EPFL

# BIO-482 Neuroscience. Cellular and Circuit Mechanisms

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

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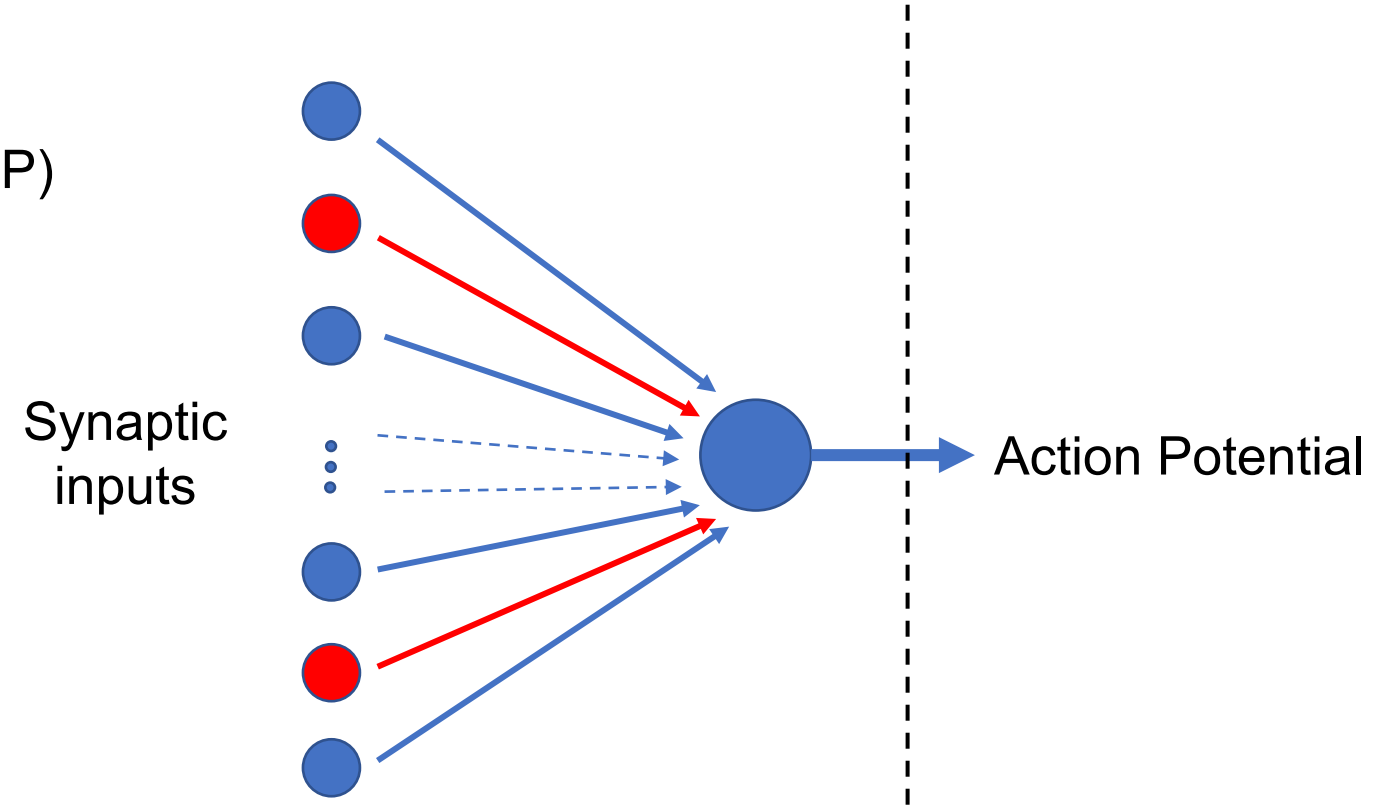
# Cortical neurons as synaptic integrators

Cortical Neurons:

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

*Synaptic inputs*
*=> Subthreshold Activity*

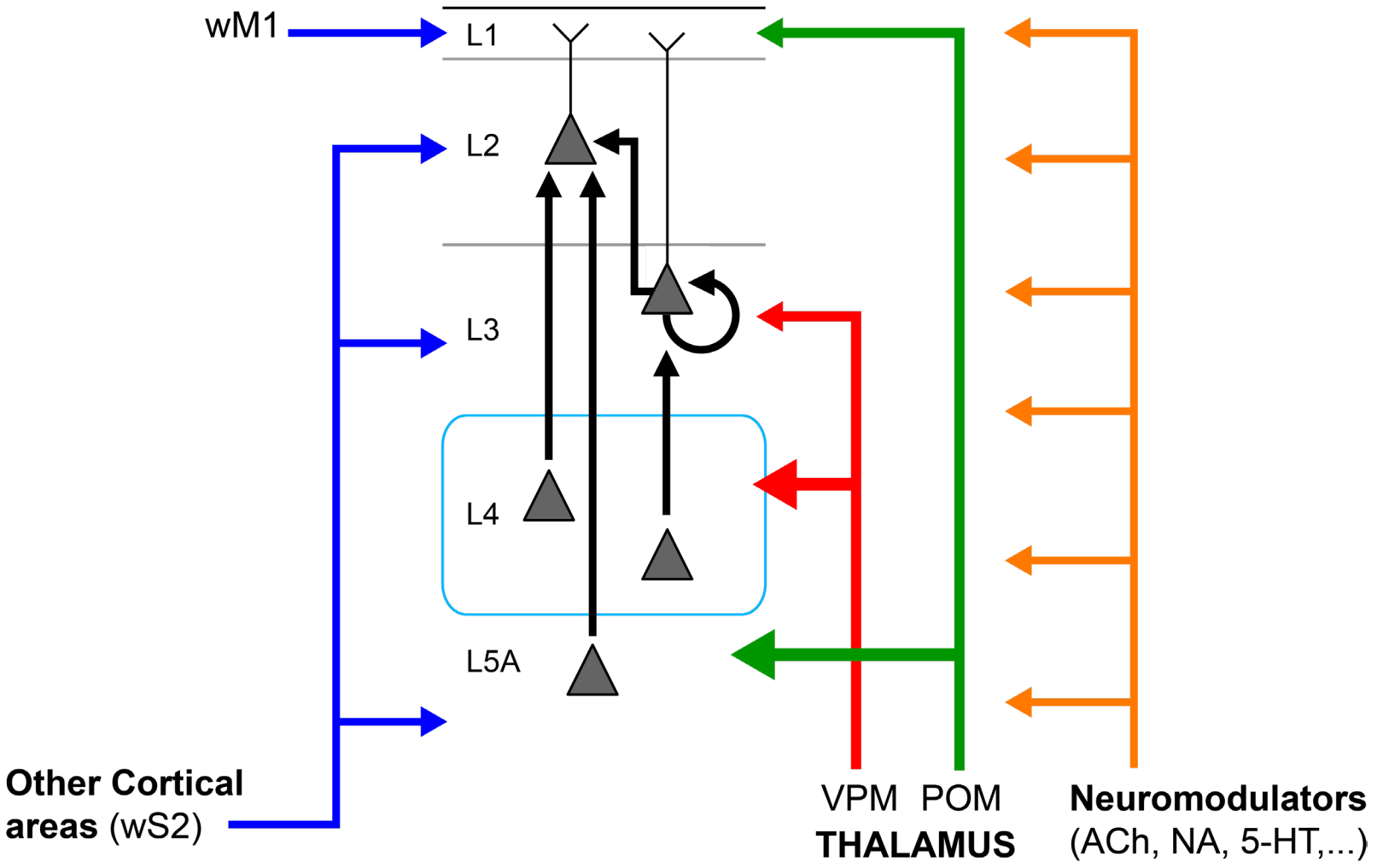
*Action potential output*
*=> Suprathreshold Activity*

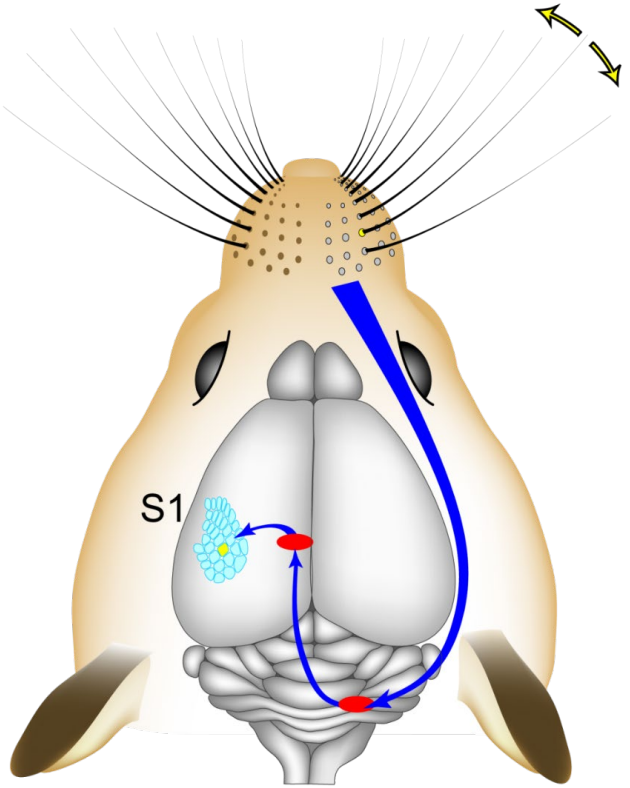



**Synaptic integration**

**Neuronal Coding**

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

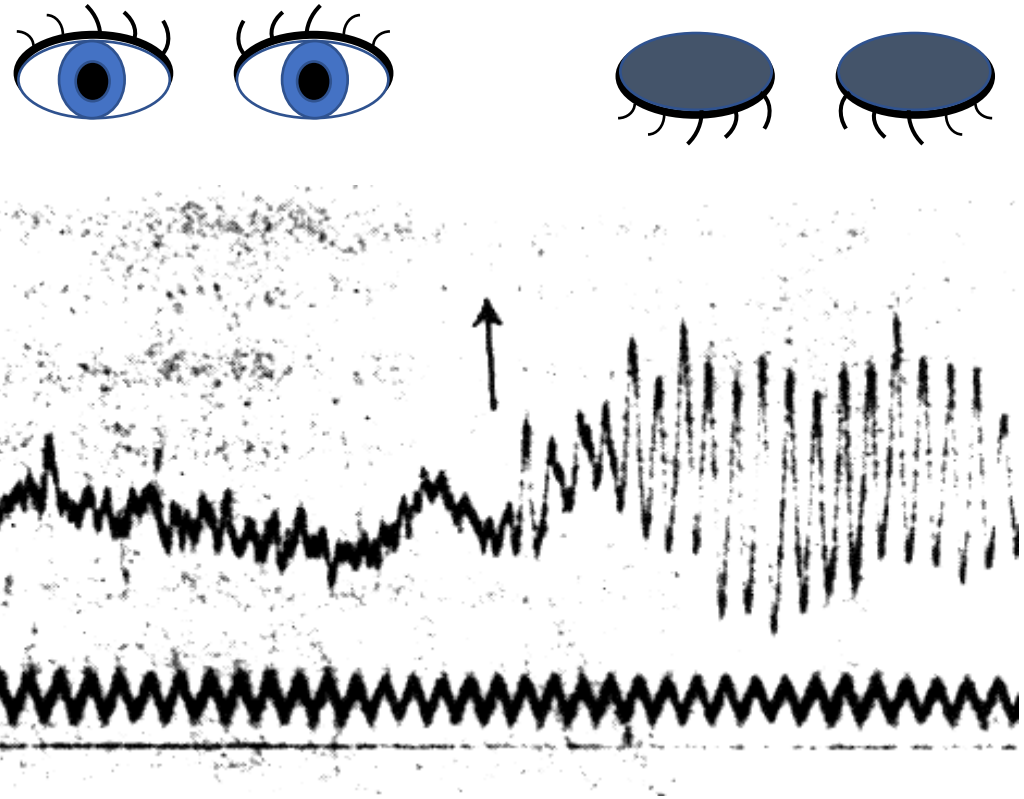


# 1. Cellular mechanisms underlying cortical state changes in awake mice

# At the origin of *cortical states*

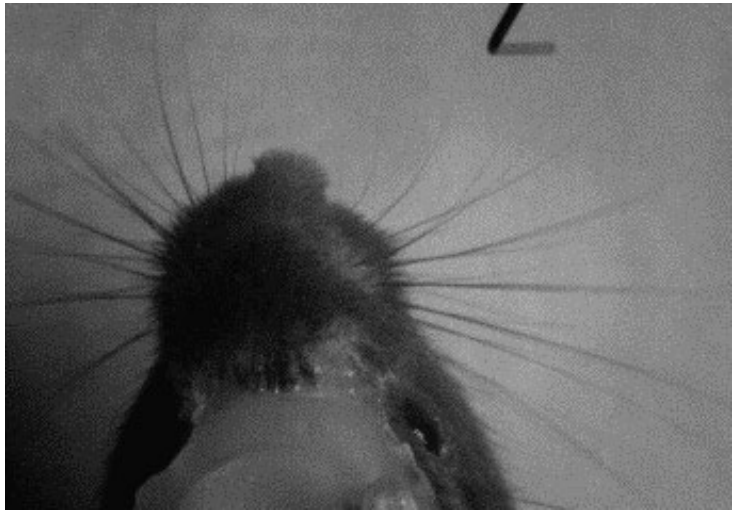
Cortical states are usually defined by the spontaneous activity of the cortical network

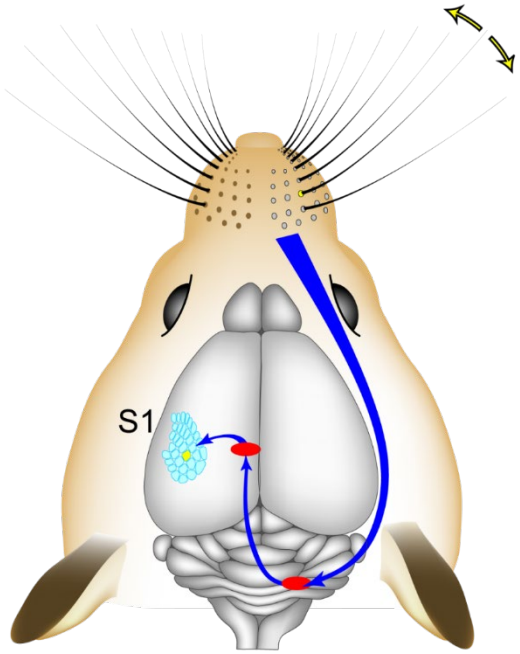



*(Hans Berger, 1929)*

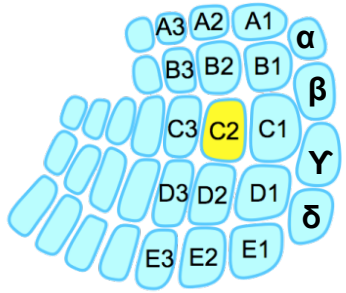
**First demonstration of cortical state change correlated with behavior**

# Experimental model






**Cortex**



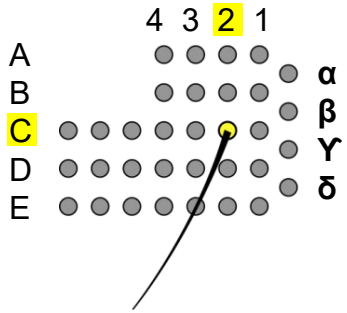

Primary somatosensory area (wS1) ***"Barrel cortex"***

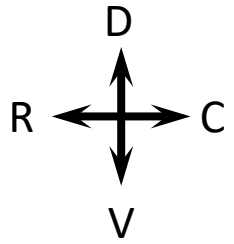
**Thalamus** VPM/POM

**Brainstem** Trigeminal nuclei

Whiskers

**Periphery**

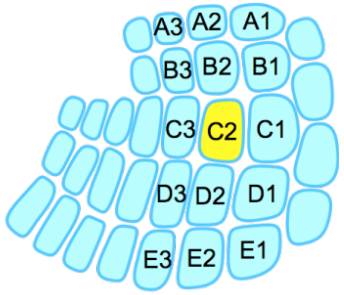


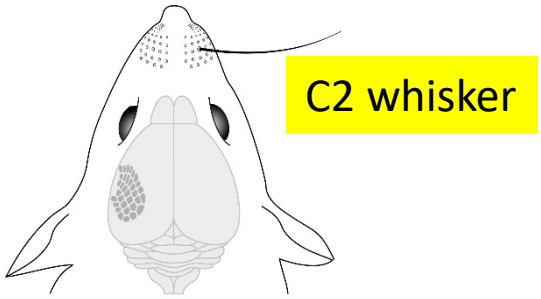
# Experimental model

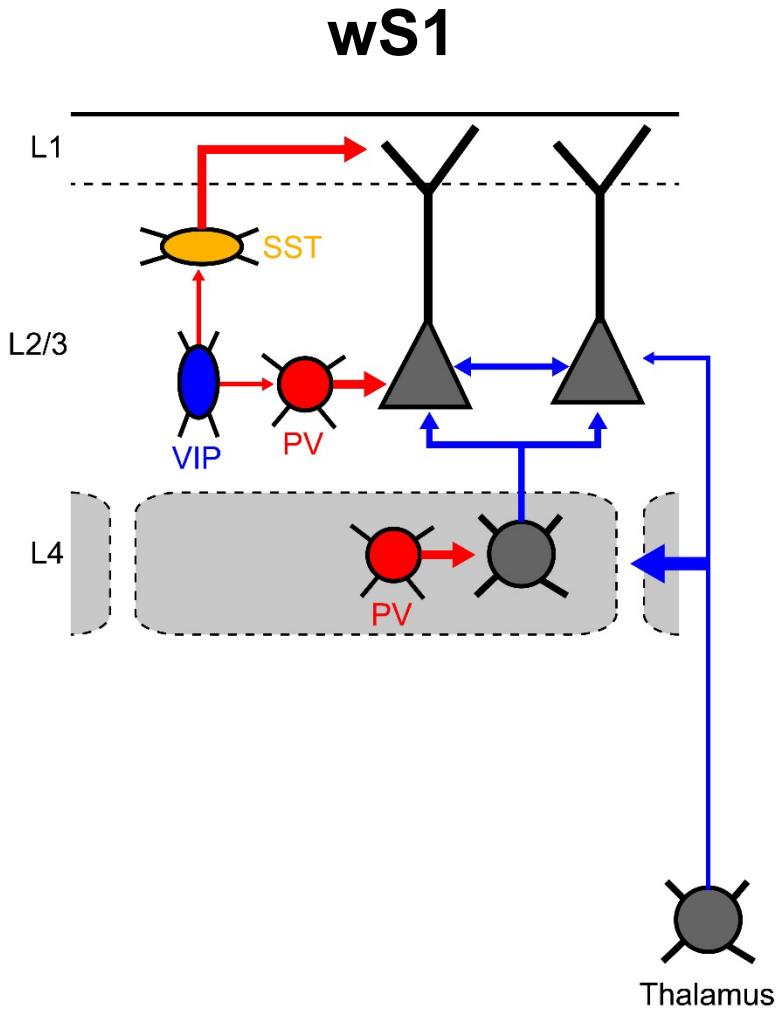
Primary somatosensory area (wS1) ***"Barrel cortex"***

**Cortex**




**Thalamus** VPM/POM



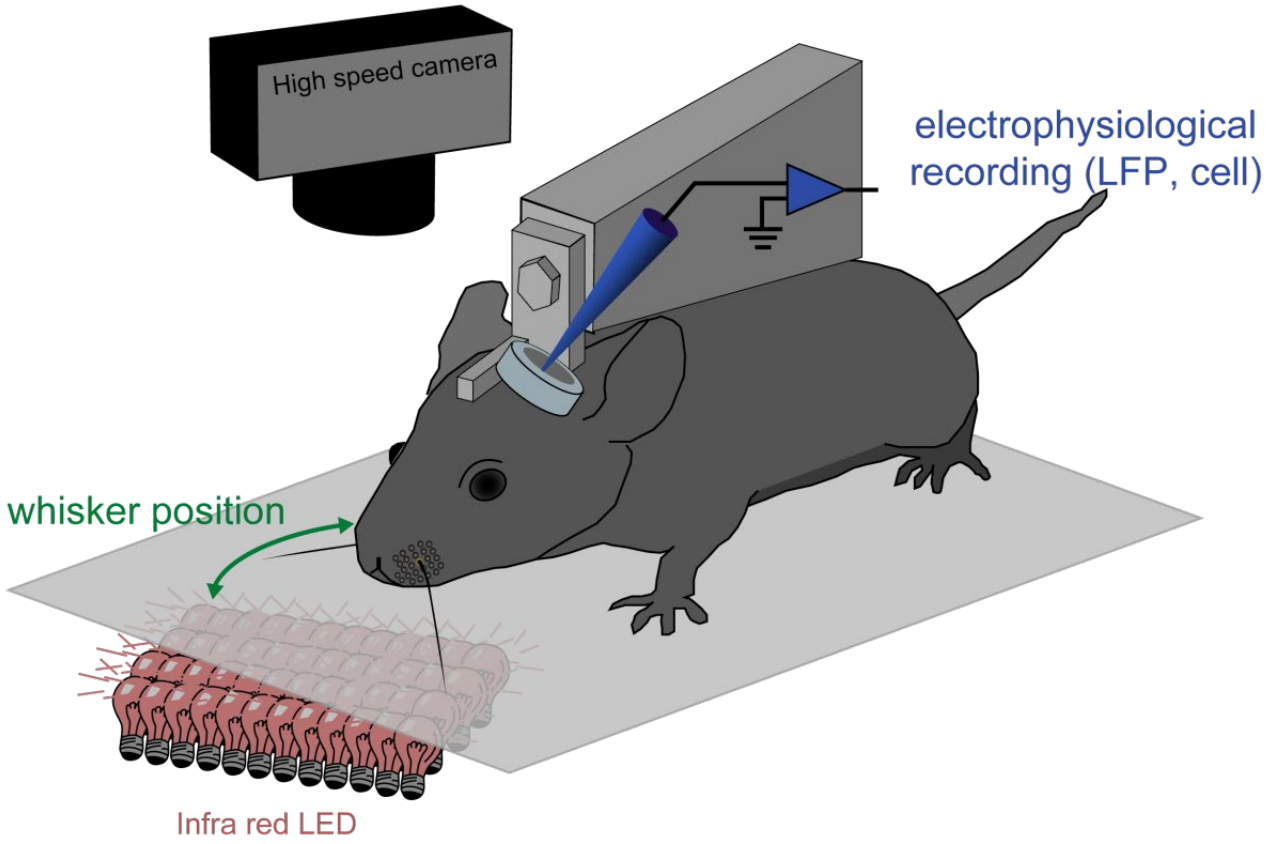




Excitatory cells (Glutamate)

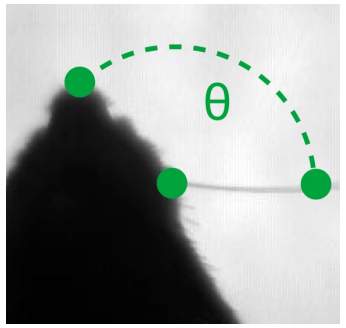
Inhibitory interneurons (GABA):

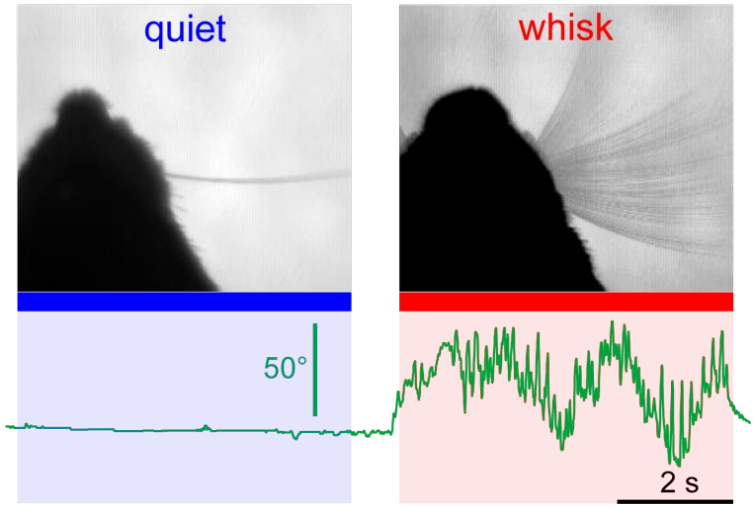
- Parvalbumine (PV)
- Vasointestinal peptide (VIP)
- Somatostatin (SST)

