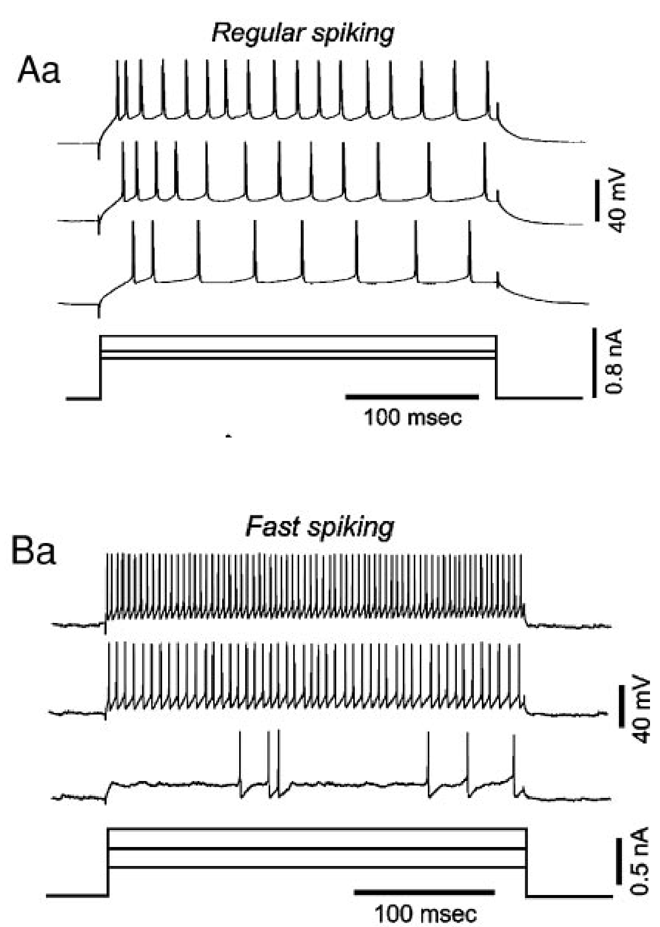
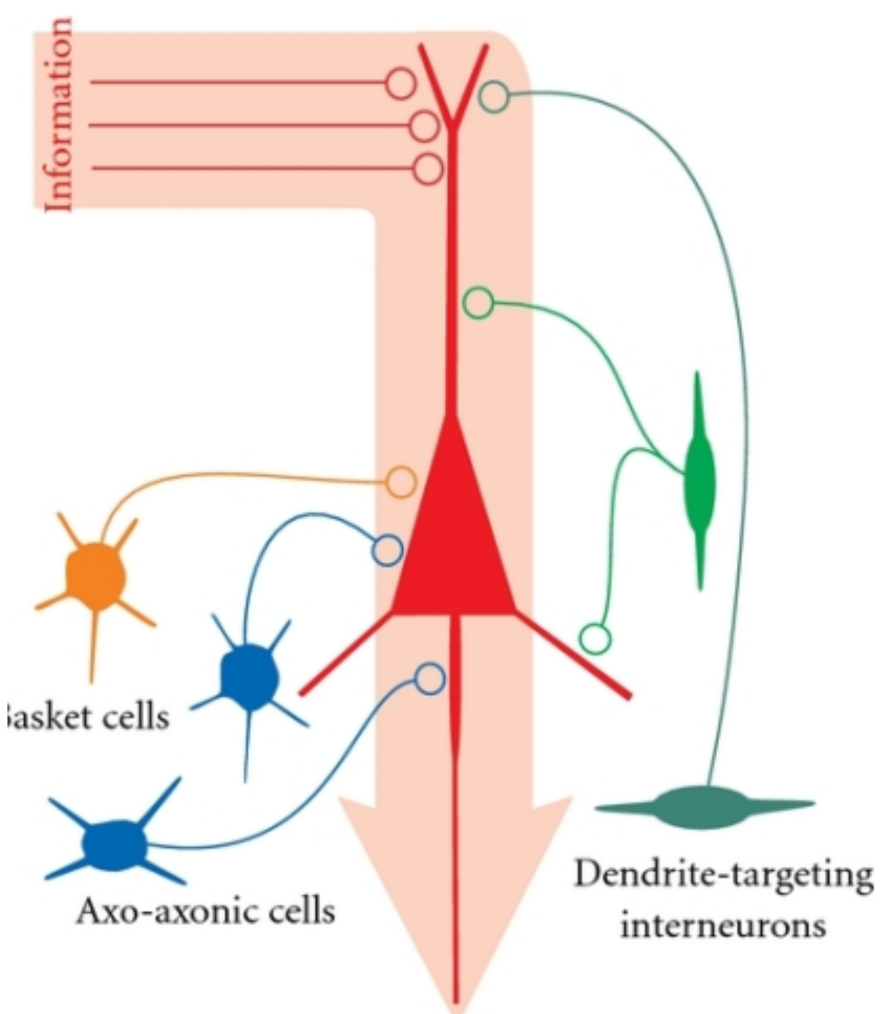
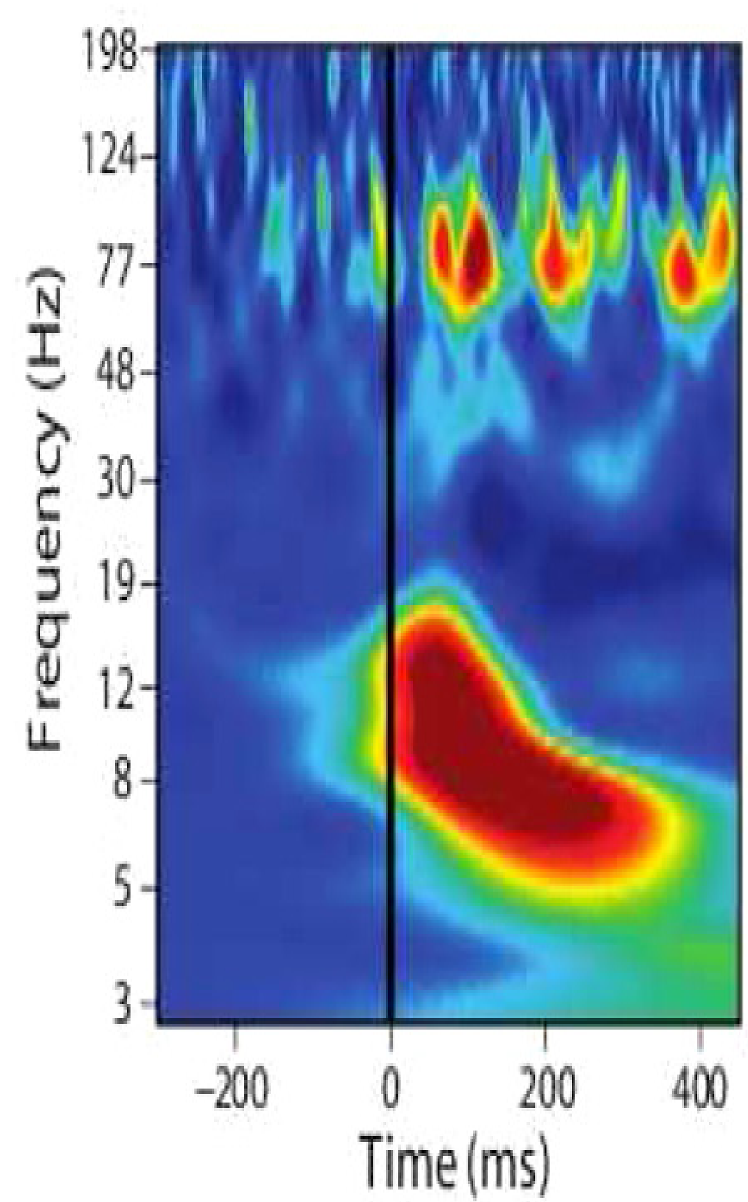
Cellular Biophysics & Modeling

Lecture 21
electrophysiological classes of cortical neurons,
networks of inhibitory interneurons in the cortex,
cortical oscillations and synchrony



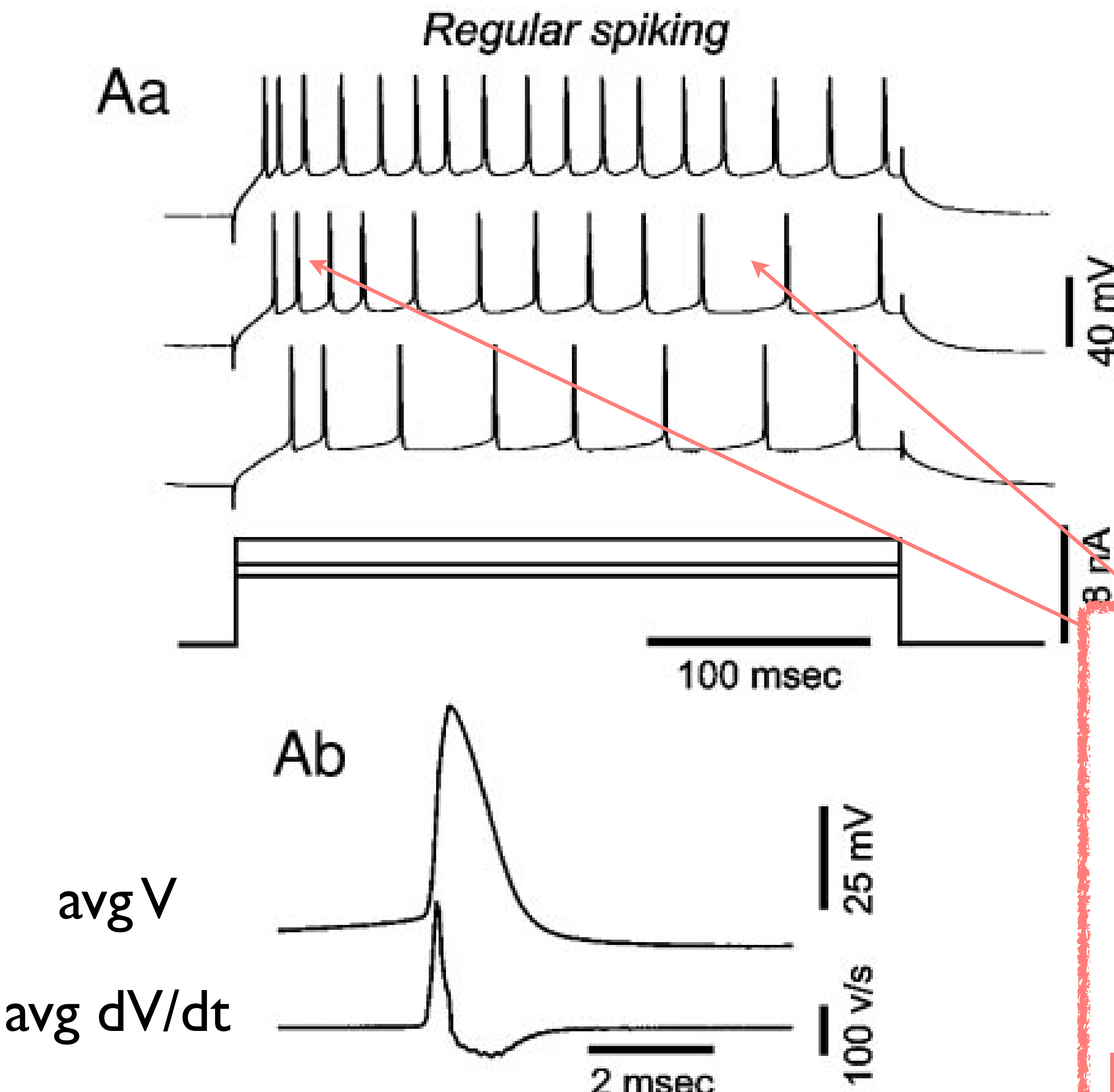




Electrophysiological classes of cortical neurons

…in cat cortical neurons of primary visual cortex
…correspondence to morphology not entirely clear

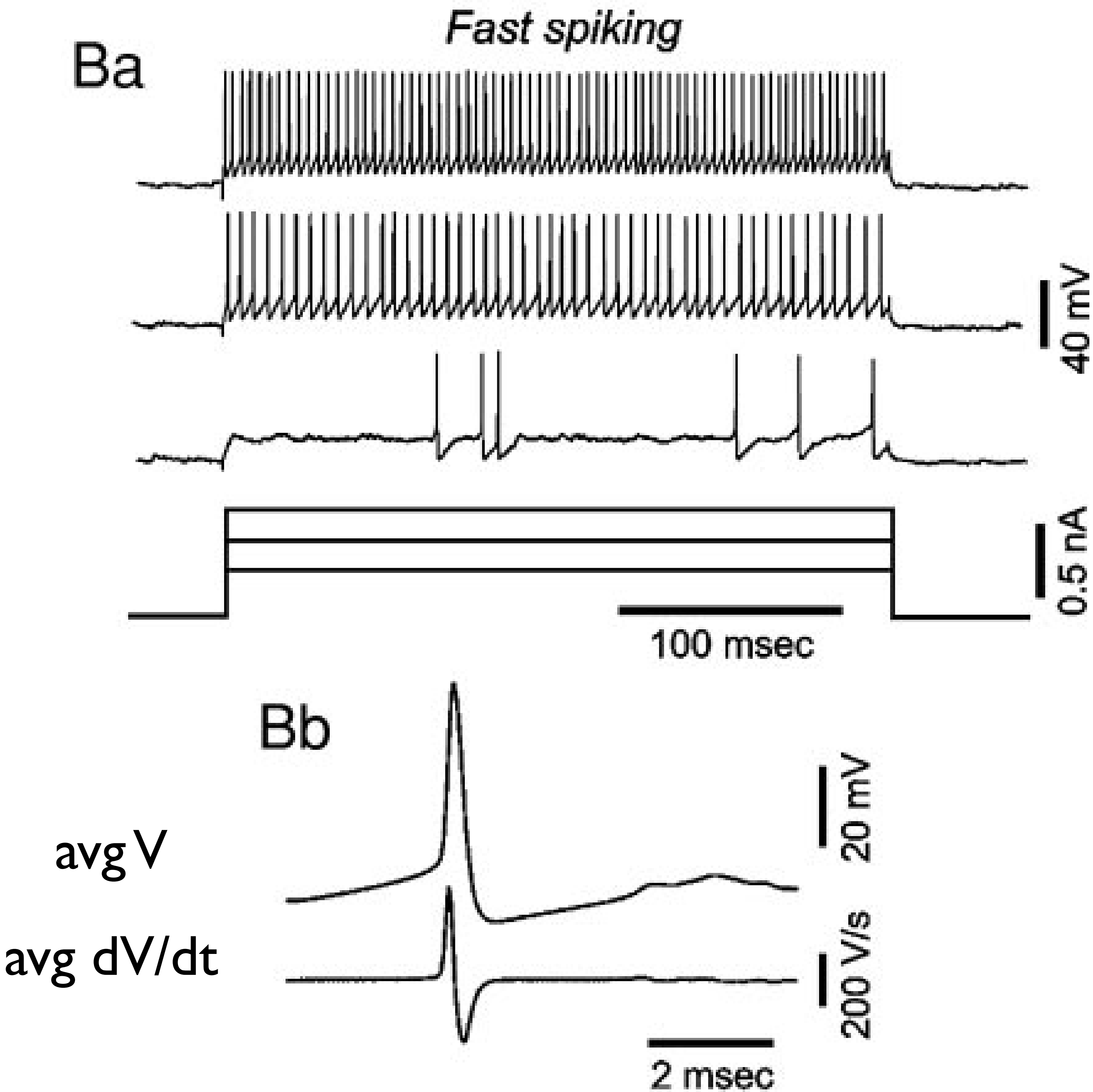
- Regular Spiking (RS)
- Fast Spiking (FS)
- Intrinsic Bursting (IB)
- Chattering (CH)



