Hippocampus: from cells to physiology and human pathology

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Physiology of Cells and Synapses


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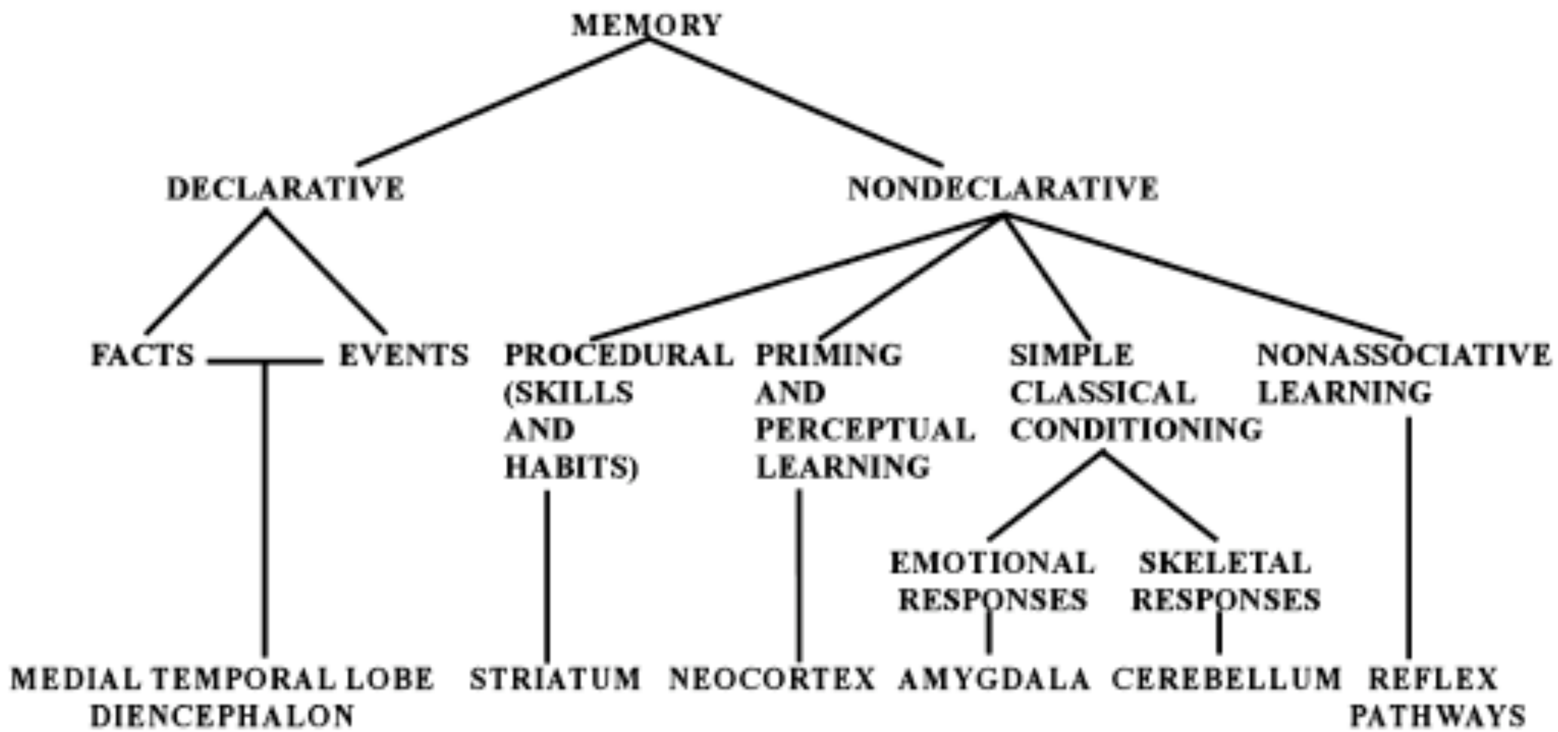
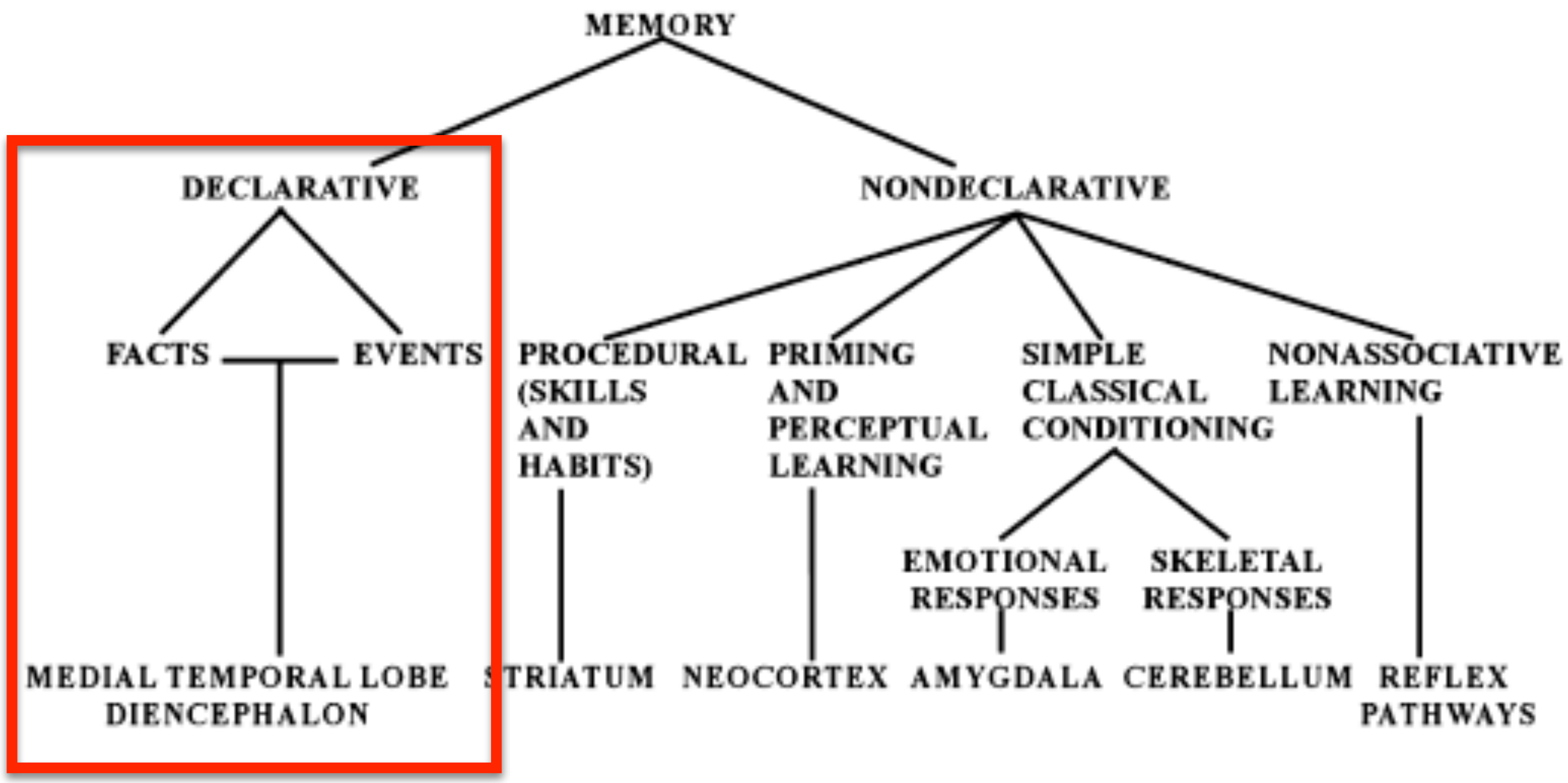
Forms of Memory



Larry Squire, *Memory systems of the brain: A brief history and current perspective.* Neurobiology of Learning and Memory. (2004) 82:171-177

Forms of Memory



Larry Squire, *Memory systems of the brain: A brief history and current perspective.* Neurobiology of Learning and Memory. (2004) 82:171-177

Declarative memory / Episodic memory

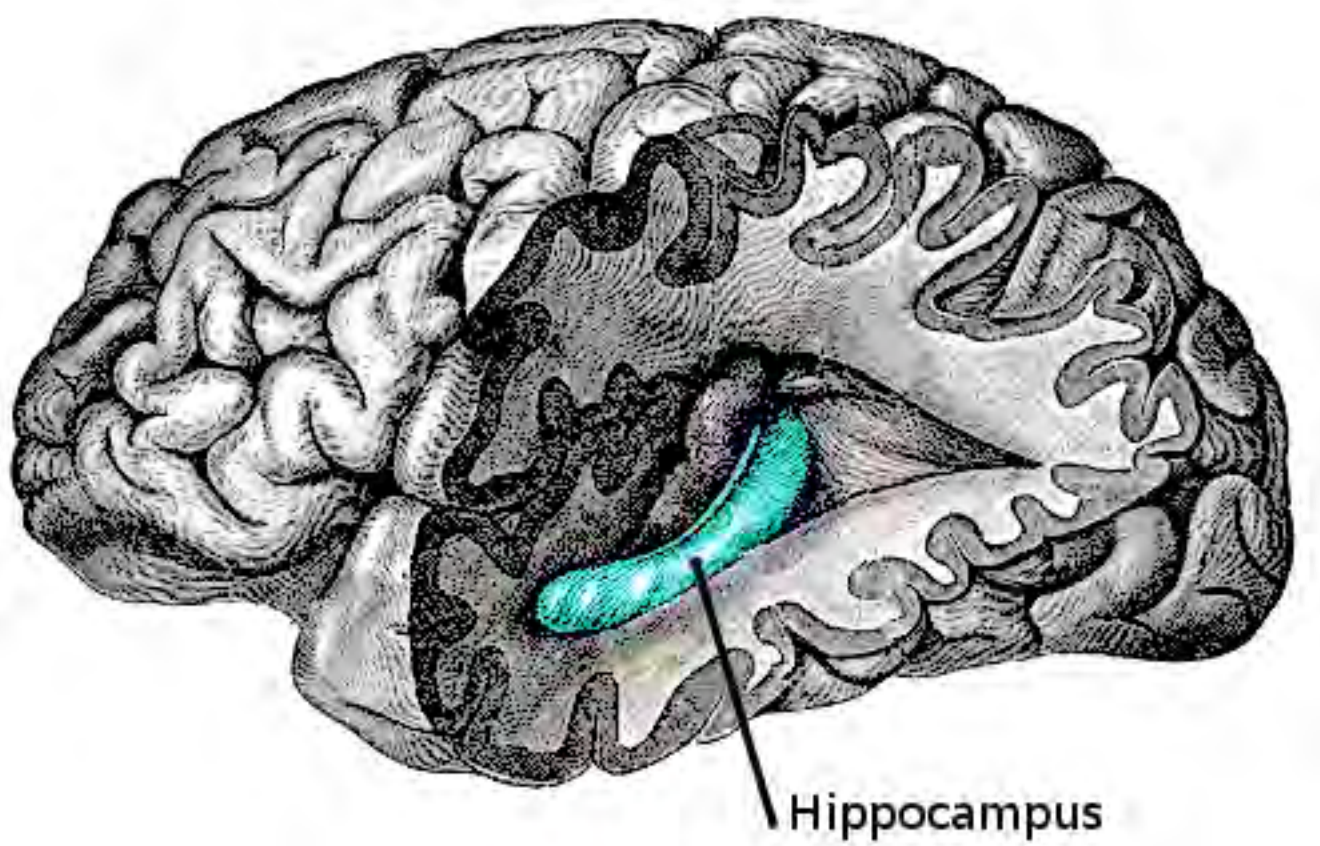
Declarative memory / Episodic memory

Episode - Event in time

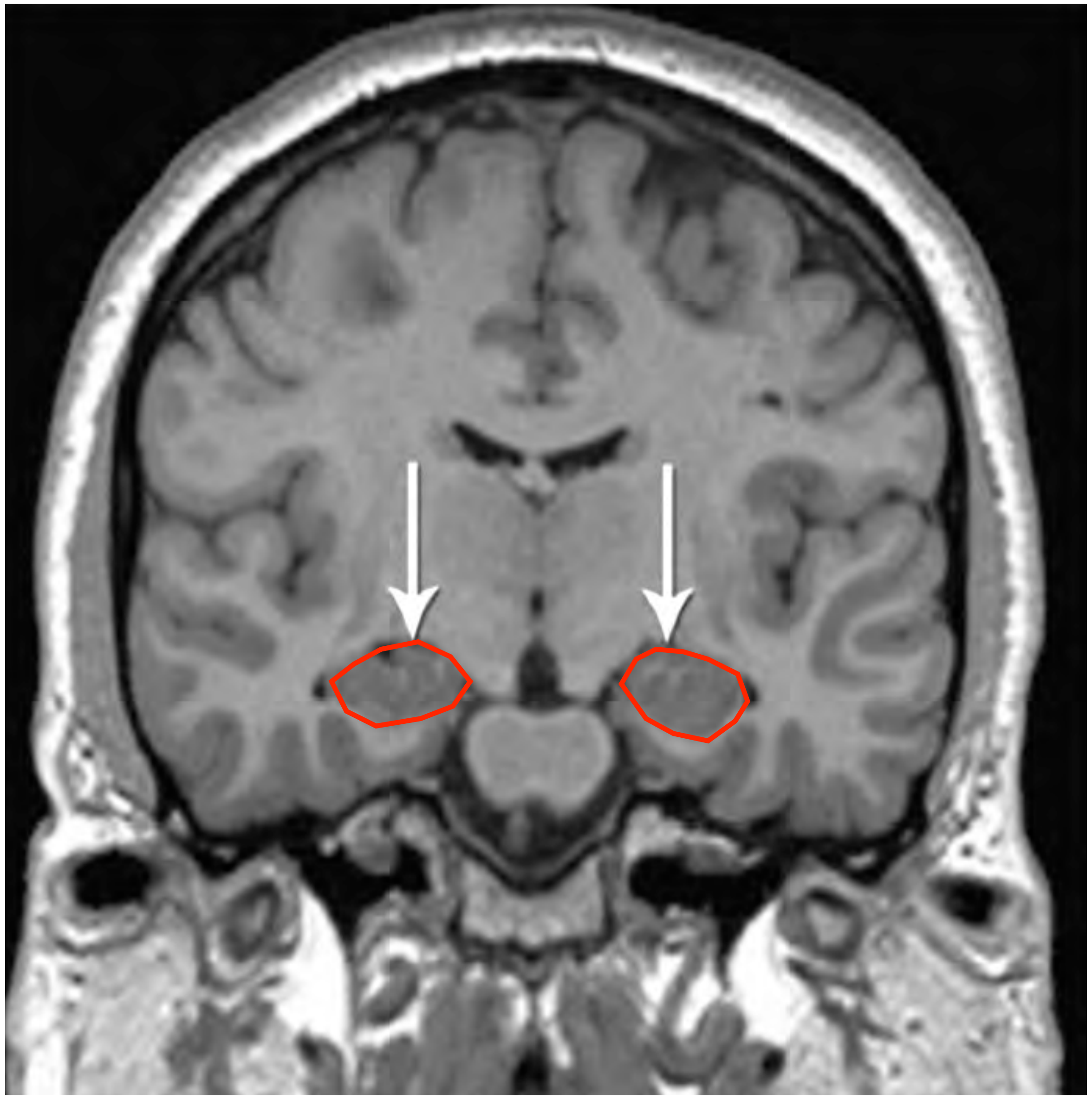
Collection of past personal experiences that occurred at a particular place and time.

Explicit: who, what, when, where and why

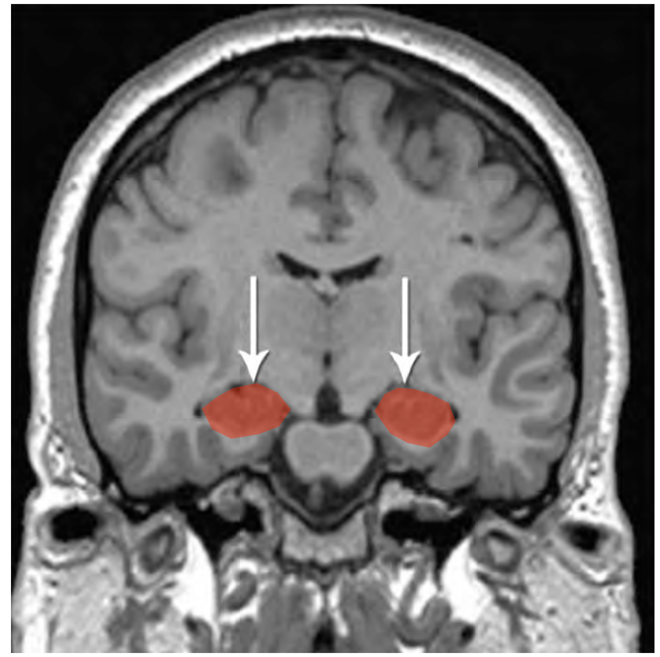
Memory formation is central to our sense of self and attachment to others.

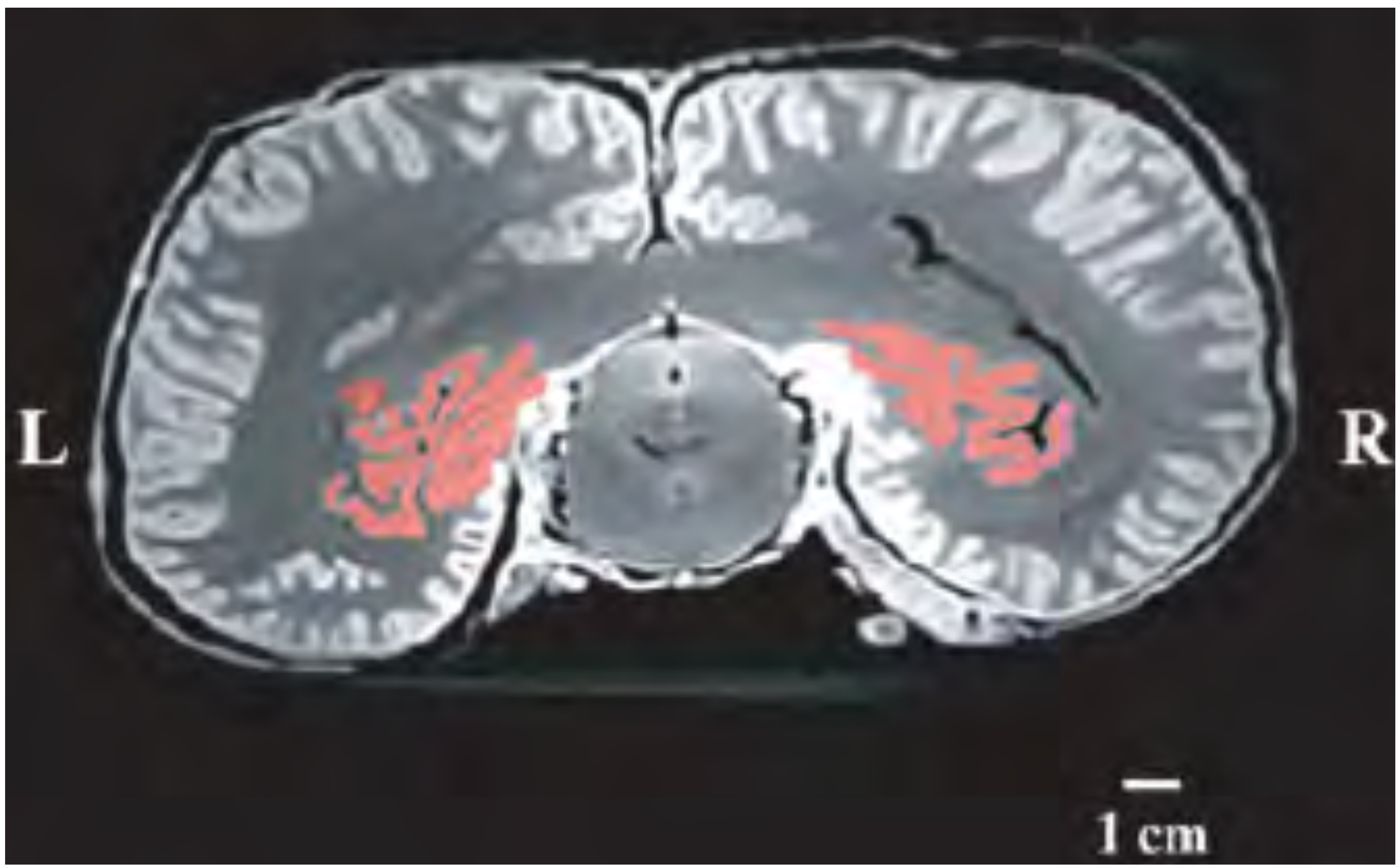


from 20th U.S. Edition of *Gray's Anatomy,* 1918



Goodrich-Hunsaker N J et al. Chem. Senses 2009




L
R
1 cm

Patient H.M.

Henry Molaison (1926 - 2008)

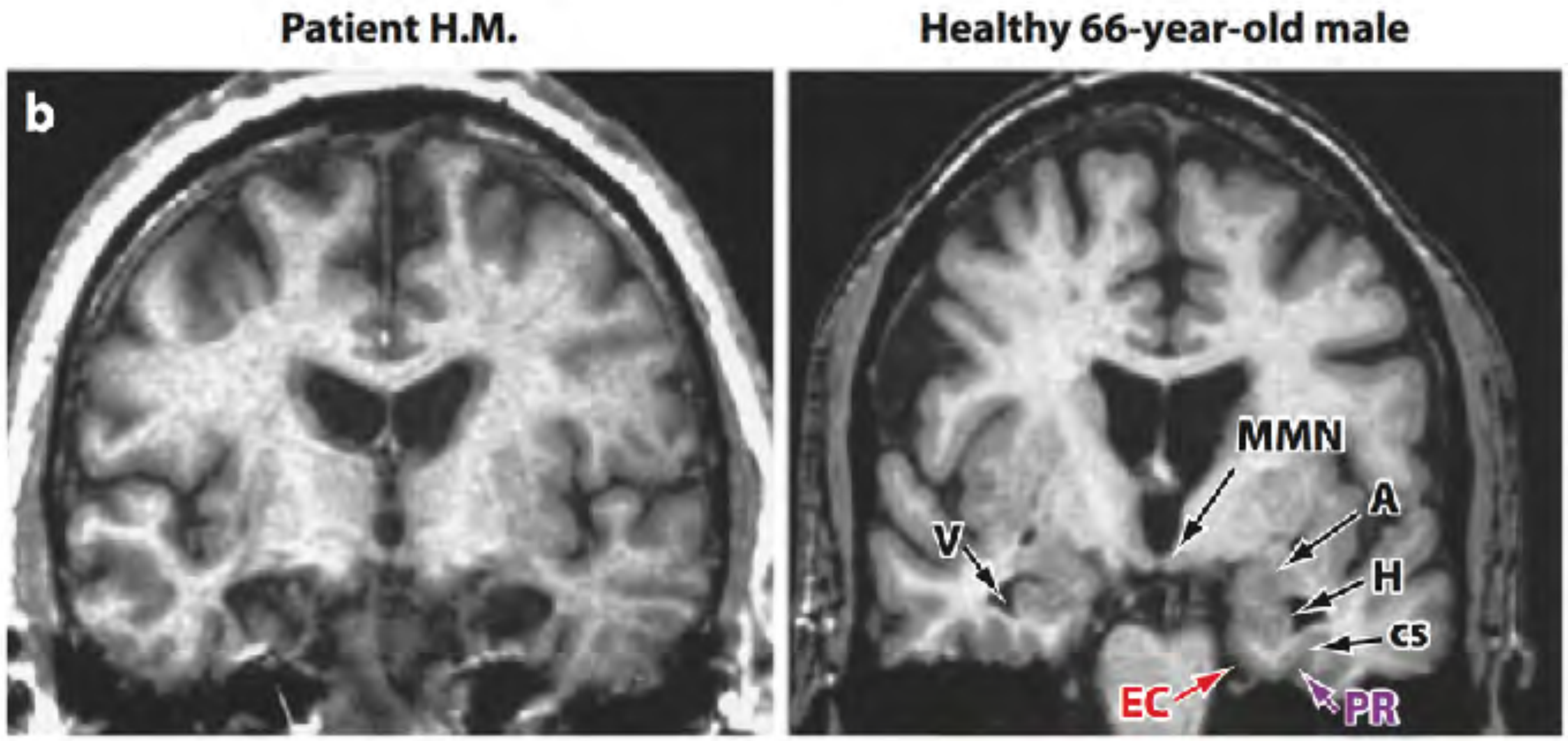
Photo © Public Broadcasting Online by WGBH

Very intelligent and agreeable young man.

Suffered from terrible life-threatening epileptic seizures.

In 1953, when he was 27 years old, he underwent experimental brain surgery. Most of both the left and right hippocampus were removed from H.M.'s brain.

Patient H.M.



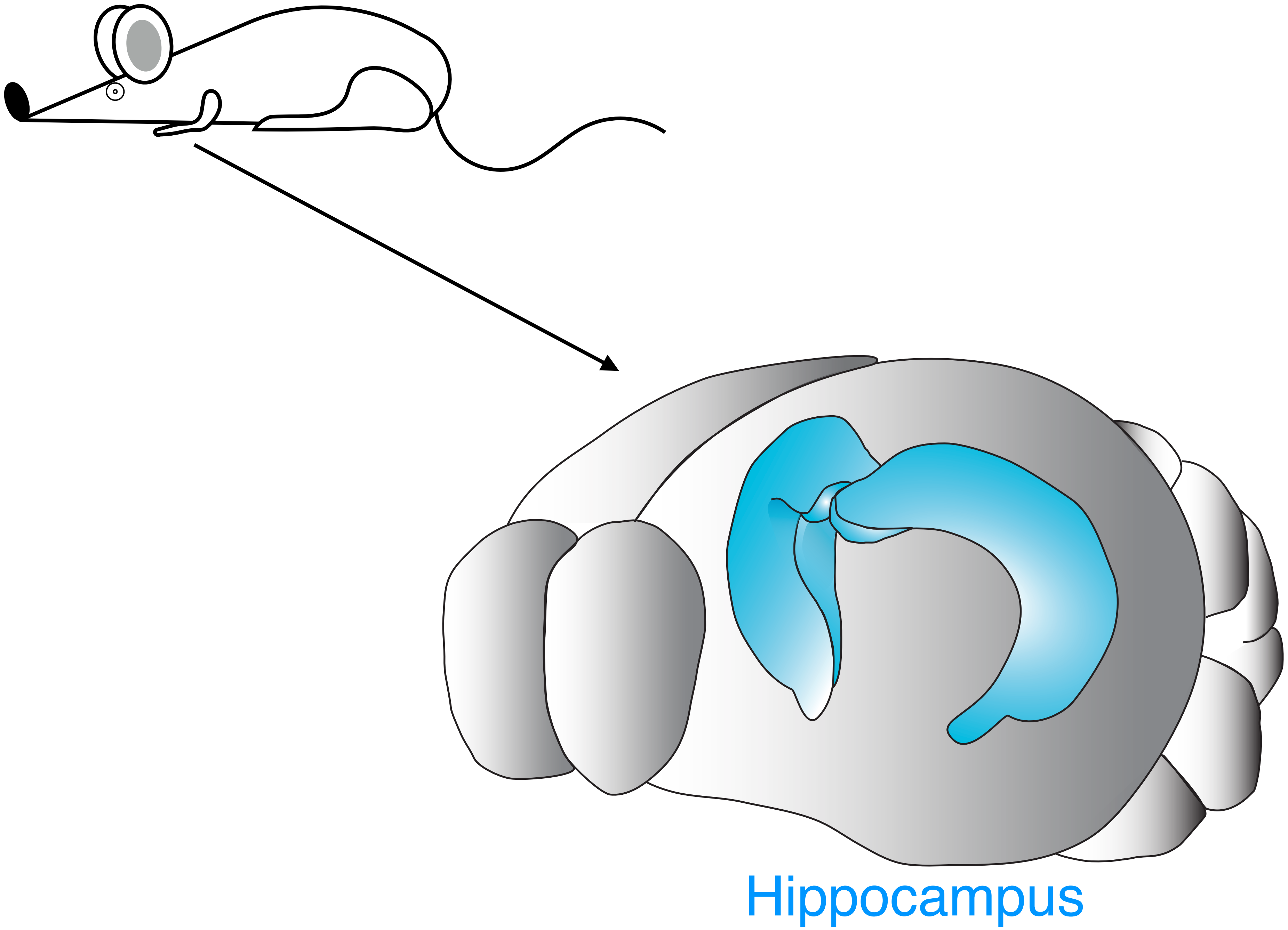
Larry Squire and John Wixted, “The cognitive neuroscience of human memory since H.M.”, *Annual Reviews of Neuroscience.* 2011

Before and after his surgery, he had an above-average I.Q.

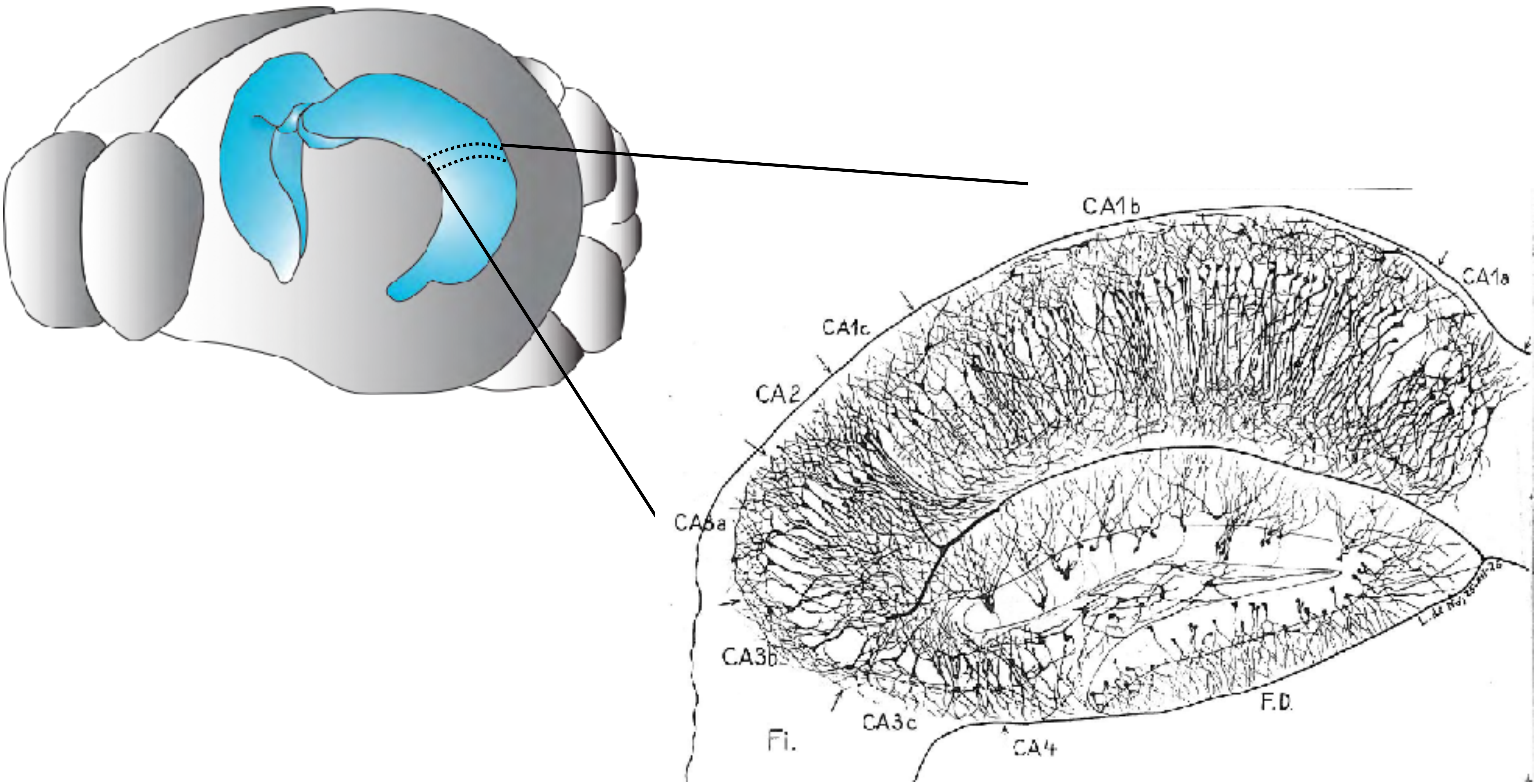
After the surgery he had no trouble moving or speaking.

Psychologically, he was very healthy.

Following the surgery, H.M. suffered from severe anterograde amnesia.
He lost the ability to form new memories.

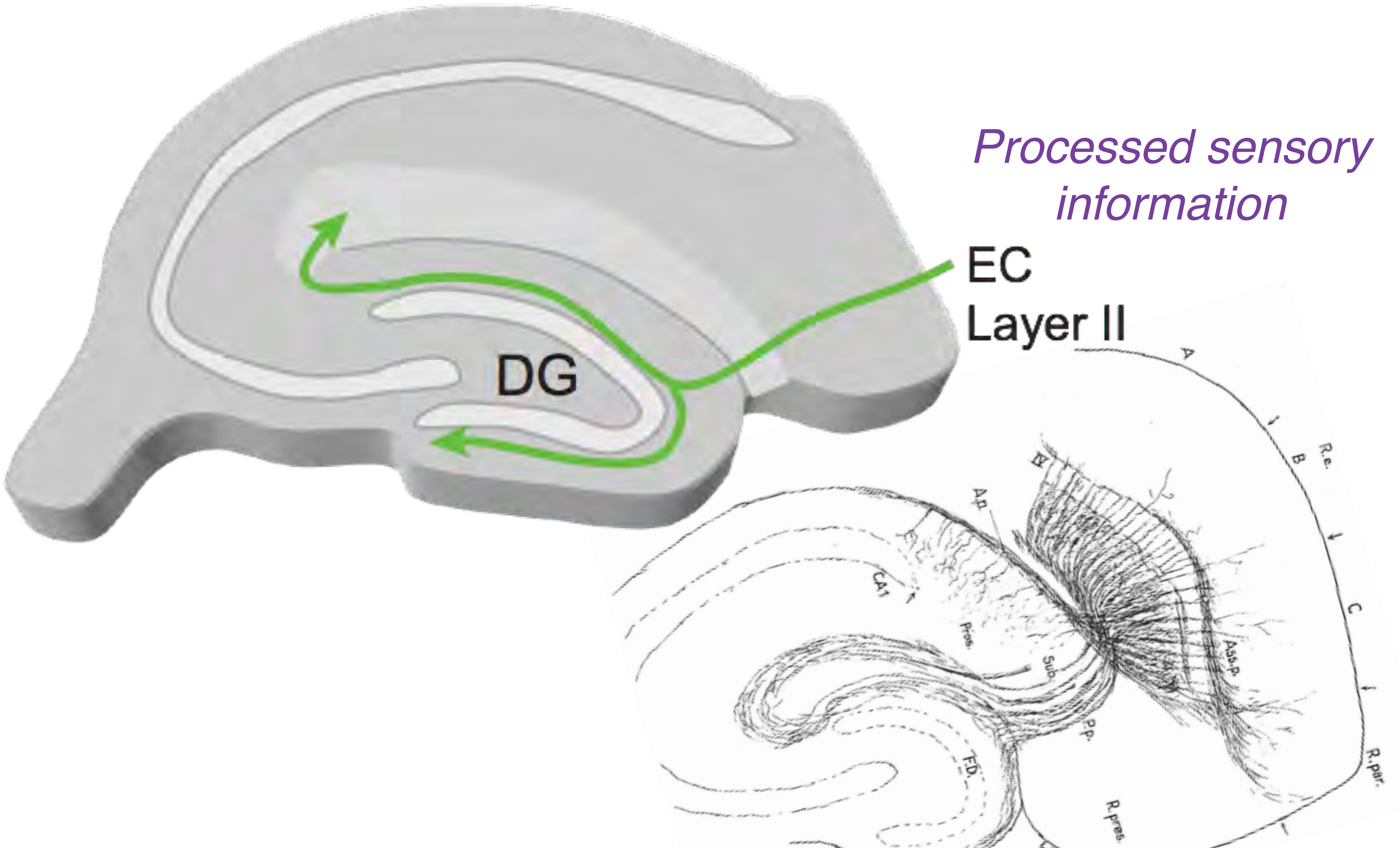

Hippocampus

Canonical model



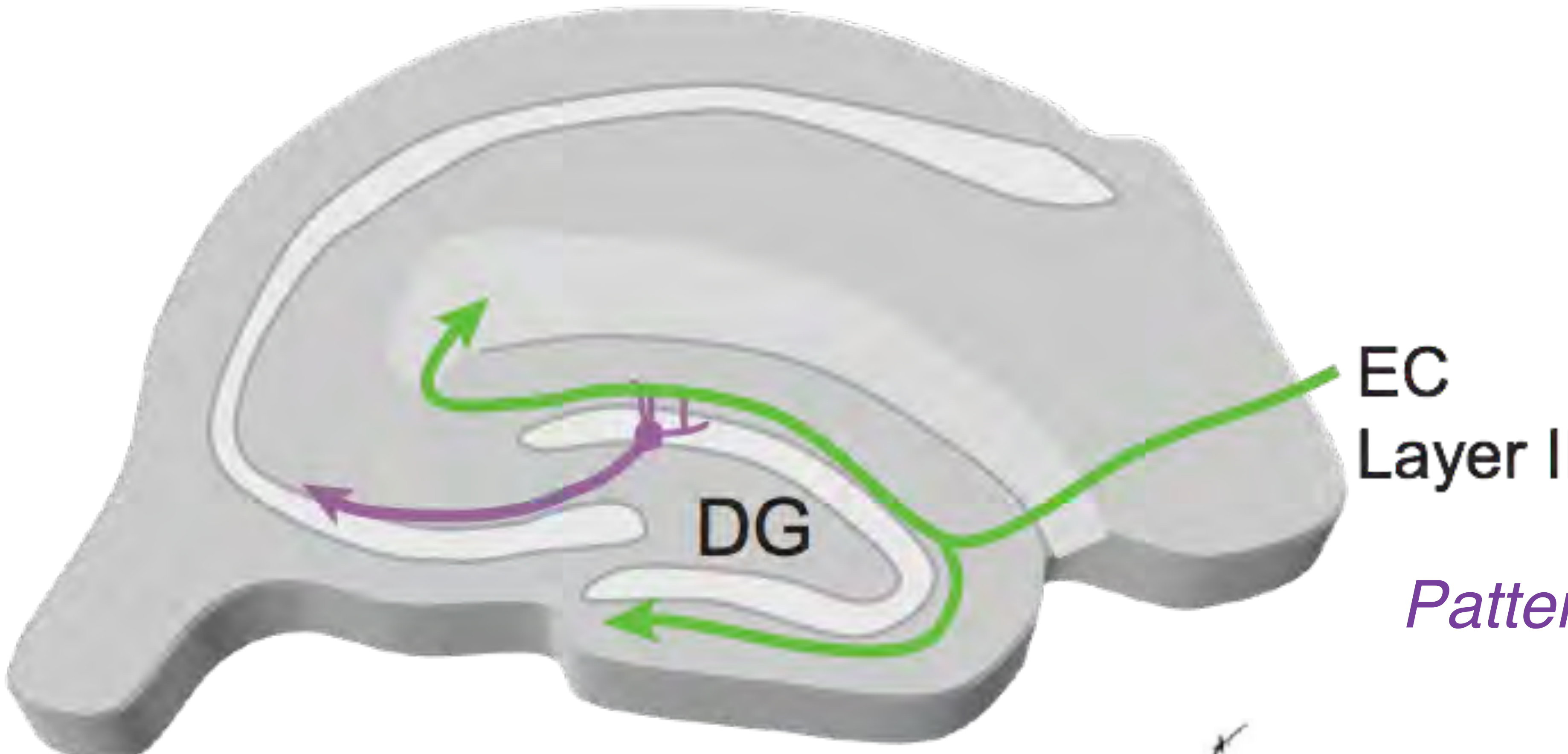
Lorente de Nó *J Psychology and Neurologie,* 1934.

Canonical model



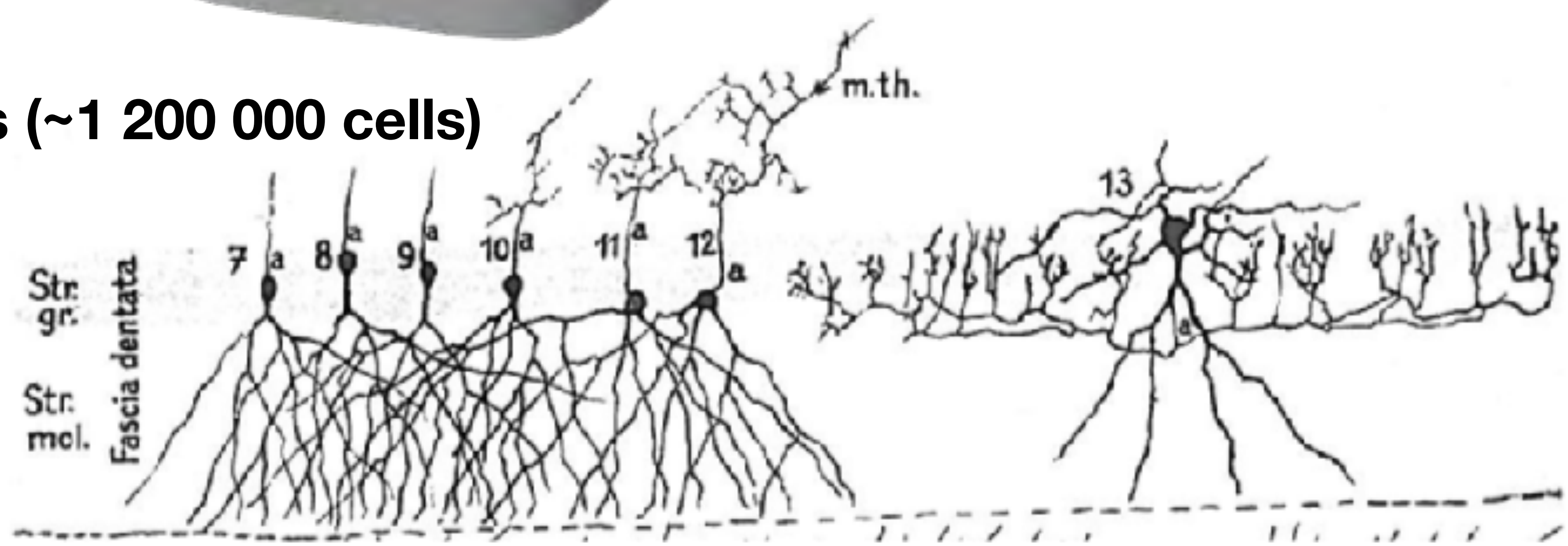
R Lorente de No, 1934

Canonical model



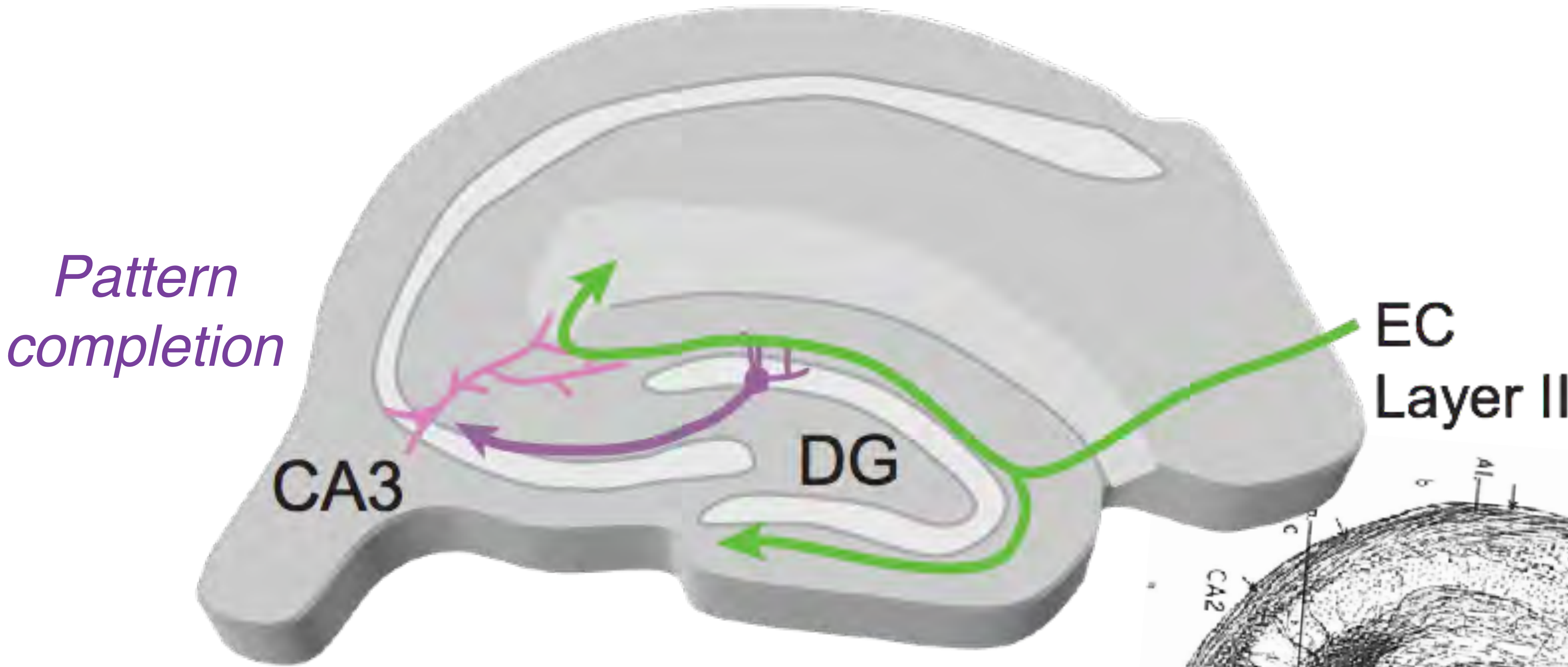
Pattern separation

Dentate granule cells (~1 200 000 cells)

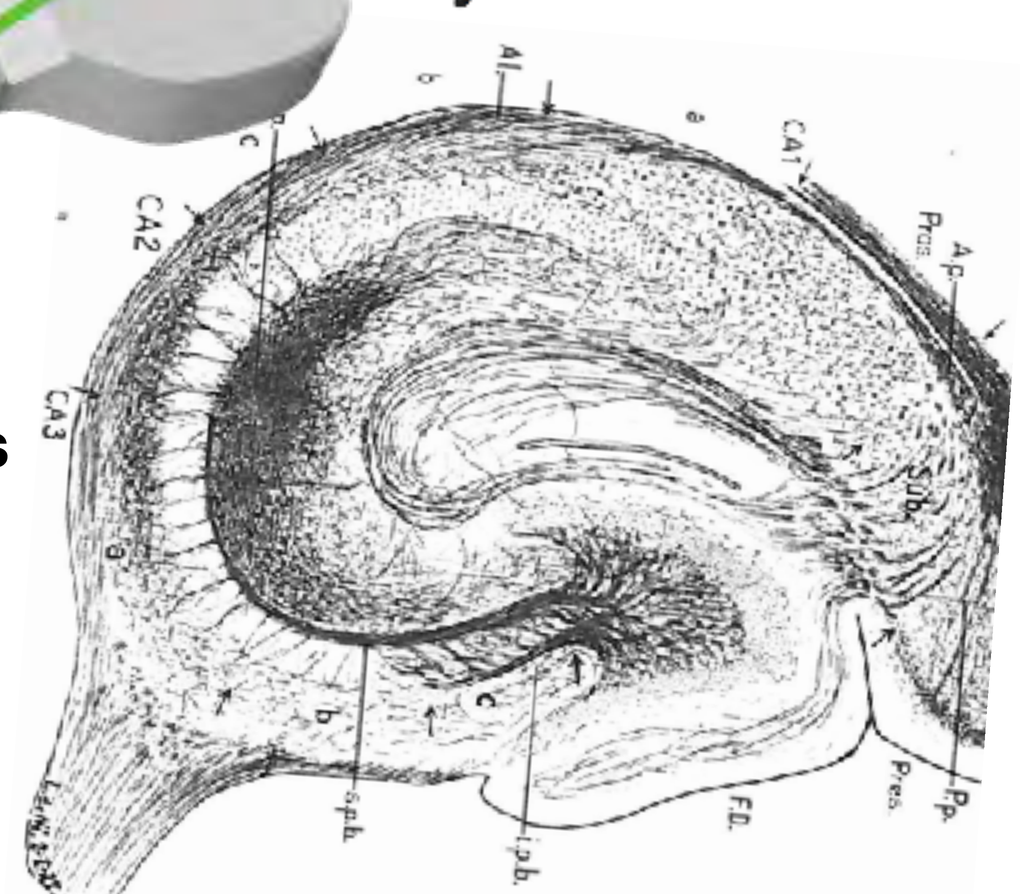


R Lorente de No, 1934

Canonical model



Mossy fibers

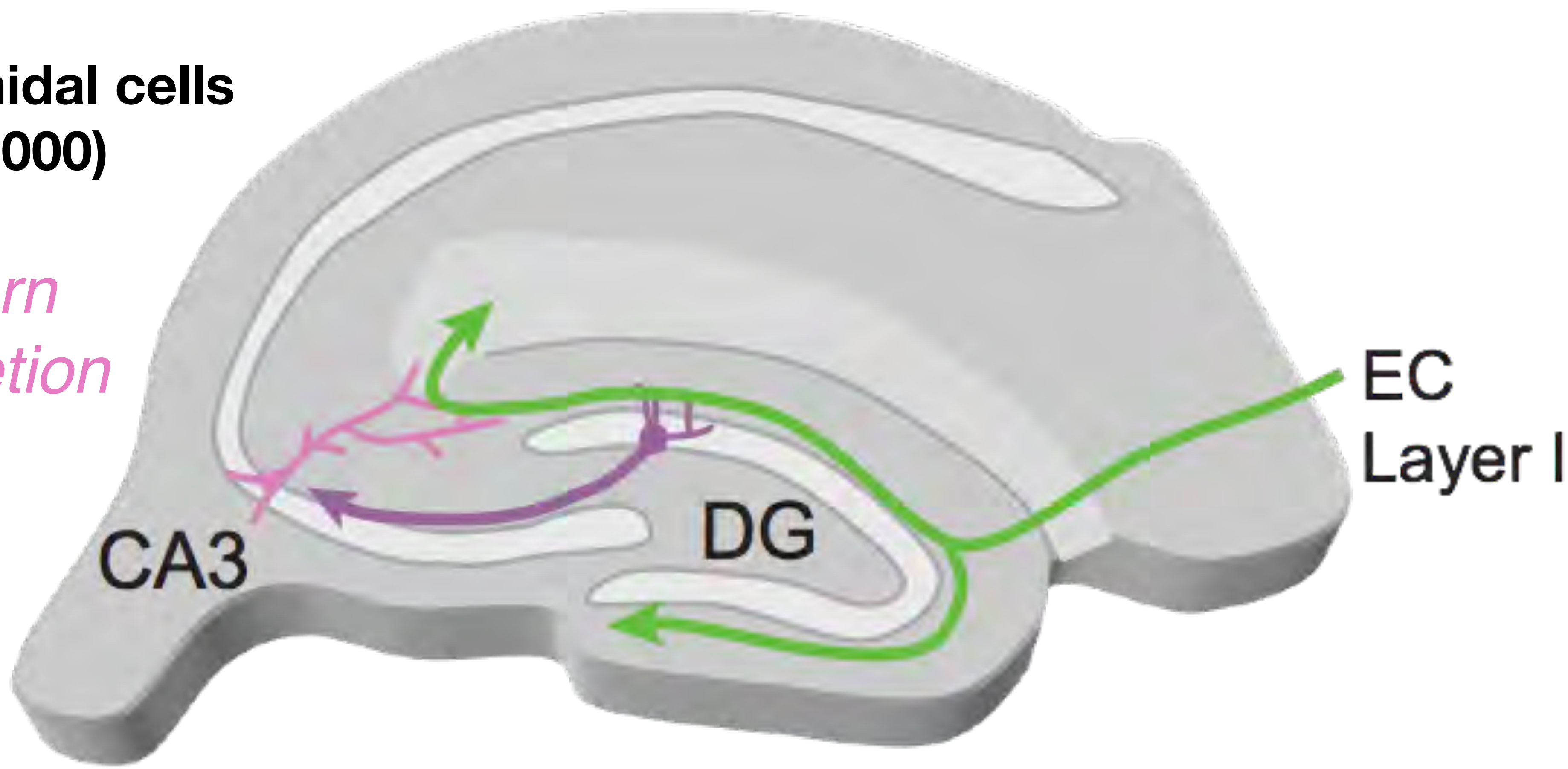


R Lorente de No, 1934

Canonical model

CA3 pyramidal cells
(~250 000)

Pattern completion

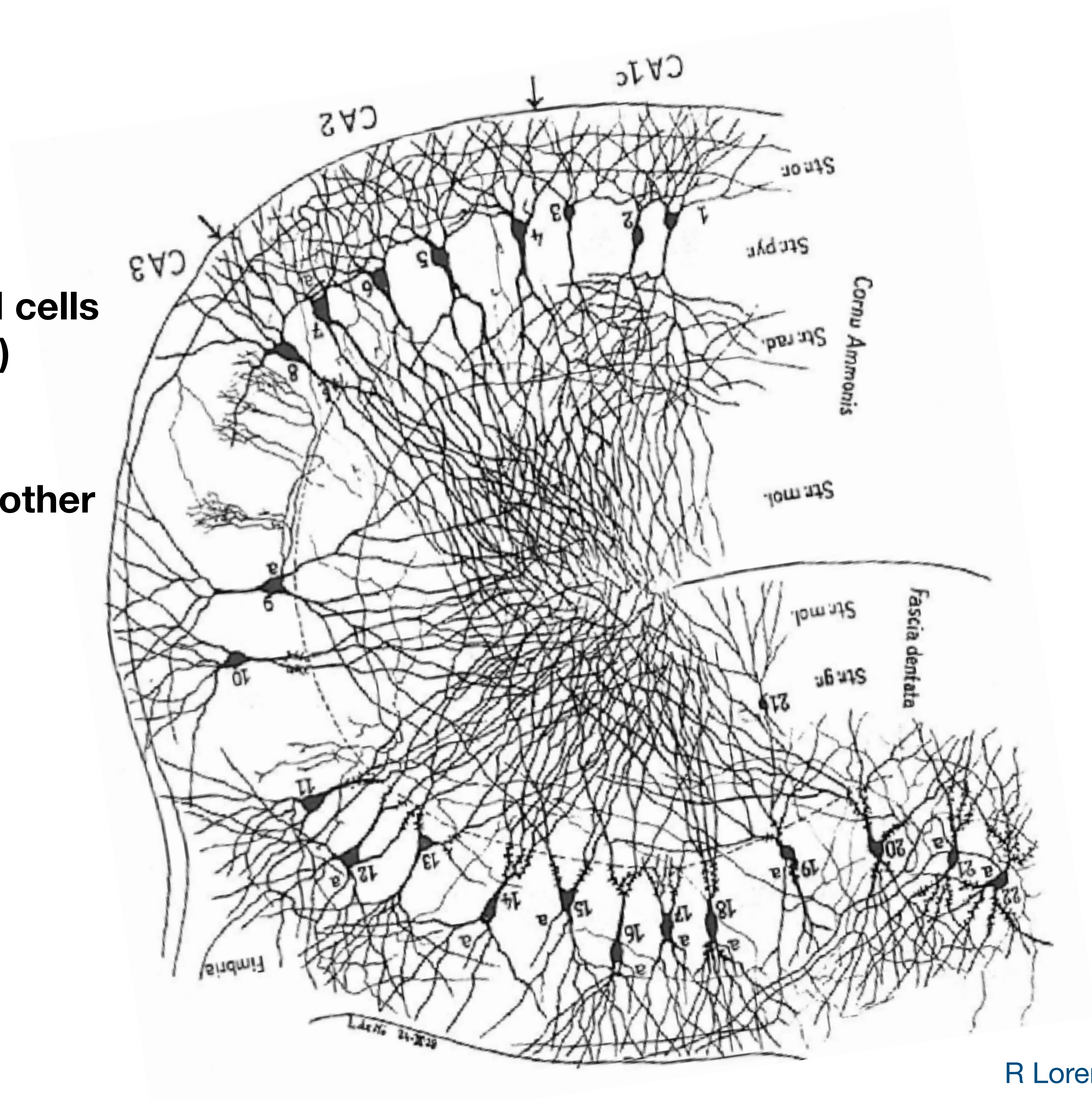


Canonical model

CA3 pyramidal cells (~250 000)

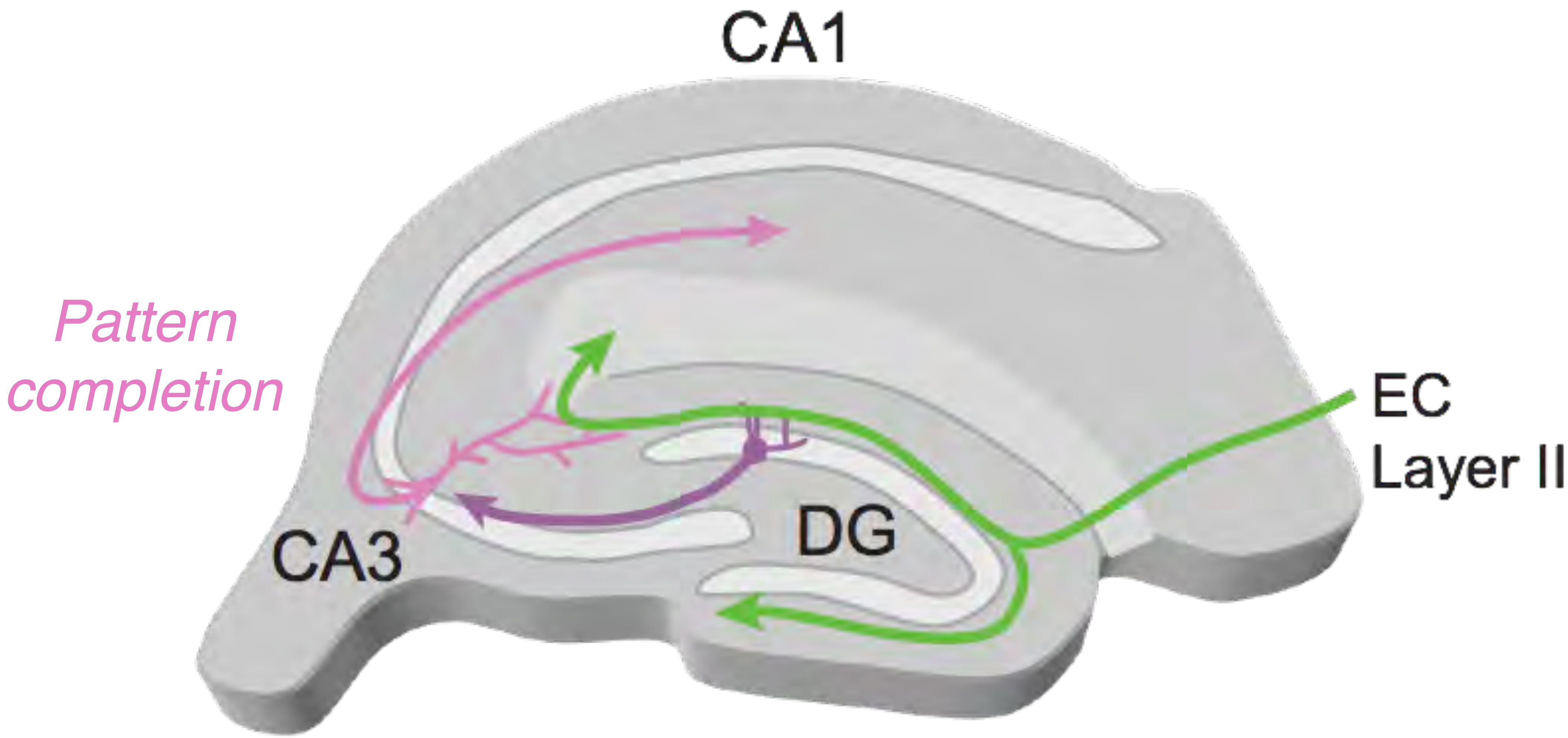
Project to each other

Highly plastic



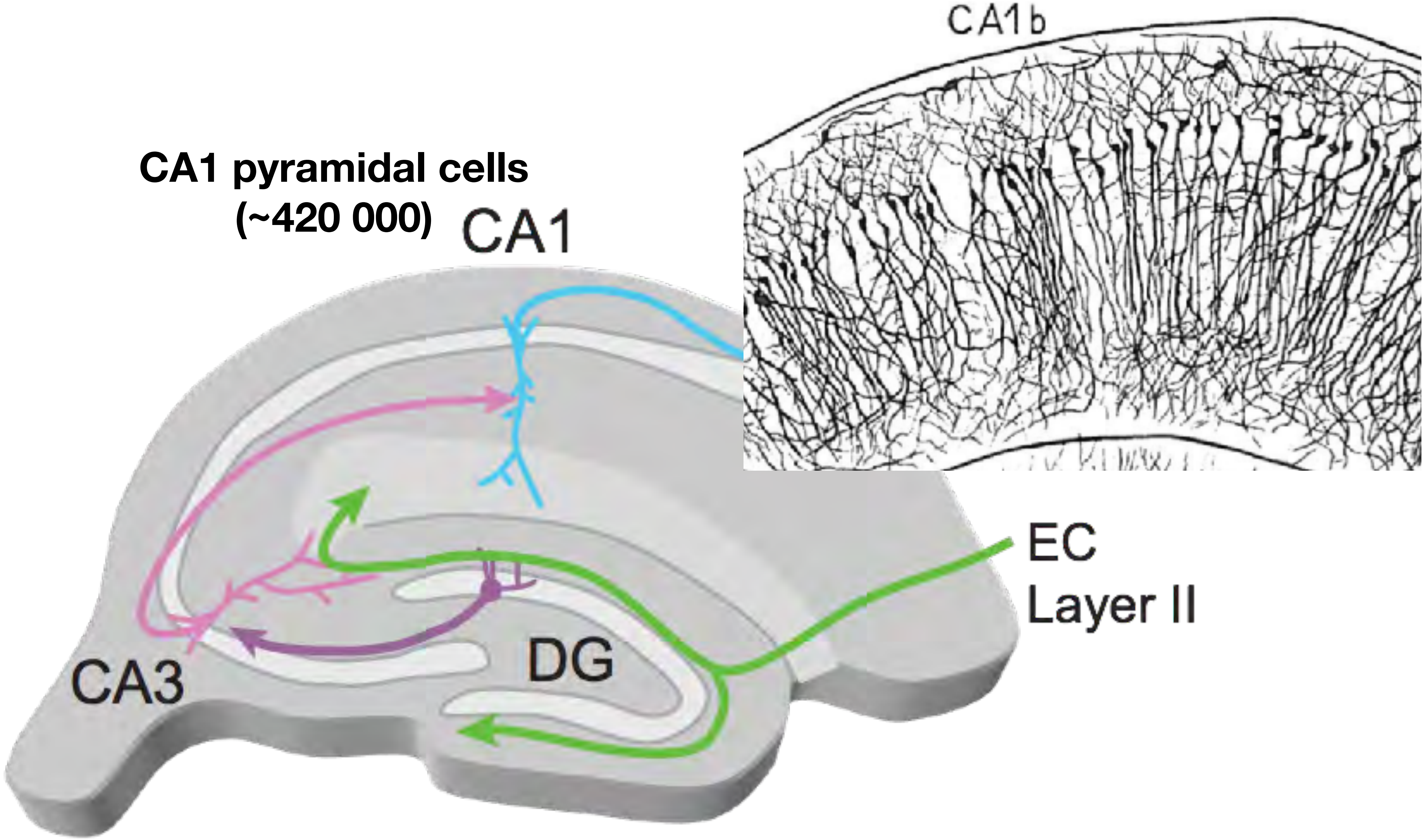
R Lorente de No, 1934

Canonical model



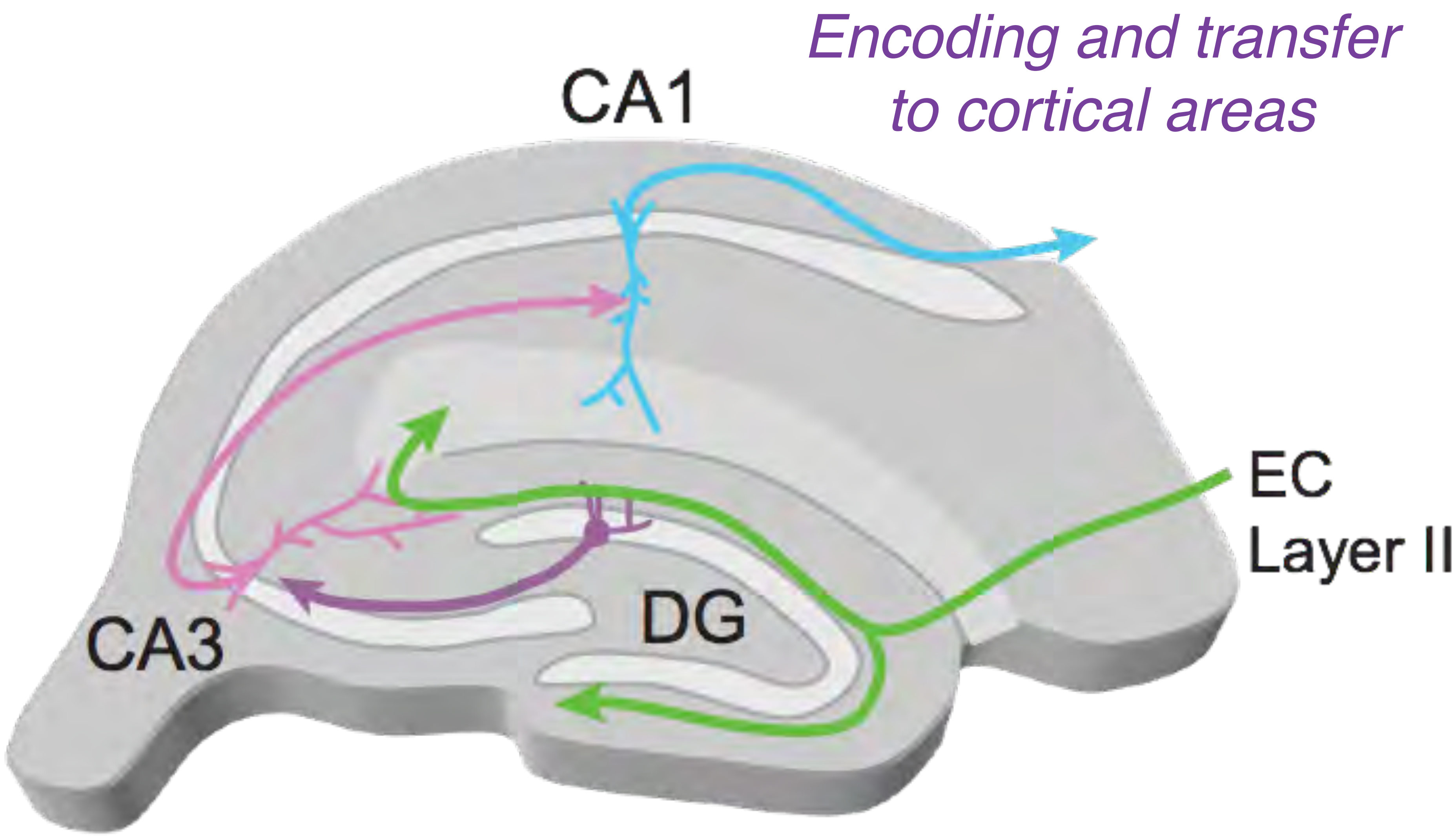
Canonical model

CA1 pyramidal cells (~420 000)



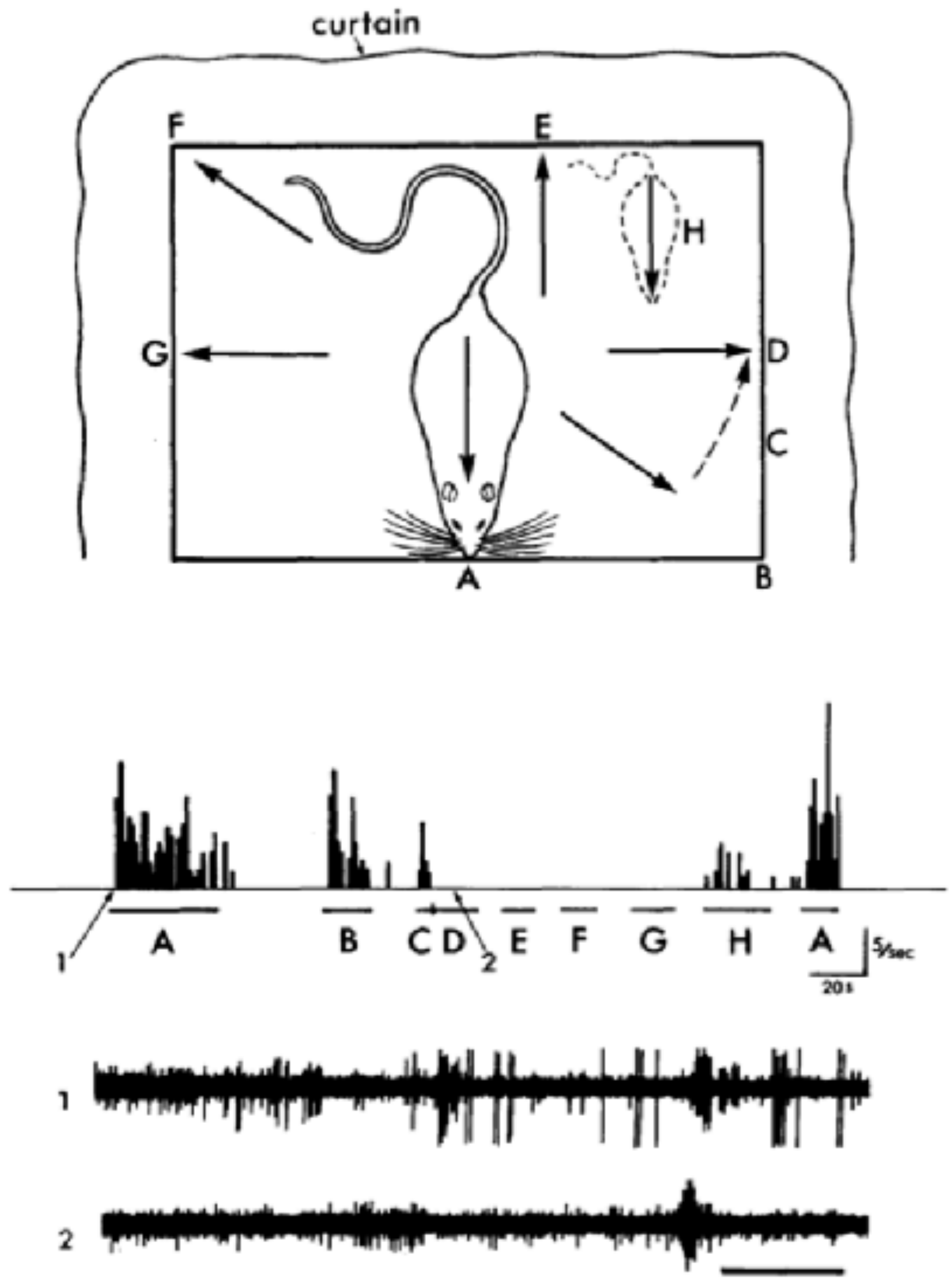
R Lorente de No, 1934

Canonical model



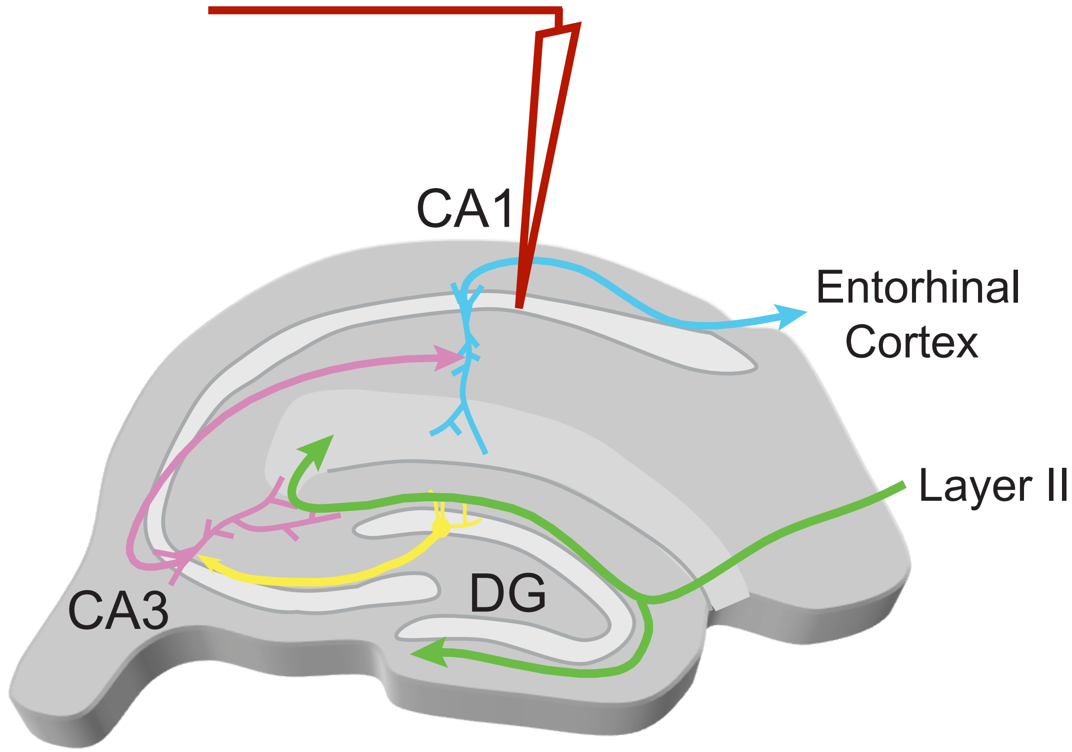
Short Communications

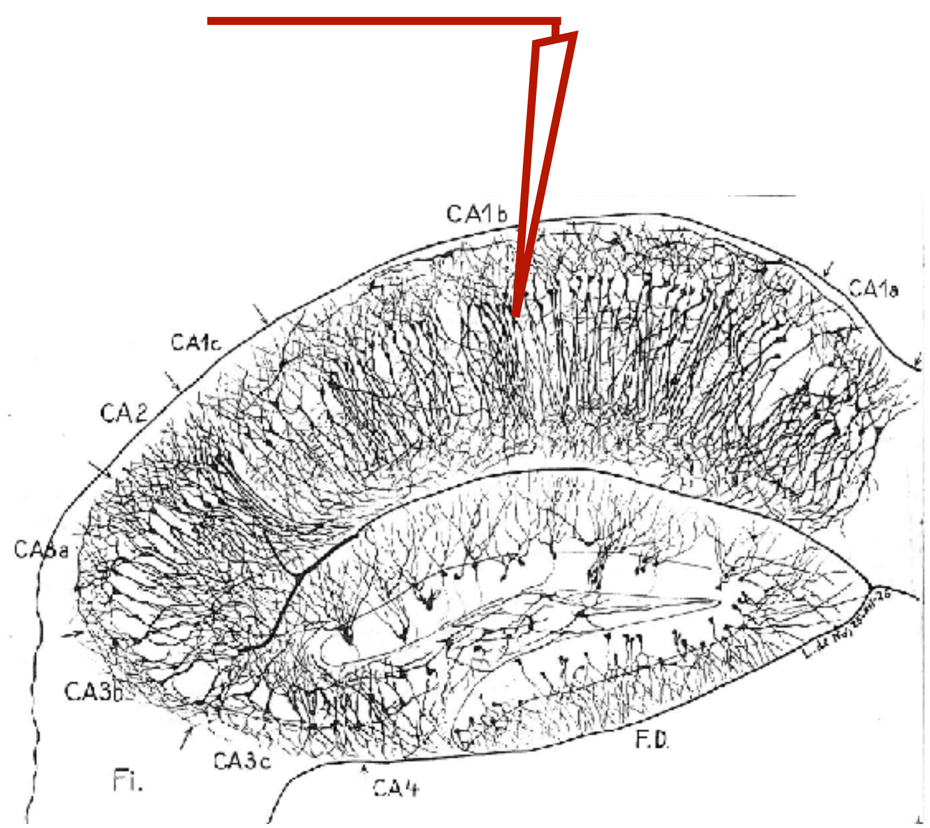
The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat



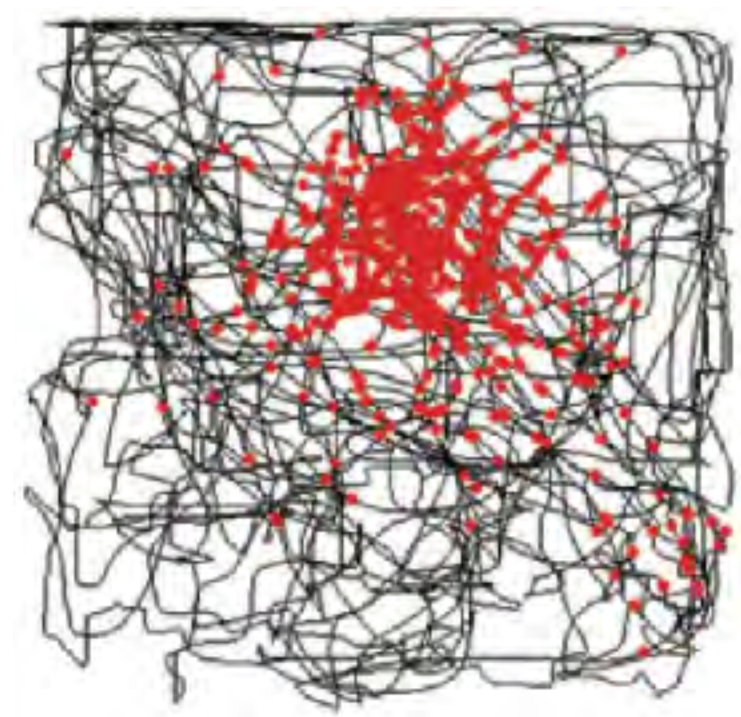
O'Keefe and Dostrovsky, 1971

Extensive progress has been made in understanding spatial learning



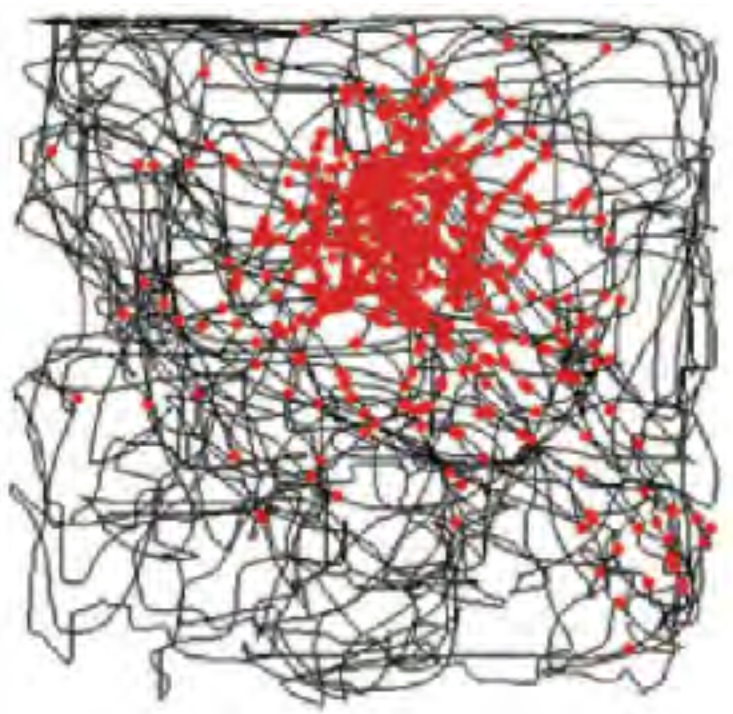


Extracellular Recording



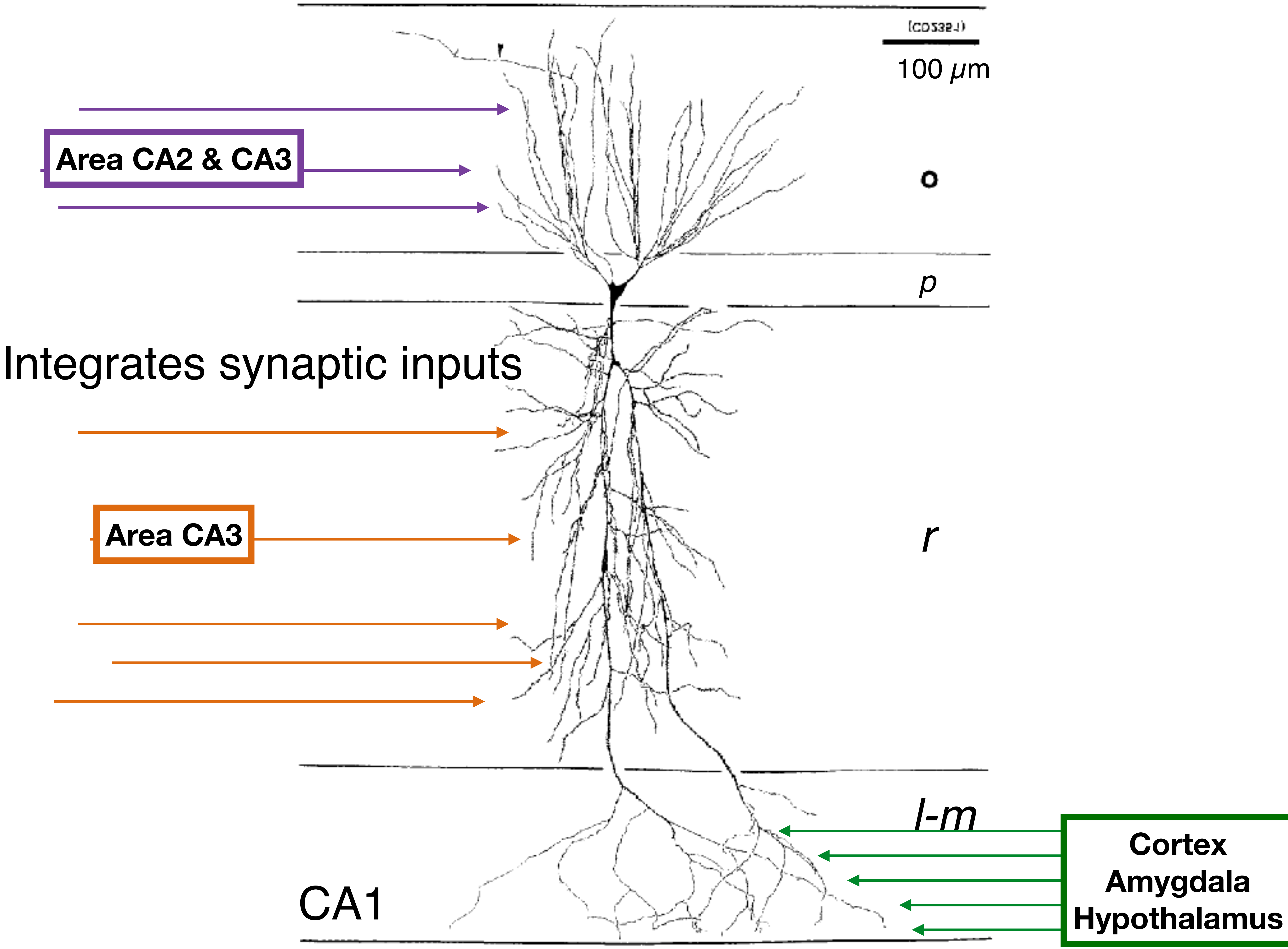
place field

Lorente de Nó *J Psychology and Neurologie*, 1934.

