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Review Article

# The elegant complexity of fear in non-human animals

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Activation of the fear system is adaptive, and protects individuals from impending harm; yet, exacerbation of the fear system is at the source of anxiety-related disorders. Here, we briefly review the 'why' and 'how' of fear, with an emphasis on models that encapsulate the elegant complexity of rodents' behavioral responding in the face of impending harm, and its relevance to developing treatment interventions.

*Mrs. Burridge has made her own pickles since 1952, which was the first year she had the garden. […] When the second batch is on and simmering on the stove she goes to the back door, opens it, and stands with her arms folded across her stomach, looking out. She catches herself doing this four or five times a day now and she doesn't quite know why. […] About now men begin to appear on the back road, the gravel road that goes past the gate, walking usually by themselves, sometimes in pairs. […] It's been so long since she has seen anyone* walking *along this road that she becomes alarmed. […] Suddenly, her eye is caught by a flicker of red, and before she can turn back — how can this happen so quickly? — it takes shape, it is a small fire, off to the right, and two men are crouching near it. They have seen her, too; one of them rises and comes towards her. […] Mrs. Burridge knows what she must do. She must wait until they are close enough and then she must raise the gun and shoot them. Using one barrel for each, aiming at the faces. Otherwise, they will kill her, she has no doubt about that.*

*–Margaret Atwood, "When it Happens", Dancing Girls and Other Stories*

*In this excerpt from "When it happens", a short story by Canadian author Margaret Atwood, the protagonist is first experiencing anxiety, which eventually turns to fear, and finally on the verge of acute fear, or panic.*

## Introduction

Fear, distress, panic, are emotions that one might experience in the face of impending harm [1,2]. Anxiety, dread, apprehension, and worry are emotions experienced when harm is not immediately present, but may be on the horizon, usually in relatively close proximity in time and space [1,2]. The differences among these emotions may appear subtle, but they are important, since the emotions engage different neural circuitry, and map onto different psychiatric disorders [1,2]. Still, the constellations of emotions overlap considerably in their neural underpinnings. As a construct, fear can be defined from a psychological, as well as a physiological perspective. The psychological definition refers to the thoughts, feelings, and behavioral responses that arise from engagement of our fear system. The physiological definition pertains to the direct biological changes that arise as a result of the same — e.g. irregular heart rate, increased sweating, increased blood pressure. In this brief article, we review the

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'why' and 'how' of fear, with an emphasis on models that encapsulate the elegant complexity of rodents' behavioral responding in the face of impending harm, and its relevance to developing treatment interventions.

## Why do we experience fear?

Fear is adaptive. As a result of experiencing some degree of uneasiness, some fear, the protagonist in the epigraph to this article makes the wise choice to protect herself in the face of impending harm. In this case, as in many that involve triggering the fear system, timely engagement of a neural network deploys our body's resources to enable us to respond in savvy and rapid ways in the face of impending harm. The fear system also powerfully encodes and stores emotional memories, which then enables us to cope more effectively when we encounter similar threats in the future. Still, as finely tuned as our fear system may be, it isn't without pitfalls. Aversive memories can be quite enduring and overgeneralized to activate fear in the absence of real danger. This type of overexpression of fear can be the source of anxiety-related disorders and post-traumatic stress disorder [3].

## How is fear acquired, stored, and expressed?

How can we best understand fear? One approach is to ask people how they are feeling; however, since there is a significant portion of our emotional lives that we are not consciously aware of, verbal reports are not enough [4]. We can ask a war veteran if they are experiencing a negative emotion in the face of a situation that reminds them of war, and while they might say no (and believe it), their body may suggest otherwise [4,5], as evidenced by physiological manifestations of fear. With this in mind, scientists can approach the study of fear in a couple of different ways. We can study fear responding in non-human animals, or we can use experimental tricks to ask questions of humans. This article is concerned with the former strategy.