# ▪ Membrane potential (*Vm*) recording in awake mice

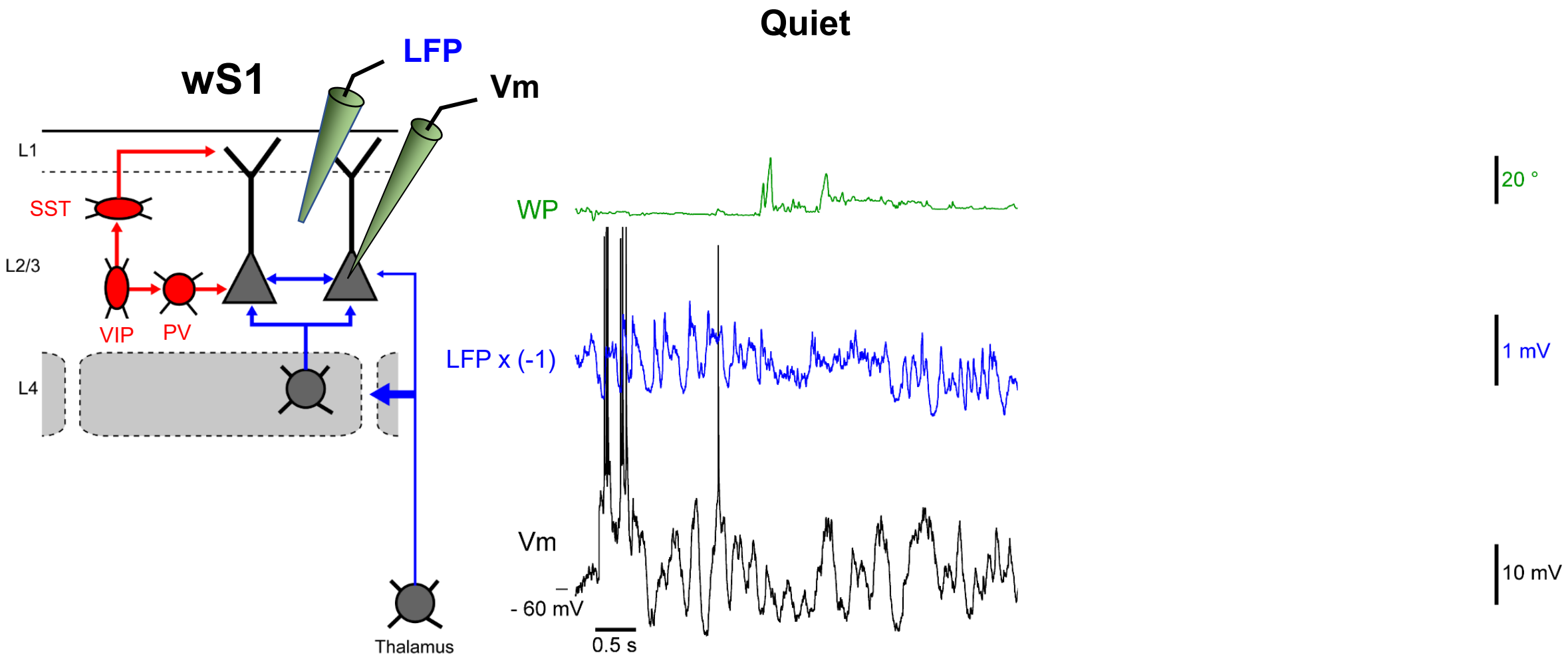



Whisker
Position (WP)

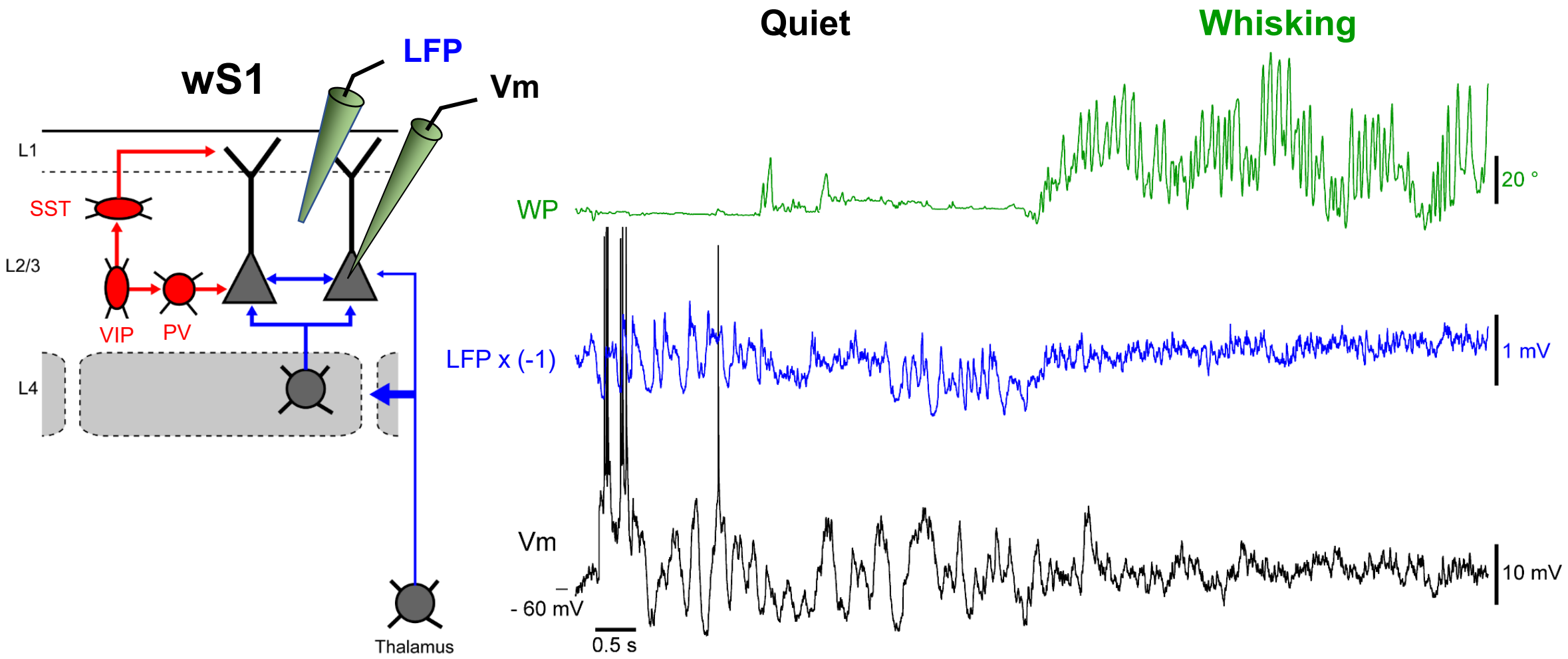


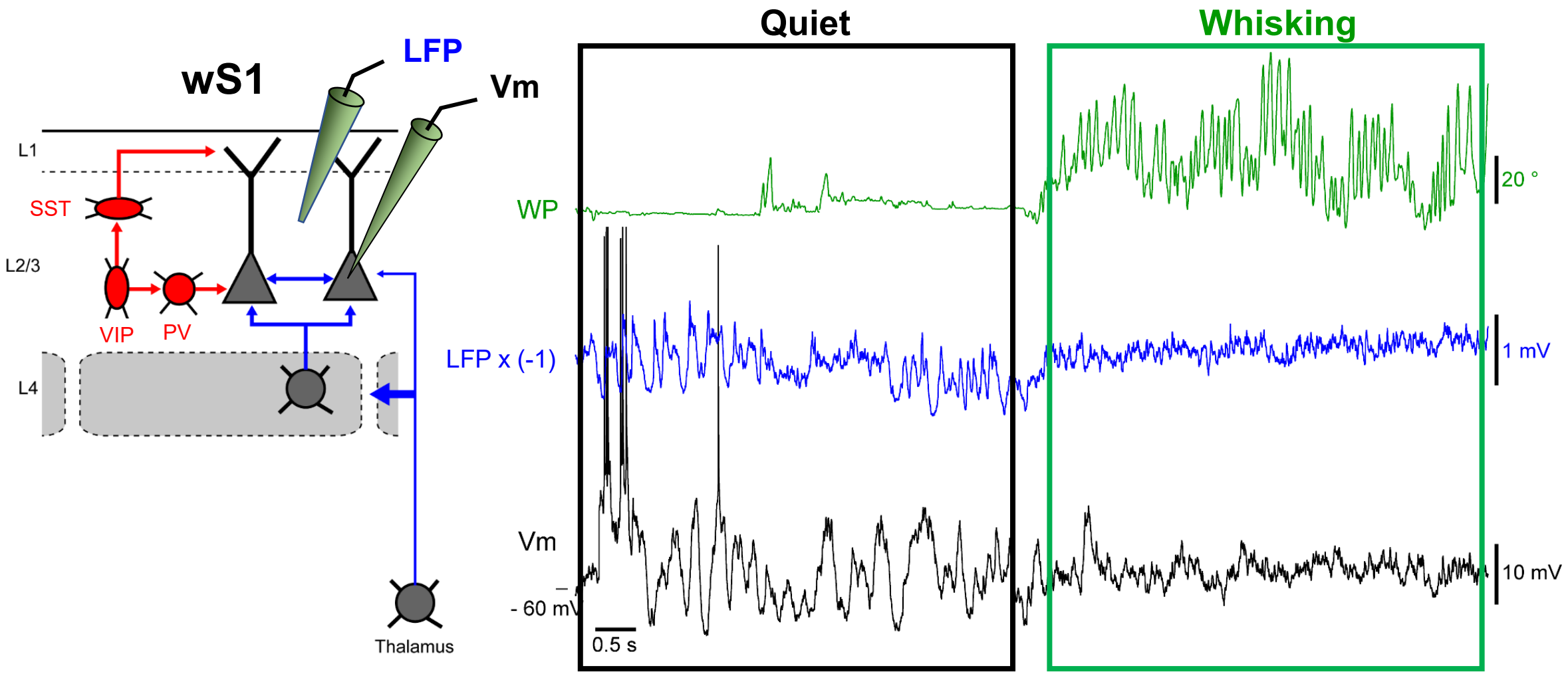
# State change in wS1



# State change in wS1

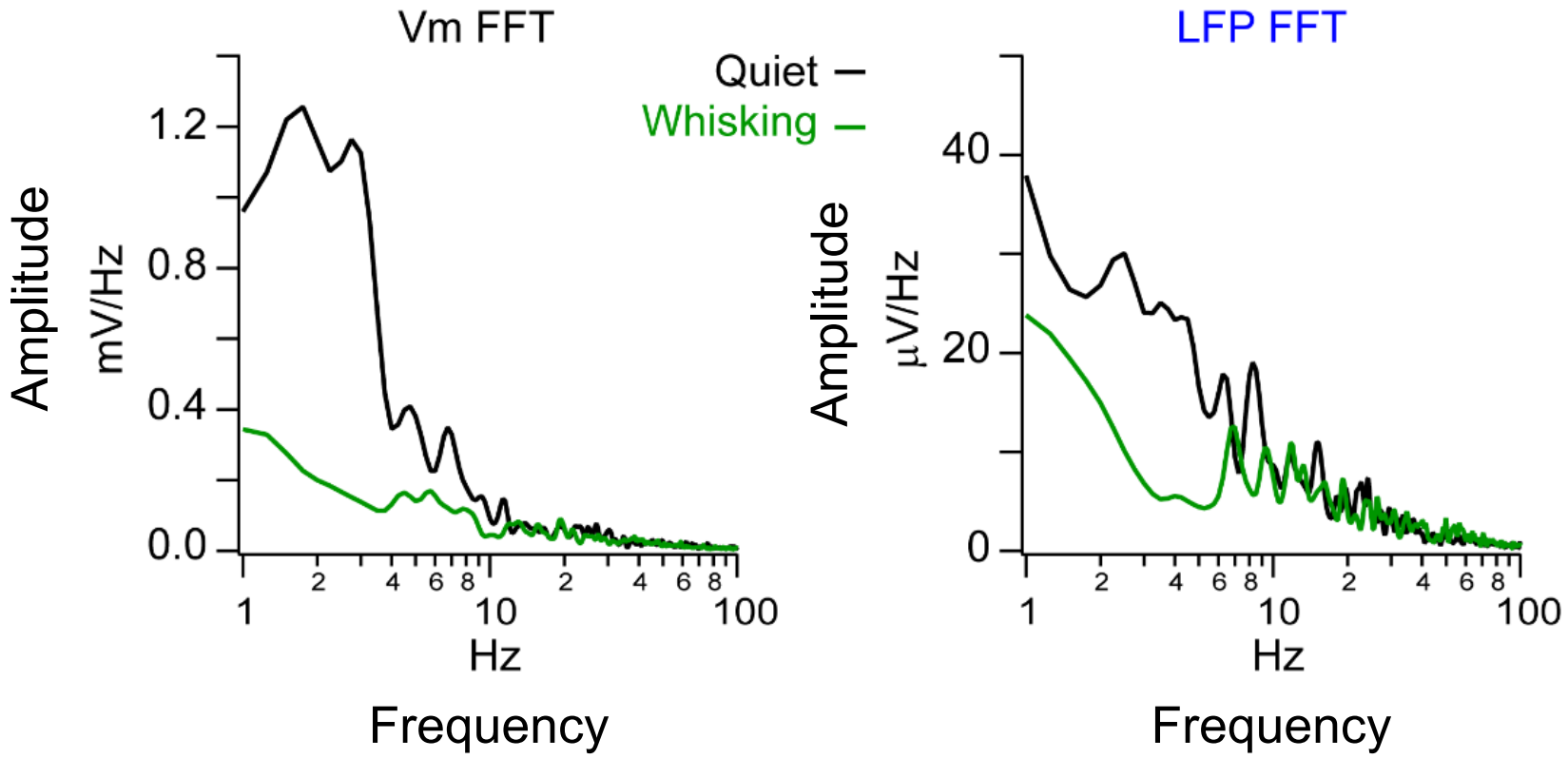


# State change in wS1



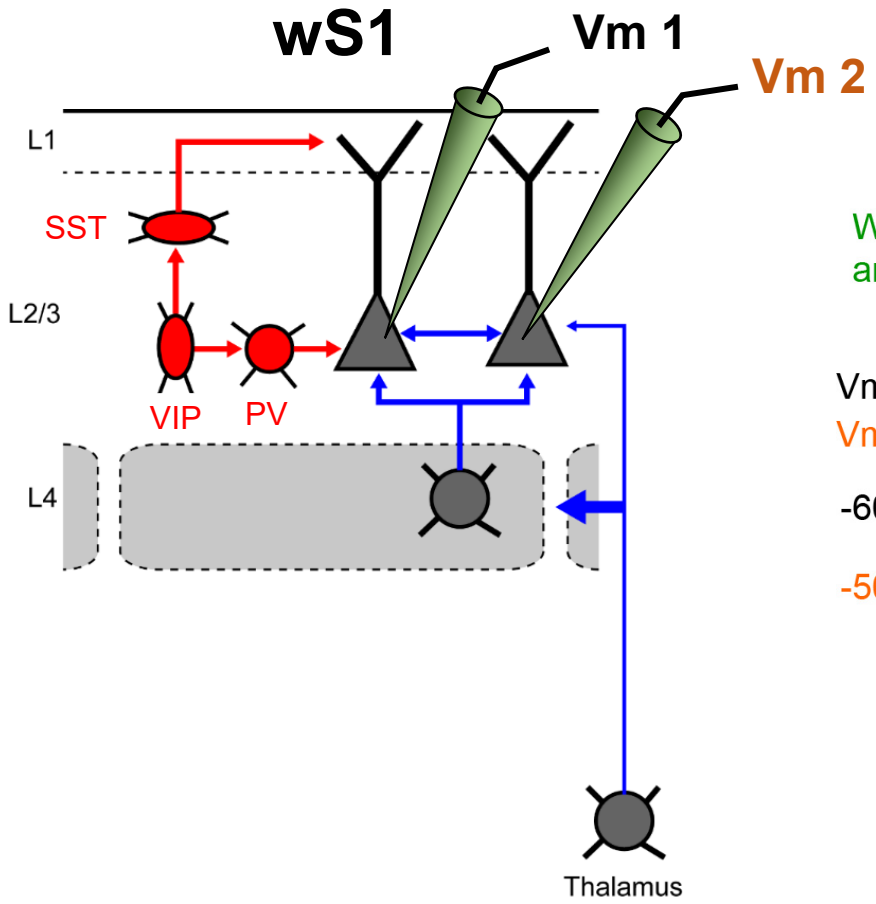
# State change in wS1

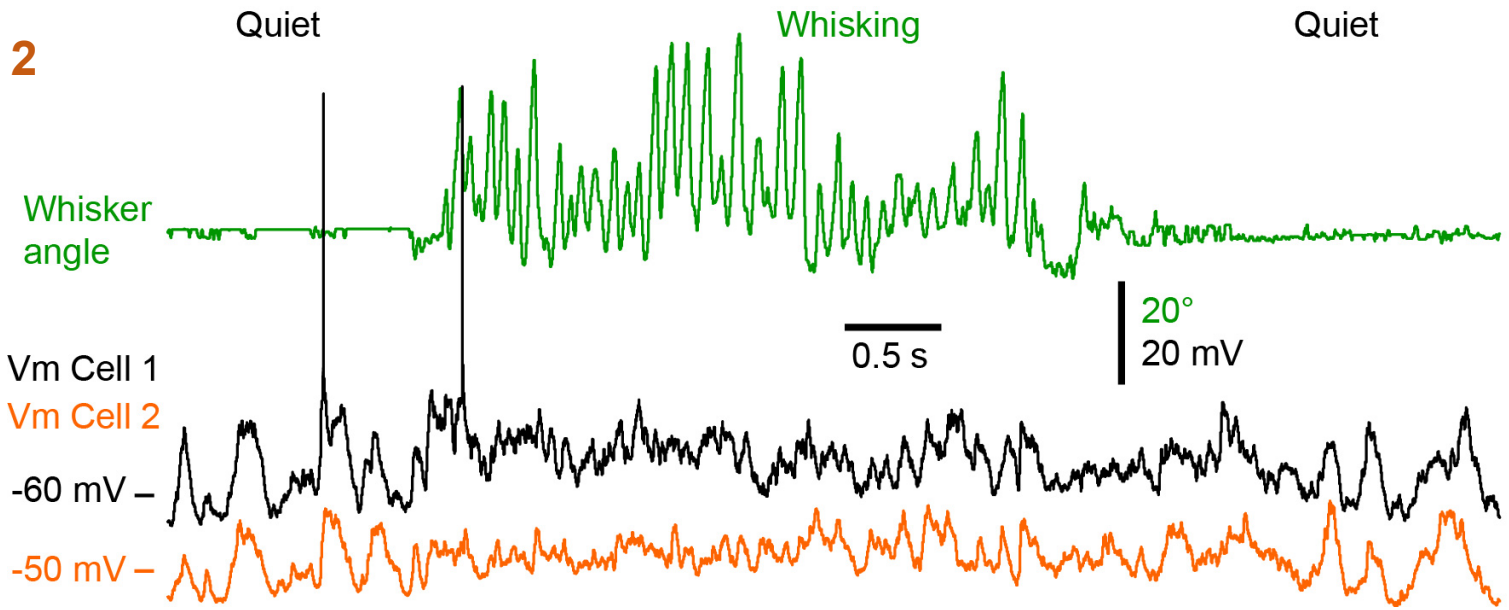
Fast-Fourier Transform => frequency domain



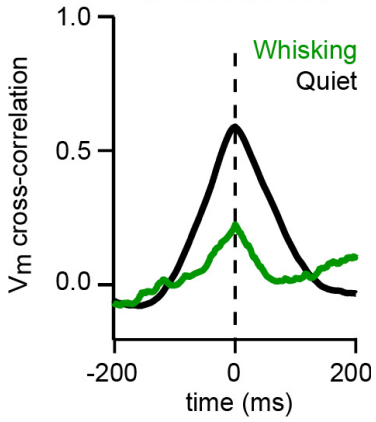

**=> Decrease in low-frequency (1-10 Hz) activity during whisking**

# State change in wS1




Vm-Vm cross-correlograms




*(Poulet and Petersen, Nature 2008)*

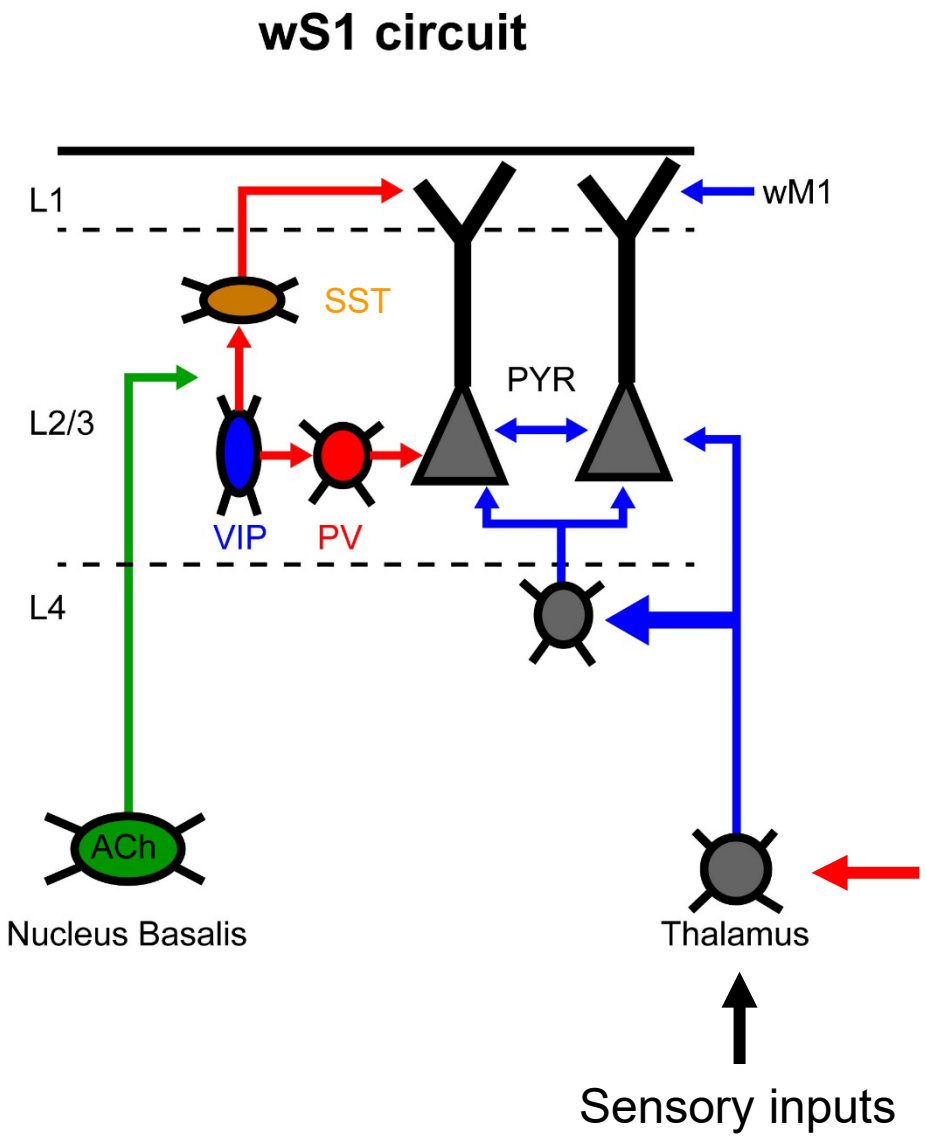
# State change in wS1

**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)*

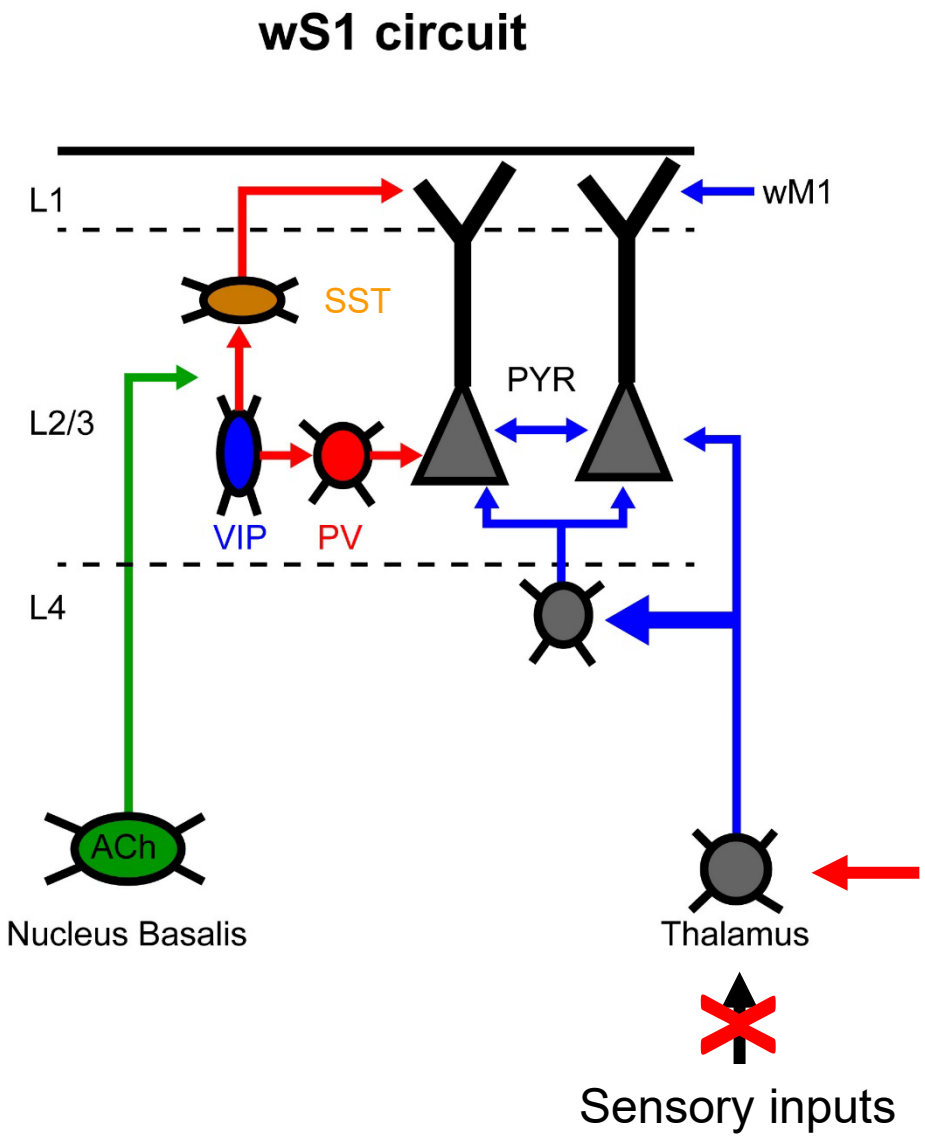
# The origins of state change in wS1




**What are the possible origins of the state change?**

Modulatory inputs
Brainstem (ACh, NA …)

