BIO-482 Neuroscience. Cellular and Circuit Mechanisms

What can we learn from membrane potential recordings in awake behaving mice?

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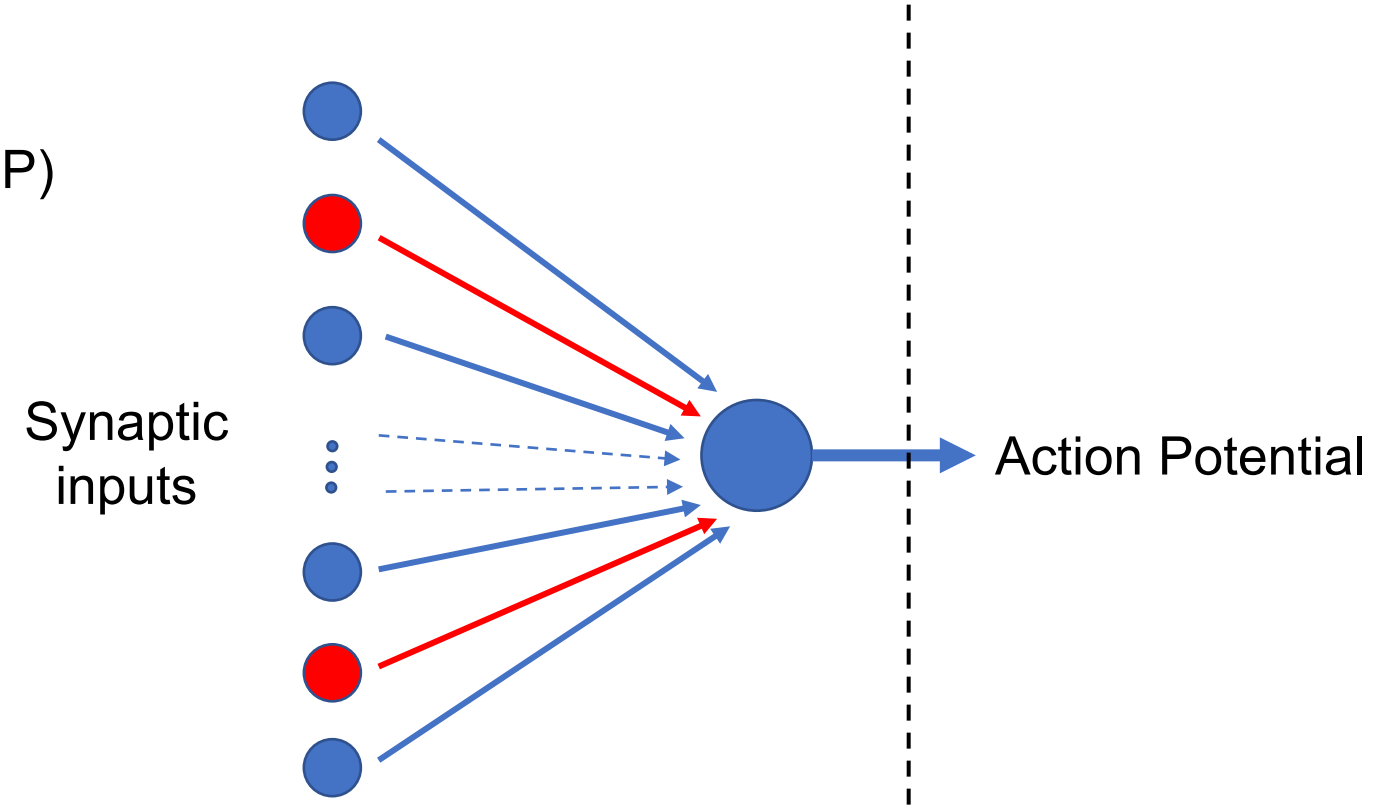
Cortical neurons as synaptic integrators

Cortical Neurons:

- > 1 000 Synaptic inputs
- Mainly from cortex
- 70-90 % Excitatory (EPSP)

Synaptic inputs
=> Subthreshold Activity

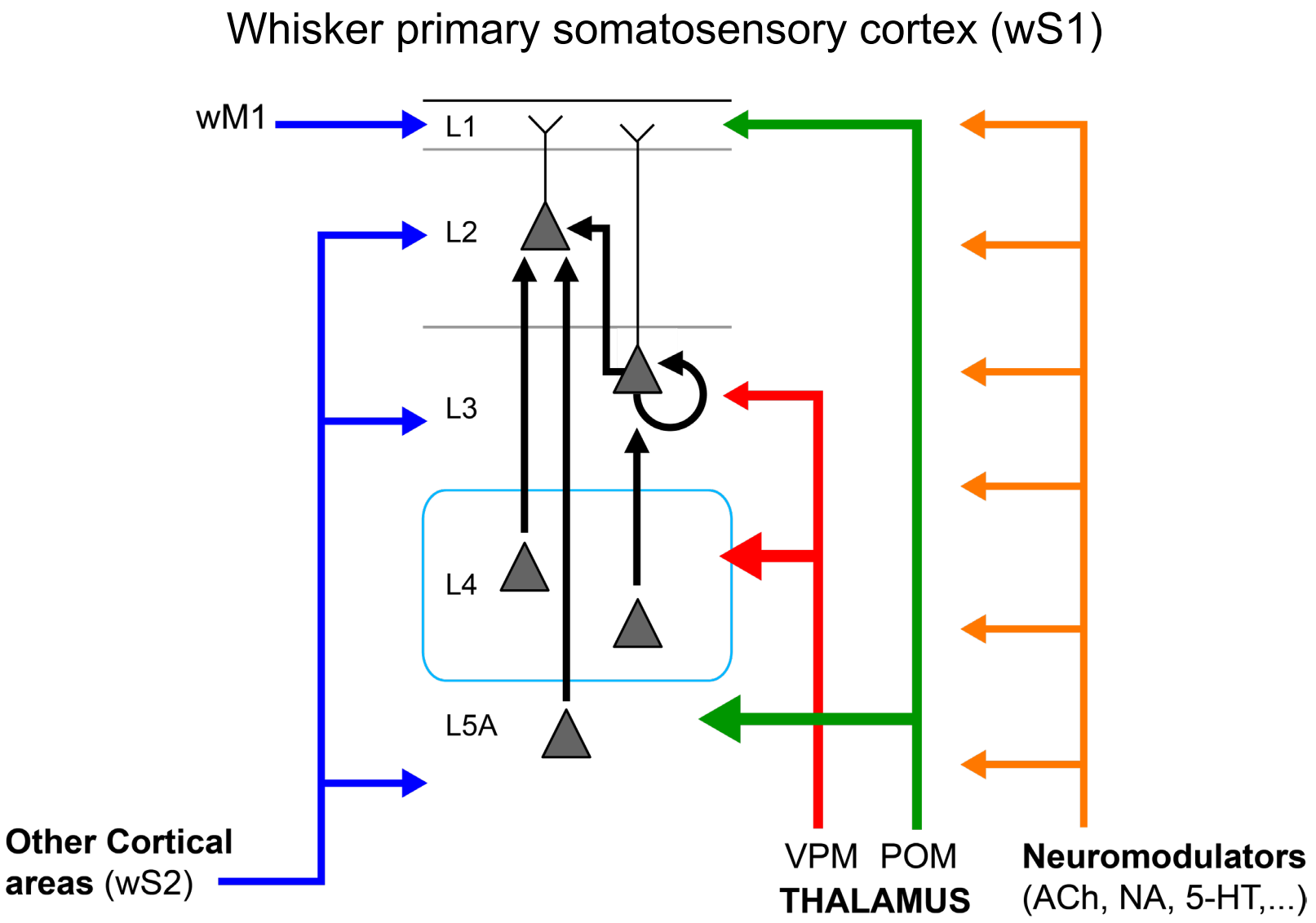
Action potential output
=> Suprathreshold Activity

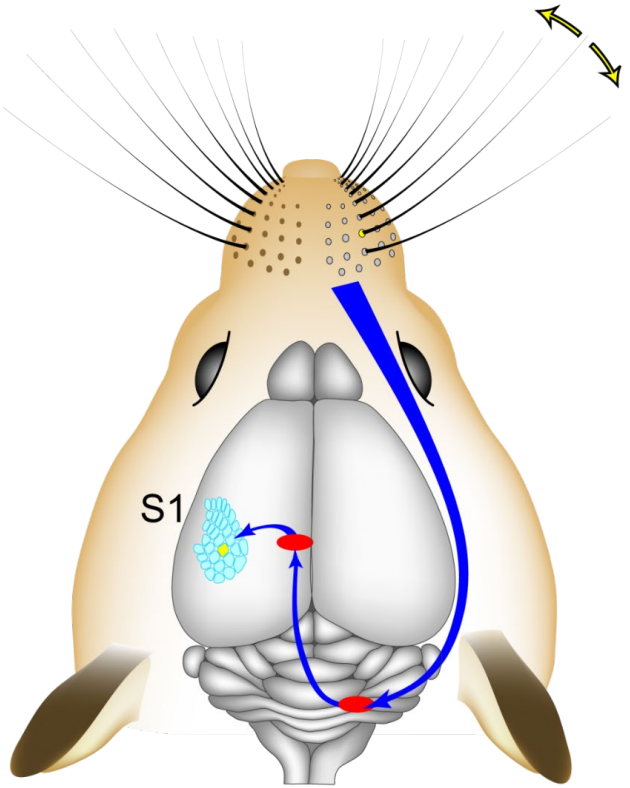


Synaptic integration

Neuronal Coding

Synaptic inputs to L2/3 of the *barrel* cortex (wS1)

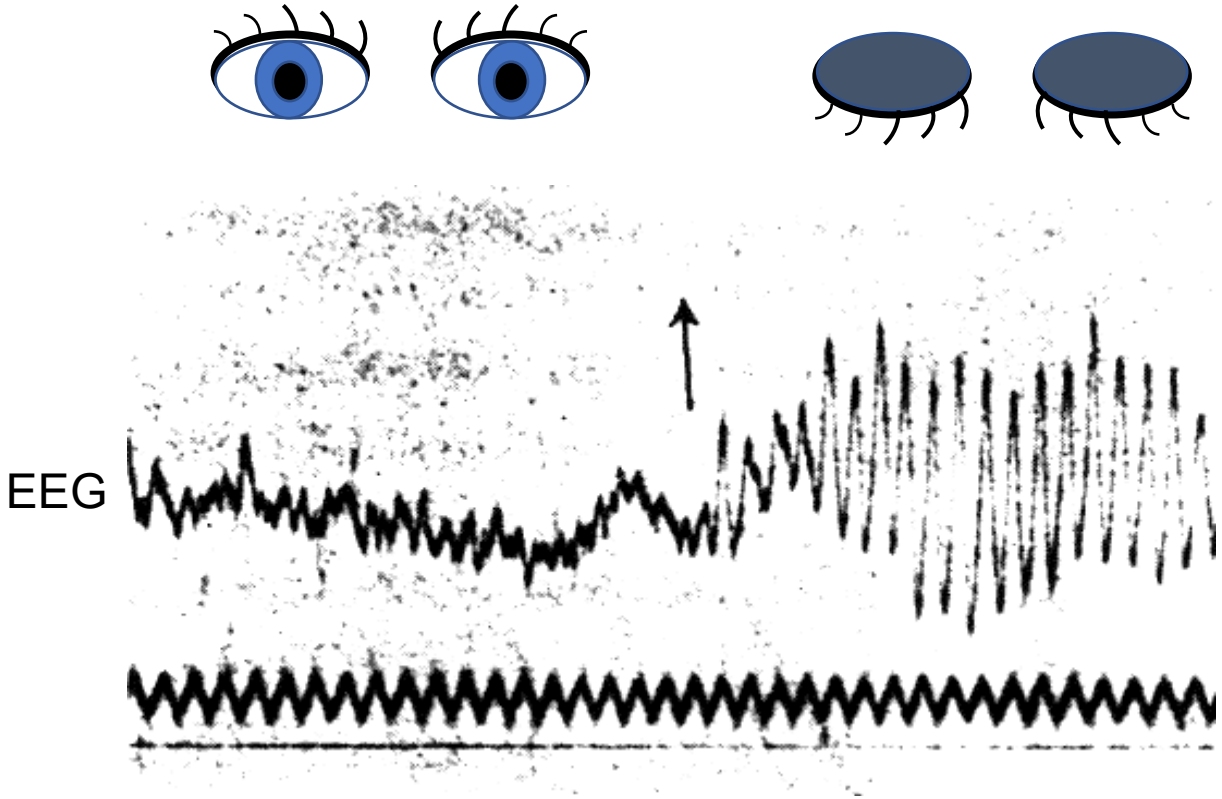




1. Cellular mechanisms underlying cortical state changes in awake mice

At the origin of *cortical states*

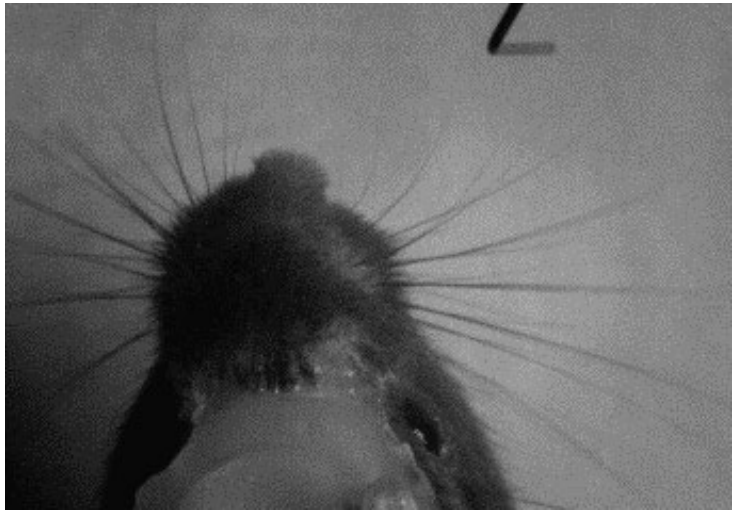
Cortical states are usually defined by the spontaneous activity of the cortical network

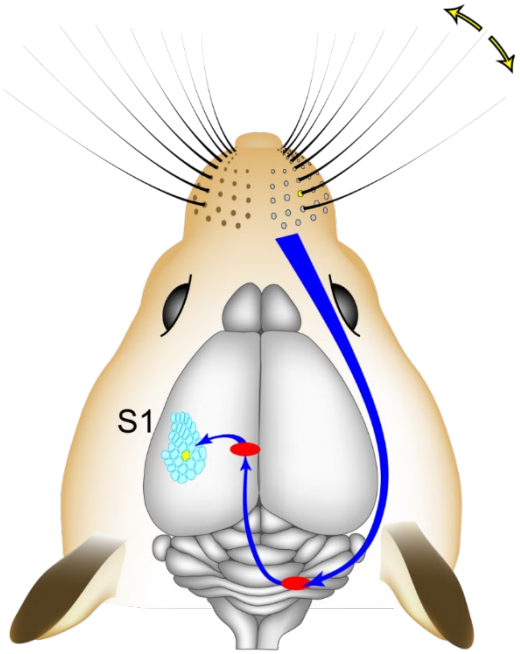


(Hans Berger, 1929)

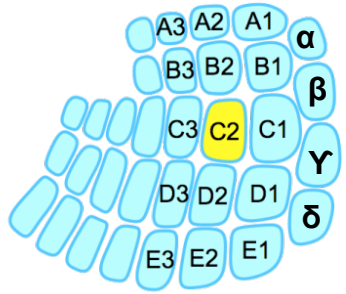
First demonstration of cortical state change correlated with behavior

Experimental model





Cortex



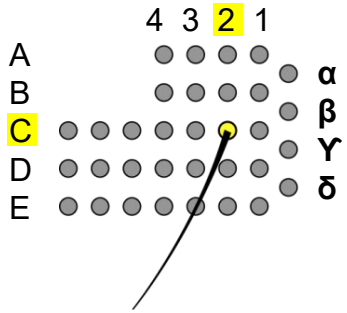
Primary somatosensory area (wS1) ***"Barrel cortex"***

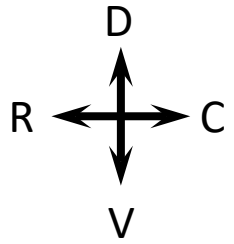
Thalamus VPM/POM

Brainstem Trigeminal nuclei

Whiskers

Periphery

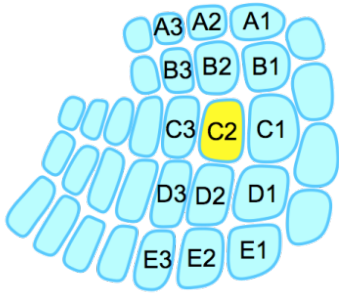




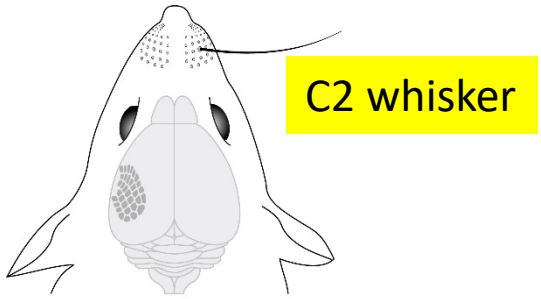
Experimental model

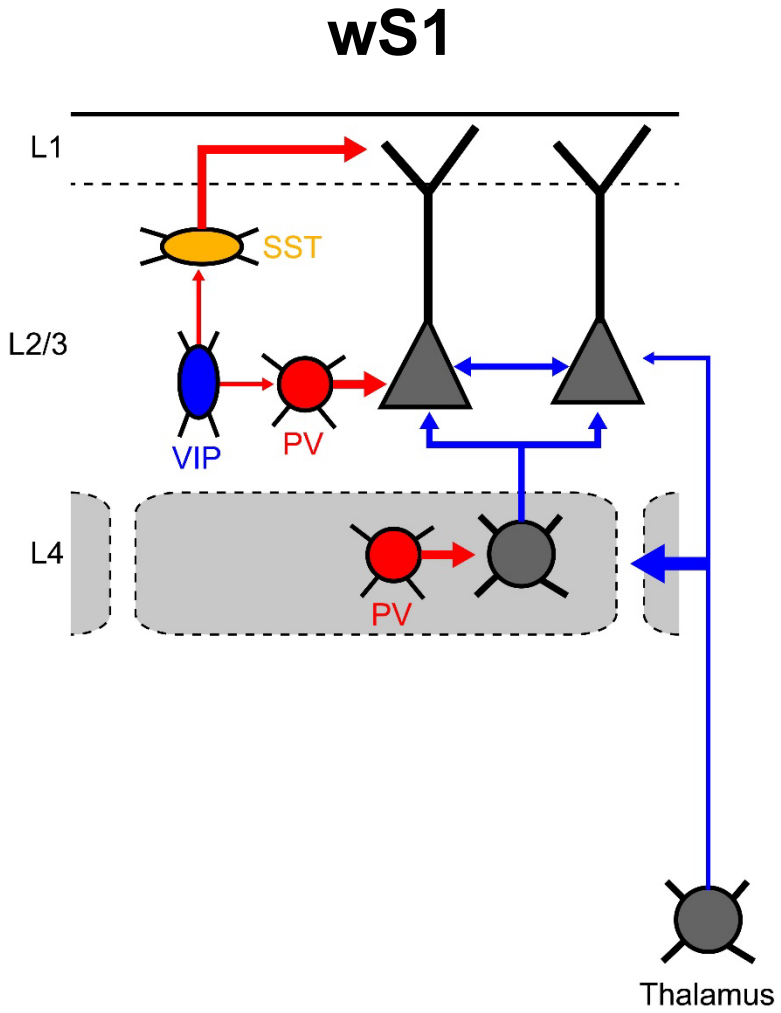
Primary somatosensory area (wS1) ***"Barrel cortex"***

Cortex



Thalamus VPM/POM



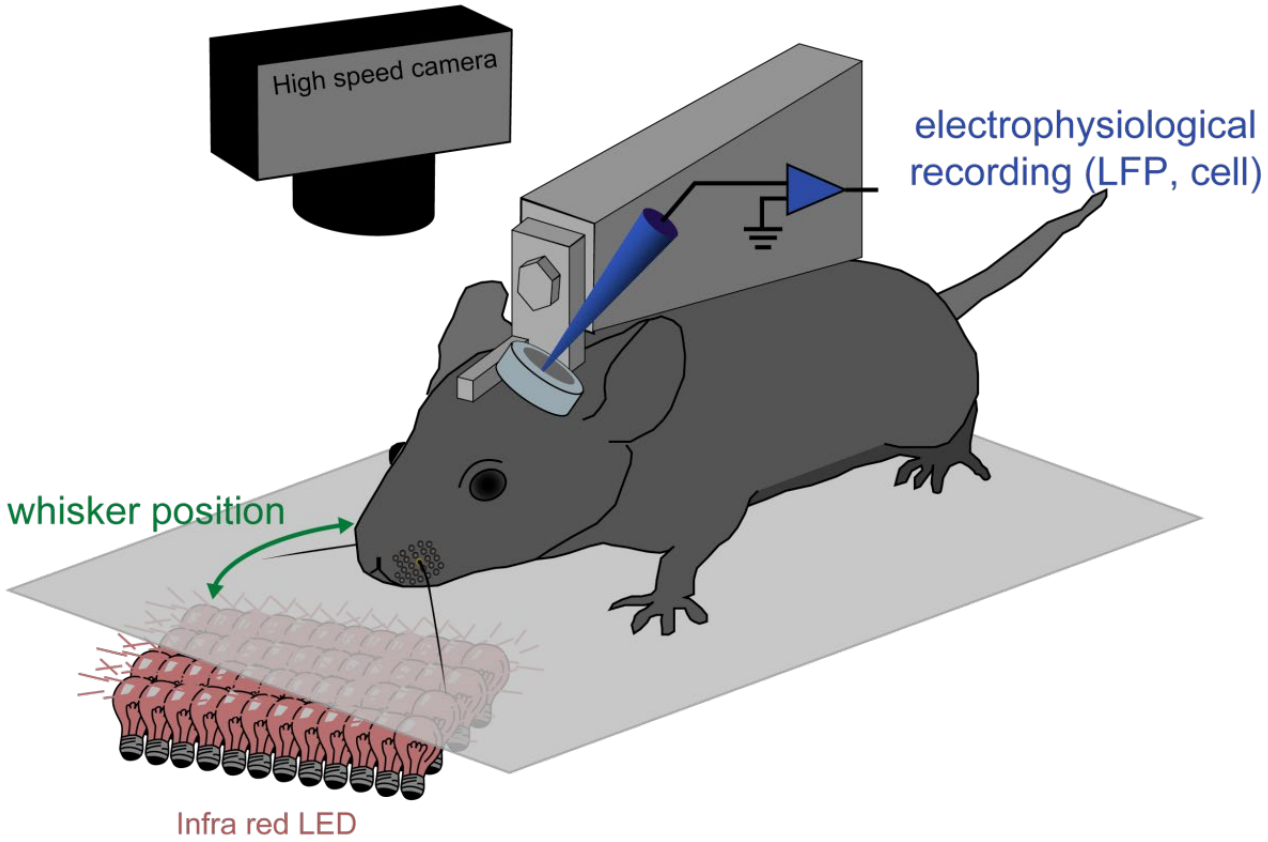


Excitatory cells (Glutamate)

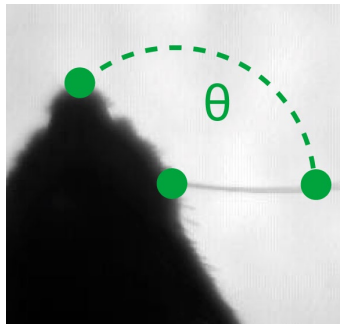
Inhibitory interneurons (GABA):

