Chapter 11

Computational Models of the Amygdala in Acquisition and Extinction of Conditioned Fear

Guoshi Li

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/67834

Abstract

The amygdala plays a central role in both acquisition and expression of conditioned fear associations and dysregulation of the amygdala leads to fear and anxiety disorders such as posttraumatic stress disorder (PTSD). Computational modeling has served as an important tool to understand the cellular and circuit mechanisms of fear acquisition and extinction. This review provides a critical appraisal of existing computational modeling studies of the amygdala and extended circuitry in acquisition and extinction of learned fear associations. It gives a broad overview of the computational techniques applied to amygdala modeling with an emphasis on how computational models could shed light on the neural mechanisms of fear learning, inform experimental design, and lead to specific, experimentally testable hypotheses. It covers different types of published models including rule-based models, connectionist type models, phenomenological spiking neuronal models, and detailed biophysical conductance-based models. Specific attention is given to the evolution of amygdala models from simple rule-based and connectionist type models to more sophisticated and biologically realistic models. Future direction on computational modeling of the amygdala and associated networks in emotional learning is also discussed.

Keywords: learning, plasticity, biophysical, neuron, network

1. Introduction

Anxiety and fear are normal human emotional states and the ability to efficiently learn about and appropriately respond to cues and contexts that predict or signal danger is critical for survival across species [1]. However, when fear becomes too generalized, this response mechanism might become very harmful [2]. Over-generalized fear could lead to anxiety disorders, especially disorders of fear regulation, including phobia, panic disorder, and posttraumatic stress disorder (PTSD). Posttraumatic stress disorder (PTSD), in particular, posts a great threat

to human health. Posttraumatic stress disorder (PTSD) is a serious psychiatric disorder that develops after exposure to a terrifying event or ordeal in which grave physical harm occurred or was threatened. People with PTSD may startle easily, become emotionally numb, more aggressive, or even violent [2]. In addition, they lose interest in life and have great difficulty in feeling affectionate. If not treated appropriately, PTSD may also lead to other mental complications such as depression, causing great suffering to the patients and their families. Posttraumatic stress disorder (PTSD) is the fifth most common psychiatric disorder with an occurrence rate of about 8% in the United States [3]. Overall, PTSD affects about 7.7 million American adults, but it can occur at any age, including childhood [4].

As the gateway to understand the pathophysiology of PTSD and other anxiety disorders, researchers used the fear conditioning paradigm, based on Pavlovian classical conditioning, which involves pairing an emotionally neutral conditioned stimulus (CS) with an innately aversive unconditioned stimulus (US). Animals appear to respond to the US with a constellation of physiological changes collectively known as the unconditioned response (UR). Following pairing of the CS in presentation with the US, the CS comes to elicit a conditional response (CR), which is generally similar to the UR [5]. Pavlov also noted that after successful conditioning, repeated presentation of the CS in the absence of US causes conditioned fear responses to rapidly diminish, a phenomenon termed fear extinction [6, 7]. Following extinction training, the animal would no longer respond to a CS that no longer predicts aversive stimuli [5]. The classical Pavlovian fear conditioning paradigm is the most valuable model to understand the pathological neural mechanism of PTSD and other anxiety disorders. Studies indicated that patients with PTSD demonstrate behavioral sensitization to stress and over-generation of the CS-US responses [8–10]. In addition, PTSD patients show delayed or impaired extinction learning as compared to controls [11, 12]. Thus, understanding the neurobiological mechanisms of fear conditioning and extinction is of great significance to understand the pathogenesis of PTSD and other fear-related mental disorders.

Taking advantage of the tractability of the fear conditioning paradigm, numerous studies have identified that the amygdaloid complex, an almond-shaped brain structure located within the medial temporal lobe, plays a central role in the acquisition and expression of learned fear associations [13, 14]. Indeed, damage of the amygdala impairs fear acquisition and expression, while electrical stimulation of the amygdala produces autonomic fear behaviors [15]. Anatomically, the amygdala receives sensory inputs from a wide range of cortical and subcortical areas including the thalamus, olfactory bulb and sensory cortex and polymodal sensory information from the prefrontal cortex (PFC), perirhinal cortex and hippocampus [16]. The projection of the amygdala is also widespread including cortical regions (especially PFC and the medial temporal lobe), striatum, hypothalamus, and brain stem areas [16, 17]. The amygdala could thus integrate a variety of sensory information and influence executive, motor, and memory functions via its divergent projections to downstream brain areas. The interactions between the amygdala, PFC and hippocampus are particularly important for the regulation and maintenance of fear memory [18, 19]. Indeed, subjects with PTSD show hyperactivation in the amygdala as well as reduced volume and activation of PFC and hippocampus [18, 20]; the reduced top-down control from the PFC and hippocampus may lead to hyper-responsive amygdala output to fearful stimuli [21].

http://dx.doi.org/10.5772/67834

Due to the central role of amygdala in mediating fear acquisition and expression, computational modeling of signal processing within the amygdala circuit and its interactions with other brain areas such the PFC and hippocampus has been a subject of continuous interest. With improved understanding of the neurobiology of fear learning and rapid advance in computational power, computational models of the amygdala and extended circuits have evolved from the early simple rule-based models (e.g., [22]) to anatomically constrained connectionist type models (e.g., [23, 24]), to large-scale spiking neuron models (e.g., [25]), and more biophysically realistic conductance-based models [26–31]. These models addressed the various aspects of the functional roles of the amygdala in emotional learning including relative contribution of the thalamo-amygdala and cortical-amygdala pathways in fear conditioning [23, 32], contextual modulation of fear acquisition and extinction [25, 33], neural mechanisms of extinction [26], impact of infralimbic cortex in fear suppression [27, 34], and the role of competitive synaptic interactions in fear memory formation [28, 29]. These computational studies have significantly improved our understanding of the acquisition, maintenance, and regulation of learned fear associations. Below is a brief description of the amygdala circuitry critical for fear learning followed by a detailed review of the major computational studies of the amygdala in acquisition and extinction of conditioned fear.

2. The amygdala circuit

The amygdala consists of four major components that are critical for the acquisition and expression of conditioned fear including lateral amygdala (LA), basal amygdala (BA), central amygdala (Ce), and the intercalated (ITC) cell clusters (**Figure 1A**; [15, 35]). In auditory fear

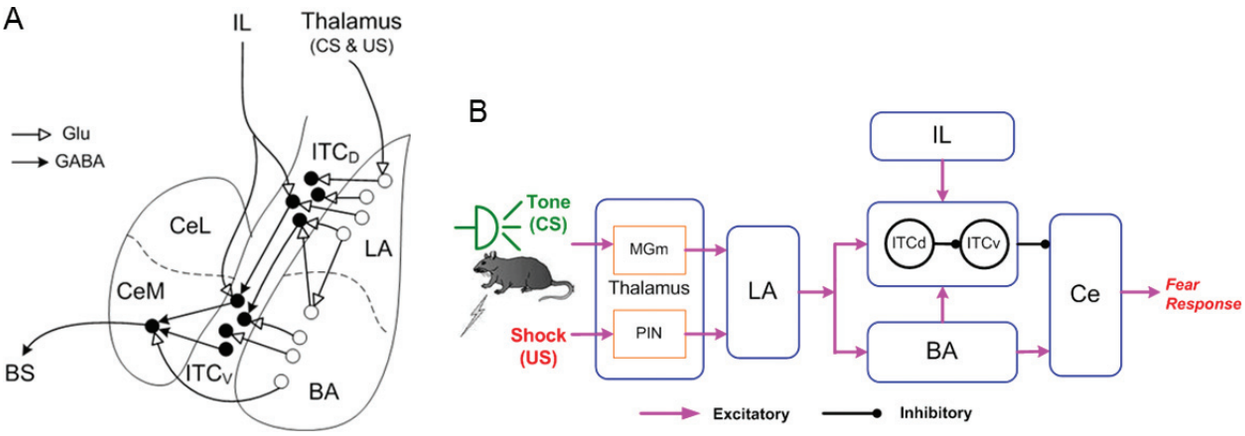

Figure 1. The amygdala circuitry for processing conditioned fear. (A) Scheme showing connectivity of the amygdala (adapted from Ref. [27]). The LA receives thalamic inputs conveying CS and US information. LA projects to the BA, and ITC neurons located dorsally (ITC_D), which in turn project to ITC cells located more ventrally (ITC_V). Intercalated cells located more ventrally (ITC_V) contribute GABAergic projections to CeM. The BA sends excitatory inputs to both ITC_D and ITC_V cells and to CeM. The infralimbic (IL) cortex also projects to both ITC_D and ITC_V cells. The CeM projects to brainstem structures mediating fear responses. (BS) Brainstem; (Glu) glutamate. (B) In auditory fear conditioning, convergence of tone (CS) and foot-shock (US) inputs in LA leads to potentiation of CS inputs, resulting in larger tone responses in LA. Increased LA responses are relayed to the Ce via the BA and the ITC cell clusters, eliciting fear responses via successive projections to brain stem and hypothalamic sites. As a result, rats learn to freeze to tones that predict foot shock. MGm: medial genicular body; PIN: posterior intralaminar nucleus.

conditioning, paring of the tone (CS) and foot-shock (US) inputs in LA potentiates the CS inputs, resulting in larger tone responses in LA (**Figure 1B**; [36–38]). Increased LA responses are relayed to the Ce via the BA [39] and the ITC cell clusters [35], eliciting fear responses via successive projections to brain stem and hypothalamic sites [13]. As a result, animals learn to freeze to tones that predict foot-shock. Those four nuclei (LA, BA, Ce, and ITC) have different physiological properties and serve distinct roles in fear conditioning and extinction, which are descried below.

