Inhibitory circuitry mechanisms for cortical processing and dynamics

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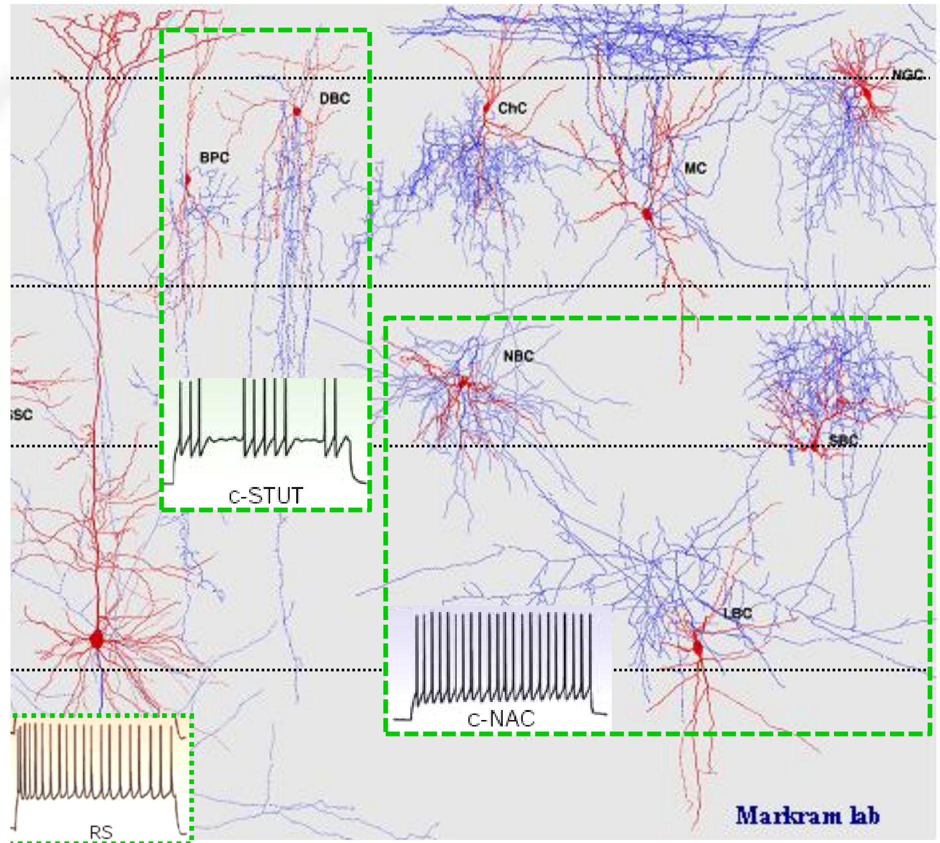
Cell constituents constructing the brain



Inhibitory GABAergic interneruon (‘‘butterflies of the soul”- R.S. Cajal, 1932)

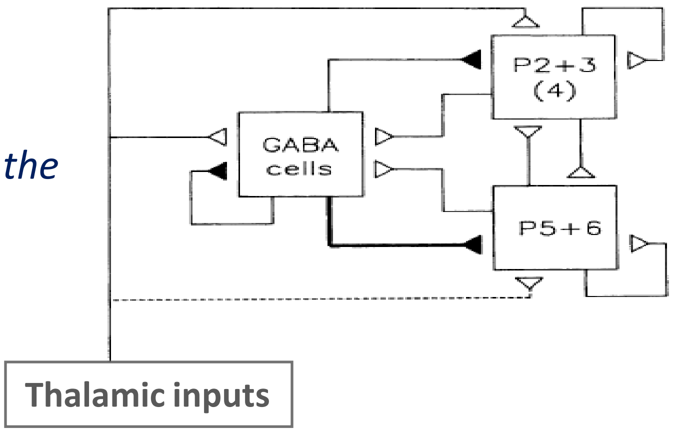
-More than 20 types, each possessing unique connectivity, territory & firing;

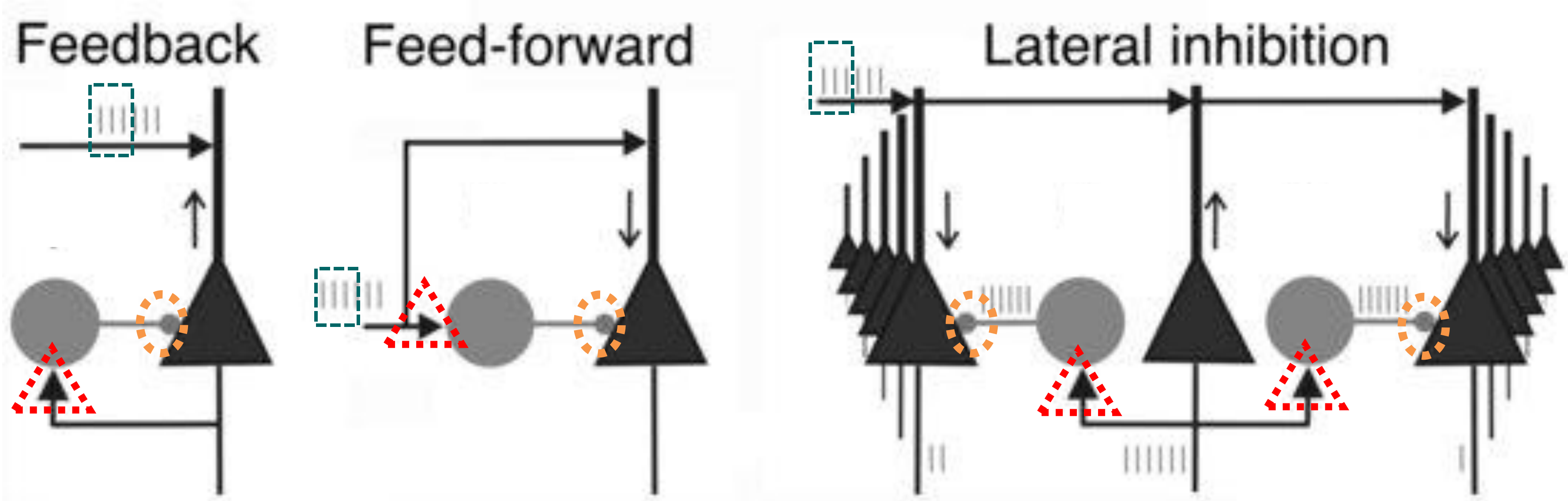
-Highly related to neural disease, e.g. epilepsy, schizophrenia, autism et al.

Working scenarios of GABA inhibitory circuits

Canonical Cortical Circuit

… All regional anatomical explorations implicate this postulate: a common functional identity [is determined by] the same type of structure and connections, whatever the mammal examined. *—Cajal, 1922*





Stabilizing

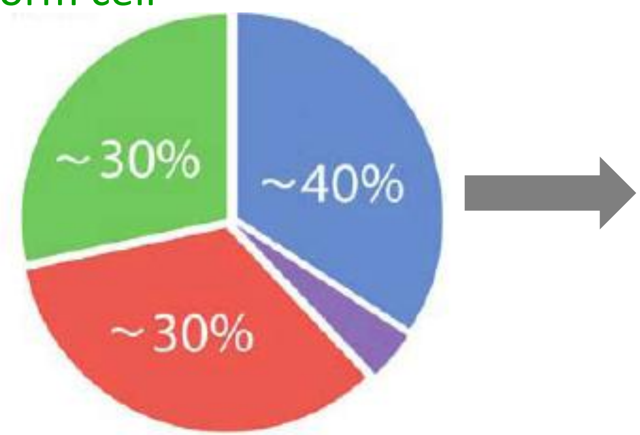
Filtering

Segregating

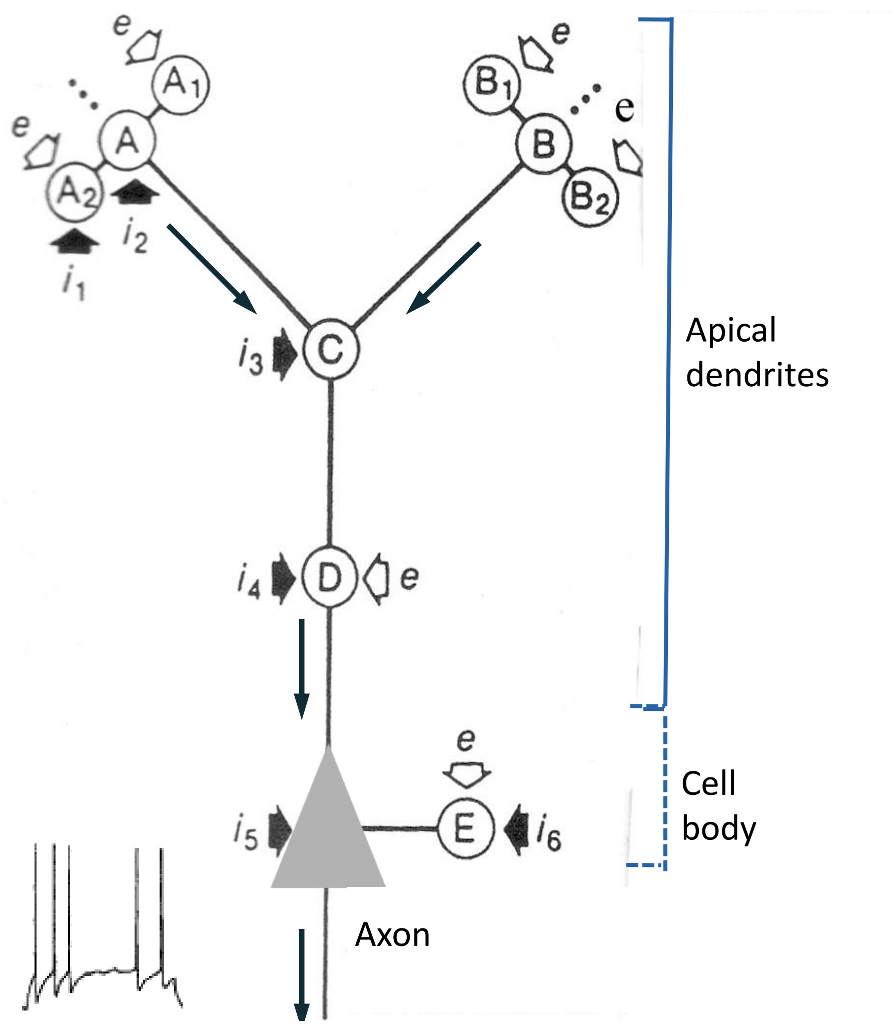
Fine-control of cortical vocabulary by enriched inhibitions from three major subtypes of inhibitory interneurons

PV expressing cells:
Basket cell
Chandelier cell
(somatic targeting)

5-HT3aR cells:
Neurogliaform cell



SOM expressing cells:
Martinotti cell
Double bouquet cell
(dendritic targeting)



e: excitatory input; i_j: inhibitory inputs

Hensch et al., (2004) *Nat. Rev. Neurosci*; Rudy et al., (2011) *Dev. Biol.*

Outline:

On the neuronal processing function

1. Single cells processing of synaptic inputs:

   A simple arithmetic rule of dendritic integration of synaptic information.

   - Hao et al., (2009) PNAS; Zhou et al., (2013) PLoS One; Li et al., (2014) PLoS Compt Biol

2. Emergence of sensory cortical selectivity: Synaptic integration mechanism.

   -Ye et al., (2010) J Neurosci

On cortical dynamics (oscillatory activities)

1 Differential regulation of cortical β and γ oscillations by subtypes of cortical GABAergic interneurons.

Role of GABA inhibition in single cell processing

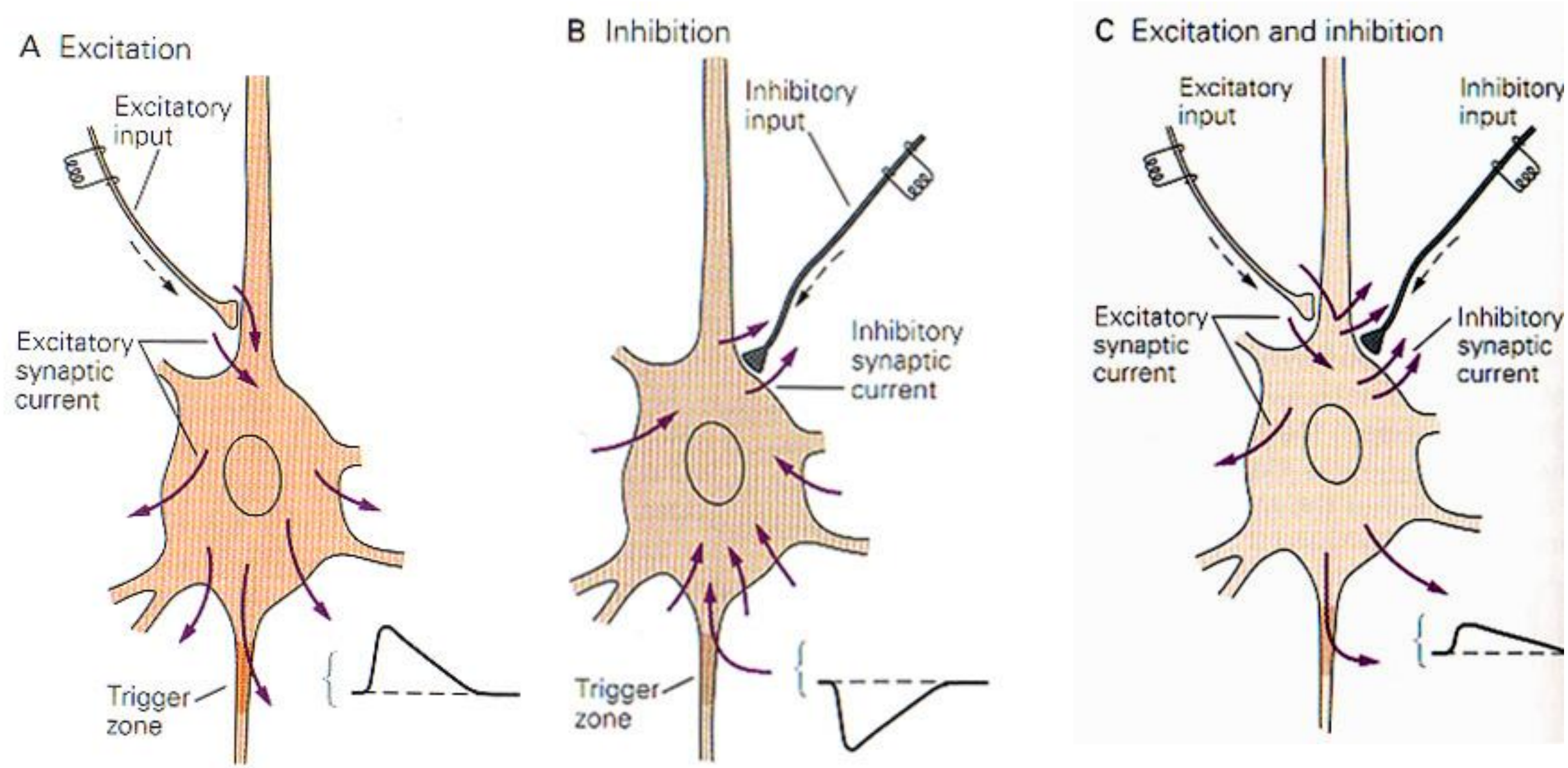
Question (*on cellular function of GABA inhibition*)

How the cellular subdomain-specific GABA inhibition interacts (or integrates) with synaptic excitation in a principle/pyramidal cell?

How does a neuron do a subtraction at its different compartments?

GABA Inhibition: *hyperpolarization* and *shunting inhibition*

EPSP (+) **IPSP (-)** **EPSP + IPSP**

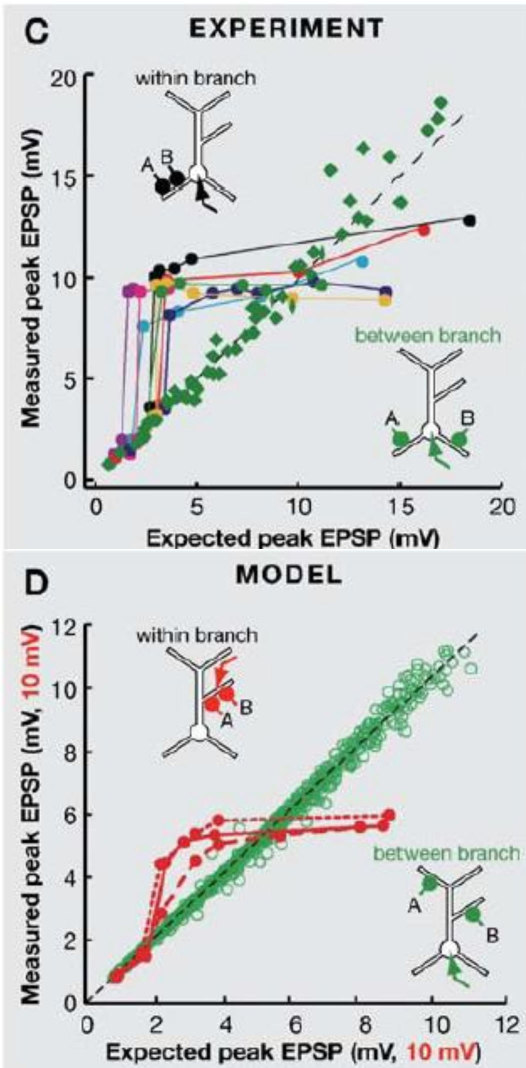


from "The principle of neural science"