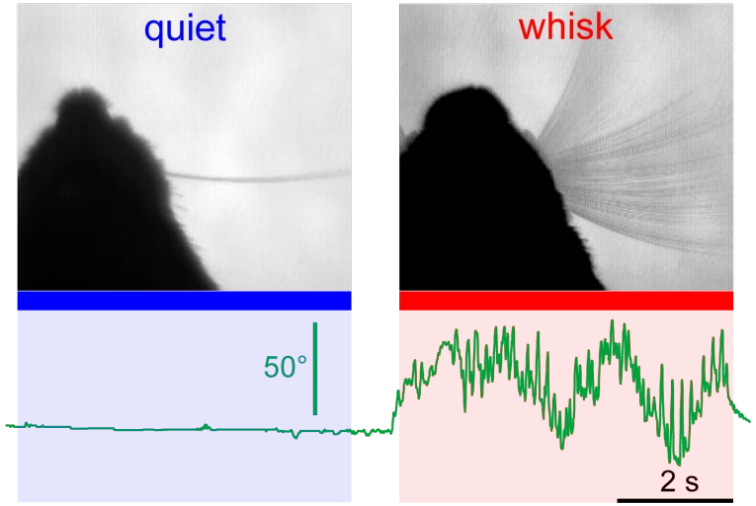
- Parvalbumine (PV)
- Vasointestinal peptide (VIP)
- Somatostatin (SST)

Membrane potential (*Vm*) recording in awake mice

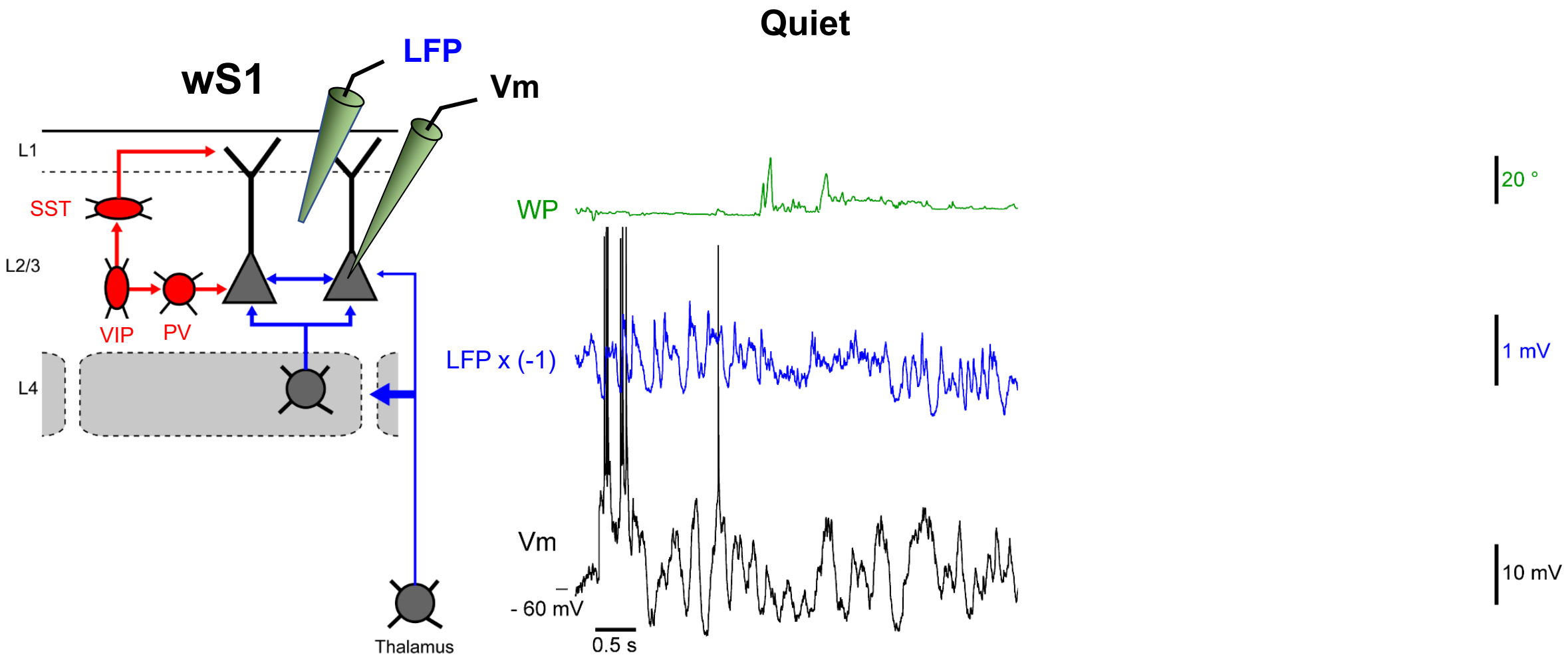


Whisker
Position (WP)

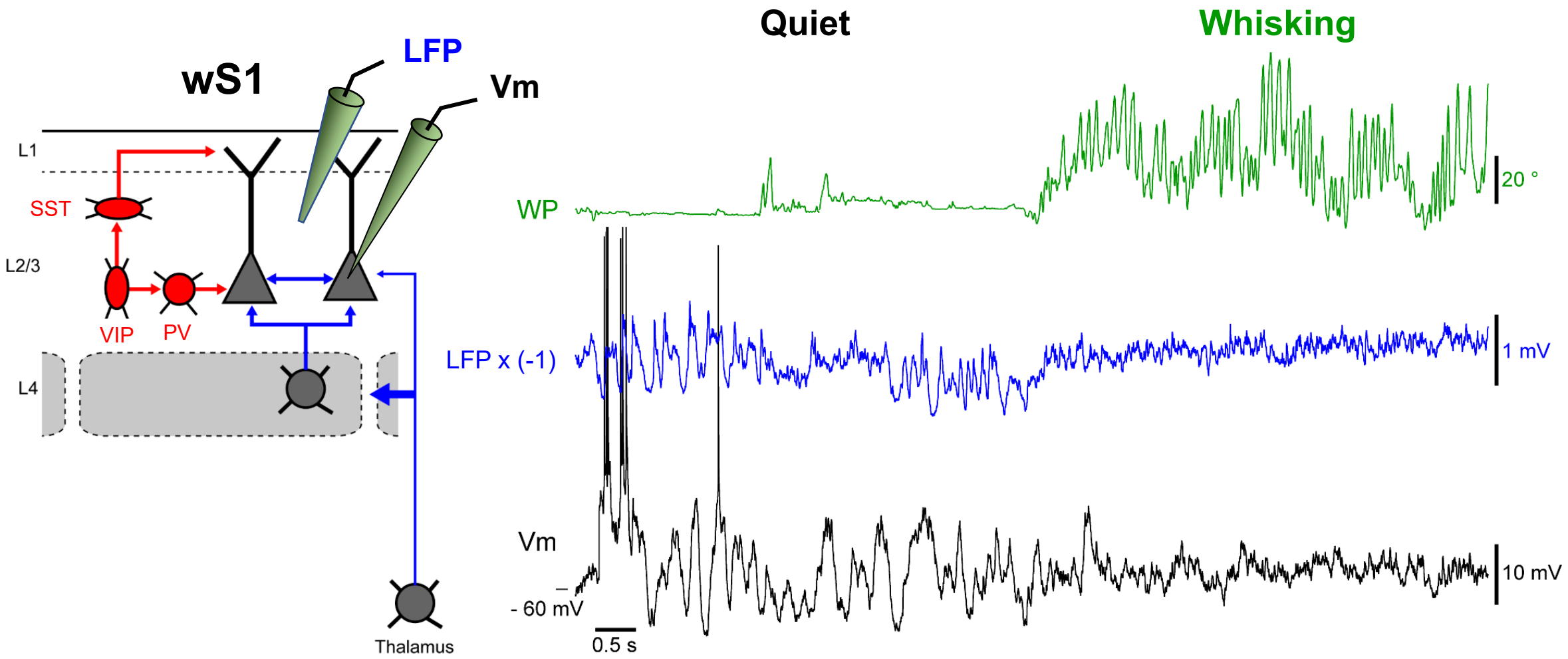




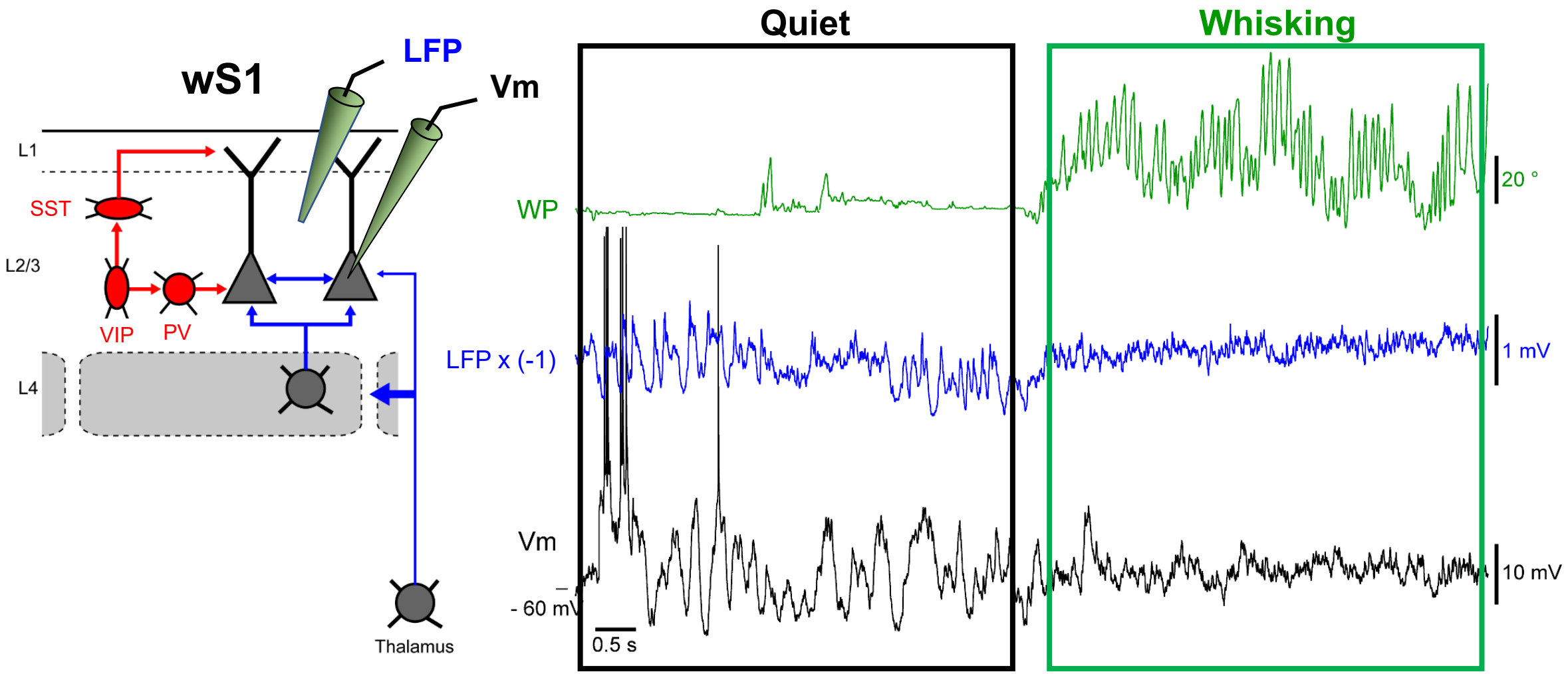
State change in wS1



State change in wS1

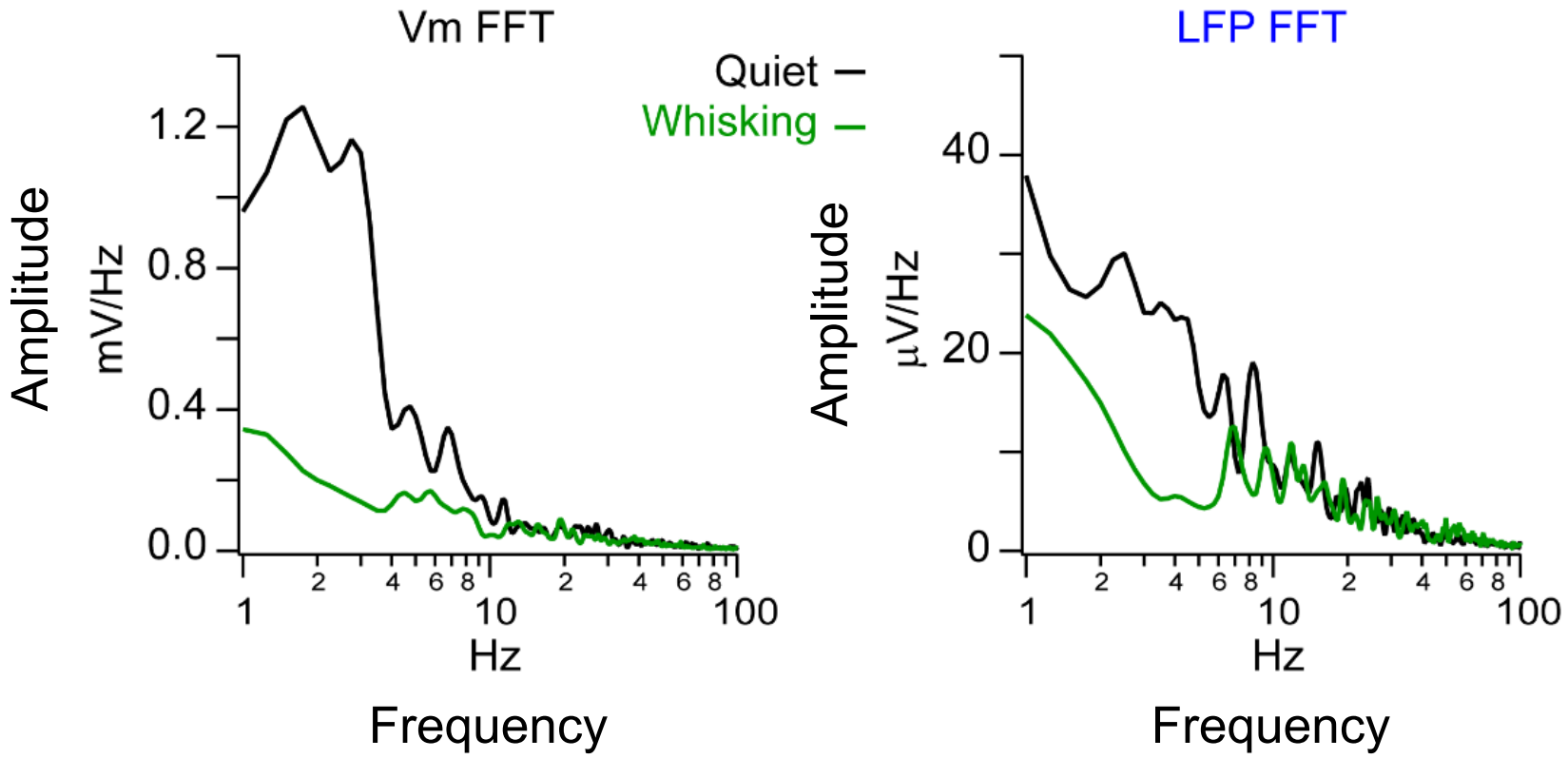


State change in wS1



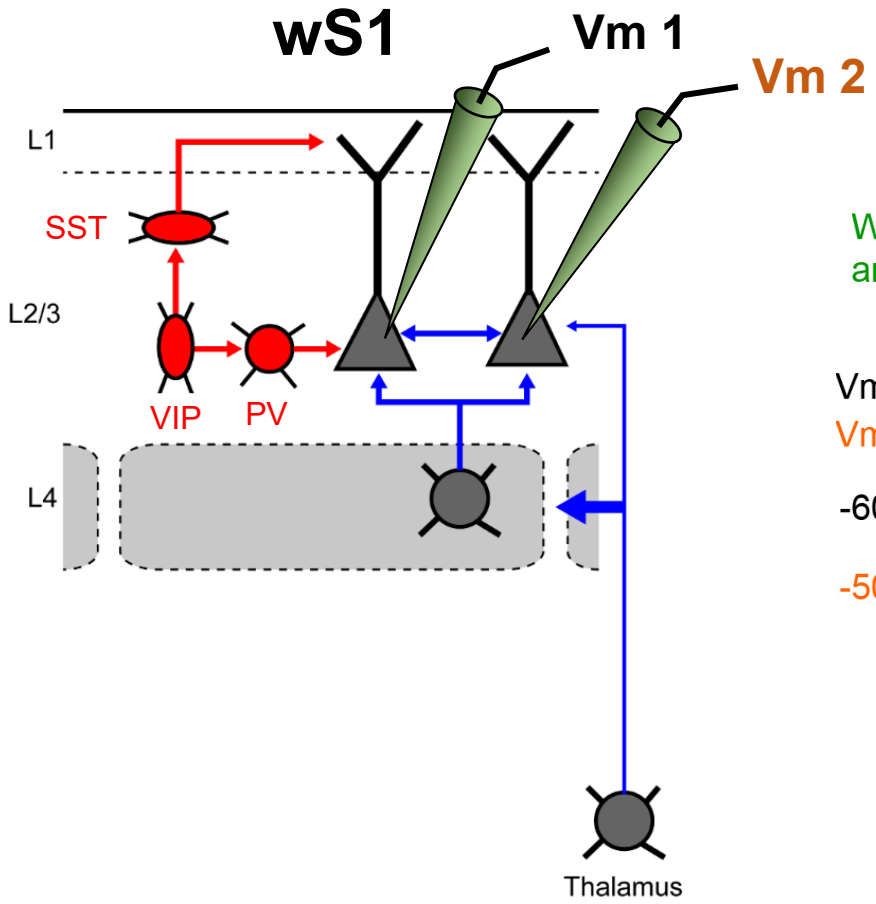
State change in wS1

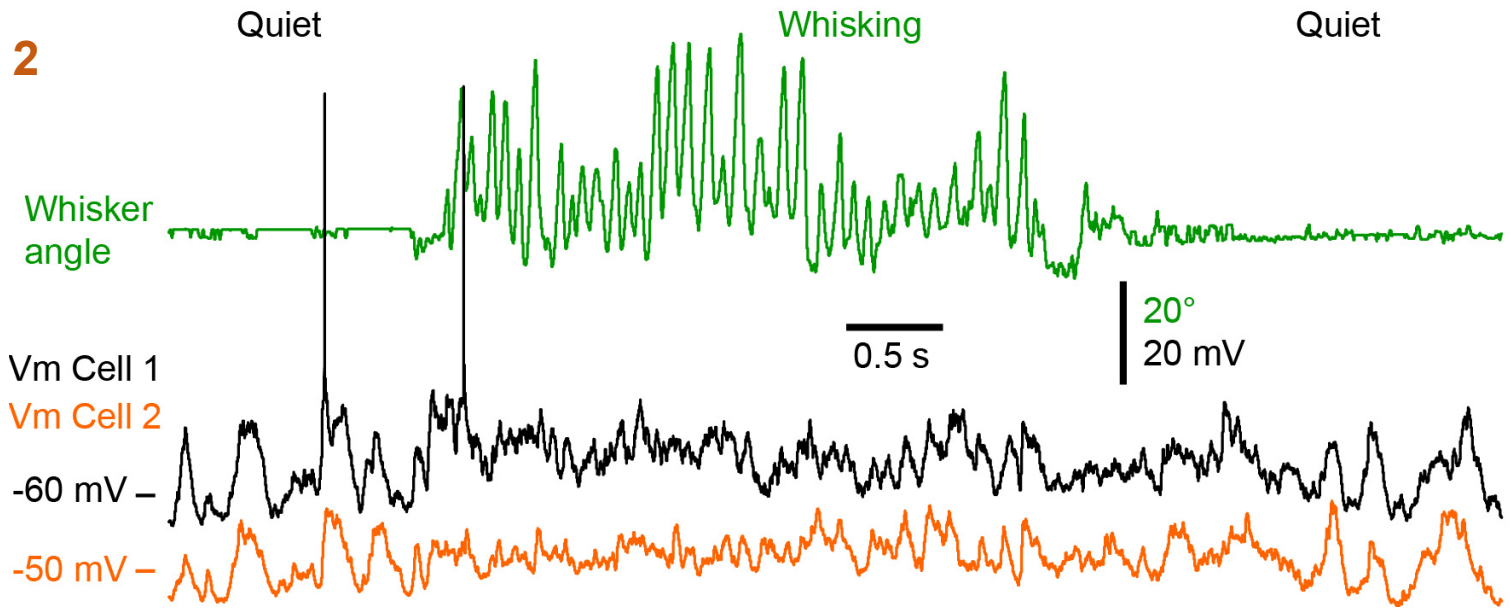
Fast-Fourier Transform => frequency domain



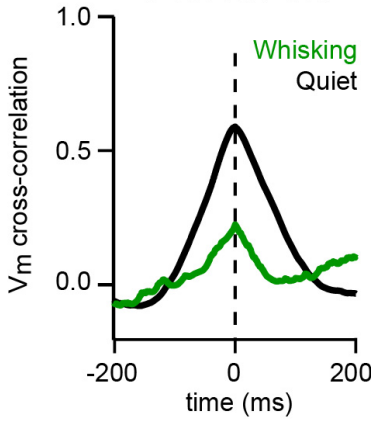
=> Decrease in low-frequency (1-10 Hz) activity during whisking

State change in wS1





Vm-Vm cross-correlograms



(Poulet and Petersen, Nature 2008)

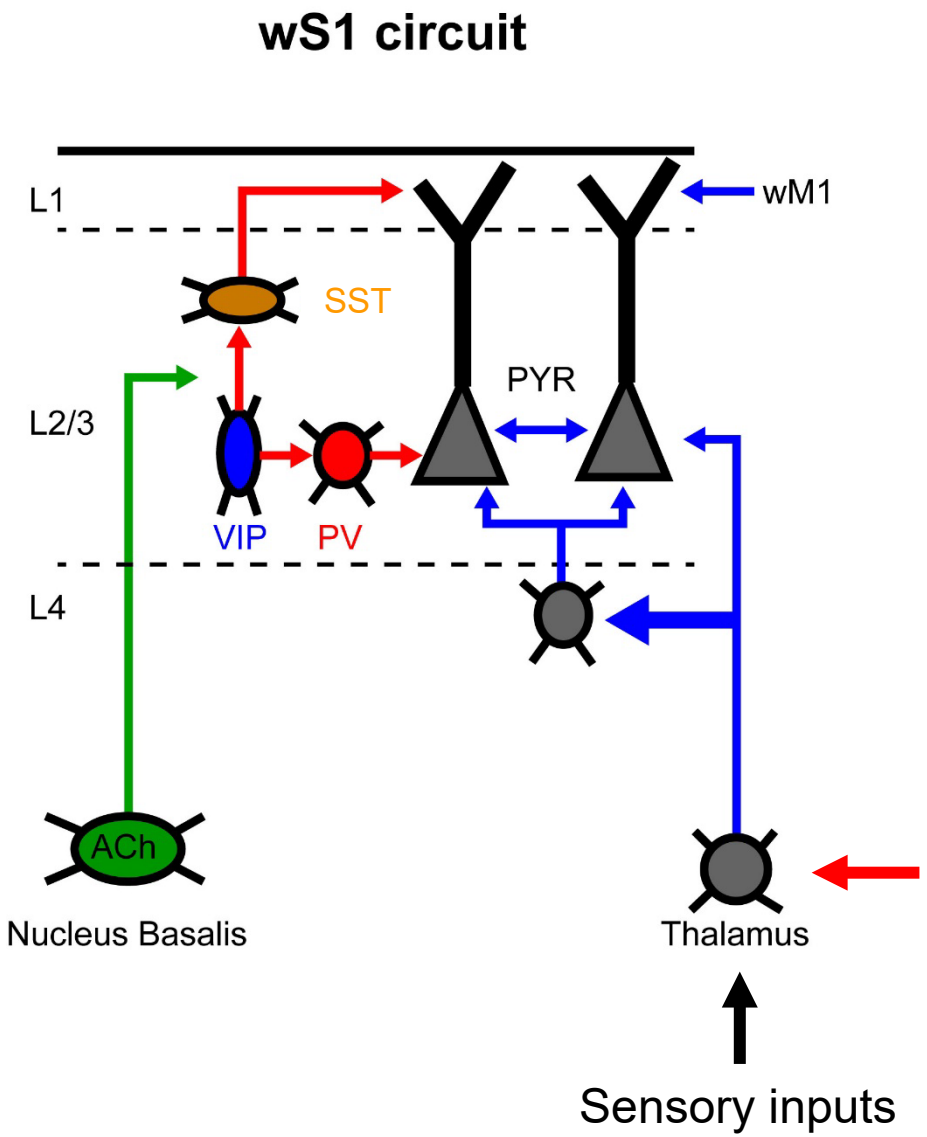
State change in wS1

Quiet => Whisking :

