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A model of amygdala–hippocampal–prefrontal interaction in fear conditioning and extinction in animals

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ABSTRACT

Empirical research has shown that the amygdala, hippocampus, and ventromedial prefrontal cortex (vmPFC) are involved in fear conditioning. However, the functional contribution of each brain area and the nature of their interactions are not clearly understood. Here, we extend existing neural network models of the functional roles of the hippocampus in classical conditioning to include interactions with the amygdala and prefrontal cortex. We apply the model to fear conditioning, in which animals learn physiological (e.g. heart rate) and behavioral (e.g. freezing) responses to stimuli that have been paired with a highly aversive event (e.g. electrical shock). The key feature of our model is that learning of these conditioned responses in the central nucleus of the amygdala is modulated by two separate processes, one from basolateral amygdala and signaling a positive prediction error, and one from the vmPFC, via the intercalated cells of the amygdala, and signaling a negative prediction error. In addition, we propose that hippocampal input to both vmPFC and basolateral amygdala is essential for contextual modulation of fear acquisition and extinction. The model is sufficient to account for a body of data from various animal fear conditioning paradigms, including acquisition, extinction, reacquisition, and context specificity effects. Consistent with studies on lesioned animals, our model shows that damage to the vmPFC impairs extinction, while damage to the hippocampus impairs extinction in a different context (e.g., a different conditioning chamber from that used in initial training in animal experiments). We also discuss model limitations and predictions, including the effects of number of training trials on fear conditioning.

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1. Introduction

Several brain structures – including the amygdala, hippocampus, and ventromedial prefrontal cortex (vmPFC) – are involved in fear conditioning and extinction, yet the functional contribution of each brain area and the nature of their interactions are not clearly understood. Here, we propose a neural network model that addresses the function of these brain areas in fear conditioning and extinction.

In classical conditioning, a previously-neutral stimulus (the conditioned stimulus or CS) is repeatedly paired with an unconditioned stimulus (US) that evokes a reflexive response. Over time, the CS itself can come to evoke an anticipatory response, the conditioned response or CR. In somatomotor conditioning, the US may be an airpuff or mild periorbital shock that evokes a protective eye closure; the CR is then an anticipatory eyeblink, so that the eye is partially closed at the time of expected US arrival. Prior work has shown that the cerebellum is the necessary and sufficient substrate for eyeblink conditioning (Christian & Thompson, 2003), but that other areas including the hippocampus may also participate and may even be critical, depending on the nature and timing of the various stimuli.

Other kinds of classical conditioning depend on other brain substrates. For example, fear conditioning in animals refers to a broad class of paradigms in which the CS is paired with an aversive stimulus, such as electric shock; with repeated pairings, the CS

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can come to evoke a range of "fear responses," including physiological responses (changes in heart rate, blood pressure, etc.), and behavioral responses (freezing, startle, etc.). The choice of CR to be measured in a particular experiment depends on many factors including the species under study. For example, heart rate conditioning has been used in rabbits (Gibbs, Prescott, & Powell, 1992; Kapp, Frysinger, Gallagher, & Haselton, 1979), which typically show a decrease in heart rate (e.g., bradycardia) in response to a CS paired with shock. In contrast, a large body of research on rats has considered the freezing CR, a brief cessation of ongoing behavior in response to a CS paired with shock (Duvarci, Popa, & Pare, 2011; LeDoux, 1992). Fear conditioning shares many features with somatomotor conditioning, including a negatively accelerated learning curve, extinction of learned responses when the CS no longer predicts the US, and sensitivity to context. However, there are also differences: for example, whereas eyeblink CRs are typically acquired following hundreds of CS–US pairings in the rabbit, fear responses such as heart-rate changes and freezing can be acquired within a few (or even a single) CS–US pairings.

Below, we first review literature on behavioral results obtained from fear conditioning paradigms in animals, then review the known neural substrates of this learning, and finally discuss how the model proposes these brain substrates interact during fear conditioning. We then describe the model simulations, and present simulation data showing that this model of amygdala–hippocampal–prefrontal interaction provides a qualitative fit to a range of data obtained from animal fear conditioning studies.

1.1. Relevant empirical background: behavioral paradigms and neural substrates

Below, we discuss behavioral paradigms of fear conditioning, and then discuss neural substrates of fear conditioning.

1.1.1. Behavioral paradigms of fear conditioning

Whereas acquisition involves increased expression of the CR as a result of CS–US pairing, extinction refers to the reduction of CR expression when the CS is no longer paired with the US. As with other kinds of learning, extinction of fear CRs could be a consequence of either erasing previously acquired fear memories or forming inhibitory fear responses that overcome or compete with previously acquired fear responses. Most studies have shown that fear extinction involves forming new extinction memories that overrule the previously-acquired fear response (Bouton, Westbrook, Corcoran, & Maren, 2006; Milad & Quirk, 2002; Myers & Davis, 2007).

