Public Abstract
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Title:COMPUTATIONAL MODELING OF THE FEAR CIRCUIT: A SYSTEM APPROACH TO UNDERSTAND ANXIETY AND STRESS DISORDER

Computational models are becoming increasingly important to systems neuroscience. In fear learning, although there have been a few attempts at modeling emotional learning and memory in the past, most were limited to simplified connectionist or artificial neural network models which did not incorporate current knowledge about the biophysical properties of accurate neurons. This research focused on extending our understanding of the neural mechanisms underlying fear learning and extinction using biophysically realistic network models. Since disruption of the fear circuit is thought to underlie the pathology of post traumatic stress (PTSD) and other anxiety disorders, such models could potentially provide ideas and approaches for the development of new medications.

We initiate modeling of the overall fear circuit starting with the most critical component, the lateral amygdala (LA), and attempts to describe how a single structure (i.e., LA) can encode both acquisition and extinction memories learned during auditory fear conditioning. A conditioning protocol consisting of unpaired/paired tone and shock stimuli was used to train the LA network and synaptic plasticity is determined by intracellular calcium levels, according to the calcium control hypothesis. The LA model provided several insights including the prediction that extinction, which has been thought to be due to a Hebbian unlearning process, is critically dependent on the potentiation of GABAergic synapses that serve to inhibit the fear memory stored in the pyramidal cells.

Next, we developed a biophysical model of another critical element of the fear circuit, the ITC (intercalated cells) to understand how strongly adaptive BLA (basolateral amygdala) signal can lead to sustained fear expression and to study the impact of infra-limbic (IL) vmPFC input in suppressing fear. Model experiments showed that persistent network activity can be maintained in ITC neurons and strongly adaptive fear/extinction signal from BLA can be transformed into more sustained output. They also showed that activation of the IL input effectively increases the responses of ITC neurons which inhibit the central amygdala (CE) output, regardless of the inter-ITC inhibition.

After successful development of component model for the LA and ITC network, an overall amygdala network model was developed to investigate how conditioning-induced potentiation of LA response leads to activation of the CE output, by inclusion of another important unit of the circuit, basal amydala (BA). Results showed that expression of fear was regulated by both the LA-BA-CE and the LA-ITC-CE pathways and interruption of each pathway resulted in impaired fear acquisition or extinction. Furthermore, the model provided insights into neural mechanisms underlying acquisition and extinction, and about the specific role of each amygdala component in fear learning by simulating a series of lesioning experiments.