- **Strong decrease in low-frequency (1-10 Hz) Vm fluctuations**
- **Strong decrease in Vm variance**
- **Decrease in Vm correlation in nearby neurons (*desynchronization*)**
- **Slight but significant depolarization**
- **No significant change in firing rate at population level**

(Crochet and Petersen, Nat. Neurosci 2006; Crochet et al., Neuron 2011; Poulet and Petersen, Nature 2008)

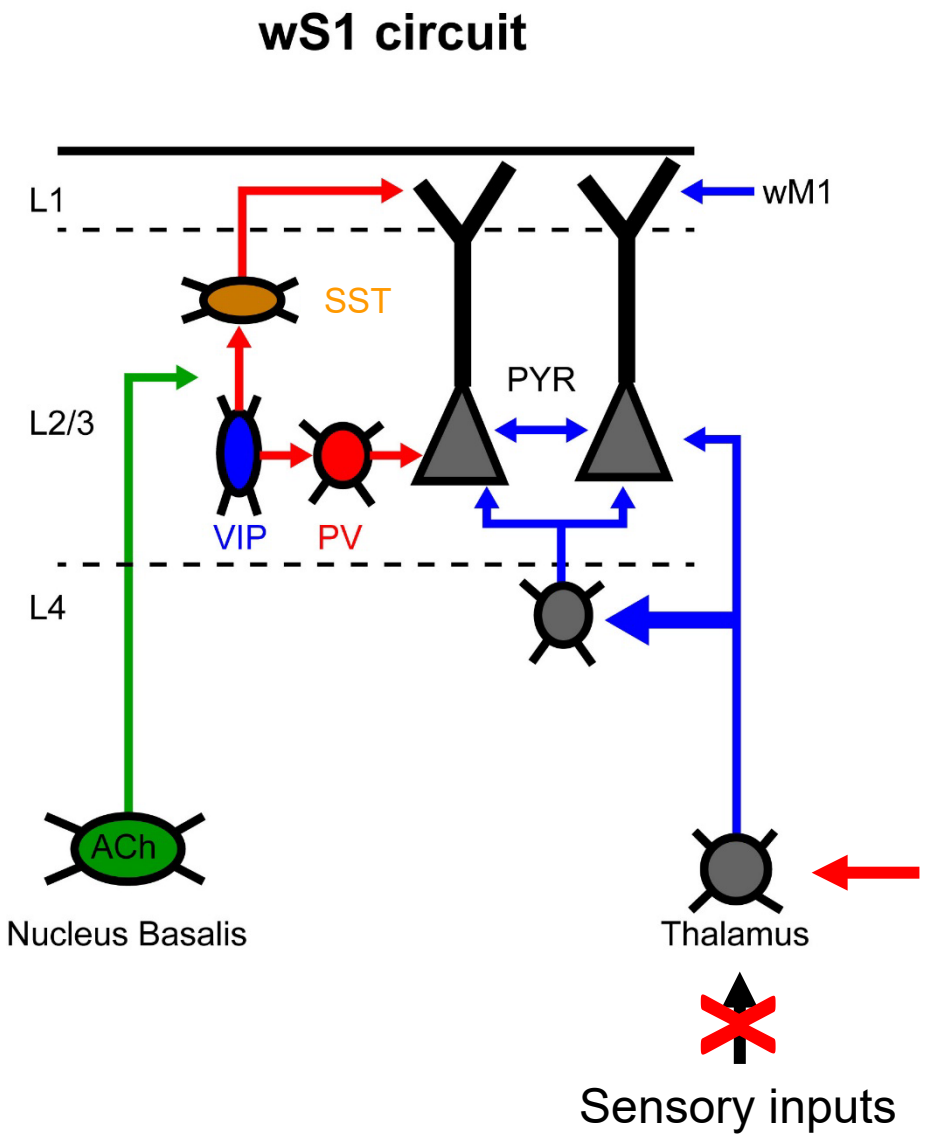
The origins of state change in wS1



What are the possible origins of the state change?

Modulatory inputs
Brainstem (ACh, NA …)

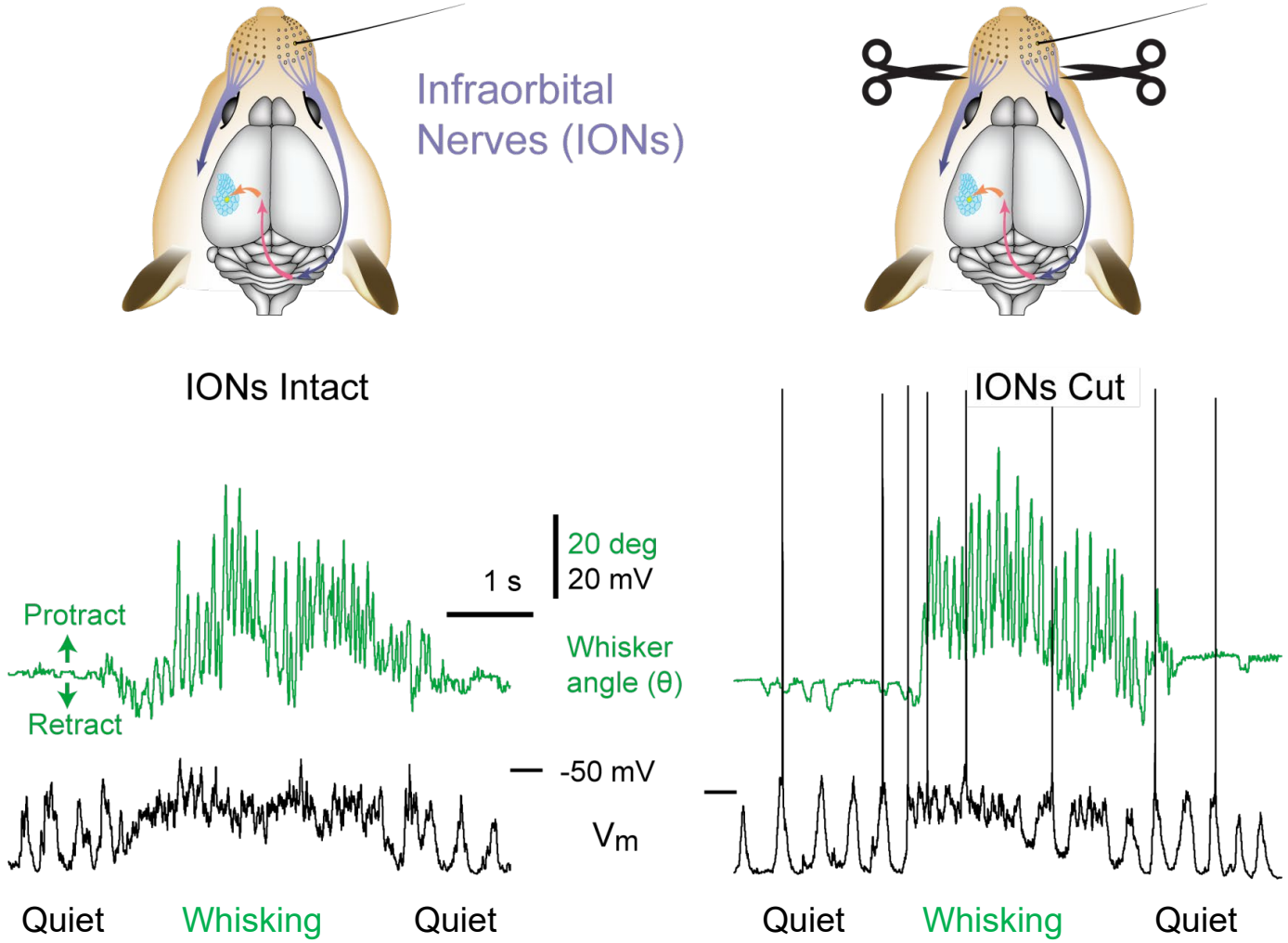
The origins of state change in wS1



What is the contribution of sensory inputs?

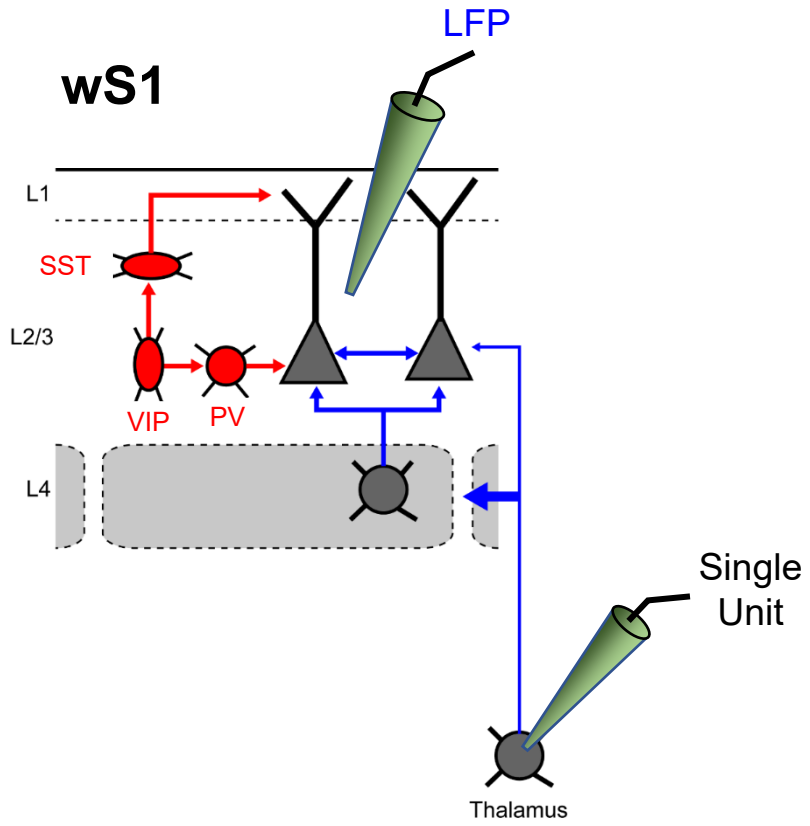
Modulatory inputs
Brainstem (ACh, NA …)

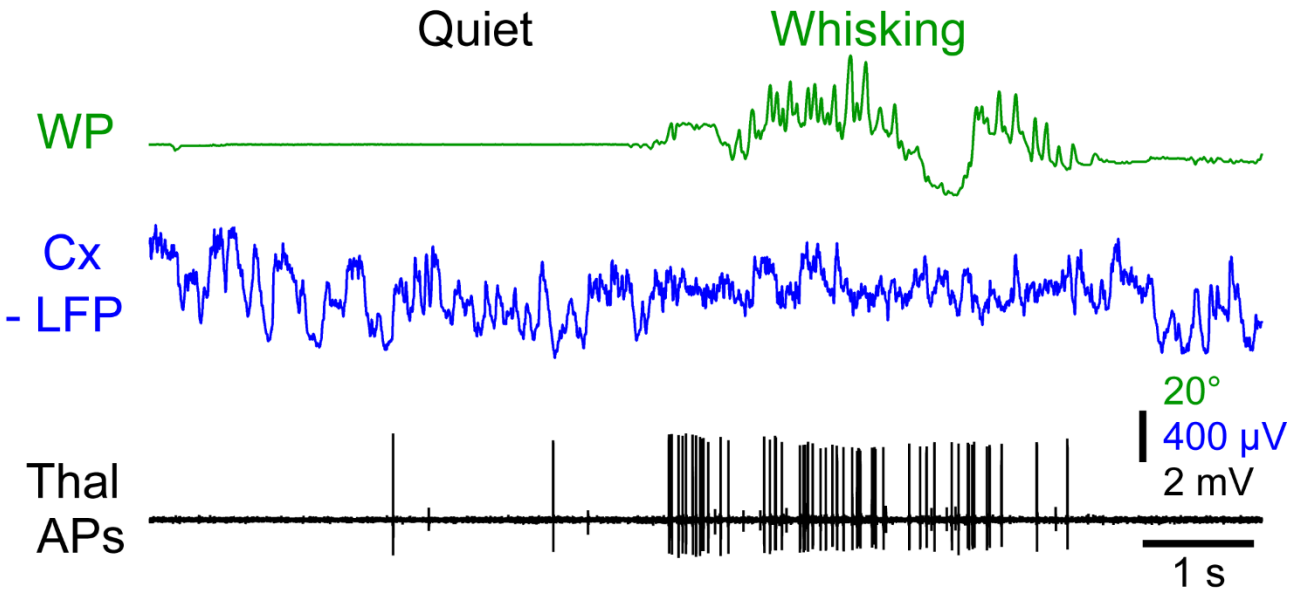
State change in wS1 is centrally generated

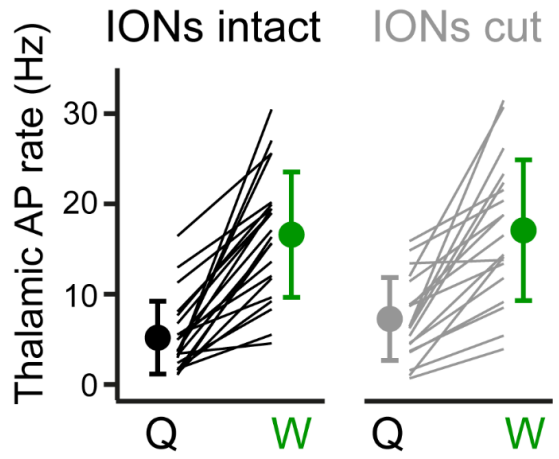


(Poulet and Petersen, Nature 2008; Poulet, Fernandez, Crochet et al., Nat. Neurosci. 2012)

Thalamic contribution





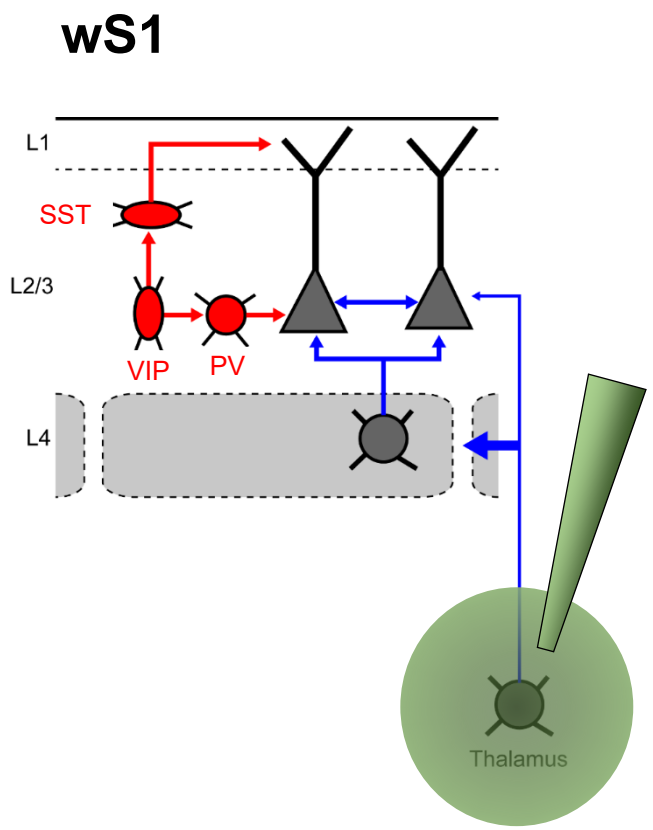


=> Activity of thalamic neurons increases with whisking and correlates with state change in wS1

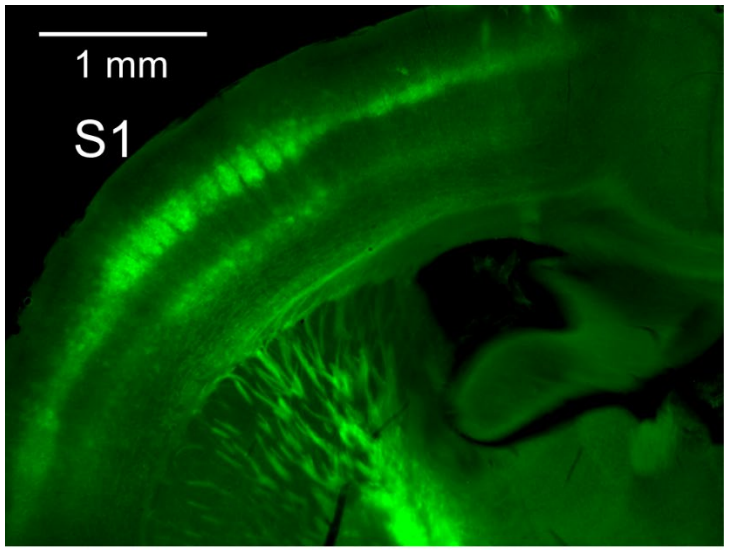
(Poulet, Fernandez, Crochet et al., Nat. Neurosci. 2012; Urbain et al., Cell Rep. 2015)

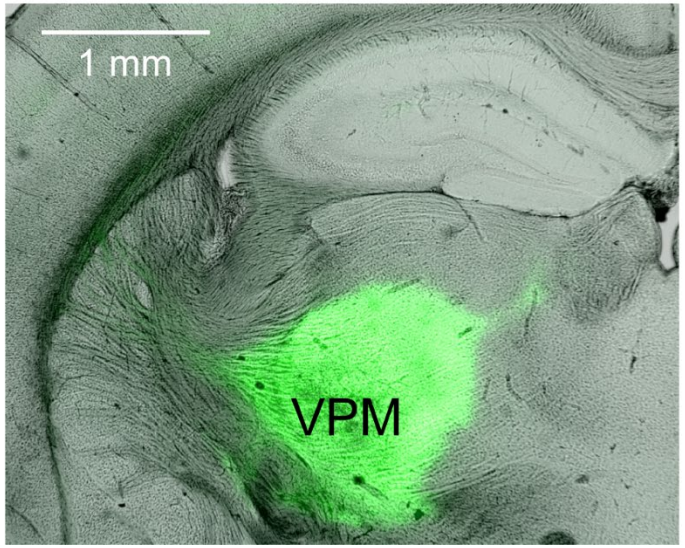
Thalamic contribution

Optogenetic stimulation of thalamic neurons



AAV2/1.CAG.ChR2-Venus.W.SV40

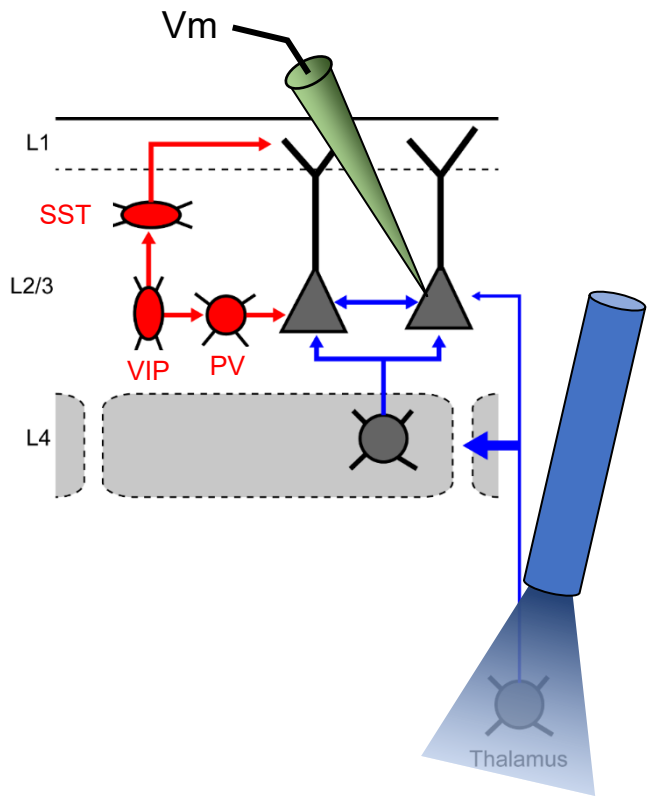


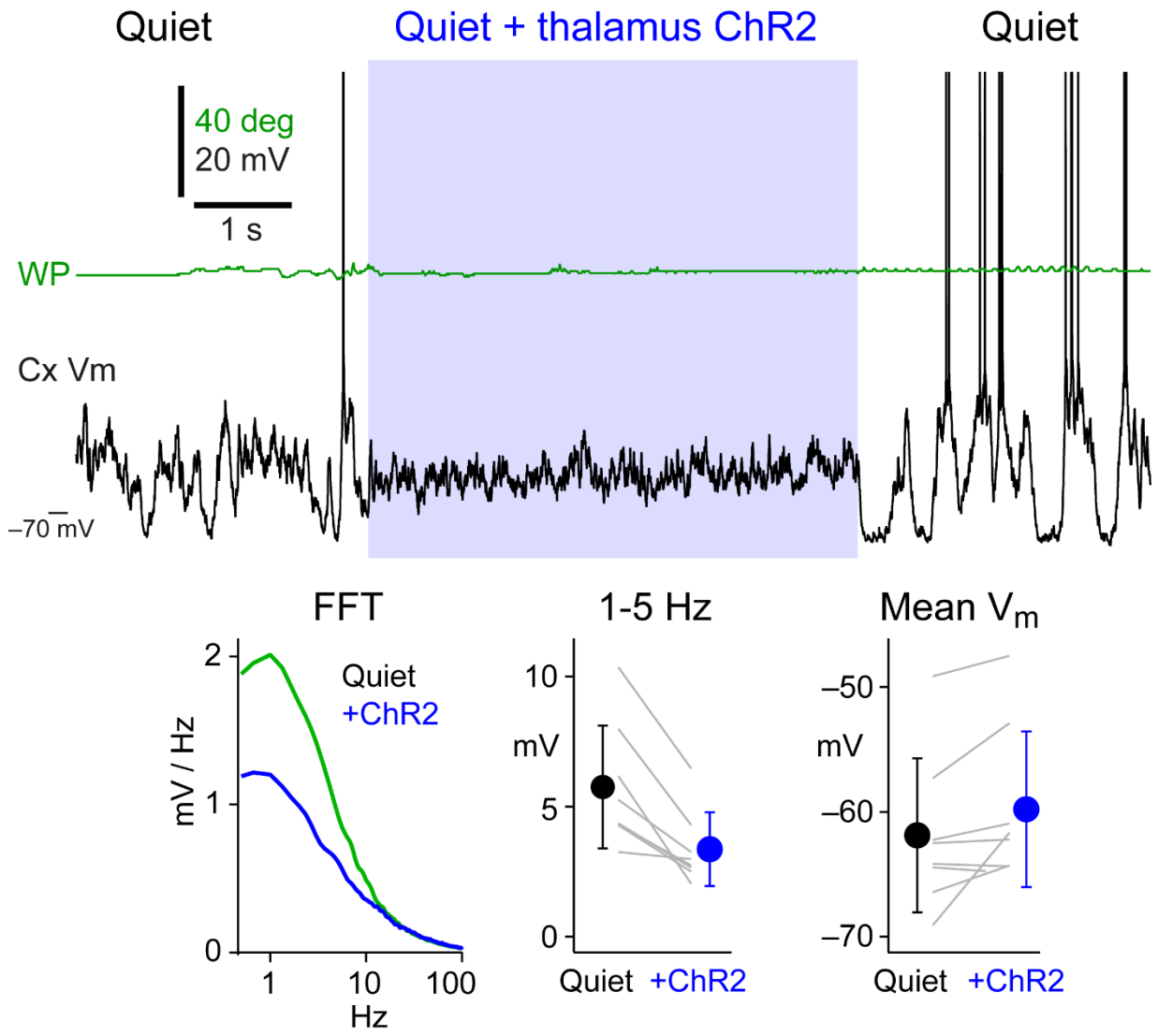


(Poulet, Fernandez, Crochet et al., Nat. Neurosci. 2012)