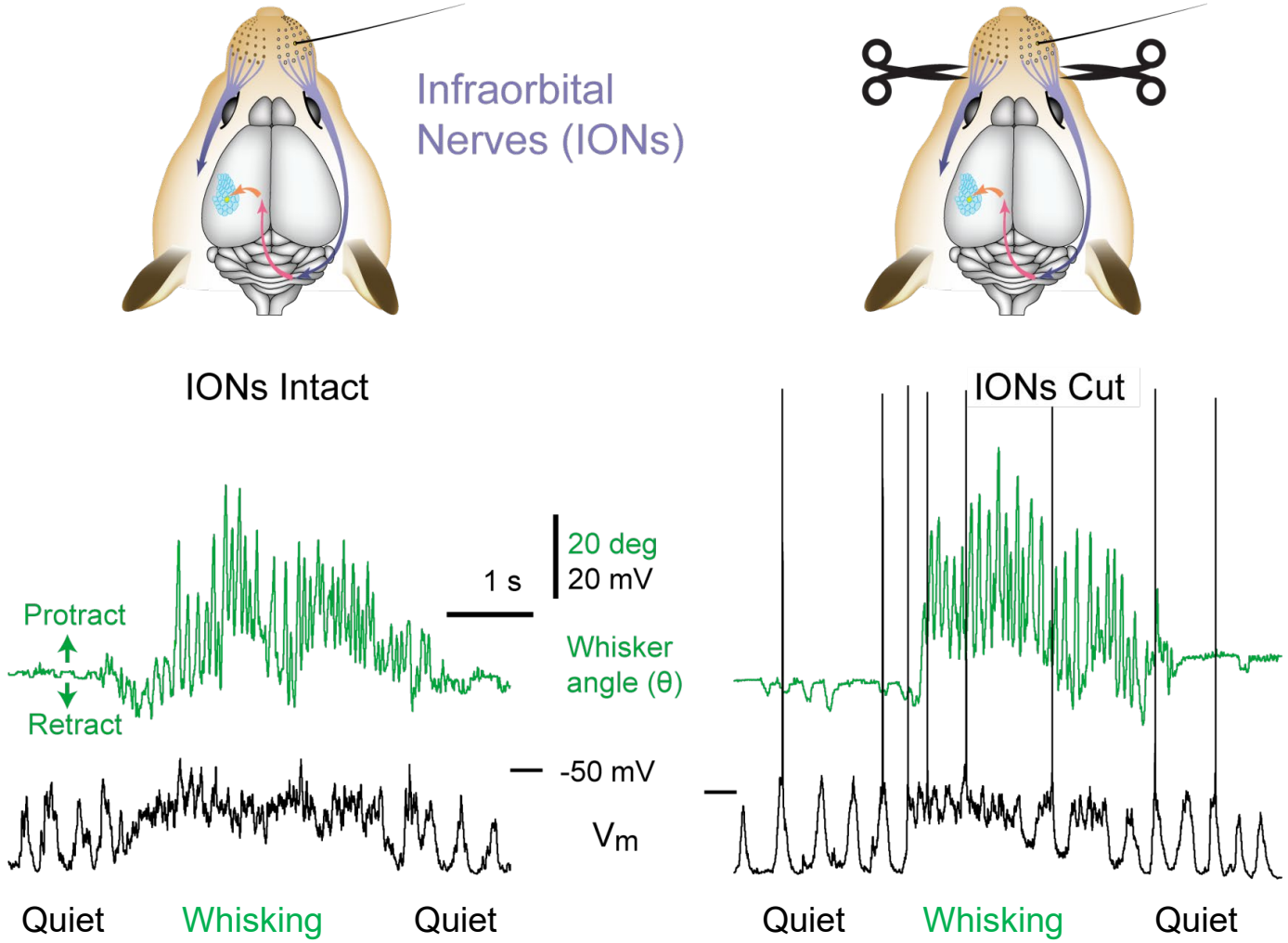
# The origins of state change in wS1




**What is the contribution of sensory inputs?**

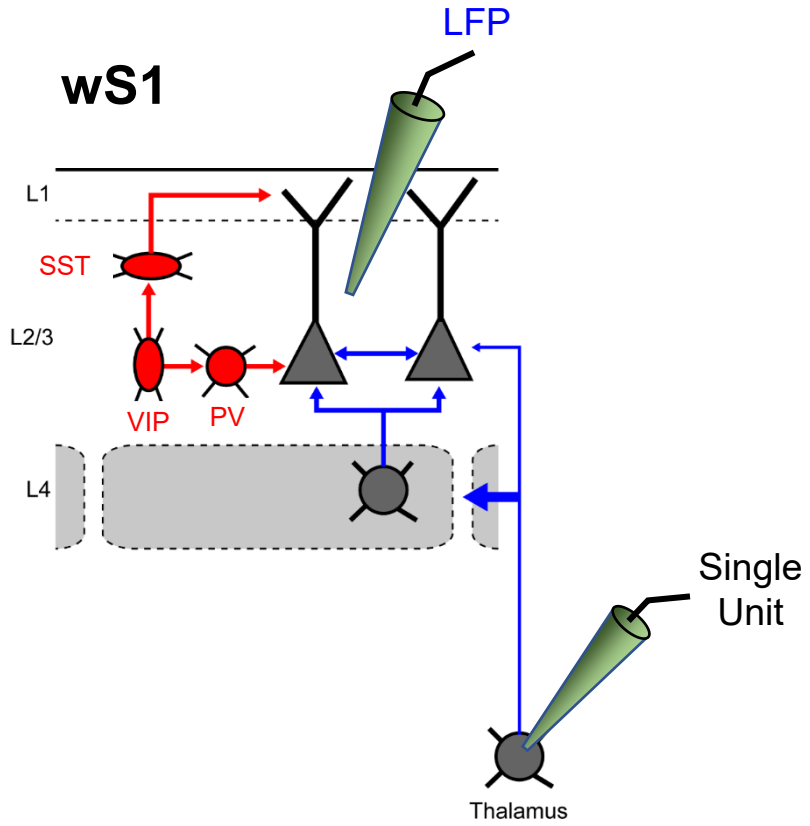
Modulatory inputs
Brainstem (ACh, NA …)

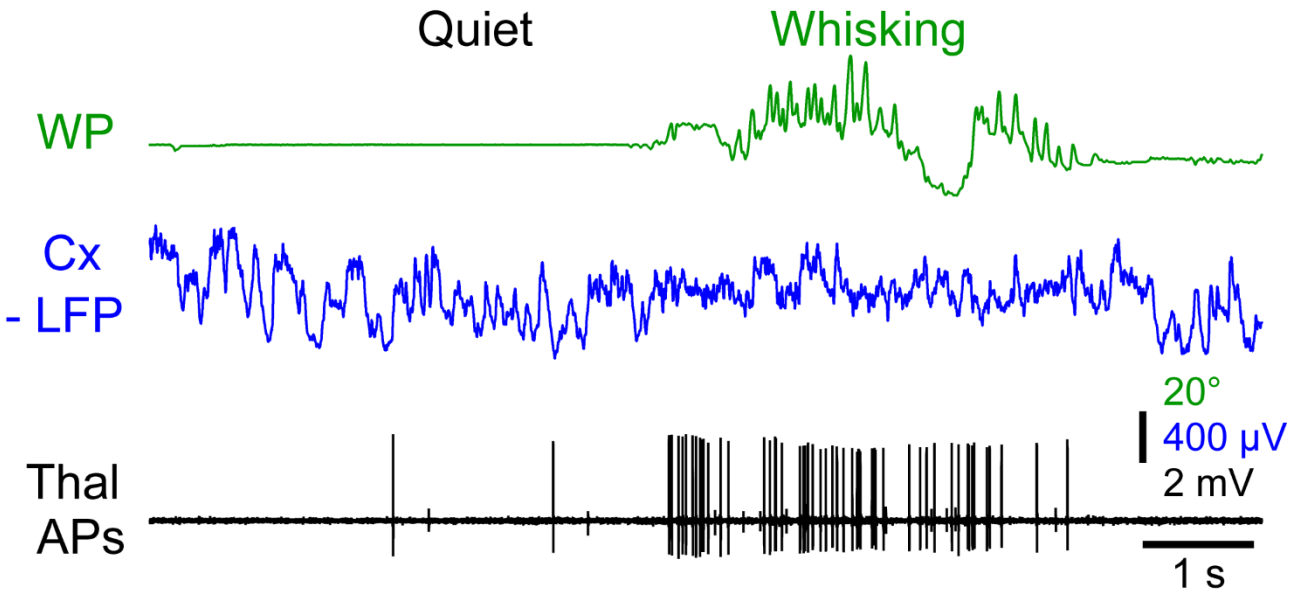
# State change in wS1 is centrally generated

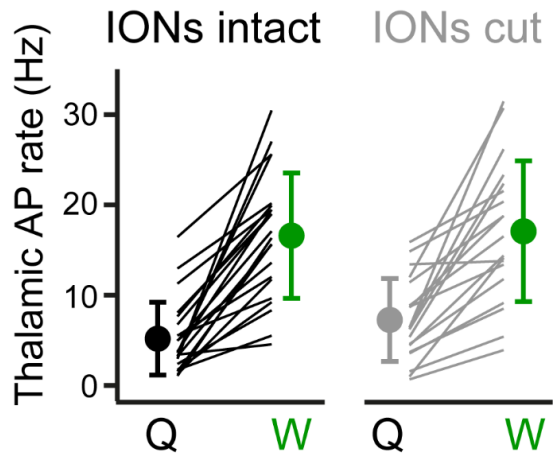



*(Poulet and Petersen, Nature 2008; Poulet, Fernandez, Crochet et al., Nat. Neurosci. 2012)*

# Thalamic contribution



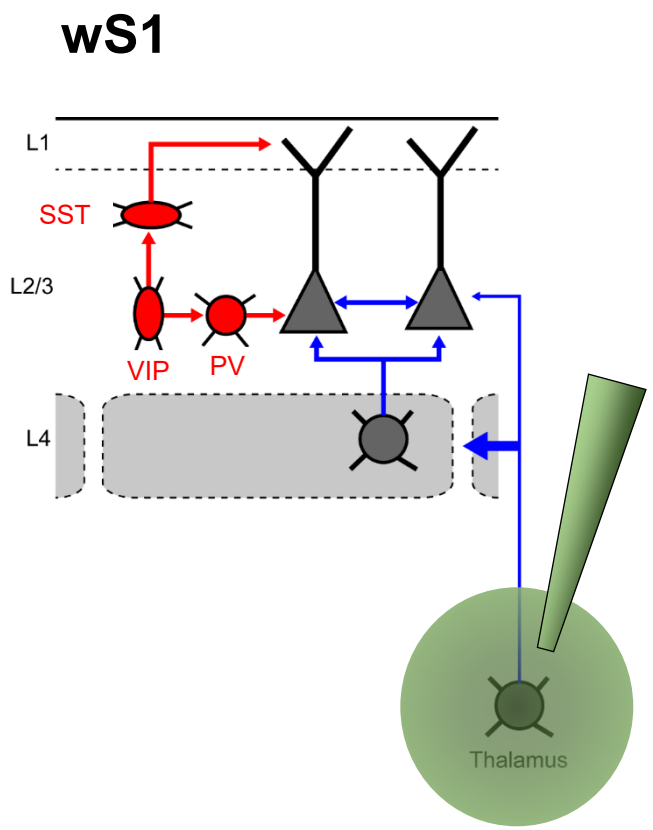




**=> Activity of thalamic neurons increases with whisking and correlates with state change in wS1**

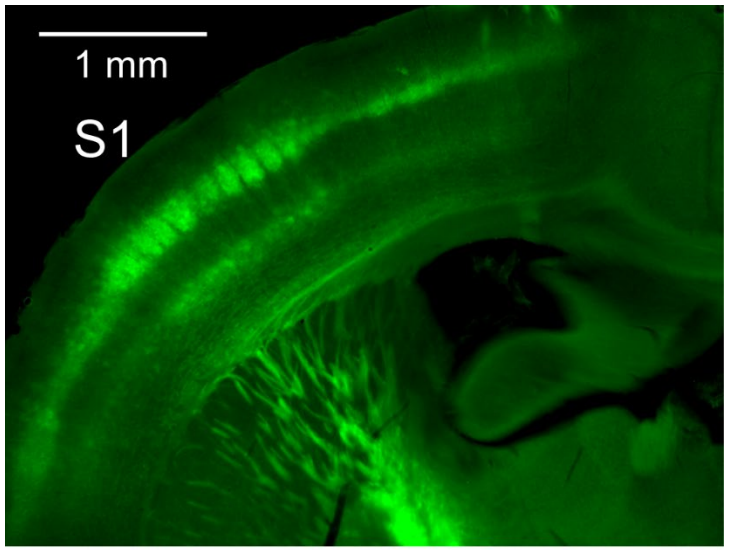
*(Poulet, Fernandez, Crochet et al., Nat. Neurosci. 2012; Urbain et al., Cell Rep. 2015)*

