Master's Thesis Research Proposal
Singing neurons: emergent oscillations in the amygdalar fear circuit in silico

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Here we investigate the biophysical mechanisms that evoke oscillations in the neuronal circuit responsible for fear learning in the basolateral amygdala (BLA) using computational models. Oscillations are patterns of waxing and waning of extracellular field potentials that occur because of changes in neuronal population activity (e.g. what proportion of cells in the population is spiking). BLA undergoes synaptic changes in the classical conditioning paradigm, which has been used to study the encoding of fearful experience (for reviews see 1,2). During classical conditioning experiments, a neutral stimulus (tone) is presented to the animal, followed by an aversive stimulus (footshock). After several trials, the animal forms a fearful memory and learns that the neutral stimulus predicts a negative outcome. Computational studies have used spiking neural networks (3,4) and more detailed two-compartmental models(5) to model the dynamics of the amygdalar fear learning circuit. However, there are no computational studies that address oscillations in the basolateral amygdala. Modeling studies can complement recent experimental work (6) that has revealed how gamma frequency oscillations change their power and coupling to the local theta rhythm during fearful experiences. The ability to simulate this system can reveal which parameters change its behavior. This leads to an improved mechanistic understanding of the underlying circuit.

We hypothesize that the oscillations in the basolateral amygdala emerge from the disinhibitory circuit that has recently been characterized experimentally(7). In this circuit, the interaction between two types of interneurons, expressing parvalbumin (PV) and somatostatin (SOM), gate learning. The SOM neurons synapse onto the distal dendrites of the principal cells and the PV neurons synapse onto the SOM cells, the perisomatic region of the principal cells and other PV cells. The pv cells play a different role during the neutral stimulus and the aversive stimulus. When optogenetics is used to activate the PV neurons during the footshock, fear learning is impaired. Conversely, when the PV neurons are silenced during the footshock, fear learning is enhanced. The proposed mechanism behind this is the disinhibition of the principal cells by dis-activation of the PV cells that increases principal cell activity, acting as a permissive gate for learning. In contrast, if the PV neurons are activated during the tone, this leads to an increase in the responses of principal cells. This happens because the PV neurons inhibit the SOM cells that are activated during the tone. The SOM cells inhibit the dendrites of the principal cells, thereby controlling the integration of thalamic input. When this inhibition is silenced through the inhibition of SOM cells by PV cells, the principal cells become more active. The patterns of inhibition exhibited by PV neurons have been shown to be necessary for the emergence of gamma oscillations in the cortex(8, 9, 10,11). Basolateral amygdala is similar in organization to the cortex (1), hence the same mechanisms may be playing a role in the BLA circuit. We propose to use real neuron morphologies (12) to simulate the dynamics of disinhibition, because these multi-compartmental models can capture the differential effects of perisomatic and dendritic inhibition, which has been marked as important by the experimental work.

Furthermore, our aim is to characterize how the oscillatory activity during neutral and aversive stimulus encodes the prediction that one will be followed by another. The coupling between neutral and aversive stimuli forms a multi-item message that hypothetically can be encoded in the theta-gamma oscillation neural code (13). The coding of information through oscillations has been demonstrated in the hippocampus, where spatial information is encoded in gamma subcycles of a theta cycle. The mechanisms for encoding the predictive information that the neutral stimulus holds about the aversive stimulus have not been fully elucidated in the amygdala. Simulations can both reveal aspects of these mechanisms and provide an informative context for the design of experiments for unraveling the learning of temporal sequences in the amygdala.

Oscillations are the consequence of synaptic currents flowing between cells. The relationship between excitatory and inhibitory currents can impact the amplitude and instantaneous frequency of the oscillations (14,15). Simulations allow to determine how cellular connectivity and the location and abundance of synapses can impact the currents flowing through the simulated cells. Experimental work has revealed how dendritic inhibition in the hippocampus controls the input-output characteristics (gain) of principal cells (16). Systematically studying how the characteristics of oscillations are modulated by factors such as cellular currents and connectivity can lead to an improved characterization of the amygdalar fear circuit and to the formulation of new experimental hypotheses.

Finally, oscillations and synchronization play a key role in transmitting signals from one area of the brain to the other (17,18,19). Gating the transmission of signals has been investigating through the lense of the balance between excitation and inhibition(20). Normally, excitation and inhibition are balanced and the spiking is driven by fluctuations in synaptic currents. Transmission of signals to further processing areas can be switched 'on' by disrupting the balance between excitation and inhibition at specific subsets of synaptic inputs(20). We intend to investigate how network oscillations create “windows of opportunity” to transfer excitatory signals to downstream areas, such as the central nucleus of the amygdala, which mediates the freezing response.

In summary, we plan to investigate how the disinhibitory circuit in the amygdala gives rise to oscillations through detailed biophysical simulations. Simulations permit a mechanistic understanding of the circuit, because different properties such as the relationship between excitation and inhibition and synaptic connectivity can be manipulated to quantify their impact on the dynamics of the system. The work has the potential to shed light on how the circuit learns to predict the occurrence of the aversive stimulus based on the neutral stimulus through an oscillatory neural code and how orchestrated disinhibition serves to transmit signals to other brain areas.

Citations

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