Thalamic contribution

Optogenetic stimulation of thalamic neurons



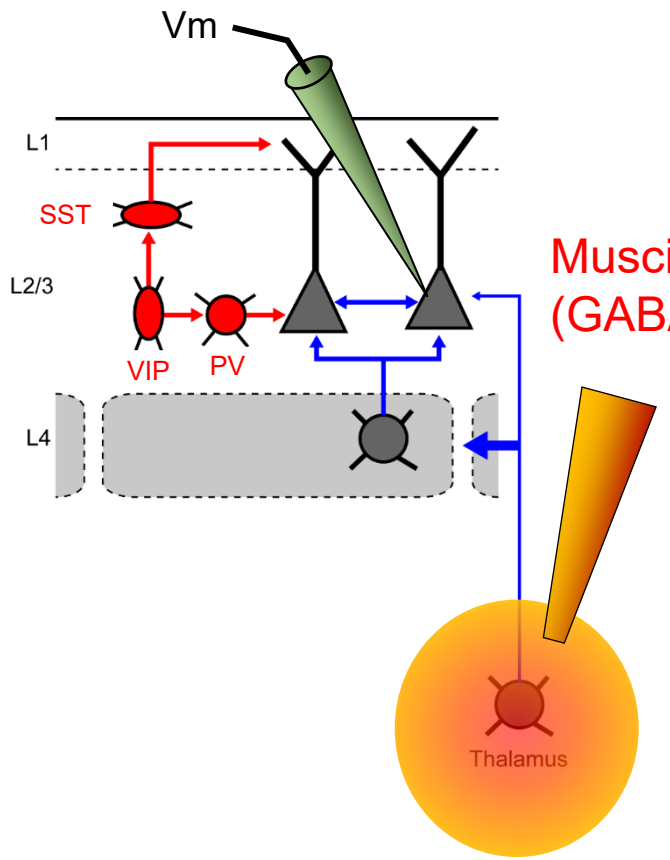


=> Activation of thalamic neurons induces state change in wS1 during quiet wakefulness

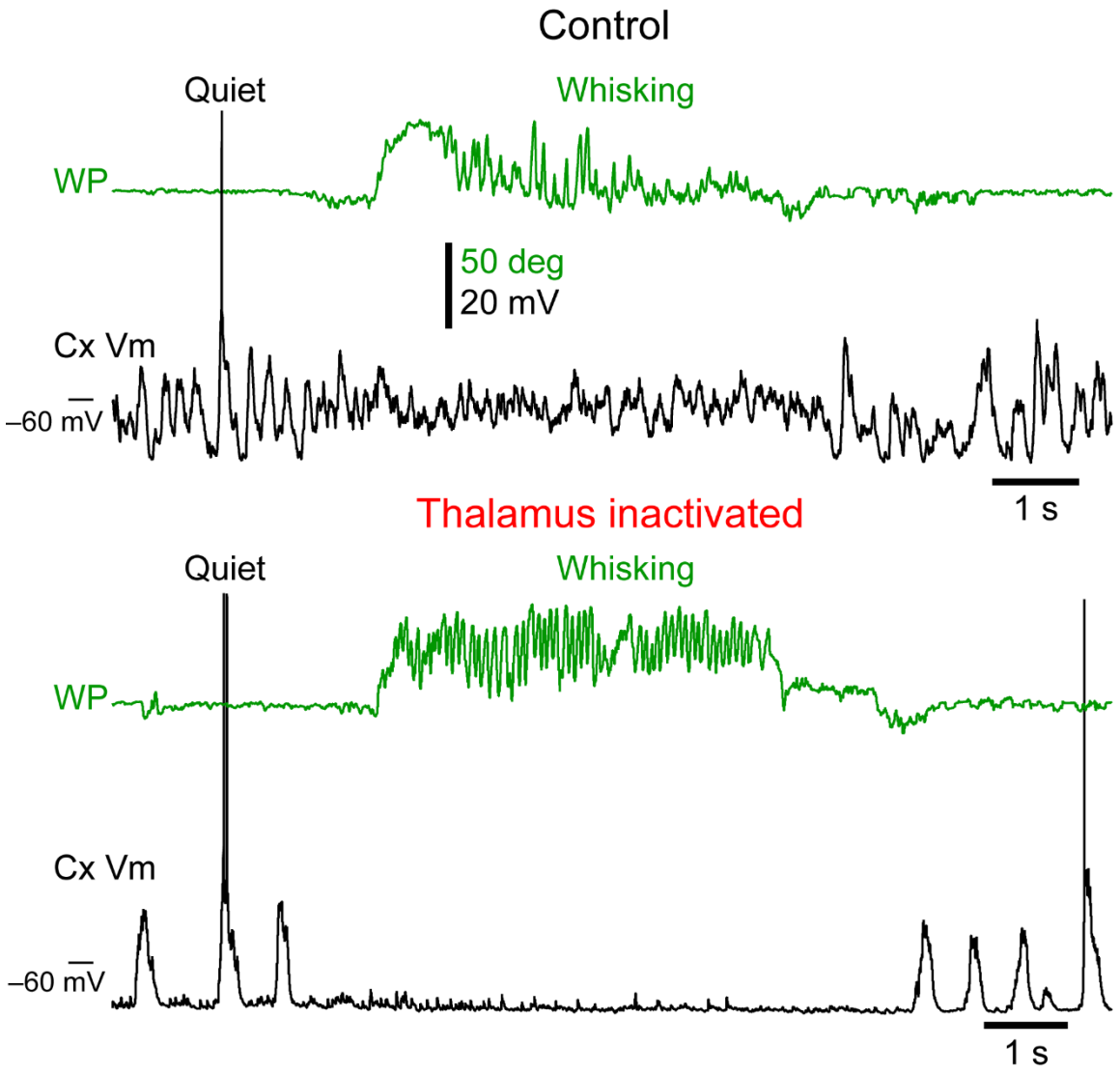
(Poulet, Fernandez, Crochet et al., Nat. Neurosci. 2012)

Thalamic contribution

Pharmacological inhibition of thalamic neurons



Muscimol
($GABA_A$ agonist)

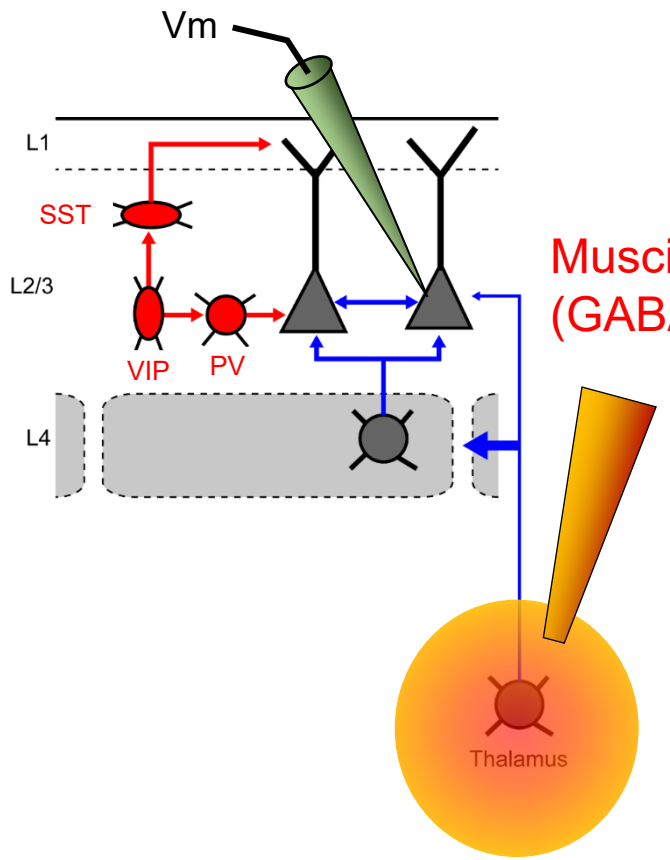


=> Inhibition of thalamic neurons suppresses the high-frequency activity in wS1 during whisking

(Poulet, Fernandez, Crochet et al., Nat. Neurosci. 2012)

Thalamic contribution

Pharmacological inhibition of thalamic neurons



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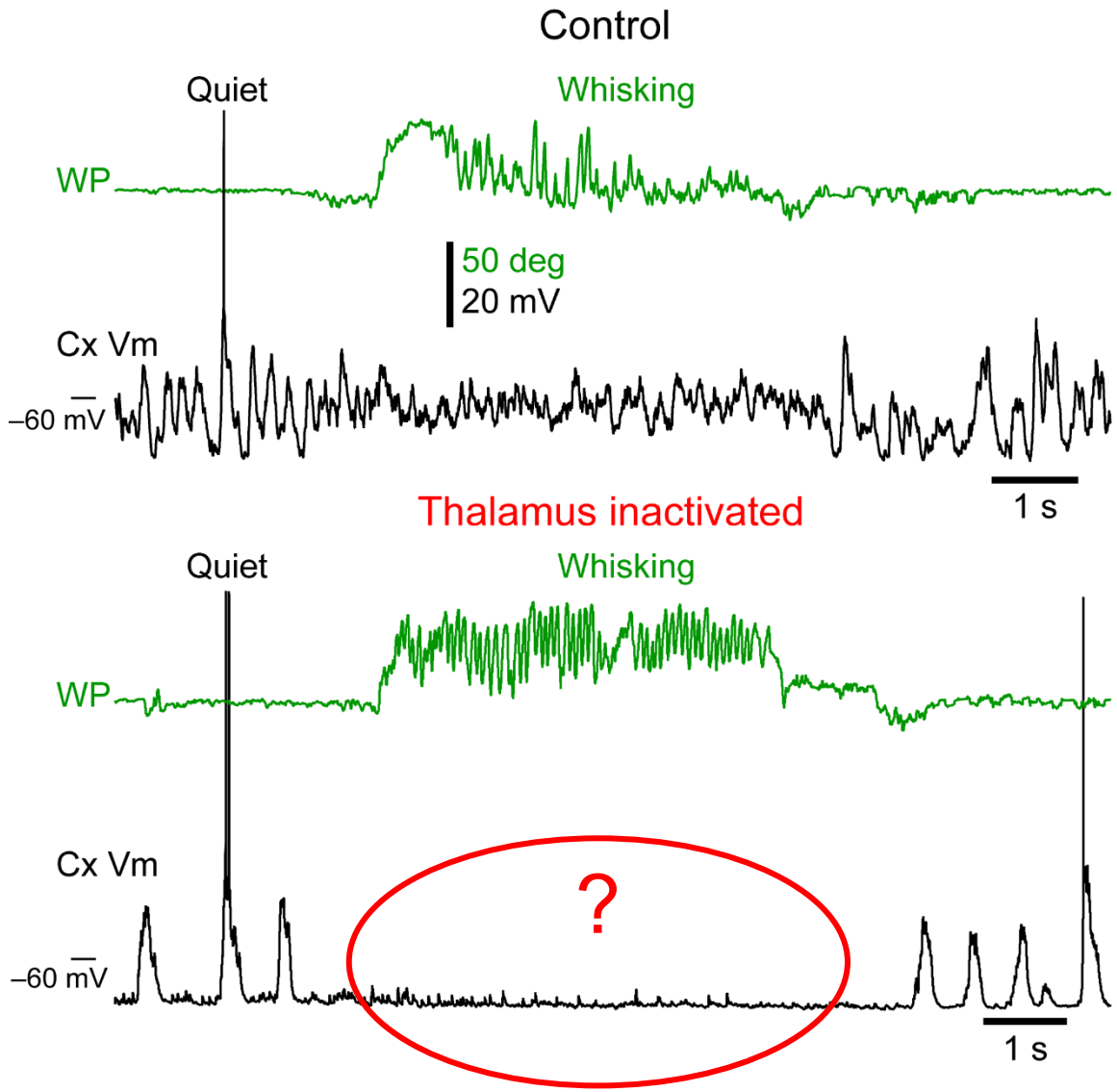
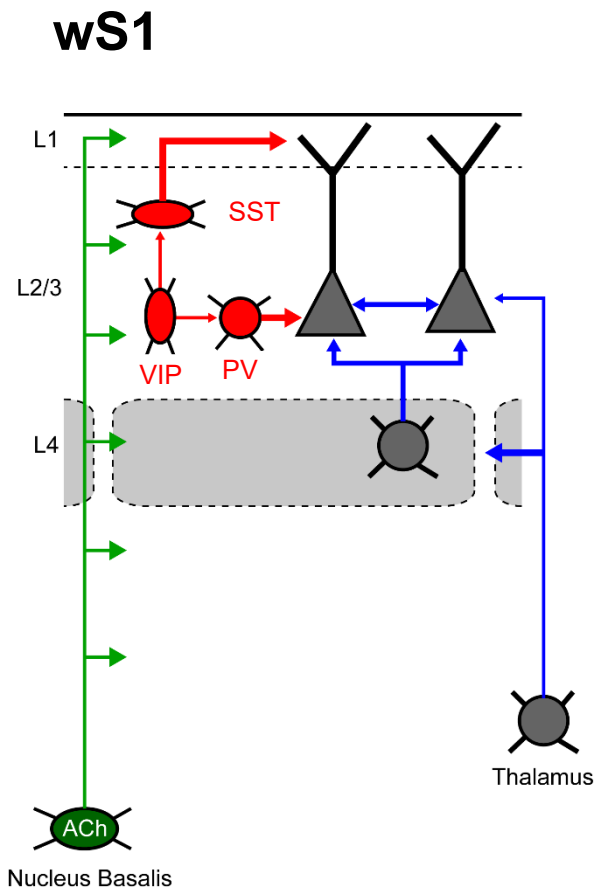
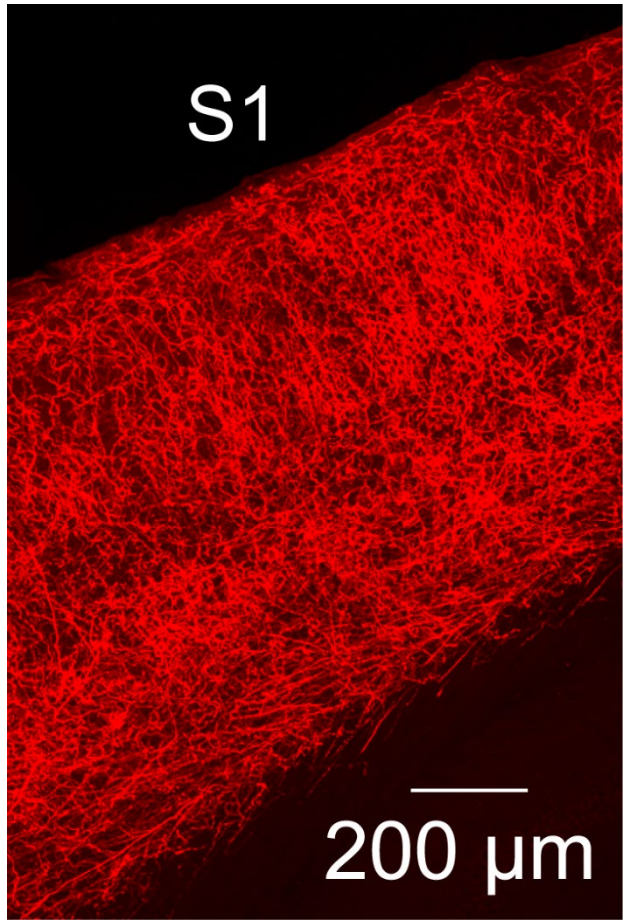


(Poulet, Fernandez, Crochet et al., Nat. Neurosci. 2012)

Cholinergic contribution

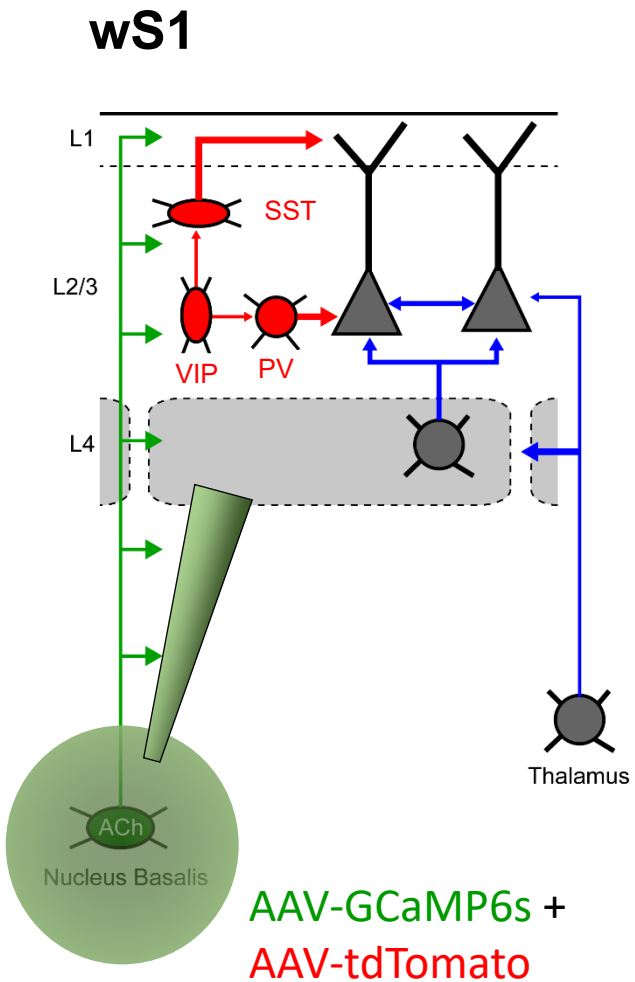


Cholinergic axons in S1 (tdTomato)

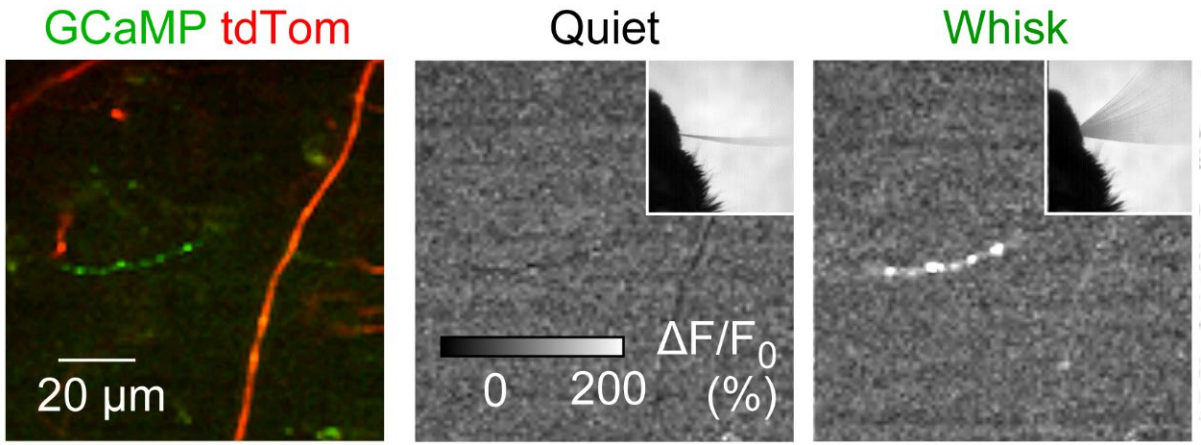


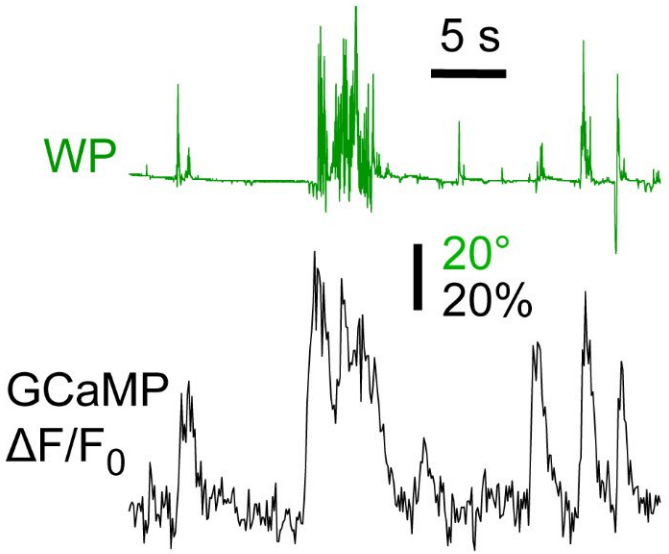
(Eggermann et al., Cell Rep. 2014)

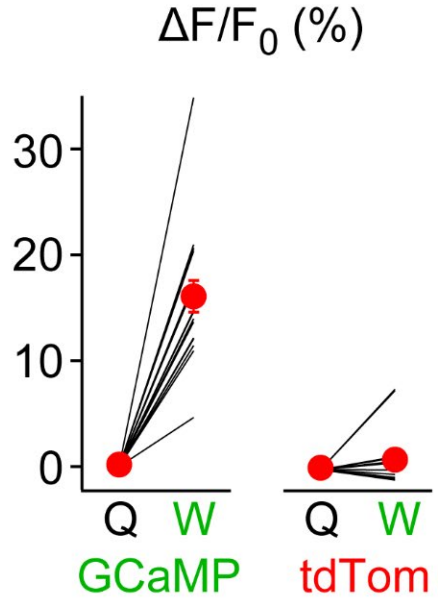
Cholinergic contribution



AAV-GCaMP6s +
AAV-tdTomato





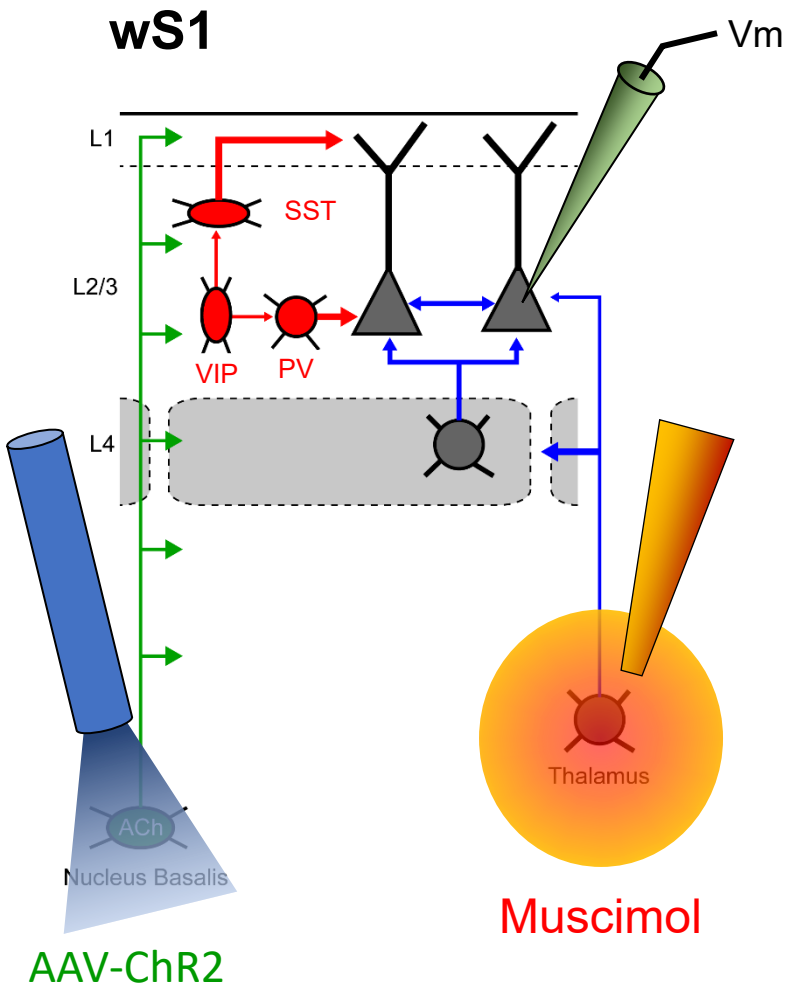


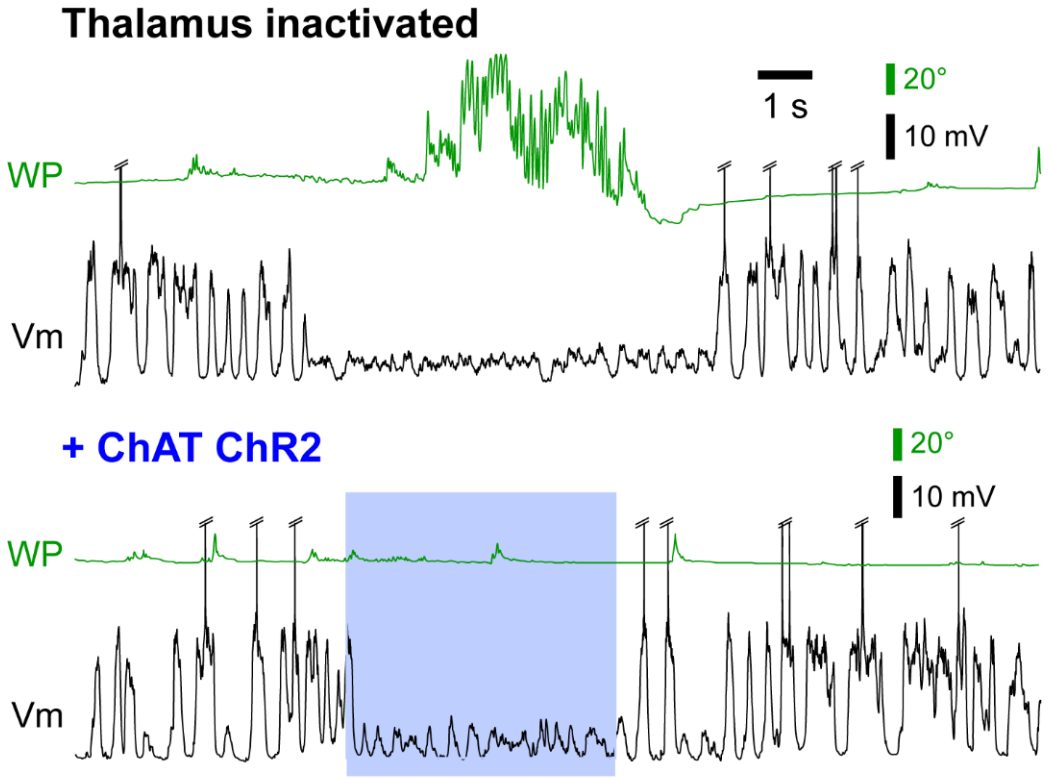
=> ACh axons in wS1 increase activity during whisking