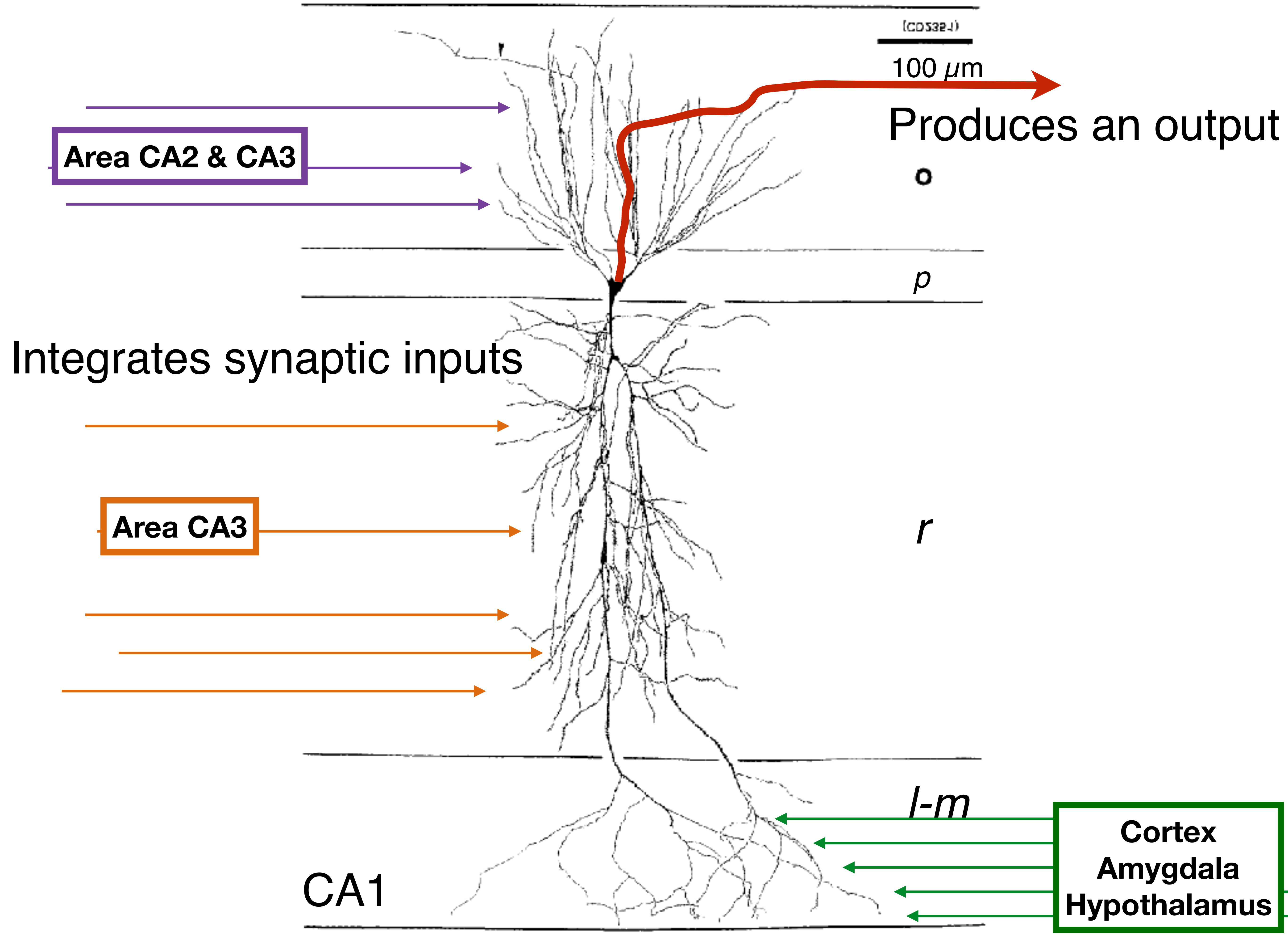


place field

= Action Potential Firing



Ishizuka et al, Journal of Comparative Neurobiology, 1995.



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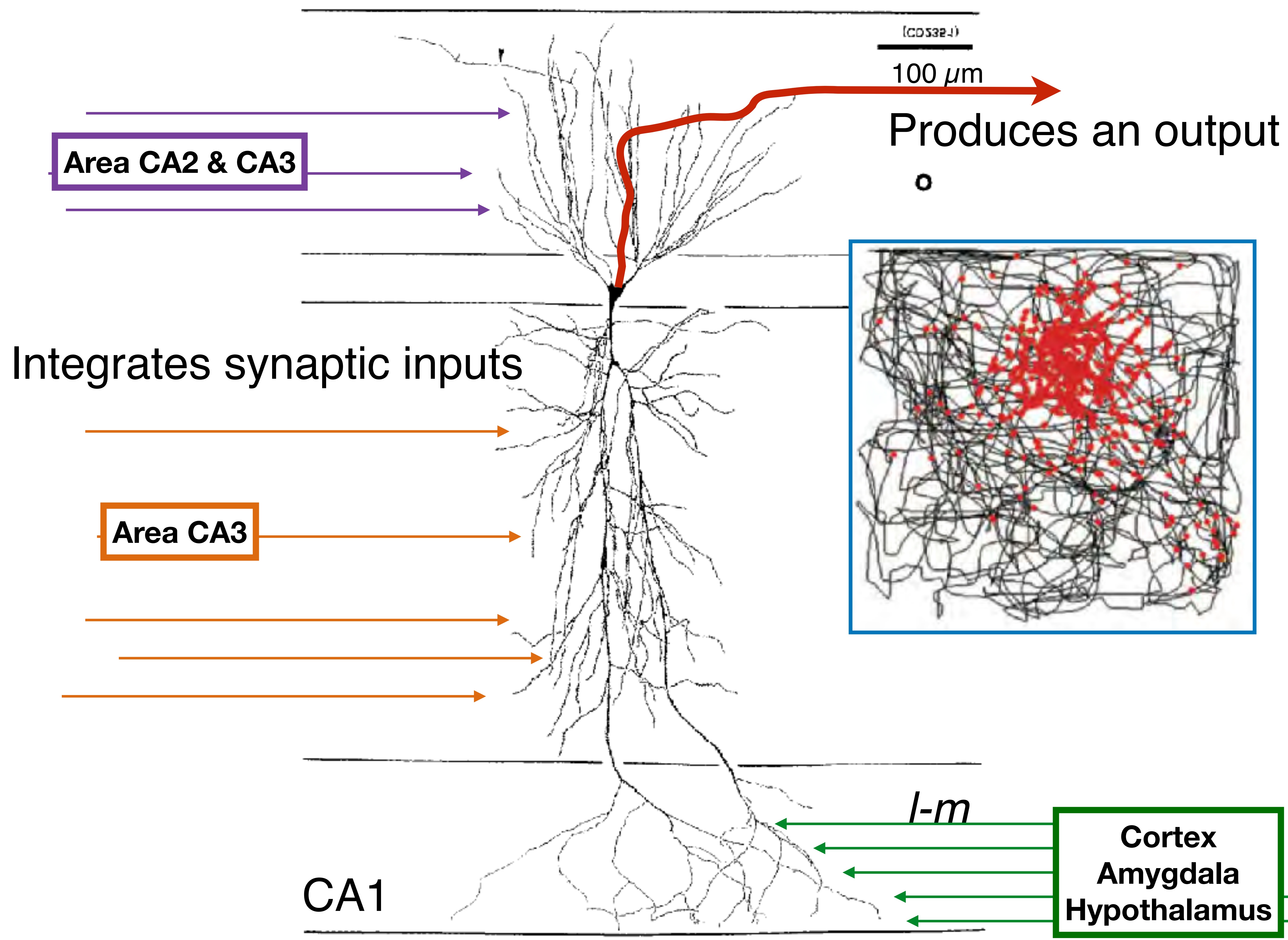
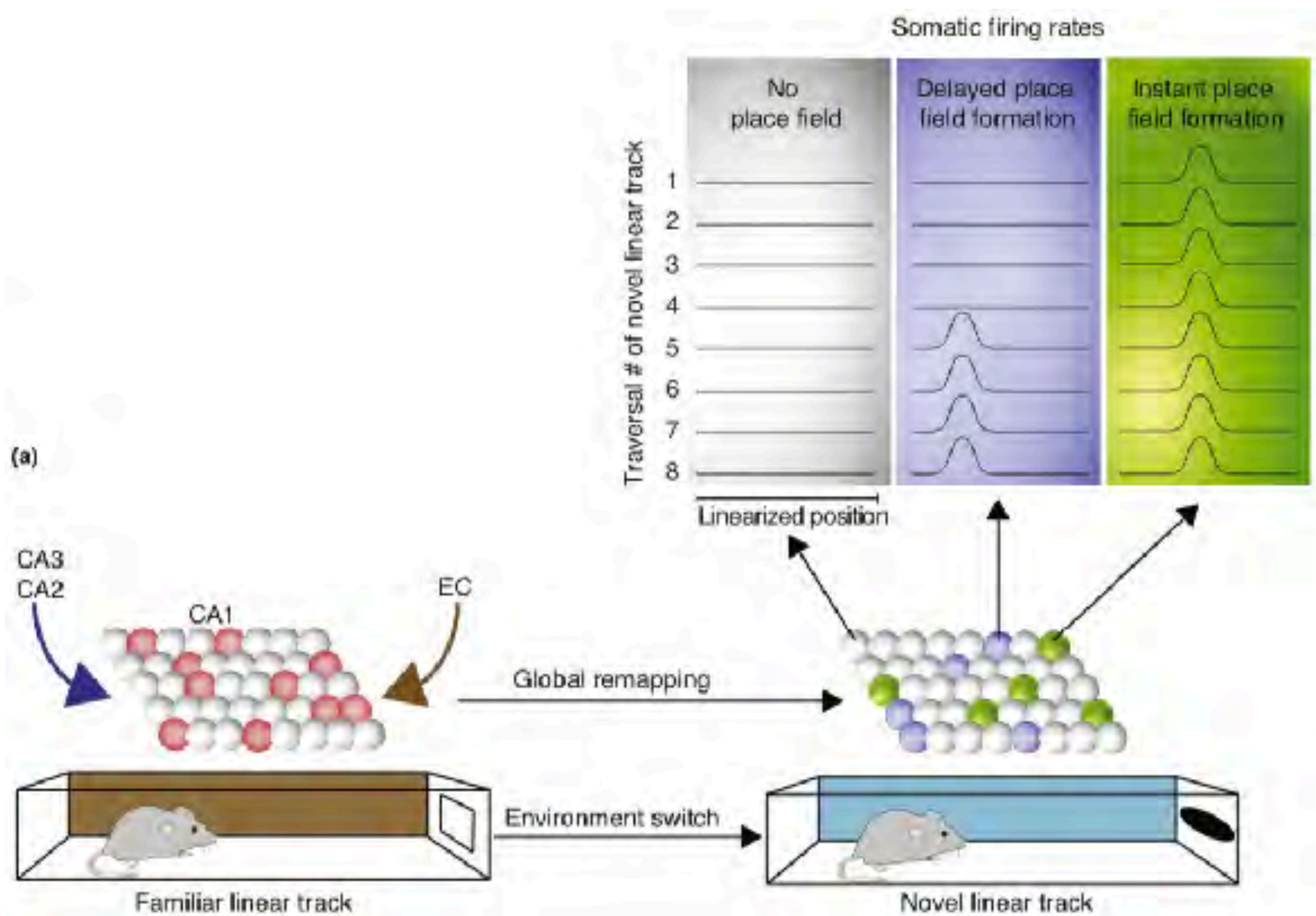


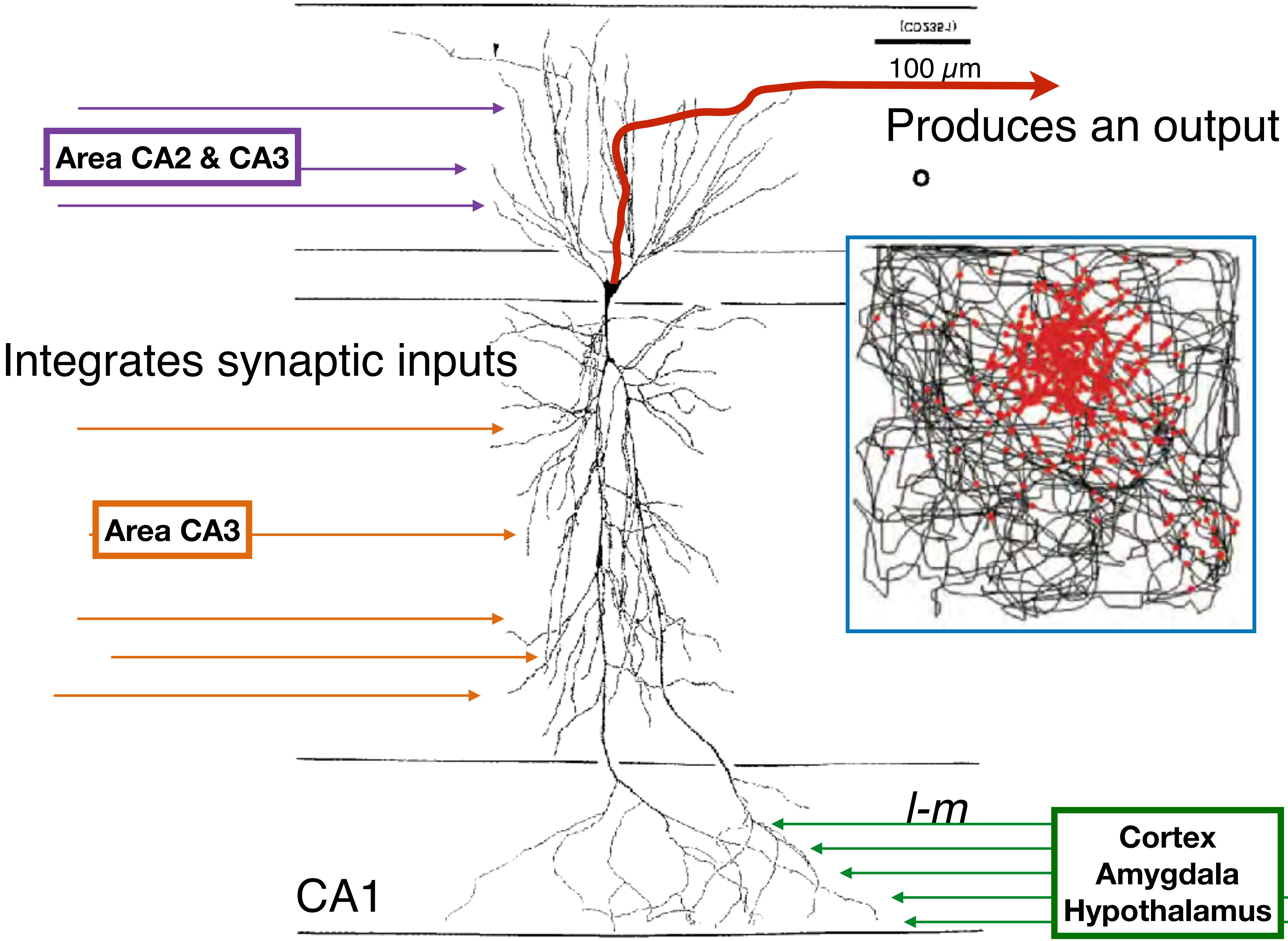
Ishizuka et al, Journal of Comparative Neurobiology, 1995.

Questions:

How do hippocampal neurons become encode information?

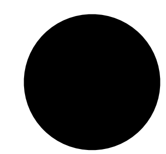


Sheffield & Dombeck *Current Opinion Neurobiology,* 2019



Ishizuka et al, Journal of Comparative Neurobiology, 1995.

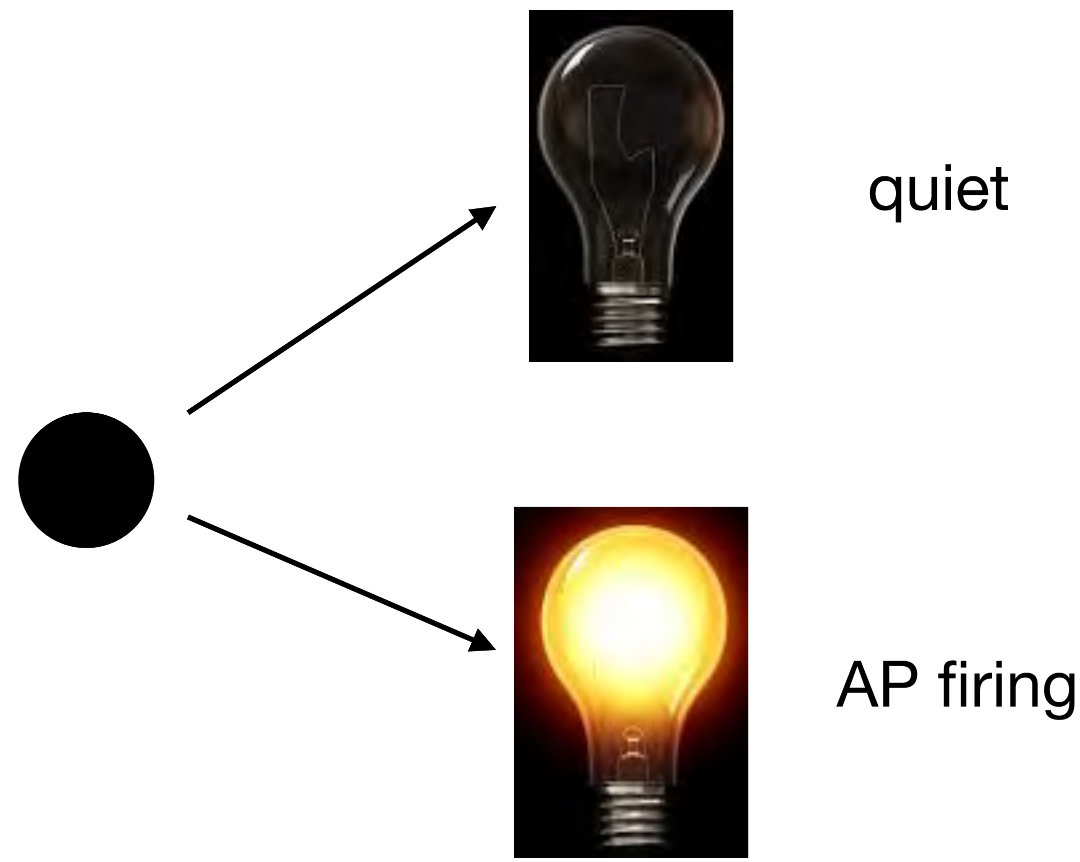
Logic operations



Point neuron
Single-node integrating neuron

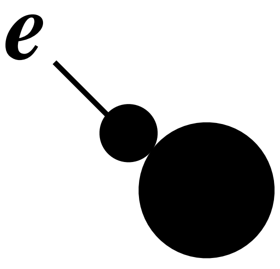
Logic operations

Point neuron



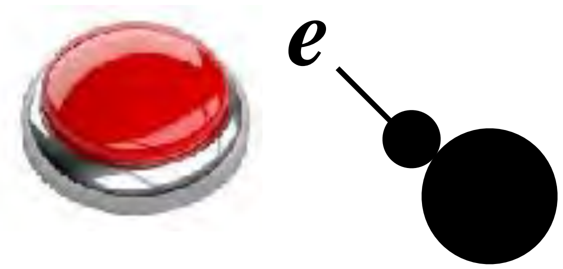
Logic operations

excitatory input

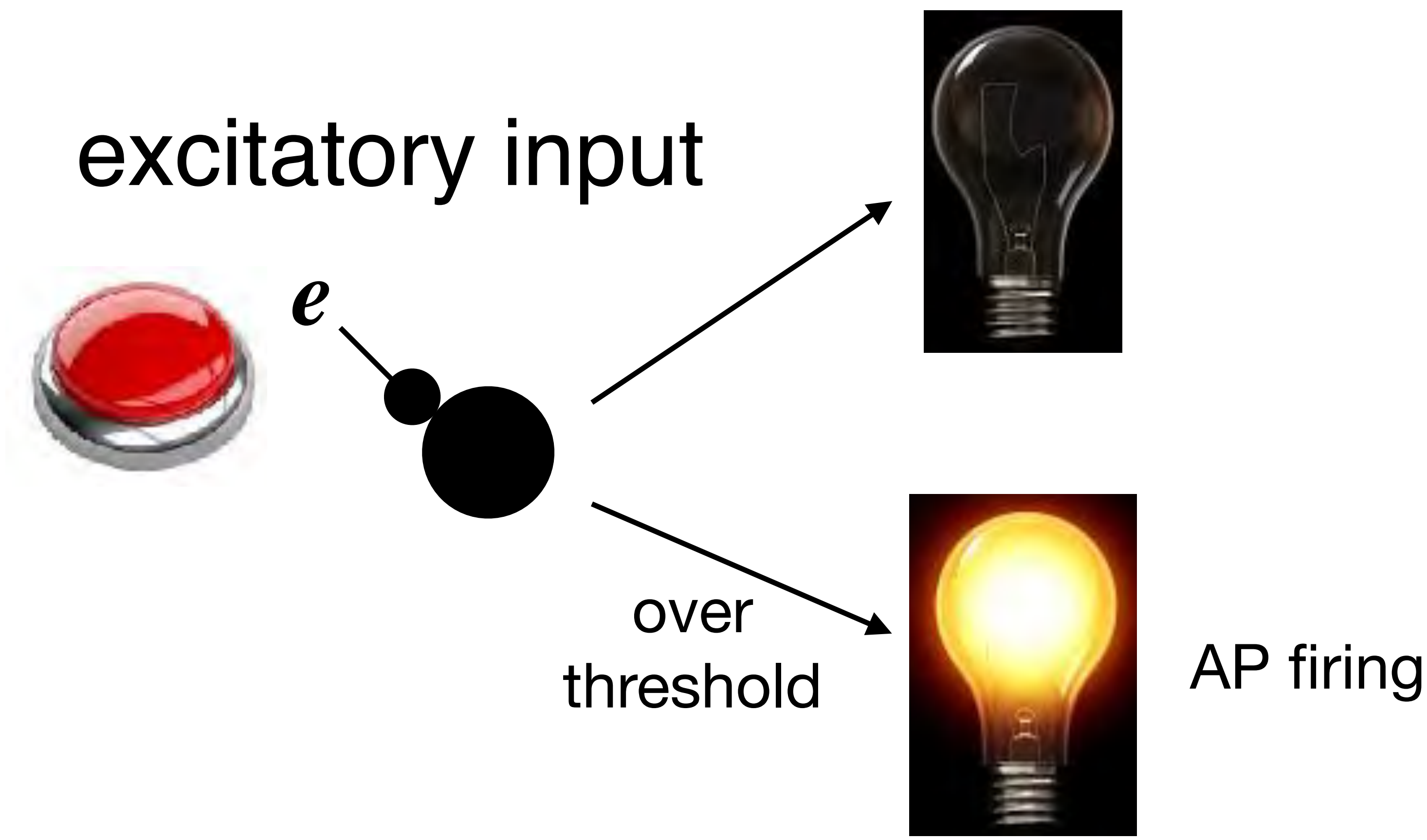


Logic operations

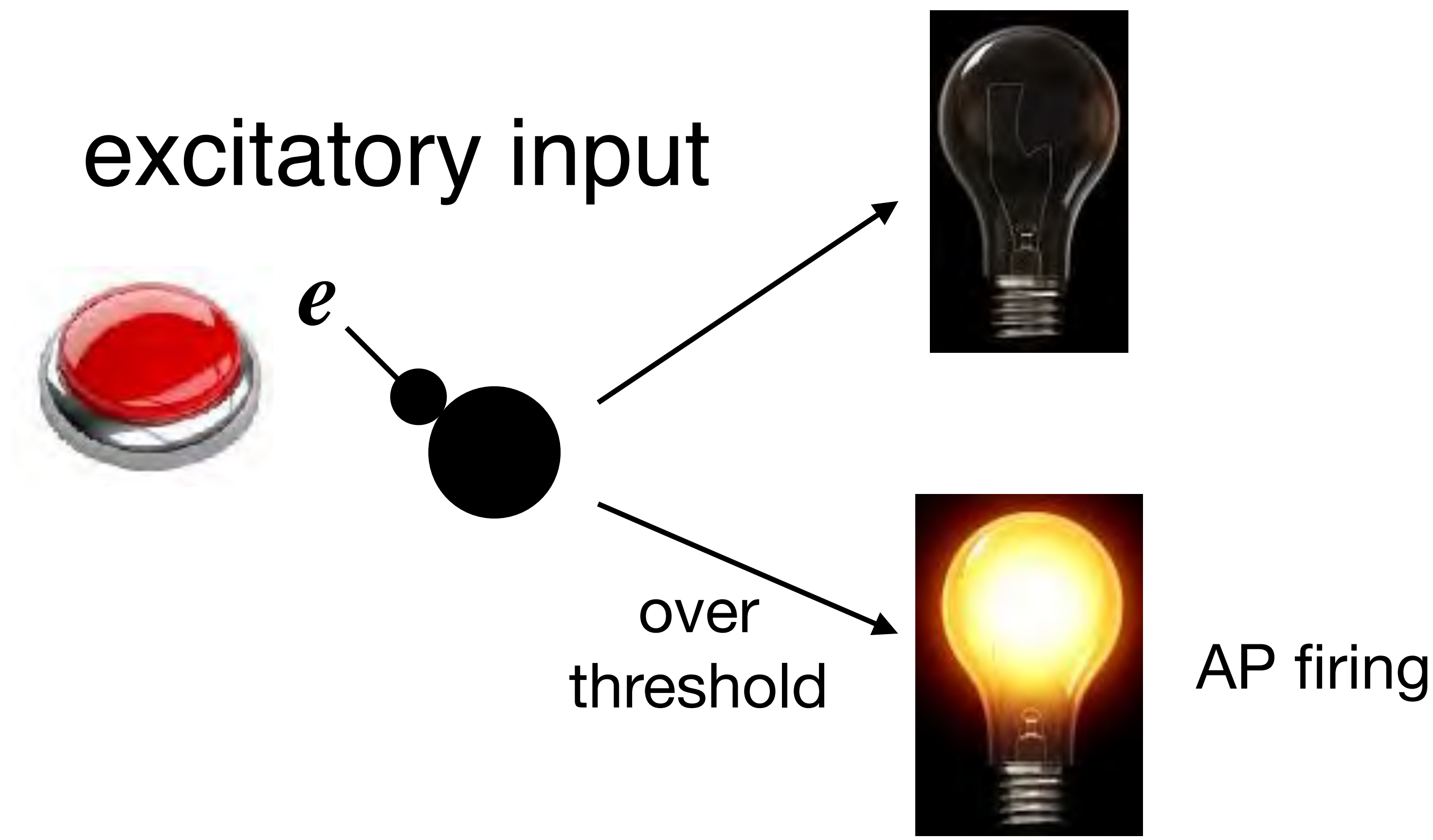
excitatory input



Logic operations



Logic operations



How does this happen?

Ionic currents and the membrane potential:

	Extracellular	Intracellular
Na^+	150	15
K^+	3	140
Cl^-	130	8
A^-	25	147

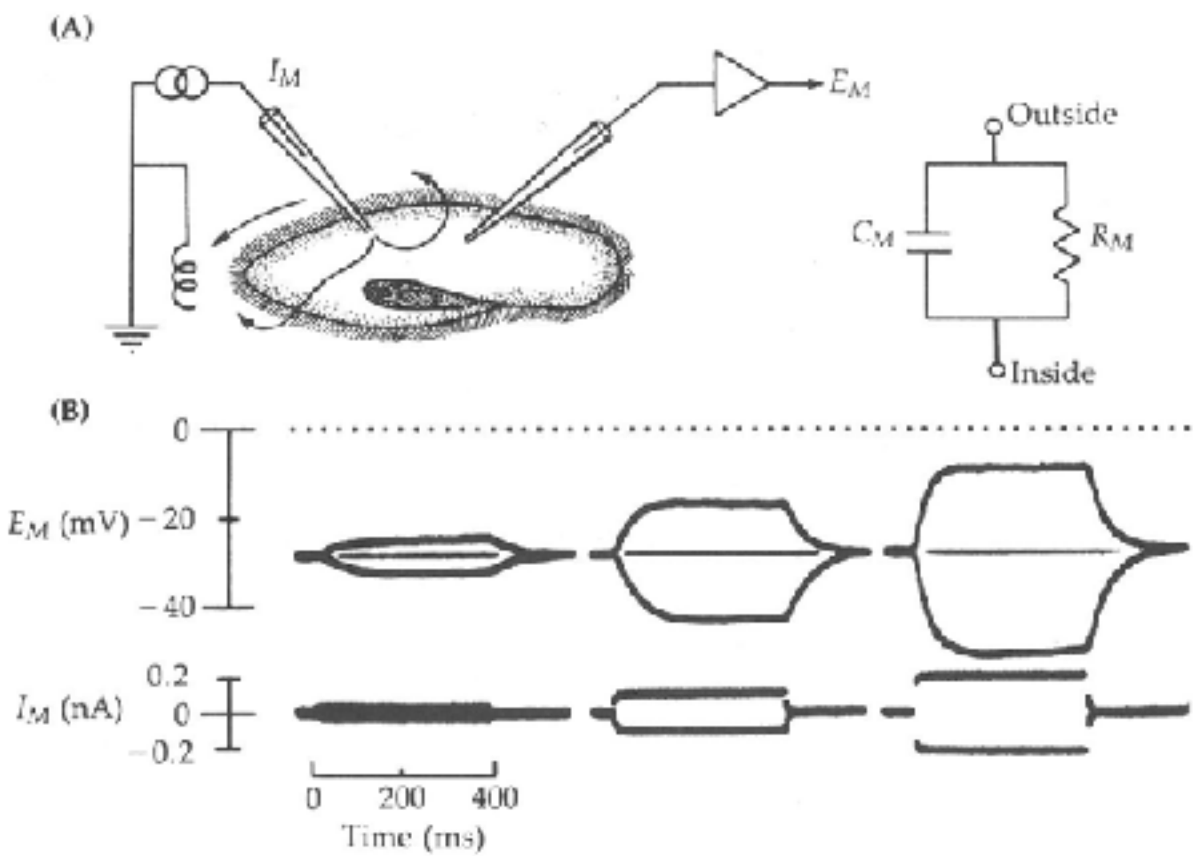
$$E_{Na} = 58 \log \frac{[Na]_o}{[Na]_i}$$

GHK equation: $$V_m = 58 \log \frac{p_{Na}[Na]_o + p_K[K]_o + p_{Cl}[Cl]_i}{p_{Na}[Na]_i + p_K[K]_i + p_{Cl}[Cl]_o}$$

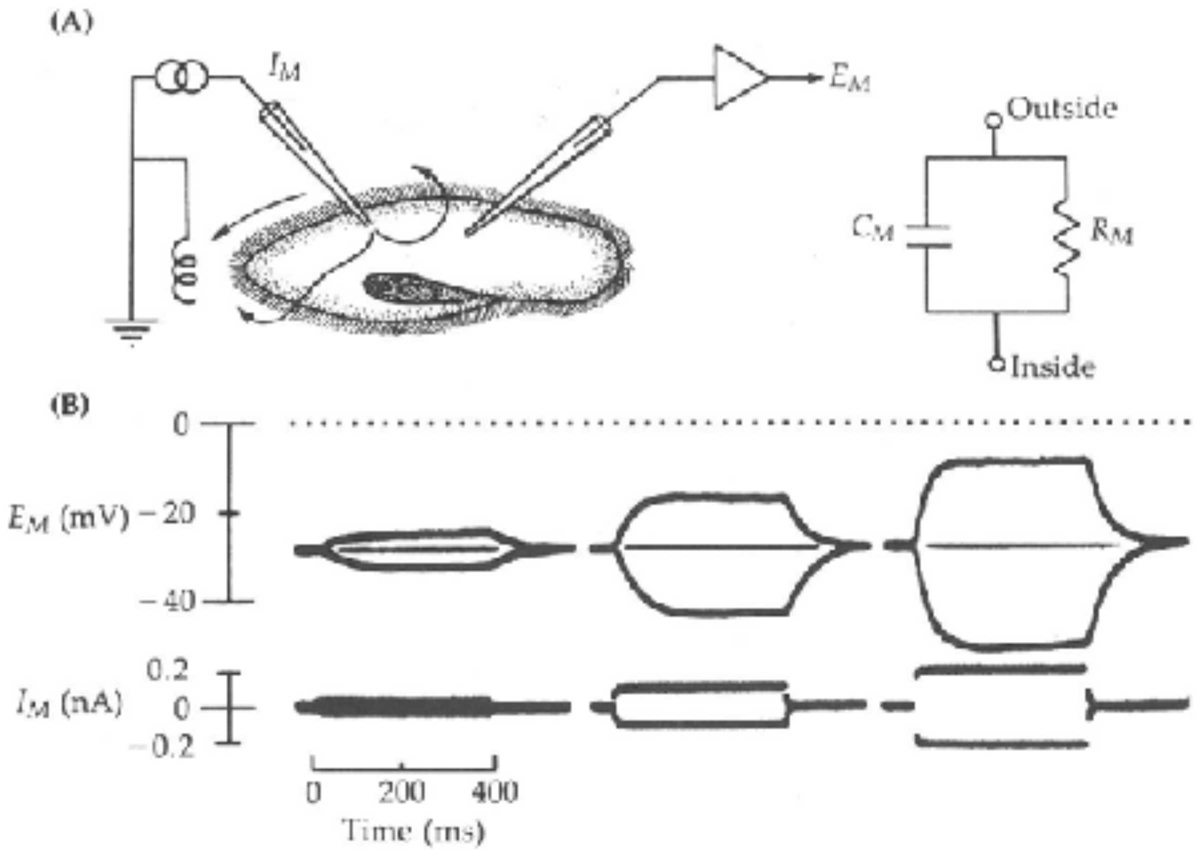
p : membrane permeability

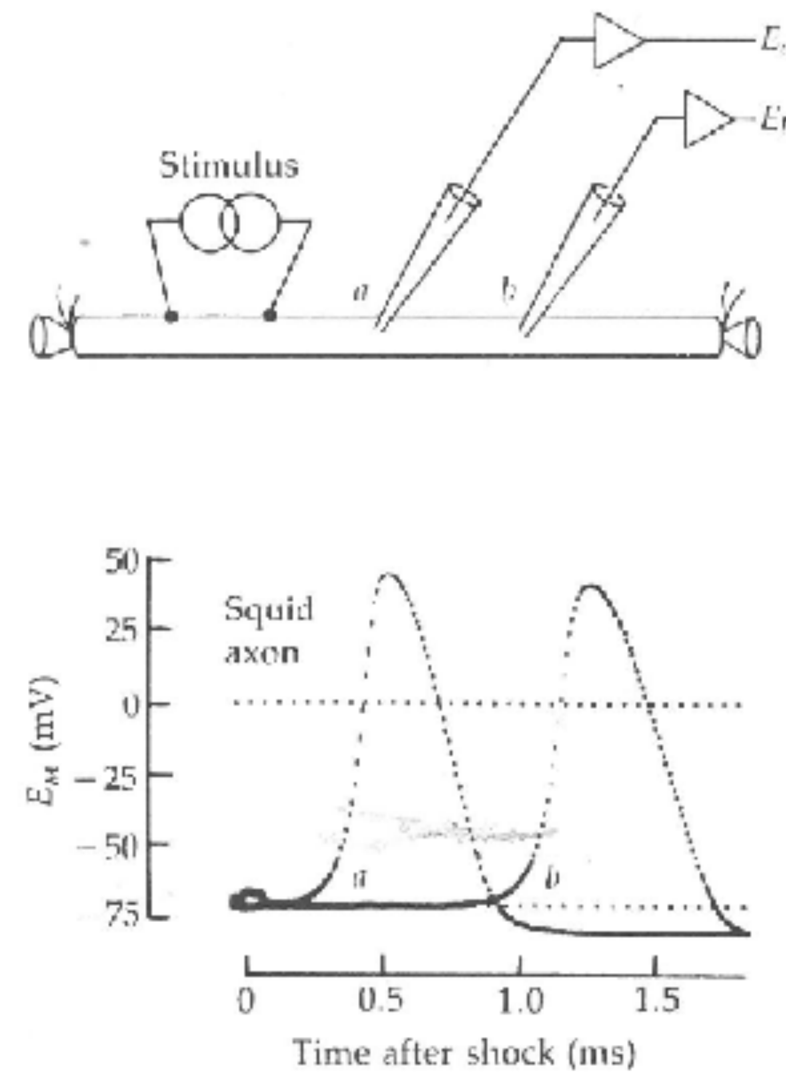
Goldman, DE, 1943, *JGP* 27:37-60
Hodgkin AL and Katz B 1949. *J physiol.* 180:37-77

Electrical properties of cell membranes



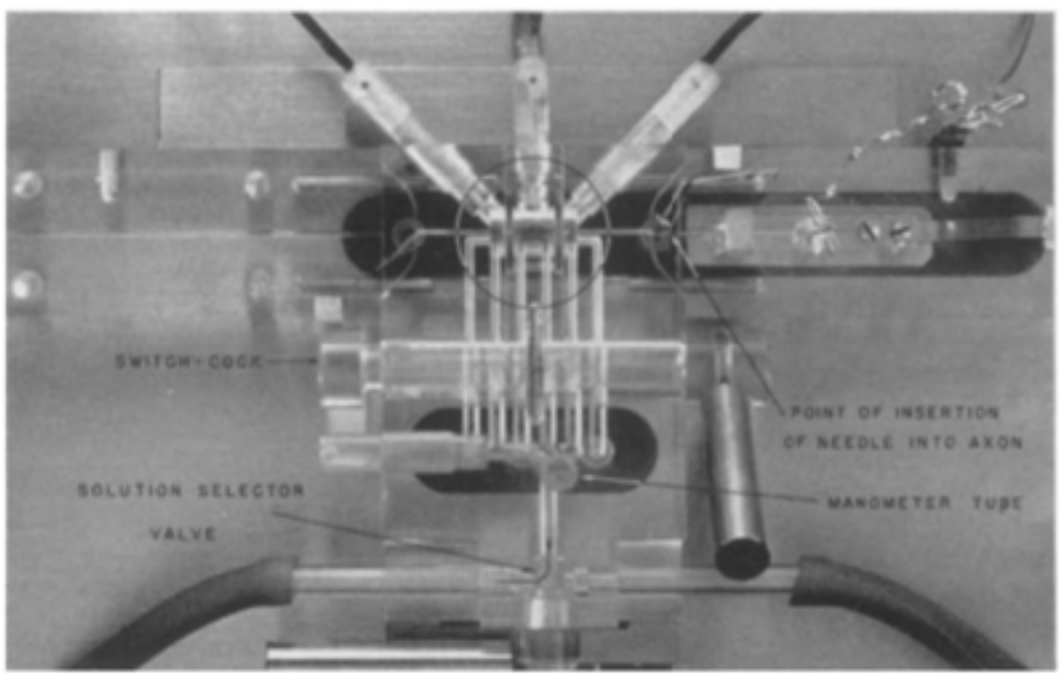
Electrical properties of cell membranes

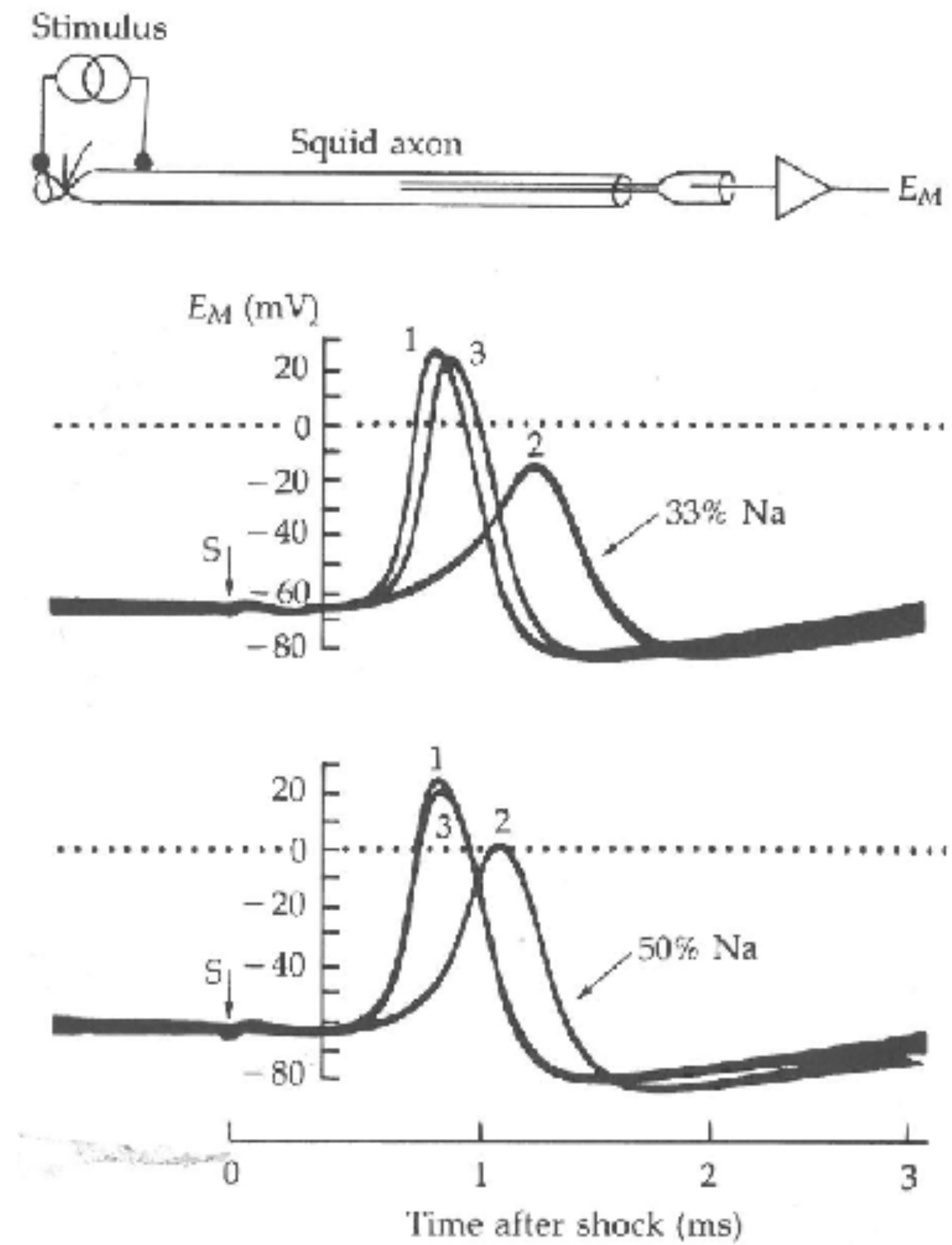




squid axon

Ionic basis of action potential

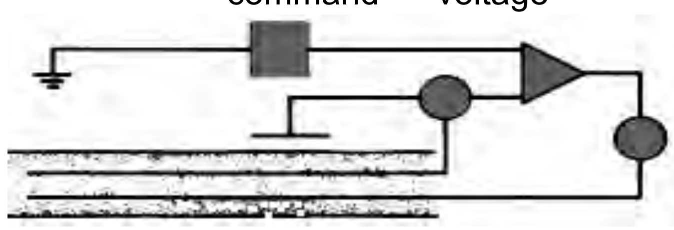


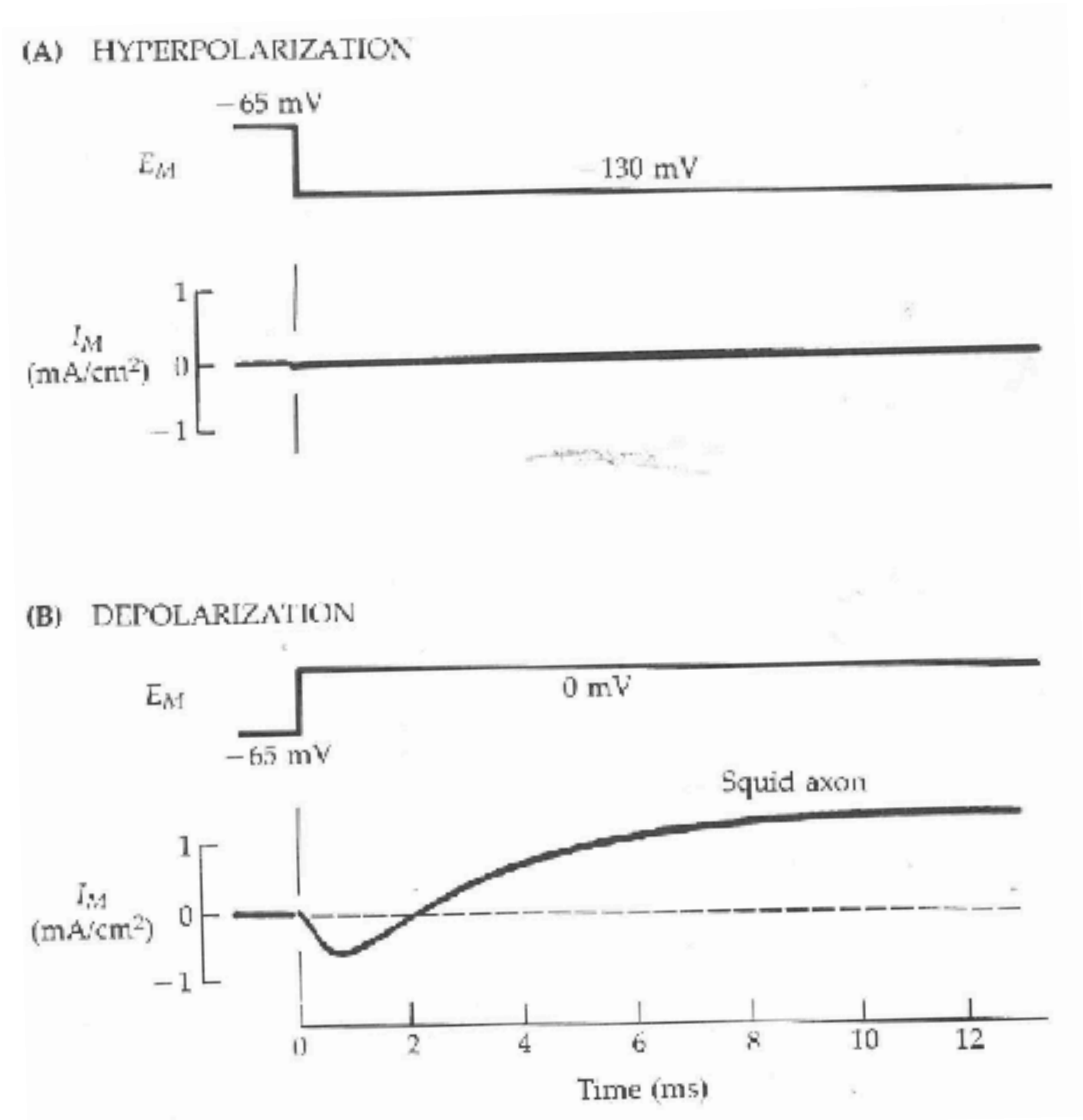


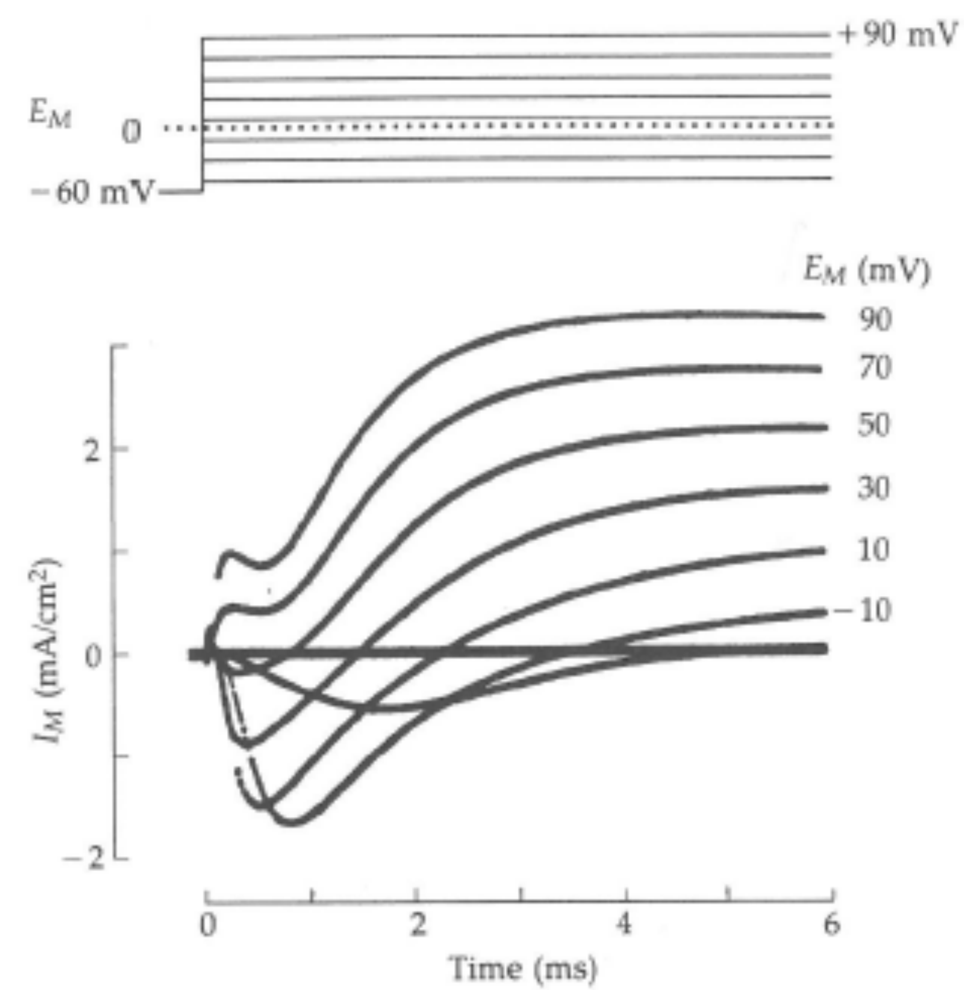
Hodgkin & Huxley, 1951

Ionic basis of action potential

Voltage clamp

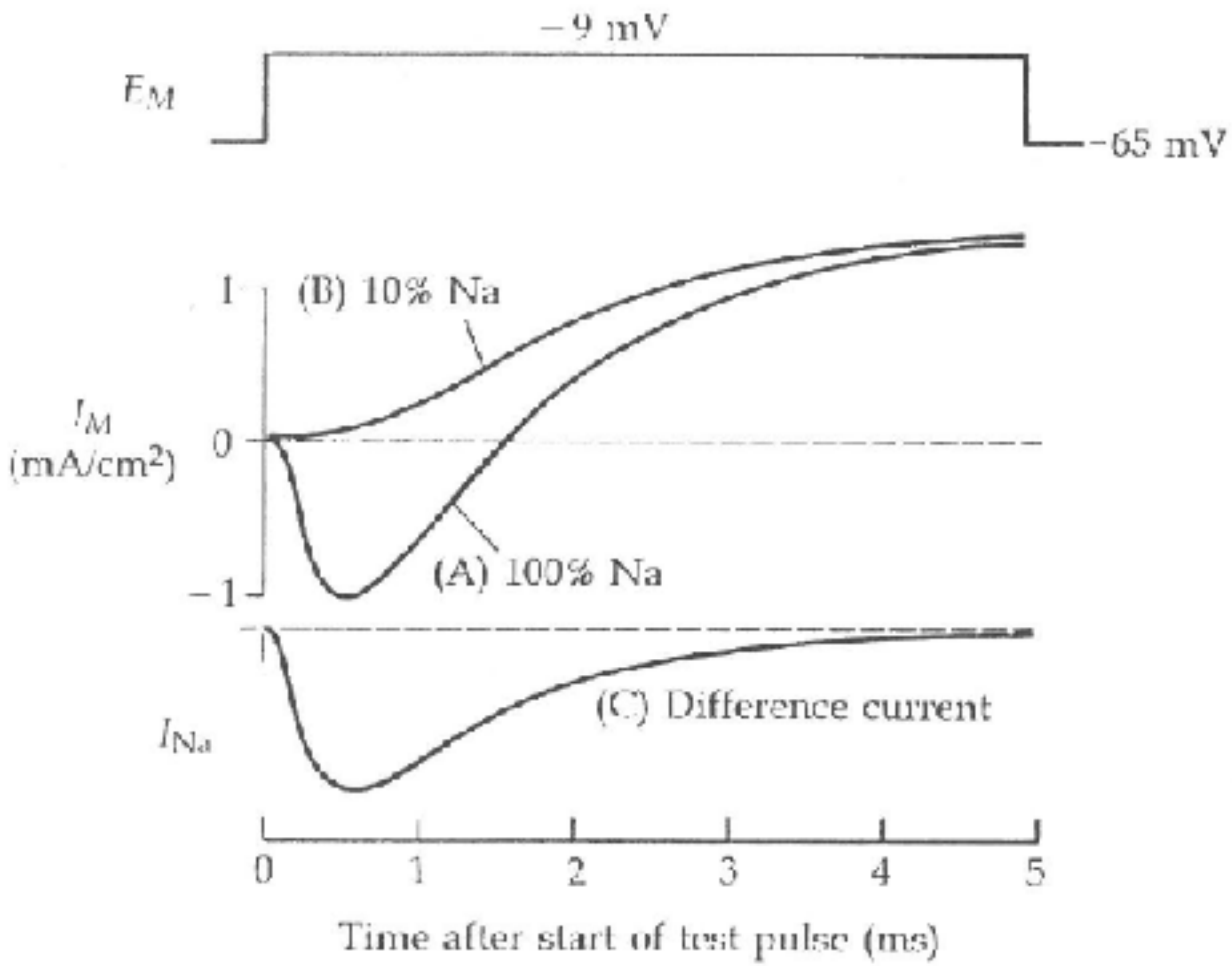






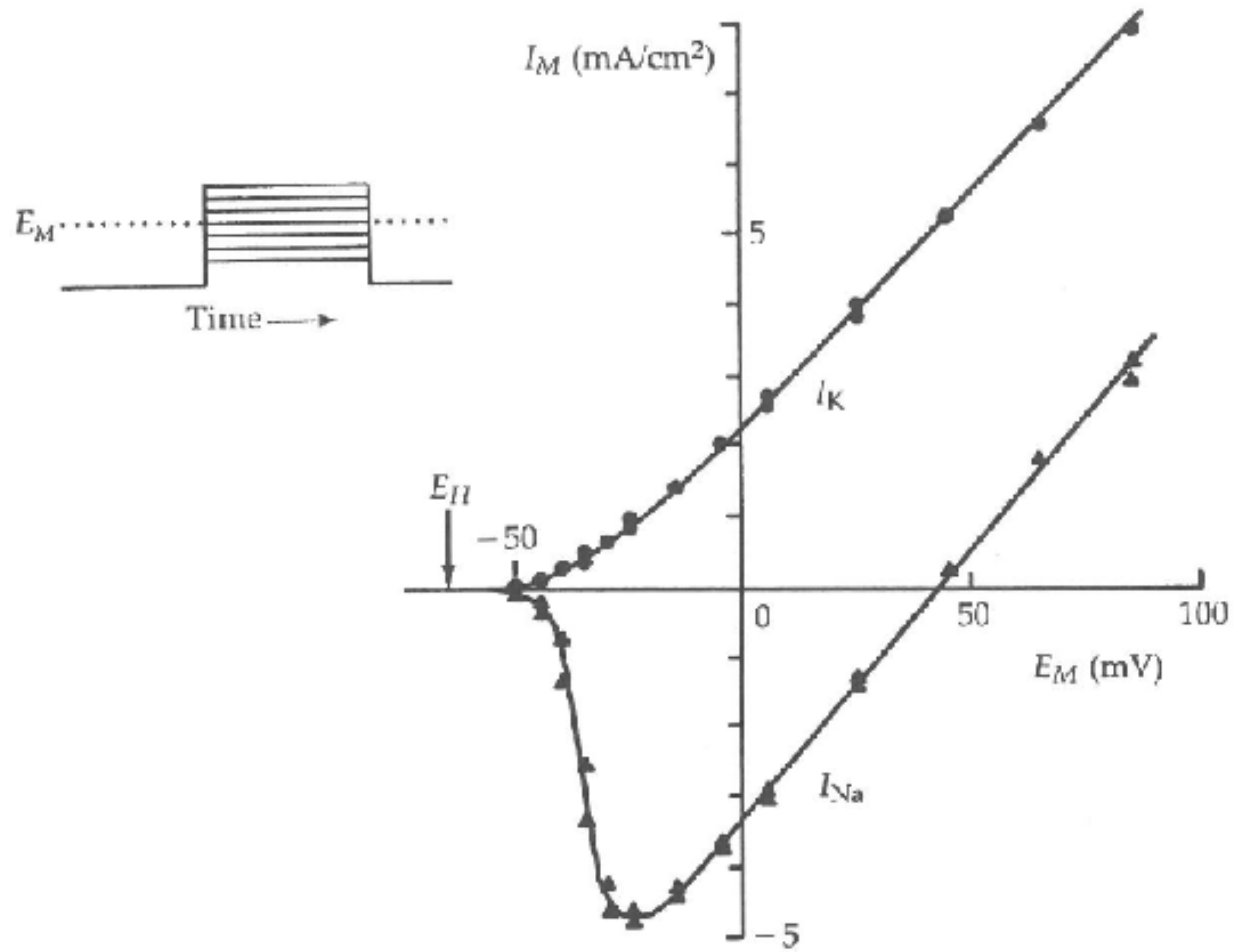
Hodgkin & Huxley, 1951

Ionic basis of action potential



Hodgkin & Huxley, 1951

Ionic basis of action potential

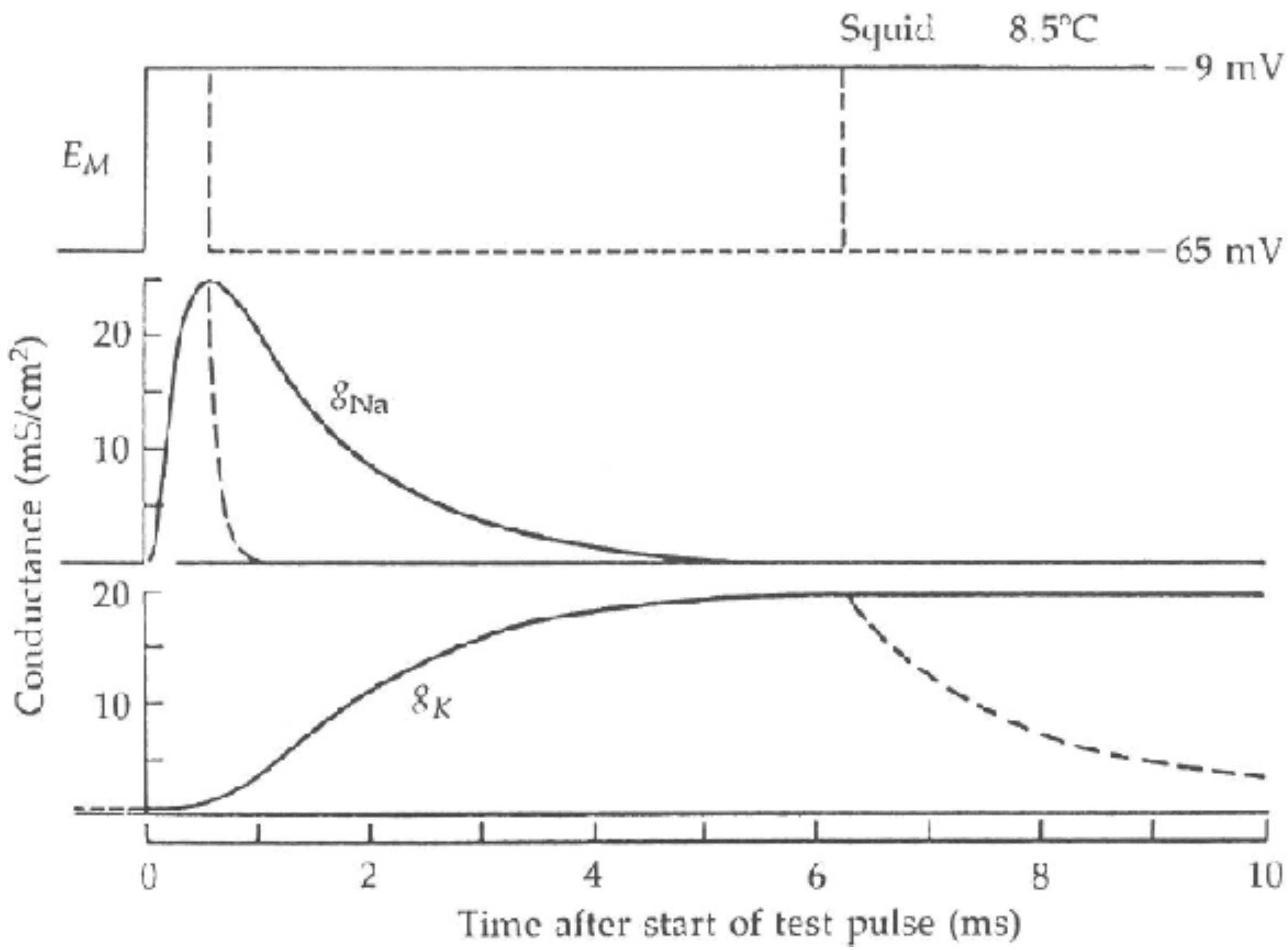


$$V = I\,R$$

$$V = \frac{I}{g}$$

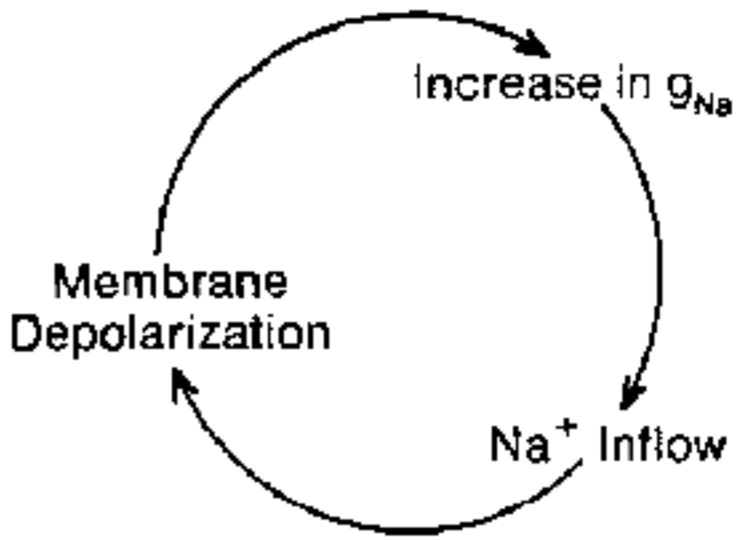
Hodgkin & Huxley, 1951

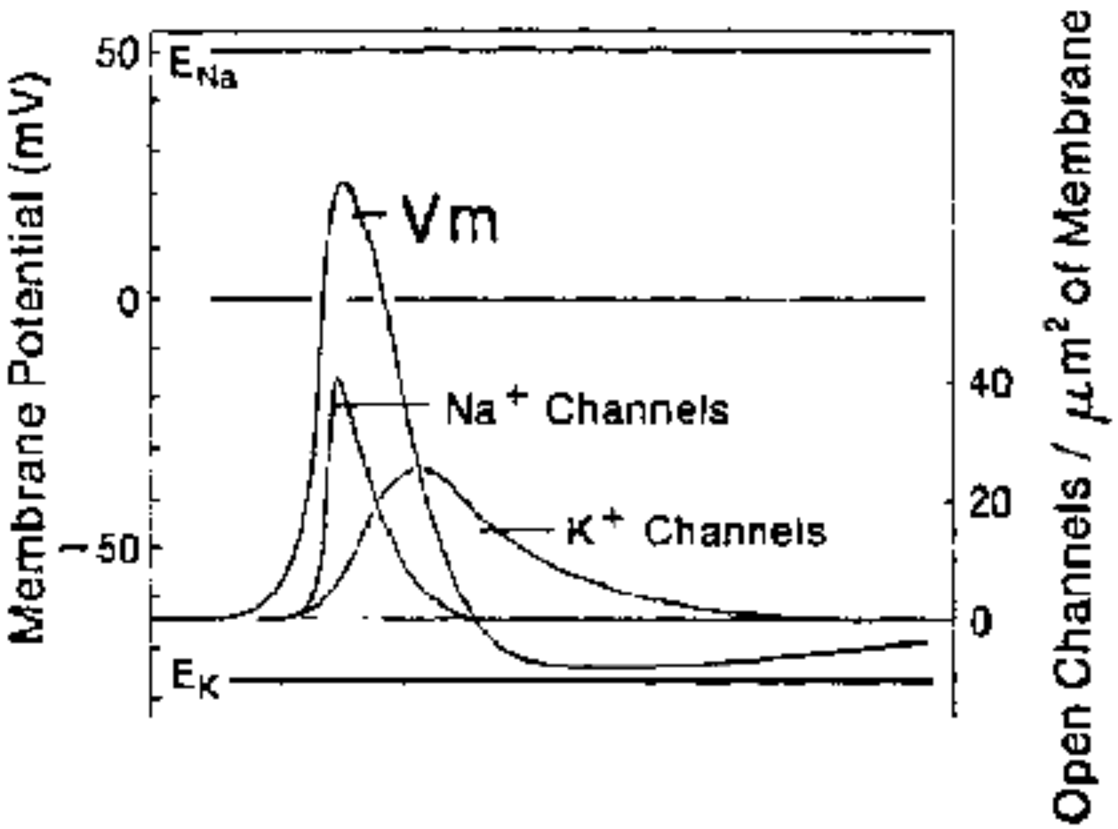
Ionic basis of action potential



Hodgkin & Huxley, 1951

Ionic basis of action potential





Hodgkin & Huxley, 1951

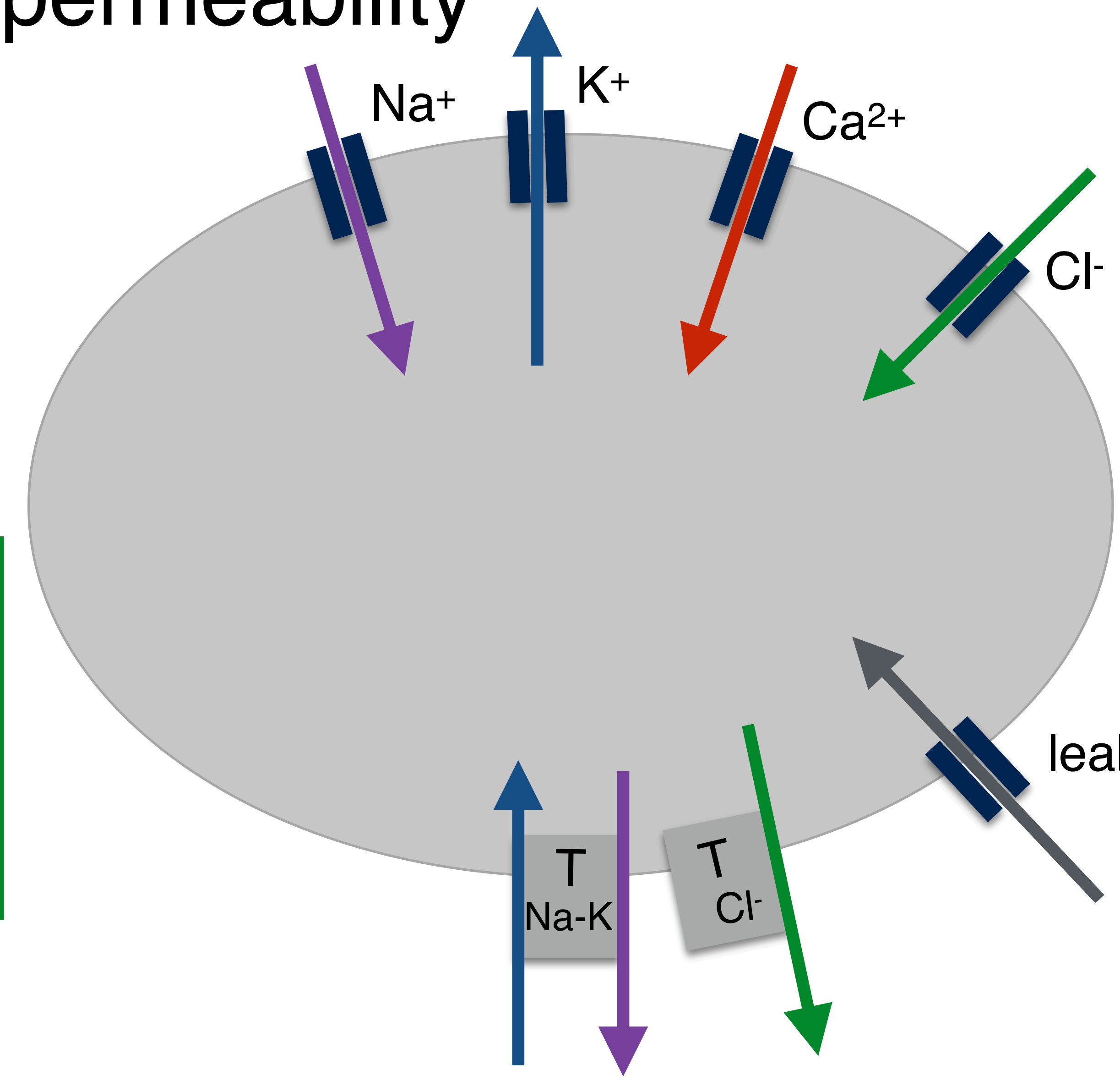
Transient changes in membrane permeability

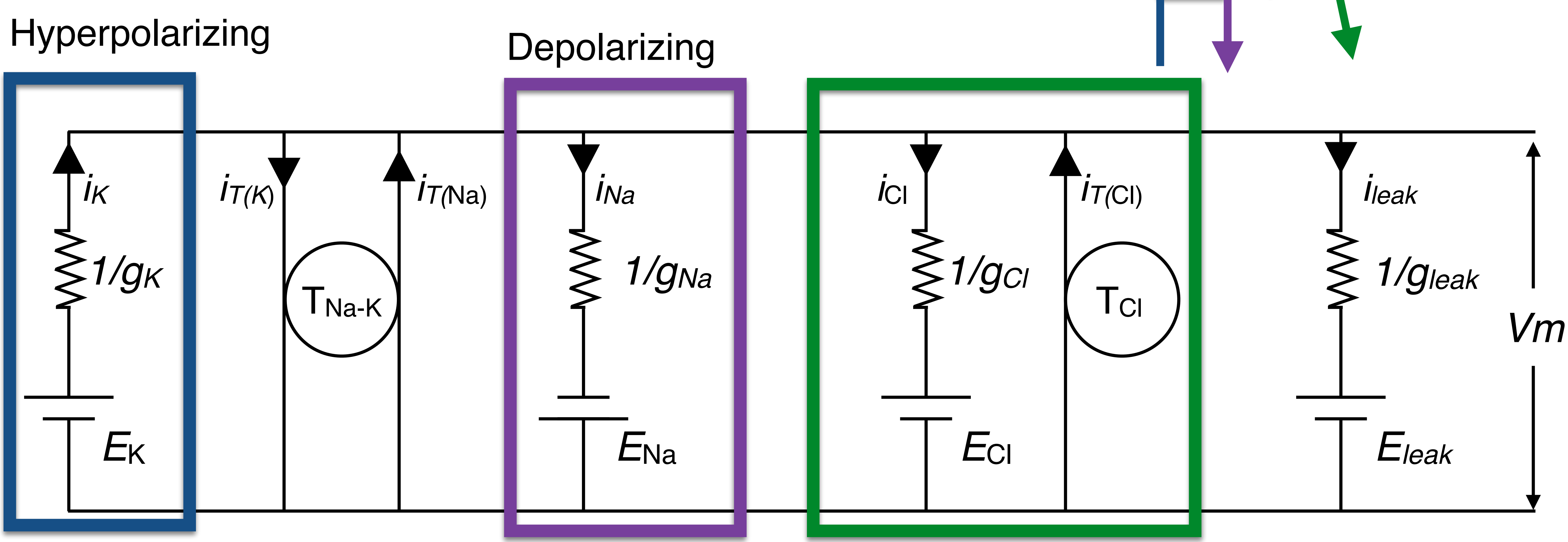
E_{Ca} is around 120 - 150 mV : Depolarization

Cl^- is a bit quirky…

E_{Cl} is quite close to Vm, and can change.

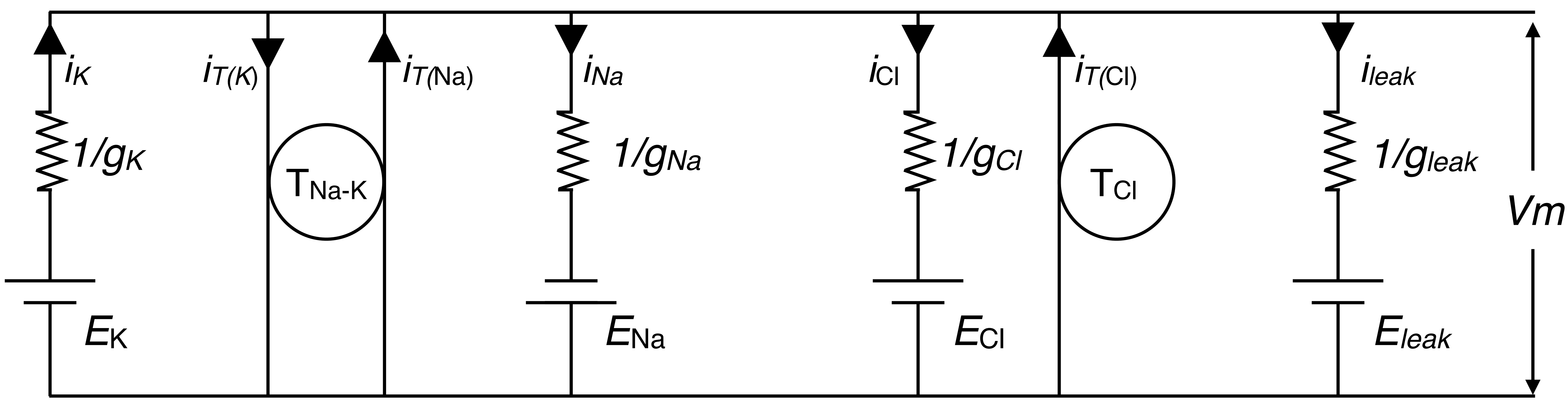
Early in development, for example, an increase in Cl^- permeability is depolarizing, whereas during adulthood it is hyperpolarizing.