“Addition” and “Subtraction” processes at the neuronal dendrite

“Addition”: Summation of EPSPs

<u>Two layer component model</u>

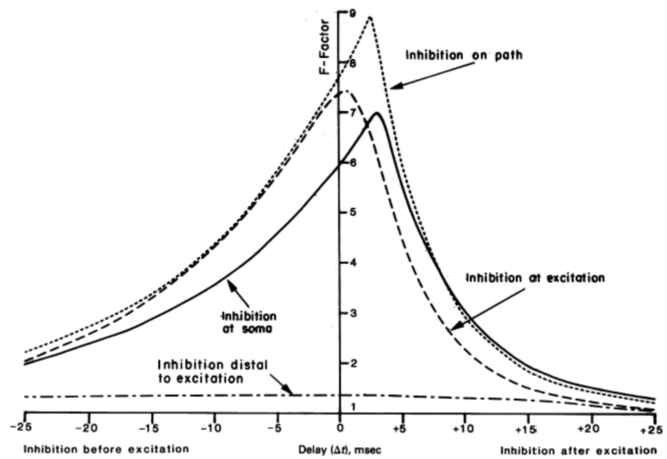


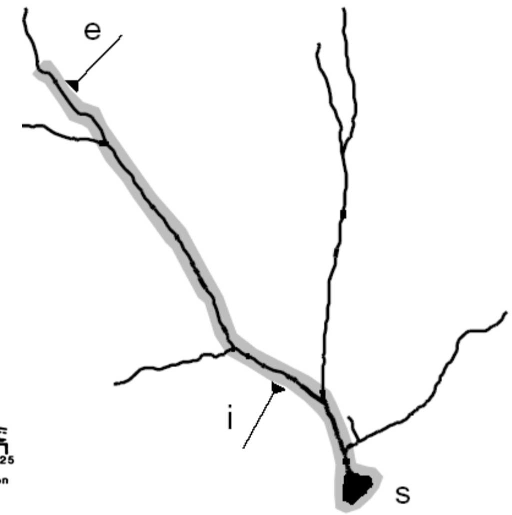
London and Hausser, 2005

“Subtraction”: Summation of EPSPs and IPSPs

Modeling prediction: **<u>On-the-path theorem</u>.**

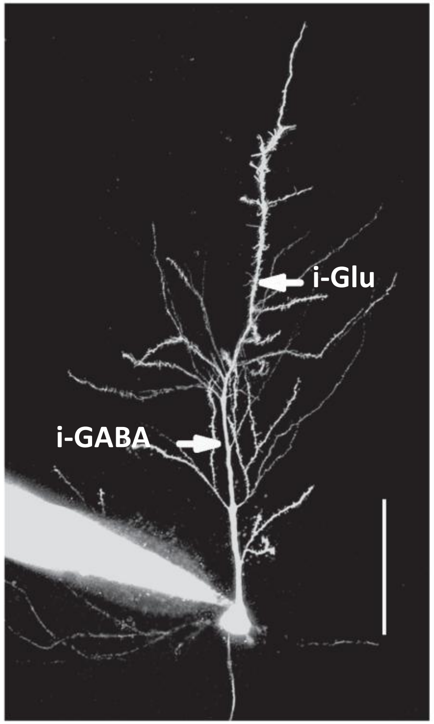
For arbitrary values of ge > 0. gi >0, Ee>0 and Ei ≤ 0, the location where ***inhibition is maximally effective*** *is always* ***on the direct path*** *from the location of the excitatory synapse to the some.*





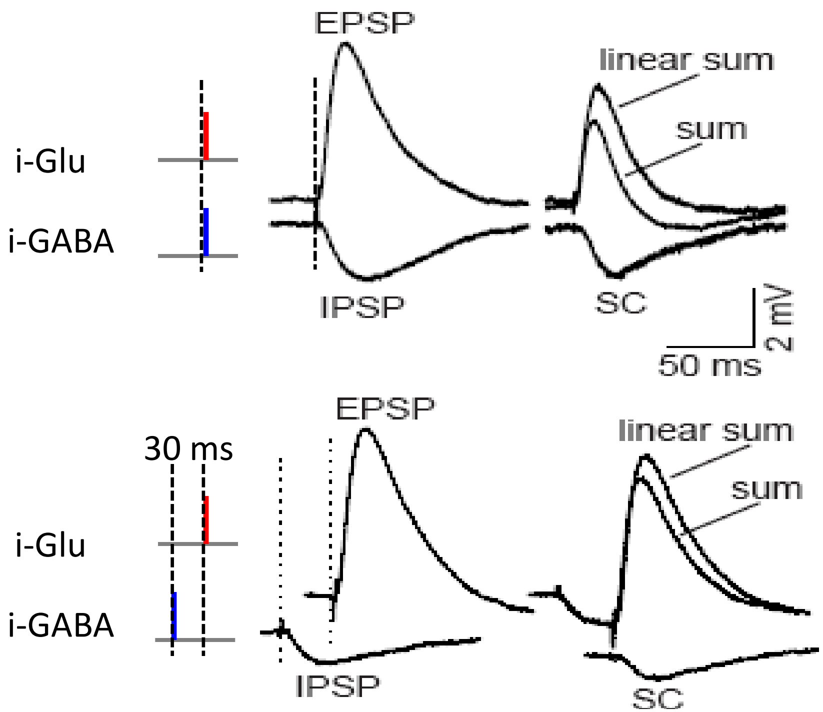
Rall (1964) in *Neural theory and model*
Koch (1999) in *Biophysics of Computation*.

Experimental measurement of E-I summation at the soma

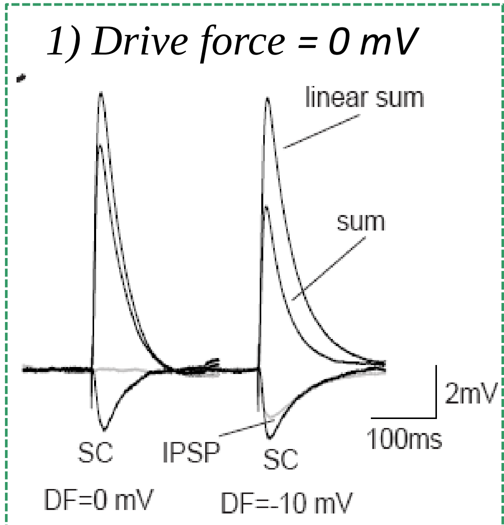


CA1 pyramidal cell loaded with Alexa dye in acute brain slice

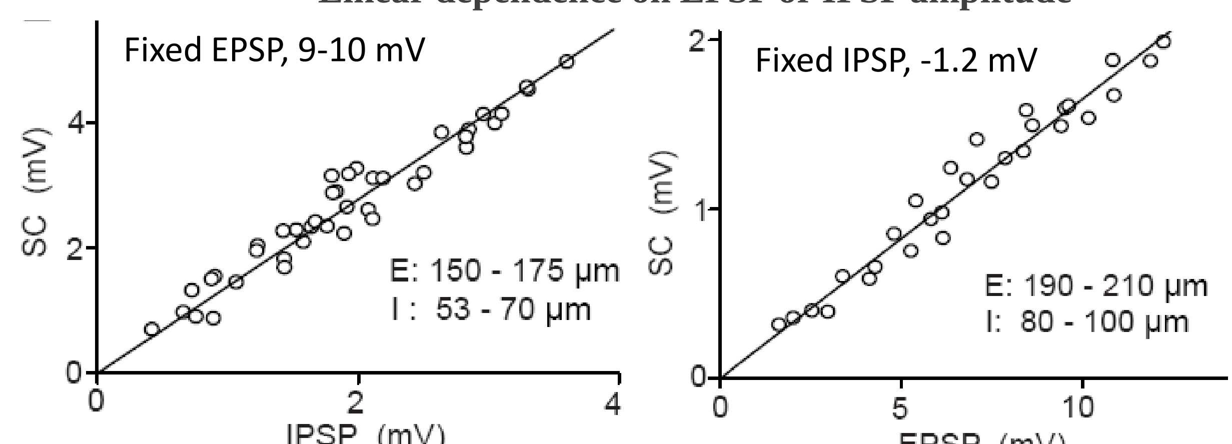
➡ iontophoretic application of glutamate or GABA



SC: Shunting component



Linear dependence on EPSP or IPSP amplitude



Hao et al., (2009) *PNAS*

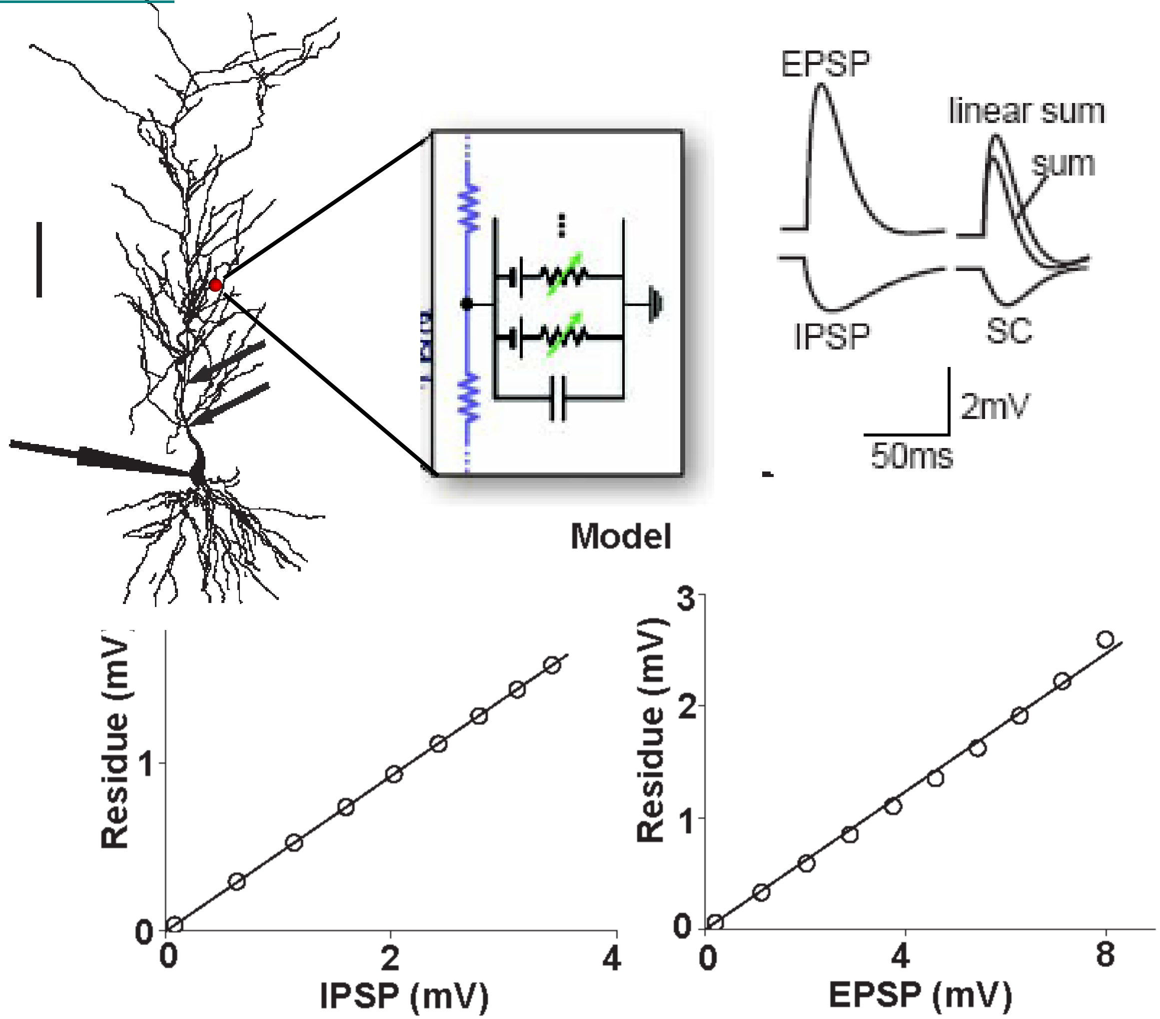
Realistic simulation in NEURON (http://www.neuron.yale.edu/neuron/)

Detailed compartmental models

Reconstructed 3D morphology of CA1 cell (Cannon et al., 1998)

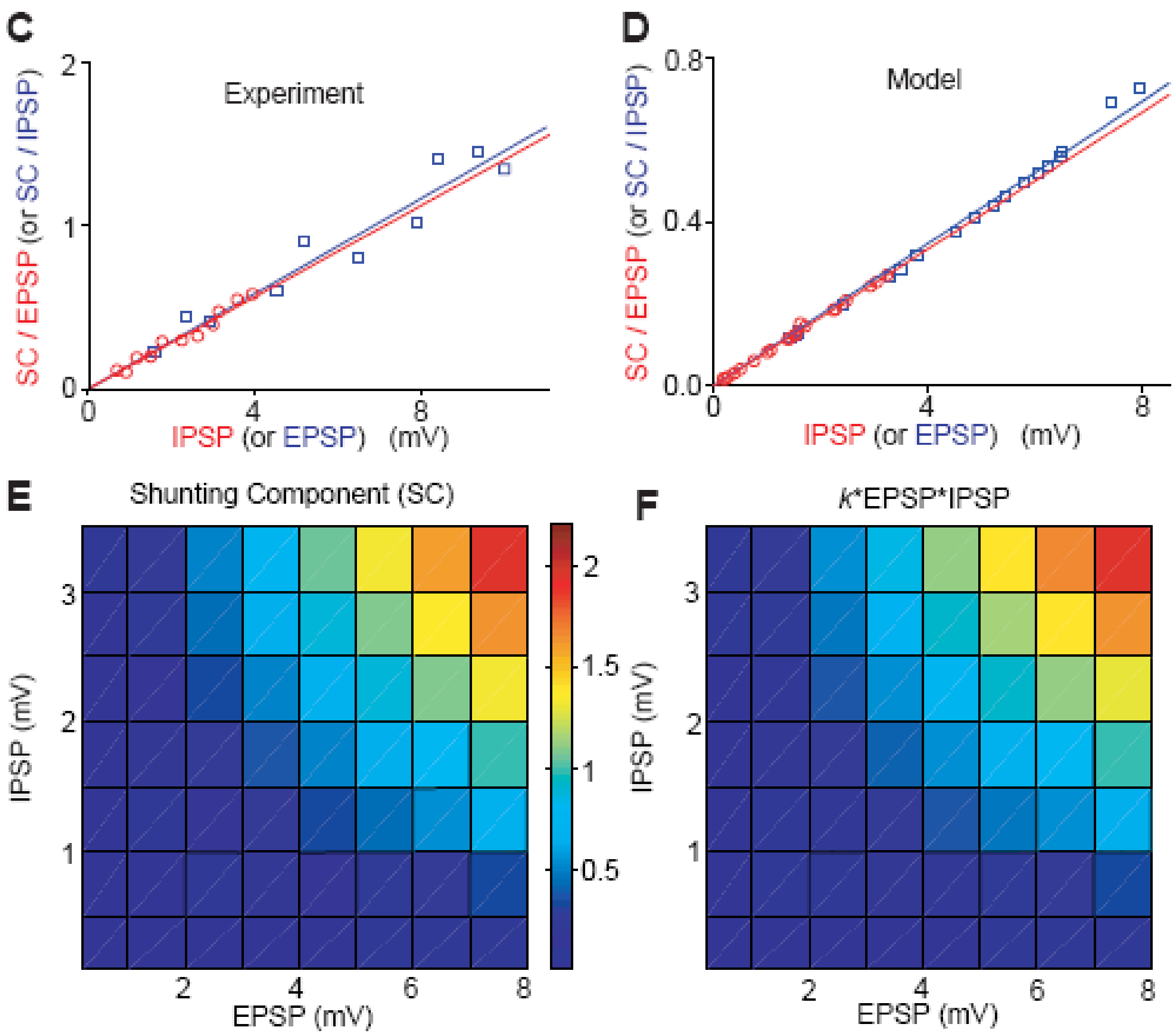
Passive cable properties

Active conductances: *gNa, gKd,* gK_A *gIh* and AMPA, NMDA, $GABA_A$ and $GABA_B$. receptors



$f(r) = k_i * V_{EPSP}$ and $f(r) = k_j * V_{IPSP}$.

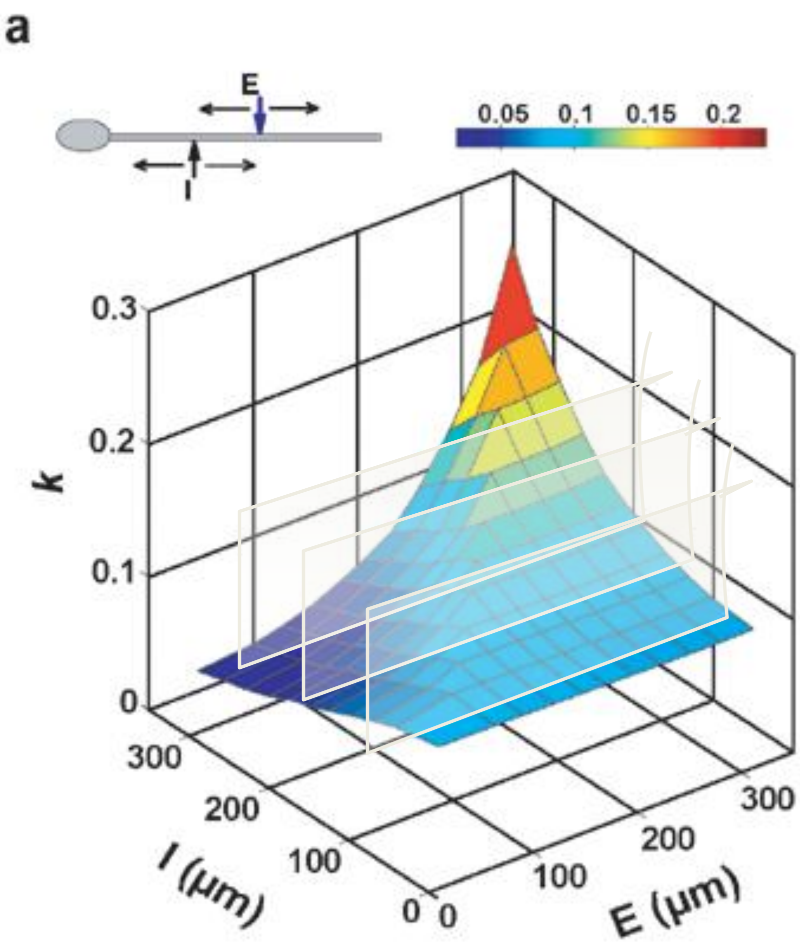
Derivation of an empirical arithmetic rule