But how does one create such a state of mind in non-human animals? And how can we quantify what animals are feeling as a result of such experiences or be sure that what other animals are feeling corresponds to what humans experience? We can also reasonably ask: does the answer to this question matter for the purpose of developing therapies to attenuate fear? There is evidence for a disconnect between the subjective reports of feeling fearful and physiological evidence of defensive circuits being engaged. Even if someone reports *not* being fearful, their life nevertheless may be adversely affected by an exacerbated fear system. For example, in contrast with healthy controls and those with mild symptoms, individuals with high PTSD symptoms cannot inhibit their startle response even when they are cognitively aware of safety [6]. We argue, therefore, that whether non-human animals possess a conscious awareness of subjective fear is an interesting and important continuing conversation (see the following references for differing opinions on this topic; [7–11]), but this issue does not have to be unambiguously resolved in order for behavioral approaches in non-humans to guide treatment interventions. Approaches known to diminish the engagement of defensive circuits are generally effective in diminishing the negative impact of untamed aversive memories in individuals who suffer from anxiety-related disorders [3].

### The 'behavioral how' of fear

In the laboratory, simple experimental procedures can be employed in which rats or other animals (including humans) acquire fear memories. The most commonly employed methodology to examine the learning of fear is Pavlovian fear conditioning. In fear conditioning (also sometimes called threat conditioning; [7]), the pairing of an initially innocuous conditioned stimulus (CS; e.g. tone) with an unconditioned stimulus (US; e.g. mild footshock) leads to associative learning such that, when presented at a later time, the CS leads to fear expression (e.g. freezing) [12].

Interestingly, individuals possess a range of adaptive responses they can deploy to protect themselves in the face of impending harm [13]. The variability in the behavioral repertoire is a product of the proximity of impending harm as well as the situational constraints encountered by the individual. Furthermore, these two factors are intimately intertwined. The dominant hypothesis that has been proposed to explain how defensive responses are organized is the predatory imminence continuum. According to predatory imminence, defensive behaviors fall along a continuum predicated on the spatial and temporal distance from impending harm (see Figures 1 and 2) [14]. Simply put, a cornered rat may be left with no choice but to fight, whereas a rat that identifies a predator without itself having been detected may freeze in place to continue avoiding detection. Another rat may flee in the face of impending harm, if it has space (and hopefully time) to do so. Most laboratory experiments have not explored all of these various response strategies. Rather, investigators have generally

