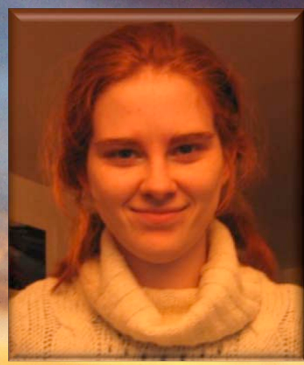
David McCormick, Yale Medical School *KITP, Oct 13, 2010*

McCormick Lab

YouSheng Shu

Andrea Hasenstaub



Bilal Haider

Alvaro Duque

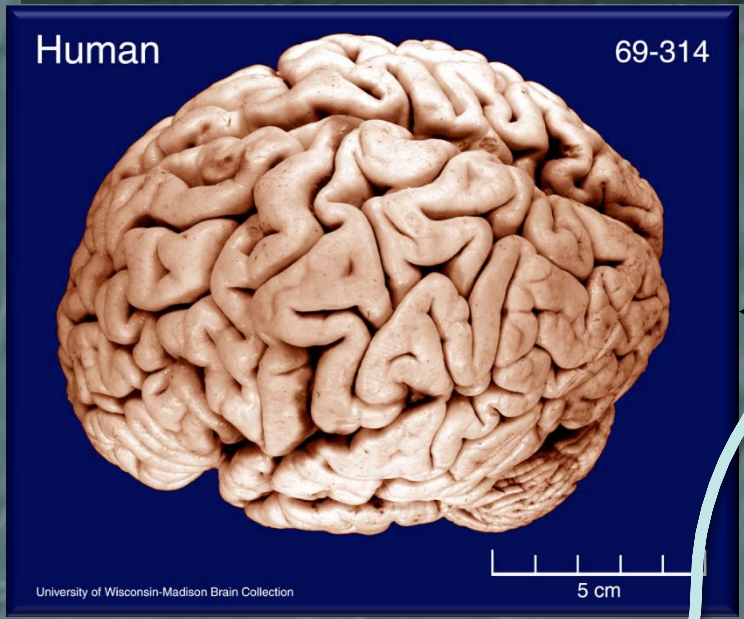
Carlos Mauriera

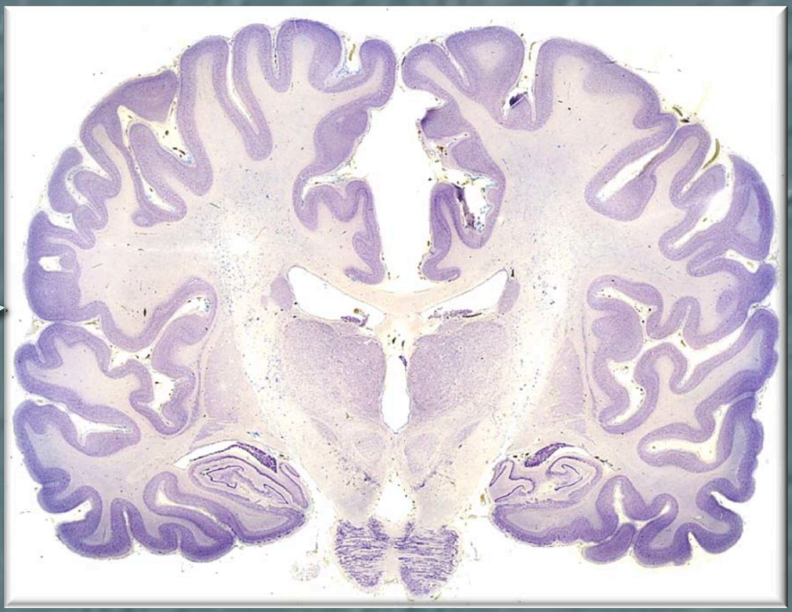
Carolina Oliva

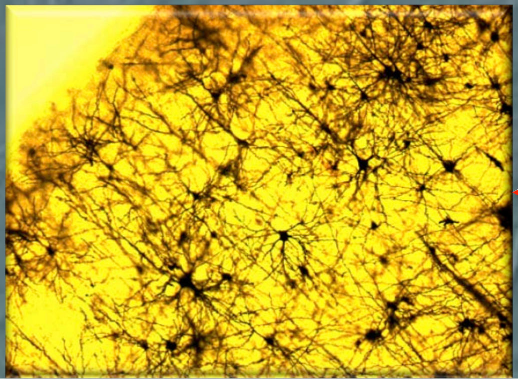
Yuguo Yu

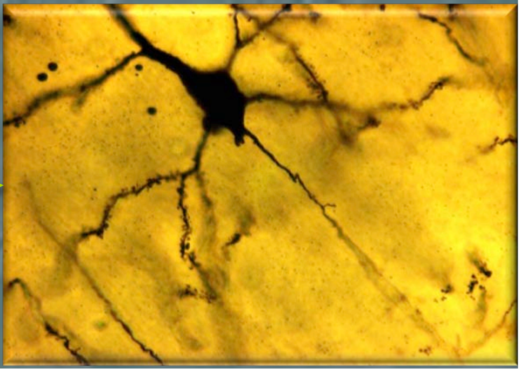
Robert Sachdev

Neocortex: Made for Flexible Behavior - What is its basic mode of operation?

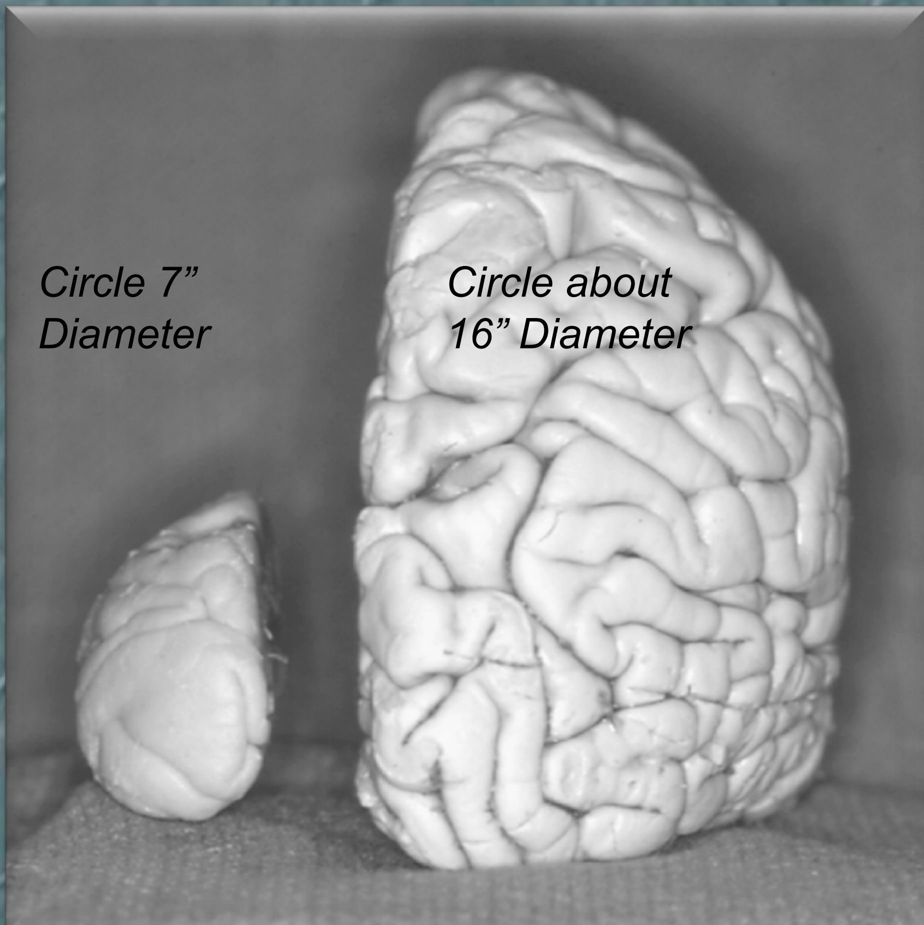


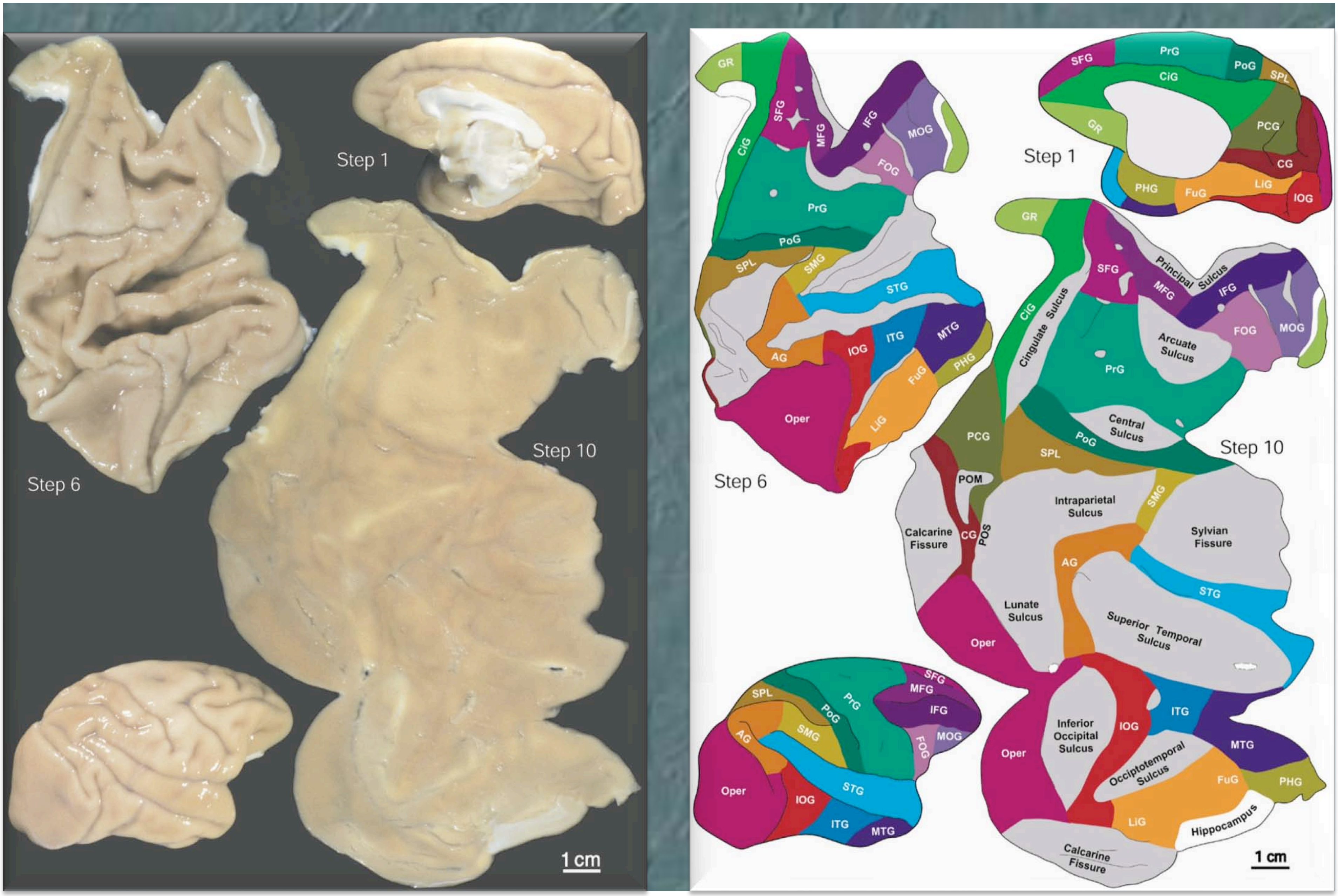






The Cortical Sheet



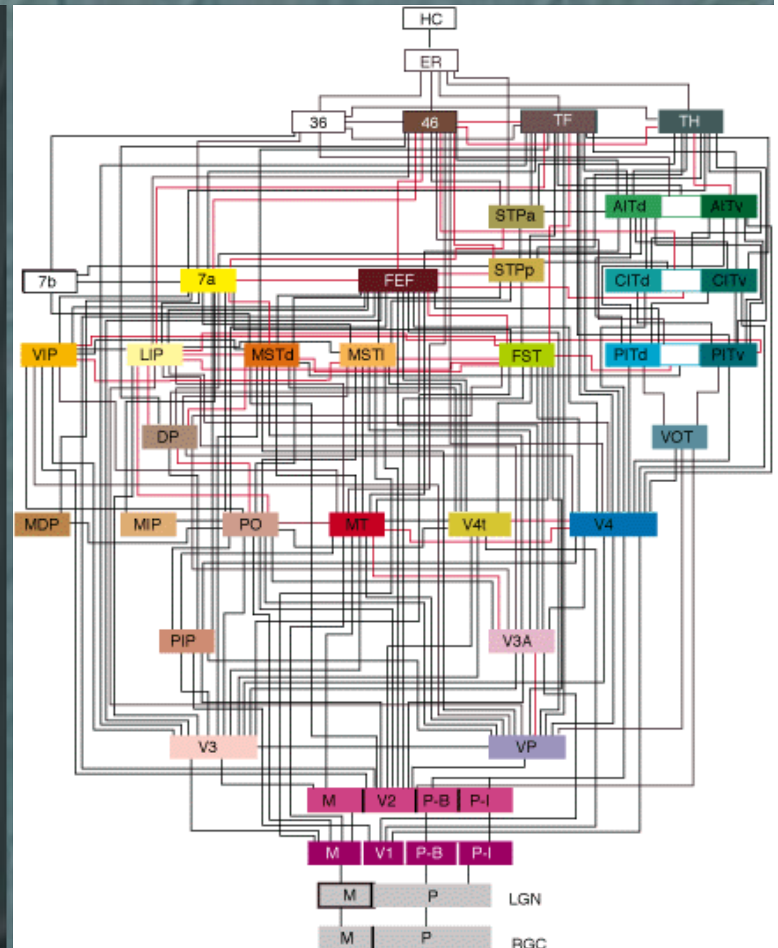

Step 1
Step 6
Step 10
1 cm
GR
CiG
SFG
MFG
IFG
MOG
FOG
PrG
PoG
SPL
SMG
STG
AG
IOG
ITG
MTG
PHG
FuG
LiG
Oper
PCG
CG
Principal Sulcus
Cingulate Sulcus
Arcuate Sulcus
Central Sulcus
POM
POS
Intraparietal Sulcus
Sylvian Fissure
Calcarine Fissure
Lunate Sulcus
Superior Temporal Sulcus
Inferior Occipital Sulcus
Occipitotemporal Sulcus
Hippocampus

Cortical Networks Are Widely Interconnected and Complex.

This Highly Interconnected Nature is Designed to Allow Flexible Behavior.

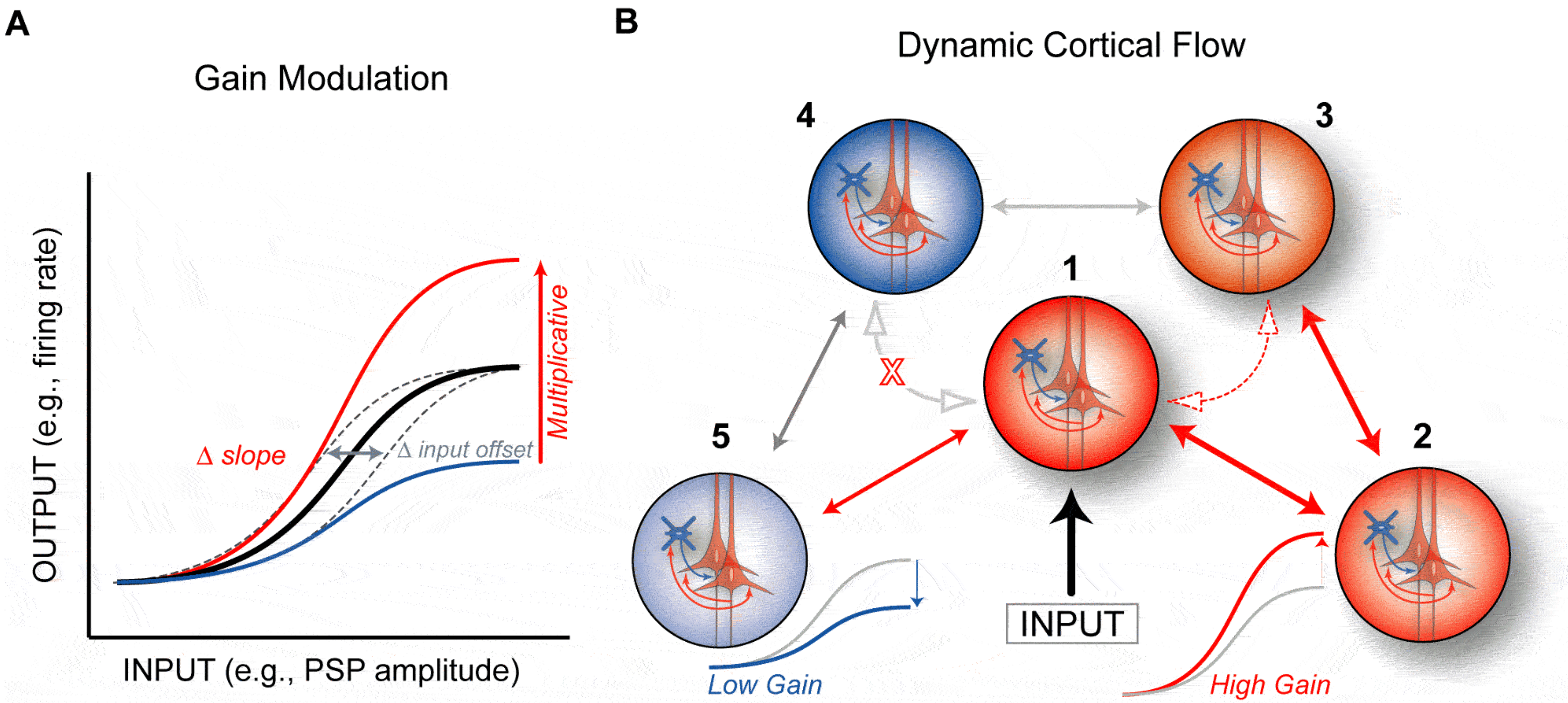
Flexible Behavior is Possible Because Functional Connections are Highly Dynamic on a Rapid (10's msec) Time Scale.

This Flexible Behavior of the Cortex Allows Activity to Flow According to Context and Behavioral Demands.