RS neurons are often
pyramidal
or
spiny stellate
cells

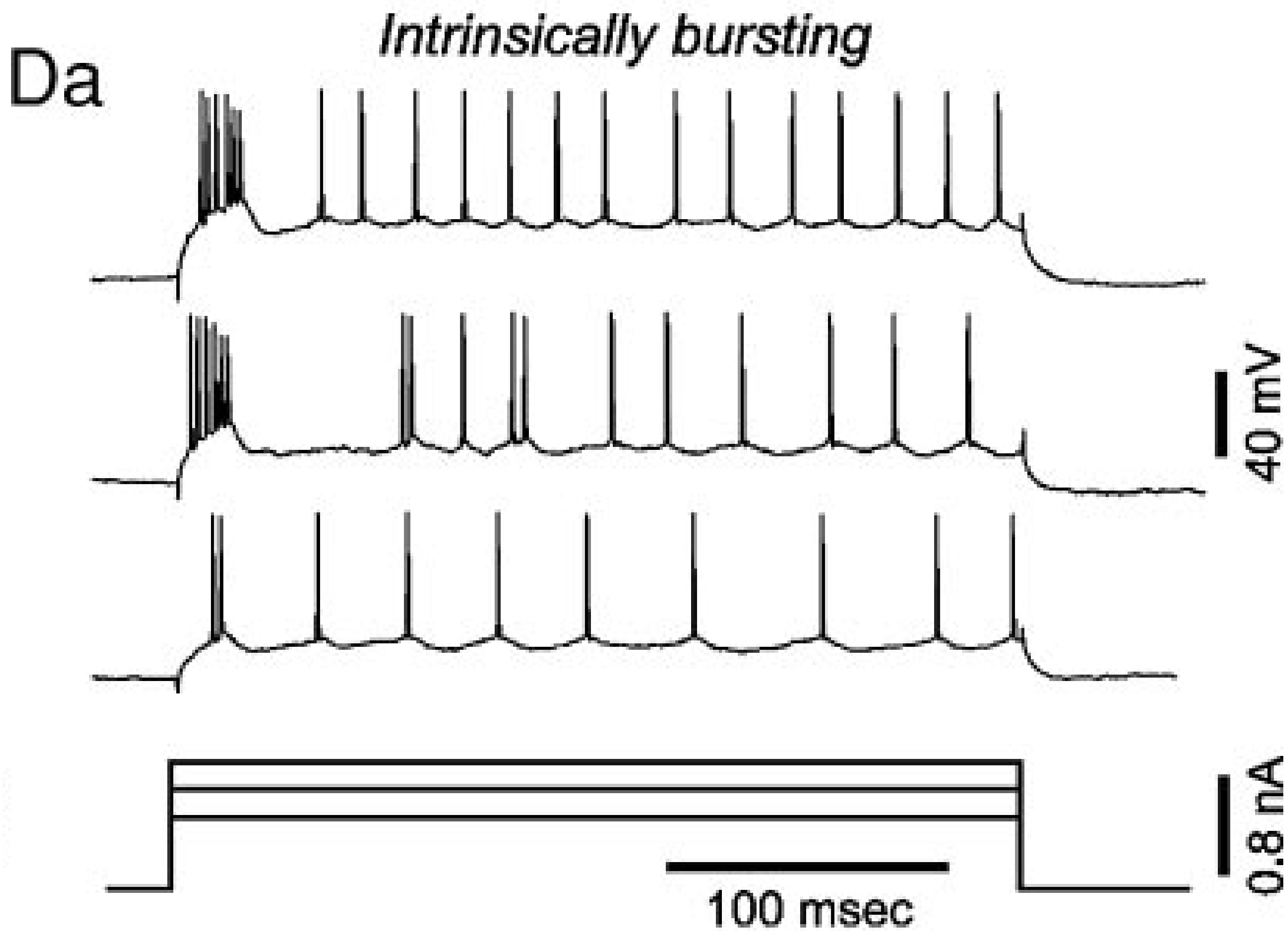
RS neurons often show
spike-frequency adaptation
(inter-spike intervals
increase in length
during current pulse)

presumably ... recruitment of
hyperpolarizing current,
perhaps I-KCa

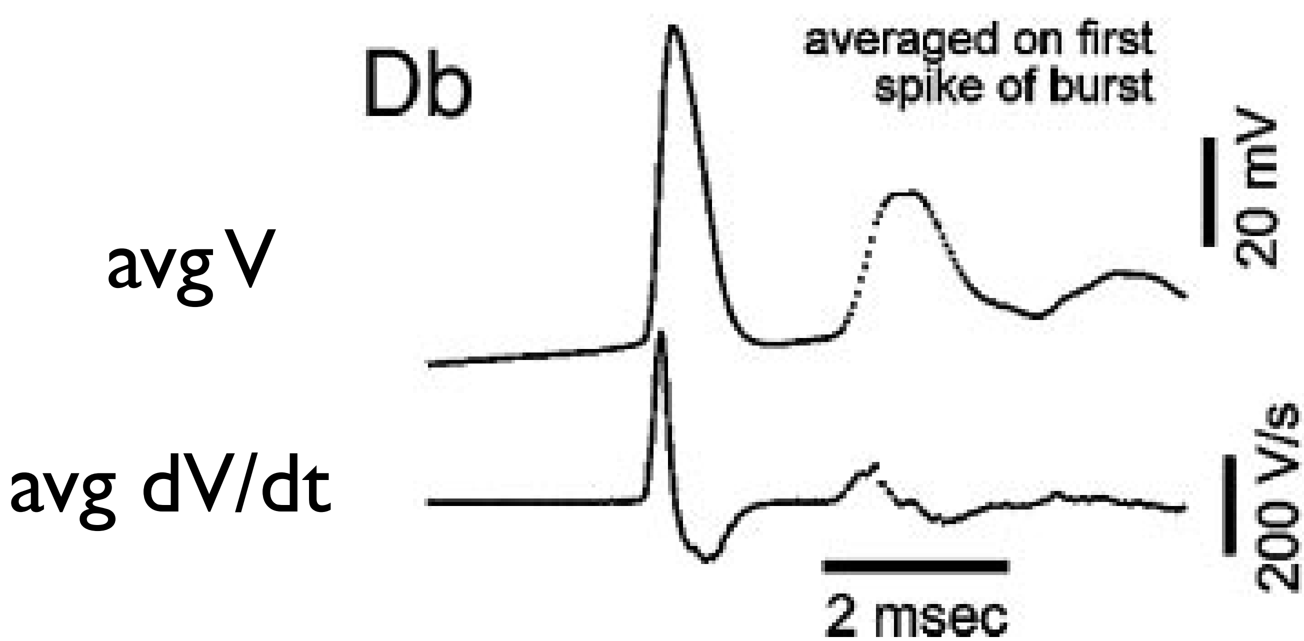


FS: various and sundry inhibitory neurons

Why do inhibitory neurons tend to spike faster than excitatory neurons???

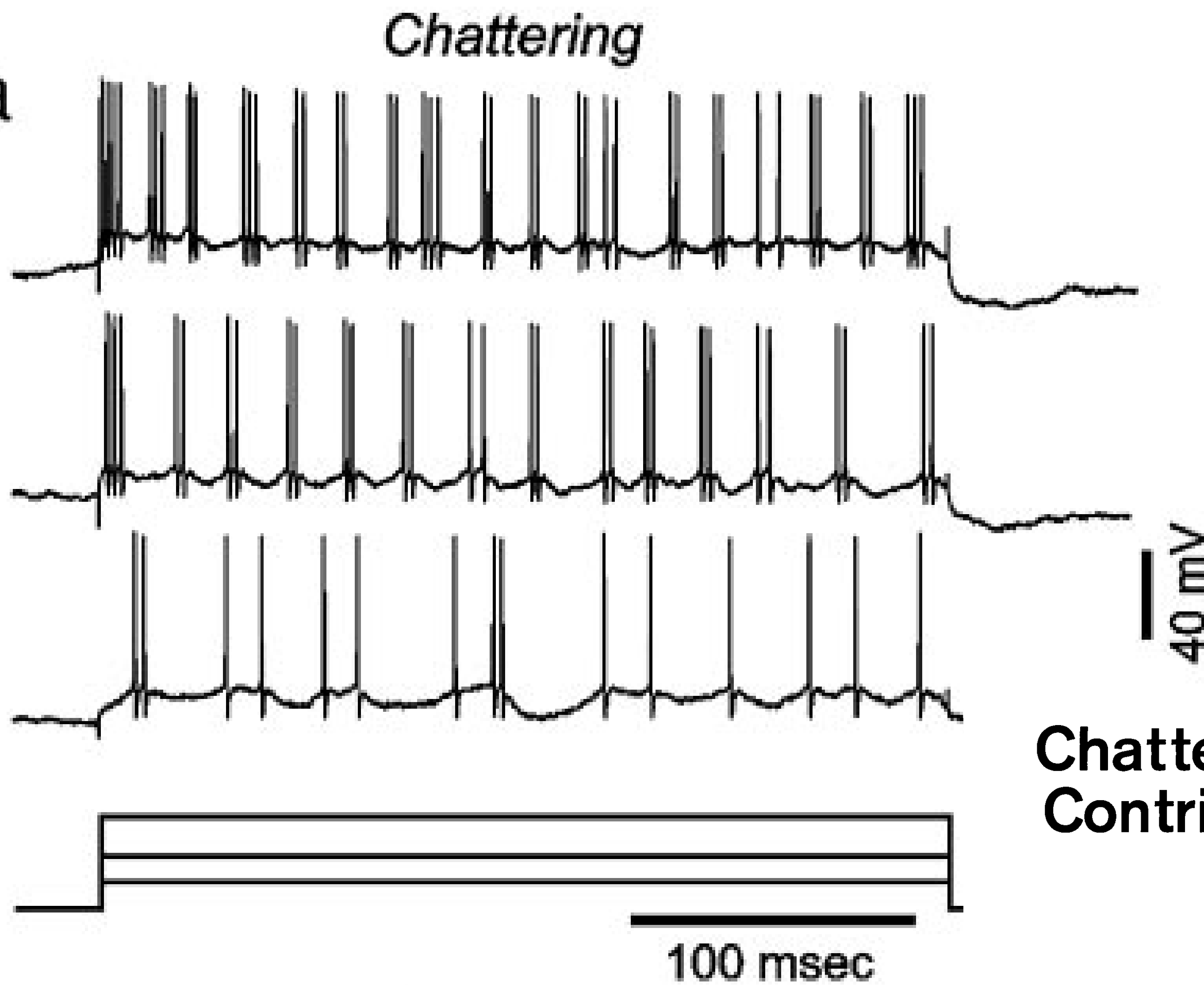


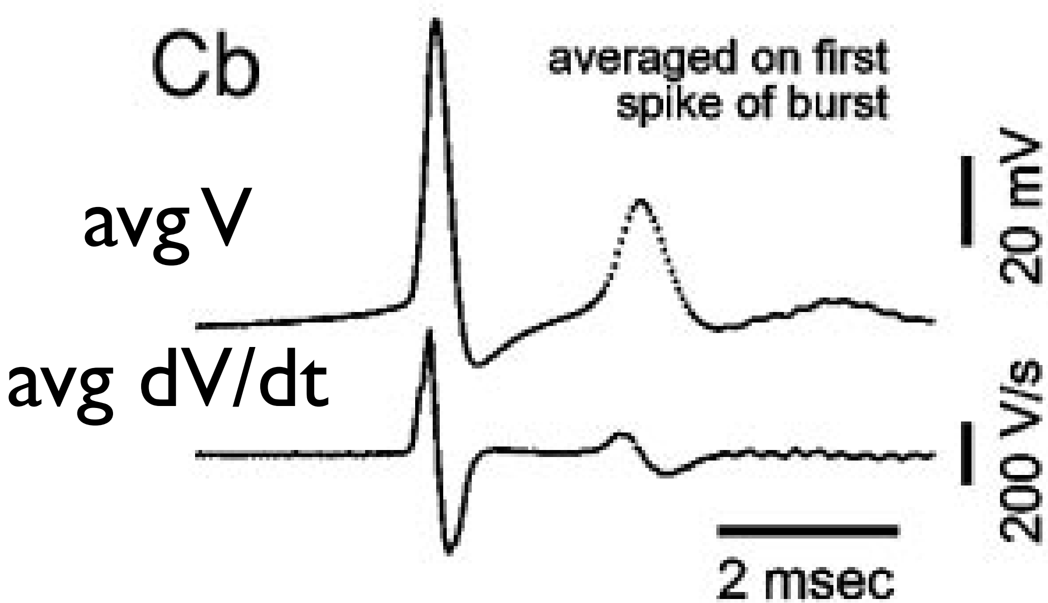
IB cells are often large pyramidal cells (principal neurons that project to another cortical or subcortical area)



Note that these authors use "intrinsically bursting" (IB) to indicate that the low-threshold calcium current is de-inactivated at resting membrane potentials.

They do not mean to imply that isolated cells will rhythmically burst.





Chattering cells are observed in visual cortex

Relationship to gamma oscillations?

Chattering Cells: Superficial Pyramidal Neurons Contributing to the Generation of Synchronous Oscillations in the Visual Cortex

Charles M. Gray and David A. McCormick

In response to visual stimulation, a subset of neurons in the striate and prestriate cortex displays synchronous rhythmic firing in the gamma frequency band (20 to 70 hertz). This finding has raised two fundamental questions: What is the functional significance of synchronous gamma-band activity and how is it generated? This report addresses the second of these two questions. By means of intracellular recording and staining of single cells in the cat striate cortex in vivo, a biophysically distinct class of pyramidal neuron termed "chattering cells" is described. These neurons are located in the superficial layers of the cortex, intrinsically generate 20- to 70-hertz repetitive burst firing in response to suprathreshold depolarizing current injection, and exhibit pronounced oscillations in membrane potential during visual stimulation that are largely absent during periods of spontaneous activity. These properties suggest that chattering cells may make a substantial intracortical contribution to the generation of synchronous cortical oscillations and thus participate in the recruitment of large populations of cells into synchronously firing assemblies.

these results are drawn from…

Electrophysiological Classes of Cat Primary Visual Cortical Neurons In Vivo as Revealed by Quantitative Analyses

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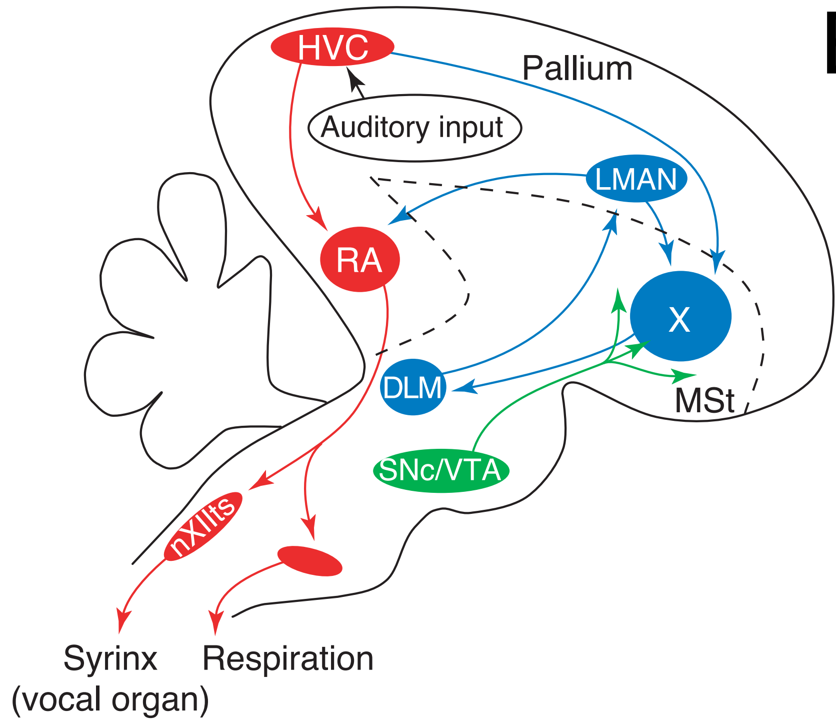
FIG. 1. Examples of action potential responses to depolarizing current injection in the 4 subjectively classified subtypes of cortical neuron. *A*: regular spiking (RS) cell. *B*: fast spiking (FS) cell. *C*: chattering (CH) cell. *D*: intrinsic bursting (IB) neuron. *Top* of each panel shows responses to 3 different current intensities. *Bottom plots* show average action potential and *dV/dt*. The individual action potentials and *dV/dt* in each panel are the result of averaging of ≥10 spikes. Therefore the amplitude and time course of the 2nd spikes in Cb and Db are not accurate, owing to jitter in the timing of these events.

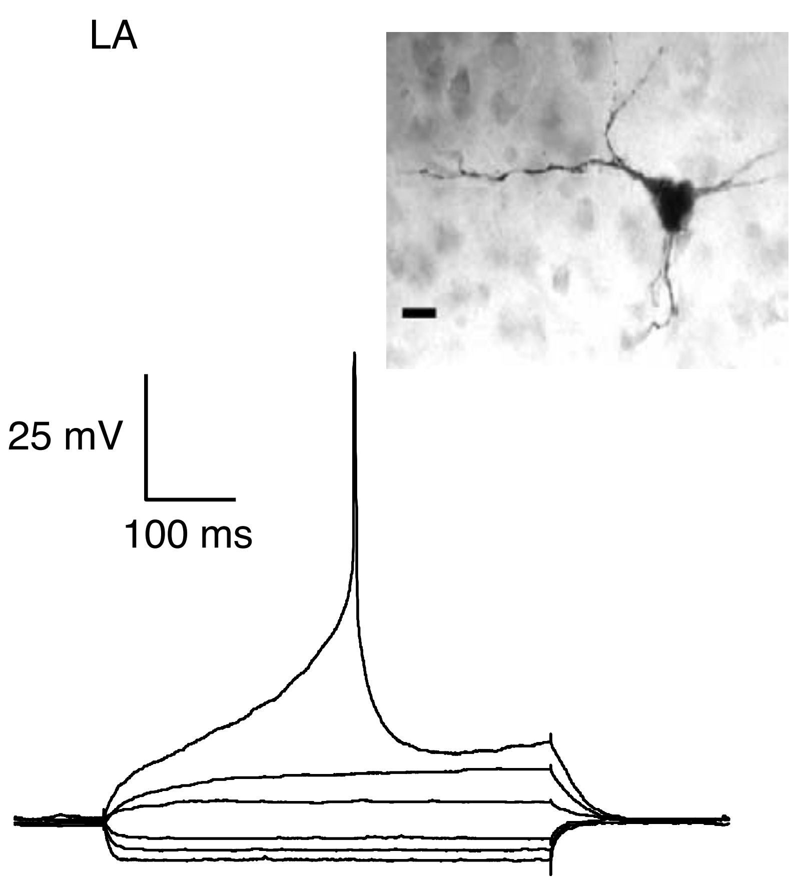
Nowak, Lionel G., Rony Azouz, Maria V. Sanchez-Vives, Charles M. Gray, and David A. McCormick. Electrophysiological classes of cat primary visual cortical neurons in vivo as revealed by quantitative analyses. *J Neurophysiol* 89: 1541–1566, 2003; 10.1152/jn.00580.2002. To facilitate the characterization of cortical neuronal function, the responses of cells in cat area 17 to intracellular injection of current pulses were quantitatively analyzed. A variety of response variables were used to separate the cells into subtypes using cluster analysis. Four main classes of neurons could be clearly distinguished: regular spiking (RS), fast spiking (FS), intrinsic bursting (IB), and chattering (CH). Each of these contained significant subclasses. RS neurons were characterized by trains of action potentials that exhibited spike frequency adaptation. Morphologically, these cells were spiny stellate cells in layer 4 and pyramidal cells in layers 2, 3, 5, and 6. FS neurons had short-duration action potentials ($<$0.5 ms at half height), little or no spike frequency adaptation, and a steep relationship between injected current intensity and spike discharge frequency. Morphologically, these cells were sparsely spiny or aspiny nonpyramidal cells. IB neurons typically generated a low frequency ($<$425 Hz) burst of spikes at the beginning of a depolarizing current pulse followed by a tonic train of action potentials for the remainder of the pulse. These cells were observed in all cortical layers, but were most abundant in layer 5. Finally, CH neurons generated repetitive, high-frequency (350–700 Hz) bursts of short-duration ($<$0.55 ms) action potentials. Morphologically, these cells were layer 2–4 (mainly layer 3) pyramidal or spiny stellate neurons. These results indicate that firing properties do not form a continuum and that cortical neurons are members of distinct electrophysiological classes and subclasses.