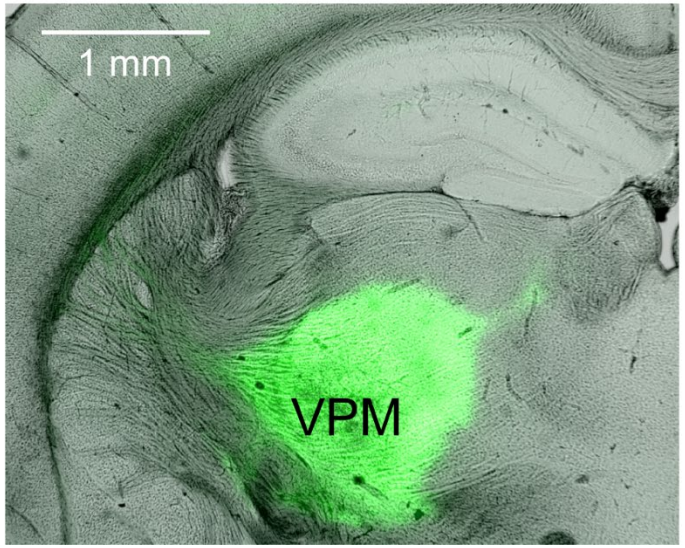
# Thalamic contribution

Optogenetic stimulation of thalamic neurons




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

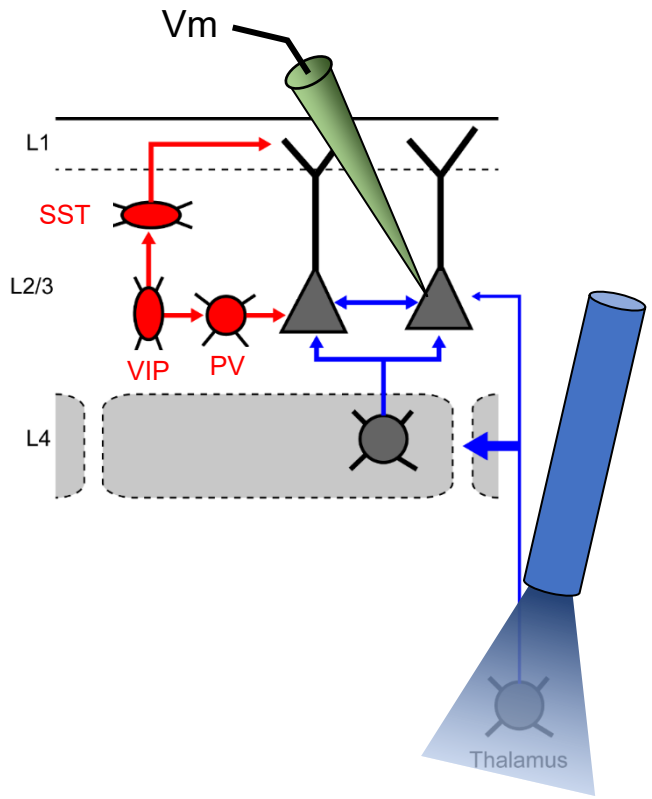


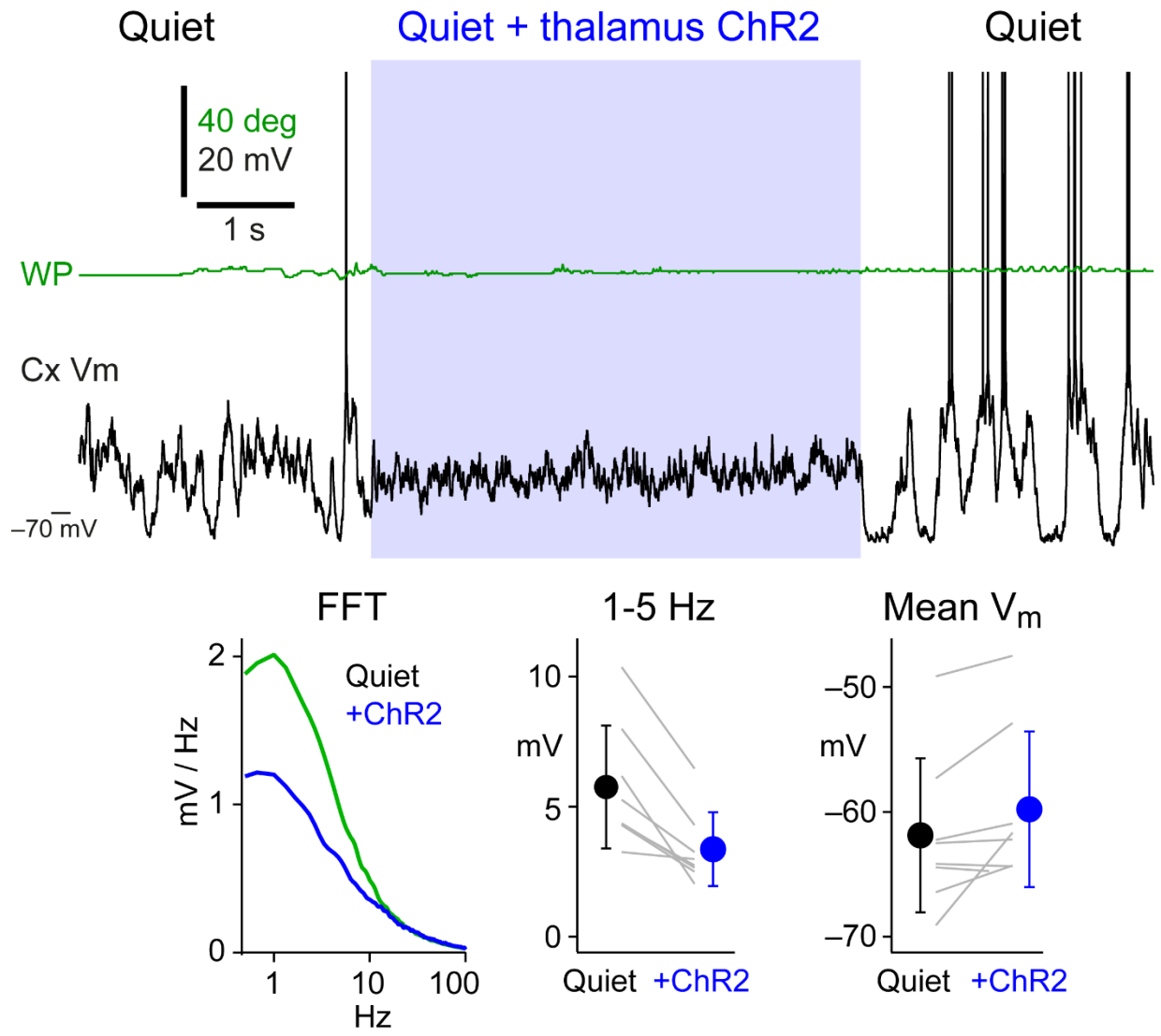




*(Poulet, Fernandez, Crochet et al., Nat. Neurosci. 2012)*

# Thalamic contribution

Optogenetic stimulation of thalamic neurons



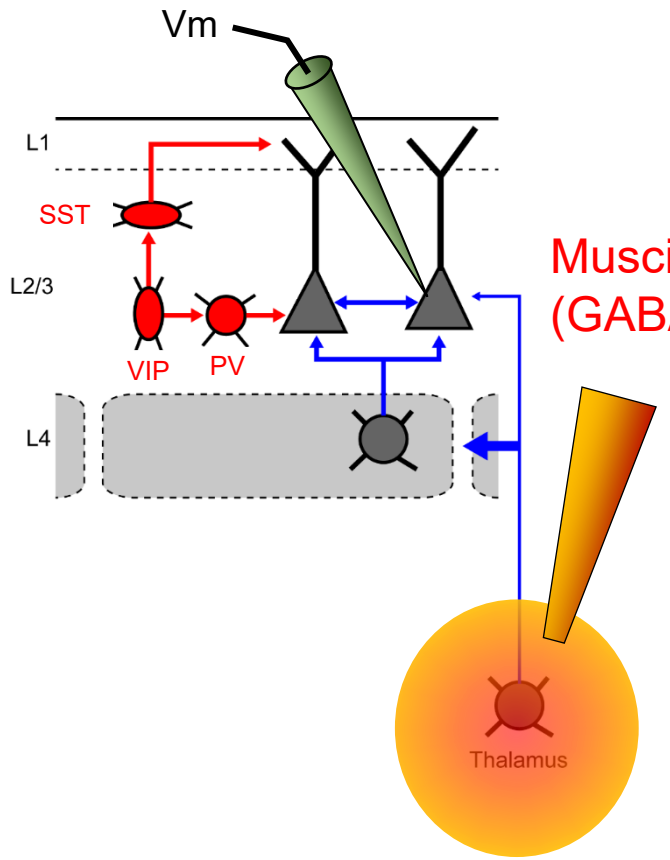




**=> Activation of thalamic neurons induces state change in wS1 during quiet wakefulness**

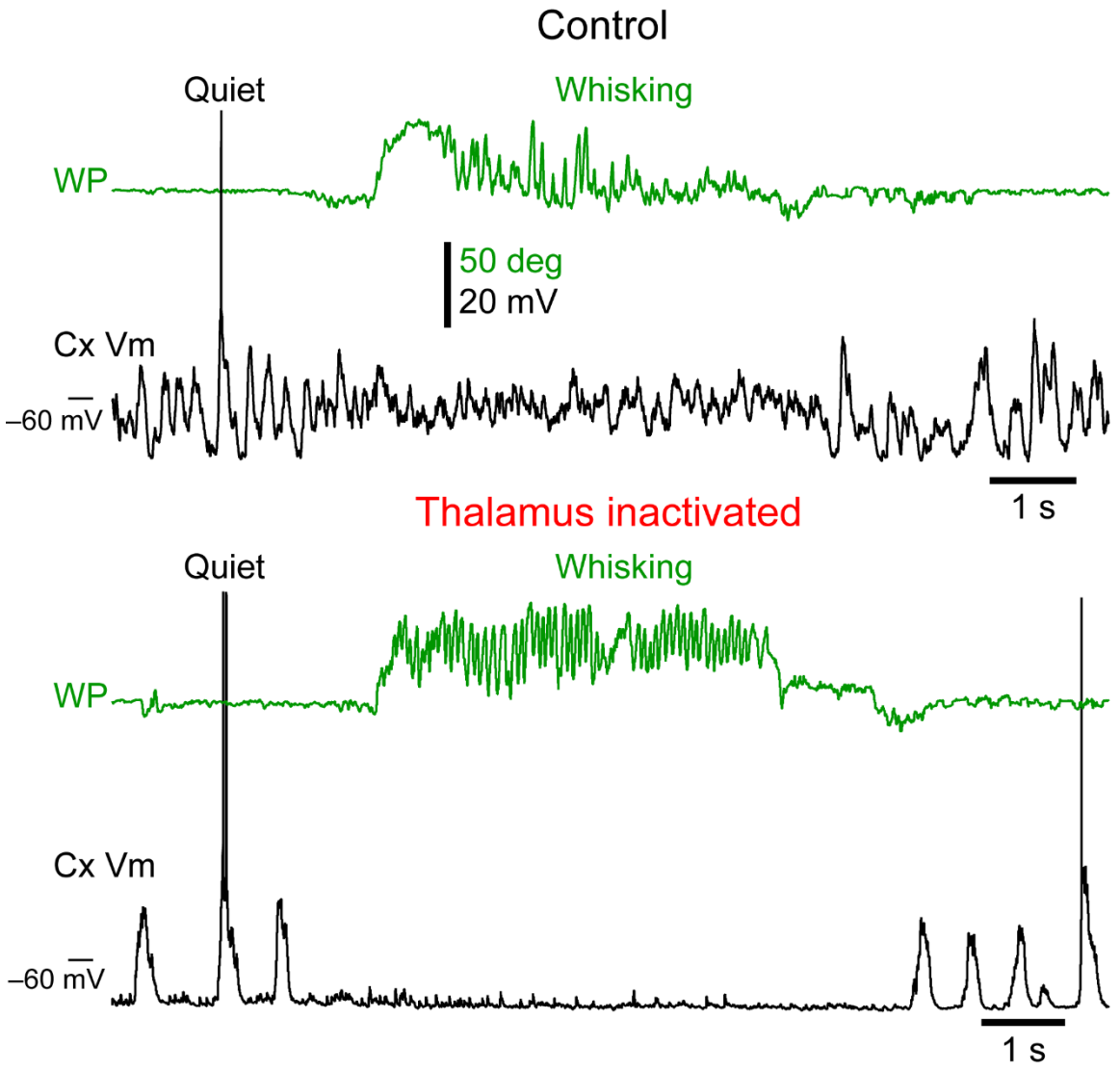
*(Poulet, Fernandez, Crochet et al., Nat. Neurosci. 2012)*

# Thalamic contribution

Pharmacological inhibition of thalamic neurons




Muscimol
($GABA_A$ agonist)

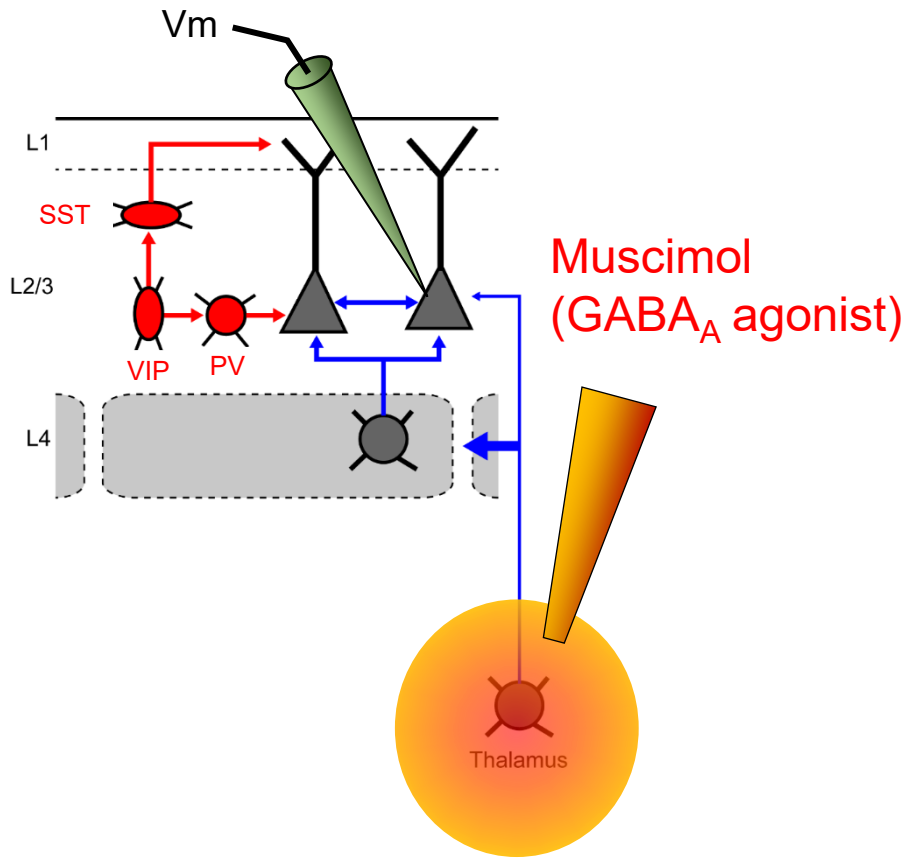



**=> Inhibition of thalamic neurons suppresses the high-frequency activity in wS1 during whisking**

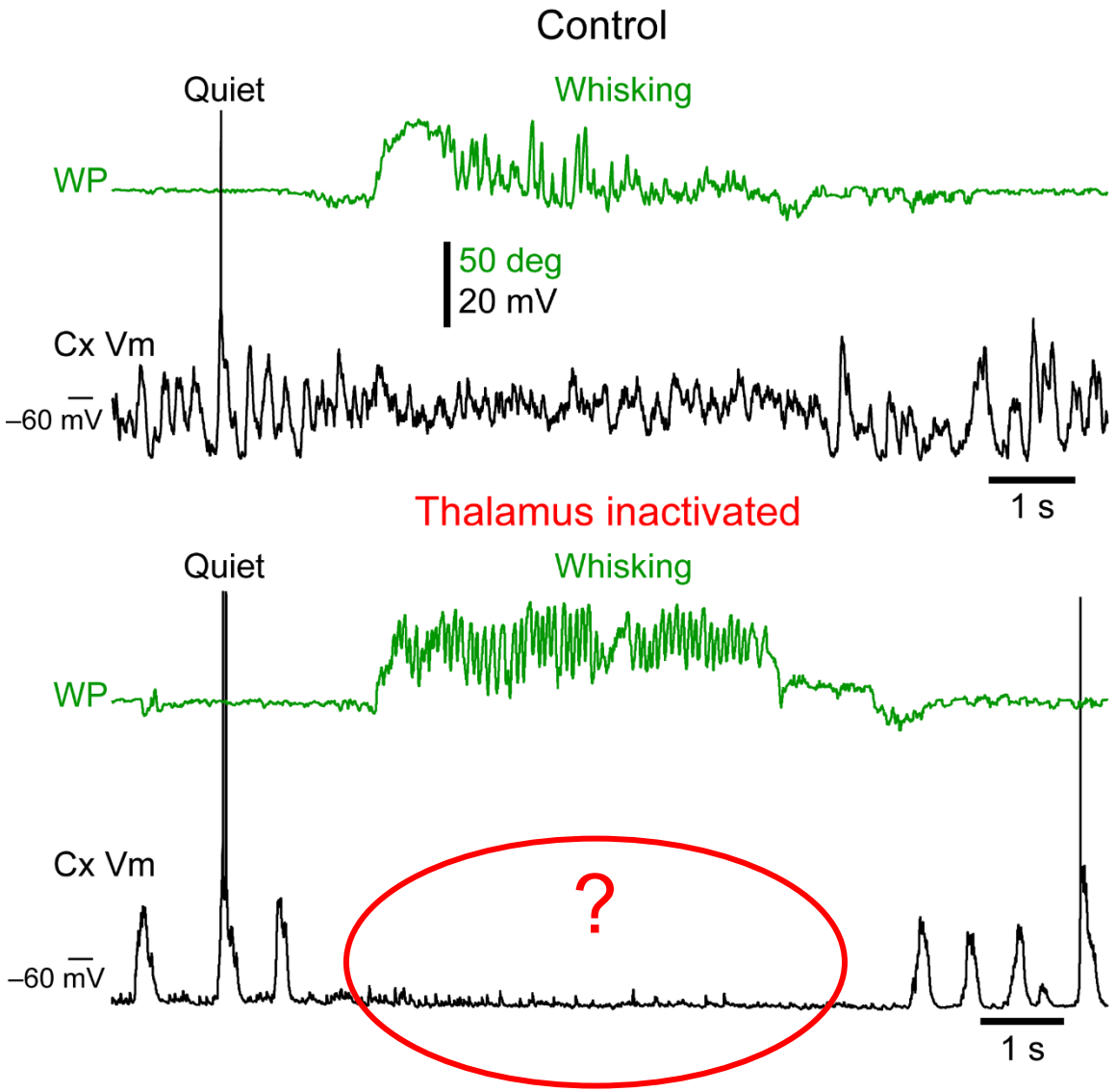
*(Poulet, Fernandez, Crochet et al., Nat. Neurosci. 2012)*

# Thalamic contribution

Pharmacological inhibition of thalamic neurons

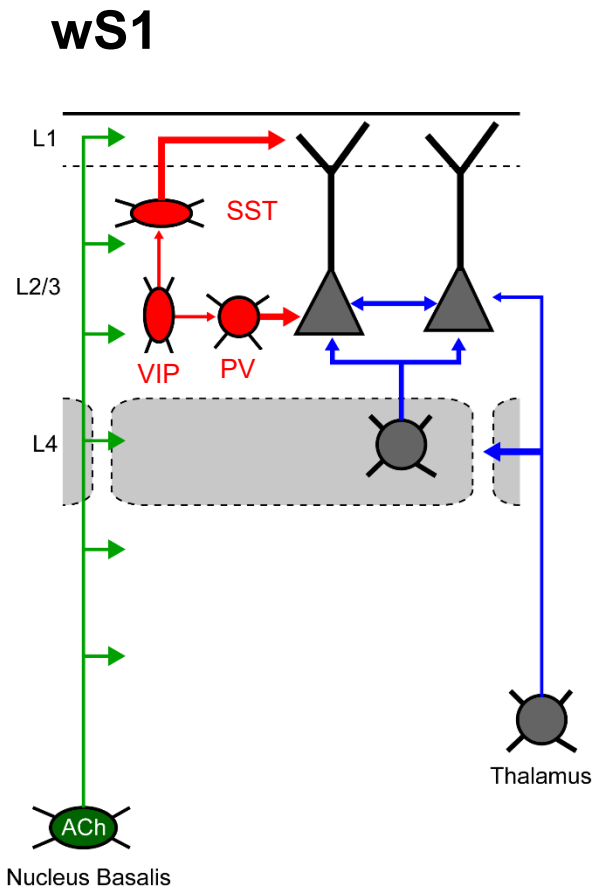



Muscimol
($GABA_A$ agonist)

