410.22

The role of higher-order thalamic inputs in generating oscillatory dynamics in sensory neocortex: Integrated electrophysiological, interluminescence and fluorescence studies

Jeremy Murphy[1], Eric Klein[1], Emmanuel L. Crespo[2], Mansi Prakash[2], Stephanie Jones[1], Ute Hochgeschwender[2], Christopher I. Moore[1]

1 Brown University, Providence, RI | 2 Central Michigan University, Mount Pleasant, MI

bioluminescencehub.org
Powered by NSF NeuroNex 1707352

ROBERT J. & NANCY D. CARNEY INSTITUTE FOR BRAIN SCIENCE
BROWN UNIVERSITY

The selective and flexible prioritization of specific sensory inputs aligned to behavioral goals is central to complex behavior. The enhancement of some sensory representations as well as the suppression of others occurs in the neocortex during this goal driven perceptual prioritization. A question that remains to be fully answered is how this enhancement and suppression is implemented at the neuronal circuit level.

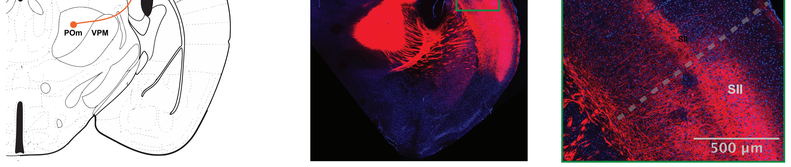
Nuclei of the thalamus are well situated to implement top-down prioritization signals as well as organize context across distinct cortical areas [1]. The posterior medial nucleus (POm) is a higher-order thalamic nucleus that is highly interconnected with the rodent somatosensory and motor systems. It provides excitatory inputs to layers 1 and 5 of barrel field of primary somatosensory cortex (SI) [2]. This canonical top-down arrangements of inputs situates it excellently to modulate perceptual representations in cortex [3]. Oscillatory activity in the field potentials of neural ensembles are associated with selective prioritization by a large body of work [1,4,5]. Interactions between thalamus and cortex have been implicated in a variety of oscillatory rhythms [4].

Here we present preliminary data from anesthetized mice in which laminar extracellular recordings were preformed in cortex. We then,
1) Simultaneously recorded from spontaneous spiking in POm
2) Briefly optogenetically inhibition POm, and
3) Imaged the spontaneous activity of POm axons in superficial cortical layers using widefield fluorescence imaging of genetically encoded calcium indicators

Our data indicate that POm may play a role in the induction of a wide band of oscillations in cortex, and we believe this may be context dependent. We present our group's bioluminescent optical synapse tool that can be utilized to exclusively target specific pre- and post-synaptic partners with optogenetically driven up- or down regulation of synaptic efficacy in an activity dependent manner. We present preliminary data demonstrating that this tool can be used to dissect the role of specific interactions between POm excitatory projections and different neuronal sub-types.

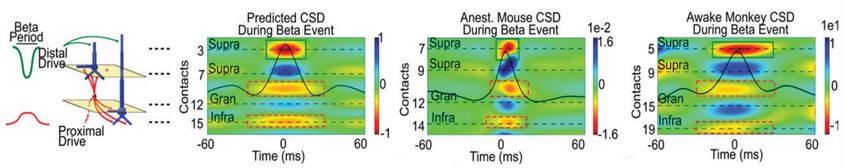
Paralemniscal thalamic nuclei likely play a role in selective prioritization of sensory representations in cortical regions. These nuclei include the pulvinar in humans and primates in the visual system and POm in the rodent somatosensory system [3]. POm is interconnected with SI in a manner that parallels the pulvinar in the visual system, sending excitatory projections to layers 1 and 5 and receiving abundant projections back from layer 6 CT cells [2]. POm is also heavily interconnected with other cortical and subcortal regions, particularly with sencondary somatosensory cortex, primary motor cortex and the striatum. This suggests that POm may serve as an important coordinator and modulator of top-down selective prioritization.