Resting membrane potential:

Electrical model of the steady-state cell membrane



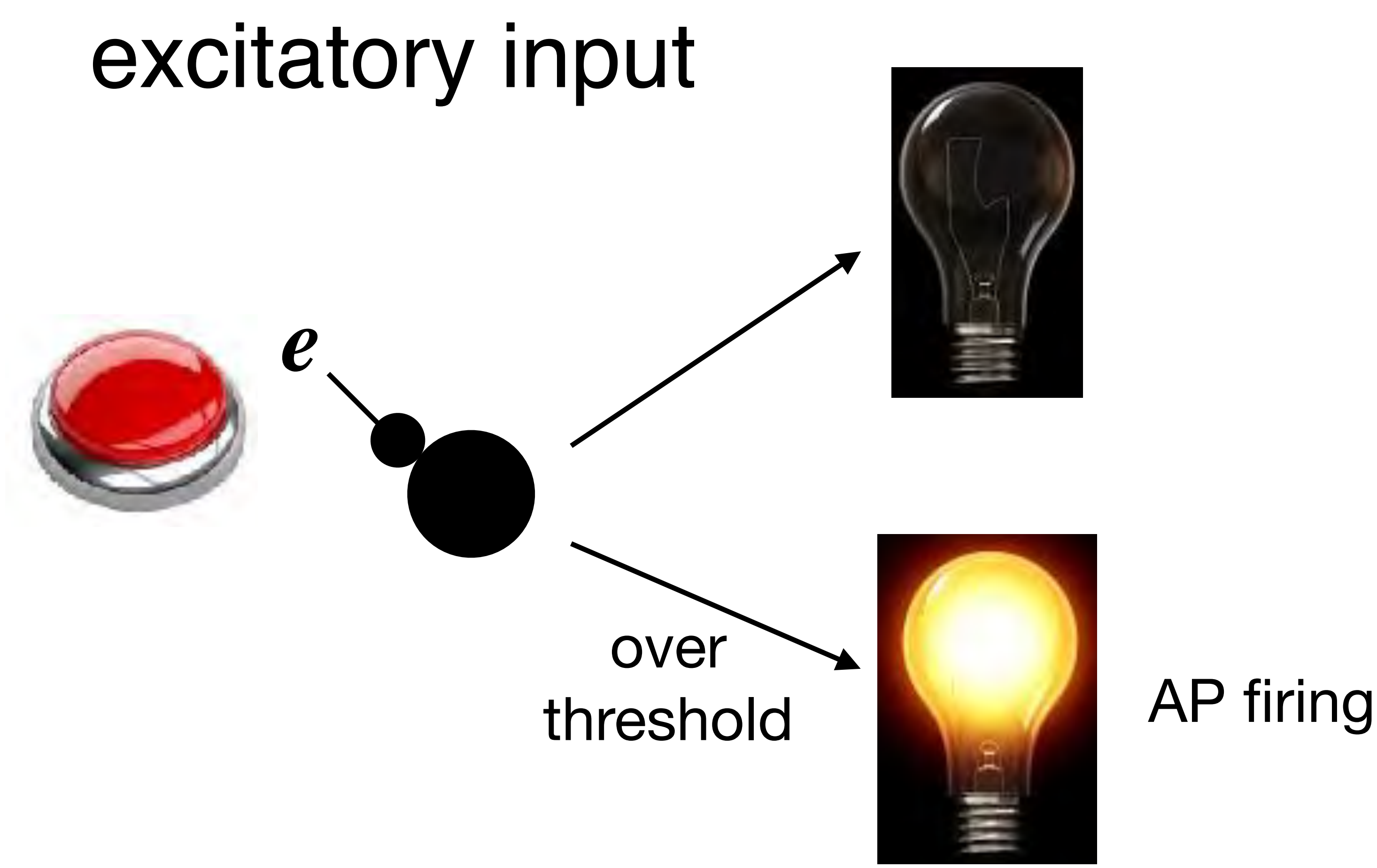
Other contributors to the resting membrane potential:

Sodium-Potassium ATPase
Chloride transporters
Leak currents

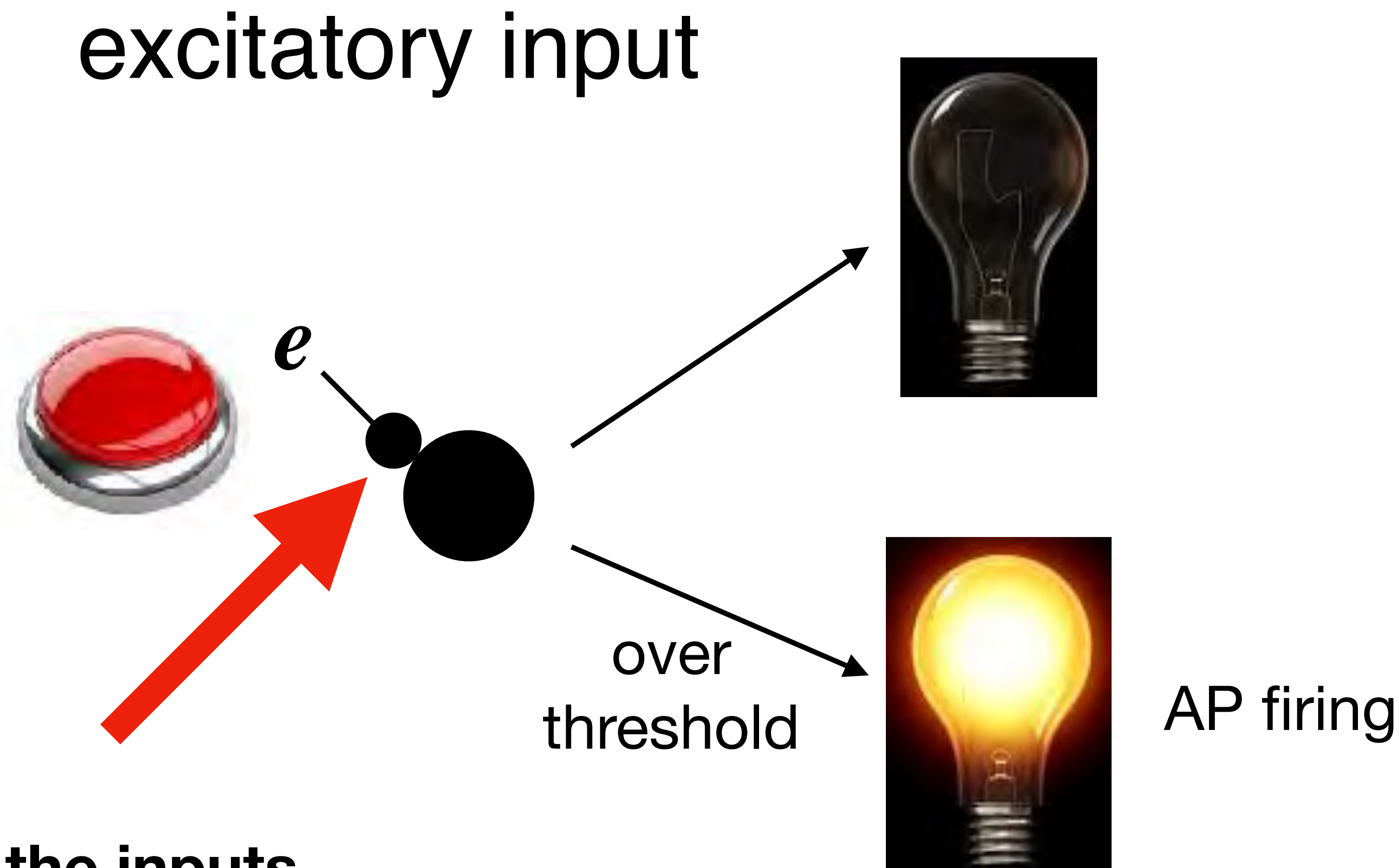
Ion channels

Ion Selectivity	*Rev, mV*	*Pharmacological nomenclature*		*Genes*
Na^+	+40 to +60	I_{Nat} , I_{Nap}	Nav1, Nav2, …Nav12.X	*scn1a, scn1b, scn2a,* ect.
K^+	-90 to -100	I_C I_A I_K I_{DR} I_{AHP}	Kv1, Kv2, Kv3, Kv4.X…	*kcna1, kcna2, kcnb, ect.*
Ca^{2+}	+120 to +150	I_T I_L I_N I_R $I_{P/Q}$	Cav1, Cav2, Cav3.X	*cacna1a, cacna1g, etc*
Cl^-	-70 to -75***	I_{Cl}	CLC1, CLC2, CLC3, CLC4	*clcn1, clcn2, etc*
$Na^+/K^+/Ca^{2+}$	-30	I_h	HCN1, HCN2, HCN3, HCN4	*hcn1, hcn2, hcn3, hcn4*
Na^+ or K^+	+40 or -90	I_{leak}	NALCN, ect … and K2P channels (TREK, ect)	*nalcn, kcnk2, ect*

Logic operations



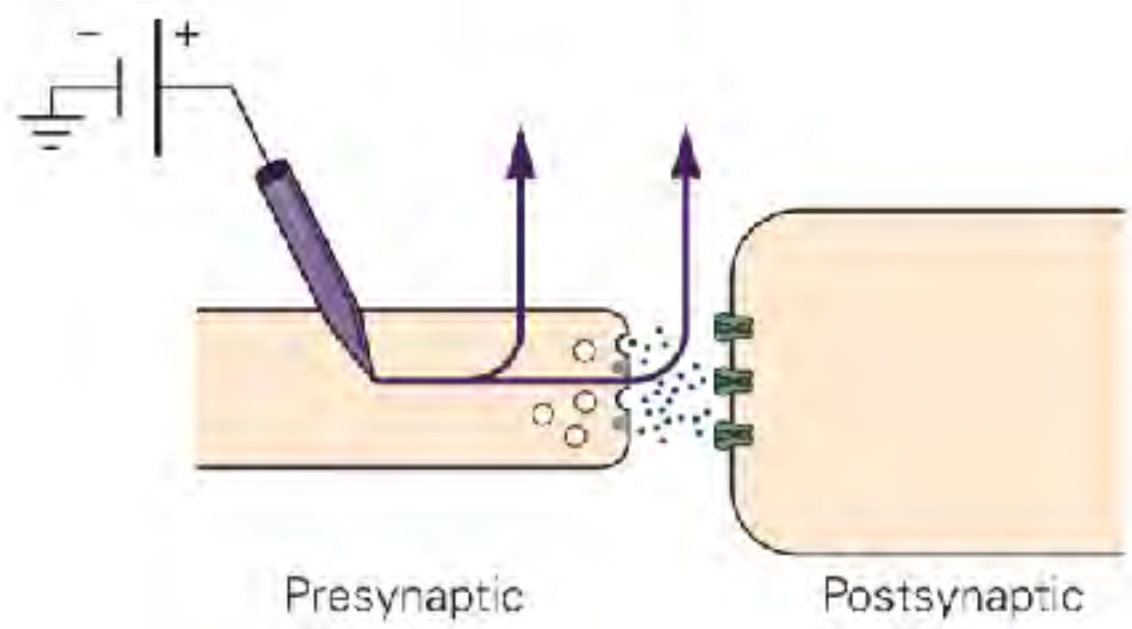
Logic operations



Now let's talk about the inputs

Synaptic transmission!!

Chemical Synapses

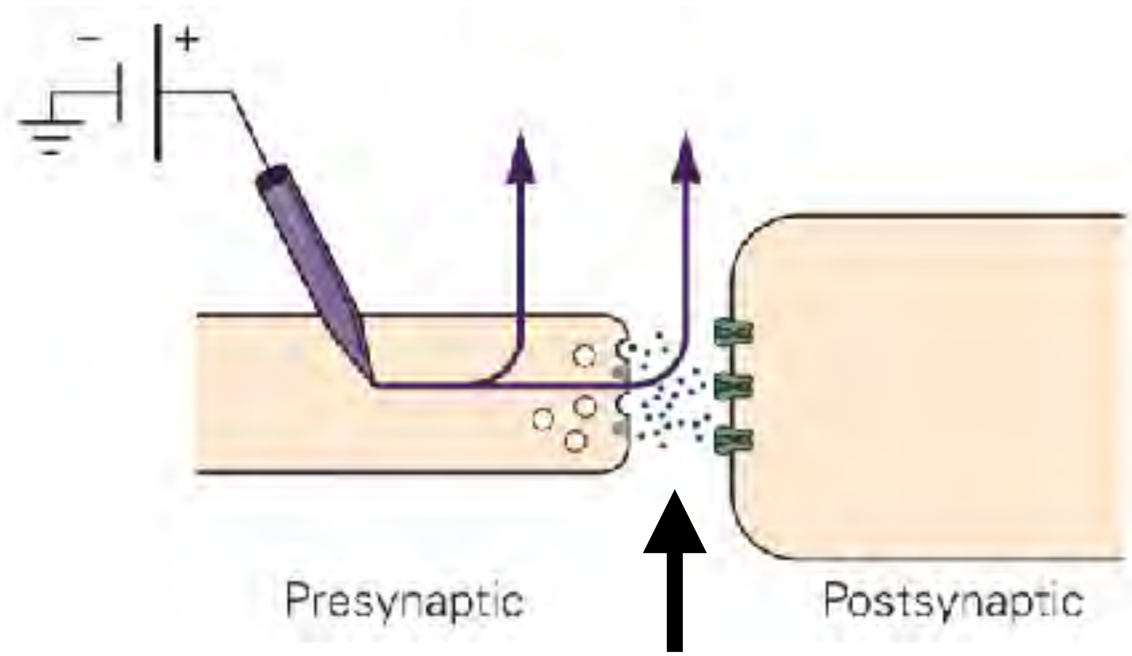


1) Fast, ionotropic transmission

2) Slower, metabotropic transmission

Synaptic transmission!!

Chemical Synapses

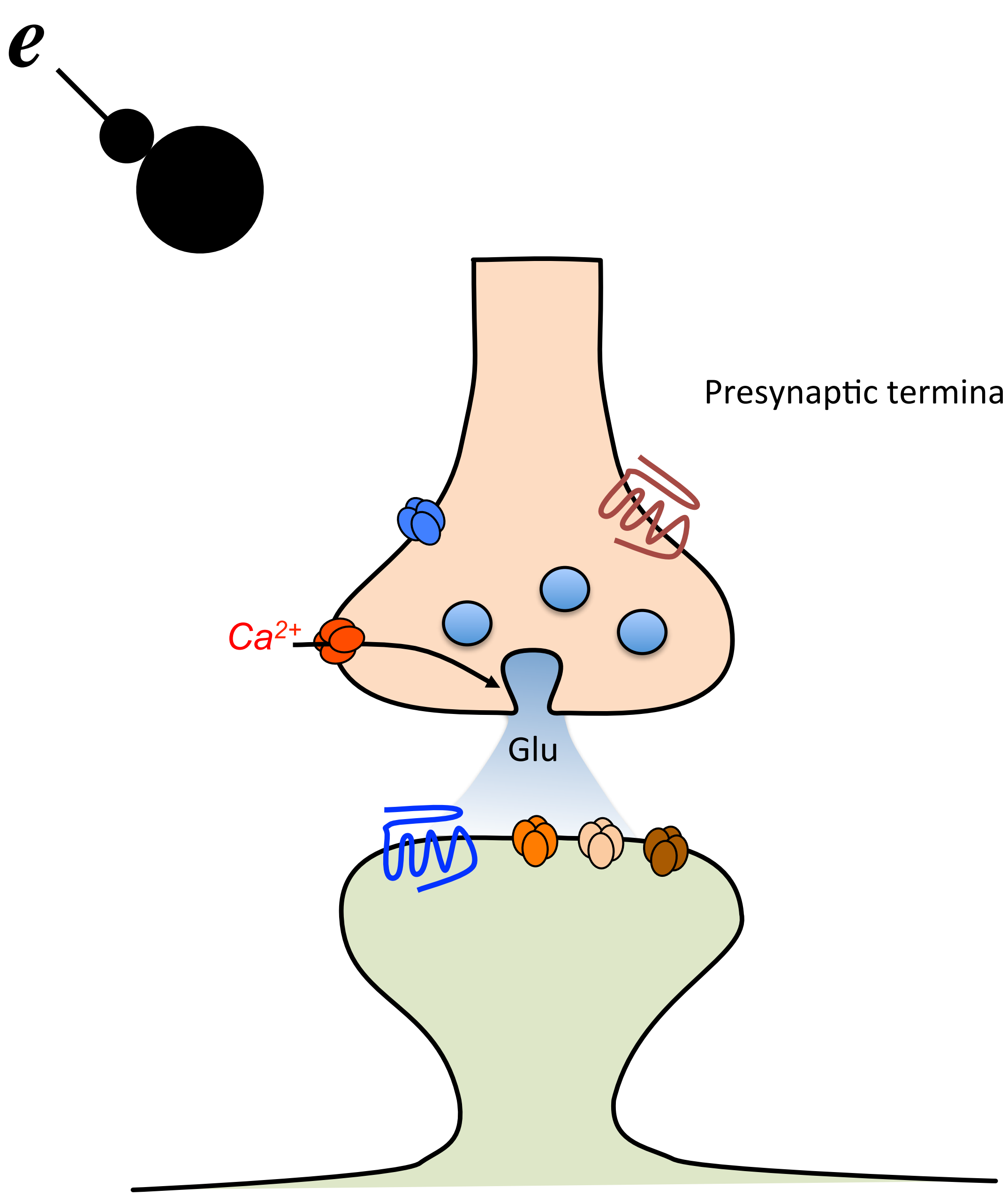


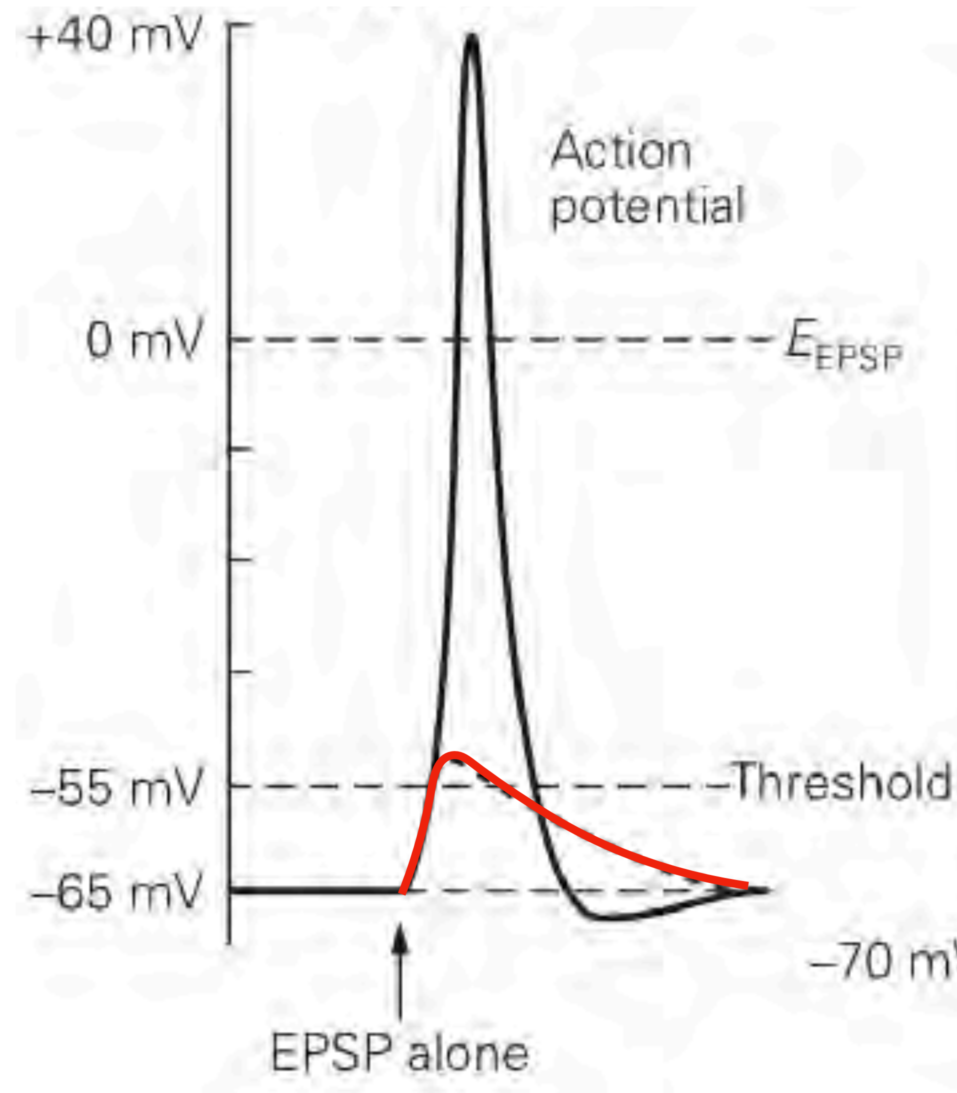
Neurotransmitters

Transmitter	Receptor	Ions	Effect
Glutamate	AMPA-R Kainite-R	Na^+, K^+, (bit of Ca^{2+})	Excitatory
	NMDA-R	Na^+, K^+, Ca^{2+}	
GABA	$GABA_A$	Cl^- (and HCO_3)	Inhibitory
Glycine	Gly-R 1-3	Cl^-	Inhibitory
Acetylcholine	nAChR1 - 7	Na^+, K^+, Ca^{2+}	Excitatory
Serotonin (5-HT_3)	5HTR3	Na^+, K^+	Excitatory

Communication between cells: ***Chemical synapses***

Glutamate receptors



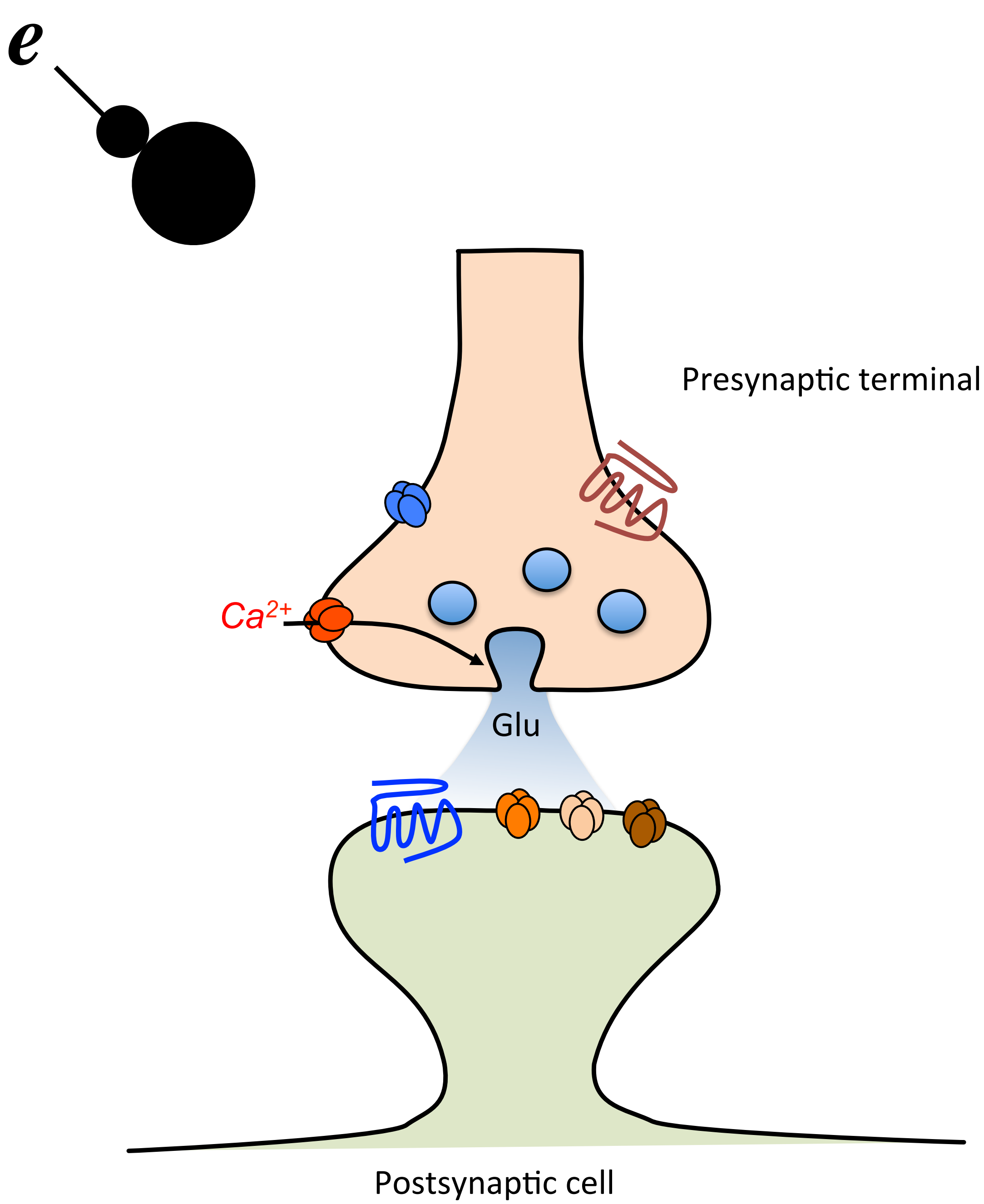


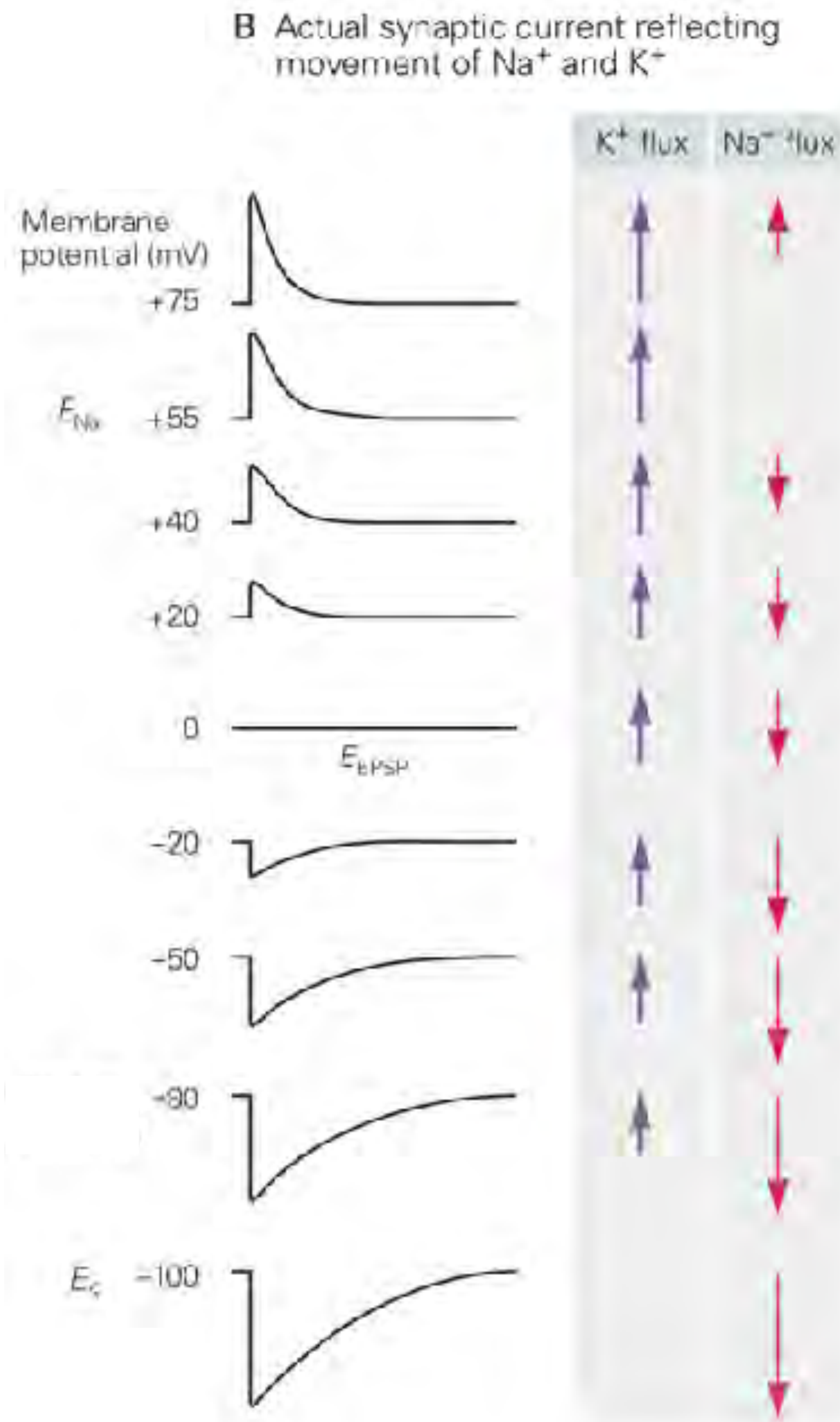
Current clamp

Kandel et al, *Principles of Neuroscience*, 2013

Communication between cells: ***Chemical synapses***

Glutamate receptors

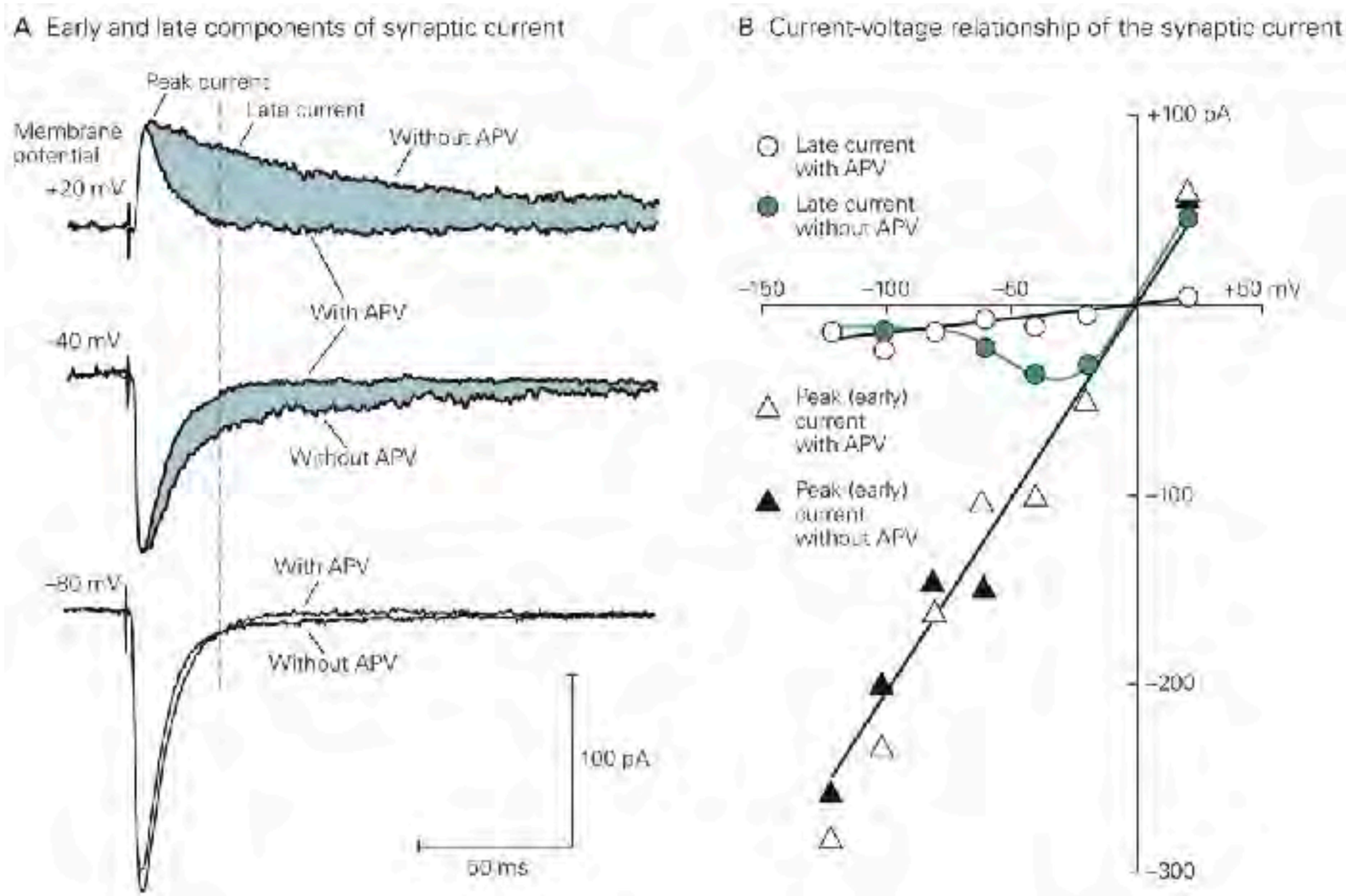




Voltage clamp

Kandel et al, *Principles of Neuroscience*, 2013

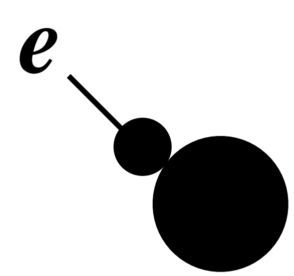
AMPA and NMDA receptors



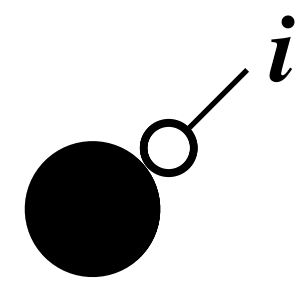
Kandel et al, *Principles of Neuroscience*, 2013

Logic operations

excitatory input



inhibitory input

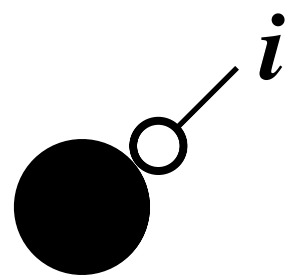


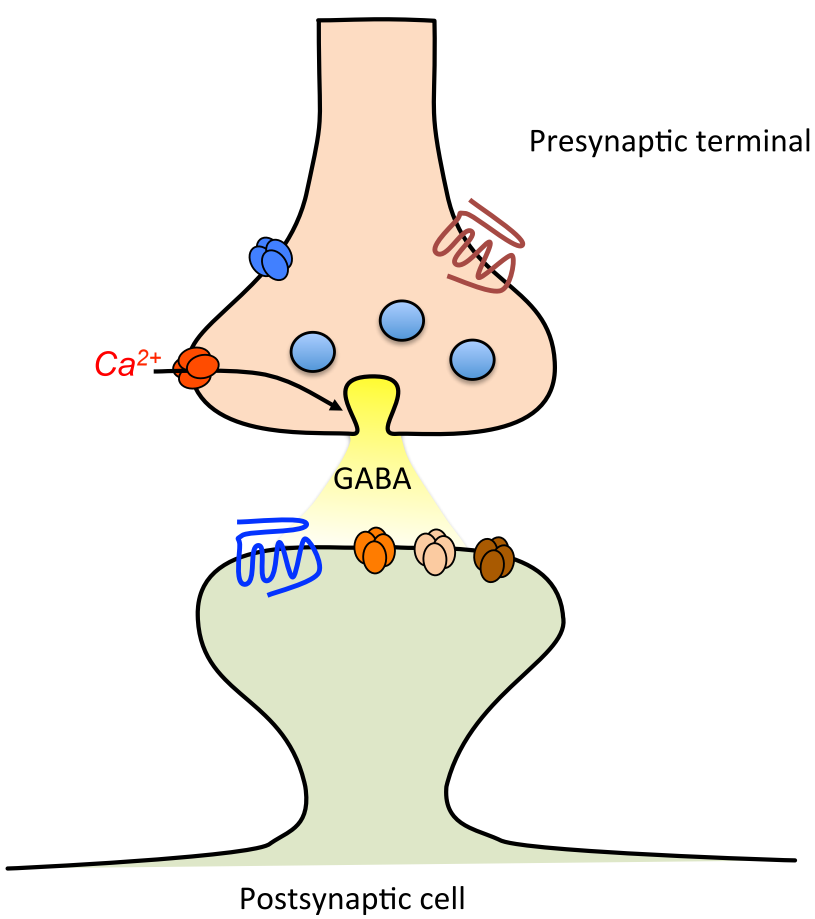
Logic operations

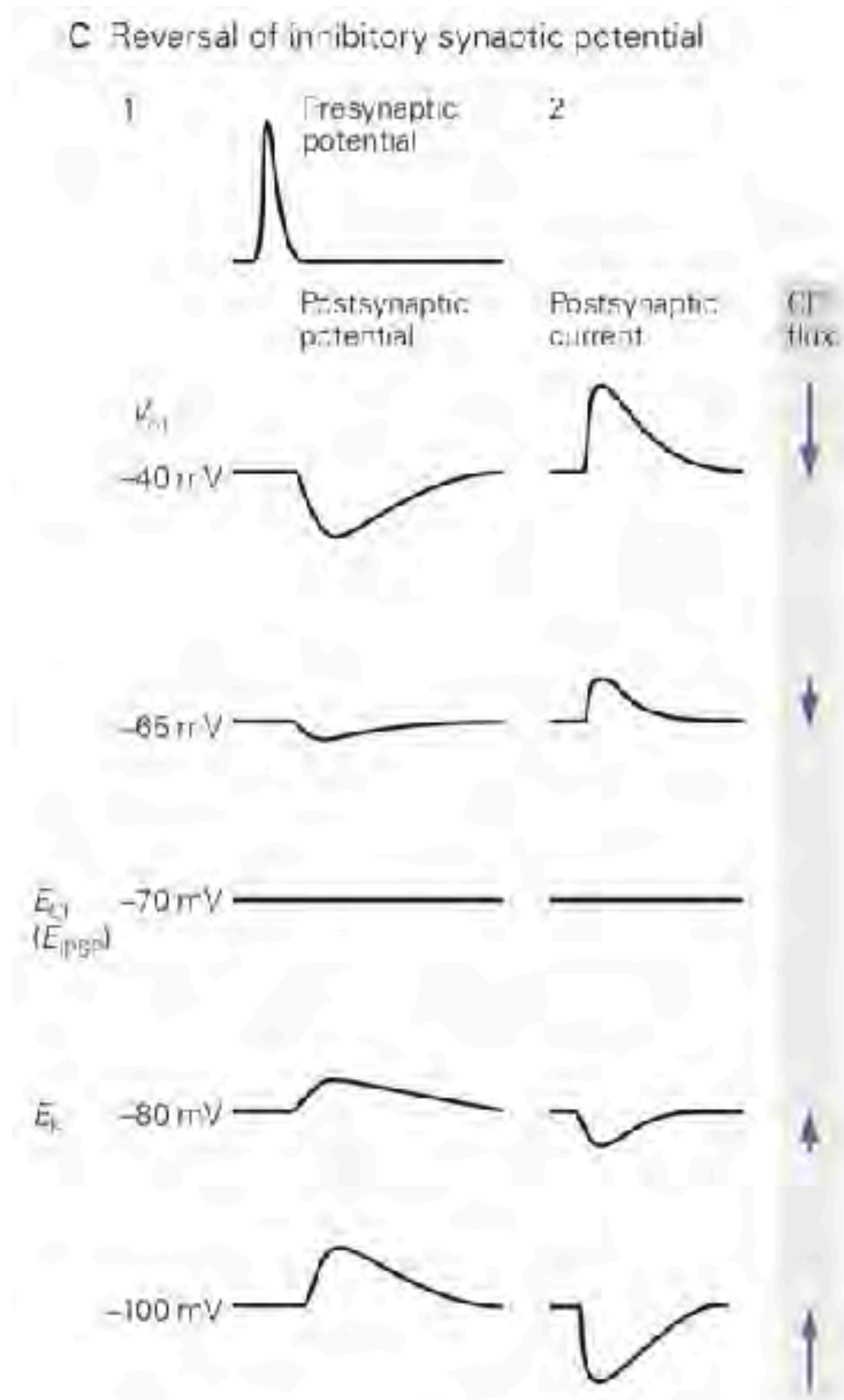
inhibitory input

Communication between cells: ***Chemical synapses***

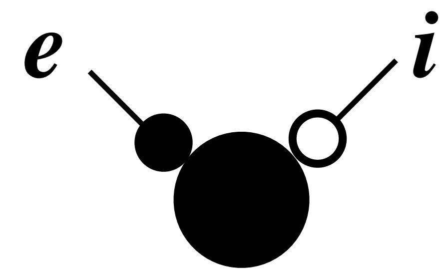
GABA receptors







Voltage clamp



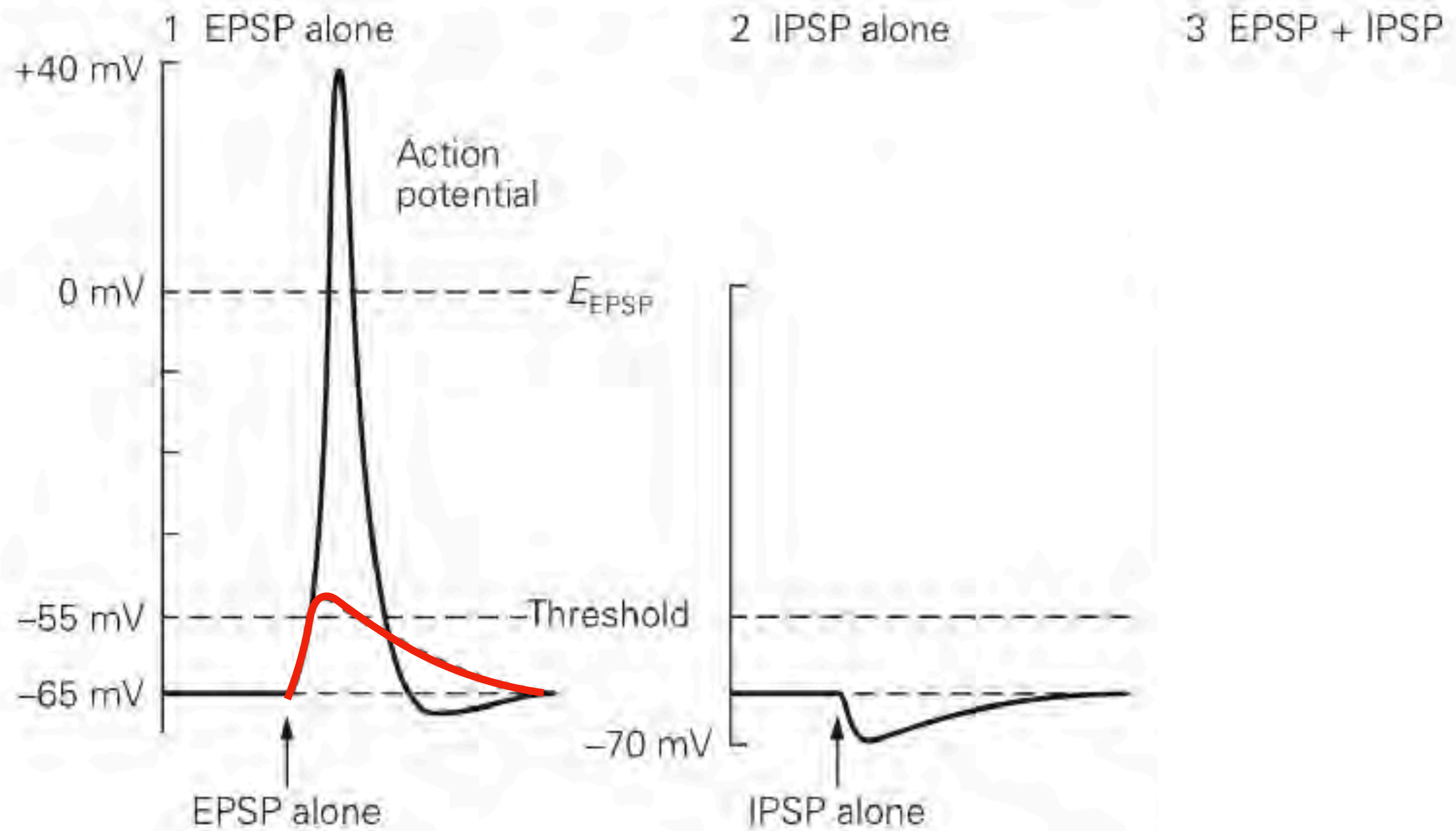
Excitatory transmission leads to membrane depolarisation

How does inhibition work?

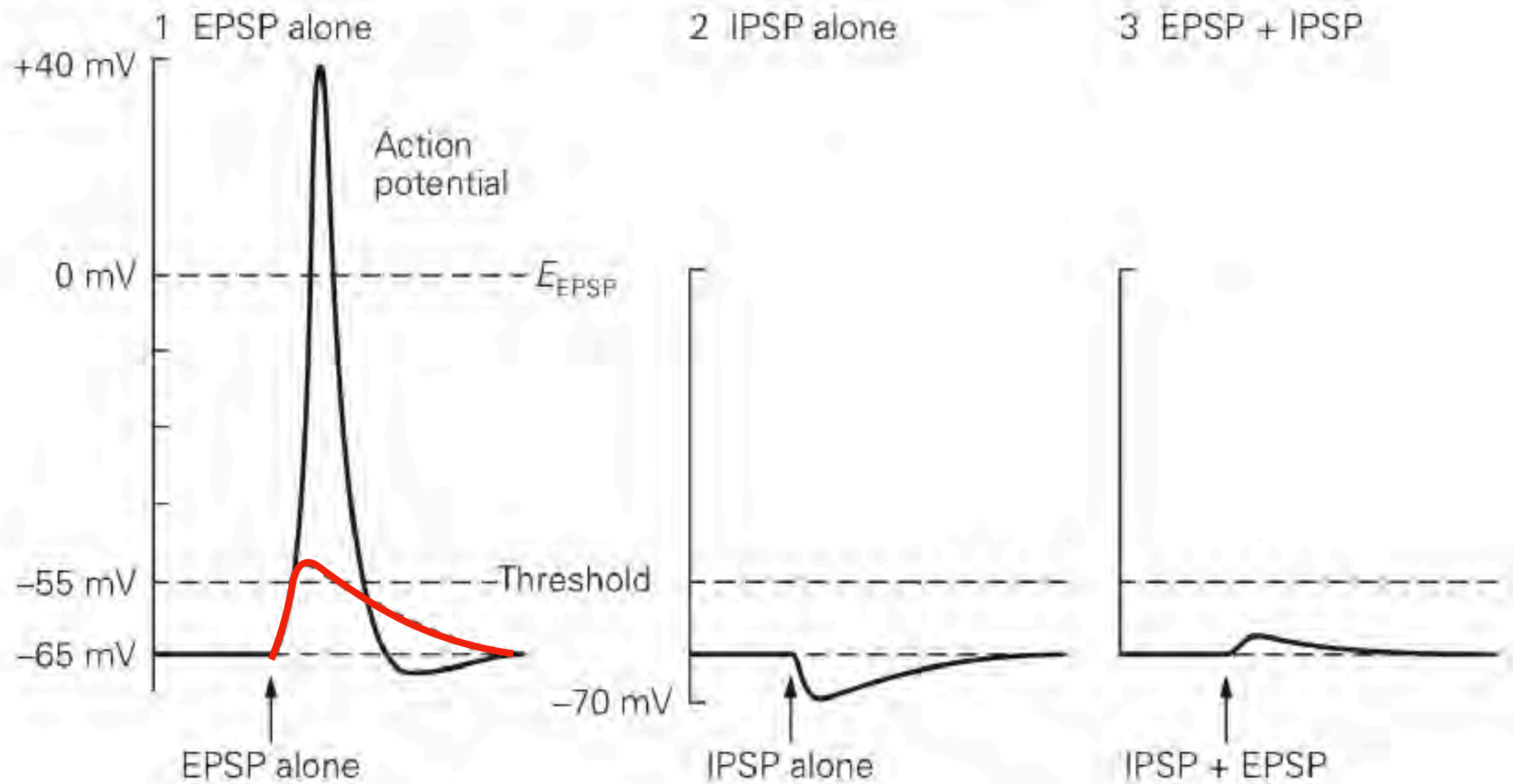
Shunting current

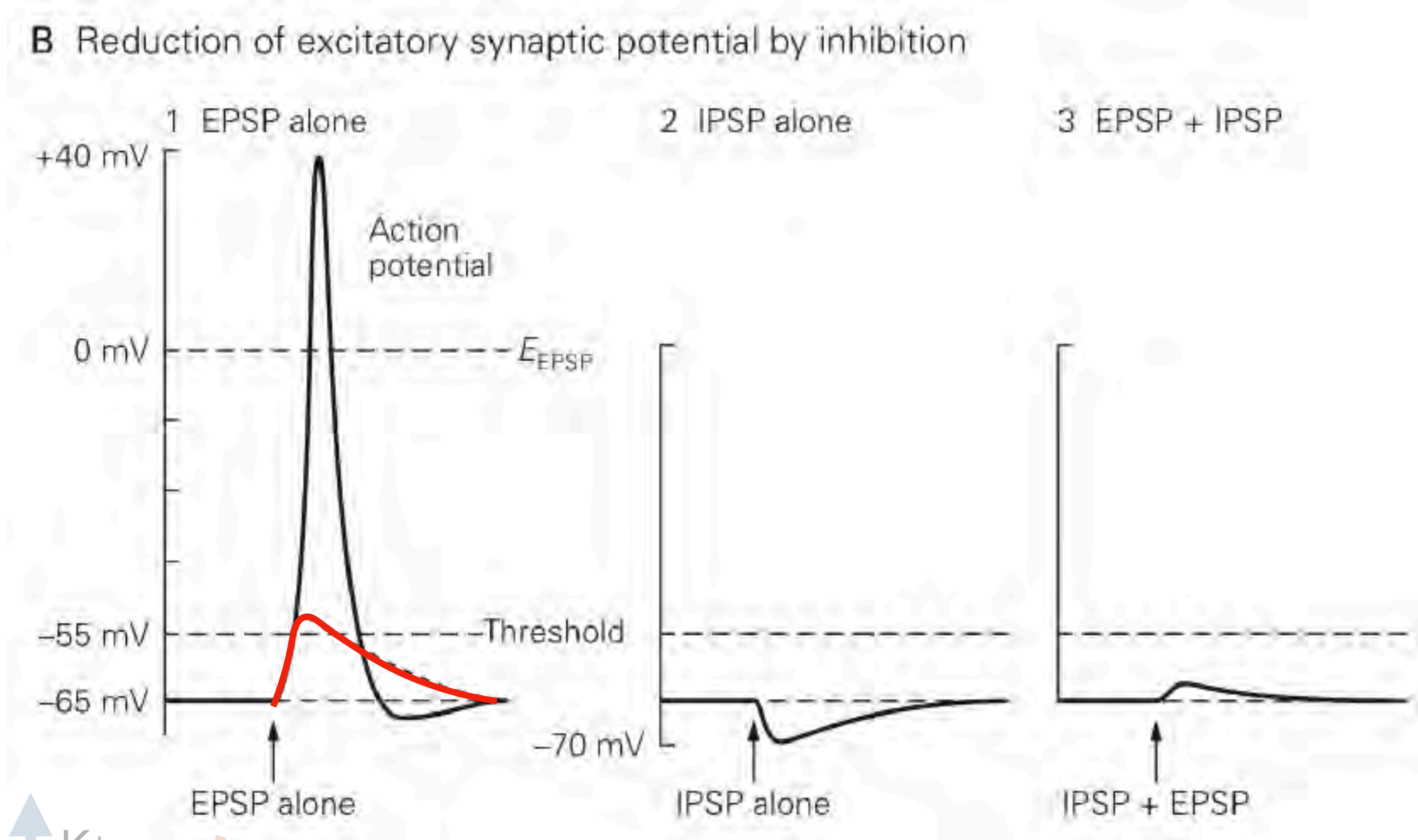
(this is important)

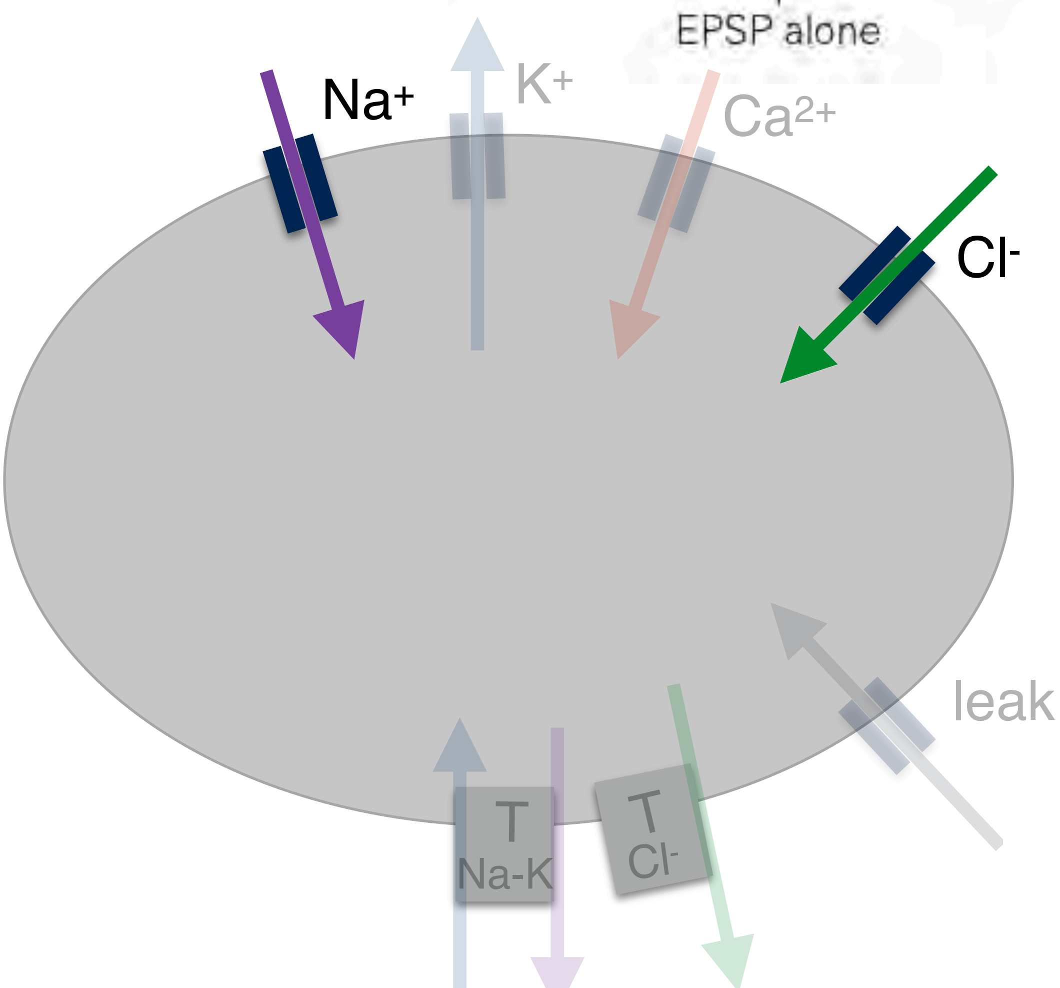
B Reduction of excitatory synaptic potential by inhibition



B Reduction of excitatory synaptic potential by inhibition

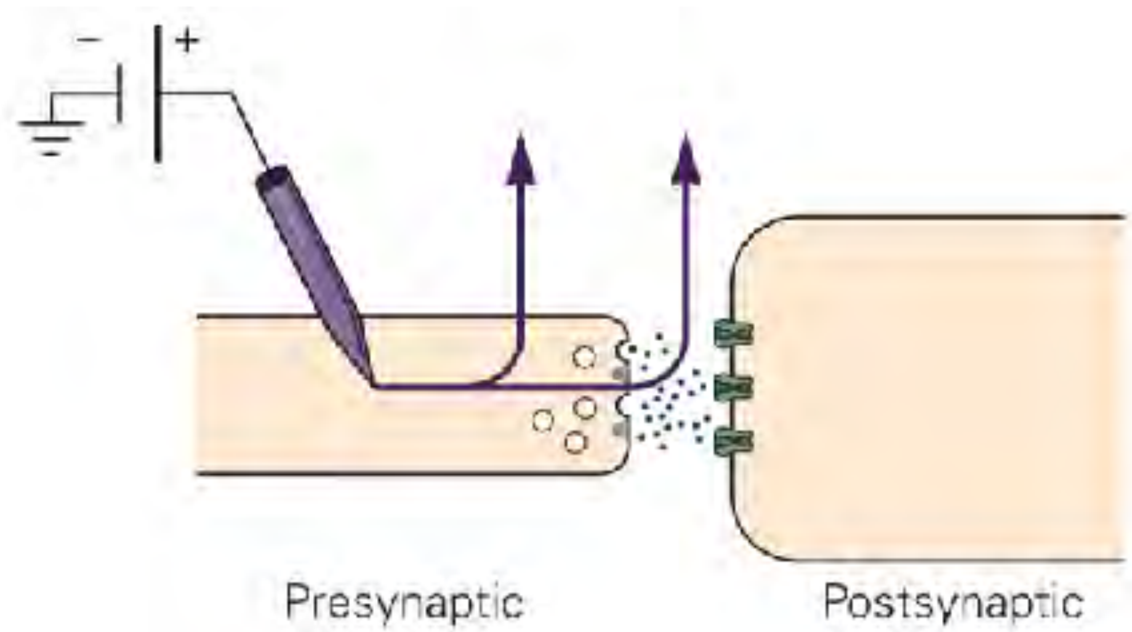



B Reduction of excitatory synaptic potential by inhibition
1 EPSP alone
2 IPSP alone
3 EPSP + IPSP
+40 mV
Action potential
0 mV
E EPSP
–55 mV
Threshold
–65 mV
–70 mV
EPSP alone
IPSP alone
IPSP + EPSP


Na+
K+
Ca2+
Cl-
leak
T
Na-K
T
Cl-

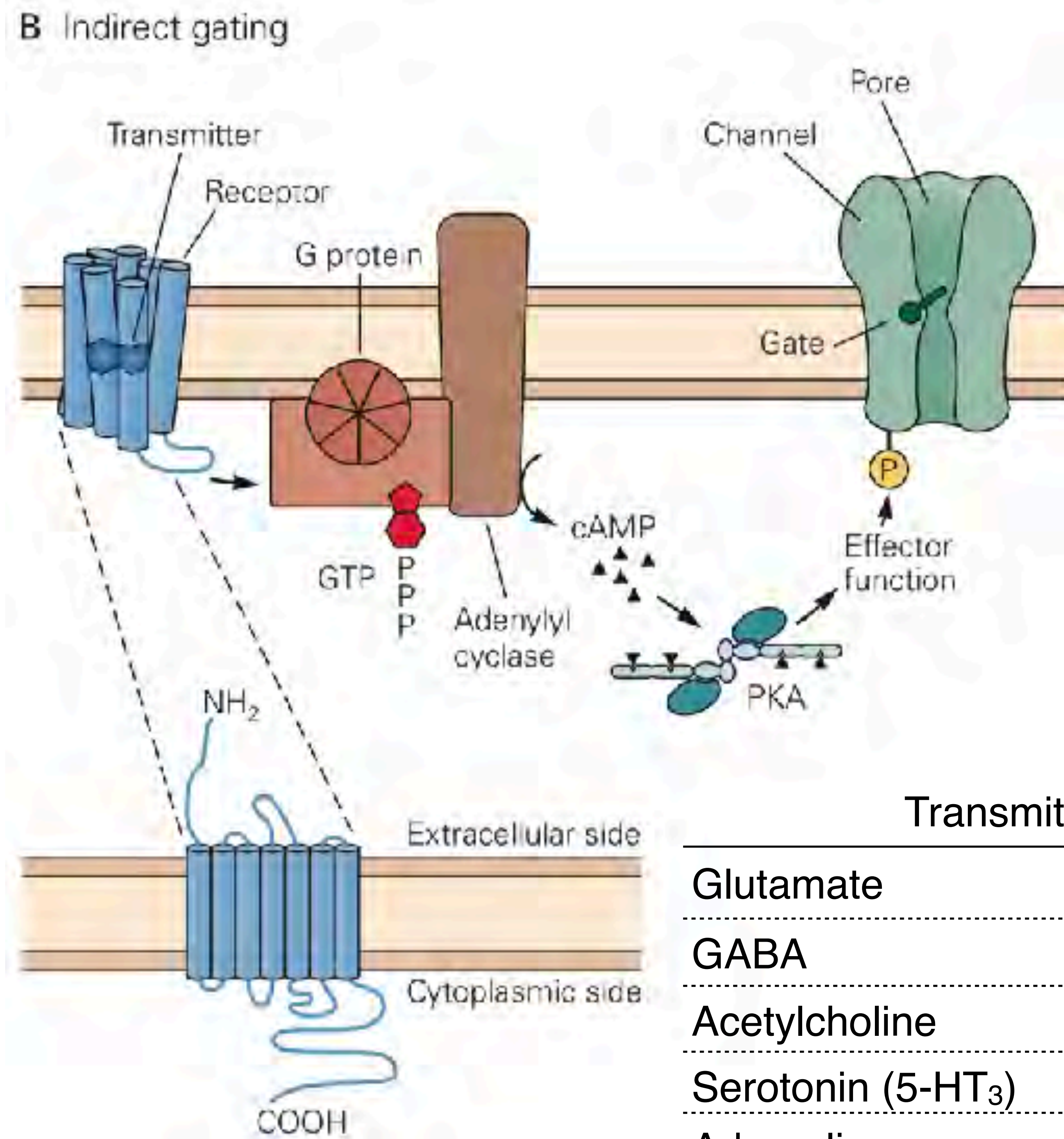
Synaptic transmission!!

Chemical Synapses



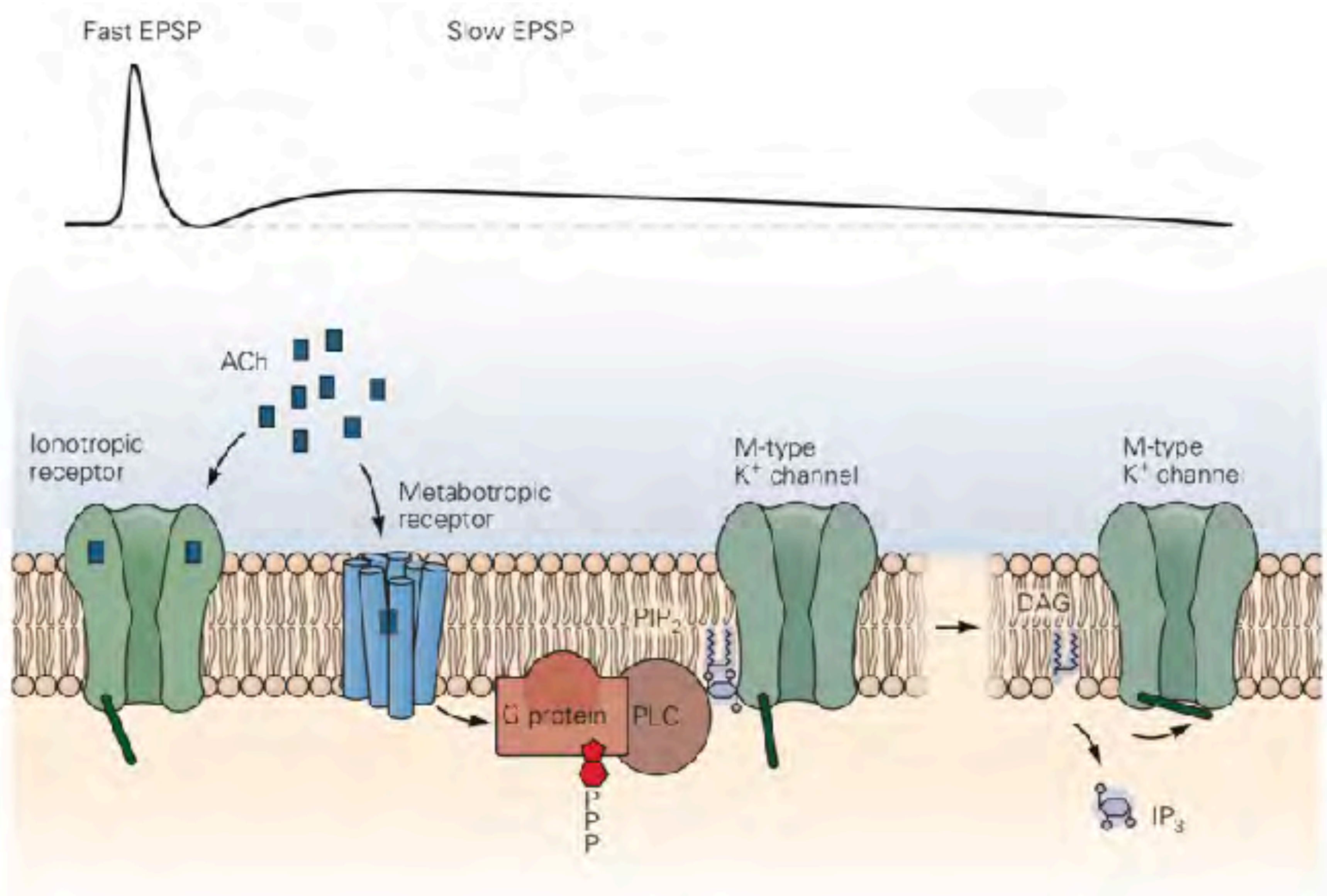
1) Fast, ionotropic transmission

2) Slower, metabotropic transmission

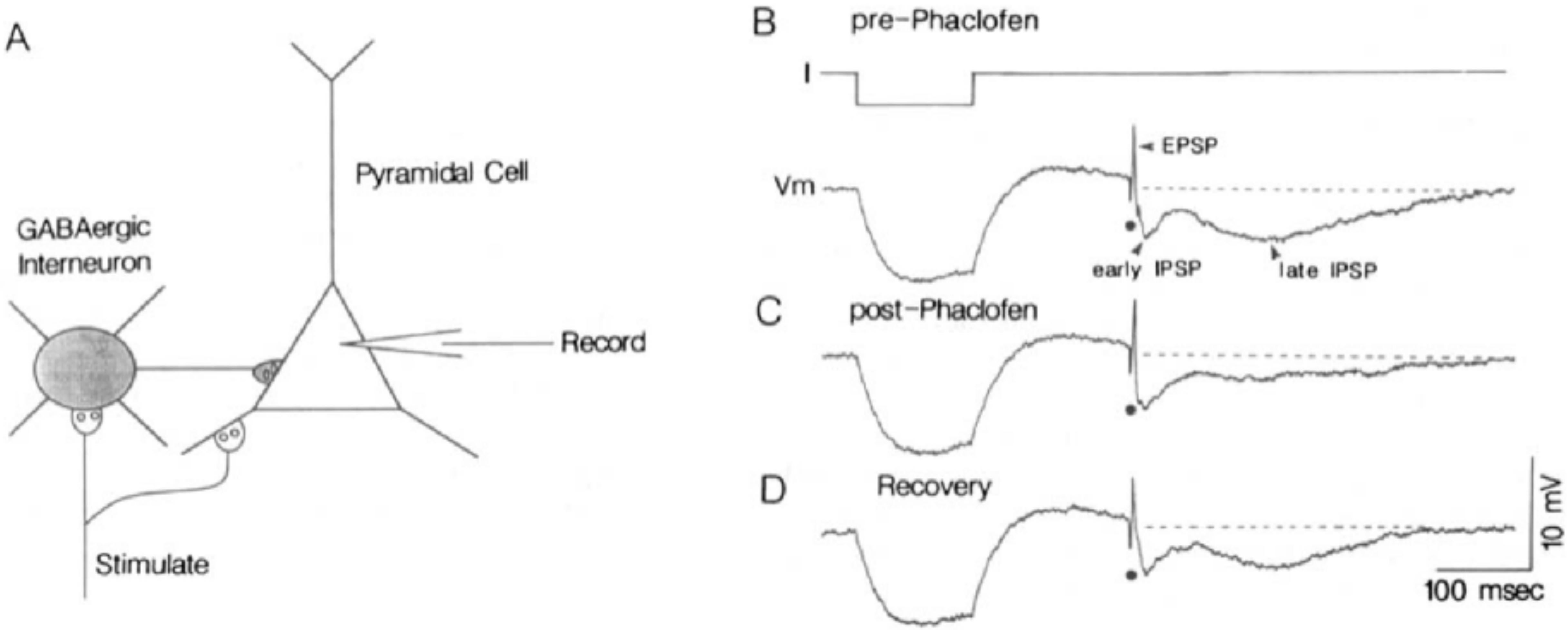


Transmitter	Receptor
Glutamate	mGluR 1-8
GABA	$GABA_B$
Acetylcholine	mAChR
Serotonin ($5\text{-}HT_3$)	5HTR 1-5
Adrenaline	NAR
Dopamine	D1-4
Epinephrine	α1, α2, β1-3

Kandel et al, *Principles of Neuroscience*, 2013

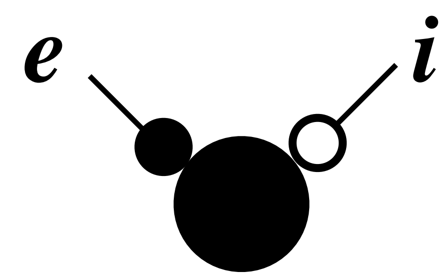


Kandel et al, *Principles of Neuroscience*, 2013



David McCormick, *Synaptic Organisation of the Brain,* Chapter 2, “Membrane Properties and Neurotransmitter Action,” edited by Gordon Shepherd, 2003.

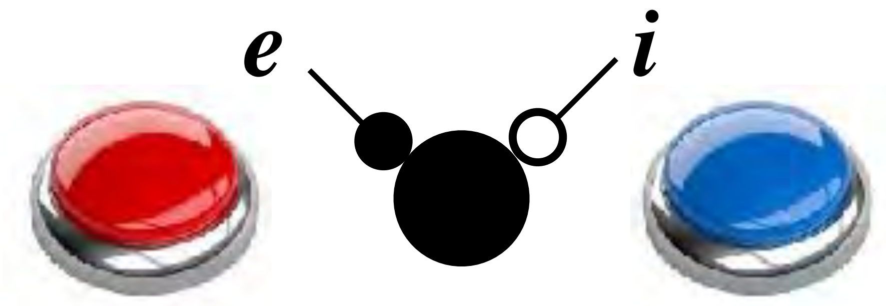
Logic operations



Integration of inputs

Timing, relative strength of inputs

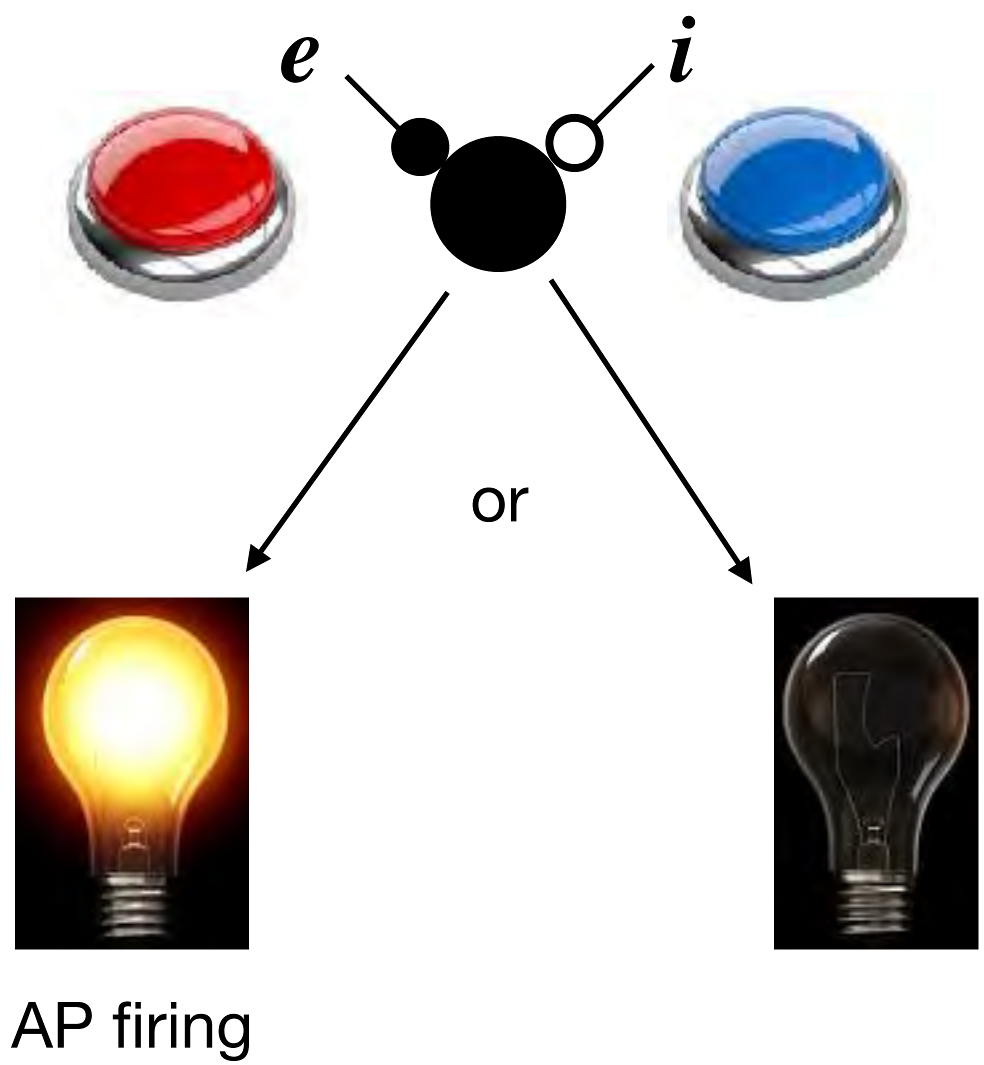
Logic operations

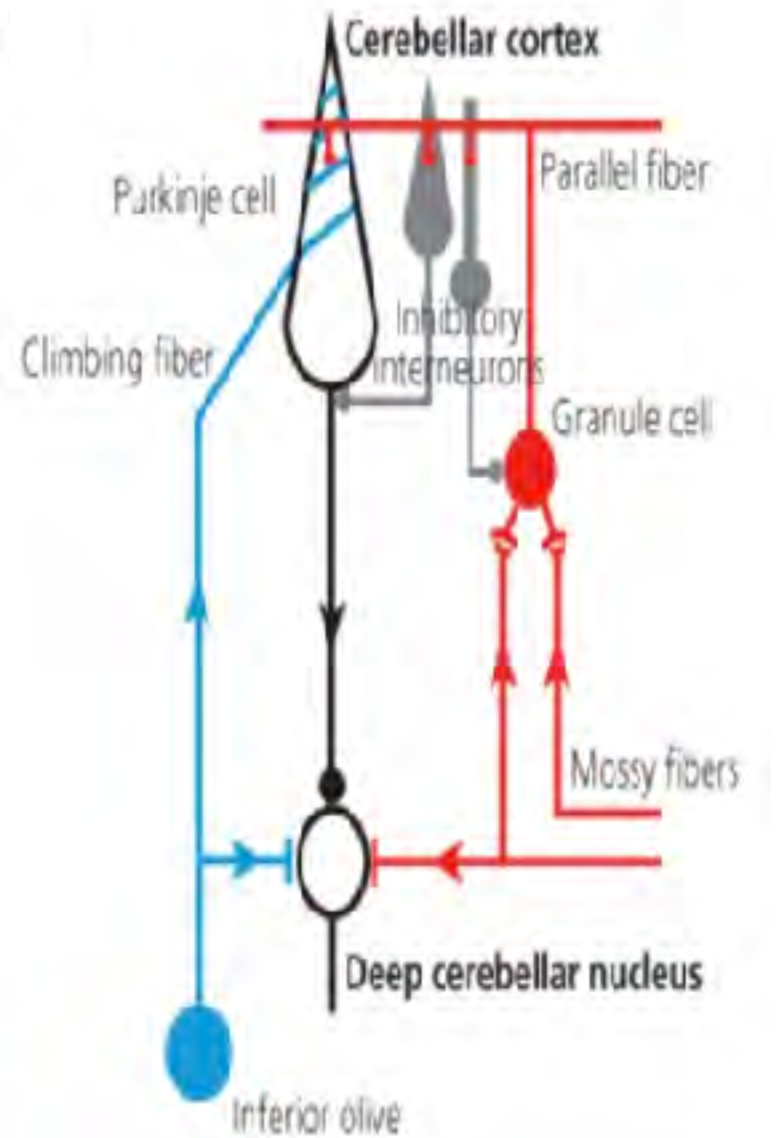


Integration of inputs

Timing, relative strength of inputs

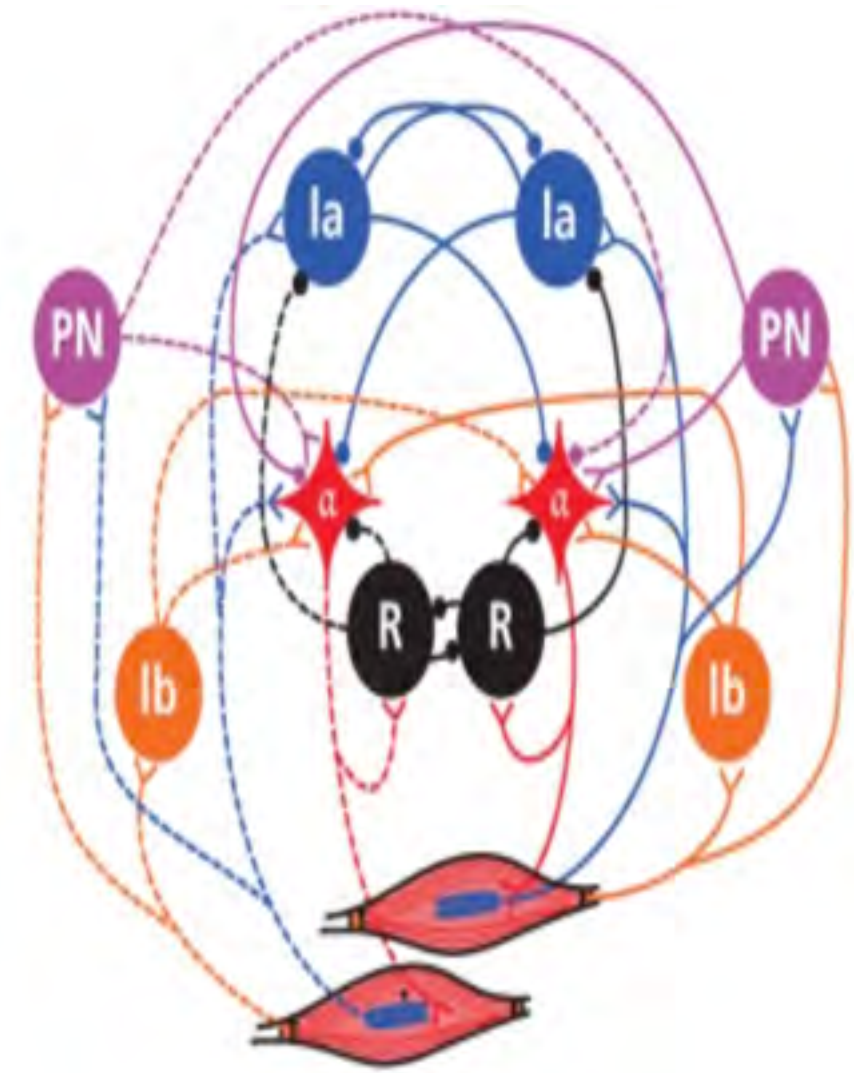
Logic operations





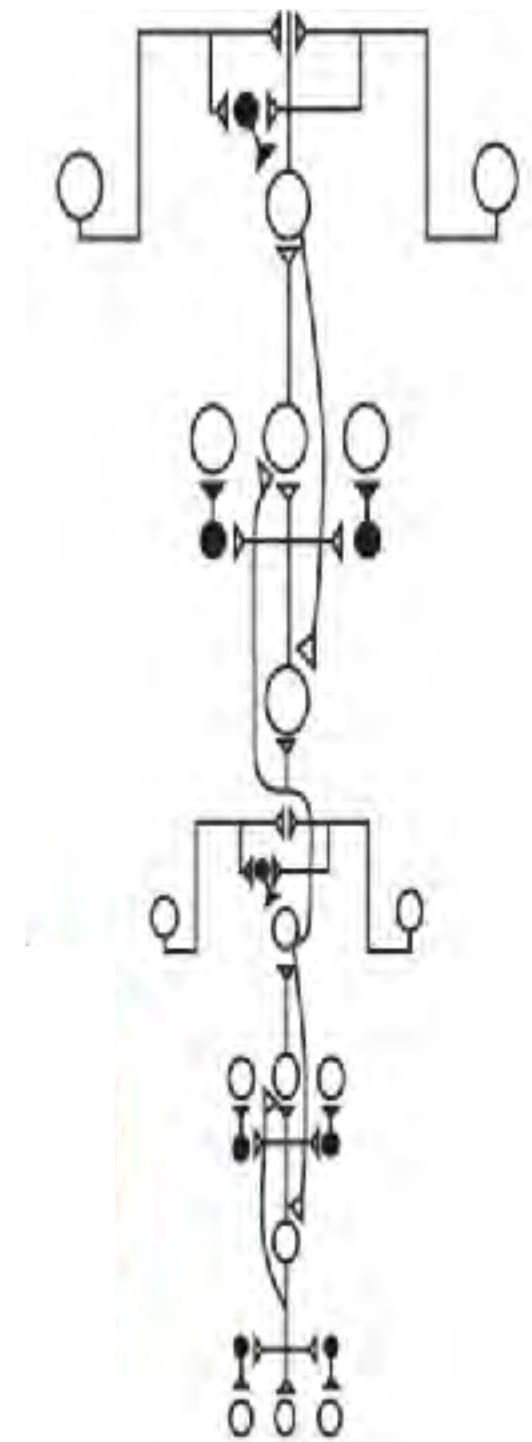
Cerebellar circuit

(Raymond et al 1996)



Spinal cord

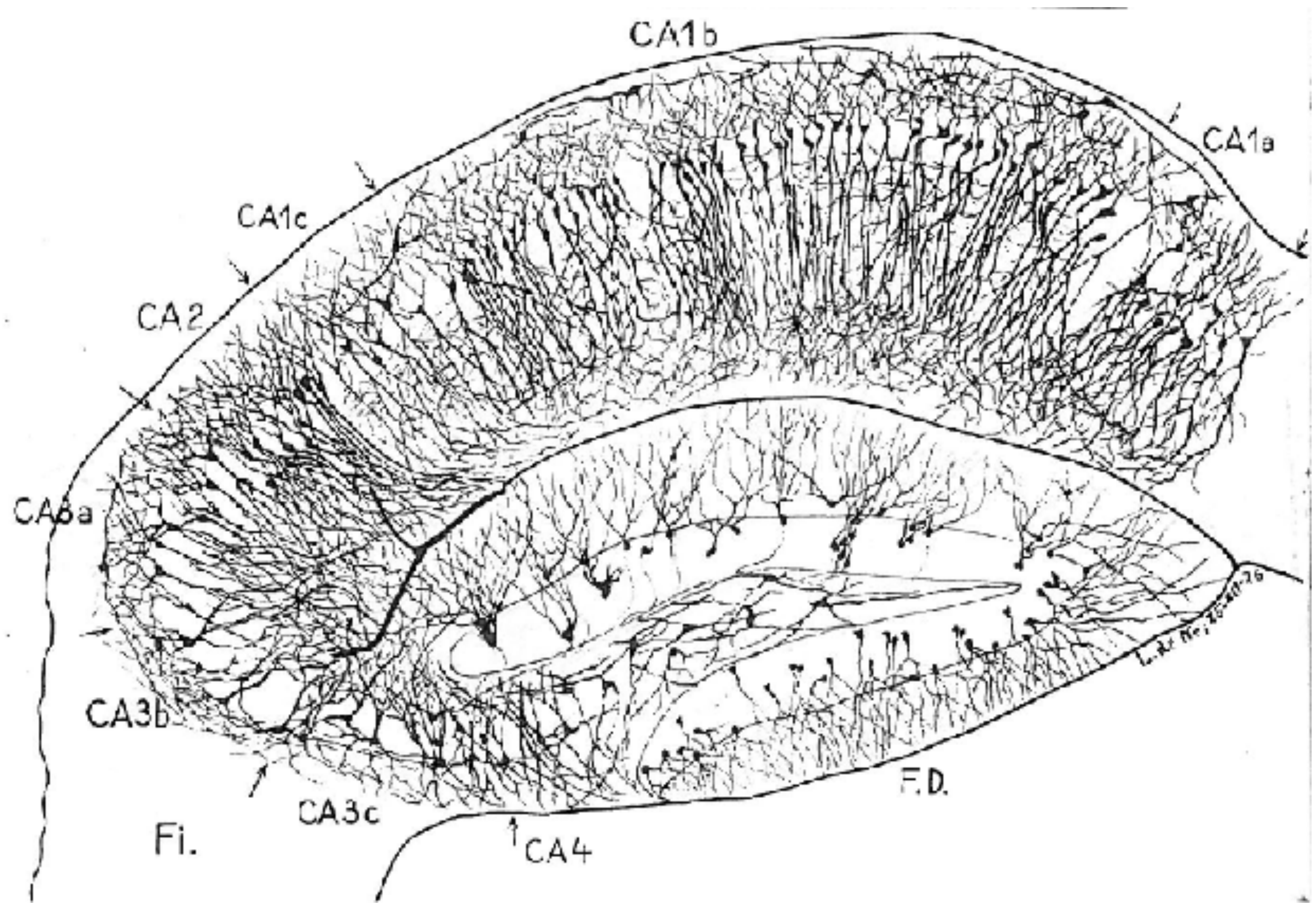
(Raphael et al 2010)



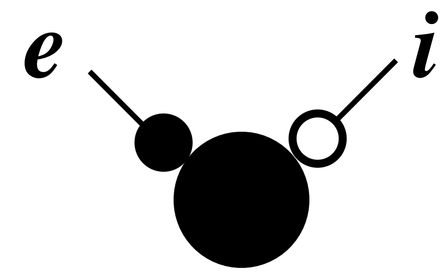
Visual cortex

(Grossberg et al 1997)

Neurons in the hippocampus are typically more complex than single nodes.