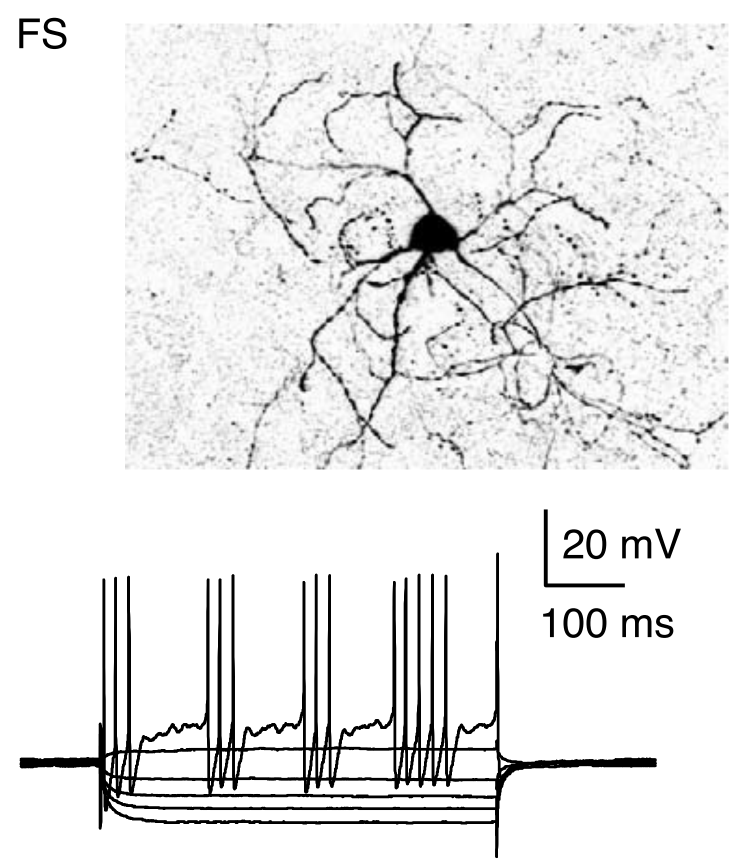
Electrophysiological classes of local **interneurons** …in the **striatum** of song **birds**

- long lasting after-hyperpolarization (LA)
- fast spiking (FS)
- low threshold spike (LTS)

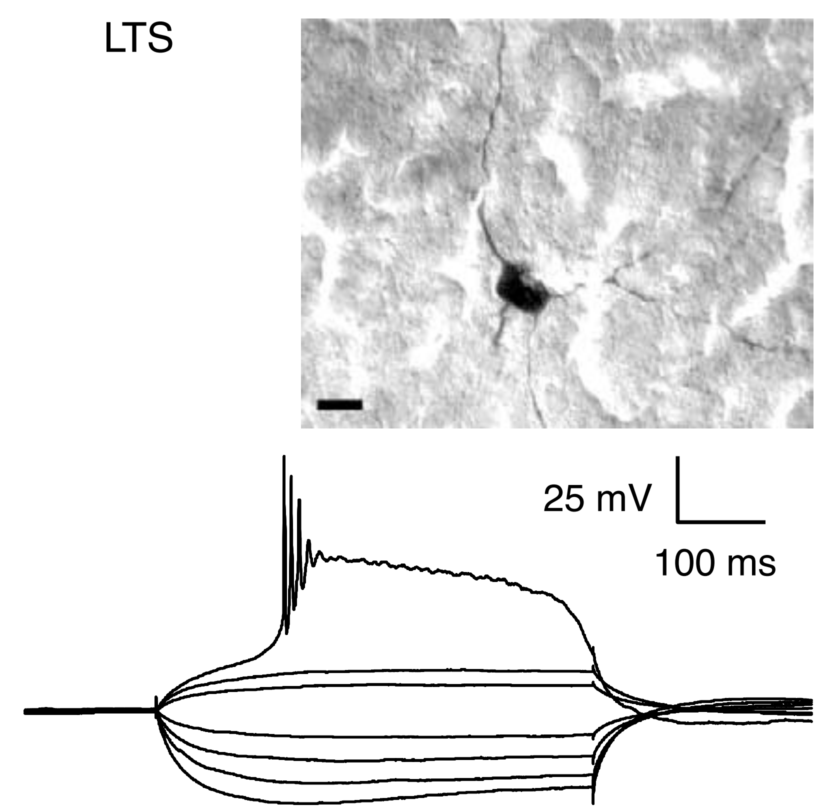
long lasting AHP neurons



fast spiking neurons



low threshold spike neurons



Birdbrains could teach basal ganglia research a new song

Allison J. Doupe[1], David J. Perkel[2], Anton Reiner[3] and Edward A. Stern[4]

Recent advances in anatomical, physiological and histochemical characterization of avian basal ganglia neurons and circuitry have revealed remarkable similarities to mammalian basal ganglia. A modern revision of the avian anatomical nomenclature has now provided a common language for studying the function of the cortical–basal-ganglia–cortical loop, enabling neuroscientists to take advantage of the specialization of basal ganglia areas in various avian species. For instance, songbirds, which learn their vocal motor behavior using sensory feedback, have specialized a portion of their cortical–basal ganglia circuitry for song learning and production. This discrete circuit dedicated to a specific sensorimotor task could be especially tractable for elucidating the interwoven sensory, motor and reward signals carried by basal ganglia, and the function of these signals in task learning and execution.

Spatial Profile and Differential Recruitment of $GABA_B$ Modulate Oscillatory Activity in Auditory Cortex

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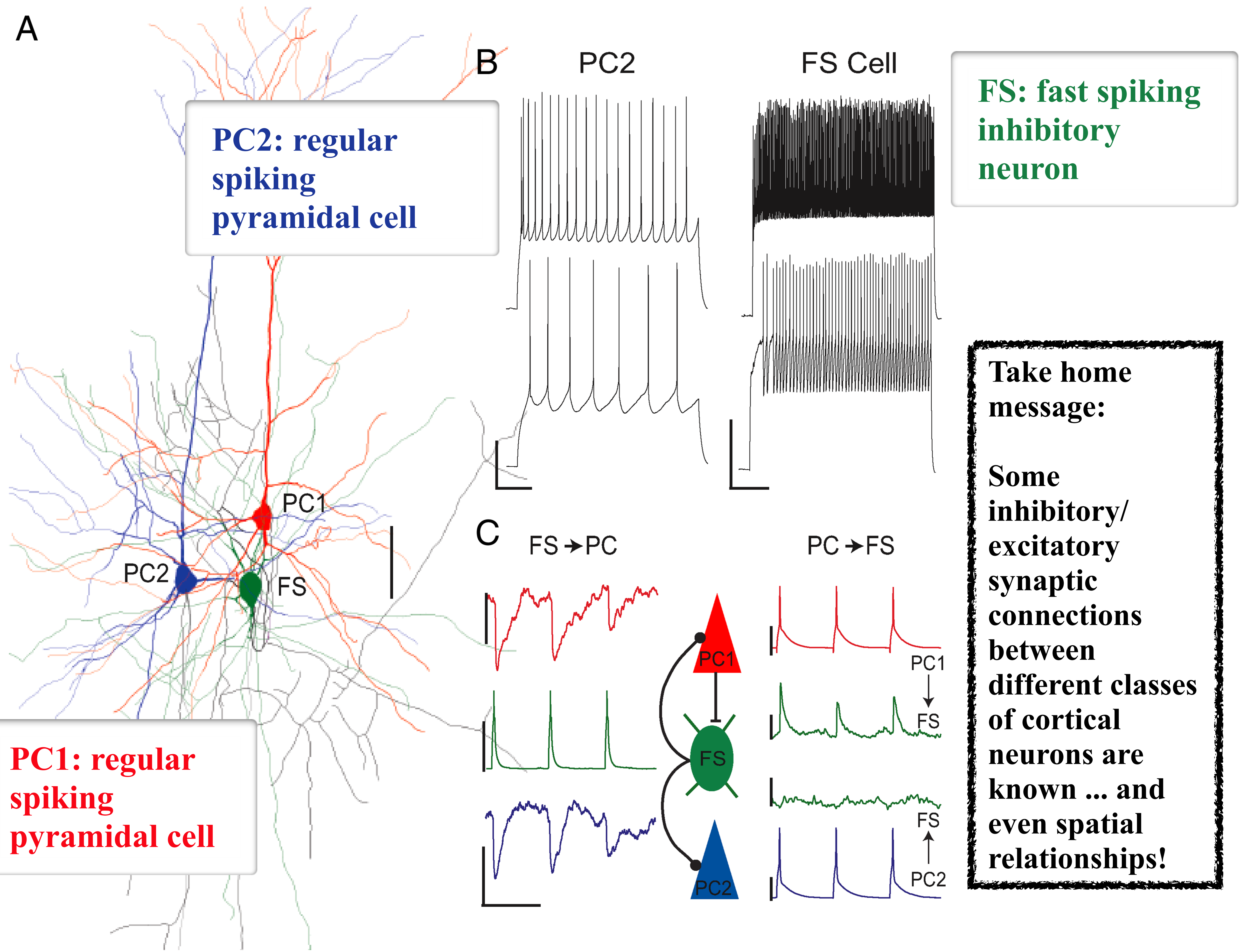
The interplay between inhibition and excitation is at the core of cortical network activity. In many cortices, including auditory cortex (ACx), interactions between excitatory and inhibitory neurons generate synchronous network gamma oscillations (30–70 Hz). Here, we show that differences in the connection patterns and synaptic properties of excitatory–inhibitory microcircuits permit the spatial extent of network inputs to modulate the magnitude of gamma oscillations. Simultaneous multiple whole-cell recordings from connected fast-spiking interneurons and pyramidal cells in L2/3 of mouse ACx slices revealed that for intersomatic distances <50 μm, most inhibitory connections occurred in reciprocally connected (RC) pairs; at greater distances, inhibitory connections were equally likely in RC and nonreciprocally connected (nRC) pairs. Furthermore, the $GABA_B$-mediated inhibition in RC pairs was weaker than in nRC pairs. Simulations with a network model that incorporated these features showed strong, gamma band oscillations only when the network inputs were confined to a small area. These findings suggest a novel mechanism by which oscillatory activity can be modulated by adjusting the spatial distribution of afferent input.

Figure 1. The intrinsic and synaptic properties of fast spiking interneurons and pyramidal cells. ***A***, A representative FS cell (green) that was an RC pyramidal cell (PC1; red) and an nRC to another (PC2; blue). Scale bar, 50 μm. ***B***, Responses evoked with depolarizing step current injection for the cells shown in ***A*** [left, PC2, 0.2 nA (bottom) and 0.4 nA (top); right, FS cell, 0.6 nA (bottom) and 0.8 nA (top)]. Calibration: vertical, 40 mV; horizontal, 200 ms. ***C***, Left, Suprathreshold stimulation (10 Hz) of the FS cell (green trace) resulted in IPSPs in both PC1 (red trace) and PC2 (blue trace). Right, Stimulation of the RC PC1 (10 Hz; red trace) produced EPSPs in the FS cell (top; green trace). Stimulation of the nRC PC2 (blue trace) did not evoke EPSPs (bottom; green trace). Calibration: vertical, PSPs, 0.5 mV; action potentials, 40 mV; horizontal, 100 ms.

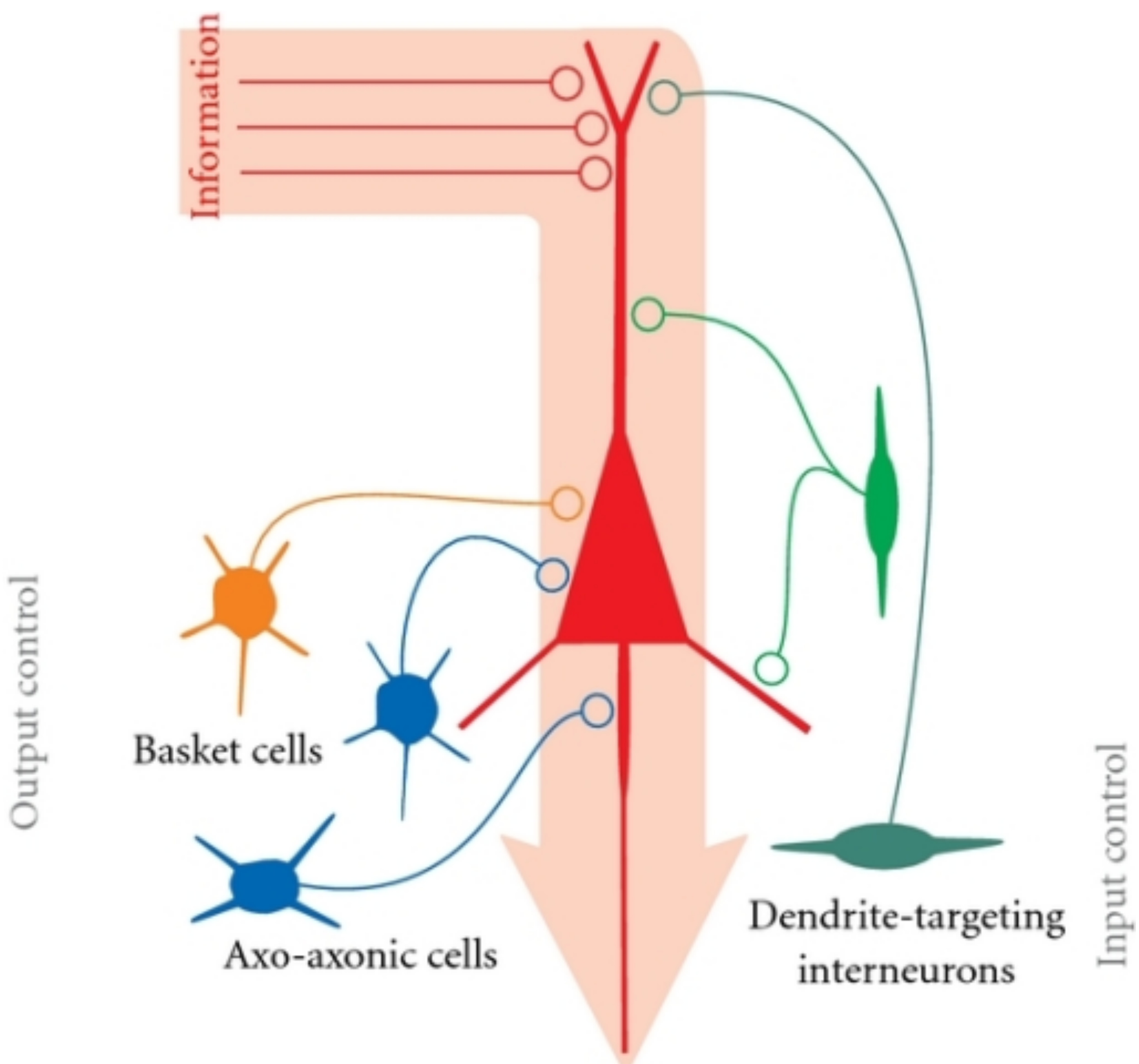


Take home message:

Some inhibitory/ excitatory synaptic connections between different classes of cortical neurons are known ... and even spatial relationships!

inhibitory interneuronal systems within cortical structures

Cortical structures have a diversity of inhibitory GABA-ergic interneurons with diverse properties governing including intrinsic excitability as well as the strength and location of inhibitory synapses on pyramidal neurons.

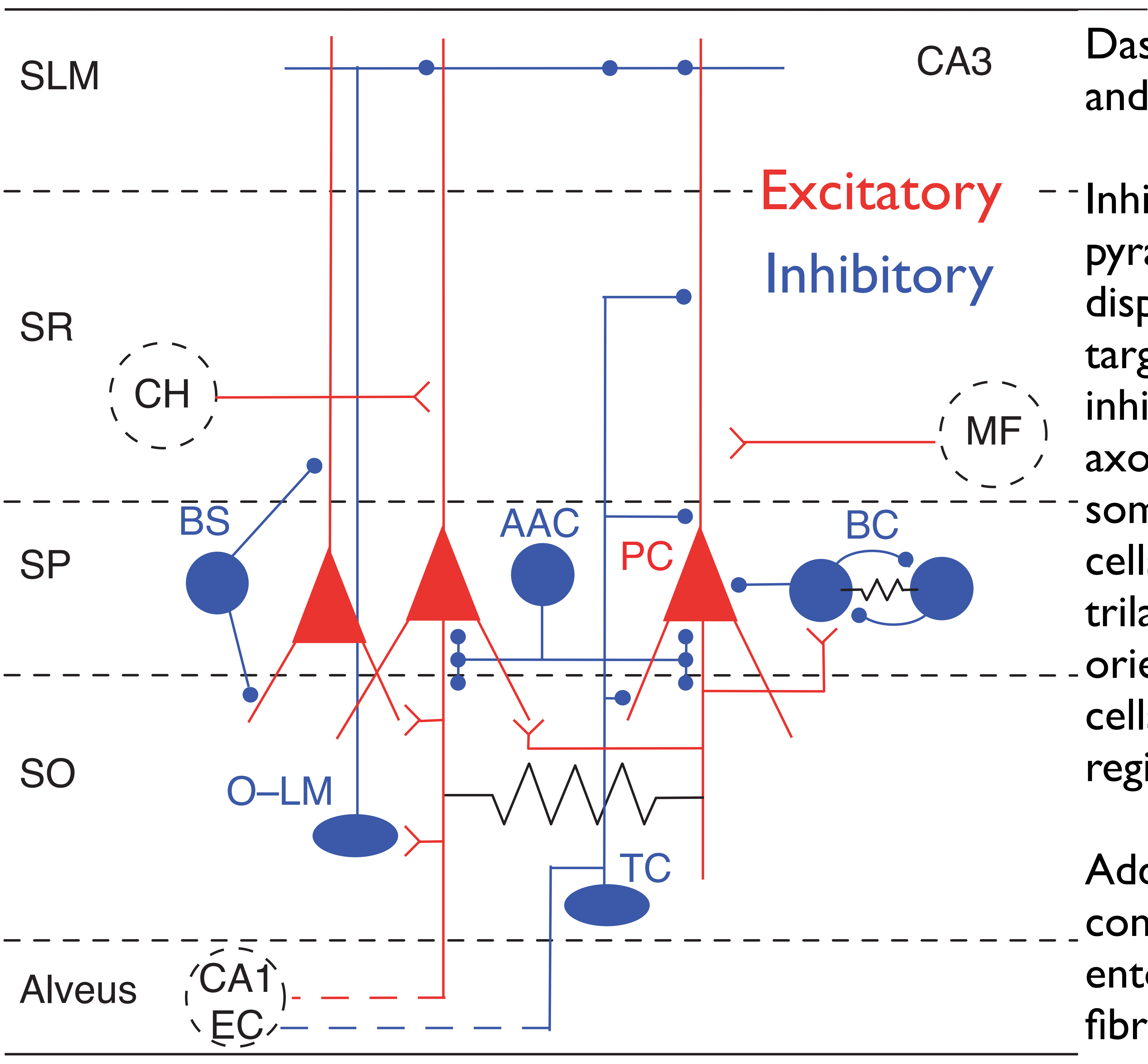


Both excitatory and inhibitory synapses can undergo activity-dependent changes in their strength.

