Computational neural modeling study of contrasting high- (28-80Hz) and low-frequency (8-32Hz) resonance properties with optogenetic drive to fast-spiking interneurons or regular-spiking pyramidal cells *in vivo*

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1 Introduction

- Gamma oscillations at 20-80Hz in the cortex predict increased attention and are thought to bind sensory representations into coherent percepts.
- Theoretical work predicts synchronous activity of fast-spiking (FS) inhibitory interneurons generates gamma oscillations, with the time course of FS-evoked GABA_A inhibition controlling frequency (Borgers and Kopell, 2003, 2005).
- ***In vivo* optogenetic activation of of Fast Spiking (FS) interneurons in mouse somatosensory cortex leads to gamma resonance (28-80 Hz),** in agreement with prevailing theoretical work (Cardin et al., Nature, 2009)
- In contrast, **activation of Pyramidal cells enhances low frequency power (8-32 Hz),** which is not readily explained by the prevailing theoretical view.
- We develop **biophysically based computational models of layer II/III somatosensory cortex** to identify possible mechanisms for these contrasting resonance behaviors.
- **We focus on distinct roles for two classes of interneurons, FS and low threshold spiking (LTS/SOM/GIN),** based on a growing body of evidence suggesting they play distinct roles in rhythmic network activity (Kapfer et al., Nature Neuroscience, 2007, Fanselow et al, J. Neurophysiol, 2008)

3 Modeling Methods

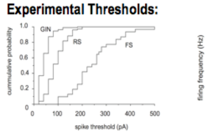
3 cell classes, tuned for in vitro cell properties:

Pyramidal Cell (RS)
- na, k, m, ca and kca currents
- 7 compartments
- slow spiking at threshold
- adapting
- τ_m = 16.35 ms

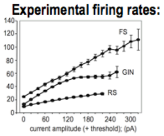
FS Interneuron
- na & k currents
- 16 compartments
- fast spiking
- τ_m = 9.6 ms

LTS/GIN/SOM Interneuron
- na, k, m, ca, kca, h and T currents
- slow periodic spiking at threshold
- 16 compartments
- sag current
- adapting
- τ_m = 17 ms

Experimental Thresholds:



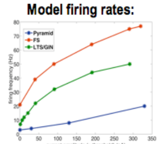
Experimental firing rates:



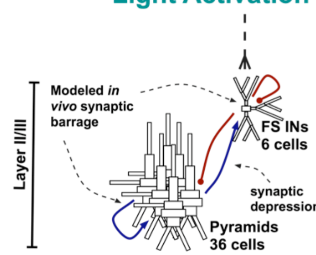
Fanselow et al., J Neurophysiol, 2008

Model Thresholds:
- LTS/GIN/SOM: 9 pA
- Pyramid: 70 pA
- FS: 110 pA

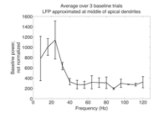
Model firing rates:

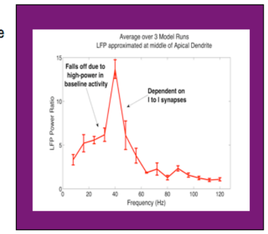


4 Pyramidal & FS Network: Drive to FS generates high frequency (gamma) resonance

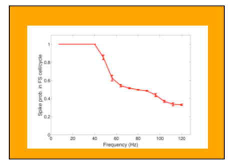


- Gamma resonance depends on time course of $GABA_A$ inhibition

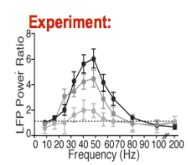


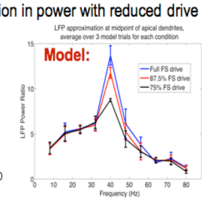


- Probability of FS response to modeled light drive falls off at high frequencies due to FS-FS connectivity



Model reproduces reduction in power with reduced drive :





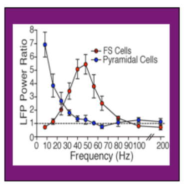
7 Summary and Conclusions

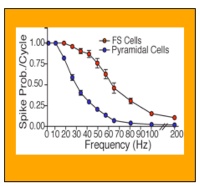
- In vivo optogenetic **activation of cortical FS cells (8-200Hz) exposes gamma resonance in normalized LFP (28-80 Hz).**
- In contrast, **activation of cortical pyramidal cells enhances low frequency LFP power (8-32 Hz).**
- Biophysically principled computational model reproduces cell spike response probabilities and dual resonance property and predicts:

FS Drive, high-frequency (28-80 Hz) resonance:
- **Short time course of FS $GABA_A$ inhibition generates gamma resonance.**
- **Pyramidal activity present during FS drive is insufficient to recruit LTS/SOM inhibition.**

Pyramidal Drive, enhanced low-frequency (8-32 Hz):
- **Decreased pyramidal cell response at high-frequency drive is insufficient generate low-frequency response.**
- **LTS/SOM interneurons are selectively recruited by highly synchronous excitatory activity with pyramidal drive.**
- The **long time course of LTS inhibition slows network,** preventing entrainment to fast driving frequencies with pyramidal drive.