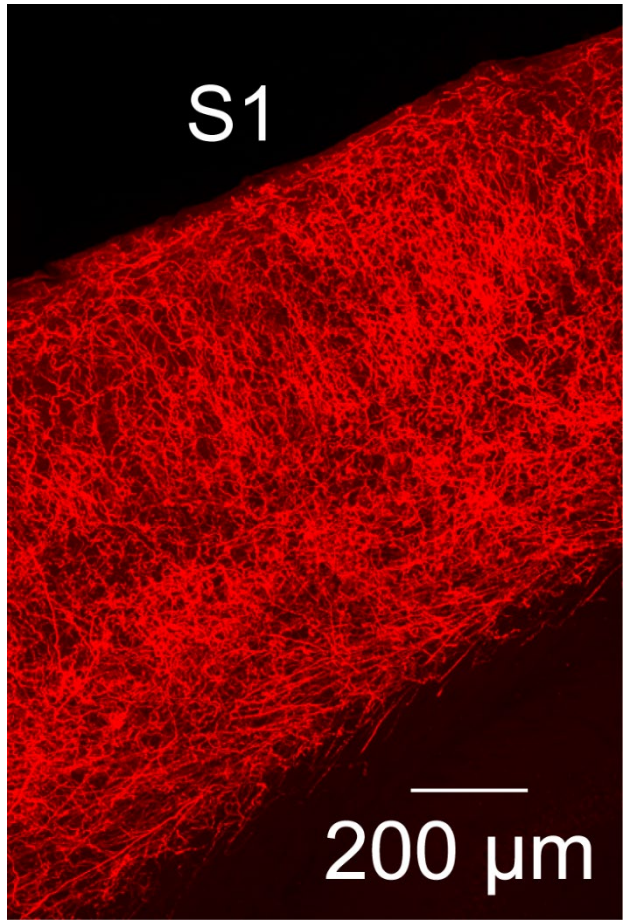



*(Poulet, Fernandez, Crochet et al., Nat. Neurosci. 2012)*

# Cholinergic contribution

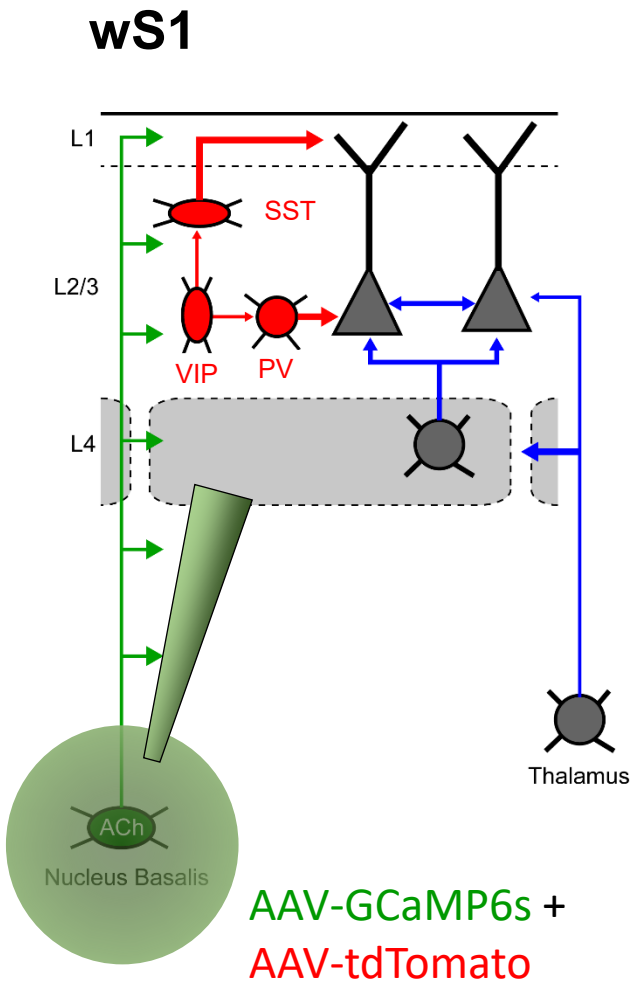



**Cholinergic axons in S1 (tdTomato)**

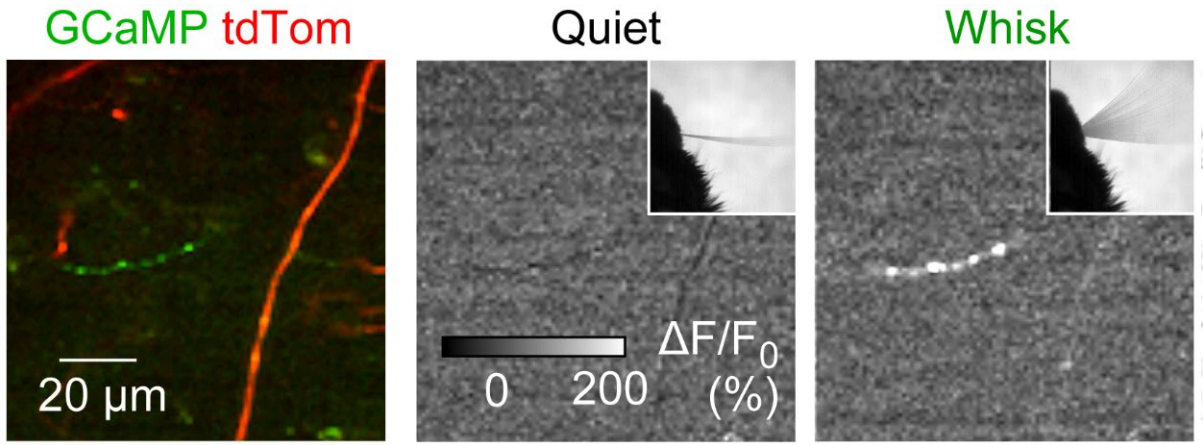


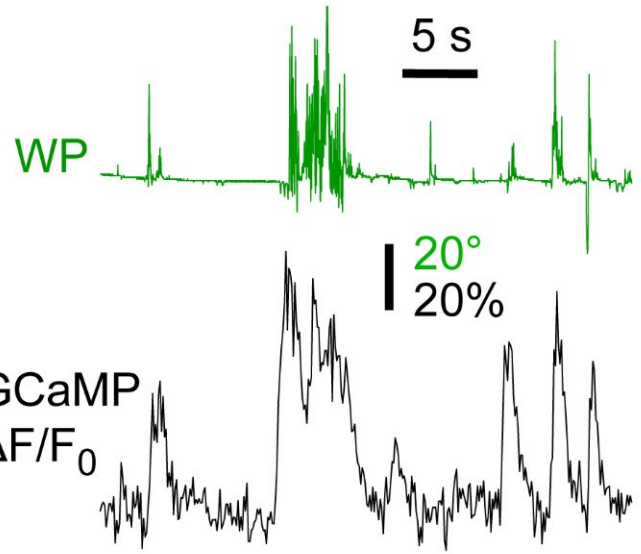

*(Eggermann et al., Cell Rep. 2014)*

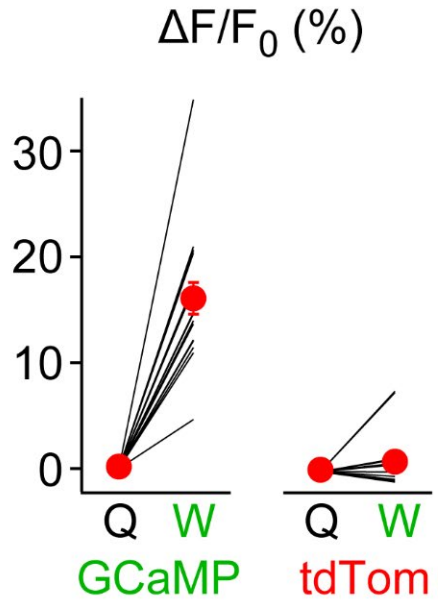
# Cholinergic contribution




AAV-GCaMP6s +
AAV-tdTomato



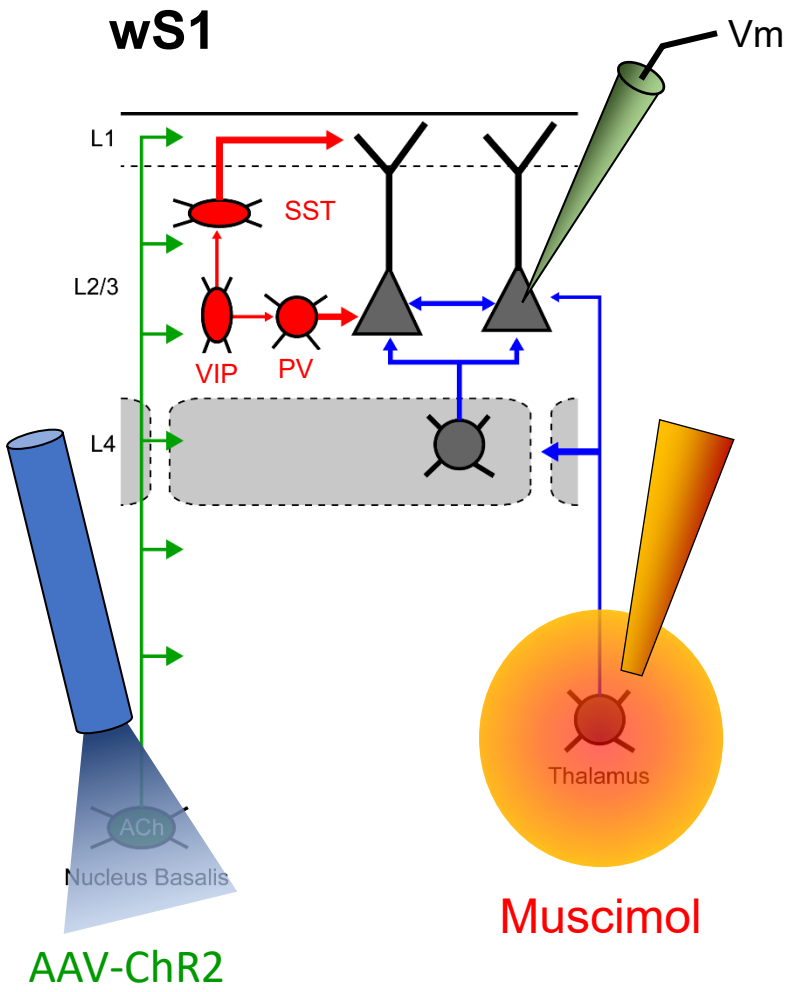



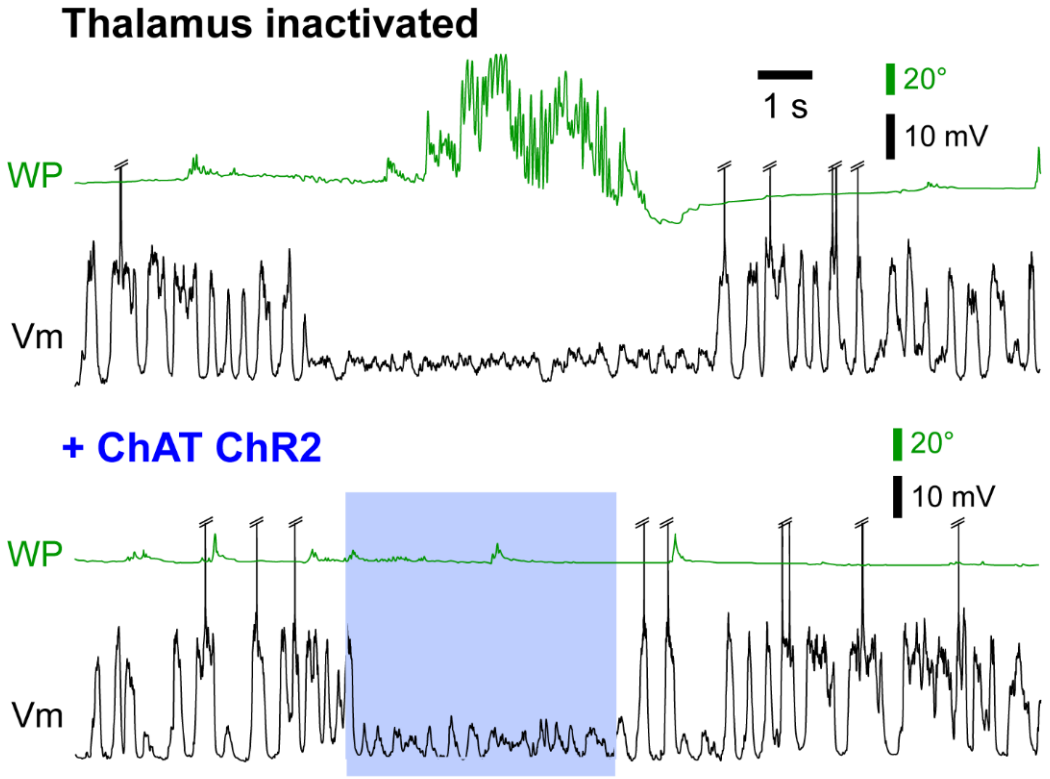

**=> ACh axons in wS1 increase activity during whisking**

*(Eggermann et al., Cell Rep. 2014)*

# Cholinergic contribution

Optogenetic activation of cholinergic neurons

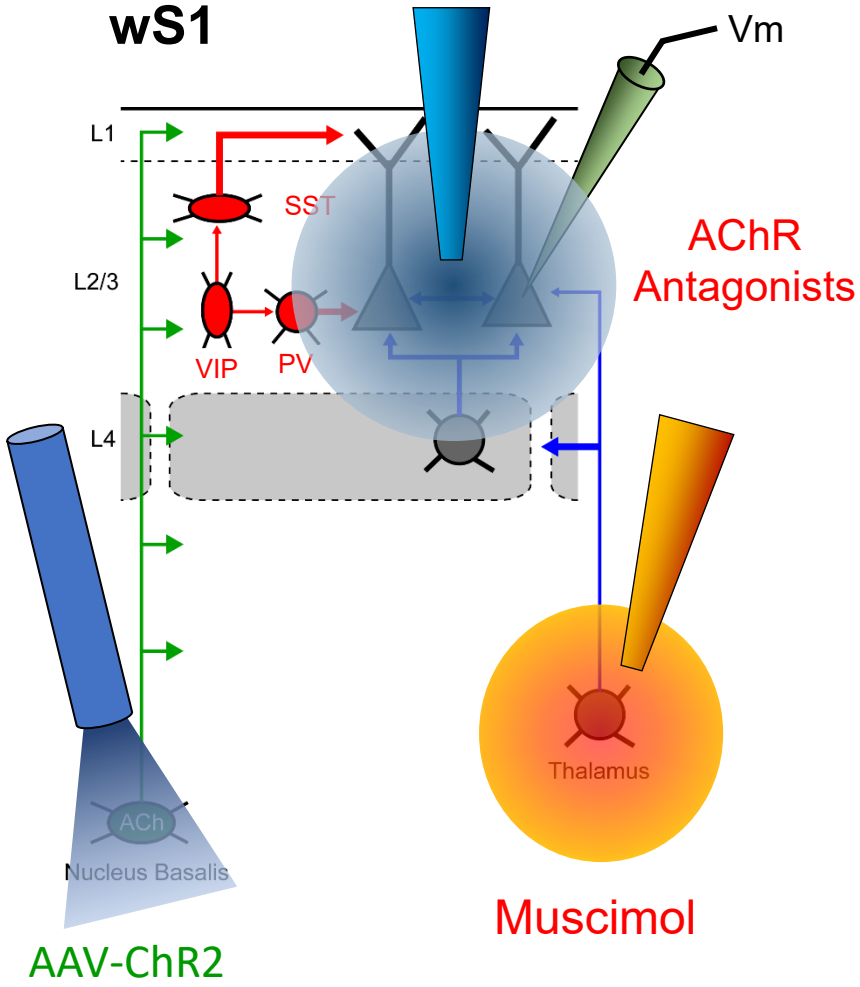


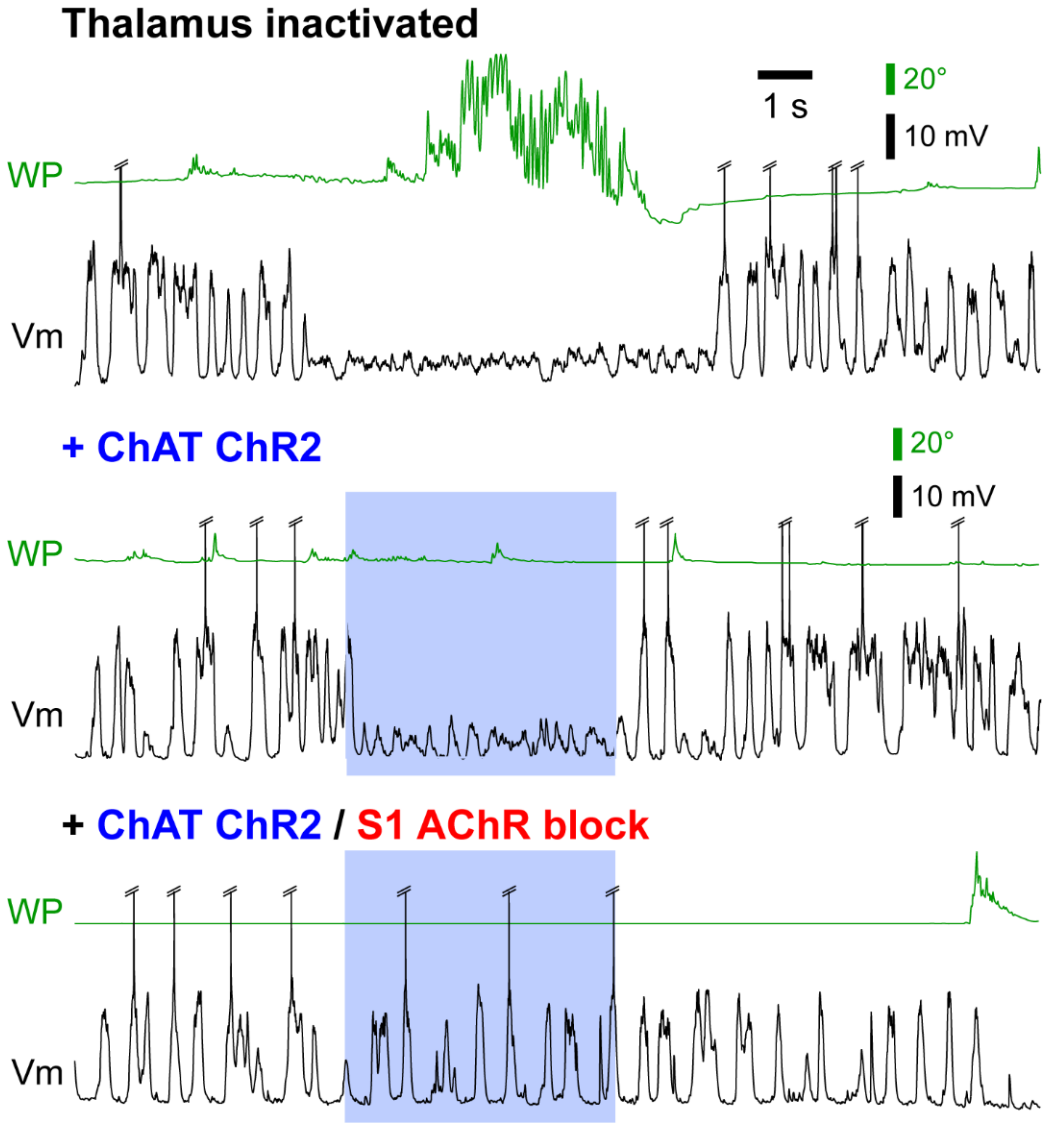




*(Eggermann et al., Cell Rep. 2014)*

# Cholinergic contribution

Pharmacological blockade of ACh receptors



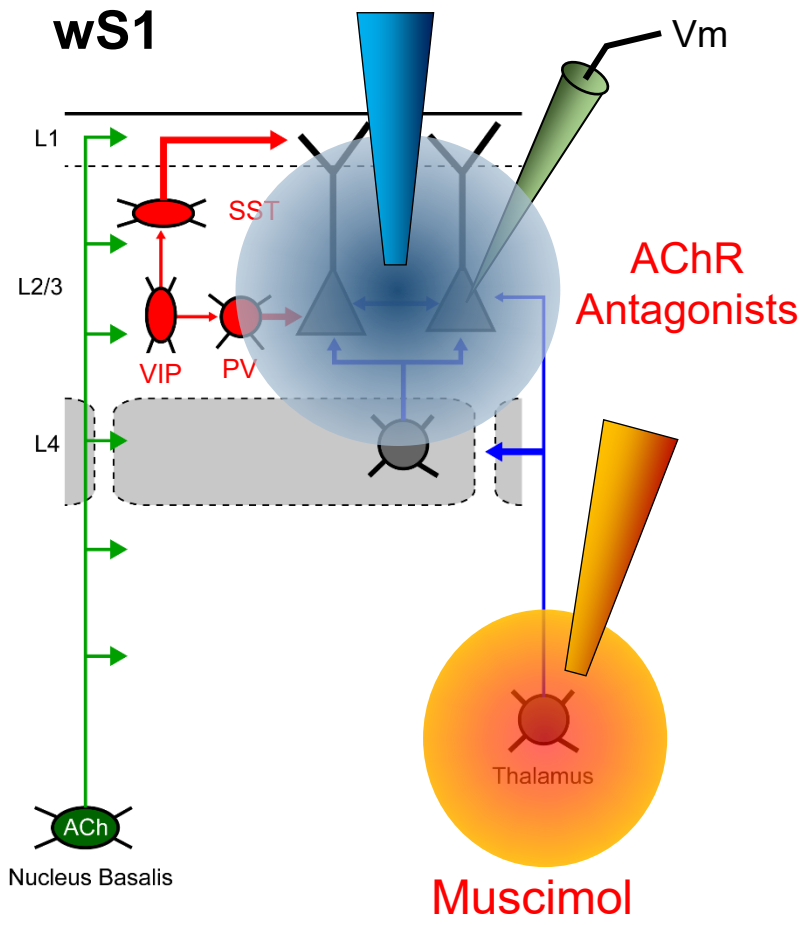



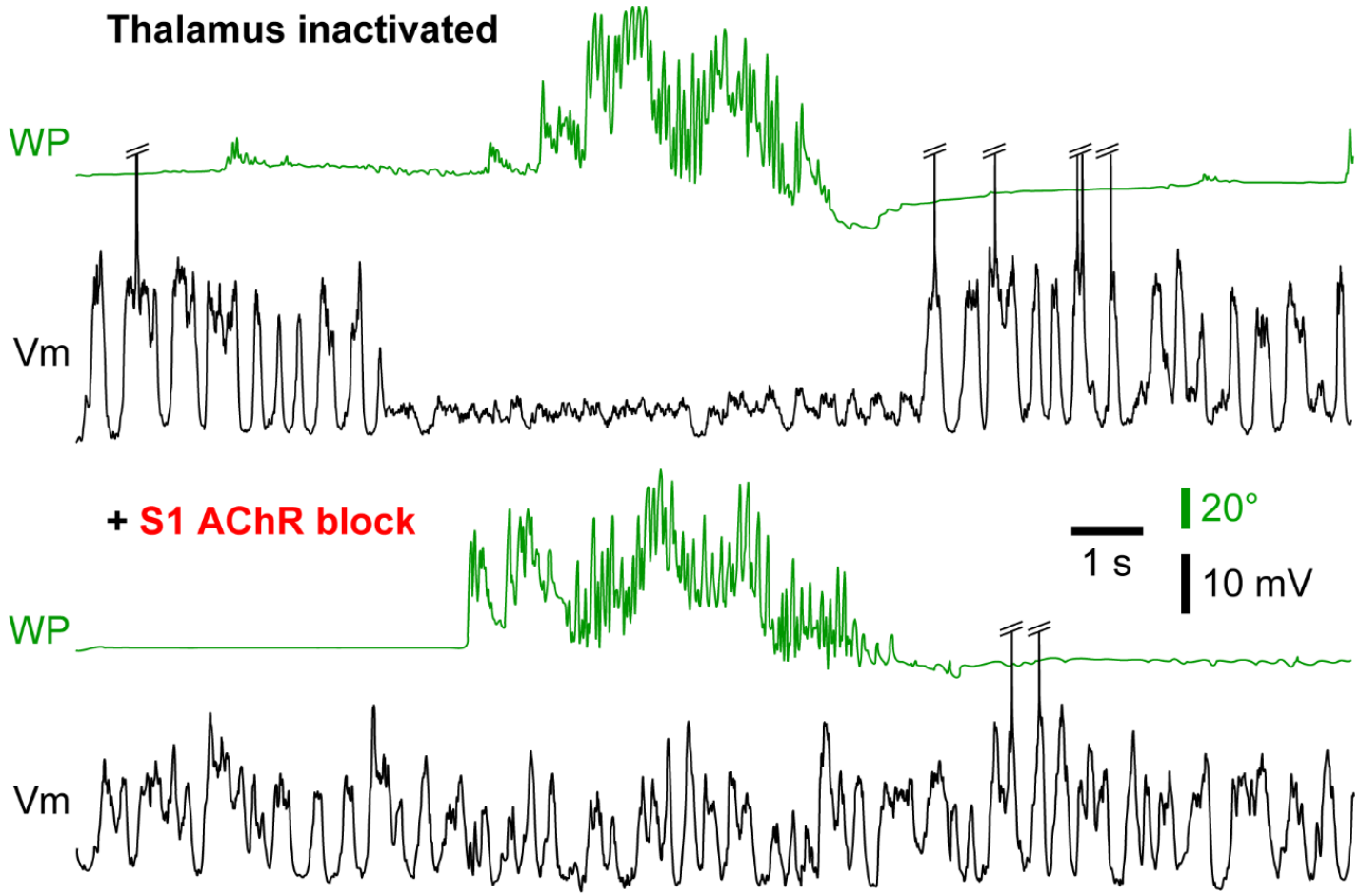

**=> Activation of ACh neurons induces state change in wS1**

*(Eggermann et al., Cell Rep. 2014)*

# Cholinergic contribution

Pharmacological blockade of ACh receptors

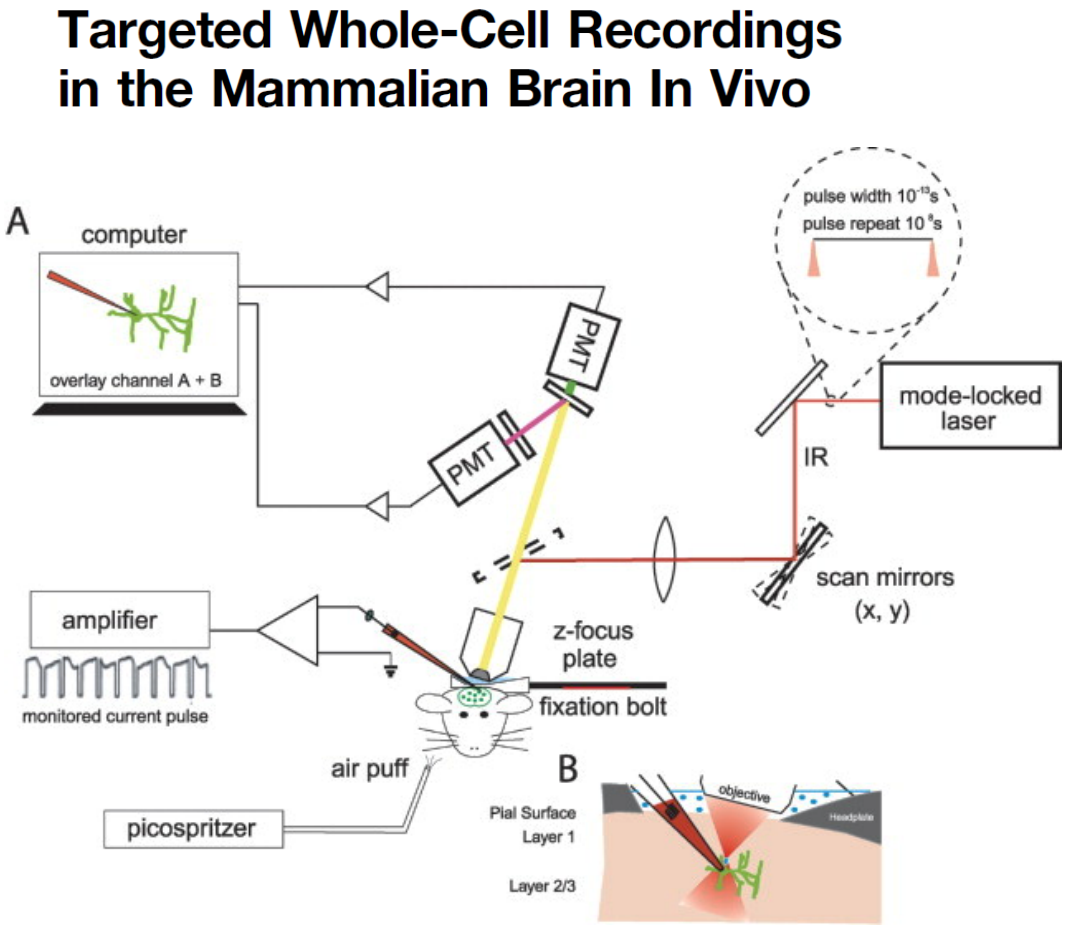


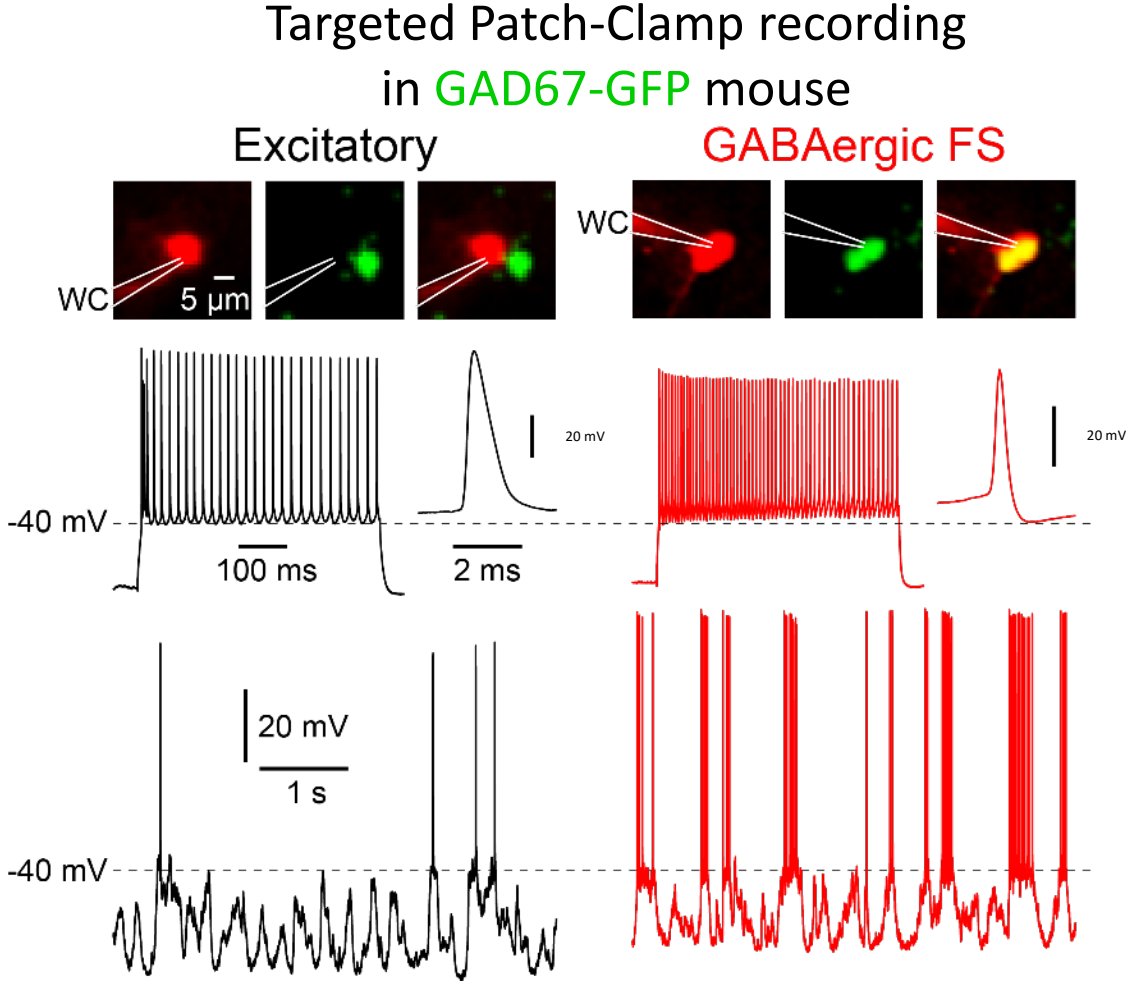

**=> Blockage of AChR in wS1 & inhibition of thalamus block the state change in wS1**

*(Eggermann et al., Cell Rep. 2014)*