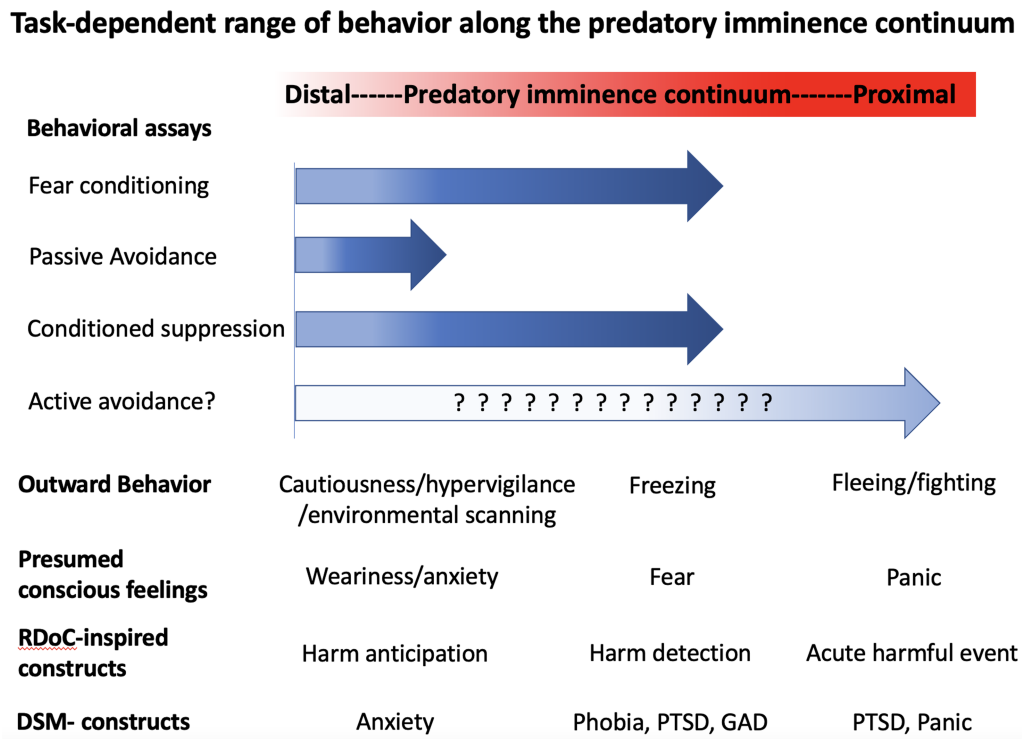


**Figure 1. Task-dependent range of behavioral responding along the predatory imminence continuum.**
Imminence is influenced by the proximity (in time and space) of impending harm. Here, we display the hypothesized relationship between the outward observed behavior, the presumed conscious feelings experienced, and their possible mapping onto revised constructs inspired by the RDoC as well as DSM-derived constructs for broadly employed behavioral fear assays. RDoC: Research Domain Criteria from the National Institute of Mental Health (see https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/development-of-the-rdoc-framework); DSM: Diagnostic and Statistical Manual of Mental Disorders.

focused on one or another form of defensive behavior in any given experiment (for an exception, see [15]). The various behavioral manifestations of conditioned fear that have attracted the most experimental attention are described in the following sections.

## Freezing

The most commonly measured 'fear' response in laboratory experiments with rats and mice is freezing: a complete cessation of movement (with the exception of breathing) in the face of impending harm. Freezing often captures whether an individual is recalling a painful experience, and is appealing in its simplicity. Measures of conditioned freezing are generally reliable, simple, and can be easily quantified and even automated. Considering the popularity of conditioned freezing as a measure of fear in research with non-human species, it is gratifying to see efforts to extend this methodology to translational research with people [16]. However, freezing is just one of a range of behavioral manifestations of fear. What follows are additional paradigms that provide a more comprehensive picture of the various ways in which conditioned fear can change behavior.

## Fear-potentiated startle

Another behavioral technique that has been used in many studies of the neurobiology of fear conditioning is the fear-potentiated startle procedure. In this procedure, fear is initially conditioned in the usual manner by pairing a conditioned stimulus (CS) with mild shock (the US). To see if the CS elicits conditioned fear, a sudden loud noise is presented during the CS. Conditioned fear results in a potentiated or exaggerated startle response [17]. A real-life example of fear potentiated startle would be an exaggerated response to a shoulder tap when you are looking at the pile of leaves where you previously saw a dangerous snake.

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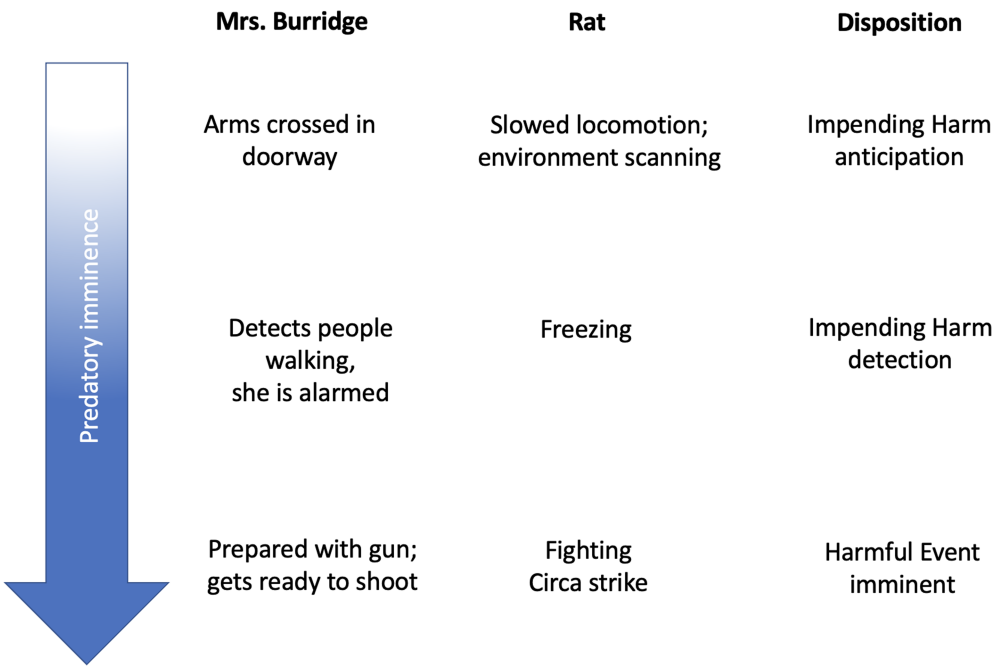


