

Dynamics of whisking and touch responses in layer-4 cortical barrels with several types of interneurons

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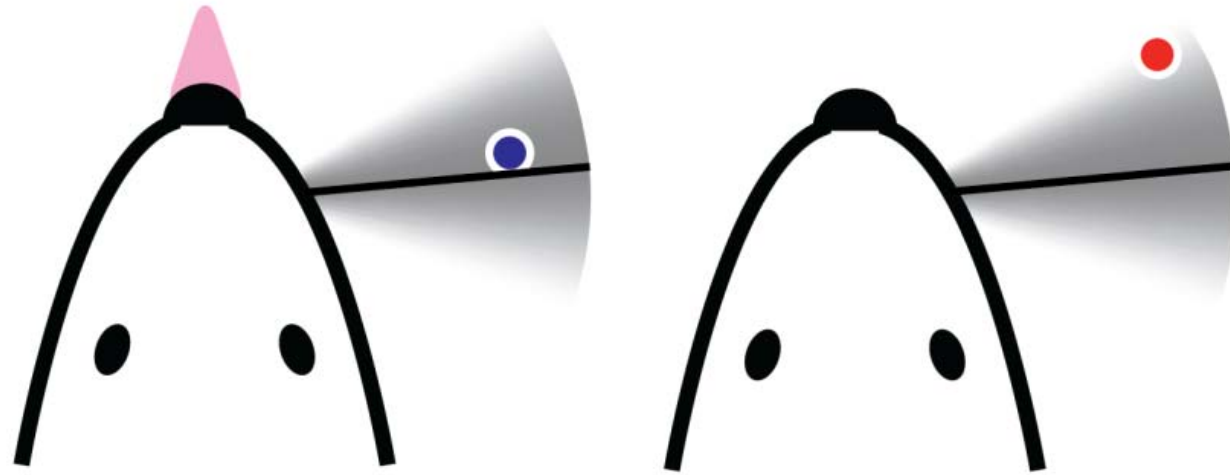
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Content

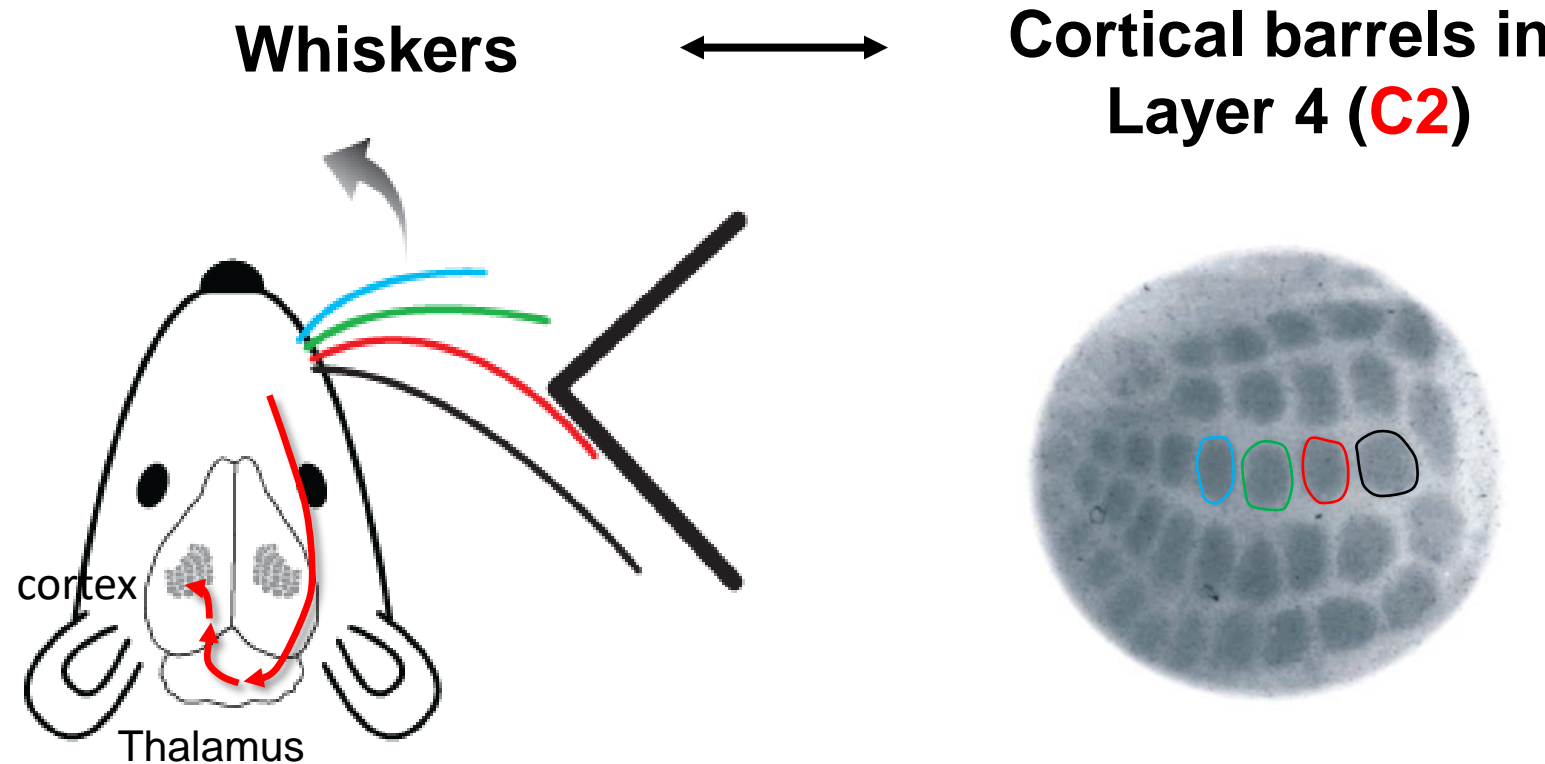
- The whisker somatosensory system.
- Theory: dynamics of strongly-coupled cortical circuits.
- Electrophysiological results.
- Models of cortical networks with excitatory (E) and PV inhibitory neurons.
- Models of cortical networks with E, PV and SOM neurons.

The whisker somatosensory-motor system

Object (pole) localization by head-fixed mice

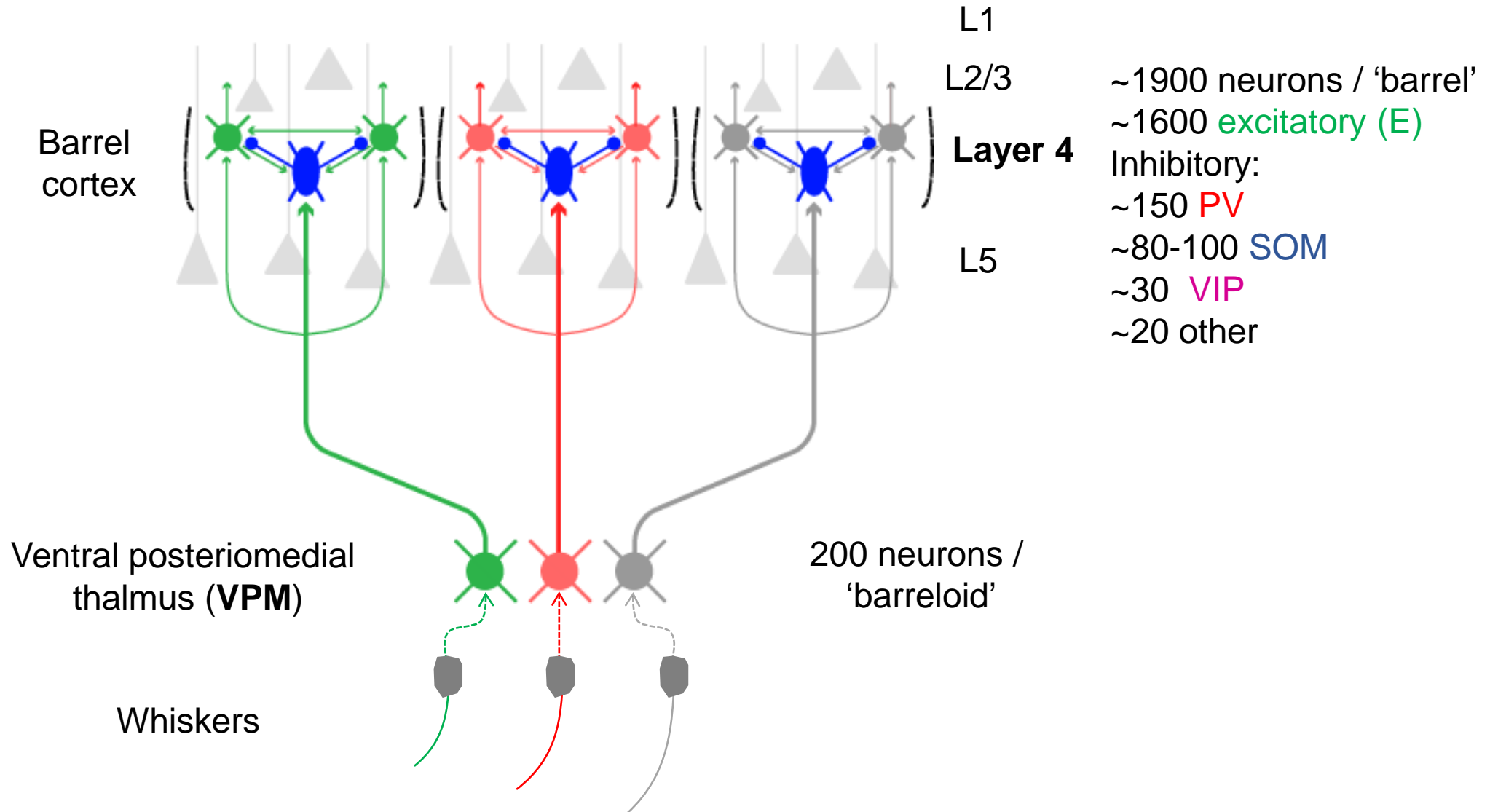


The flow of information underlying tactile sensation



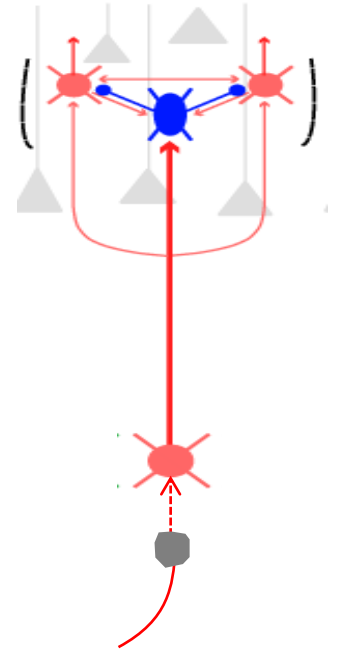
- Mice move their whiskers to detect, localize and identify objects by touch.
- Information from each whisker is processed in one barrel in Layer 4.
- Experiments:
 - Video recording of whisker movement.
 - Recording from neurons in thalamic barreloids and cortical barrels.

