Emerging Topics in Life Sciences (2022) **6** 467–477
https://doi.org/10.1042/ETLS20220003

Review Article

Negative valence systems: sustained threat and the predatory imminence continuum

Michael S. Fanselow[1,2,3]

[1]Staglin Center for Brain and Behavioral Health, University of California, Los Angeles, California, U.S.A.; [2]Department of Psychology, University of California, Los Angeles, California, U.S.A.; [3]Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, California, U.S.A.

Correspondence: Michael S Fanselow (fanselow@psych.ucla.edu)

This review describes the relationship between the National Institute of Mental Health (U.S.A.) Research Domain Criteria (RDoC) Negative Valence System related to responses to threat and the Predatory Imminence Continuum model of antipredator defensive behavior. While the original RDoC constructs of Potential Threat (anxiety) and Acute Threat (fear) fit well with the pre-encounter and post-encounter defense modes of the predatory imminence model, the Sustained Threat construct does not. Early research on the bed nuclei of the stria terminalis (BST) suggested that when fear responding needed to be sustained for a prolonged duration this region was important. However, follow-up studies indicated that the BST becomes critical not because responses needed to be sustained but rather when the stimuli triggering fear were more difficult to learn about, particularly when aversive stimuli were difficult to accurately predict. Instead, it is argued that the BST and the hippocampus act to expand the range of conditions that can trigger post-encounter defense (Acute Threat). It is further suggested that sustained threat refers to situations where the predatory imminence continuum becomes distorted causing defensive behavior to intrude into times when organisms should be engaging in other adaptive behaviors. Stress is seen as something that can cause a long-term disturbance of the continuum and this disturbance is a state of sustained threat.

Introduction

The National Institute of Mental Health (U.S.A.) developed the Research Domain Criteria (RDoC) as a framework to relate Psychiatric disorders to their underlying biology. The motivation was that the traditional, symptom-based diagnosis, described by the Diagnostic and Statistical Manual (DSM) of the American Psychiatric Association [1] was not well connected with the substantial accumulation of basic neurobiological research knowledge related to these disorders. The strategic plan of the RDoC was to 'Develop new ways of classifying disorders based on dimensions of observable behaviors and brain functions [2]'. During March 2011, a large group of basic and translational scientists was brought to NIMH to develop the 'Negative Valence Systems that are primarily responsible for responses to aversive situations or context, such as fear, anxiety, and loss[1]'. The group considered fear and anxiety to be responses to environmental threat and proposed three threat related constructs: Potential Threat, Acute Threat and Sustained Threat. These constructs were grounded in specific research topics that had received laboratory attention. The focus of this article is on the sustained threat construct. Below I describe the research findings that formed the basis for including Sustained Threat as a construct. Then, I will describe recent research findings subsequent to the development of this category that challenge the initial conception of sustained threat. Then I will suggest a revision and revised integration of the three threat constructs. To do so, it will be helpful to provide a brief overview of how the Potential and Acute constructs relate to a particular theoretical understanding of the function of threat related behavior, Predatory Imminence Continuum (PIC) Theory [3].

Received: 22 May 2022
Revised: 25 July 2022
Accepted: 18 August 2022

Version of Record published:
26 October 2022

Emerging Topics in Life Sciences (2022) **6** 467–477
https://doi.org/10.1042/ETLS20220003

The relationship between fear and anxiety and natural antipredator behavior

In a landmark paper, Bolles [4] argued that the major function of fear was to limit an organism's behavior to its species-specific defense reactions (SSDRs). Prior to that, fear was considered to be a source of motivational drive that nonspecifically stimulated behavior and that fear-reduction served as a reinforcer for any arbitrary behavior coincident with fear reduction[5,6]. So Bolles' view produced a sea-change in our understanding of aversively motivated behavior. Rather than producing arbitrary changes in behavior, fear caused a behavioral inflexibility. SSDRs are adaptive in the phylogenetic sense, evolution selected them because probabilistically they were effective at thwarting predation. However, such responses may in fact be maladaptive in any specific current situation and fear-induced inflexibility leaves the organism with little behavioral choice. The behavioral inflexibility that comes with fear is one reason why fear-related disorders are so problematic for those who suffer from them.

Bolles' assumed that a species has several different SSDRs. This raises a major question; if there is a repertoire of SSDRs, how does an animal select one? From the standpoint of natural selection, this would be the most effective one for the current situation confronting the prey. A satisfactory answer to this question did not emerge immediately [7]. A dominant idea in the ethological literature was flight-initiation distance, which is simply how close does the prey let the predator approach before it flees. Field observations showed that this was not a fixed distance. For example, Thompson's Gazelle lets a hyena get nearer than the more dangerous lion before it flees [8]. Indeed, the gazelle will let an approaching automobile get closer when it is on a tangential, rather than a directly intercepting course [8]. Speed of approach is also a factor in determining flight initiation distance. The gazelle has a greater flight initiation distance for the faster cheetah than the larger but slower lion [8]. In simulation studies in humans, speed of approach also alters which circuits mediate flight initiation distance, with hippocampus and prefrontal cortex engagement when approach is slow but midbrain periaqueductal gray engagement when approach is rapid [9,10]. It seems that flight initiation distance is determined by the psychological perception of threat and not an absolute spatial measure. To capture this idea of multiply determined psychological distance, Fanselow & Lester [3] coined the term Predatory Imminence Continuum (PIC). The PIC ranges from no threat to fatal contact with the predator.

The concept of flight initiation distance says when an organism will engage in a specific SSDR (e.g. flight) but it does not say which SSDR is selected from the available repertoire of SSDRs. PIC theory extends this conceptualization proposing that the prey's perception of the psychological distance of threat is a determinant of both the vigor and topography of SSDRs (Figure 1). A certain level of predatory imminence selects a specific SSDR. As predatory imminence increases that SSDR increases in vigor, but only up to a point. With sufficient increases in threat imminence the behavioral topography will shift to a new SSDR. By analogy to a car's transmission, the level of predatory imminence is the speed of a car. The current gear is the specific defensive response, and the tachometer (engine speed) is the vigor of that particular behavior (Figure 1).

Potential threat and pre-encounter defense

Three defensive modes lie along this continuum. The lowest level is Pre-encounter defense. This occurs when an organism leaves a position of maximum safety to one that poses the potential of predation. It is pre-encounter because no actual threat has been detected. An example would be leaving a burrow to forage in a potentially risky environment. Here, threat is uncertain and is guided by prospective reasoning. Under such situations animals change their foraging patterns and engage in high vigilance postures [3]. Rats will take less frequent but larger meals under such risk [3,11]. Predatory imminence applies to humans as well [12,13]. One example is that during the initial threat of Covid-19 people adjusted their shopping (i.e. foraging) patterns, hoarding items such as toilet paper and were highly vigilant of others that coughed [14,15]. The RDoC category of Potential Threat, and its connection with anxiety, was built on the concept of pre-encounter defense. The activating conditions for both are when 'harm may potentially occur but is distant, ambiguous, or low/uncertain in probability[2]'. Neural structures that serve pre-encounter defense include the medial prefrontal cortex and ventral hippocampus [16,17,18].