From Felleman and Van Essen Cerebral Cortex (1991) 1: 1-47

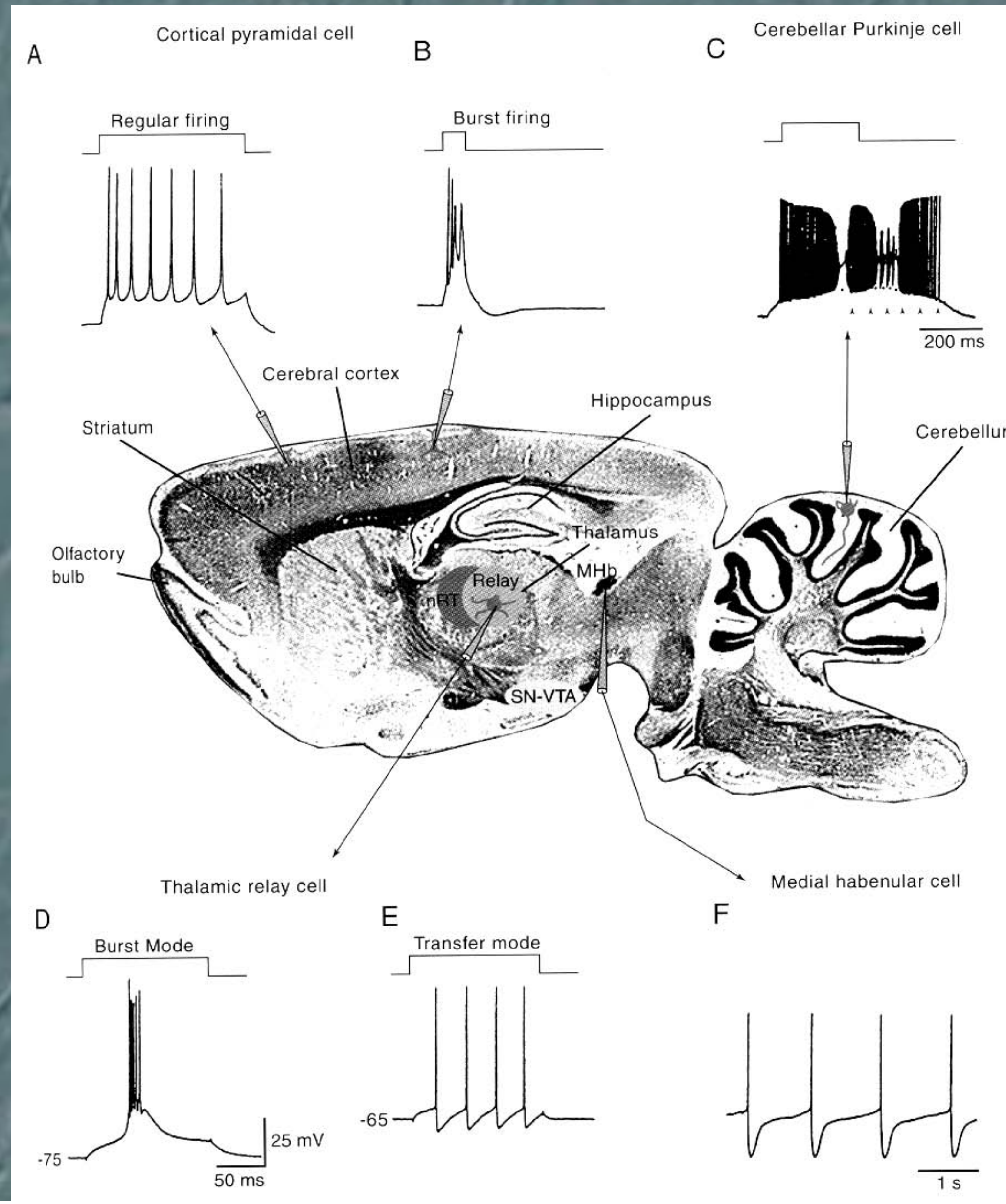
Rapid Changes in Synaptic Barrages Control Functional Cortical Connectivity



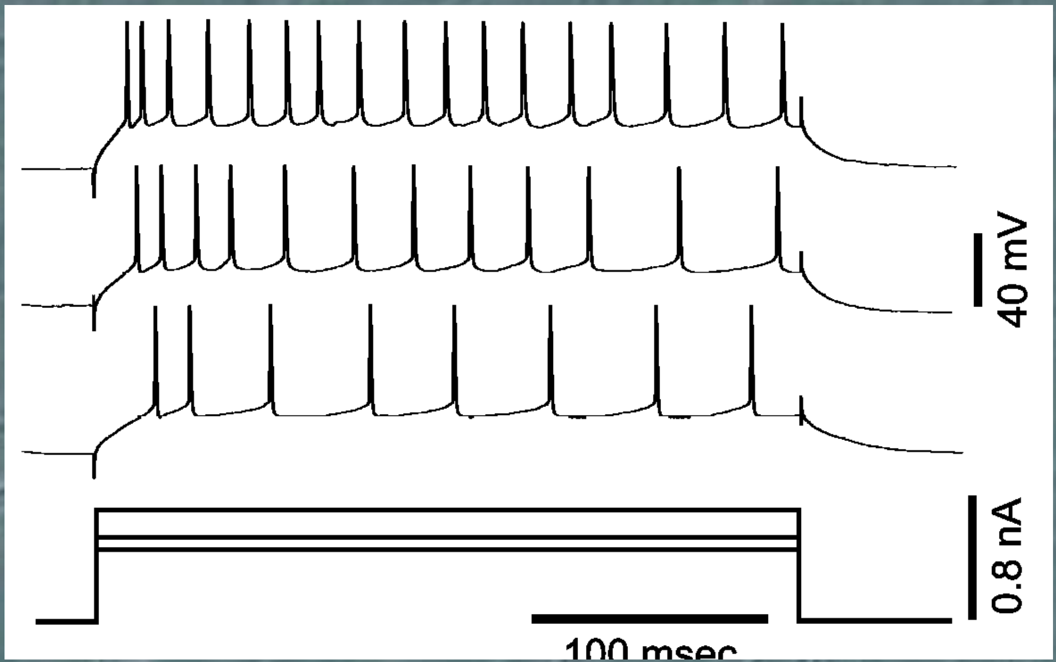
Neurons in Different Brain Regions Exhibit Unique Electrophysiological Properties.

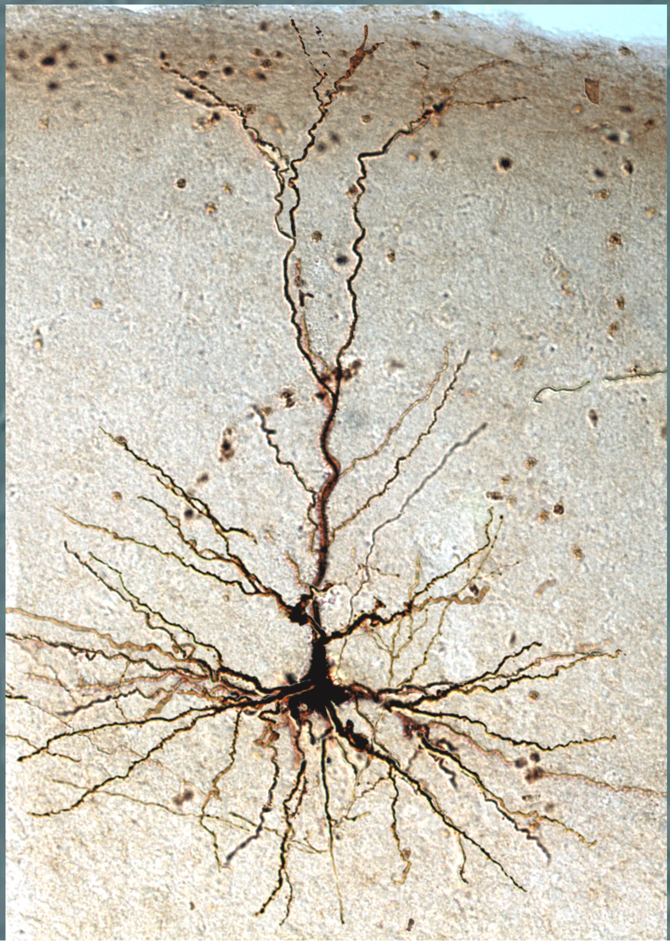
Some are Spontaneously Active, but Most Cells Types are Not.

In Particular Cortical Neurons are Often Many mV Away From Spike Threshold in the Absence of Synaptic Activity



The Combination of Synaptic Barrages Arriving in the Neuron Must Culminate in the Axon Initial Segment to Depolarize by About 20 mV to Discharge





What is the Ongoing State of Cortical Networks and How Does this Influence Neural Transmission?

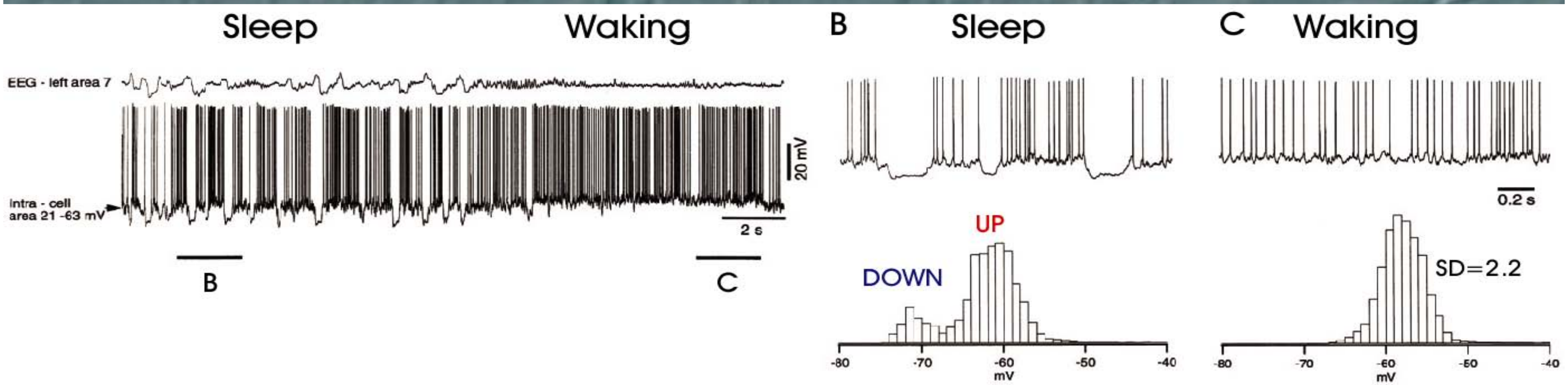
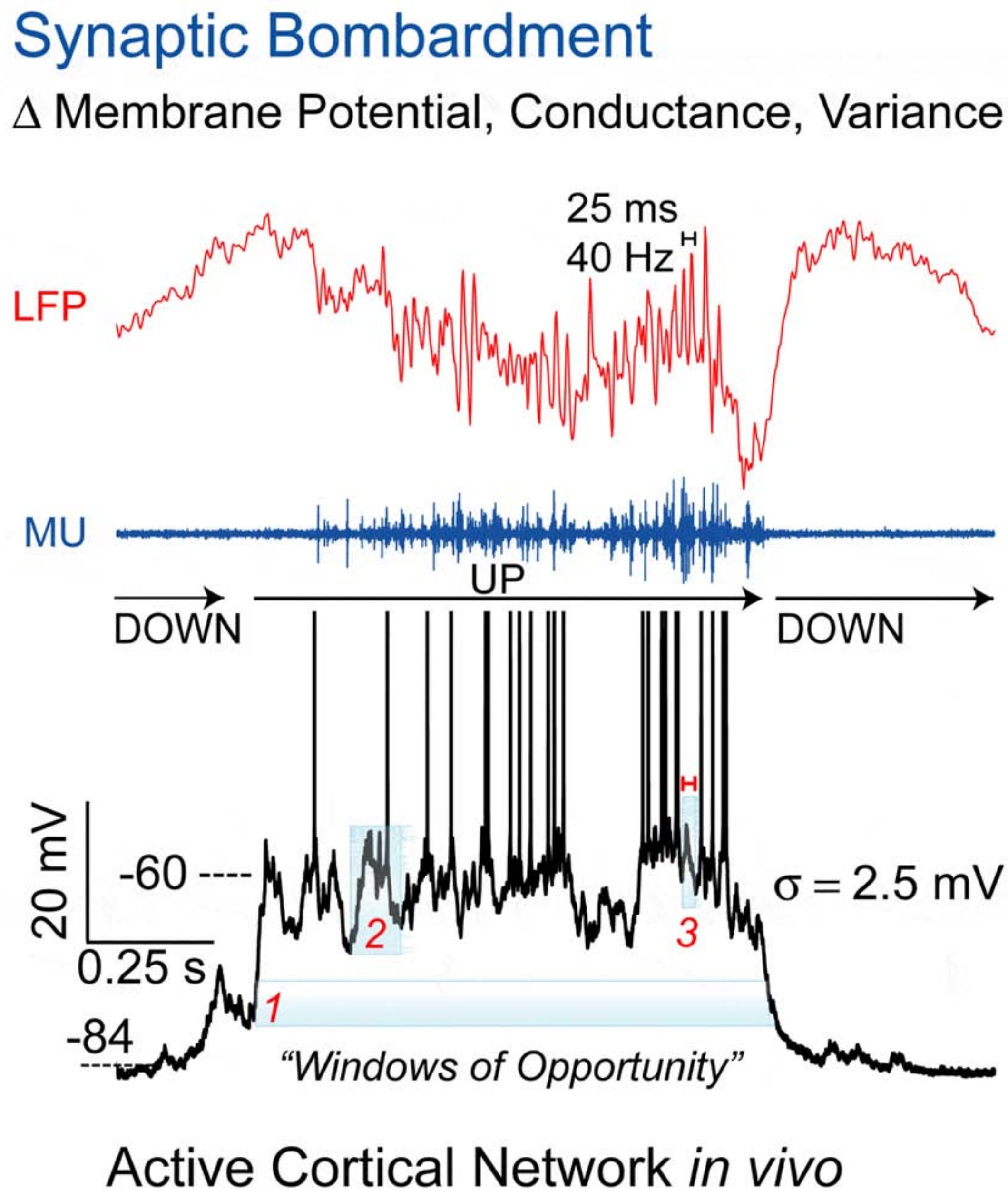


Figure adapted from Steriade et al, J. Neurophysiol 85:1969, 2001

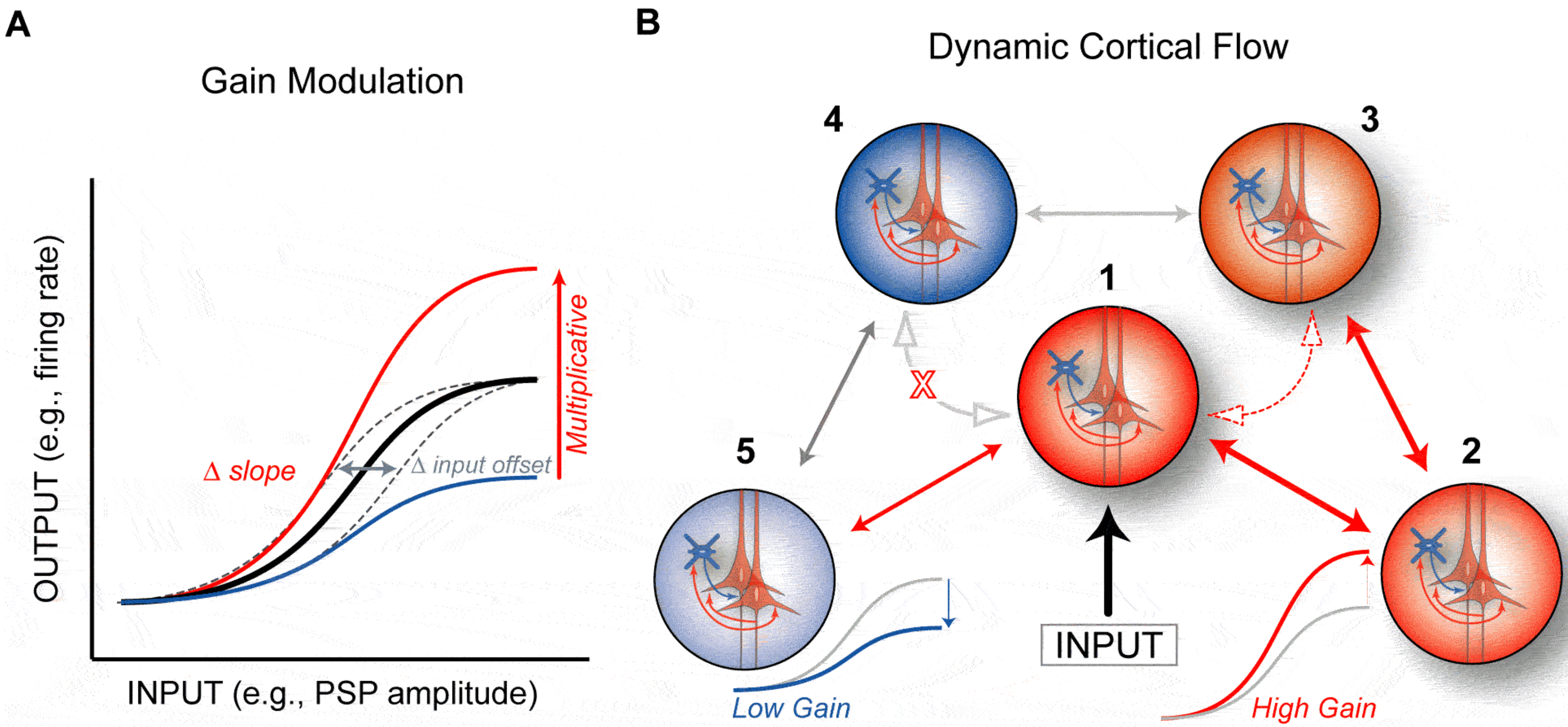
What is the synaptic Basis of Ongoing Activity?

How Does this Influence Neuronal Responsiveness?