The thalamocortical circuit

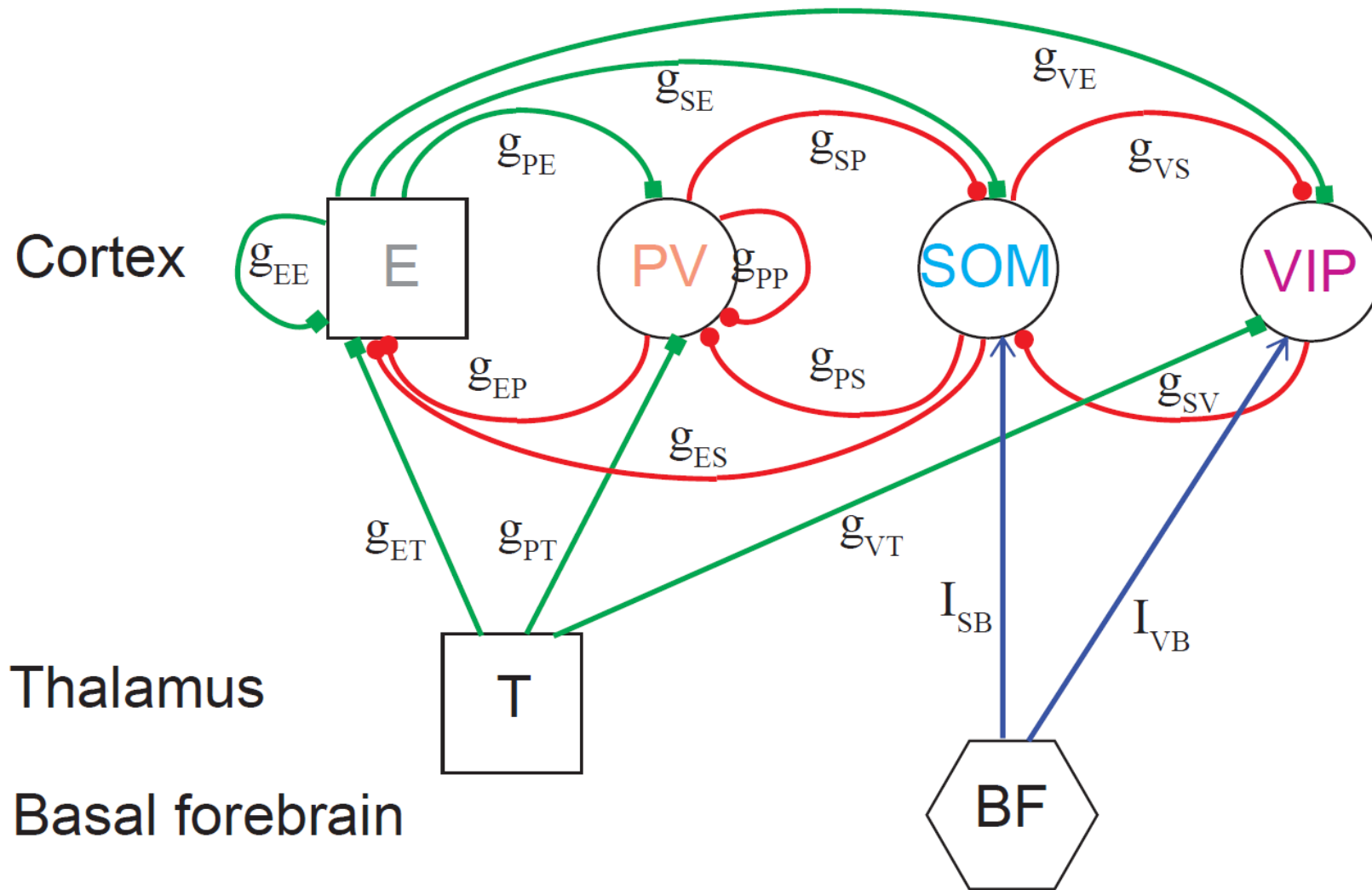


The layer-4 (L4) circuit in the barrel cortex is relatively simple because:

- Neurons in different barrels are hardly connected.
- E and PV neurons in each barrel are synaptically innervated by other neurons in the barrel and VPM thalamic (T) neurons only.
- SOM neurons mainly target L4. They preferentially inhibit L4 PV neurons (Lee... Rudy, Neuron, 2013).

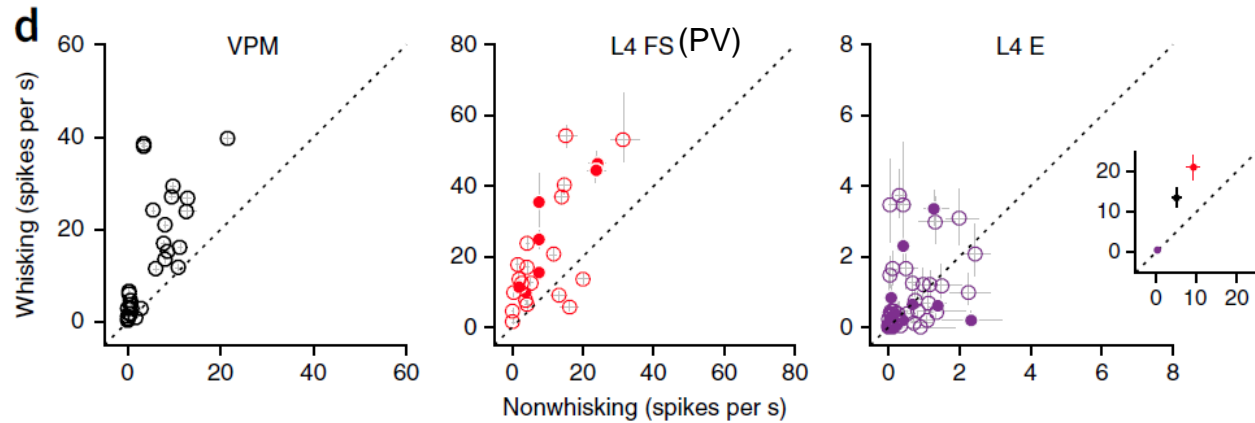


Connectivity diagram – chemical synapses

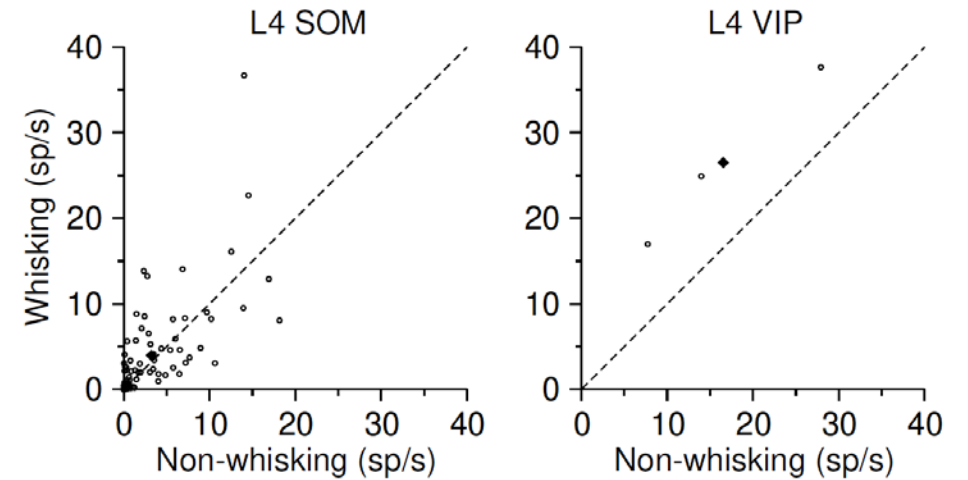


Recording from behaving, head-fixed mice

Response to baseline (non-whisking) and whisking

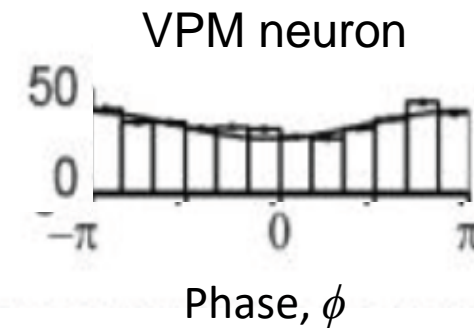


Yu et al., 2016.



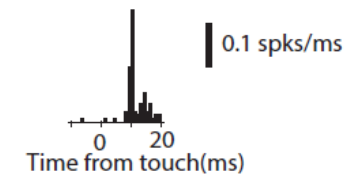
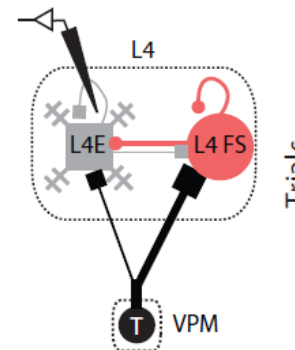
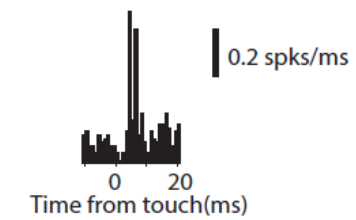
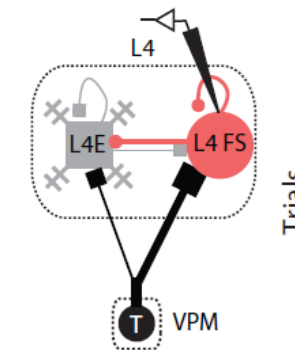
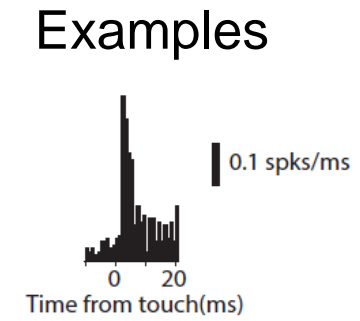
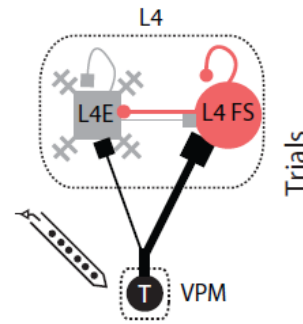
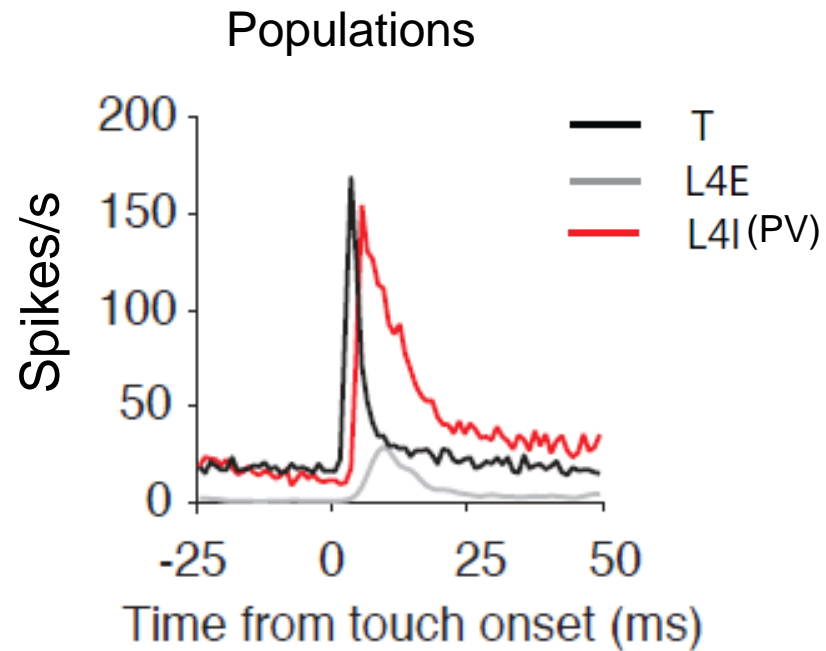
Yu and Svoboda, unpublished.