# Cell-type specific changes with cortical states

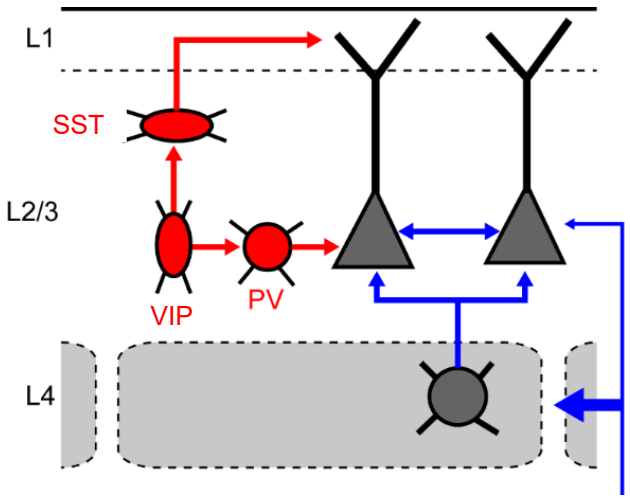



*(Margrie et al., 2003; Komai et al., 2006)*




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

# Cell-type specific changes with cortical states

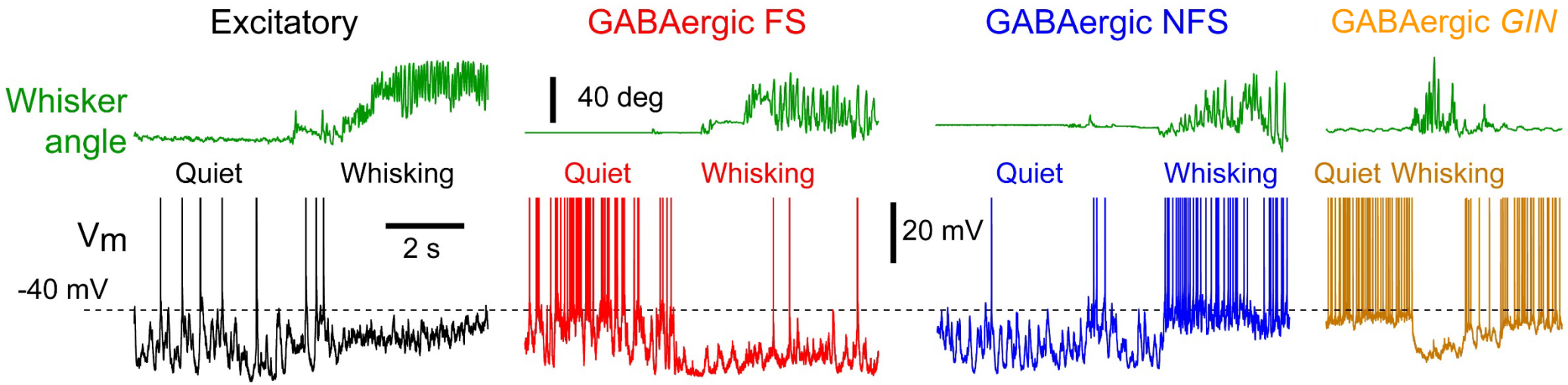



Excitatory Pyramidal

Fast Spiking (FS) ~ GABAergic PV

Non Fast-Spiking (NFS) ~ GABAergic VIP

*GIN* ~ GABAergic SST



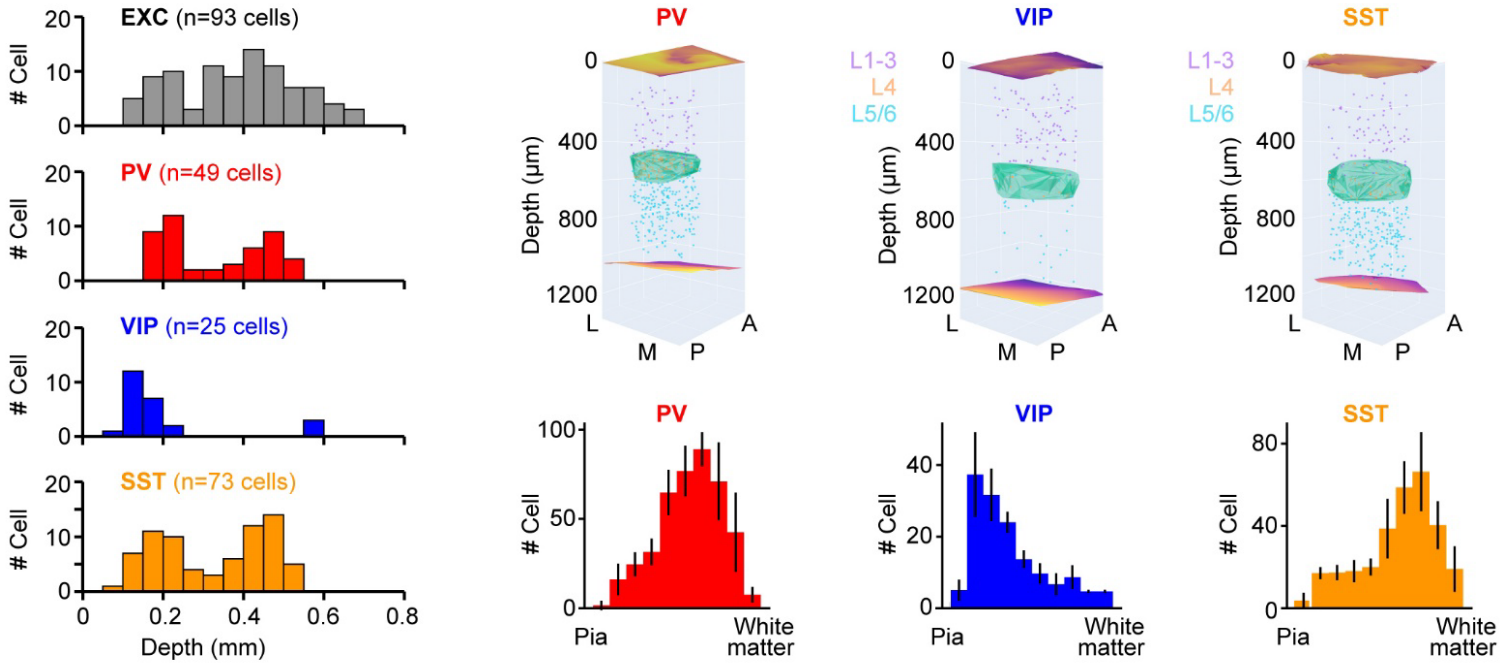

**=> But cell-type identification approximative and limitation to superficial L2/3**

*(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

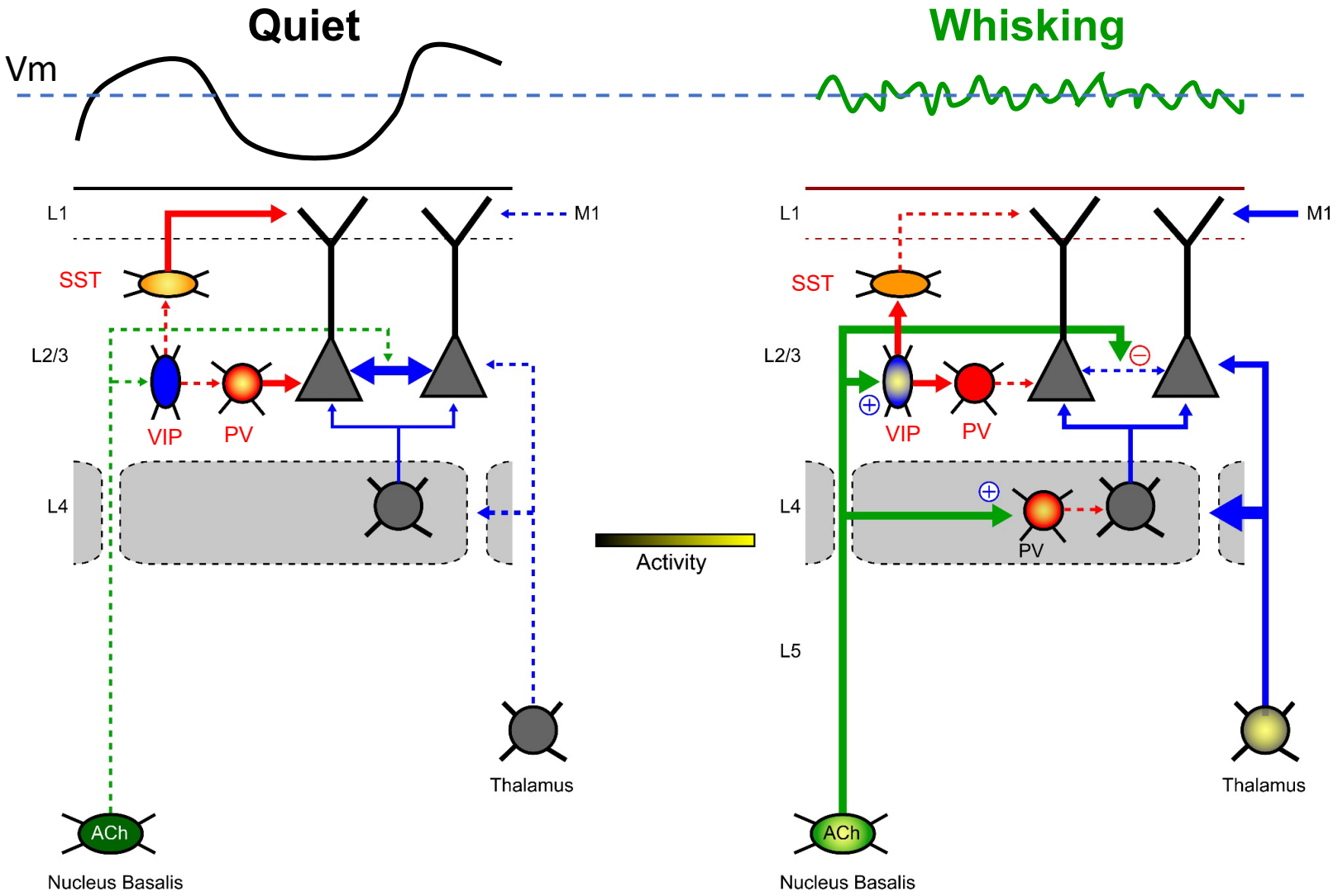



*(Kiritani et al., PLOS One 2024)*

***=> BIO482 Miniproject:***

***Learn more about these different cell-types by yourself***

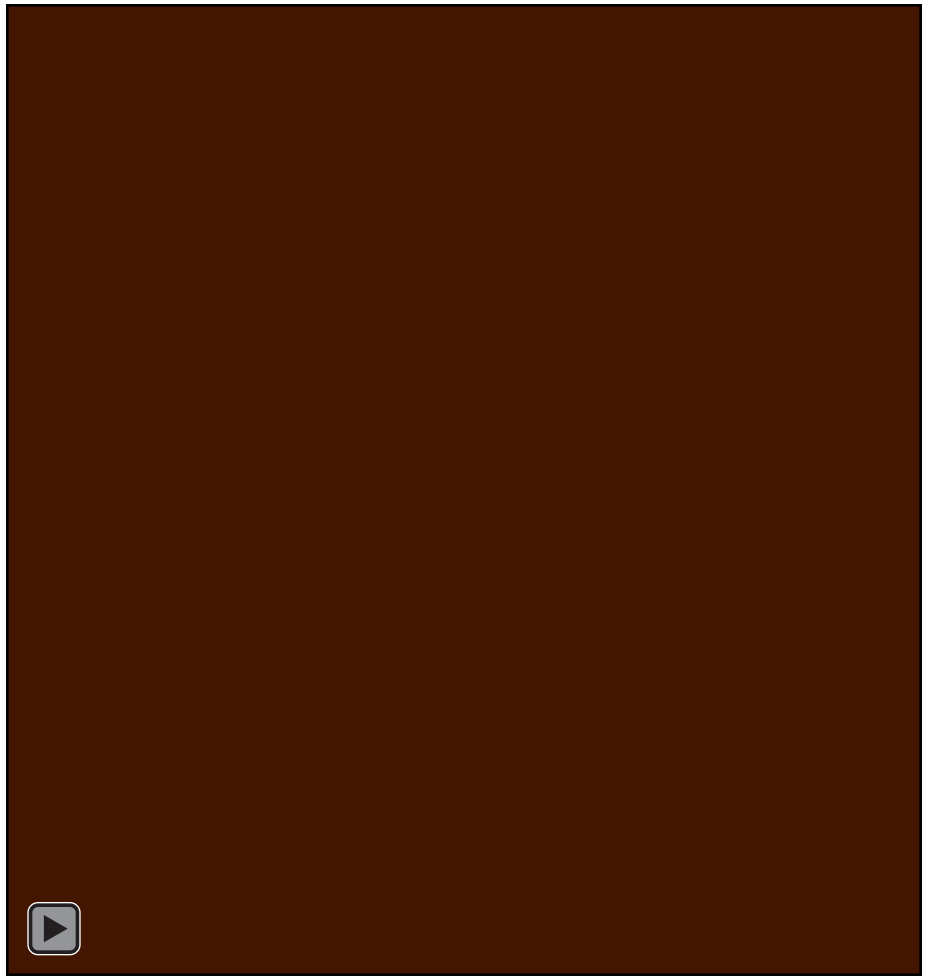
# Cellular mechanisms of the state change in wS1




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

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

# Membrane potential recording during active touch



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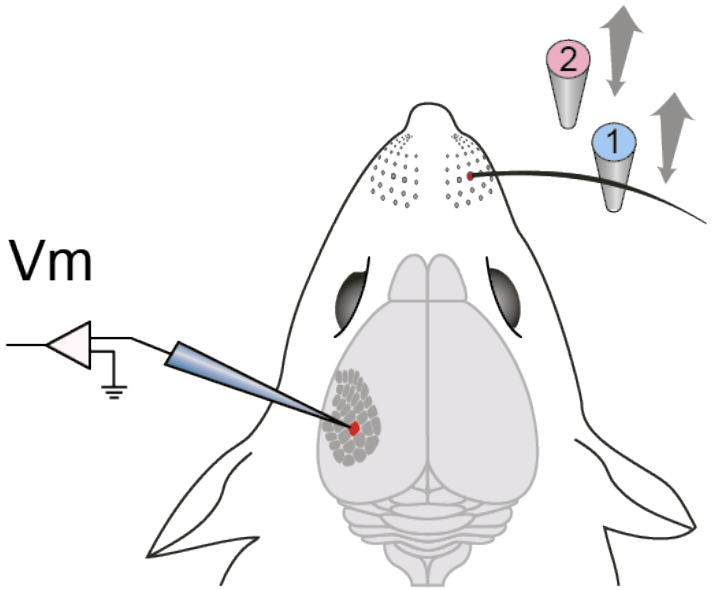


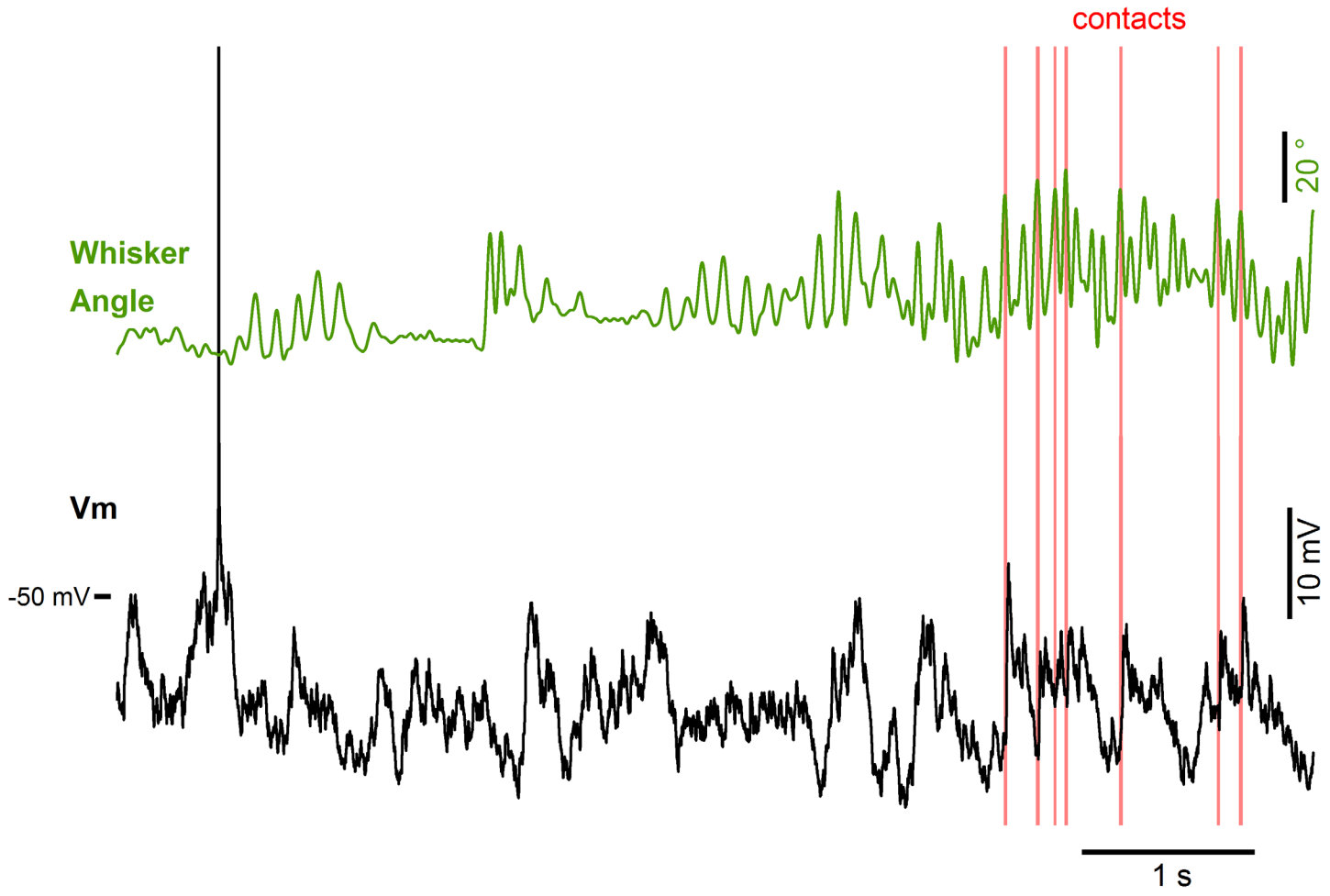

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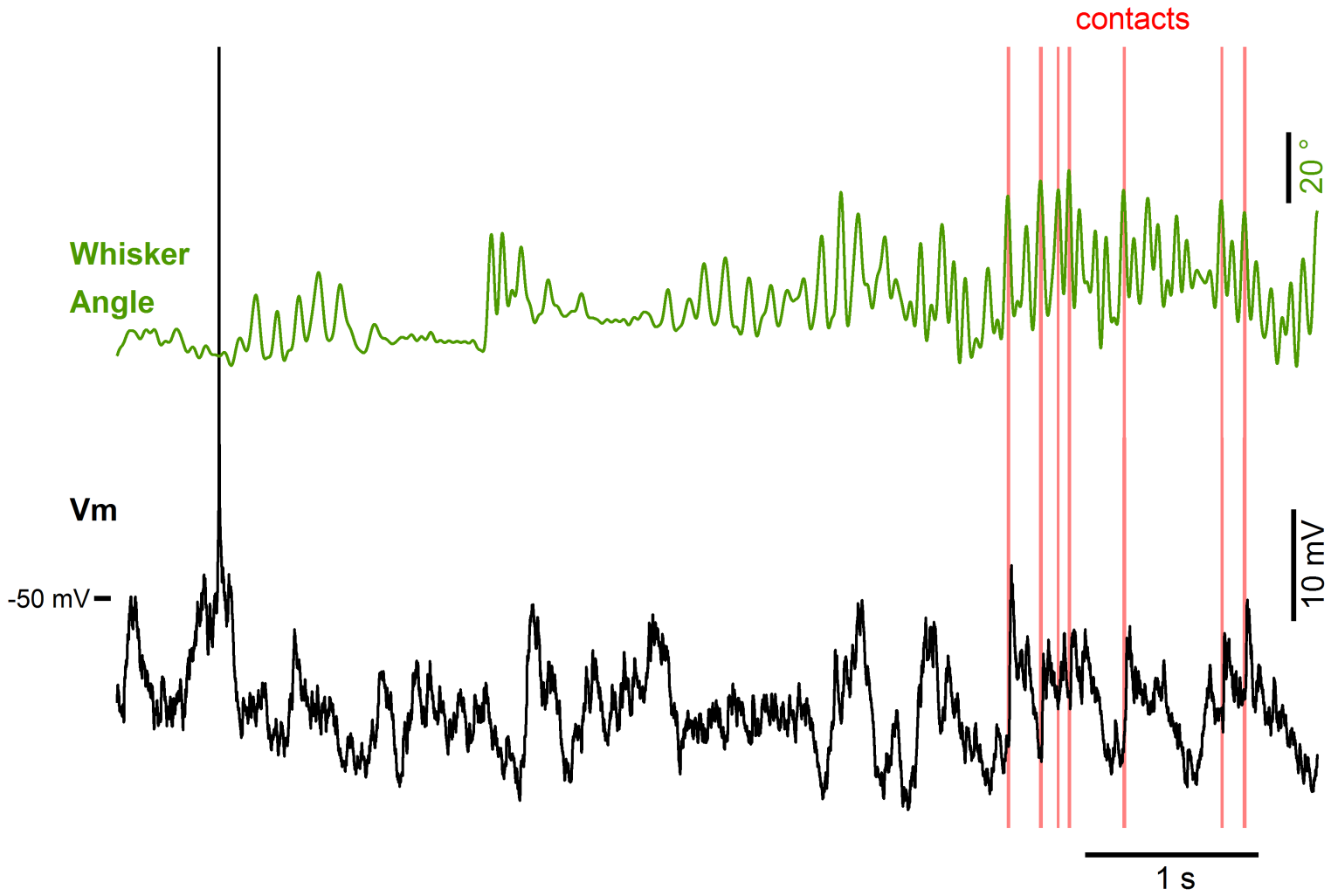
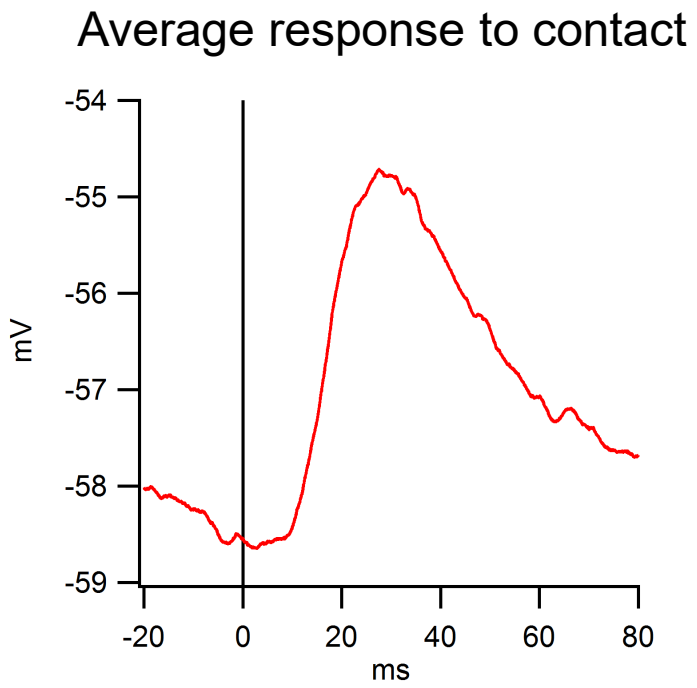
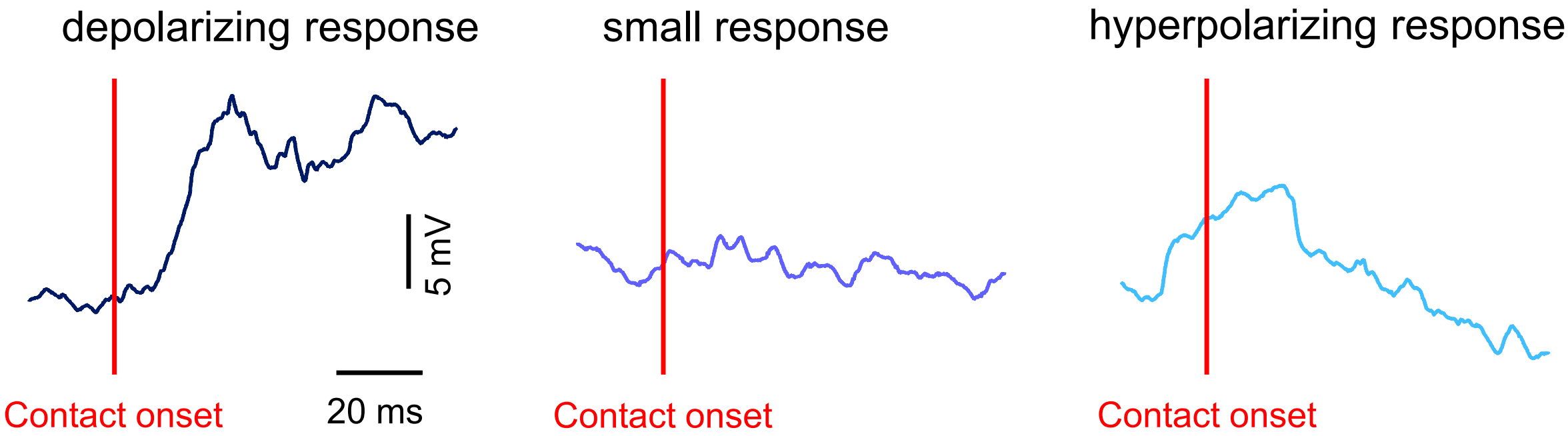