Acute threat and post-encounter defense

Obviously, pre-encounter defense will not always succeed. If a predator is detected, imminence increases, and the post-encounter mode is activated. This mode is characterized by behaviors that help the prey avoid detection and if detected reduce the likelihood of attack. One of the major post-encounter defensive behaviors is

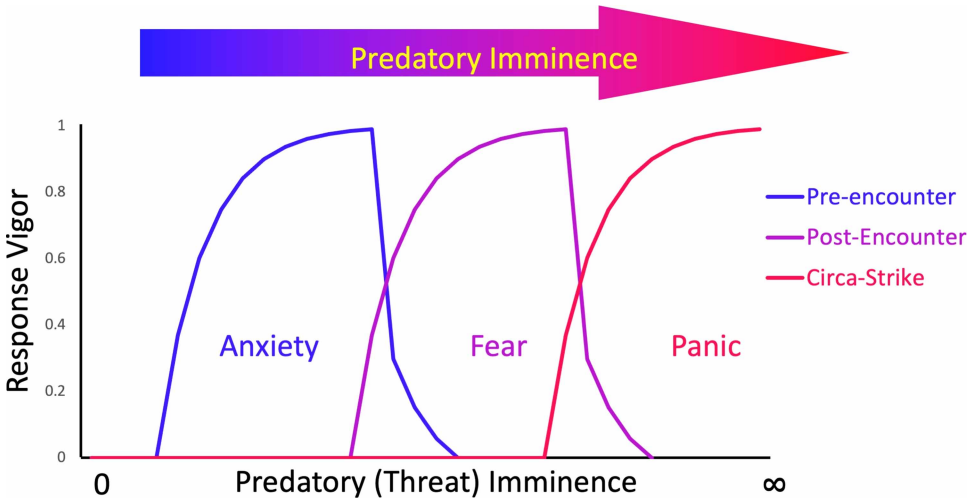

Figure 1. Hypothetical illustration of how predatory imminence determines both the response topography and the vigor of each response.

The continuum starts with a situation where there is no threat on the left (predatory imminence is 0) and ends when the prey is consumed on the right (predatory imminence is infinite). Note that besides the specific behaviors that characterize each mode, the mode also consists of preparatory responses that facilitate transitions to the next mode. For example, the frightened organism freezes but also prepares to burst into activity should the situation suddenly change [75].

movement suppression (i.e. freezing) because moving prey are more easily detected and movement often releases the predator's attack [3,19]. While most often studied in rodents, freezing has been reported in species ranging from marine mollusks [20] to humans [21,22]. At this point along the PIC the threat is actually present and acute, so the activating conditions are quite different from pre-encounter defense. Also, the behaviors are qualitatively different; foraging patterns are not simply modified they are actively suppressed [23]. The emotional state has moved from anxiety to fear. The Acute Threat (fear) construct of the RDoC has post-encounter defense as its basis[3].

The major preclinical methodological approach to understanding post-encounter defense has been fear conditioning, where a stimulus that initially does not provoke a fear response (e.g. a 30 s tone) comes to do so because it has become associated with an aversive unconditional stimulus (US) such as electric shock. The initially innocuous stimulus is called a conditional stimulus (CS) after this learning has occurred because the response is dependent or conditional on experience [24]. Following conditioning, which can occur with a single pairing [25], the CS produces a suite of behaviors including autonomic changes, overt defensive behaviors such as freezing, and potentiation of startle reflexes [26]. All these reactions are components of post-encounter defensive behavior. Some of these behaviors, such as potentiation of startle are preparations for a potential transition to the next, circa-strike, mode.

The brain circuit that generates post-encounter defense critically depends on communication between the Basolateral Amygdala (BLA), Central Nucleus, and ventral periaqueductal gray [27–29]. Traditionally this has been thought of as a descending circuit with the cortex-like BLA processing sensory information and passing it on to the striatal-like CN [28,30]. The CN, in turn, drives fear-related responses by descending projections to the midbrain periaqueductal gray (freezing and analgesia), hypothalamus (blood pressure, hormonal responses), and brainstem (heart rate and potentiated startle, [24,26]). While recent evidence paints a more complex and subtle picture of how the circuit operates (e.g. [30]), it will be important for the later discussion of sustained threat to recognize the CN as the primary driver of responses to acute threat.

Potentiation of startle and the bed nuclei of the stria terminalis

Very loud noises normally provoke a startle response that is mediated by a short circuit entirely in the brain stem [31]. During a fear state produced by the presentation of a shock-associated CS, this startle response is

Emerging Topics in Life Sciences (2022) **6** 467–477
https://doi.org/10.1042/ETLS20220003

magnified, and this increased startle is referred to as fear-potentiated startle [32]. Fear-potentiated startle has been a valuable tool advancing our understanding of fear [33,34]. Enhanced startle reactivity has long been recognized as a common symptom of anxiety disorders (e.g. [35,36]). The CN has projections to the brain stem circuit that mediates startle [37]. Stimulation of the CN will potentiate startle and inactivation or lesions of the CN will prevent fear's potentiation of startle, while leaving baseline startle intact [37–39]. These findings contributed greatly to our knowledge of the pharmacology and circuitry mediating responses to acute threat (post-encounter defense).

Davis and colleagues discovered that there were several conditions that would produce a similar enhancement of startle, but this altered startle reactivity was not dependent on the CN. These researchers looked to the Bed Nuclei of the Stria Terminalis (BST) as a potential mediator of these effects (e.g. [26]). Like the CN these nuclei are striatal-like and project to similar fear response generation regions as the CN [40–44]. A striking set of double dissociations between CN and BST were discovered [45,46]. For example, exposing the nocturnal rat to a 15 min light will unconditionally potentiate startle. A brief (3.7 s) presentation of the same light will also potentiate startle but only if the light is paired with shock. The potentiated startle to the long untrained light was blocked by BST but not CN lesions and inactivations. However, as previously reported potentiated startle to the brief shock-paired light was blocked by CN but not BST lesions [47].

Certain pharmacological agents can also potentiate startle. Starting ∼30 min after systemic administration, corticotropin releasing hormone (CRH) will enhance startle and this effect lasts on the order of hours [48]. Several lines of converging evidence again identified the BST, but not CN, as a mediator of this effect [45].