2.1. The lateral amygdala (LA)

The LA is widely accepted to be a key site of synaptic events that contribute to fear learning [26, 35, 40]. It contains pyramidal-like glutamatergic projection neurons and local circuit γ-aminobutyric acid (GABA)-ergic interneurons [41]. In auditory fear conditioning, the tone (CS, auditory information) and foot-shock (US, somatosensory information) inputs are delivered to LA from the auditory cortex and auditory thalamus [37, 42]. Individual neurons within the LA respond to both auditory and somatosensory stimuli, suggesting convergence of CS and US inputs at the cellular level [40]. Conditioning significantly enhances the responses of LA neurons to CS input, which correlates tightly with the freezing behaviors of animals [36, 37]. Consistent with the anatomical data, lesioning or functionally inactivating the LA prior to training leads to deficits in fear conditioning [43, 44], suggesting that the LA is critically involved in the formation and storage of conditioned fear memories [13, 15, 40].

2.2. The basal amygdala (BA)

The BA plays an important role in contextual fear conditioning, fear extinction, and context-dependent fear renewal [44–46]. First, the BA constitutes a major route to relay CS and US information from LA to Ce, the output station of the amygdala that generates fear responses [39]. Consistently, posttraining BA lesions block the expression of conditioned fear responses [47]. Second, the BA receives contextual information from the hippocampus, a brain structure responsible for assembling contextual representations and transmitting these representations to the amygdala for association with US [15, 48]. Indeed, pharmacological inactivation of the BA prevents context-dependent fear renewal [45, 46]. Last, the BA also receives afferent inputs from the infralimbic (IL) cortex, a cortical region in the medial prefrontal cortex (mPFC) that is implicated in extinction of conditioned fear responses [49]. When BA is inactivated in a targeted and controlled manner, fear extinction is blocked completely, demonstrating that BA is necessary for the acquisition of extinction [46].

Interestingly, the differential functional roles of BA in fear acquisition and extinction are mediated by distinct neuronal circuits within the BA. Herry et al. identified that BA contains two distinct subpopulations of neurons (fear neurons and extinction neurons) whose activities correlate tightly with expression of high and low fear [46]. The fear neurons acquire CS responses as a result of fear conditioning but lose them following extinction training. By comparison, extinction cells remain unresponsive during fear conditioning, but become CS responsive during extinction training. The study demonstrated that a switch in the balance of the activity of fear and extinction neurons is essential to trigger behavioral transition

between fear and extinction. It was further revealed that fear and extinction neurons are differentially connected with the hippocampus and mPFC, respectively, consistent with the well-documented roles of these two structures in contextual fear conditioning and extinction [50–52].

2.3. The central amygdala (Ce)

The Ce is the output station of the amygdala, which constitutes the interface to fear response systems [15]. Electrical stimulation of Ce generates fear behavioral responses [53], while lesions of the Ce impair both the acquisition and expression of conditioned fear [54, 55]. The Ce receives projections from both the BA and the ITC cells and sends dense projections to various brain stem structures involved in generating the behavioral and autonomic fear responses [56]. Anatomically, Ce can be divided into two subnuclei, the lateral sector of the Ce (CeL) and the medial sector of the Ce (CeM) (**Figure 1A**; [56]). Both the CeL and CeM contain GABAergic inhibitory neurons and CeL inhibits CeM [56].

2.4. The intercalated (ITC) cell cluster

Another component that is critical for conditioned fear responses is the intercalated (ITC) cell cluster that is located at the basolateral amygdala (LA & BA; BLA) and Ce border [57, 58]. Intercalated (ITC) cell clusters are GABAergic neurons and constitute an important alternate pathway (besides the BA) to relay CS/US information from the LA to Ce (**Figure 1B**; [35]). When ITC cells are damaged with pharmacological manipulation in rats, extinction memory is disrupted, mimicking the behaviors observed in anxiety disorders [59, 60]. Intercalated (ITC) cell clusters are ideally positioned to control Ce excitability because they receive glutamatergic inputs from principal LA and BA neurons and in turn generate feedforward inhibition in Ce cells (**Figure 1B**; [61, 62]). In addition, ITC neurons located dorsally (ITC_D) at the BLA-Ce border inhibit more ventral ones (ITC_V) [63], thereby allowing for a spatiotemporally differentiated gating of impulse traffic between BLA and Ce [62]. Moreover, ITC neurons receive massive projection from the IL cortex [64, 65] and stimulation of the IL substantially reduces conditioned fear responses [50, 66, 67], an inhibitory process believed to be mediated by ITC clusters [19, 35].

3. Computational models of the amygdala

3.1. Early computational models of fear conditioning

Early computational models of fear conditioning focused on learning theory or rules that describe the association between CS and US, i.e., associative learning theories (for an excellent review, see Ref. [68]). One representative early model of associative learning is the Rescorla-Wagner model, which proposed a learning rule based on prediction error [22]. Based on the Rescorla-Wagner rule, the change in associative strength of the individual components of a compound CS (e.g., AB) when paired with the US can be represented as:

$$\begin{aligned} \Delta V_{\mathrm{A}} &= \alpha_{\mathrm{A}}\beta(\lambda - V_{\mathrm{AB}}) \\ \Delta V_{\mathrm{B}} &= \alpha_{\mathrm{B}}\beta(\lambda - V_{\mathrm{AB}}) \end{aligned} \tag{1}$$

where V_{AB} is the associative strength of the compound AB and must be specified in terms of the strengths of the individual components, e.g., $V_{\mathrm{AB}} = V_{\mathrm{A}} + V_{\mathrm{B}}$. The parameters α_{A} and α_{B} represent the stimulus salience, β is the learning rate, and λ represents the asymptotic value of associative strength for a particular US. According to Eq. (1), the associative change for the stimulus A after the compound AB is reinforced with the US is determined by the difference between the asymptotic value λ and the combined associative strength of A and B. Thus, the predictive error for associative strength change of a particular stimulus is governed by the combined associative strength of all stimuli present on a trial instead of that particular stimulus only. The introduction of such combined predictive error enables the model to explain the phenomena of blocking and conditioned inhibition [22].

Following the Rescorla-Wagner model, many other models of associative learning have been developed to extend or improve the Rescorla-Wagner rule [69–71]. For example, to account for the variations in the associability of stimuli with reinforcement, Mackintosh proposed a theory of selective attention by incorporating the notion of variable associability [69]. The learning rule is slightly modified from the Rescorla-Wagner rule:

$$\Delta V_{\mathrm{A}} = S\alpha_{\mathrm{A}}(\lambda - V_{\mathrm{A}}) \tag{2}$$

where S is the learning rate parameter. The main difference between the Mackintosh rule and the Rescorla-Wagner rule (Eq. (1)) is that the associability parameter α_{A} is modifiable dependent on the predictability of the stimulus A. If the stimulus A can predict the outcome better than other stimuli present on a particular trial, α_{A} will increase and decrease otherwise. With that modification, the Mackintosh model ensures that the associative change is not only dependent on a cue's associative strength, but also on the past relative predictive power of the cue. As each of those rule-based models attempts to best explain certain phenomena of the classical conditioning, they fail to offer a complete and satisfactory account of varying effects of associative history. To overcome this limitation and construct a "unified" theory of associative learning, Le Pelley proposed a hybrid model of associative learning that reconciles the effects of associative history [68].

Most of the early computational models of fear conditioning can be categorized as behavioral models in the sense that they attempted to reproduce many observed phenomena in classical conditioning such as generalization, blocking, and conditioned inhibition. Although these early models are useful in describing the associative process between the CS and US, they did not address how the CS and US information is processed within the amygdala circuit nor they took into account the neuroanatomical substrates underlying associative learning. Hence, these models provide little insights on the neuronal mechanisms of fear conditioning and extinction.

3.2. Connectionist models

As the neurobiological data of fear conditioning accumulated, connectionist or artificial neural network models of the amygdala were developed by researchers (e.g., [23, 24, 32]). Compared

with early rule-based models, these connectionist models consist of multiple connected computational units (corresponding to a single neuron or a group of neurons) and take into consideration the anatomical structures of the amygdala circuit. There are two main features of connectionist-type models. First, the output of computational or neural units usually represents the firing rate or activation level of individual neurons, neural populations or a brain region. Second, the connection strength between computational units is usually modified based on Hebbian-type learning algorithm. For example, the activation levels of all neural units in a connectionist model of amygdala-hippocampal-prefrontal interaction [33] are computed as:

$$A_j(t) = f\left(\sum_{i=1}^{n} u_{ji}(t)x_i(t)\right) \tag{3}$$

where $u_{ji}(t)$ is the connection weight from unit i to unit j, n is the number of input units, and $x_i(t)$ is the input unit with binary value of either 0 (inactive) or 1 (active); f is the logistic sigmoid function

$$f = \frac{1}{1+e^{-x}} \tag{4}$$

Another way to capture amygdala activation is to use the classical mean-field formalism [72]:

$$\frac{dV_i}{dt} = \frac{F\left(\sum_j W_{ij}^{\text{Input}} * U_j^{\text{Input}}\right) - V_i}{\tau} \tag{5}$$

$$U_i = f_{\text{sigmoid}}(V_i) - \sum_k W_{ik}^{IN} * U_k^{IN} \tag{6}$$

where τ is the time constant, V_i and U_i represent membrane potential and firing rate of neuron i, U_j^{Input} and U_k^{IN} are the firing rates of input neuron j and inhibitory neuron k, respectively; W_{ij}^{Input} and W_{ik}^{IN} are the synaptic weights of the input and inhibitory connections; and F and f are nonlinear threshold and sigmoid functions, respectively. The synaptic weight is updated according to a Hebbian-type learning rule, which depends on the firing rates of pre and postsynaptic neurons [72]:

$$\frac{dW_{ij}}{dt} = ERR * \alpha U_j^{\text{Pre}} U_i^{\text{Post}} \tag{7}$$

where ERR is the prediction error (difference between the US value and amygdala output), α is the learning rate, U_j^{Pre} and U_i^{Post} are the firing rates of pre and postsynaptic neurons, respectively.