# Variable evoked responses to active touch

Example of individual postsynaptic potentials (PSPs) evoked by contact



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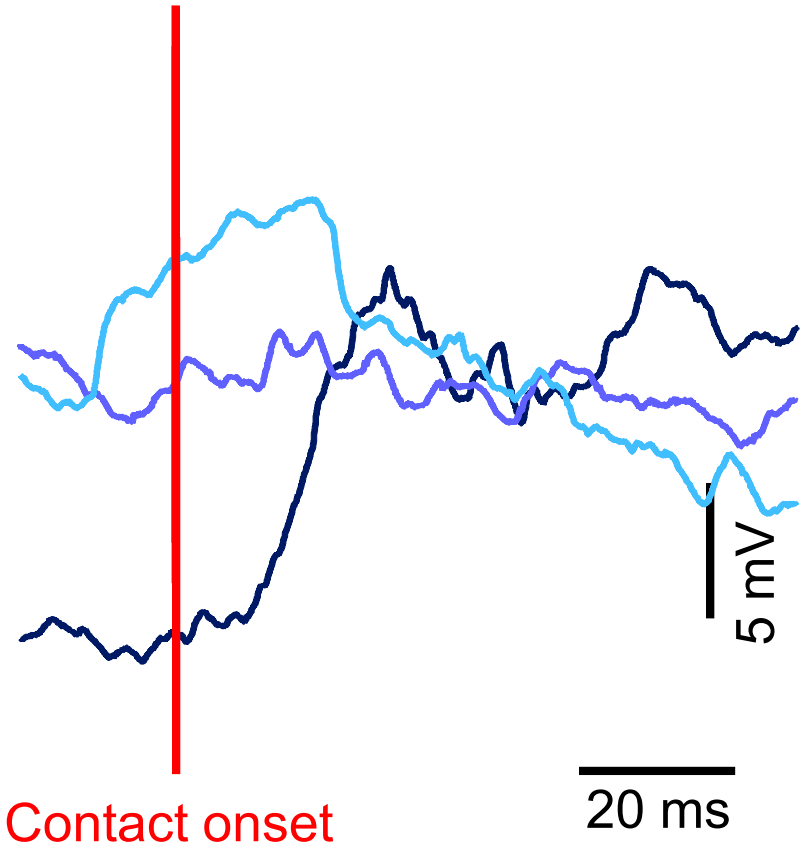

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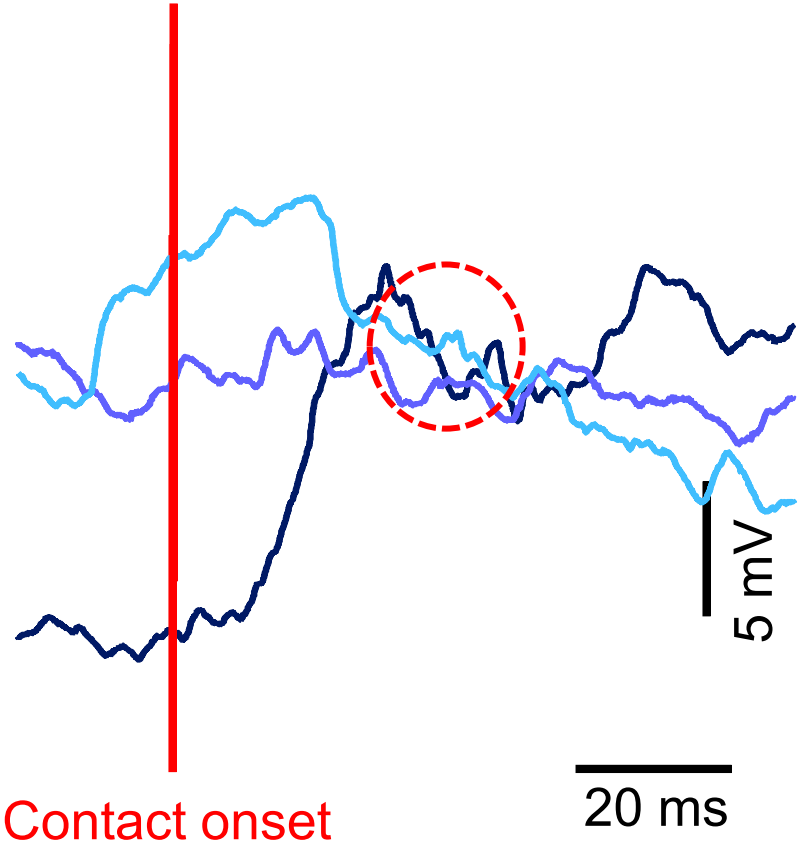
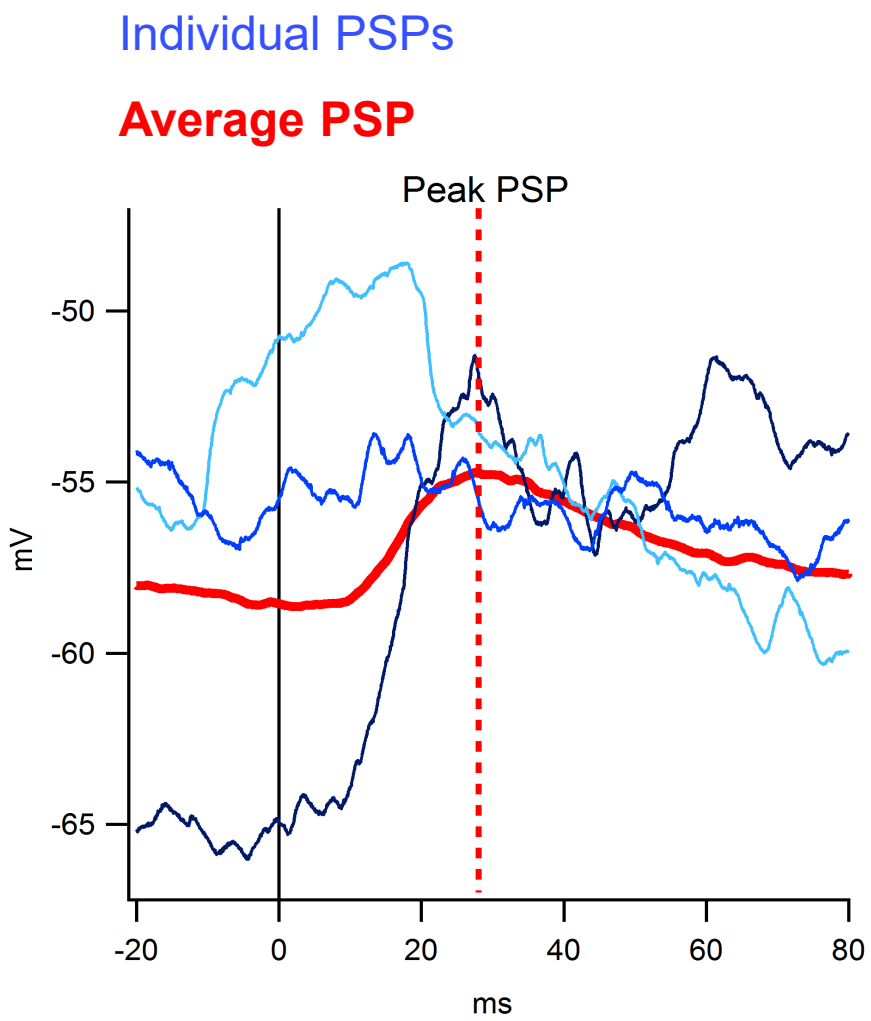
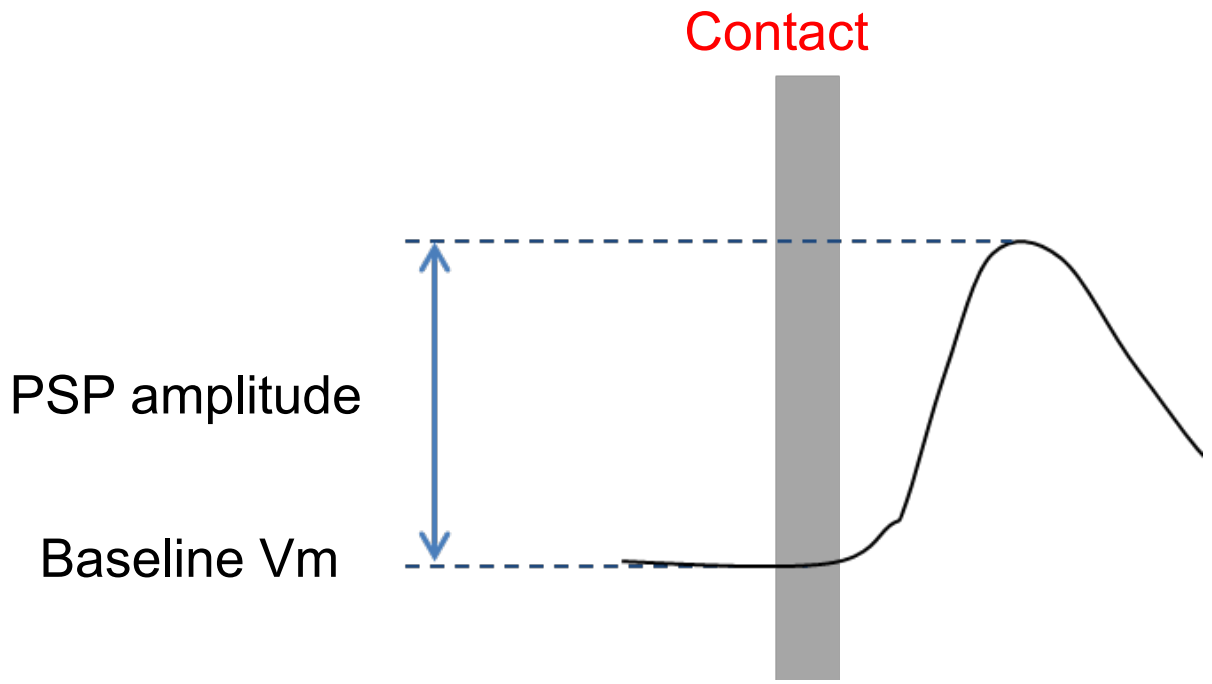



**=> Individual PSPs converge to a fixed-point of the Vm**

# Variable evoked responses to active touch

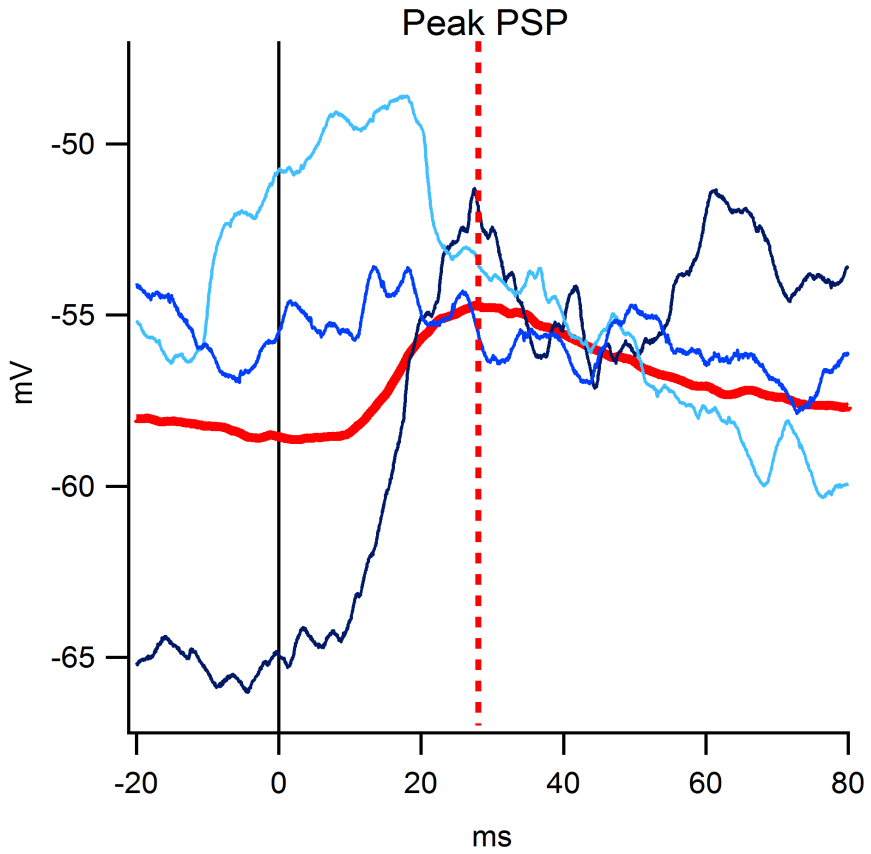


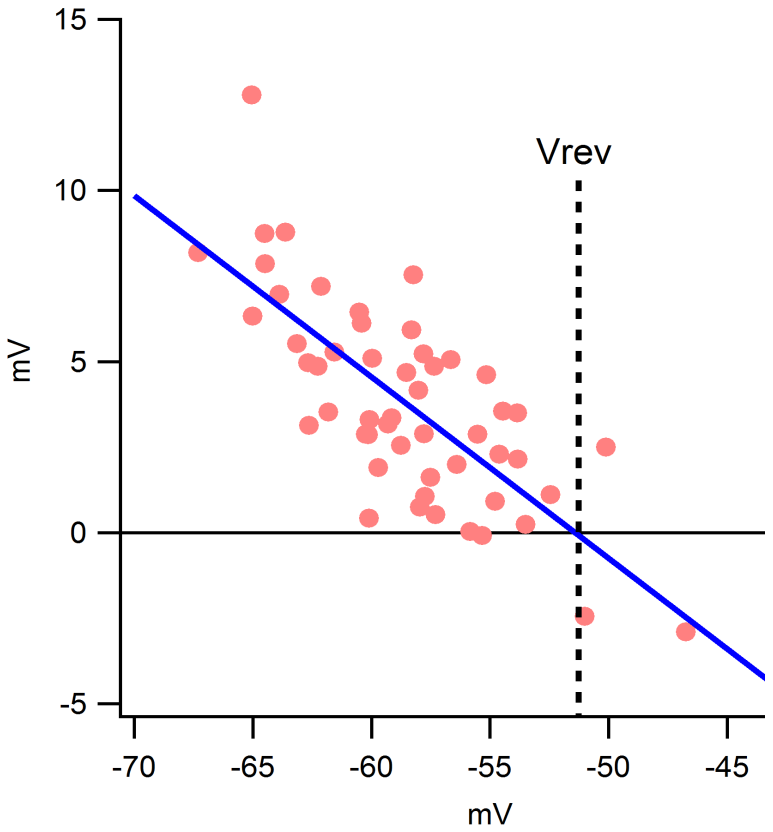
# ▪ Reversal potential ($V_{rev}$) of the sensory evoked response

Individual PSPs

**Average PSP**




PSP amplitude vs Baseline Vm

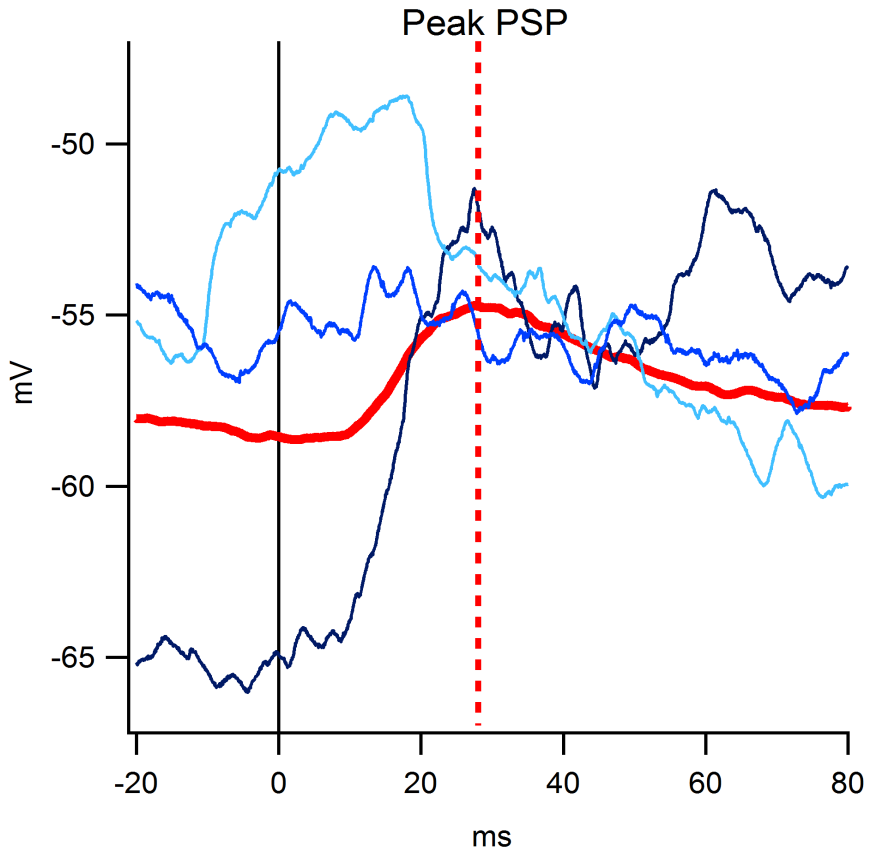



**=> Negative $V_{rev}$ of the PSP**

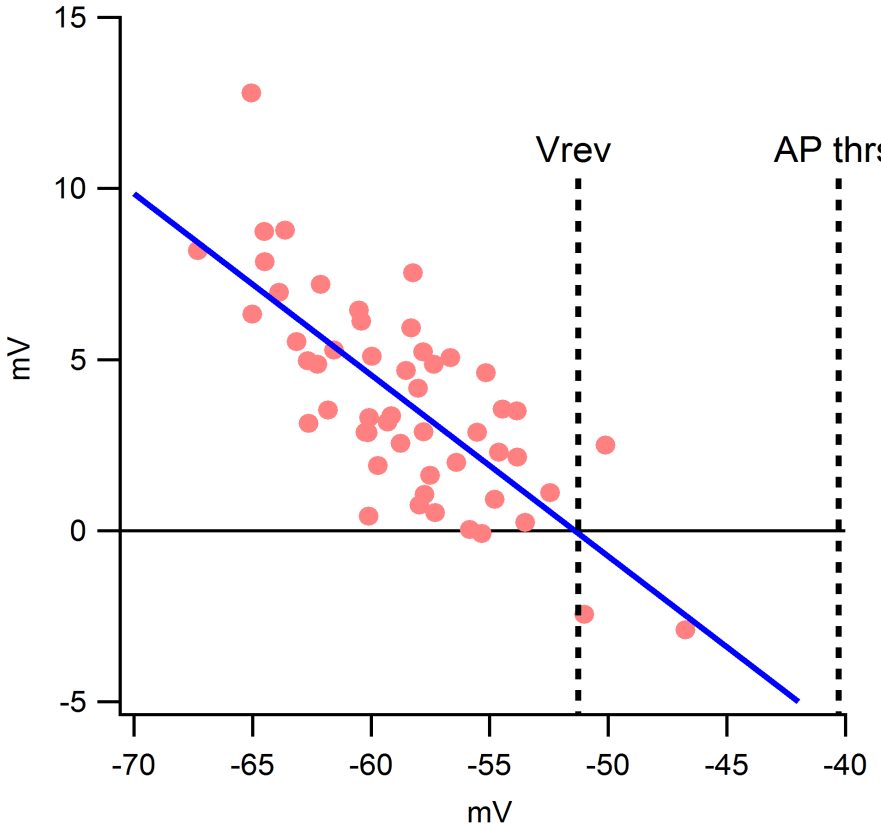
# Reversal potential ($V_{rev}$) of the sensory evoked response