Note that both the CN-dependent and the BST-dependent startle reactions required the BLA. Thus, it seemed that the BLA detected the disturbance and generated similar behaviors but through different outputs ([26], see Figure 2). This naturally raises the question of why are two independent pathways used to generate similar behaviors? Davis and colleagues noted that the stimuli that caused BST-dependent potentiated startle were of longer duration than the typical CSs used in fear conditioning experiments. They suggested that the BST is necessary when fear reactions are sustained and the CN serves fear responses that are generated for a brief time. A general characteristic of the BST-mediated potentiation was that the response had a slow onset, persisted throughout the stimulus even if it was prolonged and had a slow decay once the stimulus terminated. Walker et al. [26] concluded that the BST controls a sluggish response system that once activated continues to influence behavior long after the initiating stimulus has been terminated.

In these experiments from the Davis lab, the CN-dependent potentiation of startle was produced by a conditional fear stimulus; it was a learned reaction. The stimuli used to produce a BST-dependent increase in startle

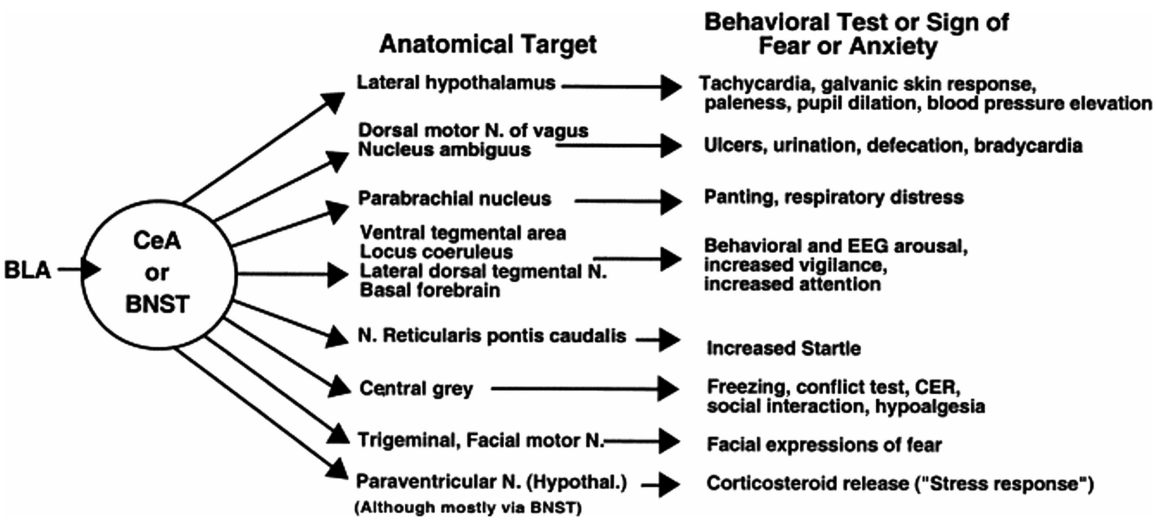

Figure 2. Threat related information is detected by the basolateral amygdala (BLA), which ultimately leads to defensive behaviors.

Note how the Central Nucleus (CeA) and Bed Nuclei (BNST) are both seen as roughly equivalent output structures projecting to the same anatomical regions. This figure was taken from Walker et al. [26].

magnitude such as bright light or CRH administration did so without any prior training. Thus, rather than duration the difference could be the use of conditional vs unconditional fear-provoking stimuli. To test between these alternatives Walker et al. [46] trained rats with a variable duration CS (3 s to 8 min) and tested them with only the 8 min CS. Inactivation of the BST reduced fear-potentiated startle specifically during the last half of the test presentation, while CN activation had no effect. Thus, the BST mediates conditional fear-induced potentiation of startle when a very long-duration CS is used. Therefore, the critical variable appeared to be stimulus duration and not learned vs unlearned reactions. This pattern was confirmed in a conditioning experiment by Waddell et al.[49]. Rather than using fear-potentiated startle they assessed fear by examining a fear CS's ability to suppress ongoing food-reinforced behavior. Rats received pairing of either a 1 min or a 10 min tone with shock. BST lesions reduced suppression to the long- but not short-duration CS.

Sustained threat vs anxiety

The BST seems to mediate behaviors when the reaction to threatening stimuli was prolonged but not brief. Davis and colleagues argued that such sustained reactions are more akin to anxiety than fear [26]. One problem with this fear/anxiety distinction is that it is entirely based on the eliciting stimulus and not the specific responses generated. Both the short and long-duration CS are producing exactly the same responses, potentiated startle and freezing. In this way the BST activated responses seem more like chronic fear than an entirely separate state. This can be contrasted with the distinction of pre-encounter and post-encounter defensive behavior. These states are differentiated both in terms of the stimulus conditions that bring them about and the responses they generate. This was recognized during the discussions of the negative valence RDoC panel. The system was organized linking the neurobehavioral system for pre-encounter defense with anxiety[2]. To capture the data surrounding the prolonged responses mediated by the BST, the RDoC system developed the sustained threat construct[4]. Note that the sustained threat category is specifically tied to situations where fear responses are maintained for long periods, indeed as written in the RDoC sustained threat may be a state that lasts from weeks to months; which is far longer than any of the experimental conditions actually tested.

Stimulus processing vs response generation

The canonical fear circuit serving post-encounter defense places the BLA primarily in a stimulus processing role. The BLA has neurons where CS information and US information converge and through long-term potentiation these cells will come to recognize these learned danger signals [50–54]. The BLA acts as a stimulus processing structure that signals downstream structures to generate fear behavior. Consistent with this, neural activity in the BLA spikes at danger stimulus onset and rapidly wanes even if the stimulus continues, suggesting that the BLA is sending an initiate signal that is interpreted by down-stream response generating structures (e.g. [53,54]). Within this model the principal response generating structure is the CN. The work by Davis and colleagues saw the BST as a substitute for the CN to generate fear responses that were prolonged [26,46]. The focus on the BST came about specifically because it projected to the same response producing regions as the CN. Thus, the initial conceptualization placed the BST clearly on the response generation side of the circuit (Figure 2). More recent evidence strongly challenges this view.

Consistent with the orientation that the BST is involved with prolonged duration responses, the initial experiments focused on testing of stimuli presented for a long duration. However, it is entirely possible the critical variable is not the length of the stimulus at test but at the time of induction. In the Davis experiments using a 15 min light, not only is the test longer but so is the duration of the threatening stimulus. The same could be said for the administration of CRH. Fear conditioning experiments offer an opportunity to more thoroughly evaluate this issue because the duration of the CS can be manipulated between the time of training and testing. Walker et al.[46] manipulated CS duration by having a variable CS during training and a long, fixed, duration 8 min CS at testing. While they attributed their findings to the long test stimulus duration at testing, the rats did receive pairings of the 8 min CS with shock during training. This question was more effectively addressed by Hammack et al. [55], who trained rats with either a 1 min or 10 min CS and tested them for 10 min. Their results were unequivocal; duration during training was critical. BST lesions had no effect on freezing in the rats trained with the 1 min CS. Importantly, even during the 10th min of testing, the freezing conditioned by a 1-min CS was equivalent in the lesioned and control rats. However, in animals trained with a 10 min CS, BST lesions reduced freezing across the entire test session. Even during the first minute of testing the BST lesion had an impact and there was no interaction of duration of testing and the lesion condition. It is not the prolonged nature of the response but the prolonged nature of the stimulus during training that matters.