Early connectionist models of fear conditioning focused on the relative contribution of the thalamic versus the cortical pathway in fear conditioning. Armony et al. developed an anatomically constrained neural network model of fear conditioning based on known anatomical

and physiological observations [23]. The connectionist model focused on areas of convergence of CS and US pathways and specifically examined information processing via the two parallel sensory pathways to the amygdala from the auditory thalamus and the auditory cortex. The model considered tone input with a specific frequency associated with a mild foot-shock and was trained by a modified Hebbian-type learning rule. The model was able to reproduce frequency-specific changes of the receptive fields known to exist in the auditory thalamus and amygdala. In a following study [32], the model was used to simulate processing capacity of the thalamo-amygdala pathway by making lesions of the auditory cortex. The model predicted that lesions of the cortical pathway would not affect the specificity of the behavioral response to a range of frequencies centered on the training frequency and were consistent with experimental observations. However, in both studies [23, 32], extinction and other related phenomena were not included in the model.

Later connectionist models of fear conditioning aimed to replicate a wide range of conditioning phenomena. For example, Balkenius and Morén [24] proposed a model for emotional learning dependent on classical conditioning, which relied on crude representations and mathematically oriented circuits. The neural network model focused on the amygdala and the orbitofrontal cortex and their interactions. The amygdala was the locus of conditioning acquisition, and the orbitofrontal cortex was the site for extinction learning. Using two arbitrary subsystems (a base system and an auxiliary system) for reinforcement prediction and error tracking, respectively, the model simulated basic phenomena related to emotional conditioning including acquisition, extinction, blocking, and habituation. More recently, Burgos and Murillo-Rodríguez [73] used a neural-network model to simulate two context-dependent phenomena in Pavlovian conditioning: context specificity and renewal. Prior to that, the computational framework was used to simulate a wide range of conditioning phenomena such as reacquisition savings [74], reinforcement reevaluation [75], superstition [76], and latent inhibition [77]. Although these neural-network models were inspired by biological data of Pavlovian fear conditioning, there was no correspondence between the models and exact neural structures, and the amygdala circuit was not modeled explicitly.

Earlier connectionist models treated the amygdala as a "black box" or one homogeneous structure characterized by input-output function (e.g., [24]). With the advance of neurophysiology, we now know the amygdala can be divided into several functionally distinct nuclei in the processing of CS/US information (reviewed above). In keeping with new emerging neurobiological data, recent connectionist models of fear learning have started to model finer details of the amygdala circuitry and evolved from modeling only one or two brain structures to multiple regions and their interactions [33, 34, 72, 78]. For example, to understand the cognitive-emotional interaction mediating flexible behaviors, John et al. [34] developed an amygdala circuit model that consists of three subnetworks: (1) the BLA subnetwork; (2) the ITC subnetwork; and (3) the central output subnetwork. The BLA subnetwork contains LA and BA; the ITC subnetwork includes both the dorsal (ITC_D) and ventral groups (ITC_V), and the central network consists of the medial subnucleus of Ce (CeM). In the model, simultaneous presentation of the CS and US potentiated the cortical synapses on LA cells, LA synapses on BA, and LA synapses on ITC_D. This led to inhibition of ITC_V and excitation of CeM resulting in fear response. In contrast, presentation of the CS in the absence of US decreased the synaptic

http://dx.doi.org/10.5772/67834

weight at LA-ITC_D synapses while potentiating the synaptic weight at BA-ITC_V synapses. As a result, CeM was inhibited and fear responses were suppressed. Besides normal fear acquisition and extinction, the model showed that cortical inputs from IL could bidirectionally modulate the circuit's behavior toward fear or extinction: stronger IL inputs to ITC_D could further disinhibit CeM promoting fear responses, while larger IL inputs to ITC_V enhanced the inhibition on CeM facilitating extinction. Moreover, model simulation indicated that if learning in ITC was faster than the BLA, the system could rapidly switch between the states of fear and extinction. Interestingly, cortical modulation from IL can be used to bias the system toward the "cautious" fear mode or the "rapid switch" mode.

In another study [78], the authors constructed a conceptual and computational neural model of fear conditioning (referred to as "FART") that included the structures and interactions of the amygdala, hippocampus, and PFC. Guided by a number of design targets based on known physiological data, the model was designed specifically to replicate many salient phenomena of fear conditioning including conditioning, extinction, secondary reinforcement, blocking, the immediate shock deficit, renewal, and a range of functional manipulation effects such as pre and posttraining inactivation of amygdala and hippocampus components. This model represents the first attempt to use one conceptual and computational model to simulate a wide range of empirically observed phenomena and effects of fear conditioning. One potential issue of such approach is that the model was designed specifically to account for those phenomena, which were not generated naturally from a biologically constrained model. It remains unclear whether the assumptions and parameters adopted by the model are biologically valid.

3.3. Phenomenological spiking neuron models

Though connectionist models are able to capture certain phenomenon of fear conditioning, such models have inherent limitation in that the output of computational units represents the firing rate or general activation, rather than the spiking activities of real neurons. Due to this limitation, connectionist models cannot be used to study specific spike patterns of individual neurons, nor the correlation in spike timing. On the other hand, although detailed conductance-based compartmental models can accurately reproduce the spiking dynamics of real neurons, these models are difficult to analyze because of intrinsic complexity. Phenomenological spiking neuron models have the advantage of emulating spiking behaviors while remaining analytically tractable and computationally feasible. As such, spiking neuron models are widely used to study neural coding, network dynamics, and learning and memory. Phenomenological spiking neuron models of fear conditioning are sparse with the exception of a large-scale spiking network model of the basal amygdala [25].

As mentioned earlier, the basal amygdala (BA) contains two types of neurons (fear neurons and extinction neurons) whose activation is correlated with the fear and extinction states, respectively [46]. However, the neural mechanisms underlying the differential activation of these two neuronal subpopulations remain unclear. To elucidate possible neural mechanisms involved in the encoding of fear and extinction memories in BA, Vlachos et al. [25] developed a large-scale spiking network model of the BA consisting of 3400 excitatory and 600 inhibitory neurons interconnected with both feedback and recurrent synapses. The excitatory neurons

were divided into two subpopulations, A and B, each receiving a different context input (CTX_A and CTX_B). In addition, all neurons in the network received CS-US input. The BA neurons were modeled with leaky-integrate-and-fire (LIF) scheme. Specifically, the subthreshold dynamics of the LIF neurons is described by the following differential equation:

$$\tau_m \frac{dV}{dt} = (E_0 - V) + g_{\text{exc}}(E_{\text{exc}} - V) + g_{\text{inh}}(E_{\text{inh}} - V) \tag{8}$$

where V is the membrane potential, τ_m is the membrane time constant, g_{exc} and g_{inh} are the excitatory and inhibitory conductance, and E_0, E_{exc}, and E_{inh} are resting membrane potential, excitatory, and inhibitory reversal potentials, respectively. When the membrane potential V crosses a static threshold θ in the upward direction, a spike is generated and the membrane potential is rest to a value E_k and clamped for 2 ms [25].

In simulation, conditioning was trained in context A while extinction was performed in context B. The strength of the CS and contextual inputs to excitatory neurons is modifiable according to a phenomenological rule, which specifies that the synapses are strengthened if the CS and contextual inputs overlap within a temporal window of ~100 ms. Based on this learning rule, the CS and CTX_A inputs to population A neurons were potentiated during fear conditioning leading to increased firing rates of population A cells. On the other hand, presentation of CS and CTX_B inputs to population B neurons during extinction potentiated those inputs resulting in activation of population B cells, which suppressed the activity of population A neurons through increased competitive inhibition. Since the behaviors of population A and B neurons resembled the fear and extinction neurons observed in [46], they were interpreted as fear and extinction neurons, respectively [25]. The model was also used to study renewal, extinction over-training, and extinction of contextual conditioning. In particularly, the model predicted that gamma oscillations will be generated if the connectivity between the excitatory and inhibitory neurons in BA is high. The main conclusion of this modeling study is that differential activation of fear and extinction neurons is a result of context specificity, i.e., fear and extinction neurons are innervated by different contextual inputs. Questions remain whether fear and extinction neurons would emerge differentially if both conditioning and extinction are trained in the same context. Also, the model assumes that both the CS and contextual inputs are potentiated if they are temporally coincided. This suggests that fear could be developed even without US inputs, which is not consistent with experimental observation.