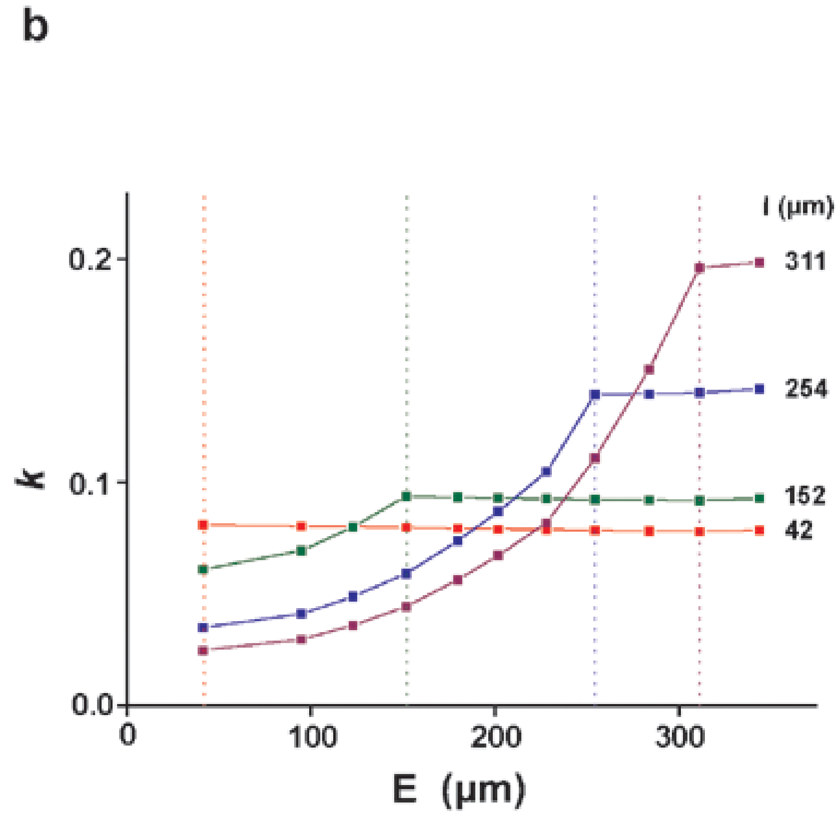


k = 0.142
RMS error: 4.9%

Somatic $V_{SUM} \approx V_{EPSP} + V_{IPSP} + k * V_{EPSP} * V_{IPSP}$

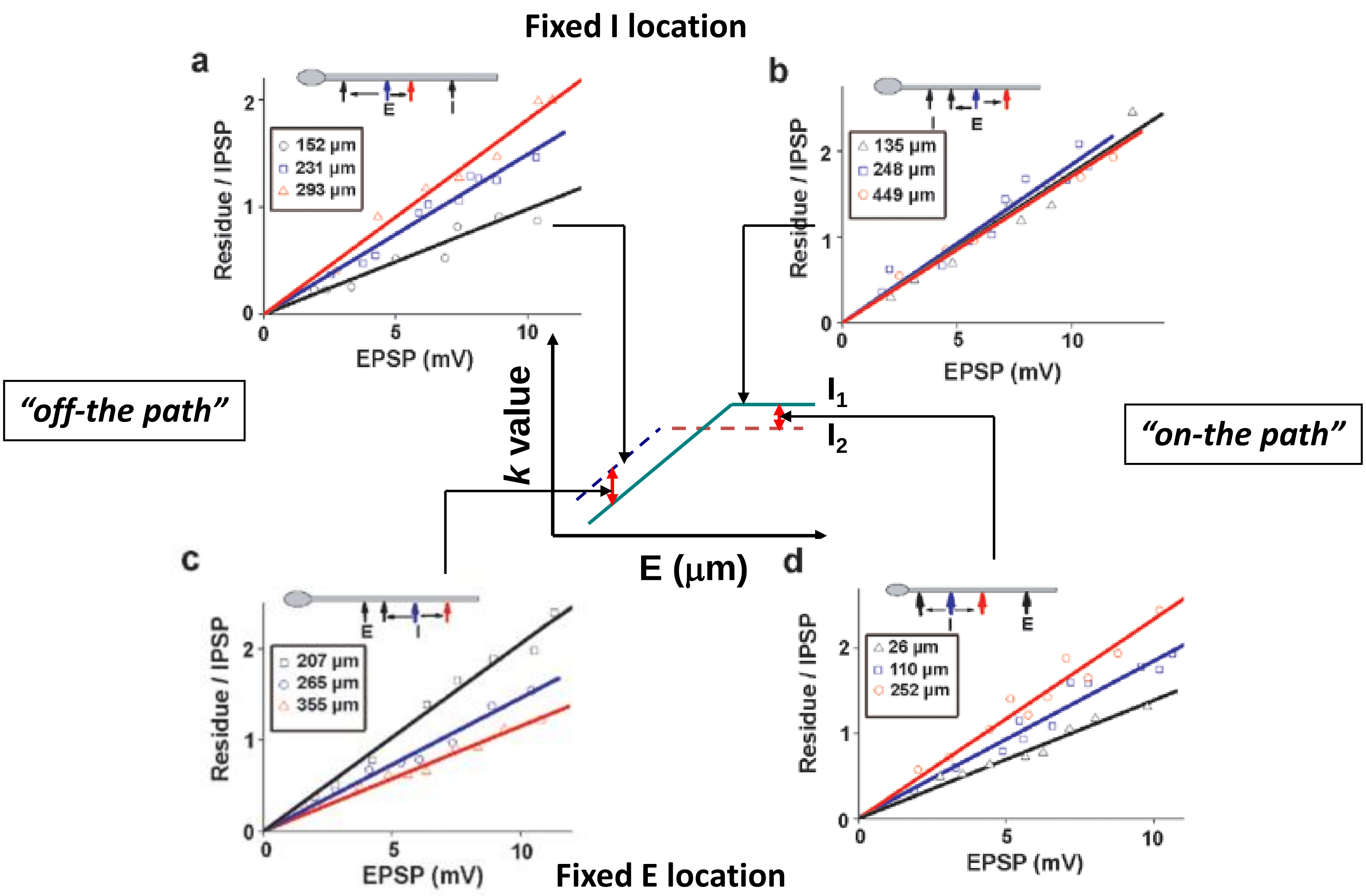
Dependence of *k* on the E and I locations – simulation results.





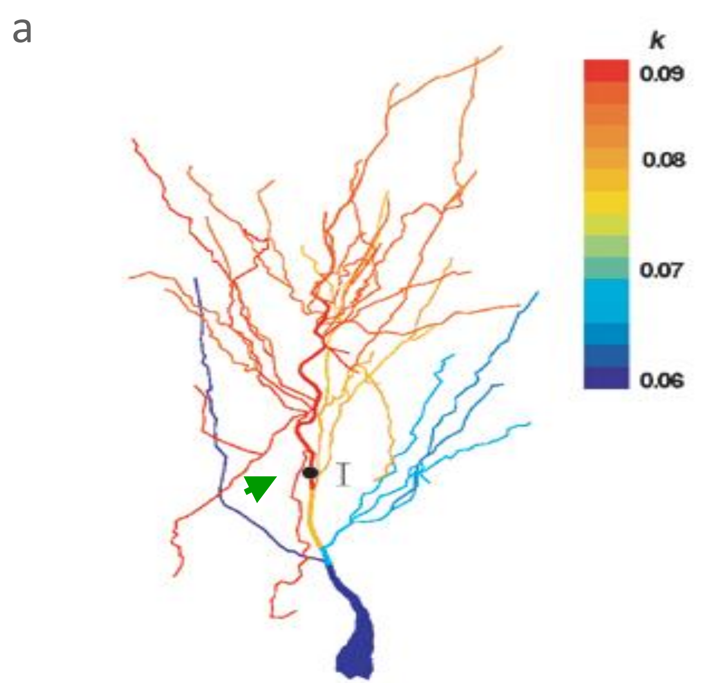
$$k_{i,j} = \frac{(V_{\mathrm{EPSP},i} + V_{I\mathrm{PSP},j} - V_{\mathrm{SUM},i,j})}{V_{\mathrm{EPSP},i} V_{I\mathrm{PSP},j}}$$

Experimental test of the dependence of *k* on the E and I locations



Dendritic domain-specific GABA shunting inhibition

Distal-proximal Asymmetry

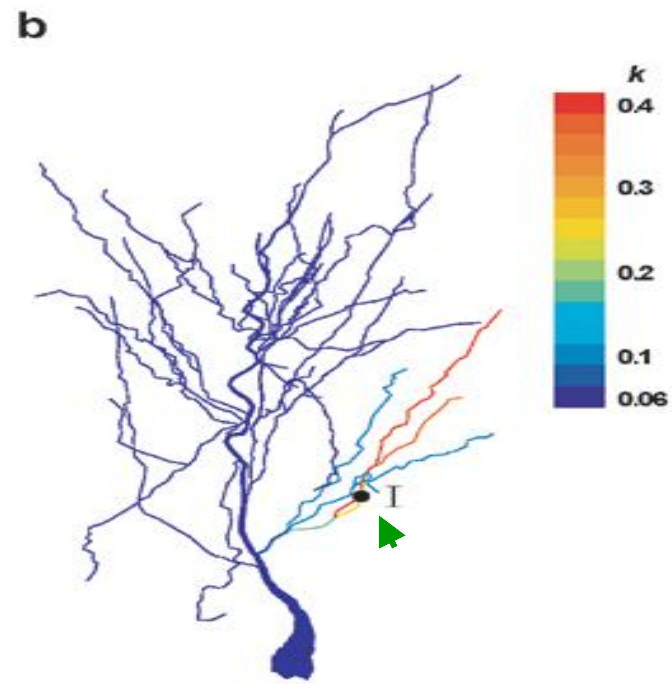


GABA input (*I*) located at the trunk

(1)*k (shunting efficacy)* remains largely constant for distal excitatory inputs (*E*s);

(2) *k* decays rapidly with *E-I* distance for proximal *E*s.

-- "on-the-path" effect



GABA input (*I*) at oblique branch

(1) Shunting effect restricted within the branch, but higher efficacy (*k values*)

(2) Same distal-proximal asymmetry.

-- local operator in branches

Summary I

1. A simple empirical function quantitatively describing spatial summation of excitatory and inhibitory inputs in single principal cell:

$$\text{Somatic } V\text{sum} \approx V_{\text{EPSP}} + V_{\text{IPSP}} + k * V_{\text{EPSP}} * V_{\text{IPSP}}$$

2. A biophysical base for understanding domain-specific inhibition produced by different types of inhibitory interneuron.

Hao et al., (2009) PNAS

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Bilinearity in Spatiotemporal Integration of Synaptic Inputs

Songting Li[1], Nan Liu[2], Xiao-hui Zhang[2], Douglas Zhou[1]*, David Cai[1,3,4]*

The simple empirical rule is further generalized to a bilinear dendritic integration rule, in which the spatiotemporal summation of all synaptic inputs at discrete times can be decomposed into the sum of all possible pair-wise integration as follows.

$$V_S(t) = \sum_p V_E^p(t) + \sum_q V_I^q(t) + \sum_{i,j} \kappa_{EI}^{ij}(t) V_E^i(t) V_I^j(t) + \sum_{k,l} \kappa_{EE}^{kl}(t) V_E^k(t) V_E^l(t) + \sum_{m,n} \kappa_{II}^{mn}(t) V_I^m(t) V_I^n(t)$$

where V_S denotes the SSP, V_E^p denotes the p^{th} individual EPSP, V_I^q denotes the q^{th} individual inhibitory postsynaptic potential (IPSP), κ_{EI}^{ij}, κ_{EE}^{kl}, and κ_{II}^{mn} are the corresponding proportionality coefficients with superscripts denoting the index of the synaptic

Li , S.T., Liu N., Zhang X.H., Zhou D, & Cai D. (2014) **PLoS Compt. Biol.** *10(12): e1004014. doi:10.1371/journal.pcbi.1004014.*

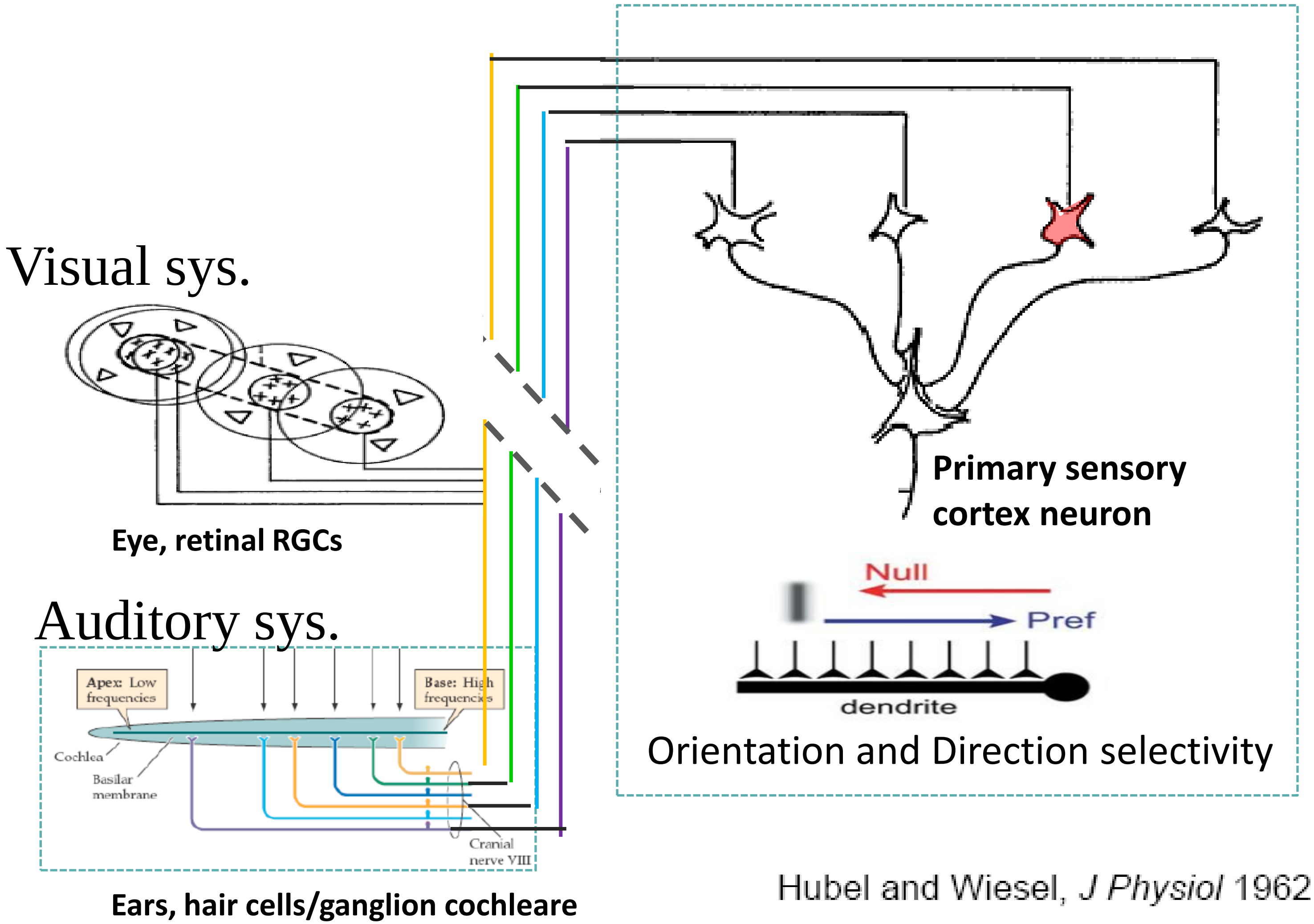
Role of GABA inhibition in circuit processing

2. **How does the integration of excitatory and inhibitory inputs determine the functional selectivity of sensory cortical cells?**

   How a sensory neuron is selectively tuned ?

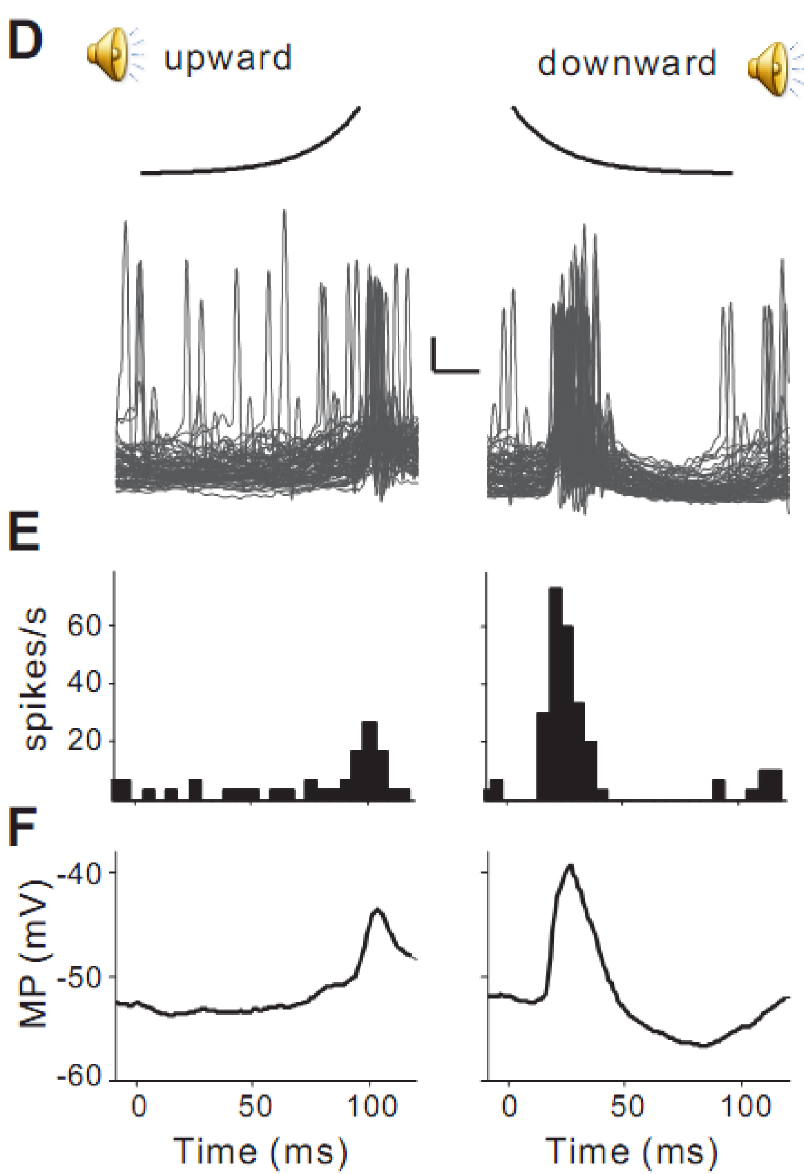
Selectivity of cortical neurons resposnes to sensory inputs

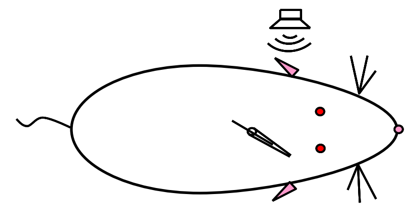
Feed-forward Model



Hubel and Wiesel, *J Physiol* 1962

Direction selective A1 neuron – Spiking rate *vs.* membrane potentials

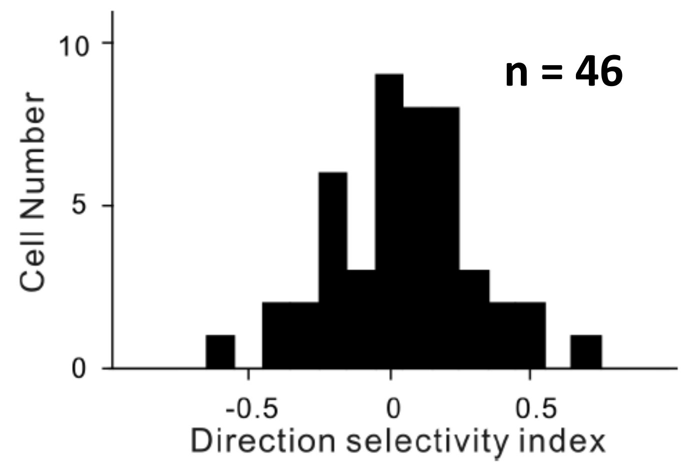




- Sound stimuli:
  - FM: 70 octave/s, either direction
  - Tone pips at pseudo-random order