Neurons tends to fire more during maximal retraction.
Modulation depth ~ 0.25 .

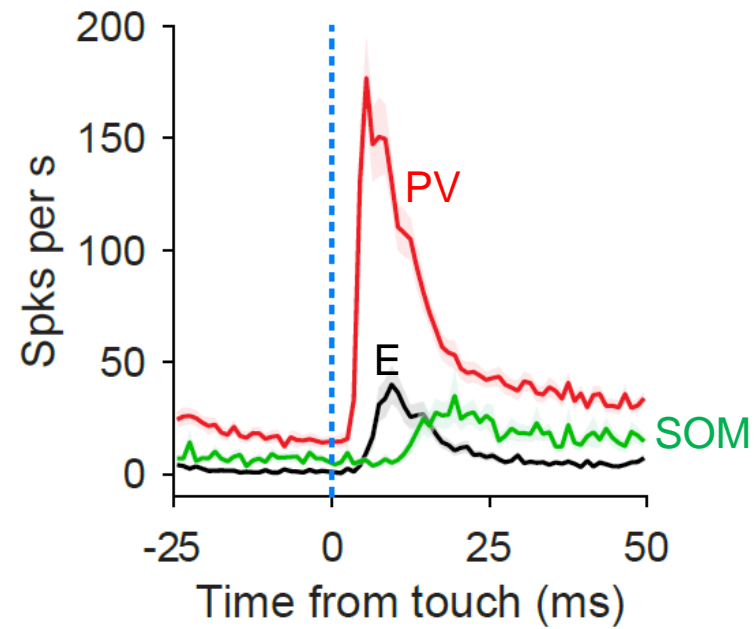


Response to touch

Hires et al., 2015; Yu et al., 2016; Gutnisky et al., 2017.

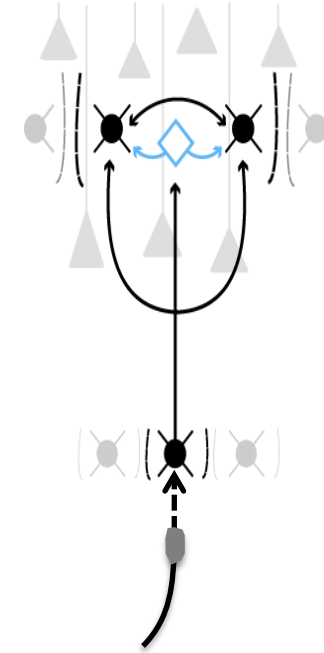


SOM neurons respond to touch with delay



Electrophysiology: summary of results

	Firing rate NW, ν (Hz)	Firing rate W, ν (Hz)	Spikes/Touch R
T (VPM)	5 ± 6	14 ± 13	0.6 ± 0.5
L4 PV	9 ± 9	21 ± 16	1.9 ± 1
L4 SOM	3.2 ± 4.3	4 ± 5.7	0.7 ± 0.7
L4E	0.4 ± 0.6	0.6 ± 0.9	0.3 ± 0.4

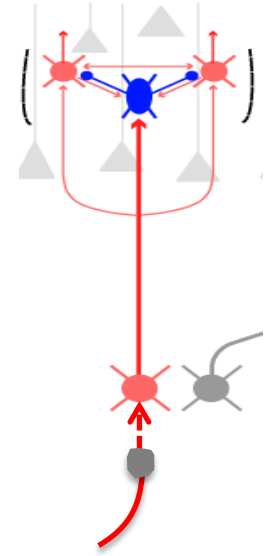


The L4 micro circuit enhances touch representation and suppresses self-movement signals

Dynamics of cortical circuits

Conditions:

- Localized networks:
Probabilities and strengths of synaptic conductances do not depend on distance between neurons.
- Strong coupling:
total excitatory (inhibitory) synaptic conductance \gg threshold.
- Asynchronized firing patterns
is obtained if connectivity is very sparse.



Measures of population firing activities

- Population firing rate, v_α , $\alpha=T, E, P, S, V$.
- Population coefficient of variation $CV_{ISI,\alpha}$.
- Synchrony measure – χ_α :

Normalized temporal fluctuations of the population voltage.

$\chi = 1$ Full synchrony

$\chi \sim 1 / \sqrt{N}$ Asynchrony

Golomb and Rinzel, 1993;
Golomb, Scholarpedia, 2007.

- Population touch response, R_α .

Theory: balanced state

(van Vreeswijk and Sompolinsky, 1996; 1998)

Constant or slowly-varying stimulus.

$$\alpha, \beta = T, E, P$$

$$p_{\alpha\beta} = K_{\alpha\beta} / N_{\beta}$$

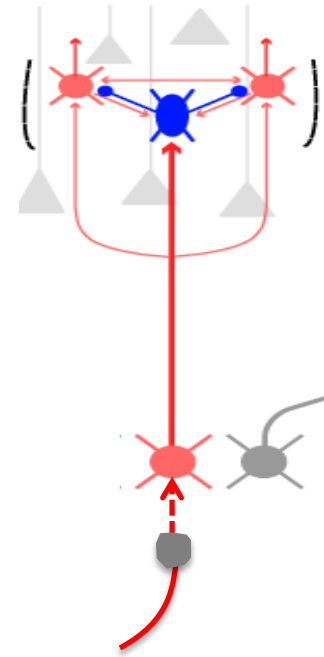
probability of coupling from population β to population α .

$$1 \square K_{\alpha\beta} \square N_{\beta}$$

$$G_{\alpha\beta} = g_{\alpha\beta} / \sqrt{K_{\alpha\beta}}$$

$$K_{\alpha\beta} = K k_{\alpha\beta}$$

$$J_{\alpha\beta} = \sqrt{k_{\alpha\beta}} g_{\alpha\beta} \Delta V_{\alpha\beta} \quad \Delta V_{\alpha\beta} = V_{\text{syn},\beta} - V_{\text{rest},\alpha}$$



The firing rate of the α th population is v_α .

$$\mu_E = \sqrt{K} (J_{ET}v_T + J_{EE}v_E + J_{EP}v_P)$$

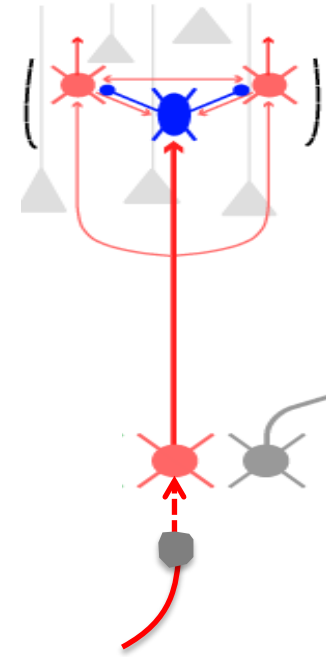
$$\mu_P = \sqrt{K} (J_{PT}v_T + J_{PE}v_E + J_{PP}v_P)$$

To prevent saturation of the single-cell dynamic range, excitation and inhibition should adjust so as to nearly cancel each other.

$$J_{ET}v_T + J_{EE}v_E + J_{EP}v_P = 0$$

$$J_{PT}v_T + J_{PE}v_E + J_{PP}v_P = 0$$

Neuronal nonlinearities are effectively washed out.



Conditions for non-zero v_E and v_I :
 (existence and stability to rate fluctuations)

$$\frac{|J_{PP}|}{J_{PT}} > \frac{|J_{EP}|}{J_{ET}}, \quad \frac{J_{PE}}{J_{PT}} > \frac{J_{EE}}{J_{ET}}$$

The solution of the linear equations is

$$v_E = \frac{J_{ET} |J_{PP}| - J_{PT} |J_{EP}|}{J_{PE} |J_{EP}| - J_{EE} |J_{PP}|} v_T$$

$$v_P = \frac{J_{PE} J_{ET} - J_{EE} J_{PT}}{J_{PE} |J_{EP}| - J_{EE} |J_{PP}|} v_T$$

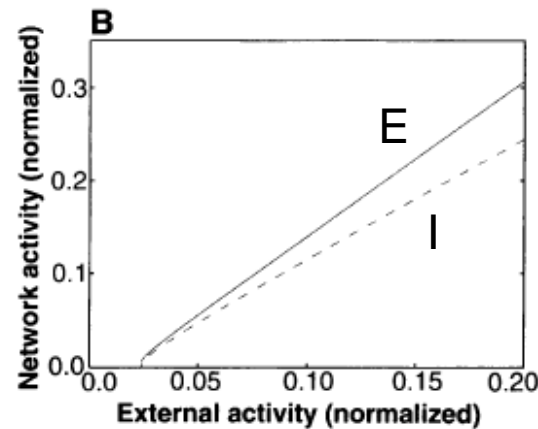
v_E and v_P are linearly proportional to v_T .

Properties of balanced networks

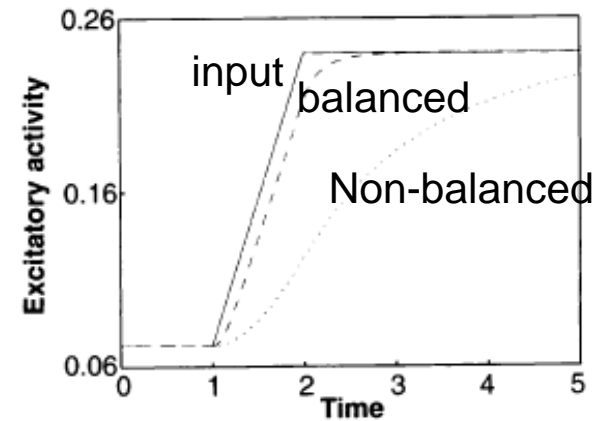
van Vreeswijk and Sompolinsky, 1996; Pehlevan and Sompolinsky 2014

$$1 \ll K \ll N$$

- Linear response at the population level.



- Fast tracking of external inputs.



- Heterogeneity in in-degrees threatens the balance of excitation and inhibition (Landau et al. 2016) .

What happens in real cortical circuits?