2 Experimental Summary

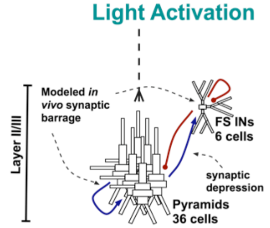




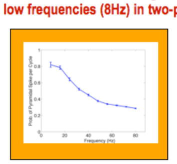
- Via a combination of genetic and viral techniques, **light-activated channelrhodopsin was inserted into specific neural subtypes** (FS and Pyramidal) in mouse somatosensory cortex.
- With pulsing light (8-200 Hz) cortical stimulation, **activation of FS inhibition led to enhanced power in the gamma frequency band, with a peak in normalized LFP at 40 Hz** (see purple box, this panel).
- In contrast, **activation of pyramidal neurons amplified lower frequency LFP (8 Hz)** (see purple box, this panel).
- **FS cells responded to higher frequency stimulus more readily than pyramidal cells** (see yellow box, this panel).

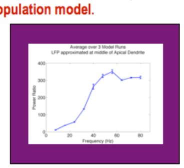
Cardin et al., Nature, 2009

5 Do less responsive pyramidal cells generate low frequency resonance?

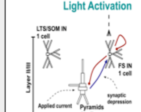


- Firing probability of pyramidal cells in response to light drive falls off for high frequencies due to intrinsic cell properties (long AHP).
- **This is not sufficient to generate enhanced relative power at low frequencies (8Hz) in two-population model.**



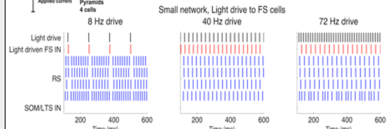


6 Hypothesis: Second Inhibitory Population (LTS) Required for Low-Frequency Enhancement



- No recruitment of LTS/SOM cell due to insufficient synchrony in the pyramidal population with RS drive
- Resonance depends on time course of $GABA_A$ inhibition (8 ms) from FS cells

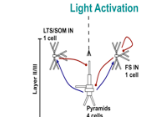
Small network, Light drive to FS cells



Lots of spiking, but not at 8 Hz
Weak 8 Hz in LFP

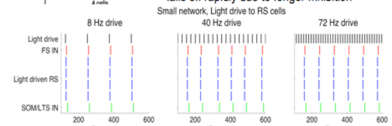
Spiking at 40 Hz Due to inhibitory timing
Strong 40 Hz in LFP

Too much inhibition to follow 72 Hz drive
Weak 72 Hz LFP



- Synchronous drive to pyramidal population recruits LTS/SOM cell
- Time constant of LTS/SOM inhibition (20 ms) slows network to 8-12 Hz, even with high frequency drive
- Firing probability for pyramidal cell drive falls off rapidly due to longer inhibition

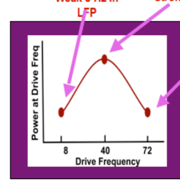
Small network, Light drive to RS cells

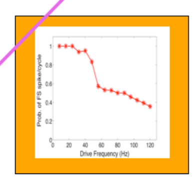


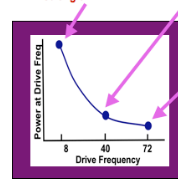
Network entrains to 8 Hz drive
Strong 8 Hz in LFP

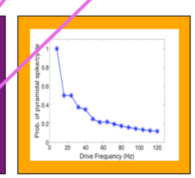
Long LTS inhibition slows network
Weak 40 Hz in LFP

Long LTS inhibition slows network
Weak 72 Hz LFP









8 Ongoing Efforts

Ongoing efforts are aimed at

- Understanding enhanced low-frequency activity resonance in fully connected larger network with pyramidal drive.
- Modeling more biophysically accurate activation of LTS population to explore whether it is reasonable to assume that LTS naturally activate with pyramidal drive but not with FS drive.
- Determining further network features that promote contrasting network resonance properties when pyramidal vs. FS cells are synchronously activated *in vivo*.

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