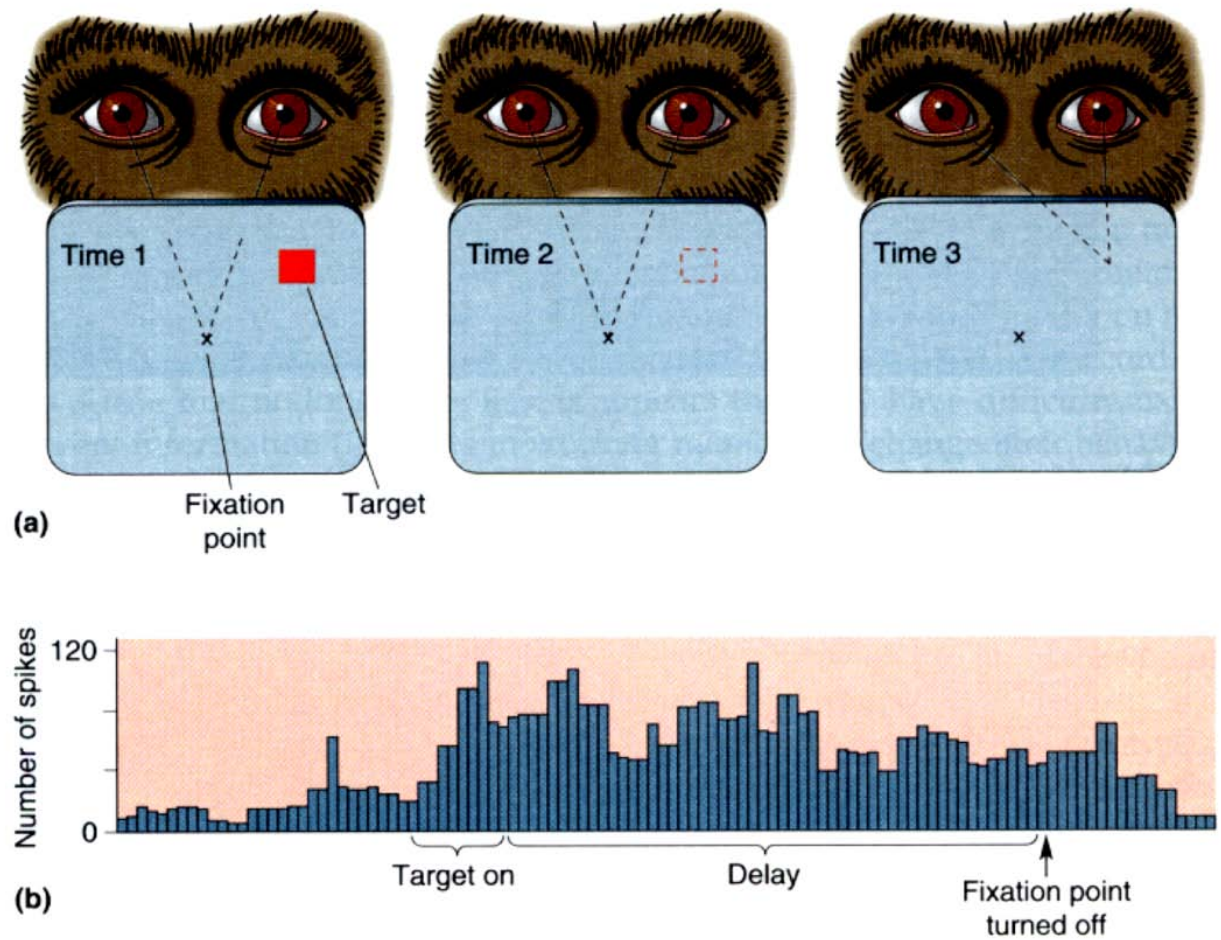
What are the Functional Consequences?



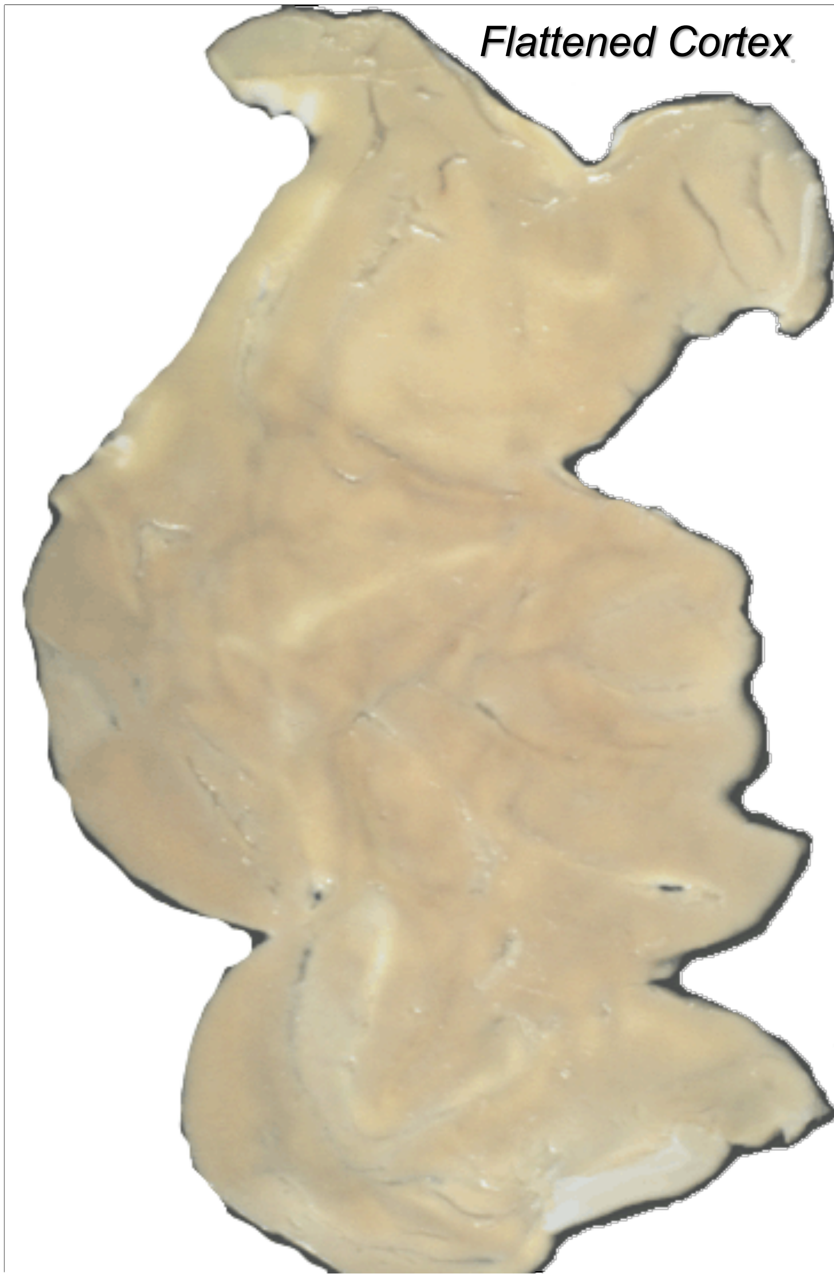
Rapid Changes in Synaptic Barrages Control Functional Cortical Connectivity

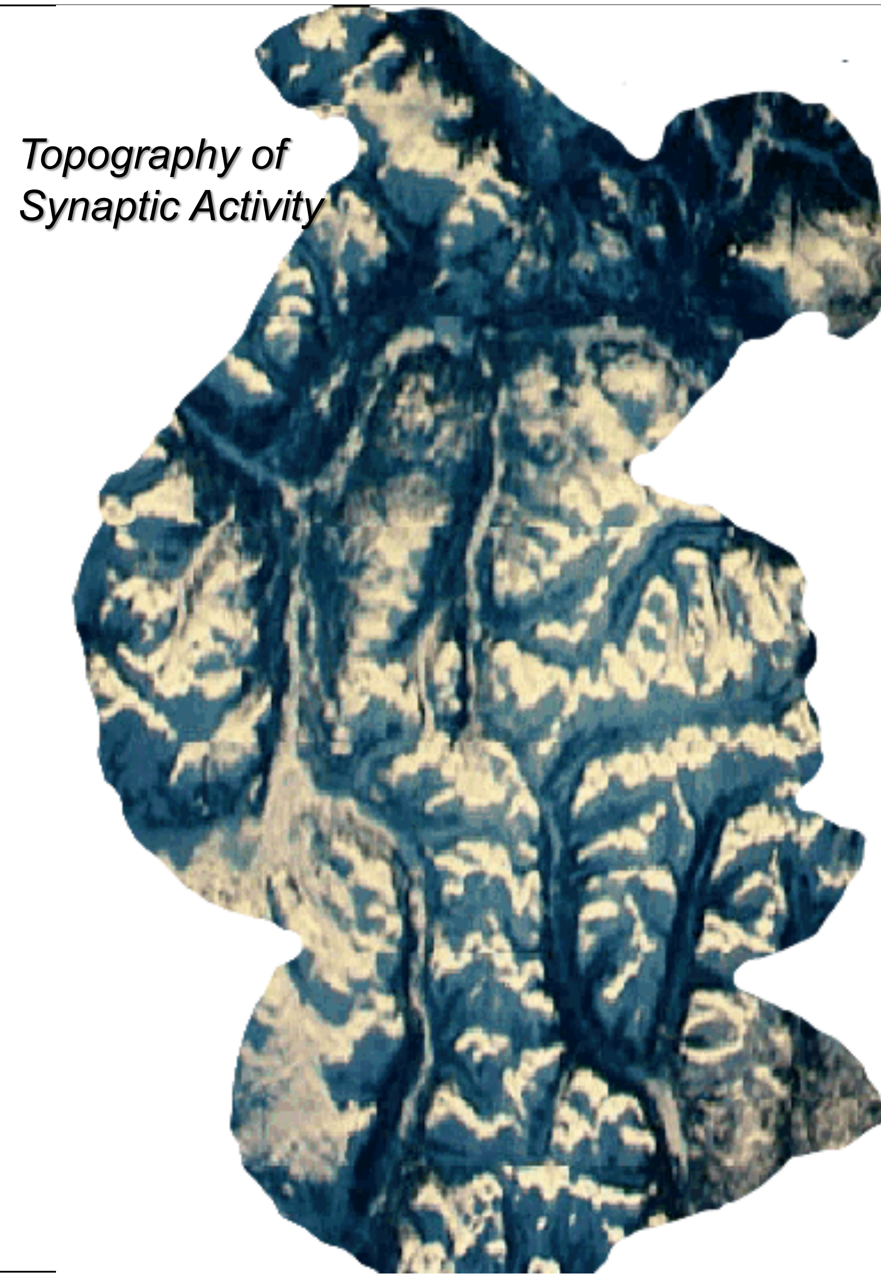


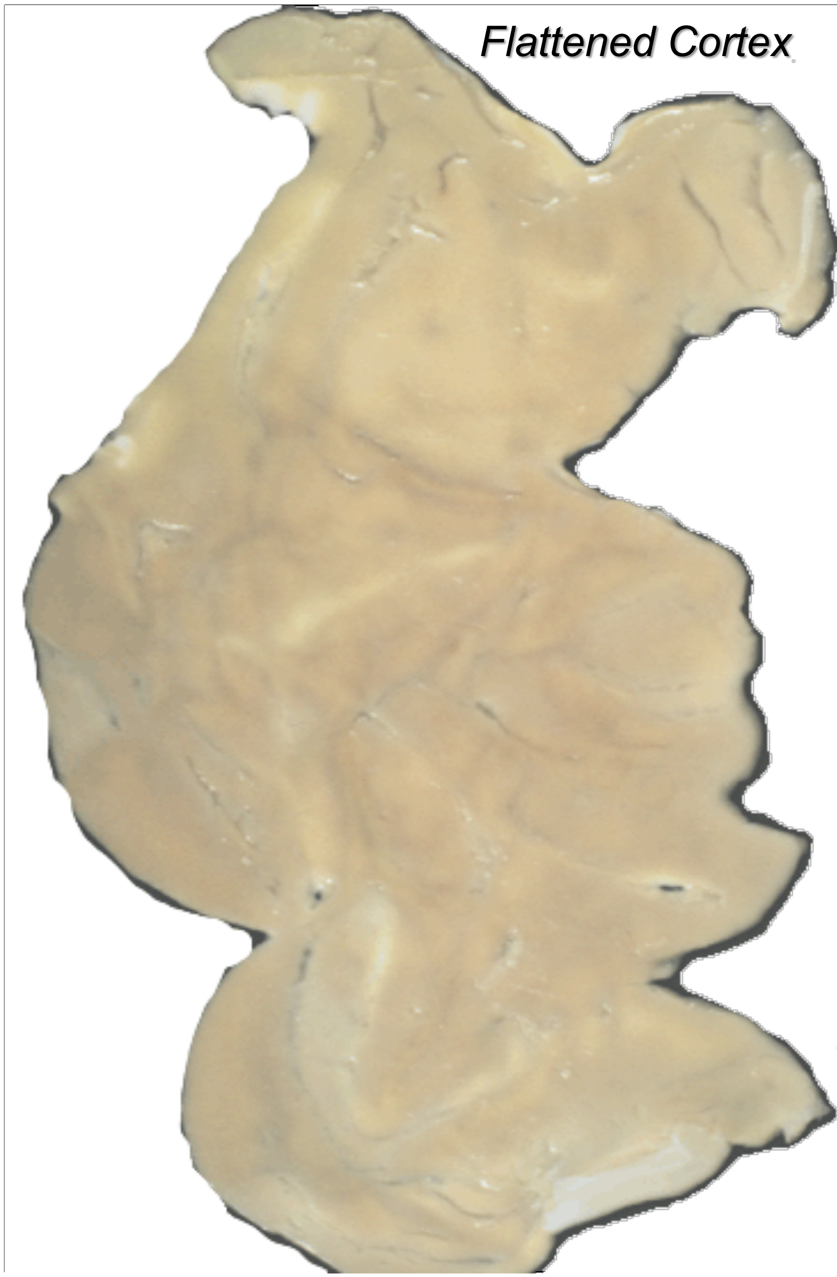
Working Memory is Associated with Persistent Activity in Cortical Neurons



