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Model of the Generation of the Amygdala Theta Rhythm

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Introduction

- The basolateral amygdala (BLA) receives a prominent basal forebrain (BF) GABAergic projection. This projection, arising from the ventral pallidum/substantia innominata nuclei (VP/SI), selectively targets GABAergic interneurons in the amygdala and forms a disinhibitory mechanism. However, the functional role of this circuit is not well-understood.
- We aim at filling the gap in the literature by revealing the fine structure and function of the BF GABAergic projection to the amygdala. We seek to understand how they contribute to the generation of local oscillations in the amygdala and shape the formation of emotional memories.
- We conceptualize that BF GABAergic projections constitute a major neuromodulatory pathway in the brain. They carry out a single, common function in all the limbic areas that they target, contributing to local network oscillations and the associated memory processes. We hypothesize that, as GABAergic septo-hippocampal projections substantially contribute to hippocampal memory processes, GABAergic BF-amygdala projections are required for emotional memory processes by regulating local theta oscillations.
- A computo-experimental approach is used to explore this hypothesis. On the experimental front, we combine tract-tracing, fluorescent immunohistochemistry, selective neural silencing/inactivation, and behavioral testing in rats. In parallel, we are developing a biophysically-realistic BLA model with afferents from known regions including the VP/SI (Figure 1).

Network Model and Hypothesis

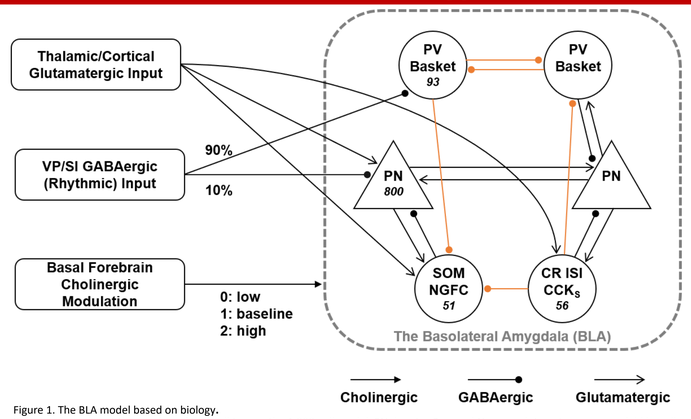

Figure 1. The BLA model based on biology.
Italic numbers depict the number of that cell type in the 1,000-cell model. PN denotes Principal Neuron, glutamatergic pyramidal-like cells of the BLA. Three most populous interneuron groups of the amygdala are included: parvalbumin- (PV), somatostatin- (SOM), and calretinin- (CR) containing interneurons. PV-Basket cells co-express CB. SOM interneurons co-express CB and NPY. These include dendrite-targeting interneurons, neurogliaform cells (NGFC) and long-range SOM+ GABAergic neurons that project to the BF. CR interneurons co-express VIP. These include the majority of small CCK+ interneurons (CCKS) that can have CR or VIP, and VIP+ interneuron-specific interneurons (ISI).

- We hypothesize that GABAergic projection neurons from the ventral pallidum/substantia innominata (VP/SI) nuclei of the BF that selectively innervate inhibitory interneurons in the BLA [1;2] are responsible for the generation of local theta oscillations in this limbic structure.
- In this realistic BLA model, local theta oscillations should emerge when both the non-rhythmic cholinergic input and the rhythmic GABAergic input of the VP/SI are present in addition to the constant excitatory thalamic/cortical input, as is the case for hippocampus [3].
- As observed for the hippocampal theta rhythm [4], removing the cholinergic or the GABAergic BF input alone should decrease the theta power in the BLA.
- In addition, the BLA theta oscillation should cease completely when the rhythmic GABAergic input is cut together with either the cholinergic or the non-rhythmic thalamic/cortical input.

Methods

- Our current experimental efforts combine tract-tracing with fluorescent immunohistochemistry to characterize VP/SI GABAergic innervation of the BLA. Fluorescent latex microspheres (RetroBeads, Lumafluor, NC) is used for retrograde tracing of the BLA-targeting BF neurons.
- Following the development in our prior hippocampal theta model [4] a 1000-cell scaled down model of the BLA was developed that included known cell types, connectivity, and extrinsic input, including the BF GABAergic projections.
- Local microcircuitry includes pyramidal-like principal neurons (PN) and three most populous interneuron groups: interneurons containing parvalbumin (PV), somatostatin (SOM), and calretinin (CR) [1;2].
- These cells were matched with biological findings regarding their passive properties and firing rates. Connectivity between cells was built using published literature. AMPA, NMDA, $GABA_A$ and $GABA_B$ currents are modeled together with rise and decay times, and synaptic weights.

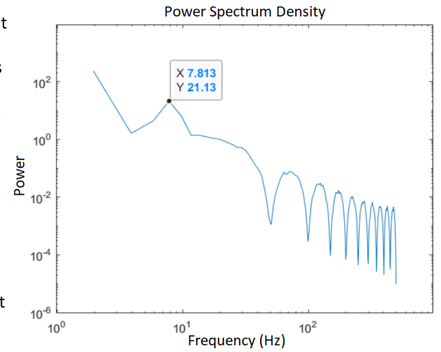

Figure 2. Simulated VP/SI GABAergic input power spectrum density. Shows the power at which different frequency inputs are provided.