Experimental system: T-L4 in whisker somatosensory cortex.

Differences from assumptions leading to “balanced networks”:

- Modest N's, K's.
- Connectivity is not very sparse.
- Synaptic delays $\tau_{\text{delay}} \sim 1$ ms.
- No SOM-to-SOM inhibitory synapses.

Questions

- **Circuit dynamics in response to (almost) constant inputs :**

Does the barrel circuit behave similarly to balanced networks?

What are the effects of heterogeneities in the levels of in-degrees?

- **Non-whisking to whisking:**

T and PV neurons fire at ~10 Hz and more than double their firing rates during the transition.

Why are the firing rates of E neurons so low? Why don't their firing rates substantially increase during the transition?

- **Whisking vs. touch:**

v_E (0.6 Hz) during whisking is much smaller than v_T (14 Hz).

The number of spikes/touch ($R_T = 0.6$, $R_E = 0.3$ spike/touch) are more similar for the T and E populations.

How does the L4 circuit filter out whisking response while transmitting touch response?

- **Activation SOM neurons:**

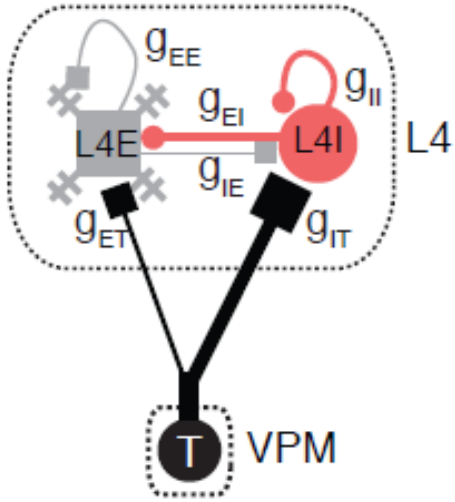
How is the activity of SOM neurons controlled by thalamic input and cholinergic activation from the brainstem?

Can the E-PV-SOM circuit exhibit approximate balance states?

A network model of the thalamocortical circuitry

Argaman and Golomb, Neurosci. 2018;

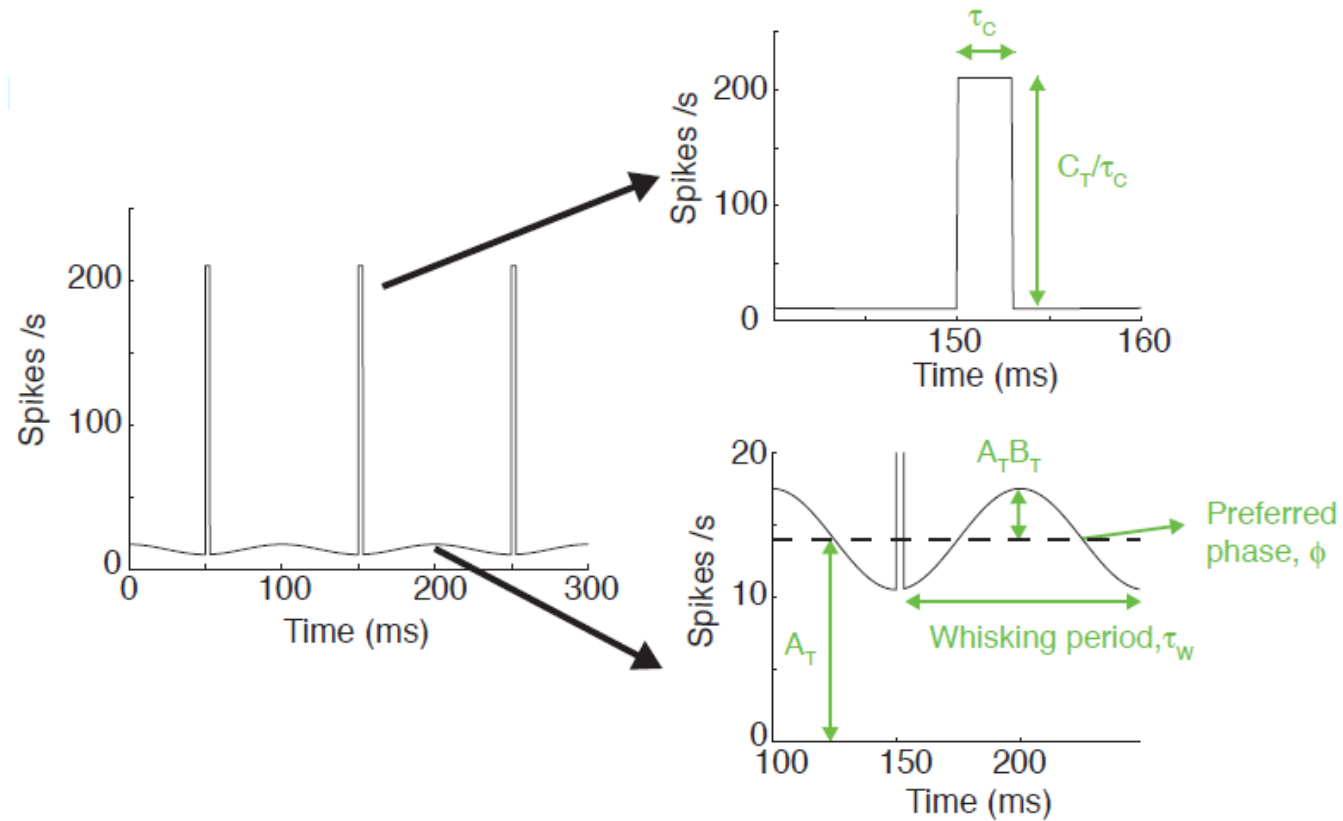
Gutnisky, Yu, Hires, To, Bale, Svoboda and Golomb, PLoS CB 2017.



- The cortical network is composed of spiking neurons from the excitatory (E) and PV and SOM inhibitory types.
- $N_E=1600$, $N_P=150$, $N_S=100$, $N_T=200$ (C2 barrel).
- Modified Wang-Buzsaki conductance-based neurons (Hansel and van Vreewijsk, 2012).
- Random connectivity.
- Synaptic conductances are in the ranges obtained in *in-vitro* experiments (within a range of 2-3).
- Synaptic delays $\tau_{\text{delay}} \sim 1$ ms.
- No short-term synaptic plasticity.

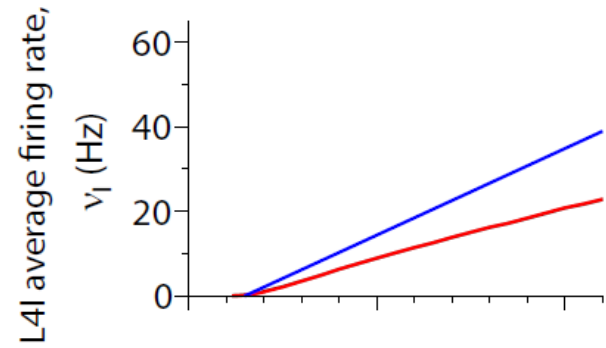
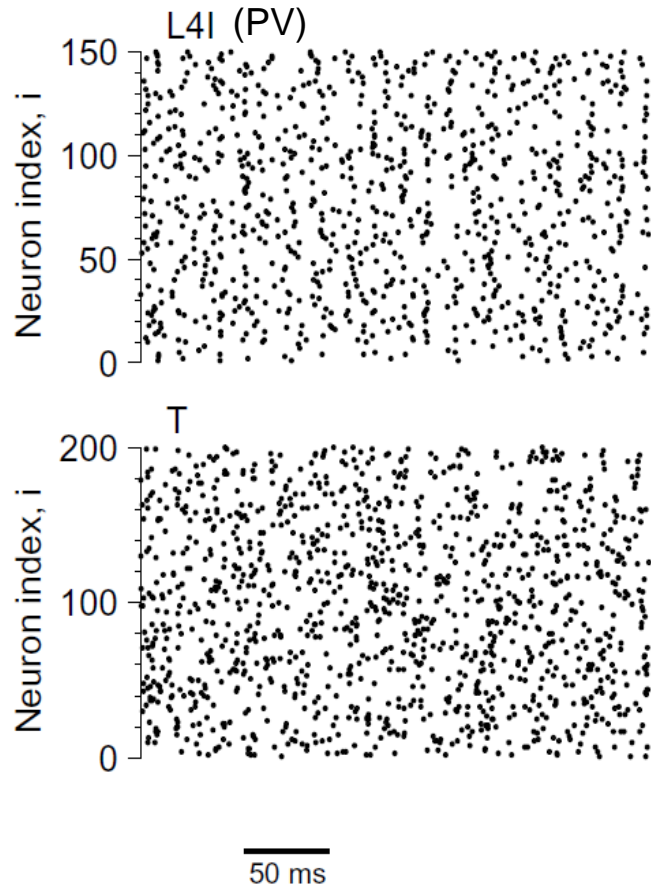
- Thalamic neurons fire according to an inhomogeneous Poisson process with a generating function $\Lambda_T(t)$.

$$\Lambda_T(t) = A_T (1 + B_T \cos(2\pi t / T + \phi)) + C_T \delta(t - t_c)$$



During non-whisking or whisking, $v_T = A_T$

Dynamics of L4 PV circuits



Poisson
Balanced state

Difference:

Small circuit

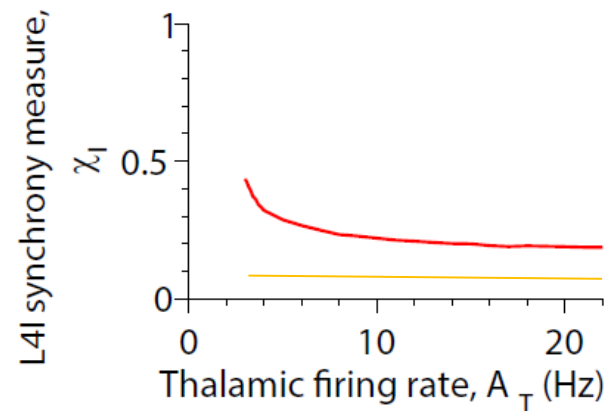
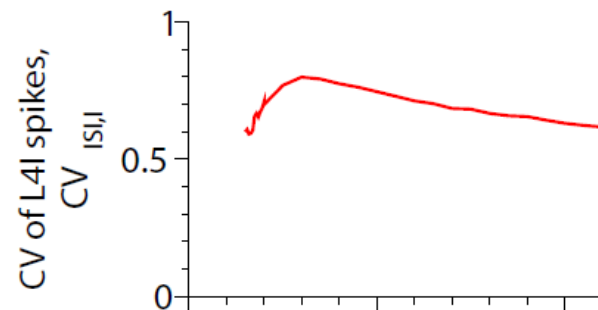
Interactions via conductances/currents