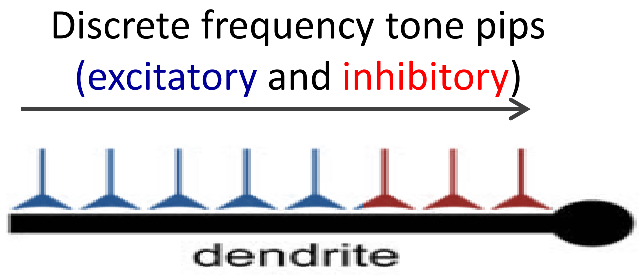
$$DI = \frac{P_u - P_d}{P_u + P_d}$$

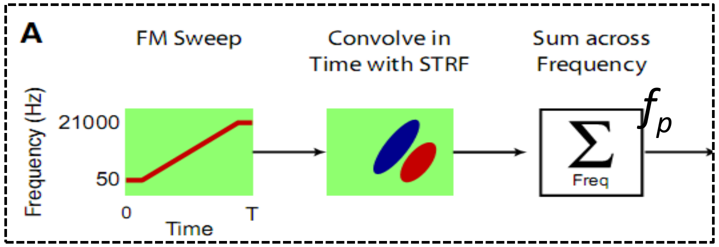
DI: Direction selectivity Index

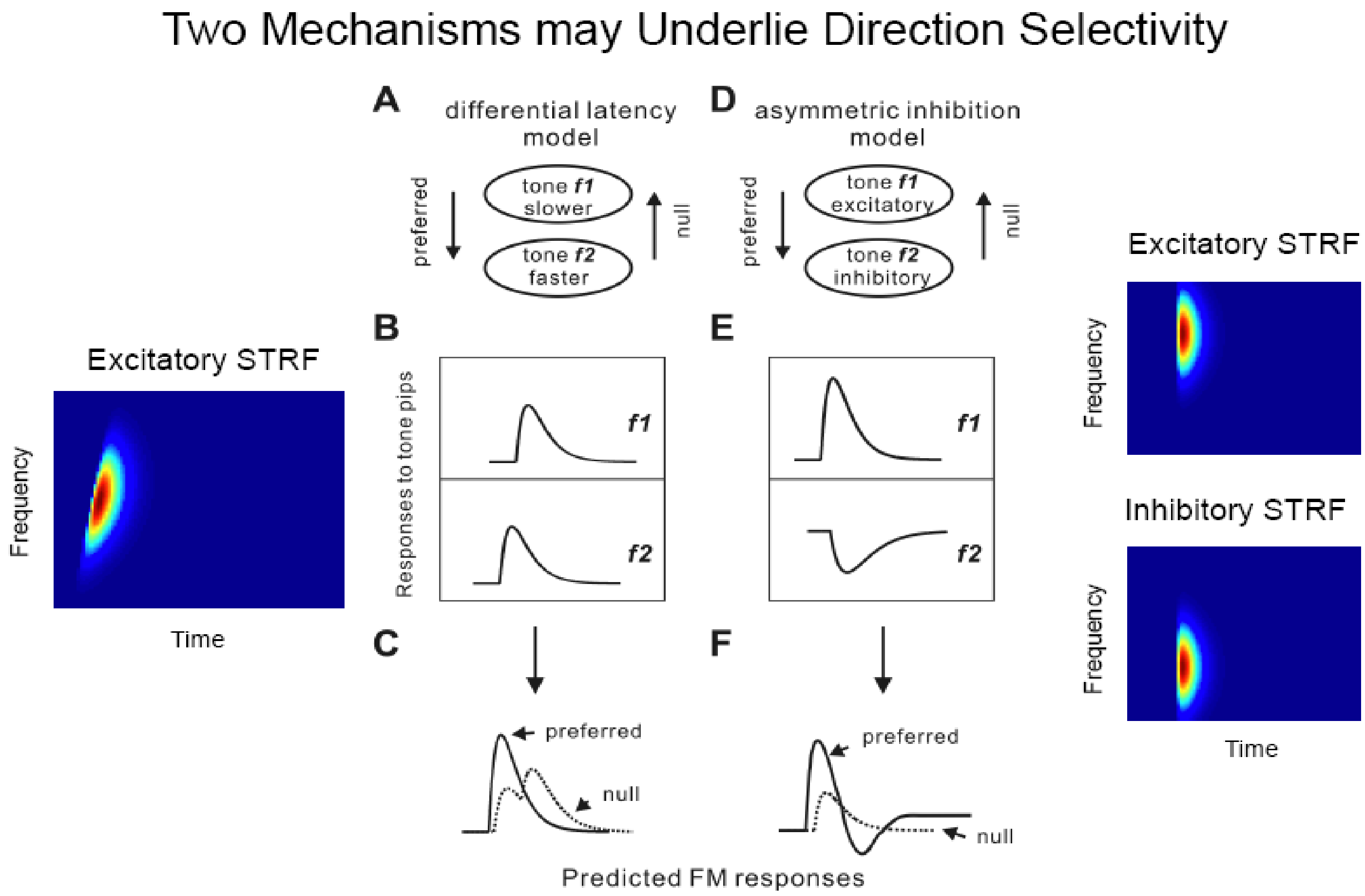


Ye CQ et al., (2010) J. Neurosci.

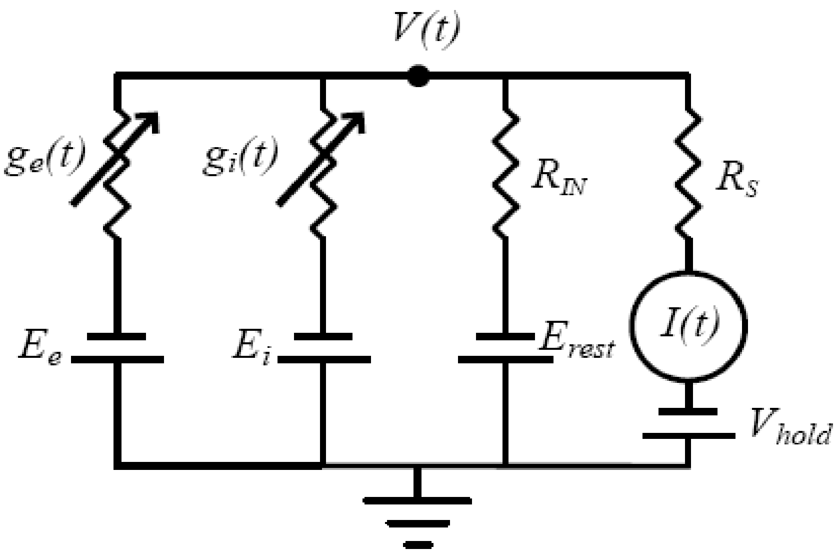
Models of integration of excitatory and inhibitory spatiotemporal receptive fields (STRF)

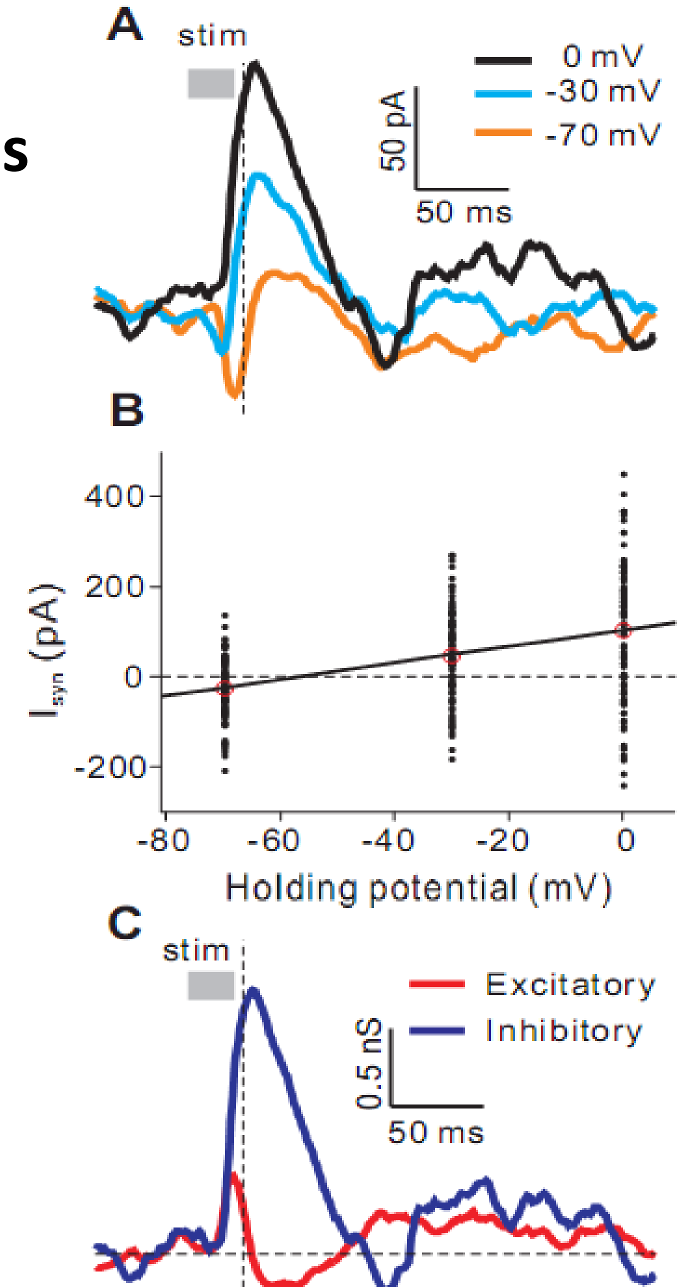






Separation of excitatory and inhibitory synaptic conductances (*Ge* & *Gi*)



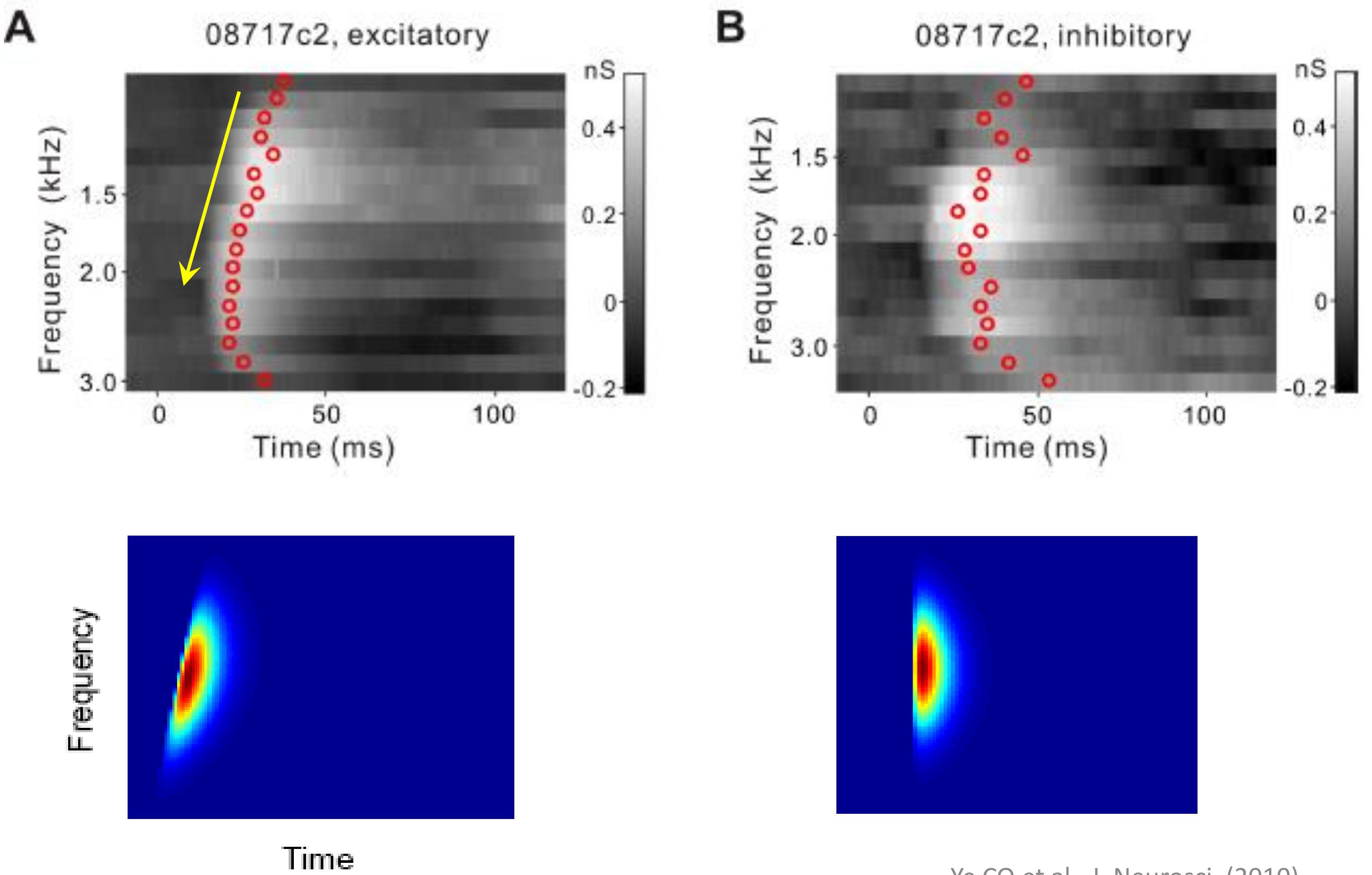


Modified from Wehr and Zador, *Nature* 2003

- **Sound stimuli: Tone pips**

Characteristics of excitatory and inhibitory STRFs from a direction selective A1 neuron (preferring upward FM sound)

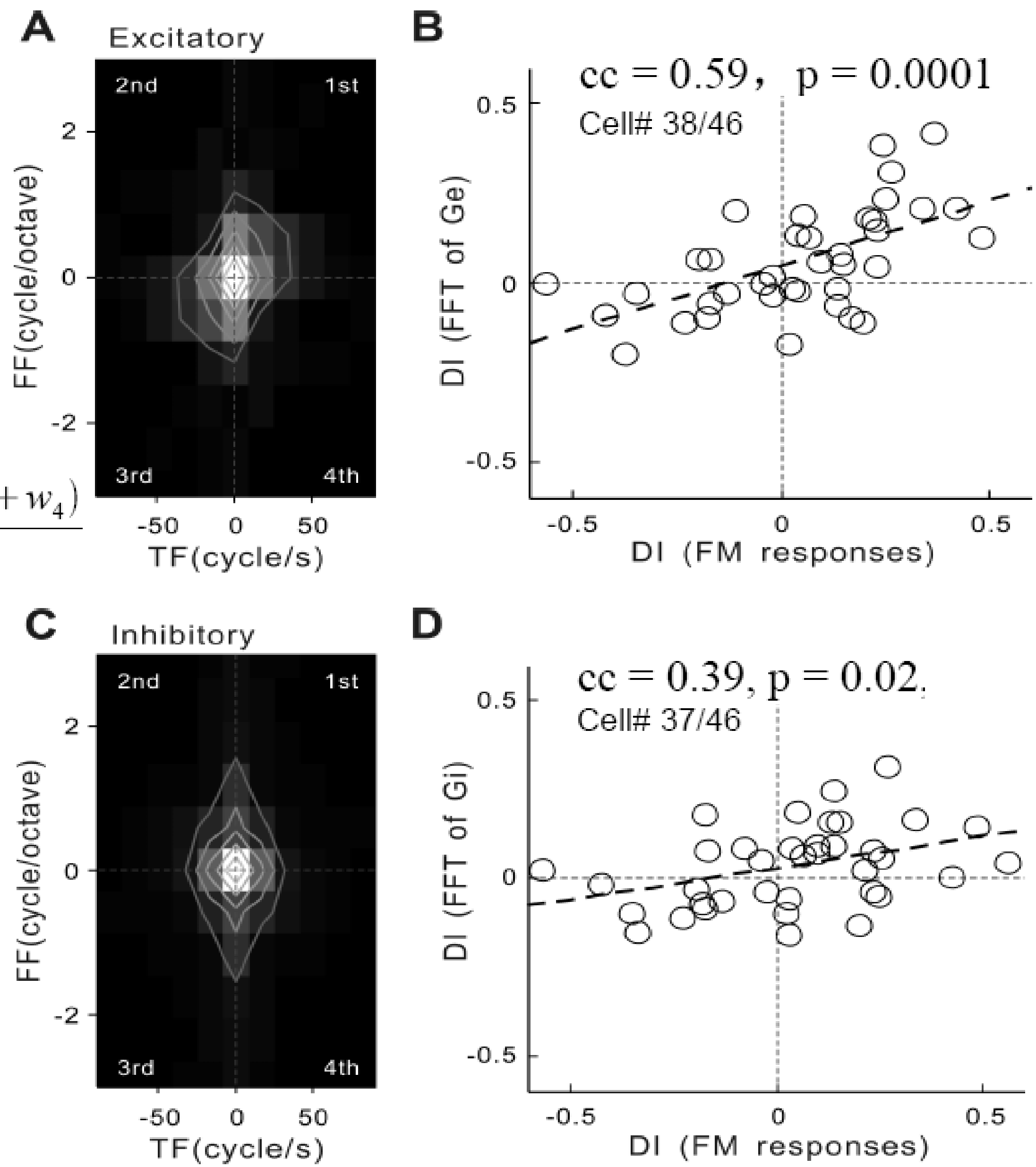
Spatiotemporal receptive fields (STRFs) of Ge and Gi

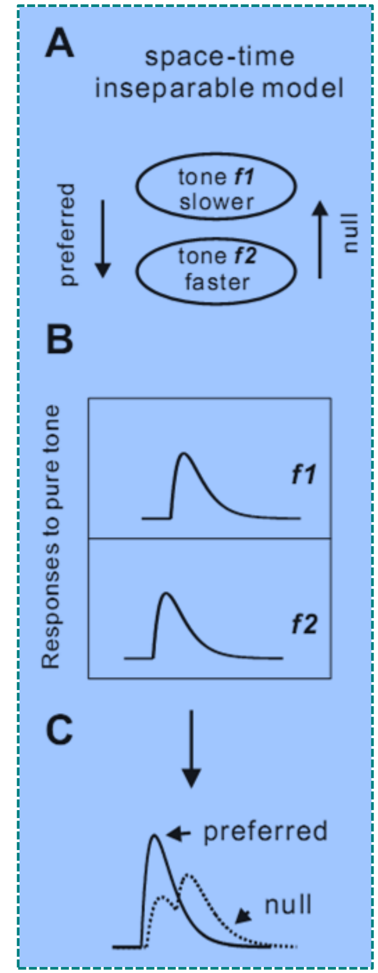


Ye CQ et al., J. Neurosci. (2010)