Goldman-Rakic


Flattened Cortex


Topography of
Synaptic Activity

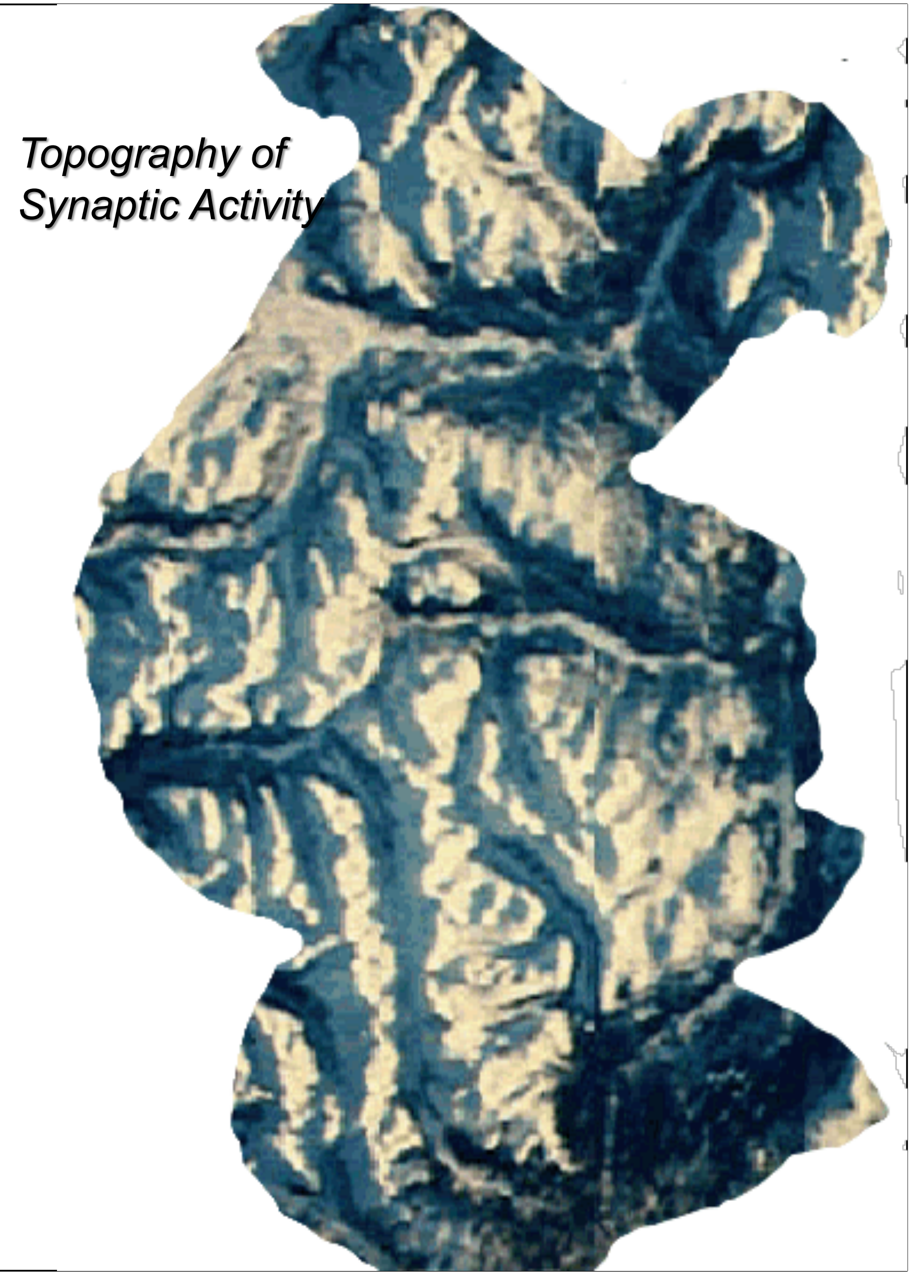

Flattened Cortex


Topography of
Synaptic Activity

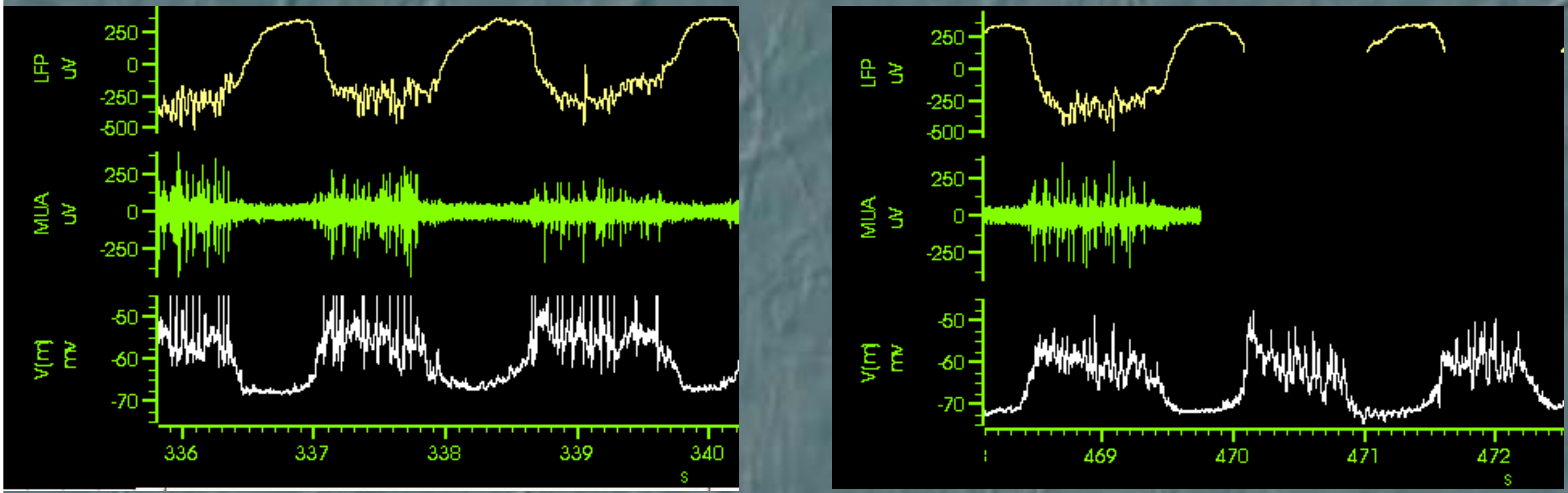

Flattened Cortex


Topography of
Synaptic Activity

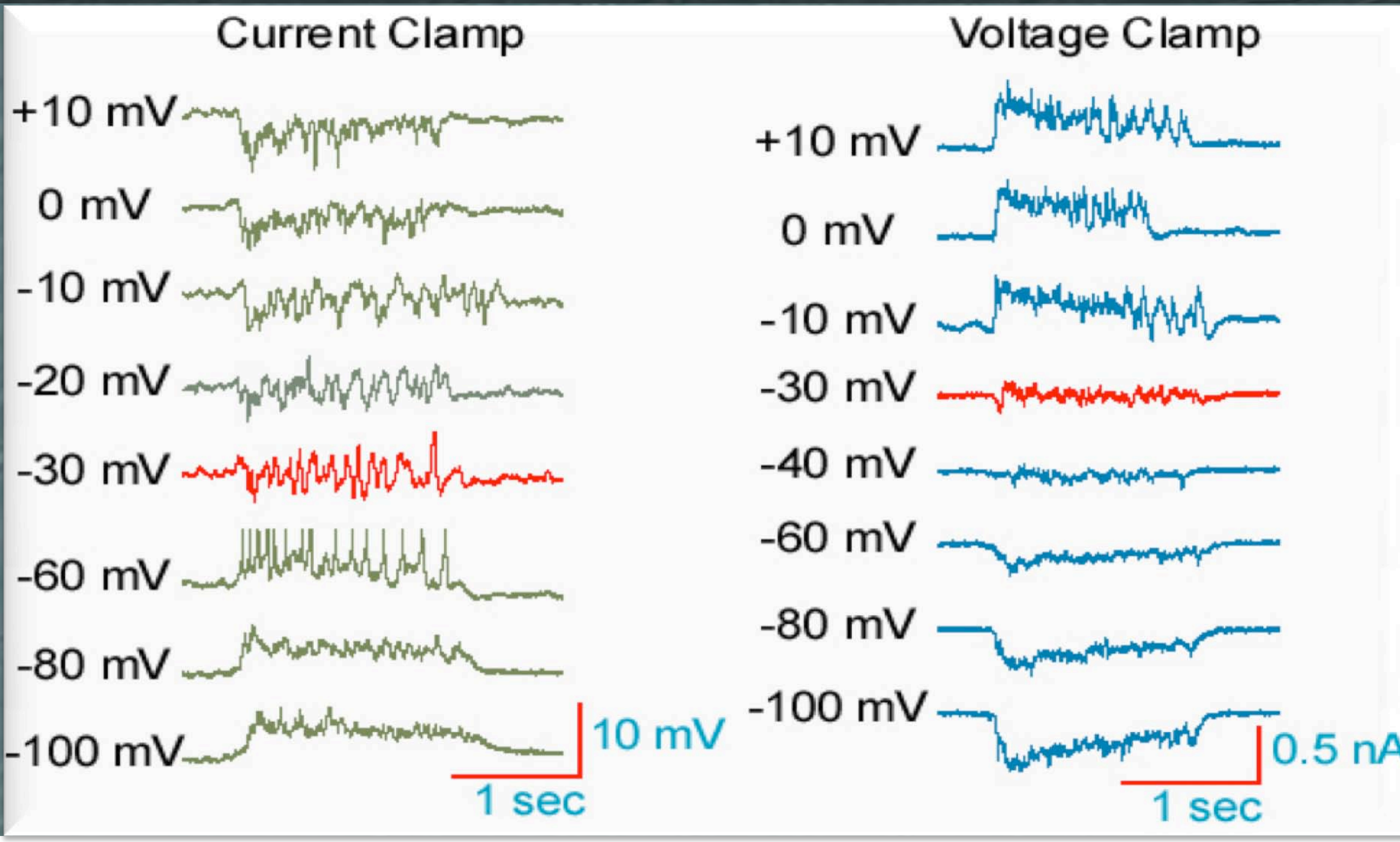

Flattened Cortex


Topography of
Synaptic Activity

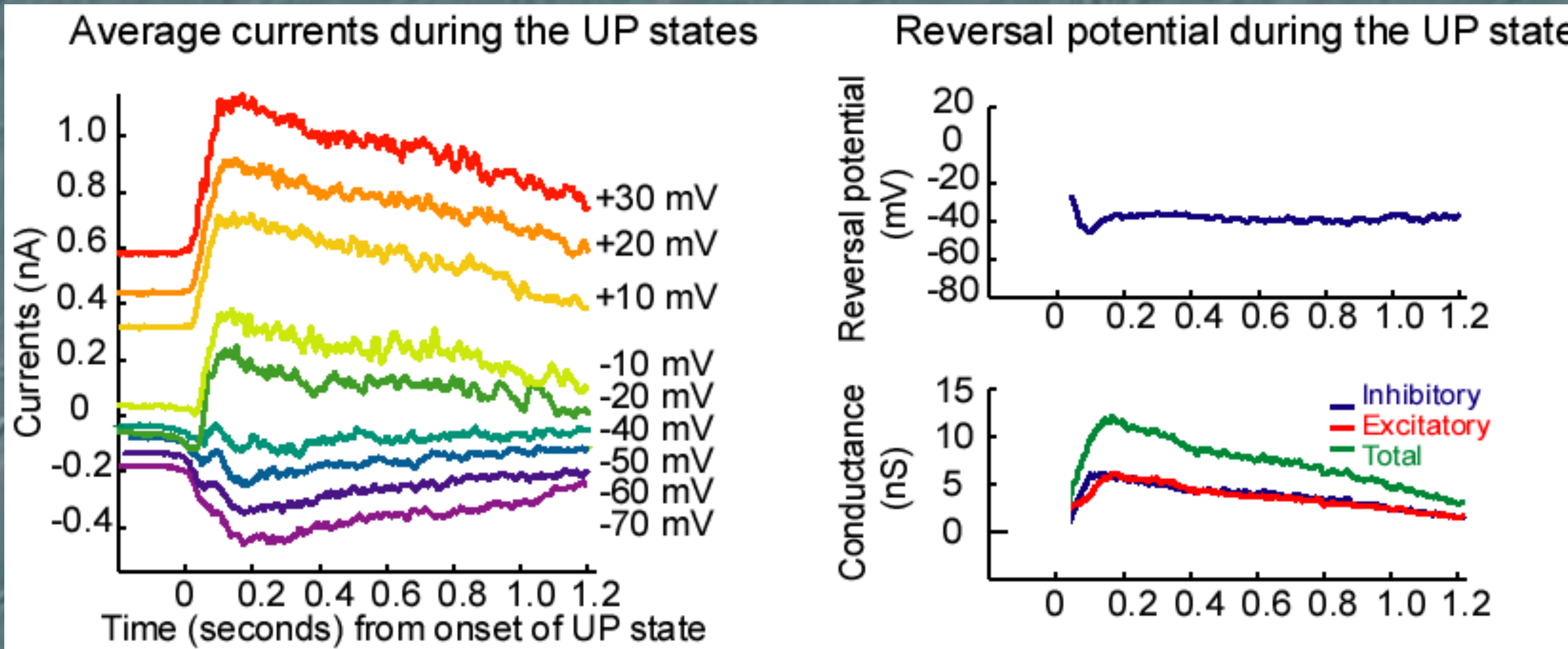
The Slow Oscillation in Ferret Prefrontal Cortex In Vivo (Anesthetized)



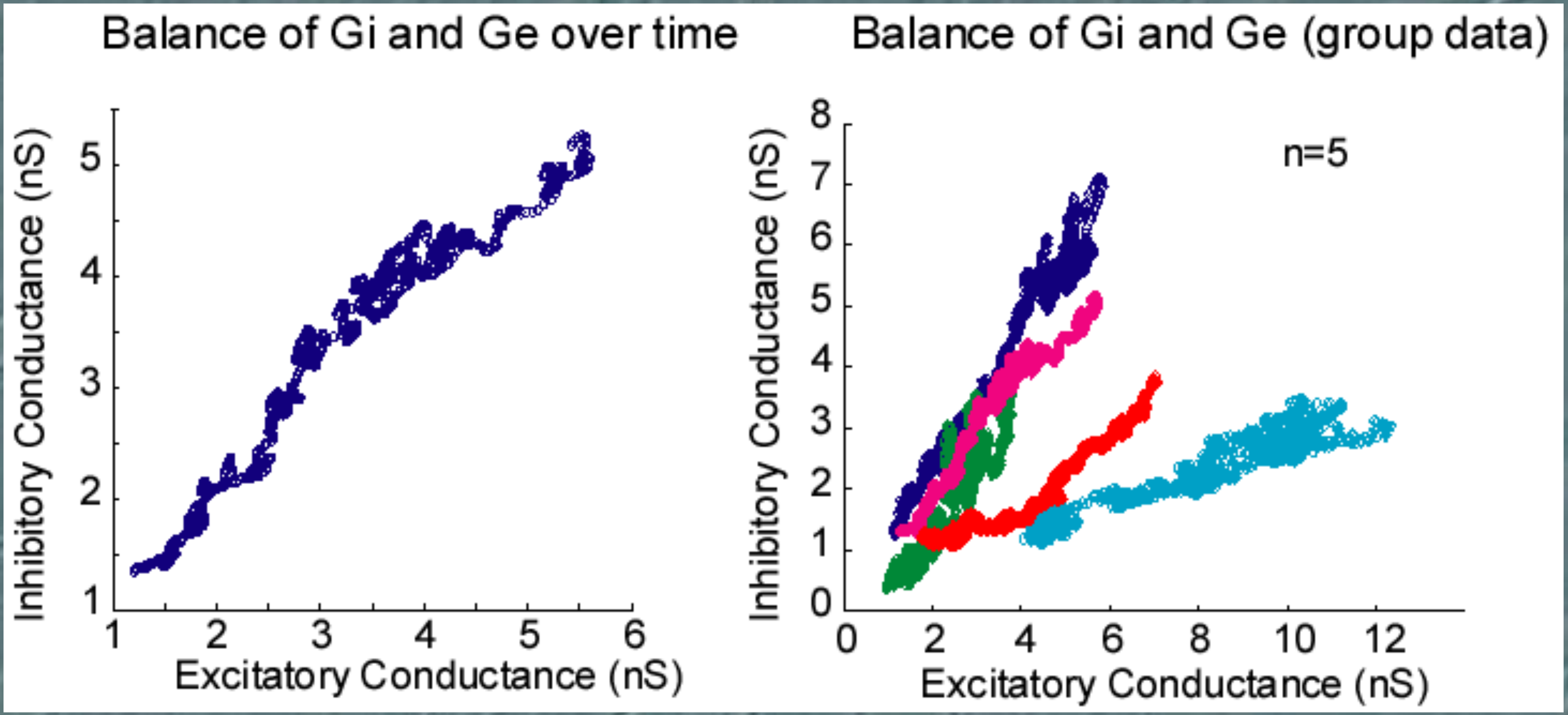
The Up State, which is at least superficially similar to waking, is Generated Through Recurrent Excitation Controlled by Local Inhibition



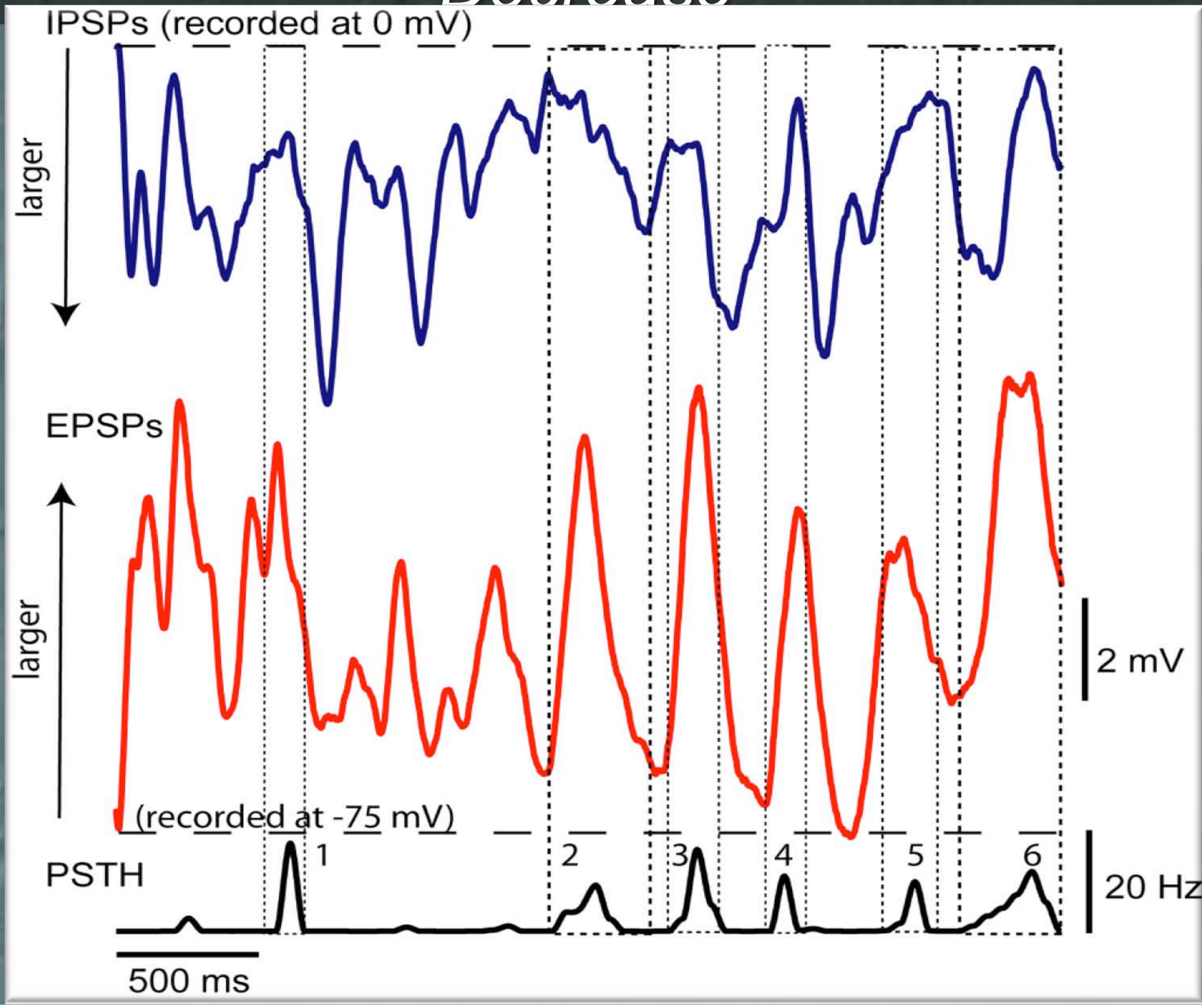
Up state Reversal Potential is Steady Throughout



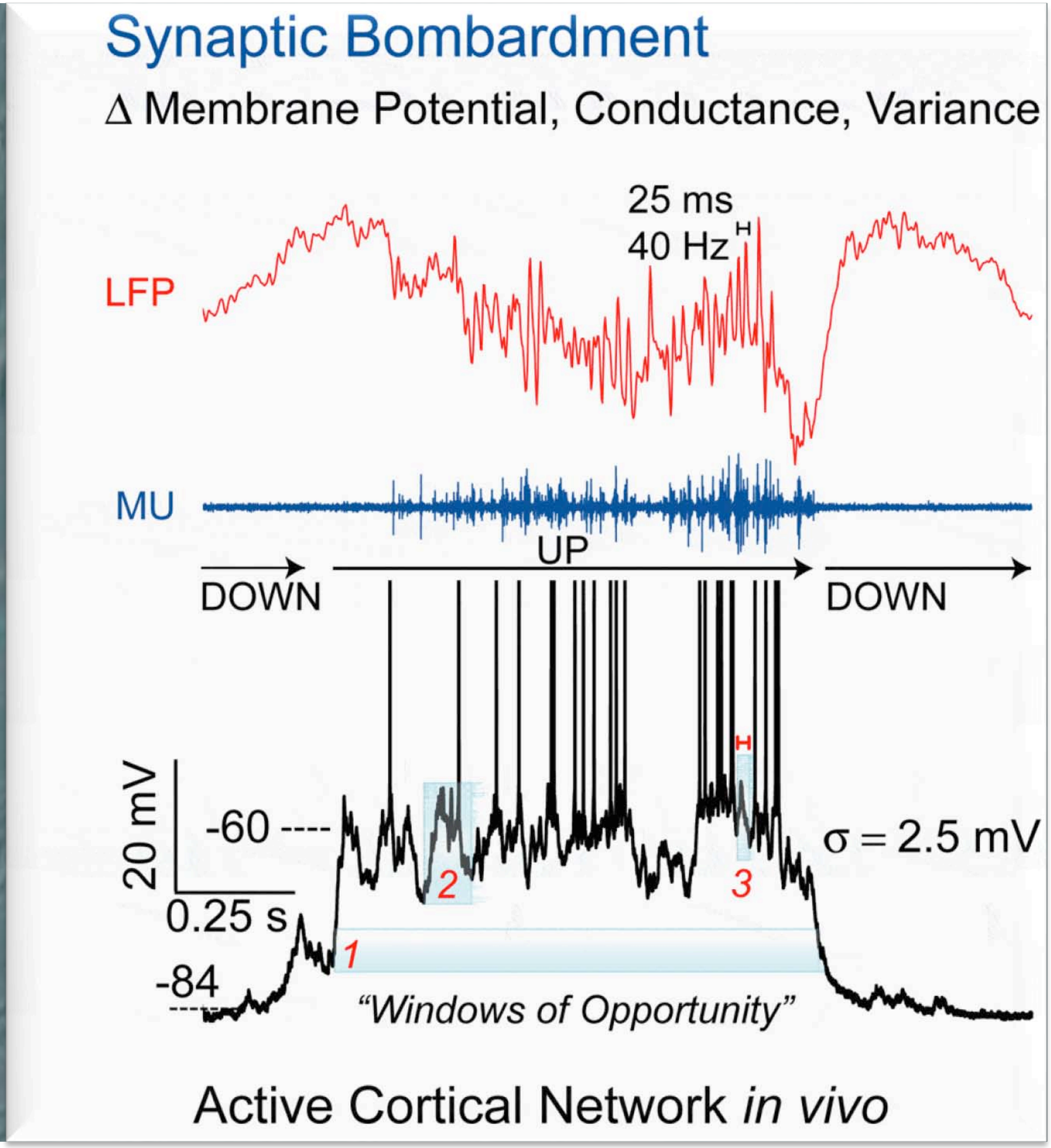
The Neocortex Operates Through a Balance of Excitatory and Inhibitory Conductances