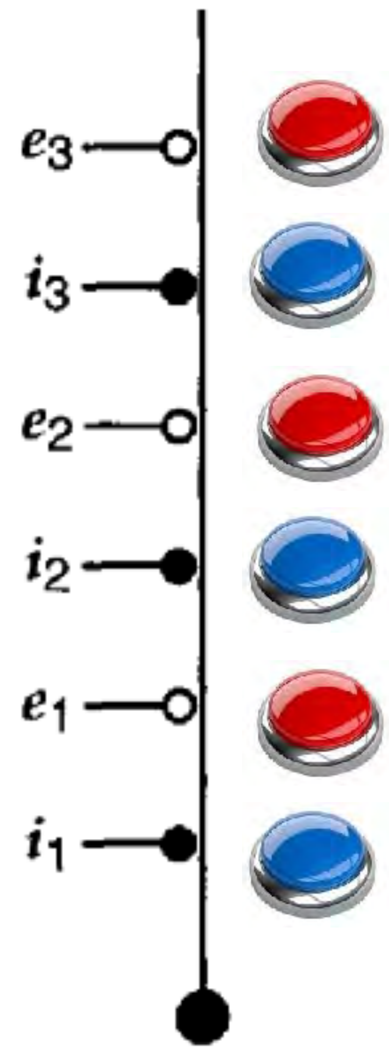
Lorente de Nó *J Psychology and Neurologie,* 1934.



Okay, so lets add some dendrites.

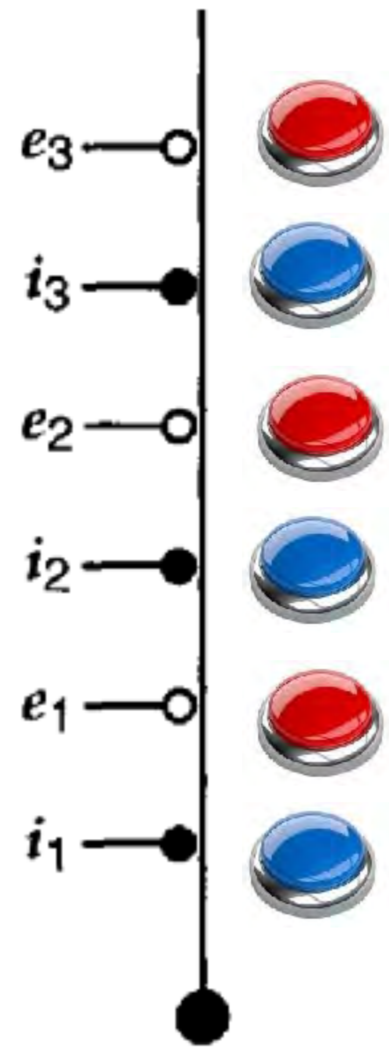
What do we gain?

Logic operations - now with dendrites



One button alone is below threshold

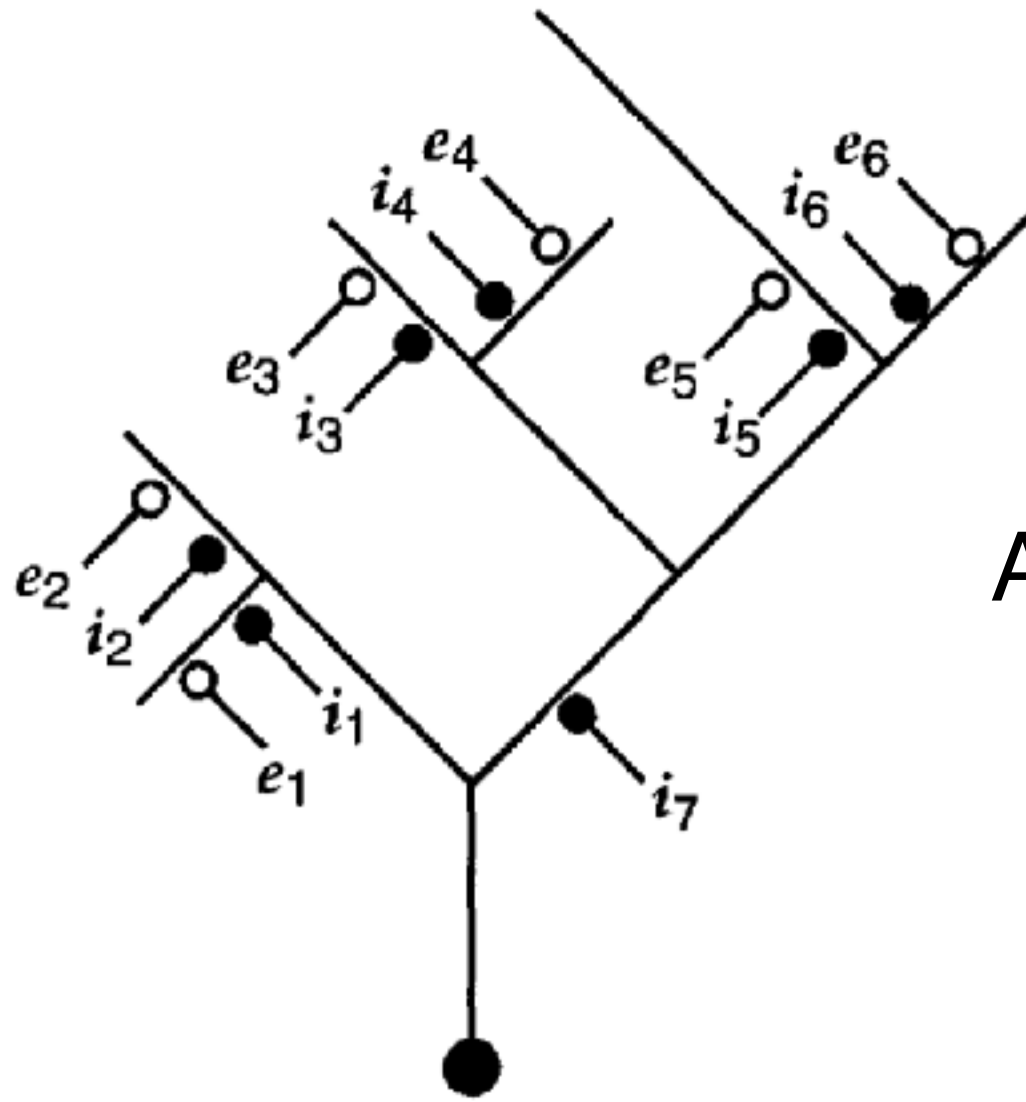
Logic operations - now with dendrites



AND NOT circuit

Red buttons together **AND NOT** blue buttons = AP firing

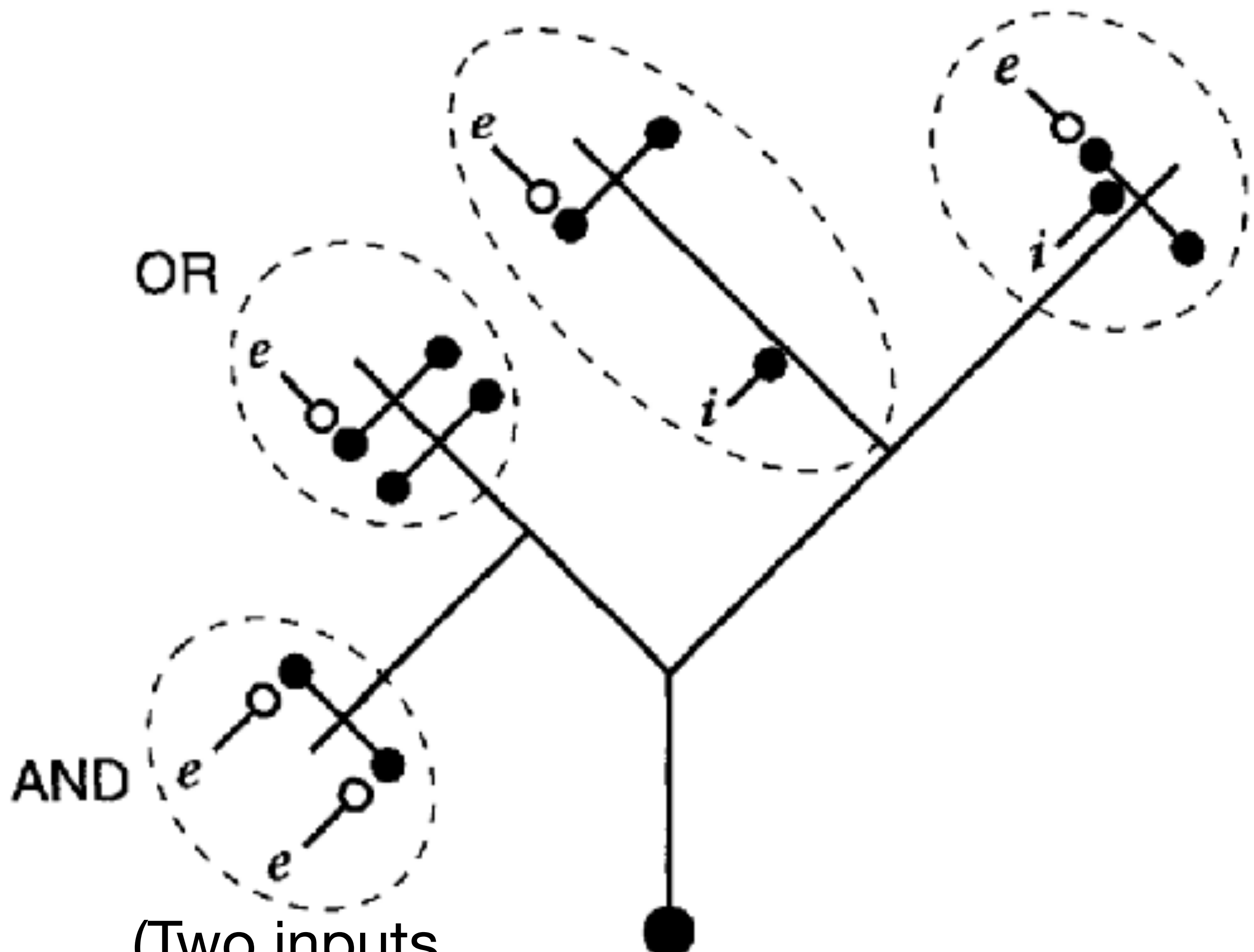
Logic operations - now with branched dendrites



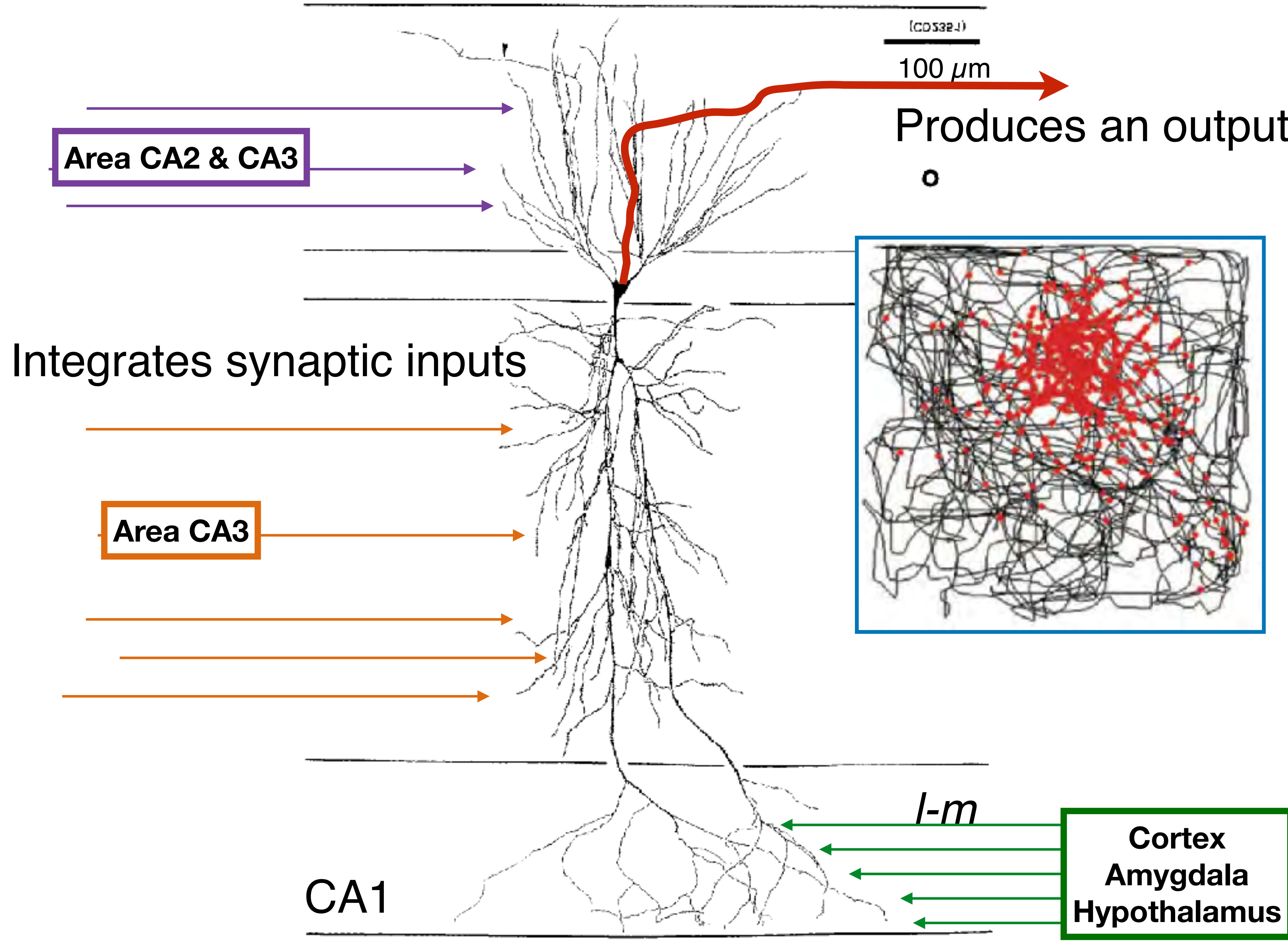
AND NOT circuit

Logic operations - now with branched dendrites with compartments

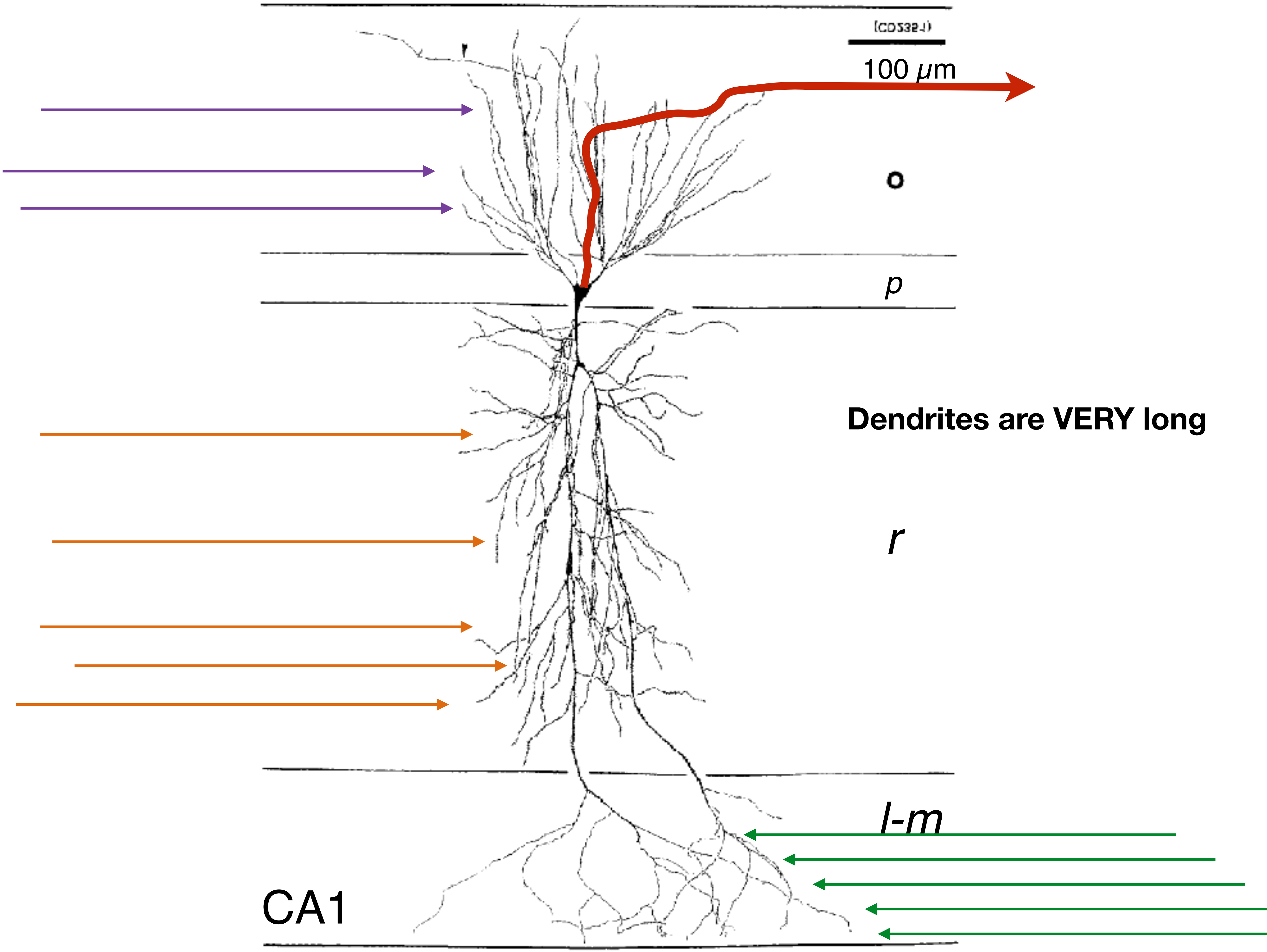
AND NOT



(Two inputs
below threshold)

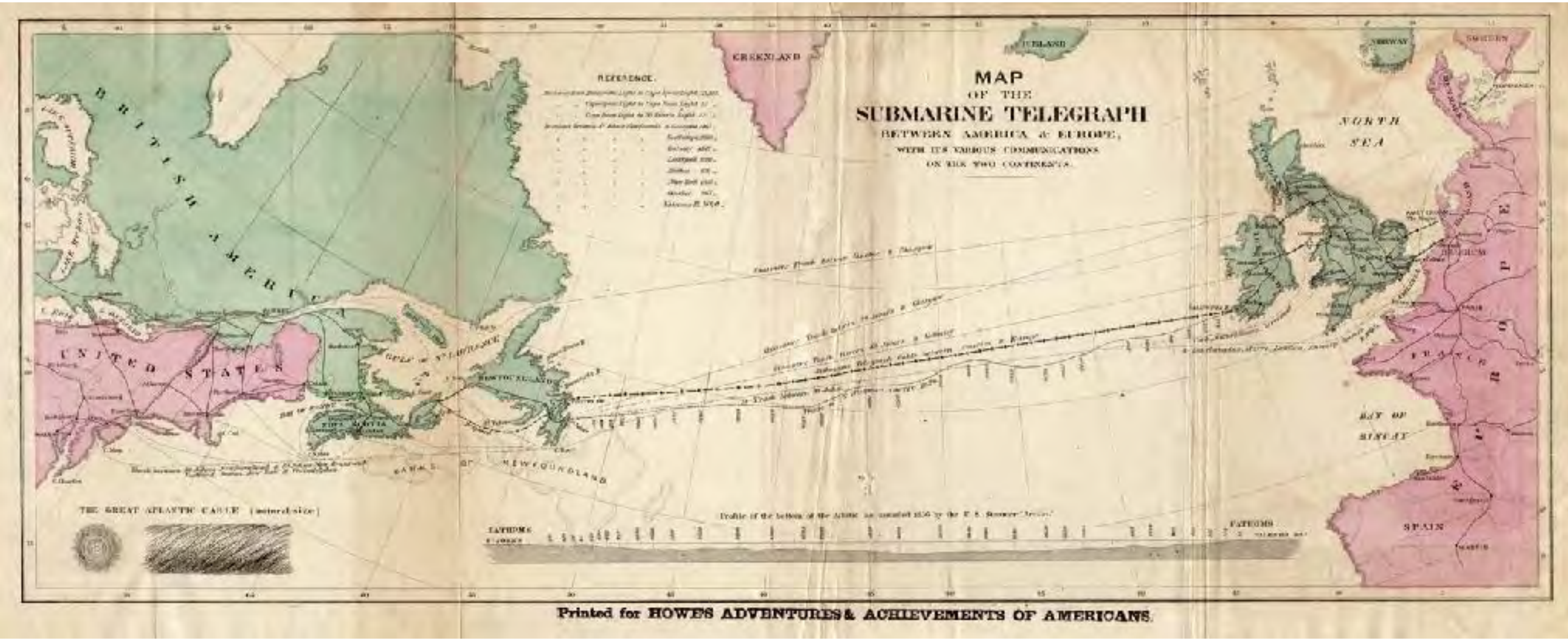


Ishizuka et al, Journal of Comparative Neurobiology, 1995.

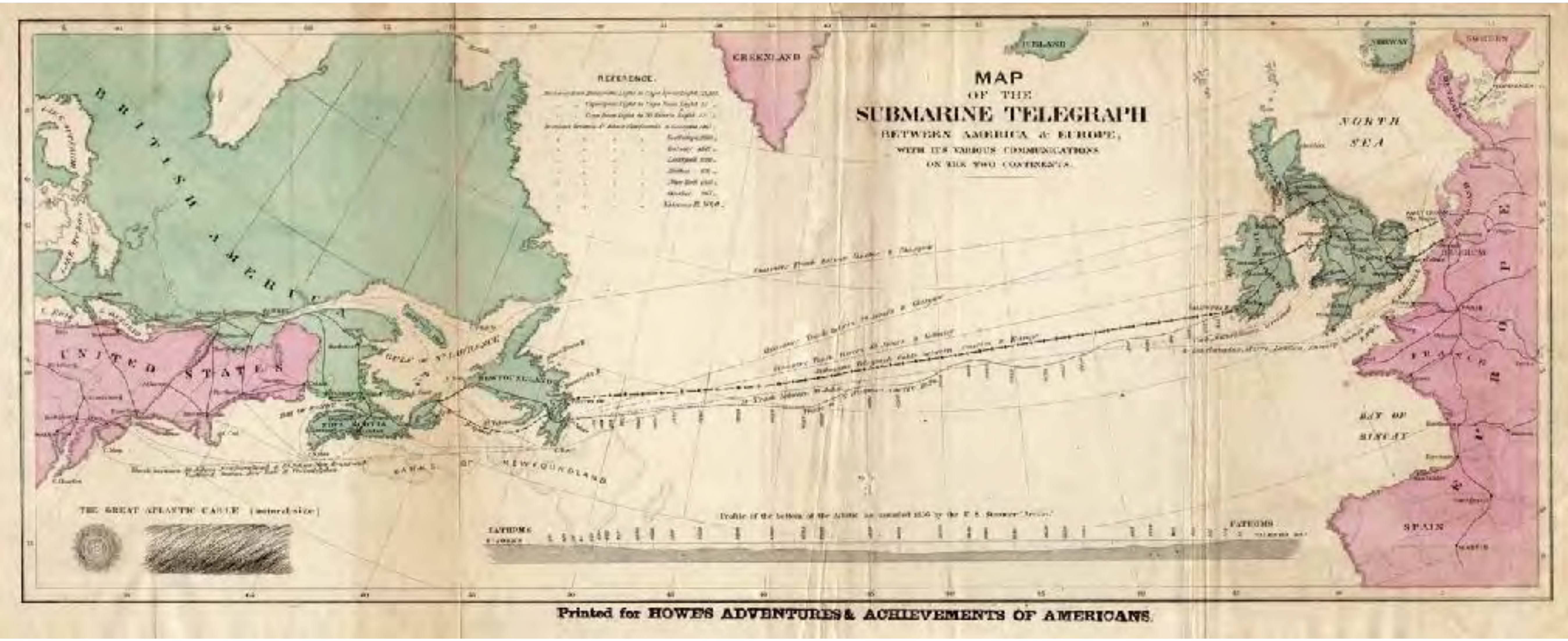


Ishizuka et al, Journal of Comparative Neurobiology, 1995.

Cable properties:



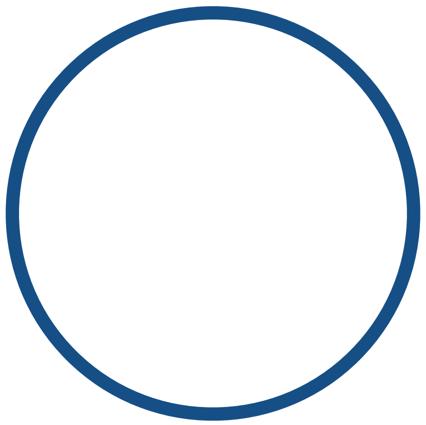
Neurons as electrical conductors:



"The tendency for membrane polarization to equalize over the neuron surface during passive decay is analogous to the tendency for temperature to equalize over an unevenly heated metal surface as it cools."

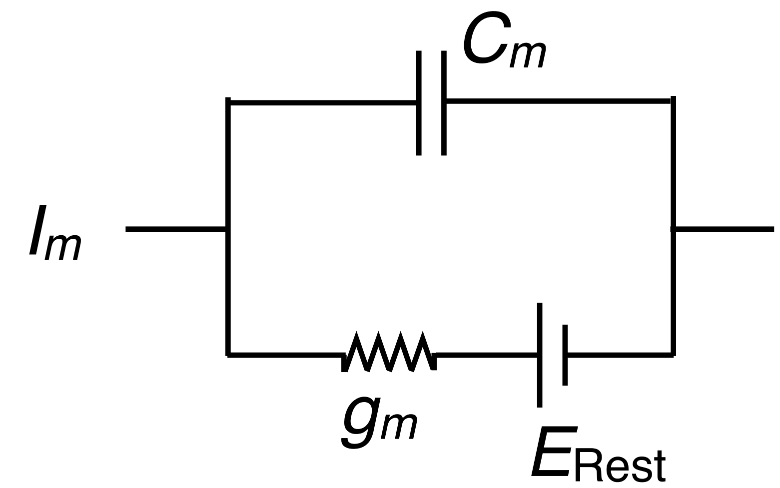
Wilfrid Rall 1957, 1962, 1964, 1969

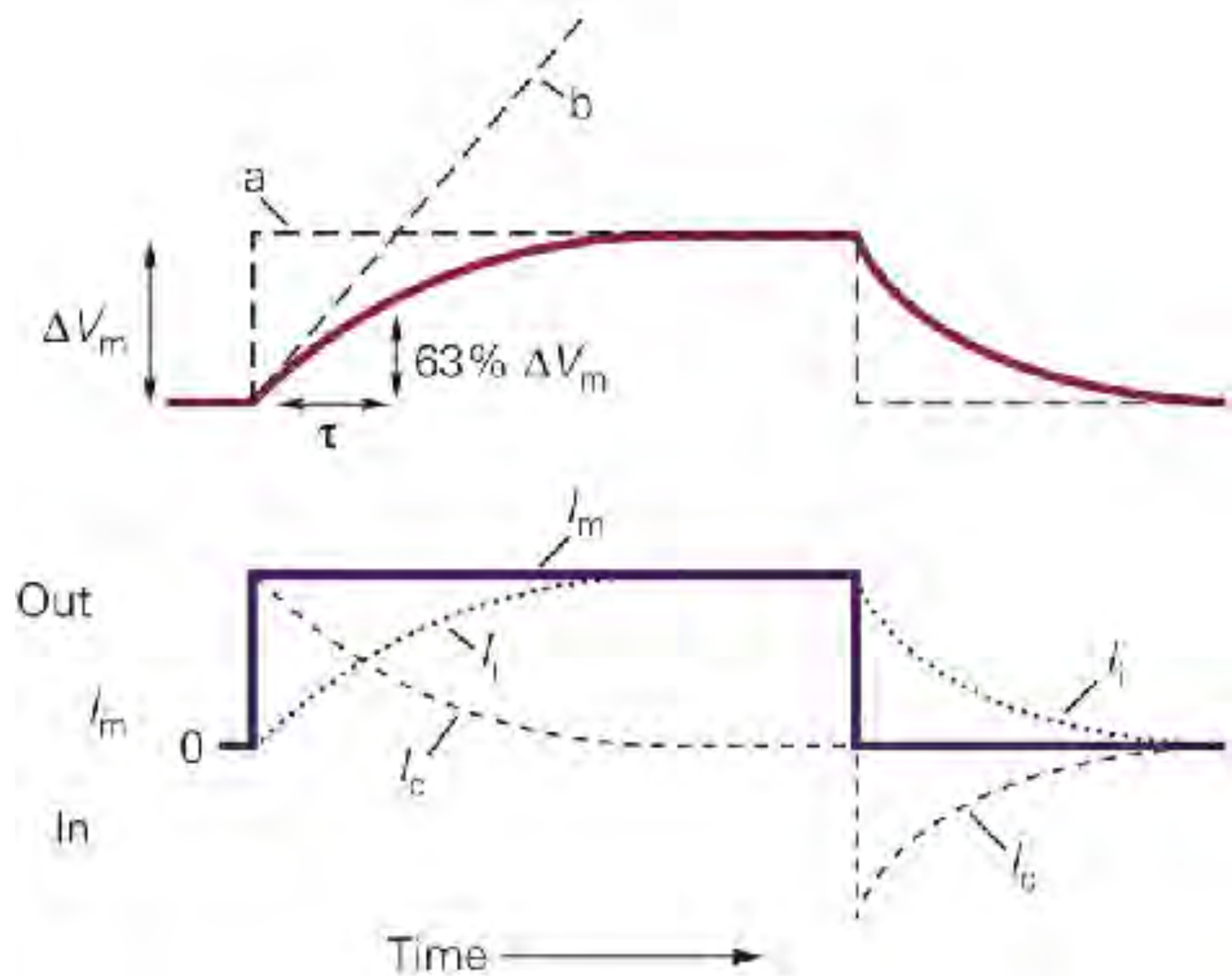
Neurons as electrical conductors



$$\Delta V_m = I_m R_m \left(1 - e^{t/\tau_m}\right)$$

$$\tau_m = C_m R_m$$



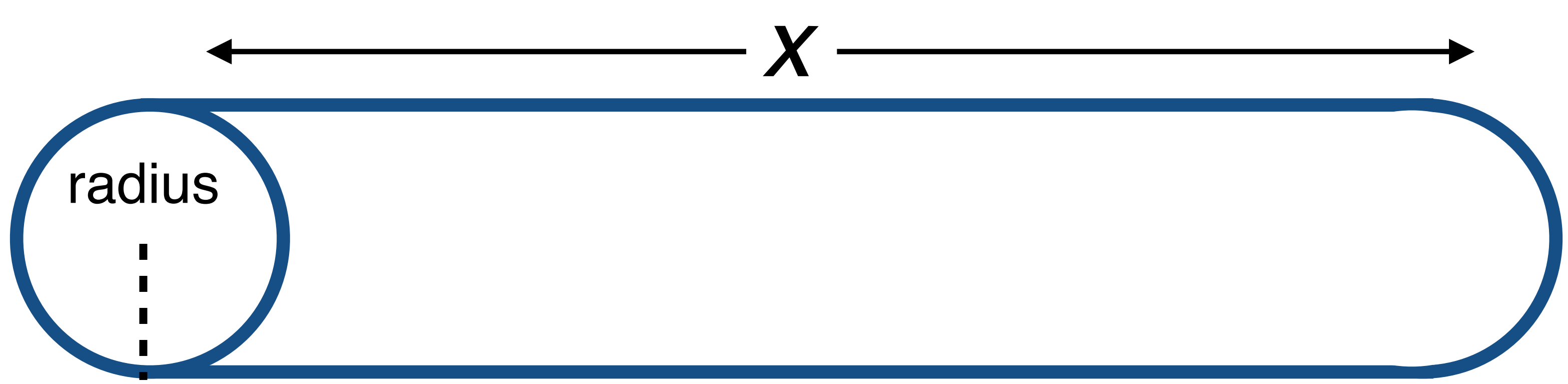


$$\Delta V(x) = \Delta V_0 \, e^{-x/\lambda}$$

$$\lambda = \sqrt{(r_m / r_a)}$$

r_m membrane resistance ($\Omega \cdot$cm)

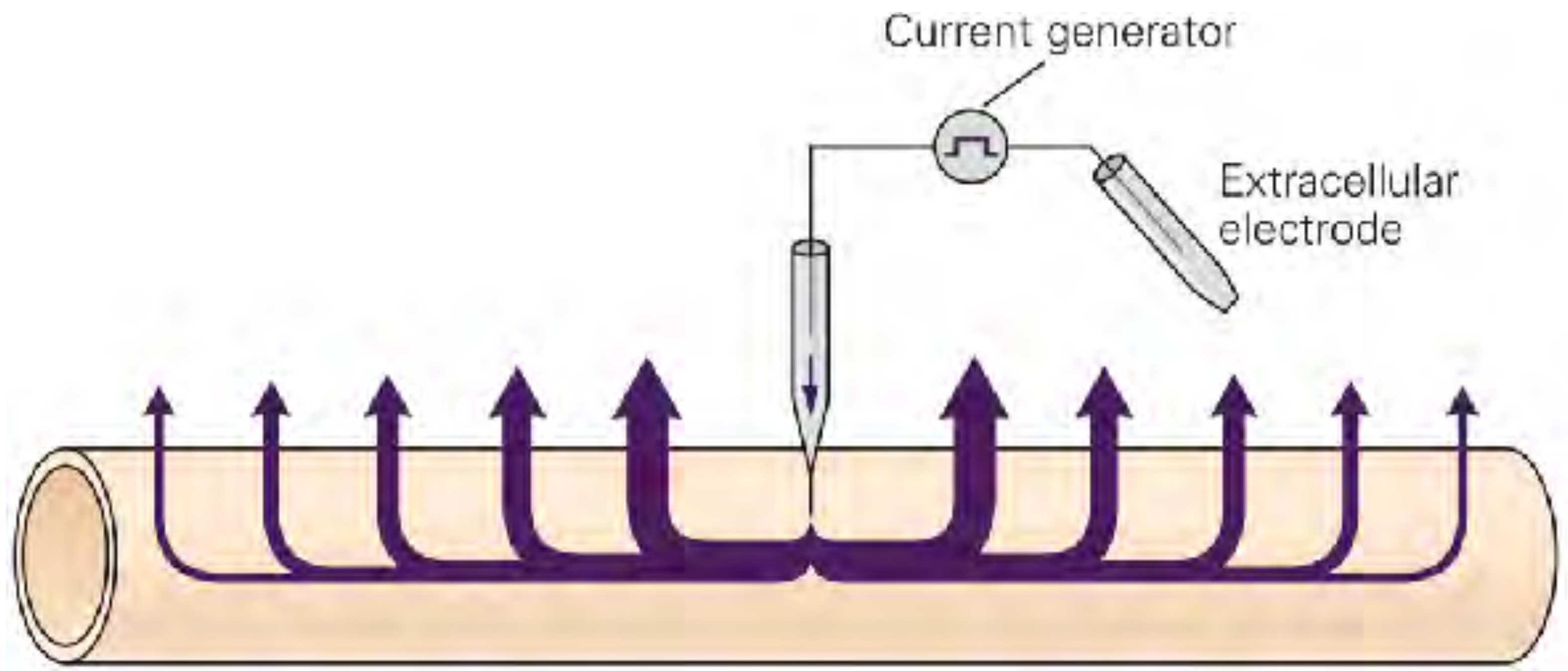
r_a axial resistance (Ω / cm)

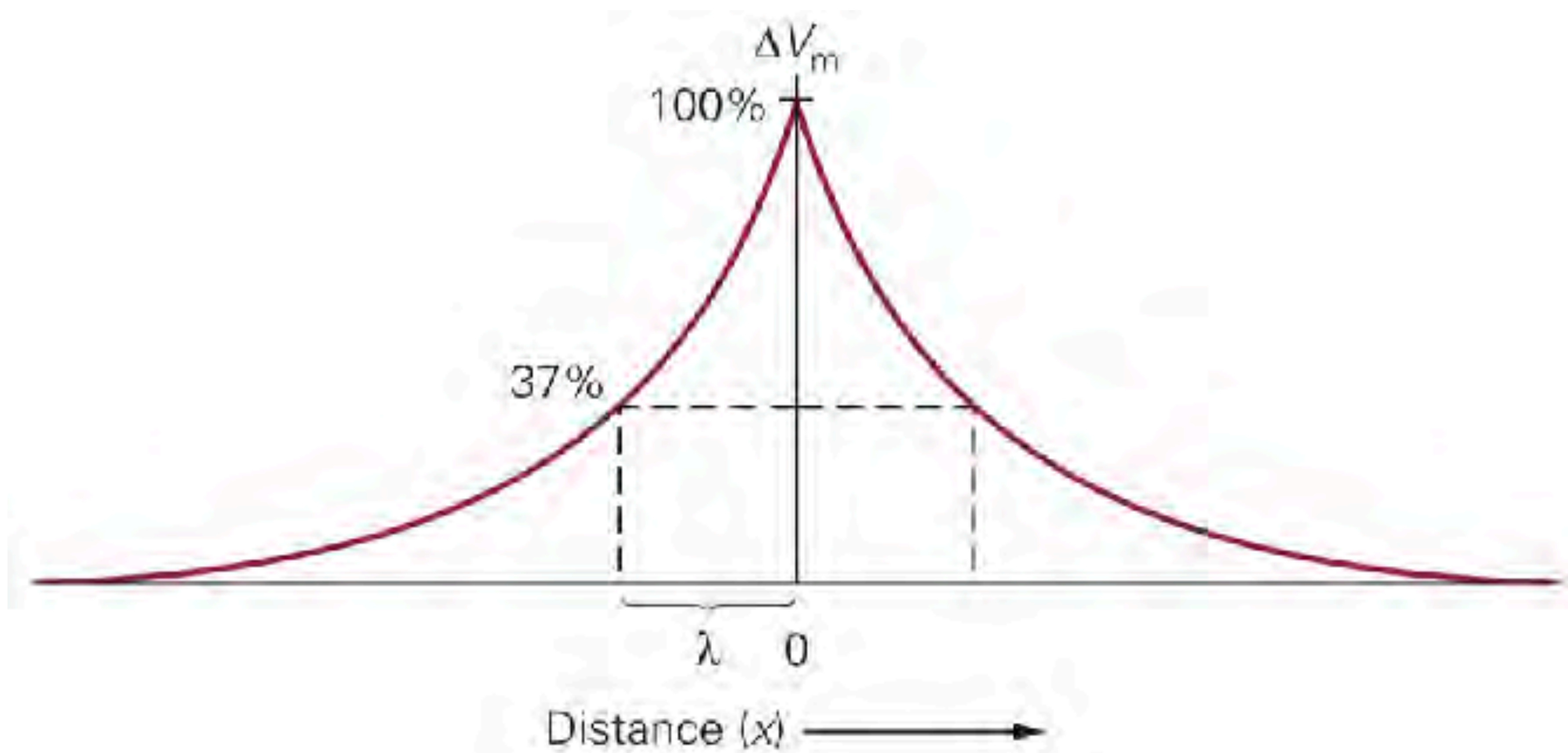


$r_m \propto 1 / (2 \pi \text{ radius})$

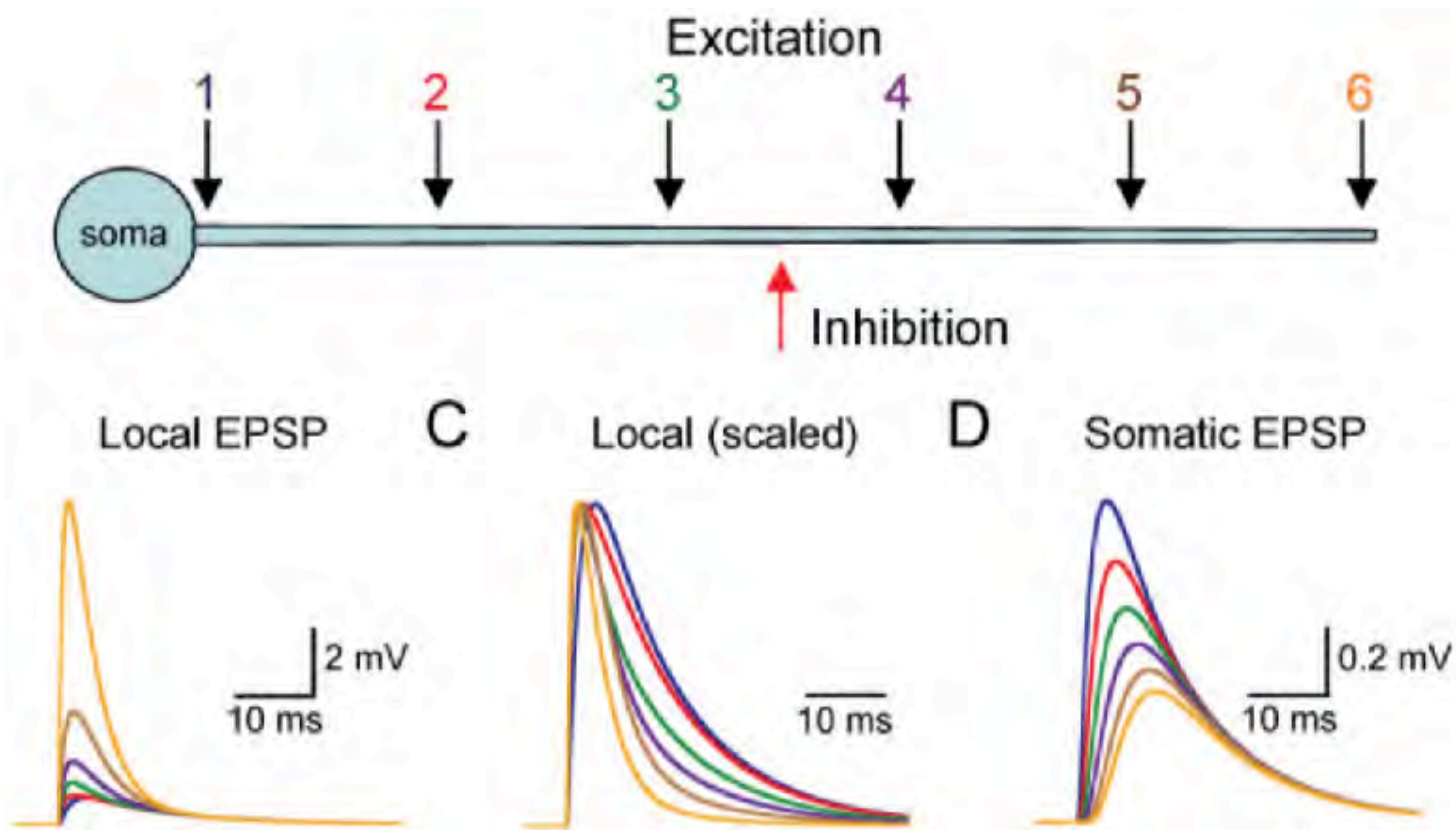
$r_a \propto 1 / (\pi \text{ radius}^2)$

(Fat versus skinny dendrites)

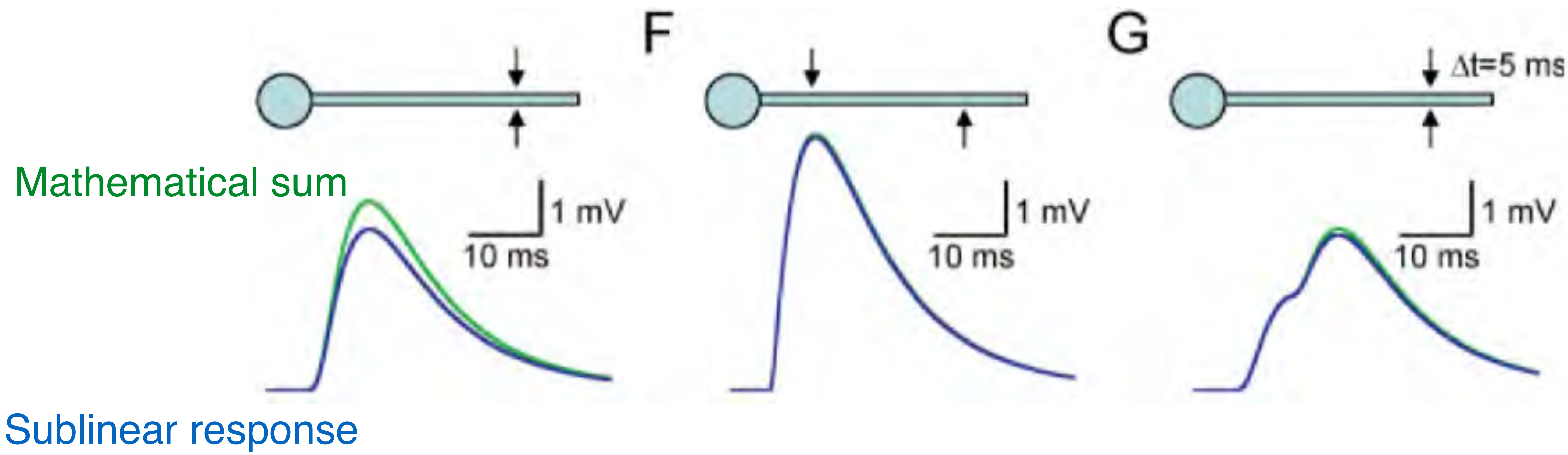




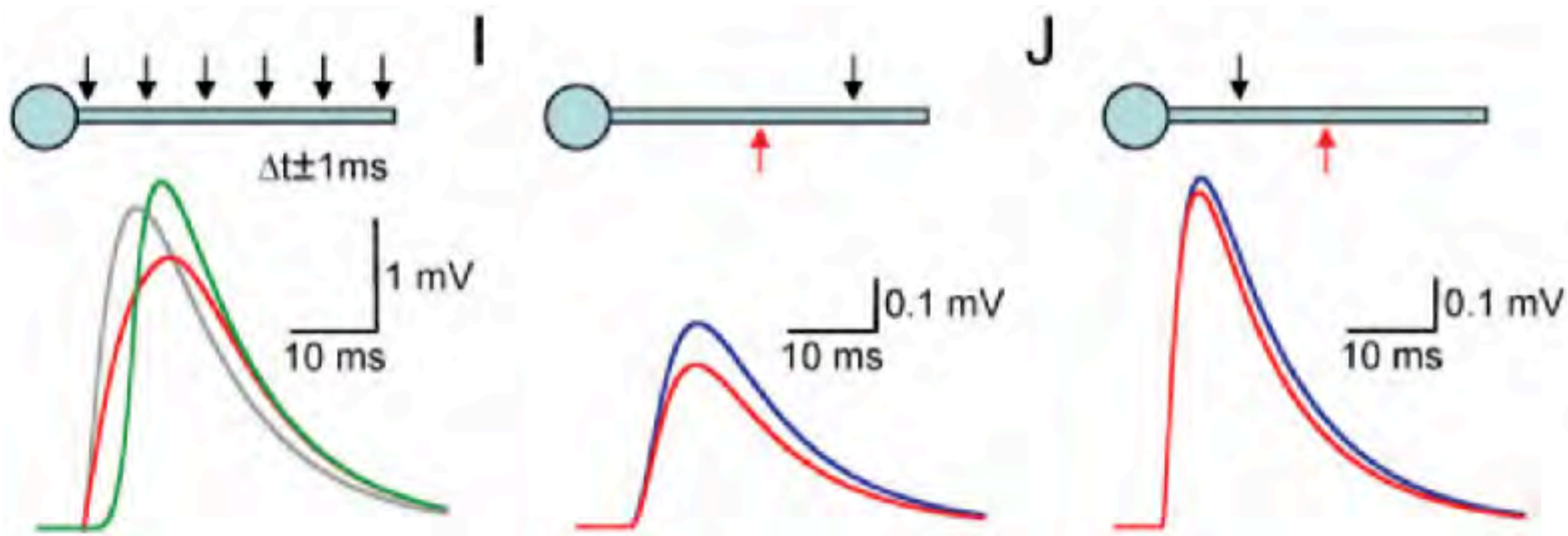
Kandel et al, *Principles of Neuroscience*, 2013



Gulledge *et al, J Neurobiology,* 2005



Gulledge *et al, J Neurobiology,* 2008

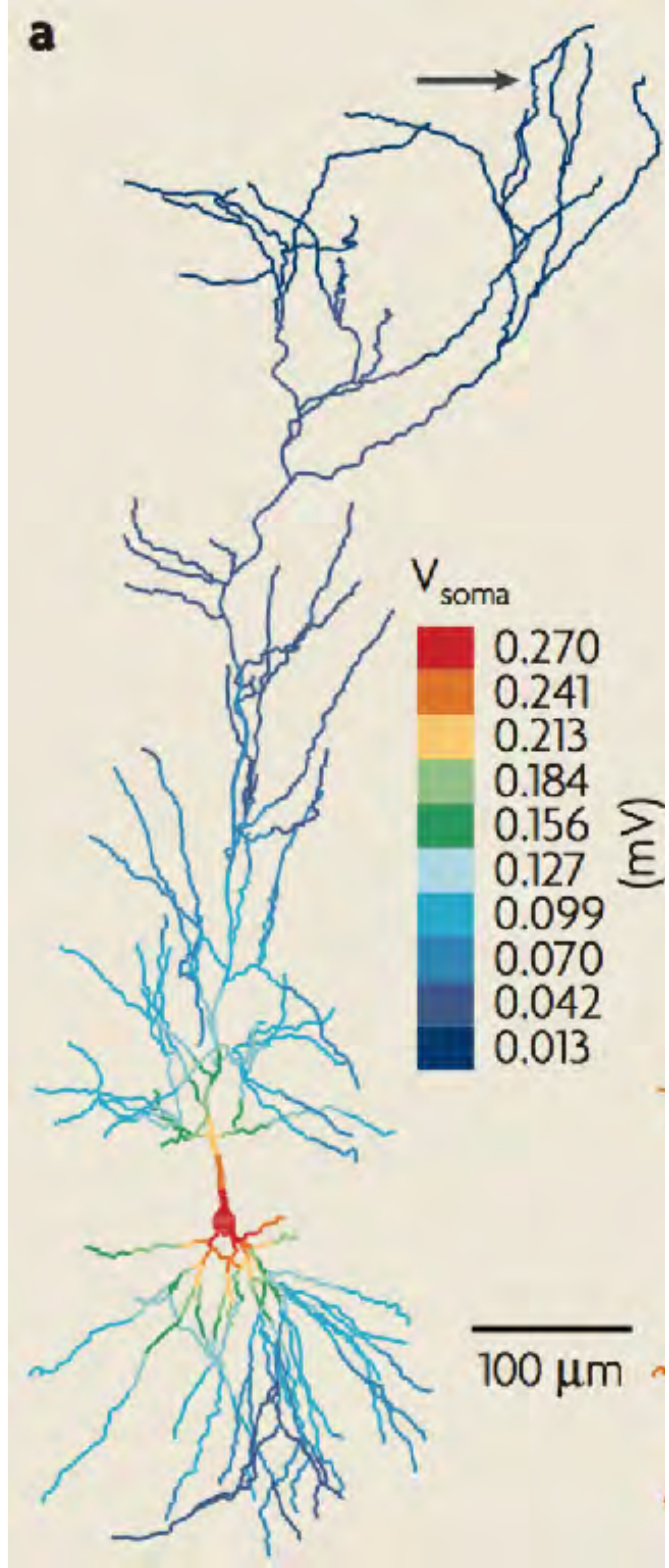


distal to proximal
proximal to distal
simultaneous

EPSP alone
combined response

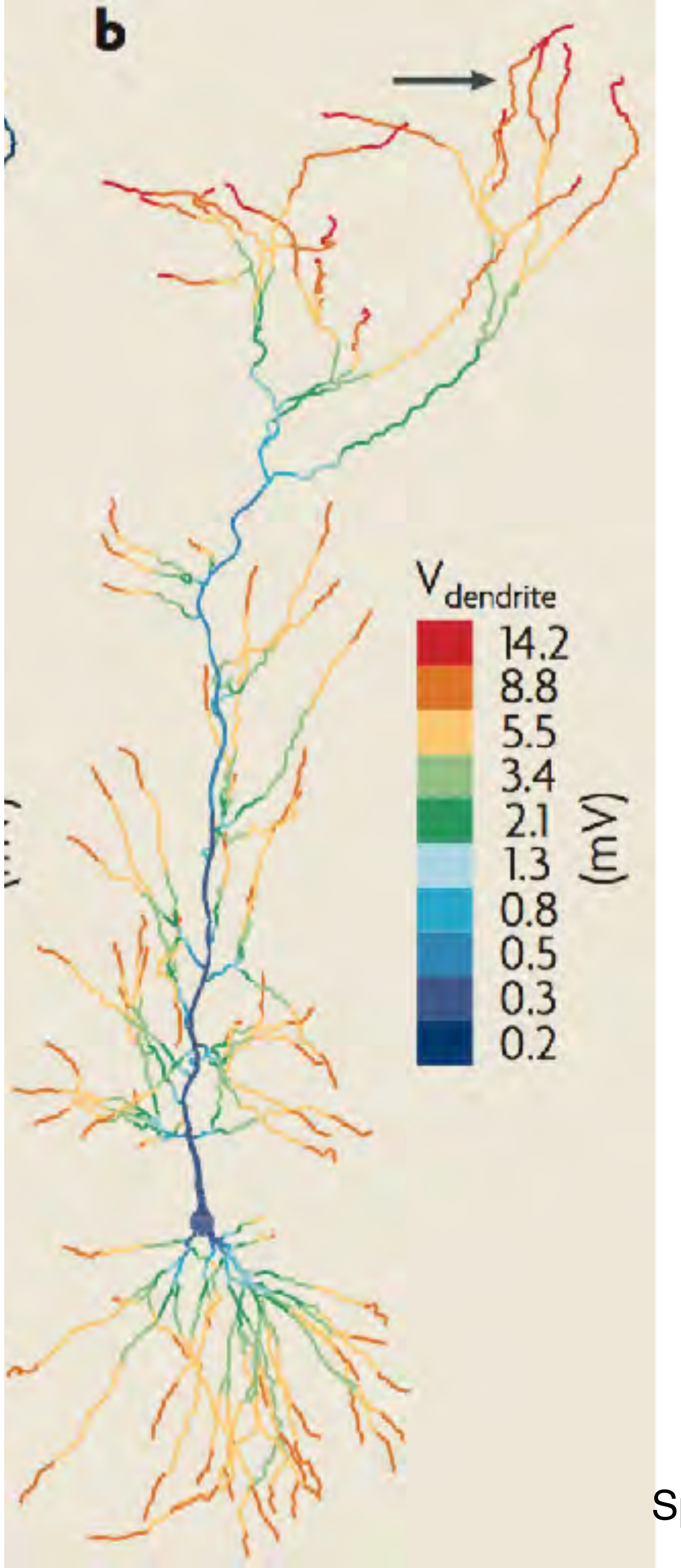
Gulledge *et al, J Neurobiology,* 2008

Relative size of synaptic potentials injected at the soma.



Spruston, *Nat Rev Neurosci,* 2008

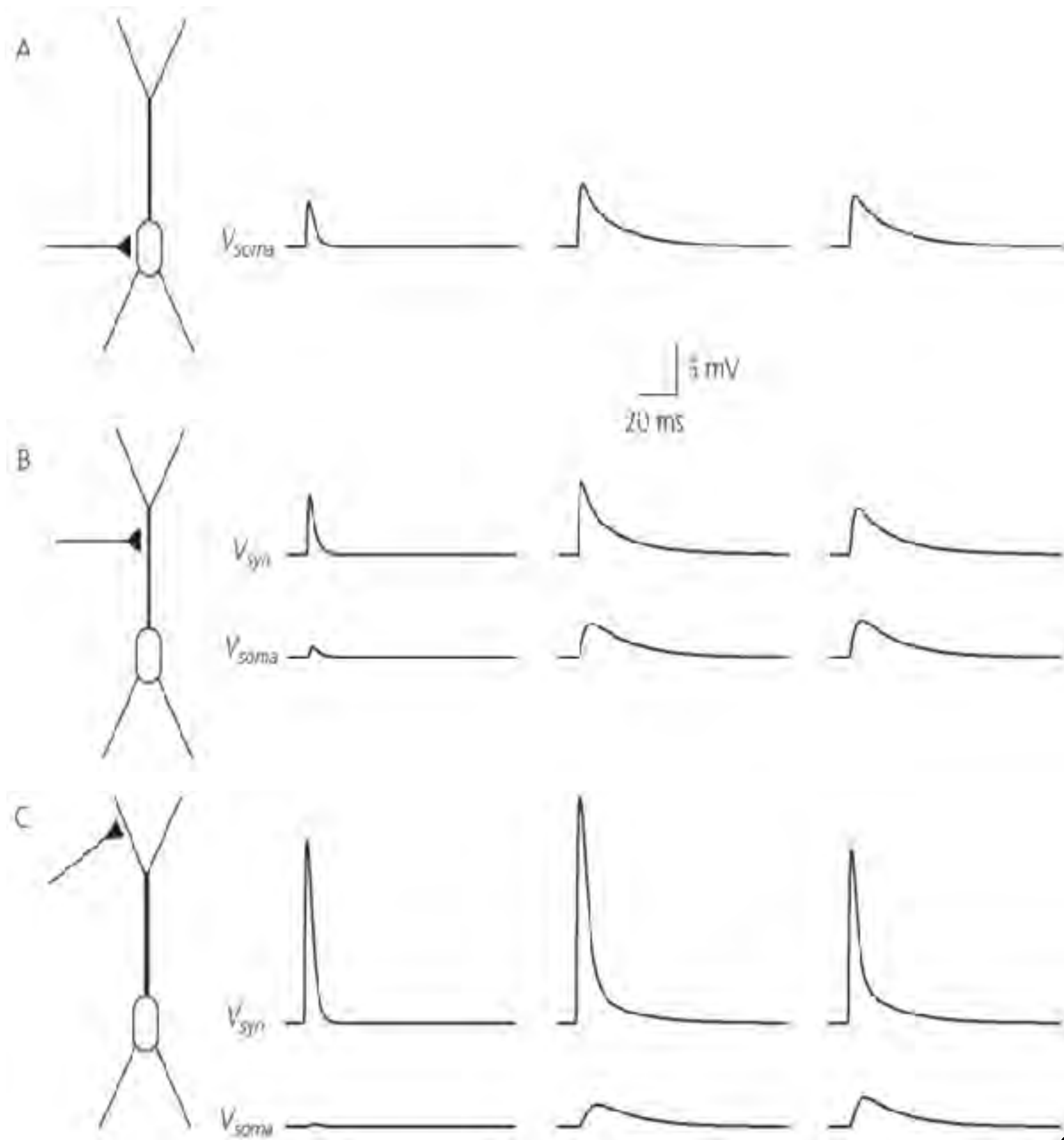
Attenuation of synaptic depolariazations relative to the soma.



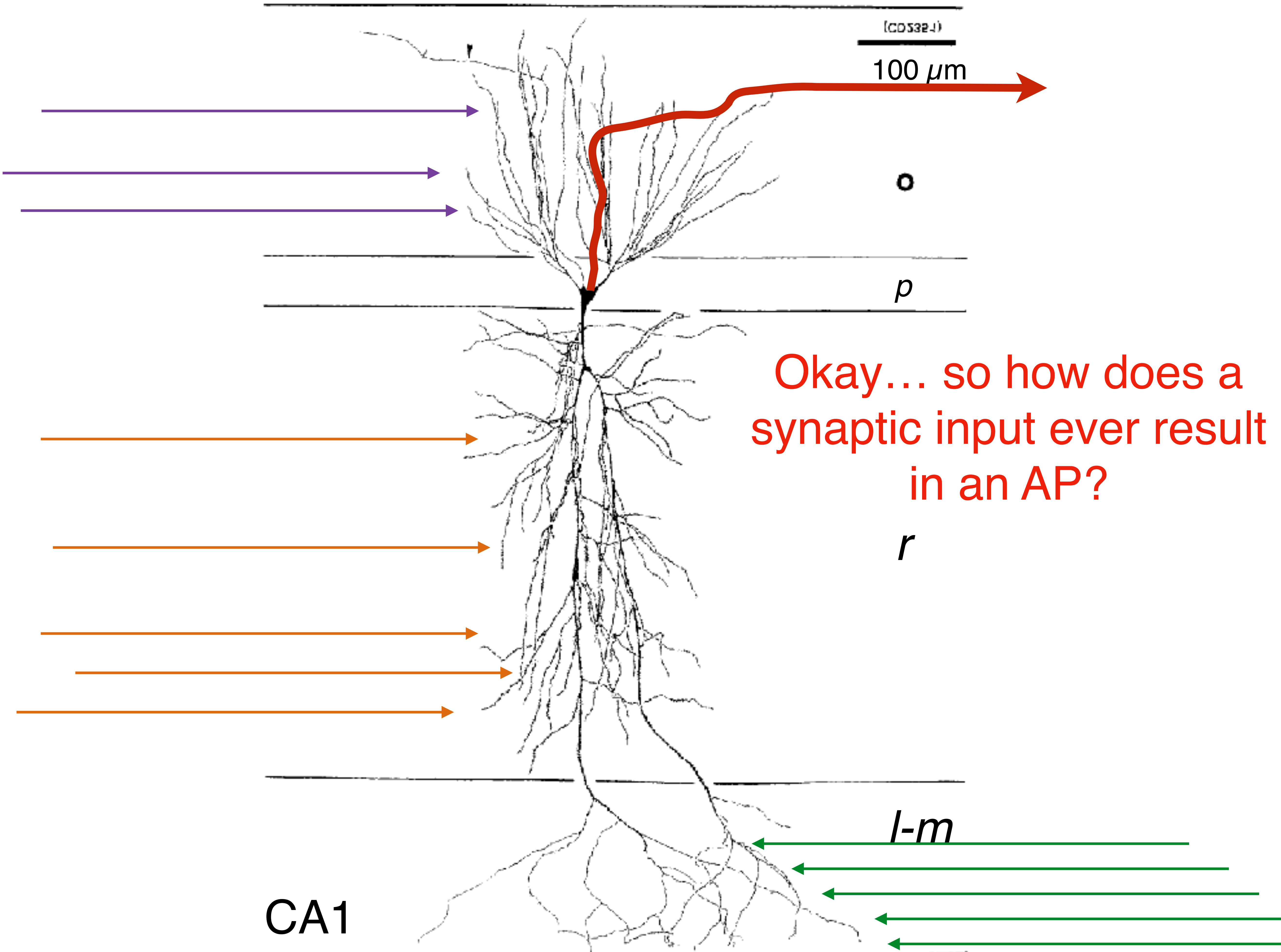
Spruston, *Nat Rev Neurosci,* 2008

Control

membrane resistance	$R_m = 2{,}000\ \Omega cm^2$	$R_m = 20{,}000\ \Omega cm^2$	$R_m = 20{,}000\ \Omega cm^2$
intracellular resistance	$R_i = 150\ \Omega cm$	$R_i = 150\ \Omega cm$	$R_i = 75\ \Omega cm$



Gordon Shepherd, 2003.



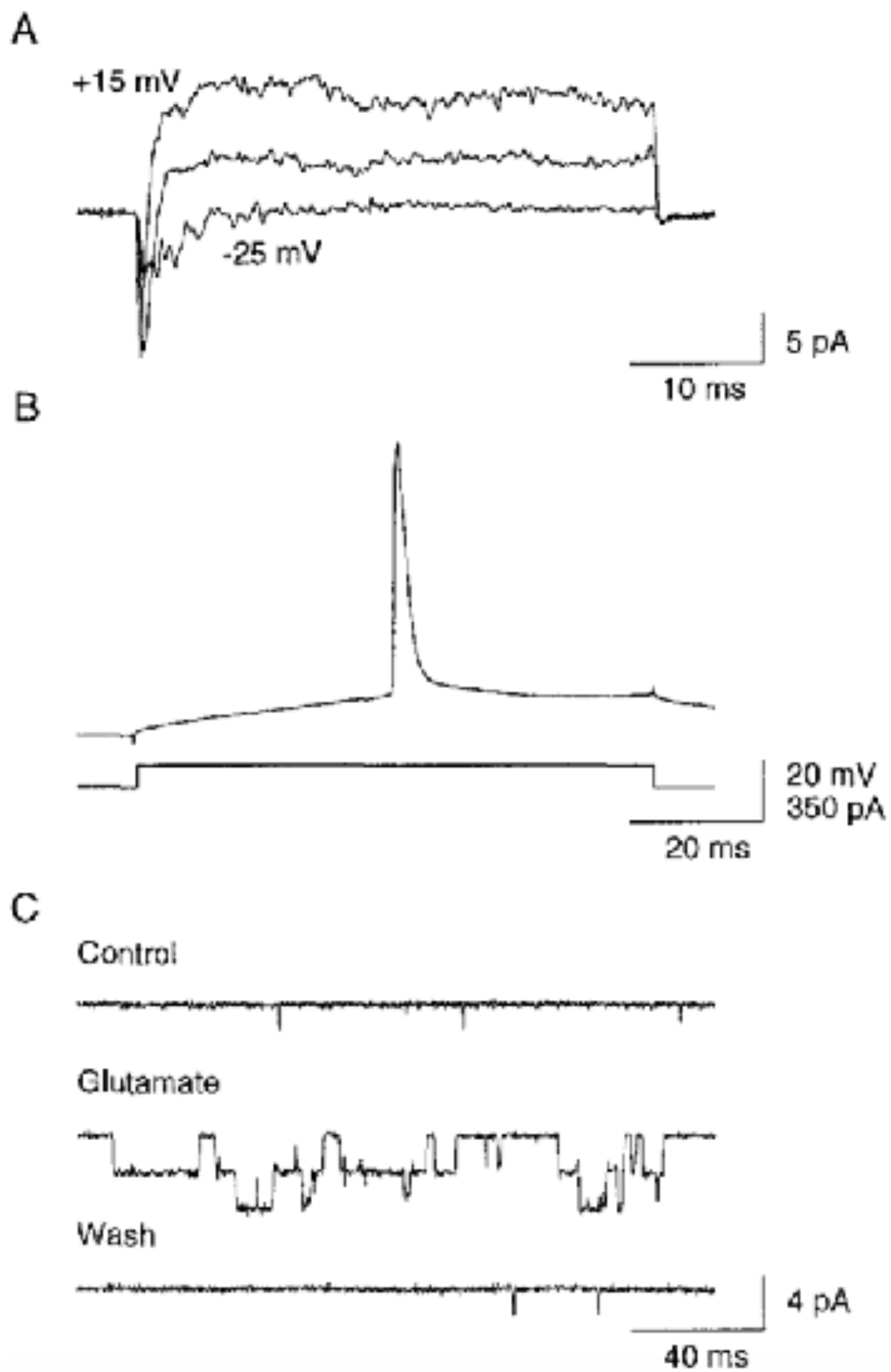
Ishizuka et al, Journal of Comparative Neurobiology, 1995.

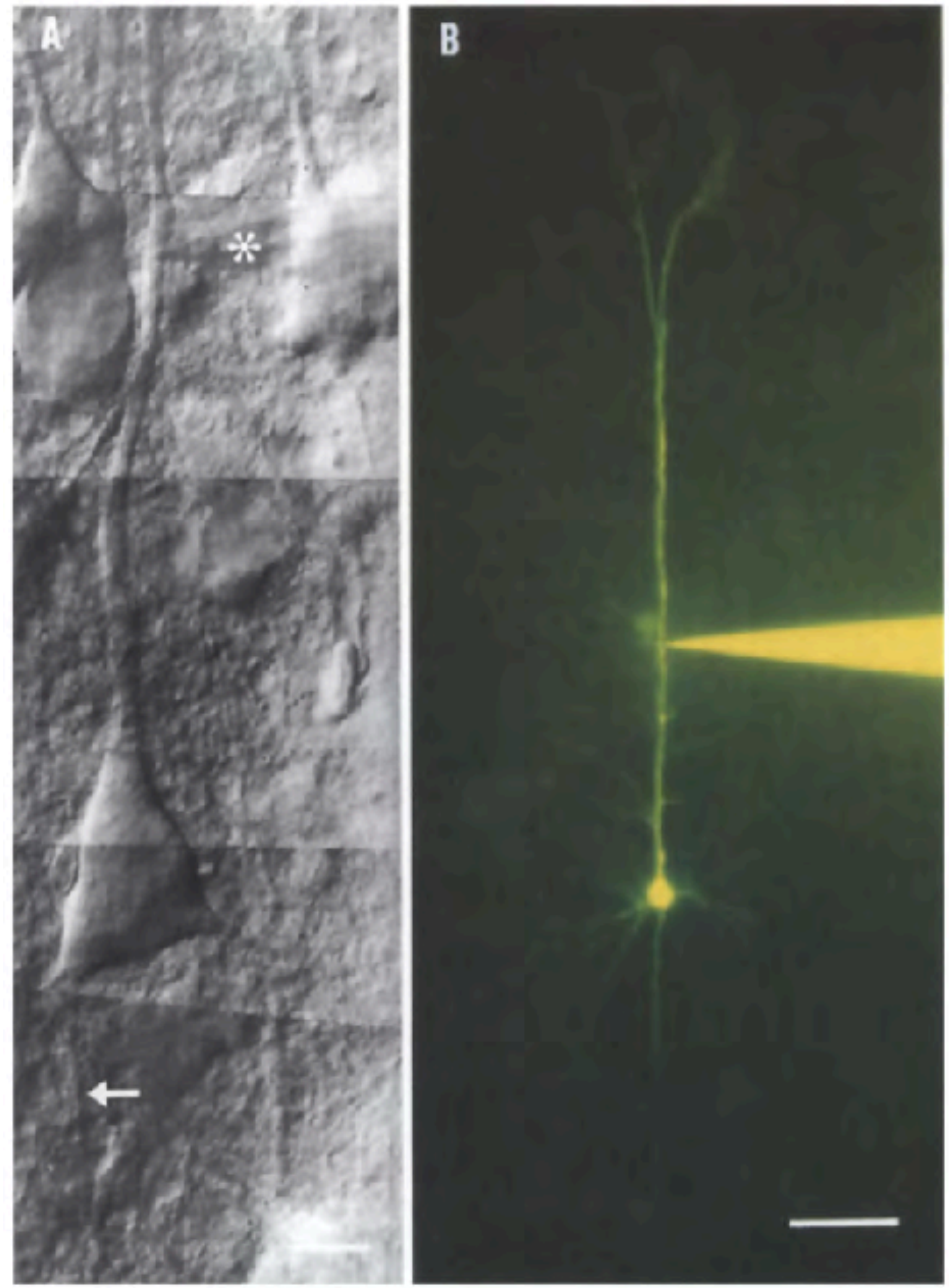
Dendrites have ***active conductances*** that shape integration

Patch-clamp recordings from the soma and dendrites of neurons in brain slices using infrared video microscopy

G. J. Stuart[1], H.-U. Dodt[2], B. Sakmann[1]

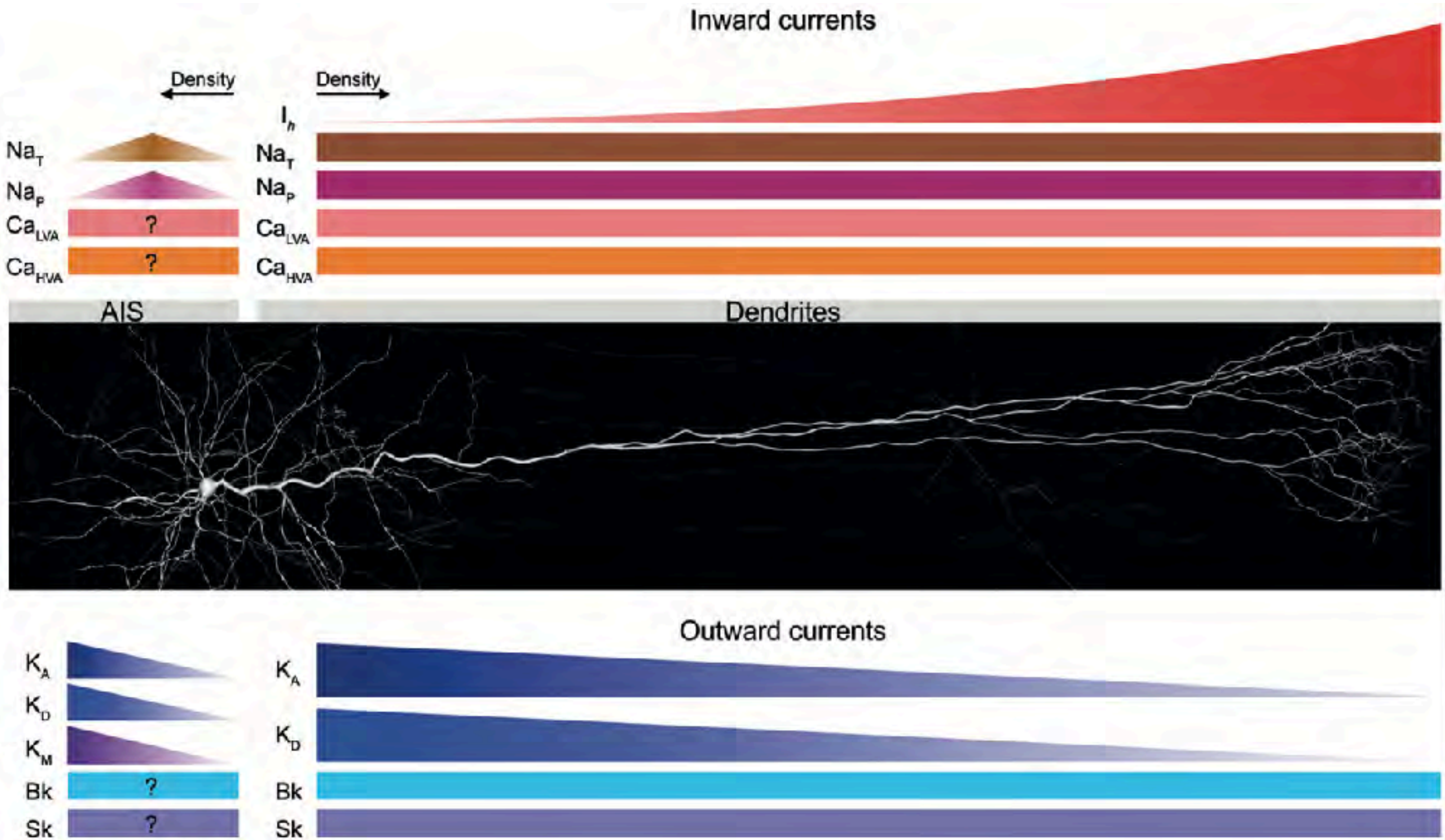
[1] Max-Planck-Institut für medizinische Forschung, Abteilung Zellphysiologie, Jahnstrasse 29, W-6900 Heidelberg, Germany
[2] Max-Planck-Institut für Psychiatrie, Klinisches Institut, Kraepelinstrasse 2, W-8000 München 40, Germany





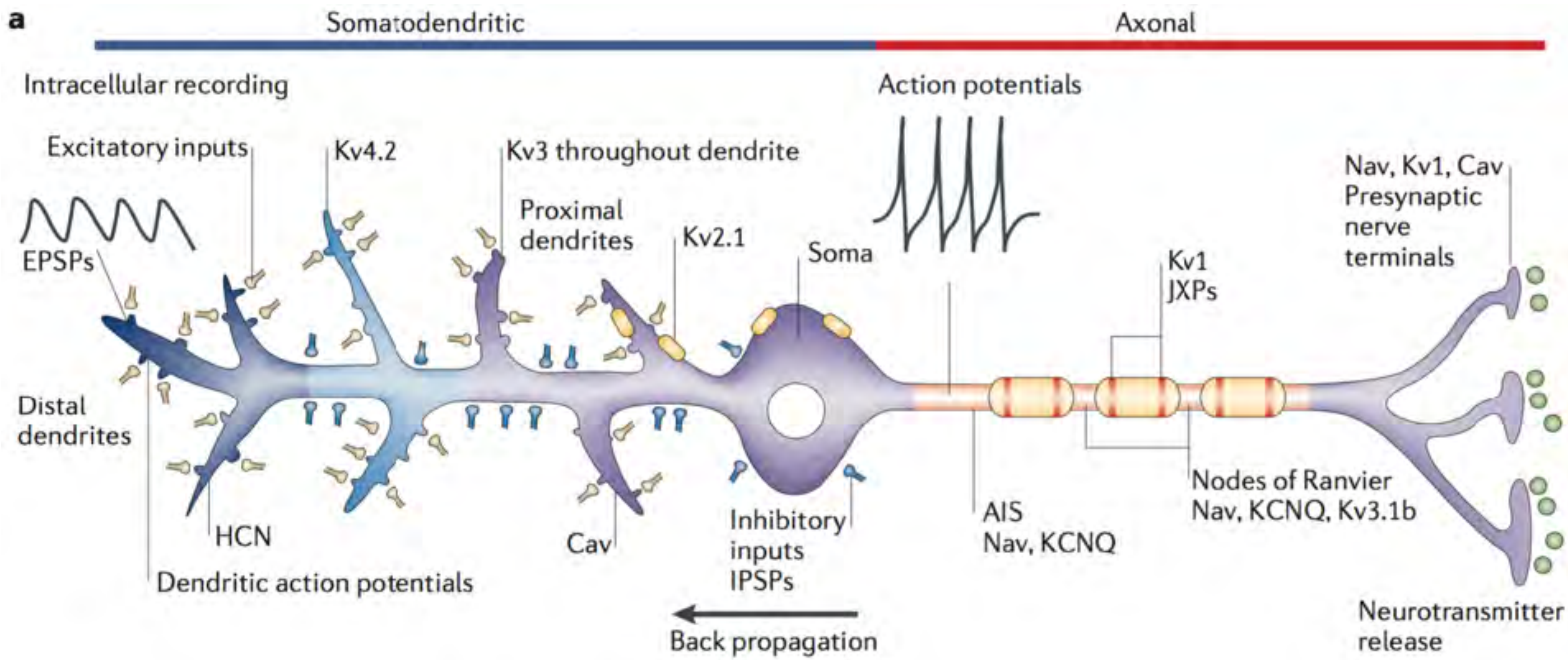
Dendrites have ***active conductances*** that shape integration

Layer 5 pyramidal neuron



Ramaswamy & Markram *Frontiers Cellular Neuroscience*, 2015

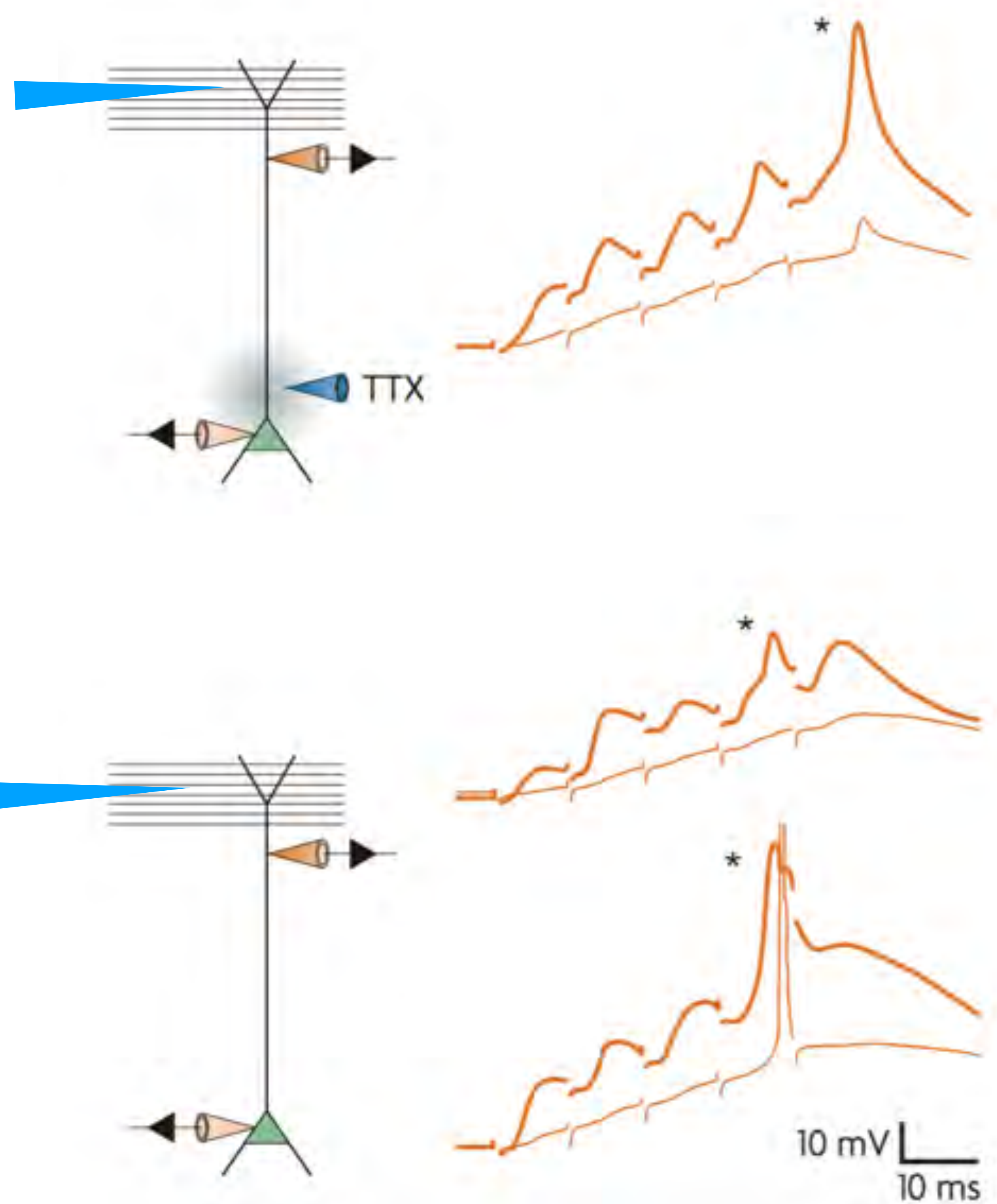
Dendrites have ***active conductances*** that shape integration



H. Lau and L. Jan, *Nat Rev Neuroscience, 2006*

Dendrites can spike!!