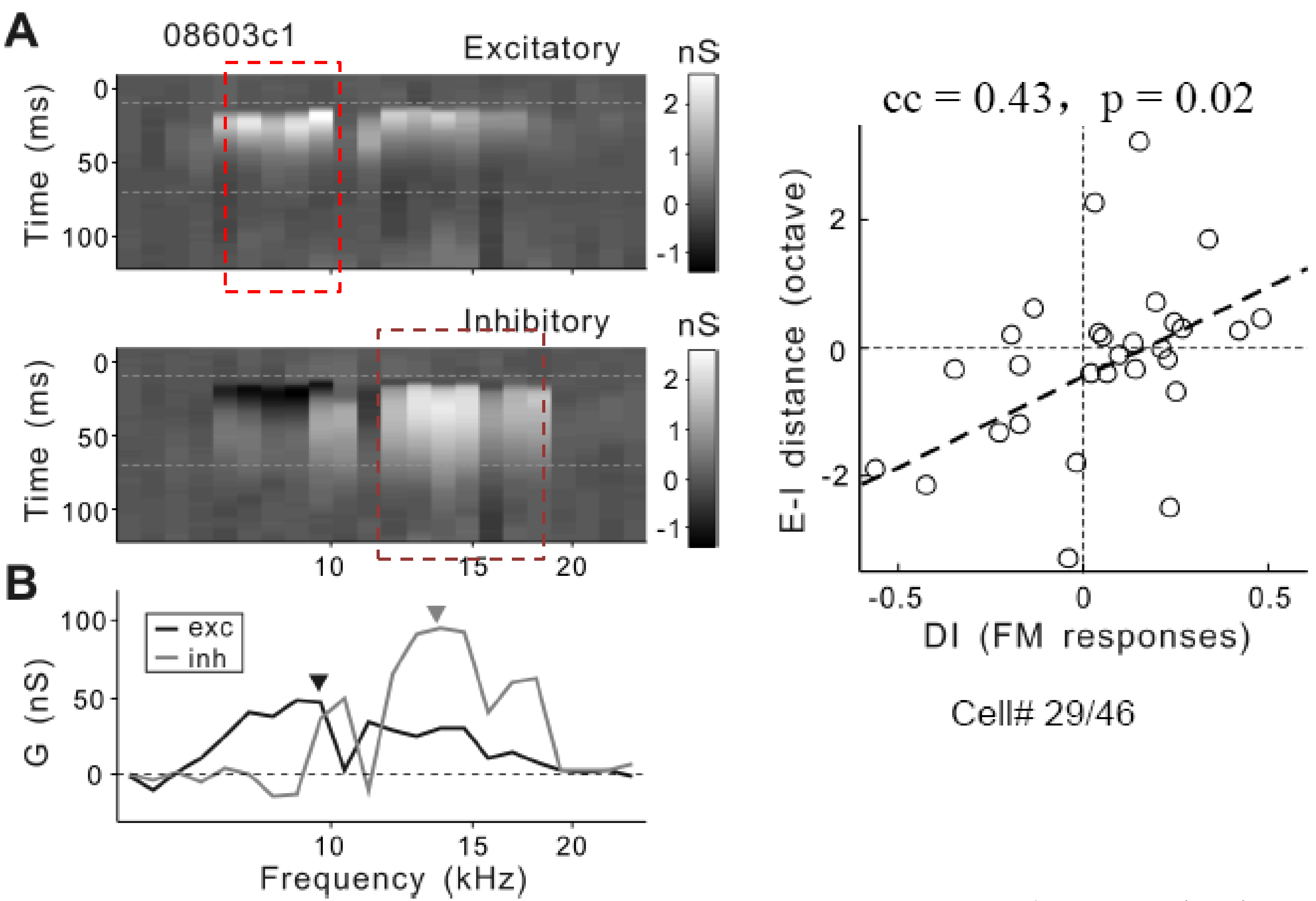
Prediction of direction selectivity (DI) from *Ge* or *Gi* STRFs

$$DI = \frac{(w_1 + w_3) - (w_2 + w_4)}{\sum w_i}$$





Spectra offset between *Ge* and *Gi* on the STRF from direction selective A1 neurons



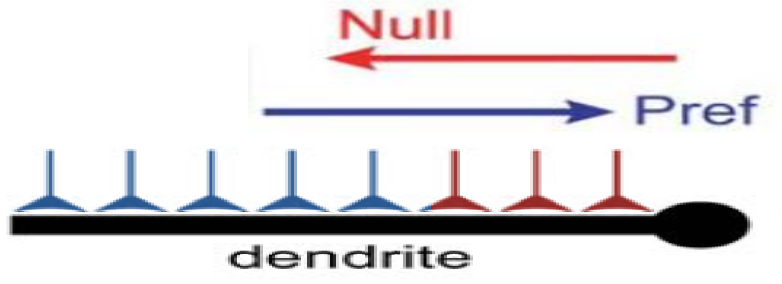
Ye CQ et al., J. Neurosci. (2010)

Summary II

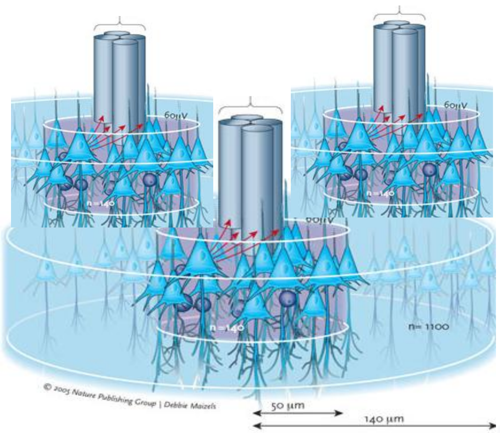
Synaptic integration mechanism underlying the emergence of direction selectivity responses to FM sound in the A1

- Differential arrival timing of excitatory inputs over the spectral (frequency) dimension
- Asymmetric excitatory (*Ge*) and inhibitory(*Gi*) receptive field (RF) over the spectral dimension
- Both two mechanisms may generally underly the feature selectivity across different sensory modalities.

Ye et al., J Neurosci (2010)



Role of GABA inhibition in regulating cortical dynamics



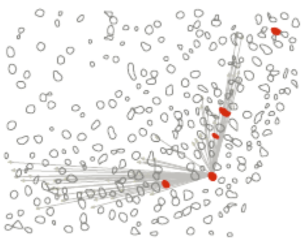
Temporal frequencies of synchronized neuronal activity in a neural network

-assayed by the spike synchrony among cells and local field potentials (LFPs, rhythmic synaptic activities)

Brainwave Type	Frequency range	Mental states and conditions
Delta	0.1Hz to 3Hz	Deep, dreamless sleep, non-REM sleep, unconscious
Theta	4Hz to 7Hz	Intuitive, creative, recall, fantasy, imaginary, dream
Alpha	8Hz to 12Hz	Relaxed, but not drowsy, tranquil, conscious
Low Beta	12Hz to 15Hz	Formerly SMR, relaxed yet focused, integrated
Midrange Beta	16Hz to 20Hz	Thinking, aware of self & surroundings
High Beta	21Hz to 30Hz	Alertness, agitation
Gamma	30Hz to 100Hz	Motor Functions, higher mental activity

Distinct connectivity and firing during neuronal oscillations

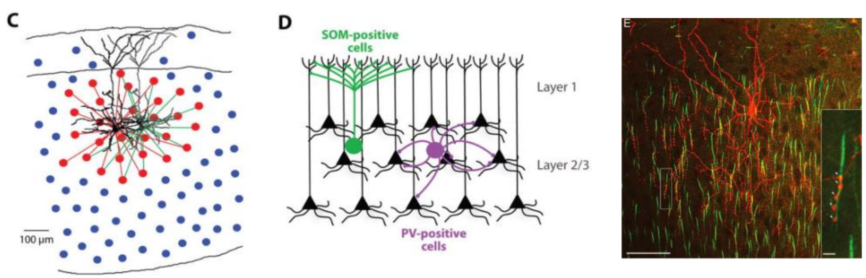
➢GABA Interneuron functions at Hub neuron orchestrate the hippocampal network activity;



Bonifizi et al., *Science* (2009)

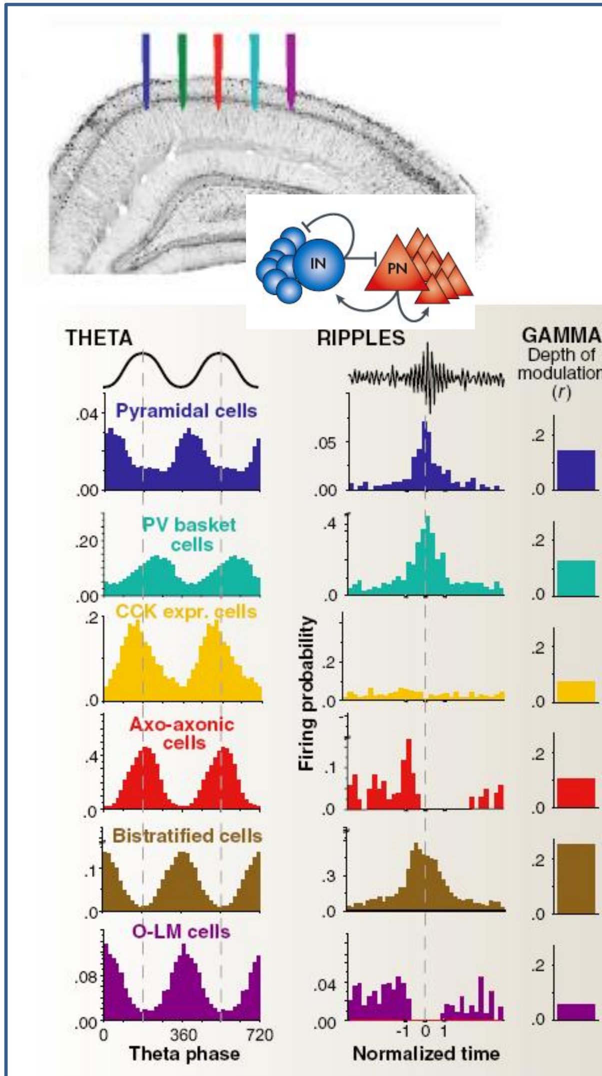
➢GABA interneurons are densely connected with neighborhood PC cells.

SOM and chandelier cells (Fino1 & Yuste , *Neuron*, 2011; Fino et al., Neuroscientist, 2013; Taniguchi, et al., *Science*, 2013)



➢A existence of long-range GABA neuron projection across different brain areas.

(Tamamaki & Tomioka, *Front. Neurosci.* 2010; Melzer, et al., *Science*, 2013)



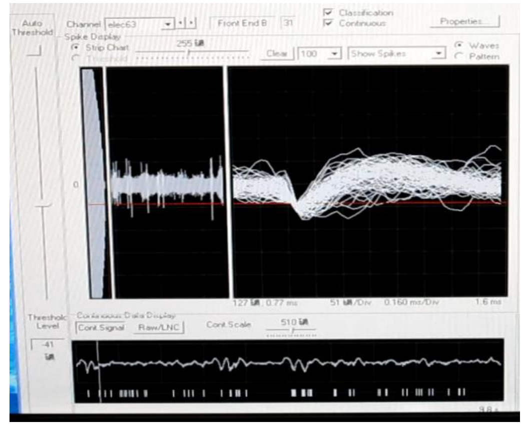
Buzsaki (2004*) Nat Neurosci*; Bartos et al., (2007) *Nat Rev Neurosci*; Klusberger & Somogyi (2008*) Science*

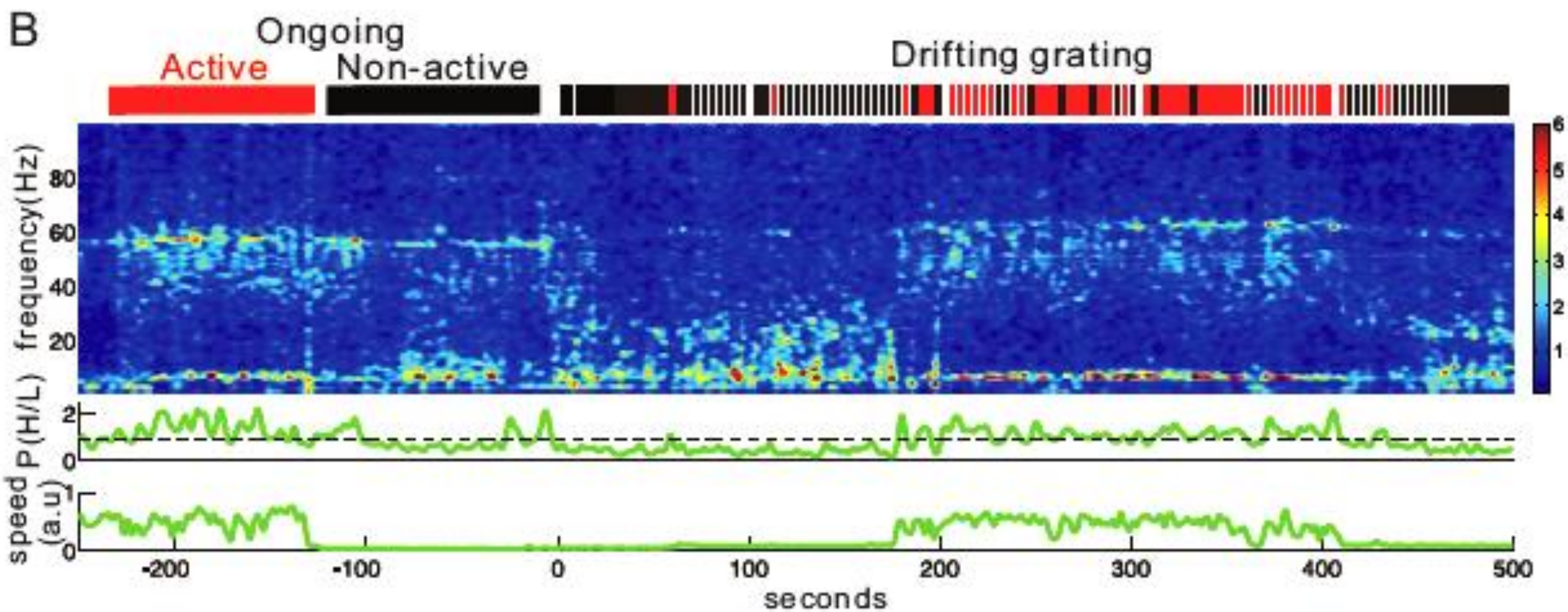
GABA circuits regulating cortical oscillations

3. How distinct subtypes of inhibitory cells and their synaptic circuits are involved in regulating synchronized cortical population activities?

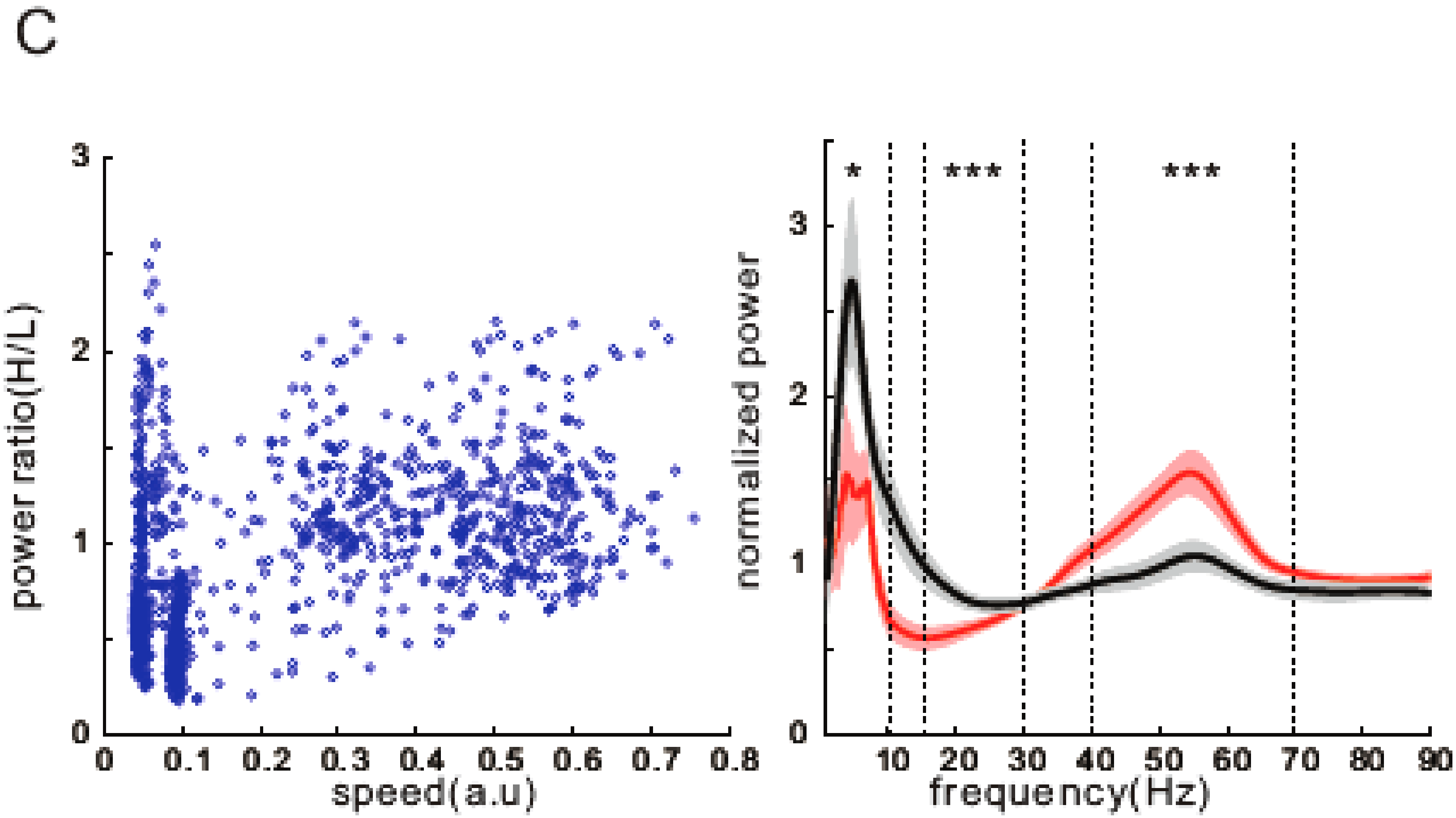
- A optogenetic study on the different inhibitory circuits