In addition to the acquisition and extinction of fear, other conditioning procedures have also examined renewal and reacquisition (Bouton & King, 1983; Herry et al., 2008; Hobin, Ji, & Maren, 2006; Ji & Maren, 2007; Milad, Orr, Pitman, & Rauch, 2005; Zelikowsky, Pham, & Fanselow, 2011). The reacquisition paradigm involves three phases. In the first phase, all subjects are trained to acquire a fear response in one context (e.g., a training chamber with certain features and odors). In the second phase, all subjects are given extinction trials in a different context (e.g., a different conditioning chamber with different features and odors). In the last phase, half of the subjects group are trained on fear acquisition using the acquisition context (i.e. as in the first phase), and the other half of subjects are trained on fear acquisition using the extinction context (i.e., as in the second phase) (Bouton & King, 1983). Interestingly, studies have found that reacquiring fear responses is faster than in the initial fear acquisition phase (Leung, Bailey, Laurent, & Westbrook, 2007). Other fear conditioning procedures have examined the effect of changing the background context during the extinction or reacquisition phase (Bouton, 1984; Bouton & King, 1983; Bouton & Peck, 1989; Corcoran & Maren, 2001). In experimental settings, context usually refers to spatial and olfactory features of the testing box and/or other external cues that might have been used by the subjects during learning. Studies have shown that extinction learning is quicker when it occurs in a different context than that used in the fear acquisition phase (Corcoran & Maren, 2001; for discussion see Delamater, 2004). Similarly, reacquisition in the third phase is quicker when using the acquisition rather than extinction context (Bouton & King, 1983; Milad et al., 2005). In sum, the goal of this project is to link all these behavioral paradigms in one coherent framework. Table 1 describes these fear conditioning tasks.

Table 1
Tasks simulated in the model. In all experiments, contexts are referred to as A and B, cues as X. "AX−" means X is presented in context A with no US, while AX + means X is presented in context A with the US in the same trial. ';' Separates different trials in the same phase. In each of these phases, the corresponding context is presented to the network by itself before cue presentation mimicking the presence of animal inside a box (see Experimental Procedure).

Simulation	Phase 1	Phase 2	Phase 3
Fear conditioning and extinction	AX+	AX−	
Extinction in a new context	AX+	BX−	
Renewal	AX+	BX−	AX−, BX−
Reacquisition	AX+	BX−	AX+, BX+

1.1.2. Neural substrates of fear conditioning

Various lesion, physiological, and imaging studies have investigated the neural basis of fear conditioning in rats and rabbits, as well as other animals. Most of these studies have found that three different brain areas have been implicated in fear conditioning: amygdala, hippocampus, and vmPFC. Fig. 1 shows a simplified anatomical map of their connectivity. Research on fear conditioning has been attempting to elucidate the specific contribution of each brain area to fear conditioning. Below, we review empirical studies on the role of amygdala, hippocampus, and vmPFC in fear conditioning and extinction (for a review, see Jovanovic & Ressler, 2010; Maren & Quirk, 2004).

1.1.2.1. Amygdala. The amygdala is a collection of highly differentiated nuclei that belong to different functional systems (Swanson & Petrovich, 1998). One subregion of the amygdala is the central nucleus (CeA), a part of the motor striatum with mainly GABAergic projections to autonomic systems. Another major subregion of the amygdala is the lateral and anterior basolateral nuclei (BLA), which may be considered ventromedial extensions of the temporal and frontal lobes with mainly glutamatergic projections (Swanson & Petrovich, 1998).

The central nucleus of the amygdala (CeA) is involved in the initiation of various fear responses, including freezing and heart rate changes (Duvarci et al., 2011). Conditioned freezing and heart rate changes appear to be driven by outputs from CeA through the lateral hypothalamus to the cardioinhibitory neurons in the dorsal vagal nucleus and/or the nucleus of the solitary tract (McCabe, Gentile, Markgraf, Teich, & Schneiderman, 1992; Wiersma, Bohus, & Koolhaas, 1993). Specifically, the CeA projects to the parasympathetic nervous system (driving freezing, heart rate changes, respiratory changes), the hypothalamus (driving the release of stress hormones), and brainstem motor areas (driving motor responses such as freezing). Stimulation of CeA can produce altered heart rate (Cox et al., 1986), and neurons in the CeA show CS-evoked learning-related responses during both heart rate and eyeblink conditioning (e.g. Rorick-Kehn & Steinmetz, 2005); these responses are correlated with the magnitude of the CR in heart rate conditioning (Pascoe & Kapp, 1985). In freezing experiments, lesioning CeA abolishes fear responses (Davis, 1992; LeDoux, 1992; McCabe et al.,