Emerging Topics in Life Sciences (2022) **6** 467–477
https://doi.org/10.1042/ETLS20220003

Such results suggest that the BST lies on the stimulus processing side and not the response generation side. Assocaitive learning degrades as the interval between CS and US increases [56–58]. The BST may be acting to promote association formation when the CS is longer and more difficult to learn about. Certainly, it is urgent to deal with a threat that is 10 min away and recruiting a brain circuit capable of forming such associations would be advantageous.

One aspect of a long duration CS is that it makes US occurrence less predictable. Animals generally do poorer at accurately predicting long intervals such that the variance in estimates of interval duration is proportional to the duration of the interval being estimated [59,60]. Consistent with this, the BST is critical when a variable duration CS is used during training [44]. This predictability hypothesis was explicitly tested by Goode et al.[61]. They used a 10 s long tone CS but altered US placement. For rats in the delay conditioned group the CS termination was coincident with US onset as is typical in most conditioning experiments. For rats in the backward group, US termination was coincident with CS initiation (backward conditioning). It should be recognized that starting with Pavlov [24], backward conditioning was known to support some, albeit reduced, conditioning compared with the optimal delay conditioning procedure. Goode et al. [61] found that BST inactivation at the time of test reduced freezing to the backward trained but not the forward trained CS. The backward CS also caused greater BST activation as assessed by immediate early gene expression. In these experiments both CSs were of equal duration and both were short (10 s). The temporal arrangement between CS and US, not CS duration, was key to BST involvement. A similar effect was seen with a long 10 min contextual CS. Goode et al. [62], placed rats in a conditioning chamber for 10 min and gave a shock either 1 min or 9 min after placement. The BST was critical with the 9 min placement to shock interval but not the shorter 1 min interval. Again, it was not the duration of the CS but the temporal placement of the US that mattered. Goode and colleagues [61,62] conclude that the BST becomes important when CS and US are related in a way that makes temporal prediction of the US difficult.

Associations between stimuli are most readily formed when the stimuli have close contiguity and are embedded in predictable or contingent relationships [56–58,63]. It is easy to see how such relationships would drive the neural plasticity needed for learning [64]. However, the real world is rarely so optimally organized. As Bolles [4] pointed out, predators are unlikely to behave in ways that maximize the prey's ability to learn about them. Therefore, the brain is likely to have evolved mechanisms to allow learning under conditions that deviate from the ideal. Such mechanisms would be specifically recruited when learning is difficult. There is precedent for the recruitment of different brain systems when forming associations becomes more challenging. For example, contextual stimuli are composed of individual features that will vary as a context is explored making the contextual features have poor contiguity and contingency with the US. To overcome this issue, the hippocampus becomes necessary for learning contextual fear [65,66]. The hippocampus plays little role when the CS is a salient, brief and accurate predictor of the US. For example, if rats are placed in a context and receive parings of a 30 s tone with shock, the hippocampus is important for fear of the context but not the auditory stimulus learned at precisely the same moment [66]. The behavior generated by both the context and the tone is the same freezing response, it is the stimulus processing demands that require the different anatomy. Another way to weaken simple associative learning is to separate CS termination from US onset, a procedure Pavlov called trace conditioning [24]. If a 28 s gap is inserted between tone and shock the hippocampus is required for fear conditioning [67].

I would argue that both the hippocampus and the BST can act as stimulus processing 'front ends' for the post-encounter defensive mode. They expand the range of stimuli that can support fear conditioning. That is not to say that the function of these regions is solely dedicated to defense. The hippocampus provides context information for many types of decisions; it is just that fear circuitry can take advantage of the information processing that the hippocampus accomplishes. Less is known about the general function of the BST. Would backwards conditioning with a food US depend on the BST? The position I am putting forth is that both hippocampus and BST are used by the post-encounter fear system. They allow post-encounter responses such as freezing to occur in situations when danger is imminent, but the conditions are suboptimal for associative learning. The level of threat imminence in Goode et al.[61,62], and Waddell et al. [49], studies range between 10 s and 10 min and they generated a freezing response regardless of CS duration. This should be contrasted with pre-encounter defense where threat is far less imminent, and the behaviors are quite different. Fanselow et al. [11] found that rats did not freeze, they altered meal-patterns, when shock receipt was occurring about once every 24 h in a live-in context.

Emerging Topics in Life Sciences (2022) **6** 467–477
https://doi.org/10.1042/ETLS20220003

Stress and the distortion of the predatory imminence continuum

To be adaptive, defensive behavior topography needs to be matched to where the prey stands with respect to the predator. Predatory imminence provides a way of conceptualizing how this match occurs by describing 3 different modes of defense. Animals have more to do than defend themselves; another aspect of adaptive behavior is to restrict defense only to times when it is needed, so there is time for other adaptive behaviors. Such a restriction of defensive behavior could be obtained by having an appropriate threshold level of threat necessary to trigger a particular defensive mode. If such thresholds were set too low, defensive behavior would intrude into times when it was unnecessary. One defining characteristic of an anxiety disorder is when such intrusions compromise day to day functioning. Low thresholds for activation of defensive modes would result in a distortion of the predatory imminence continuum that infringes on nonaversively motivated adaptive behavior. Such distortions would be akin to chronic fear or anxiety (see Figure 3).

Experiencing traumatic stress is one condition that could lead to a distortion of the PIC. To test this idea, Hoffman et al. [68], exposed mice to a potent stressor, 10 unsignaled and inescapable footshocks randomly distributed over an hour. Then they gave the mice a battery of tests targeted at each mode of defense. Pre-encounter defense (anxiety) was tested by observing exploration in an open-field. Post-encounter defense (fear) was tested by scoring freezing following one trial contextual fear conditioning. Circa-strike defense (panic) was tested by scoring the burst of activity generated by the sudden onset of a mild but novel white noise presented in the stressful context. Each of the three responses was enhanced in the stressed mice suggesting a broad distortion across the entire predatory imminence continuum. Such stress effects can be quite prolonged. Rau et al. [69] gave rats a similar stressor and found that one trial fear conditioning was still enhanced