Stimulation



Stimulation

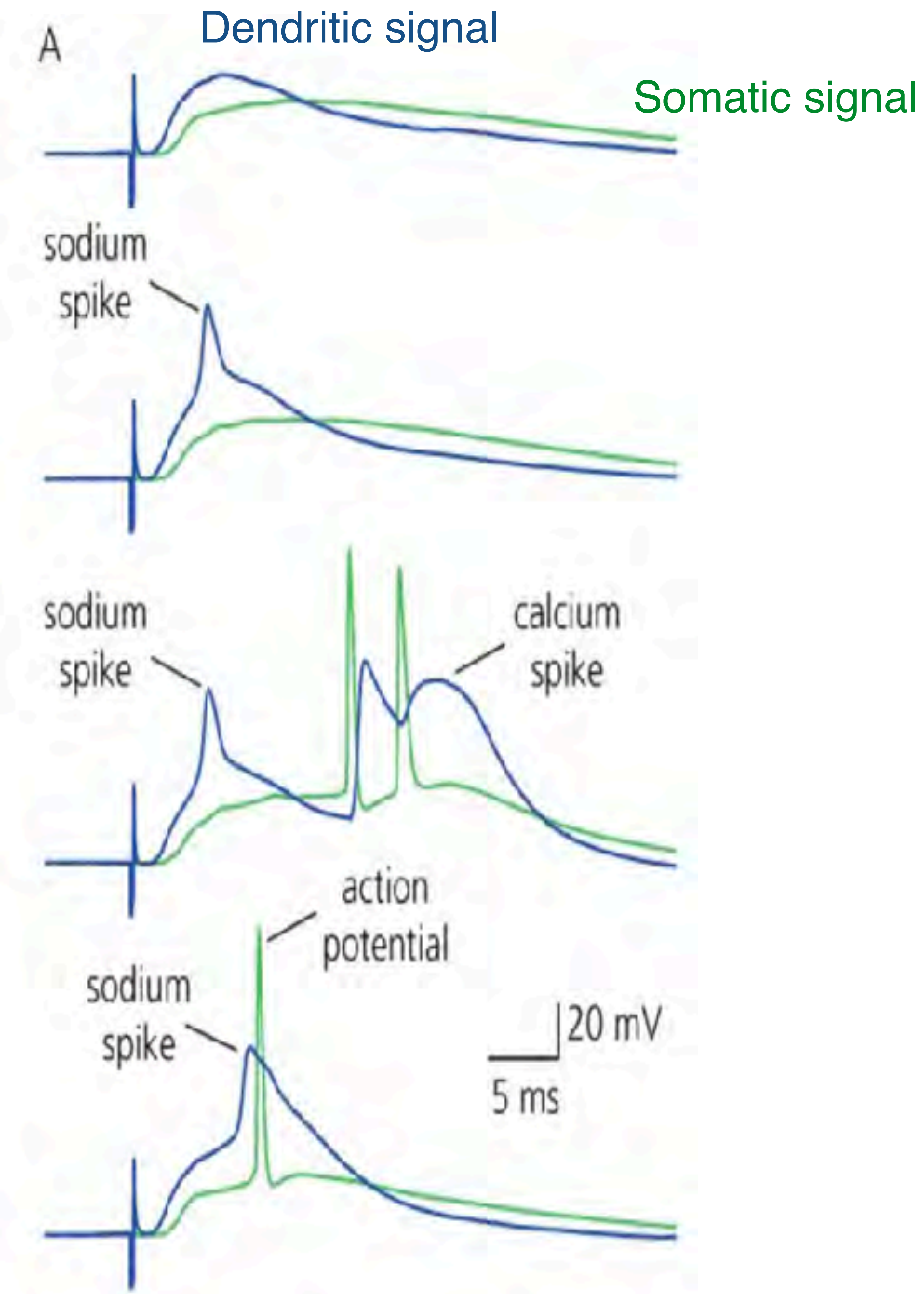
Na_V channels and K_V channels produce **sodium spikes**

low

high

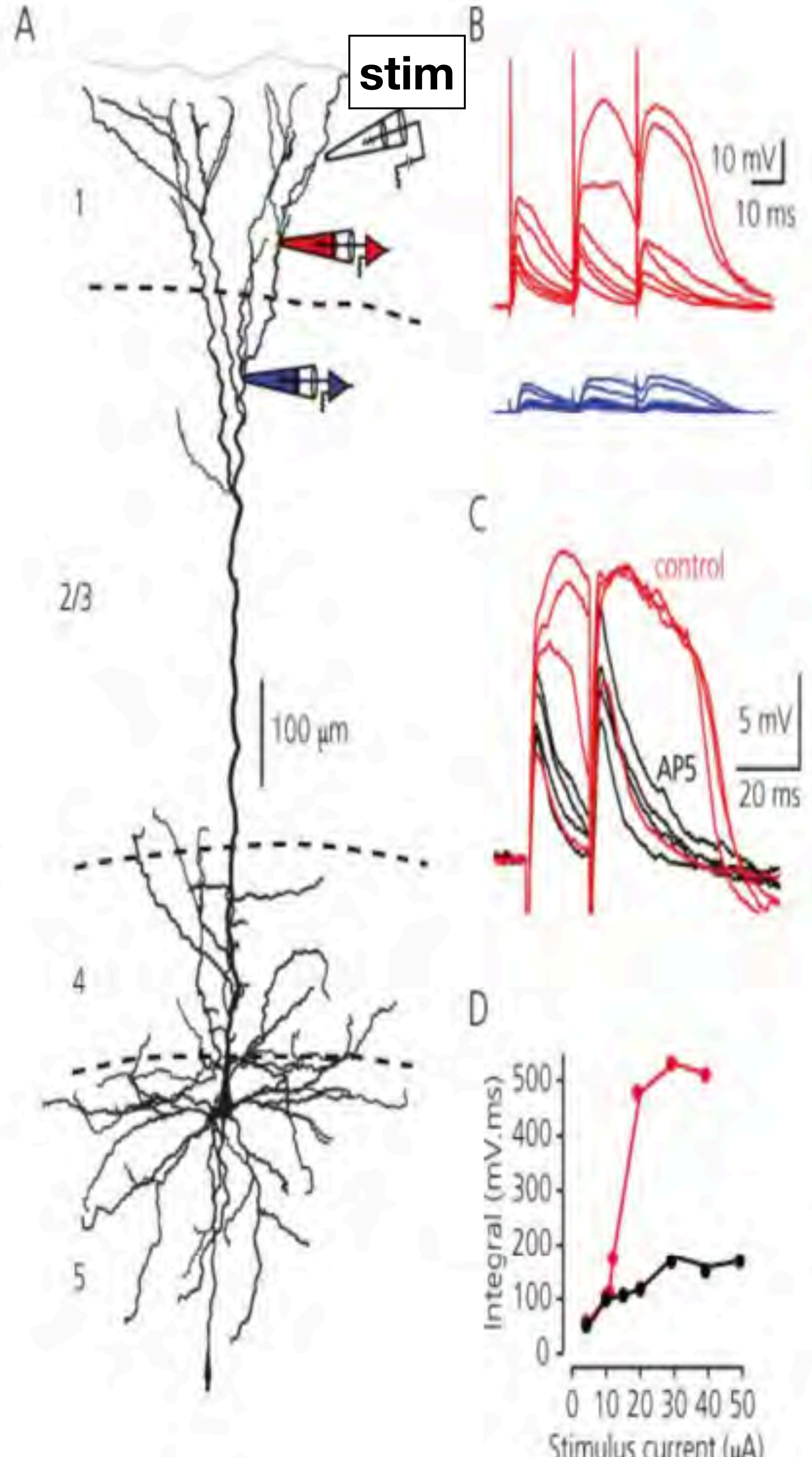
Spruston, *Nat Rev Neurosci*, 2008

Dendrites have ***active conductances*** that shape integration

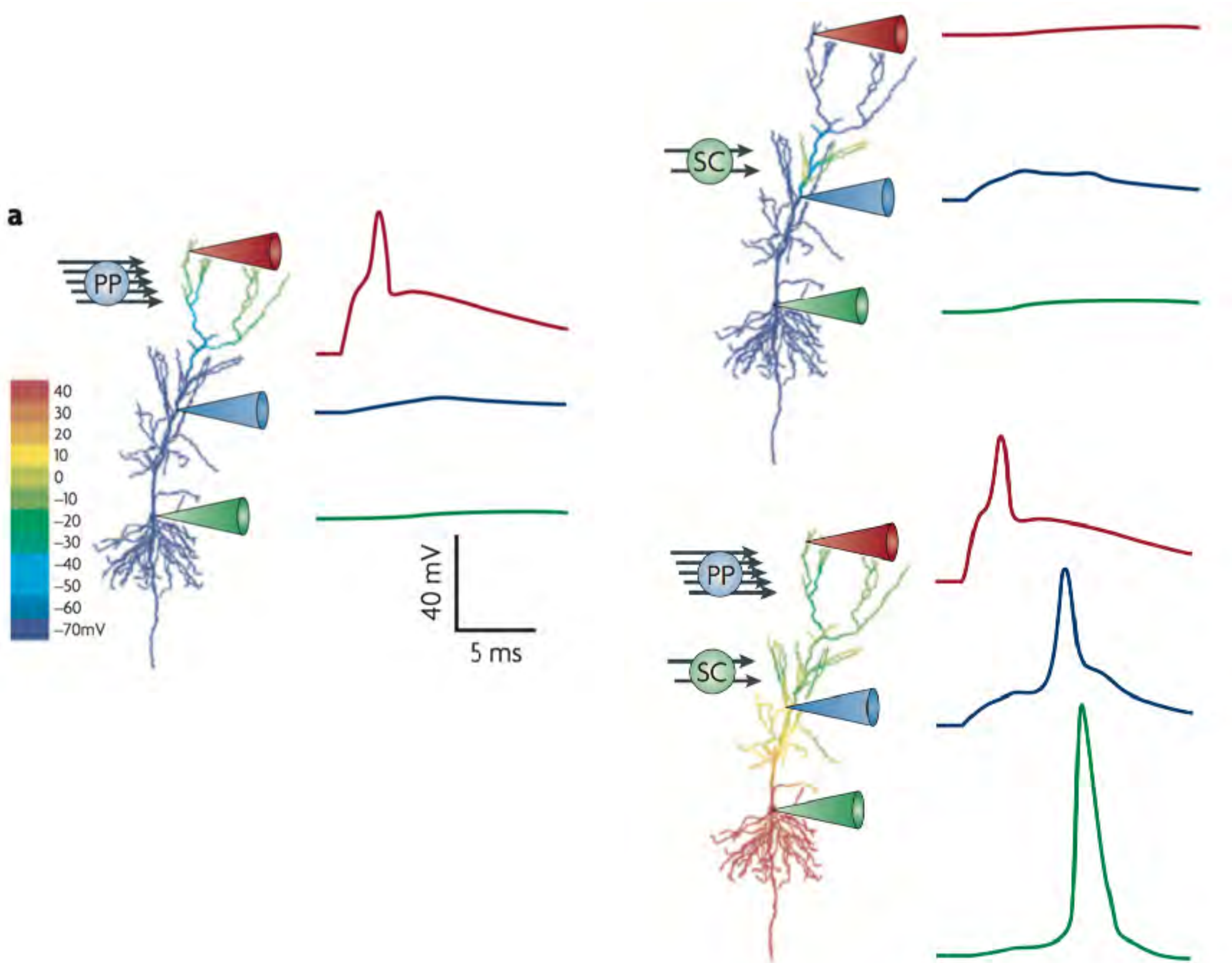


Ca_V channels and K_V channels produce **calcium spikes**

NMDA receptor activation leads to large depolarisation in dendrites

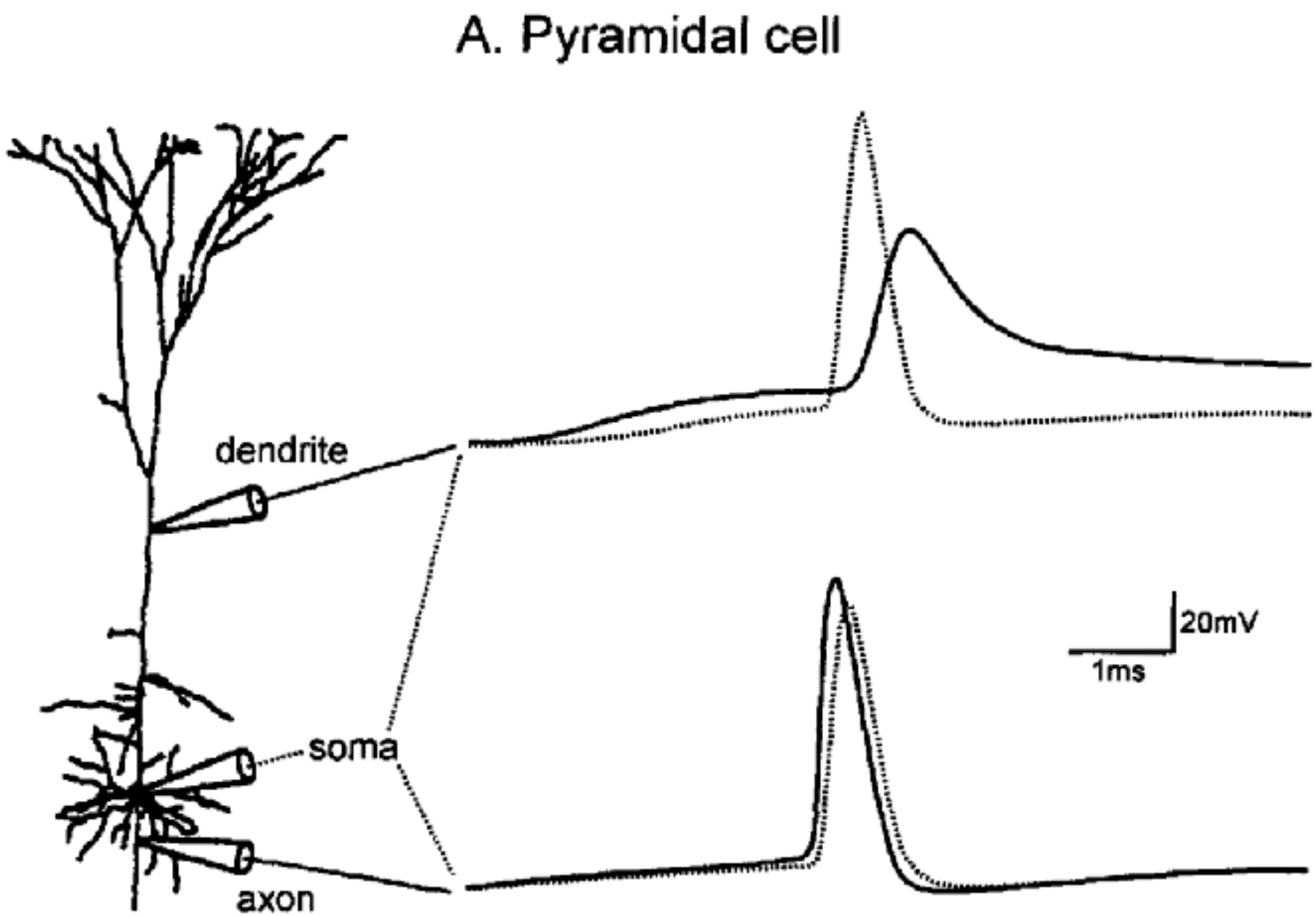


Dendrites as coincidence detectors:



Jarsky, et al, *Nature Neuroscience* 2005

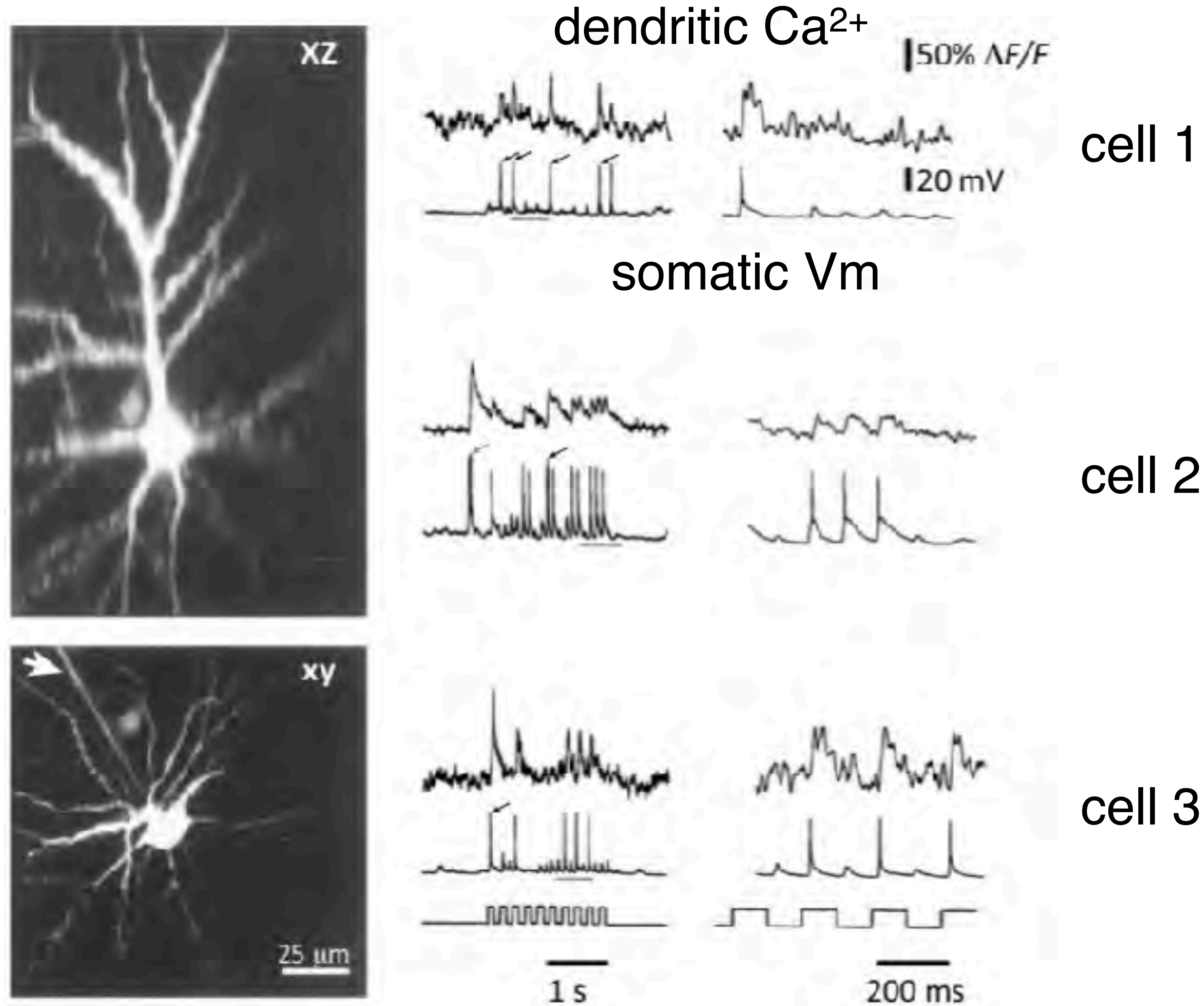
Backpropagation of action potentials to dendritic compartment



Gordon Shepherd, 2003.

Backpropagating action potential *in vivo.*

Cortical layer 2/3 pyramidal neurons



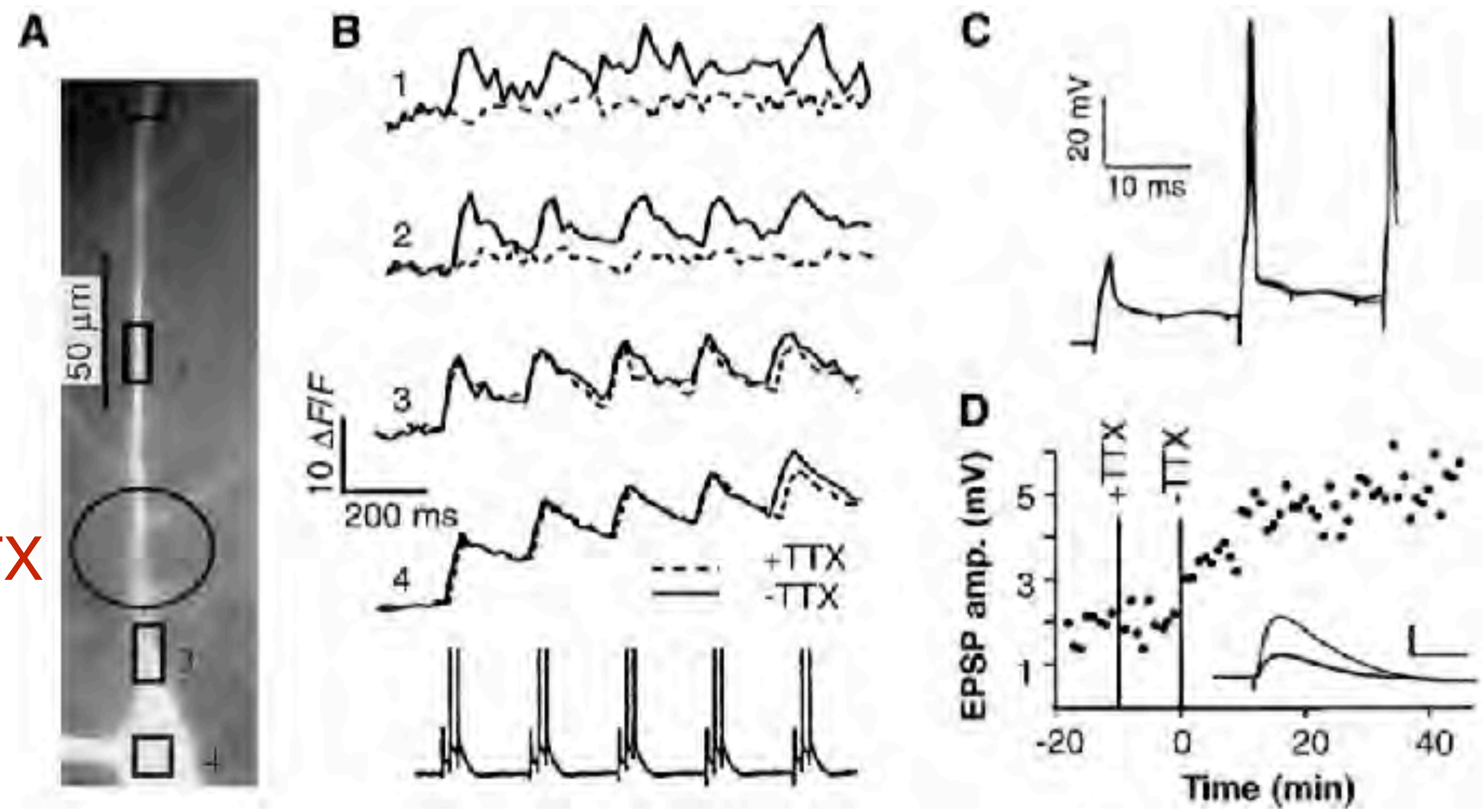
Szoboda et al, *Nature* 1997

Propagation of action potentials to dendritic compartment **strengthens synaptic input**

A Synaptically Controlled, Associative Signal for Hebbian Plasticity in Hippocampal Neurons

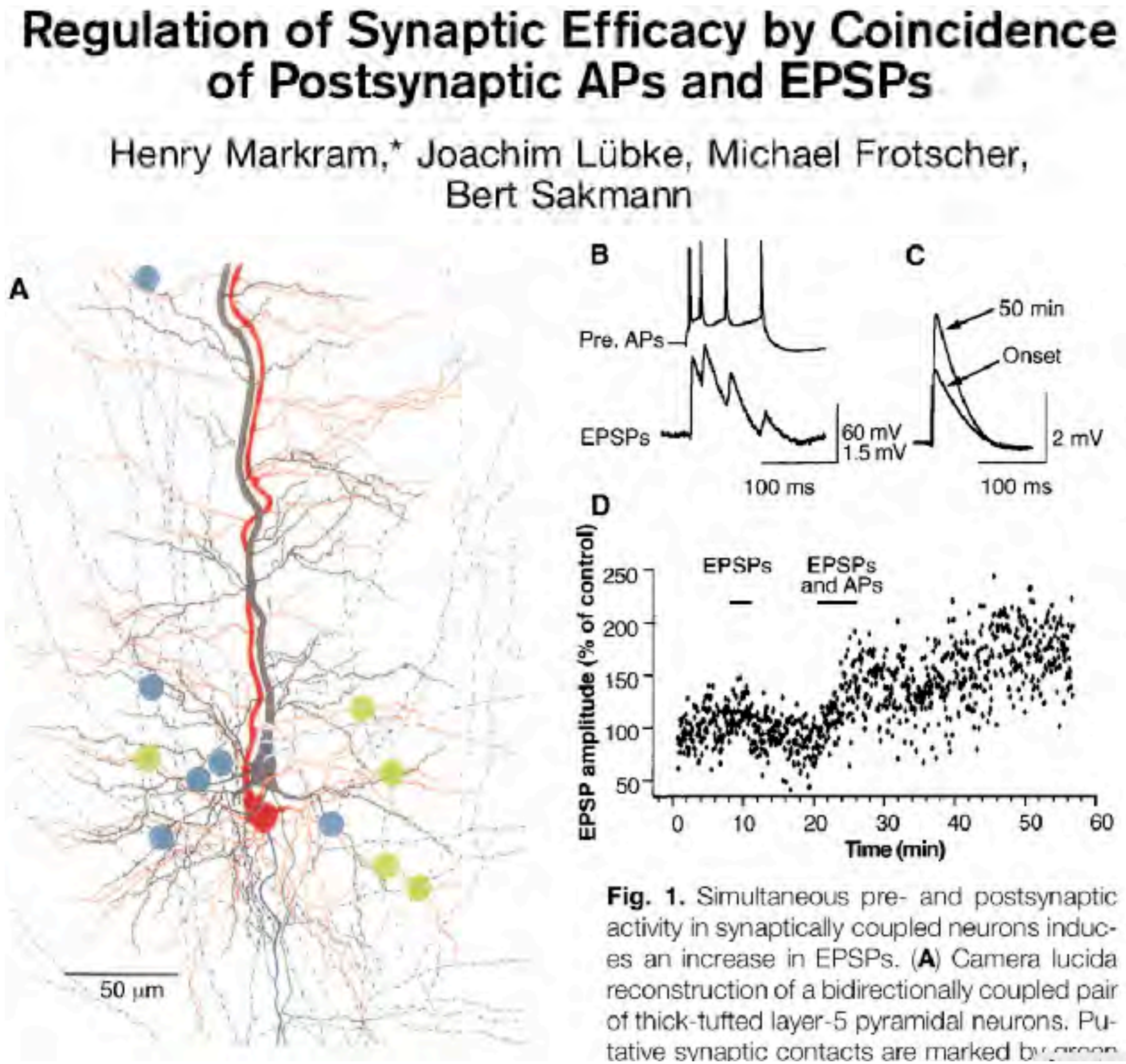
Jeffrey C. Magee and Daniel Johnston

puffed TTX



Science, 1997

Propagation of action potentials to dendritic compartment **strengthens synaptic input**



Regulation of Synaptic Efficacy by Coincidence of Postsynaptic APs and EPSPs

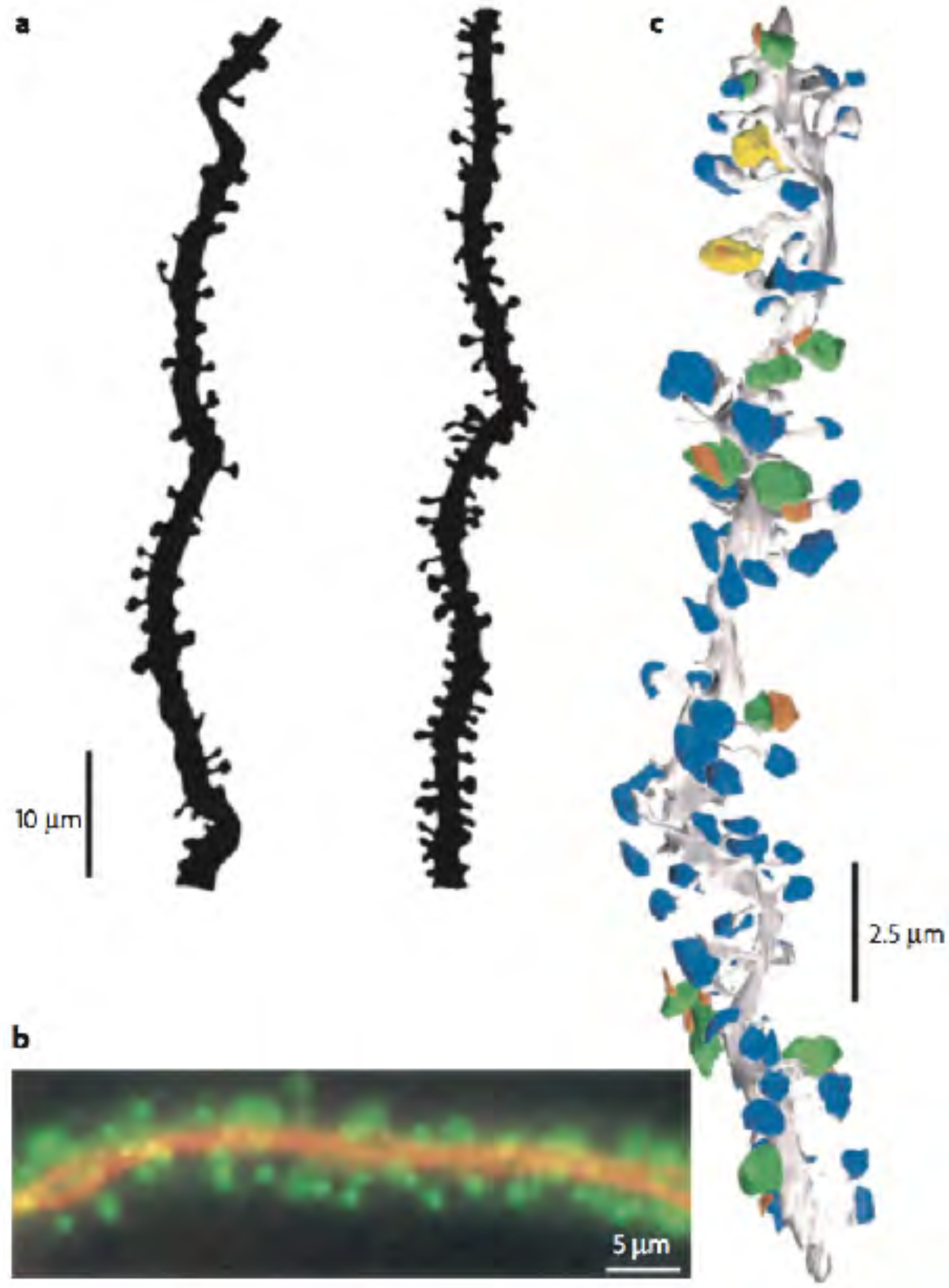
Henry Markram,* Joachim Lübke, Michael Frotscher, Bert Sakmann

Fig. 1. Simultaneous pre- and postsynaptic activity in synaptically coupled neurons induces an increase in EPSPs. (**A**) Camera lucida reconstruction of a bidirectionally coupled pair of thick-tufted layer-5 pyramidal neurons. Putative synaptic contacts are marked by green

Science, 1997

Compartments *of dendrites enable computation:*

Morphology

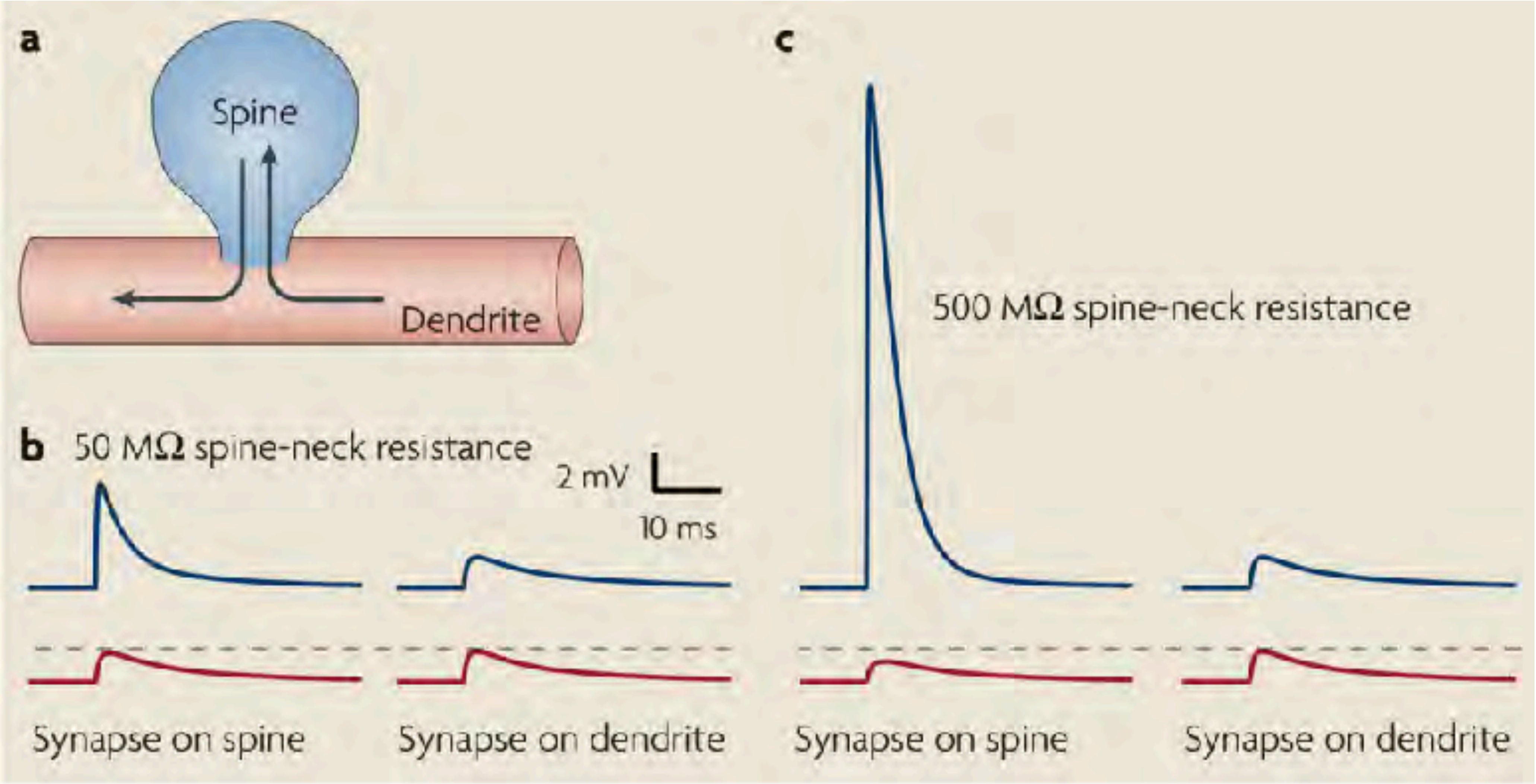


Spruston, Nat Rev Neurosci, 2008

***Compartments** of dendrites enable computation:*

Morphology

Electrical properties



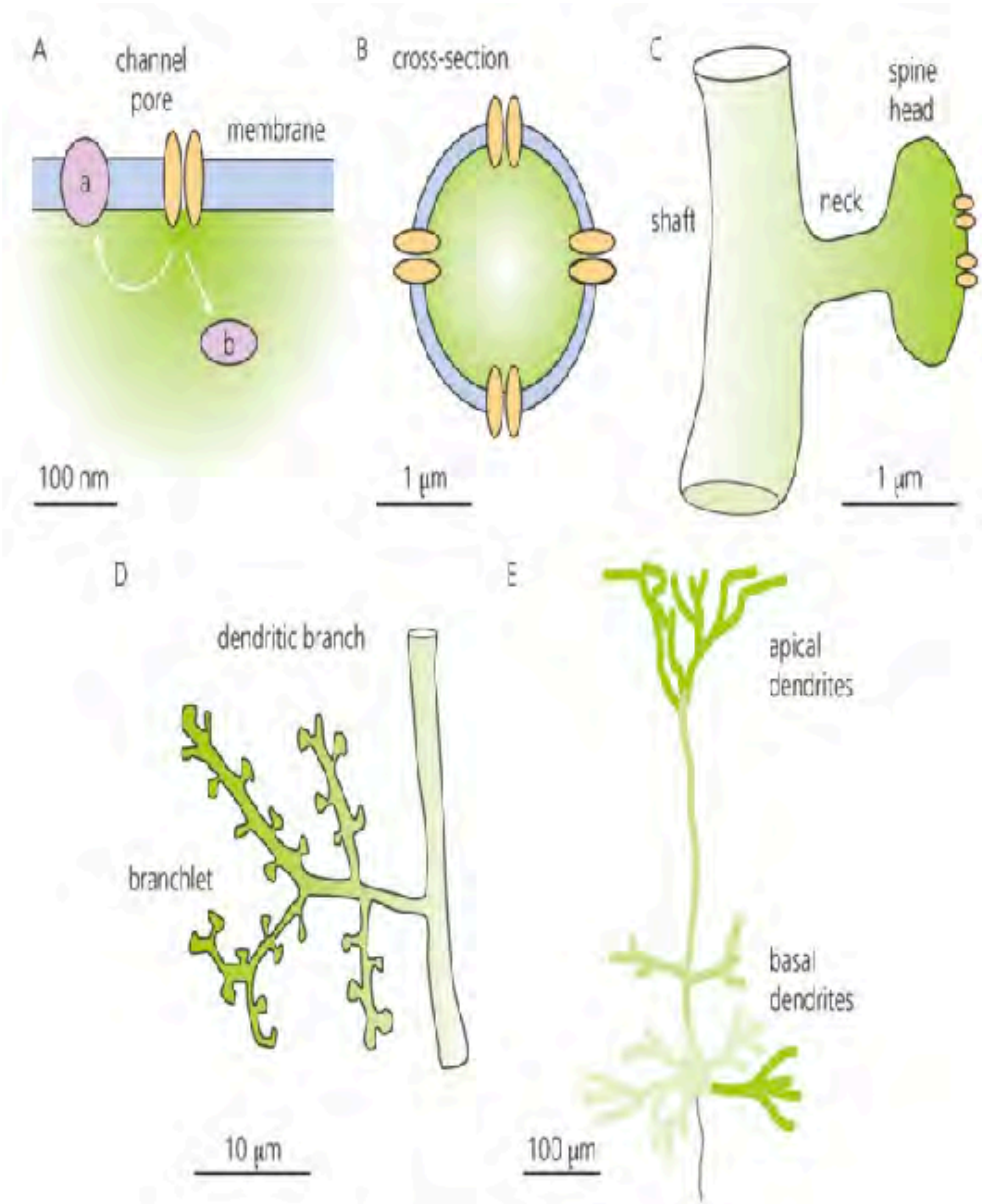
Spruston, Nat Rev Neurosci, 2008

***Compartments** of dendrites enable computation:*

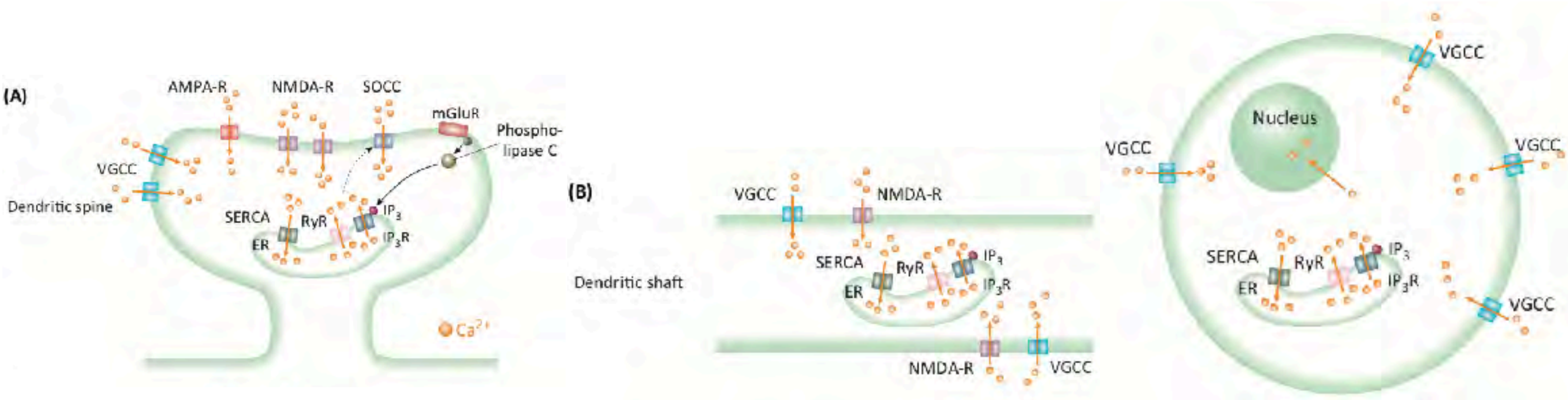
Morphology

Electrical properties

Calcium dynamics



Compartments *of dendrites enable computation:*



Grienberger et al, Trends in Neruosci, 2015

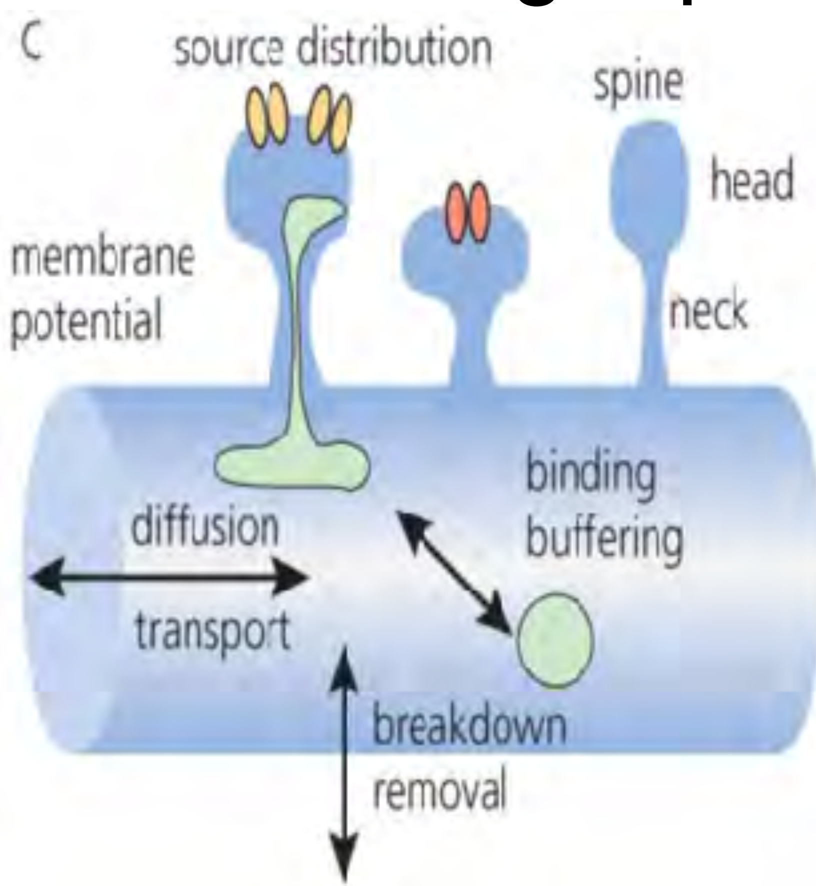
Compartments *of dendrites enable computation:*

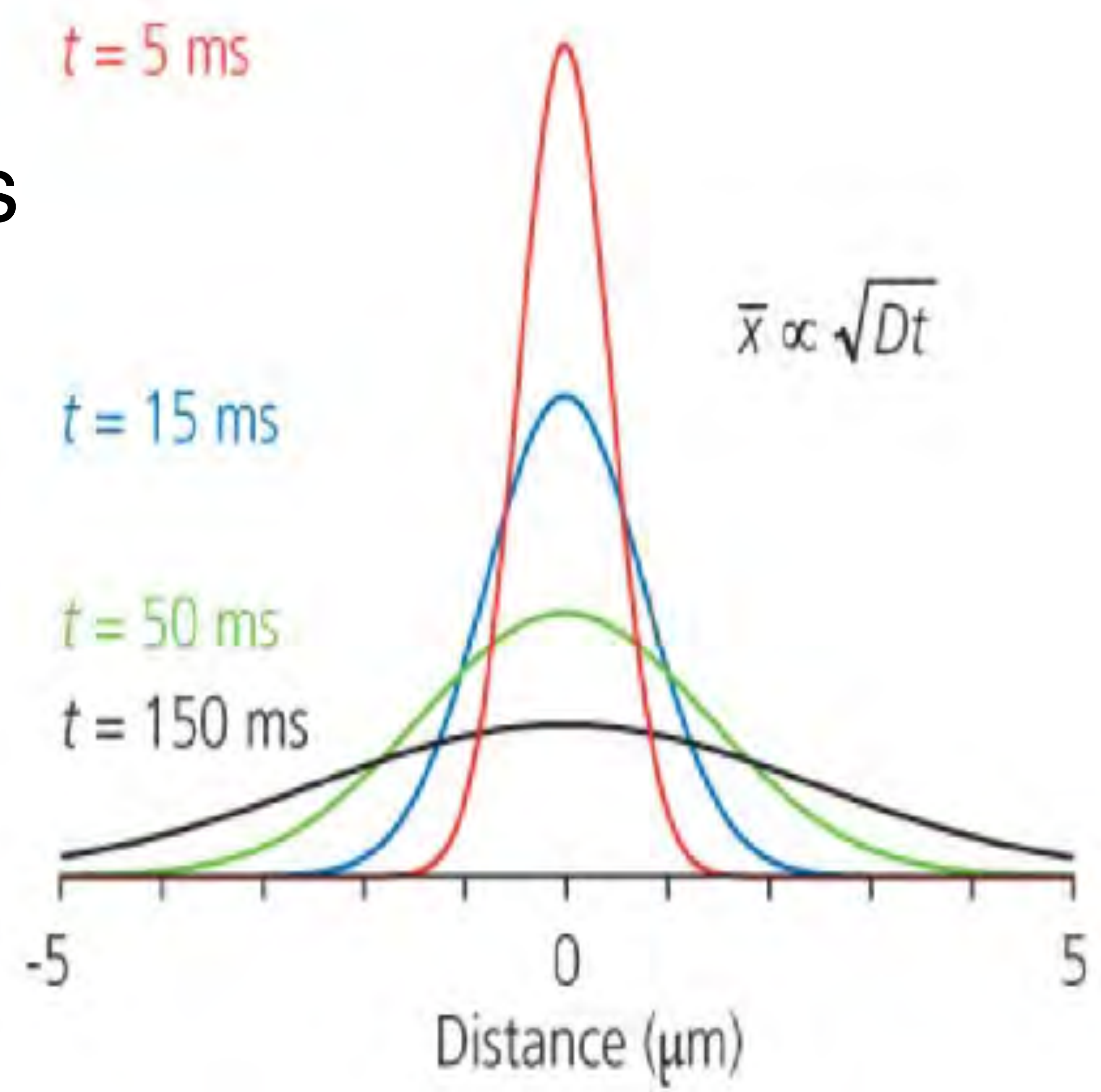
Morphology

Electrical properties

Calcium dynamics

Second messenger pathways





Dendrites consist of ***compartments*** that are distinct by:

Morphology

Electrical properties

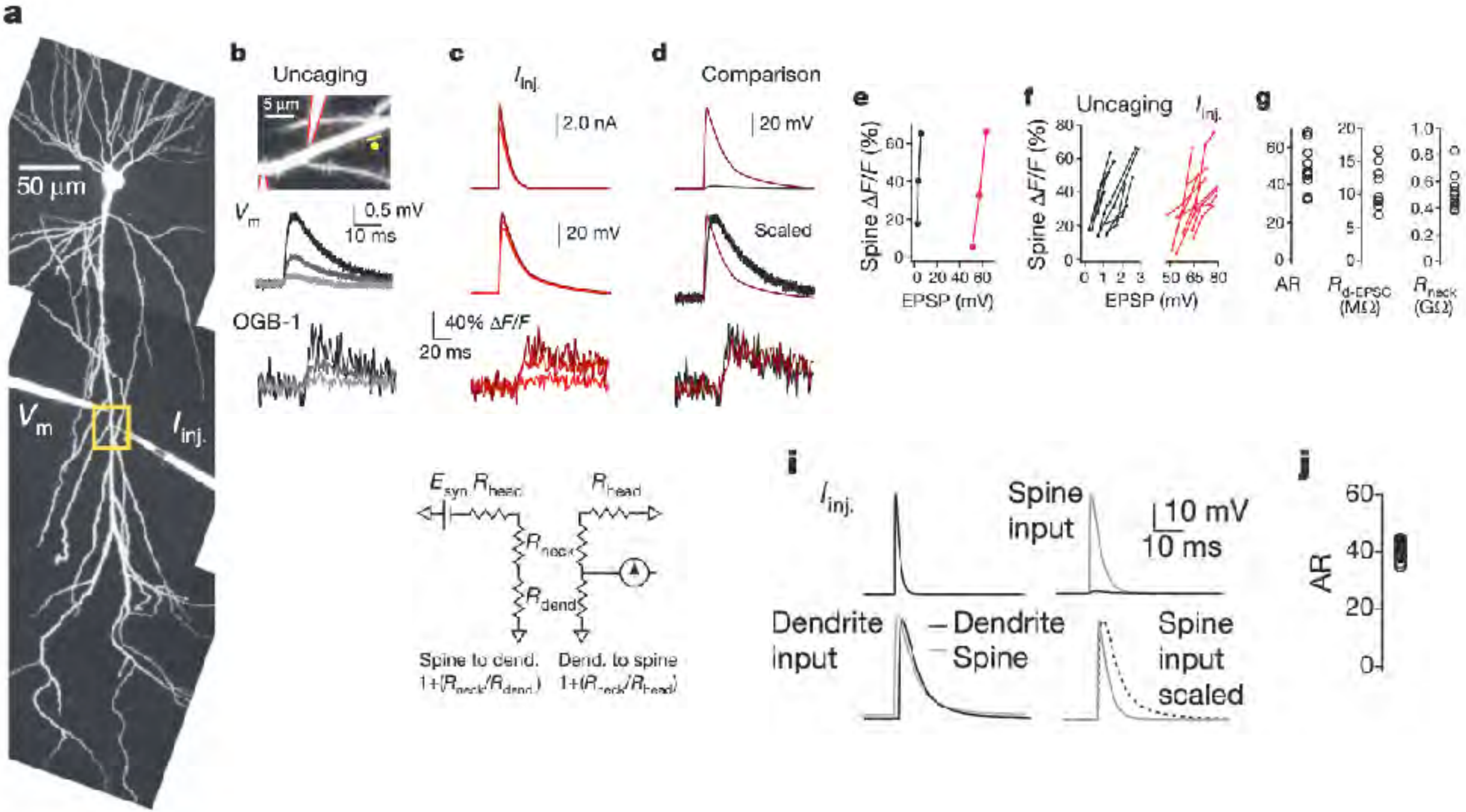
Calcium dynamics

Second messenger pathways

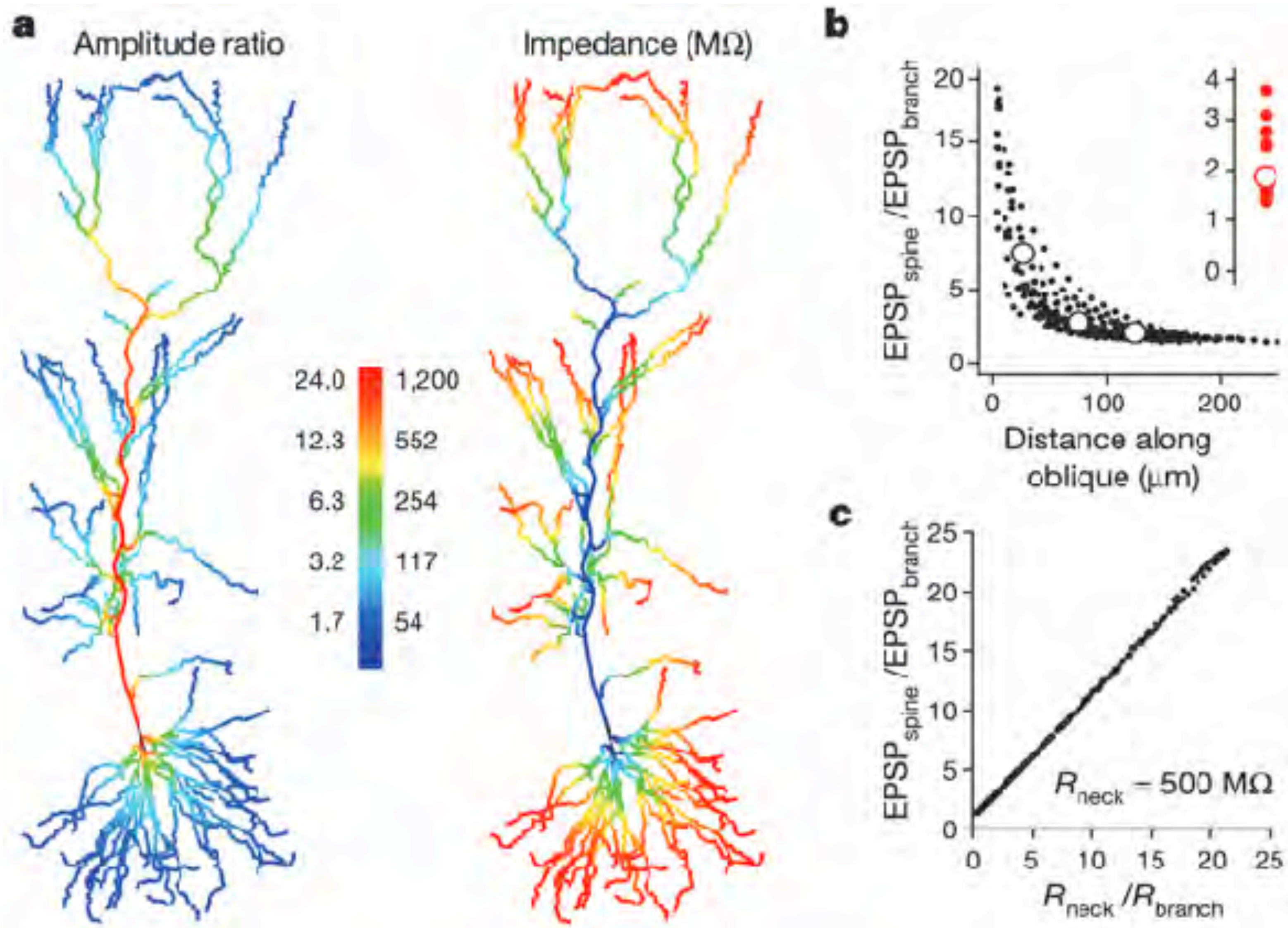
Dynamic *processes that change with experience*

Synaptic amplification by dendritic spines enhances input cooperativity

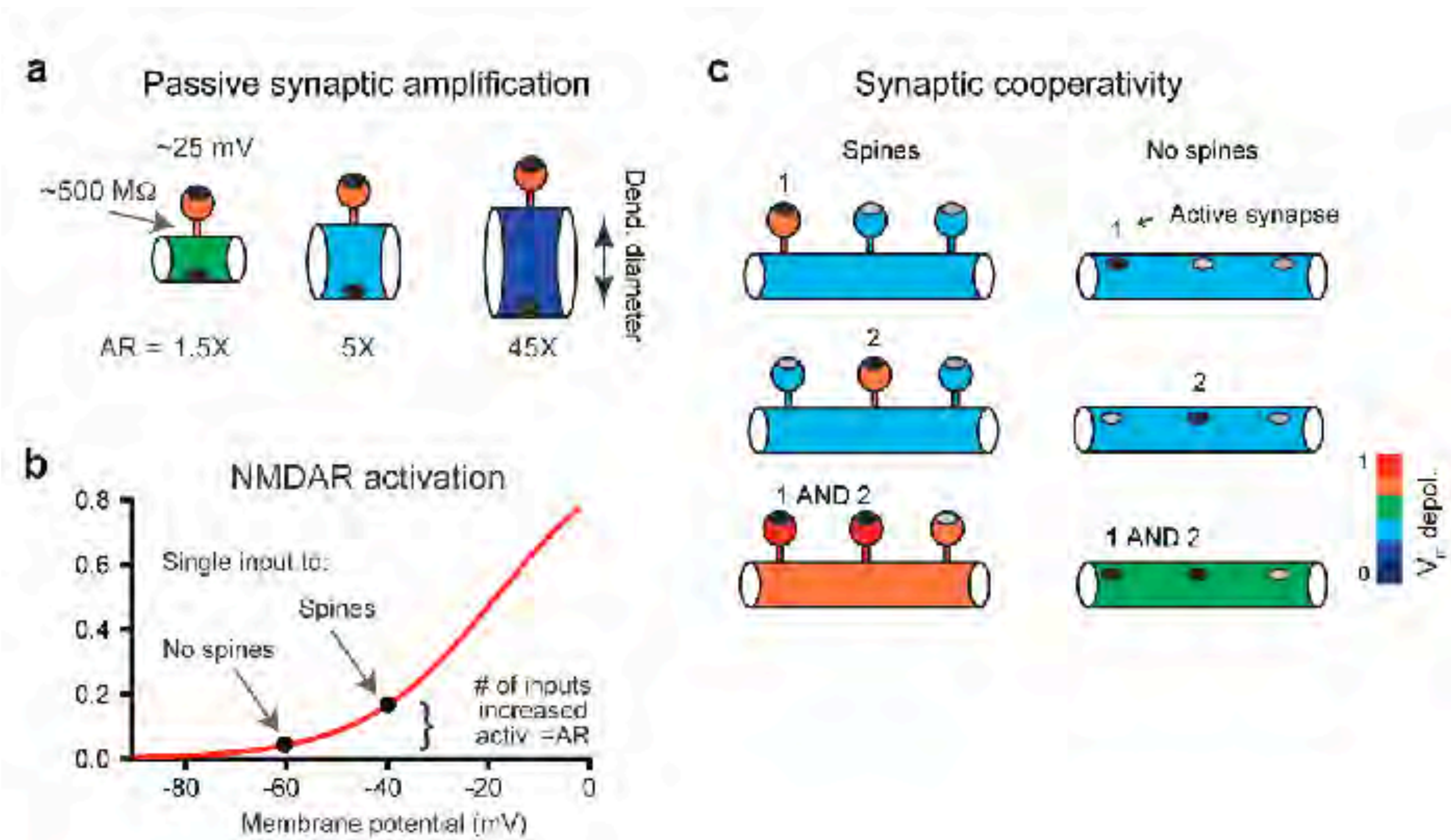
Mark T. Harnett[1]*, Judit K. Makara[1,2]*, Nelson Spruston[1], William L. Kath[3] & Jeffrey C. Magee[1]



Harnett *et al.*, *Nature*, 2012



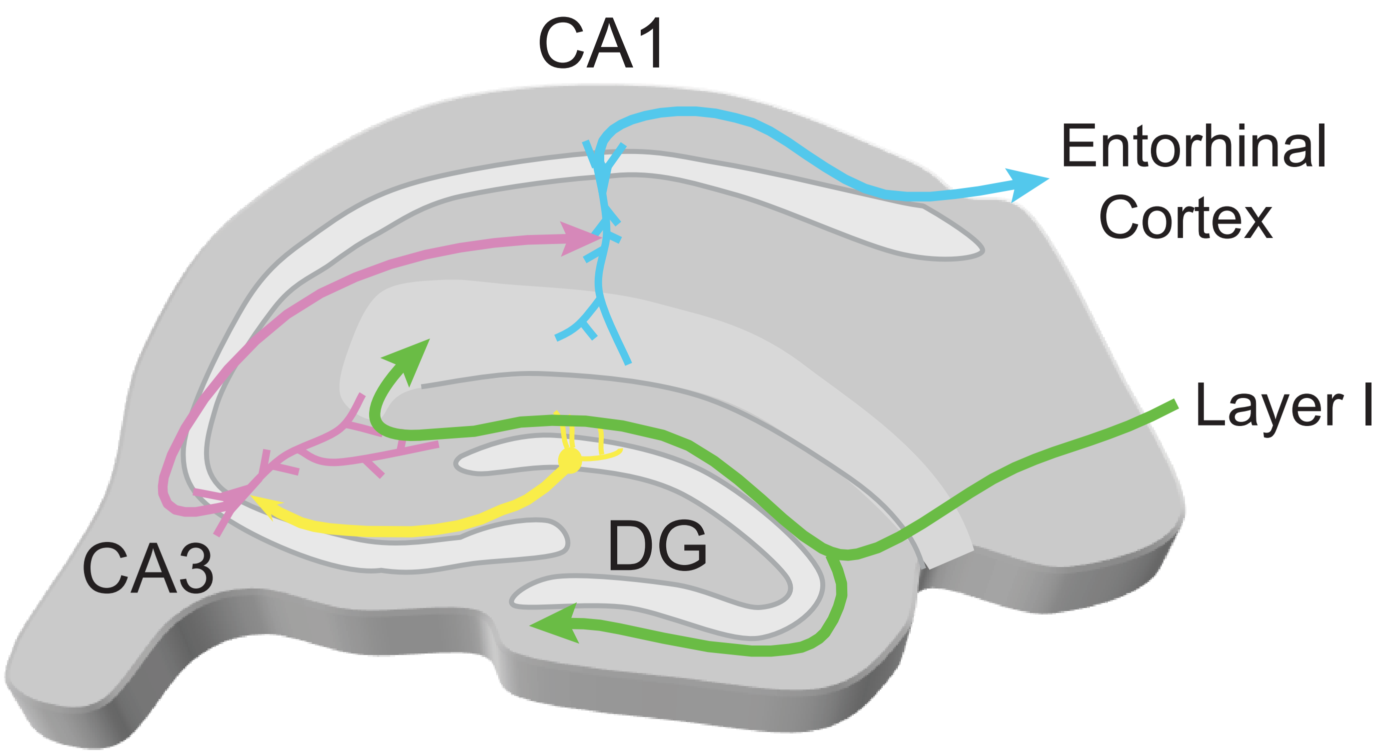
Harnett *et al.*, *Nature*, 2012

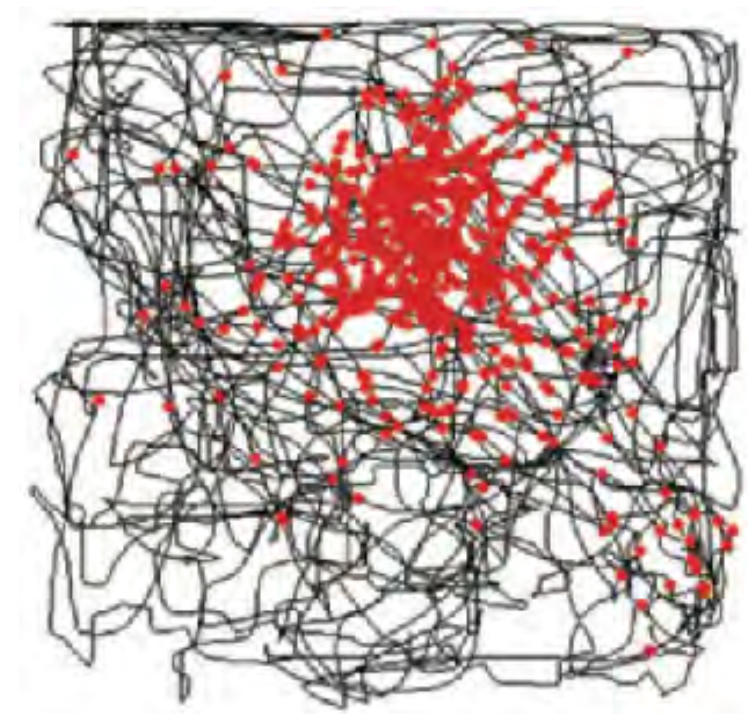


Harnett *et al.*, *Nature*, 2012

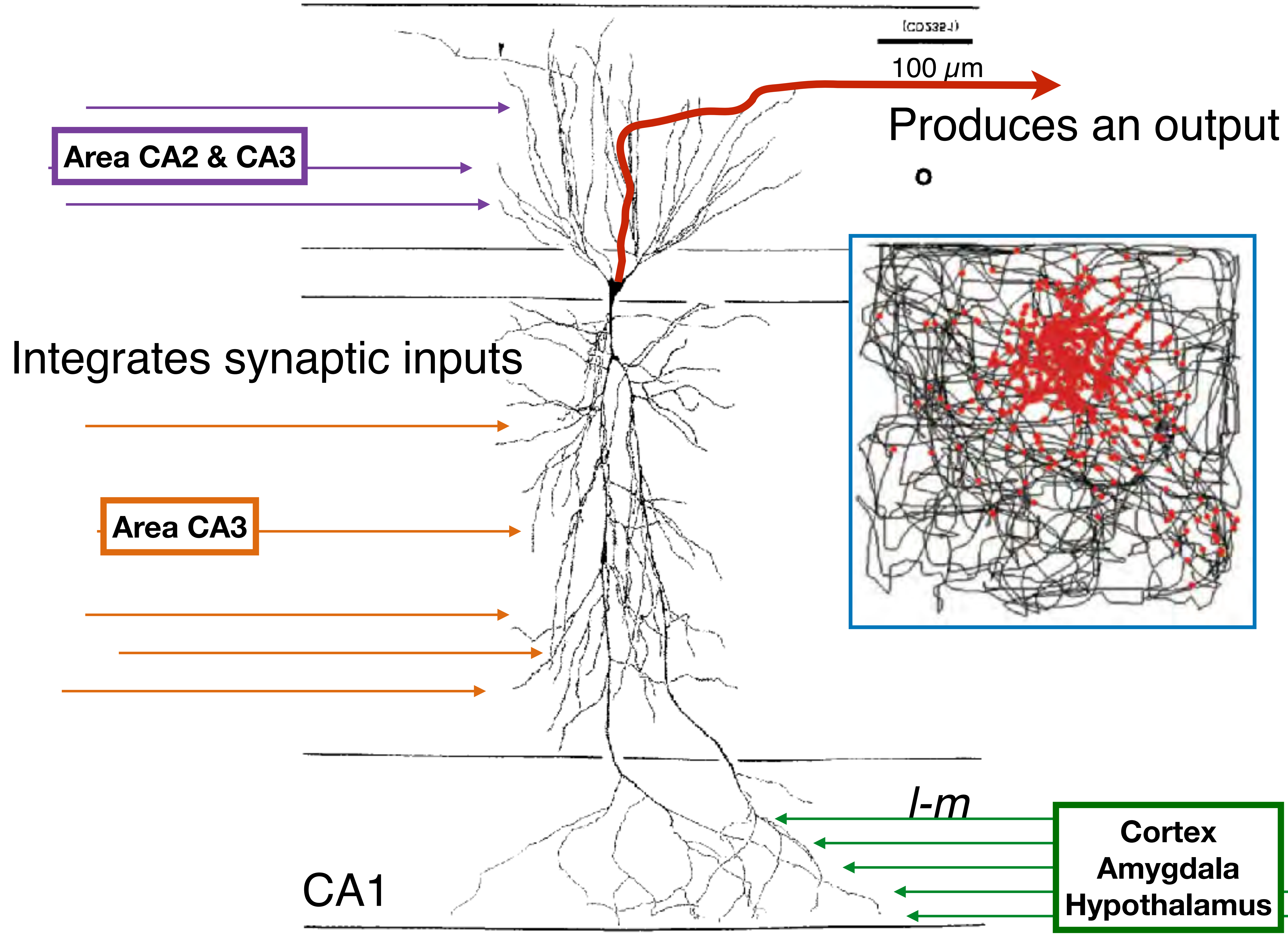
Now it will become interesting

Hippocampal encoding of space





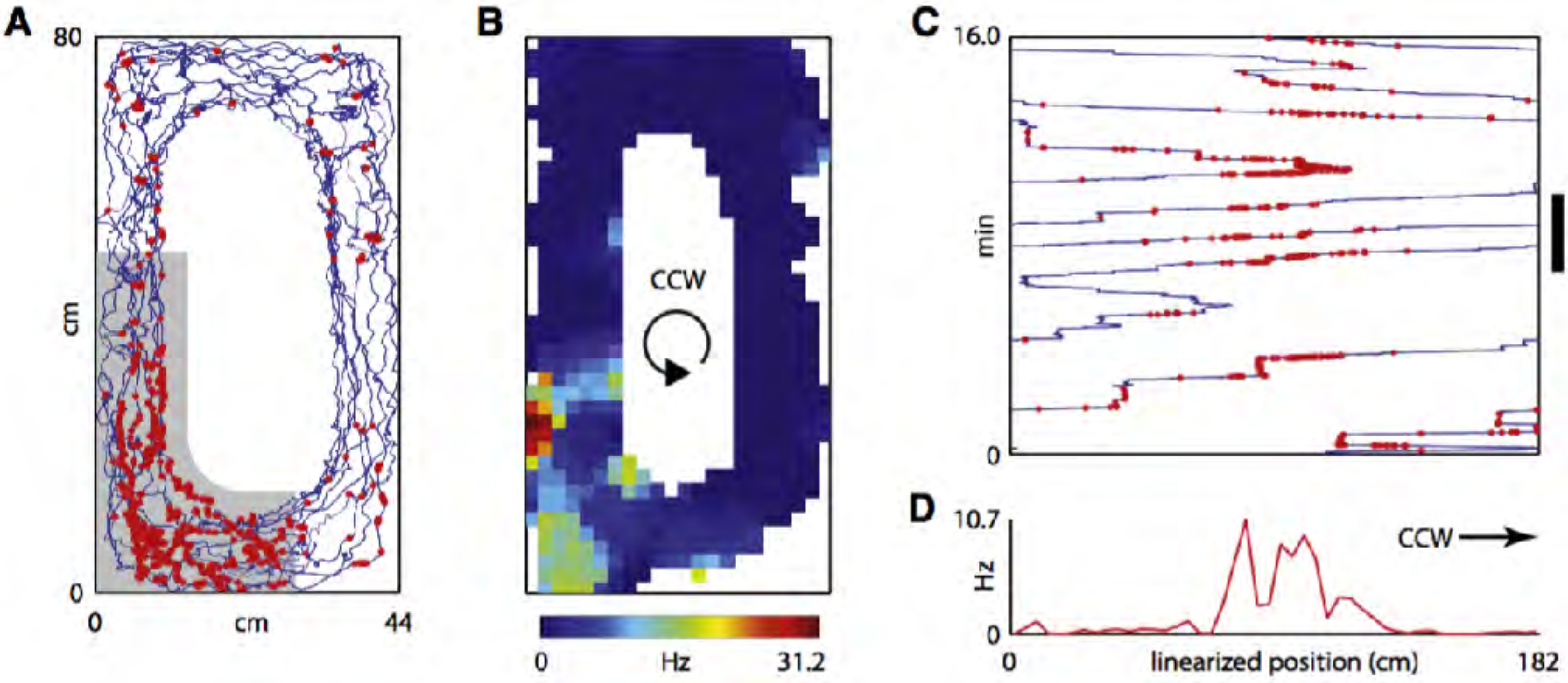
place field

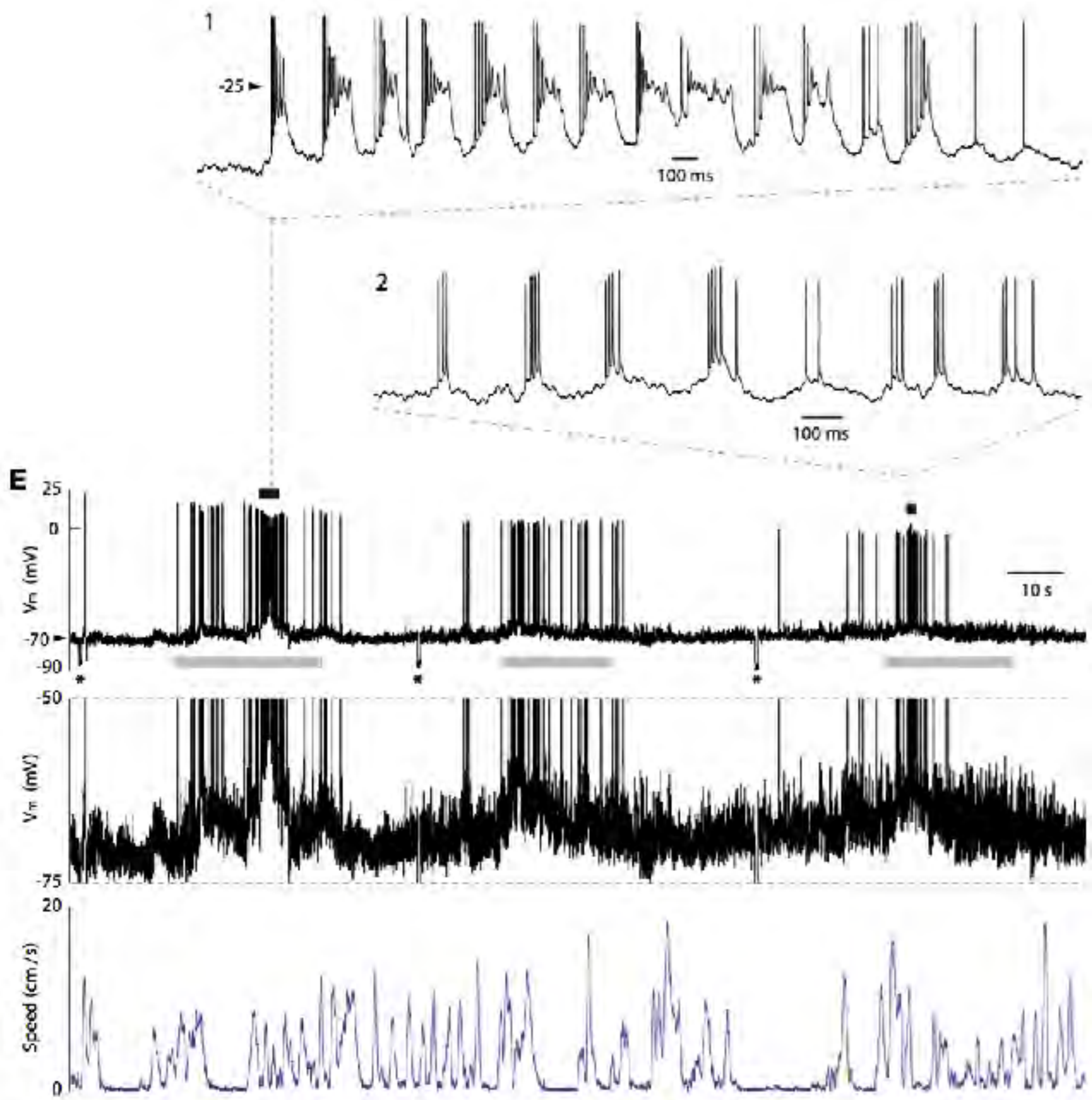


Ishizuka et al, Journal of Comparative Neurobiology, 1995.