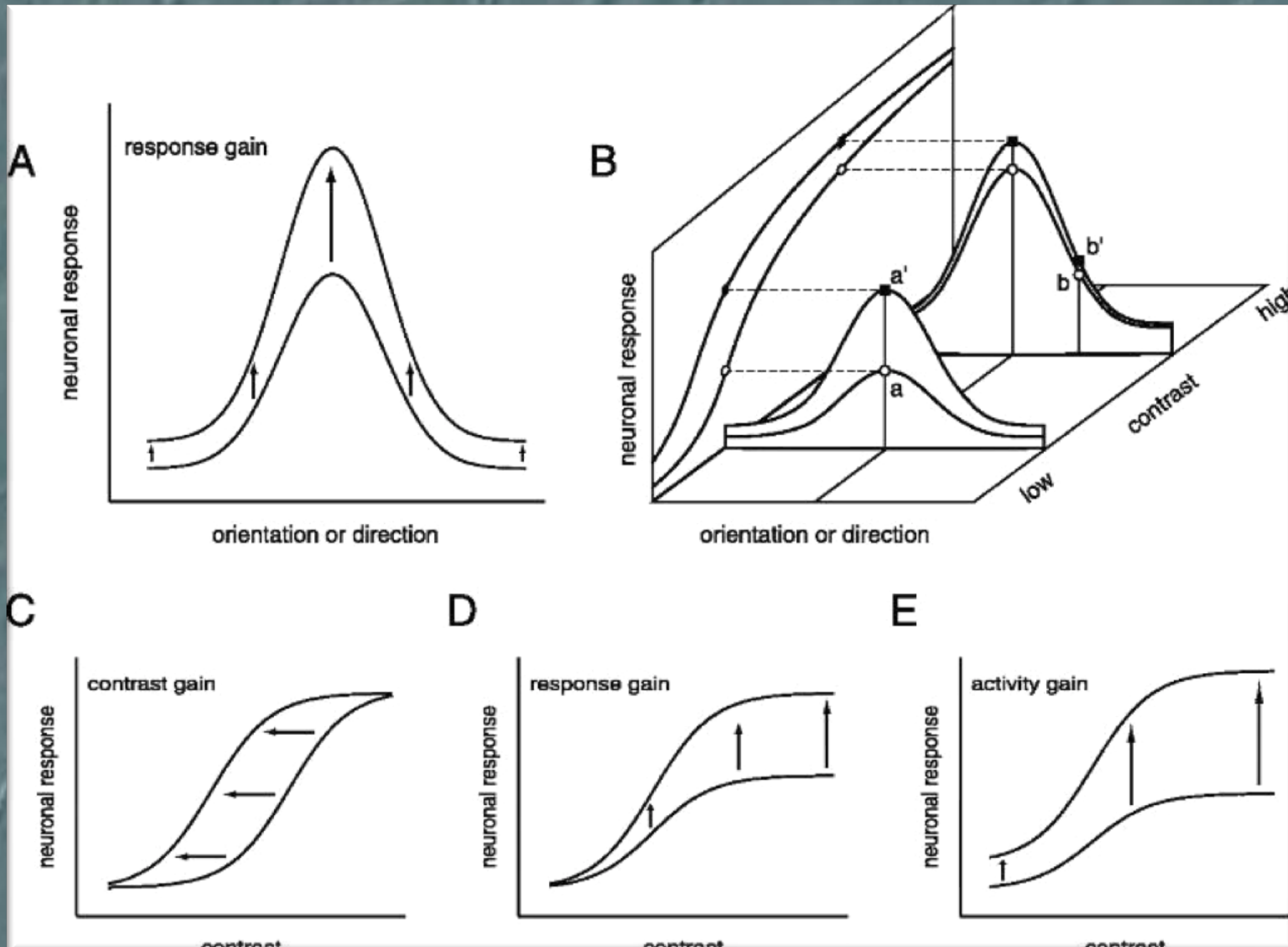
Neurons Spike When EPSPs Increase and IPSPs Decrease



Depolarizations of Variable Duration Generate Different "Windows of Opportunity" for Neuronal Interactions

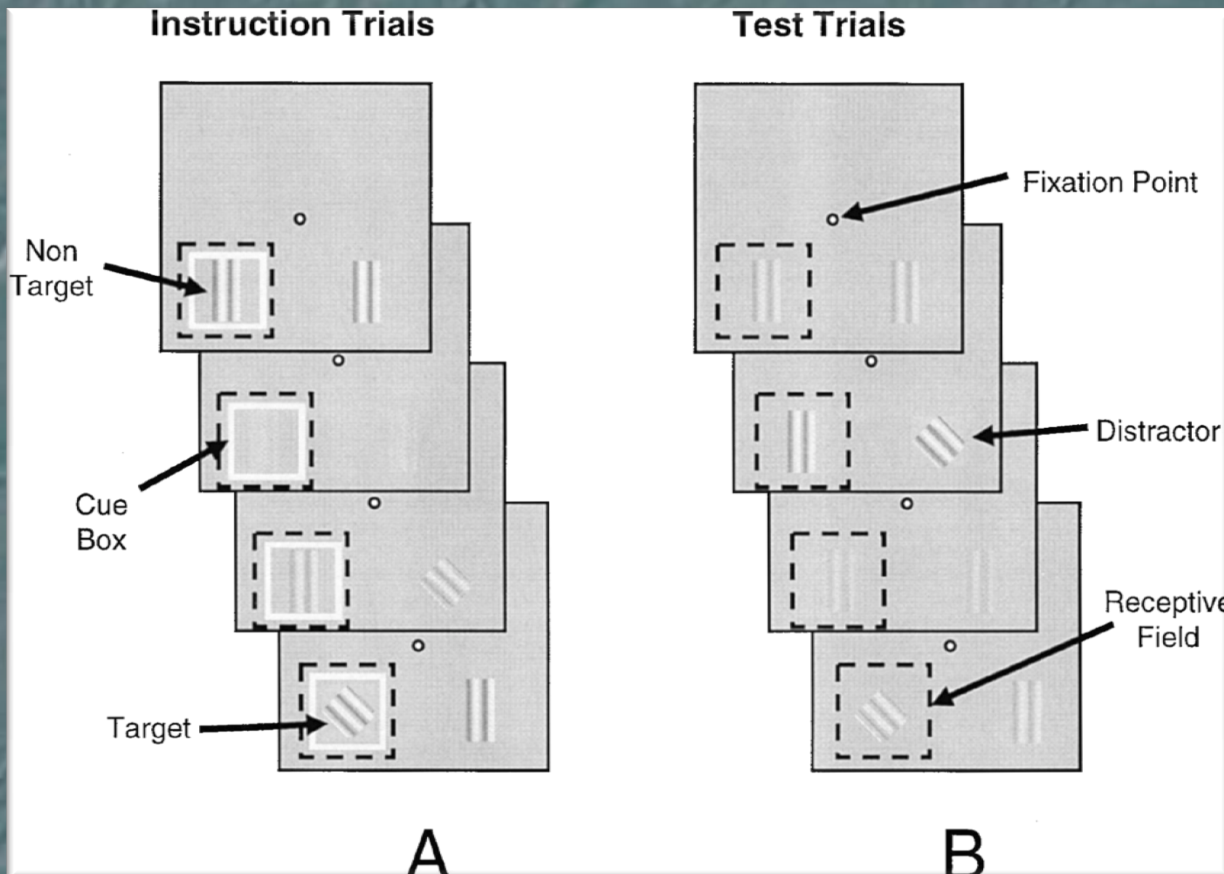


Spatial Attention – Different Ways to Modulate Input-Output Functions of Visual Cortical Neurons



Attention Modulates Input-Output Function of V4 Neurons

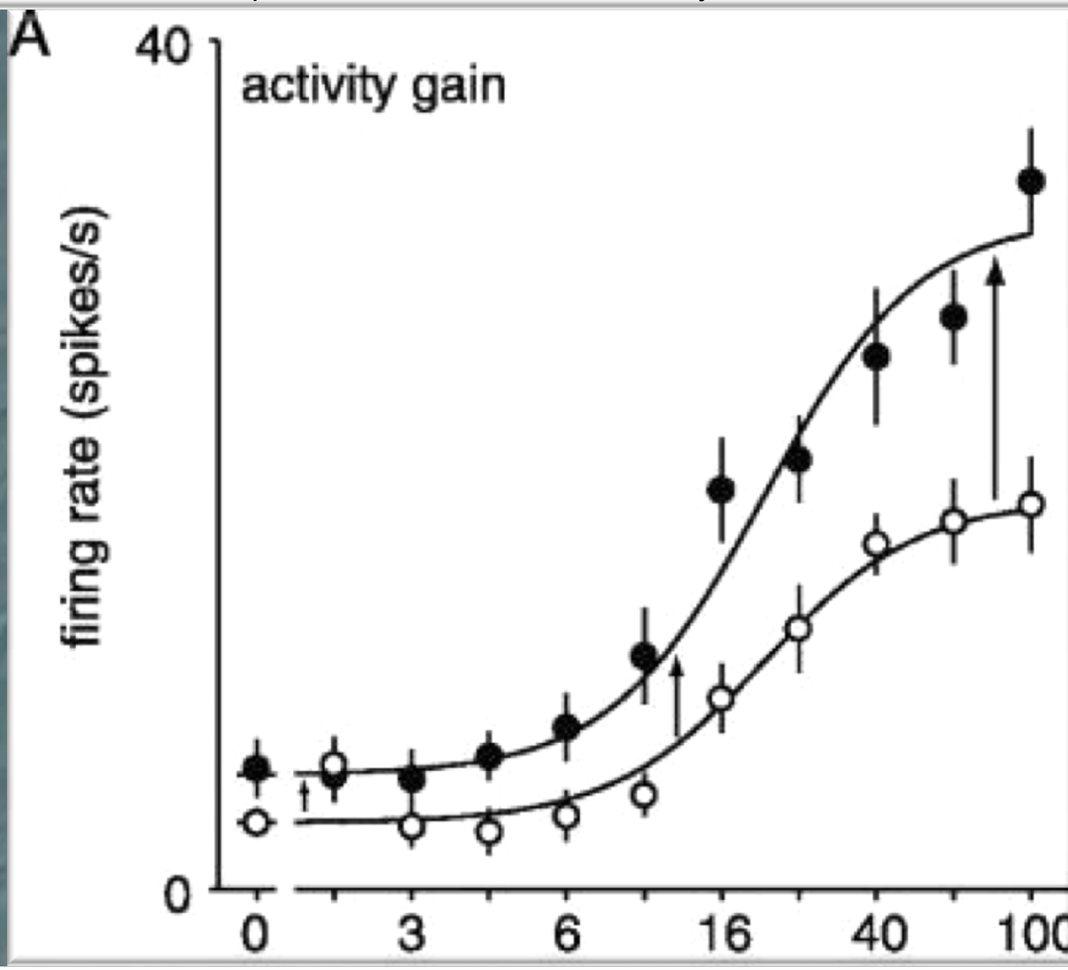
Monkeys Trained to Attend to RF or to Opposite Field

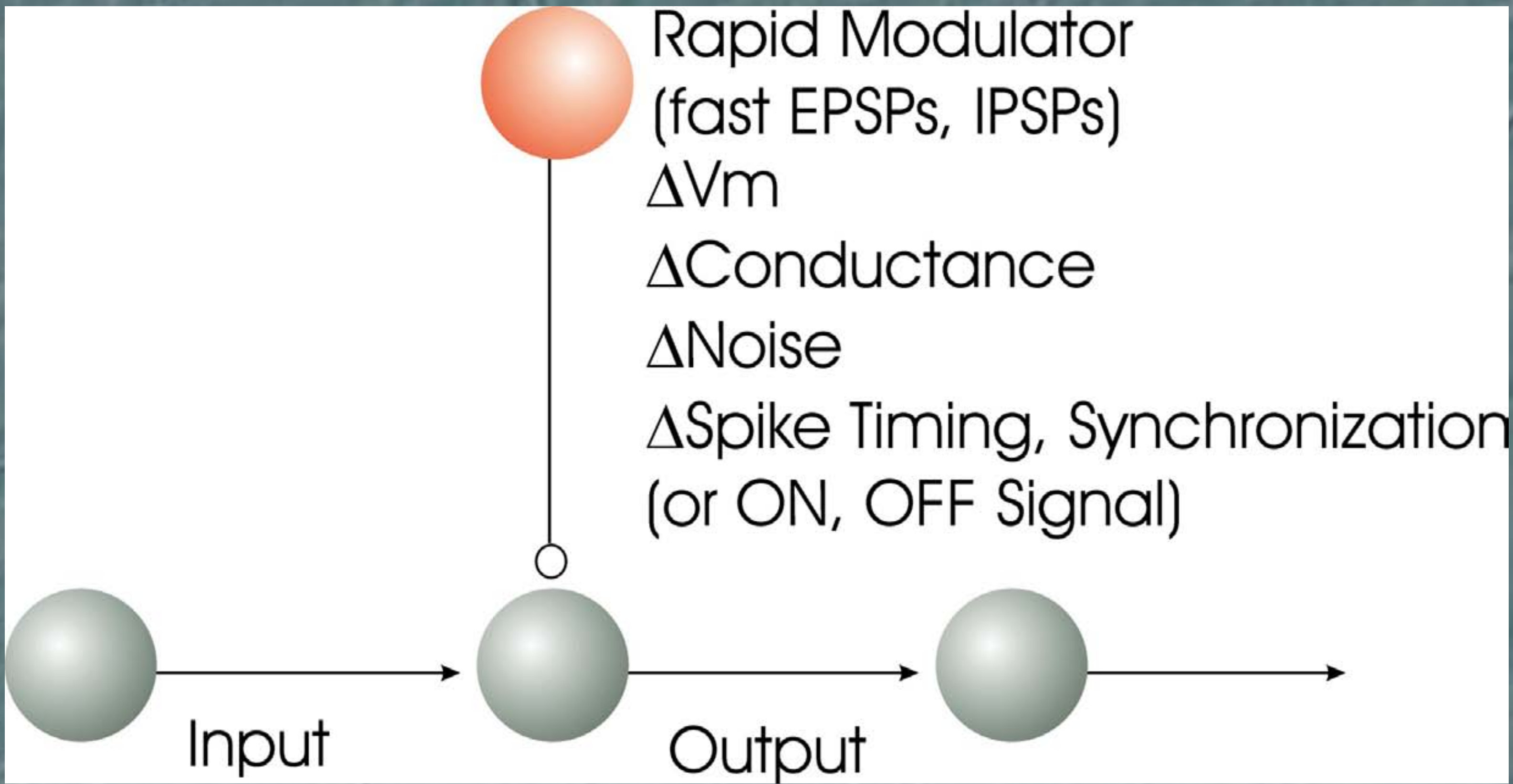


Reynolds, Pasternak, Desimone Neuron 26: 703.

Some of the effects of spatial attention can be explained by a simple rapid change in membrane potential

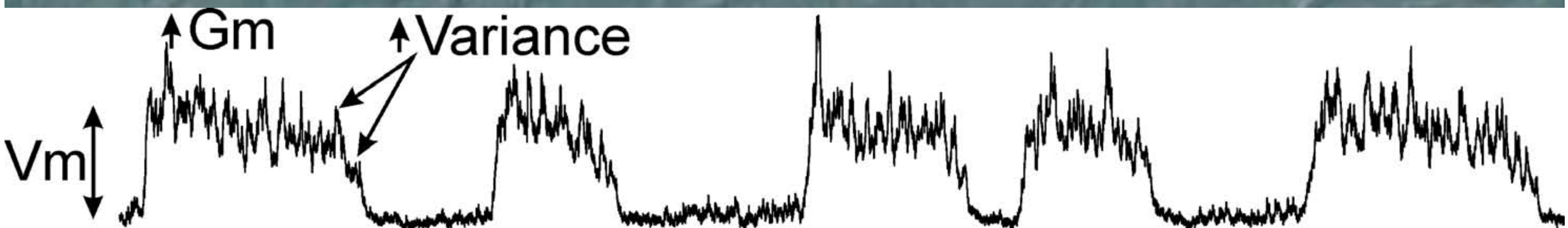
Effect of attention on contrast response function curve in monkey V4   Maunsell et al.




Rapid Modulator
(fast EPSPs, IPSPs)
ΔVm
ΔConductance
ΔNoise
ΔSpike Timing, Synchronization
(or ON, OFF Signal)
Input
Output

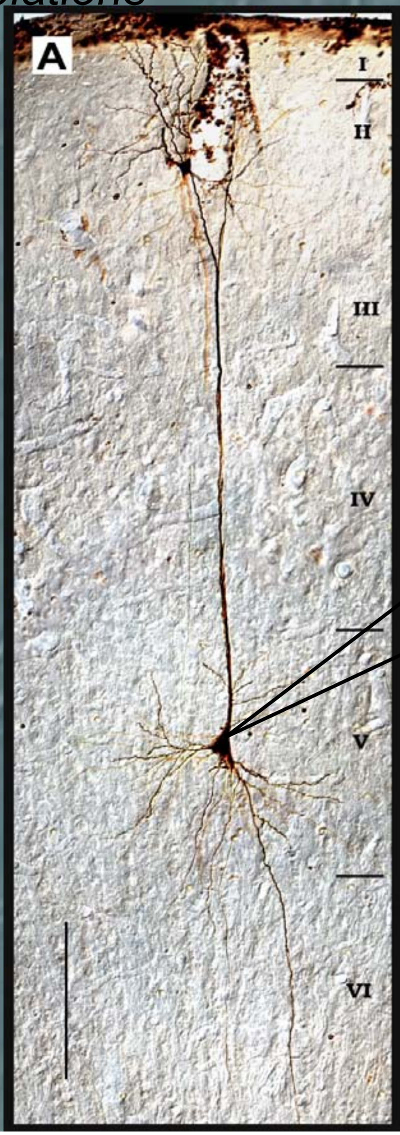
Synaptic Activity has 3 Main Effects:

Change in Membrane Potential, Conductance and Variance

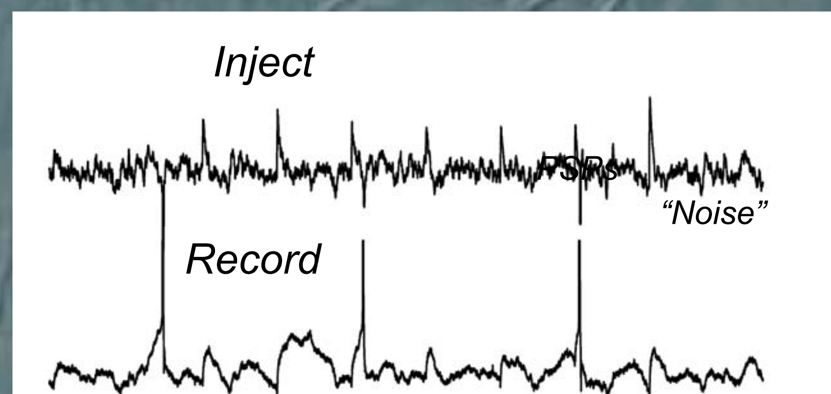


How do These Changes Affect the Input-Output Relation of Single Neurons?