Networks of inhibitory interneurons in cortex appear to control cortical oscillations and synchrony.

Neuronal oscillations and synchrony play an important role in brain function and dysfunction.

hippocampal microcircuit: cells types & synaptic connections in CA3

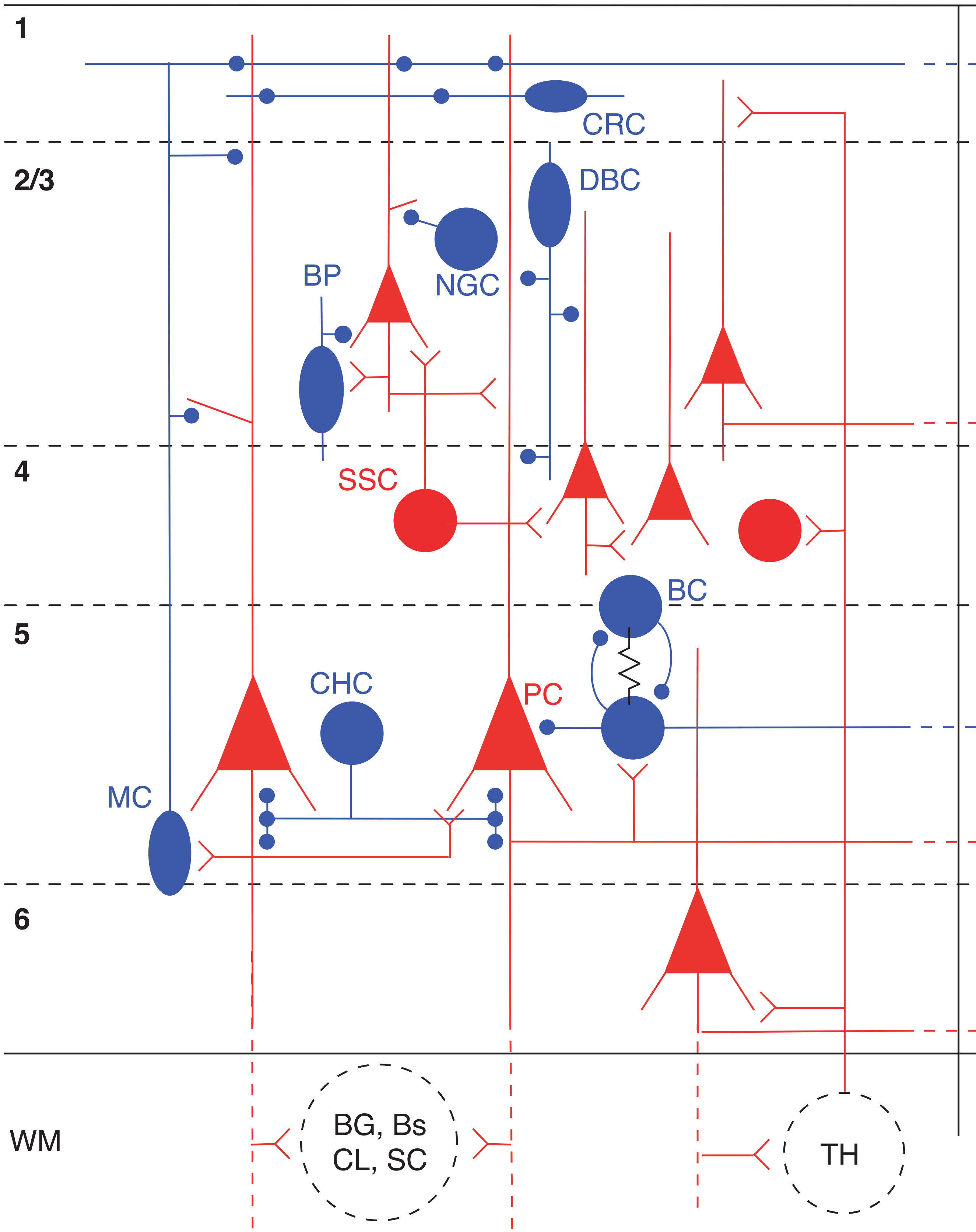


Dashed circles depict afferent and efferent extracortical input.

Inhibitory synapses onto pyramidal cells (PC) are displayed according to the target domains: axonal inhibition is provided by axo-axonic cells (AAC), and somatic inhibition by basket cells (BC). Bistratified cells (BS), trilaminar cells (TC), and oriens-lacunosum moleculare cells (O-LM) target dendritic regions.

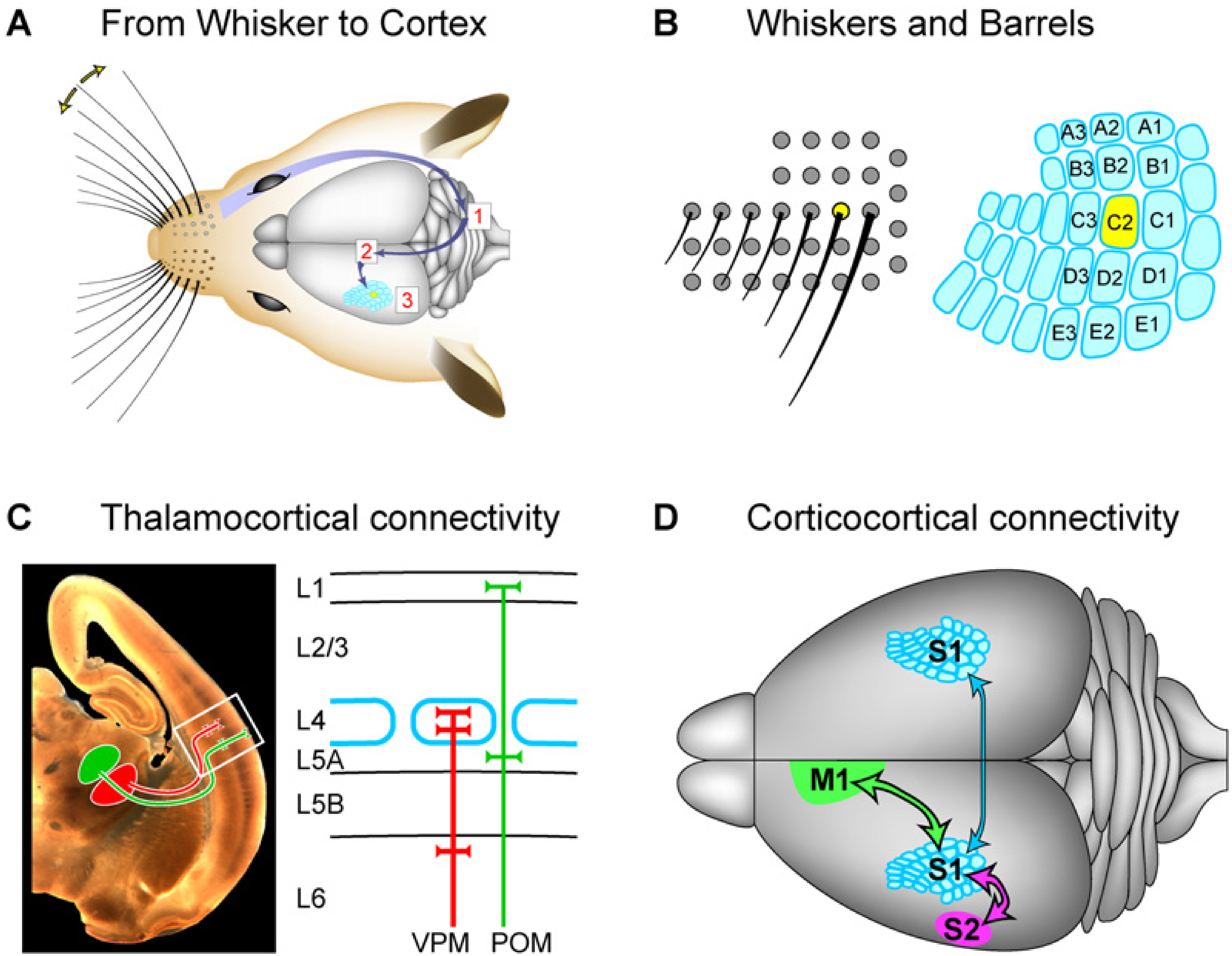
Additional abbreviations: CH, contralateral hemisphere; EC, entorhinal cortex; MF, mossy fibre.

cells types & connections in neocortex
(repeating unit: the cortical column microcircuit)

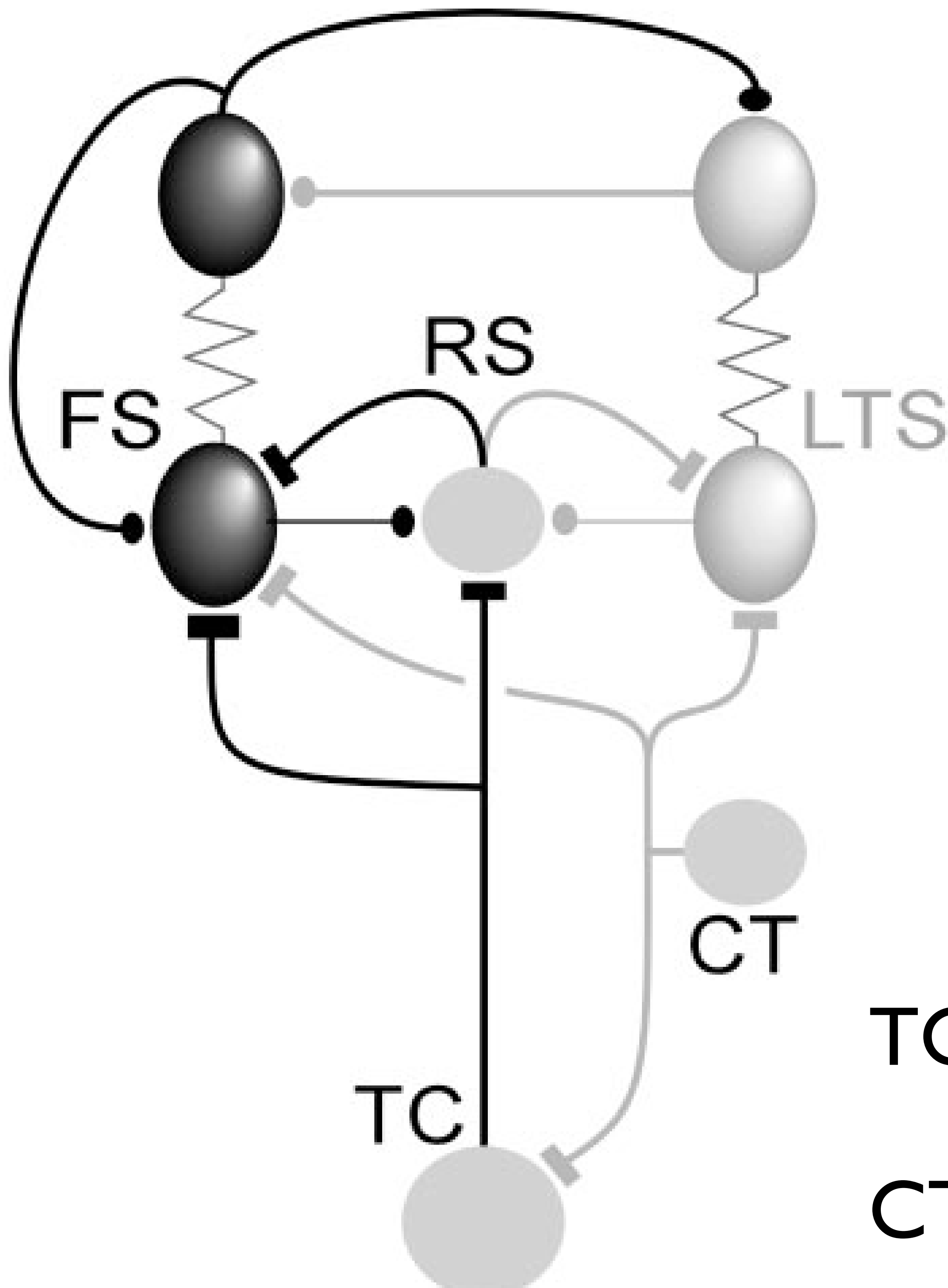


Inhibitory synapses onto pyramidal neurons (PC) are displayed according to the target domains: axonal inhibition is provided by chandelier cells (CHC), somatic inhibition by basket cells (BC), and dendritic inhibition by double-bouquet cells (DBC), bipolar cells (BP), neurogliaform cells (NGC), Martinotti cells (MC) and Cajal-Retzius cells (CRC). PCs projecting to different brain areas reside in different layers: layer 5 is the main projection layer, with PCs projecting to subcortical regions such as the brainstem (Bs), spinal cord (SC), superior colliculus, basal ganglia (BG) and thalamus (TH). Layer 6 PCs project mainly to the thalamus, and PCs in superficial layers project to other cortical targets, such as neighbouring columns and the contralateral cortical hemisphere (CL). The representation of the different interneurons also changes across layers, with NGCs and DBCs mainly located in superficial layers, and MCs dominating the deep layers. BCs of different types constitute 50% of interneurons in layers 2-6. Interneurons display diverse interlaminar targeting preferences: DBCs target dendrites that are typically located deeper than the soma, and MCs mainly target dendrites in the more superficial layers. SSC, spiny stellate cell; WM, white matter.

focus on layer 4 of rat "barrel cortex"