(Eggermann et al., Cell Rep. 2014)

Cholinergic contribution

Optogenetic activation of cholinergic neurons

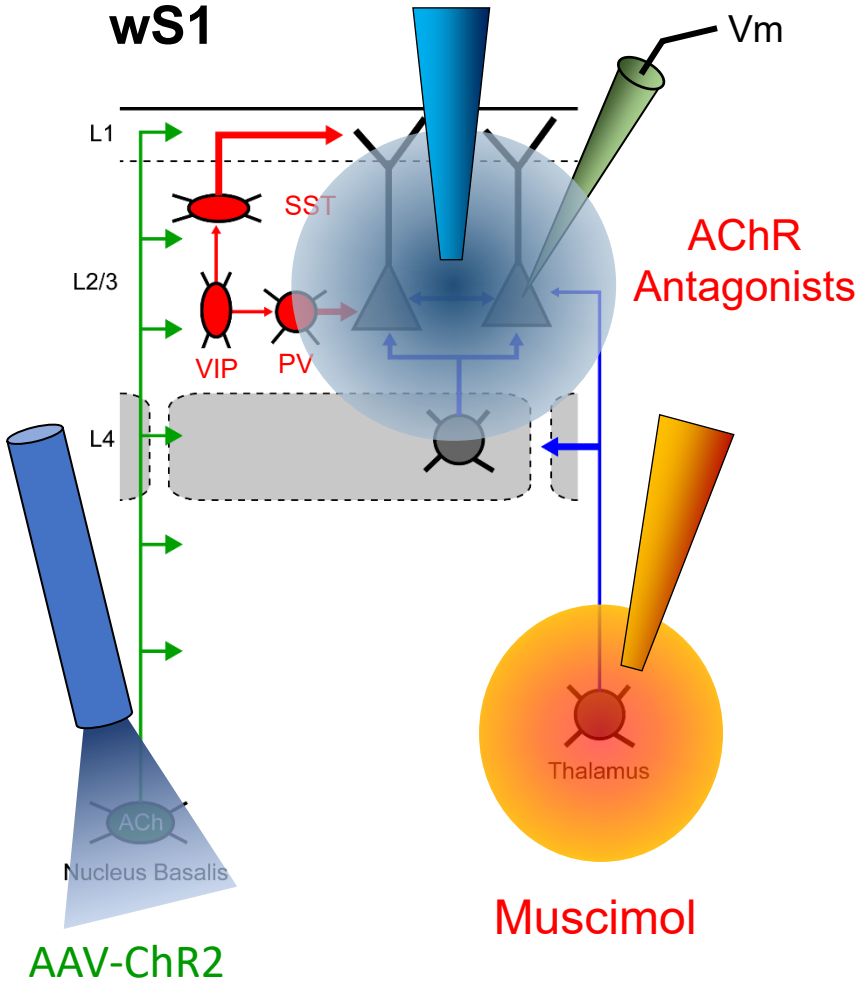


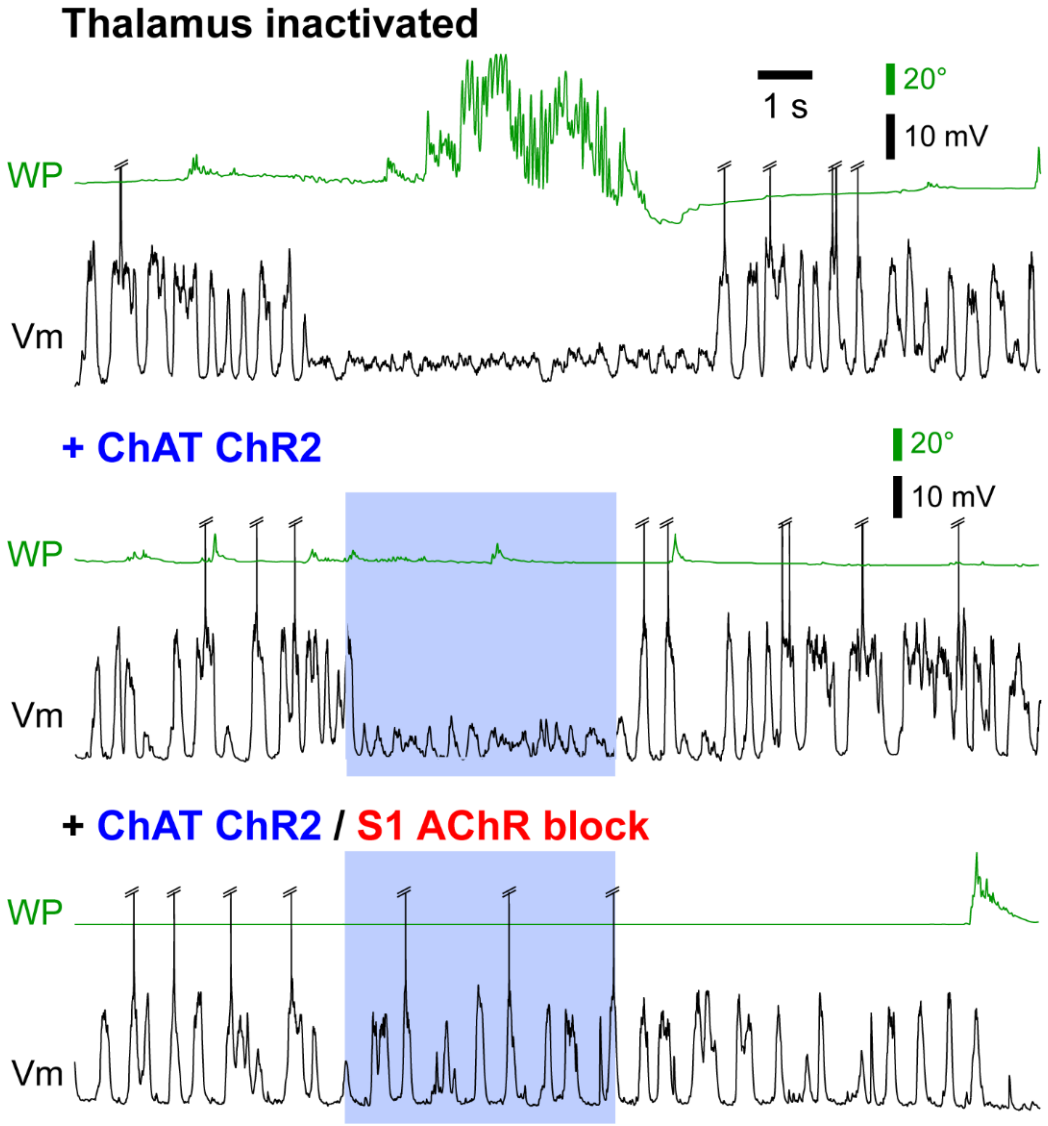


(Eggermann et al., Cell Rep. 2014)

Cholinergic contribution

Pharmacological blockade of ACh receptors



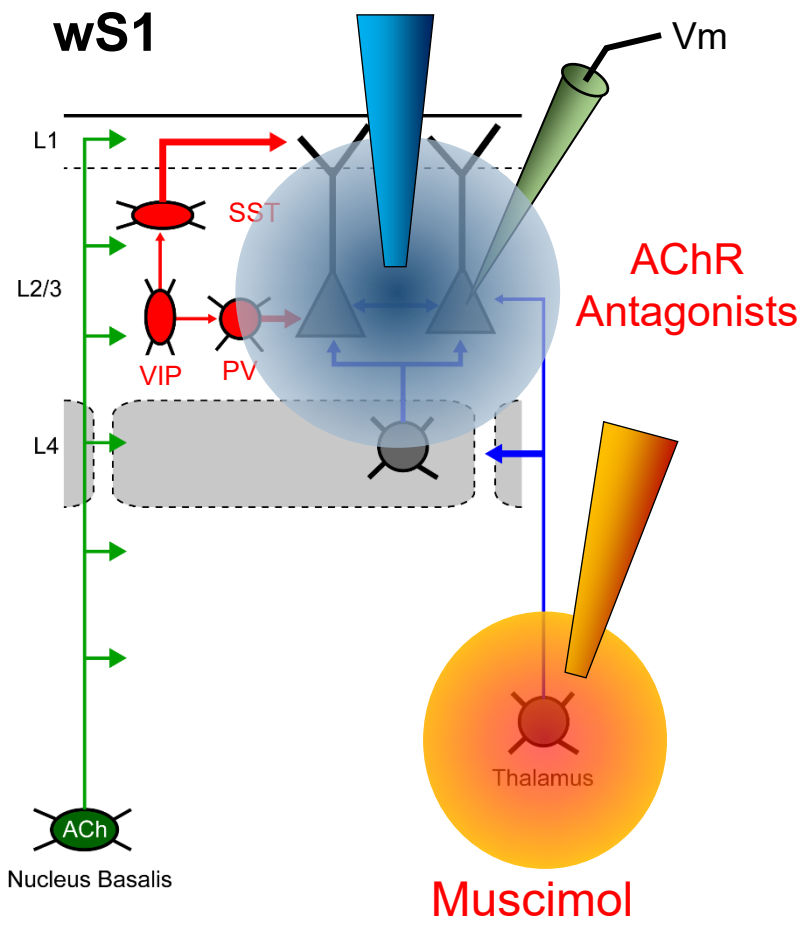


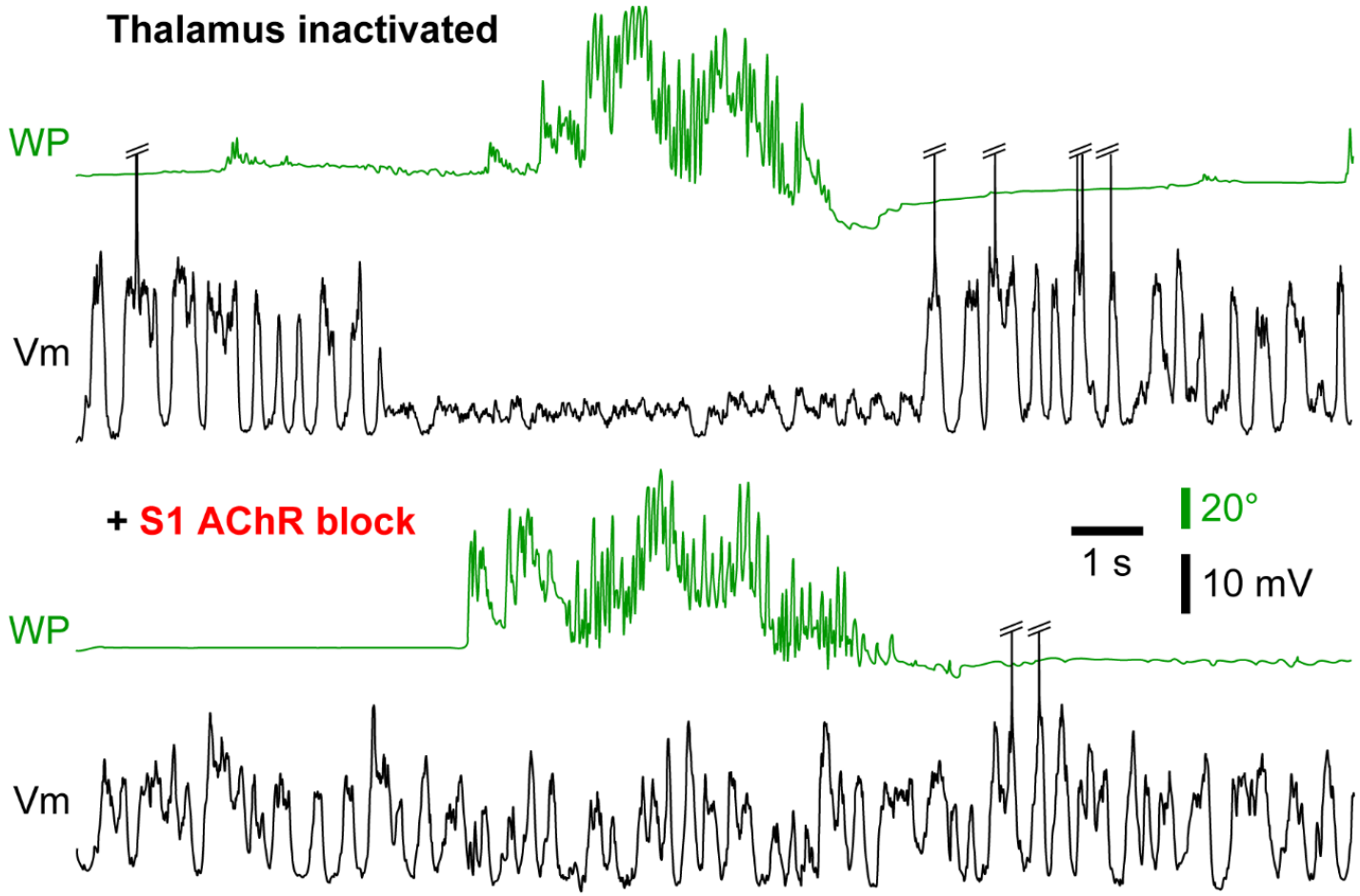
=> Activation of ACh neurons induces state change in wS1

(Eggermann et al., Cell Rep. 2014)

Cholinergic contribution

Pharmacological blockade of ACh receptors

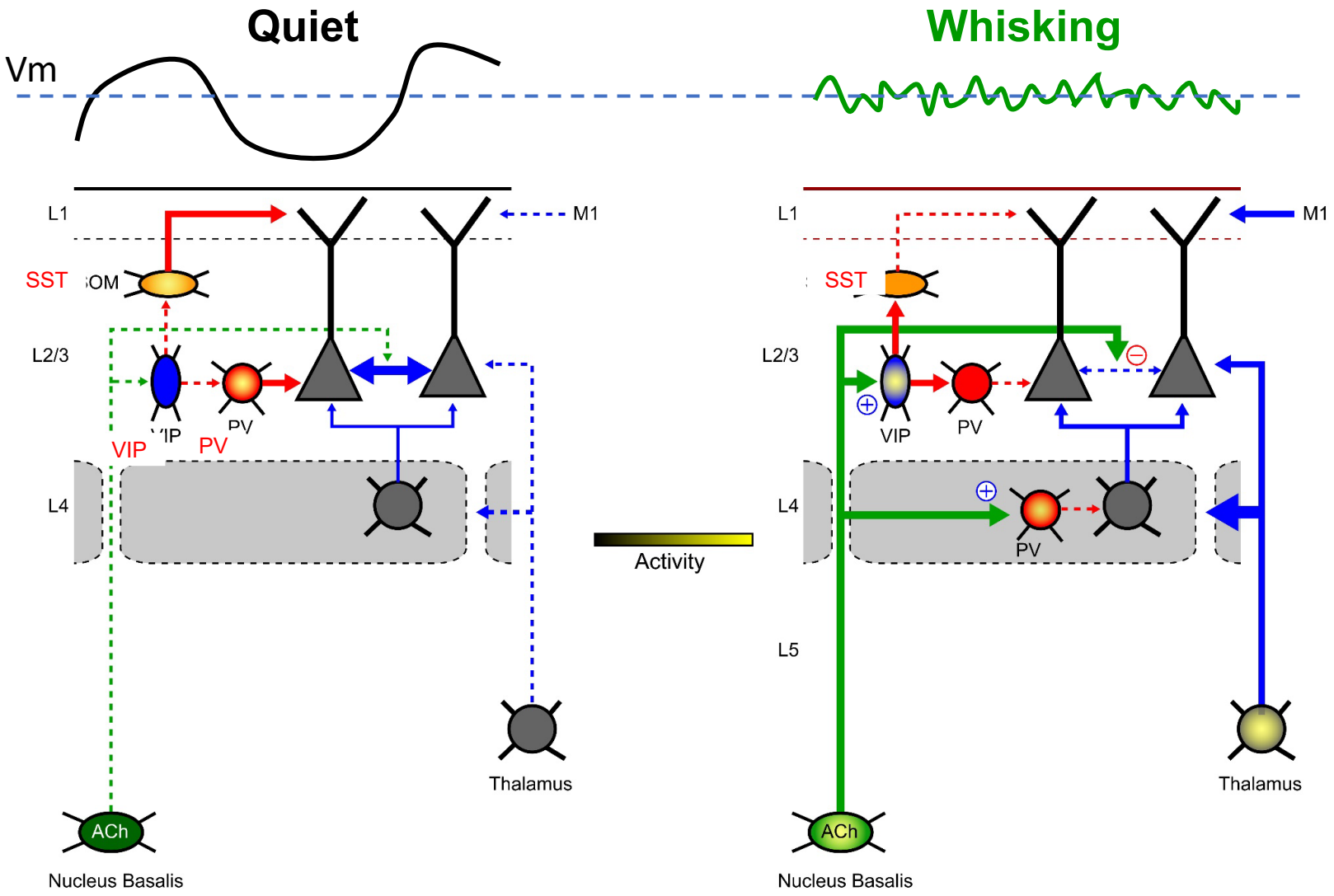




=> Blockage of AChR in wS1 & inhibition of thalamus block the state change in wS1

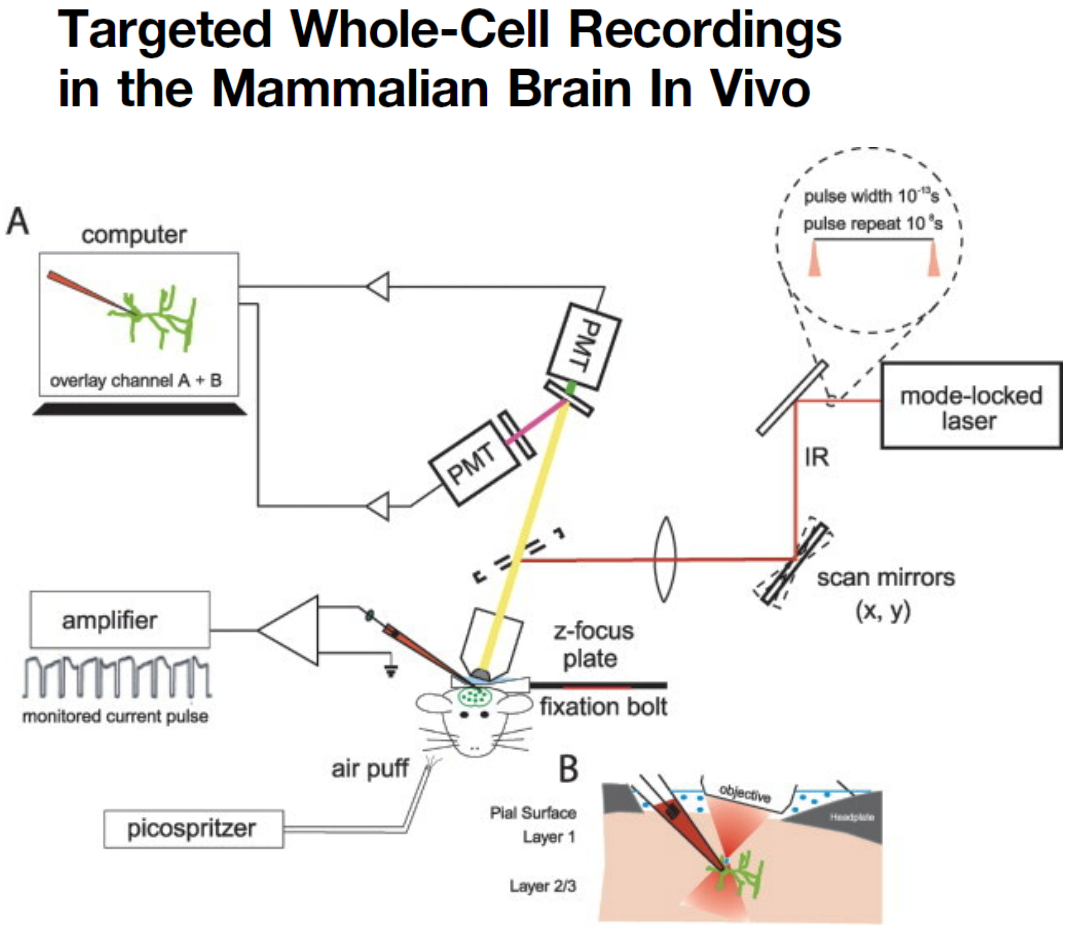
(Eggermann et al., Cell Rep. 2014)

Cellular mechanisms of the state change in wS1

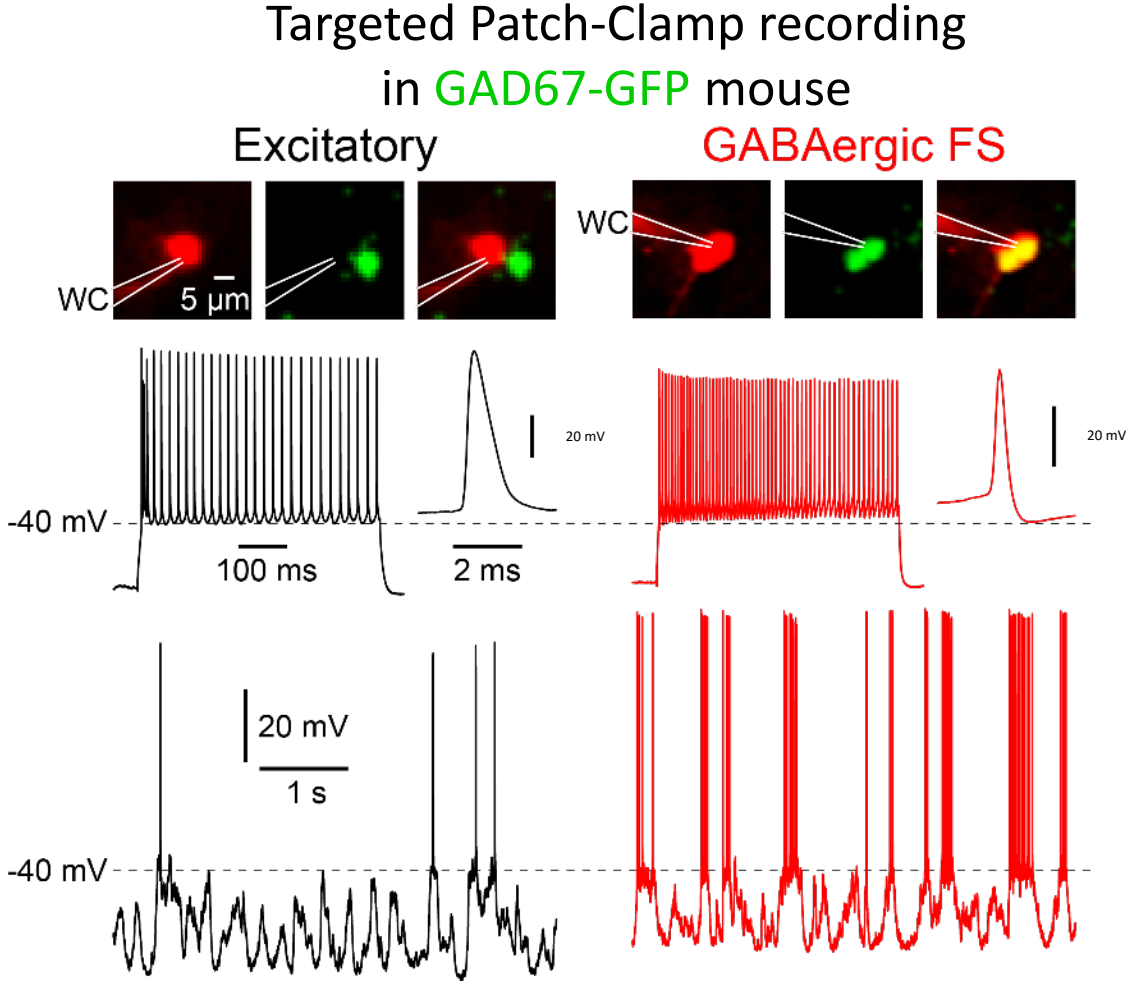


See https://www.frontiersin.org/journals/systems-neuroscience/articles/10.3389/fnsys.2018.00064/full