Use Dynamic Clamp to Examine the Effect of Synaptic Activity on Input-Output Relations



Cycle of Record, Calculate, Inject
(10,000 Hz Bridge; 3,000 Hz DCC)



John White and Alan Dorval Ann. Biomed. Eng. 29: 897

To answer this question, we investigated the effects of:

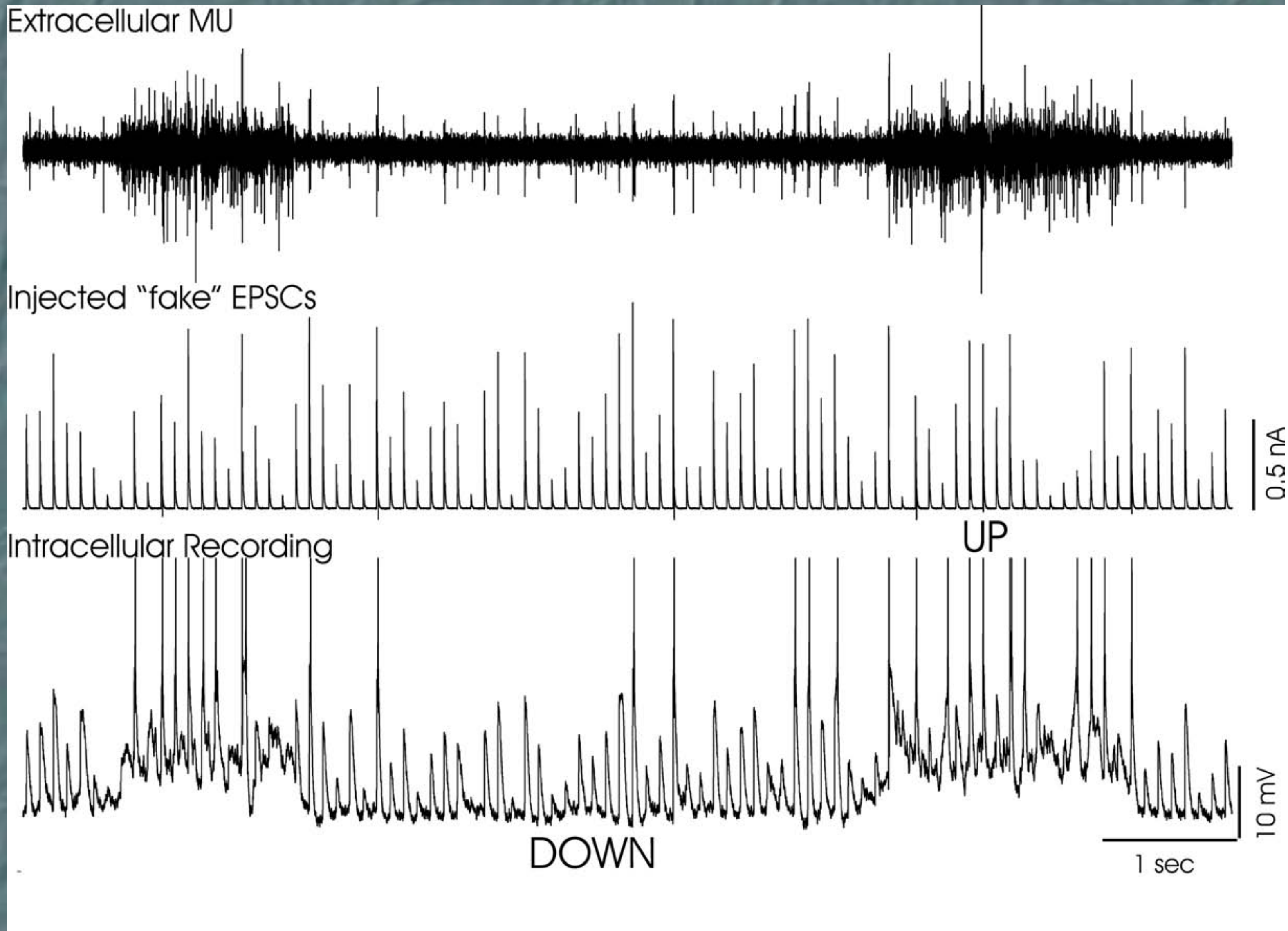
1) *Change in Membrane Potential*

2) *Change in Membrane Conductance*

3) *Change in Membrane Variance ("noise")*

On Spike Reliability, Timing, and Jitter to EPSPs, Pulses, and Complex Waveforms.

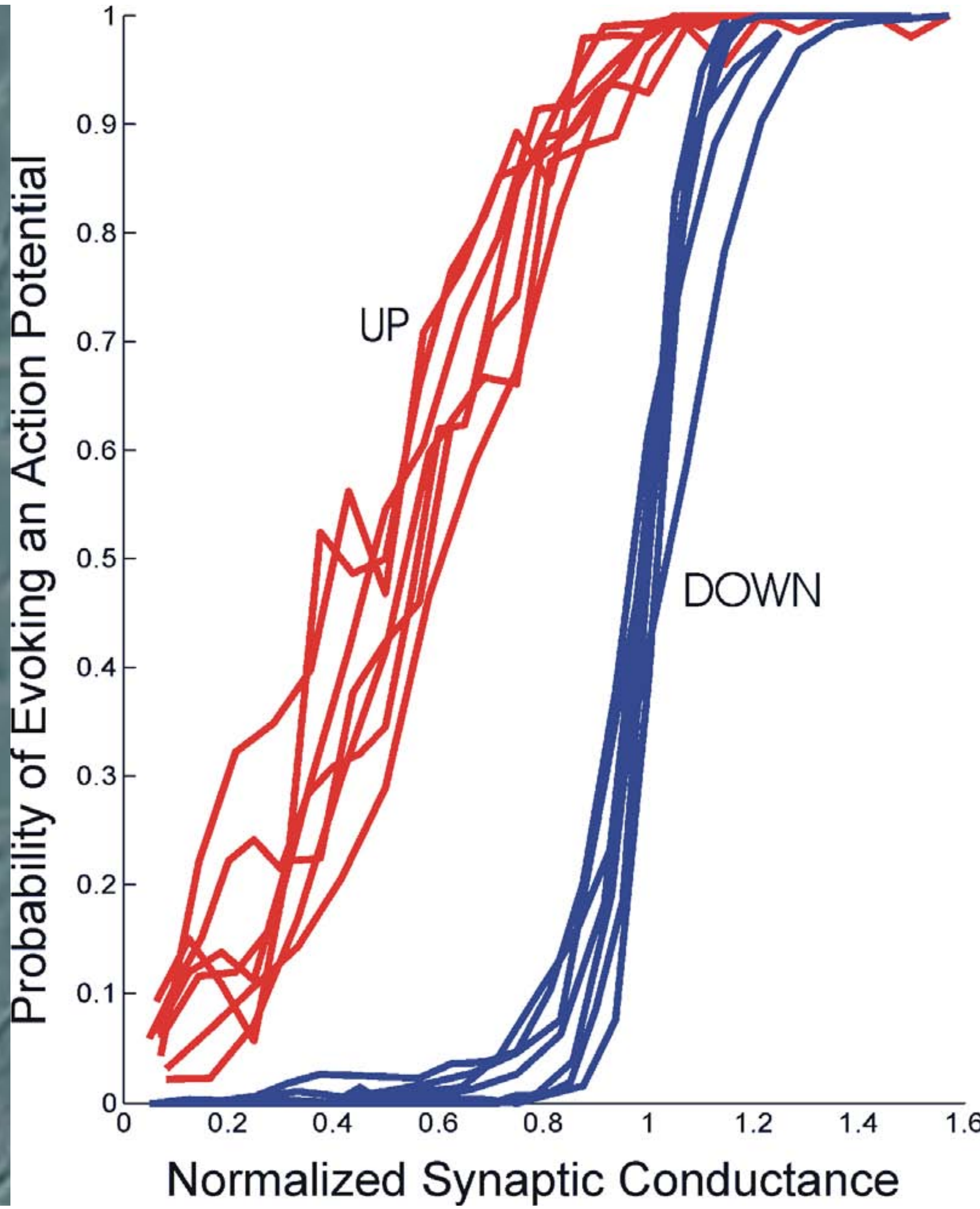
The Intracellular Injection of "fake EPSCs" was used to test the Input-output Relation of the Neuron during Different States



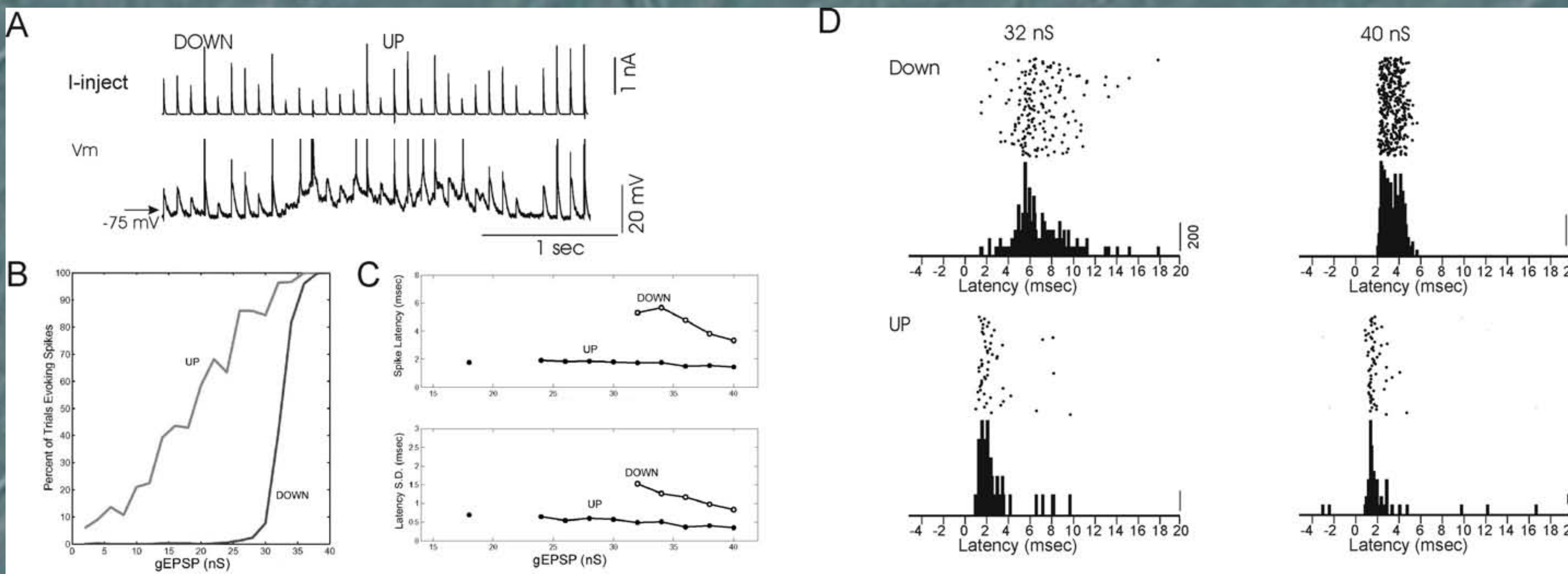
Group Data Illustrating the Effects of Network Activity on the Input-Output Curves

UP state is associated with a Leftward Shift (Increase in Responsiveness) and Decrease Slope

What is the Mechanism of These Effects and What are the Consequences?

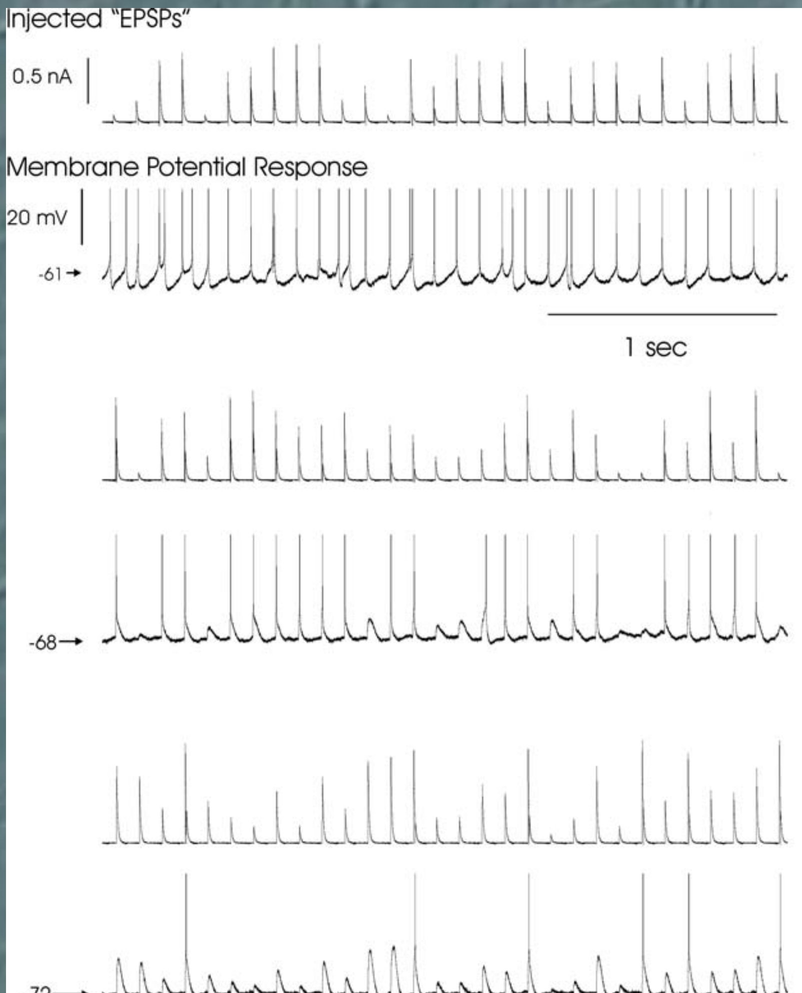


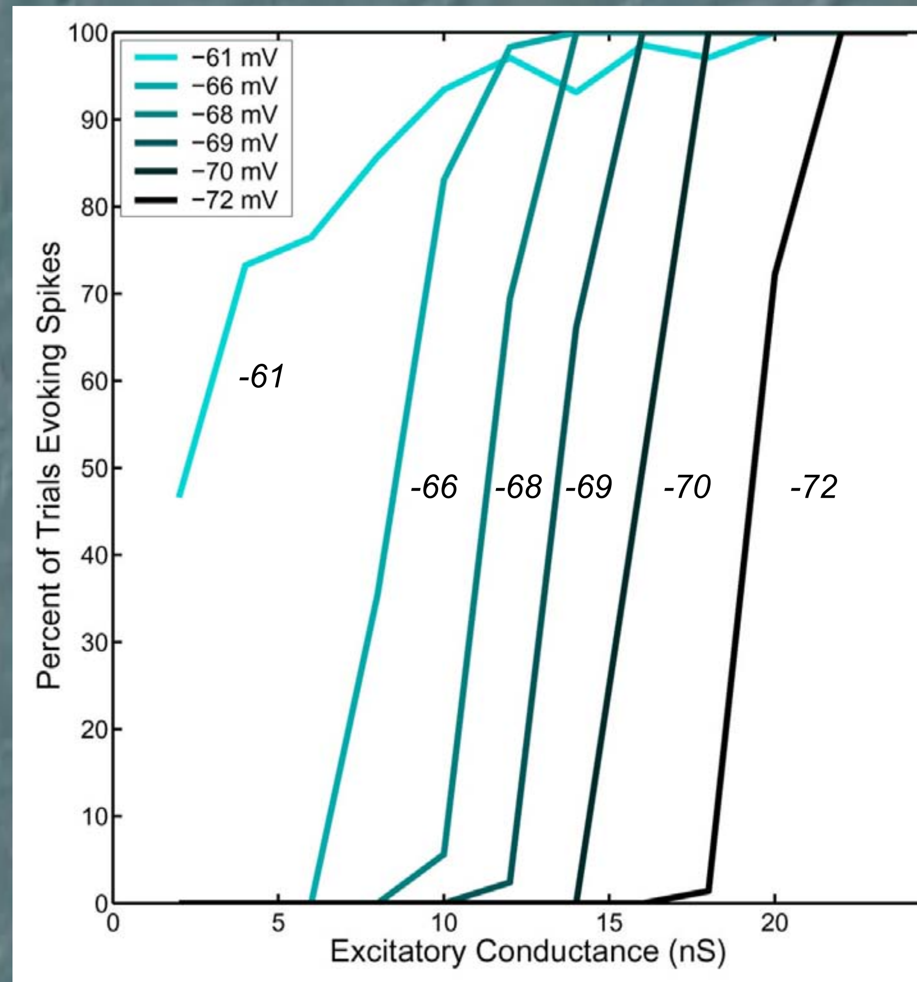
The UP state increases responsiveness to small inputs, decreases latency to spike, and decreases spike jitter



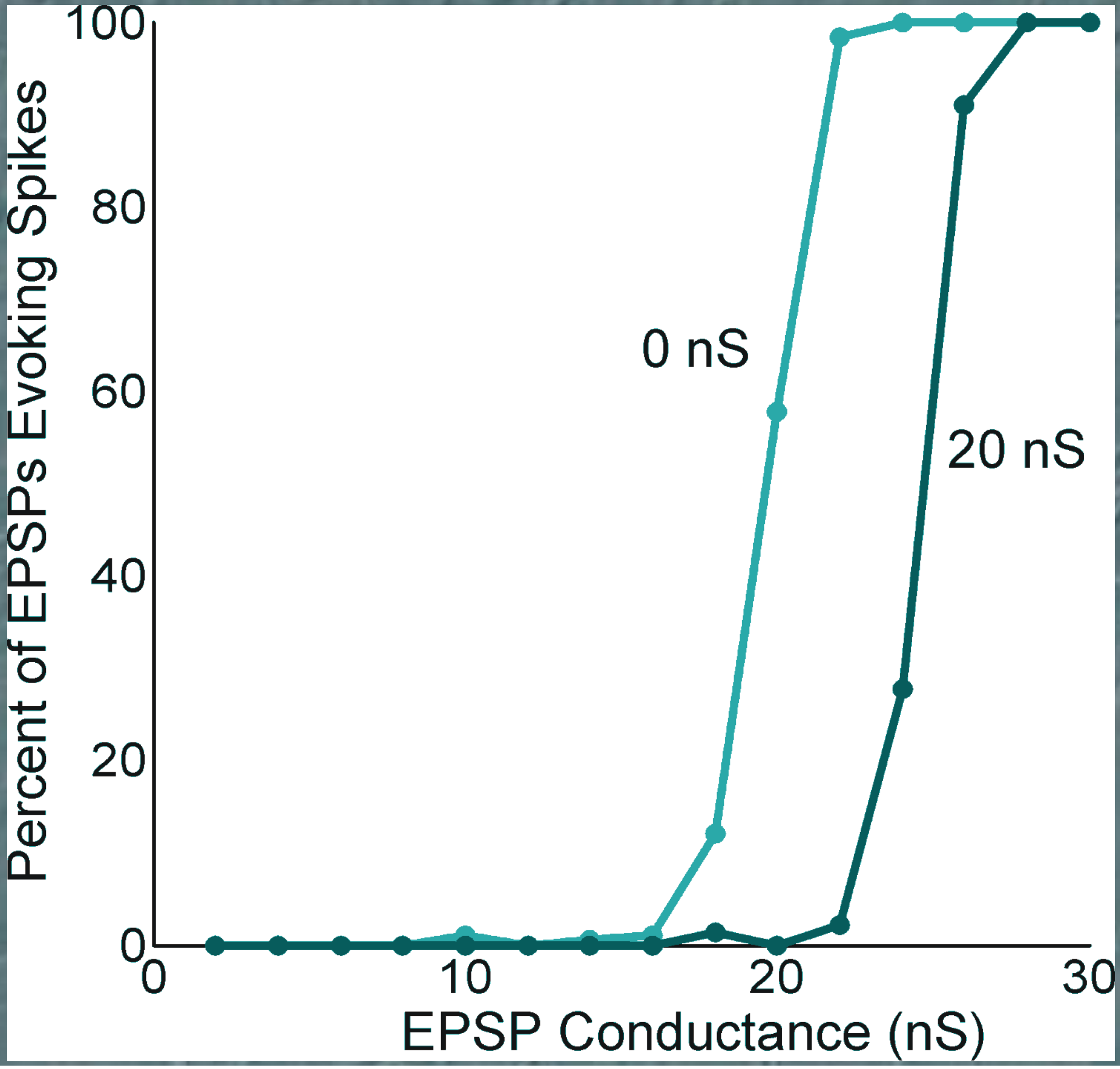
What is the Effect of Changes in Vm on Neuronal Responsiveness?

