the Pavlovian fear conditioning paradigm. Such observations can also point to mechanistic deficits at play in individuals with an anxiety disorder that might be causal to the disorder. These deficits can thereby direct pre-clinical research efforts into understanding how these processes work, as well as clinical research efforts into developing and evaluating interventions that target these processes. Mapping individual differences is therefore a critical step to unravelling what distinguishes adaptive from maladaptive fear and anxiety.

So far, research on individual differences in acquisition, extinction, generalization and avoidance has mostly focused on either acquisition alone or acquisition together with only one of the latter three processes. Although this research has hinted at relevant differences, the evidence is often inconsistent across studies. Further progress in modelling clinical anxiety might result from looking at the phenomena of extinction, generalization and avoidance in combination. Impaired extinction learning, overgeneralization and persistent avoidance might each be core mechanisms in the development of clinical fear and anxiety in their own right, but specific combinations or patterns of (deficits in) extinction, generalization and avoidance within individuals could confer even greater vulnerability for the development of anxiety (see Fig. 3a), above and beyond interindividual differences in each of these factors separately. At present, it remains unclear whether, for example, impaired extinction necessarily confers vulnerability to pathological anxiety after an aversive event in the absence of overgeneralization and excessive avoidance. If an individual keeps feeling tense when nearing the intersection where they had a car accident despite passing there repeatedly, but they do not avoid driving there and do not generalize their fear to other intersections or driving in general, they might not develop an anxiety disorder. Conversely, if someone manages to quell their tension for this particular intersection through repeated exposure, but gets anxious at the mere thought of driving over an unknown intersection and avoids situations where they need to drive on new roads with unknown intersections, they might well be on their way to developing a driving phobia even though the extinction process is intact.

These speculative examples serve to illustrate that a comprehensive understanding of the development and maintenance of pathological anxiety is unlikely to come from the characterization of extinction, avoidance or generalization alone. Instead, these processes must be studied in combination to establish whether deficits in extinction, generalization and avoidance tend to go together within individuals, whether some deficits are more important than others, and whether distinct profiles of deficits in these factors differentially predict the development of anxiety or its treatment trajectory. If such profiles can be established, an equally important task will be to establish whether they represent stable, trait-like dispositions or whether they become aggravated in response to certain triggers, such as stress[128]. This represents an important research agenda for the coming years.

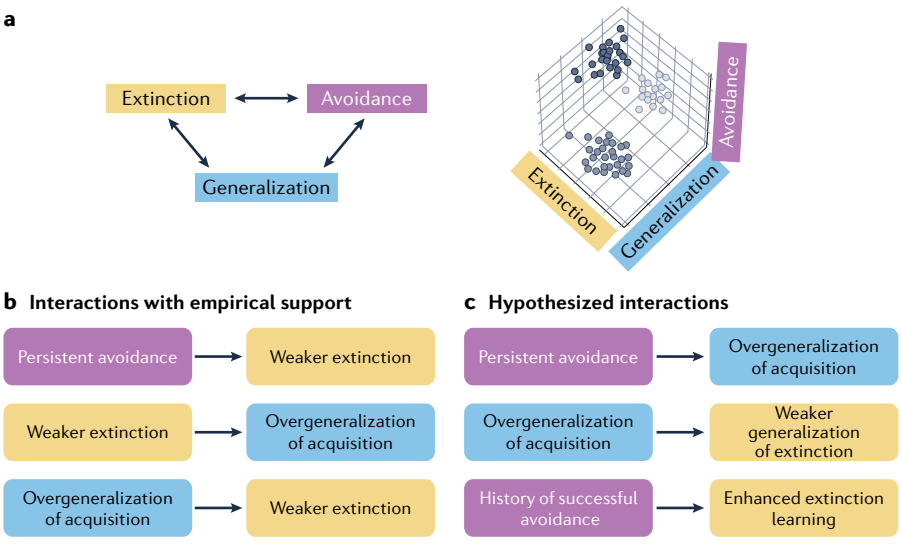

Fig. 3 | An integrated model of maladaptive fear learning. a, After a threatening event, extinction, generalization and avoidance processes collectively and interactively determine an individual's trajectory towards more or less adaptive fear responding, influenced by individual traits. As such, specific individual combinations (profiles) of extinction impairment, overgeneralization and excessive avoidance will confer differential risk for the development of clinical anxiety. **b**, Causal relations between extinction, avoidance and generalization that have been documented in the literature[116,129–135]. **c**, Further potential relationships between extinction, generalization and avoidance suggested in this article.