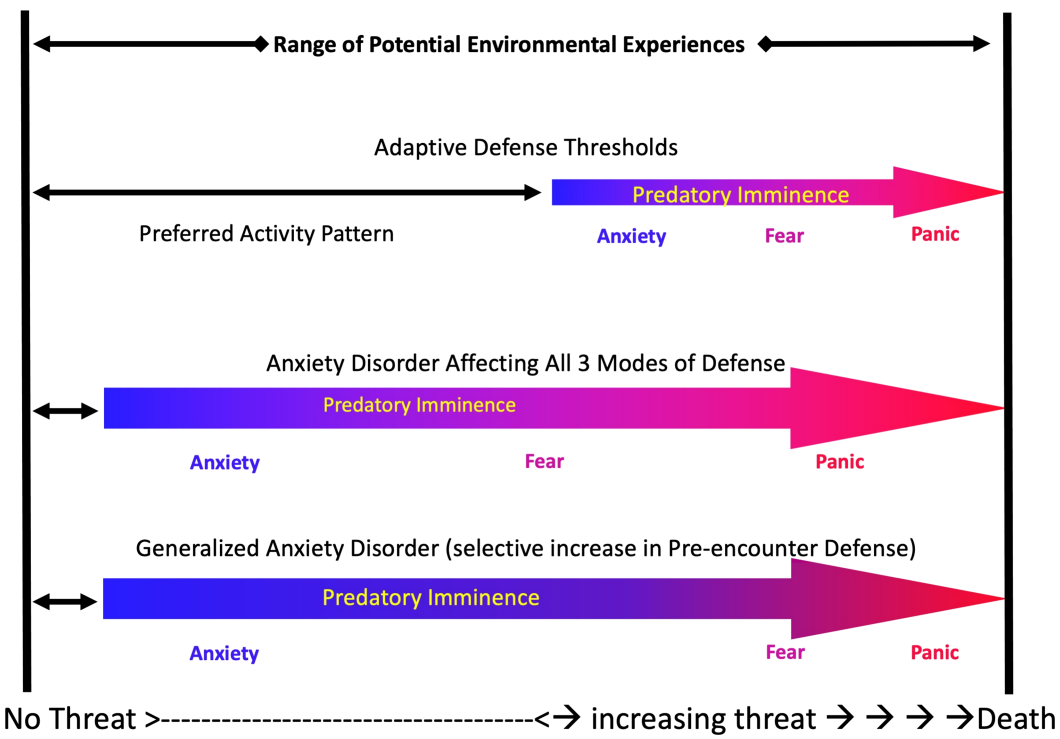

Figure 3. In the top arrow adaptive thresholds for anxiety, fear and panic confine defensive behavior to situations where threat is present leaving sufficient time for preferred activity patterns to fulfill nonthreat related needs.

The two lower arrows show distortions of the PIC such that defensive behavior occurs when unnecessary and intrudes into the preferred activity pattern. The middle arrow illustrates a situation where all three modes of defense were increased as observed by Hoffman et al. [68] following stress. The bottom arrow shows a selective distortion of the pre-encounter mode leading to chronic anxiety as in the case of generalized anxiety disorder.

Emerging Topics in Life Sciences (2022) **6** 467–477
https://doi.org/10.1042/ETLS20220003

3 months later. They did not test longer intervals, but such a prolonged impact of stress suggests some degree of permanence. Thus, stress is causing a long-term disruption of the PIC. Such findings fit well with the RDoC Sustained Threat construct, which is defined as an emotional state that is prolonged lasting weeks to months[4]. The stressed animals behave as if they were living through a condition of sustained threat.

Early-life stress may be particularly effective at causing a state of sustained threat [70]. Poulos et al. [71], gave the same stressor used in the Rau et al. study described above to young rats (19 days old) and tested them 2 months later in adulthood. They showed a heightened anxiety profile on the elevated plus maze and enhanced one trial contextual fear conditioning suggesting a distortion of at least the pre- and post-encounter defensive modes. In addition, even though the stress had happened 60 days earlier, the neuroendocrine profile of the BLA was altered. The early-life stressed rats had increased glucocorticoid receptors and decreased neuropeptide Y receptors specifically in the BLA. Additionally, the stressed rats had a severely disturbed diurnal rhythm for plasma corticosterone.

Conclusions: reconfiguring sustained threat

One of the goals of this perspective piece was to clarify the relationship and correspondence between the RDoC negative valence threat constructs and predatory imminence theory. The correspondence between Acute and Potential Threat constructs with pre-encounter and post-encounter defense is obvious [15]. To better integrate PIC and RDoC, the sustained threat construct could be reconceived of as a condition where the predatory imminence continuum has become distorted because of altered thresholds for eliciting the different states of defense. Under such conditions, defensive responses are sustained into periods when the level of threat does not warrant them. The ability for stress to cause a long-term alteration in the PIC fits well with RDoC's description of sustained threat as a state that lasts weeks to months[4]. Indeed, such changes may well be permanent. Besides stress there may be other conditions that result in a distorted PIC. Genetic factors are an obvious possible source of distortion [72]. This conceptualization of sustained threat does not suggest that defensive responses are continuous. Rather, it suggests that because of altered imminence thresholds for the different modes of defense, there will be periodic intrusions of anxiety, fear and/or panic when the environmental conditions are safe.

In our hands, stress caused a distortion across the entire continuum [68]. It is possible that some internal or external conditions would alter thresholds for eliciting just one particular mode of defense. For example, generalized anxiety disorder could stem from a low threshold for pre-encounter defense (Figure 3). If thresholds for circa-strike behavior were low, stimuli that would not necessarily generate panic would be more likely to do so and that could be a source of panic disorder. Given this conceptualization, future research should seek to determine the mechanisms that regulate these thresholds.

The overall approach taken in this review was to see the function of emotional reactivity from a neurobiological and ethological vantage. Doing so allows us to first see the adaptive function of these behaviors and provide an understanding of why these reactions evolved in the first place. Important also, is to see how these behaviors can go awry and thereby lead to anxiety disorders. I have suggested that one potential way this can happen is through conditions that change the thresholds that trigger different modes of defensive behavior distorting the PIC so that it disrupts adaptive behaviors that are not aversively motivated.

Anxiety disorders as a class are the most prevalent mental disorder and create a major emotional and economic cost on society [73]. This makes it critical to understand the causes of this prevalence and the nature of the symptoms experienced by those suffering from these disorders. Some insight into these questions is provided by taking a neuroethological approach as taken here. Prevalence stems from the phylogenetic urgency of defense [74]. Specific symptoms are not random but understandable from the specific phylogenetic protective function they serve.

Summary

- Predatory imminence continuum theory suggests that the psychological distance of threat determines both the form (topography) and vigor of defensive behavior.
- Defensive behavior is organized into 3 modes (pre-encounter, post-encounter and circa-strike) along a continuum of increasing threat.

- Two threat related constructs of the NIMH Research Domain Criteria (RDoC), potential threat and acute threat are related to pre-encounter and post-encounter defense, respectively.
- Sustained threat occurs when factors such as stress cause a long-term distortion of the predatory imminence continuum.