Cell-type specific changes with cortical states

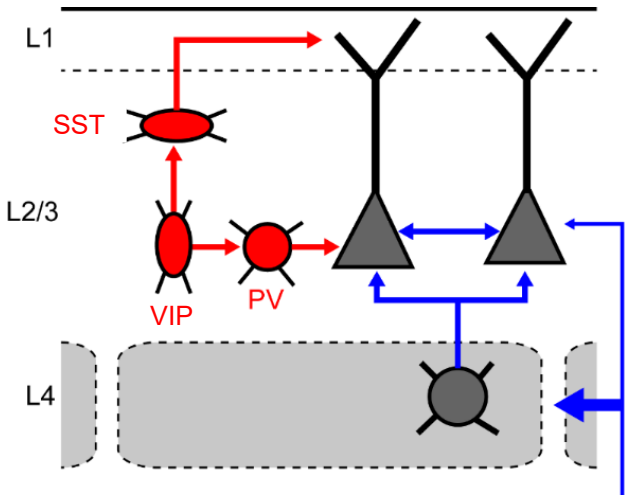


(Margrie et al., 2003; Komai et al., 2006)



(Gentet et al., Neuron 2010 ; Gentet et al., Nat. Neurosci. 2012)

Cell-type specific changes with cortical states

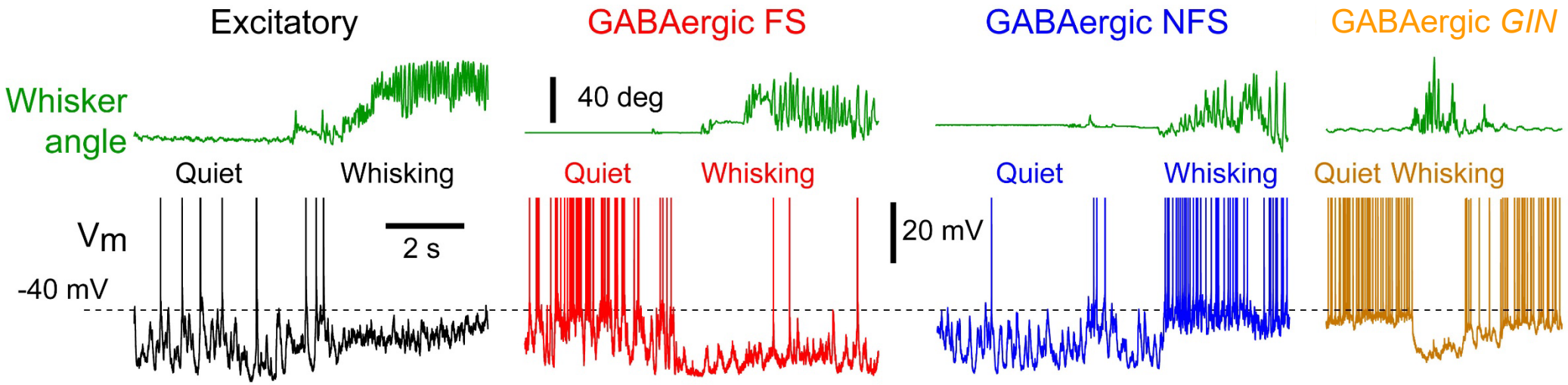


Excitatory Pyramidal

Fast Spiking (FS) ~ GABAergic PV

Non Fast-Spiking (NFS) ~ GABAergic VIP

GIN ~ GABAergic SST



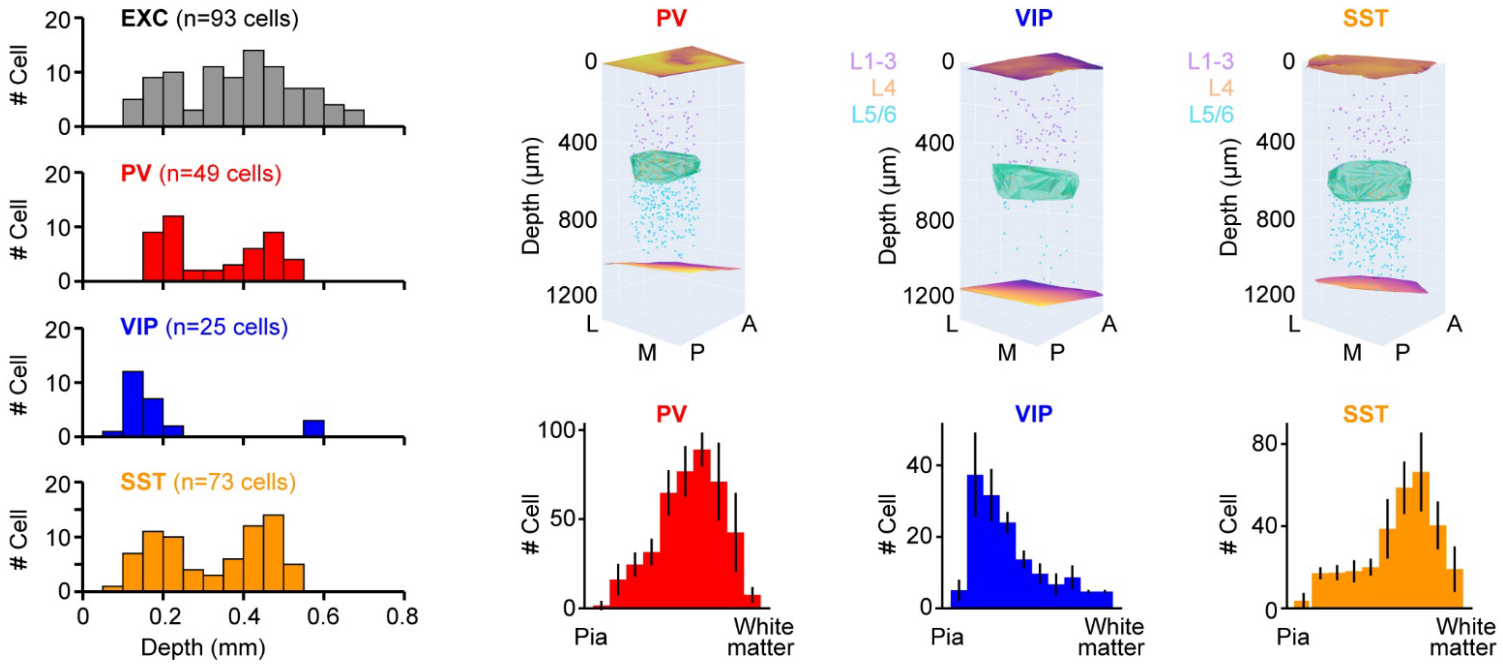
=> But cell-type identification approximative and limitation to superficial L2/3

(Gentet et al., Neuron 2010 ; Gentet et al., Nat. Neurosci. 2012)

Cell-type specific changes with cortical states

New study – Kiritani et al., PLOS One 2024

- Better cell-type identification => PV-Cre, VIP-Cre and SST-Cre mouse lines
- Recordings at lower cortical depth => improved 2-photon targeting



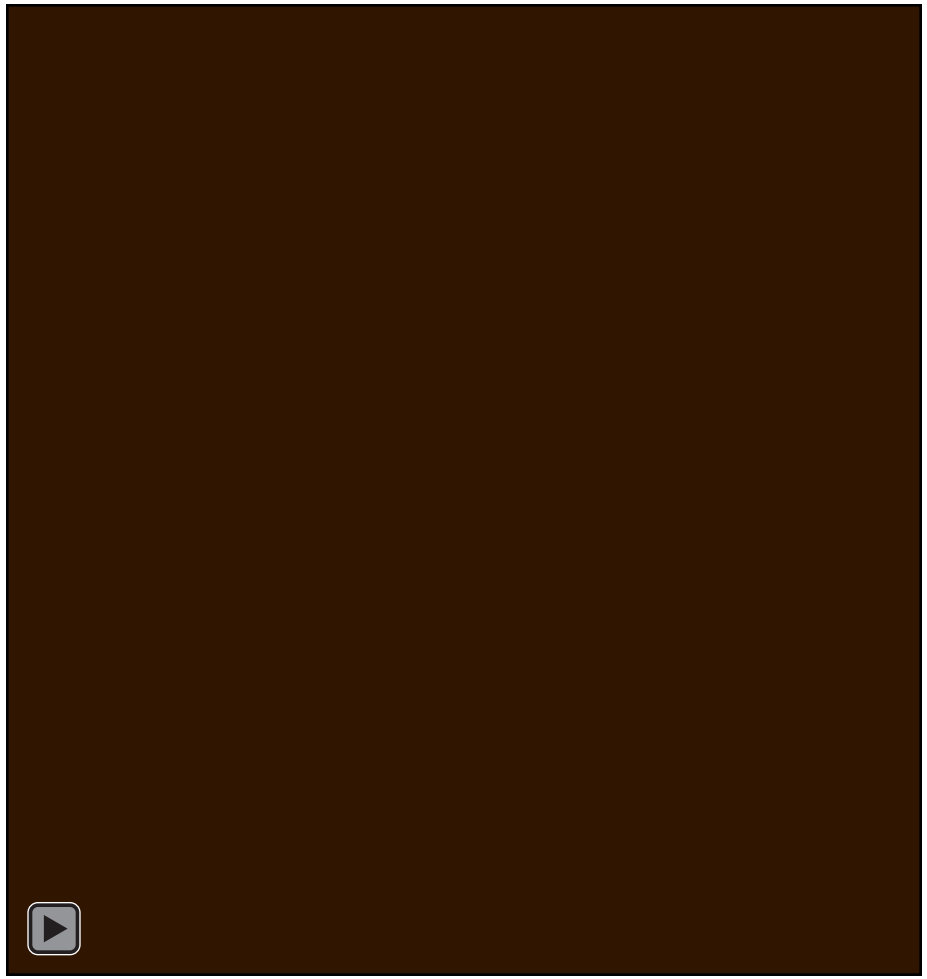
(Kiritani et al., PLOS One 2024)

=> BIO482 Miniproject:

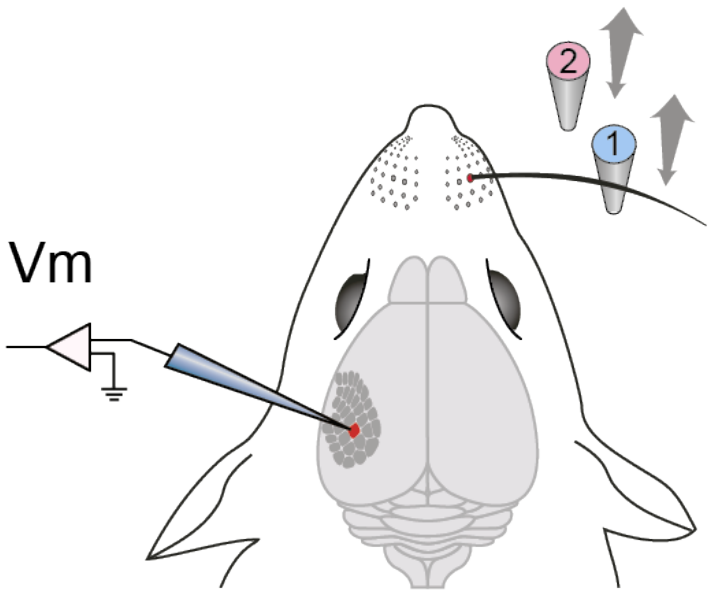
Learn more about these different cell-types by yourself

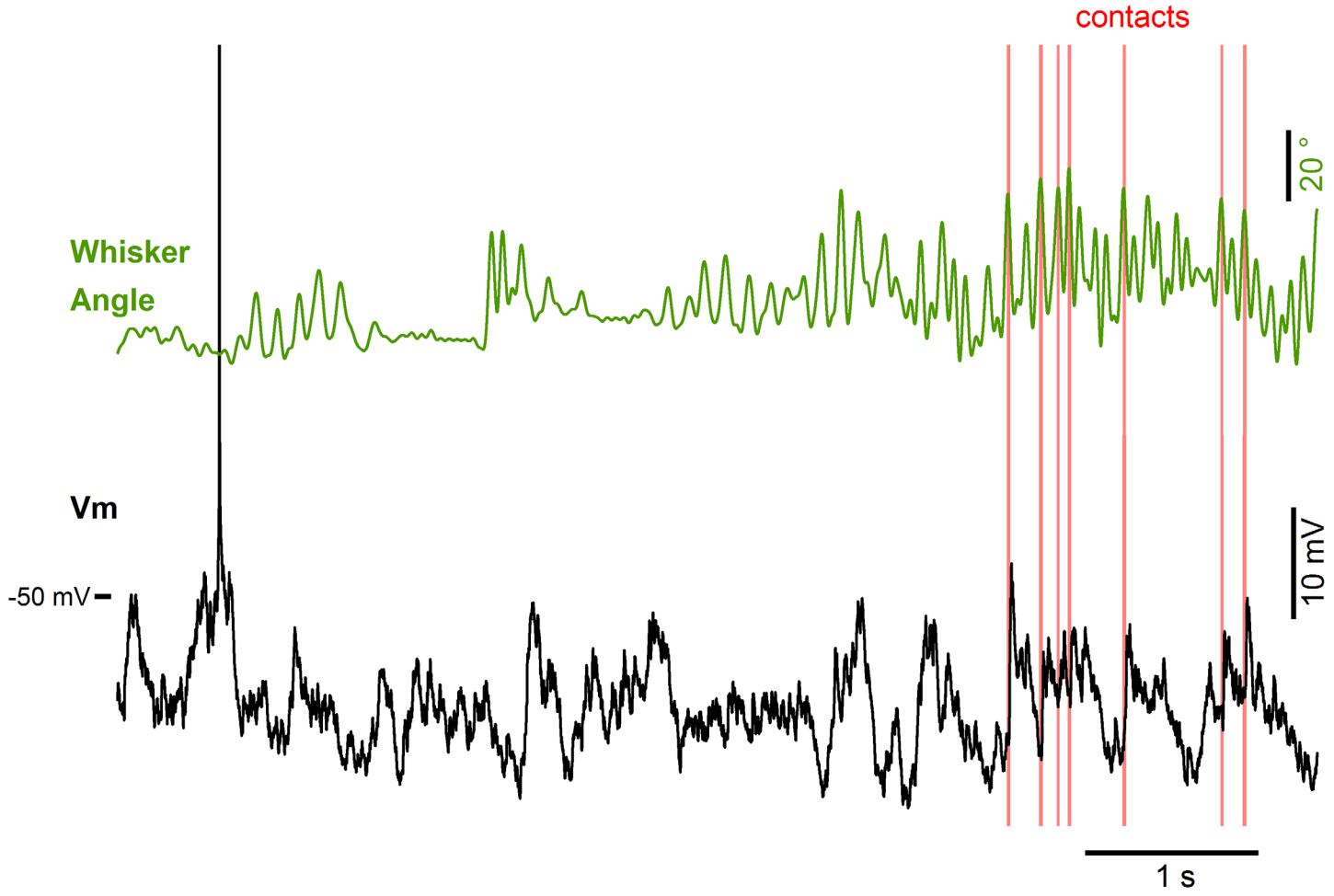
2. Sparse representation of sensory inputs in layer 2/3

Membrane potential recording during active touch

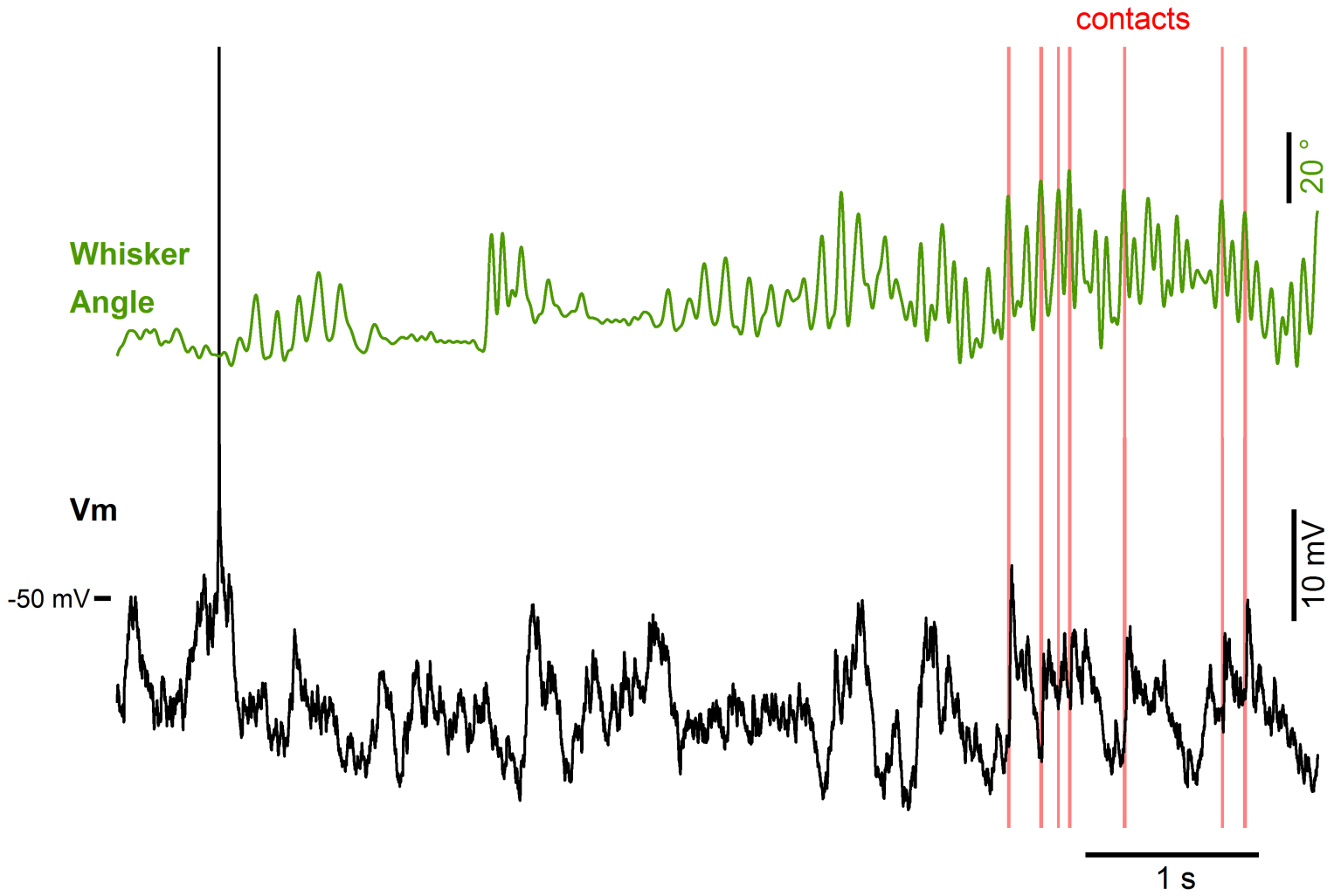


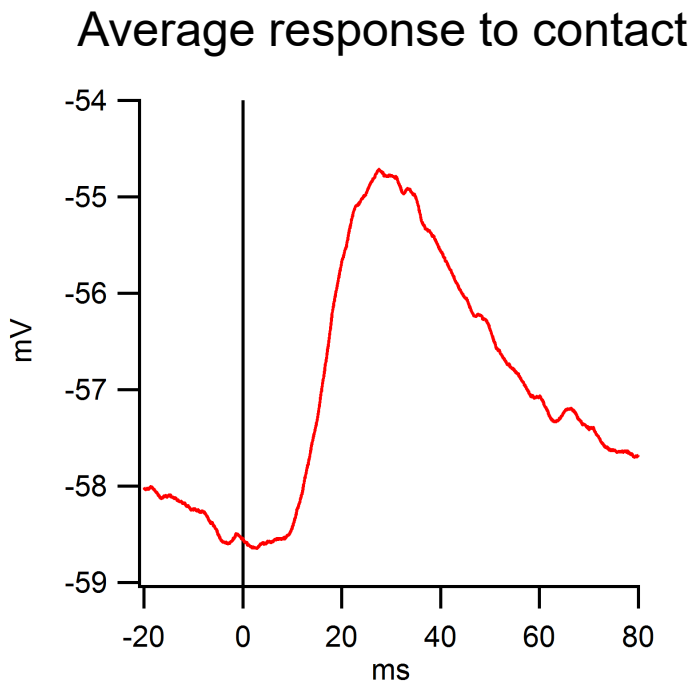
Membrane potential recording during active touch





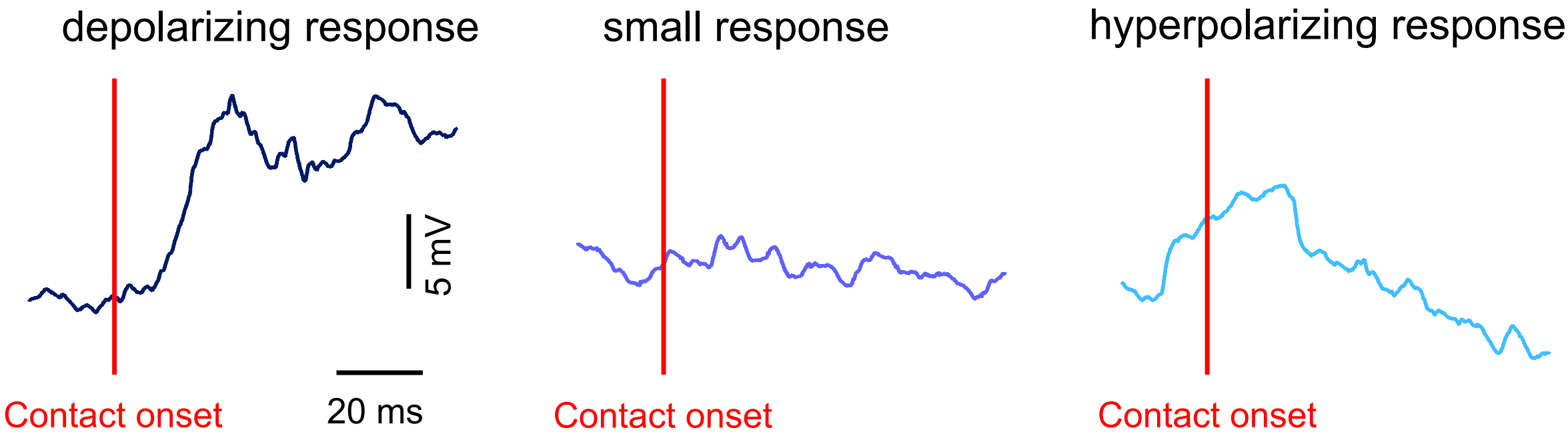
Membrane potential recording during active touch