Spike synchrony

Moderate coupling strength -

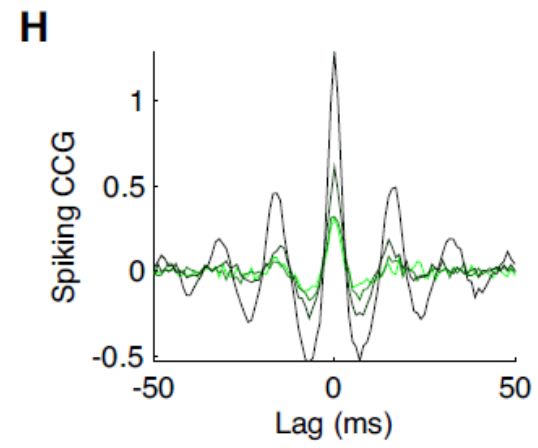
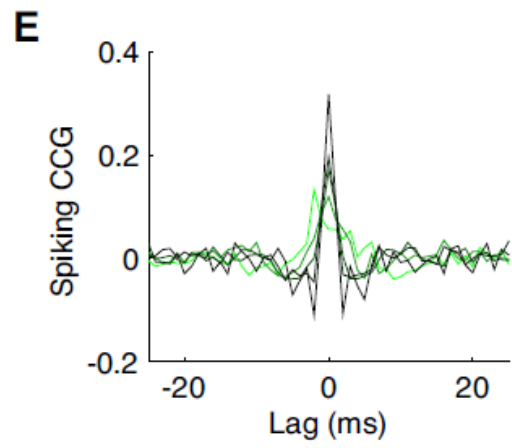
moderate CV

(Lerchner et al., 2006)