**Figure 2. Disposition along the predatory imminence continuum for Mrs Burridge and a rat.**
As impending harm increases in spatial and temporal proximity, rats and humans engage in different defensive behaviors.

## Passive vs active avoidance

In passive avoidance, an animal is trained to inhibit a natural response. Typically, the task is conducted in an apparatus with two adjacent compartments. One of the compartments is dark, and the other illuminated. Given a choice, rodents generally prefer to spend time in a dark environment, as that offers a safer space where they can avoid being detected by a predator. At the start of an experiment, a rodent would be placed in the bright chamber. When they cross over to the dark side (their natural inclination), they receive a shock. On future trials, when they are placed in the white compartment they avoid shock by remaining passive and not entering the dark side [18].

In active avoidance, individuals have to make an active response (e.g. running to the other side of a shuttle box or pressing a response lever) to avoid facing the negative or aversive outcome. Unlike Pavlovian fear conditioning, avoidance procedures allow participants to control whether or not they are exposed to the aversive outcome [18]. A simple distinction between passive and active avoidance is that in the former, individuals choose to *not engage* in a response that will increase their discomfort, whereas in the latter, they choose to engage in behaviors that decrease their discomfort [19,20].

## Escape from fear

In escape from fear, an individual learns that performing a given response will result in termination of a conditioned aversive stimulus. Escape from fear is a feature of both active and passive avoidance procedures. However, in avoidance procedures it is difficult to isolate the escape-from-fear component. That is why the typical escape from fear experiment is conducted in two stages. In the first stage, individuals receive simple Pavlovian pairings of a CS with an aversive US. In the next phase of the experiment, they received escape from fear training, during which if they perform a certain behavior (e.g. pressing a response lever) during the CS, the CS is turned off [21]. Because escaping from fear is rewarding, individuals come to perform the escape response more and more to minimize their exposure to the CS. This process can result in both adaptive and maladaptive coping strategies. On one hand, escape from fear can be a coping strategy that promotes active engagement, is likely to minimize exposure to an aversive event, and in doing so, improves long-term outcomes. On the other hand, escape from fear can be conducive to the development of stereotyped compulsive behaviors, which would interfere with clinical improvements [22].

### Conditioned suppression of reward seeking

In a prototypical conditioned suppression procedure, rodents are first trained to press a lever to receive food reward. Then, a conditioned stimulus (CS) is paired with a shock unconditioned stimulus (US). Subsequently, rats suppress lever responding when the CS is present, and the magnitude of this suppression offers an indirect measure of conditioned fear [23]. Conditioned suppression may be more relevant than freezing to the way that human beings experience fear, i.e. as something that interferes with the enjoyment of pleasurable activities [24], and provides a means of determining more subtle dispositions toward the impending harm than freezing alone. For example, a rat may show a significant reduction in freezing, but fail to resume engaging in reward seeking — an outcome that would indicate lingering weariness of the stimulus that would not be captured by looking at freezing alone, for example [25]. Elegant research by Sangha and colleagues suggests that this behavior may be sex-specific [26]. The degree of conditioned suppression also depends on the rate of reinforcement the rat obtains for pressing the lever [27,28]. This makes the conditioned suppression procedure useful for studying how the expression of fear is influenced by the availability of alternative incentives.