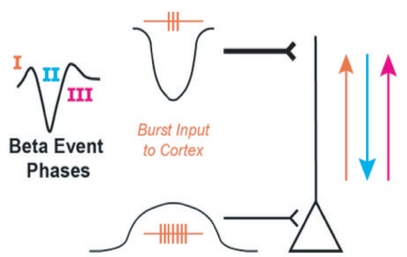
In layers 1 and 5 of SI, POm has distinctive synaptic targets, including the proximal and distal dendrites of layer 5 pyramidal cells, as well as the dendrites of layer 2/3 inhibitory interneurons. POm is thus well situated to play a role in active dendritic currents of layer 5 pyramidal neurons, a mechanism that has been proposed as a gate to perception [5].



Neocortical oscillations are associated with selective sensory prioritization by a strong body of research in humans, primates, and rodents [1]. In human studies, as measured by M/EEG, cortical oscillations in the alpha band (8-14 Hz) and short bursts of beta oscillations (15-29 Hz) are both correlated with successful detection of threshold stimuli [6]. Both alpha power and beta burst frequency increase over cortical regions that represent disattended sensory representations, suggesting that they are markers of suppression of non-relevant information [7,8].

In a biophysical model from our group of beta events in neocortex, proximal and distal excitatory drive of layer 5 pyramidal cells along with possible inhibition of interneurons that themselves tonically inhibit the apical dendrites of the layer 5 pyramidal cells, leads to the drive of current up and down the length of layer 5 pyramidal cell apical dendrites. This pattern of current flow is able to produce the distinct shape of a beta event [9]. POm's excitatory synaptic pattern of inputs to S1 make it an excellent candidate for beta event generation.

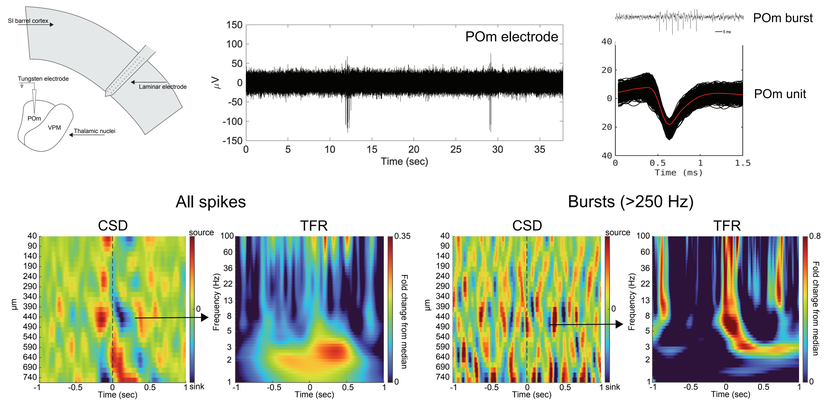




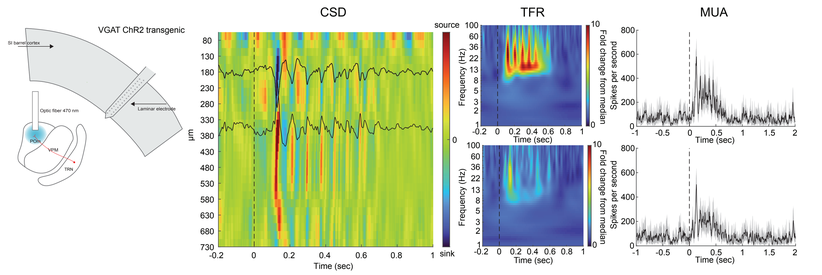
Model of cortical beta event:

I) Proximal 10 Hz bursting onto layer 5 pyramidal neurons drives Current up the apical dendrites
II) Dendritic calcium spiking in the distal dendrites drives current down the dendrites
III) Continued EPSPs in the proximal dendrites in addition to the arrival of current back from the apical dendrites initiates further bursting driving current back up the

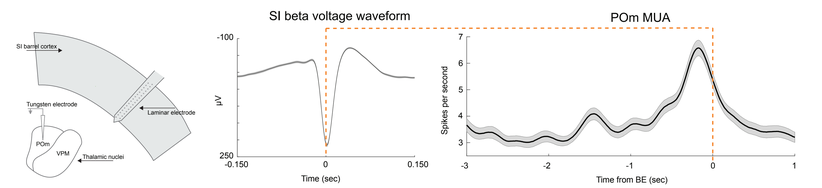
POm single unit bursts and tonic firing coincide with slow (1-8 Hz) oscillatory transients in SI