- External input includes excitatory cortical/thalamic input that target PNs, SOM+ and CR+ interneurons [5], non-rhythmic BF cholinergic input, and rhythmic BF GABAergic input.

Design of Rhythmic inputs

- Rhythmic GABAergic input from the VP/SI was designed using methods described by [6].
- In short, "the input was set to a specific frequency, and each cell responded to that input with some "jitter" to represent intercellular variability. The jitter was Gaussian distributed (N) for each cell, as defined by sigma-jitter. The time of the jth event of neuron i was therefore given by the following $t_j^i = jT + \mathcal{N}(0, \sigma^2_{jitter})$,
- A total of 893 afferent cells were designed to individually exhibit 2 Hz Poisson activity, resulting in a 8 Hz population rhythmicity. Figures 3 and 4 show the randomness of the network, with a modest but significant power increase in the theta range (Fig. 3). The afferents project onto 800 PN and 93 PV Basket cells with an average convergence of 1 and 10.1 cells, respectively.
- A similar 20 Hz rhythmic input was also produced using this method, which can also interfere with local gamma oscillations [7].

Results/Discussion

- Our computo-experimental study explores the contributions of the underlying circuit mechanisms to the BLA theta rhythm using a 1,000-cell, biophysically-realistic computational model. The model used known physiological and anatomical properties of the amygdala, incorporating different cell types, synaptic current dynamics, heterogeneous spatial connectivity, short-term plasticity and neuromodulatory inputs. Extrinsic inputs comprised cholinergic and GABAergic inputs from the BF, and an excitatory thalamic/cortical input.
- After matching single cell responses to biological data, model cells were inserted into the network and synaptic weights were tuned to successfully reproduce baseline in vivo firing rates for all cell types except for SOM+ interneurons: 1.89 Hz (± 1.03 Hz), 8.66 Hz (± 5.85 Hz) and 21.33 Hz (± 0.95 Hz) for PN, PV+ and SOM+/CR+ cell types, respectively [4].
- With a higher firing rate of 21 Hz, a distinct bump in theta frequency range was noticed in the power spectral density (PSD) plot of the LFP, suggesting that the network has the capability for producing theta intrinsically.
- We then introduced extrinsic input with firing rates at 4-8 Hz to represent theta rhythmic inputs from VP/SI. With SOM+ cells back to a baseline firing rate of 12.89 Hz (± 5.85 Hz) and an 8 Hz rhythmic input, we found that theta remained consistently high (Fig. 3) at a power level as in experiments with higher levels of SOM+ activity.
- We show that GABAergic VP/SI input should strengthen the theta-range oscillatory power albeit sufficient network resonance arising from thalamic/cortical and BF cholinergic input. However, when these excitatory inputs fail to produce theta-genesis, GABAergic afferents may provide no additional effect.

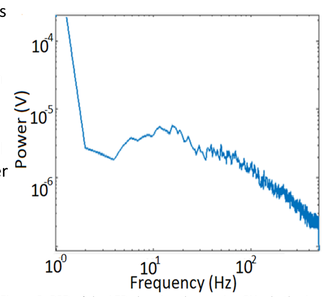

Figure 3. PSD of the LFP, showing theta using 8Hz rhythmic input from the VP/SI.

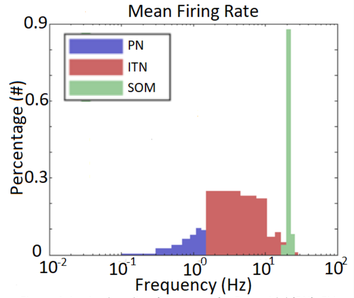

Figure 4. In vivo baseline firing rates for Pyramidal (PN), PV (ITN) and Somatostatin (SOM) cell types.

Ongoing and Future Work

- Ongoing work explores the contribution of cholinergic modulation and the role of extrinsic drive on BLA theta activity.
- While cholinergic modulation is thought to further strengthen resonance in these cell loops and contribute to the theta-frequency oscillation in the BLA, the extrinsic GABAergic projection from VP/SI provides an independent, possibly overarching resonant mechanism.
- Although there should be sufficient resonance in the network arising from non-rhythmic thalamic/cortical and modulatory cholinergic input, GABAergic VP/SI input should strengthen the theta-range oscillatory power.
- However, when these non-rhythmic excitatory inputs fail to produce theta-genesis in the BLA, GABAergic afferents may provide no additional effect, as in the hippocampus [8].
- In line with these efforts, our future experimental work will investigate the functional role of the BLA-targeting BF GABAergic neurons in amygdala-dependent learning and memory processes by selectively inactivating these cells using neurotoxins (GAT1-saporin) and chemogenetics.

Conclusions

- We developed a biophysical computational model of the BLA to explore how the external inputs and intrinsic connectivity in the amygdala supports theta rhythmic local oscillations observed during fear learning, a well-studied affective process coordinated by the amygdala.
- Intrinsic oscillatory mechanisms in the model included the PN-SOM+ and PN-CR+ cell loops. Our results show that this mechanism is indeed capable of increasing power in the theta range as reflected in the PSD plot of the LFP.

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