two systems of inhibition in layer 4



FS = fast spiking interneurons

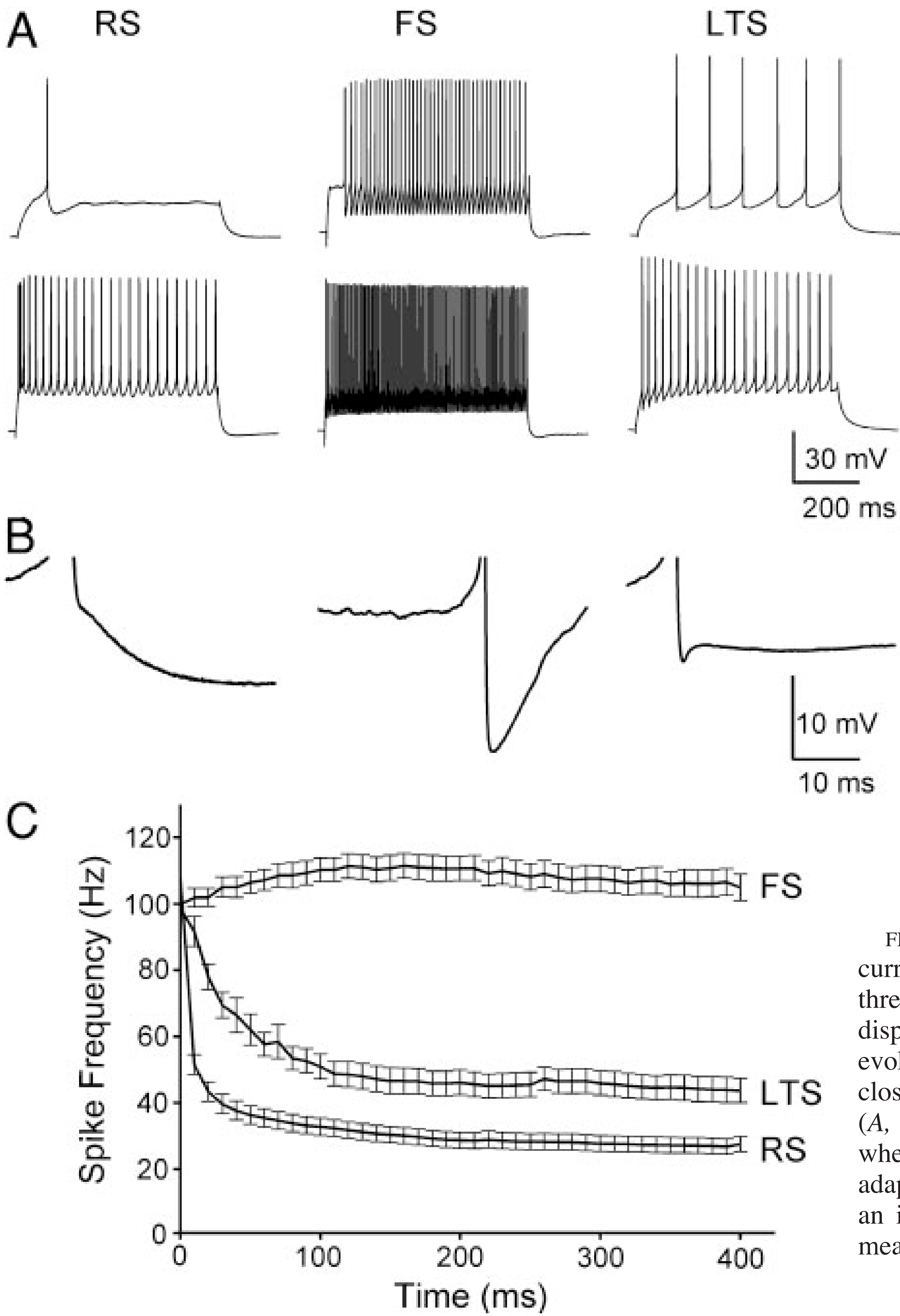
RS = regular spiking pyramidal neurons

LTS = low-threshold spike inhibitory neurons

TC = thalamocortical neuron

CT = corticothalamic neuron

intrinsic firing properties of layer 4 neurons

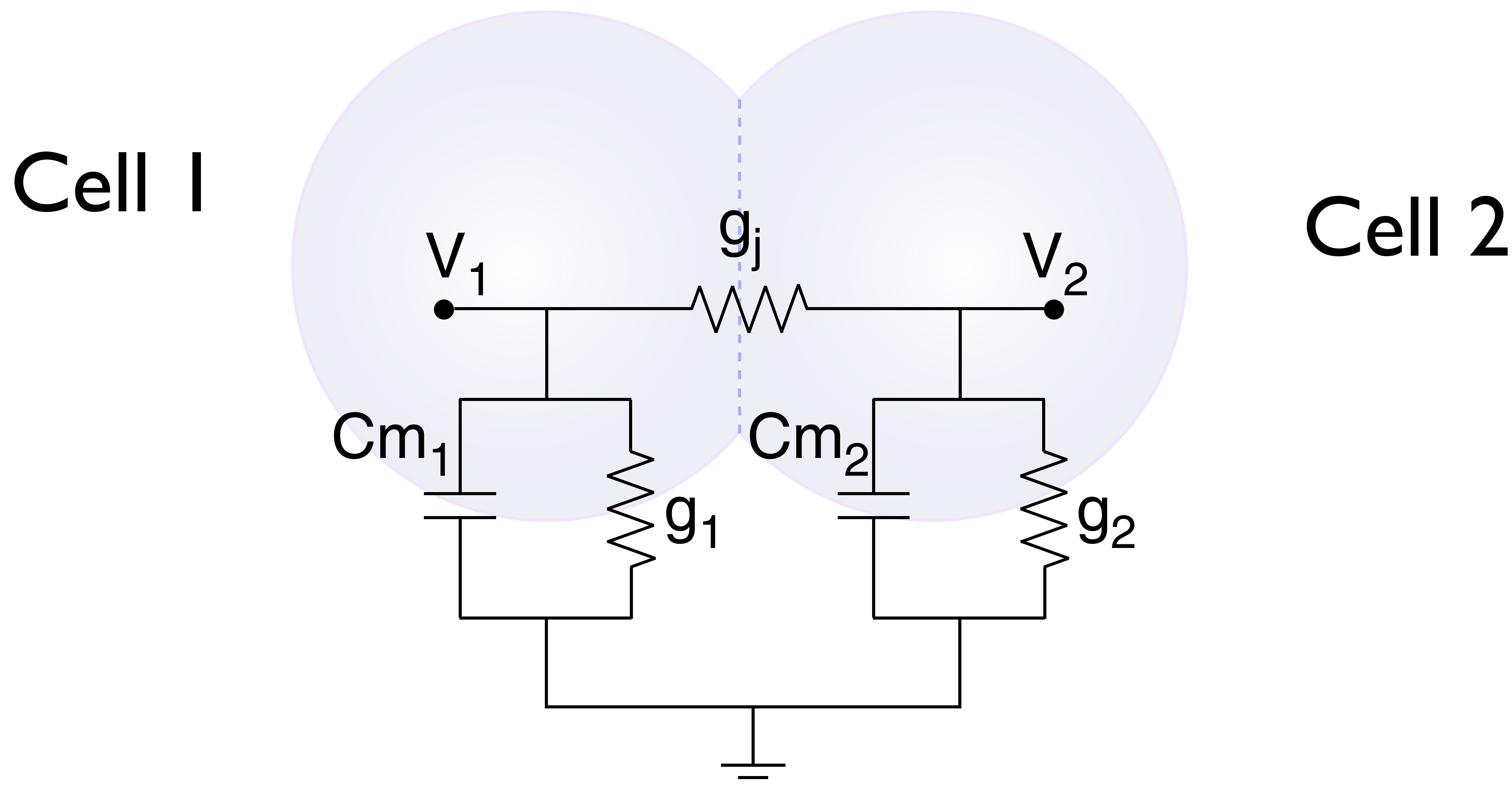


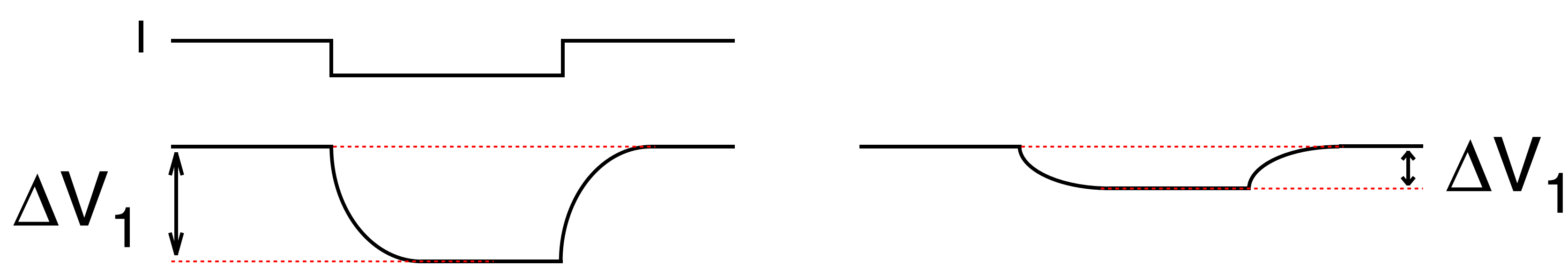
after-hyperpolarization (AHP)

spike-frequency adaptation (SFA)

FIG. 1. Intrinsic firing pattern of 3 types of layer 4 neurons. *A*: depolarizing current steps evoked low-frequency firing in regular-spiking (RS) and low-threshold-spiking (LTS) cells at threshold, whereas fast-spiking (FS) neurons displayed high minimum firing frequencies. Current steps at higher amplitudes evoked spike-frequency adaptation in RS and LTS cells but not in FS cells. *B*: close-up of the afterpotential waveforms following the 1st spikes at threshold (*A, top*). Notice the monophasic afterhyperpolarization (AHP) in the FS cell, whereas the LTS cell generated both fast and slow AHPs. *C*: spike-frequency adaptation in the 3 cell types. Current step amplitudes were adjusted to evoke an initial firing frequency of 100 Hz in all sampled cells. Data shown are means ± SD for each cell type (FS, n = 36 cells; LTS, n = 34; RS, n = 25).

gap junctional coupling of inhibitory interneurons





$$CC_{12} = \frac{\Delta V_2}{\Delta V_1} = \frac{g_j}{g_j + g_2}$$

$$CC_{21} = \frac{\Delta V_1}{\Delta V_2} = \frac{g_j}{g_j + g_1}$$

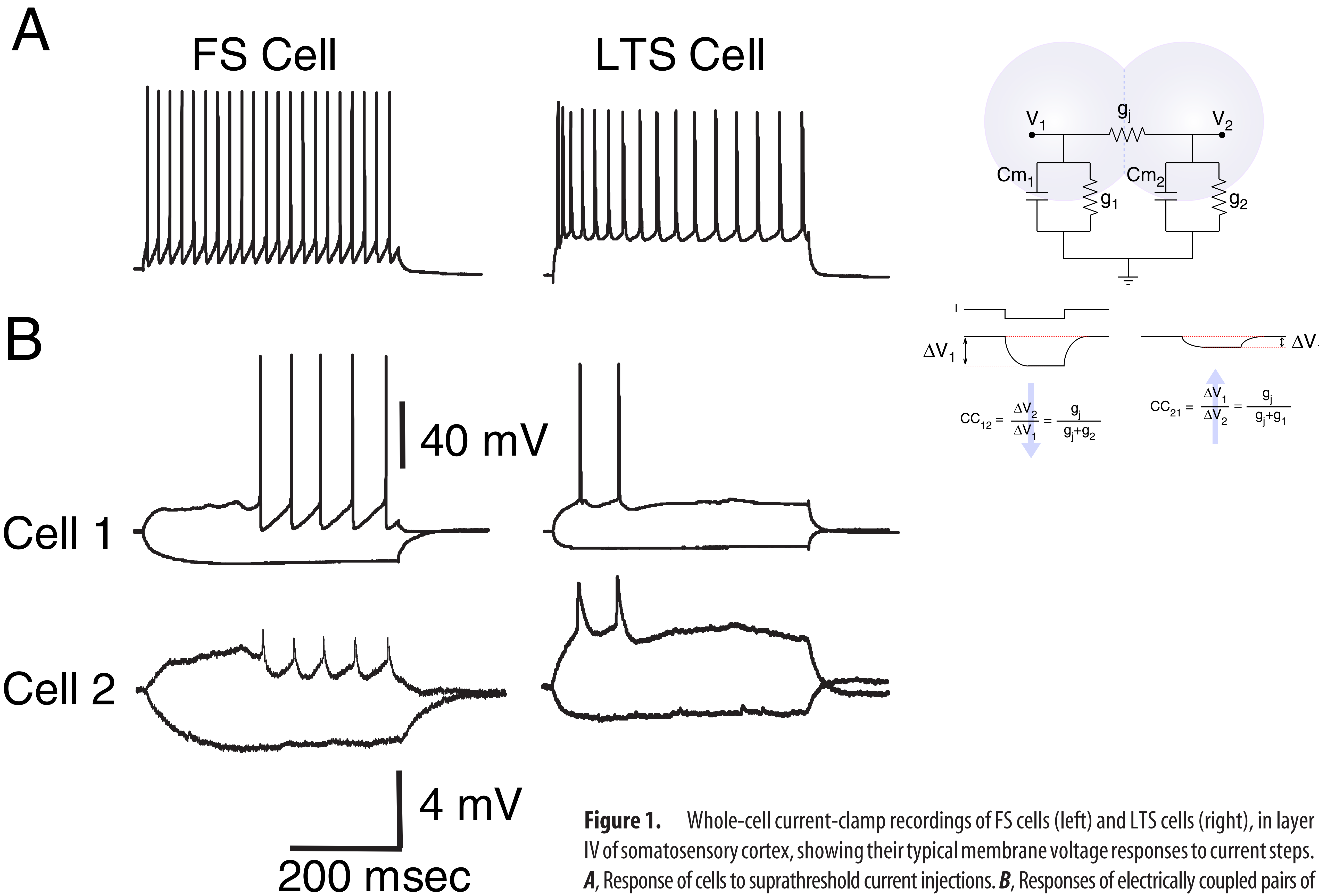
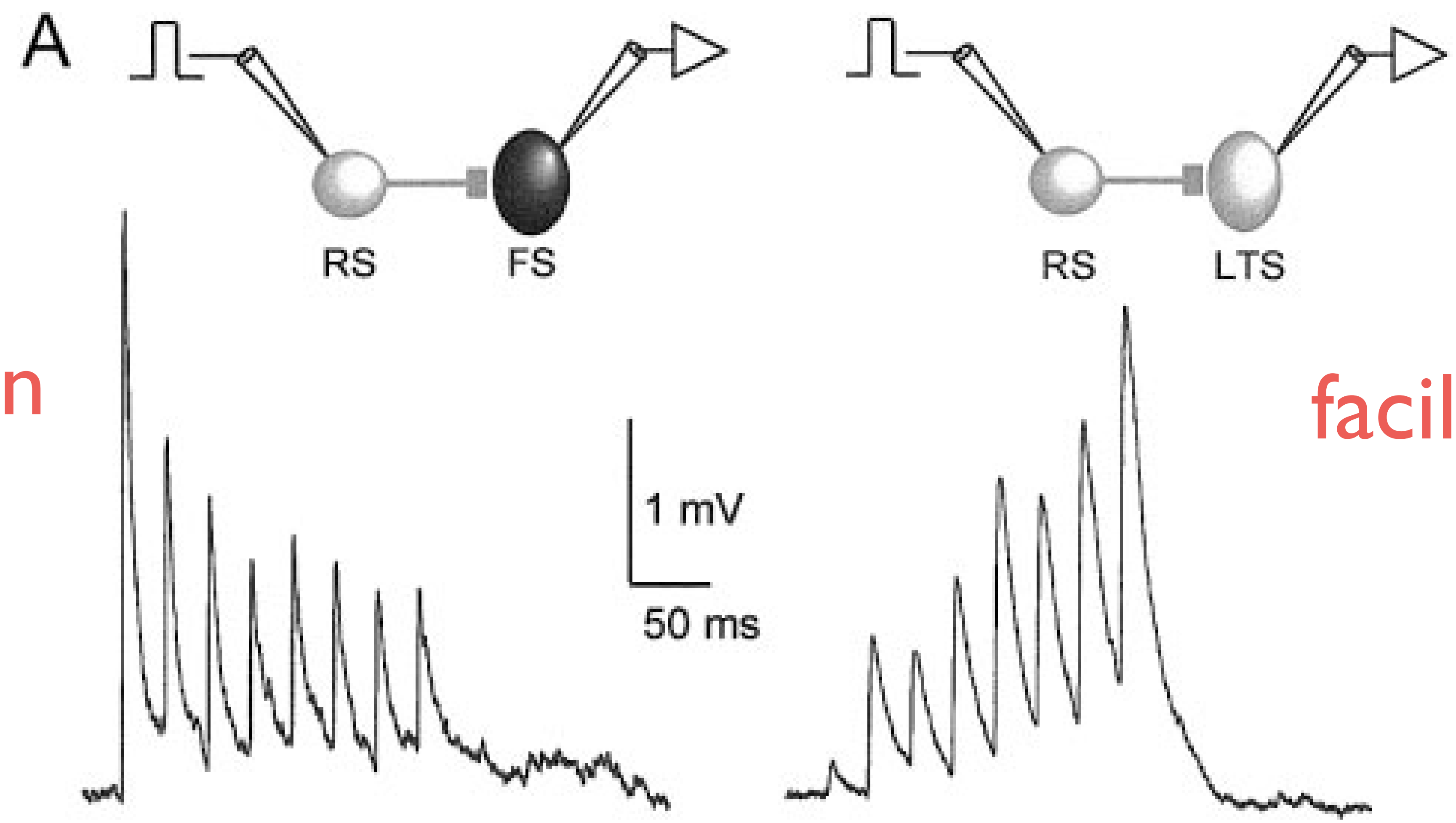


Figure 1. Whole-cell current-clamp recordings of FS cells (left) and LTS cells (right), in layer IV of somatosensory cortex, showing their typical membrane voltage responses to current steps. ***A***, Response of cells to suprathreshold current injections. ***B***, Responses of electrically coupled pairs of cells to suprathreshold and hyperpolarizing currents steps injected into cell 1. The bottom set of traces show the voltage responses attributable to coupling in the second cell (cell 2).