3.4. Biophysically realistic models

Although phenomenological spiking neuron models (e.g., LIF models) are able to simulate neuronal spiking activities, they do not take into account the morphological and electrophysiological properties of actual neurons, thus neglecting the biophysical constraints on neural learning and computation. To accurately model the underlying processes responsible for fear learning, biophysical Hodgkin-Huxley type models are required. The first biophysically realistic model of fear conditioning was developed by Li et al. [26] to study the neural mechanisms of fear acquisition and extinction in LA neurons. In this pioneering study, conductance-based compartmental models of LA pyramidal cells and interneurons are first developed by incorporating detailed ionic channels and kinetics observed in LA neurons. The schematic

http://dx.doi.org/10.5772/67834

representation of the two-compartment LA pyramidal cell and interneuron models is shown in **Figure 2A**, and the equivalent electrical circuit of two basic neural compartments is shown in **Figure 2B**. Each compartment has a membrane capacitance C_m, a fixed membrane resistance R_m, and an equilibrium potential E_m associated with the ohmic leakage current that flows across R_m. Based on the equivalent circuit, one can derive the current-balance equations for the two compartments:

$$\begin{aligned} c_m \frac{dV_s}{dt} &= -\frac{(V_s - E_m)}{R_m} - \sum_i G_{ki}(V_s - E_{ki}) - g_c(V_s - V_d) \\ c_m \frac{dV_d}{dt} &= -\frac{(V_d - E_m)}{R_m} - \sum_i G_{ki}(V_d - E_{ki}) - g_c(V_d - V_s) \end{aligned} \tag{9}$$

where V_s and V_d are the transmembrane potentials for the soma and dendrite compartments, respectively. G_{ki} and E_{ki} are the conductance and reversal potential for the channel i and g_c is

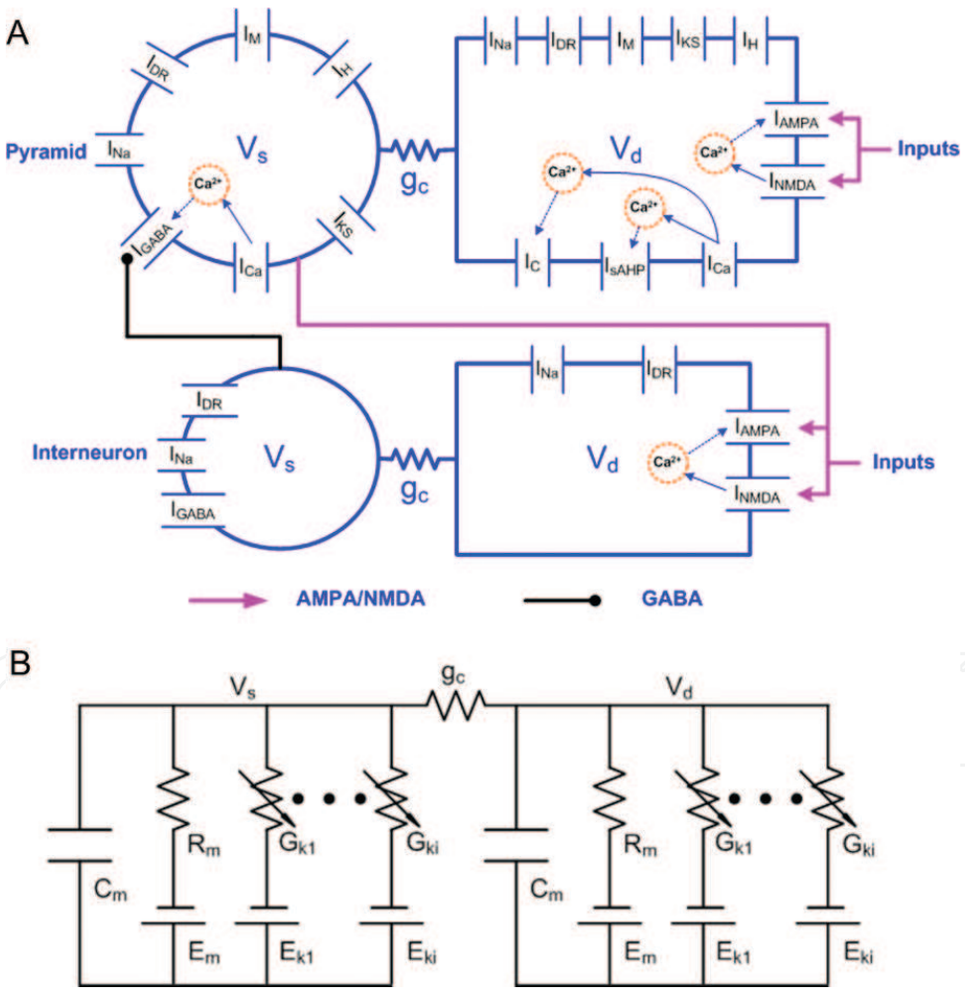

Figure 2. Conductance-based compartmental model of LA neurons. (A) Schematic representation of the LA pyramidal cell and interneuron models with distribution of active ionic conductances in each of its two compartments (adapted from Ref. [26]). (B) Equivalent electrical circuit of two interconnected neural compartments used to simulate LA cell excitability. C_m is the membrane capacitance, R_m is the membrane resistance, and E_m is the leakage reversal potential. Subscripts k1, k2, ⋯, ki denote i different active (variable) conductances and their associated reversal potentials (G_{Na}, G_{DR}, etc., with reversal potentials E_{Na}, E_K, etc.).

the coupling conductance between the soma and dendrite compartments. All ionic conductances in the LA model are modeled using the Hodgkin-Huxley kinetics [79]. Specifically, the conductance for channel *i*, G_{ki}, is modeled as:

$$G_{ki} = g_{ki} m^p h^q \tag{10}$$

where g_{ki} is its maximal conductance density, m its activation variable (with exponent p), and h its inactivation variable (with exponent q). The kinetic equation for the gating variable x (m *or* h) satisfies a first-order kinetic model,

$$\frac{dx}{dt} = \varnothing_x \frac{x_\infty(V) - x}{\tau_x(V)} \tag{11}$$

where ϕ_x is a temperature-dependent factor, $x_\infty(V)$ is the voltage-dependent steady state, and $\tau_x(V)$ is the voltage-dependent time constant. Equivalently, Eq. (11) can be written as:

$$\frac{dx}{dt} = \phi_x \left(\alpha_x(V)(1 - x) - \beta_x(V)x \right) \tag{12}$$

where $\alpha_x(V)$ and $\beta_x(V)$ are the voltage-dependent rate constants. The detailed kinetic parameters can be found in Ref. [26]. With careful parameterization, the LA neuronal models were able to accurately reproduce the firing properties of LA neurons as observed in experimental recording (**Figure 3**).

After successfully constructing single-cell models of LA neurons, Li et al. [26] developed a small network model consisting of eight pyramidal cells and two interneurons (**Figure 4A**). The network model was trained with a behavioral protocol including a sensitization, conditioning and two extinction phases (**Figure 4B**). In addition, the model implemented a biophysical learning rule termed "calcium control hypothesis" [81] to precisely model synaptic potentiation and depression during fear acquisition and extinction (**Figure 4C**). The biophysical realism enables the LA model to accurately replicate conditioning- and extinction-induced

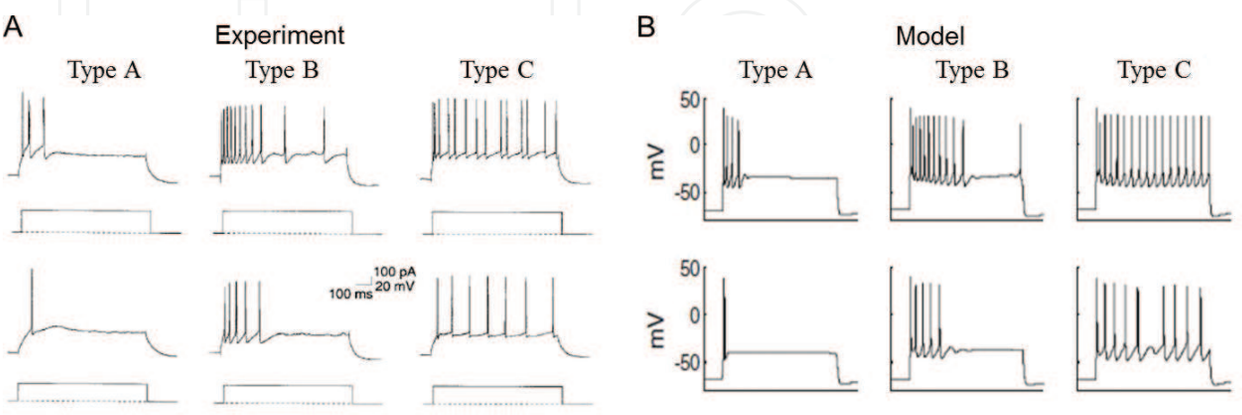

Figure 3. Biophysical LA neuronal models reproduce salient firing patterns of LA pyramidal cells. (A) Firing properties of three types of pyramidal cells (Type A, Type B, and Type C) recorded *in vitro* (adapted from Ref. [80]). (B) Responses of three types of LA model neurons to current injections (adapted from Ref. [26]).

http://dx.doi.org/10.5772/67834

changes in tone responses of LA neurons in behaving rats during the classical auditory fear conditioning experiment [37] (**Figure 5**). By closely matching experimental data, the model has provided in-depth insights into the neural mechanisms of fear conditioning and extinction. First, the LA model demonstrates that both conditioning and extinction can be learned within the LA circuitry. This has significant implication as the LA, known to be a key site for fear acquisition [35, 40], can also encode extinction memory. Second, the LA model convincingly reconciles the two contrastive theories (unlearning versus inhibition) about the extinction mechanism. In the model, extinction not only causes depression in potentiated thalamic input