To shed further mechanistic insight on the covariations between extinction, generalization and avoidance, it will also be important to chart the mutual influences between them. Existing research already reveals some of the ways in which impaired extinction, persistent avoidance and overgeneralization might directly cause or sustain one another in the laboratory and in clinical anxiety. For instance, in the laboratory, persistent avoidance can hamper extinction learning[115] if the absence of the unconditioned stimulus is attributed to the avoidance behaviour rather than a change in threat value of the conditioned stimulus (protection-from-extinction through unconditioned stimulus avoidance behaviour[116]) or if the avoidance behaviour prevents exposure to the conditioned stimulus altogether (in the case of conditioned stimulus avoidance behaviour[129]). These findings echo extensive clinical research that demonstrates that engaging in safety behaviours (a subtle form of avoidance) during exposure treatment, such as carrying hygienic wipes to clean one's hands directly after touching dirty objects during exposure treatment for contamination fear, can hamper effectiveness of the treatment[130]. In another example from the laboratory, extinction training can undo the generalization of learned fear to specific temporal or physical contexts[131]. As such, lack of extinction might sustain excessive generalization. Conversely, wide generalization of learned fear to perceptually or symbolically related stimuli dramatically expands the number of stimuli that need to be extinguished. Importantly, extinction learning for those generalization stimuli will not necessarily generalize (back) to the initial threat cue or other related stimuli[132–135]. Thus, broader generalization essentially makes extinction learning (and perhaps interventions based on principles of extinction, such as exposure treatment) less effective.

Although some specific causal relationships between extinction, avoidance and generalization have been established (Fig. 3b), several questions remain (Fig. 3c). In particular, as described above, research has teased out some of the relationships between extinction and generalization[131–135] and between avoidance and extinction[115,116,129], but little is known about the relationship between avoidance and generalization. We hypothesize that avoidance amplifies generalization. Avoidance prevents actual confrontations with threat, so there are fewer possibilities to check the memory representation of the avoided threat against reality (which can reduce the precision of threat representation) and fewer opportunities to habituate to the threat. This lack of confrontation with the avoided threat thereby leaves room for processes like incubation (a marked increase in fear of a threat over time in the absence of additional exposure to threat[136]) and catastrophizing (exaggerated conscious appraisals of the danger implied by a certain threat[137]) that amplify the aversive value of the threat memory over time (inflation). Enhanced threat aversiveness and greater overall anxiety might in turn drive overgeneralization. Experimental research has shown that fear generalization increases when a threat is more aversive. For example, individuals show stronger fear generalization after fear conditioning with high-intensity shocks than with low-intensity shocks[138,139]; also, inducing state anxiety after fear conditioning results in a broadened fear generalization gradient[140]. To the extent that a history of avoidance promotes unconditioned stimulus inflation, incubation and catastrophizing, it might give rise to enhanced generalization. In clinical terms, this would imply that avoiding feared situations might cause an anxious individual to feel tense in an increasing number of essentially harmless situations; this clinical intuition has not been investigated.

Paradoxically, enhanced generalization of acquisition might result in weaker generalization of extinction. Learned fear generalizes more broadly than its extinction: when people learn to fear a conditioned stimulus, they readily exhibit defensive reactions to perceptually similar cues (generalization stimuli) as well. However, extinction training using a generalization stimulus does not similarly reduce defensive responding to the original conditioned stimulus or other generalization stimuli[132–135]. This lack of generalization of extinction has implications for the efficacy of extinction-based exposure treatments, because exposure treatment often does not use cues that were involved in the original threatening incident (like the actual intersection that was the scene of a driving accident), but rather cues that have come to elicit fear as a result of that incident (any intersection that triggers the driving phobia that resulted from the accident).

Another related prediction that has yet to be tested is that individuals with broader generalization gradients will show a smaller reduction in fear responding to the conditioned stimulus following extinction training for a generalization stimulus. This is a strong prediction because it contradicts formal models of associative learning[141]. According to similarity-based mechanisms in those models, stronger generalization of associative strength from the conditioned stimulus to a generalization stimulus should go hand in hand with stronger generalization of extinction from that generalization stimulus to the conditioned stimulus. By contrast, the current prediction follows from a more cognitive account of fear learning and generalization[105], according to which the same mechanism that drives broad generalization (a better-safe-than-sorry strategy) might constrain the application of safety information acquired during extinction for a generalization stimulus towards the initial conditioned stimulus.