Small Depolarizations Shift the Input-Output Relation to the Left



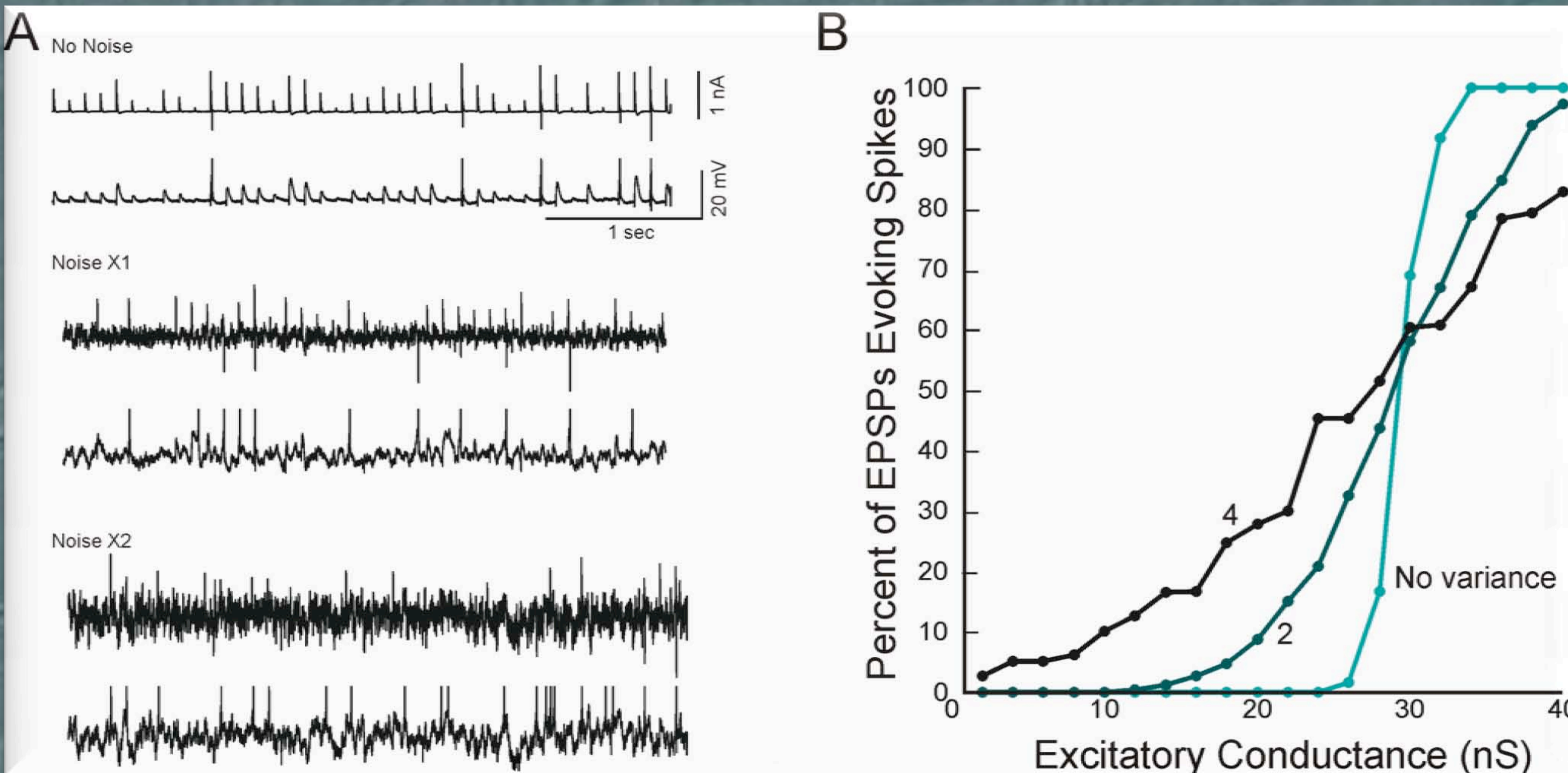


Increases in Membrane Conductance Alone Can Cause Rightward Shift in Input-Output Relation for Response Probability



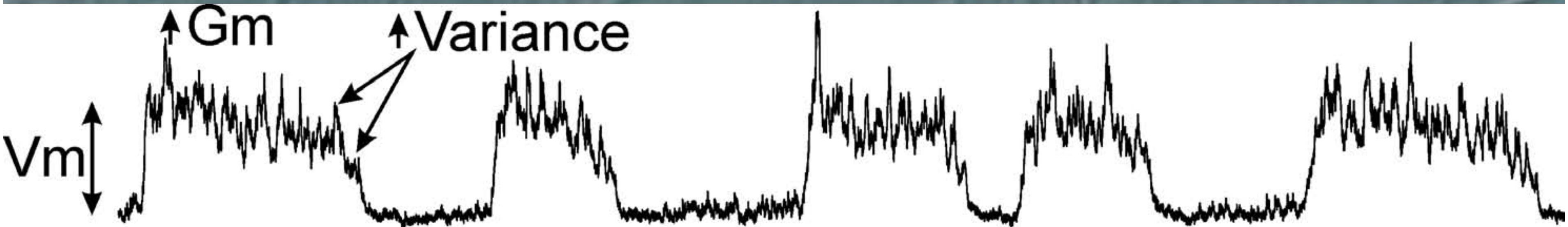
What is the Effect of Change in Membrane Variance (without tonic depolarization or change in conductance) on Neuronal Responsiveness?

Change in Variance Changes the Slope of Response Probability to "EPSPs"



Synaptic Activity has 3 Main Effects:

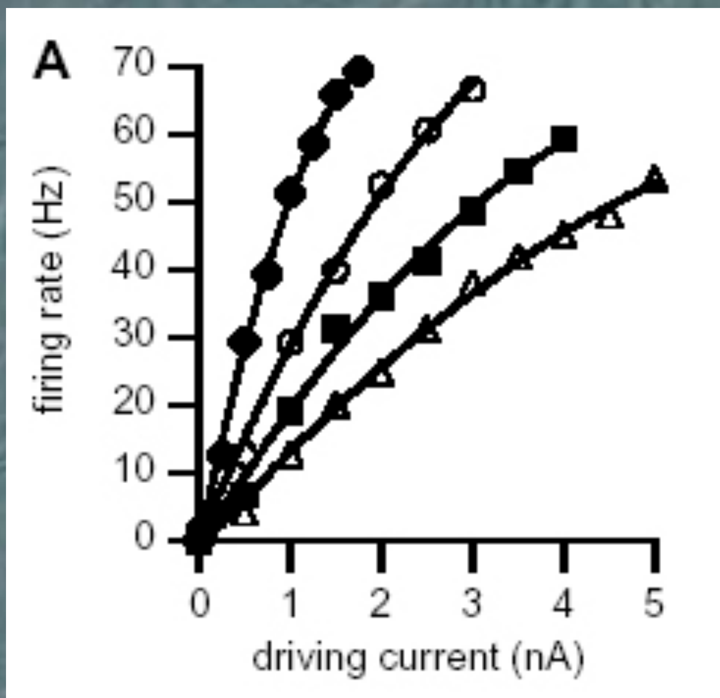
Change in Membrane Potential, Conductance and Variance

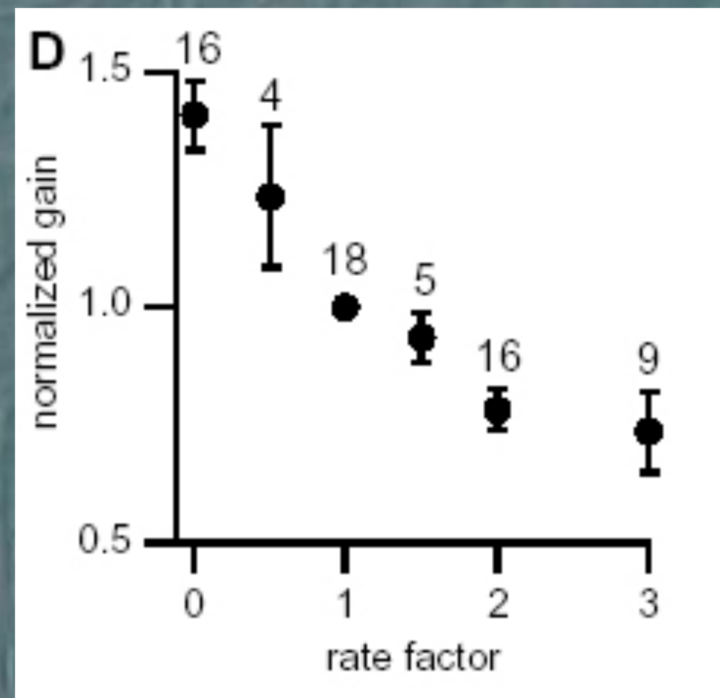


How do These Changes Affect the Input-Output Relation of Single Neurons?

Depolarizations Increases Responsiveness (Shift to Left)
Increase Conductance (reversing at rest) Reduces Responsiveness (Shift to Right)
Increase in Variance Increases Responsiveness to Small Inputs, and Decreases Slope of Input-Output Relation

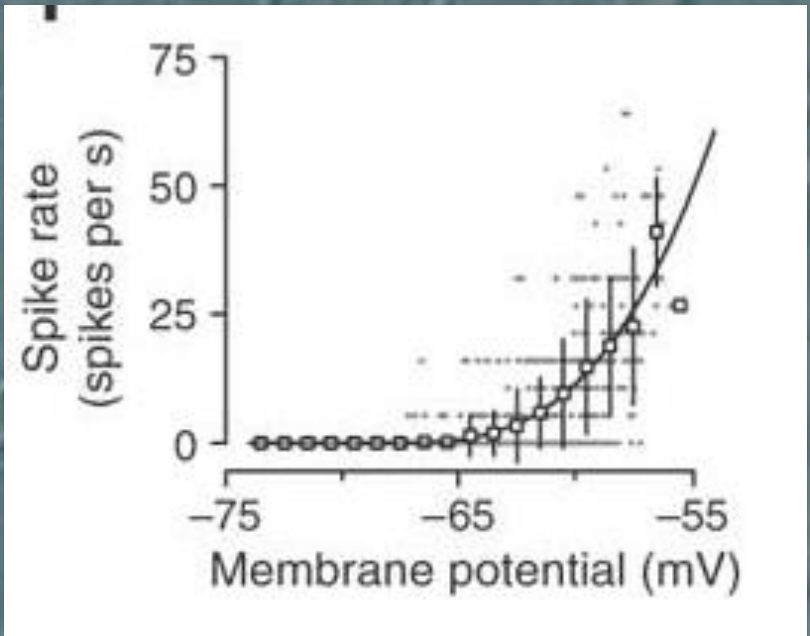
Simultaneously Increasing Noise and Conductance can Modulate just the Slope of the Input-Output Relation (so-called "Gain") of Cortical Cells

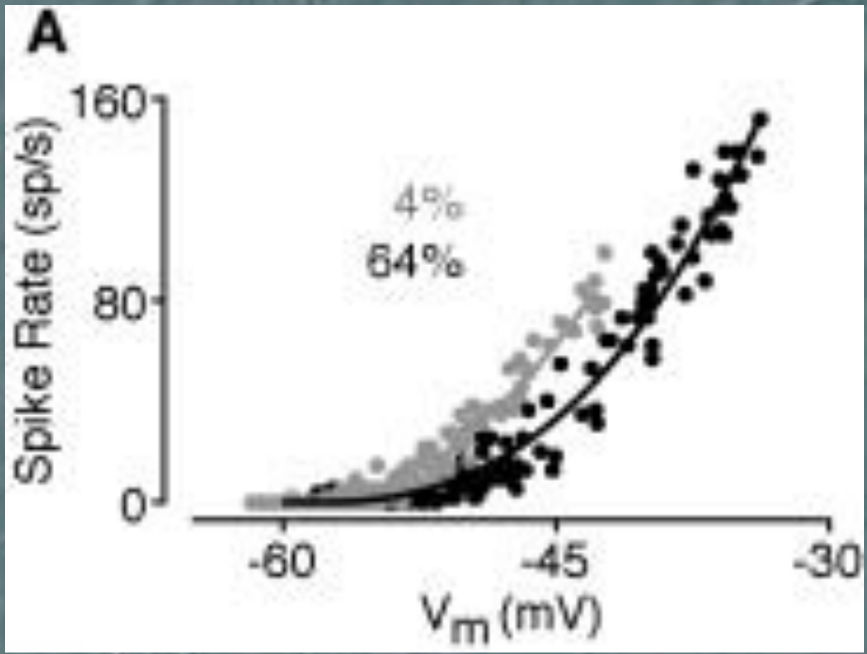




Chance, Abbott, Reyes Neuron, 35:773.

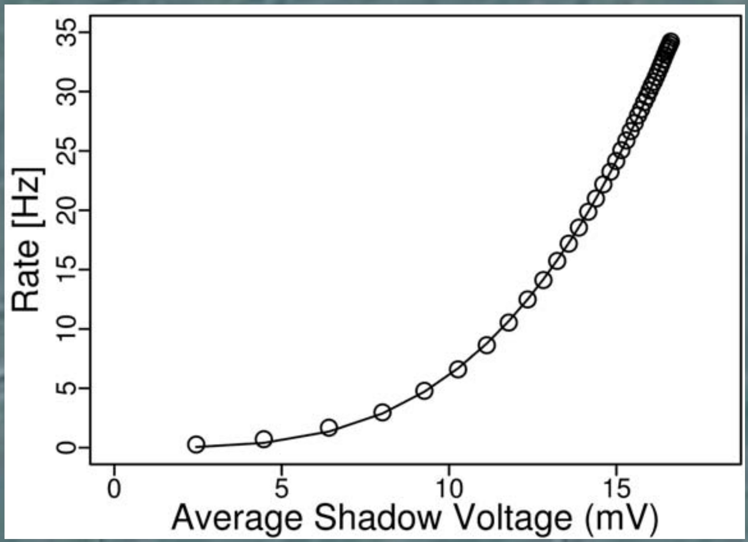
Visual Cortical Neurons Exhibit a Power Law Relationship Between Vm and Firing Rate