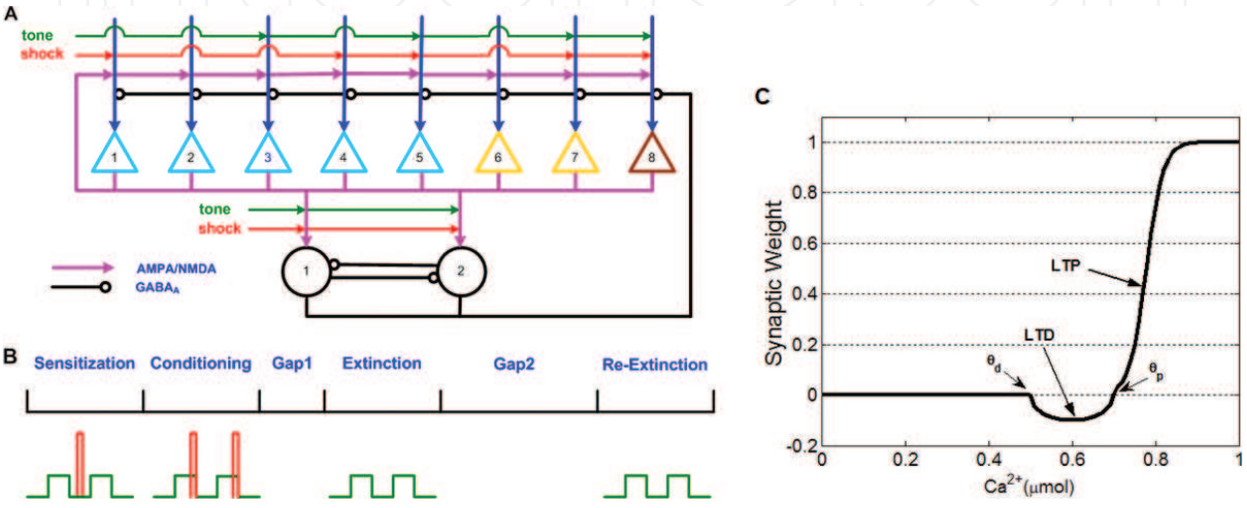

Figure 4. Architecture, training protocol and learning rule of the LA network model (adapted from Ref. [26]). (A) The LA network structure. Triangles represent pyramidal cells and circles representing interneurons. (B) Simulation schedule showing tone and shock inputs during sensitization, conditioning, and the two extinction phases. (C) Synaptic depression and potentiation as a function of the Ca^{2+} concentration. LTD: long-term depression; LTP: long-term potentiation.

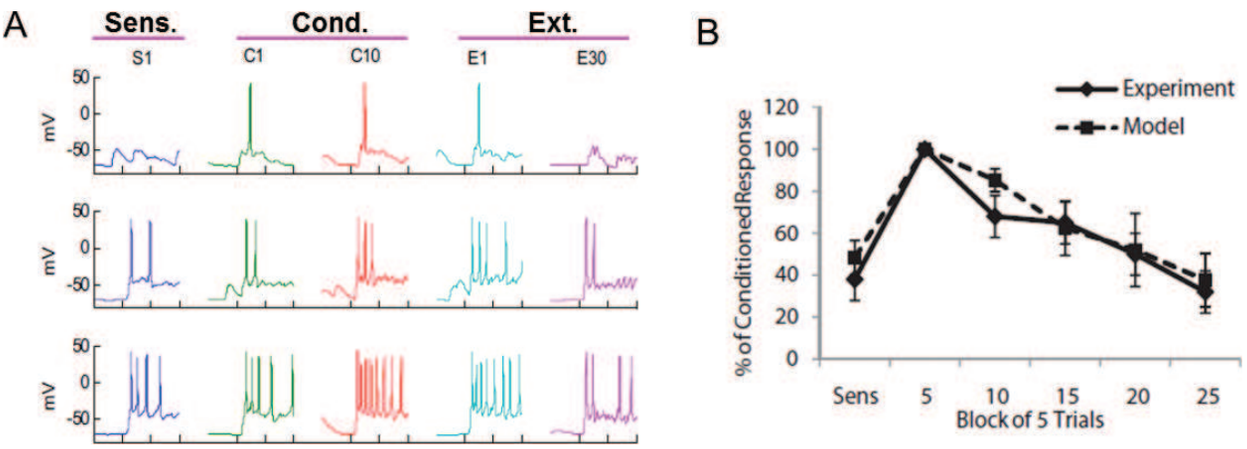

Figure 5. The LA network model reproduces conditioned tone response in behaving rats (adapted from Ref. [26]). (A) Early tone response (100 ms) of three representative pyramidal cells in the LA network during different phases of the training. S1: first tone in sensitization; C1: first tone in conditioning; C10: 10th tone in conditioning; E1: first tone in extinction; E30: 30th tone in extinction. (B) Comparison of the experimental data (**Figure 4** of Ref. [37]) and the model conditioned tone responses for the last block of five trials in sensitization and successive five-trial blocks during extinction.

synapses, but also potentiates inhibitory GABAergic synapses from local LA interneurons that inhibit conditioned responding in pyramidal cells. Therefore, both synaptic depression (unlearning) and potentiation of inhibition are required for a complete extinction of fear. Importantly, the model suggests that depotentiation induced by extinction is synapse-dependent in that the thalamus-to-LA pyramidal cell synapses will undergo stronger depotentiation than the LA pyramidal-to-pyramidal cell synapses. This finding agrees with an earlier experimental observation that a unique form of depotentiation during extinction reversed conditioning induced potentiation at thalamic input synapses onto the LA *ex vivo* [82]. Last, the LA model makes a number of important predictions that could guide experimental design. For example, the model makes specific predictions regarding the storage sites of fear and extinction memory within the LA circuitry. Also, the LA model suggests that while the low spontaneous firing rates of LA pyramidal cells serve to preserve the original fear memory, the relatively high spontaneous firing rates of interneurons lead to extinction decay and spontaneous fear recovery. The prediction that higher spontaneous firing rates result in faster decay of memory has been validated by experimental data *in vivo* [83]. Moreover, the model predicts that N-methyl-D-aspartic acid (NMDA) currents are required for extinction training, consistent with an experimental finding that depotentiation of conditioning-induced potentiation at thalamic input synapses onto the LA *ex vivo* requires GluN2B-containing NMDA receptors [84].

During conditioning, conditioned fear output in the LA is related to the Ce via both the BA and ITC cell clusters and generates fear response via successive projection to the brain stem and hypothalamic sites (**Figure 1B**). Thus, ITC cells play a critical role in regulating fear expression by controlling the impulse traffic between the LA and Ce. Also, brief stimulation of infralimbic cortex (IL) substantially reduces fear expression, an inhibitory process believed to be mediated by ITC cells [19, 35]. Thus, it is of great importance to understand how activation of ITC neurons by IL leads to fear suppression. However, ITC neurons are endowed with both unusual membrane characteristics (prolonged excitation or bistability [85]; **Figure 6A**) and synaptic properties (heterogeneous plasticity [86]; **Figure 6B**), and are embedded in complex neuronal circuit with both intercluster and within-cluster inhibition (**Figure 6C**). The functional roles of ITC cells in mediating fear extinction are precluded by such complicated cellular, synaptic, and circuit properties.

To address this critical issue, Li et al. [27] developed a biophysically realistic ITC neuronal model that precisely replicated the salient firing patterns and bistable properties of real ITC cells. By incorporating realistic heterogeneous short-term synaptic dynamics in a biophysical ITC network (**Figure 6C**), Li et al. [27] elucidated that: (1) ITC neurons could transform the transient fear signal arising in the LA/BA into a persistent pattern of activity; (2) over a wide range of stimulation frequencies and strengths, brief IL activation caused a marked increase in the firing rates of ITC neurons, resulting in a persistent decrease in Ce output, despite inter-ITC inhibition (**Figure 7**); (3) both intrinsic properties (i.e., bistability) and variations in the short-term synaptic dynamics of ITC neurons contributed to the effectiveness of IL stimulation; and (4) IL stimulation reduced Ce responses to conditioned stimulus in a temporally specific manner with the most effective inhibition given shortly after stimulus onset. All these important findings significantly improve our understanding of the functional roles of ITC cells in mediating fear conditioning and extinction. It offers the solid computational support that IL inputs are in a strategic position to control extinction of conditioned fear via the activation of