MEA recording of neuronal activities (spike and LFPs) in V1 of awake mice

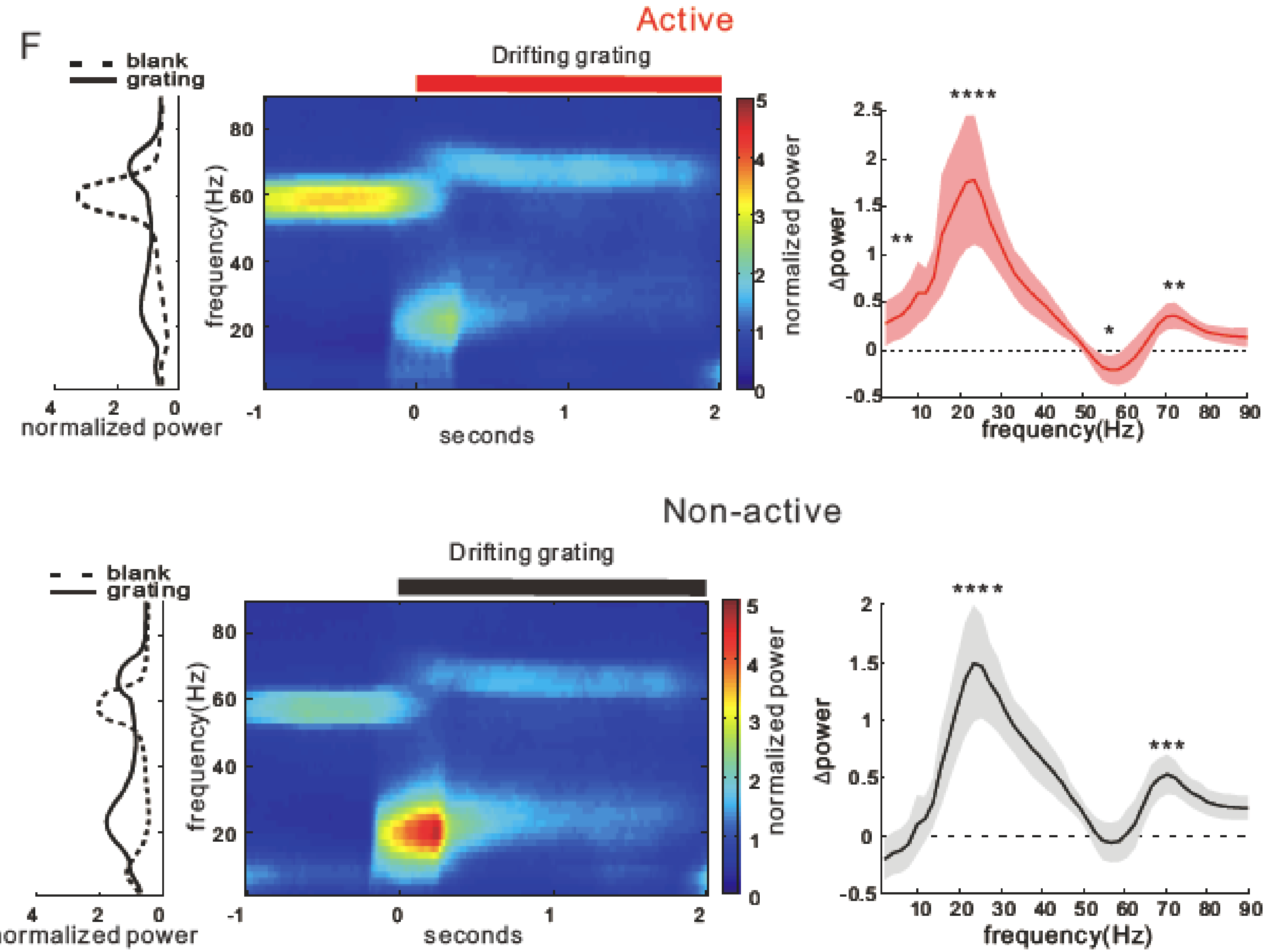




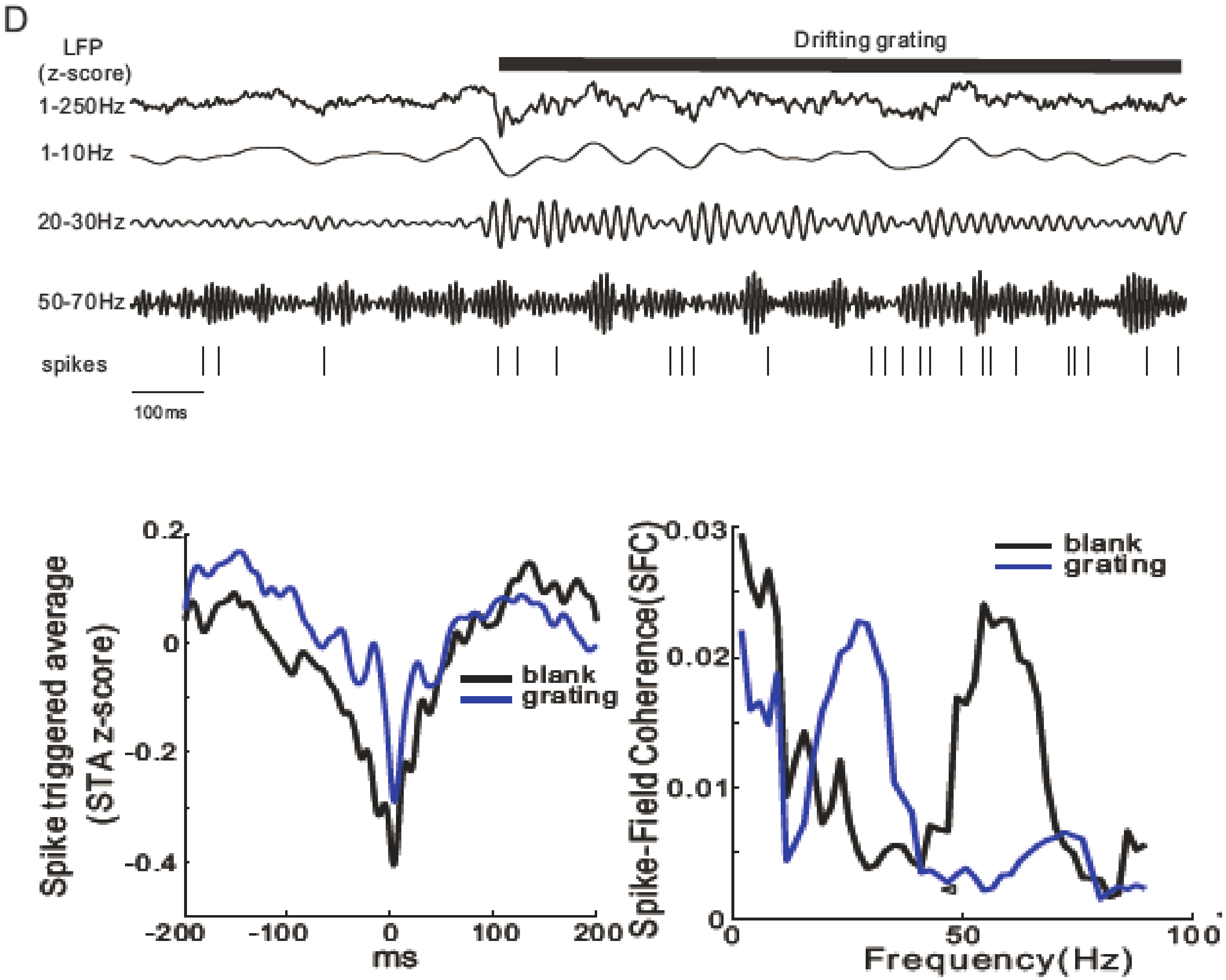
Characteristics of baseline LFPs across bands in active (running) and non-active (stationary) states

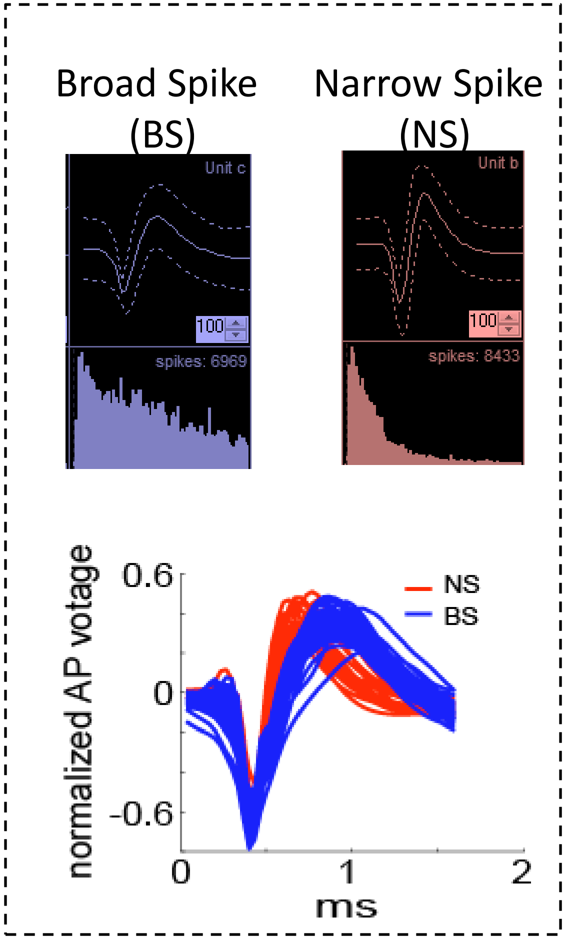


Visually evoked LFPs in active (running) and non-active (stationary) states --peaked at beta (15-30 Hz) band



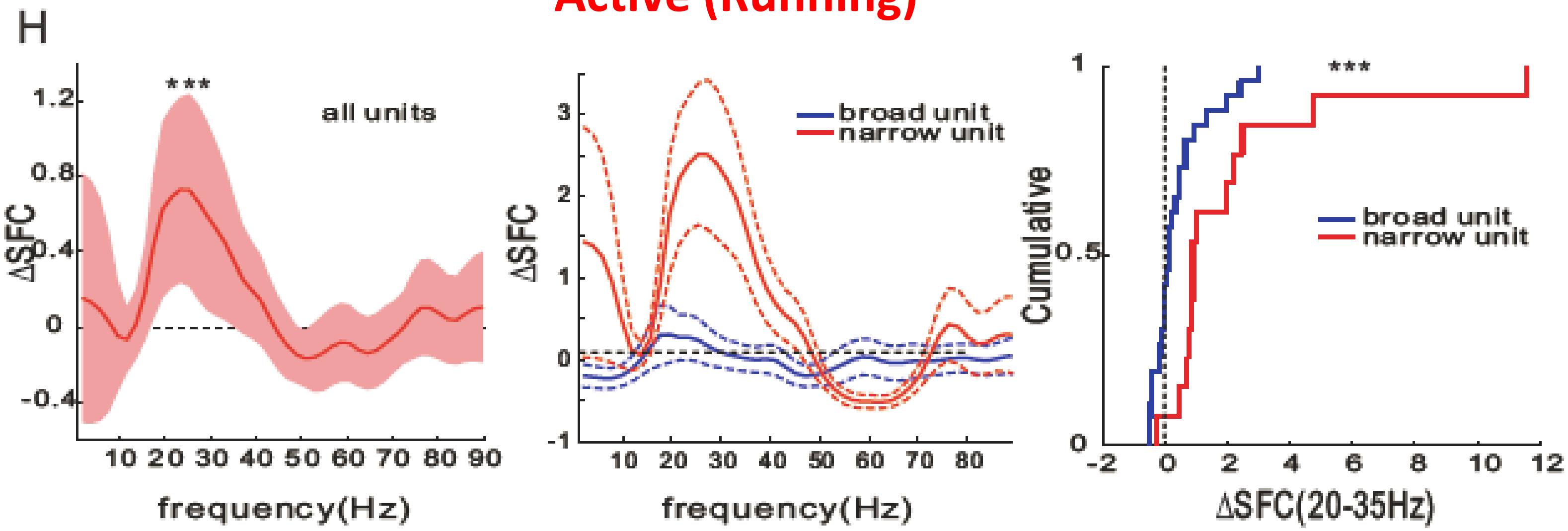
Visually evoked increase of spike field coherence (SFC)



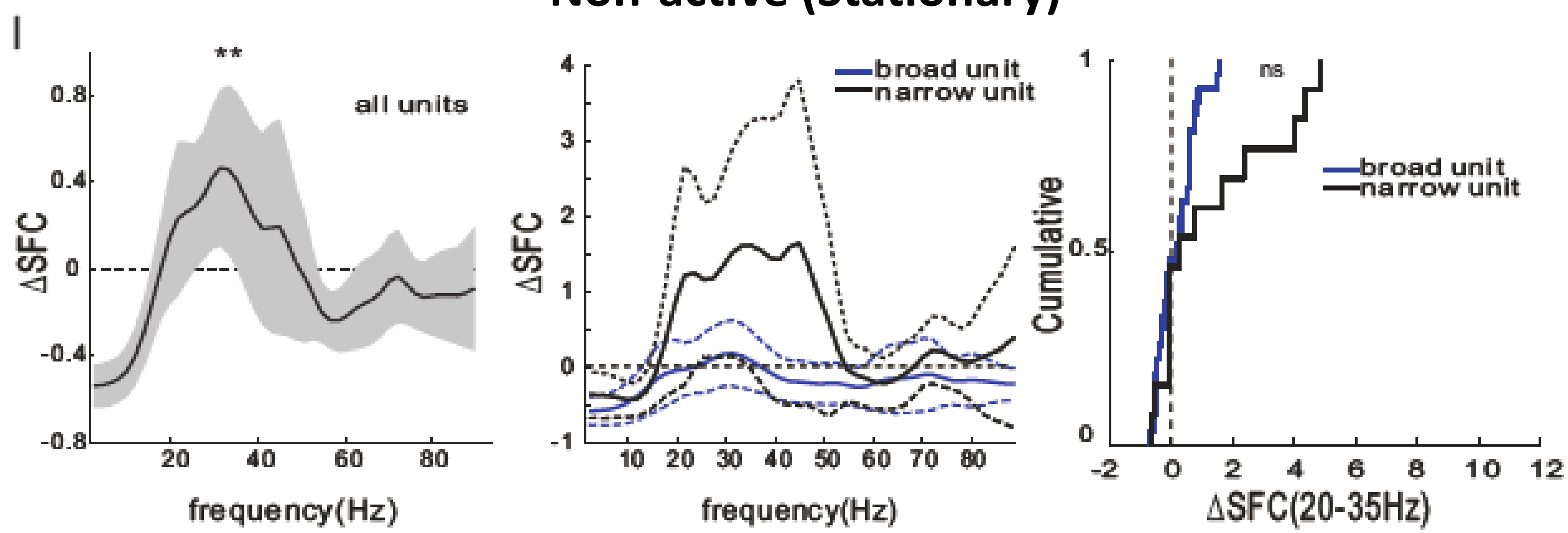


Visually-evoked increase of spike field coherence (SFC)

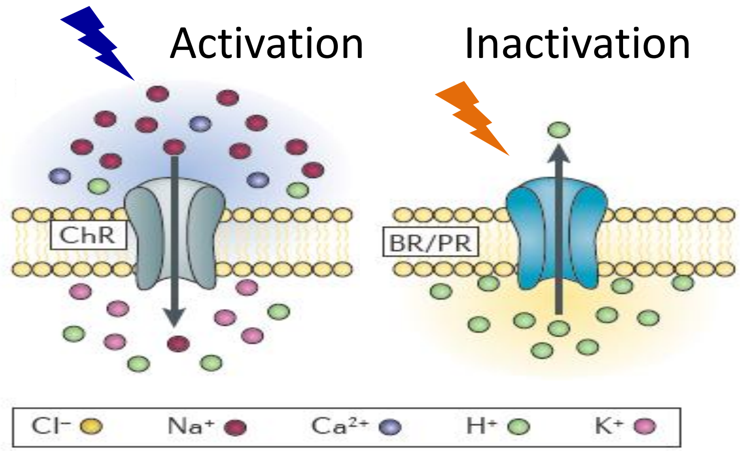
Active (Running)



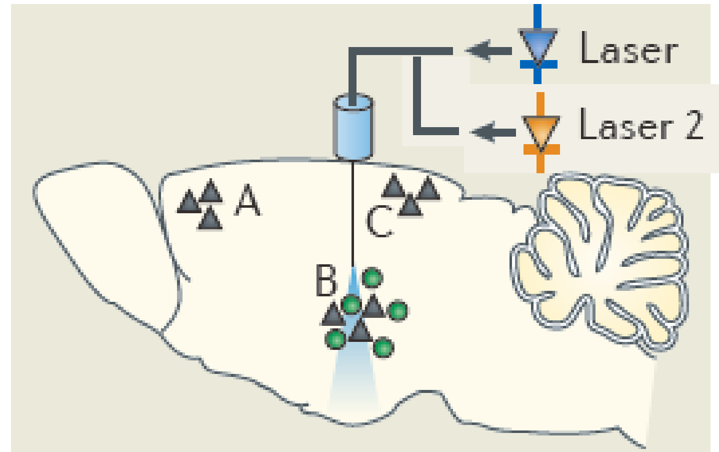
Non-active (Stationary)

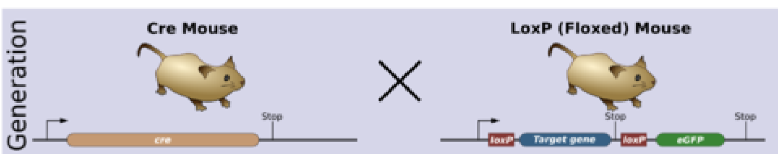


Transgenic expression of optogenetic channels (ChR2 or Arch) selectively to PV and SOM cells



Tye &Karl Deisseroth (2011) *Nat Rev Neurosci*





PV-IRES-Cre

SOM-IRES- CRE

X ***CAG-ChR2-tdTomato$^{flox/flox}$ (Ai27)*** →

Activation lines

PV-Cre::Ai27
SOM-Cre::Ai27

PV-IRES-Cre

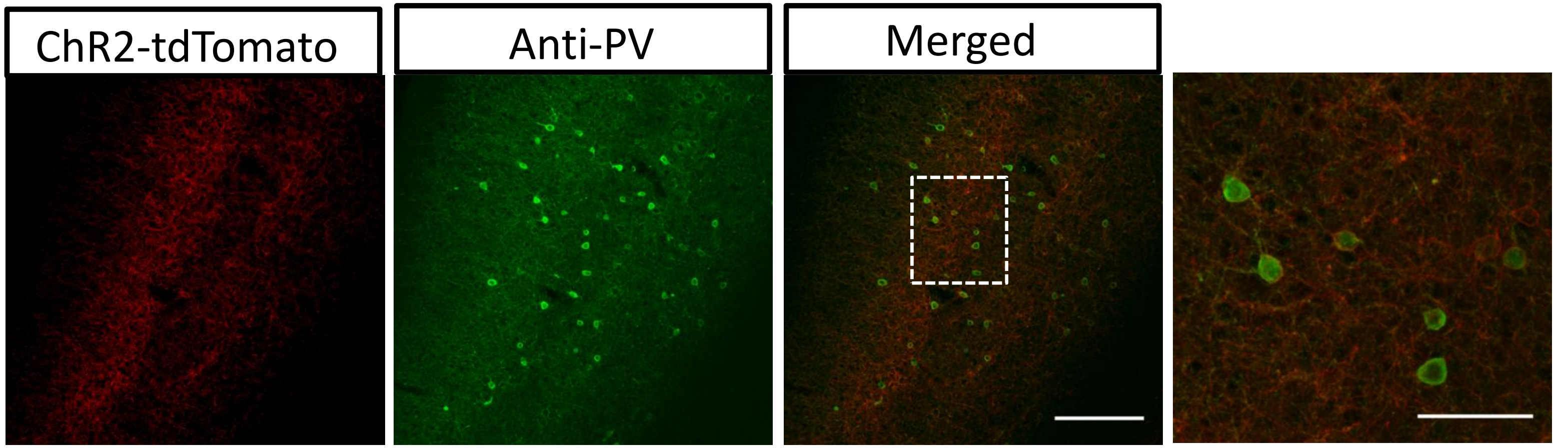
SOM-IRES- CRE

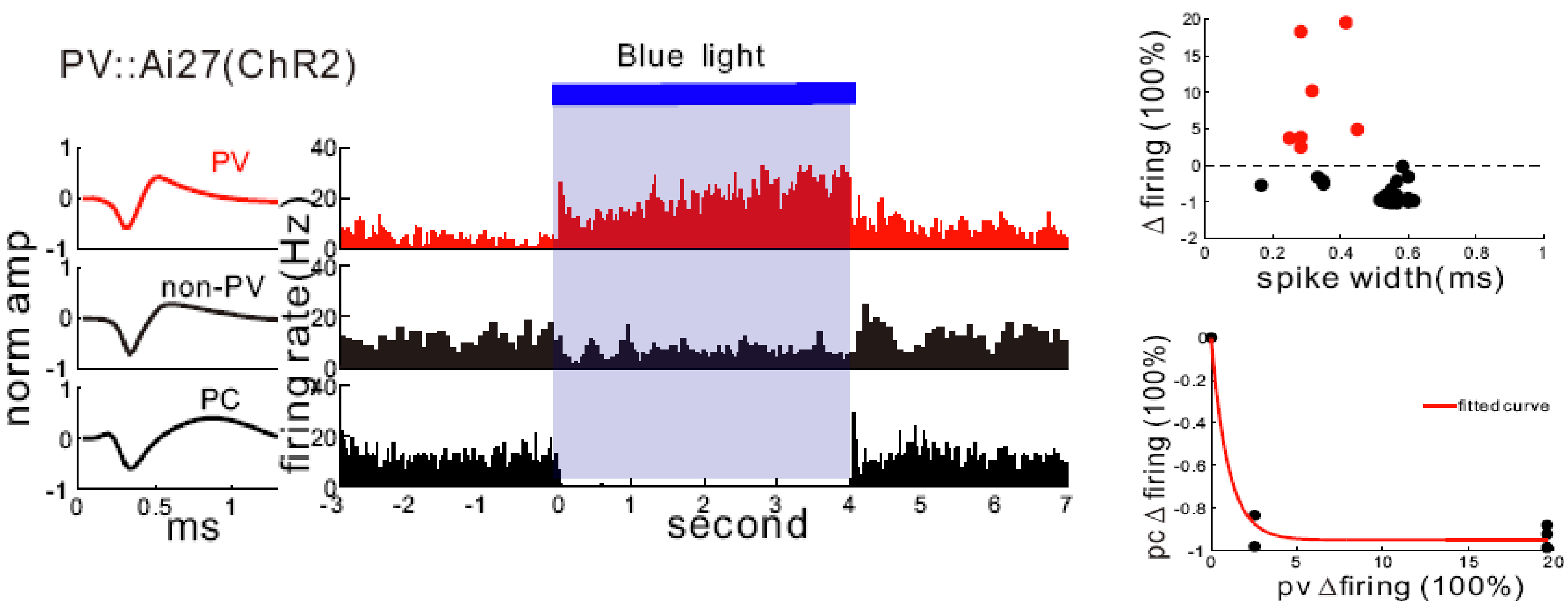
X ***CAG-Arch-EGFP$^{flox/flox}$ (Ai35)*** →