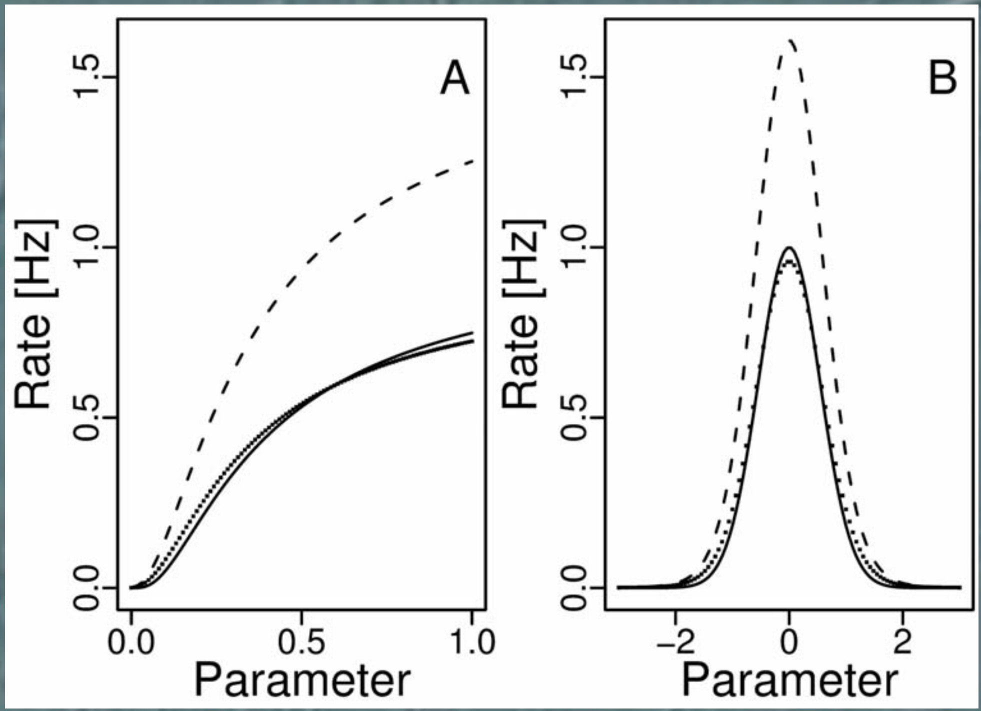




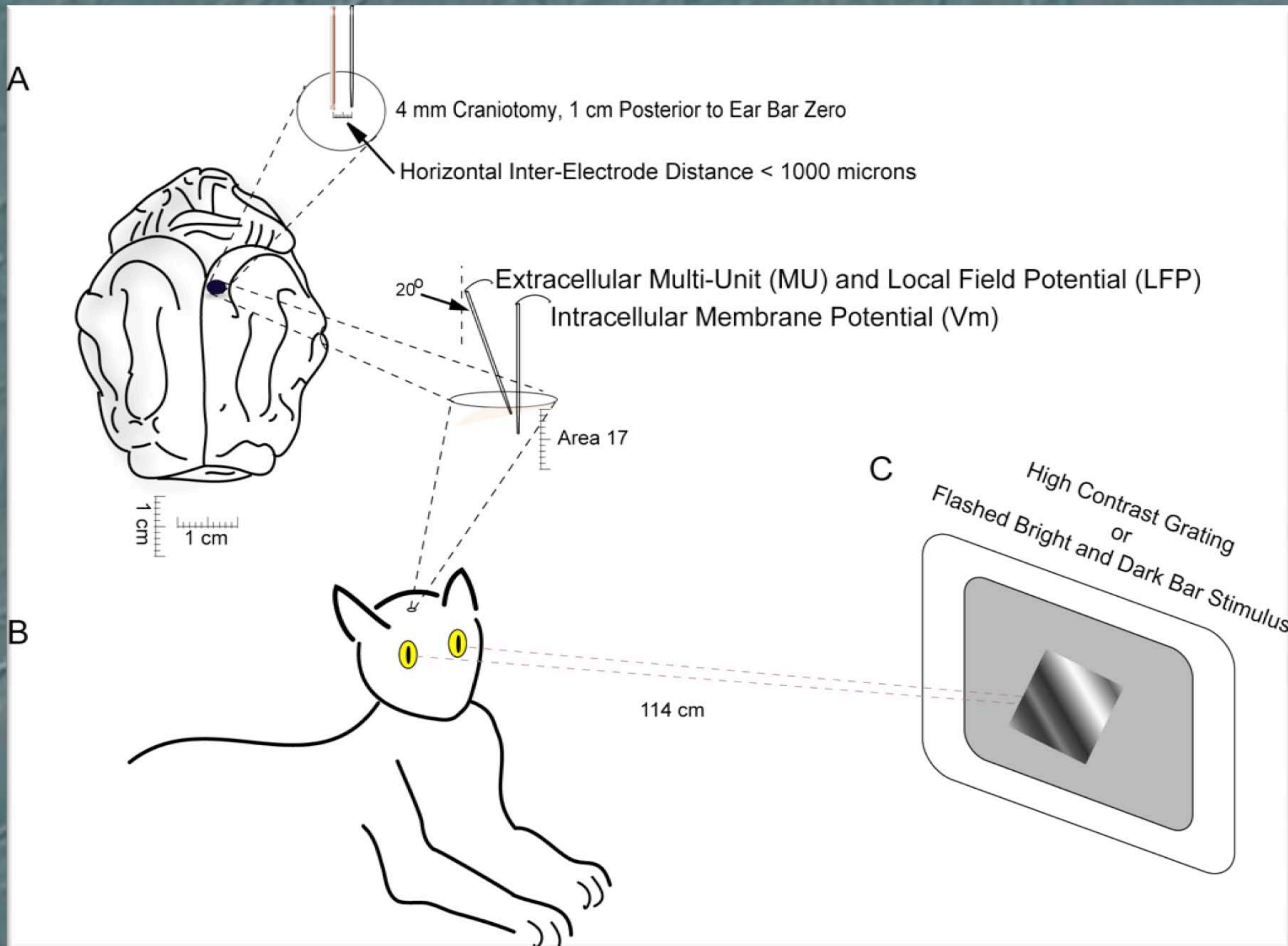
Ferster et al

Near Multiplicative Gain From Depolarization – Computational Model



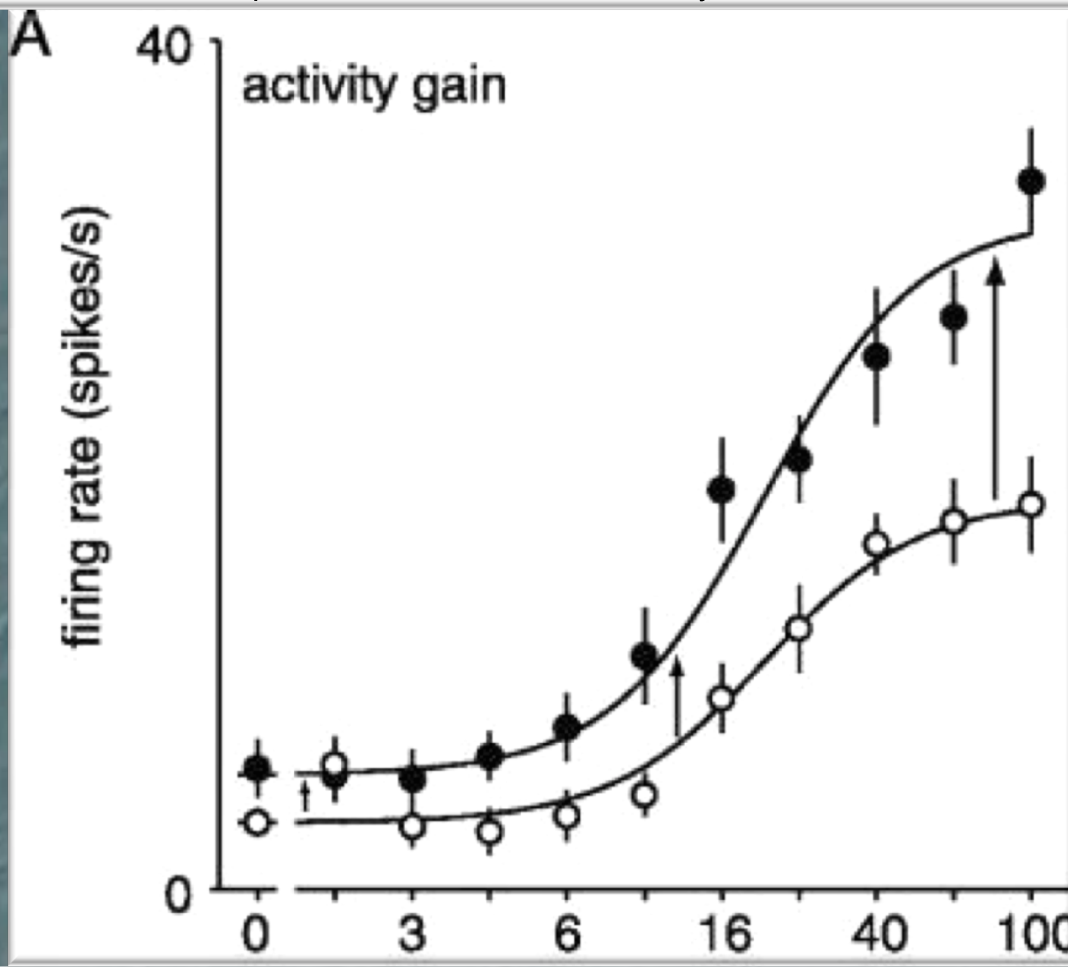


Murphy and Miller, J. Neurosci. 23: 10040 (2003)

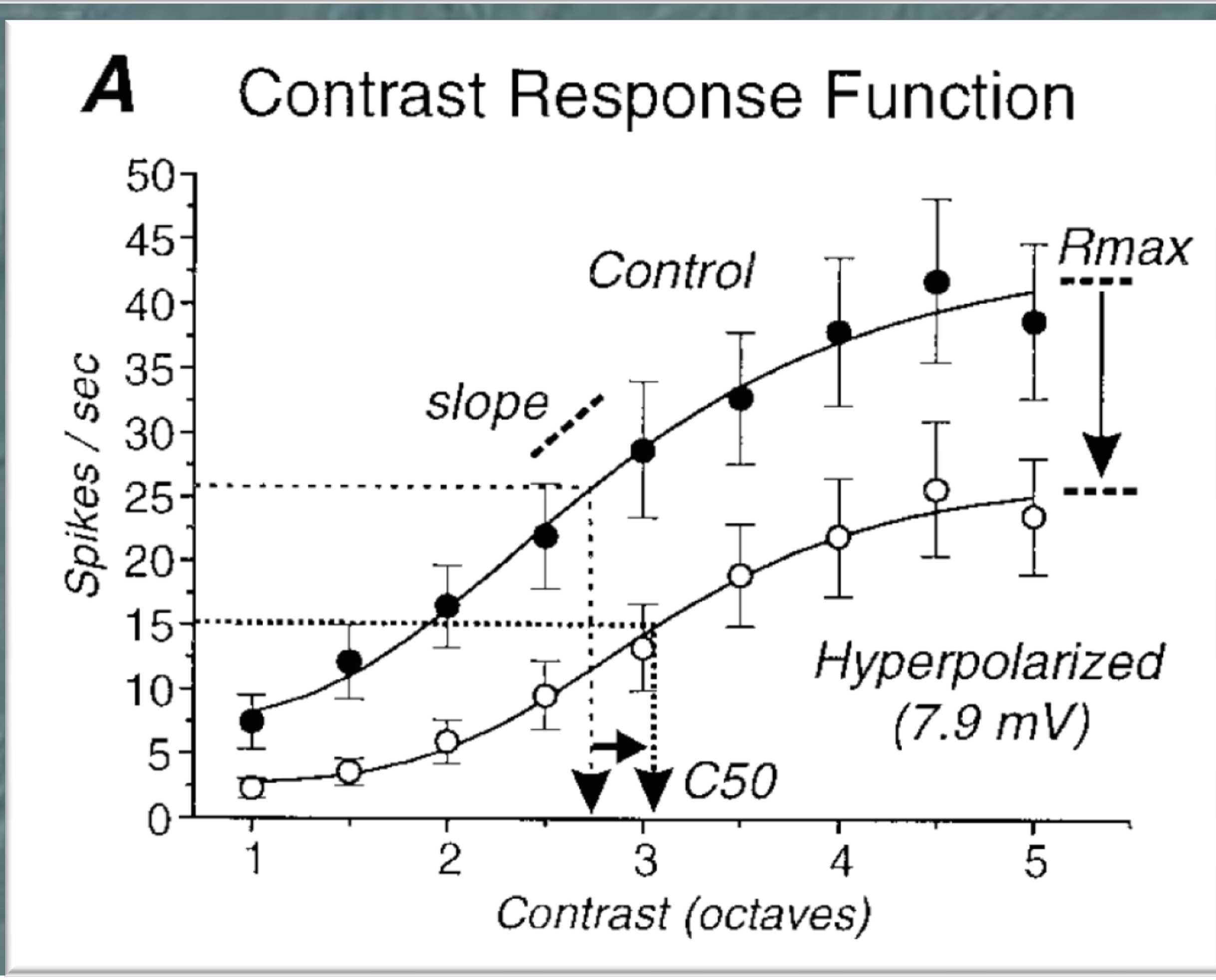

A
4 mm Craniotomy, 1 cm Posterior to Ear Bar Zero
Horizontal Inter-Electrode Distance < 1000 microns
20°
Extracellular Multi-Unit (MU) and Local Field Potential (LFP)
Intracellular Membrane Potential (Vm)
Area 17
1 cm
1 cm
B
114 cm
C
High Contrast Grating
or
Flashed Bright and Dark Bar Stimulus

Some of the effects of spatial attention can be explained by a simple rapid change in membrane potential

Effect of attention on contrast response function curve in monkey V4   Maunsell et al.

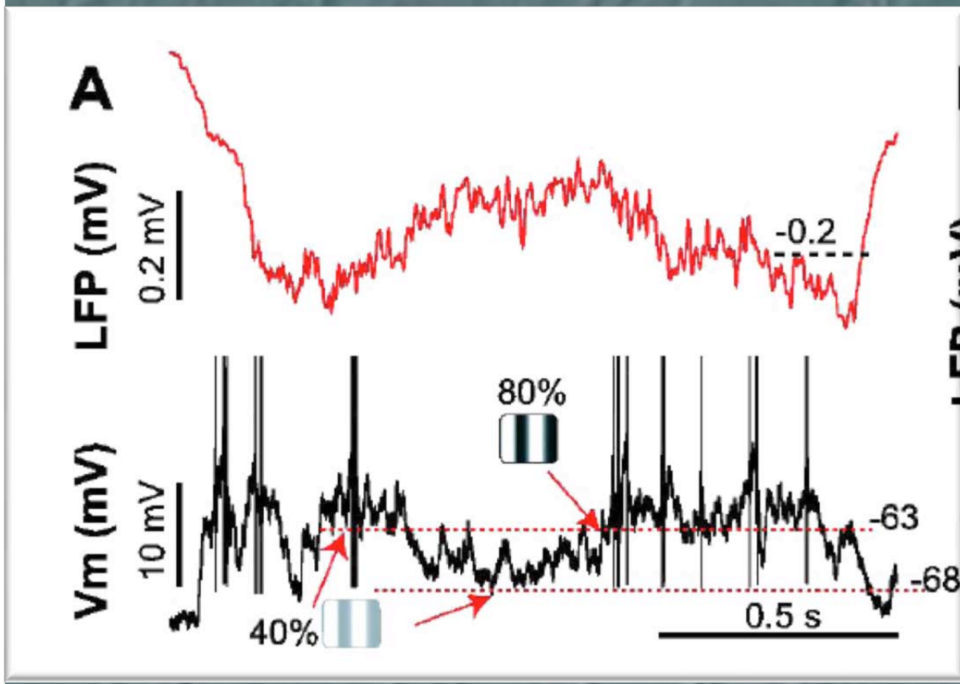


Depolarization of Membrane Potential Replicates Attention

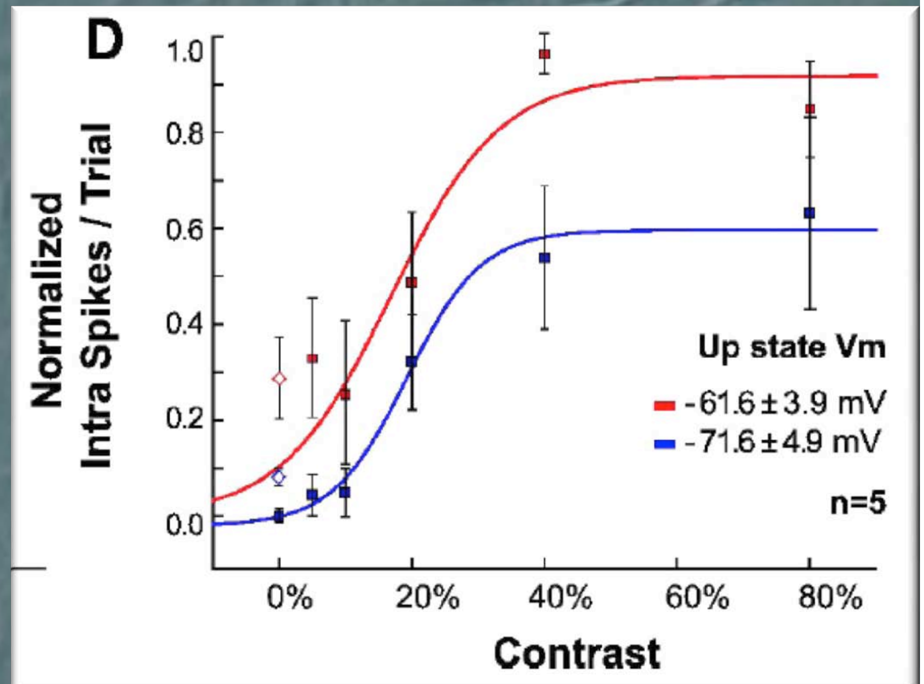


Some of the effects of spatial attention can be explained by a simple rapid change in membrane potential

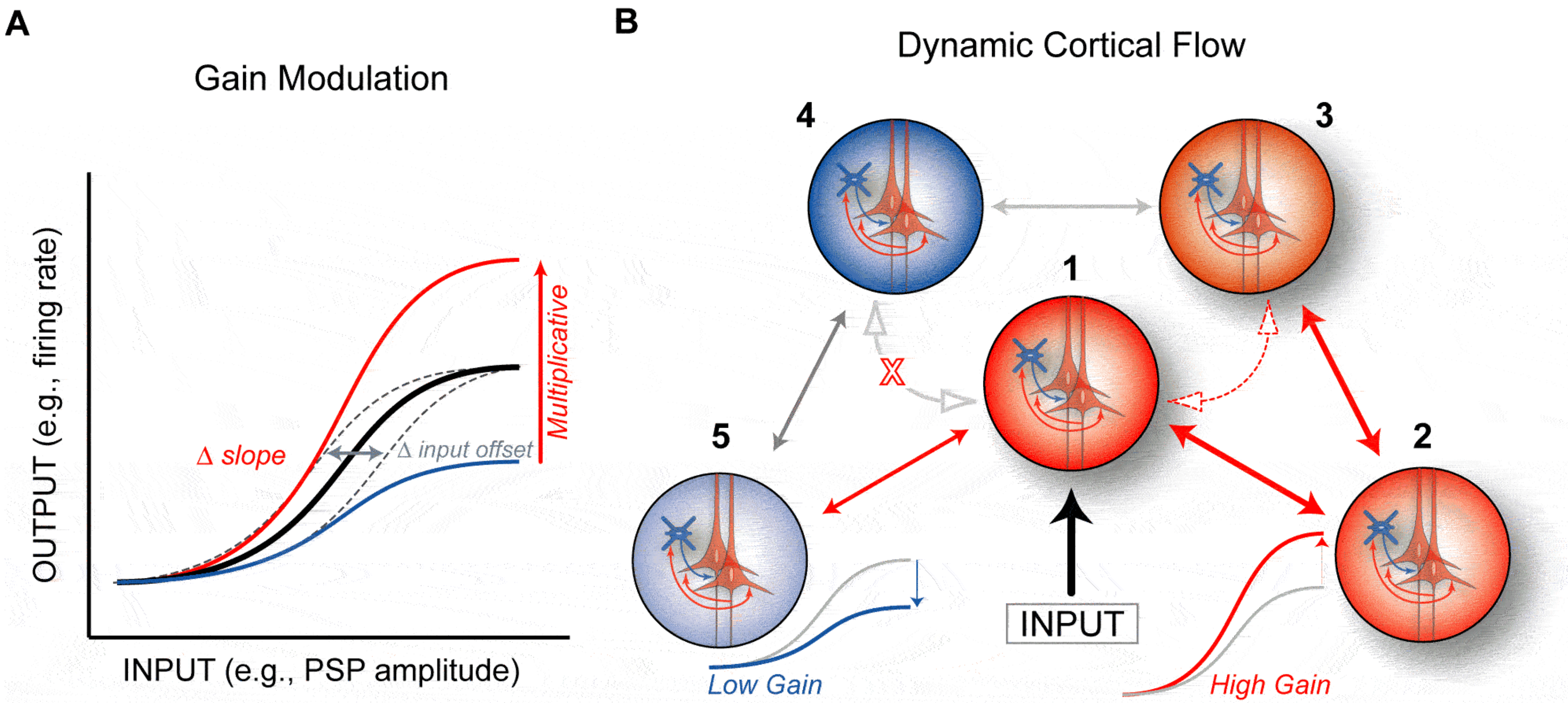
Examining visual responses during spontaneous changes in Vm in Cat V1



Effect of spontaneous changes in Vm on contrast response function in Cat V1



Rapid Changes in Synaptic Barrages Control Functional Cortical Connectivity



Conclusions: *Cortical Neurons Must Be Depolarized by Approximately 20-25 mV from True Resting Potential (-75 to -80) to Discharge an Action Potential.*

This Depolarization DOES NOT occur de novo With Each Action Potential, but Rather Consists of Two Components:

I: An ongoing, but variable Depolarization due to Recurrent Network Activity in the Cerebral Cortex (>80% of the Depolarization to Firing Threshold). This ongoing synaptic bombardment provides "context" to the cell, preparing it and determining whether or not it participates in a neuronal ensemble.

II. A temporally precise component that determines when action potentials are generated on a msec time scale.

III. Together, these components determine the pattern of activity flow in the cortex.