http://dx.doi.org/10.5772/67834

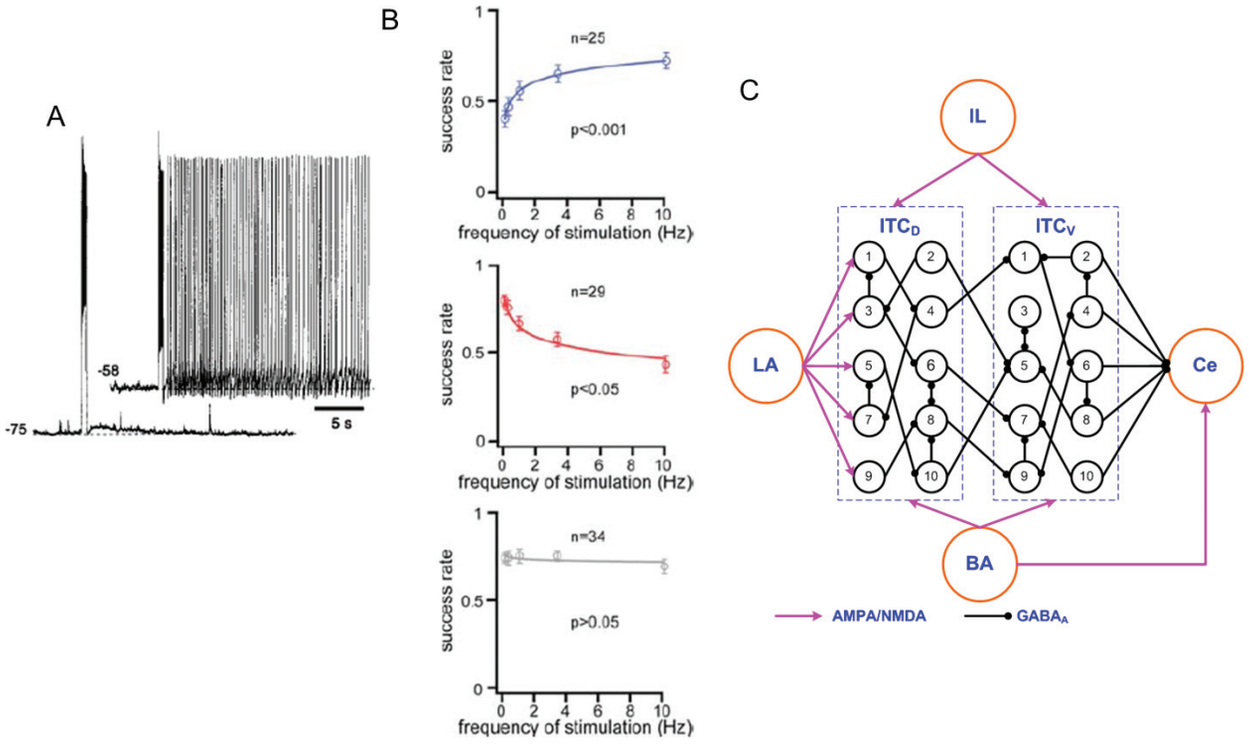

Figure 6. Intercalated (ITC) cell clusters neurons are endowed with both unusual membrane and synaptic properties, and embedded in complex neuronal circuit with both intercluster and within-cluster inhibition. (A) Bistable firing or prolonged excitation of ITC cells (adapted from Ref. [85]). Transient depolarization induces sustained firing. (B) The release probability of ITC synapses increases, decreases, or remains constant when the presynaptic stimulation frequency increases in three different types of synapses (adapted from Ref. [86]). (C) Structure of the ITC network model (adapted from Ref. [27]).

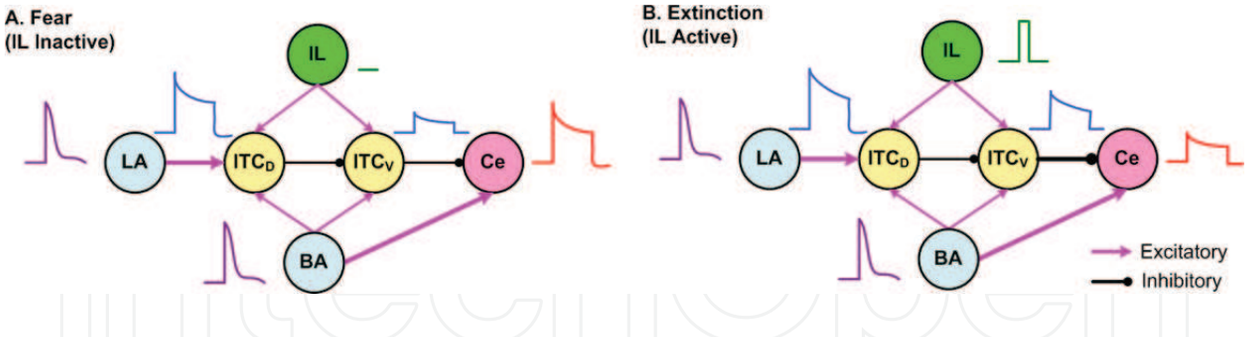

Figure 7. Effect of IL stimulation on amygdala network activity (adapted from Ref. [27]). (A) During fear conditioning, the LA-ITC$_D$ synaptic strength is potentiated. Strongly adaptive LA inputs are transformed into sustained output by ITC$_D$ neurons leading to persistent inhibition on ITC$_V$ cells allowing for sustained Ce firing in the high fear state. (B) Brief IL stimulation increases the excitability of both ITC$_D$ and ITC$_V$ neurons, with a larger impact on ITC$_V$ cells, which significantly reduces the Ce firing leading to a low fear state.

ITC neurons. Thus, targeting ITC neurons with IL stimulation or pharmacological interventions could potentially eliminate fear memories and reduce anxiety, offering new hope for the treatment of anxiety disorders such as PTSD.

As a pivot study, the network size of the LA model developed by Li et al. [26] was relatively small (eight pyramidal cells and two interneurons) and focused on the neural mechanisms of fear extinction. In a subsequent study, Kim et al. developed a large-scale biophysical model of the

dorsal portion of the LA (LAd) to study the mechanisms contributing to the induction and storage of Pavlovian fear memories [28]. The spatial LAd network model included 800 principal pyramidal cells and 200 interneurons placed in a horn-shaped 3D structure. In addition, the model network integrated spatially differentiated patterns of excitatory and inhibitory connections within the LA [87]. The model was able to replicate the behaviors of two types of LAd neurons (transient cells and long-term plastic cells) observed in experimental recording [88] as a result of differential intrinsic connectivity. Moreover, the model demonstrated that while the conditioning-induced increases in the CS responsiveness of thalamic/cortical neurons are required for fear memory formation, they are not necessary for long-term fear memory storage. Instead, the projecting synapses from thalamic/cortical neurons to LA pyramidal cells play a more important role in the storage of fear memory. In a following up study, the LAd network model was used to study an important question of how particular LA neurons are assigned to fear memory traces [29]. The model showed that LA neurons with higher intrinsic excitability have a larger chance of being recruited into the fear memory trace. Paradoxically, when the ratio of more excitably cells changed, the number of plastic cells remained relatively constant. Model analysis indicated that competitive synaptic interactions play a critical role in assigning the LA neurons to the memory trace. That is, a subset of pyramidal cells gain advantage in competition due to stronger excitatory interconnections and suppress the remaining pyramidal cells through the recruitment of inhibitory interneurons. Hence, assignment of LA neurons to a memory trace depends on a competitive process, consistent with experimental data [89]. The nature, specificity, and details of synaptic competition in fear memory trace formation are further examined in two subsequent biophysical modeling studies [31, 90].

Although the amygdala plays a central role in fear acquisition and extinction, the medial prefrontal cortex (mPFC) exerts strict top-down control over the amygdala on both the formation and expression of fear memory [52, 91]. Specifically, while prelimbic (PL) cortex increases fear expression, the infralimbic (IL) cortex reduces fear expression [67]. There is significant difference about the neural correlates of fear expression between the LA and PL. Specifically, the conditioned response in LA neurons is transient, lasting only a few hundred milliseconds after CS onset [36, 37, 88]. By comparison, the PL neurons have sustained conditioned response during the entire CS presentation which correlates closely with the fear expression [92]. This leads to the hypothesis that PL transforms transient fear signal in LA into sustained fear output in Ce via descending projections to the BA [92]. However, the neural and circuit mechanisms underlying such transformation are not clear. Using a biophysically realistic model of the BA-PL network consisting of 850 conductance-based compartmental model cells, Pendyam et al. [30] investigated three potential mechanisms involved in the LA-PL transformation including: (1) BA-PL network structure and connectivity; (2) dopaminergic and noradrenergic modulation; and (3) specific microcircuits within the BA-PL network. Model simulation indicated that BA-induced continuous release of dopamine and norepinephrine, rather than the BA-PL interconnections, plays a dominant role in sustaining PL conditioned responses. The model also predicted that specific microcircuit variations in the BA-PL network significantly modulate fear expression, which could possibly explain the individual heterogeneity in fear responses.

http://dx.doi.org/10.5772/67834

4. Summary and future direction

Computational models of the role of the amygdala in fear conditioning and extinction have enjoyed a long history of success and greatly improved our understanding of the processes underlying emotional learning and memory. With the advance of neurophysiology and high performance computation, computational models of the amygdala have evolved from simple rule-based models to anatomically constrained connectionist models, and to large-scale biologically realistic network models. These different types of models have complementary utility, and the selection of models depends on the available computational resource and the nature of the problem being investigated. In particular, the development of biophysically realistic models of the amygdala and extended circuits has opened up new avenues to study the neural and circuit mechanisms of acquisition, storage, and regulation of fear memory in the brain. In the future, large-scale biophysical network models of the amygdala and associated circuits such as PFC and hippocampus are of particular interest in order to provide an integrated account of how multiple brain regions work in concert to regulate fear memory formation and expression.

