CellPress

Review

What Can Ethobehavioral Studies Tell Us about the Brain's Fear System?

Blake A. Pellman[1] and Jeansok J. Kim[1,2,*]

Foraging-associated predation risk is a natural problem all prey must face. Fear evolved due to its protective functions, guiding and shaping behaviors that help animals adapt to various ecological challenges. Despite the breadth of risky situations in nature that demand diversity in fear behaviors, contemporary neurobiological models of fear stem largely from Pavlovian fear conditioning studies that focus on how a particular cue becomes capable of eliciting learned fear responses, thus oversimplifying the brain's fear system. Here we review fear from functional, mechanistic, and phylogenetic perspectives where environmental threats cause animals to alter their foraging strategies in terms of spatial and temporal navigation, and discuss whether the inferences we draw from fear conditioning studies operate in the natural world.

Trends

The expression of fear is shaped by an organism's evolutionary history and ecology, and fear has pervasive effects on neural systems and behavior, altering cost–benefit decision-making, spatial navigation, and even biological clocks, among others.

While the amygdala seems necessary for many forms of defensive behavior, emerging evidence suggests fear networks that include the hypothalamus, PAG, and mPFC, among others, are distributed throughout the brain and some may support fear responses without the amygdala.

Fear and reward-based decision-making are not mutually exclusive systems, and ethological experiments can examine how they interact to produce behavioral decisions that balance perceived costs and benefits.

The Nature of Fear

Fear is a defensive mechanism that rapidly activates coordinated bodily and behavioral responses to environmental stimuli that the brain, as a result of genetics and experience, has come to recognize as potentially dangerous. The fear system likely evolved because animals that successfully evade predatory threats while foraging for resources (e.g., food, water, mate, shelter) have a reproductive advantage over those that do not [1]. The brain's ability to instinctively recognize and respond accordingly to certain dangers and undergo experience-dependent plasticity to new threats is thus predicated by the **evolutionary pressure** (see Glossary) associated with each species' interactions within its ecological niche (Figure 1). For example, the main defensive behavior displayed by the woodland-living deer mouse, *Peromyscus maniculatus austerus*, is freezing, which provides a stealth function against its natural predators (e.g., the weasel's sensitivity to the prey's movement), whereas the vertical leap response of the arid region-residing deer mouse, *Peromyscus maniculatus gambeli*, is adaptive against its natural predators (e.g., the gopher snake's strike) [2]. Likewise, each species' biological history predisposes fear learning to certain stimuli and not others. A canonical example of this is the discovery that laboratory rats can easily learn, via **Pavlovian conditioning**, to associate sound/light with footshock (fear conditioning) and tastes with emetic agents (conditioned taste aversion) but cannot associate sound/light with emetics and tastes with footshock [3]. Presumably, rats have an evolutionary history of encountering the temporal coincidence of sound/visual (but not taste) cues with cutaneous pain of predatory attack and experiencing the delayed temporal overlap of taste (but not sound/visual) cues with gustatory pain of consuming poisonous food. By contrast, birds rely on visual acuity for searching for food and thus easily associate visual cues with emetic food [4], such as the monarch butterfly's wing pattern and its cardenolides poison. Thus, the rodent brain's capacities to rapidly and lastingly associate auditory and ocular inputs with cutaneous pain-inducing stimuli (including artificial footshock) and taste inputs with gustatory illness-inducing stimuli have

[1]Department of Psychology, University of Washington, Seattle, WA 98195-1525, USA
[2]Program in Neuroscience, University of Washington, Seattle, WA 98195-1525, USA

*Correspondence:
jeansokk@u.washington.edu (J.J. Kim).

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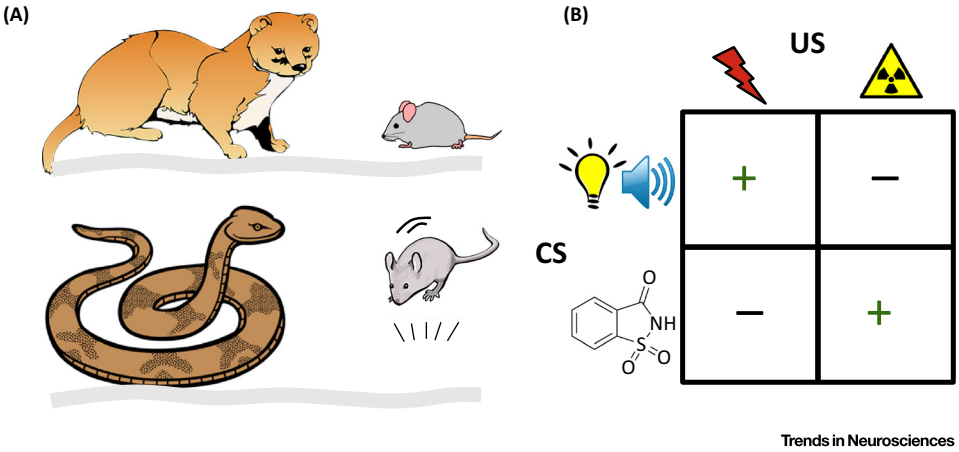