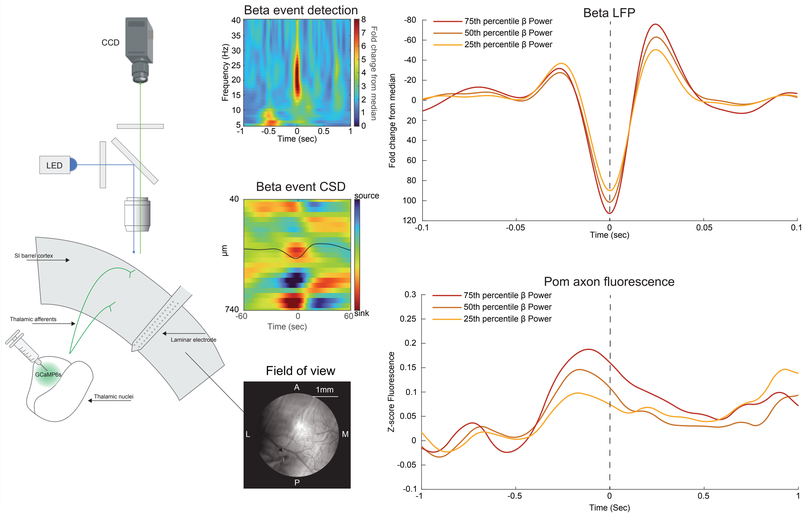
Brief (10 ms) inhibition of POm via the optogenetic excitation of GABAergic projections from TRN results in subsequent rhythmic fields in the alpha range (~13 Hz) along with phase locked population spiking



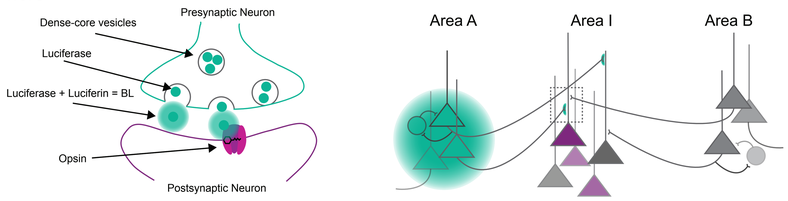
POm population firing rate increases prior to a beta event in SI



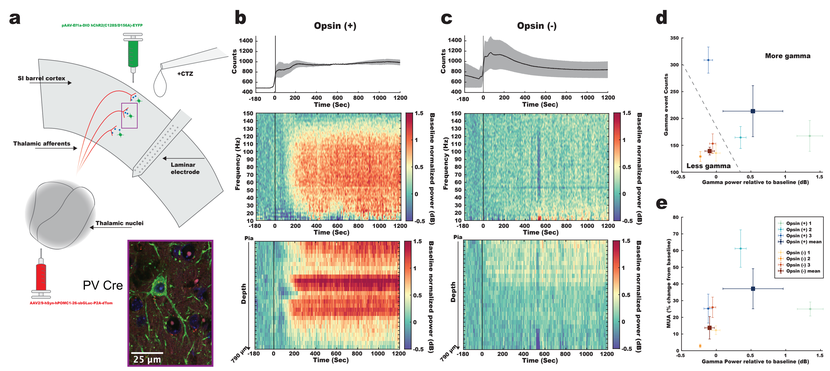
Increases in GCaMP6s fluorescence in POm axons in SI precede beta events in SI



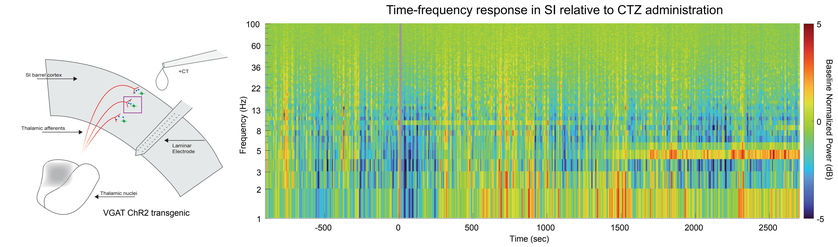
Bioluminescent optical synapses can modulate the drive of specific pre- and postsynaptic partners