Competing Interests

M. S. Fanselow is a founding board member of Neurovation, Inc.

Open Access

Open access for this article was enabled through a transformative open access agreement between Portland Press and the University of California.

Funding

This work was supported by National Institutes of Health (U.S.A.) grant R01-MH115678 and the Staglin Center for Brain and Behavioral Health.

Abbreviations

BLA, basolateral amygdala; BST, bed nuclei of the stria terminalis; CN, central nucleus; CRH, corticotropin releasing hormone; CS, conditional stimulus; FPA, fear-potentiated startle; PIC, predatory imminence continuum; RDoC, research domain criteria; SSDR, species-specific defense reaction; US, unconditional stimulus.

References

1 American Psychiatric Association. (2013) *Diagnostic and Statistical Manual of Mental Disorders (Fifth ed.)*, American Psychiatric Publishing, Arlington, VA, pp. 5–25
2 Cuthbert, B.N. (2014) The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. *World psychiatry* **13**, 28–35 https://doi.org/10.1002/wps.20087
3 Fanselow, M.S. and & Lester, L.S. (1988) A functional behavioristic approach to aversively motivated behavior: predatory imminence as a determinant of the topography of defensive behavior. In *Evolution and Learning* (Bolles, R.C. and Beecher, M.D., eds), pp. 185–211, Erlbaum, Hillsdale, N. J
4 Bolles, R.C. (1970) Species-specific defense reactions and avoidance learning. *Psychol. Rev.* **77**, 32–48 https://doi.org/10.1037/h0028589
5 Miller, N.E. (1948) Studies of fear as an acquirable drive: I. Fear as motivation and fear-reduction as reinforcement in the learning of new responses. *J. Exp. Psychol.* **38**, 89–101 https://doi.org/10.1037/h0058455
6 Mowrer, O.H. (1951) Two-factor learning theory: summary and comment. *Psychol. Rev.* **58**, 350–354 https://doi.org/10.1037/h0058956
7 Fanselow, M.S. (1997) Species-specific defense reactions: Retrospect and prospect. In *Learning, Motivation, and Cognition: The Functional Behaviorism of Robert C. Bolles* (Bouton, M.E. and Fanselow, M.S., eds), pp. 321–341, American Psychological Association, Washington, D.C
8 Walther, F.R. (1969) Flight behaviour and avoidance of predators in thomson's gazelle (Gazella Thomsoni Guenther 1884). *Behaviour* **1969**, 184–220 https://doi.org/10.1163/156853969X00053
9 Qi, S., Hassabis, D., Sun, J., Guo, F., Daw, N. and Mobbs, D. (2018) How cognitive and reactive fear circuits optimize escape decisions in humans. *Proc. Natl Acad. Sci. U.S.A.* **115**, 3186–3191 https://doi.org/10.1073/pnas.1712314115
10 Fung, B.J., Qi, S., Hassabis, D., Daw, N. and Mobbs, D. (2019) Slow escape decisions are swayed by trait anxiety. Nat. *Hum. Behav.* **3**, 702–708 https://doi.org/10.1038/s41562-019-0595-5
11 Fanselow, M.S., Lester, L.S. and Helmstetter, F.J. (1988) Changes in feeding and foraging patterns as an antipredator defensive strategy: a laboratory simulation using aversive stimulation in a closed economy. *J. Exp. Anal. Behav.* **50**, 361–374 https://doi.org/10.1901/jeab.1988.50-361
12 Mobbs, D., Marchant, J.L., Hassabis, D., Seymour, B., Tan, G., Gray, M. et al. (2009) From threat to fear: the neural organization of defensive fear systems in humans. *J. Neurosci.* **29**, 12236–12243 https://doi.org/10.1523/JNEUROSCI.2378-09.2009
13 Mobbs, D. and Kim, J.J. (2015) Neuroethological studies of fear, anxiety, and risky decision-making in rodents and humans. *Curr. Opin. Behav. sci.* **5**, 8–15 https://doi.org/10.1016/j.cobeha.2015.06.005
14 Schmidt, S., Benke, C. and Pané-Farré, C.A. (2021) Purchasing under threat: changes in shopping patterns during the COVID-19 pandemic. *PLoS ONE* **16**, e0253231 https://doi.org/10.1371/journal.pone.0253231
15 Smith, N.J., Markowitz, S.Y., Hoffman, A.N. and Fanselow, M.S. (2022) Adaptation of threat responses within the negative valence framework. *Front. Syst. Neurosci.* **16**, 886771 https://doi.org/10.3389/fnsys.2022.886771
16 Mobbs, D., Petrovic, P., Marchant, J.L., Hassabis, D., Weiskopf, N., Seymour, B. et al. (2007) When fear is near: threat imminence elicits prefrontal-periaqueductal gray shifts in humans. *Science* **317**, 1079–1083 https://doi.org/10.1126/science.1144298
17 Kjelstrup, K.G., Tuvnes, F.A., Steffenach, H.A., Murison, R., Moser, E.I. and Moser, M.B. (2002) Reduced fear expression after lesions of the ventral hippocampus. *Proc. Natl Acad. Sci. U.S.A.* **99**, 10825–10830 https://doi.org/10.1073/pnas.152112399