short-term **synaptic plasticity** of inhibitory interneurons



depression

facilitation

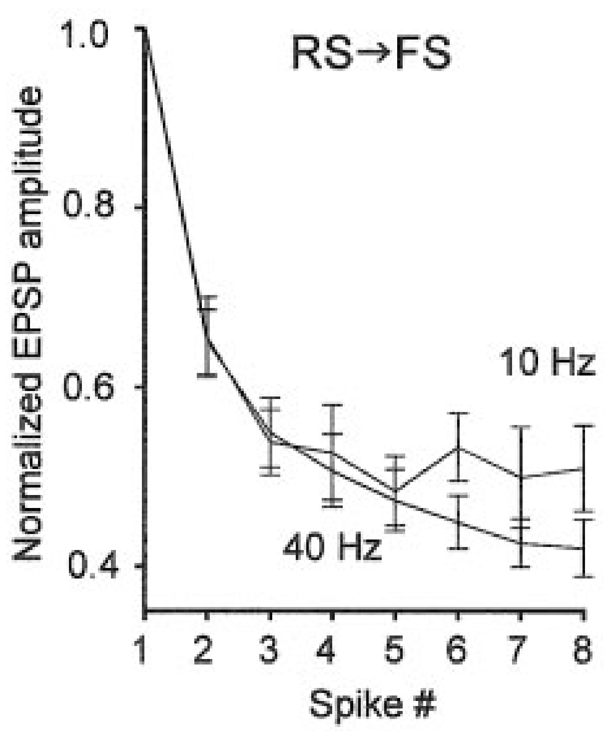
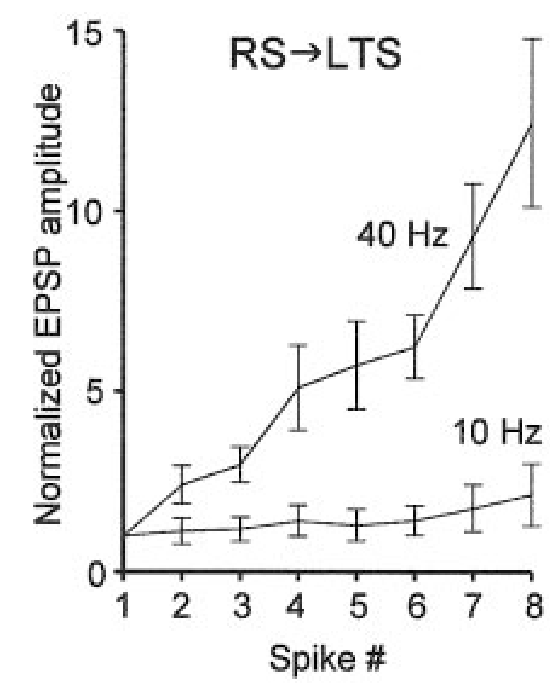
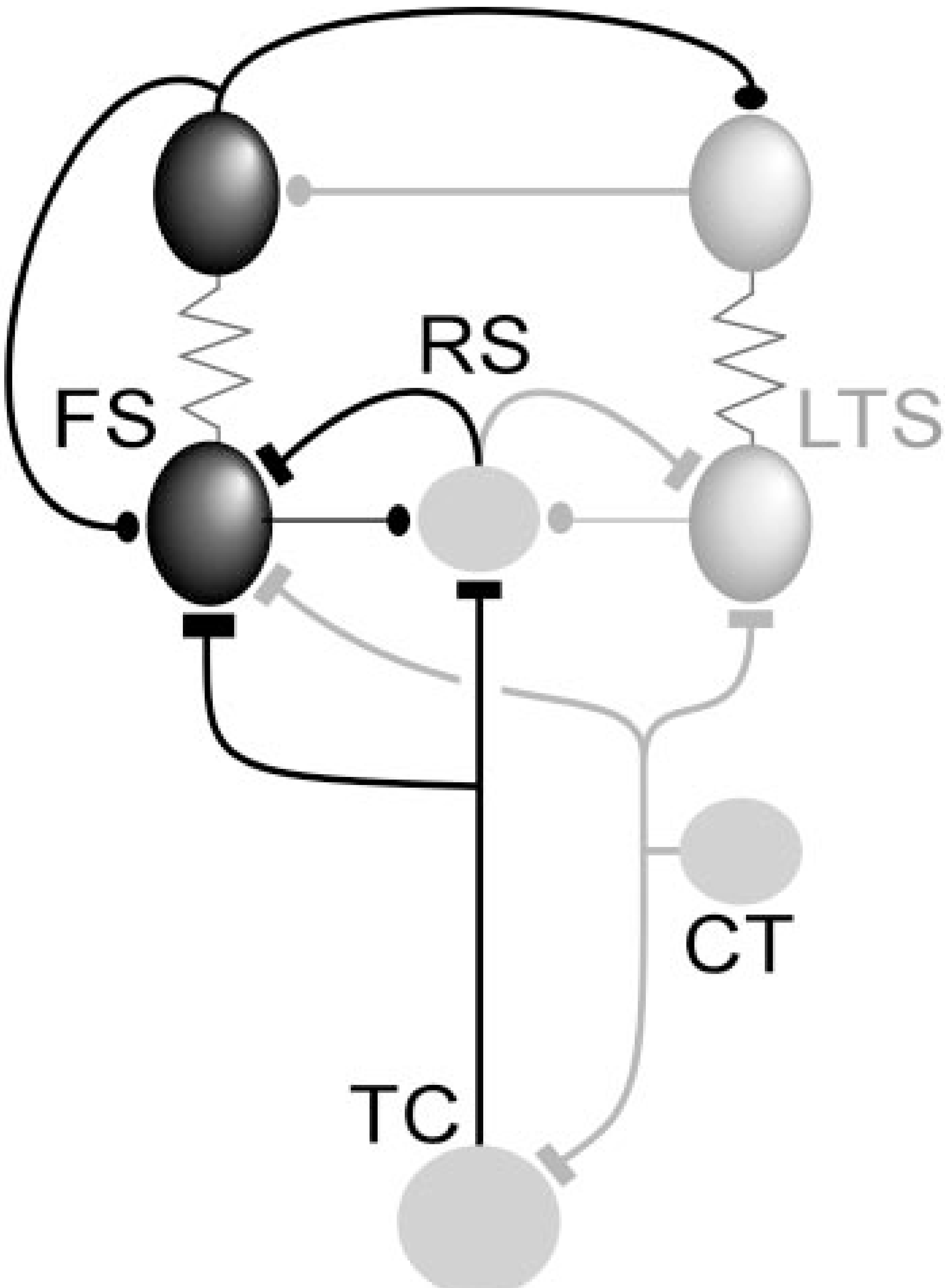
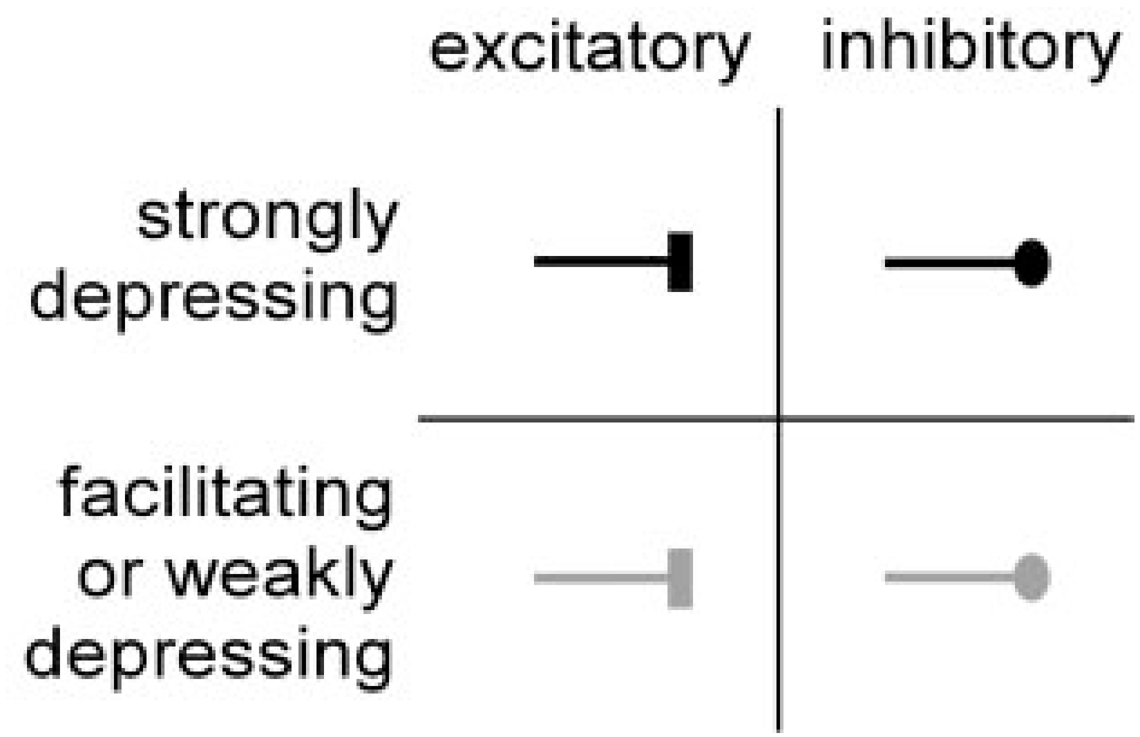


FIG. 4. EPSPs recorded from FS and LTS cells have distinctive short-term dynamics. *A*: EPSPs (averaged) recorded from FS and LTS neurons, evoked by stimulation of presynaptic RS cells (8 spikes at 40 Hz). *B*: summary data (means ± SE) of EPSPs from FS cells (24 pairs) and LTS cells (18 pairs) evoked by 10- and 40-Hz trains in RS cells. Data are normalized to 1st response in each train. FS (*left*): ratio of average amplitudes of $EPSP_{7-8}$ to $EPSP_1$ = 0.50 for 10 Hz, 0.42 for 40 Hz. LTS (*right*): ratio of average amplitudes of $EPSP_{7-8}$ to $EPSP_1$ = 1.9 for 10 Hz, 10.9 for 40 Hz.



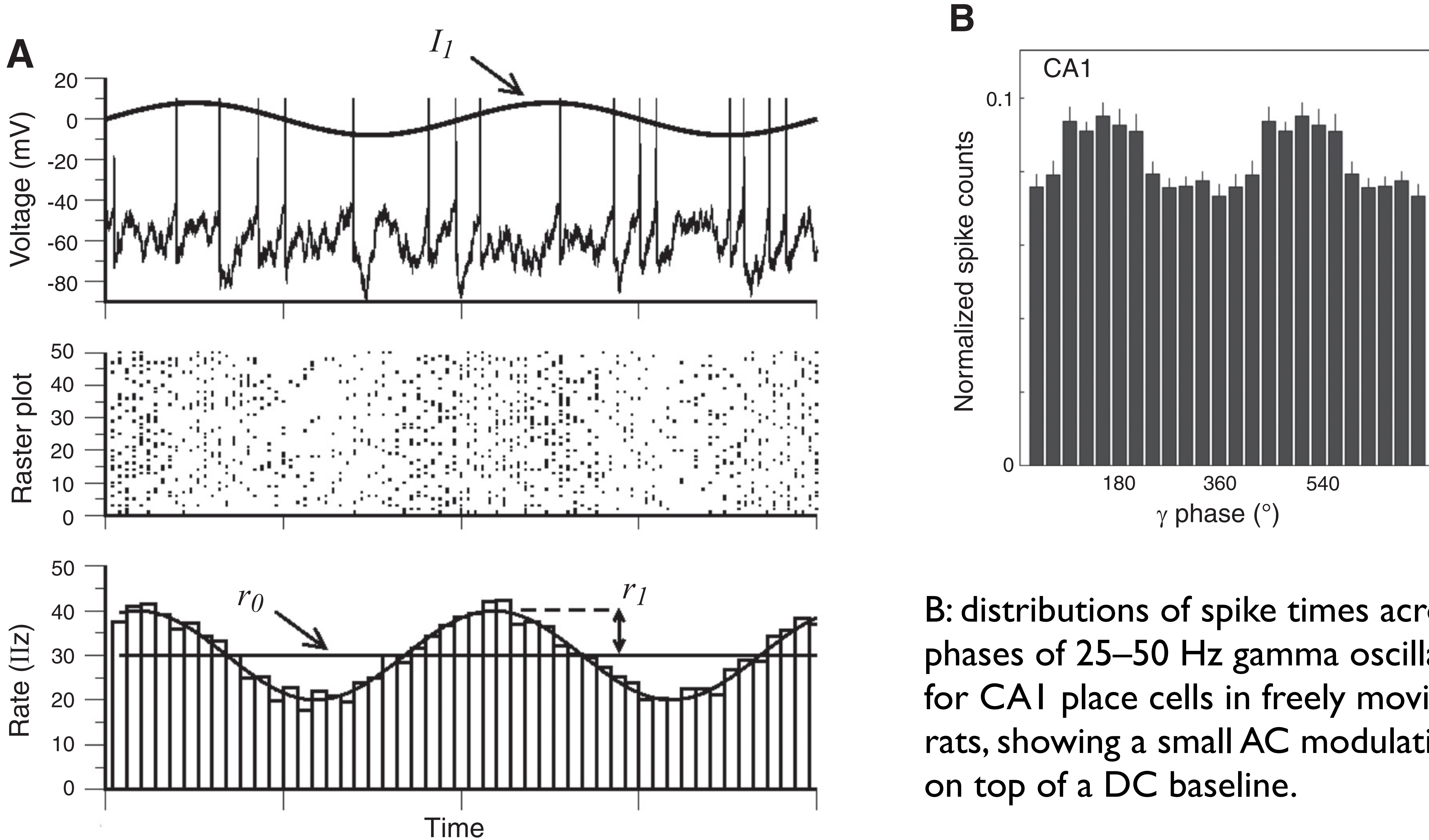
two systems of inhibition in layer 4





reciprocal
short-term
synaptic plasticity

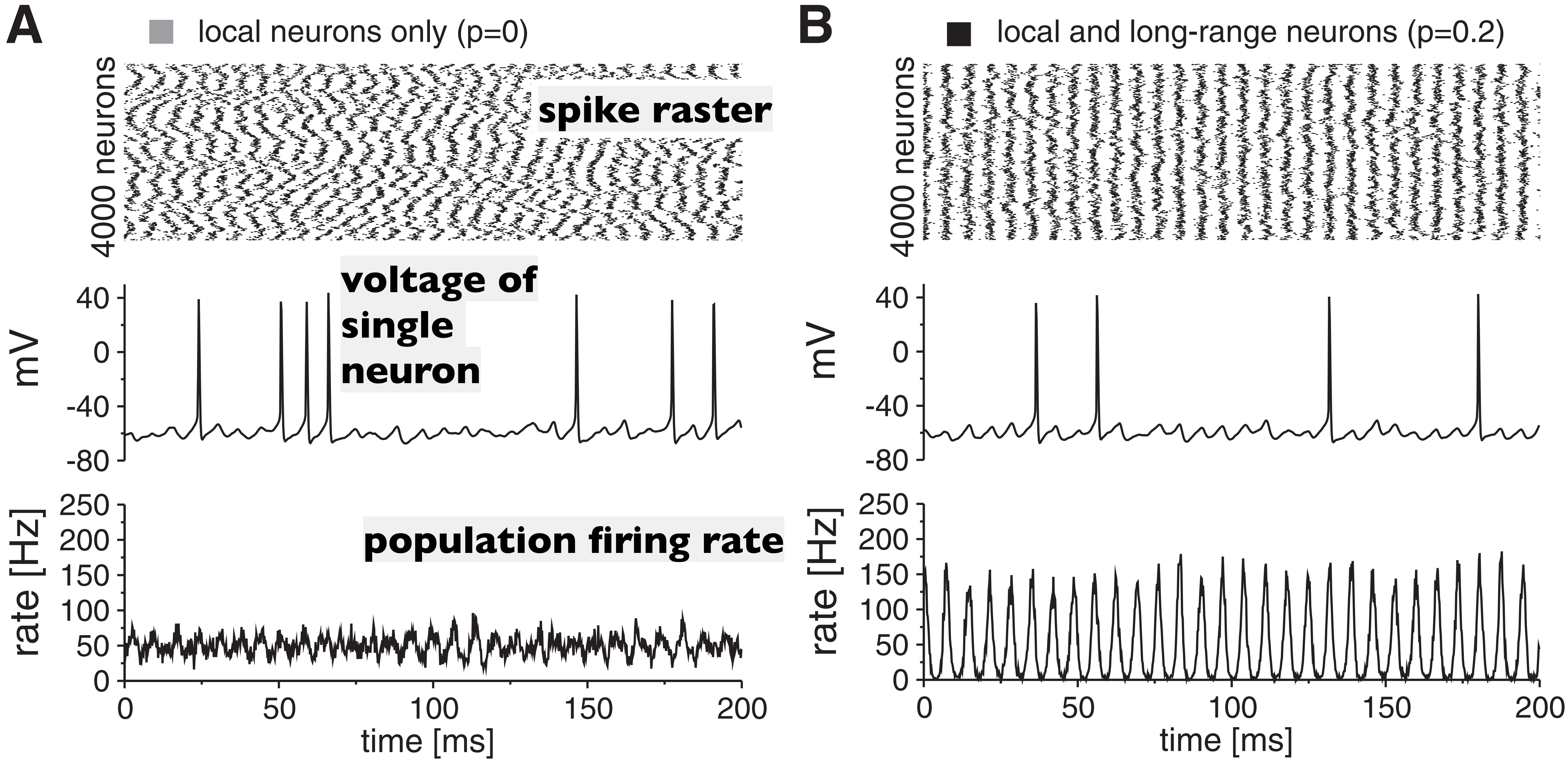
population rhythmicity with irregular spike activity of individual neurons



B: distributions of spike times across phases of 25–50 Hz gamma oscillations for CA1 place cells in freely moving rats, showing a small AC modulation on top of a DC baseline.

A: network dynamics in the form of single neuron activity in response to network inputs composed of a large amount of noise and a weak sinusoidal wave (top). The **raster plot** (middle) reveals the modulation of the instantaneous firing rate, which has a large DC component (r0) and a small AC component (r1, sinusoidal) (bottom).

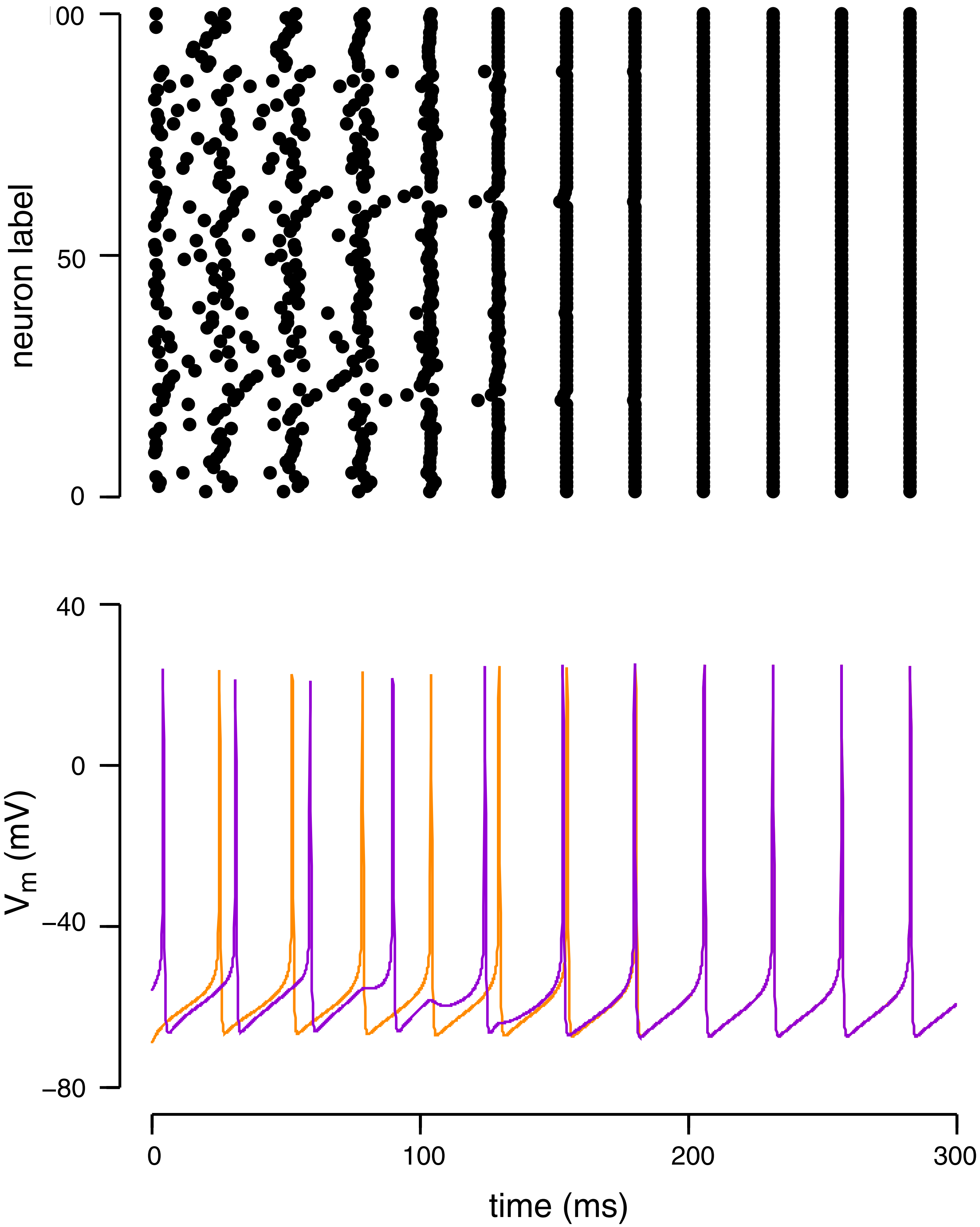
cortical inhibitory interneuron network population activity is async/sync depending on short/long range network connectivity



A: Here interneurons are coupled by inhibitory synapses with **local connectivity** (spatial length is 20 neurons, in a network of 4,000 neurons). The network is essentially asynchronous.