While much modeling progress has been made, there is still a long way to go to model pathologies associated with the fear circuit (e.g., PTSD) and assist in the development of new treatments. To achieve this goal, a new class of translational models need to be developed that could simulate the systemic neural impairments with resulting symptoms observed in fear and anxiety disorders such as PTSD. In addition, such models should explore new treatment paradigms such as invasive deep brain stimulation (DBS) and noninvasive transcranial magnetic stimulation (TMS). This may lead to the development of hybrid type models that combine the system-level analysis and detailed cellular-level operation.

Acknowledgements

This work was supported by the National Institute on Deafness and Other Communication Disorders (NIDCD) of the National Institute of Health R03 Grant DC013872 to G Li.

The author declares no competing financial interests.

Author details

Guoshi Li

Address all correspondence to: guoshi_li@med.unc.edu

Department of Psychiatry, University of North Carolina at Chapel Hill, North Carolina, USA

References

[1] Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatric stress disorder and extinction: human neuroimaging research past, present and future. Biological Psychiatry. 2006;**60**:376–382.

[2] Mahan AL, Ressler KJ. Fear conditioning, synaptic plasticity and the amygdala: implications for posttraumatic stress disorder. Trends in Neurosciences. 2012;**35**:25–35.

[3] Thakur GS, Daigle BJ, Dean KR, Zhang Y, Rodriguez-Fernandez M, Hammamieh R, et al. Systems biology approach to understanding post-traumatic stress disorder. Molecular bioSystems. 2015;**11**:980–993.

[4] Davidson JR. Trauma: The impact of post-traumatic stress disorder. Journal of Psychopharmacology. 2000;**14**:S5–S12.

[5] Pavlov I. Conditioned Reflexes. London: Oxford University Press; 1927.

[6] Rescorla RA. Comparison of the rates of associative change during acquisition and extinction. Journal of Experimental Psychology. Animal Behavior Processes. 2002;**28**: 406–415.

[7] Myers KM, Davis M. Mechanisms of fear extinction. Molecular Psychiatry. 2007;**12**: 120–150.

[8] Griffin MG. A prospective assessment of auditory startle alterations in rape and physical assault survivors. Journal of Traumatic Stress. 2008;**21**:91–99.

[9] Pole N, Neylan TC, Otte C, Henn-Hasse C, Metzler TJ, Marmar CR. Prospective prediction of posttraumatic stress disorder symptoms using fear potentiated auditory startle responses. Biological Psychiatry. 2009;**65**:235–240.

[10] McLaughlin KA, Conron KJ, Koenen KC, Gilman SE. Childhood adversity, adult stressful life events, and risk of past-year psychiatric disorder: a test of the stress sensitization hypothesis in a population-based sample of adults. Psychological Medicine. 2010;**40**:1647–1658.

[11] Orr SP, Metzger LJ, Lasko NB, Macklin ML, Peri T, Pitman RK. De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. Journal of Abnormal Psychology. 2000;**109**:290–298.

[12] Milad MR, Orr SP, Lasko NB, Chang Y, Rauch SL, Pitman RK. Presence and acquired origin of reduced recall for fear extinction in PTSD: Results of a twin study. Journal of psychiatric research. 2008;**42**:515–520.

[13] LeDoux JE. Emotion circuits in the brain. Annuals Reviews Neurosciences. 2000;**23**: 155–184.

[14] Maren S, Quirk GJ. Neuronal signalling of fear memory. Nature Review of Neurosciences. 2004;**5**:844-8402.

[15] Maren S. Neurobiology of Pavlovian fear conditioning. Annual Review of Neuroscience. 2001;**24**:897–931.

[16] Sah P, Faber ESL, Lopez De Armentia M, Power J. The amygdaloid complex: Anatomy and physiology. Physiology Review. 2003;**83**:803–834.

[17] Cardinal RN, Parkinson JA, Hall J, Everitt BJ. Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. Neuroscience & Biobehavioral Reviews. 2002;**26**:321–352.

[18] Shin LM, Rauch SL, Pitman RK. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. Annals of the New York Academy of Sciences. 2006;**1071**: 67–79.

[19] Quirk GJ, Mueller D. Neural mechanisms of extinction learning and retrieval. Neuropsychopharmacology. 2008**33**:56–72.

[20] Bremner JD. Traumatic stress: Effects on the brain. Dialogues in Clinical Neuroscience. 2006;**8**:445–461.

[21] Etkin A, Wager TD. Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. American Journal of Psychiatry. 2007;**164**:1476–1488.

[22] Rescorla RA, Wagner, AR. A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and non-reinforcement. In: Black A, Prokasy WF, editors. Classical Conditioning II: Current Research and Theory. New York: Appleton-Century-Crofts; 1972. pp. 64–99.

[23] Armony JL, Servan-Schreiber D, Cohen JD, LeDoux JE. An anatomically constrained neural network model of fear conditioning. Behavior Neurosciences. 1995;**109**:246–257.

[24] Balkenius C, Morén J. Emotional learning: A computational model of the amygdala. Cybernetics and Systems. 2001;**32**:611–636.

[25] Vlachos I, Herry C, Lüthi A, Aertsen A, Kumar A. Context-dependent encoding of fear and extinction memories in a large-scale network model of the basal amygdala. PLoS Computer Biology. 2011;**7**:e1001104.

[26] Li G, Nair SS, Quirk GJ. A biologically realistic network model of acquisition and extinction of conditioned fear associations in lateral amygdala neurons. Journal of Neurophysiology. 2009;**101**:1629–1646.

[27] Li G, Amano T, Pare D, Nair SS. Impact of infralimbic inputs on intercalated amygdala neurons: A biophysical modeling study. Learning & Memory. 2011;**18**:226–240

[28] Kim D, Pare D, Nair SS. Mechanisms contributing to the induction and storage of Pavlovian fear memories in the lateral amygdala. Learning & Memory. 2013;**20**:421–430.

[29] Kim D, Pare D, Nair SS. Assignment of model amygdala neurons to the fear memory trace depends on competitive synaptic interactions. Journal of Neurosciences. 2013;**33**: 14354–14358.

[30] Pendyam S, Bravo-Rivera C, Burgos-Robles A, Sotres-Bayon F, Quirk GJ, Nair SS. Fear signaling in the prelimbic-amygdala circuit: A computational modeling and recording study. Journal of Neurophysiology. 2013;**110**:844–861.

[31] Feng F, Samarth P, Pare D, Nair SS. Mechanisms underlying the formation of the amygdalar fear memory trace: A computational perspective. Neuroscience. 2016;**322**:370–376.

[32] Armony JL, Servan-Schreiber D, Romanski LM, Cohen JD, LeDoux JE. Stimulus generalization of fear responses: Effects of auditory cortex lesions in a computational model and in rats. Cerebal Cortex. 1997;**7**:157–165.

[33] Moustafa AA, Gilbertson MW, Orr SP, Herzallah MM, Servatius RJ, Myers CE. A model of amygdala-hippocampal-prefrontal interaction in fear conditioning and extinction in animals. Brain and Cognition. 2013;**81**:29–43.

[34] John YJ, Bullock D, Zikopoulos B, Barbas H. Anatomy and computational modeling of networks underlying cognitive-emotional interaction. Frontiers in Human Neuroscience. 2013;**7**:101.

[35] Pare D, Quirk GJ, Ledoux JE. New vistas on amygdala networks in conditioned fear. Journal of Neurophysiology. 2004;**92**:1–9.

[36] Quirk GJ, Repa C, LeDoux JE. Fear conditioning enhances short-latency auditory responses of lateral amygdala neurons: Parallel recordings in the freely behaving rat. Neuron. 1995;15:1029–1039.

[37] Quirk GJ, Armony JL, LeDoux JE. Fear conditioning enhances different temporal components of tone-evoked spike trains in auditory cortex and lateral amygdala. Neuron. 1997;**19**:613–624.

[38] Blair HT, Schafe GE, Bauer EP, Rodrigues SM, LeDoux JE. Synaptic plasticity in the lateral amygdala: A cellular hypothesis of fear conditioning. Learning & Memory. 2001;**8**:229–242.

[39] Pitkanen A. Connectivity of the rat amygdaloid complex. In: Aggleton JP, editor. The Amygdala: A Functional Analysis, 2nd ed. Oxford: Oxford University Press; 2000.

[40] Sigurdsson T, Doyere V, Cain CK, Ledoux JE. Long-term potentiation in the amygdala: A cellular mechanism of fear learning and memory. Neuropharmacology. 2007;**52**:215–227.

[41] McDonald AJ. Neuronal organization of the lateral and basolateral amygdaloid nuclei of the rat. The Journal of Comparative Neurology. 1984;**222**:589–606.

[42] Bordi F, LeDoux JE. Response properties of single units in areas of rat auditory thalamus that project to the amygdala. Experimental Brain Research. 1994;**98**:275–286.

[43] LeDoux, JE, Cicchetti P, Xagoraris A, Romanski LM. The lateral amygdaloid nucleus: sensory interface of the amygdala in fear conditioning. Journal of Neurosciences. 1990;**10**:1062–1069.

[44] Goosens KA, Maren S. Contextual and auditory fear conditioning are mediated by the lateral, basal, and central amygdaloid nuclei in rats. Learning & Memory. 2001;**8**:148–155.

[45] Muller J, Corodimas KP, Fridel Z, Ledoux JE. Functional inactivation of the lateral and basal nuclei of the amygdala by muscimol infusion prevents fear conditioning to an explicit conditioned stimulus and to contextual stimuli. Behavior Neurosciences. 1997;**111**:683–691.

[46] Herry C, Ciocchi S, Senn V, Demmou L, Muller C, et al. Switching on and off fear by distinct neuronal circuits. Nature. 2008;**454**:600–606.