## Deceptively simple?

The above paradigms showcase the range of behavioral responses that can be displayed when non-human animals are faced with impending harm. Even the simple pairing of a CS with a US belies a complexity that is rarely acknowledged. For example, individuals show a greater propensity to acquire fear of stimuli that might have caused their ancestors harm (e.g. snakes or spiders), relative to innocuous stimuli (e.g. a colored square, or a tone) — a concept known as stimulus relevance [29]. In the opposite direction, individuals will show diminished potential to associate a CS with an aversive outcome if that CS has been repeatedly experienced in an innocuous way first — a concept known as latent inhibition. Even simple CS–US associations grow more complex with a simple twist. For instance, adding a brief gap between the CS and the US presentation (a form of Pavlovian fear conditioning known as Trace conditioning) has been shown to engage different neural circuitry than a CS co-terminating with a US (known as Delay conditioning). There is also increasing evidence for sex differences in freezing and other behaviors in aversive conditioning paradigms [16,26,30–32].

On a moment-to-moment basis, we are estimators of the present based on experiences from the past. This calculus is rarely perfect, but it does allow for a rapid deployment of resources to protect us from harm. To further complicate matters, direct experience is not the only way that we and other animals sample the world and encode experiences. We can also learn from observation of others, or via social transmission [33–35]. This is sometimes called 'fear by proxy' and engages a different neural circuitry than fear acquired via first-hand encounters with harmful stimuli [36].

## The "mechanistic how' of fear

Countless articles and books have been devoted to the mechanisms that underlie fear acquisition and maintenance. Covering them extensively is beyond the scope of this article, but here is a primer. The pairing of a CS with a US leads to associative learning from convergence of their respective information to a small subnucleus in the brain called lateral amygdala (LA). Contextual information is processed in the area that is necessary for the formation of episodic memories — the hippocampus. The hippocampus synapses (that is, neurally connects with) onto a subnucleus of the amygdala (the basal nucleus), which in turn synapses onto the central amygdala (CE). The LA also synapses onto the central amygdala (CE), which sends outward projections to engage the periphery and gives rise to the behavioral responding we outwardly observe — freezing, fleeing, fighting (See Figure 3). This relatively simple fear circuit has been established thanks to countless studies that provided converging information from complementary angles: lesion studies, recordings, inactivations, behavioral observations, molecular approaches, and more recently, optogenetic manipulations (selective activation or inactivation of cells genetically modified to be sensitive to light pulses at specific wavelengths) [37]. (For a broader perspective on the neural circuitry of defensive behavior, see Barrett & Finlay [38])

Avoidance paradigms are less well characterized, but are thought to engage the striatum and the ventromedial prefrontal cortex (See Figure 2; [41]). Acquiring fear by-proxy overlaps significantly with direct acquisition, but engages and requires yet another brain region — the anterior cingulate cortex [36]. When fear memories are first acquired, they are initially somewhat fragile and malleable, but they progressively strengthen through the synthesis of new proteins — a process called consolidation [42]. Once memories have become