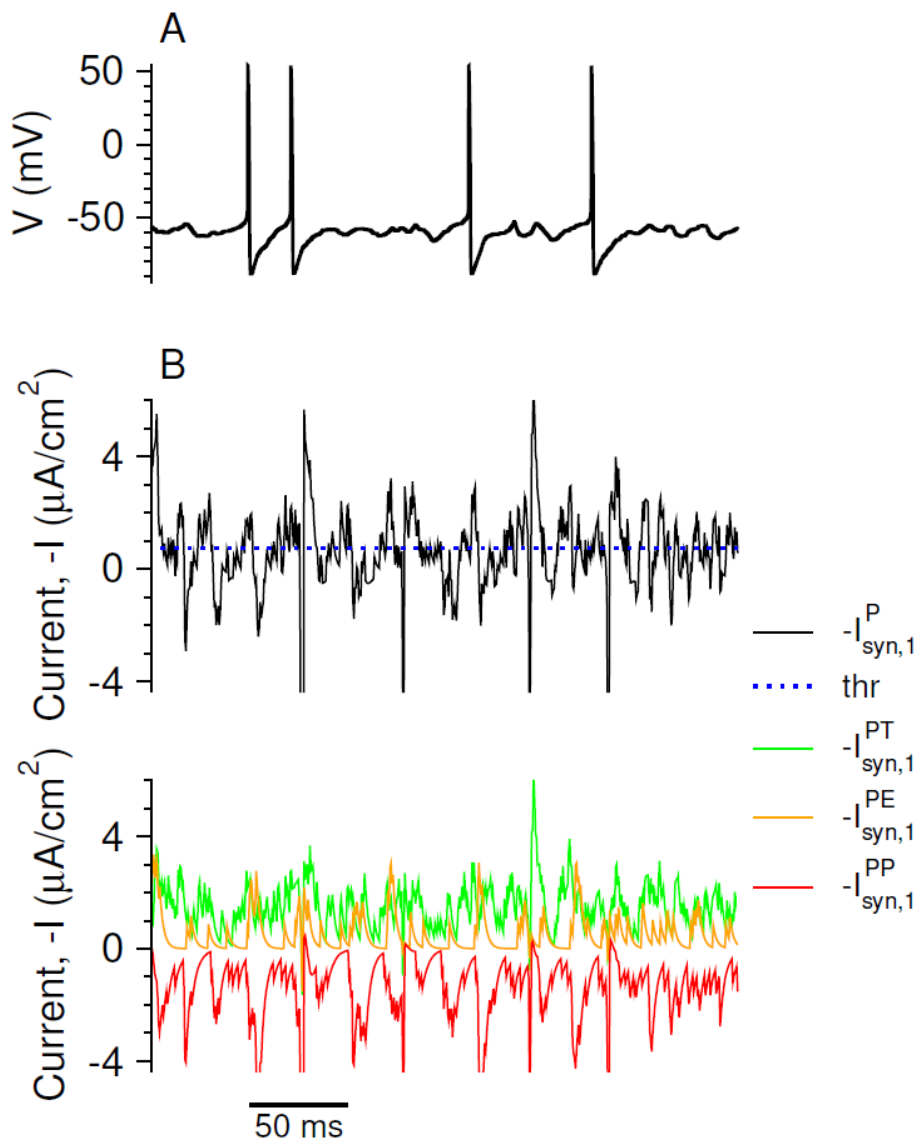


Synchrony of uncoupled
neurons firing at the same rate

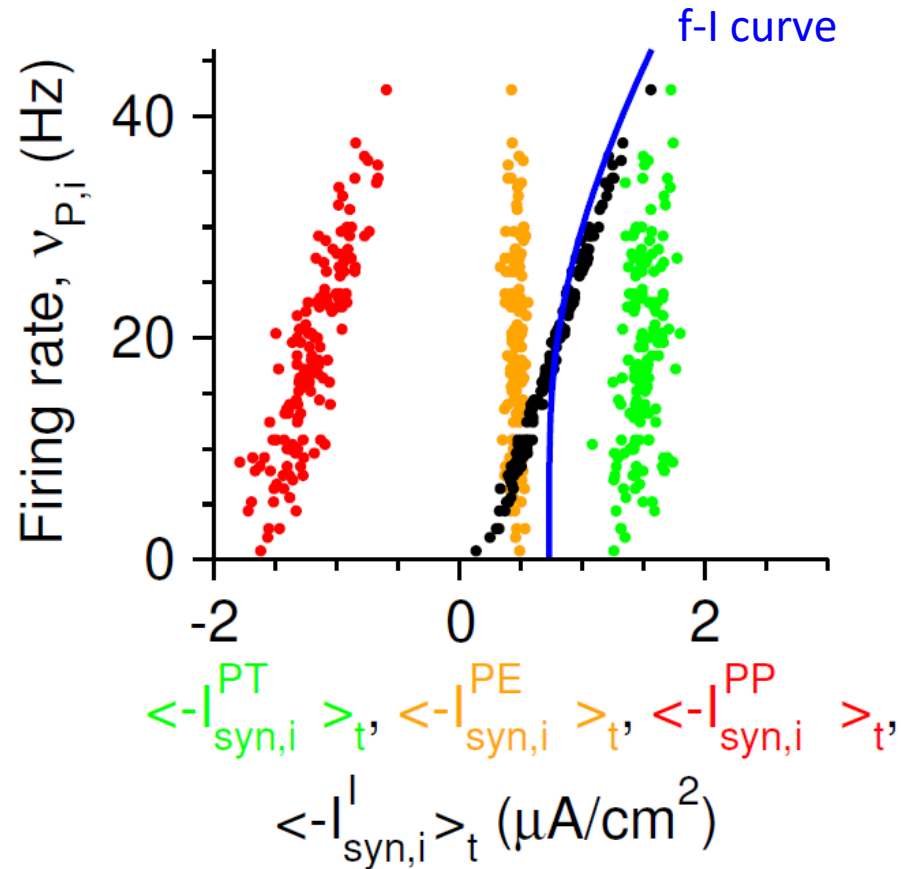
Renart et al., 2010



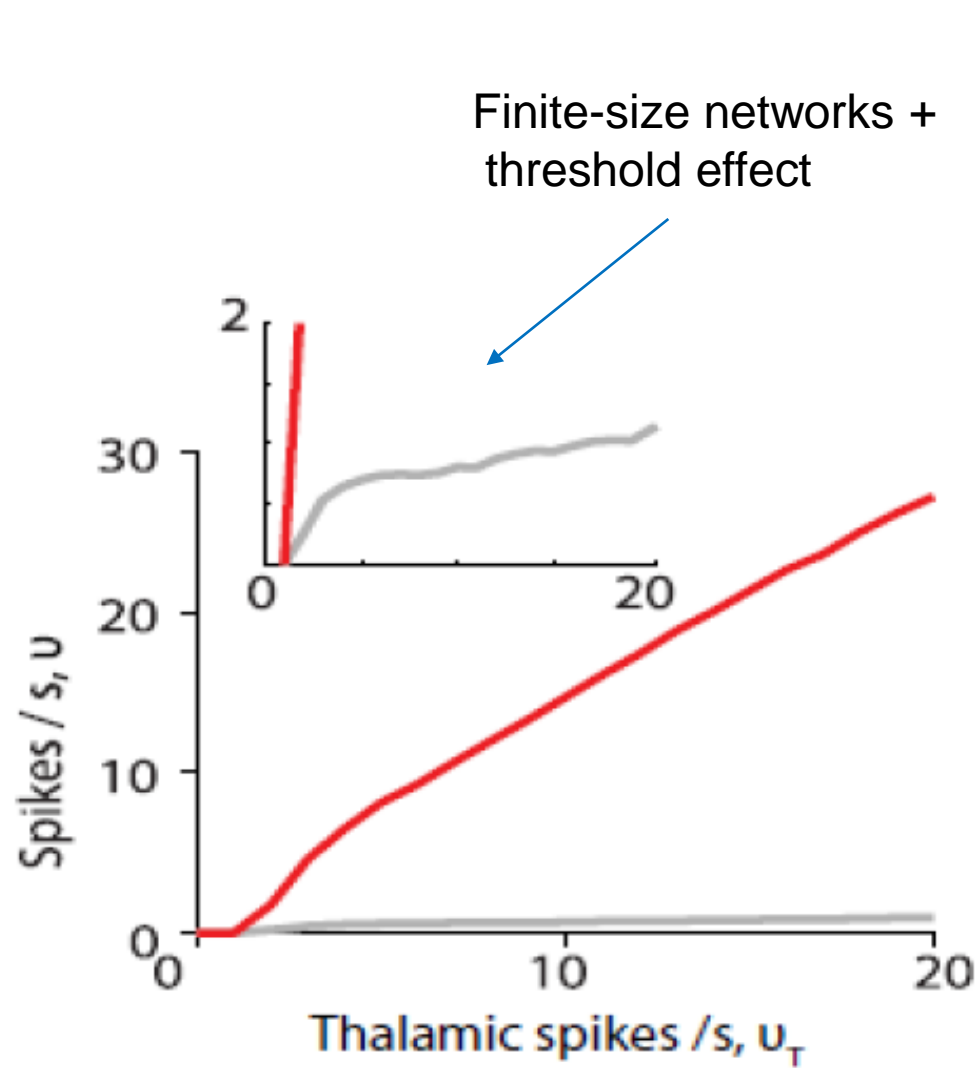
One PV neuron



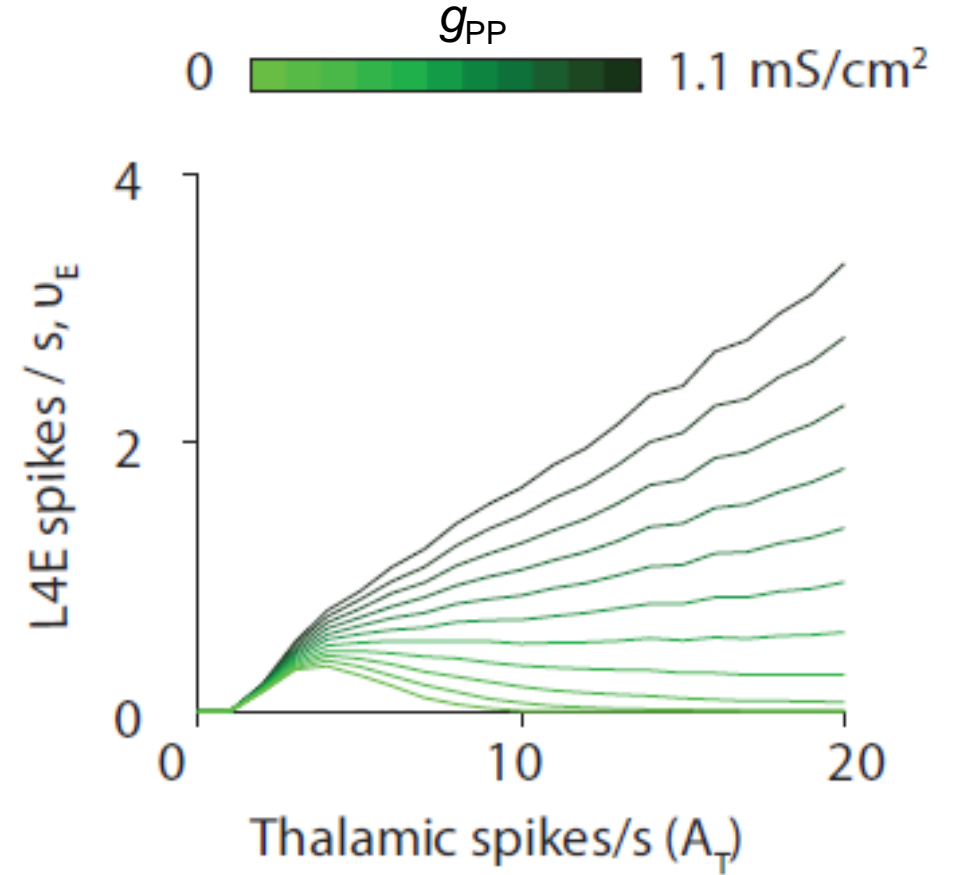
Population of PV neurons



Dynamics of L4 E-PV circuits



T
 E
 PV



- g_{PP} increases u_E .
- u_E may decrease with A_T for small g_{PP} .

Heterogeneity in in-degrees

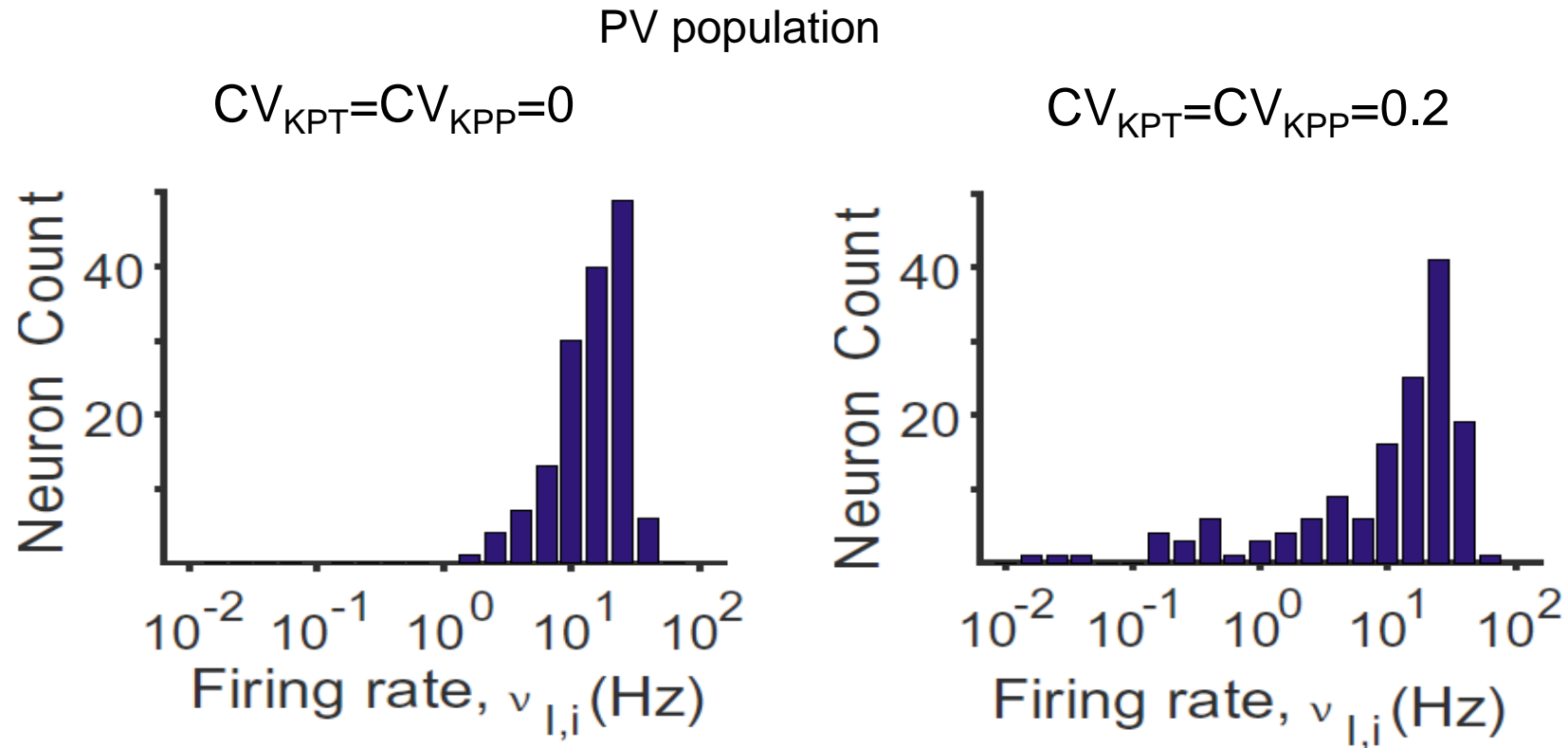
In-degree: the total number of inputs from a neuronal population projecting to an individual neuron (Landau *et al.*, 2016, Pyle and Rosenbaum 2016).

Standard deviation: $\sigma_{K_{\alpha\beta}} = \text{CV}_{K_{\alpha\beta}} K_{\alpha\beta}$

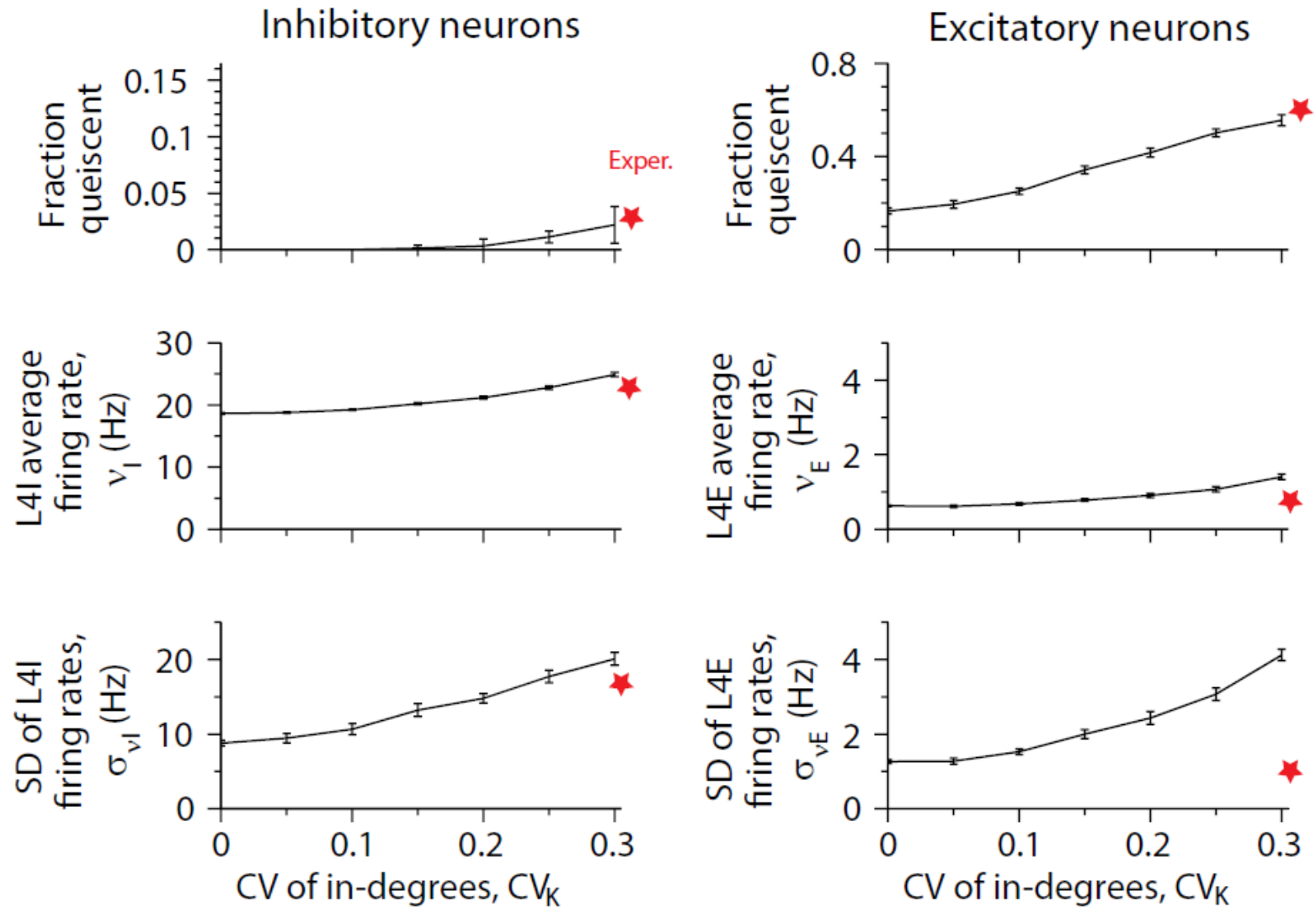
In “larger” networks ($N_I \sim 1000$, $K_{II} \sim 250$; Landau *et al.*, 2016), this heterogeneity threatens the balance of excitation and inhibition.

It increases the number of silent neurons and broadens the distribution of firing rates.