Trends in Neurosciences

Figure 1. Evolutionary Influences on Innate and Learned Fear. (A) Predatory history shapes prey's innate fear responses as illustrated by *Peromyscus maniculatus austerus* deer mouse's freezing to weasels and *Peromyscus maniculatus gambeli* deer mouse's jump (Jan Gillbank, 'Drawing of a grey mouse' October 27, 2012 via Wikimedia, Creative Commons Attribution 3.0 License) to gopher snakes [2]. *P. m. austerus* deer mice live in the coniferous forests of western Washington State and *P. m. gambeli* deer mice dwell in the arid grassland of eastern Washington State. (B) Ecological history predisposes fear learning. A classic study by John Garcia [3] found that rats easily acquired conditioned fear to bright/noisy conditioned stimulus (CS) paired to footshock unconditioned stimulus (US) and conditioned taste aversion to saccharin taste CS paired to X-rays (or LiCl) US. However, rats showed lack of conditioning to bright/noisy–X-ray (or LiCl) and saccharin–footshock pairings.

evolved as a genetic trait. Consistent with this notion, a recent study found that different populations of neurons dispersed in the basolateral nucleus of the amygdala (BLA) become activated to either context–footshock or saccharin–LiCl conditioning, but not to both [5], providing evidence of biologically predisposed learning at the cellular level within the same brain region. Similarly, a subset of distributed neurons in the dorsal pedal ganglion of the marine mollusk *Tritonia* are predetermined to develop into memory networks [6]. Such distinct neuronal information processing likely enables the same brain structures to perform diverse functions effectively.

In this review, we will examine the current status and future directions of fear research from an eco-evolutionary perspective in which animals' innate and acquired fear responses have been shaped by its ecological niche. First, we will briefly summarize recent findings from Pavlovian fear conditioning studies, the neurobiological picture of fear they have provided, and outline some major questions these studies have created. We will then discuss ethological approaches to studying fear and how they may provide a more comprehensive and naturalistic understanding of fear dynamics and its circuity.

Contemporary Models of Fear Conditioning

Current neurobiological models of fear have progressed from nearly a century of Pavlovian fear conditioning research in animals and humans (Figure 2). It is generally agreed in the field that information about the conditioned stimulus (CS; such as tones or lights for discrete 'cued' conditioning; experimental chambers for 'contextual' conditioning) and unconditioned stimulus (US; such as electric shocks, loud sounds) converge in the amygdala, where associative (Hebbian) synaptic plasticity (e.g., **long-term potentiation**, **LTP**) strengthens the CS afferents to amygdalar neurons, enabling the CS to autonomously produce conditioned fear responses (CR) [7–9]. Evidence further suggests that fear conditioning to different CS information occurs in distinct amygdalar nuclei, that is, the lateral/basolateral nucleus (LA/BLA) for tone CSs via the auditory thalamus and cortex; the basolateral complex for light CSs via the visual thalamus; and

Glossary

Circadian rhythm: rhythmic patterns of activity restricted to specific times of the daily cycle, such as the daytime (diurnal), night-time (nocturnal), or dawn-and-dusk times (crepuscular), which are generated by endogenous molecular clocks with approximately 24-h periods and 'entrained' to external cues (zeitgebers), such as sunlight, to remain environmentally relevant.

Evolutionary (or selective) pressure: any environmental factors (e.g., predation) that decrease members of a species' reproductive fitness given their current physiological and behavioral traits.

Genetic ablation: a method of using viruses to tag neurons that express a particular gene (e.g., induced by neural activation) and to selectively induce cell death in those neurons.

Hippocampal place cells: neurons that fire burst spikes preferentially when the animal visits a specific location in a familiarized environment; collectively, these cells are hypothesized to provide a neural representation of the spatial environment.

Immediate early gene: a gene that is expressed during or shortly following the onset of cellular activity (e.g., when a neuron fires an action potential).

Long-term potentiation (LTP): a sustained enhancement of synaptic transmission following high-frequency stimulation of afferent fibers that has been demonstrated in several brain structures, such as the hippocampus and amygdala, and exhibits properties desirable for information storage (rapidly induced, strengthened by repetition, input specificity, and associativity).

Optogenetics: a method of precisely controlling the activity of neurons achieved by virus-driven expression of light-sensitive receptors that can be activated or deactivated by a laser focused through optic fibers implanted in the brain.

Pavlovian (or classical) conditioning: the simplest form of associative learning where an initially neutral stimulus (conditioned stimulus, CS) – via contingent pairing with a biologically significant stimulus (unconditioned stimulus, US) that elicits an unlearned, reflexive behavior (unconditioned response, UR) – acquires a learned behavior