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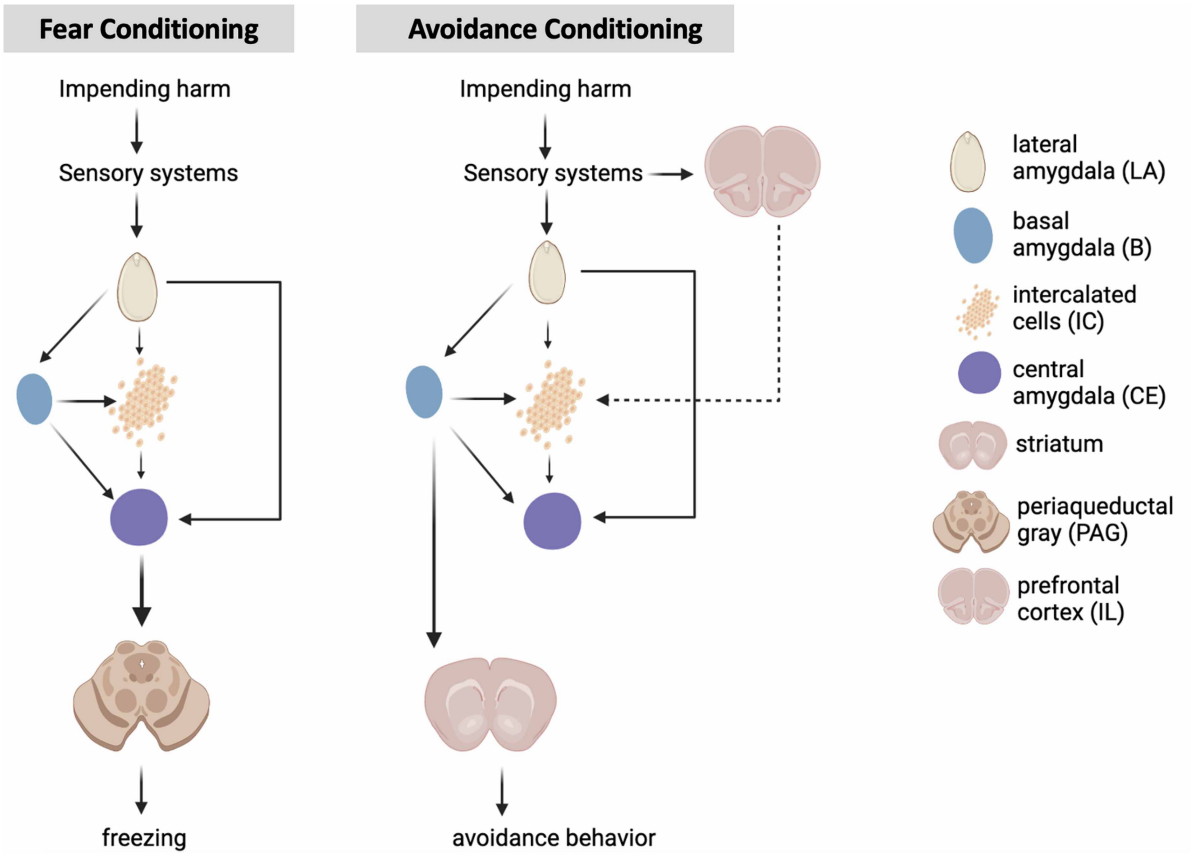


**Figure 3. Simplified schematics of the neural circuitry underlying fear conditioning and conditioned avoidance.**
Impending harm, or the pairing of a CS with a US leads to associative learning from convergence of their respective information after processing through the appropriate sensory system (e.g. auditory thalamus and cortex for sounds) to a small subnucleus in the brain called lateral amygdala (LA). Contextual information is processed in the area that is necessary for the formation of episodic memories — the hippocampus (not shown). The hippocampus synapses (that is, neurally connects with) onto the basal subnucleus of the amygdala (B), which in turn synapses onto the central amygdala (CE). The LA also synapses onto the central amygdala (CE) directly, and through the intercalated cells. The CE then sends outward projections via the periaqueductal gray to engage the periphery and gives rise to the behavioral responding we outwardly observe — freezing, fleeing, fighting. In avoidance learning, the circuit is similar to that just described early during training; however, at later stages, the basal amygdala synapses onto the striatum to control goal-directed behavior — a process that relies on the inhibition of elicited defensive responses (like freezing). The inihibition is thought to be effected via the infralimbic region of the prefrontal cortex [39]. Figure inspired by LeDoux and Daw [40] and created using BioRender.

consolidated, they are much harder to modify [43] (For additional research on this question, please see McGaugh [42] and Nader et al. [43]).

## When the fear system goes awry and how to fix it

When activation of the fear system allows us to avoid or escape harm, it is adaptive. When the same system leads us to react vigorously even in the absence of impending harm, as is the case with post-traumatic stress disorder (PTSD) and phobias, it is maladaptive. A core feature of anxiety-related disorders is hypervigilance — a state of hightened alertness characterized by scanning the environment, and increased reactivity to novel cues. One can envision hypervigilance as a shift towards a heightened perception of predatory imminence, where detecting impending harm occurs more rapidly (and may include false positives), and defensive behaviors are exaggerated for the situation at hand (See Figure 4).