Individual PSPs

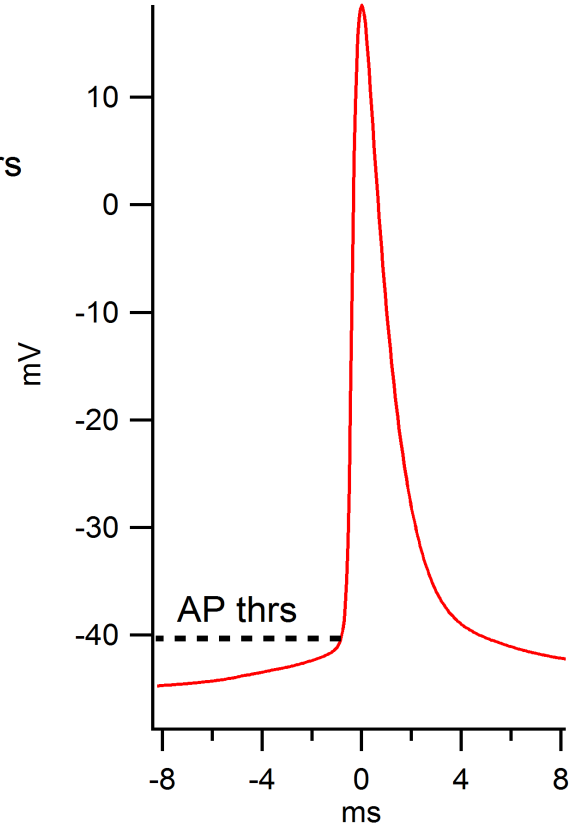
**Average PSP**




PSP amplitude vs Baseline Vm

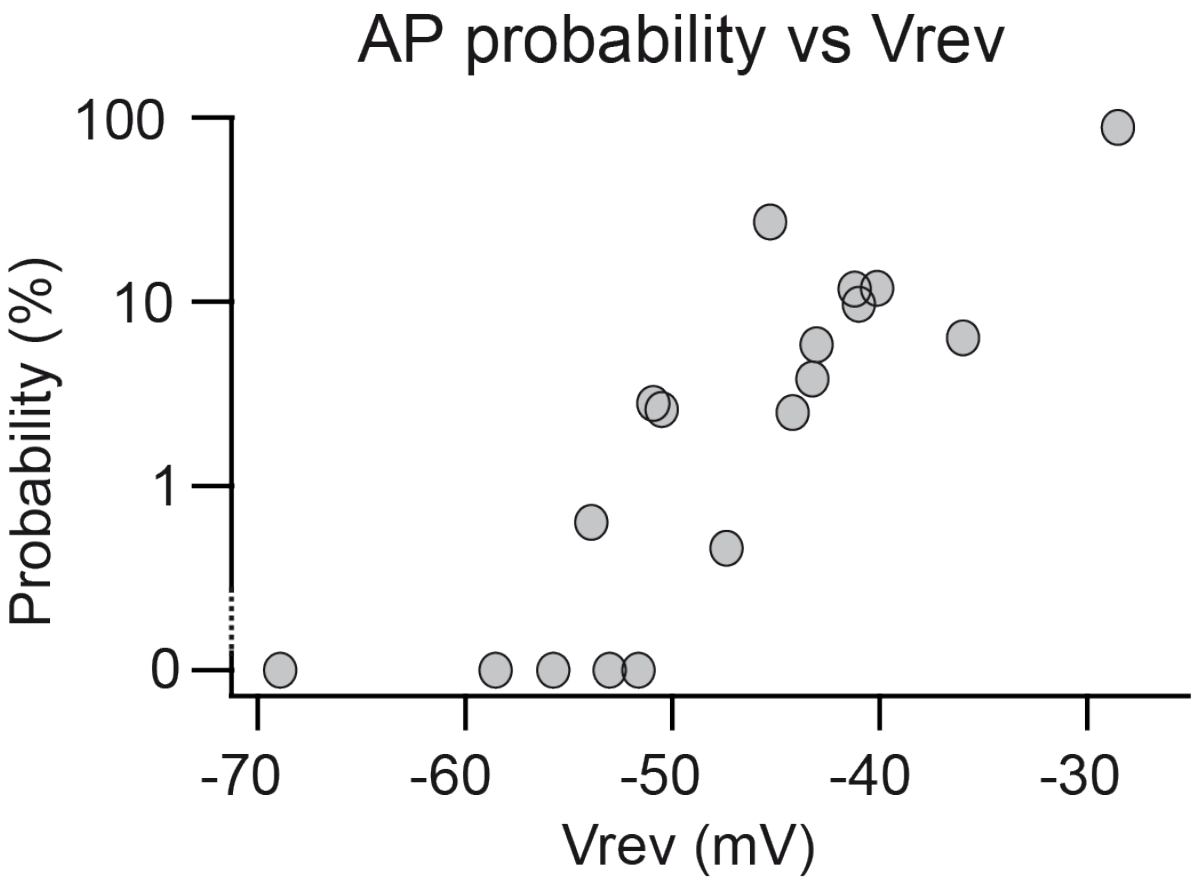


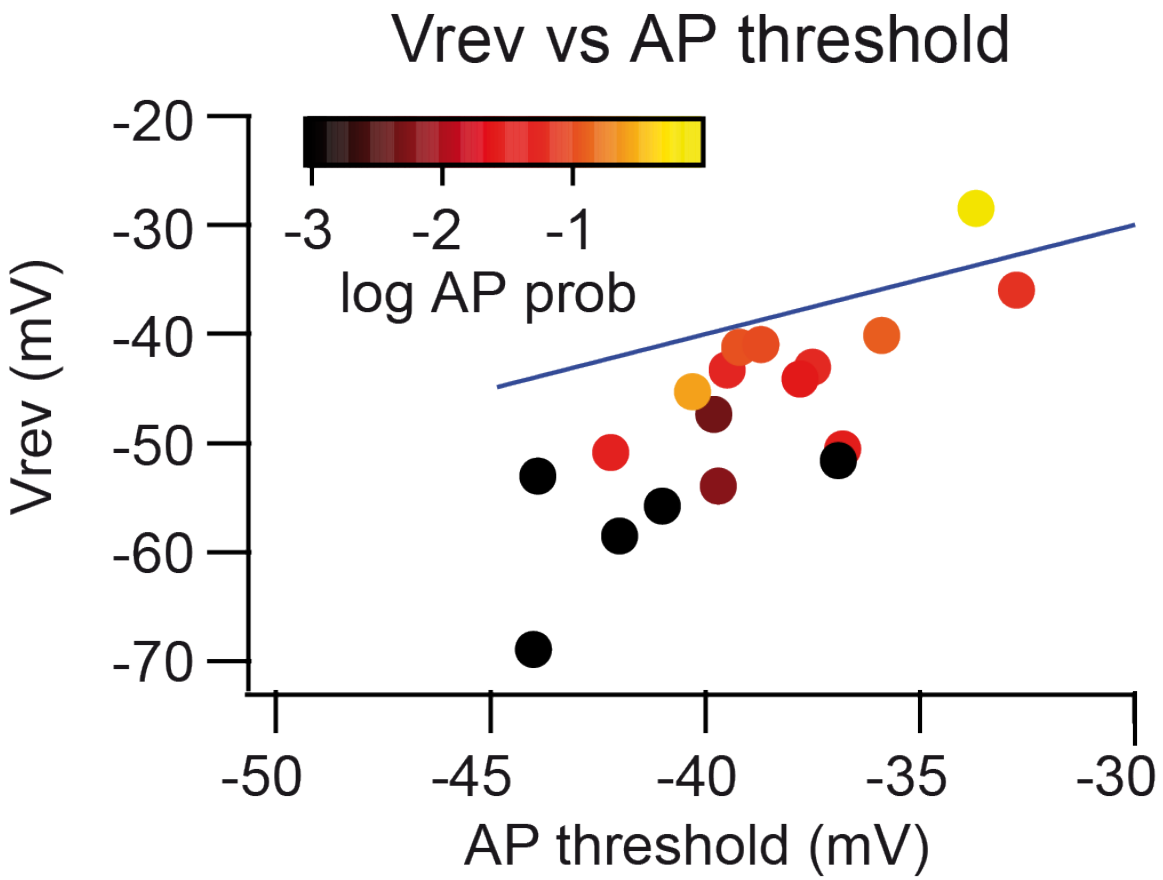

AP Threshold




**=> Negative $V_{rev}$ of the PSP**

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



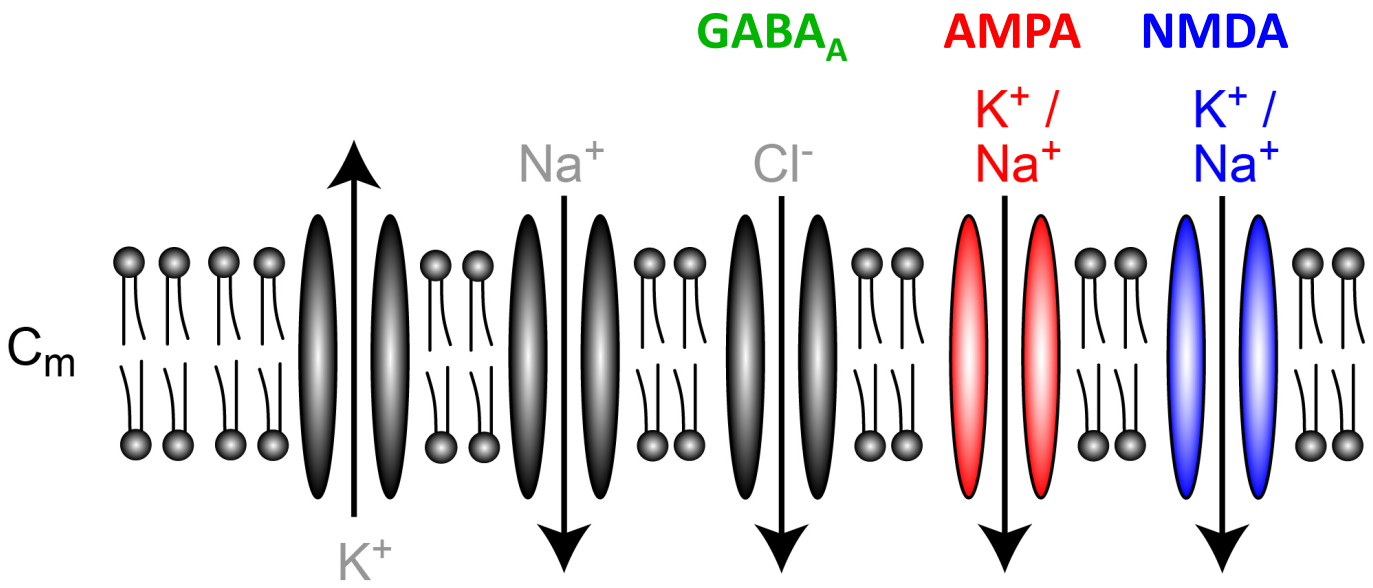




**=> $V_{rev}$ of individual cell correlates with AP firing probability**

*(Crochet et al., Neuron 2011 )*

# ▪ Cortical inhibition mediates sparse response

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




$E_{rev}$ $GABA_A$ ~ -80 mV

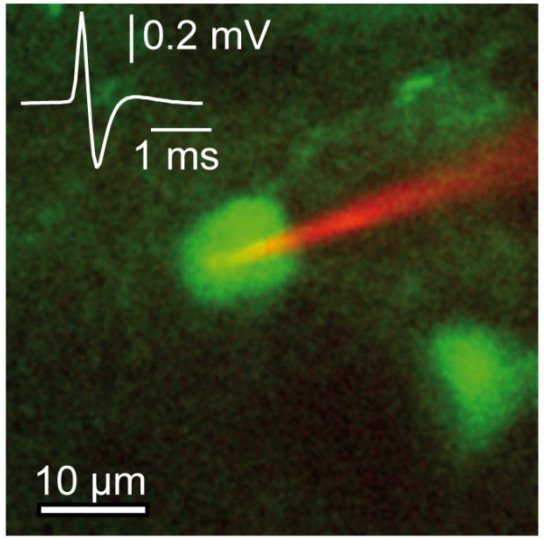
$E_{rev}$ AMPA ~ 0 mV

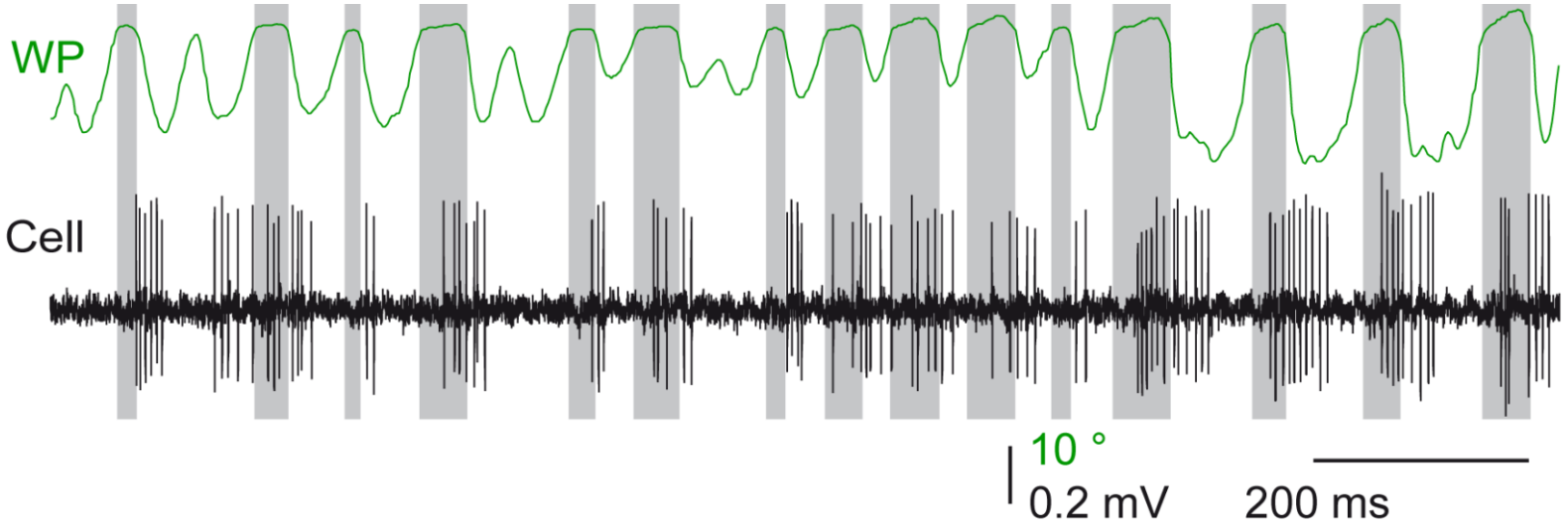
$E_{rev}$ NMDA ~ 0 mV

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

# Cortical inhibition mediates sparse response

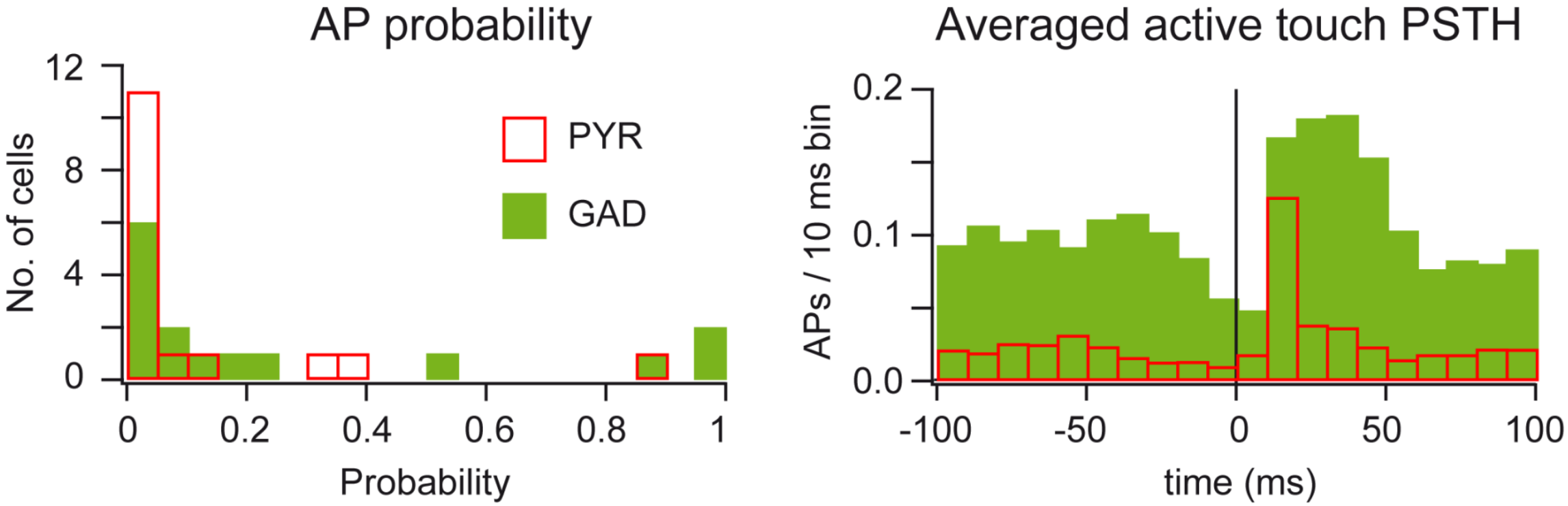
Targeted juxtacellular recording in GAD67-GFP knockin mouse




*(Crochet et al., Neuron 2011 )*

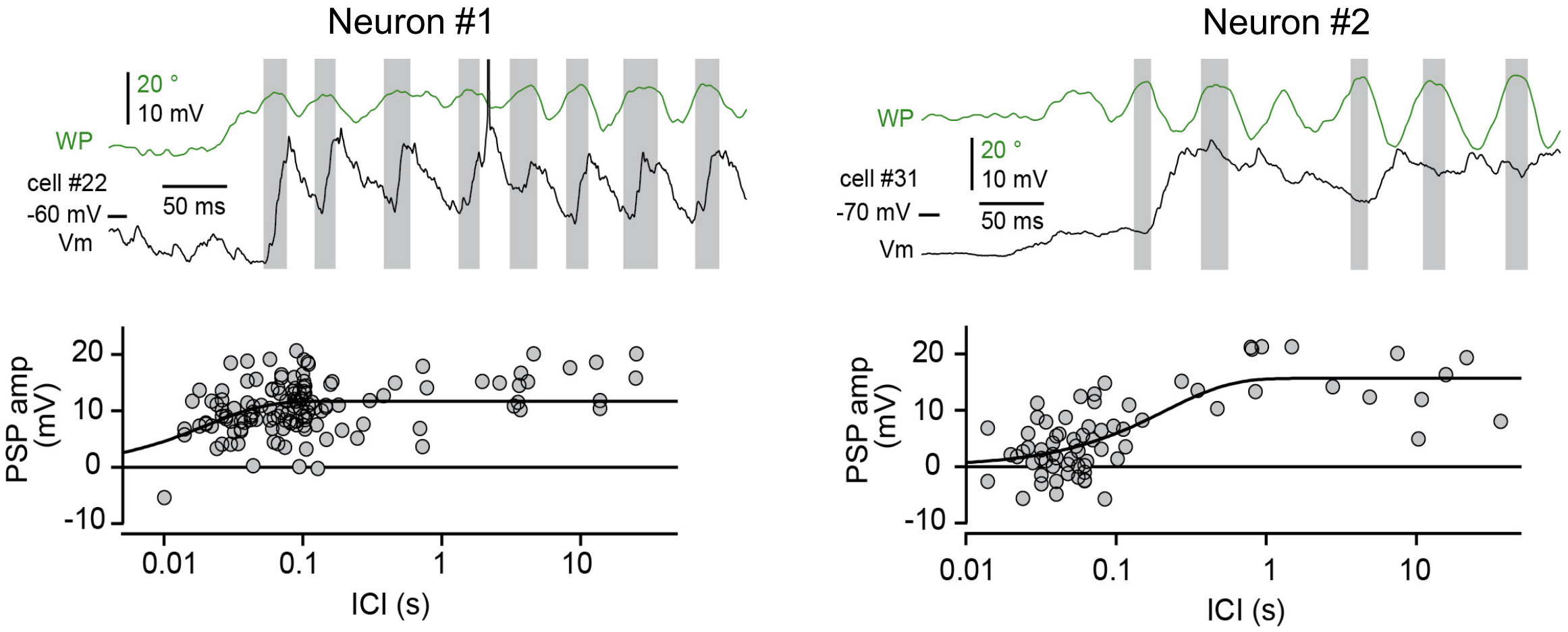
# Cortical inhibition mediates sparse response




*(Crochet et al., Neuron 2011 )*

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

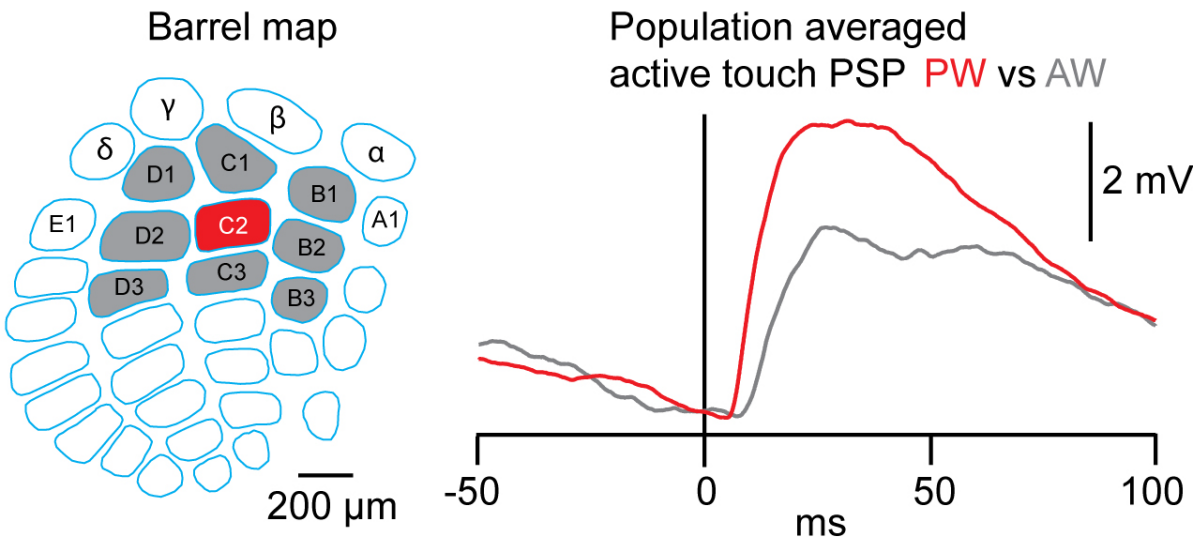
# Short-term dynamics

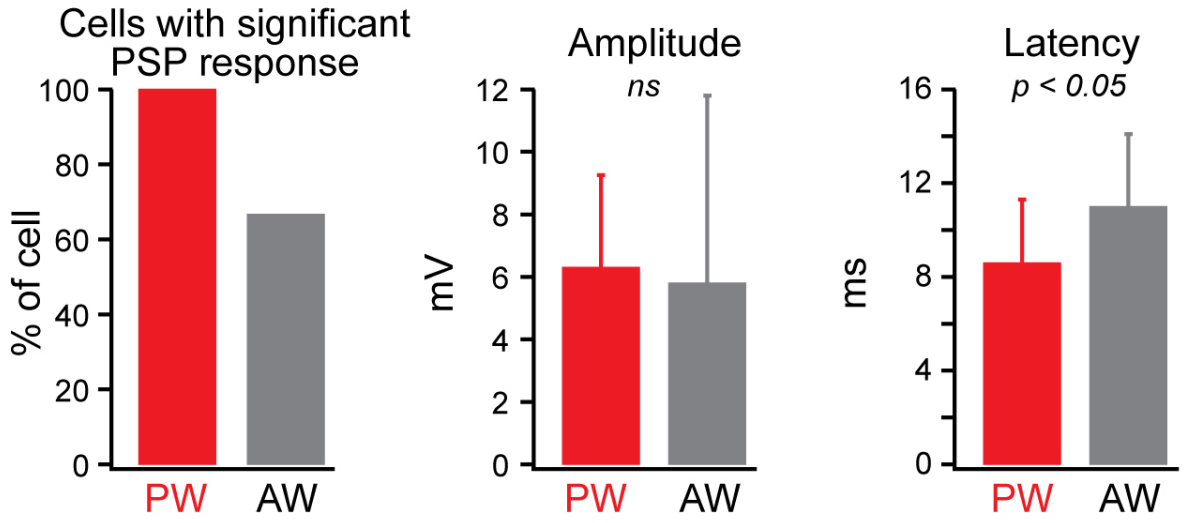



*(Crochet et al., Neuron 2011 )*

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

# Principal vs surrounding cortical columns



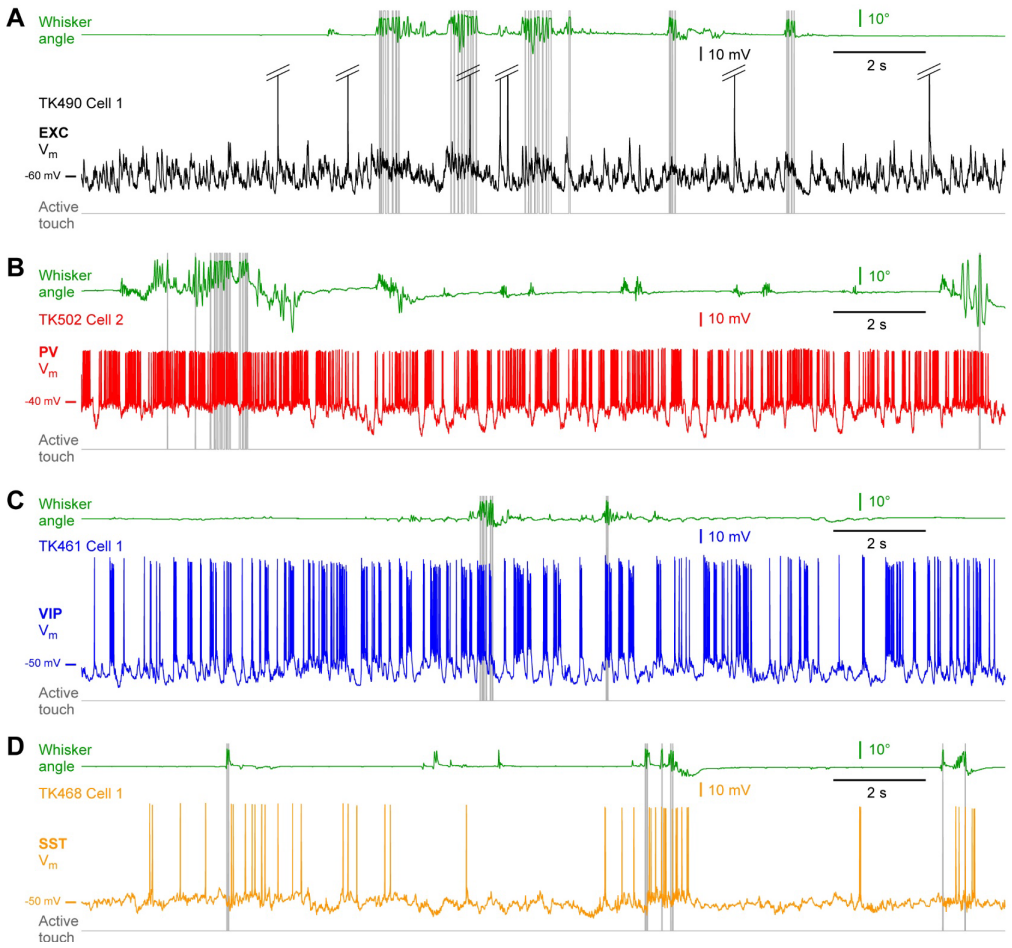

**=> Decreased response probability and longer latencies in surrounding vs principal cortical columns**

*(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 ?