Inactivation lines

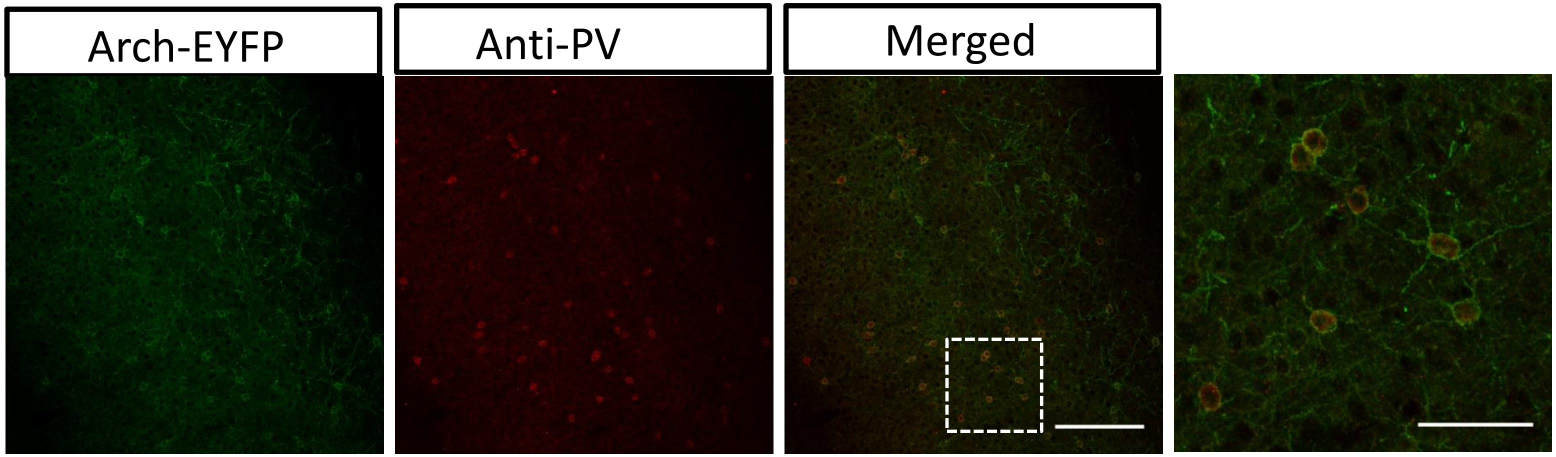
PV-Cre::Ai35
SOM-Cre::Ai35

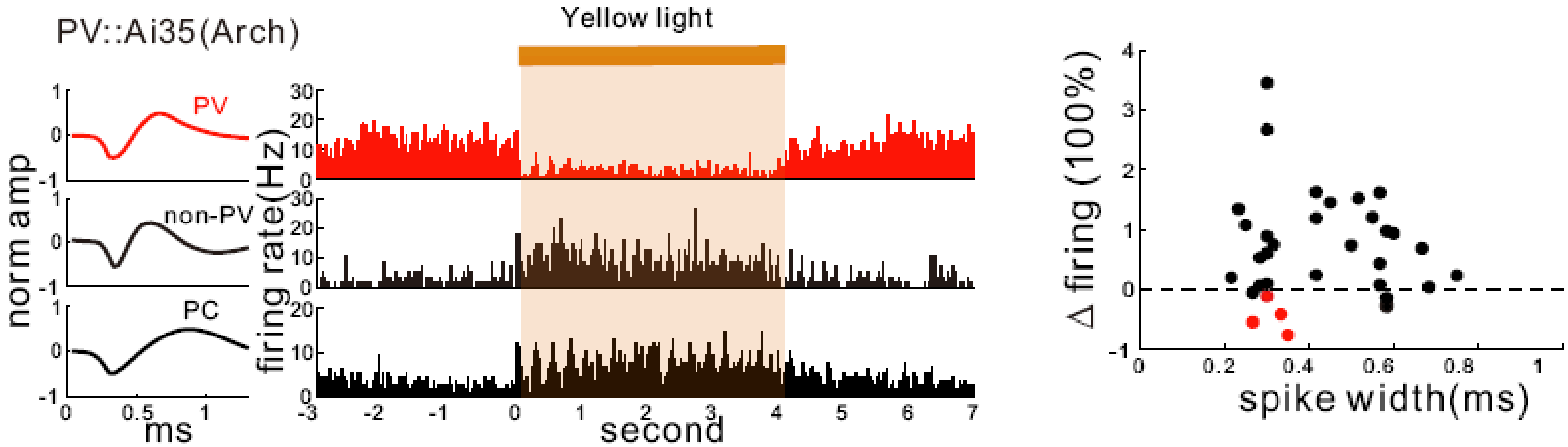
Optogenetic manipulation and identification of inhibitory cortical PV cells



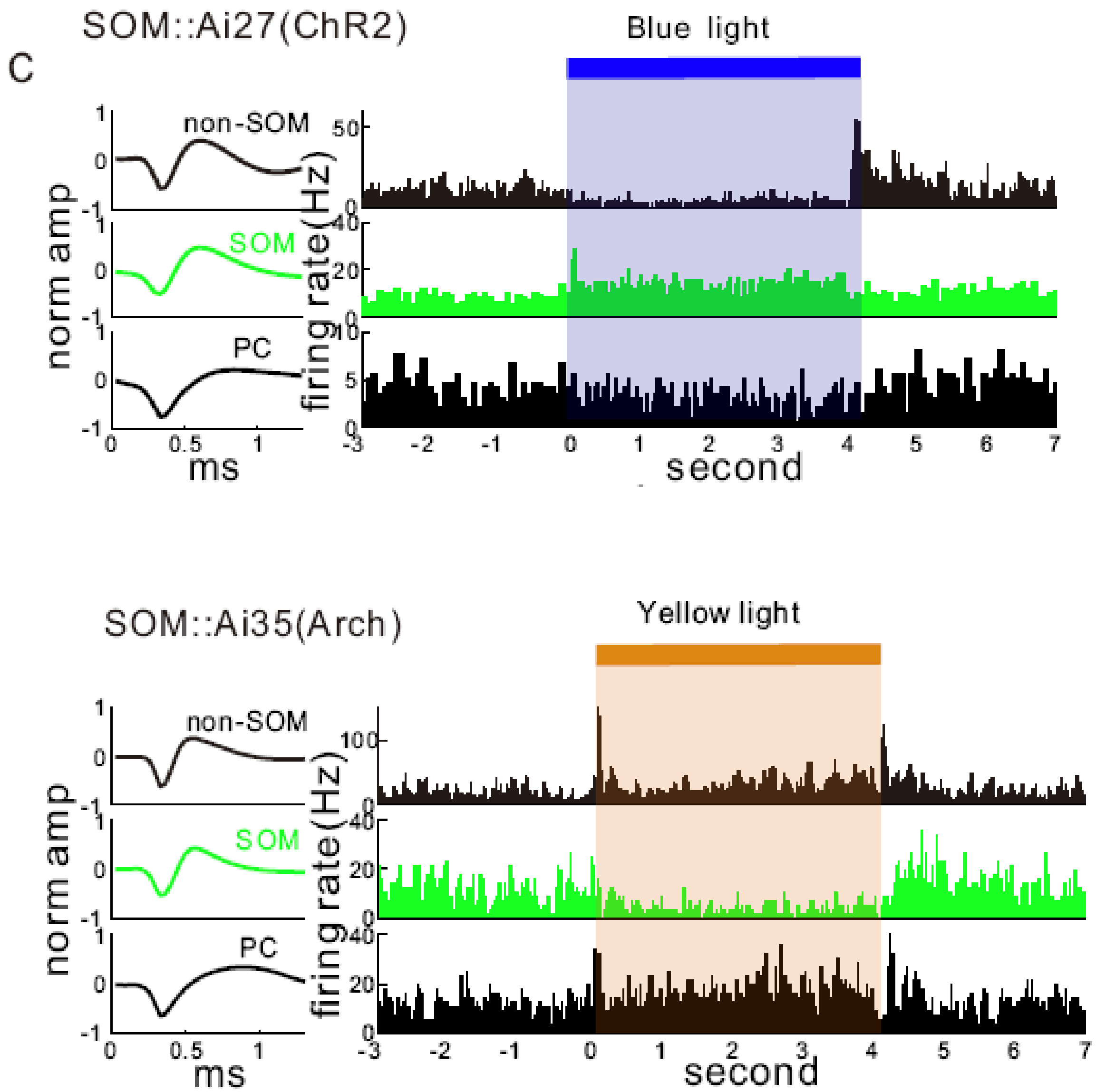


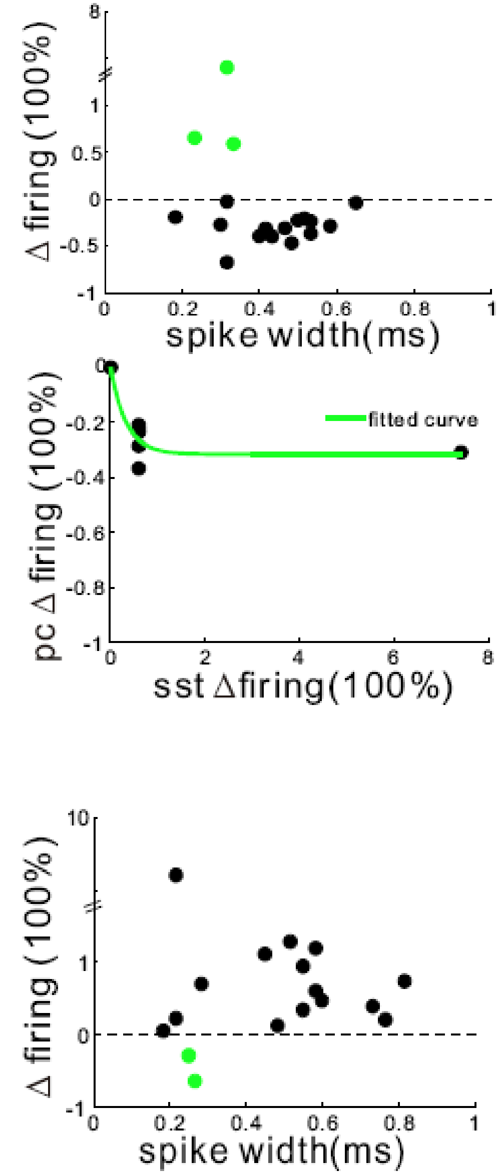
Optogenetic inactivation of inhibitory cortical PV cells



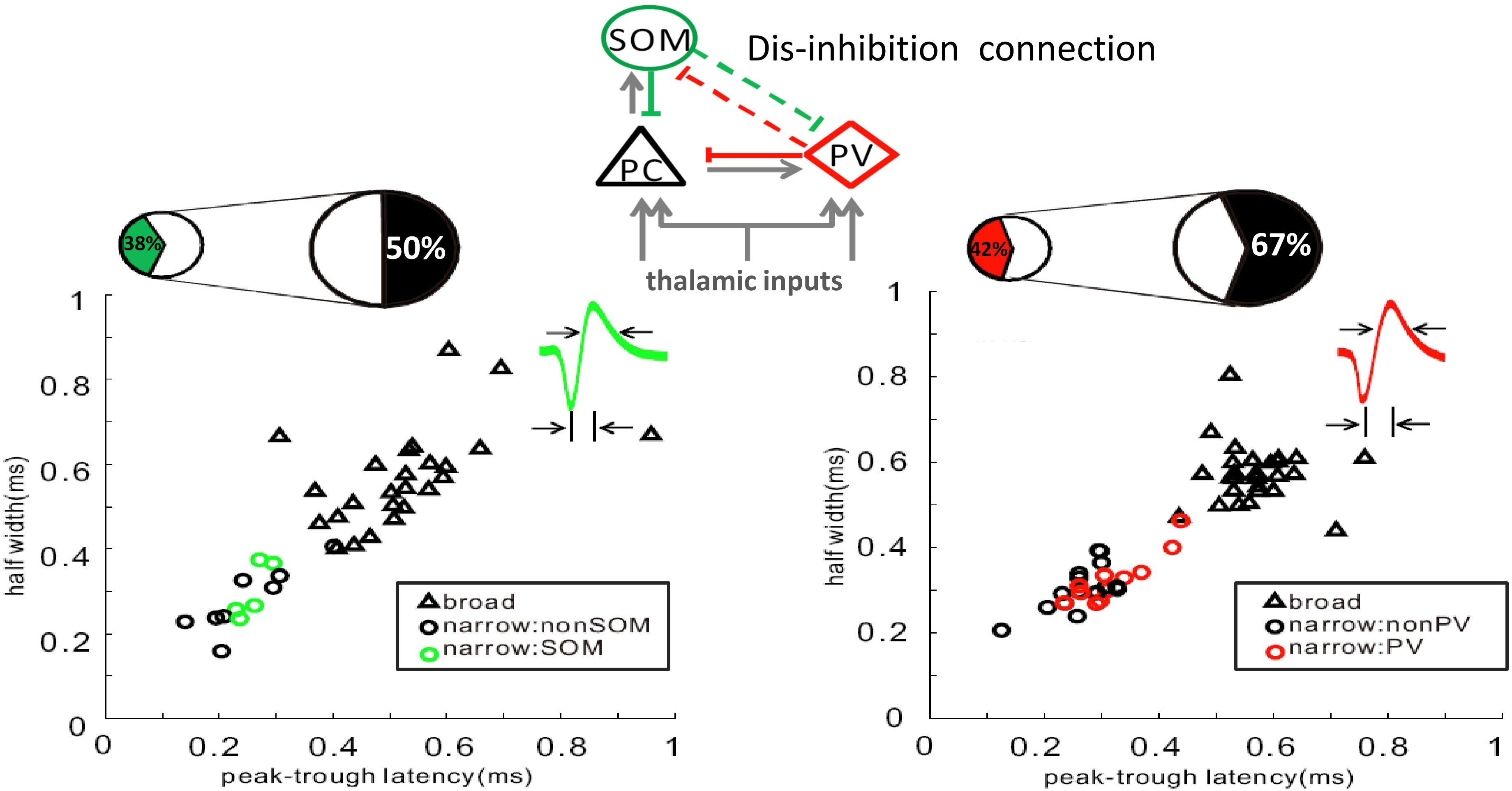


Optogenetic identification and manipulation of inhibitory SOM cells

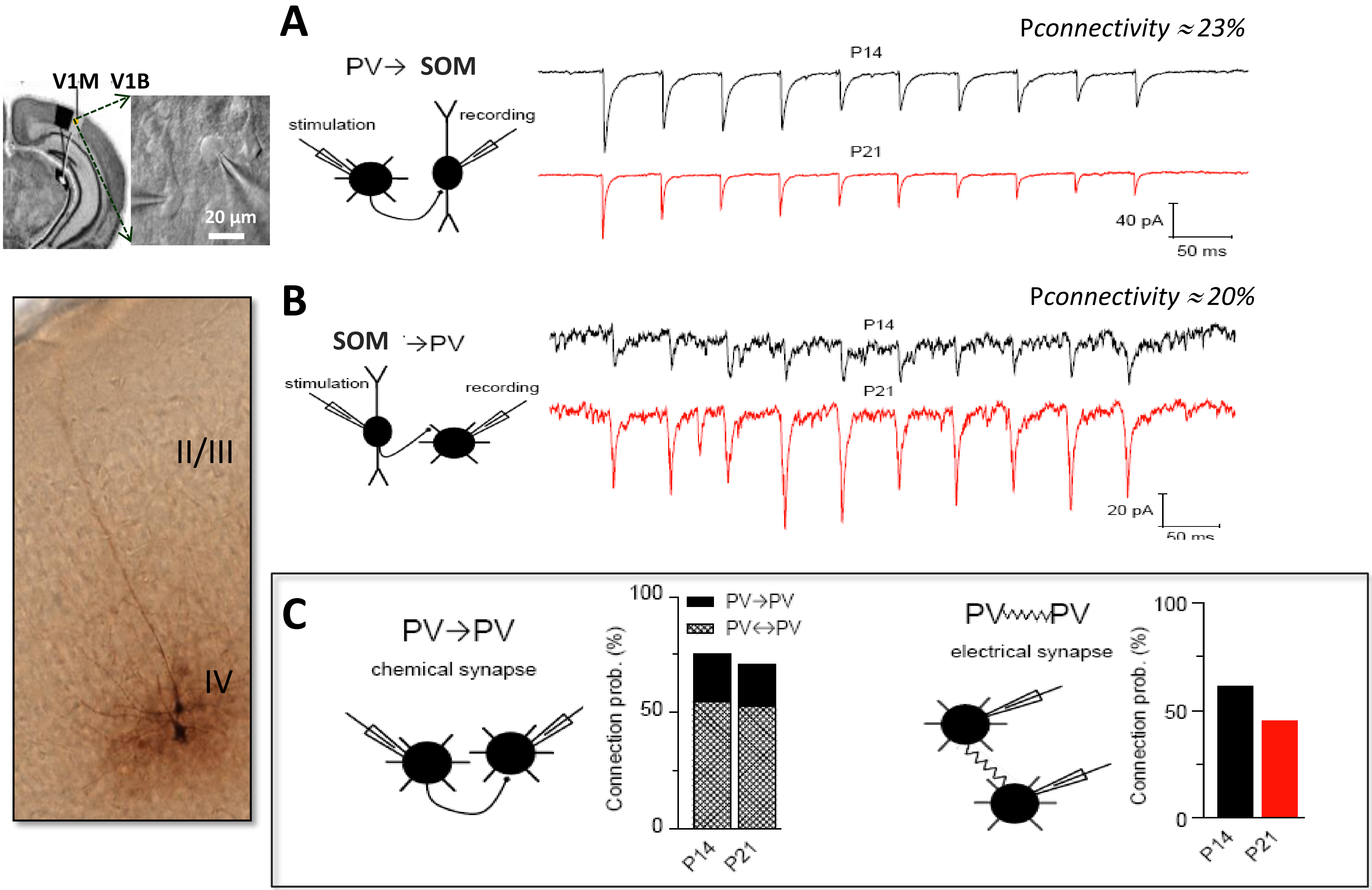




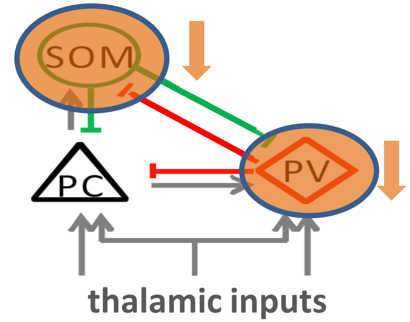
Inhibitory synapses between the cortical PV and SOM interneurons (dis-inhibition pathway)