Heterogeneity in in-degrees

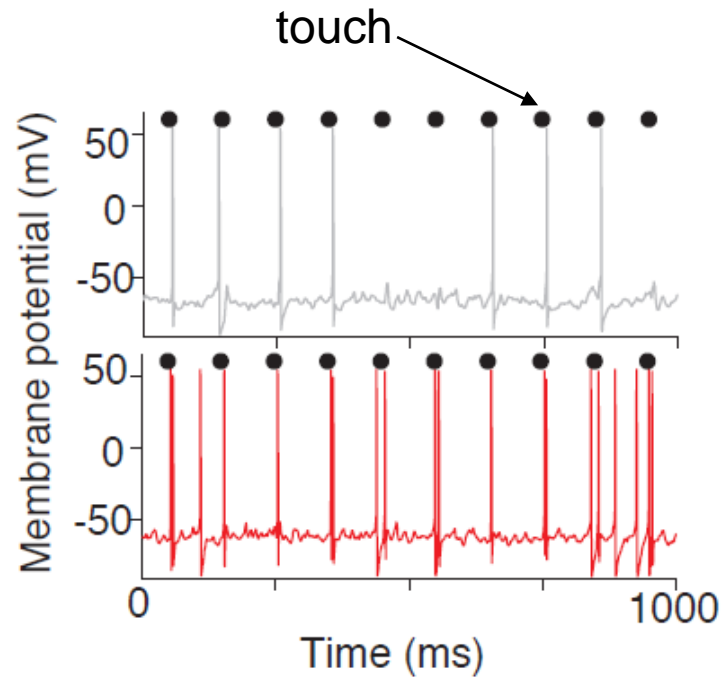


Same CV_K for all synaptic populations.

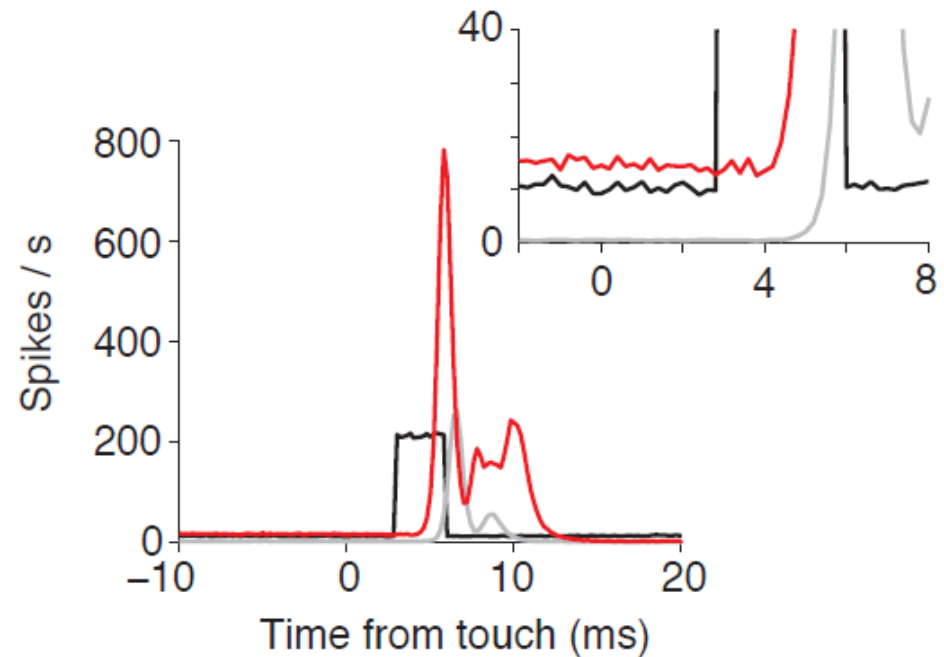


For $CV_K \sim 0.3$, the theoretically-obtained values of fractions of quiescent neurons are similar to experimentally-measured values, without the need for in-degree correlations and compensatory mechanisms.

Simulations: whisking and touch

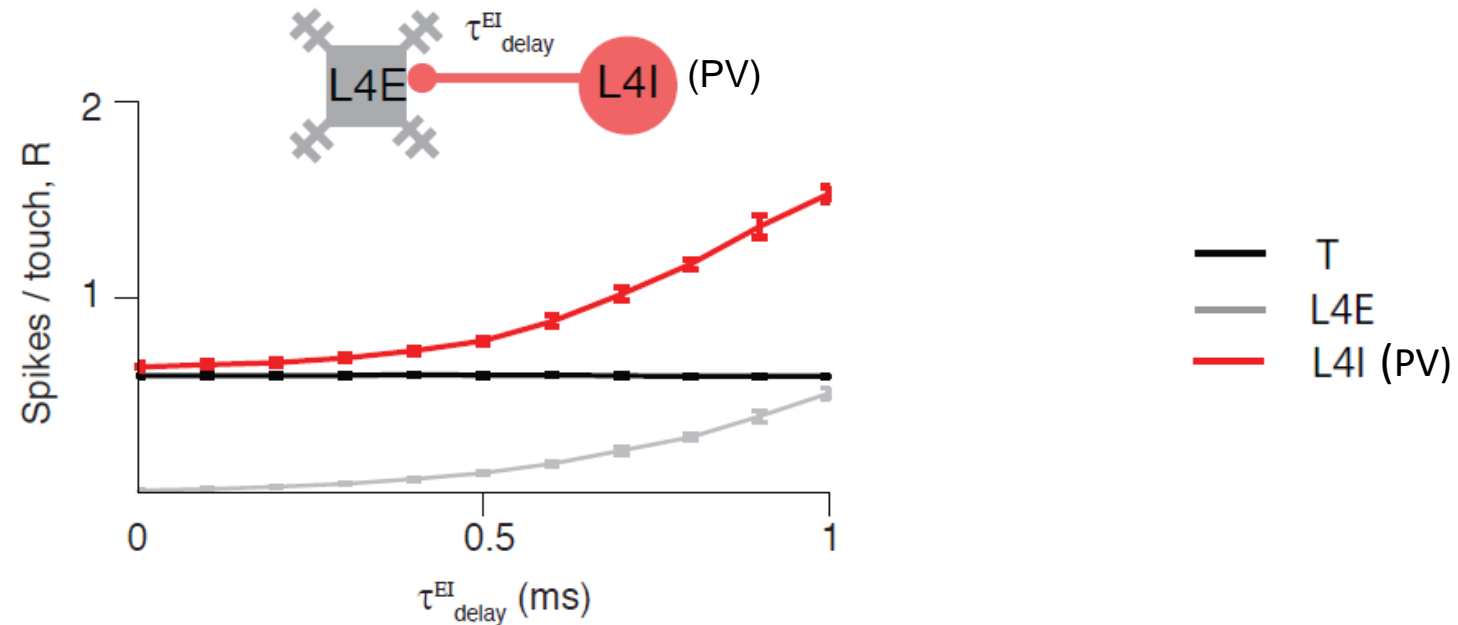


Spike histograms



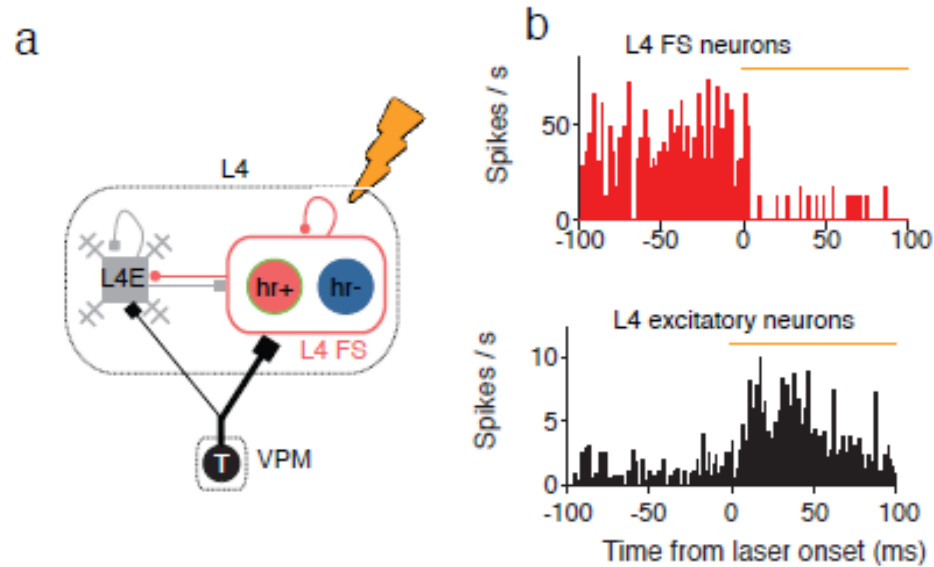
- T
- L4E
- L4I (PV)

PV-to-E synaptic delay is necessary for touch response.



An PV-to-E synaptic delay and a fast-rising stimulus allows a “window of opportunity” (Simons, 1989).

Expressing halorhodopsin in PV neurons

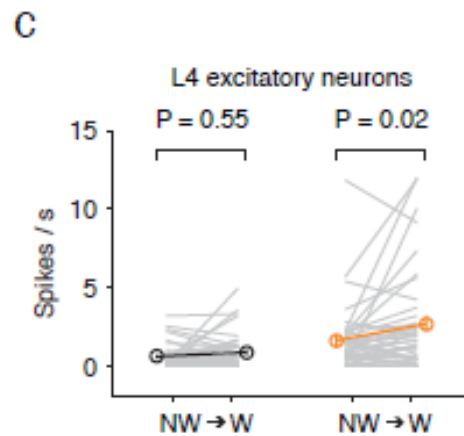


3 out of 4 PV (FS) neurons decreased their firing rate (and spikes/touch) in response to halo activation.

Halorhodopsin is a chloride pump.