The discussion so far might suggest that the relationships between impaired extinction, excessive avoidance and overgeneralization are linear, but the reality might be more complicated. For example, although avoidance can be detrimental to extinction, a history of avoidance below a certain threshold might actually benefit extinction learning. Avoidance is a way to exert control over expected aversive events, and a prior history of controllability over stressors has been shown to enhance extinction. For example, a group of participants that had been exposed to uncontrollable shocks in an unrelated task 1 week before a Pavlovian fear conditioning procedure subsequently exhibited weaker fear extinction retention than a group of participants that had control over shock administration in the unrelated task; a third group of participants that had no prior experience in stressor controllability showed intermediate extinction retention[142] (for similar results in rats, see ref. [143]). These results suggest that a history of successful avoidance might actually promote later learning of safety during extinction training, perhaps because experiencing that one's actions are causally linked to the absence of threat leads to greater sensitivity to disruptions in conditioned stimulus–unconditioned stimulus contingencies. Thus, although clinical avoidance is often detrimental because it maintains anxiety, the sense of control it entails could possibly have a beneficial effect by enhancing later extinction learning during therapeutic exposures. Again, this is an issue that requires empirical scrutiny, including a systematic comparison between avoidance and controllability and a close examination of the conditions under which they converge or diverge.

Conclusions

Pavlovian fear conditioning has provided a wealth of insight into psychological and neurobiological variables that govern defensive mobilization and the learning of threat signals[14,20,21]. Part of this success stems from the fact that Pavlovian fear conditioning represents a strong situation: fear conditioning procedures rely on unambiguous events that

are sufficiently potent to elicit similar responses across individuals[82], thereby making them well suited for studying universal principles of associative learning. In turn, research on fear conditioning phenomena beyond initial fear acquisition, such as fear extinction, fear generalization and fearful avoidance, might be particularly suited to shedding light on what demarcates adaptive and clinical anxiety because they concern weak situations that more readily allow for individual differences. However, despite that promise, research efforts to reveal clinically meaningful differences in fear extinction, generalization and avoidance between individuals with anxiety disorder and healthy controls or between individuals with varying degrees of vulnerability to develop clinical anxiety have produced inconsistent results.

We suggest that closer investigation of the myriad ways in which deficits in extinction, excessive generalization and pervasive avoidance interact, cluster and mutually reinforce one another might be pivotal for illuminating the difference between adaptive fear responding and disordered anxiety. Compelling theoretical and empirical arguments exist for extensive interactions and covariations between these phenomena, but there is a lack of sufficient data. Studying these phenomena in combination is a challenging task that requires the development of Pavlovian fear conditioning procedures that can assess extinction, generalization and avoidance patterns within a single individual and provide robust and comparable metrics. Efforts to enhance standardization of Pavlovian fear conditioning procedures[15,20,144] and improve measure calibration[145,146] will provide indispensable groundwork to this end.

Improved understanding of the interrelations and covariations between extinction, generalization and avoidance has scientific importance for understanding defensive behaviour, as well as clinical relevance. Clinical research on the optimization of exposure-based treatments focuses heavily on improving extinction[147], based on the assumption that reducing fear through extinction will also curb generalized fear and decrease avoidance. However, laboratory evidence suggests that this is not always the case. For instance, after extinction to the conditioned stimulus, some degree of fear responding to generalization stimuli can remain[148]. Moreover, under some circumstances, successful fear extinction can leave avoidance behaviour intact[149]. This latter observation aligns with clinical evidence that compulsive rituals (often conceptualized as a form of avoidance) in obsessive–compulsive disorder can persist despite successful fear reduction through exposure[150]. A tunnel view on one specific factor like impaired extinction might therefore detract from other factors that could contribute to relapse (such as overgeneralization and excessive avoidance)[151]. We expect that fundamental insights into how processes of extinction, avoidance and generalization correlate and interact causally, coupled with tools to assess profiles of extinction, avoidance and generalization individually, will provide crucial input for future treatment optimization and personalization.

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Author contributions

T.B. and B.V. developed the outline of the article in consultation with D.H., I.L., L.L. and S.S. All authors researched data and contributed substantially to discussion of the content and writing of the article, and reviewed and/or edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

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