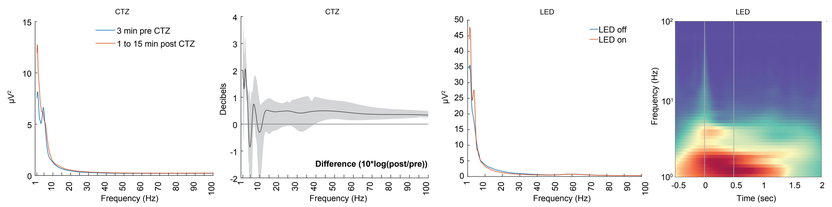


Prakash, Murphy, et al. (2022): Up-regulating the synaptic pairing of thalamic excitatory projections to cortical PV interneurons using a bioluminescent optical synapse increases gamma band (30-100 Hz) oscillations



Preliminary data suggest that the up-regulation excitatory drive from POm to broad GABAergic interneurons in S1b produces slow oscillations in S1b (1-8 Hz). By using available transgenic lines we plan to target specific interneuron subtypes with this setup





The oscillatory markers of sensory prioritization are irregular in many neurological disorders, such as ADHD, autism spectrum disorders, Parkinson's disease, and schizophrenia [10]. Understanding the mechanistic, circuit level processes that give rise to the various oscillatory events in the brain would provide tremendous insight in the pathology of these disorders. Our work aims to understand these circuit mechanisms. We are currently implementing imaging (wide field and 2-p) and high-density extracellular electrophysiology of neocortex and thalamic nuclei in awake behaving mice.

References

1. Fiebelkorn, I. C., & Kastner, S. (2020). Functional specialization in the attention network. Annual review of psychology, 71, 221.
2. El-Boustani, S., Sermet, B. S., Foustoukos, G., Oram, T. B., Yizhar, O., & Petersen, C. C. (2020). Anatomically and functionally distinct thalamocortical inputs to primary and secondary mouse whisker somatosensory cortices. Nature communications, 11(1), 1-12.
3. Schuman, B., Dellal, S., Prönneke, A., Machold, R., & Rudy, B. (2021). Neocortical layer 1: an elegant solution to top-down and bottom-up integration. Annual review of neuroscience, 44, 221-252.
4. Jones, S. R., Pritchett, D. L., Sikora, M. A., Stufflebeam, S. M., Hämäläinen, M., & Moore, C. I. (2009). Quantitative analysis and biophysically realistic neural modeling of the MEG mu rhythm: rhythmogenesis and modulation of sensory-evoked responses. Journal of neurophysiology, 102(6), 3554-3572.
5. Foxe, J. J., & Snyder, A. C. (2011). The role of alpha-band brain oscillations as a sensory suppression mechanism during selective attention. Frontiers in psychology, 2, 154.
6. Bourgeois, A., Guedj, C., Carrera, E., & Vuilleumier, P. (2020). Pulvino-cortical interaction: an integrative role in the control of attention. Neuroscience & Biobehavioral Reviews, 111, 104-113.
7. Takahashi, N., Ebner, C., Sigl-Glöckner, J., Moberg, S., Nierwetberg, S., & Larkum, M. E. (2020). Active dendritic currents gate descending cortical outputs in perception. Nature Neuroscience, 23(10), 1277-1285.
8. Shin, H., Law, R., Tsutsui, S., Moore, C. I., & Jones, S. R. (2017). The rate of transient beta frequency events predicts behavior across tasks and species. Elife, 6, e29086.
9. Sherman, M. A., Lee, S., Law, R., Haegens, S., Thorn, C. A., Hämäläinen, M. S., ... & Jones, S. R. (2016). Neural mechanisms of transient neocortical beta rhythms: Converging evidence from humans, computational modeling, monkeys, and mice. Proceedings of the National Academy of Sciences, 113(33), E4885-E4894.
10. Başar, E., Schmiedt-Fehr, C., Mathes, B., Femir, B., Emek-Savaş, D. D., Tolay, E., ... & Başar-Eroğlu, C. (2016). What does the broken brain say to the neuroscientist? Oscillations and connectivity in schizophrenia, Alzheimer's disease, and bipolar disorder. International Journal of Psychophysiology, 103, 135-148.