Intracellular Determinants of Hippocampal CA1 Place and Silent Cell Activity in a Novel Environment

Jérôme Epsztein,[1,2,3,4] Michael Brecht,[1] and Albert K. Lee[1,5,*]
[1]Bernstein Center for Computational Neuroscience, Humboldt University, Berlin 10115, Germany
[2]Institut de Neurobiologie de la Méditerranée, Marseille 13273, France
[3]Institut National de la Santé et de la Recherche Médicale U901, Marseille 13273, France
[4]Université de la Méditerranée Aix-Marseille II, UMR S901, Marseille 13273, France
[5]Howard Hughes Medical Institute, Janelia Farm Research Campus, Ashburn, VA 20147, USA
*Correspondence: leea@janelia.hhmi.org
DOI 10.1016/j.neuron.2011.03.006



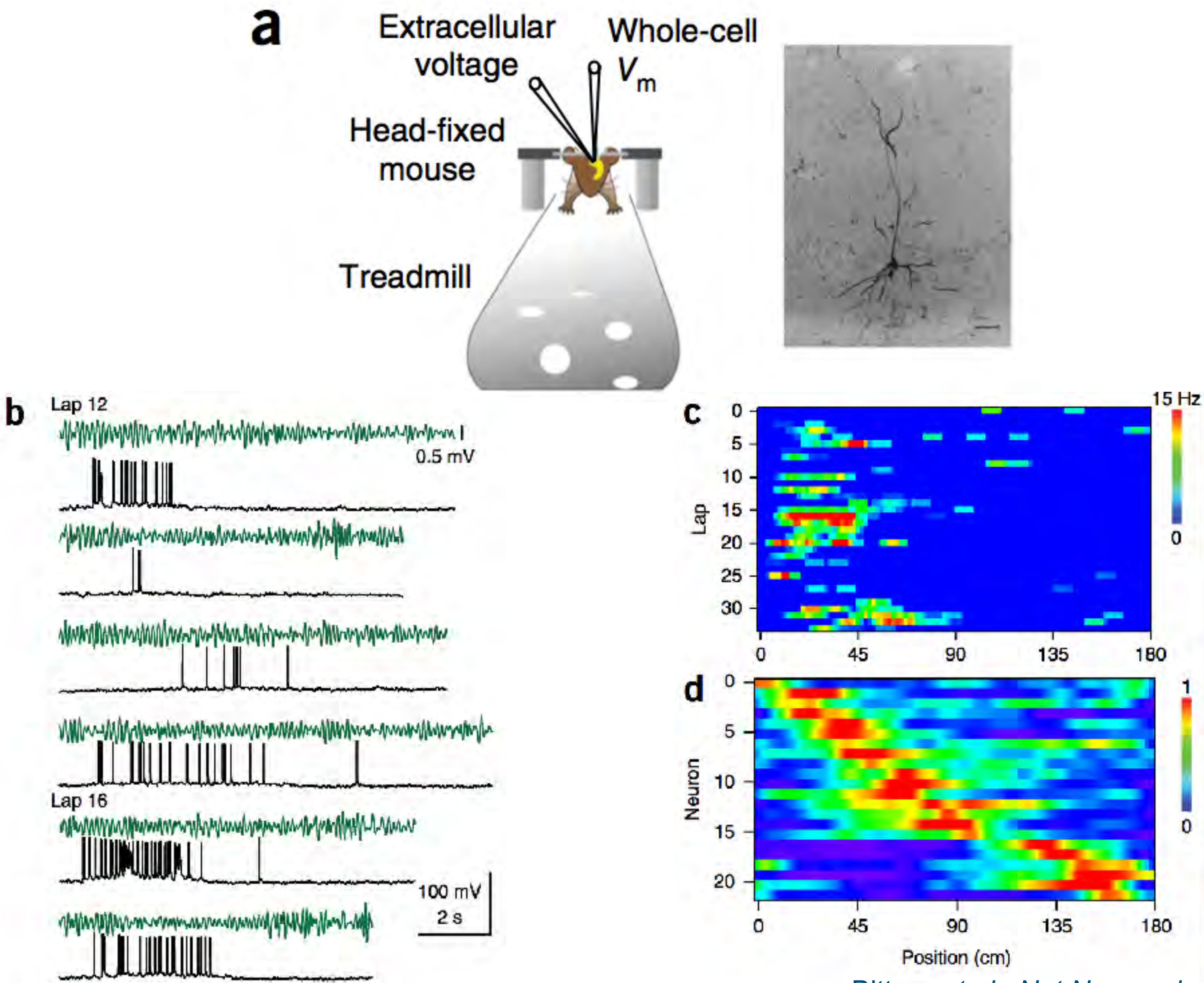


Epsztein *et al., Neuron,* 2011

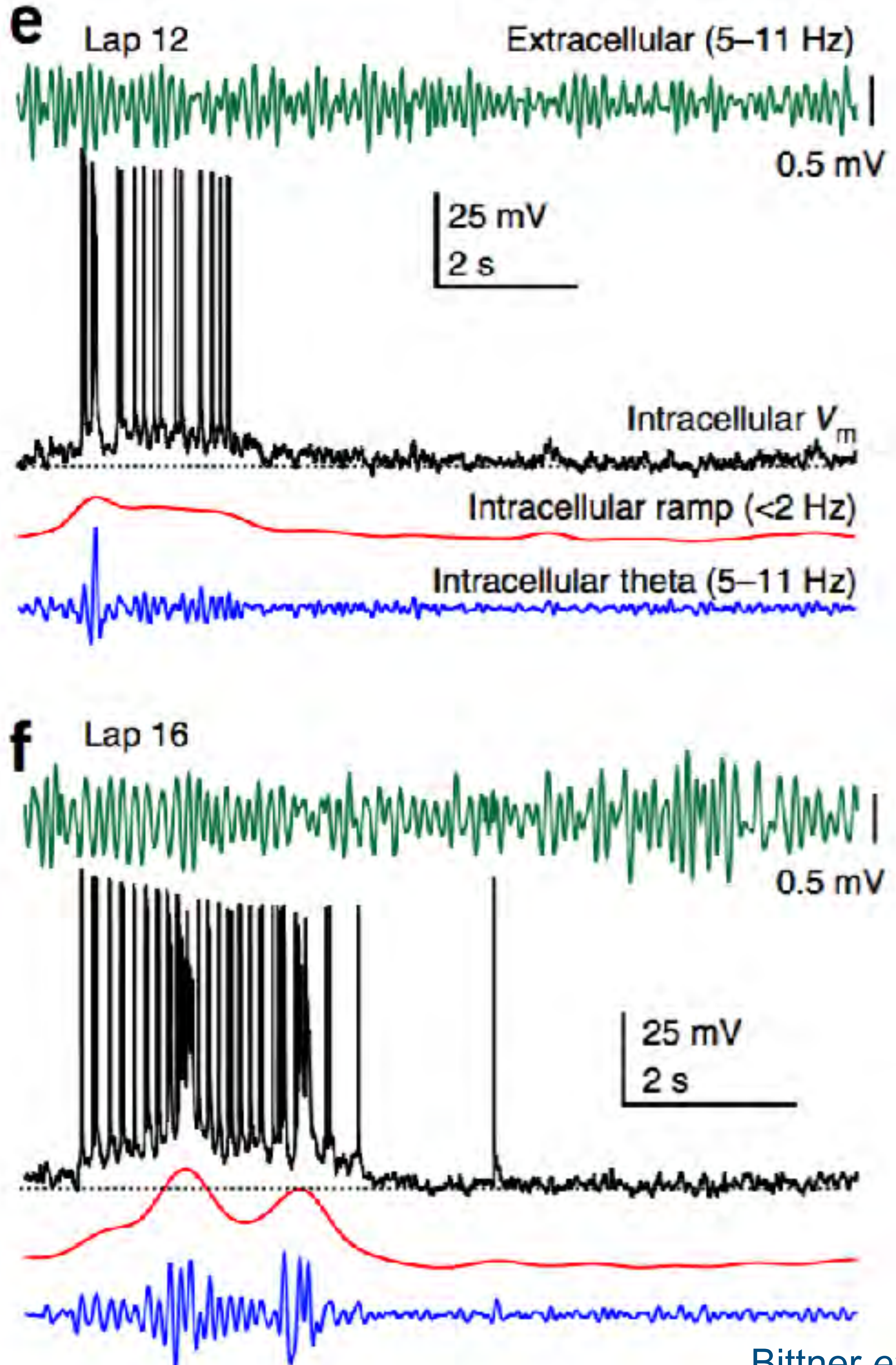
nature
neuroscience

Conjunctive input processing drives feature selectivity in hippocampal CA1 neurons

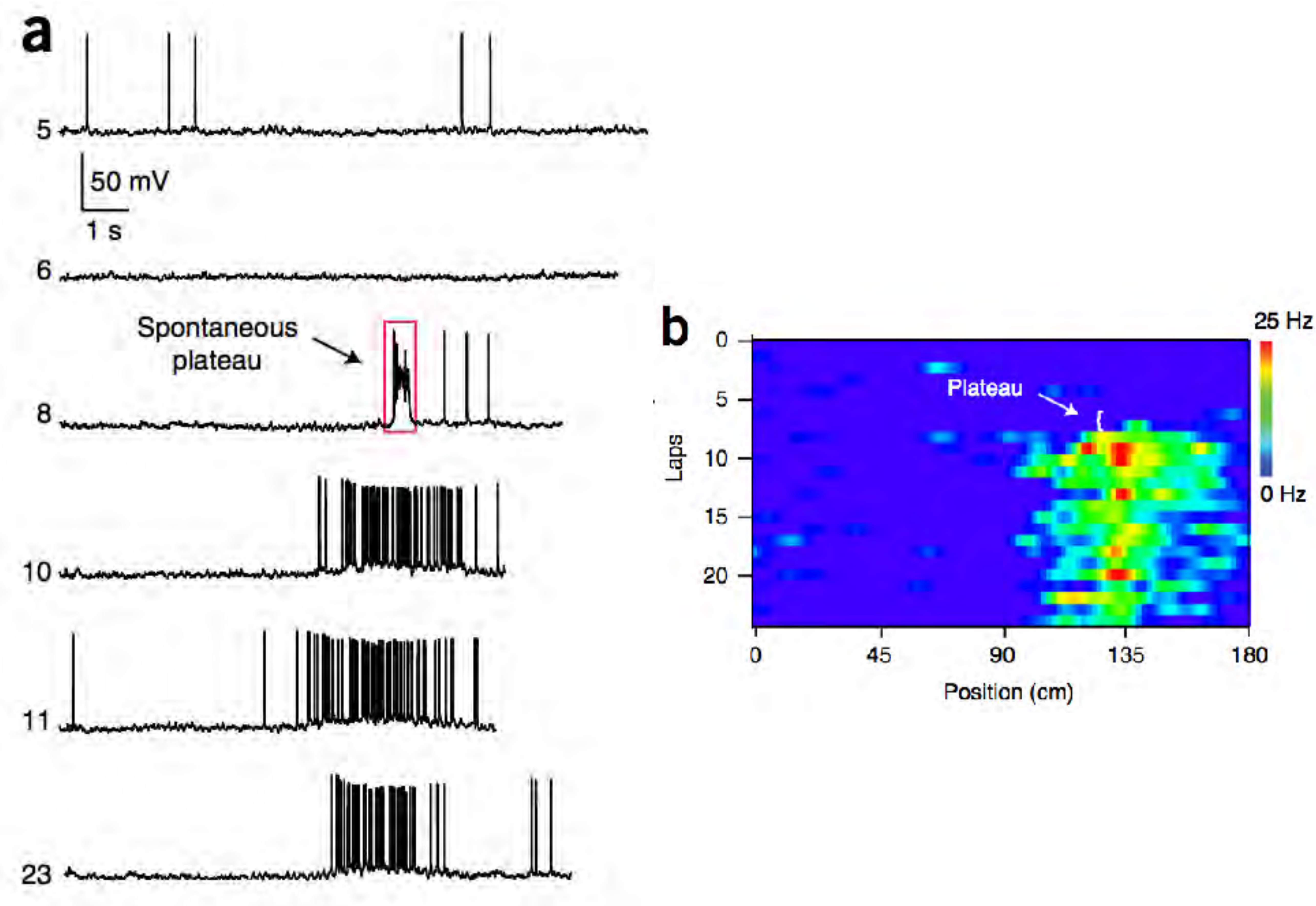
Katie C Bittner[1], Christine Grienberger[1], Sachin P Vaidya[1], Aaron D Milstein[1], John J Macklin[1], Junghyup Suh[2,3], Susumu Tonegawa[2,3] & Jeffrey C Magee[1]



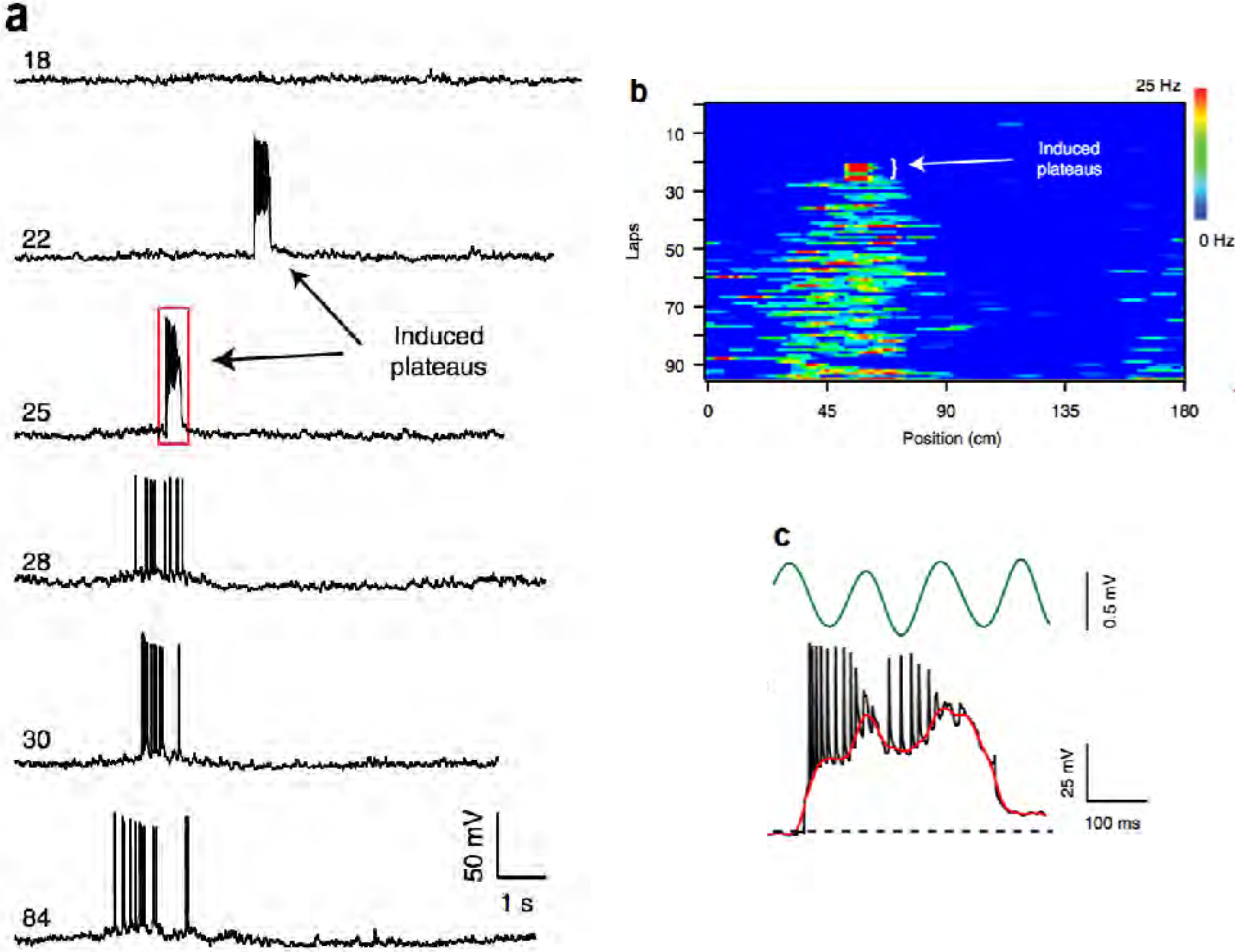
Bittner *et al.*, *Nat Neuroscience*, 2017



Bittner *et al., Nat Neuroscience*, 2017



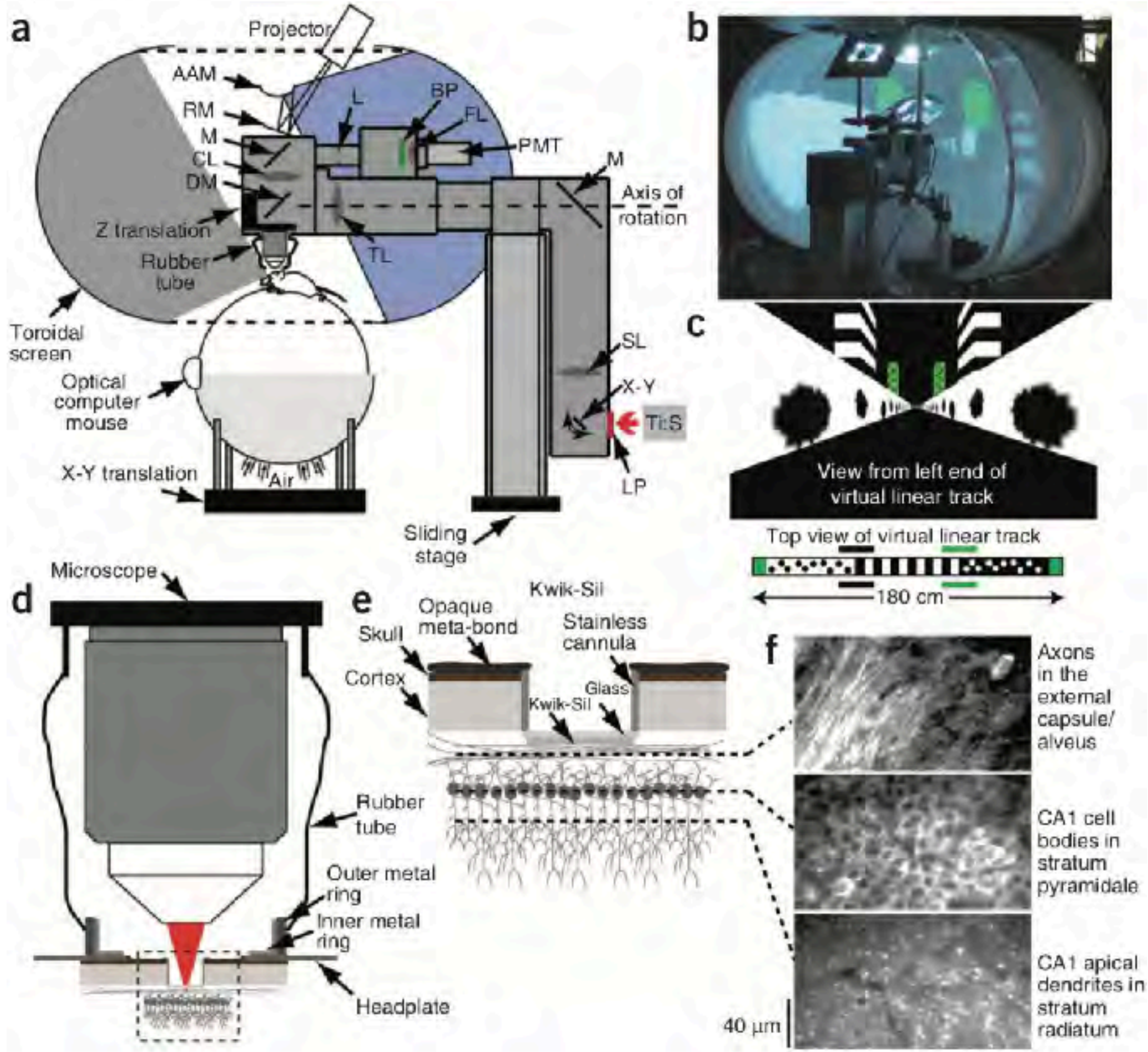
Bittner *et al., Nat Neuroscience*, 2017



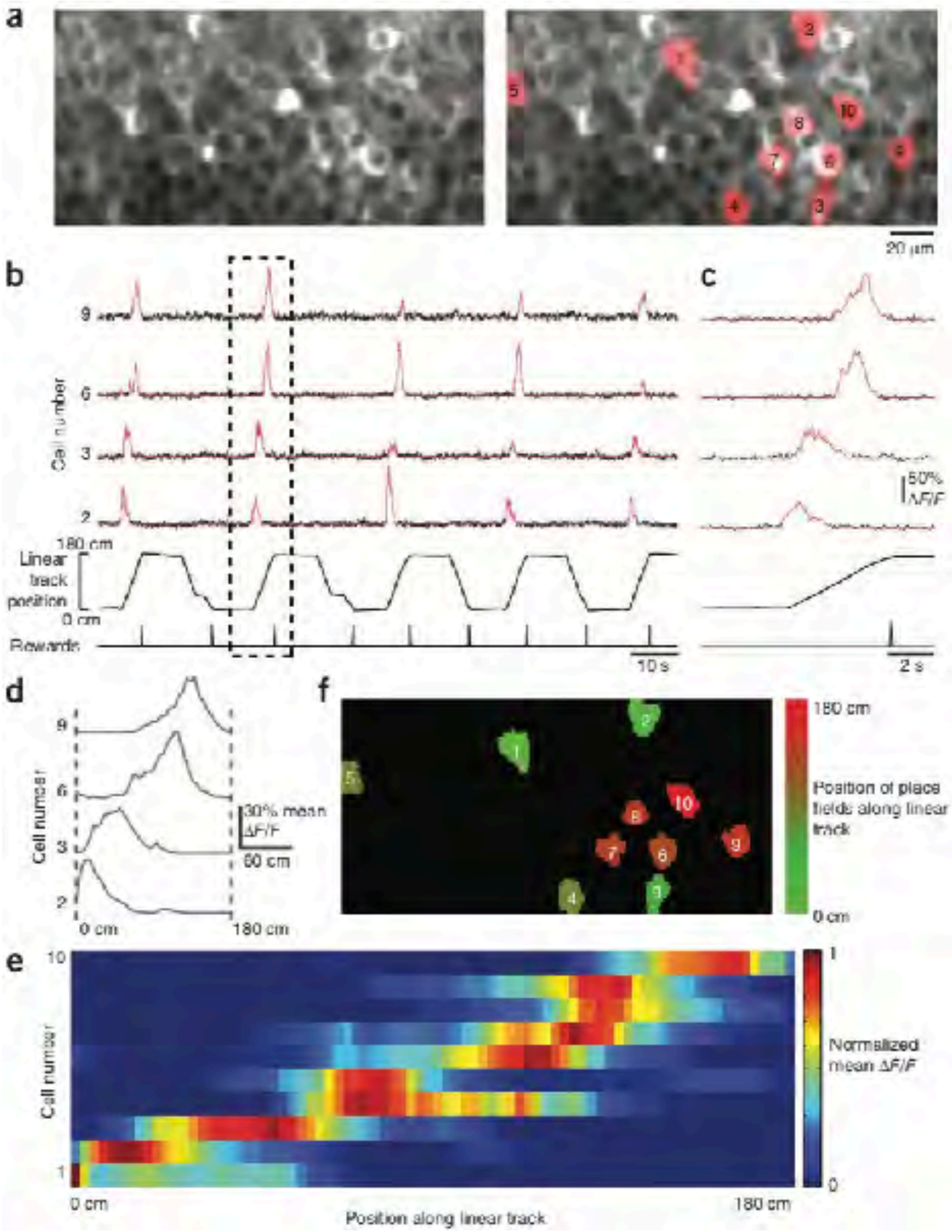
a
18
22
25
28
30
84
Induced
plateaus
50 mV
1 s
b
25 Hz
0 Hz
Induced
plateaus
Laps
10
30
50
70
90
0
45
90
135
180
Position (cm)
c
0.5 mV
25 mV
100 ms

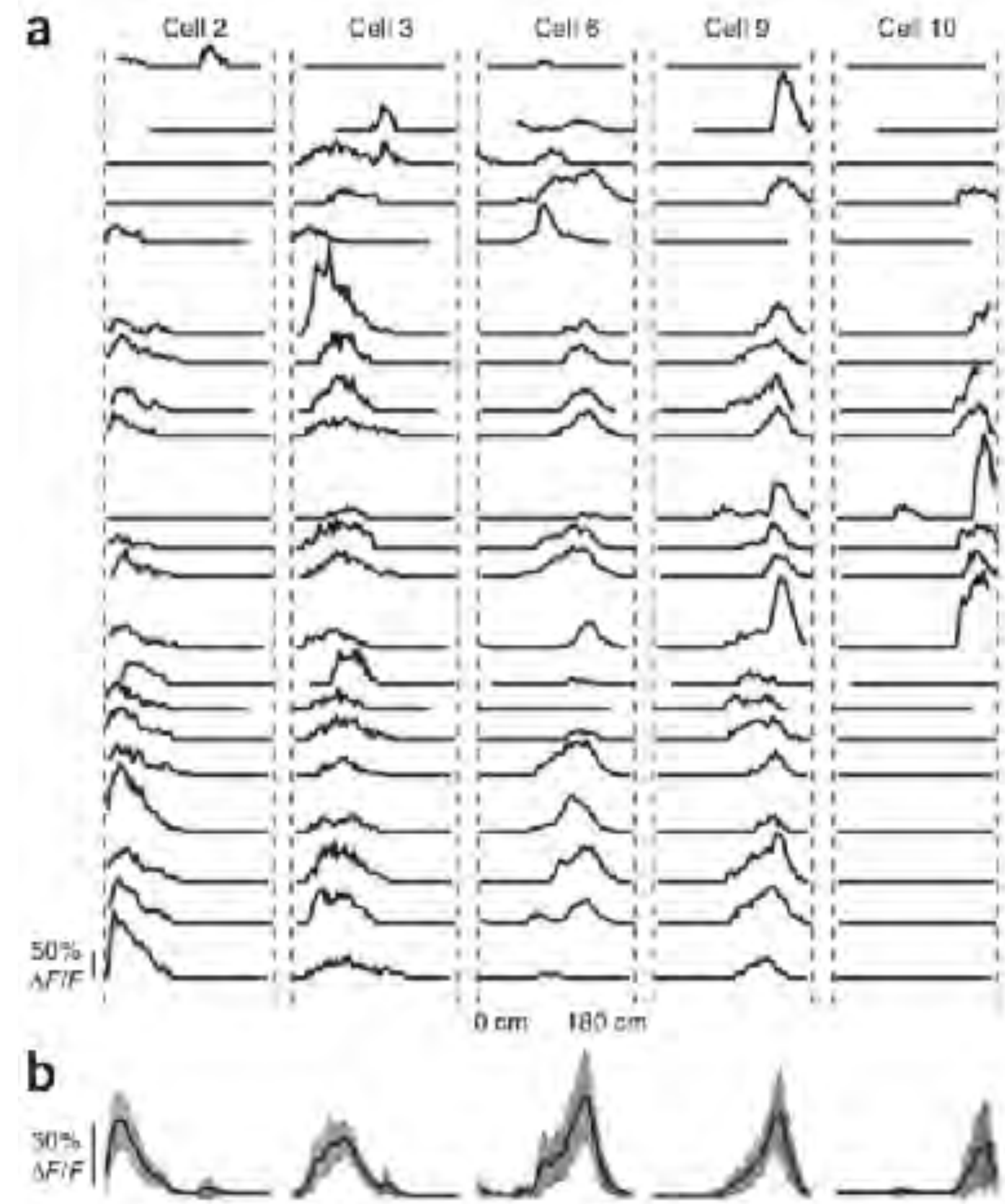
Functional imaging of hippocampal place cells at cellular resolution during virtual navigation

Daniel A Dombeck[1], Christopher D Harvey[1], Lin Tian[2], Loren L Looger[2] & David W Tank[1]

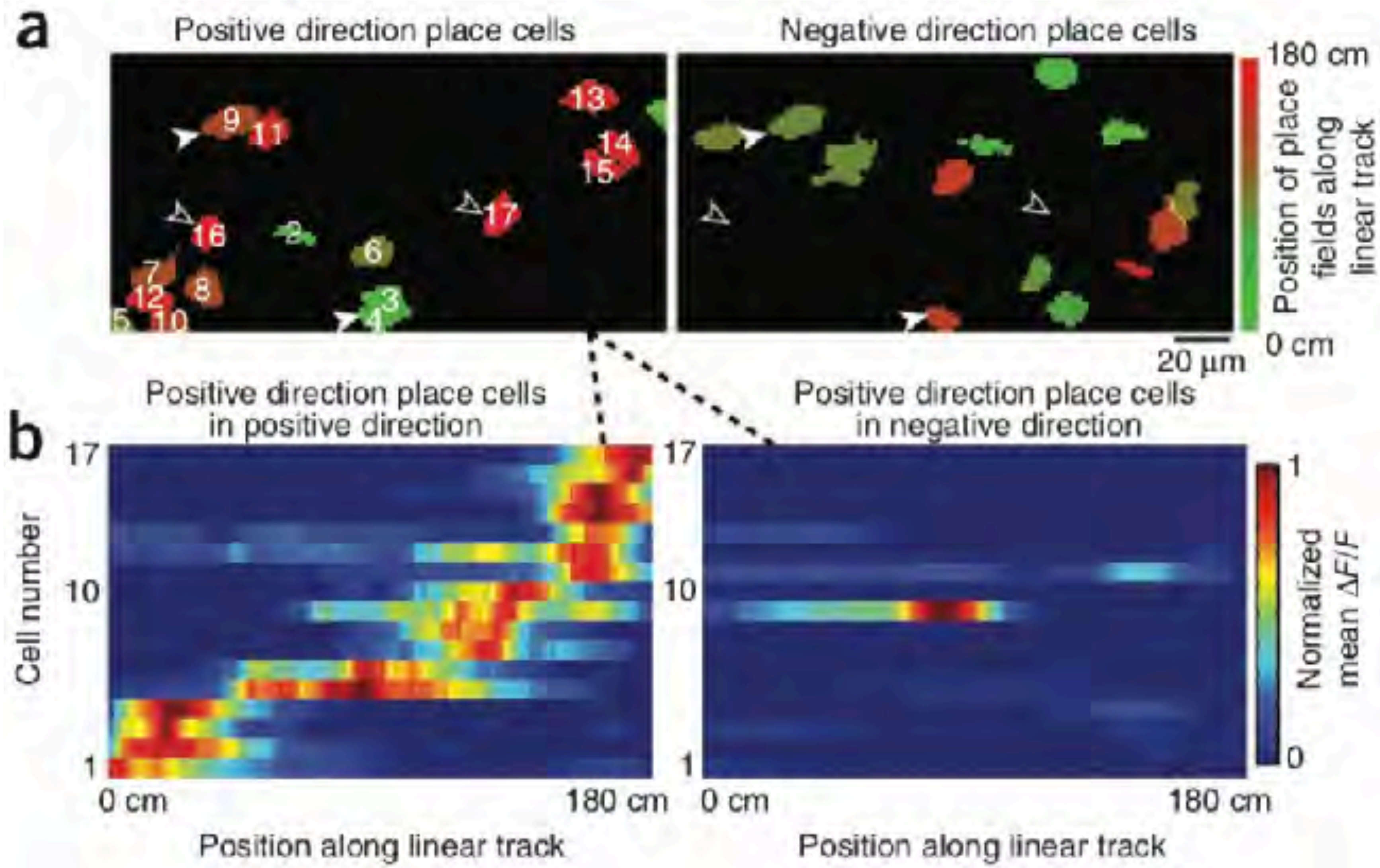


Dombeck *et al., Nat Neuroscience,* 2010





Dombeck *et al.*, *Nat Neuroscience*, 2010



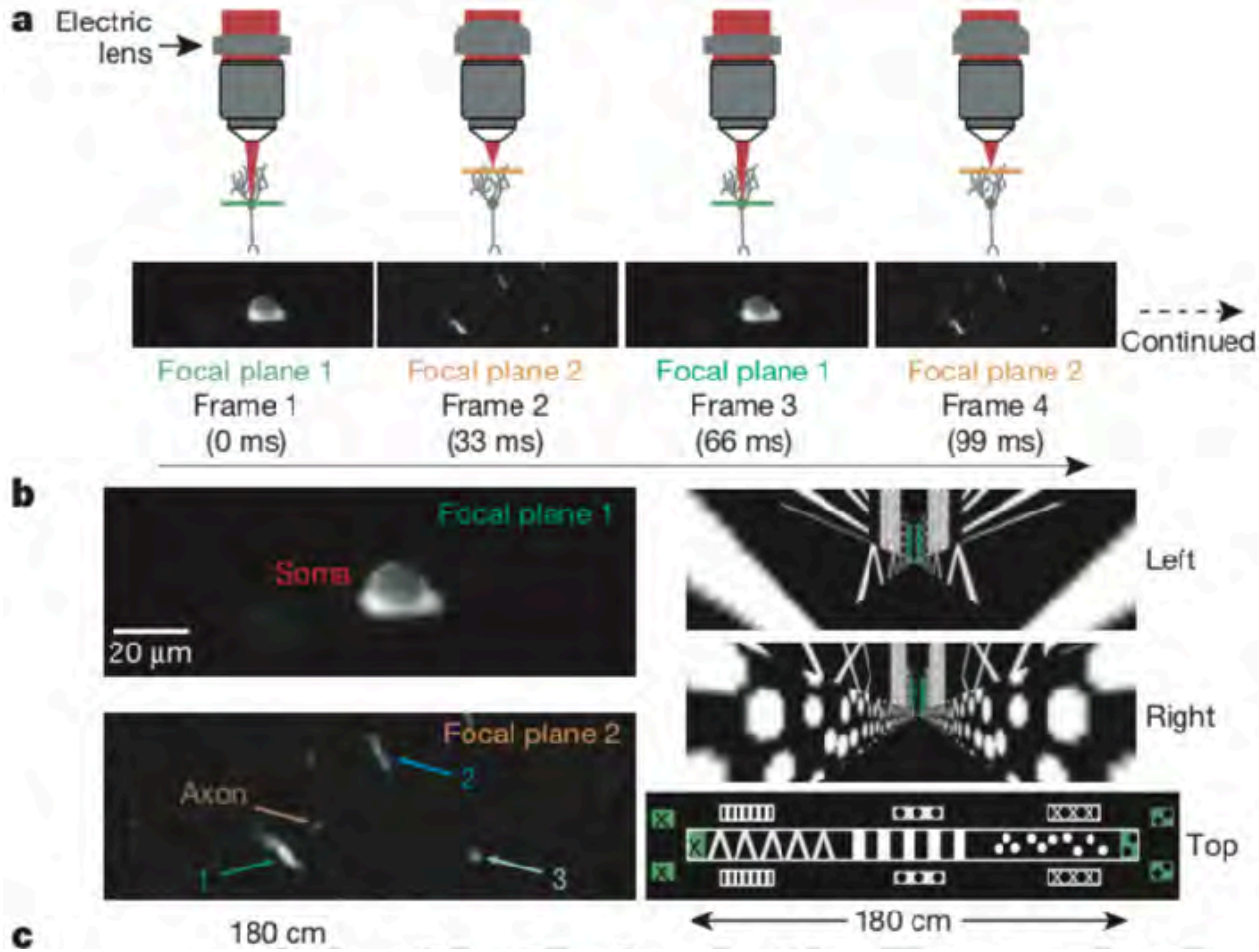
Dombeck *et al., Nat Neuroscience,* 2010

LETTER

doi:10.1038/nature15871

Calcium transient prevalence across the dendritic arbour predicts place field properties

Mark E. J. Sheffield[1] & Daniel A. Dombeck

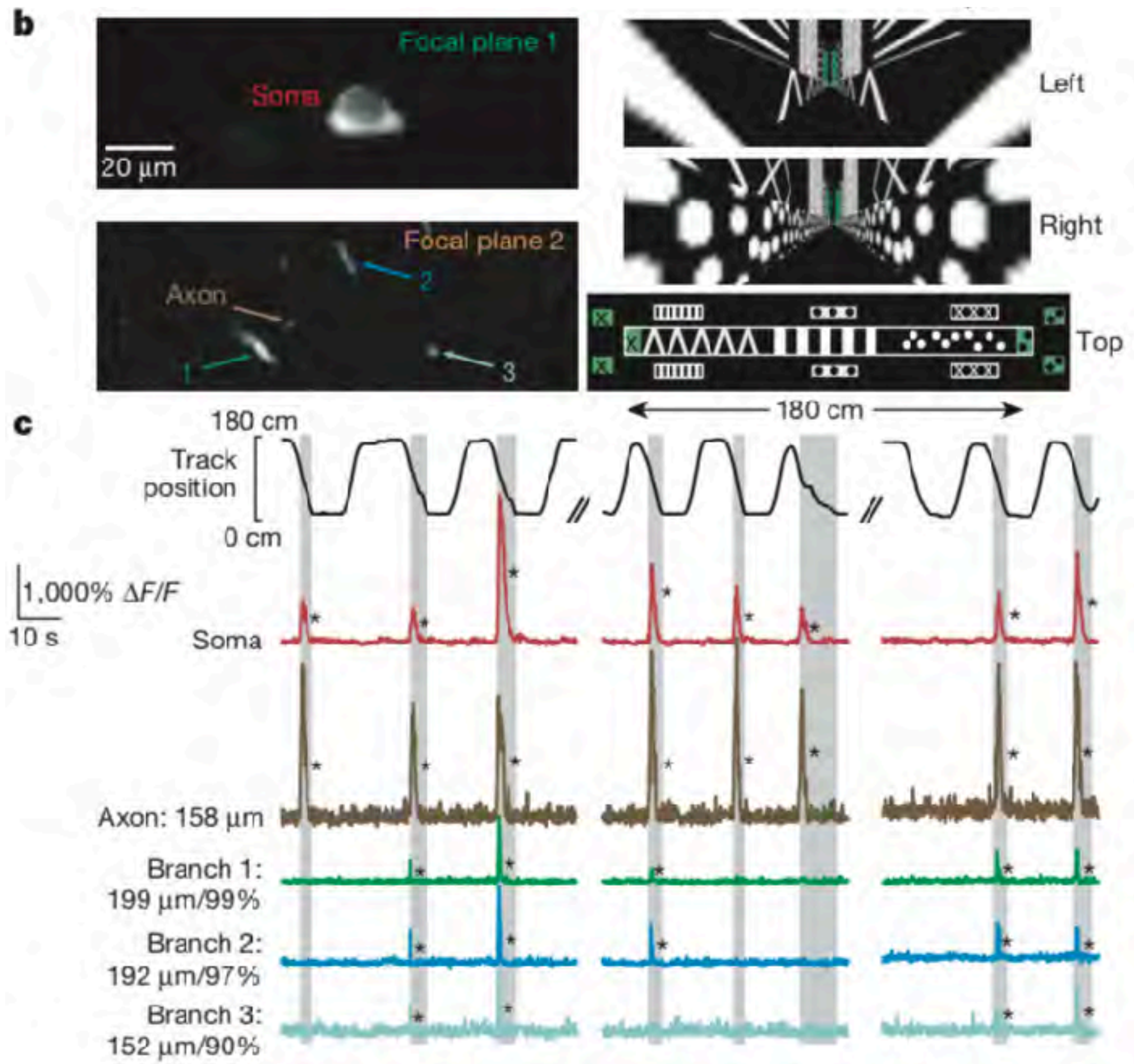


Sheffield & Dombeck *Nature*, 2015

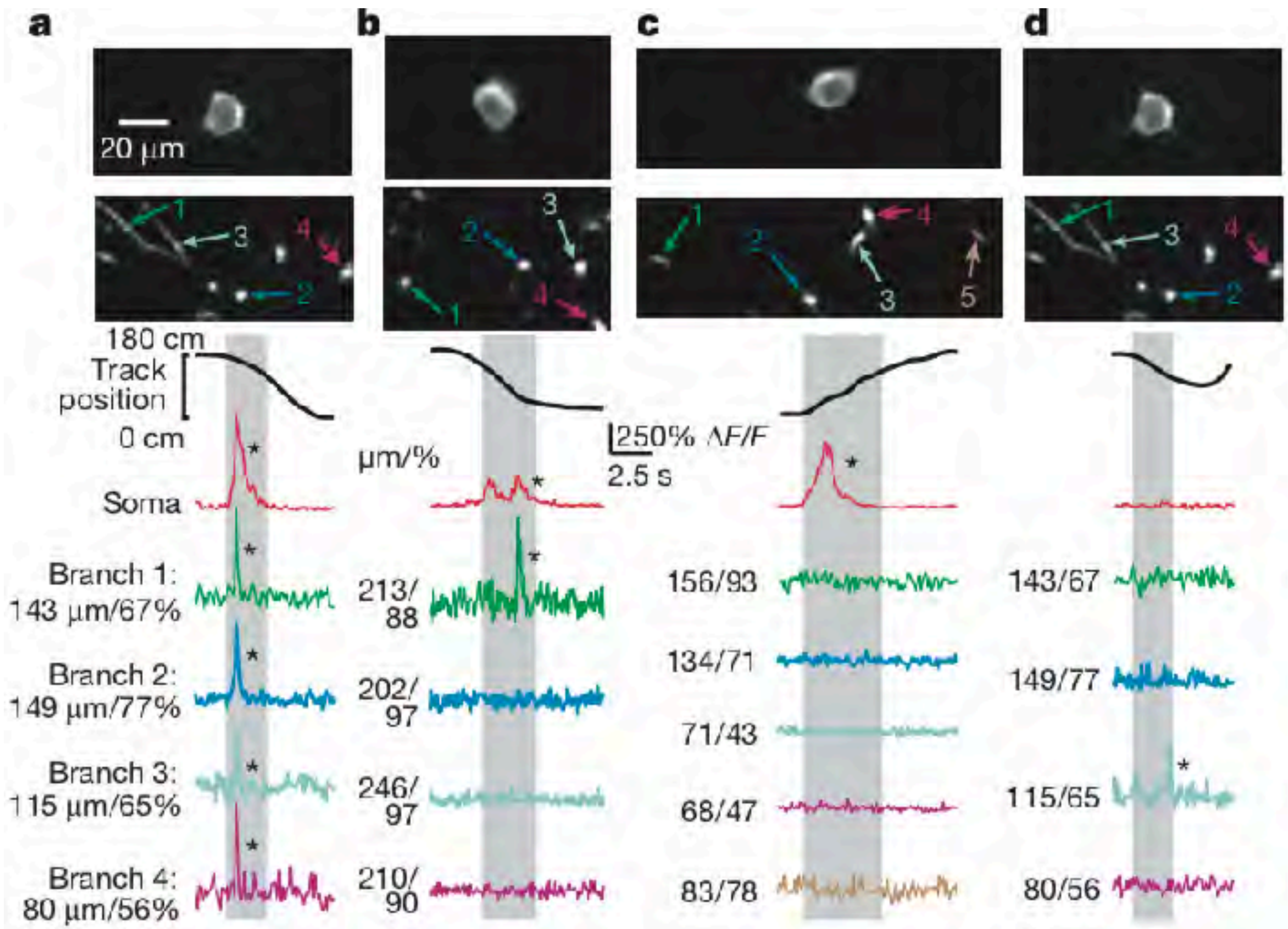
LETTER

Calcium transient prevalence across the dendritic arbour predicts place field properties

Mark E. J. Sheffield & Daniel A. Dombeck

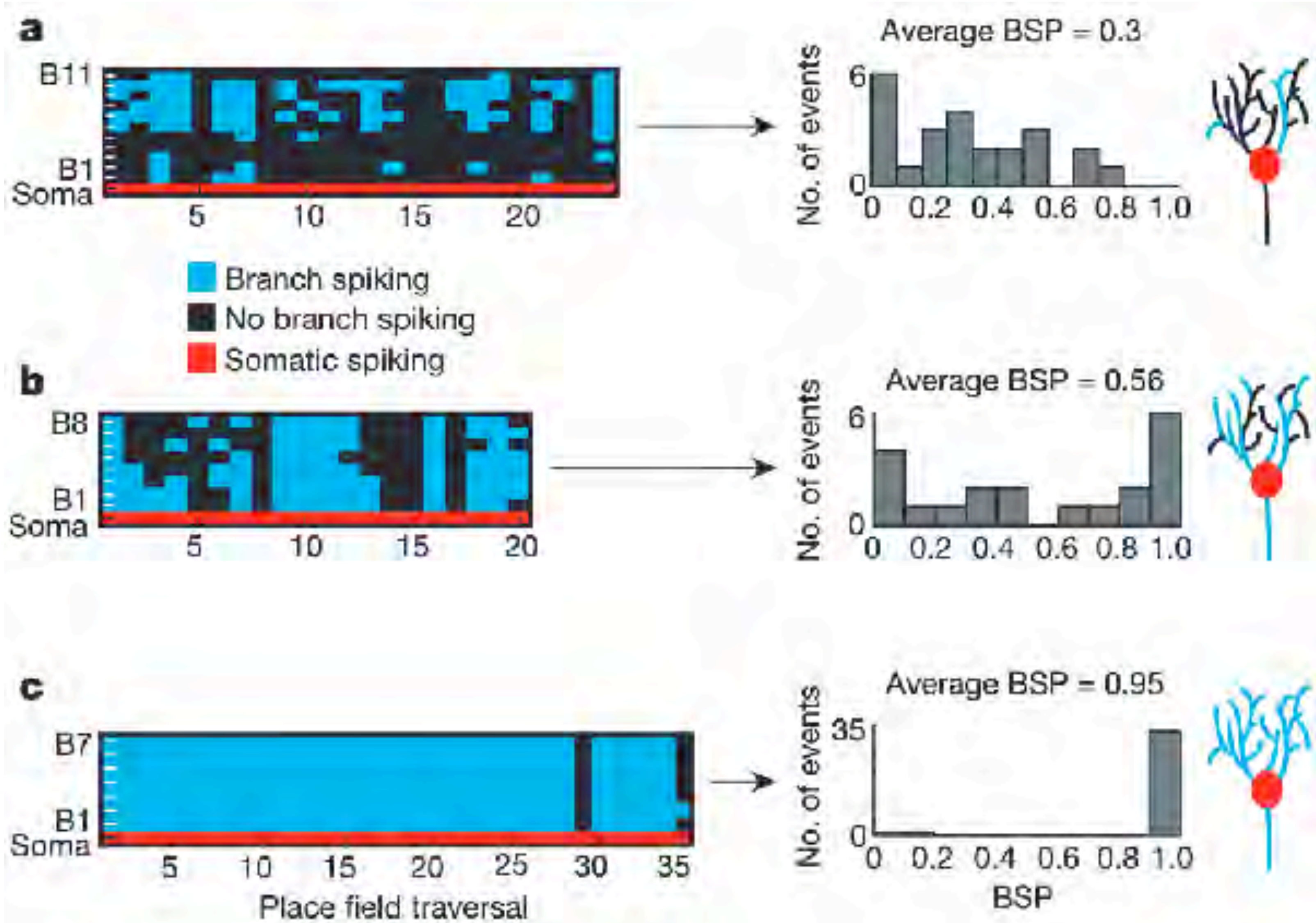


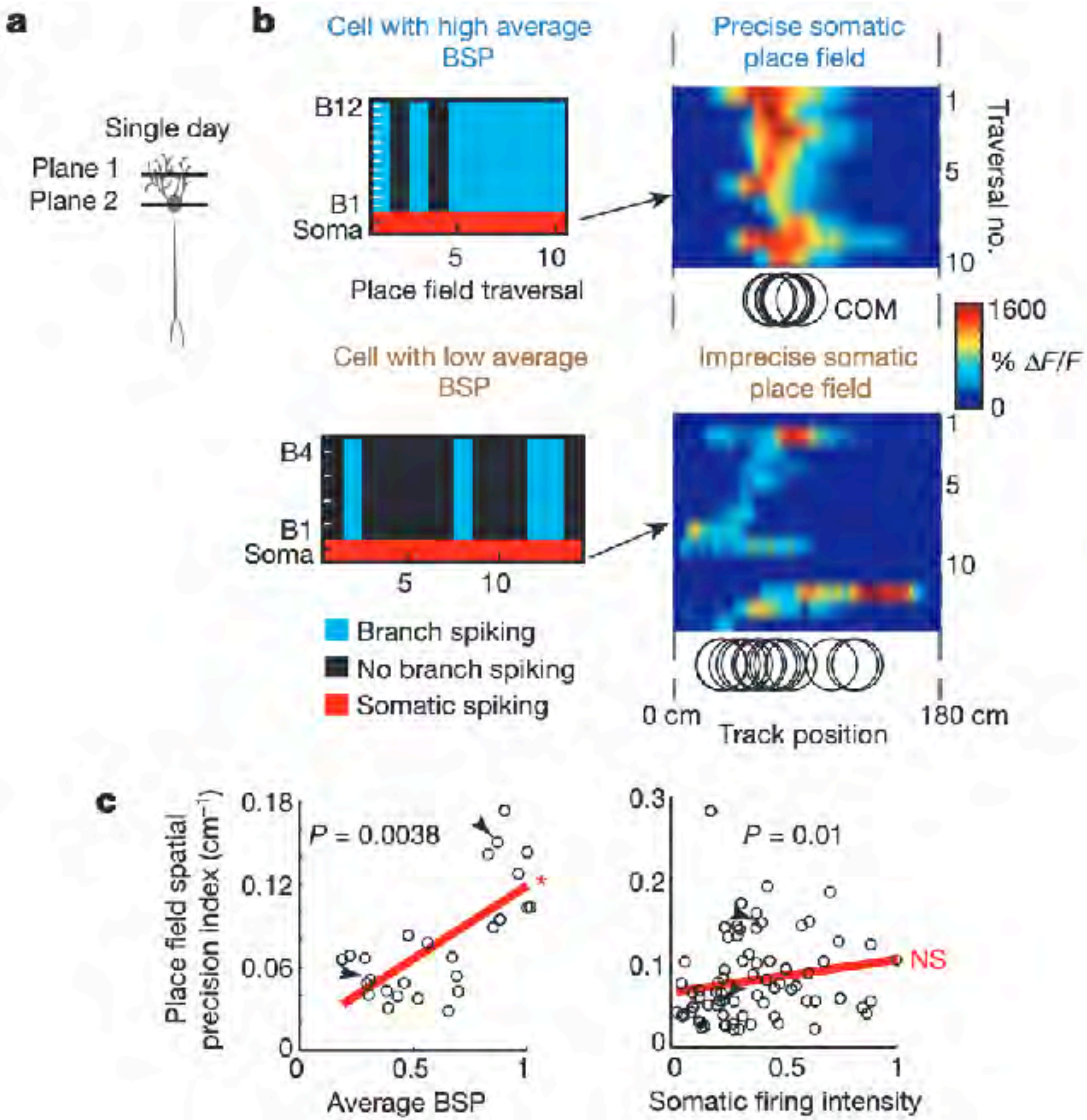
Sheffield & Dombeck *Nature*, 2015



all **some** **none** **branch without soma**

Sheffield & Dombeck *Nature*, 2015

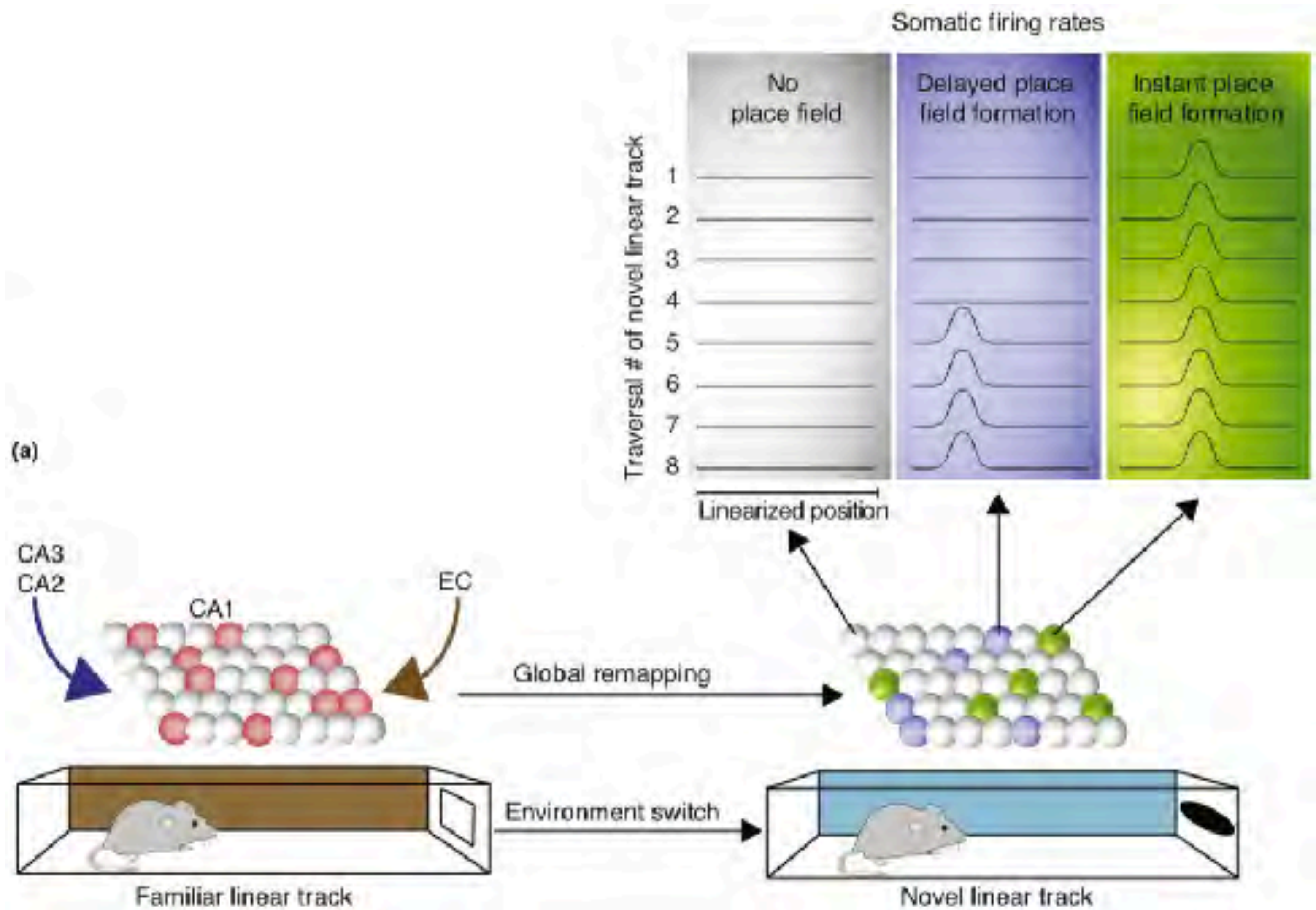

a
B11
B1
Soma
5
10
15
20
Average BSP = 0.3
No. of events
6
0
0 0.2 0.4 0.6 0.8 1.0
Branch spiking
No branch spiking
Somatic spiking
b
B8
B1
Soma
5
10
15
20
Average BSP = 0.56
No. of events
6
0
0 0.2 0.4 0.6 0.8 1.0
c
B7
B1
Soma
5 10 15 20 25 30 35
Place field traversal
Average BSP = 0.95
No. of events
35
0
0 0.2 0.4 0.6 0.8 1.0
BSP



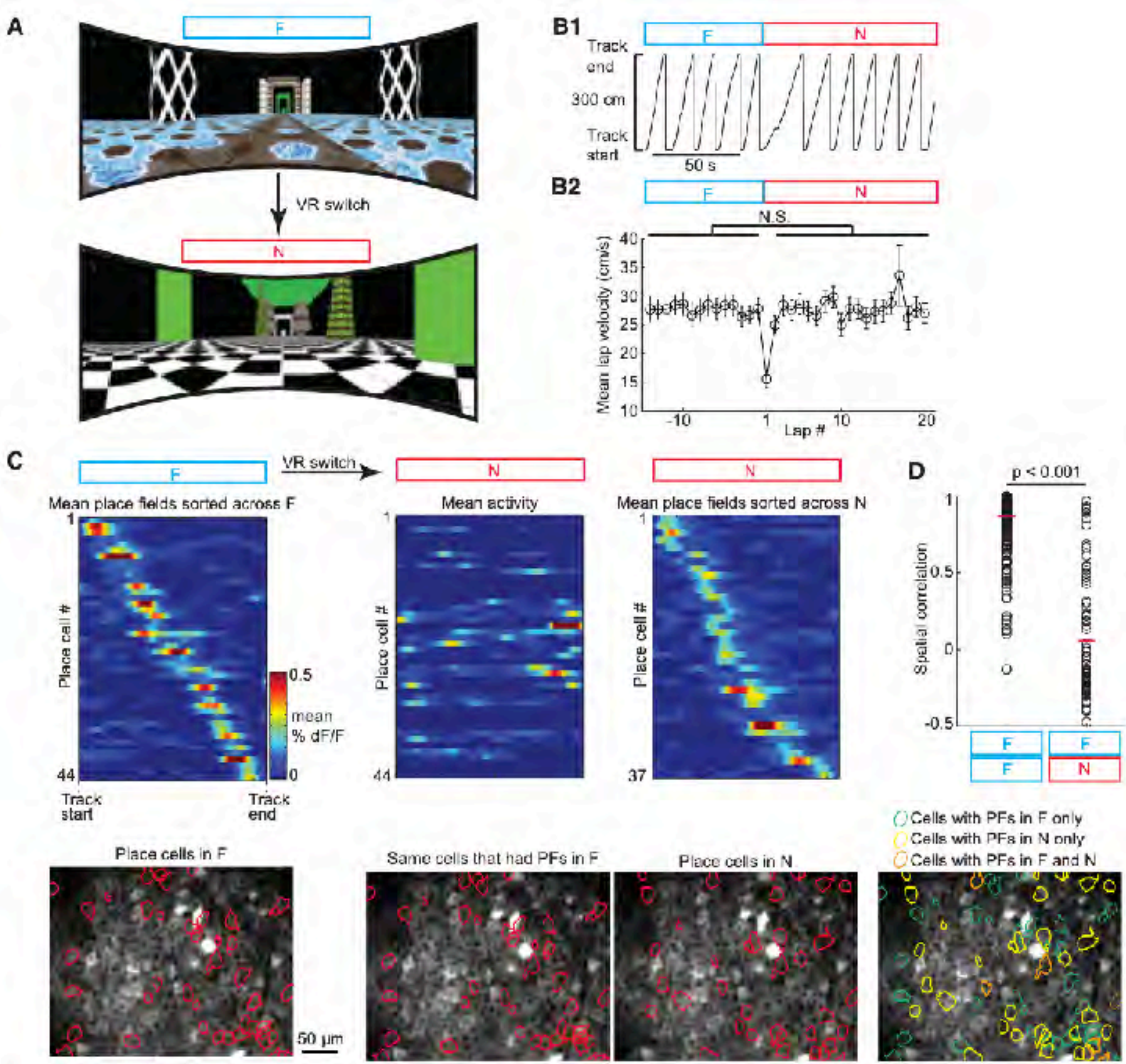
a
Single day
Plane 1
Plane 2
b
Cell with high average BSP
B12
B1
Soma
5
10
Place field traversal
Precise somatic place field
1
5
10
Traversal no.
COM
1600
% ΔF/F
0
Cell with low average BSP
B4
B1
Soma
5
10
Imprecise somatic place field
1
5
10
Branch spiking
No branch spiking
Somatic spiking
0 cm
Track position
180 cm
c
Place field spatial precision index (cm⁻¹)
0.18
0.12
0.06
0
P = 0.0038
*
0
0.5
1
Average BSP
0.3
0.2
0.1
0
P = 0.01
NS
0
0.5
1
Somatic firing intensity

Increased Prevalence of Calcium Transients across the Dendritic Arbor during Place Field Formation

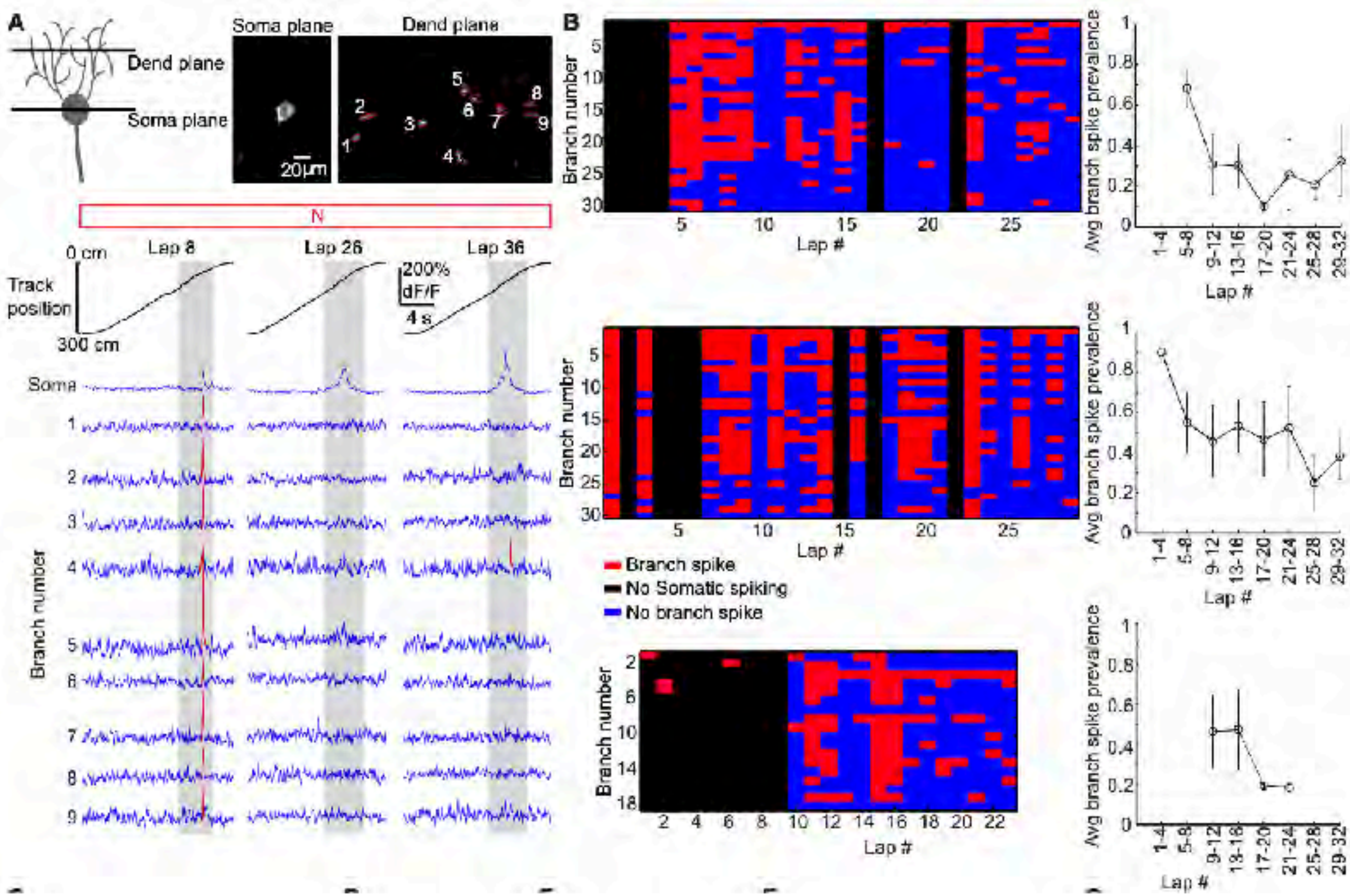
Mark E.J. Sheffield,[1,2] Michael D. Adoff,[1] and Daniel A. Dombeck[1,3,*]
[1]Department of Neurobiology, Northwestern University, Evanston, IL 60208, USA
[2]Present Address: Department of Neurobiology, Grossman Institute for Neuroscience, The University of Chicago, Chicago, IL 60637, USA
[3]Lead Contact
*Correspondence: d-dombeck@northwestern.edu
https://doi.org/10.1016/j.neuron.2017.09.029



Sheffield & Dombeck *Current Opinion Neurobiology,* 2019



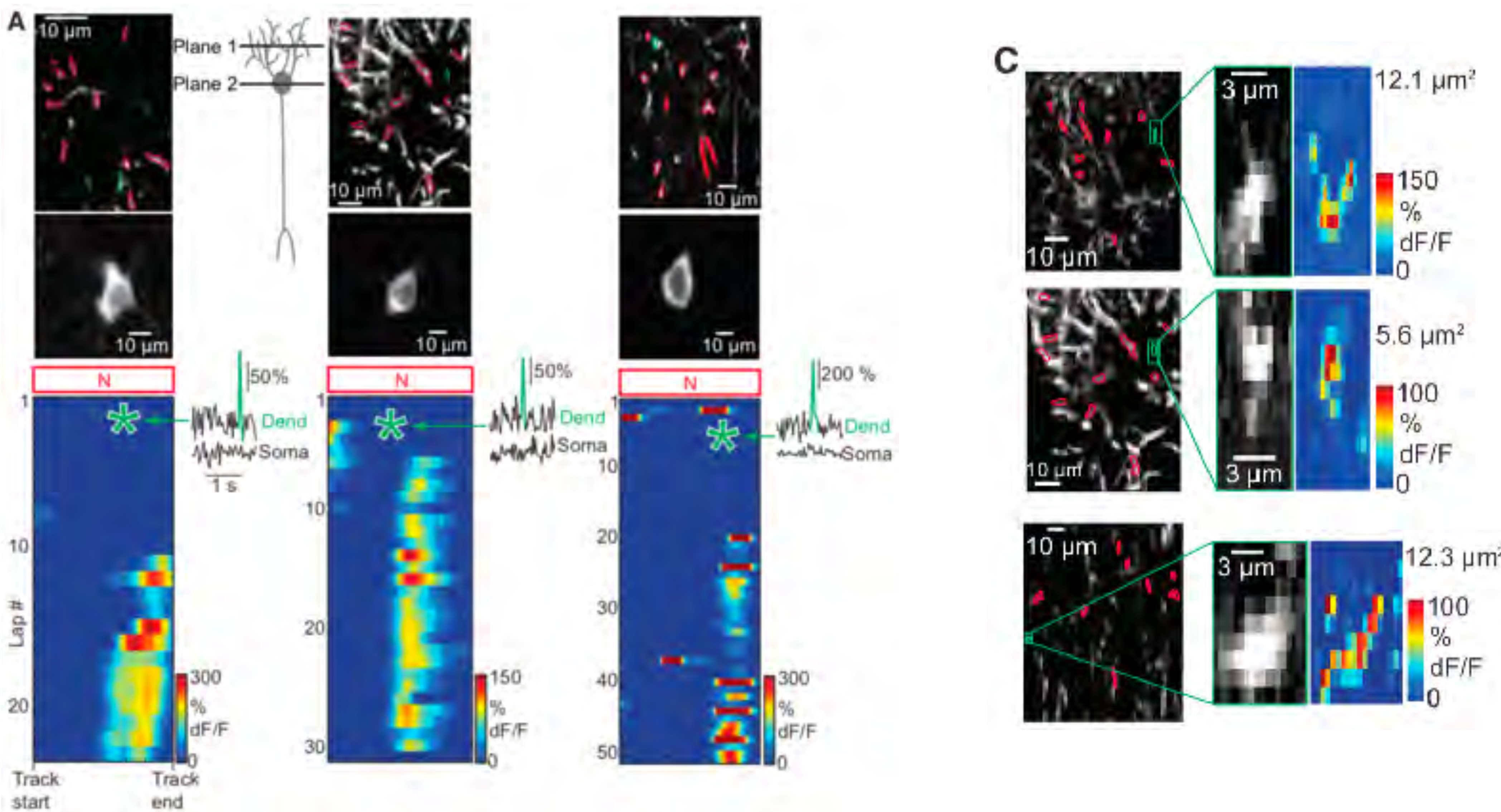
Sheffield & Dombeck *Neuron*, 2017



Sheffield & Dombeck *Neuron,* 2017

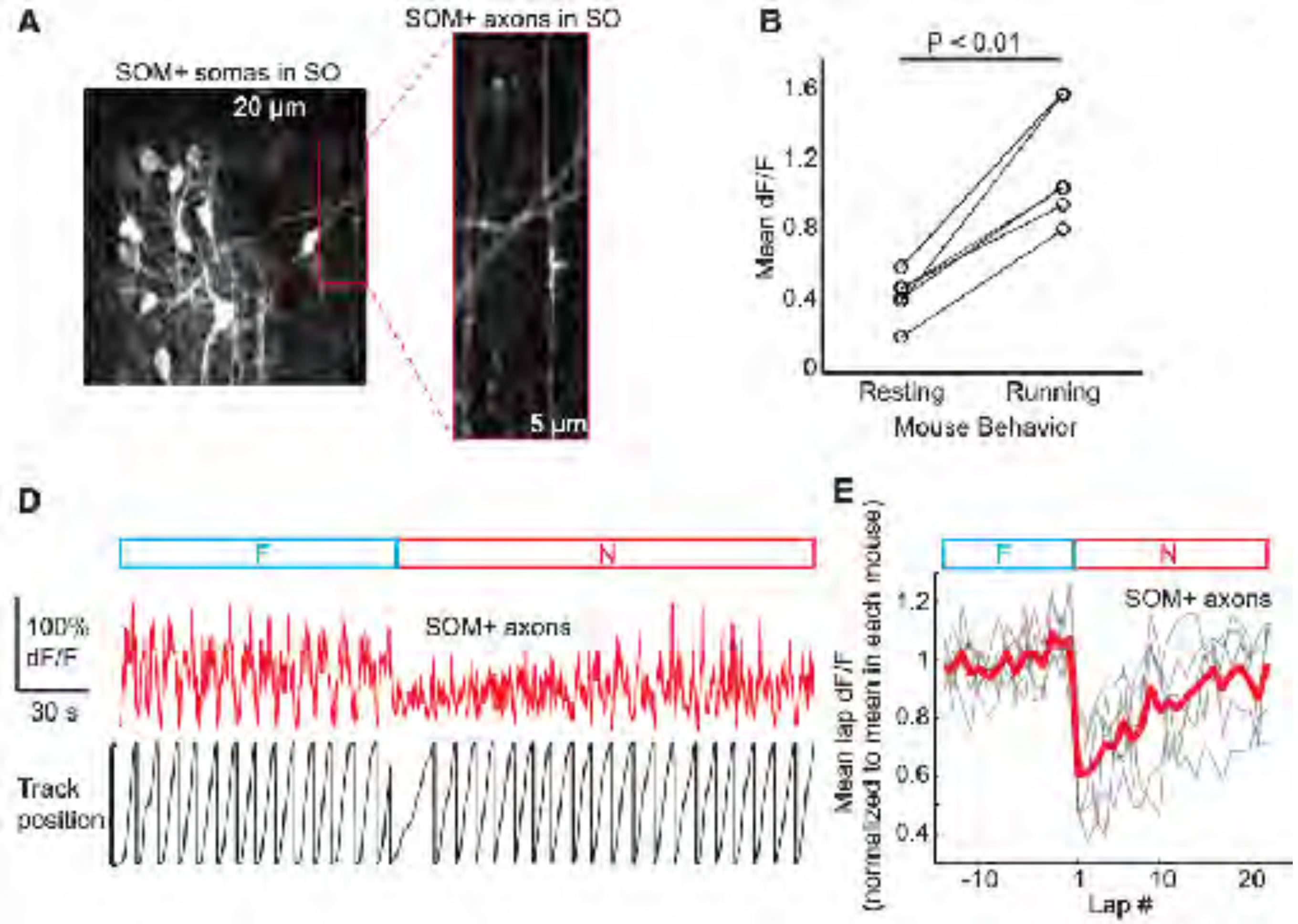
Signal in soma

Signal in dendrite

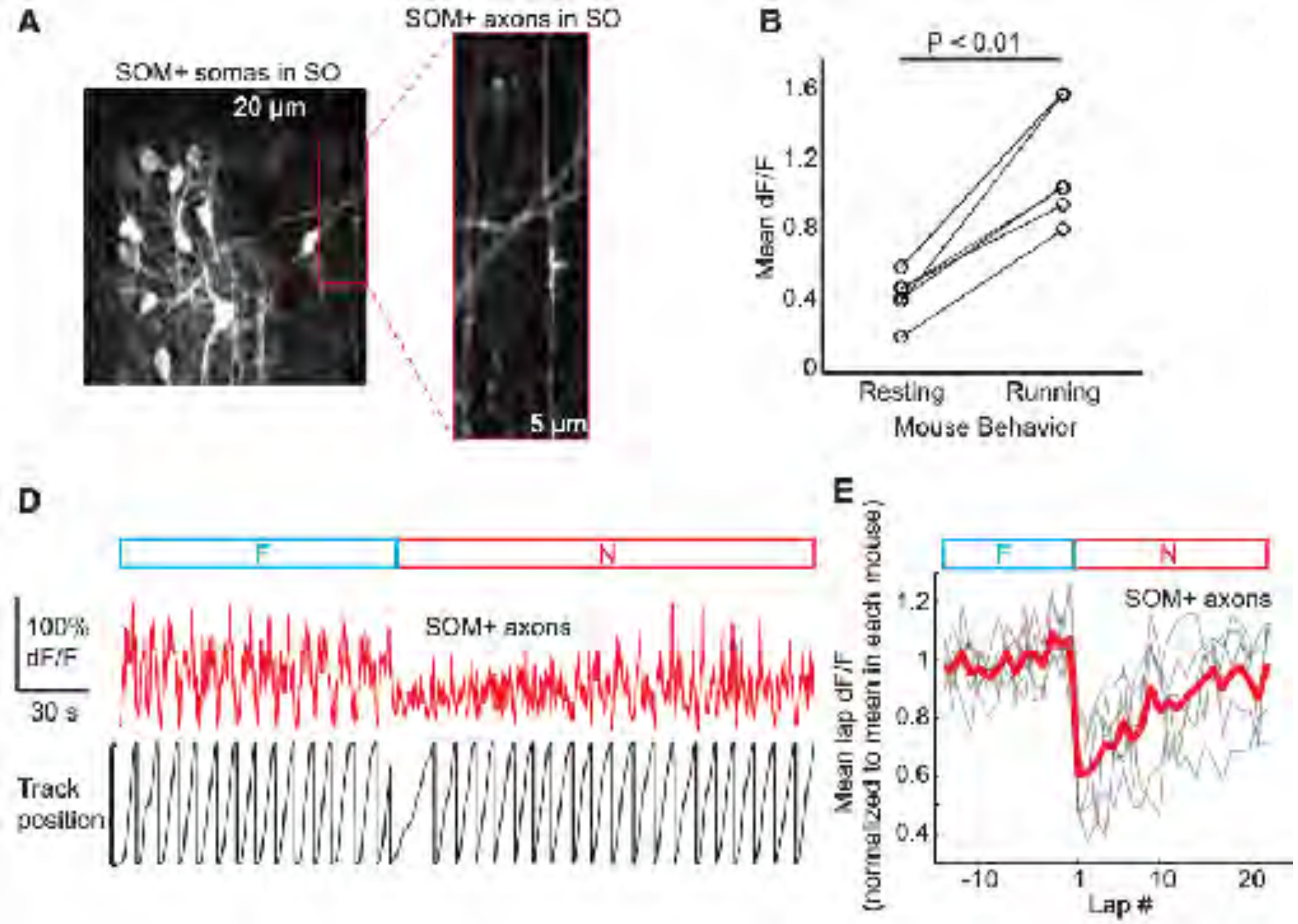


Sheffield & Dombeck *Neuron,* 2017

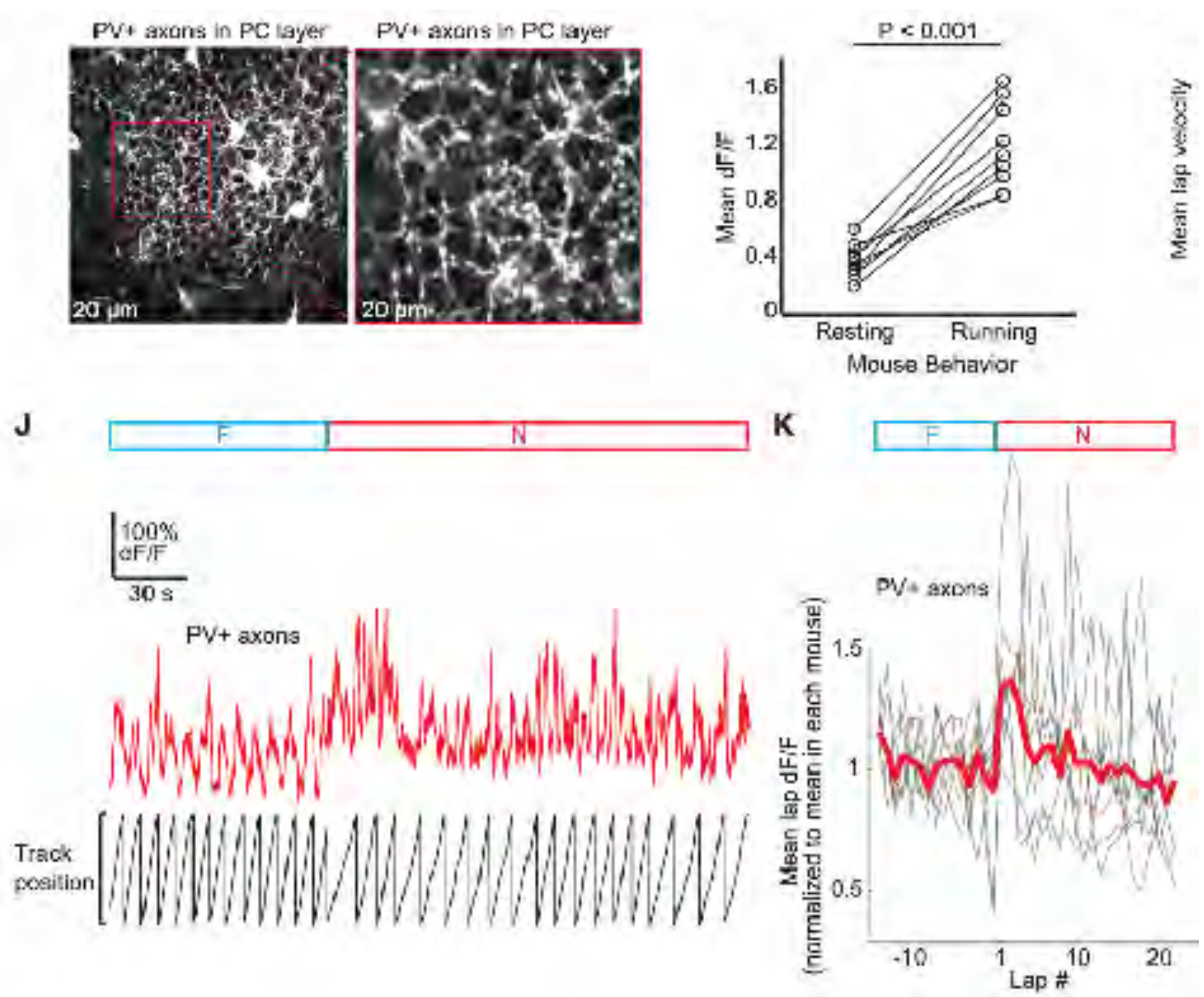
Dendritic inhibition

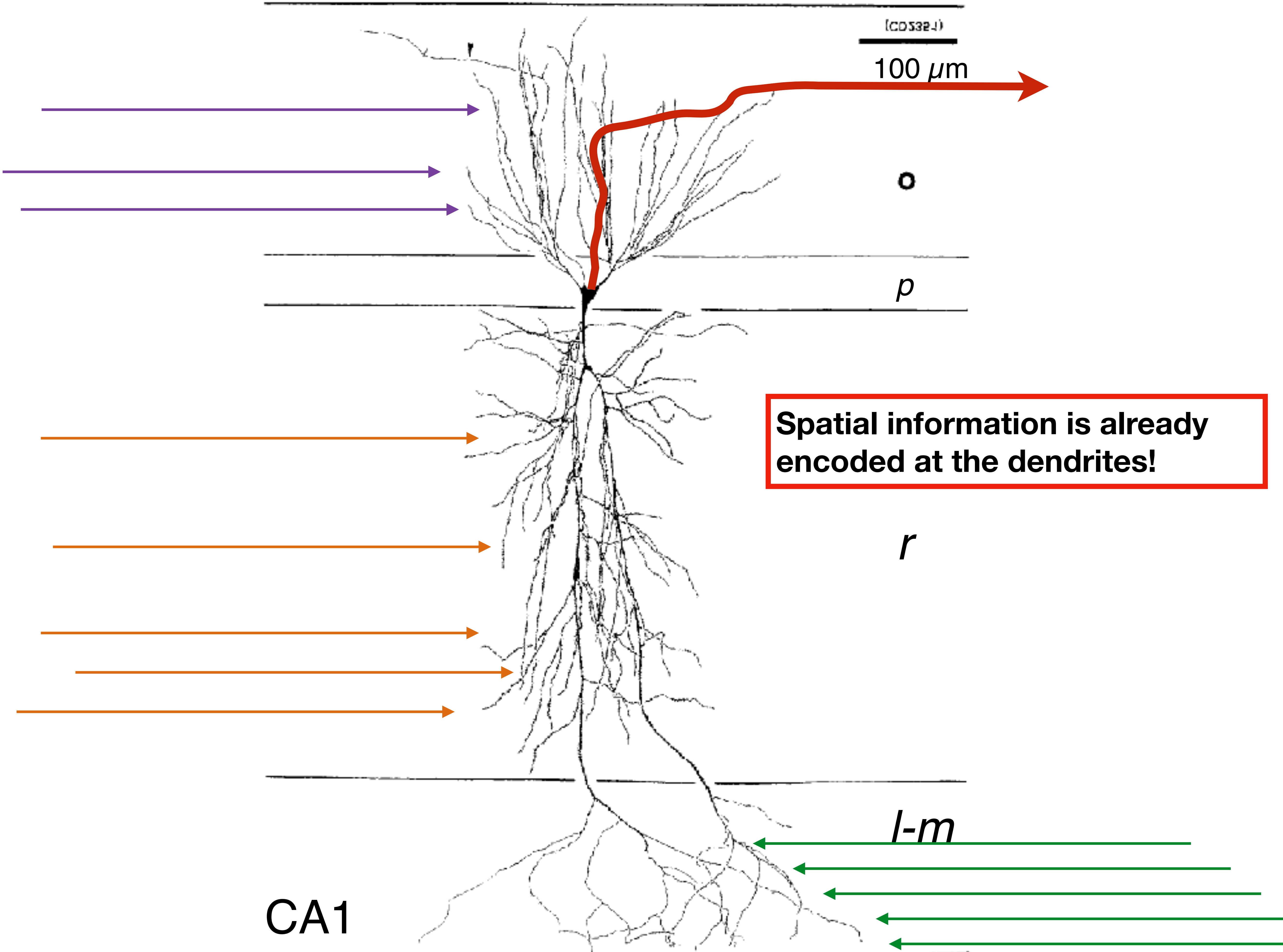


Dendritic inhibition



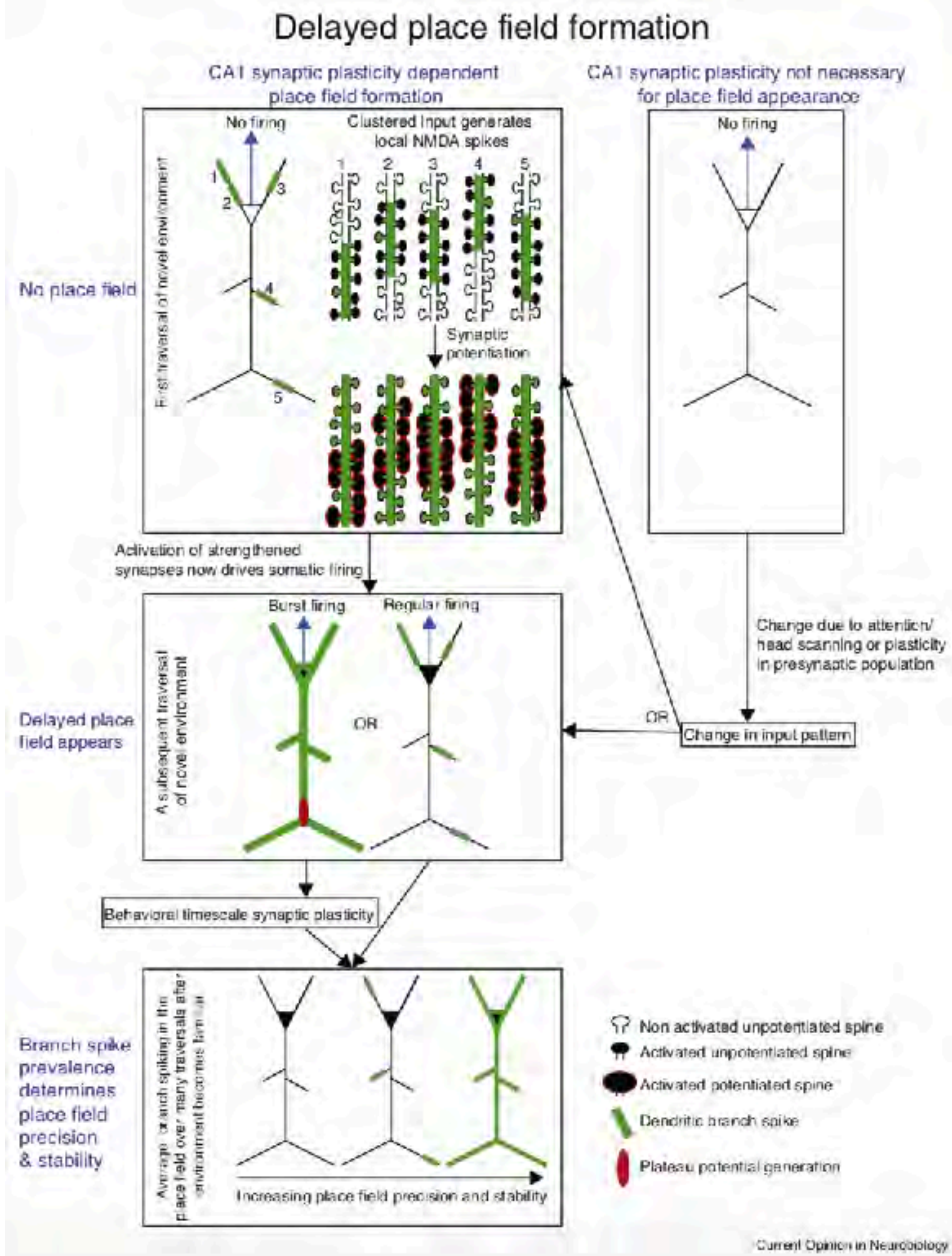
Somatic inhibition





Spatial information is already encoded at the dendrites!