Variable evoked responses to active touch

Example of individual postsynaptic potentials (PSPs) evoked by contact



Variable evoked responses to active touch

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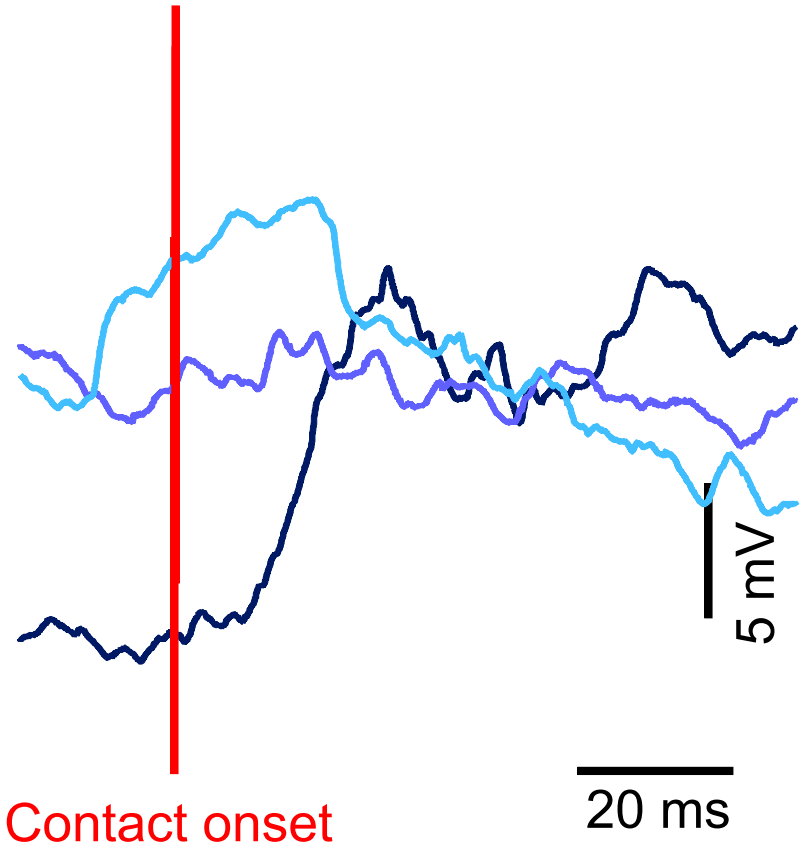
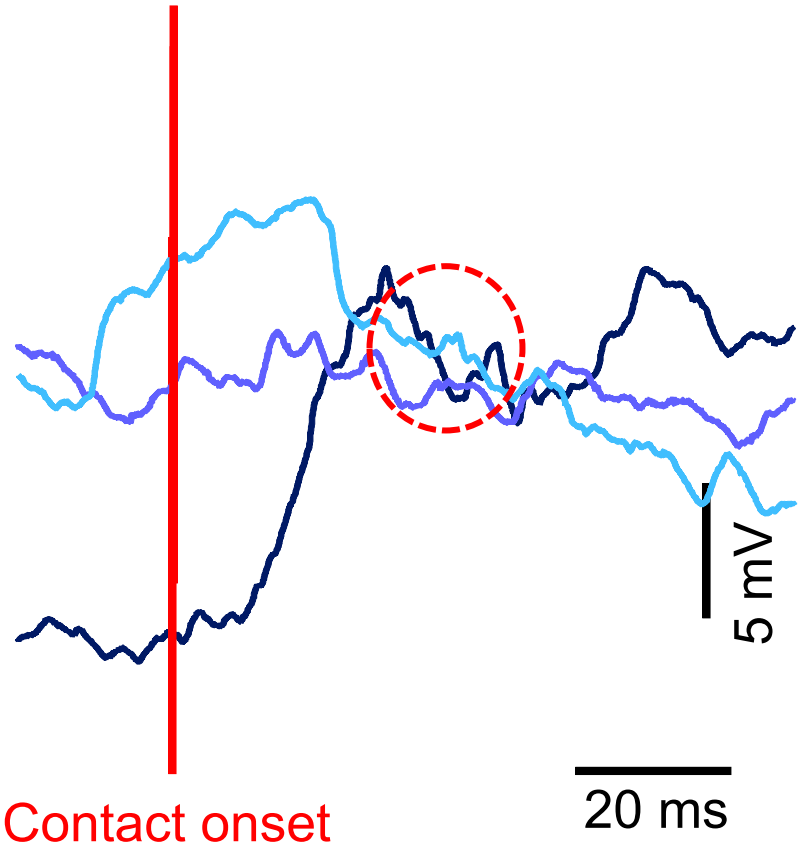


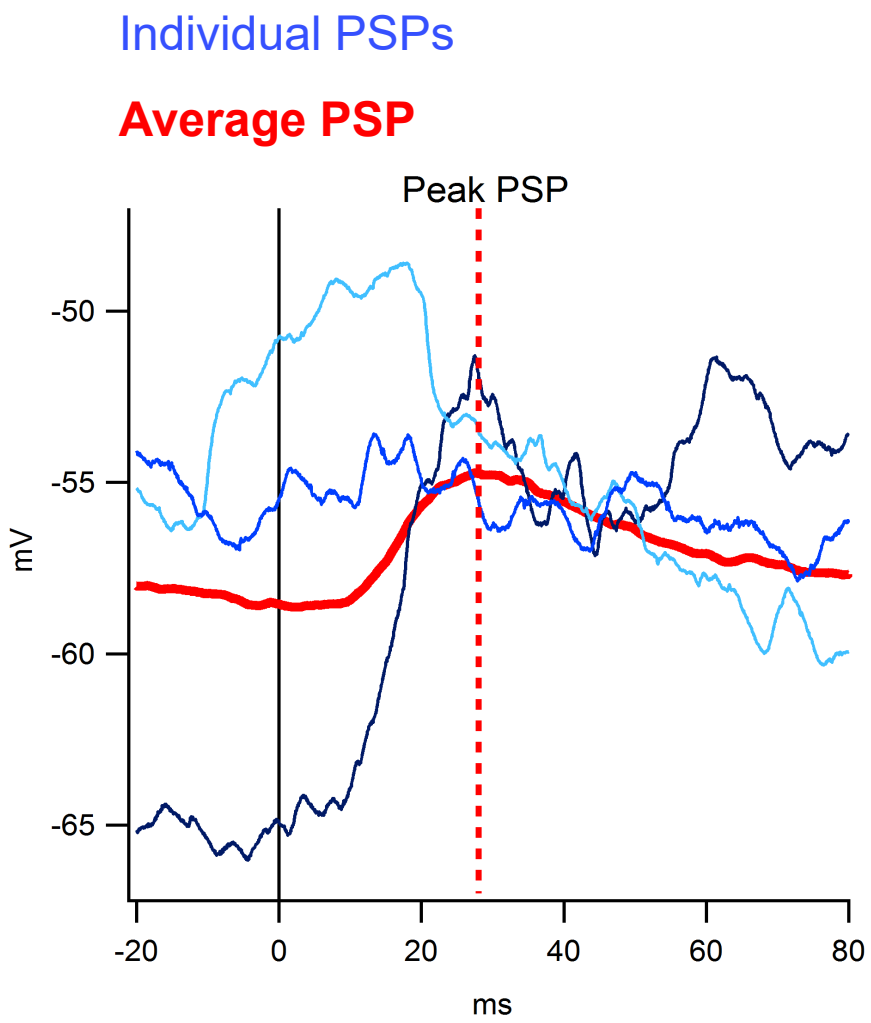
▪ Variable evoked responses to active touch

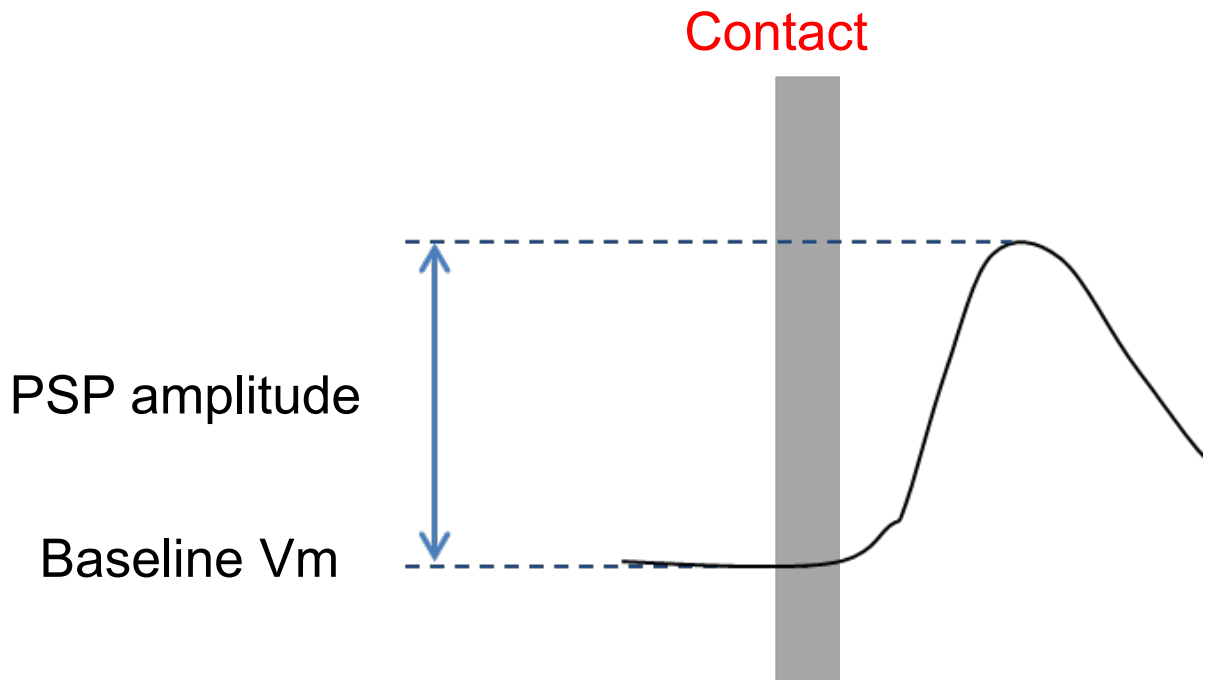
Example of individual postsynaptic potentials (PSPs) evoked by contact



=> Individual PSPs converge to a fixed-point of the Vm

Variable evoked responses to active touch

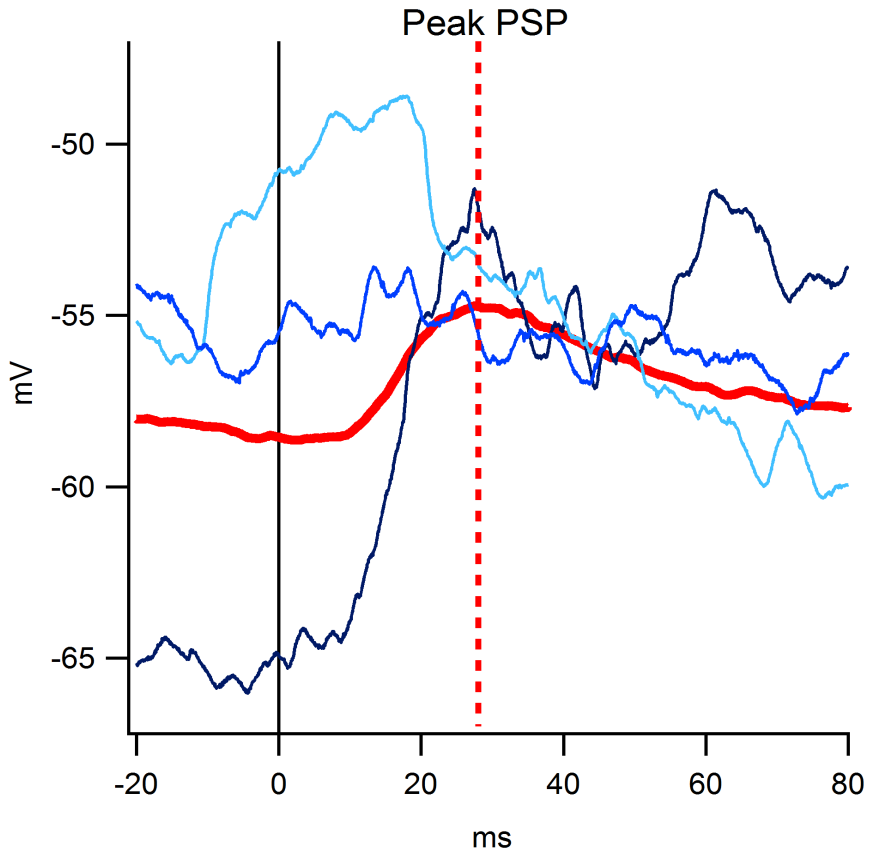




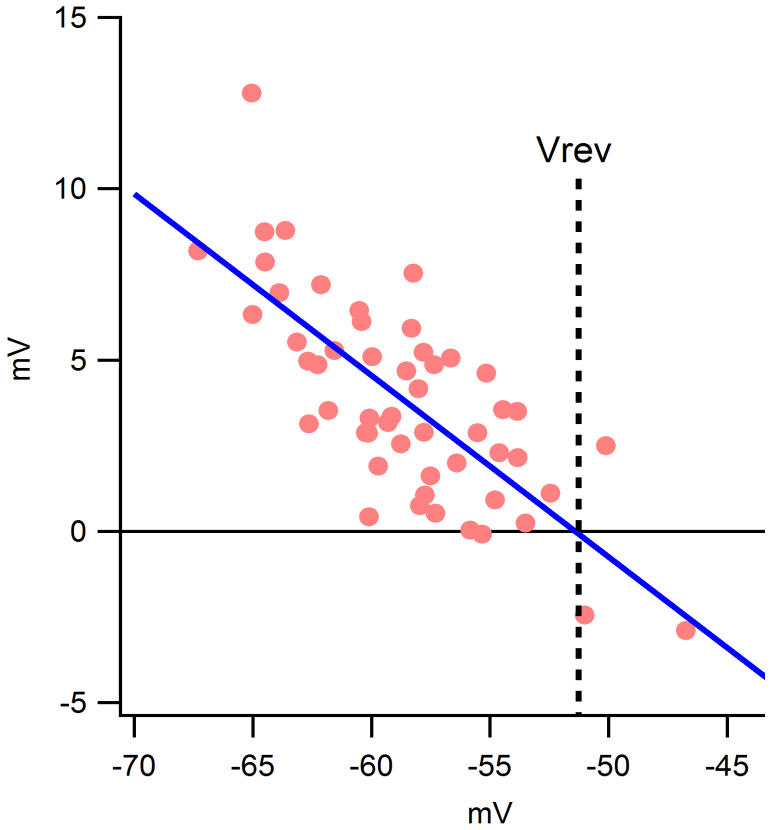
Reversal potential of the sensory evoked response

Individual PSPs

Average PSP



PSP amplitude vs Baseline Vm

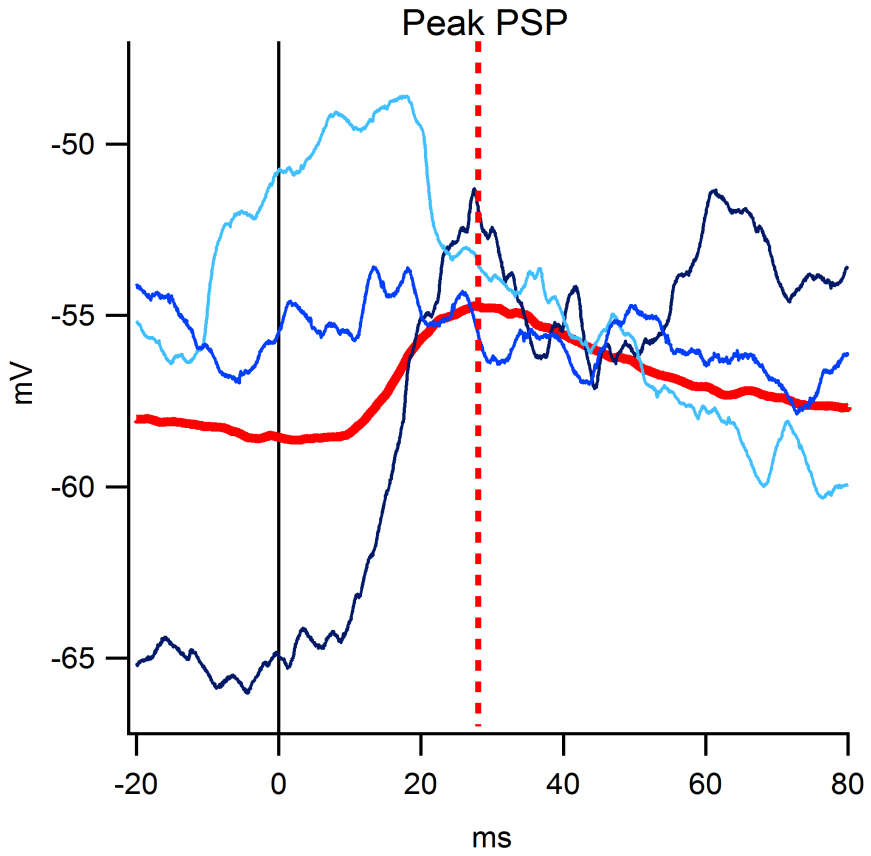


=> Negative V_{rev} of the PSP

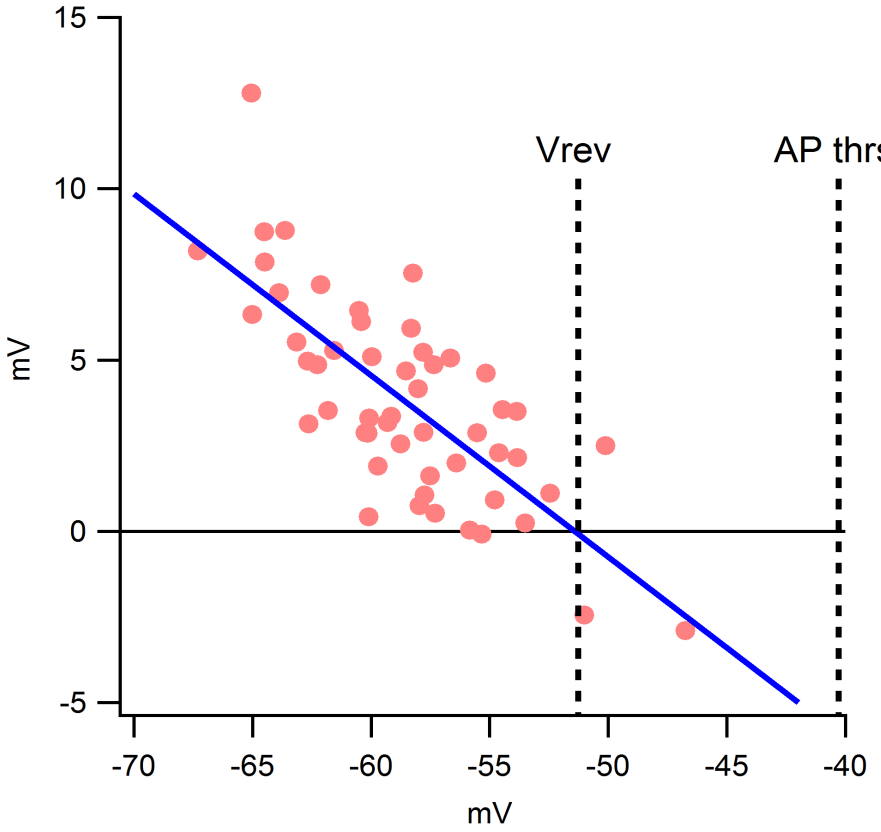
Reversal potential (V_{rev}) of the sensory evoked response