B: Here the network has 75% local and 25% **long-range connections**. Note strong oscillatory rhythm.

synchronization in an inhibitory interneuronal network (type 1 neurons)

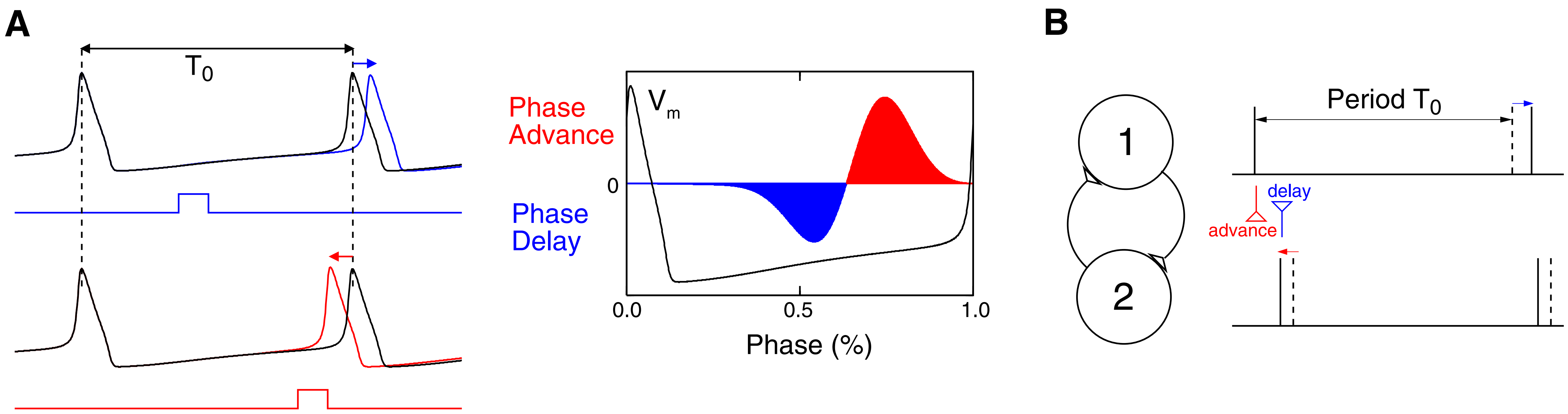


rastergram where each row of dots represents spikes discharged by one of the neurons in the network

Membrane potentials show two neurons initially **asynchronized**, but quickly become perfectly **synchronized by mutual inhibition**

Different(!) from phase plane analysis of coupled relaxation oscillators (type 2)

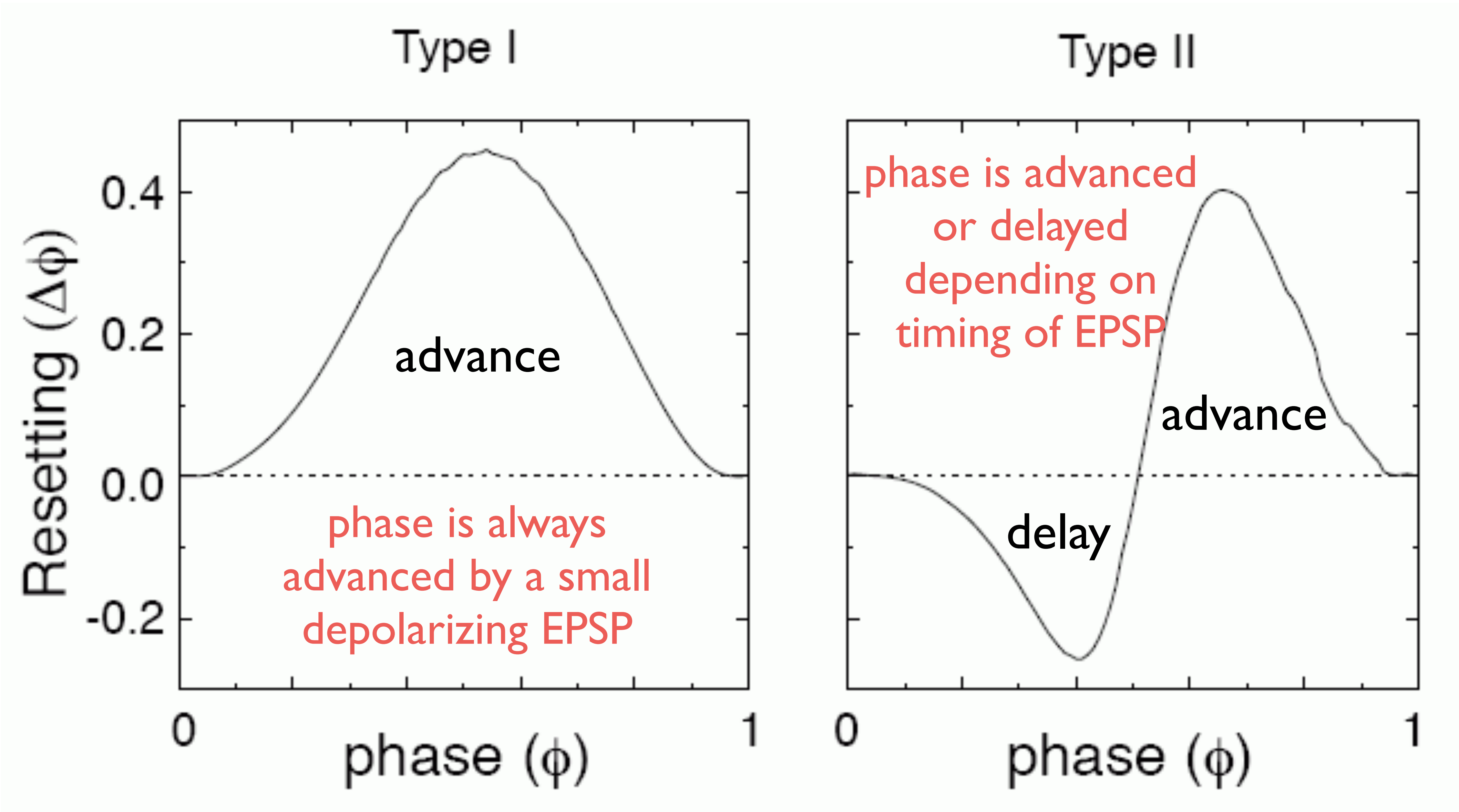
our phase plane methods don't apply when neurons are not relaxation oscillators
instead: theory of "weakly coupled" oscillators - the "phase response curve"
shows that excitation synchronizes type 2 neurons



A: Phase response curve of the type 2 neuron model. Left: a small and brief depolarizing current pulse leads to either a phase delay (blue) or phase advance (red), depending on the timing of the pulse perturbation. T0 is the oscillation period in the absence of perturbation. Right: induced phase change (positive for advance, negative for delay) as a function of the oscillatory phase at which the pulse perturbation is applied. Superimposed is the membrane potential for a full oscillation cycle (spike peak corresponds to zero phase).

B: Fast mutual excitation naturally gives rise to synchrony for two coupled type-2 Hodgkin-Huxley model neurons, as a cell firing slightly earlier advances the firing of the other cell, while the synaptic input back from the other cell delays its own firing, leading to reduced phase difference between the two in successive cycles.

but phase response curves for type I neurons are different



theoretical neuroscientists have shown:
type 2 neurons are more easily synchronized by excitation;
type I neurons are more easily synchronized by inhibition

neural oscillations

an important aspect of brain function

Table 1 | **Neural oscillations in cortical networks**

Frequency band	Anatomy	Function
Theta (4–7 Hz)	Hippocampus[134], sensory cortex[140] and prefrontal cortex[141]	Memory[142,143], synaptic plasticity[18], top-down control[9] and long-range synchronization[9]
Alpha (8–12 Hz)	Thalamus[144], hippocampus[145], reticular formation[145], sensory cortex[146] and motor cortex[147]	Inhibition[148], attention[149], consciousness[150], top-down control[9] and long-range synchronization[151]
Beta (13–30 Hz)	All cortical structures, subthalamic nucleus[152], basal ganglia[152] and olfactory bulb[153]	Sensory gating[154], attention[155], motor control[156] and long-range synchronization[157]
Gamma (30–200 Hz)	All brain structures, retina[158] and olfactory bulb[159]	Perception[7], attention[160], memory[161], consciousness[162] and synaptic plasticity[16]

power in this frequency range

when exhibited by this brain structure

seems to have something to do with this function

neural oscillations in cortical function

mediated by inhibitory interneuronal systems

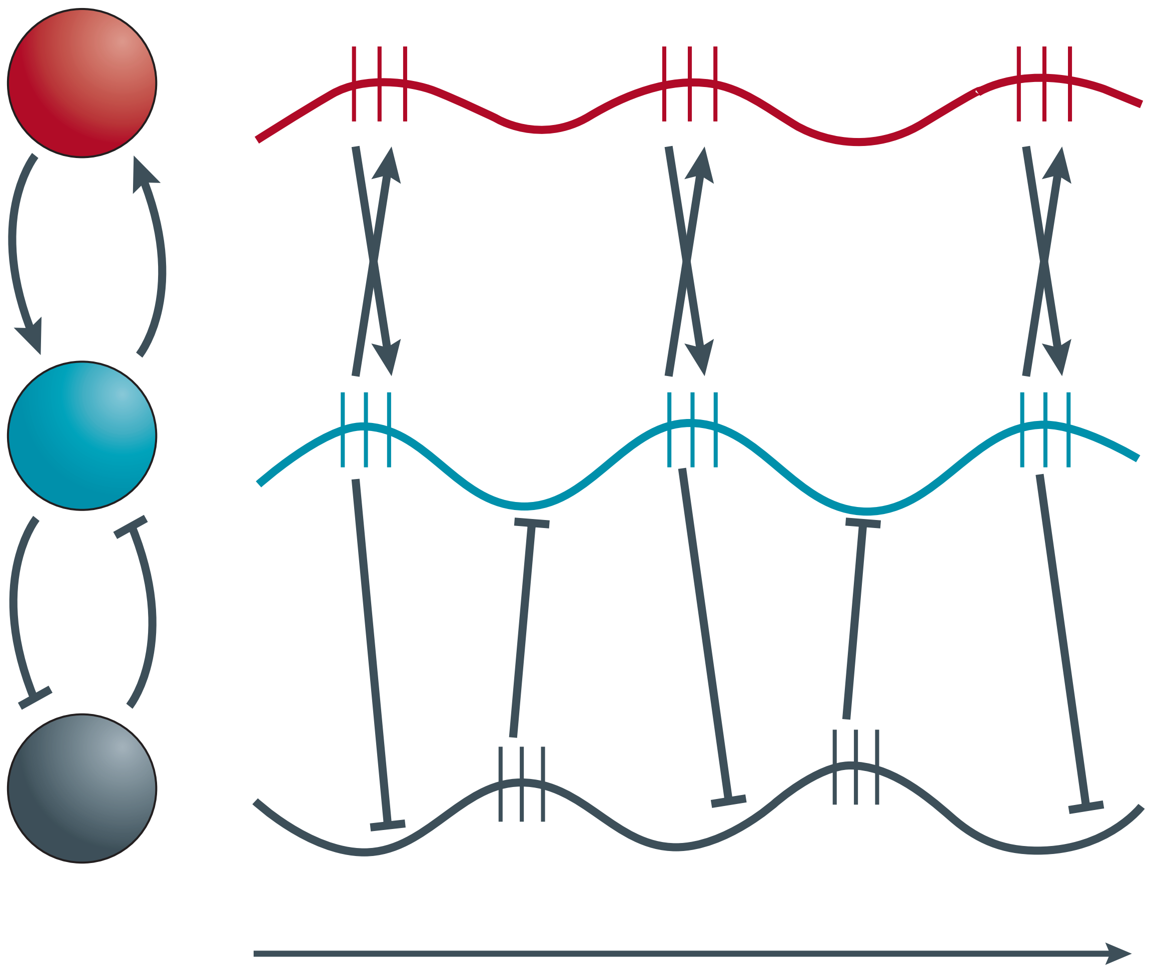
power spectrum of EEG or LFP - amount of signal at various frequencies

coherence - correlation of EEG or LFP at particular frequencies

correlation as a measure of **synchrony** of action potentials

phase synchrony - an estimate of synchrony that is independent of amplitude of oscillations.

Measures of action potential timing or synchronization with respect to oscillatory stimulus or population-level activity (e.g., EEG or LFP).



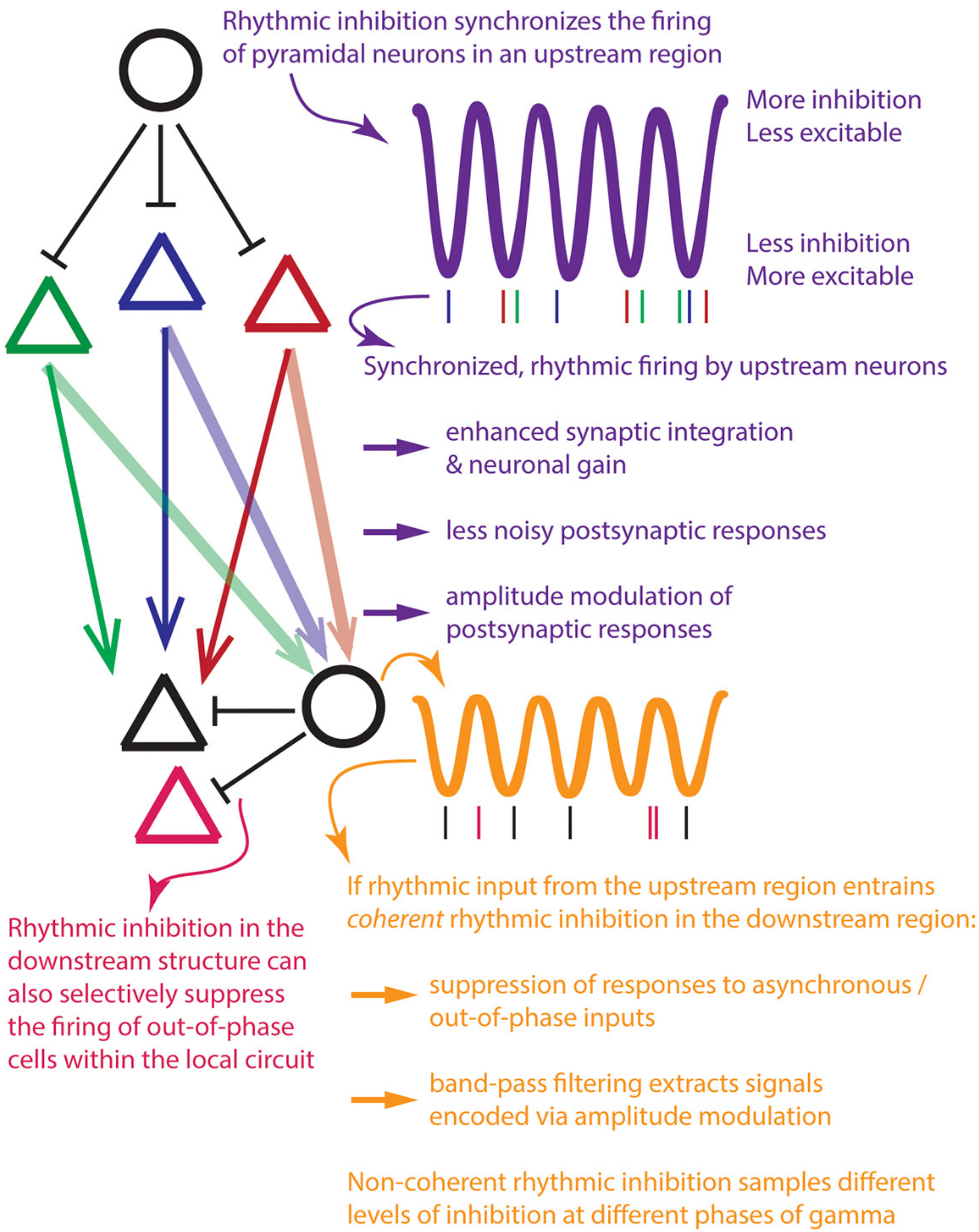
timing of spikes in relation to phase of population activity (e.g., local field potential) influences post-synaptic response probability

assume **excitatory** neurons:

- → Spike arriving at peak excitability
- ⊣ Spike missing peak excitability

Figure 1 | **Neural oscillations and synchrony in cortical networks. a** | The timing of rhythmic activity in cortical networks influences communication between neuronal populations. Three groups of interconnected neurons, each of which is rhythmically active, are shown on the left. On the right are local field potential oscillations and action potentials (spikes; indicated by vertical lines) in the three populations. Spikes either arrive at the postsynaptic neuron during a peak in its local field potential (arrows), corresponding to a peak in its excitability, or miss these peaks (blunt arrows). The timing of the activity of two groups of neurons is thus either aligned, enabling effective communication (red and blue group), or not aligned (blue and grey group), preventing communication. **b** | Synchronization between neurons in local cortical

inhibitory interneurons generates gamma oscillations and synchrony



Gamma oscillations, which can be identified by rhythmic electrical signals 30–100 Hz, consist of interactions between excitatory and inhibitory neurons that result in rhythmic inhibition capable of entraining firing within local cortical circuits.