18 Fanselow, M.S. and Dong, H.-W. (2010) Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron* **65**, 7–19 https://doi.org/10.1016/j.neuron.2009.11.031
19 Suarez, S.D. and Gallup, G.G. (1981) An ethological analysis of open-field behavior in rats and mice. *Learn. Motiv.* **12**, 342–363 https://doi.org/10.1016/0023-9690(81)90013-8
20 Bedore, C.N., Kajiura, S.M. and Johnsen, S. (2015) Freezing behaviour facilitates bioelectric crypsis in cuttlefish faced with predation risk. *Proc. R. Soc. B* **282**, 20151886 https://doi.org/10.1098/rspb.2015.1886
21 Roelofs, K. (2017) Freeze for action: neurobiological mechanisms in animal and human freezing. *Philos. Trans. R. Soc. B Biol. Sci.* **372**, 20160206 https://doi.org/10.1098/rstb.2016.0206
22 Roelofs, K., Hagenaars, M.A. and Stins, J. (2010) Facing freeze. *Psychol. Sci.* **21**, 1575–1581 https://doi.org/10.1177/0956797610384746
23 Helmstetter, F.J. and Fanselow, M.S. (1993) Aversively motivated changes in meal patterns of rats in a closed economy: the effects of shock density. *Anim. Learn. Behav.* **21**, 168–175 https://doi.org/10.3758/BF03213397
24 Pavlov, I.P. (in press) *Pavlov on the Conditional Reflex: Papers, 1903–1936. O. T. Yokoyama (Translator/Editor)*, Oxford University Press, London
25 Fanselow, M.S. (1990) Factors governing one trial contextual conditioning. *Anim. Learn. Behav.* **18**, 264–270 https://doi.org/10.3758/BF03205285
26 Walker, D.L., Toufexis, D.J. and Davis, M. (2003) Role of the bed nucleus of the stria terminalis versus the amygdala in fear, stress, and anxiety. *Eur. J. Pharmacol.* **463**, 199–216 https://doi.org/10.1016/S0014-2999(03)01282-2
27 Fanselow, M.S. (1994) Neural organization of the defensive behavior system responsible for fear. *Psychon. Bull. Rev.* **1**, 429–438 https://doi.org/10.3758/BF03210947
28 Fendt, M. and Fanselow, M.S. (1999) The neuroanatomical and neurochemical basis of conditioned fear. *Neurosci. Biobehav. Rev.* **23**, 743–760 https://doi.org/10.1016/S0149-7634(99)00016-0
29 Kim, J.J., Rison, R.A. and Fanselow, M.S. (1993) Effects of amygdala, hippocampus and periaqueductal gray lesions on short- and long-term contextual fear. *Behav. Neurosci* **107**, 1093–1098 https://doi.org/10.1037/0735-7044.107.6.1093
30 Yu, K., Ahrens, S., Zhang, X., Schiff, H., Ramakrishnan, C., Fenno, L. et al. (2017) The central amygdala controls learning in the lateral amygdala. *Nat. Neurosci.* **20**, 1680–1685 https://doi.org/10.1038/s41593-017-0009-9
31 Davis, M., Gendelman, D.S., Tischler, M.D. and Gendelman, P.M. (1982) A primary acoustic startle circuit: lesion and stimulation studies. *J. Neurosci.* **2**, 791–805 https://doi.org/10.1523/JNEUROSCI.02-06-00791.1982
32 Brown, J.S., Kalish, H.I. and Farber, I.E. (1951) Conditioned fear as revealed by magnitude of startle response to an auditory stimulus. *J. Exp. Psychol.* **41**, 317–328 https://doi.org/10.1037/h0060166
33 Davis, M. (1986) Pharmacological and anatomical analysis of fear conditioning using the fear-potentiated startle paradigm. *Behav. Neurosci.* **100**, 814–824 https://doi.org/10.1037//0735-7044.100.6.814
34 Davis, M., Falls, W.A., Campeau, S. and Kim, M. (1993) Fear-potentiated startle: a neural and pharmacological analysis. *Behav. Brain Res.* **58**, 175–198 https://doi.org/10.1016/0166-4328(93)90102-v
35 Landis, C. and Hunt, W. (1939) *The Startle Pattern*, Farrar & Rinehart, New York
36 Ray, W.J., Molnar, C., Aikins, D., Yamasaki, A., Newman, M.G., Castonguay, L. et al. (2009) Startle response in generalized anxiety disorder. *Depress. Anxiety* **26**, 147–154 https://doi.org/10.1002/da.20479
37 Rosen, J.B., Hitchcock, J.M., Sananes, C.B., Miserendino, M.J.D. and Davis, M. (1991) A direct projection from the central nucleus of the amygdala to the acoustic startle pathway: anterograde and retrograde tracing studies. *Behav. Neurosci.* **105**, 817–825 https://doi.org/10.1037/0735-7044.105.6.817
38 Campeau, S. and Davis, M. (1995) Involvement of the central nucleus and basolateral complex of the amygdala in fear conditioning measured with fear-potentiated startle in rats trained concurrently with auditory and visual conditioned stimuli. *J. Neurosci.* **15**, 2301–2311 https://doi.org/10.1523/JNEUROSCI.15-03-02301.1995
39 Rosen, J.B. and Davis, M. (1988) Enhancement of acoustic startle by electrical stimulation of the amygdala. *Behav. Neurosci.* **102**, 195–202 https://doi.org/10.1037/0735-7044.102.2.195
40 Swanson, L.W. and Petrovich, G.D. (1998) What is the amygdala? *Trends Neurosci.* **21**, 323–333 https://doi.org/10.1016/S0166-2236(98)01265-X
41 Gray, T.S. and Magnuson, D.J. (1992) Peptide immunoreactive neurons in the amygdala and the bed nucleus of the stria terminalis project to the midbrain central gray in the rat. *Peptides* **13**, 451–460 https://doi.org/10.1016/0196-9781(92)90074-d
42 Gray, T.S. and Magnuson, D.J. (1987) Neuropeptide neuronal efferents from the bed nucleus of the stria terminalis and central amygdaloid nucleus to the dorsal vagal complex in the rat. *J. Comp. Neurol.* **262**, 365–374 https://doi.org/10.1002/cne.902620304
43 Holstege, G., Meiners, L. and Tan, K. (1985) Projections of the bed nucleus of the stria terminalis to the mesencephalon, pons, and medulla oblongata in the cat. *Exp. Brain Res.* **58**, 379–391 https://doi.org/10.1007/BF00235319
44 Schmued, L.C. (1994) Diagonal ventral forebrain continuum has overlapping telencephalic inputs and brainstem outputs which may represent loci for limbic/autonomic integration. *Brain Res.* **667**, 175–191 https://doi.org/10.1016/0006-8993(94)91495-8
45 Lee, Y. and Davis, M. (1997) Role of the hippocampus, bed nucleus of the stria terminalis and amygdala in the excitatory effect of corticotropin releasing hormone on the acoustic startle reflex. *J. Neurosci.* **17**, 6434–6446 https://doi.org/10.1523/JNEUROSCI.17-16-06434.1997
46 Walker, D.L., Miles, L.A. and Davis, M. (2009) Selective participation of the bed nucleus of the stria terminalis and CRF in sustained anxiety-like versus phasic fear-like responses. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **33**, 1291–1308 https://doi.org/10.1016/j.pnpbp.2009.06.022
47 Hitchcock, J.M. and Davis, M. (1991) Efferent pathway of the amygdala involved in conditioned fear as measured with the fear-potentiated startle paradigm. *Behav. Neurosci.* **105**, 826–842 https://doi.org/10.1037//0735-7044.105.6.826
48 Liang, K.C., Melia, K.R., Miserendino, M.J.D., Falls, W.A., Campeau, S. and Davis, M. (1992) Corticotropin-releasing factor: long-lasting facilitation of the acoustic startle reflex. *J. Neurosci* **12**, 2303–2312 https://doi.org/10.1523/JNEUROSCI.12-06-02303.1992
49 Waddell, J., Morris, R.W. and Bouton, M.E. (2006) Effects of bed nucleus of the stria terminalis lesions on conditioned anxiety: aversive conditioning with long-duration conditional stimuli and reinstatement of extinguished fear. *Behav. Neurosci.* **120**, 324–336 https://doi.org/10.1037/0735-7044.120.2.324
50 Barot, S.K., Chung, A., Kim, J.J. and Bernstein, I.L. (2009) Functional imaging of stimulus convergence in amygdalar neurons during pavlovian fear conditioning. *PLoS ONE* **4**, e6156 https://doi.org/10.1371/journal.pone.0006156
51 Fanselow, M.S. and LeDoux, J.E. (1999) Why we think plasticity underlying pavlovian fear conditioning occurs in the basolateral amygdala. *Neuron* **23**, 229–232 https://doi.org/10.1016/S0896-6273(00)80775-8