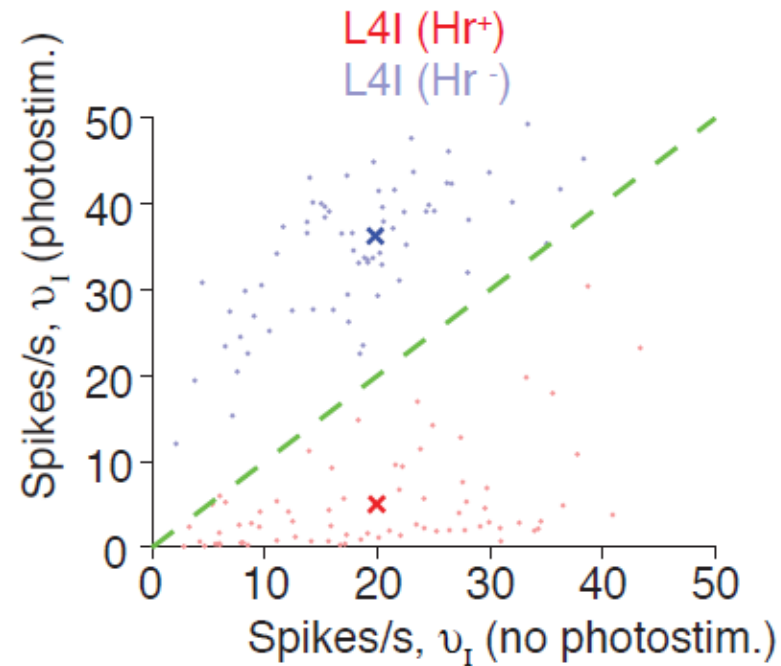
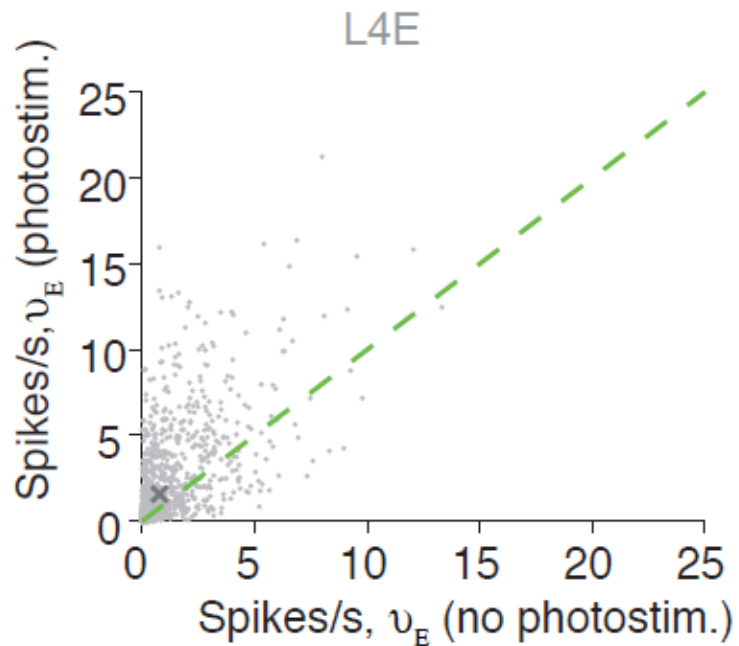
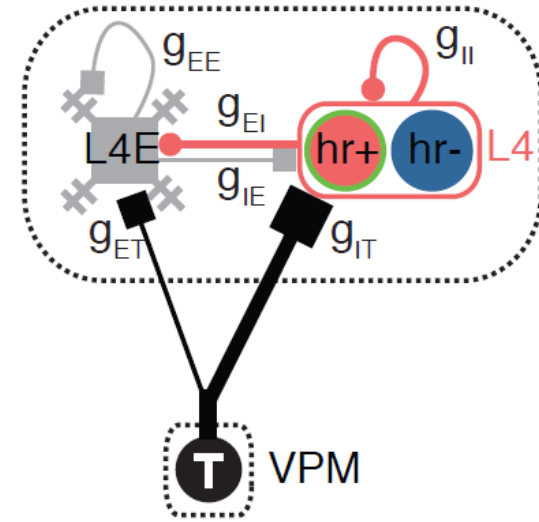
Effects:

1. Negative “current injection”.
2. Depolarization of $GABA_A$ reversal potential (negligible).

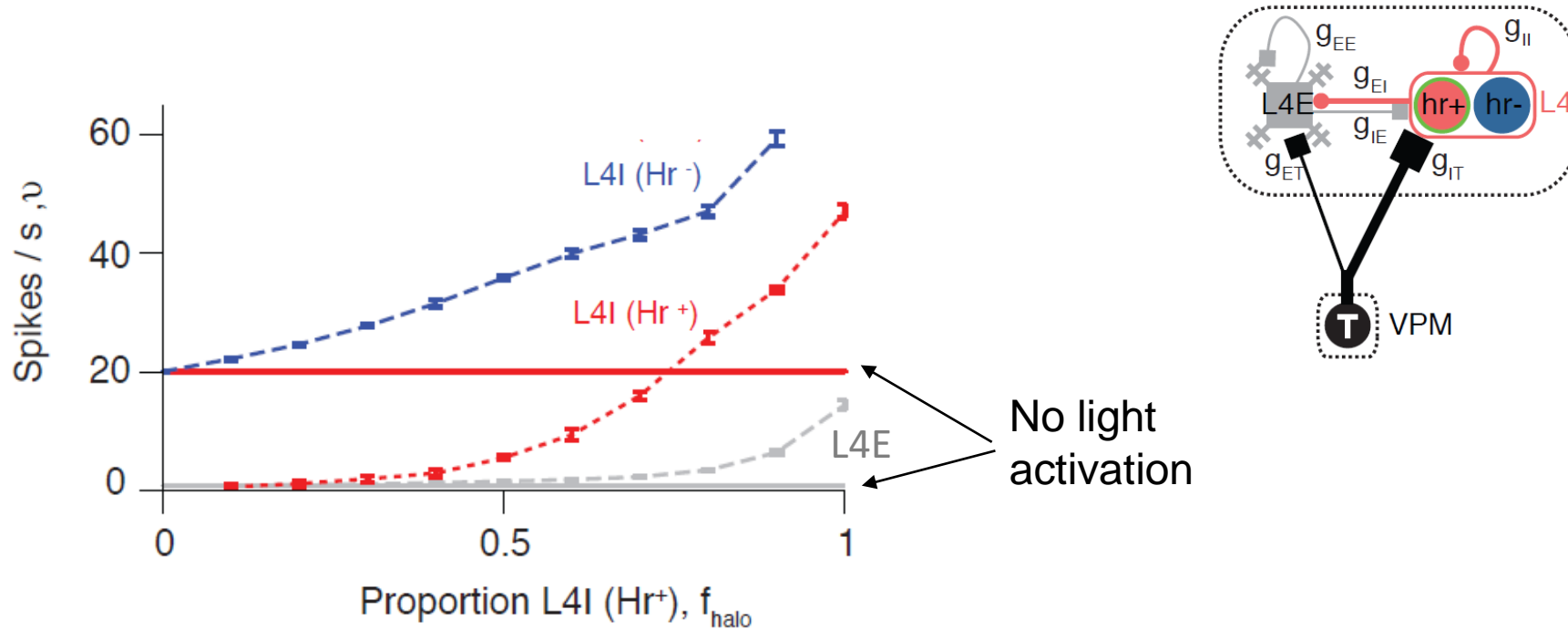


Yu et al., 2016;
Gutnisky et al., 2017.

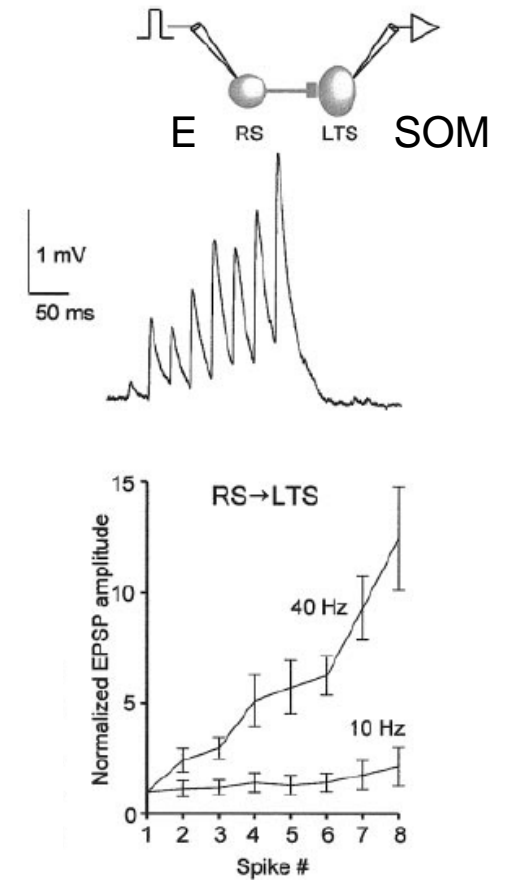
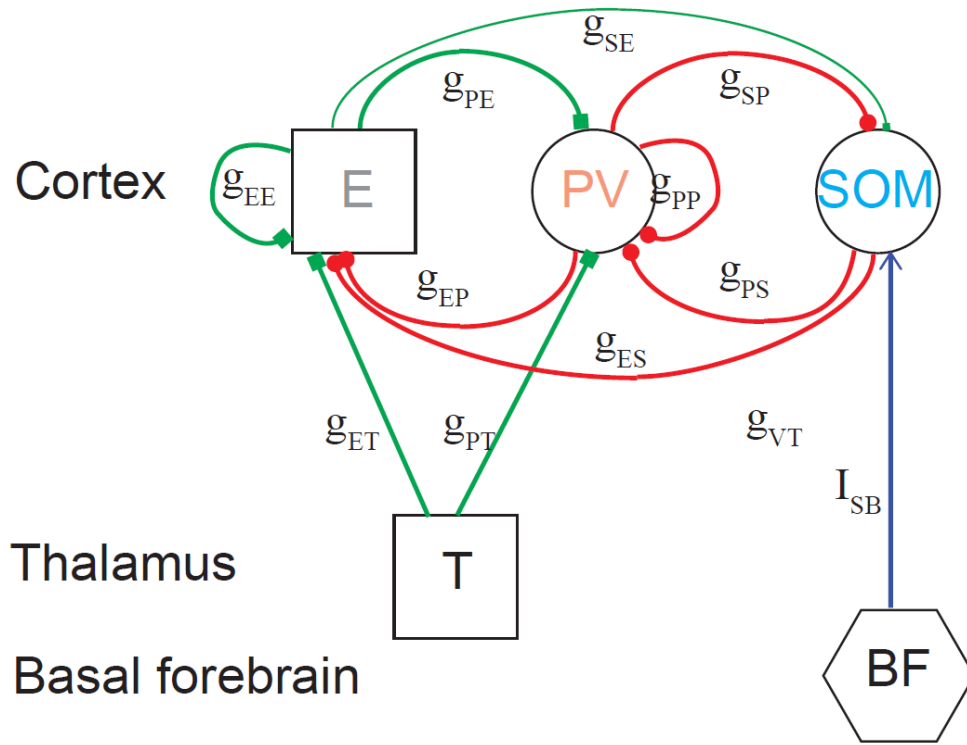
Light activation of halorodopsin expressed in a fraction $f_{\text{halo}}=0.5$ of FS neurons of FS neurons



Hr⁺ neurons reduced their v_E if their ratio f_{halo} is below a certain value.



Dynamics of L4 E-PV-SOM circuits



- No SOM-to-SOM inhibitory synapses.
- E-to-SOM synapses are weak without facilitation.
- ACh drives the activity of SOM neurons via muscarinic receptors (Munoz... Rudy, 2017).

Beierlein, Gibson and Connors, 2003.

Conclusions

- Despite the relatively small size of L4 barrels and some synchrony among neurons, the dynamics of PV and E neurons in PV-E L4 circuits during non-whisking and whisking states are consistent with balanced state ideas with finite-size corrections.
- The strong response of L4E neurons to touch is explained by the “window of opportunity” mechanism, and demands $\tau_{\text{delay}}^{\text{EP}} \sim 1 \text{ ms}$.
Brief thalamic stimulation breaks the balance between excitation and inhibition.