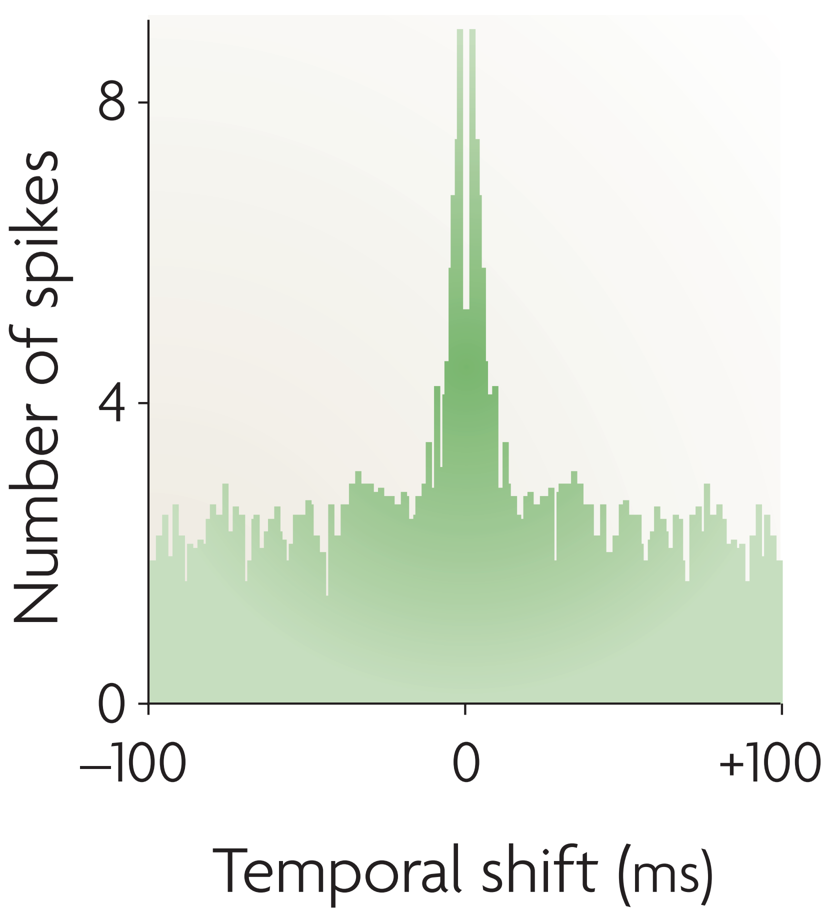
Many possible mechanisms have been described through which oscillations could act on cortical circuits to modulate their responses to input, alter their patterns of activity, and/or enhance the efficacy of their outputs onto downstream targets.

measures of synchronization

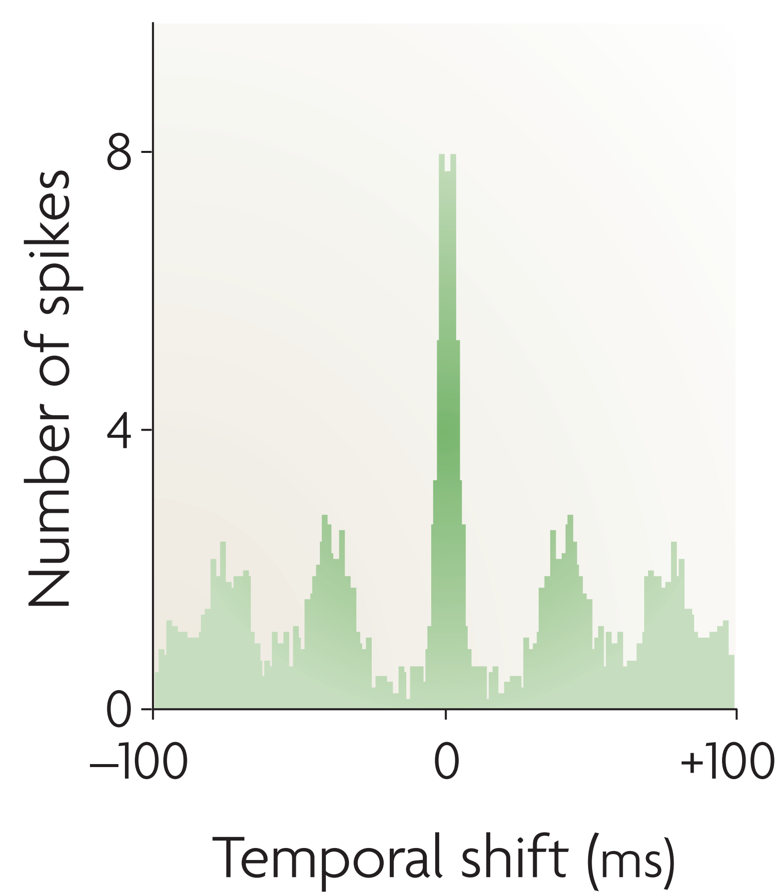
auto-correlation: average correlation of a signal with itself at two times separated by a shift tau

$$c(\tau) = \langle s(t)s(t-\tau) \rangle_t$$

gamma oscillations absent



gamma oscillations present

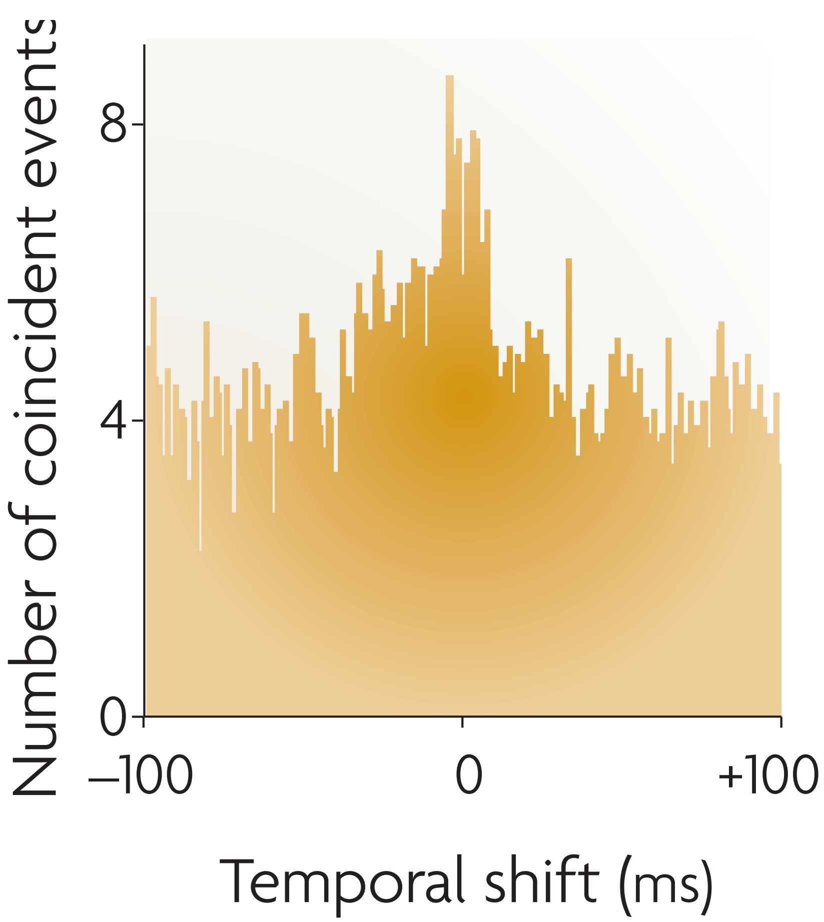


measures of synchronization

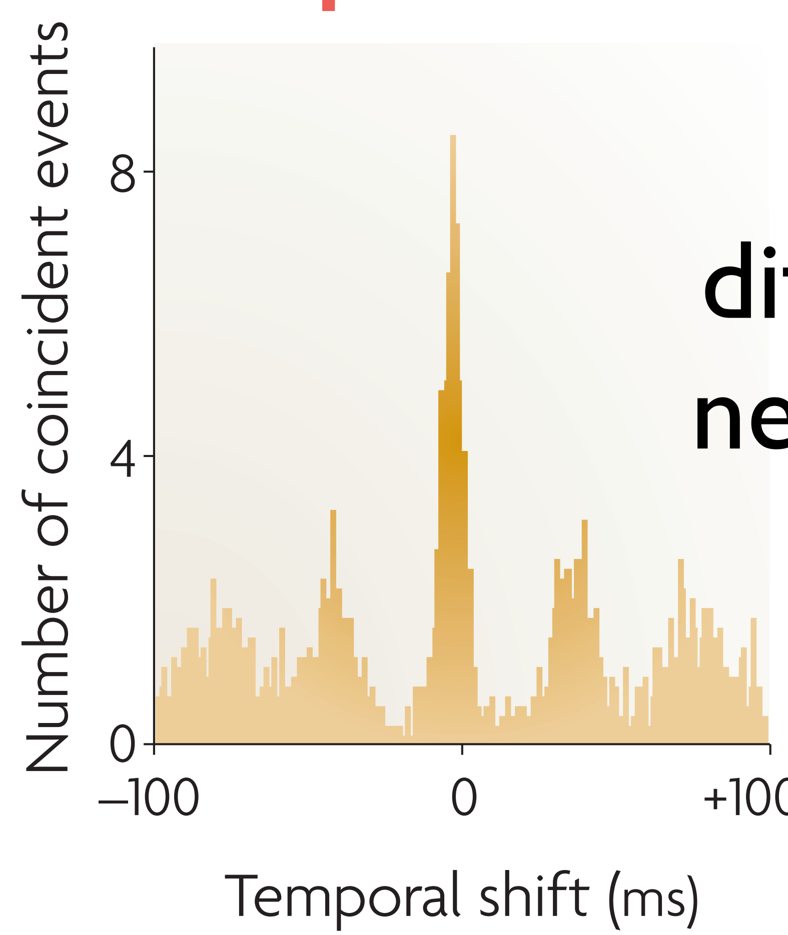
cross-correlation: the correlation of two signals as a function of temporal shift

$$c_{ab}(\tau) = \langle s_a(t) s_b(t-\tau) \rangle_t$$

gamma oscillations absent



gamma oscillations present



two different neurons!

gamma oscillations and long-range synchrony

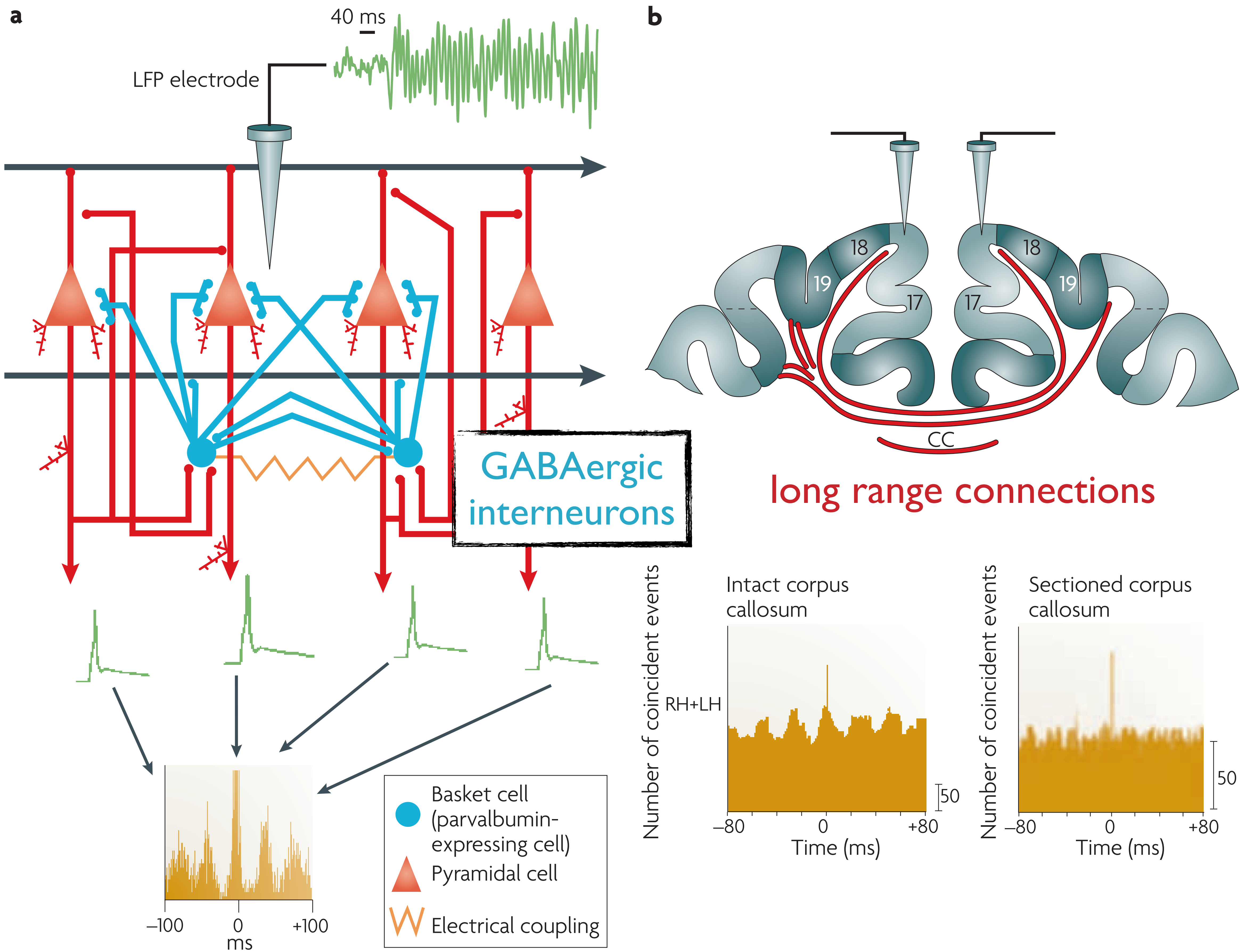


Figure 3 | **Mechanisms underlying the generation of gamma oscillations and synchrony. a** | A neocortical circuit involved in the generation of gamma-band oscillations. Generation of synchronized neural activity in neocortical circuits is dependent on negative feedback inhibition of pyramidal cells by GABA (γ-aminobutyric acid)-ergic interneurons that express the Ca^{2+}-binding protein parvalbumin. These receive glutamate receptor-mediated feedforward excitatory inputs, which makes them susceptible to changes in glutamatergic drive. Transient excitation of parvalbumin-expressing interneurons leads to a depolarization of many interneurons, which are themselves reciprocally interconnected through gap junctions and chemical GABAergic synapses. Electrical synapses are important for the synchronization of network activity because they rapidly propagate activity. Conversely, mutual inhibition through chemical synapses is a crucial determinant of the network frequency, as the duration of inhibitory postsynaptic potentials determines the dominant oscillation frequency. The resulting rhythmic inhibitory postsynaptic potentials can synchronize the firing of a large population of pyramidal neurons as the axon of an individual GABAergic neuron makes multiple postsynaptic contacts onto several pyramidal cells. This phasic inhibition leads to the synchronization of spiking activity that can be recovered with a cross-correlogram. A local field potential (LFP) recorded with an extracellular electrode reflects the average of the transmembrane currents that fluctuate at gamma-band frequency. Its extracranial counterpart can be reflected in electroencephalography (EEG) or magnetoencephalography (MEG) signals. **b** | Cortico-cortical connections mediate long-distance synchronization. The relationship between the integrity of the corpus callosum and interhemispheric synchronization of gamma-band oscillations in the cat visual cortex is illustrated. Recording electrodes were placed in the vicinity of the border of areas 17 and 18 of the right (RH) and left (LH) cortical hemispheres during stimulation with a light bar. In the bottom panels are cross-correlograms between responses from different recording sites in the LH and RH that indicate the degree of interhemispheric synchronization. When the corpus callosum was intact (left-hand panel), strong interhemispheric synchronization occurred with no phase lag between the LH and RH recording sites. Sectioning of the corpus callosum (right-hand panel) abolished interhemispheric synchronization while leaving synchronization within hemispheres intact. These data show that synchronization can occur over long distances with high precision and is crucially dependent on the integrity of cortico-cortical connections. The upper panel of part b is modified with permission, from REF. 163 © (1972) Elsevier. The lower panel of part **b** is modified, with permission, from REF. 70 © (1991) American Association for the Advancement of Science.

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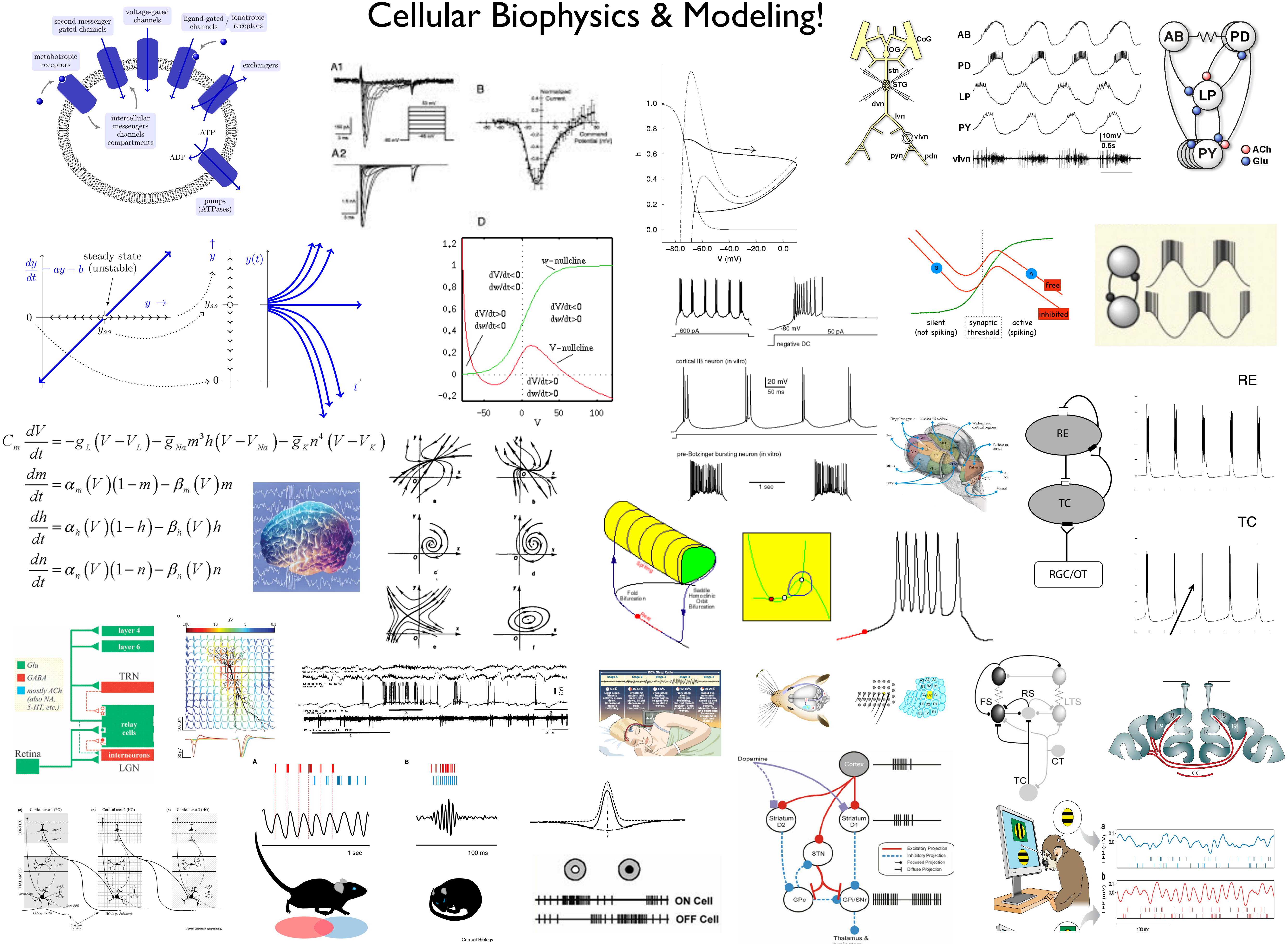

$$C_m \frac{dV}{dt} = -g_L\left(V - V_L\right) - \overline{g}_{Na} m^3 h \left(V - V_{Na}\right) - \overline{g}_K n^4 \left(V - V_K\right)$$

$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m$$

$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h$$

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n$$

further reading