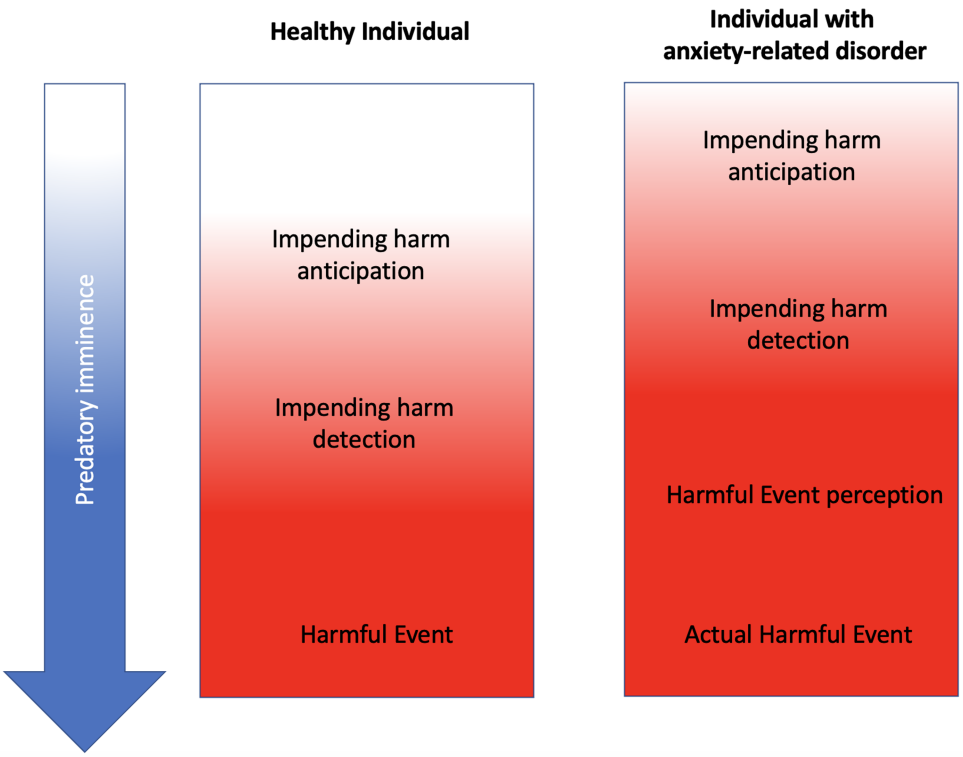


**Figure 4. Mapping hypervigilance onto the predatory imminence continuum.**

Hypervigilance, a state of increased alertness that influences a person's thoughts, perceptions, and actions, is a core feature of individuals with anxiety-related disorders. Here, we map a theoretical account of impending harm detection and commensurate behavioral responding along the predatory imminence continuum based on a possible shift in the threshold to anticipate and detect a harmful event. Note that as a result of hypervigilance, an individual with an anxiety-related disorder may anticipate impending harm pre-emptively relative to a healthy individual.

Approaches that are commonly used in the clinic to attenuate fear and traumatic memories generally rely on learning principles derived from non-human animal studies. The most commonly used approach is a form of cognitive behavioral therapy called exposure therapy [44]. The procedure and mechanisms of exposure therapy overlap considerably with extinction. In extinction, the repeated presentation of a CS in the absence of a reinforcer leads to a progressive decrease in behavioral responding. Like extinction, exposure therapy is thought to engage inhibitory neural circuitry that serves to suppress the fear responding, though it is not permanent, and as such, leaves an individual susceptible to the return of fear. Still, there are a number of tactics that can be employed that maximize the efficacy of extinction-based approaches, including pharmacological enhancement, deepened extinction, extinction generalization, and fading of safety behaviors. A successful exposure therapy session can be further improved with the administration of the glutamate agonist D-Cycloserine [44,45], or the mitochondrial enhancer methylene blue [46,47]. In deepened extinction, an individual first receives extinction to one stimulus, then, a second stimulus is presented in combination with the first for another round of extinction [48–50]. This results in a deeper extinction effect that is less susceptible to the return of fear [48]. Administering exposure therapy or extinction in a number of different contexts leads to better generalization of extinction [49] creating an extinction memory that is more enduring across different contexts. On the other hand, there is evidence that engaging in safety behaviors can interfere with extinction success [51]. For example, Sloan & Telch [52] found greater fear reactions in claustrophobic patients who used safety behaviors (e.g. opening a window) during exposure therapy than those who did not. A possible explanation for this outcome is that the safety behavior is a form of avoidance that can influence impending harm expectancy, and prevent extinction learning [53]. For extinction learning to be effective, an individual must experience a prediction error — that is, a difference between the harm they anticipate, and the absence of harm that actually