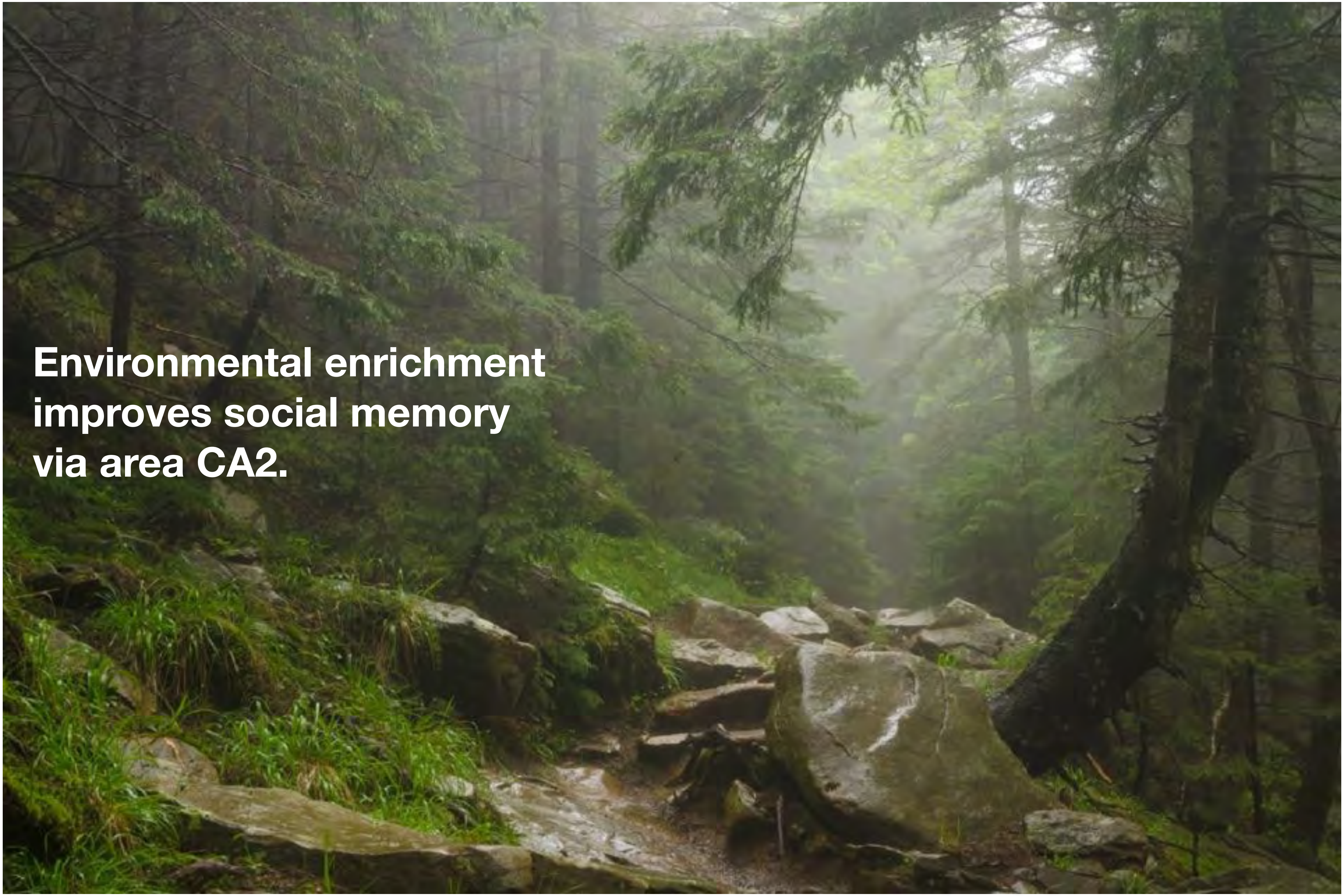
Ishizuka et al, Journal of Comparative Neurobiology, 1995.



Sheffield & Dombeck
Current Opinion Neurobiology, 2019

Extra Stuff

Environmental enrichment improves social memory via area CA2.



Rebecca Piskorowski
Team Synaptic Plasticity and Neural Networks
Institute of Psychiatry and Neuroscience of Paris

Inserm
Institut national de la santé et de la recherche médicale

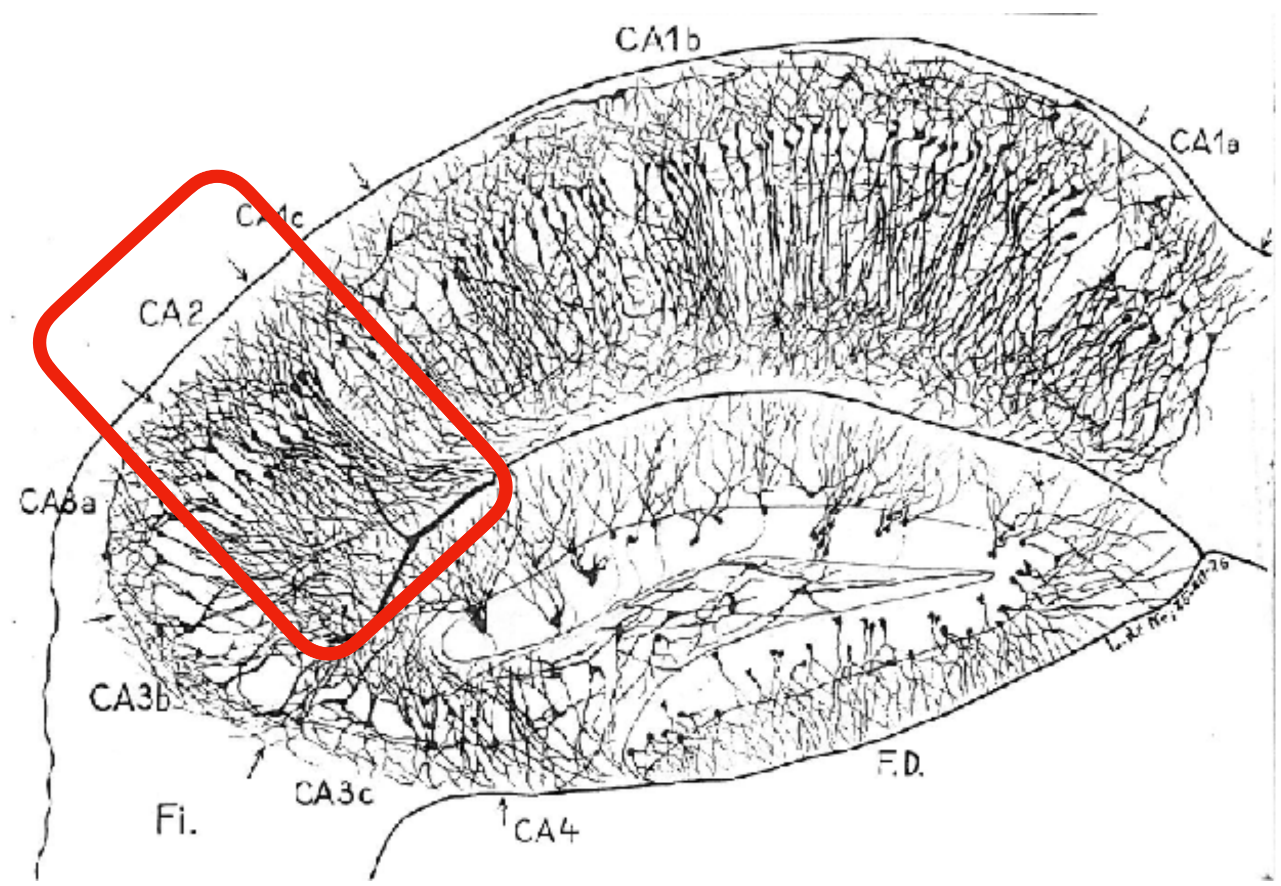
Institut de Psychiatrie et Neurosciences de Paris

Université de Paris

CA regions identified by Lorente de Nó

Primate hippocampus

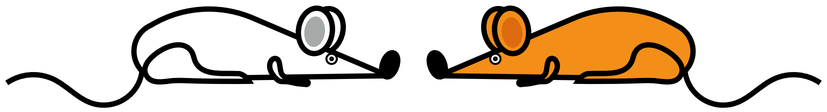
Rodent hippocampus



Lorente de Nó *J Psychology and Neurologie,* 1934.

Hippocampal area CA2

1) Plays an important role in social recognition memory



(Stevenson and Caldwell. *Eur J Neurosci.* 2014)
(Hitti F and Siegelbaum SA. *Nature.* 2014)

Hippocampal area CA2

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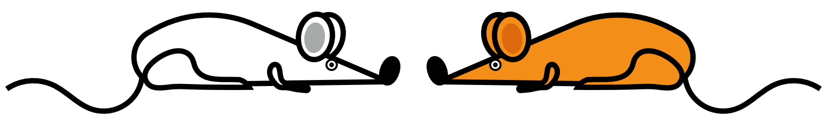
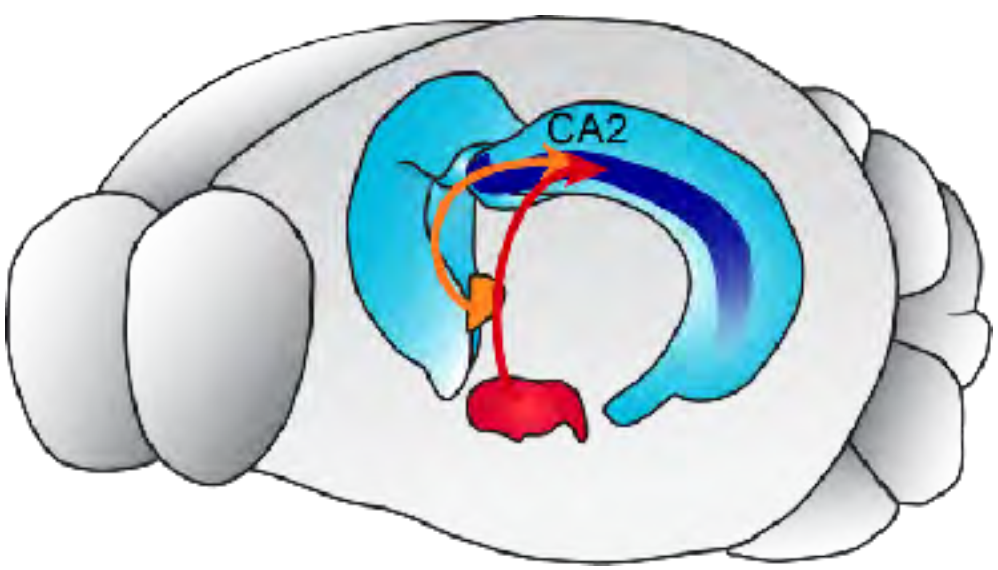
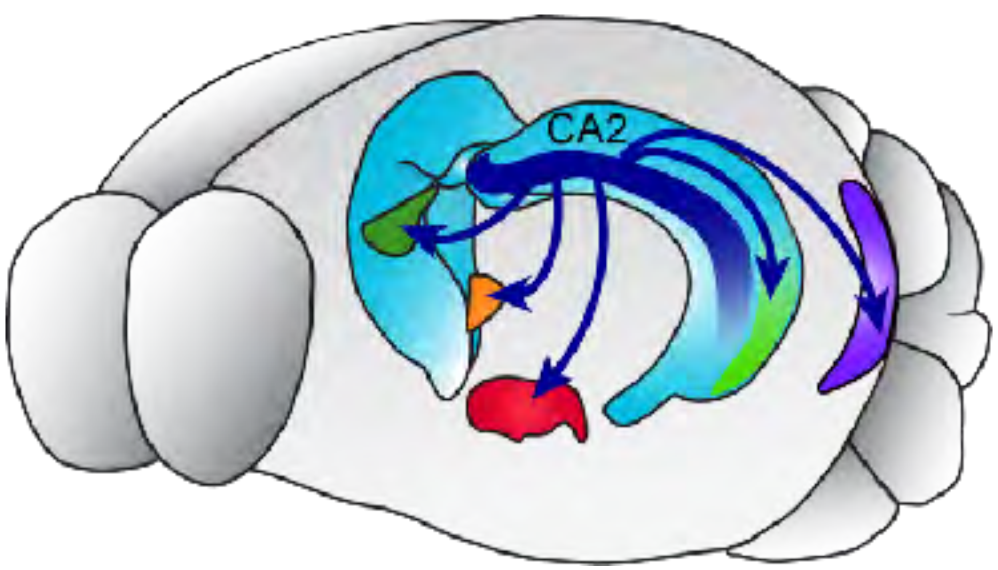


(Stevenson and Caldwell. *Eur J Neurosci.* 2014)
(Hitti F and Siegelbaum SA. *Nature.* 2014)

2) Receives unique input from the hypothalamus and projects to numerous brain regions



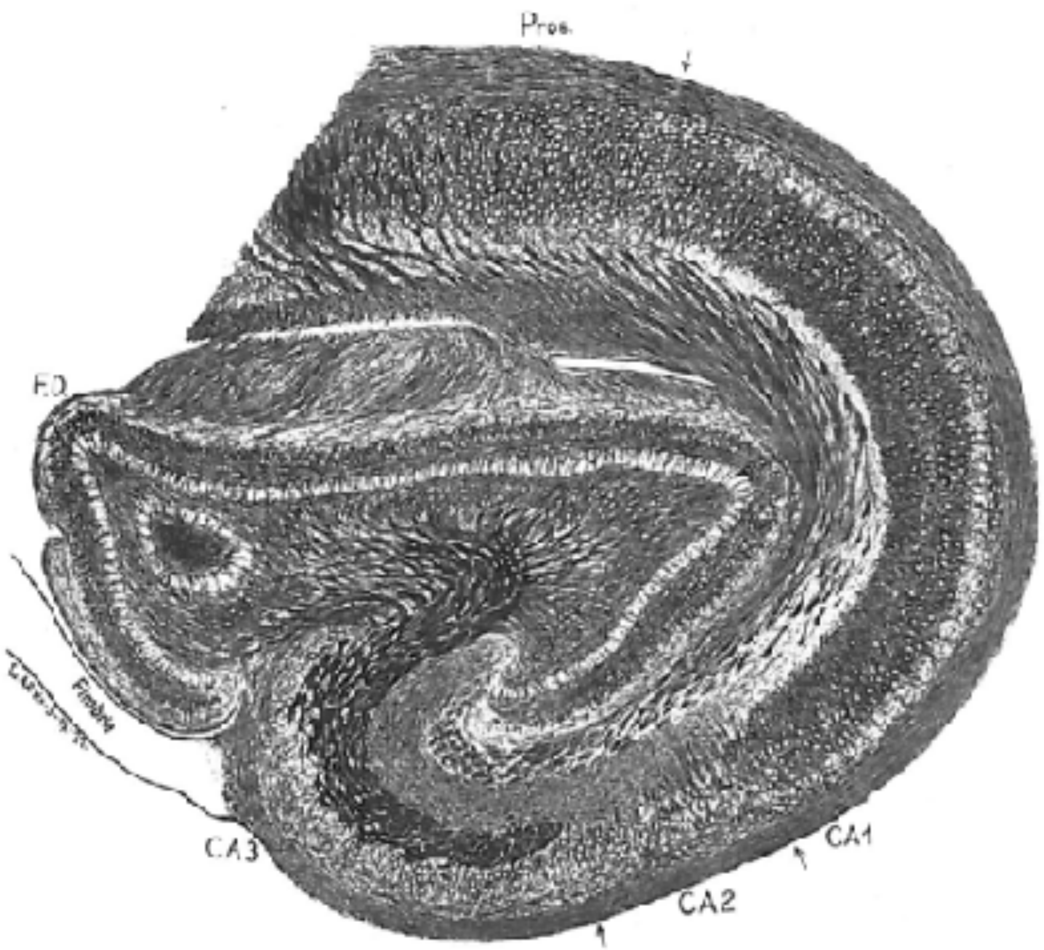
CA2 receives input from hypothalamus



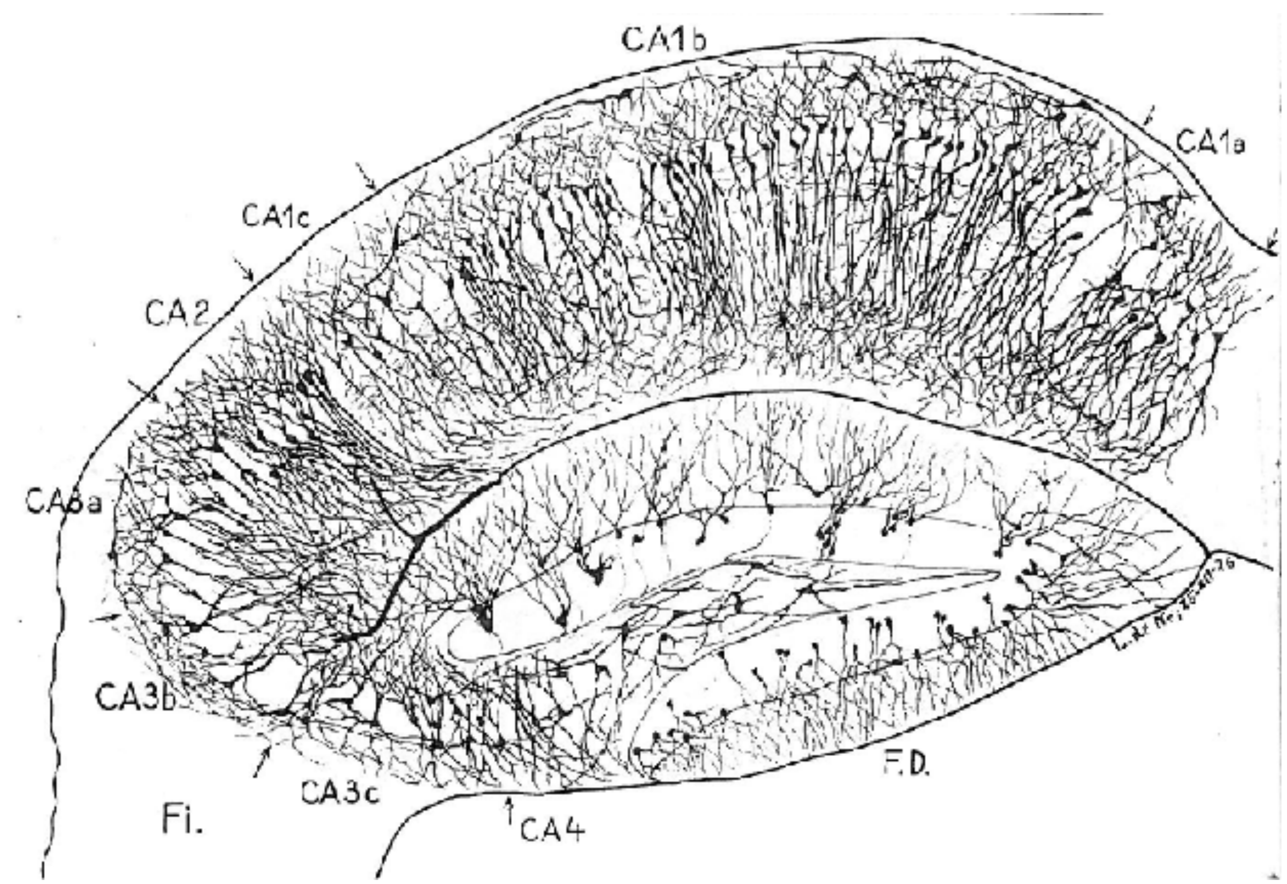
CA2 projects to several brain regions

Area CA2 was understudied for 70 years by physiologists…

Macaca hippocampus



Rodent hippocampus



Lorente de Nó *J Psychology and Neurologie,* 1934.

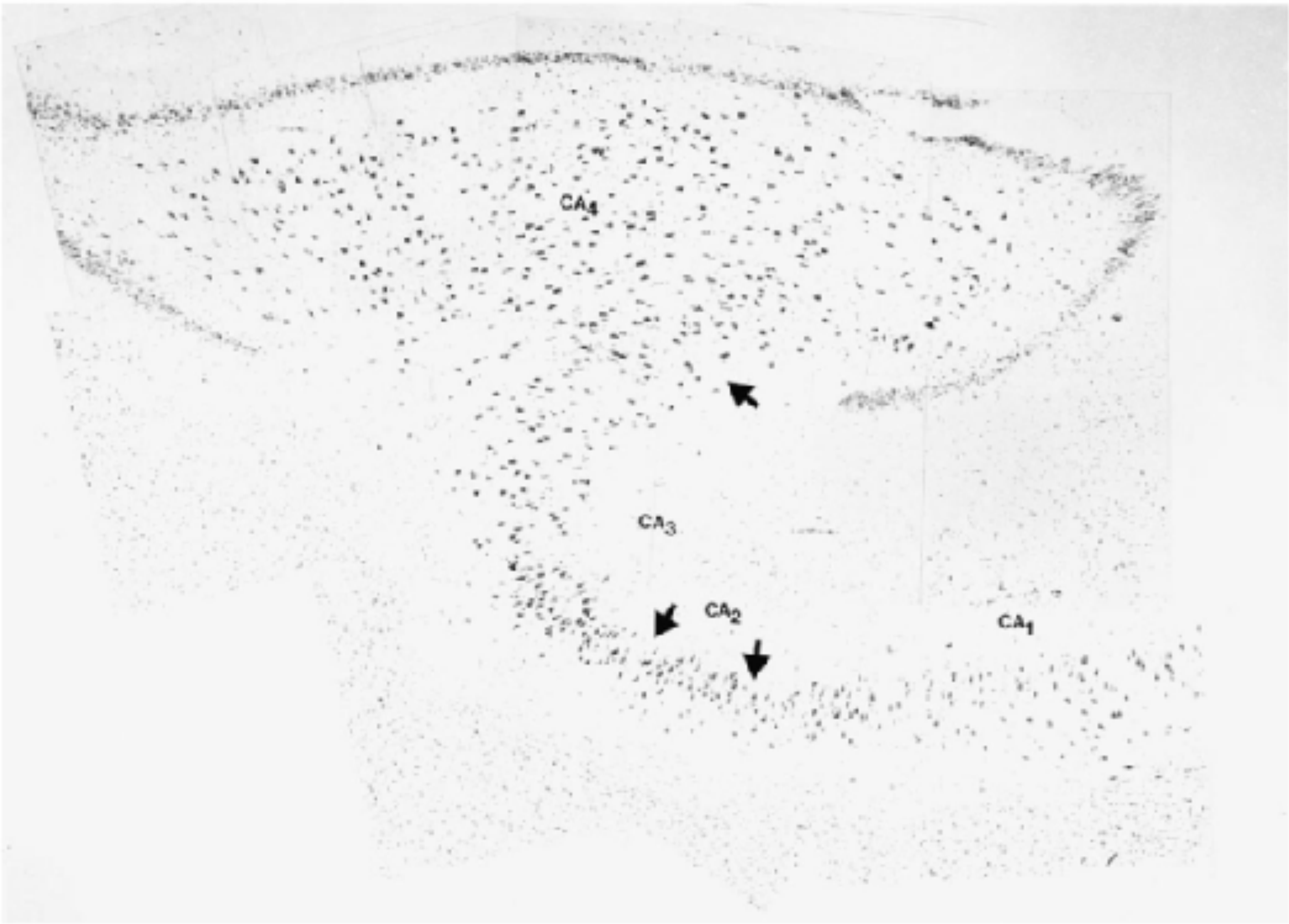
…but NOT by neuroanatomists

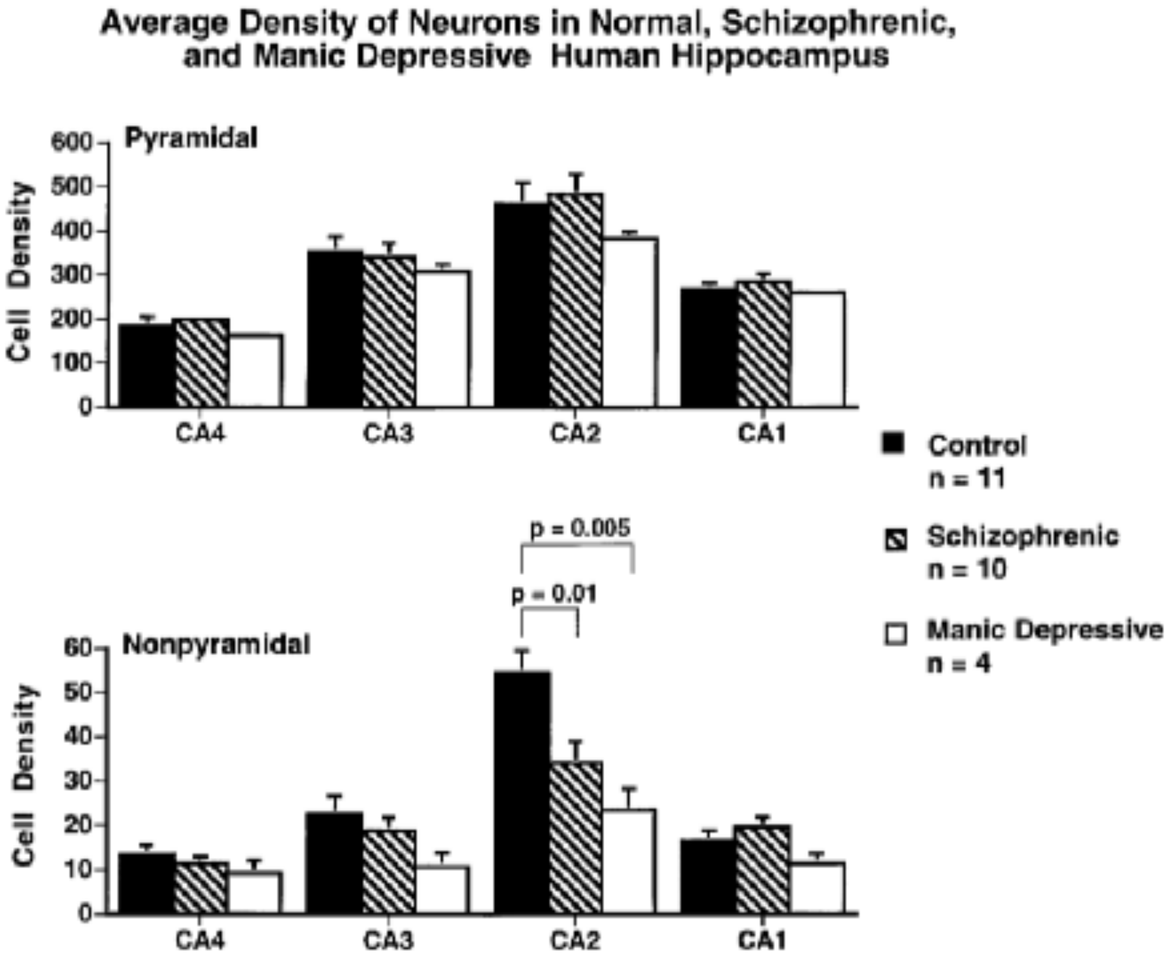
Area CA2 is altered in psychiatric disorders

A Reduction of Nonpyramidal Cells in Sector CA2 of Schizophrenics and Manic Depressives

Francine M. Benes, Esther W. Kwok, Stephen L. Vincent, and Mark S. Todtenkopf

BIOL PSYCHIATRY 1998; 44:88-97





Area CA2 is altered in psychiatric disorders

Molecular abnormalities of the hippocampus in severe psychiatric illness: postmortem findings from the Stanley Neuropathology Consortium

MB Knable[1], BM Barci[1], MJ Webster[2], J Meador-Woodruff[3] and EF Torrey[1,2]

[1]The Stanley Medical Research Institute, Bethesda, MD, USA; [2]Stanley Brain Research Laboratory, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD, USA; [3]Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA

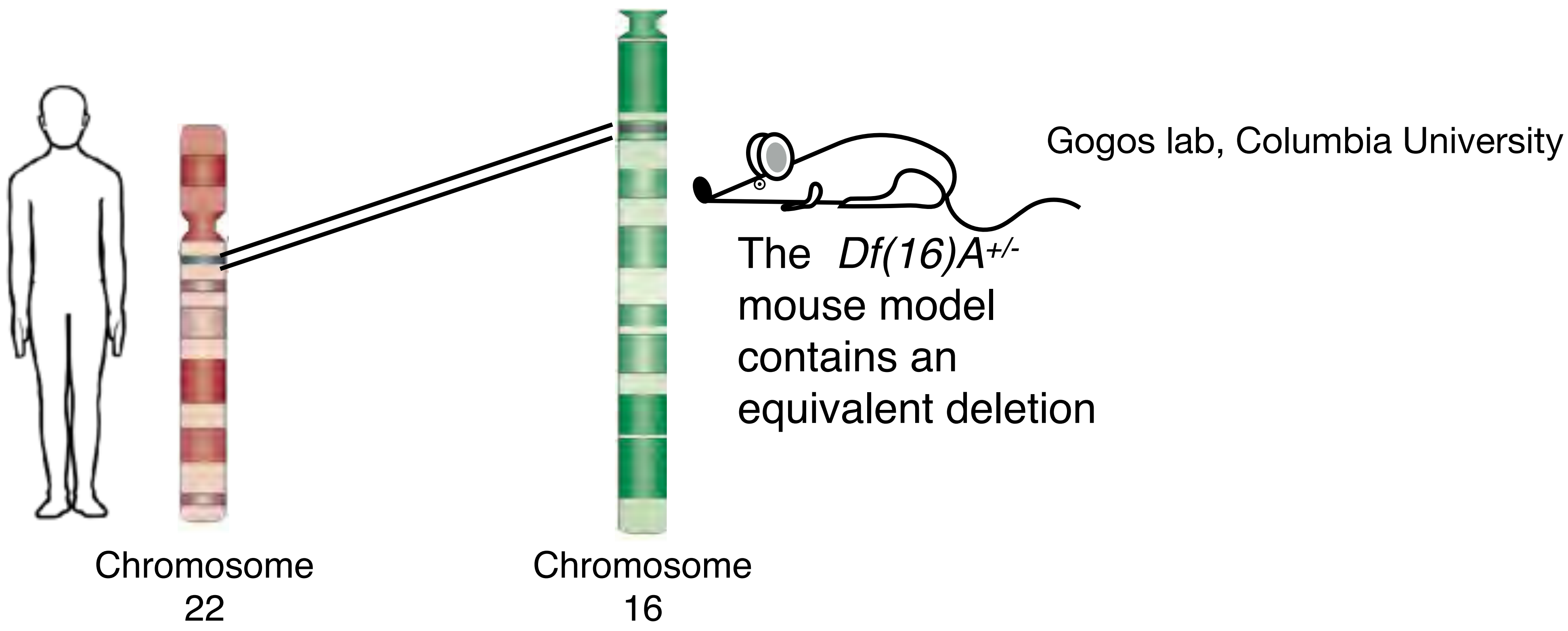
Out of 224 measures…

Table 2 *Post hoc* Mann–Whitney *U* test results and fold change (Δ) for abnormal hippocampal measures after correction for multiple comparisons

Measure	*Schizophrenia*		*Bipolar*		*Depression*	
	P	*Δ*	*P*	*Δ*	*P*	*Δ*
Reelin dentate gyrus molecular layer[a]	0.0002	0.53	0.004	0.73	0.04	0.67
Parvalbumin total CA2	<0.0001	0.20	0.04	0.80		
Parvalbumin density CA2	<0.0001	0.27				

22q11.2 Deletion Syndrome (De DiGeorge Syndrome)

Deletion of ~36 genes ⟶ 30% risk of schizophrenia diagnosis



22q11.2 Deletion Syndrome (De DiGeorge Syndrome)

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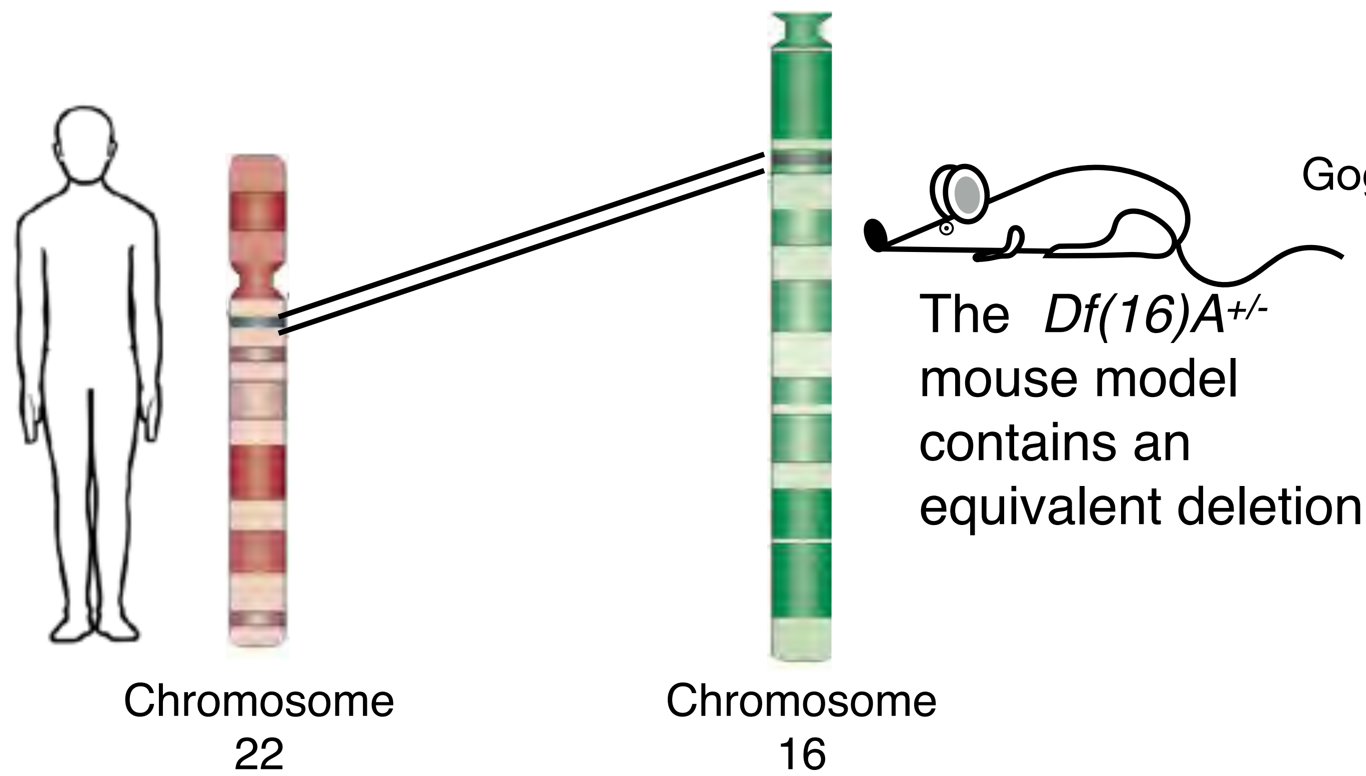


Disruption in hippocampal-prefrontal synchrony that accompanies compromised memory.

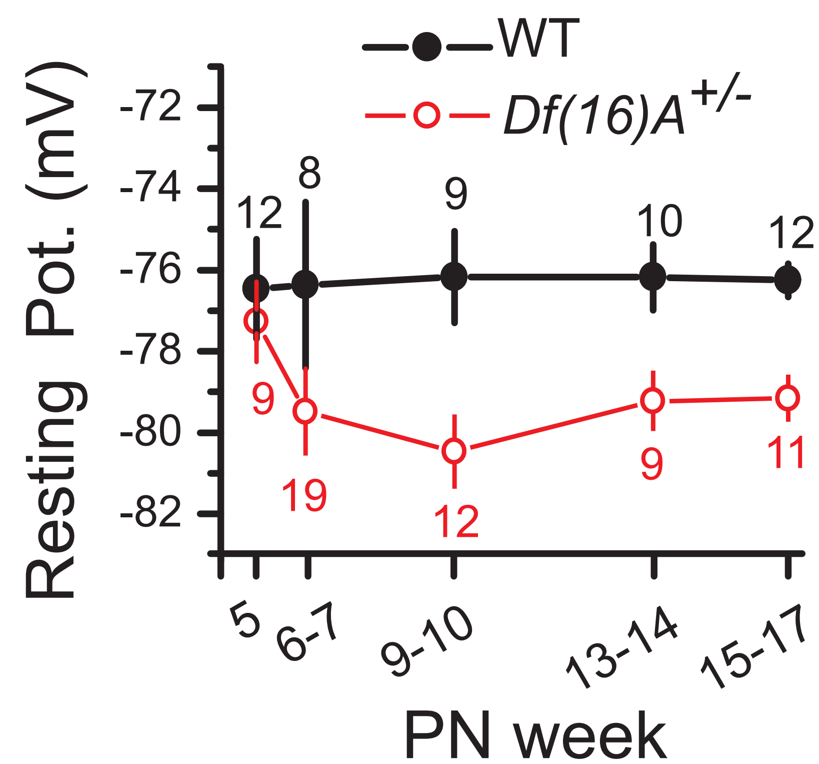
Sigurdsson, Stark, Karayiorgou, Gogos and Gordon, *Nature* 2010.

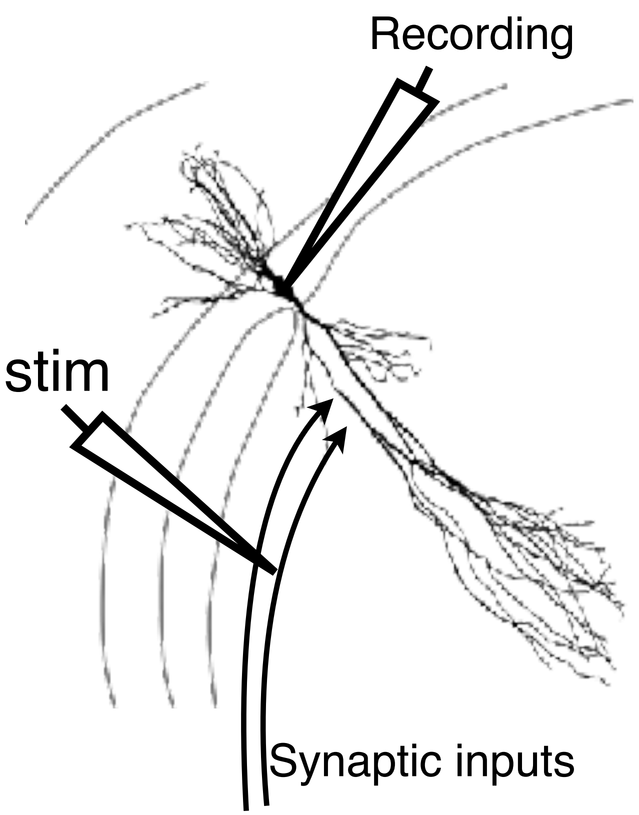
Several cognitive and behavioral phenotypes, yet no major change in CA1 pyramidal neuron physiology.

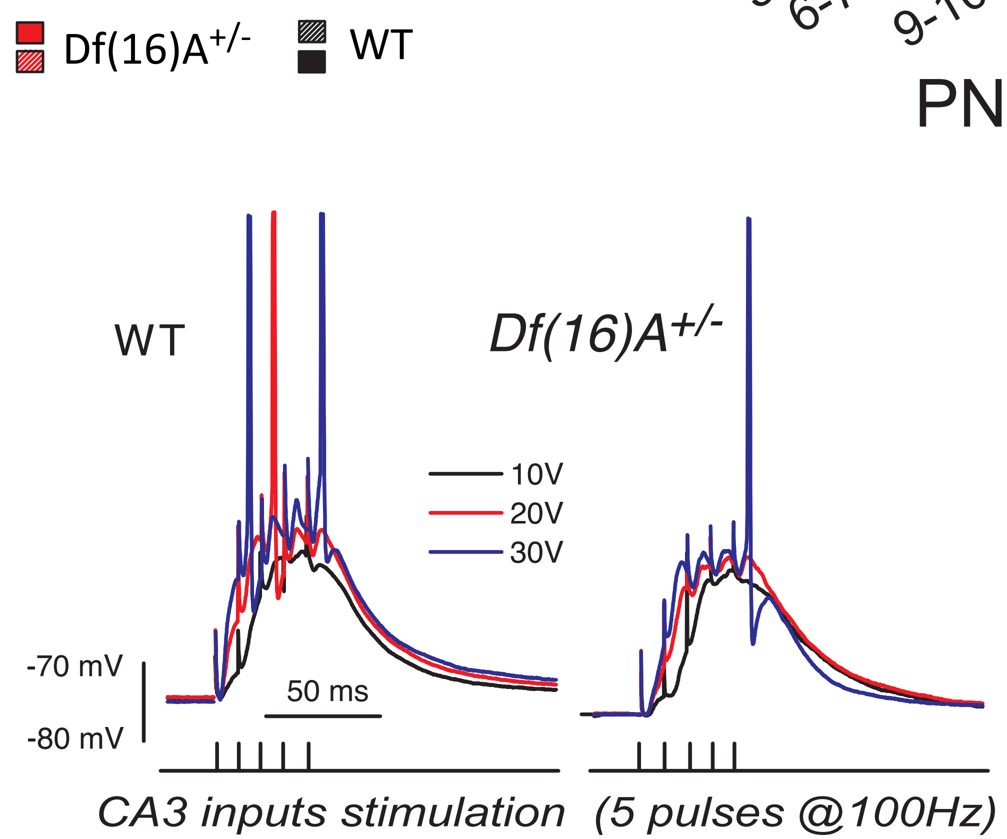
Drew LJ, Stark KL, Fénelon K, Karayiorgou M, MacDermott AB, Gogos JA, *Molecular and Cellular Neuroscience*, 2011

Age-dependent changes in hippocampal area CA2 in a mouse model of schizophrenia.

CA2 pyramidal neurons show age-dependant changes in intrinsic properties.



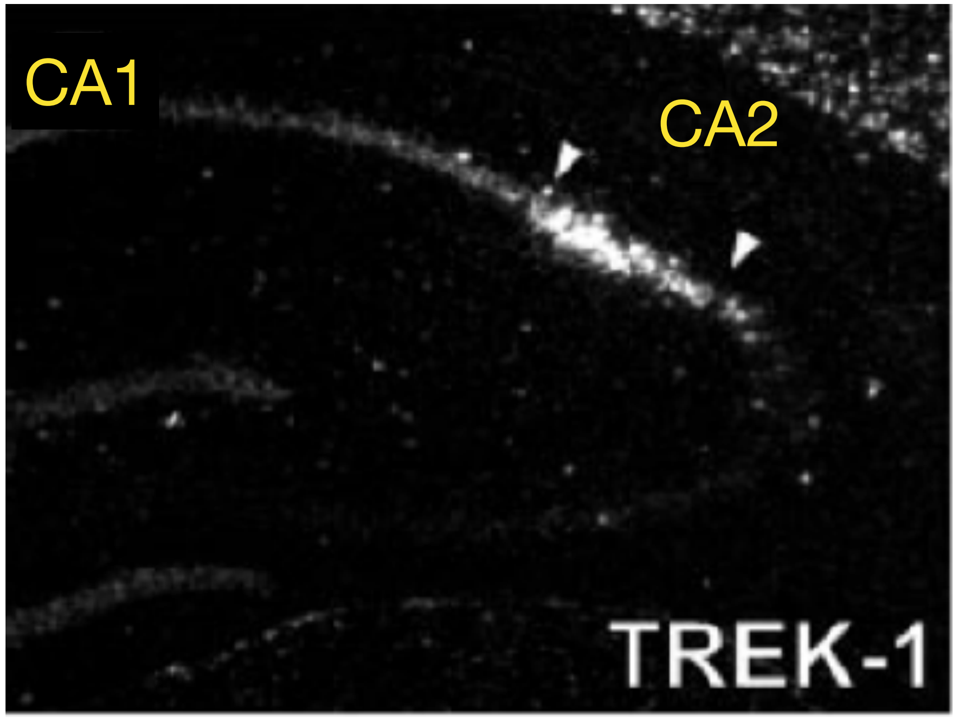




Making it extremely difficult to evoke action potentials in CA2 pyramidal cells in the Df(16)A$^{-/+}$ mice.

Piskorowski et al, *Neuron* 2016.

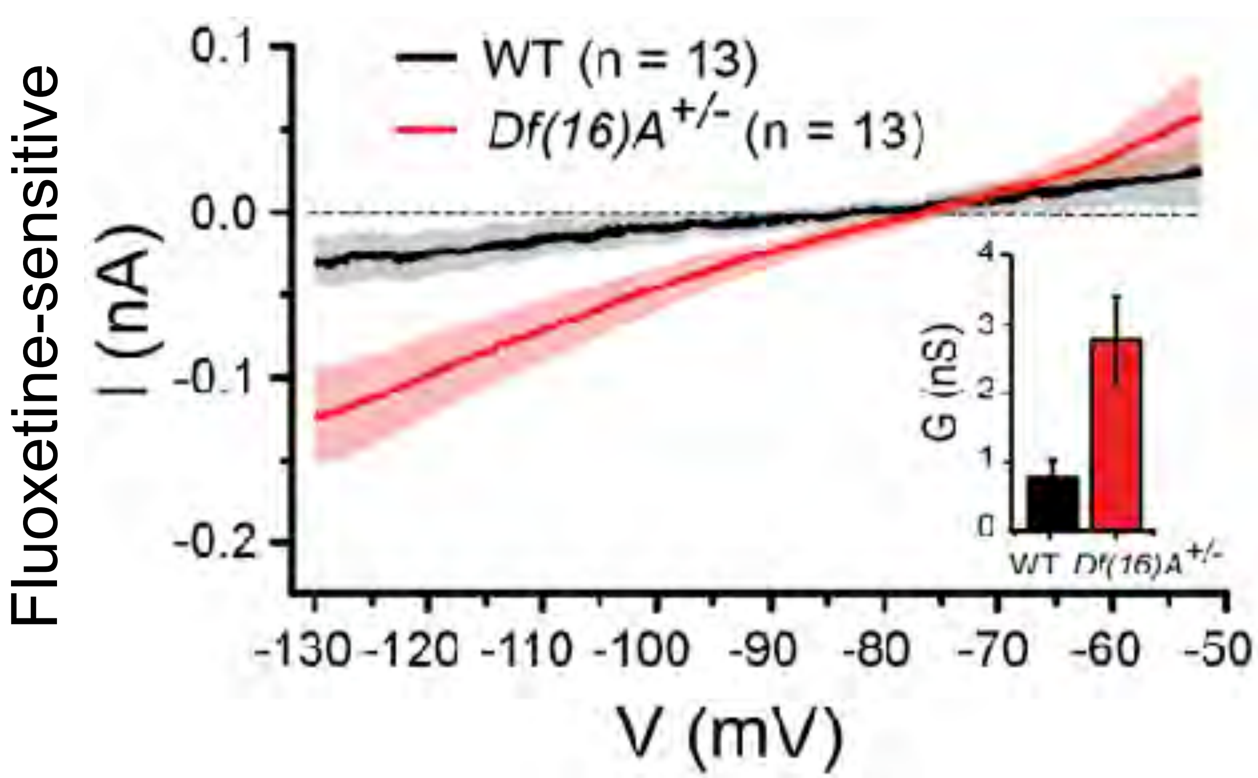
Age-dependent changes in hippocampal area CA2 in a mouse model of schizophrenia.

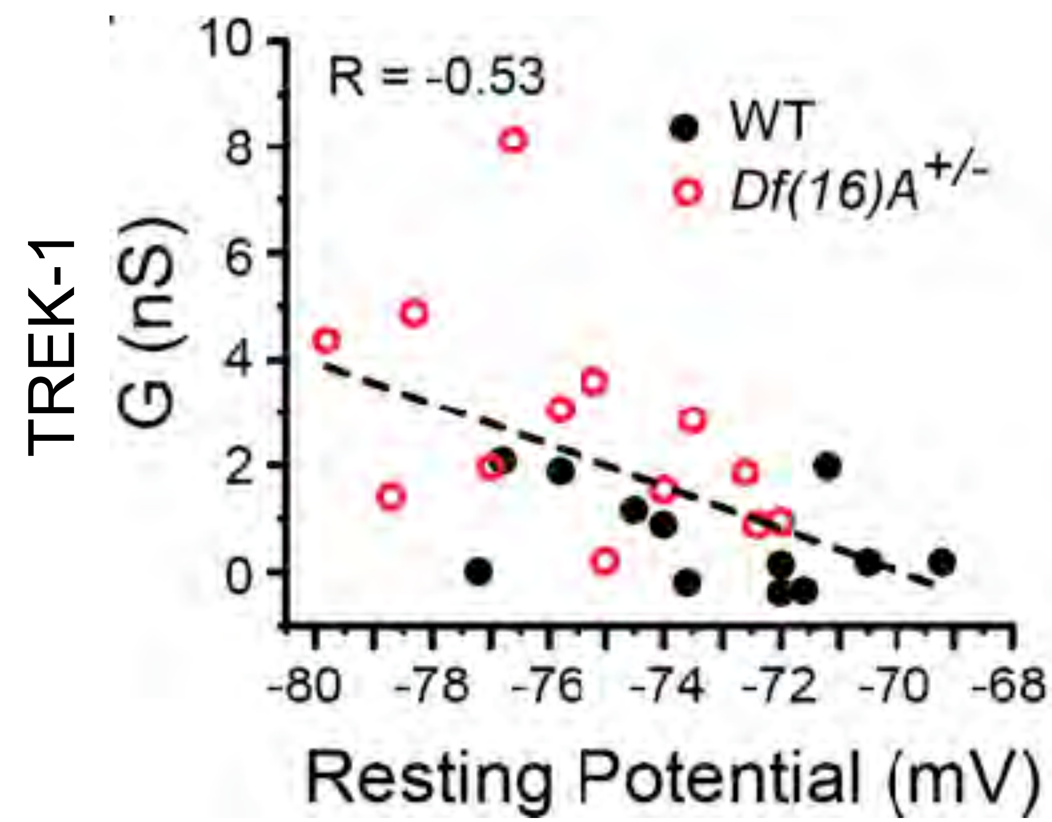


Two-Pore Domain Potassium Channel (TREK-1)
Talley et al, 2001

Leak conductance, open at V_M

Play a role in neuroprotection

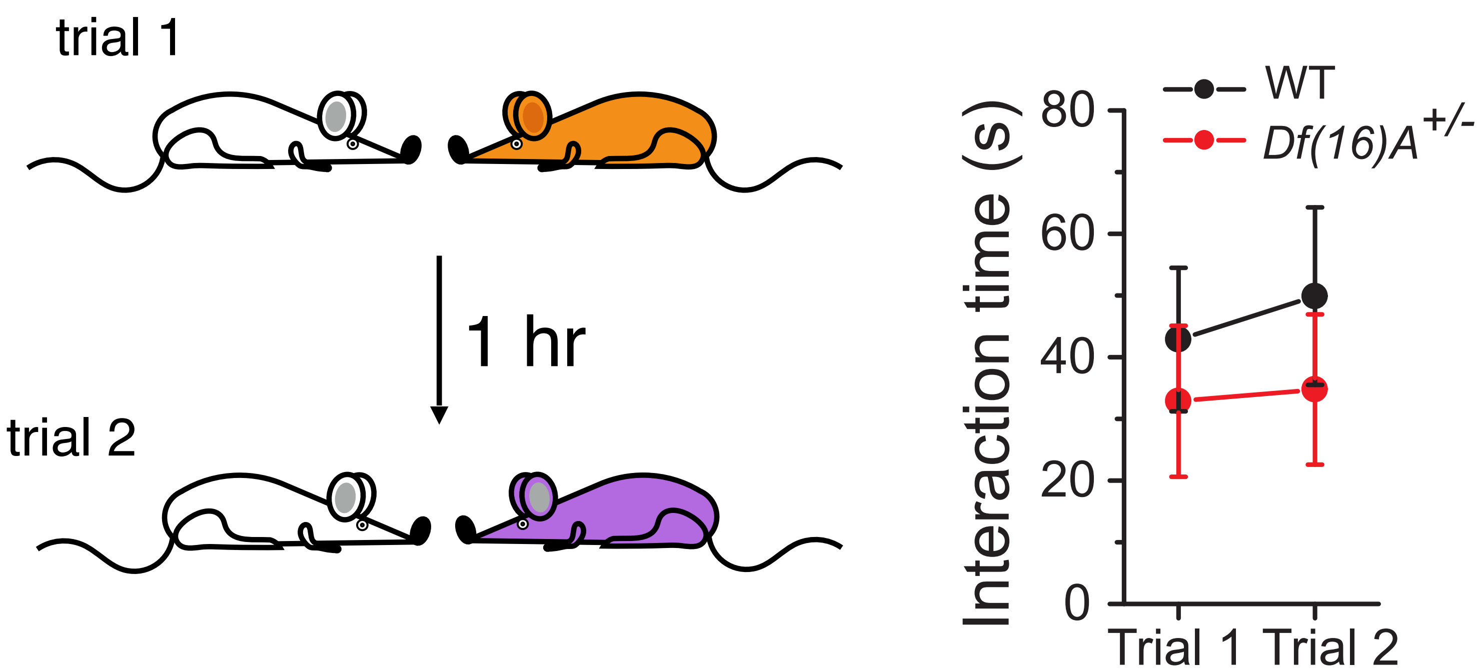


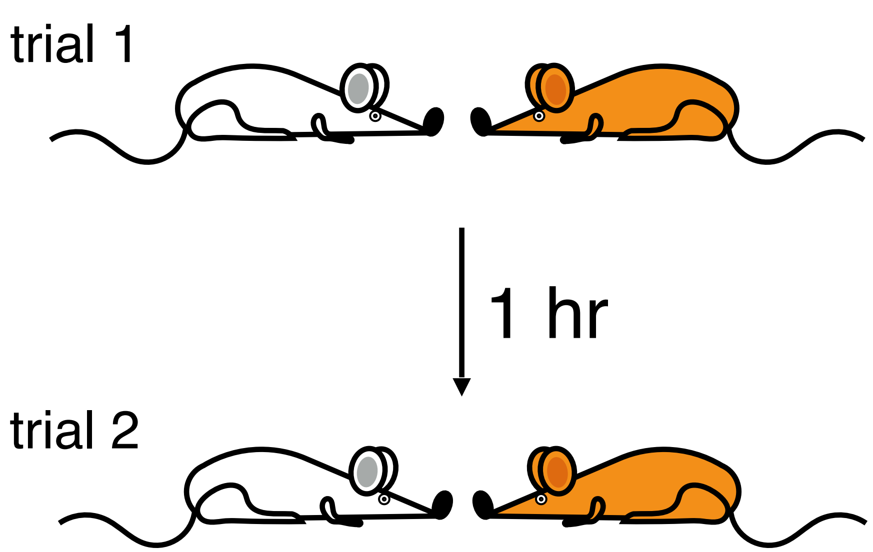


Piskorowski et al, *Neuron* 2016.

The is in increase in TREK-1 conductance in CA2 PNs in the Df(16)A$^{-/+}$ mice.

Age-dependent changes in hippocampal area CA2 in a mouse model of schizophrenia.





Piskorowski et al, *Neuron* 2016.

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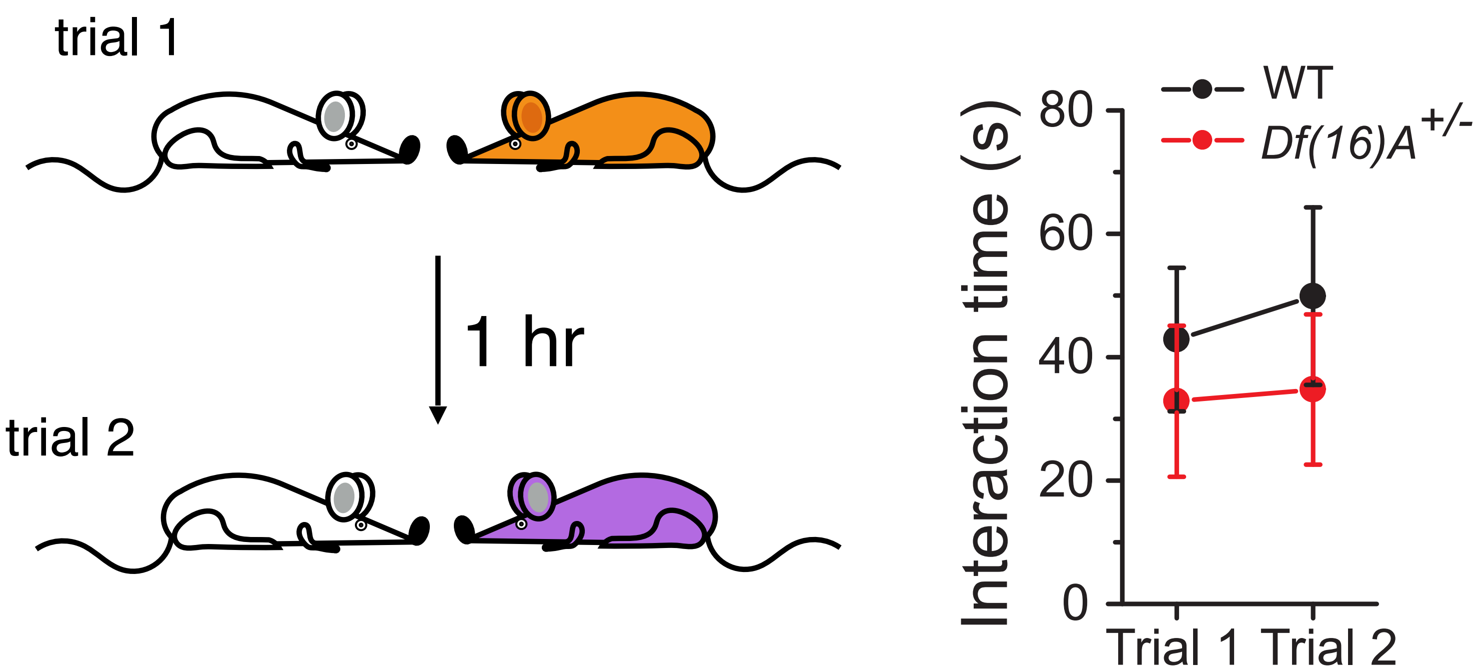

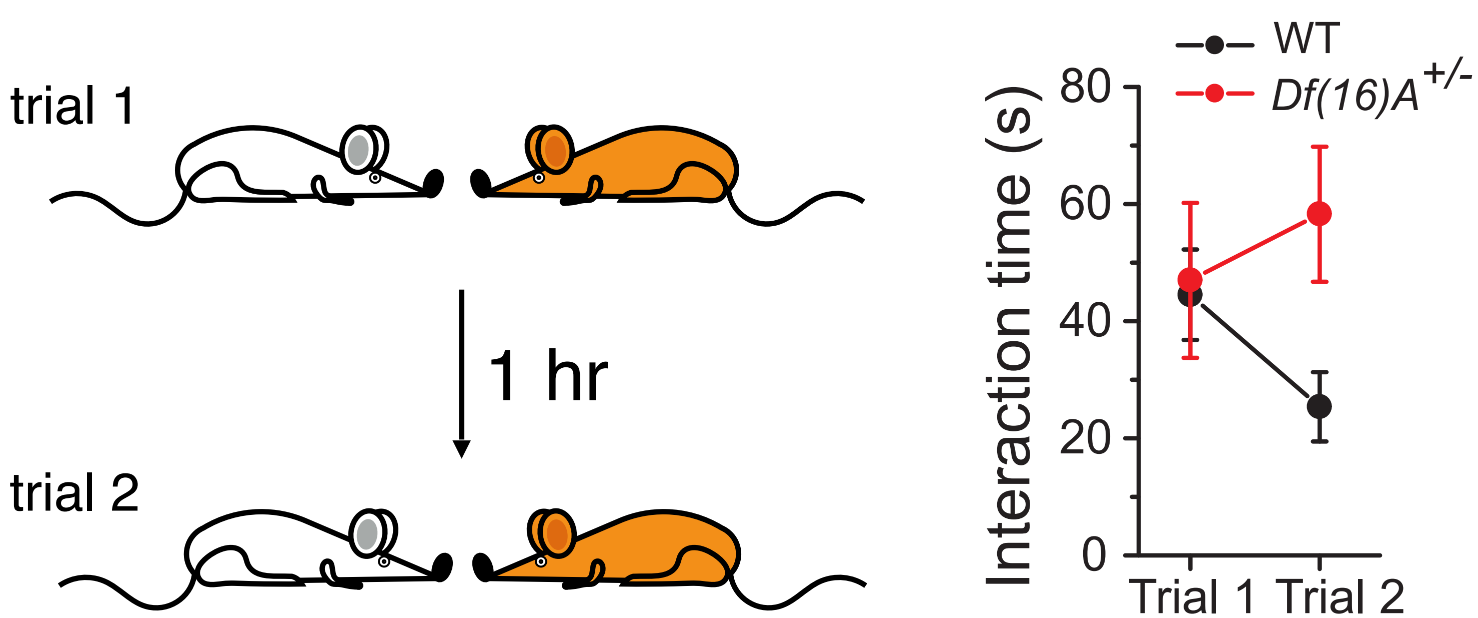

Piskorowski et al, *Neuron* 2016.

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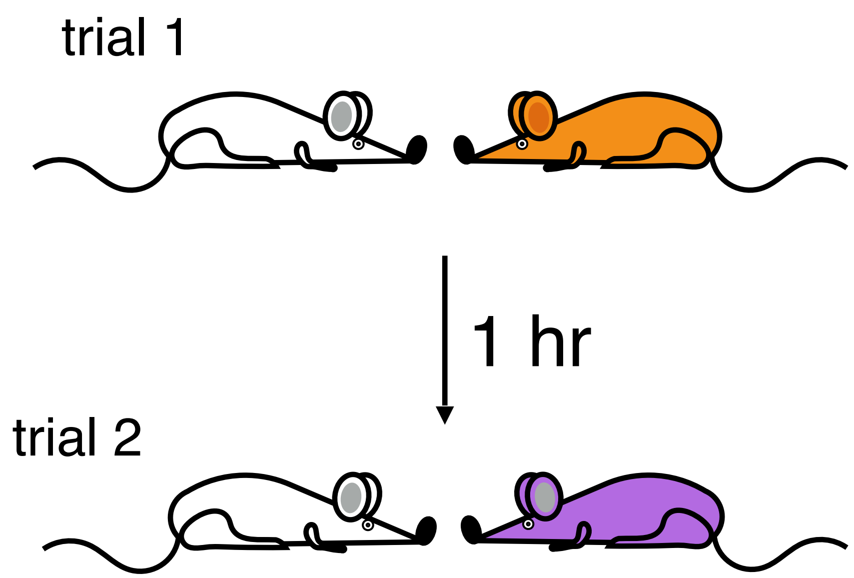
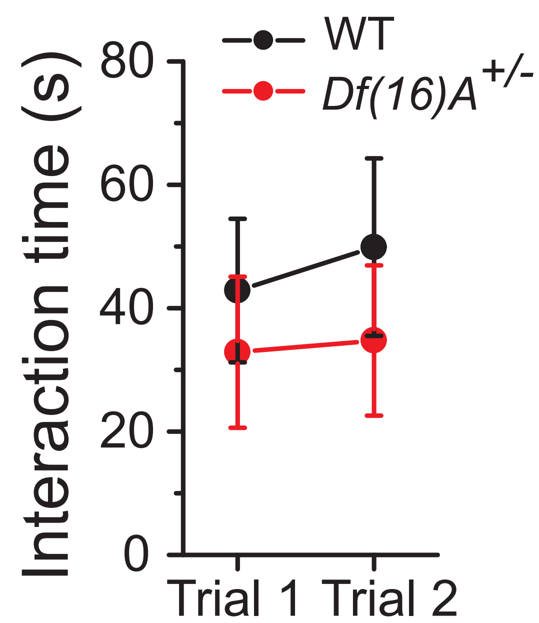
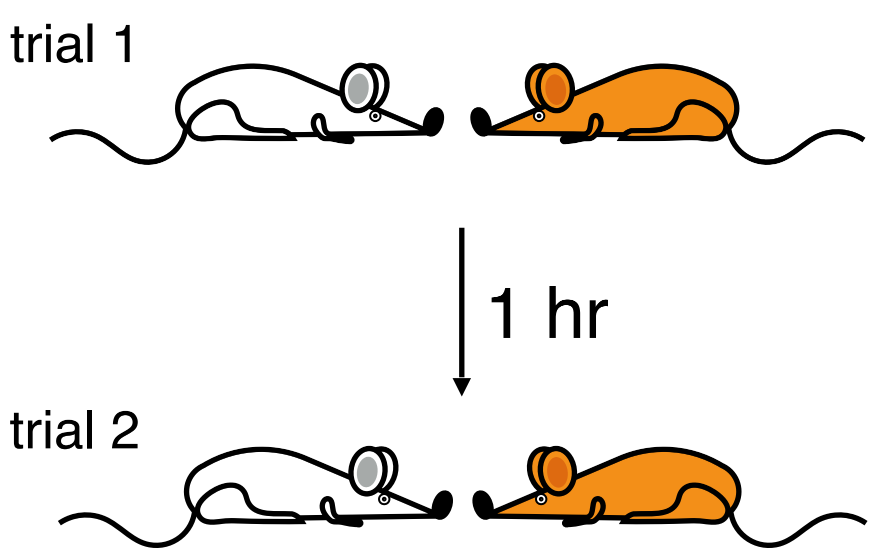
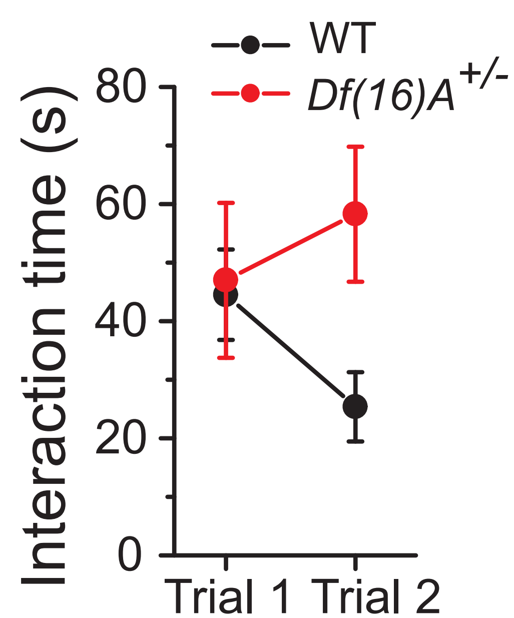
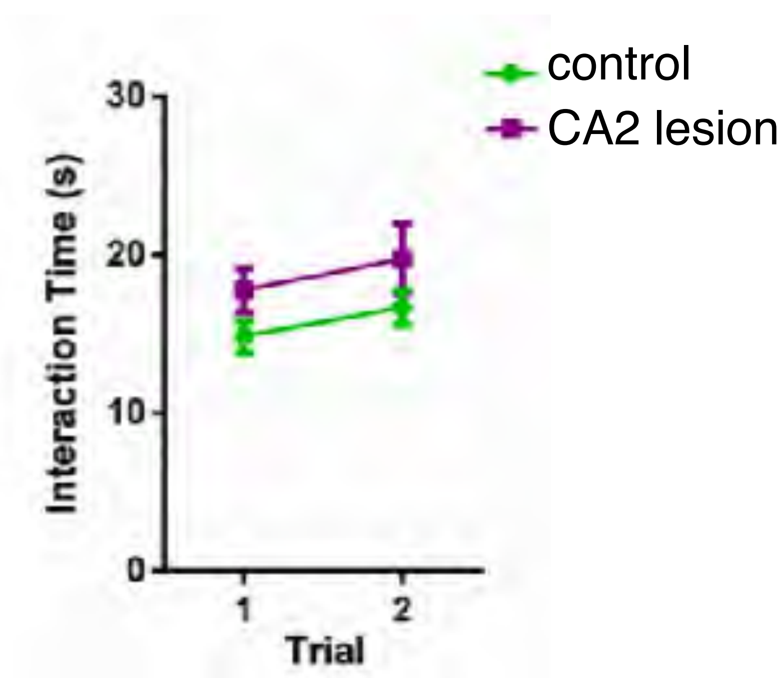


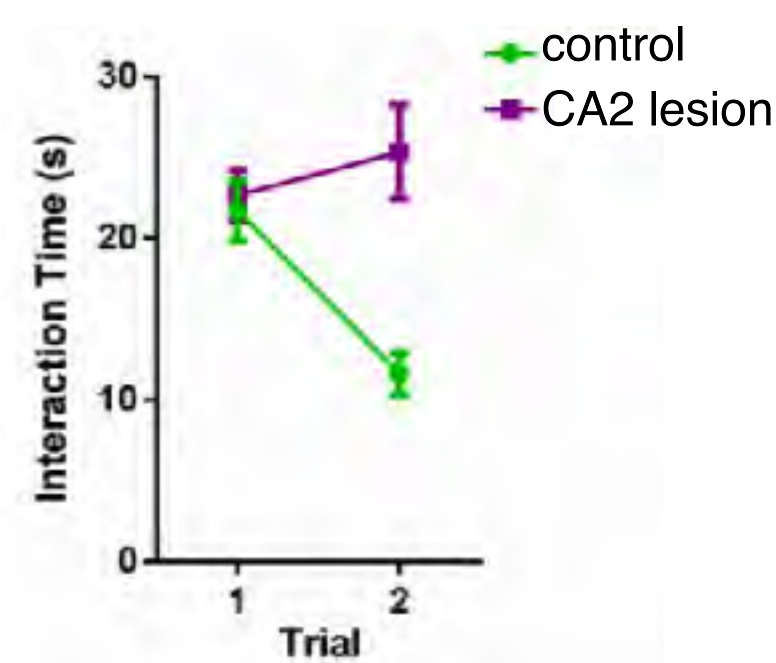






Specific CA2 lesion





(Hitti F and Siegelbaum SA. *Nature.* 2014)

Piskorowski et al, *Neuron* 2016.