52 Romanski, L.M., Clugnet, M.C., Bordi, F. and LeDoux, J.E. (1993) Somatosensory and auditory convergence in the lateral nucleus of the amygdala. *Behav. Neurosci.* **107**, 444–450 https://doi.org/10.1037//0735-7044.107.3.444
53 Quirk, G.J., Repa, J.C. and LeDoux, J.E. (1995) Fear conditioning enhances short-latency auditory responses of lateral amygdala neurons: parallel recordings in the freely behaving rat. *Neuron* **15**, 1029–1039 https://doi.org/10.1016/0896-6273(95)90092-6
54 Liu, J., Totty, M.S., Melissari, L., Bayer, H. and Maren, S. (2022) Convergent coding of recent and remote fear memory in the basolateral amygdala. *Biol. Psychiatry* **91**, 832–840 https://doi.org/10.1016/j.biopsych.2021.12.018
55 Hammack, S.E., Todd, T.P., Kocho-Schellenberg, M. and Bouton, M.E. (2015) Role of the bed nucleus of the stria terminalis in the acquisition of contextual fear at long or short context-shock intervals. *Behav. Neurosci.* **129**, 673–678 https://doi.org/10.1037/bne0000088
56 Kamin, L.J. (1954) Traumatic avoidance learning: the effects of CS-US interval with a trace-conditioning procedure. *J. Comp. Physiol. Psychol.* **47**, 65–72 https://doi.org/10.1037/h0061380
57 McAllister, W.R. (1953) Eyelid conditioning as a function of the CS-US interval. *J. Exp. Psychol.* **45**, 417–422 https://doi.org/10.1037/h0059534
58 Schneiderman, N. and Gormezano, I. (1964) Conditioning of the nictitating membrane of the rabbit as a function of CS-US interval. *J. Comp. Physiol. Psychol.* **57**, 188–195 https://doi.org/10.1037/h0043419
59 Gibbon, J. (1977) Scalar expectancy theory and Weber's law in animal timing. *Psychol. Rev.* **84**, 279–325 https://doi.org/10.1037/0033-295X.84.3.279
60 Treisman, M. (1963) Temporal discrimination and the indifference interval: implications for a model of the 'internal clock'. *Psychol. Monogr.* **77**, 1–31 https://doi.org/10.1037/h0093864
61 Goode, T.D., Ressler, R.L., Acca, G.M., Miles, O.W. and Maren, S. (2019) Bed nucleus of the stria terminalis regulates fear to unpredictable threat signals. *eLife* **8**, e46525 https://doi.org/10.7554/eLife.46525
62 Goode, T.D., Acca, G.M. and Maren, S. (2020) Threat imminence dictates the role of the bed nucleus of the stria terminalis in contextual fear. *Neurobiol. Learn. Mem.* **167**, 107116 https://doi.org/10.1016/j.nlm.2019.107116
63 Rescorla, R.A. (1967) Pavlovian conditioning and its proper control procedures. *Psychol. Rev.* **74**, 71–80 https://doi.org/10.1037/h0024109
64 van Rossum, M.C., Bi, G.Q. and Turrigiano, G.G. (2000) Stable Hebbian learning from spike timing-dependent plasticity. *J. Neurosci.* **20**, 8812–8821 https://doi.org/10.1523/JNEUROSCI.20-23-08812.2000
65 Fanselow, M.S. (2000) Contextual fear, gestalt memories, and the hippocampus. *Behav. Brain Res.* **110**, 73–81 https://doi.org/10.1016/S0166-4328(99)00186-2
66 Kim, J.J. and Fanselow, M.S. (1992) Modality-specific retrograde amnesia of fear following hippocampal lesions. *Science* **256**, 675–677 https://doi.org/10.1126/science.1585183
67 Quinn, J.J., Oommen, S.S., Morrison, G.E. and Fanselow, M.S. (2002) Post-training excitotoxic lesions of the dorsal hippocampus attenuate forward trace, backward trace, and delay fear conditioning in a temporally specific manner. *Hippocampus* **12**, 495–504 https://doi.org/10.1002/hipo.10029
68 Hoffman, A.N., Trott, J.M., Makridis, A. and Fanselow, M.S. (2022) Anxiety, fear, panic: an approach to assessing the defensive behavior system across the predatory imminence continuum. *Learn. Behav.* **50**, 339–348 https://doi.org/10.3758/s13420-021-00509-x
69 Rau, V., Decola, J.P. and Fanselow, M.S. (2005) Stress-induced enhancement of fear learning: an animal model of posttraumatic stress disorder. *Neurosci. Biobehav. Rev.* **29**, 1207–1223 https://doi.org/10.1016/j.neubiorev.2005.04.010
70 Sheth, C., McGlade, E. and Yurgelun-Todd, D. (2017) Chronic stress in adolescents and Its neurobiological and psychopathological consequences: an RDoC perspective. *Chronic stress (Thousand Oaks, Calif.)* **1**, 2470547017715645 https://doi.org/10.1177/2470547017715645
71 Poulos, A.M., Reger, M., Mehta, N., Zhuravka, I., Sterlace, S.S., Gannam, C. et al. (2014) Amnesia for early life stress does not preclude the adult development of posttraumatic stress disorder symptoms in rats. *Biol. Psychiatry* **76**, 306–314 https://doi.org/10.1016/j.biopsych.2013.10.007
72 Domschke, K. and Maron, E. (2013) Genetic factors in anxiety disorders. *Mod. Trends Pharmacopsychiatry* **29**, 24–46 https://doi.org/10.1159/000351932
73 Bandelow, B. and Michaelis, S. (2015) Epidemiology of anxiety disorders in the 21st century. *Dialogues Clin. Neurosci.* **17**, 327–335 https://doi.org/10.31887/DCNS.2015.17.3/bbandelow
74 Fanselow, M.S. and Sterlace, S.R. (2014) Pavlovian fear conditioning: Function, cause, treatment. In *The Wiley Blackwell Handbook of Operant and Classical Conditioning* (McSweeney, F.K. and Murphy, E.S., eds), pp. 117–141, John Wiley & Sons, Ltd, Oxford, U.K
75 Trott, J.M., Hoffman, A.N., Zhuravka, I. and Fanselow, M.S. (2022) Conditional and unconditional components of aversively motivated freezing, flight and darting in mice. *eLife* **11**, e75663 https://doi.org/10.7554/eLife.75663