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occurs during extinction ([53]; but see also [54]). With a safety behavior in place, they have a diminished impending harm anticipation, thus, the difference between what is expected and what actually occurs is smaller, and this interferes with the extinction process [49,55].

Other approaches are emerging but are more experimental for the time-being (e.g. reconsolidation-based approaches). When a memory is retrieved, it is thought to be temporarily fragile and susceptible to disruption. During this 'reconsolidation window', pharmacological blockade of the molecular cascade engaged by the retrieval results in a decrease in the fear response the next day [44]. Most drugs that have been employed experimentally to block reconsolidation cannot safely be used in humans, with the beta-blocker propranolol being an exception [55,56]. Propranolol has been used with mixed success [57,58]. Monfils et al. [59] also developed a reconsolidation-based approach that is strictly behavioral. In this procedure an extinction session is presented after an isolated retrieval trial to open the reconsolidation window. This approach has been found to result in a decrease in fear responding in rats, in fear conditioned humans, and was successfully employed in a number of studies with clinical or analog samples ([50,59–61]; see Monfils & Holmes, for Review [3]), but is not universally effective [62,63].

The experimental approaches described above could ultimately prove useful, especially as we consider individual differences in suitability to respond to any given treatment [29]. Detailing the mechanisms of fear extinction and reconsolidation blockade or updating is beyond the scope of this review, but there is mounting evidence that they engage different neural circuitry [64–66]. This will be important, moving forward, as we strive to identify what approach works best for whom [66]. In doing so, researchers and clinicians will continue to work to identify safe and effective candidates to modulate memory (for a recent review on candidate drugs that may be vetted for this purpose, please refer to Raut et al. [67]).

Rats display individual differences in extinction that, at least on the surface, correspond nicely with the range of individual differences in humans [30]. As we develop more tailored treatments, incorporating behavioral assays that capture a broad range of responses will prove important. An increased emphasis on sex differences will be also be crucial. There are marked differences in the propensity for women and men to suffer from anxiety-related disorders, as well as evidence for sex differences in extinction [26,32]. Indeed, females also display a range of behaviors in response to aversive stimuli that is different from that of males [31]. Ultimately, detailed behavioral assessments may prove to be a good indicator of whether an individual's behavioral repertoire would make them conducive to improvements with exposure sessions. For example, continued avoidance following treatment in the absence of impending harm would likely prove more challenging to treat than cases in which there is no such persistence. Though imperfect, behavior in the face of impending harm provides a proxy assessment of an animal's appraisal of that possibility — a construct with translational validity [68–70]. Ultimately, while a multi-level analysis is often warranted, there really is no substitute for good behavioral assessment. Even in humans, we do not at this point have a reliable measure to predict exposure success. Translationally speaking, identifying a good non-human animal predictor of extinction responding that we can easily assess in humans would be ideal.

## Summary

- Anticipation of impending harm engages the fear system.
- Behavioral responding in the face of impending harm is situation-dependent.
- Engagement of the fear system in the absence of immediate impending harm is maladaptive.
- Development of therapeutic interventions needs to take into account the behavioral complexity of the fear system.

### Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

## Abbreviations

CE, central amygdala; CS, conditioned stimulus; LA, lateral amygdala; PTSD, post-traumatic stress disorder.

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