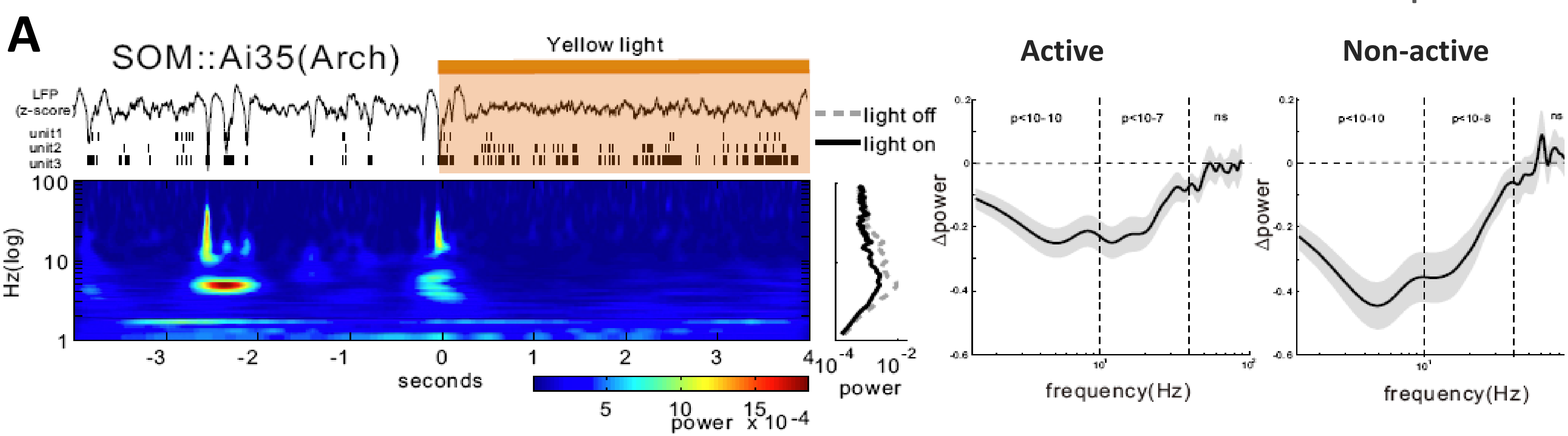


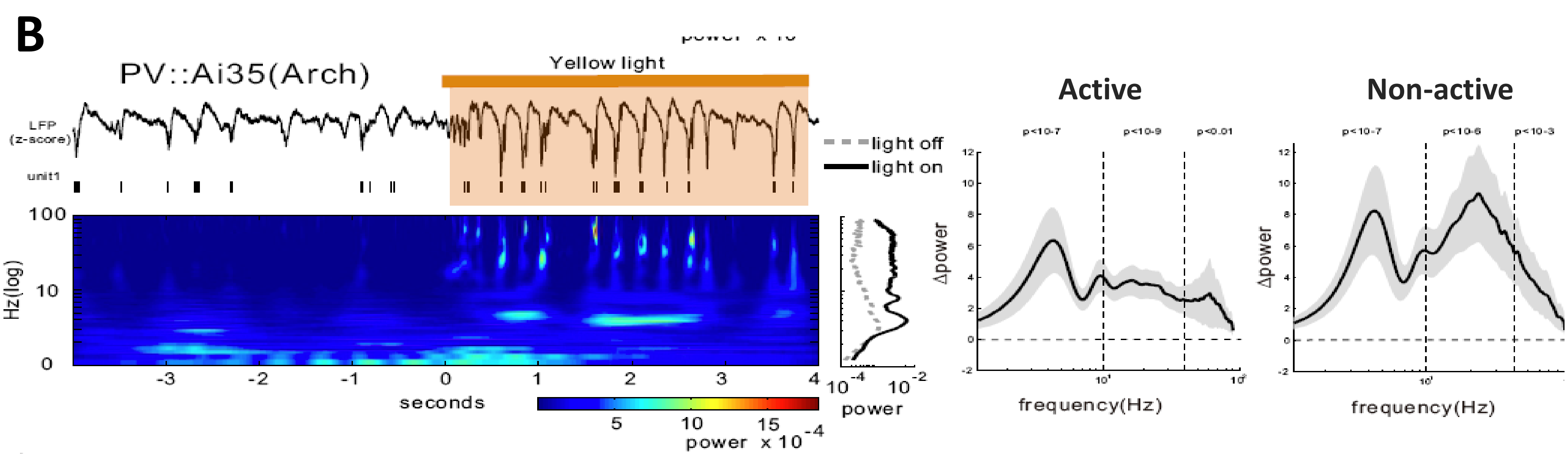
Dis-inhibitory synapses in the layer 4 circuit of mouse V1



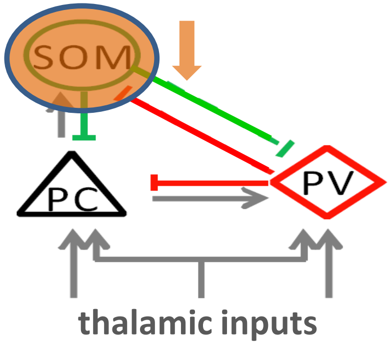
Baseline activities: optogenetic inactivation (by Arch) of cortical SOM and PV cells

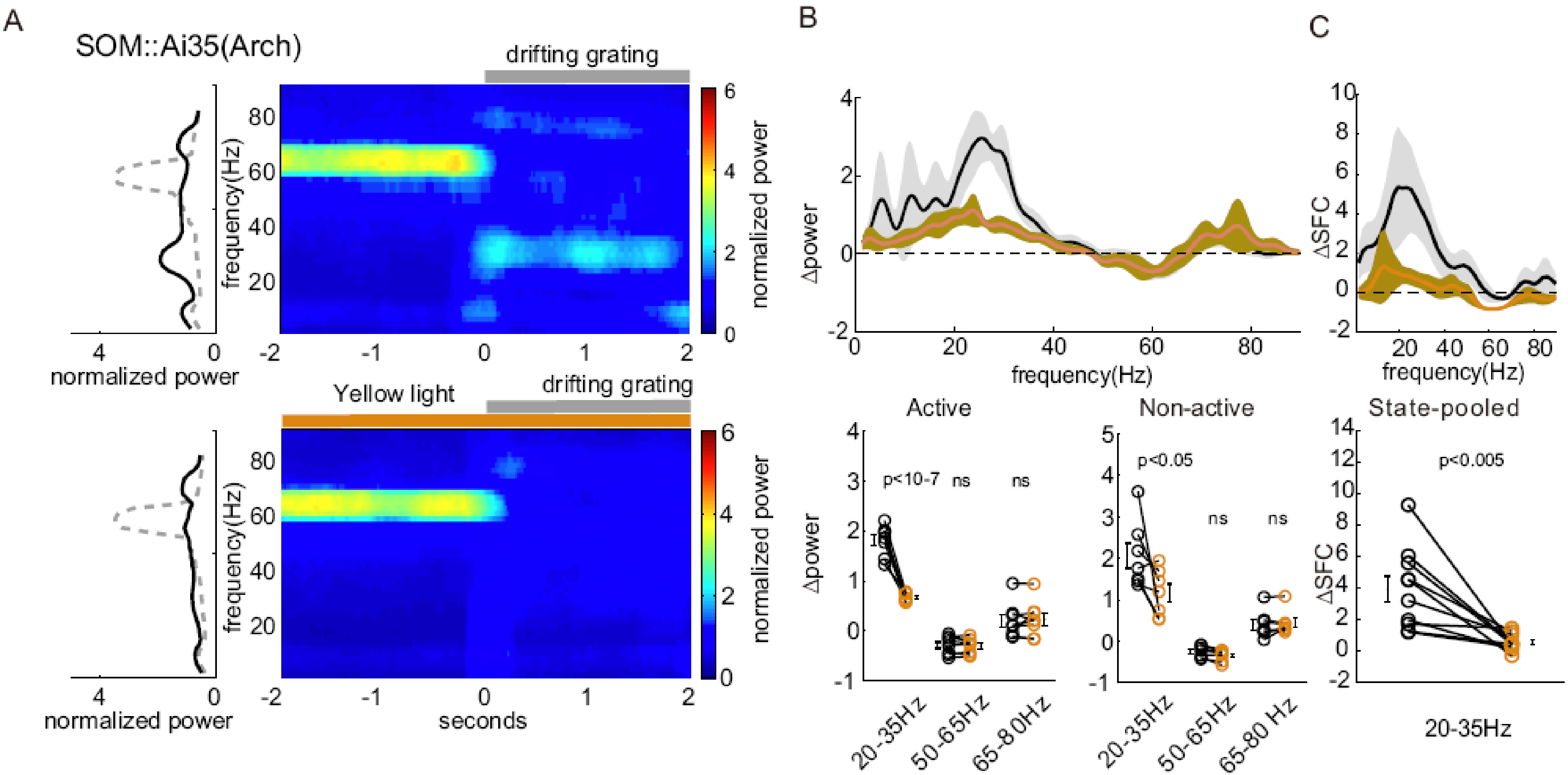




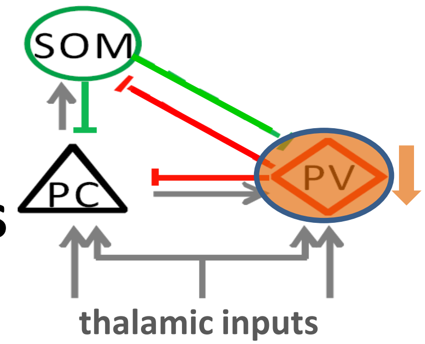


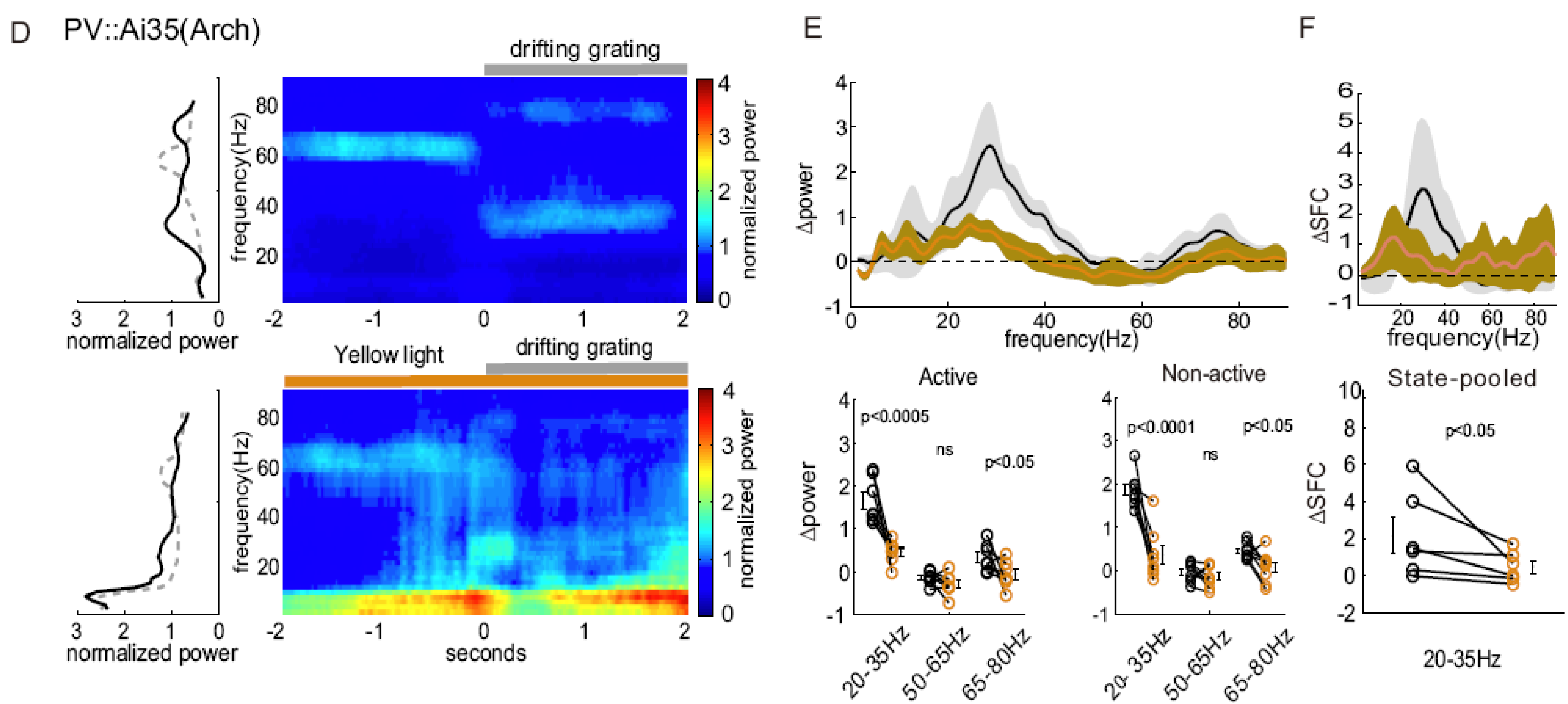
Optogenetic inactivation of cortical SOM cells selectively suppresses the evoked beta-band activities



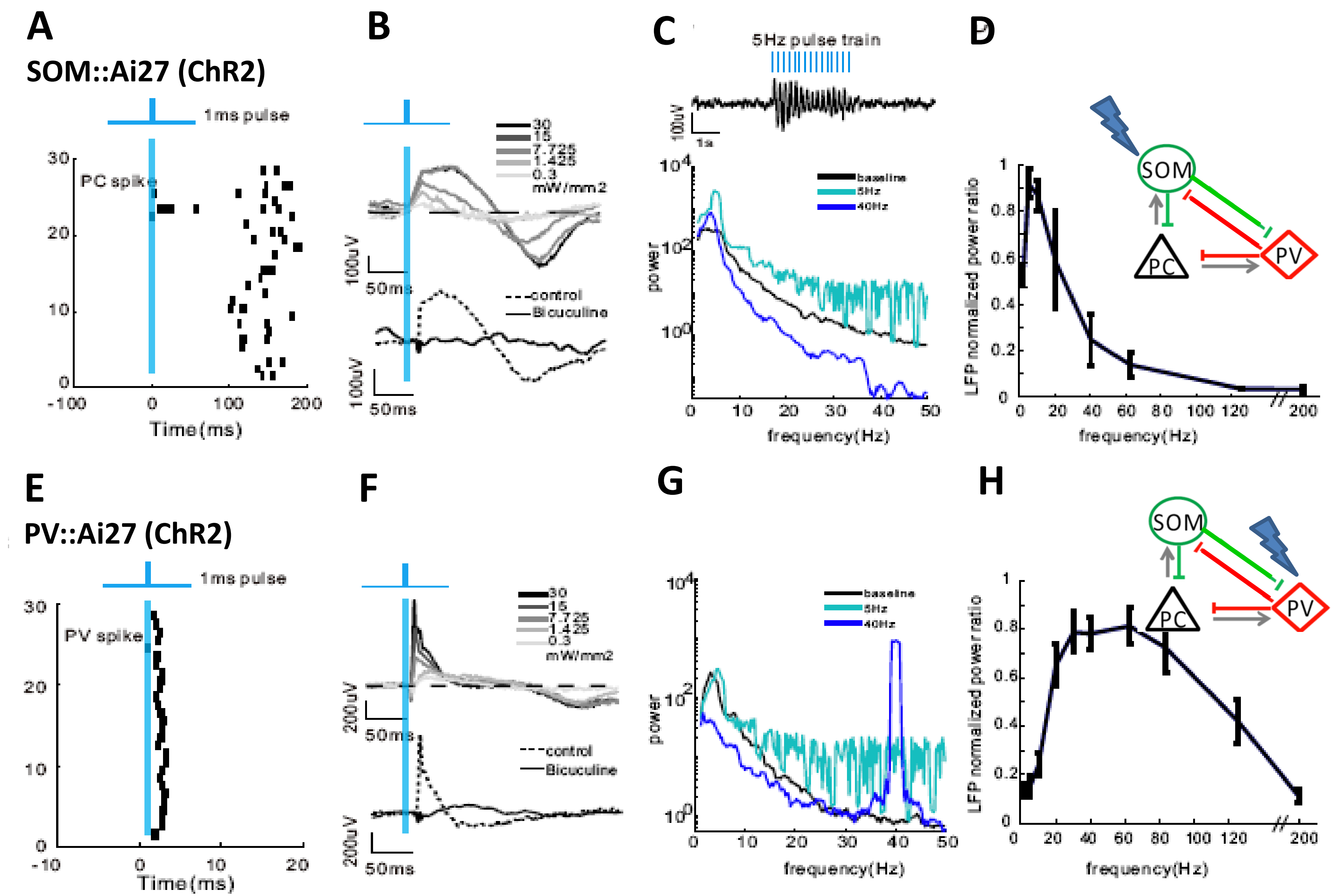


Optogenetic inactivation of cortical PV cells globally suppresses evoked beta- / higher bands





Rhythmic activation of cortical SOM and PV cells evokes different temporal-frequency responses in local circuits



Summary III

1) Drifting grating preferentially evokes beta-band activity.

2) Differential regulation of cortical oscillations by inhibitory cortical PV and SOM cells :
   - ➢ SOM cell / PCs sub-circuit exclusive for beta-band generation
   - ➢ PV cell / PCs sub-circuit for producing higher bands
   - ➢ Dis-inhibition connections between PV and SOM cells may contribute to the modulation cortical oscillations.

Take-home message:

1. Synaptic integration rule or mechanisms in the neuronal information processing.
   - The simple empirical and generalized arithmetic rules.
   - Synaptic mechanisms underlying the emergence of cortical functional selectivity.

2. Differential sub-interneuronal circuits regulates distinct frequency bands of cortical population activities.

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