Individual PSPs

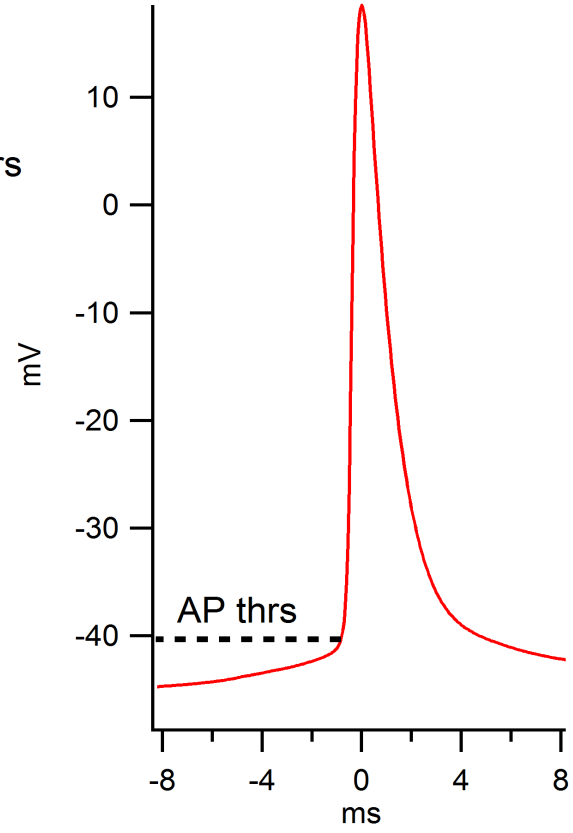
Average PSP



PSP amplitude vs Baseline Vm

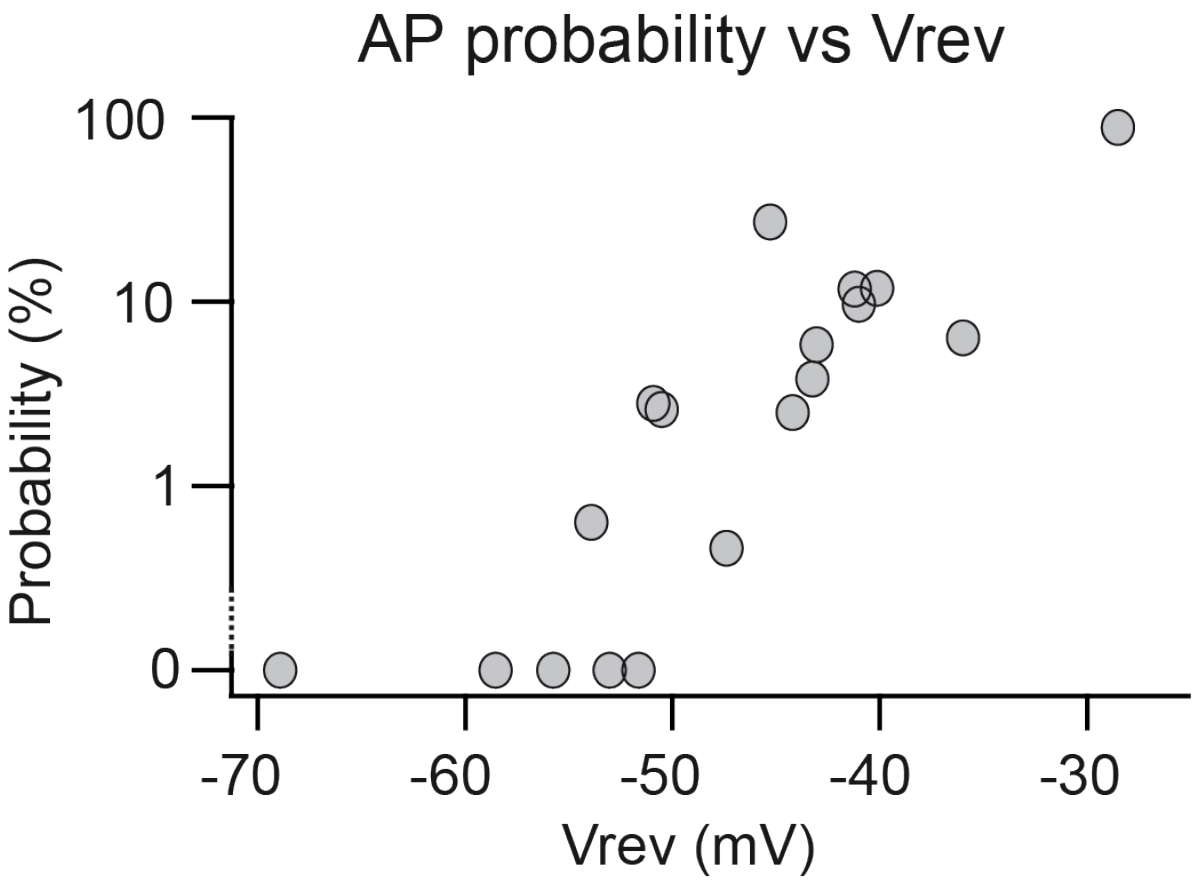


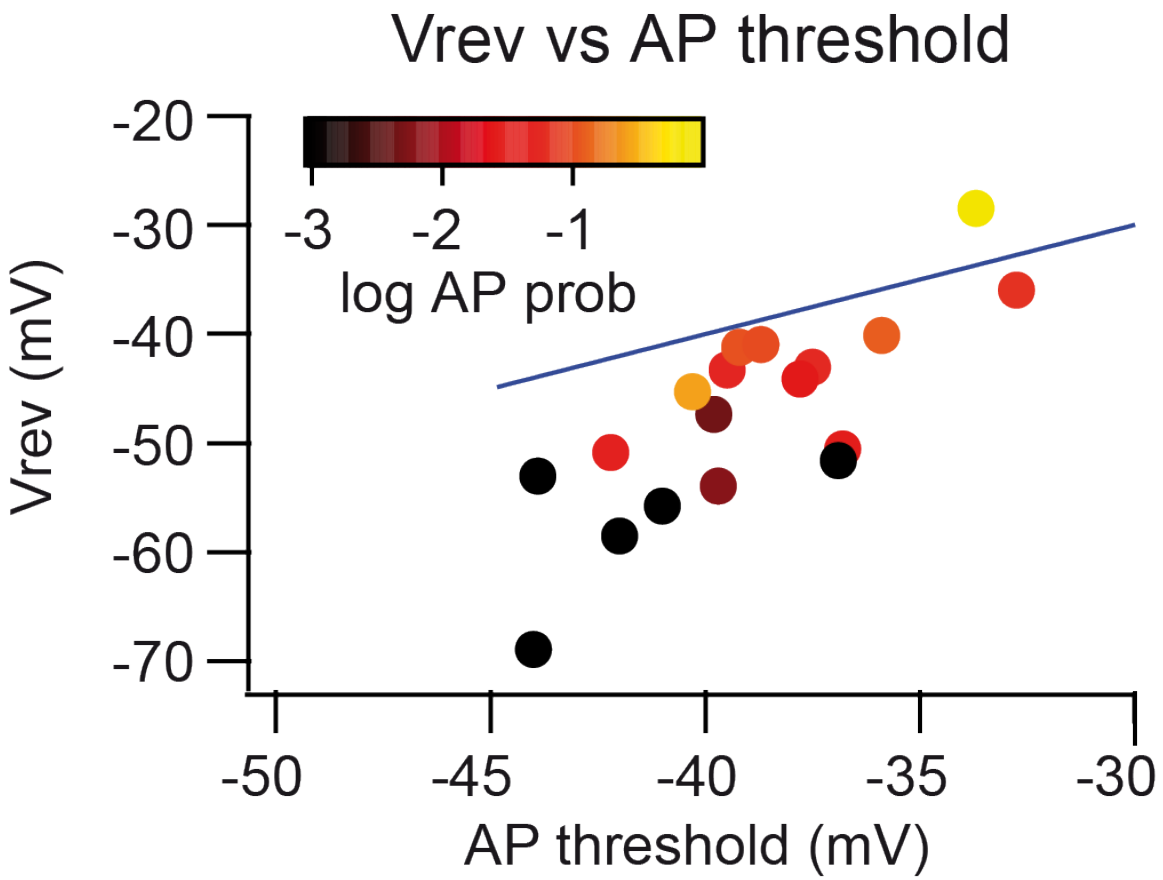
AP Threshold



=> Negative V_{rev} of the PSP

▪ V_{rev} of the evoked response accounts for AP probability



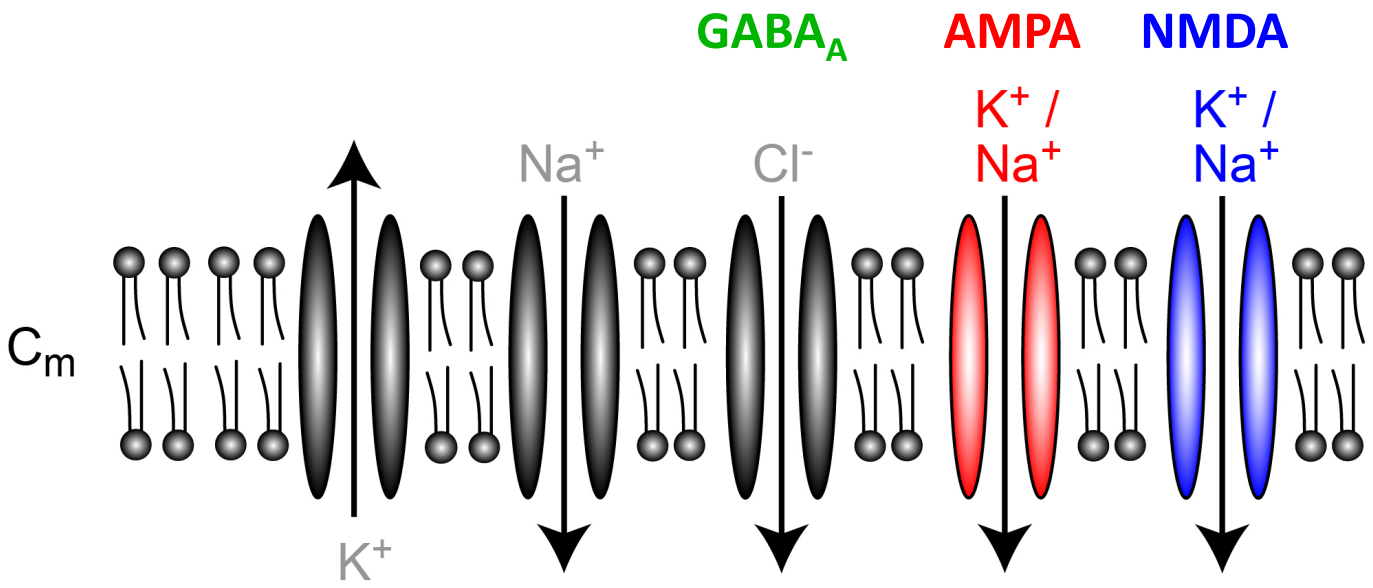


=> V_{rev} of individual cell correlates with AP firing probability

(Crochet et al., Neuron 2011)

▪ Cortical inhibition mediates sparse response

Synaptic Inputs => Inhibition (GABA) Excitation (Glutamate)



E_{rev} $GABA_A$ ~ -80 mV

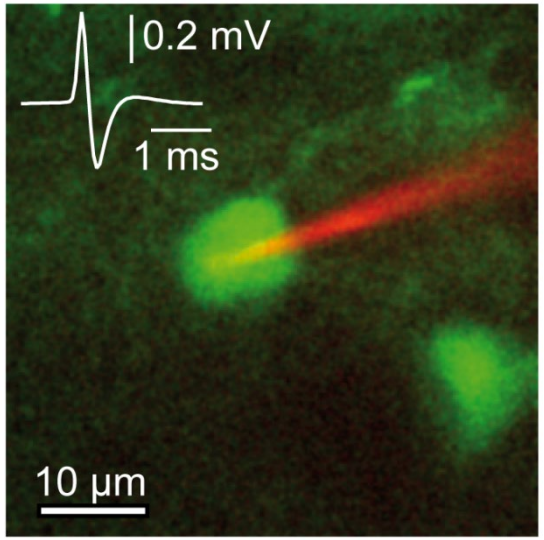
E_{rev} AMPA ~ 0 mV

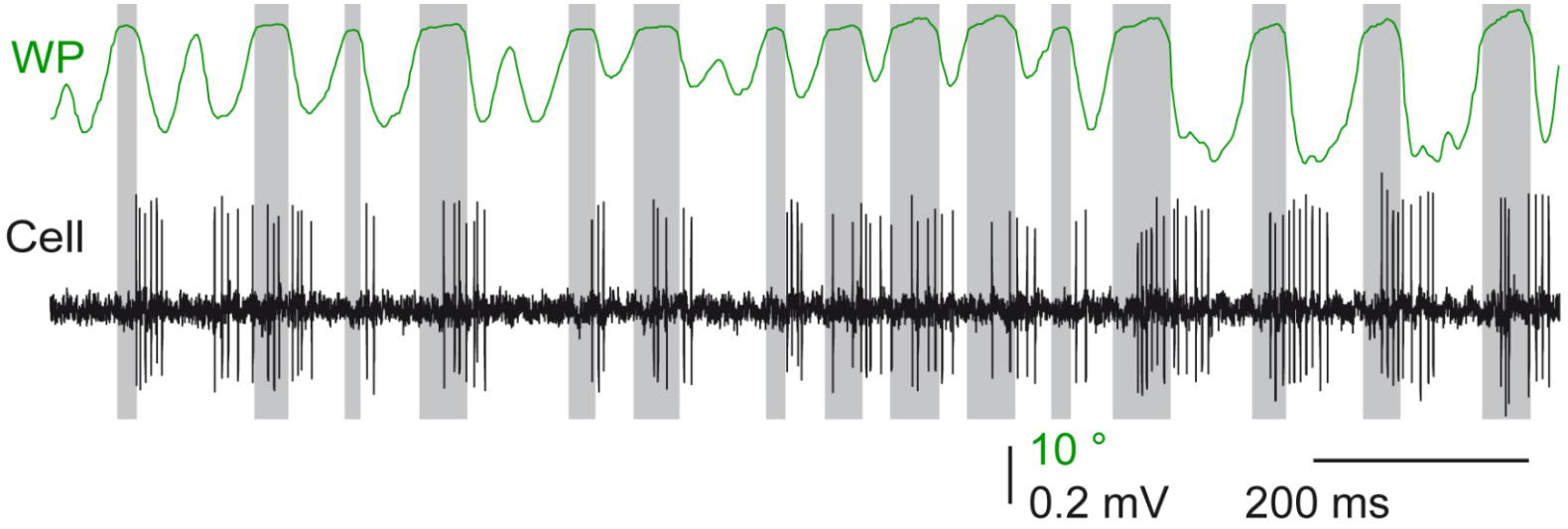
E_{rev} NMDA ~ 0 mV

=> Negative V_{rev} of the PSP implies contribution of inhibition

Cortical inhibition mediates sparse response

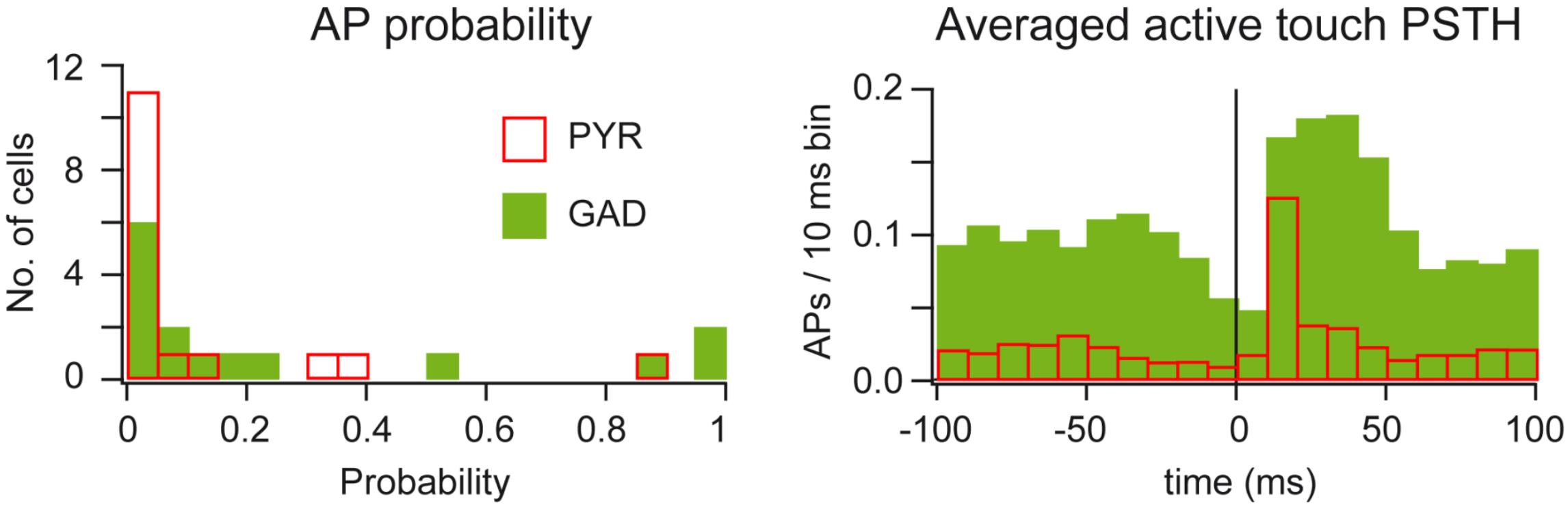
Targeted juxtacellular recording in GAD67-GFP knockin mouse





(Crochet et al., Neuron 2011)

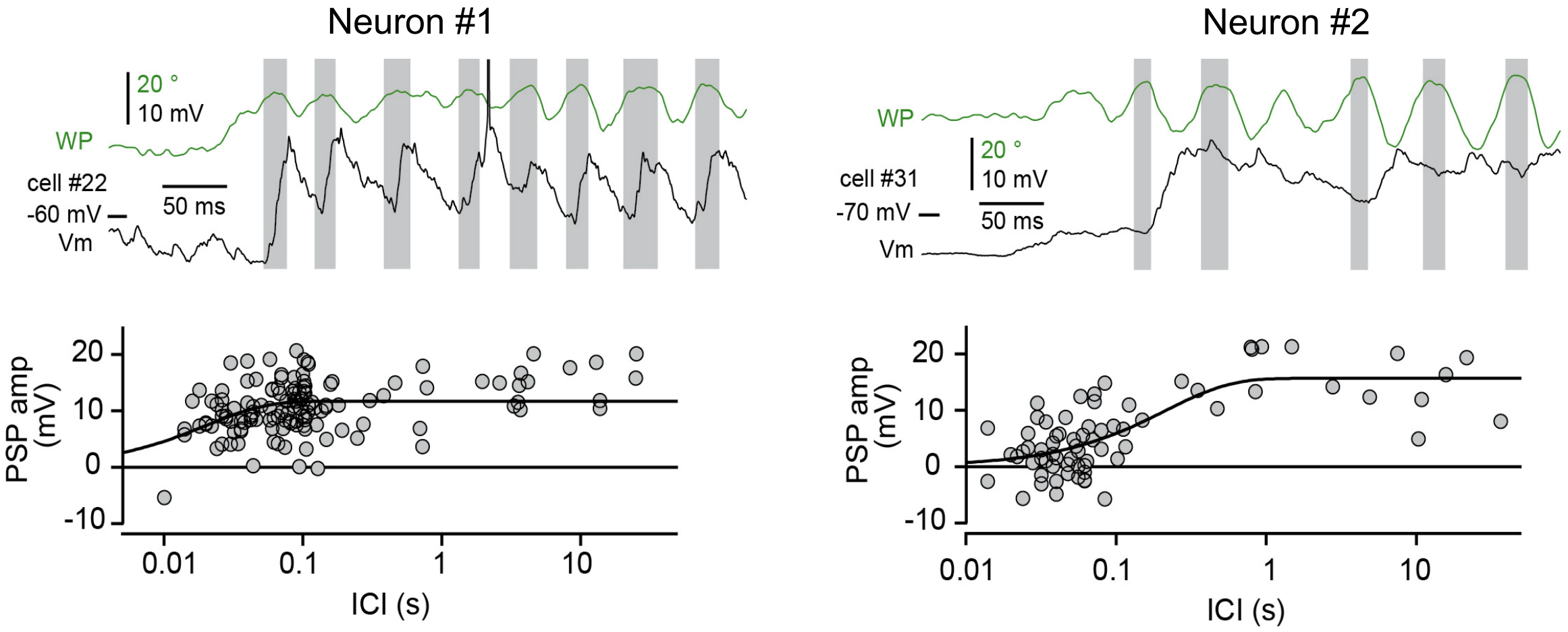
Cortical inhibition mediates sparse response



(Crochet et al., Neuron 2011)

=> GABAergic neurons fire more reliably in response active touch than EXC neurons

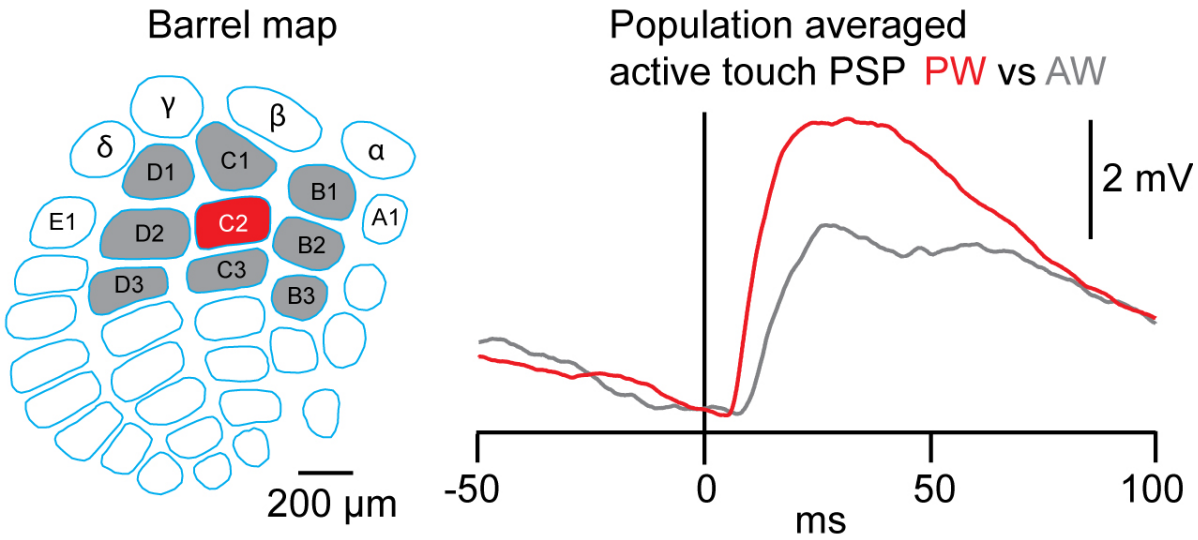
Short-term dynamics

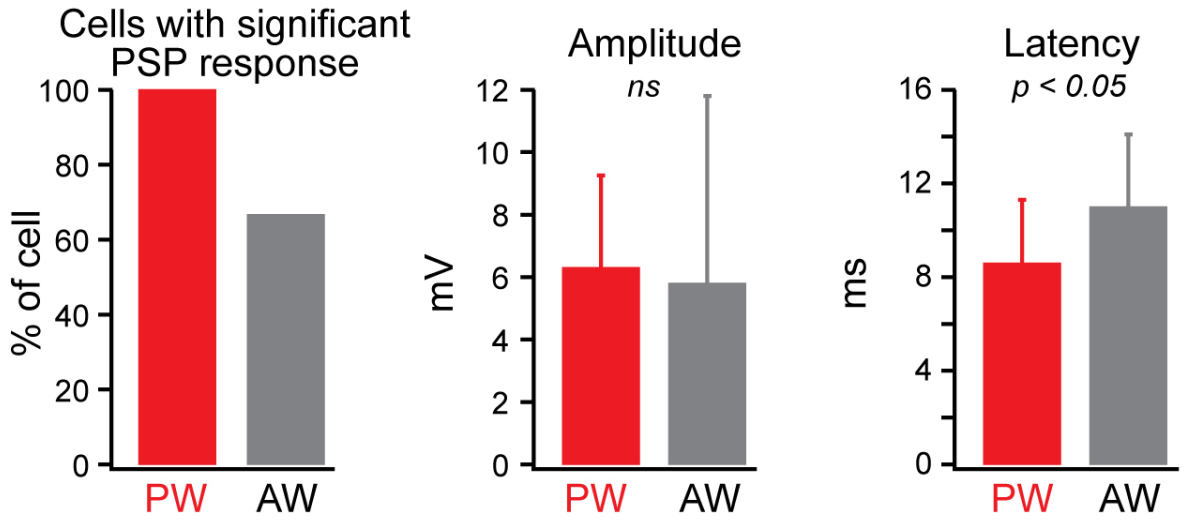


(Crochet et al., Neuron 2011)

=> EXC neurons have different short-term dynamics in response to succesive active contacts

Principal vs surrounding cortical columns





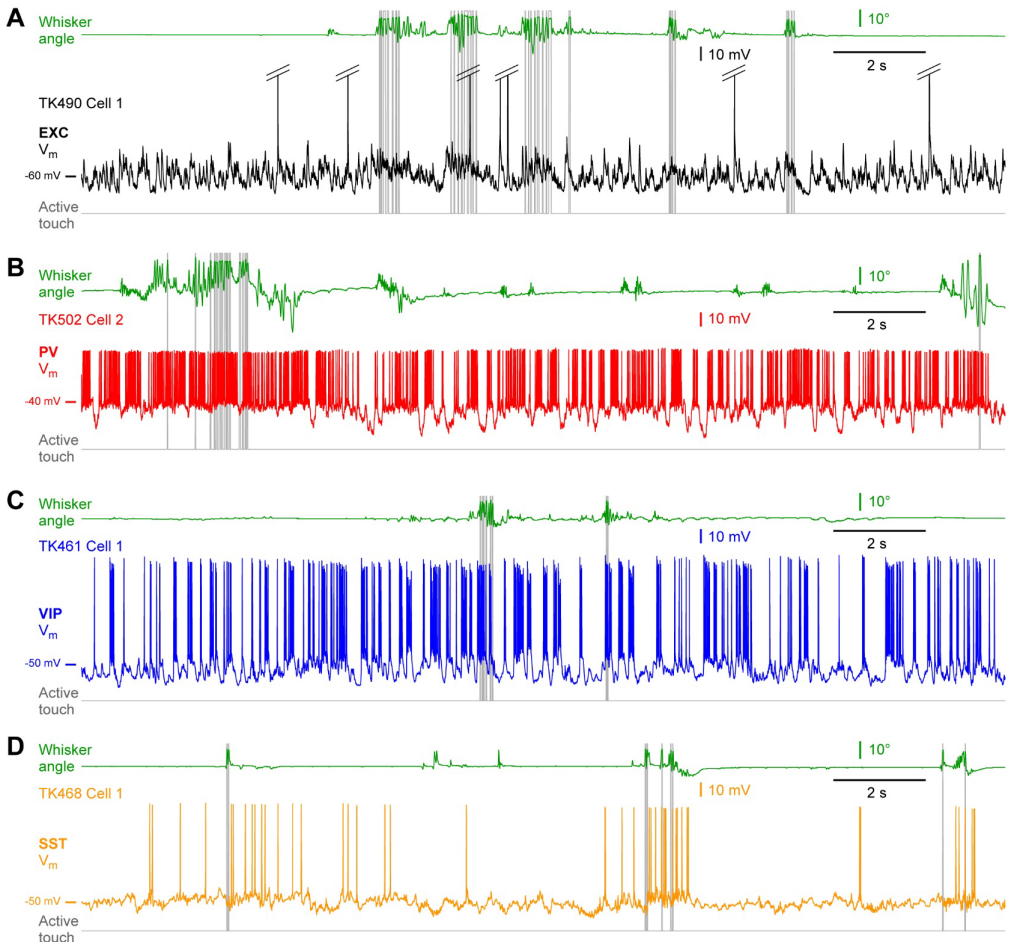
=> Decreased response probability and longer latencies in surrounding vs principal cortical columns

(Crochet et al., Neuron 2011)

Active touch responses in different cell-types

New study – Kiritani et al., PLOS One 2024

- Also active touch



(Kiritani et al., PLOS one 2024)

=> BIO482 Miniproject:

Learn more about active touch responses in different cell-types by yourself

QUESTIONS ?