[47] Anglada-Figueroa D, Quirk GJ. Lesions of the basal amygdala block expression of conditioned fear but not extinction. Journal of Neurosciences. 2005;**25**:9680–9685.

[48] Hobin JA, Ji J, Maren S. Ventral hippocampal muscimol disrupts context-specific fear memory retrieval after extinction in rats. Hippocampus. 2006;**16**:174–182.

[49] Sierra-Mercado D, Padilla-Coreano N, Quirk GJ. Dissociable roles of prelimbic and infralimbic cortices, ventral hippocampus, and basolateral amygdala in the expression and extinction of conditioned fear. Neuropsychopharmacology. 2011;36:529–538.

[50] Milad MR, Quirk GJ. Neurons in medial prefrontal cortex signal memory for fear extinction. Nature. 2002;**420**:70–74.

[51] Bouton ME, Westbrook RF, Corcoran KA, Maren S. Contextual and temporal modulation of extinction: Behavioral and biological mechanisms. Biological Psychiatry. 2006;**60**:352–360.

[52] Quirk GJ, Garcia R, Gonzalez-Lima F. Prefrontal mechanisms in extinction of conditioned fear. Biological Psychiatry. 2006;**60**:337–343.

[53] Iwata J, Chida K, LeDoux JE. Cardiovascular responses elicited by stimulation of neurons in the central amygdaloid nucleus in awake but not anesthetized rats resemble conditioned emotional responses. Brain Research. 1987;**418**:183–88

[54] Hitchcock J, Davis M. Lesions of the amygdala, but not of the cerebellum or red nucleus, block conditioned fear as measured with the potentiated startle paradigm. Behavior of Neurosciences. 1986;**100**:11–22

[55] Iwata J, LeDoux JE, Meeley MP, Arneric S, Reis DJ. Intrinsic neurons in the amygdaloid field projected to by the medial geniculate body mediate emotional responses conditioned to acoustic stimuli. Brain Research. 1986;**383**:195–214

[56] Pape HC, Paré D. Plastic synaptic networks of the amygdala for the acquisition, expression, and extinction of conditioned fear. Physiology Reviews. 2010;**90**:419–463

[57] McDonald AJ, Augustine JR. Localization of GABA-like immunoreactivity in the monkey amygdala. Neuroscience. 1993;**52**:281–294.

[58] Pare D, Smith Y. Distribution of GABA immunoreactivity in the amygdaloid complex of the cat. Neuroscience. 1993;**57**:1061–1076.

[59] Jungling K, Seidenbecher T, Sosulina L, Lesting J, Sangha S, Clark SD, Okamura N, Duangdao DM, Xu YL, Reinscheid RK, et al. Neuropeptide S-mediated control of fear expression and extinction: Role of intercalated GABAergic neurons in the amygdala. Neuron. 2008;59:298–310.

[60] Likhtik E, Popa D, Apergis-Schoute A, Fidacaro GA, Pare D. Amygdala intercalated neurons are required for expression of fear extinction. Nature. 2008;**454**: 642–645.

[61] Pare D, Smith Y. The intercalated cell masses project to the central and medial nuclei of the amygdala in cats. Neuroscience. 1993;**57**:1077–1090.

[62] Royer S, Martina M, Pare D. An inhibitory interface gates impulse traffic between the input and output stations of the amygdala. Journal of Neurosciences. 1999;**19**:10575–10583.

[63] Royer S, Martina M, Pare D. Polarized synaptic interactions between intercalated neurons of the amygdala. Journal of Neurophysiology. 2000;**83**:3509–3518.

[64] McDonald AJ, Mascagni F, Guo L. Projections of the medial and lateral prefrontal cortices to the amygdala: A phaseolus vulgaris leucoagglutinin study in the rat. Neuroscience. 1996;**71**:55–75.

[65] Freedman LJ, Insel TR, Smith Y. Subcortical projections of area 25 (subgenual cortex) of the macaque monkey. The Journal of Comparative Neurology. 2000;**42**:172–188.

[66] Milad MR, Vidal-Gonzalez I, Quirk GJ. Electrical stimulation of medial prefrontal cortex reduces conditioned fear in a temporally specific manner. Behavior of Neurosciences. 2004;**118**:389–394.

[67] Vidal-Gonzalez I, Vidal-Gonzalez B, Rauch SL, Quirk GJ. Microstimulation reveals opposing influences of prelimbic and infralimbic cortex on the expression of conditioned fear. Learning & Memory. 2006;**13**:728–733.

[68] Le Pelley ME. The role of associative history in models of associative learning: A selective review and a hybrid model. The Quarterly Journal of Experimental Psychology. 2004;**57**: 193–243.

[69] Mackintosh NJ. A theory of attention: Variations in the associability of stimuli with reinforcement. Psychological Review. 1975;**82**:276–298.

[70] Pearce JM, Hall, G. A model for Pavlovian conditioning: Variations in the effectiveness of conditioned but not of unconditioned stimuli. Psychological Review. 1980;**87**:532–552.

[71] Schmajuk NA, Moore JW. Real-time attentional models for classical conditioning and the hippocampus. Physiological Psychology B. 1985;**13**:278–290.

[72] Carrere M, Alexandre F. A Pavlovian model of the amygdala and its influence within the medial temporal lobe. Frontiers in Systems Neuroscience. 2015:9:41.

[73] Burgos JE, Murillo-Rodríguez E. Neural-network simulations of two context-dependence phenomena. Behavior of Processes. 2007;**75**:242–249.

[74] Donahoe JW, Burgos JE, Palmer DC. A selectionist approach to reinforcement. Journal of the Experimental Analysis of Behavior. 1993;**60**:17–40.

[75] Donahoe JW, Burgos JE. Behavior analysis and revaluation. Journal of the Experimental Analysis of Behavior. 2000;**74**:331–346.

[76] Burgos JE. Superstition in artificial neural networks: A case study for selectionist approaches to reinforcement. Mexican Journal of Behavior Analysis. 2000;**26**:159–189.

[77] Burgos, JE. Theoretical note: Simulating latent inhibition with selection neural networks. *Behavioural Processes. 2003;***62**:183–192.

[78] Krasne FB, Fanselow MS, Zelikowsky M. Design of a neurally plausible model of fear learning. Frontiers in Behavioral Neuroscience. 2011;5:41.

[79] Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. Journal of Physiology. 1952;**117**:500–544.

[80] Faber ESL, Callister RJ, Sah P. Morphological and electrophysiological properties of principal neurons in the rat lateral amygdala in vitro. Journal of Neurophysiology. 2001;**85**:714–723.

[81] Shouval HZ, Bear MF, Cooper LN. A unified model of NMDA receptor-dependent bidirectional synaptic plasticity. Proceedings of the National Academy of Sciences of United States of America. 2002;**99**:10831–10836.

[82] Kim J, Lee S, Park K, Hong I, Song B, Son G, Park H, Kim WR, Park E, Choe HK, Kim H, Lee C, Sun W, Kim K, Shin KS, Choi S. Amygdala depotentiation and fear extinction. Proceedings of the National Academy of Sciences of United States of America. 2007;**104**:20955–20960.

[83] Lin FG, Galindo-Leon EE, Ivanova TN, Mappus RC, Liu RC. A role for maternal physiological state in preserving auditory cortical plasticity for salient infant calls. Neuroscience. 2013;**247**:102–116.

[84] Park S, Lee S, Kim J, Choi S. Ex vivo depotentiation of conditioning-induced potentiation at thalamic input synapses onto the lateral amygdala requires GluN2B-containing NMDA receptors. Neuroscience Letters. 2012;**530**:121–126.

[85] Royer S, Martina M, Pare D. Bistable behavior of inhibitory neurons controlling impulse traffic through the amygdala: Role of a slowly deinactivating K^+ current. Journal of Neuroscience. 2000;**20**:9034–9039.

[86] Geracitano R, Kaufmann WA, Szabo G, Ferraguti F, Capogna M. Synaptic heterogeneity between mouse paracapsular intercalated neurons of the amygdala. Journal of Physiology. 2007;**585**:117–134.

[87] Samson RD, Pare D. A spatially structured network of inhibitory and excitatory connections directs impulse traffic within the lateral amygdala. Neuroscience. 2006;**141**:1599–1609.

[88] Repa JC, Muller J, Apergis J, Desrochers TM, Zhou Y, LeDoux JE. Two different lateral amygdala cell populations contribute to the initiation and storage of memory. Nature Neuroscience. 2001;**4**:724–731.

[89] Han JH, Kushner SA, Yiu AP, Cole CJ, Matynia A, Brown RA, Neve RL, Guzowski JF, Silva AJ, Josselyn SA. Neuronal competition and selection during memory formation. Science. 2007;**316**:457–460.

[90] Kim D, Samarth P, Feng F, Pare D, Nair S. Synaptic competition in the lateral amygdala and the stimulus specificity of conditioned fear: A biophysical modeling study. Brain Structure and Function. 2016;**221**:2163–2182.

[91] Gilmartin MR, Balderston NL, Helmstetter FJ. Prefrontal cortical regulation of fear learning. Trends in Neurosciences. 2014;**37**:455–464.

[92] Burgos-Robles A, Vidal-Gonzalez I, Quirk GJ. Sustained conditioned responses in prelimbic prefrontal neurons are correlated with fear expression and extinction failure. Journal of Neurosciences. 2009;**29**:8474–8482.