Summary of changes in area CA2 of the 22q11.2 DS model:

Reduction in CA2 principle cell activity

Compromised social recognition memory

Parallels with human neuroanatomy (loss of interneurons in area CA2)

Summary of changes in area CA2 of the 22q11.2 DS model:

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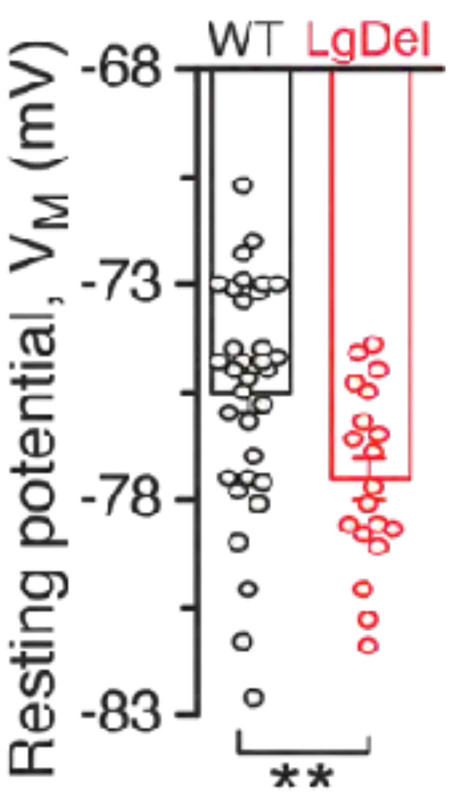
Next steps:

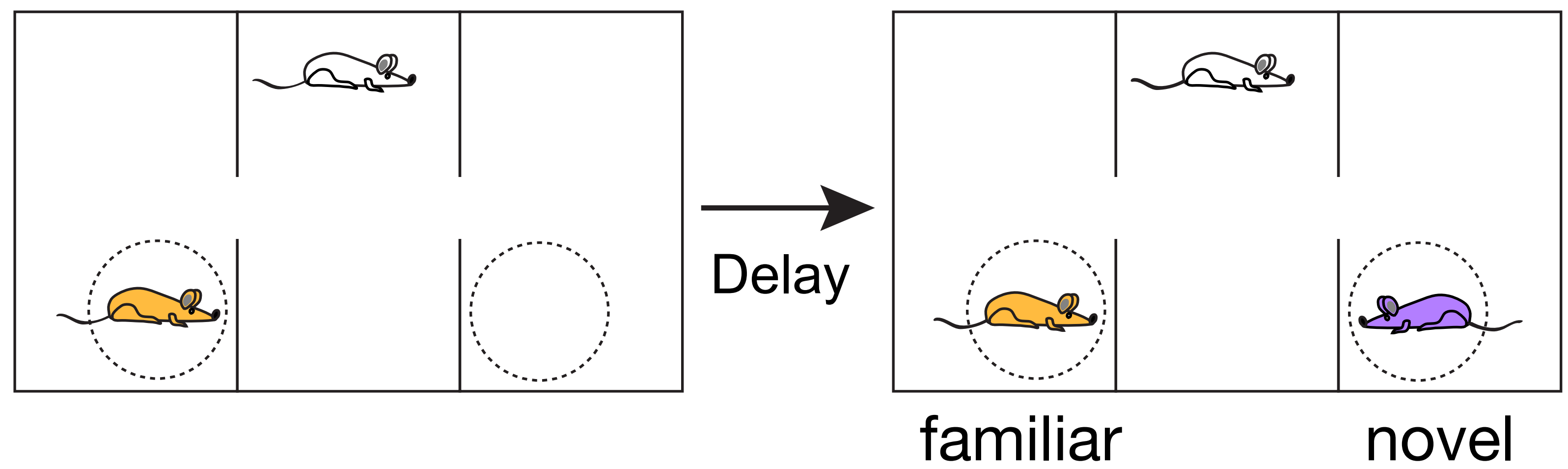
Genetics ⟷ **Environment**

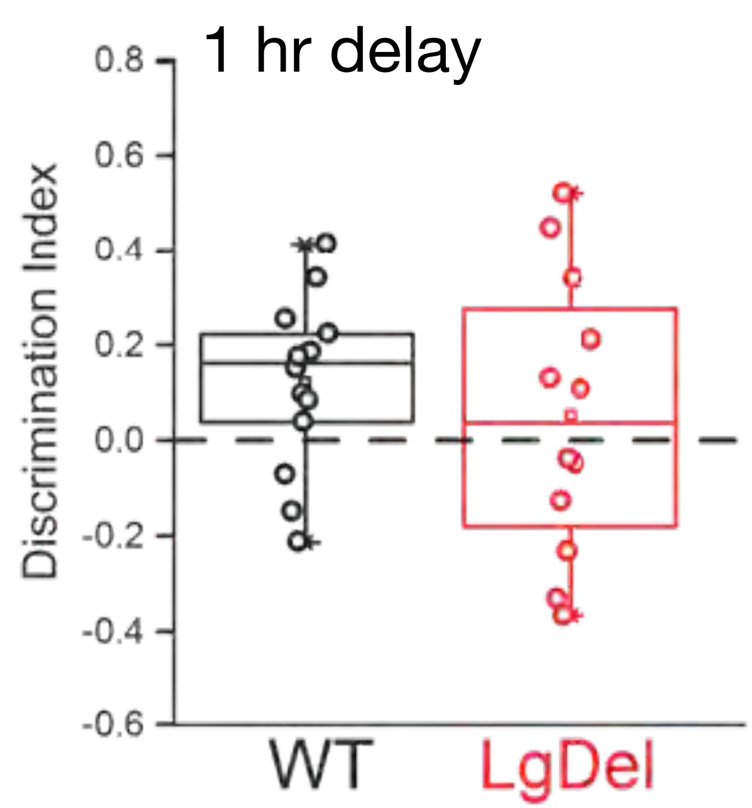
22q11.2DS

Using the LgDel mouse model of 22q11.2DS

(Merscher et al, *Cell* 2001)







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Summary of changes in area CA2 of the 22q11.2 DS model:

Next steps:

Genetics

Environment

22q11.2DS

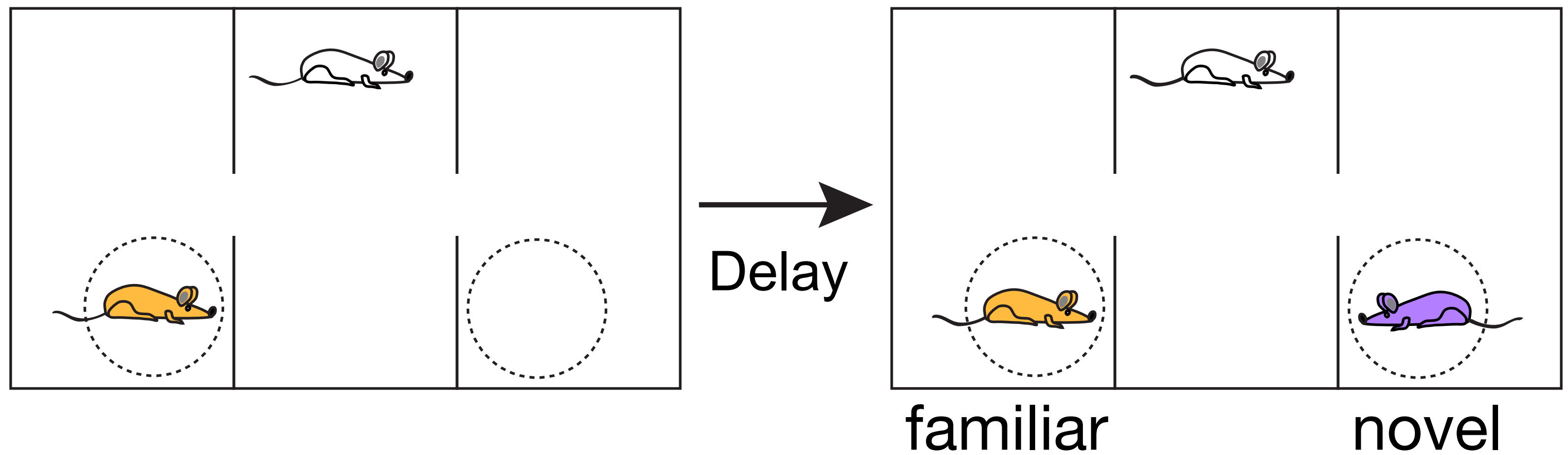
Examining area CA2 with environmental enrichment

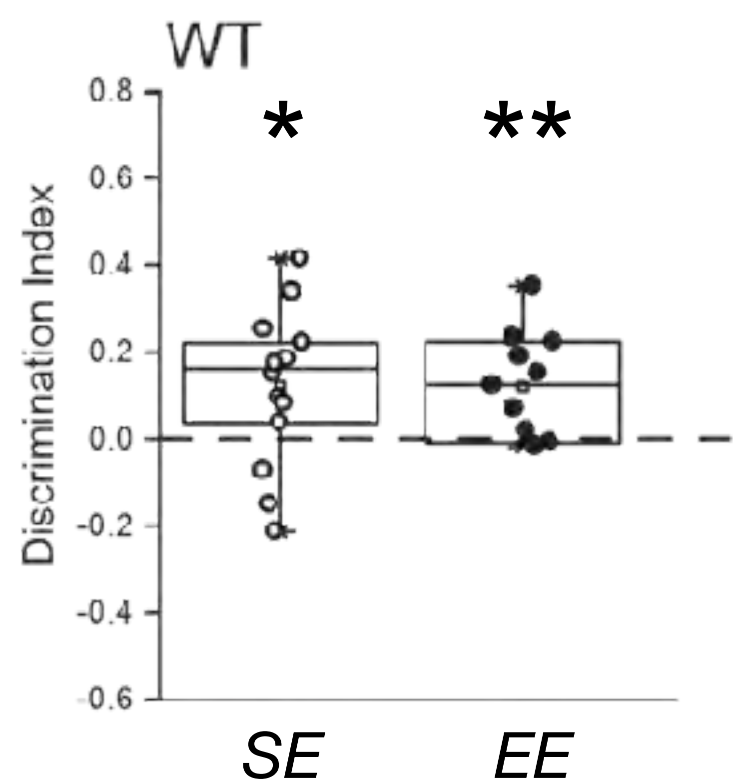
Standard Environment, SE

Enriched Environment, EE

3 weeks

Social recognition memory with environmental enrichment





1 hr delay

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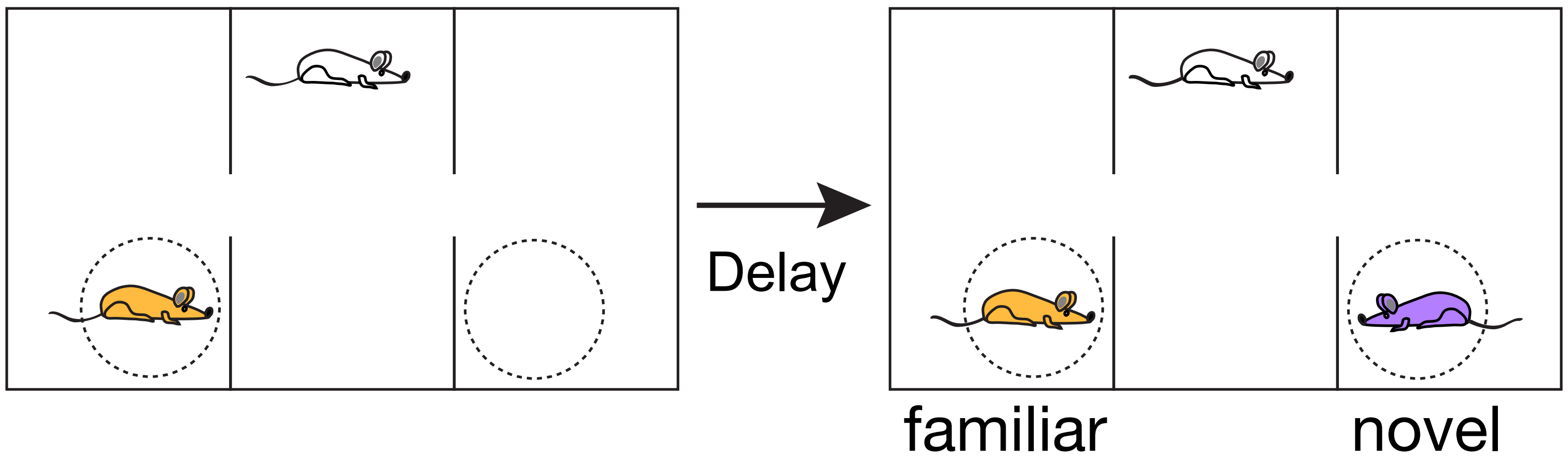
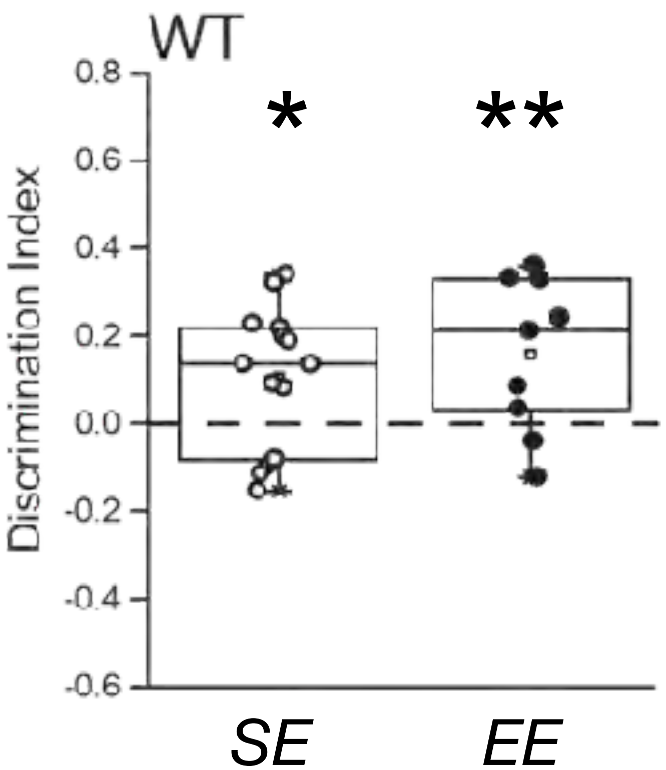
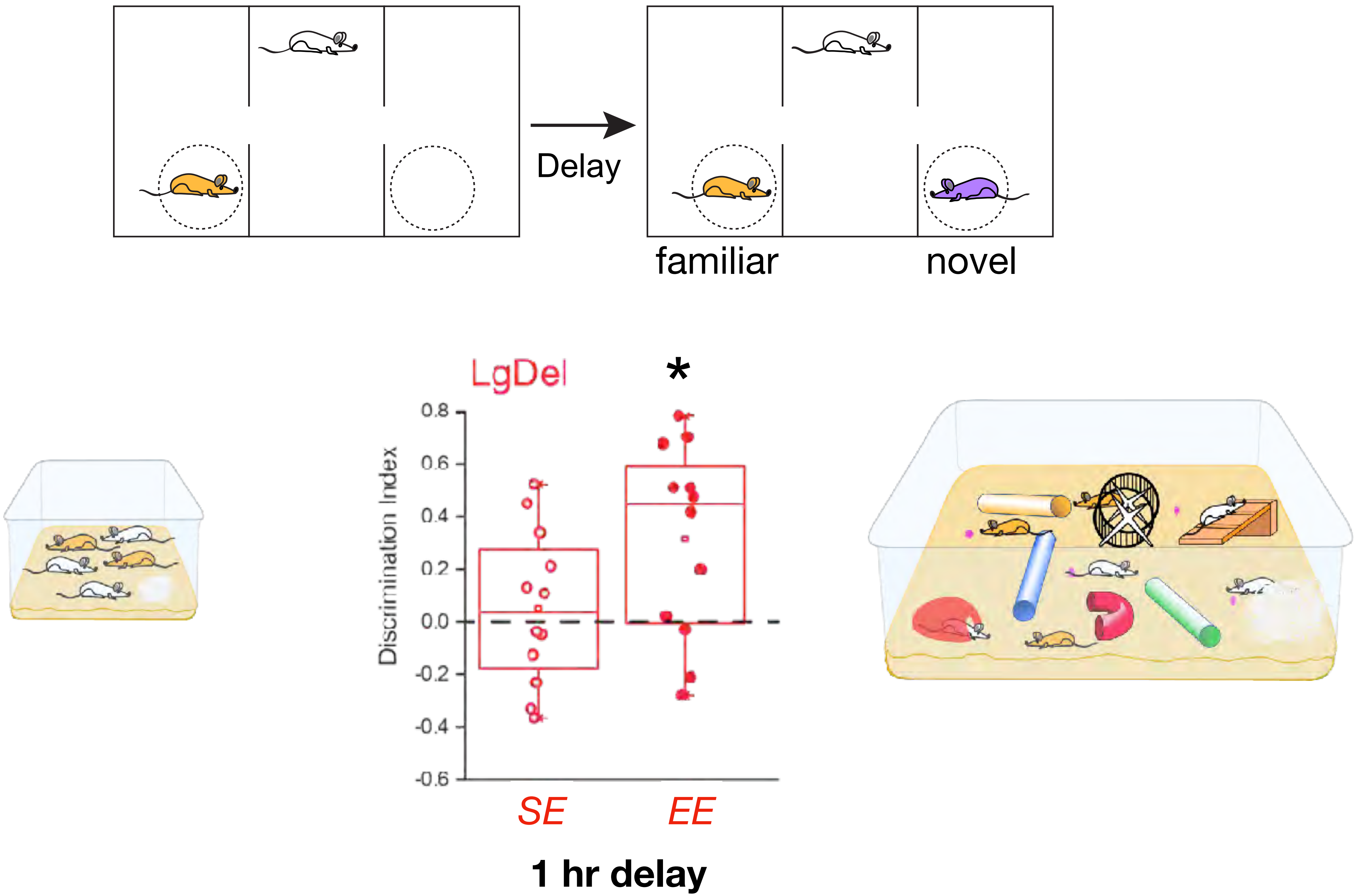
Social recognition memory with environmental enrichment





24 hr delay

Social recognition memory with environmental enrichment



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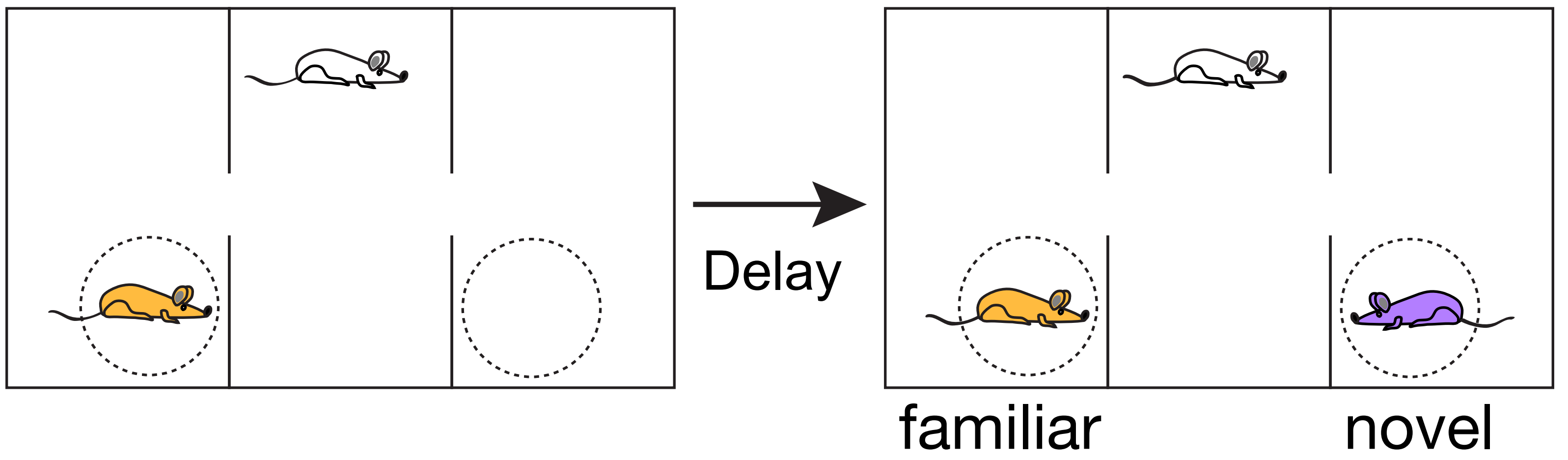
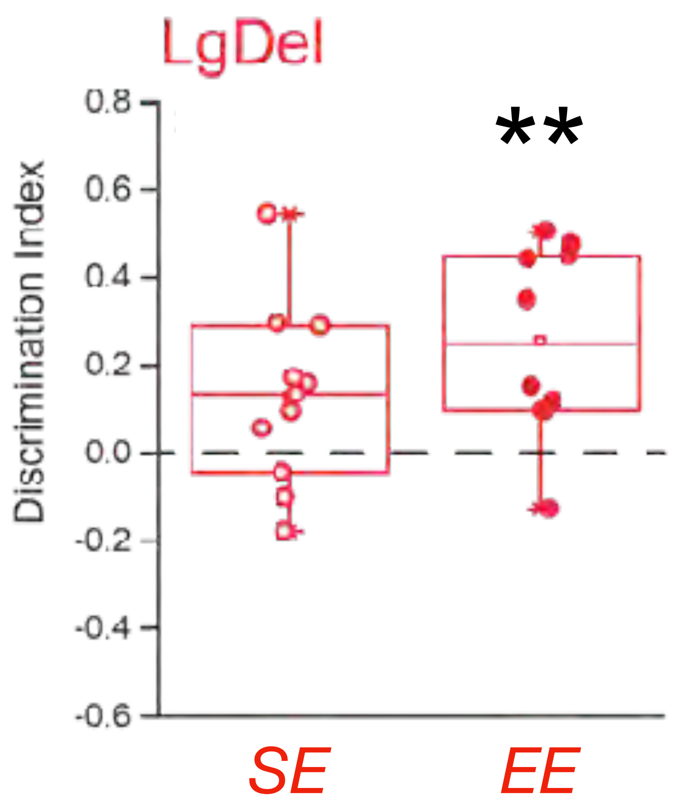
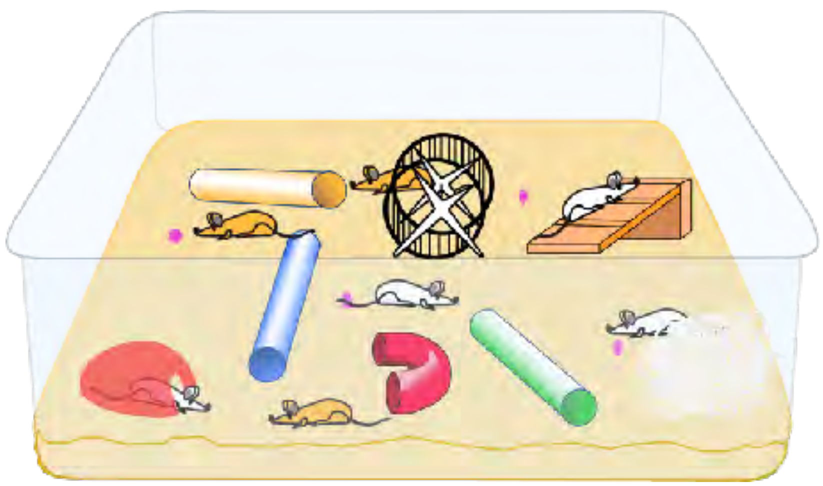
Social recognition memory with environmental enrichment







24 hr delay

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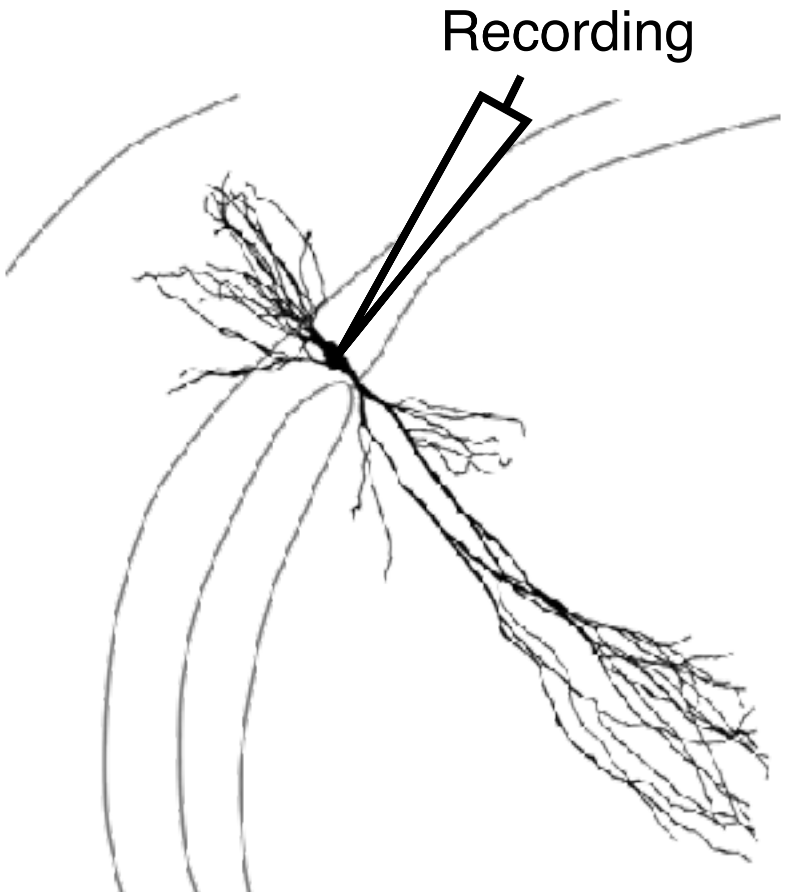
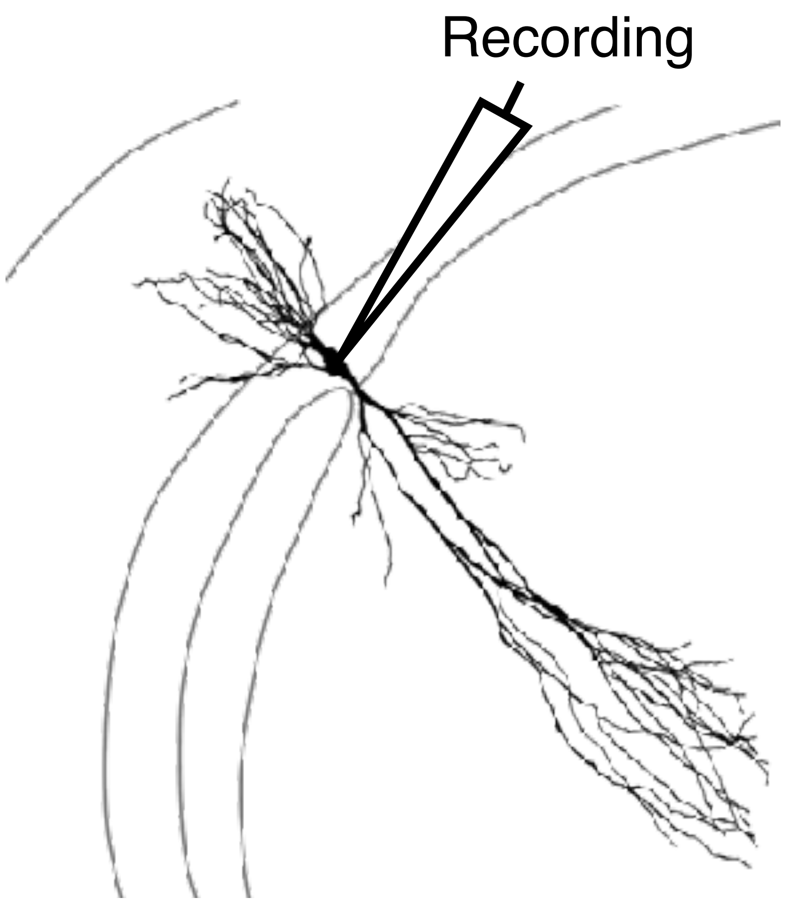
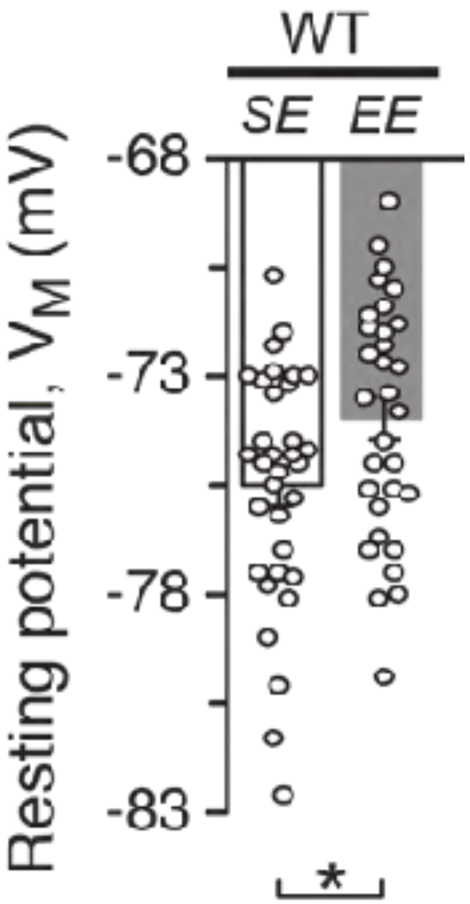
Do CA2 neurons undergo changes with environmental enrichment?

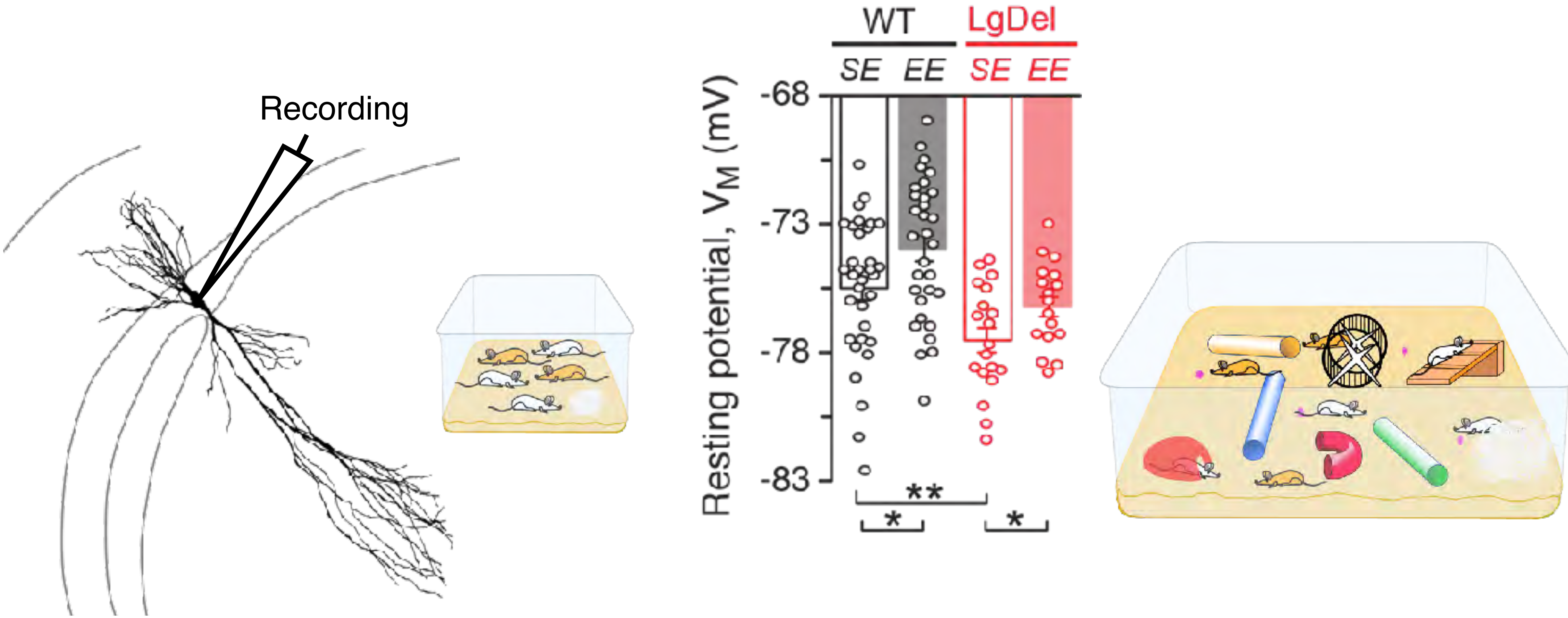


Do CA2 neurons undergo changes with environmental enrichment?





CA2 neurons undergo changes with environmental enrichment



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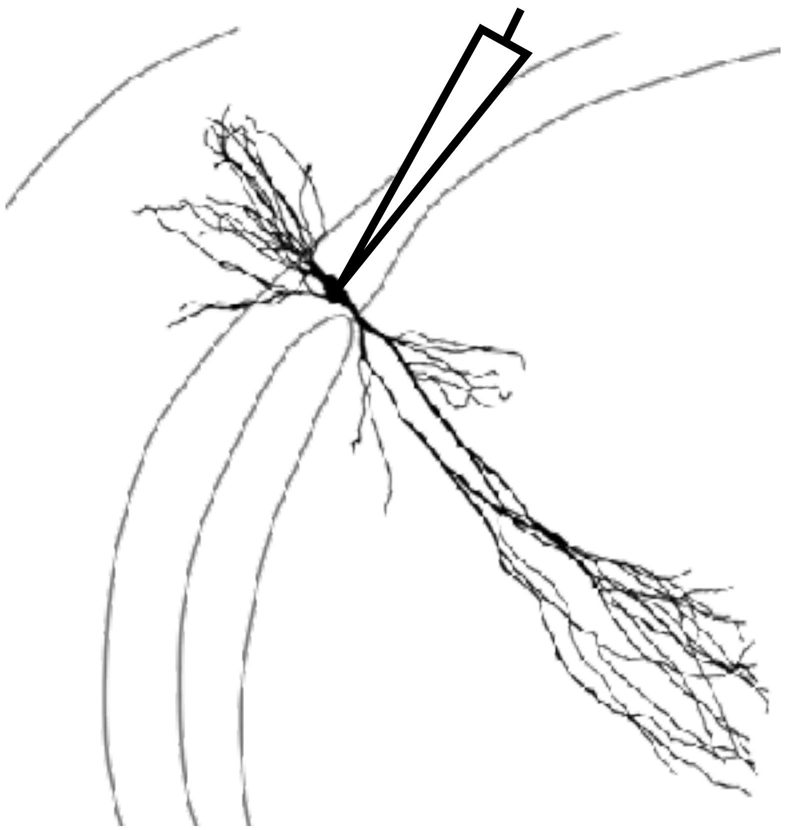
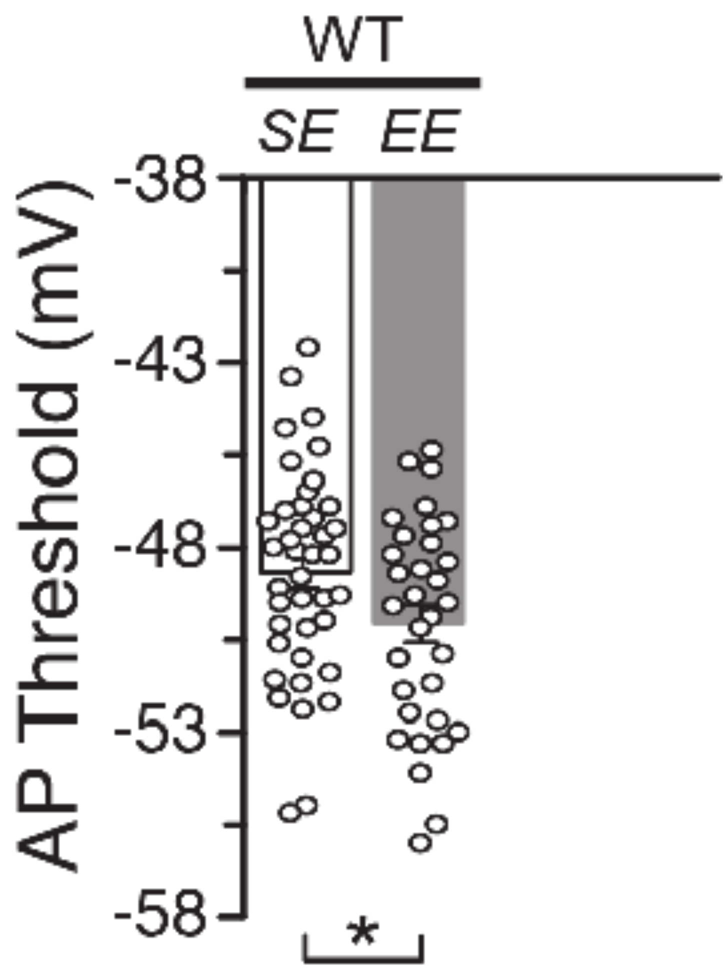
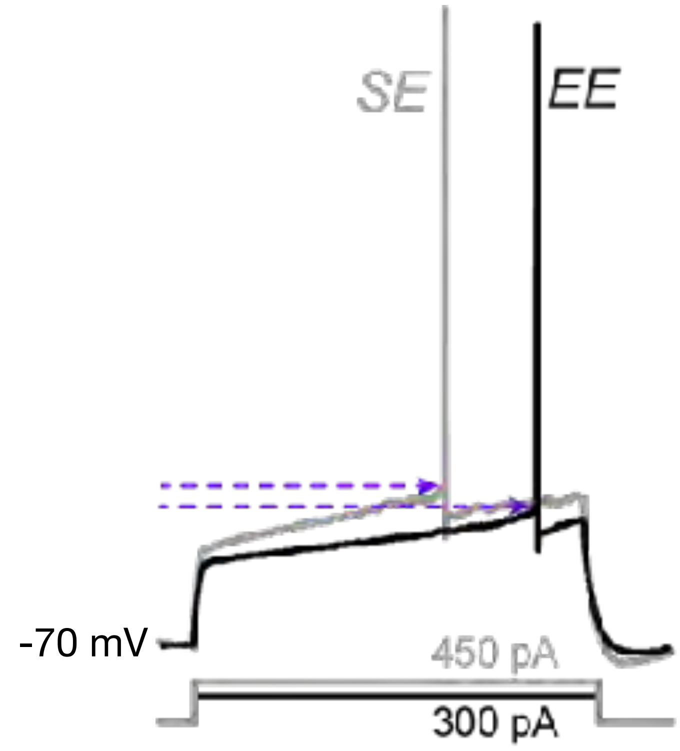
CA2 neurons undergo changes with environmental enrichment







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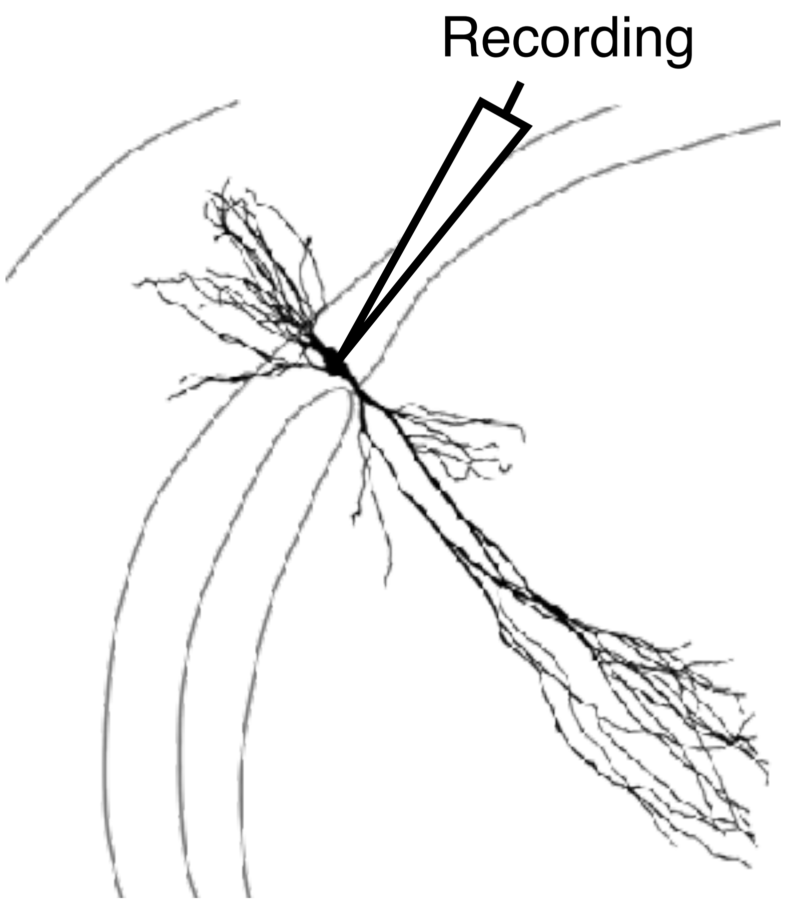

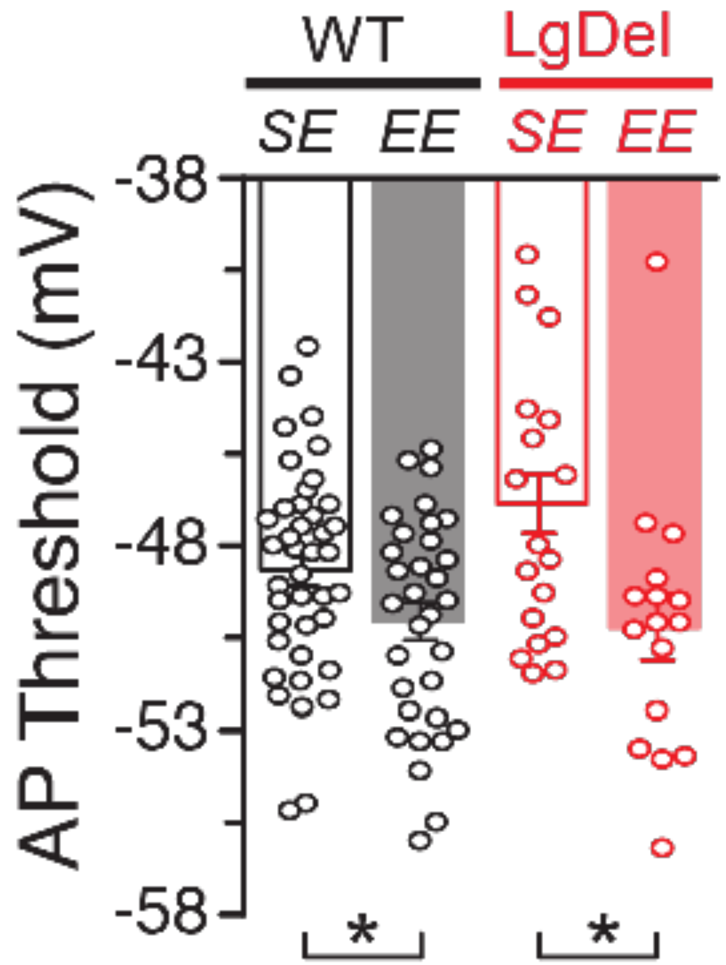

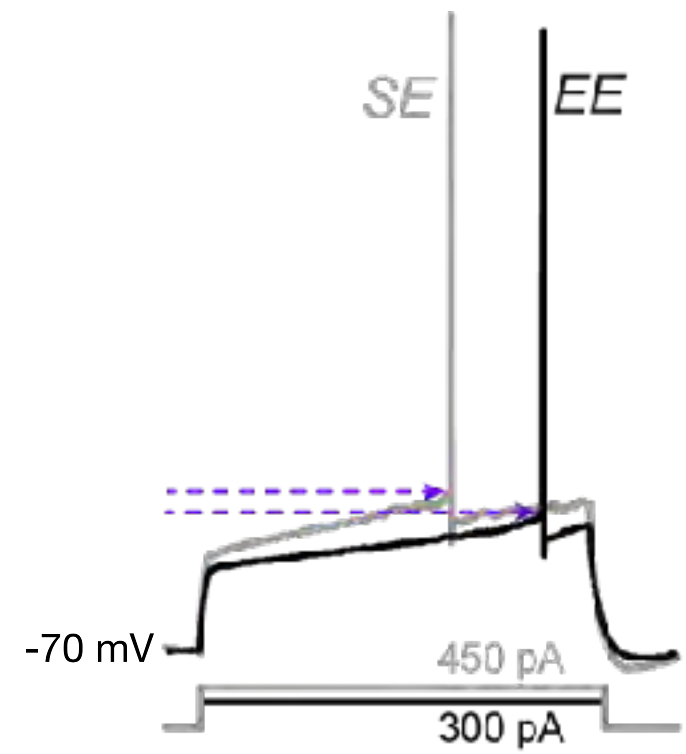

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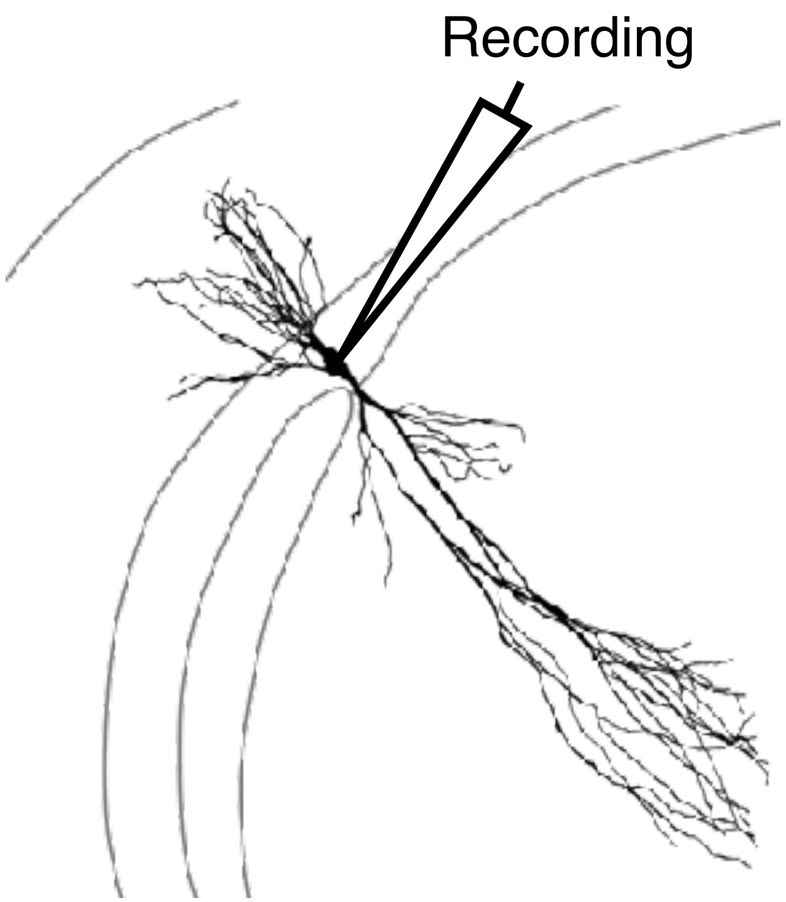
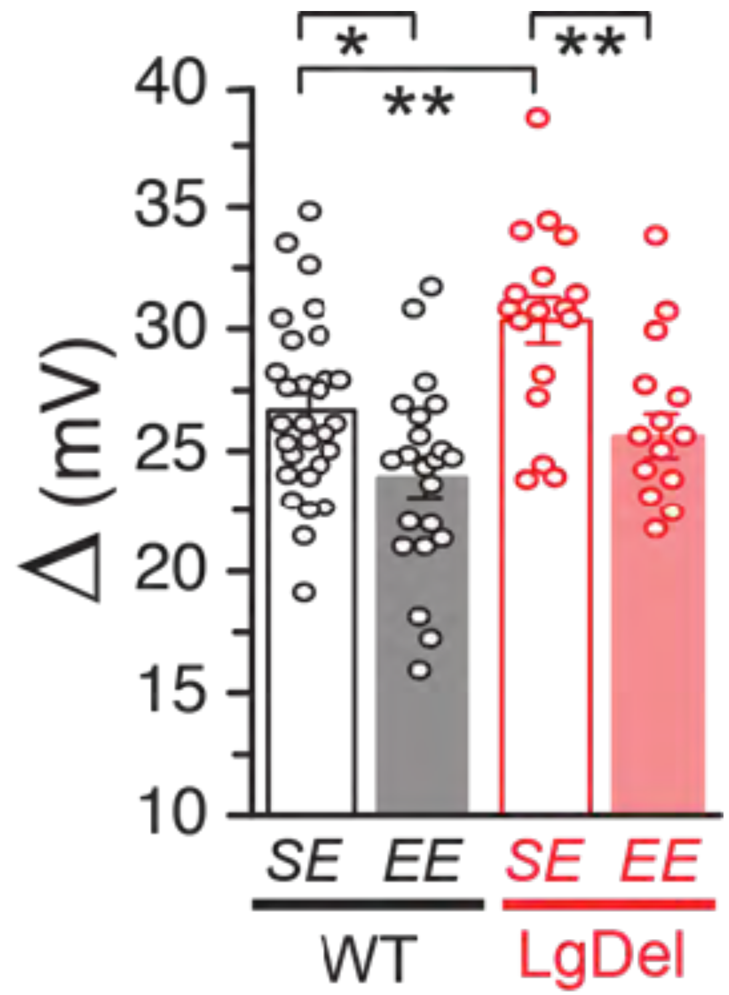
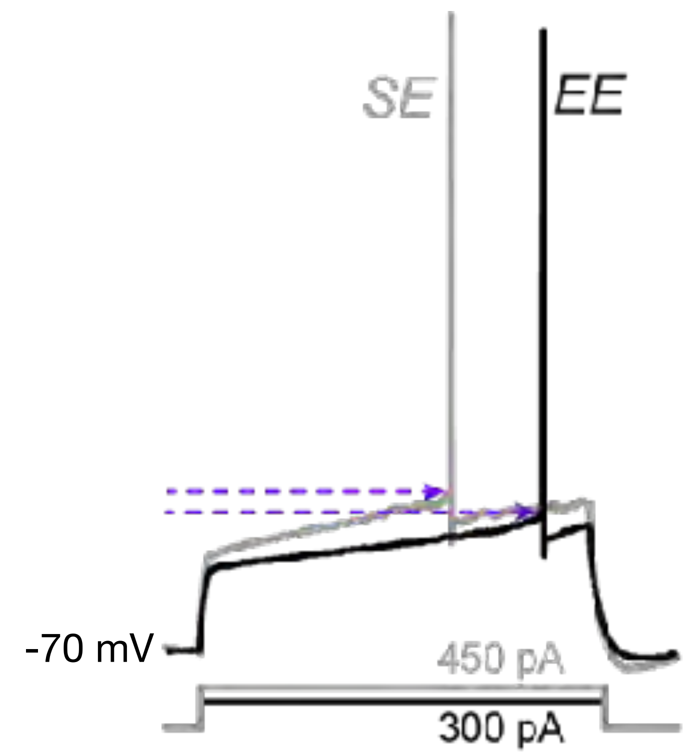
CA2 neurons undergo changes with environmental enrichment







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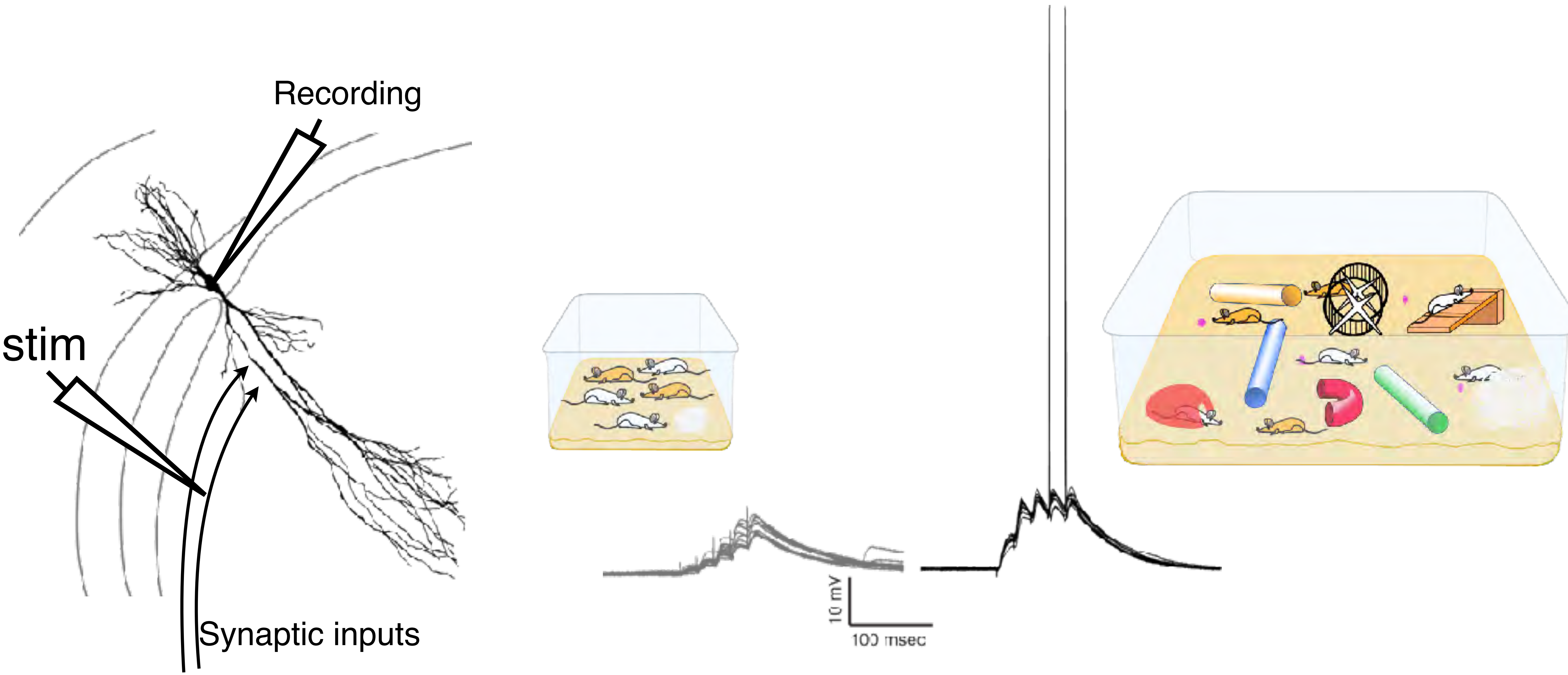
CA2 neurons undergo changes with environmental enrichment



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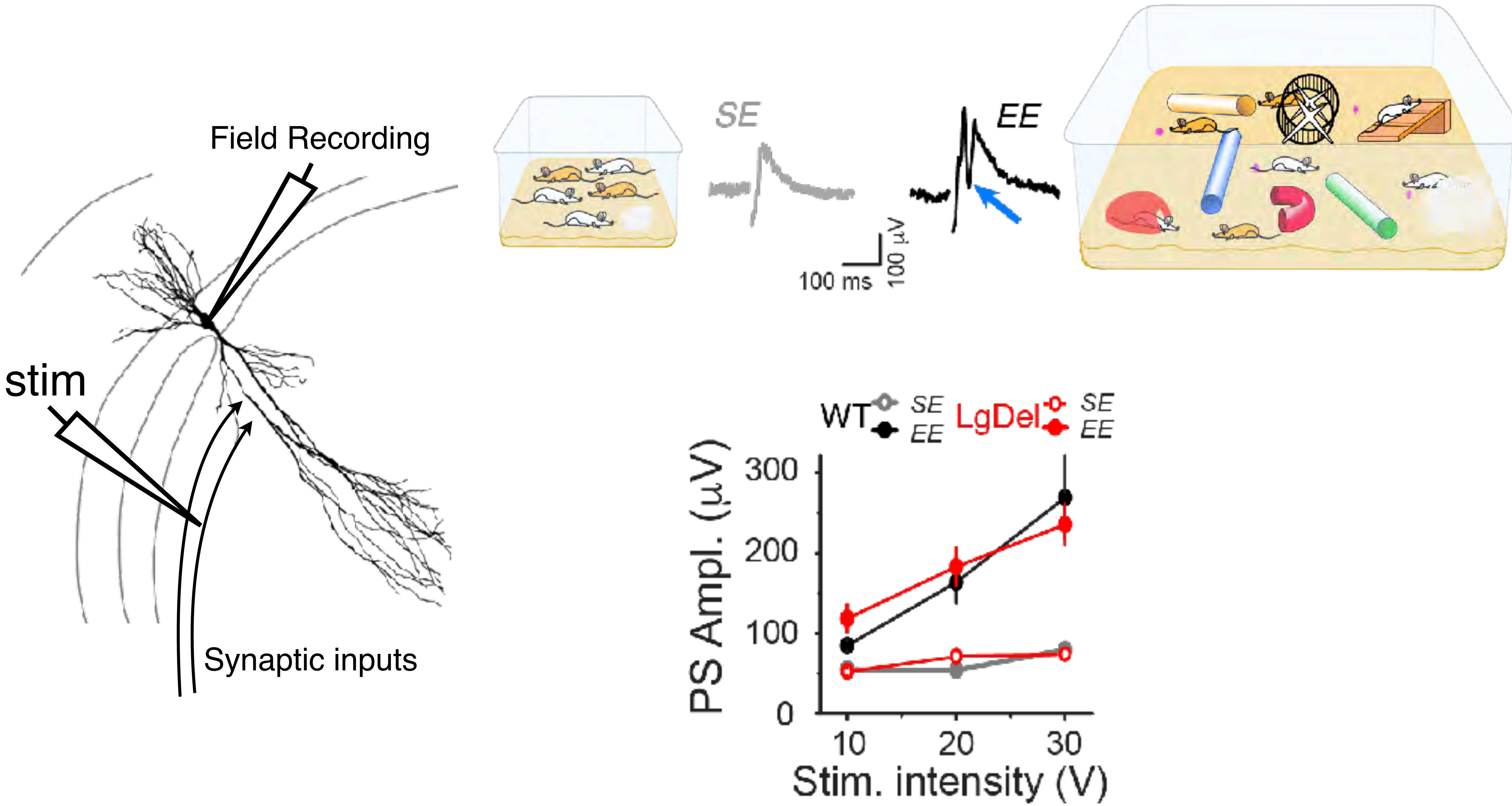

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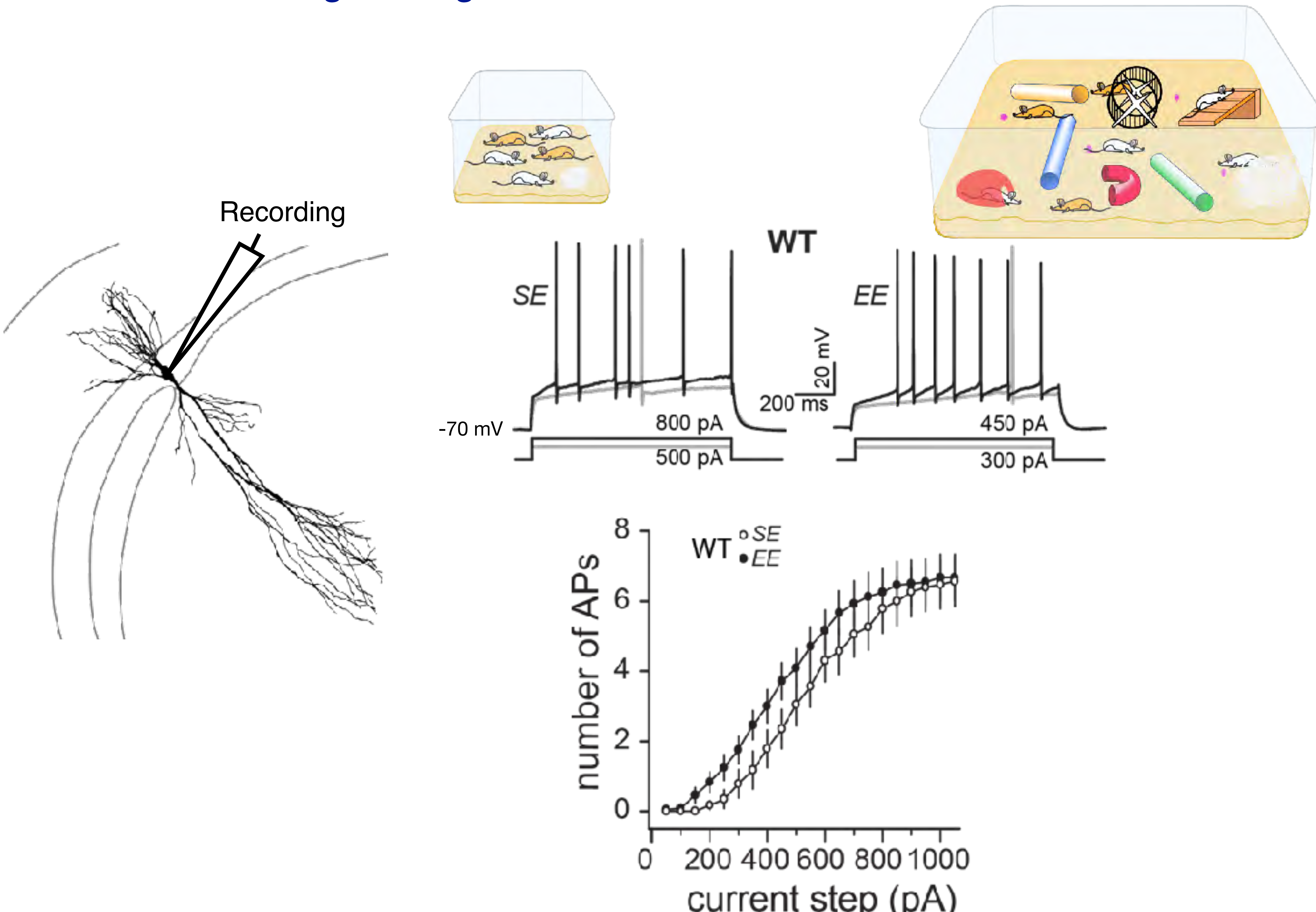

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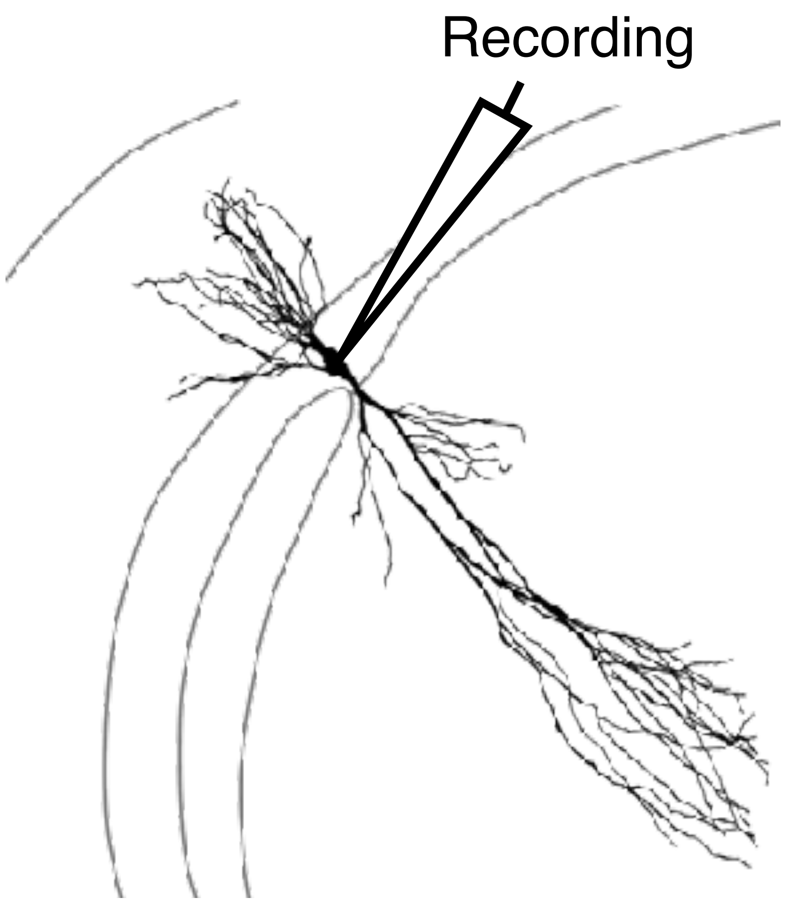

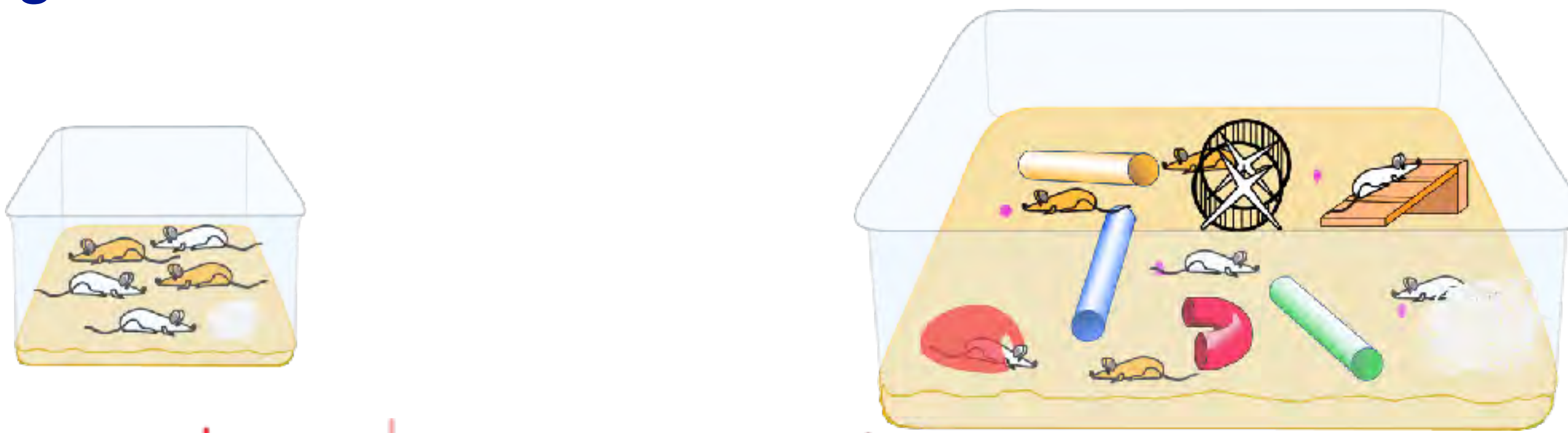

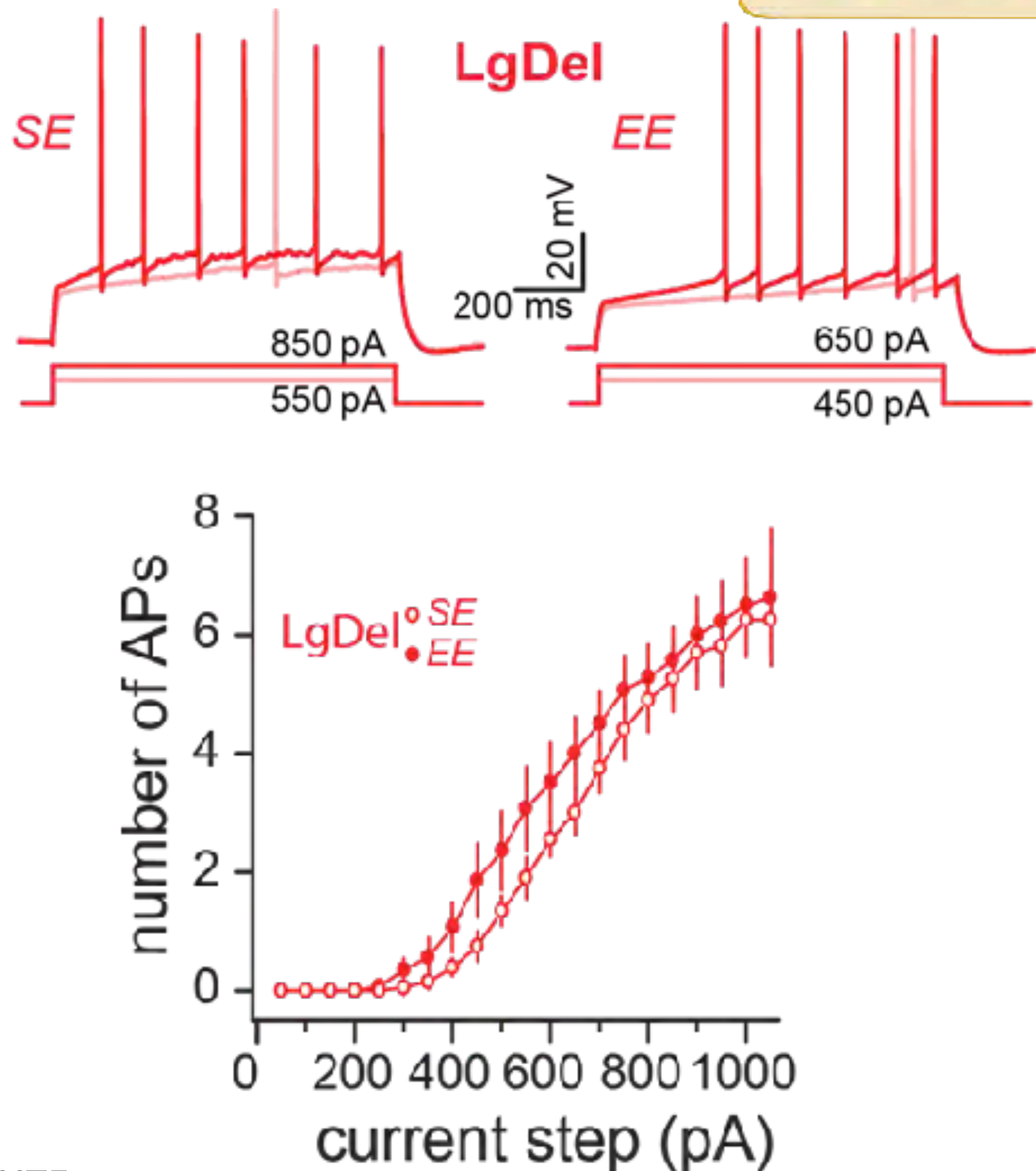

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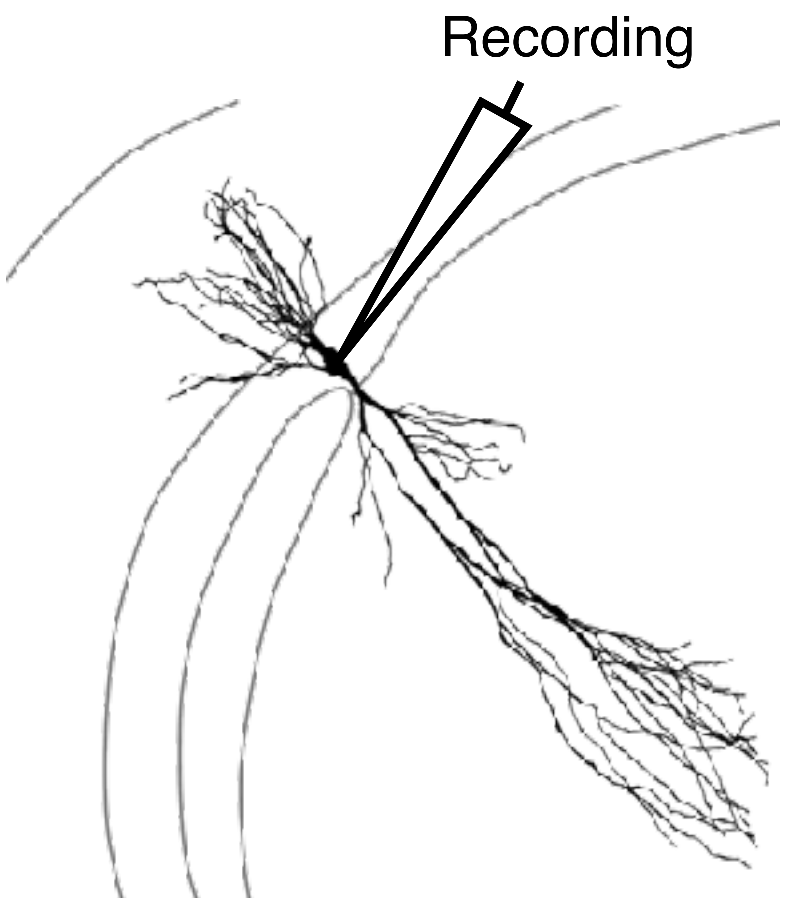

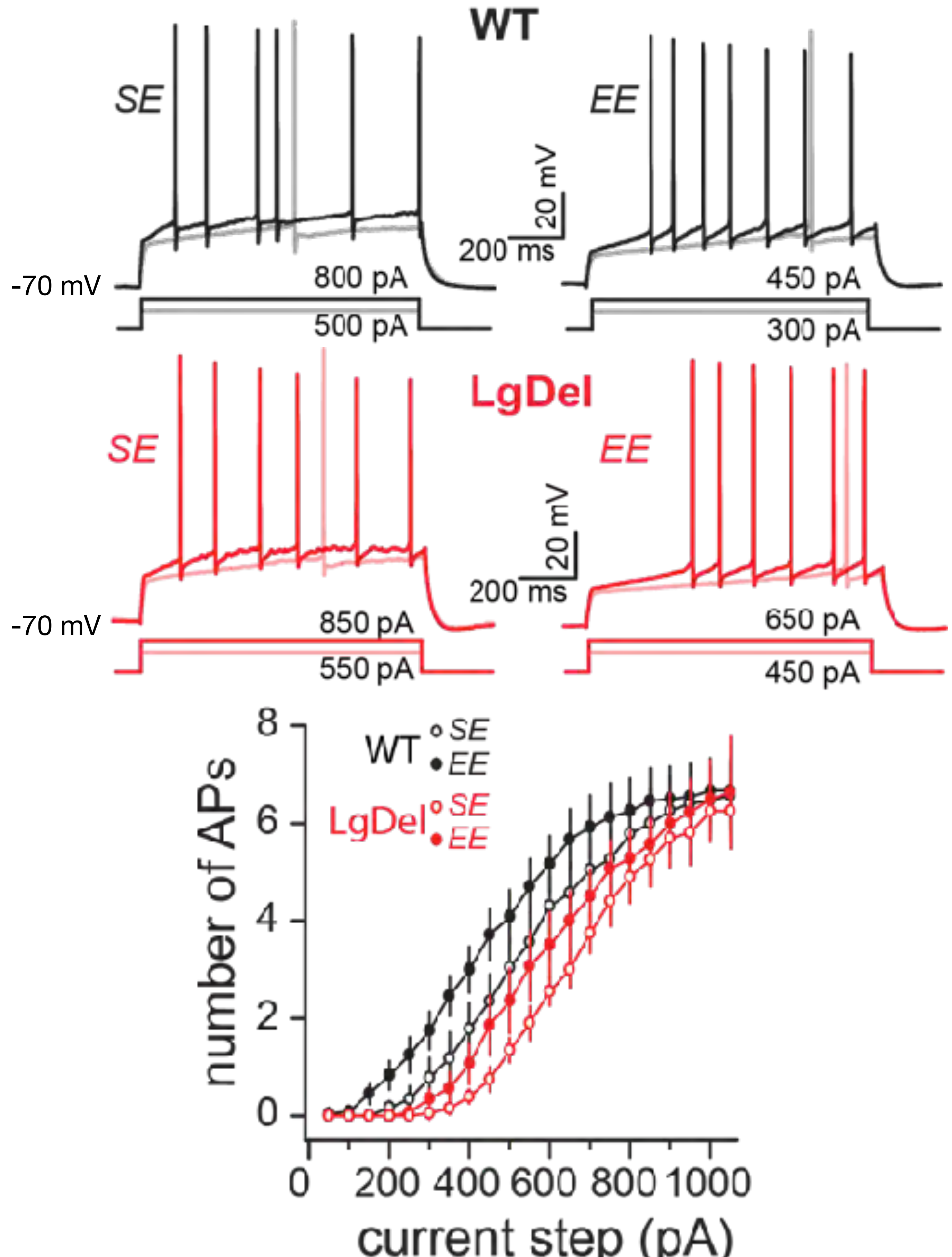

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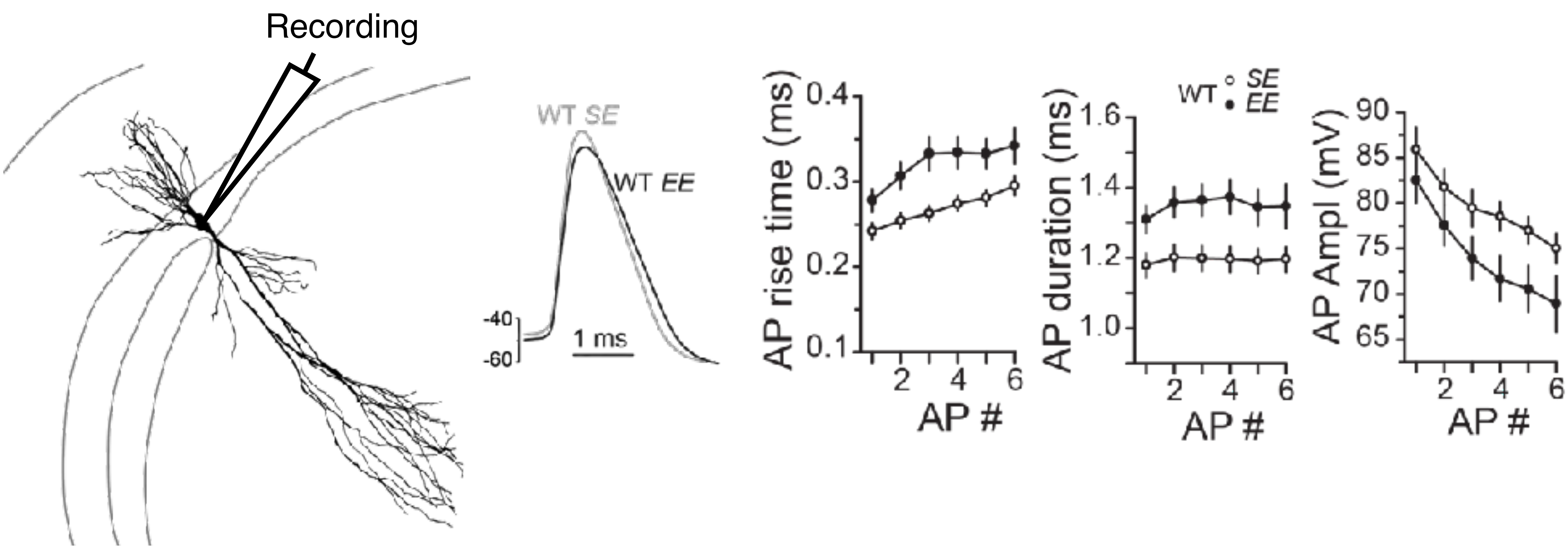

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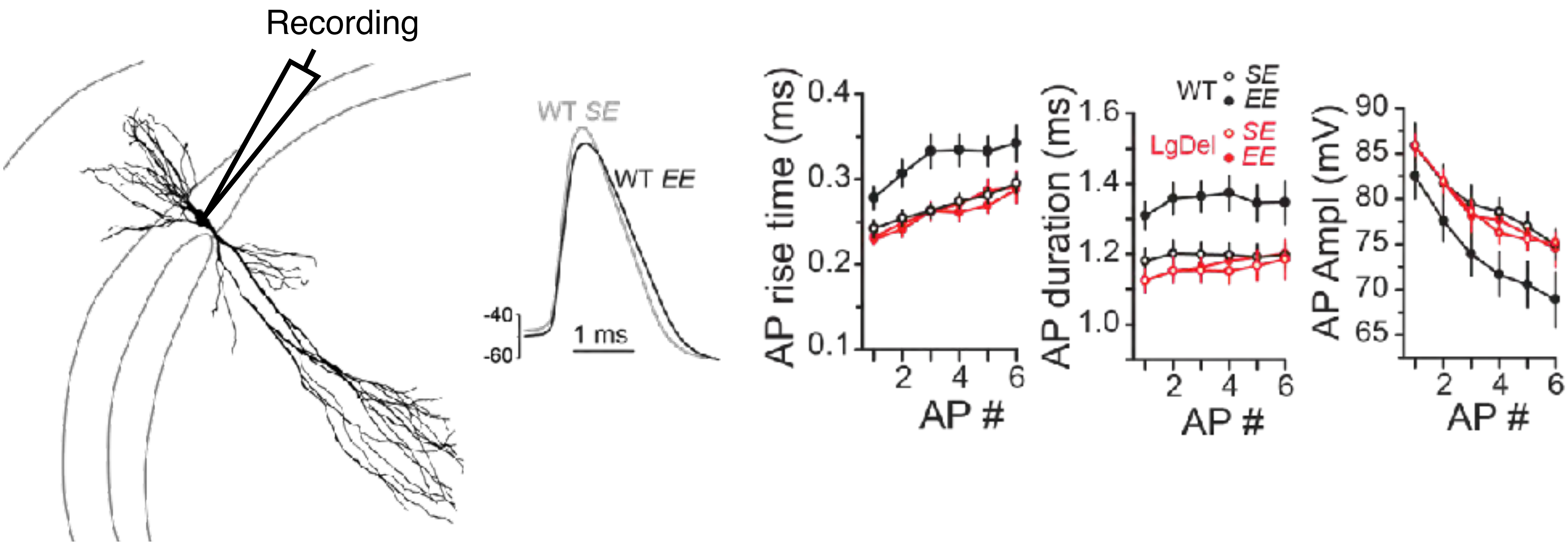

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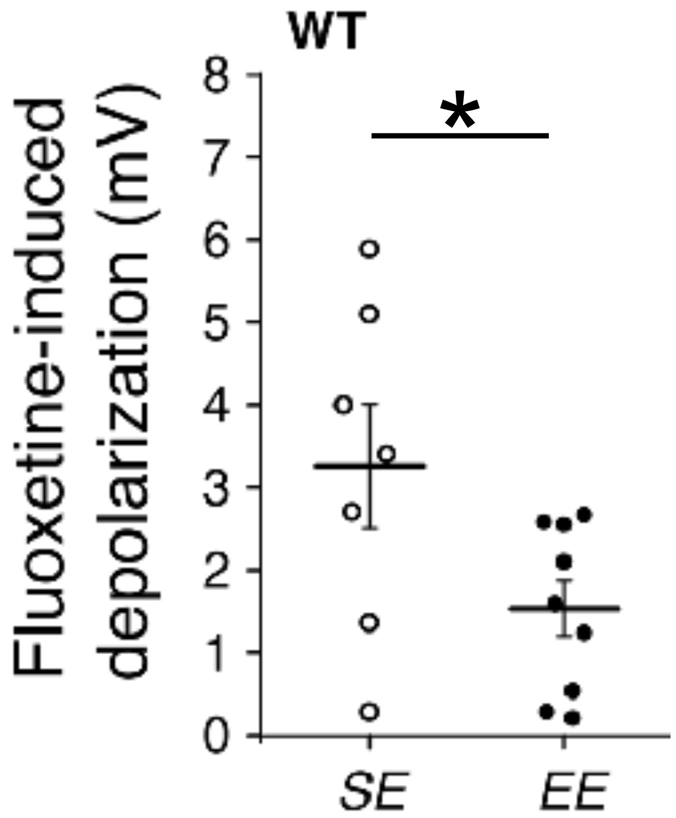
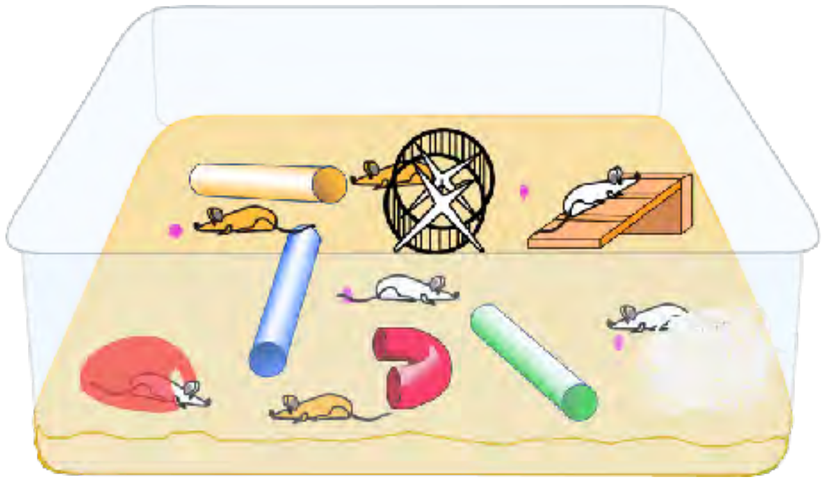
Mechanism

There is a reduction in TREK-1 conductance with EE





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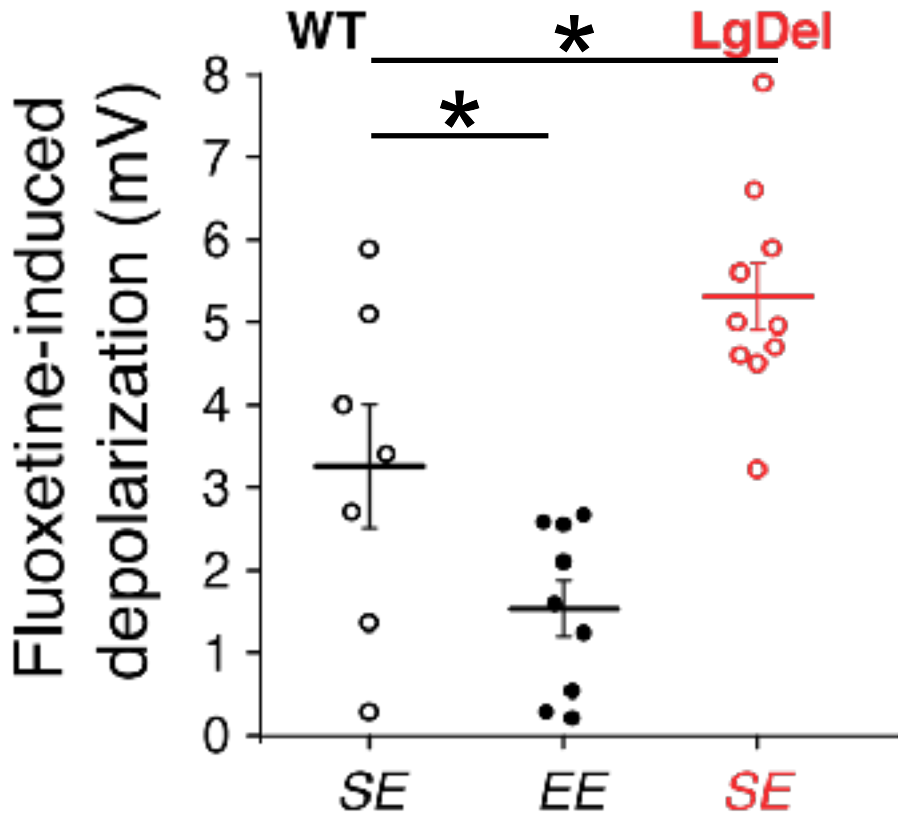

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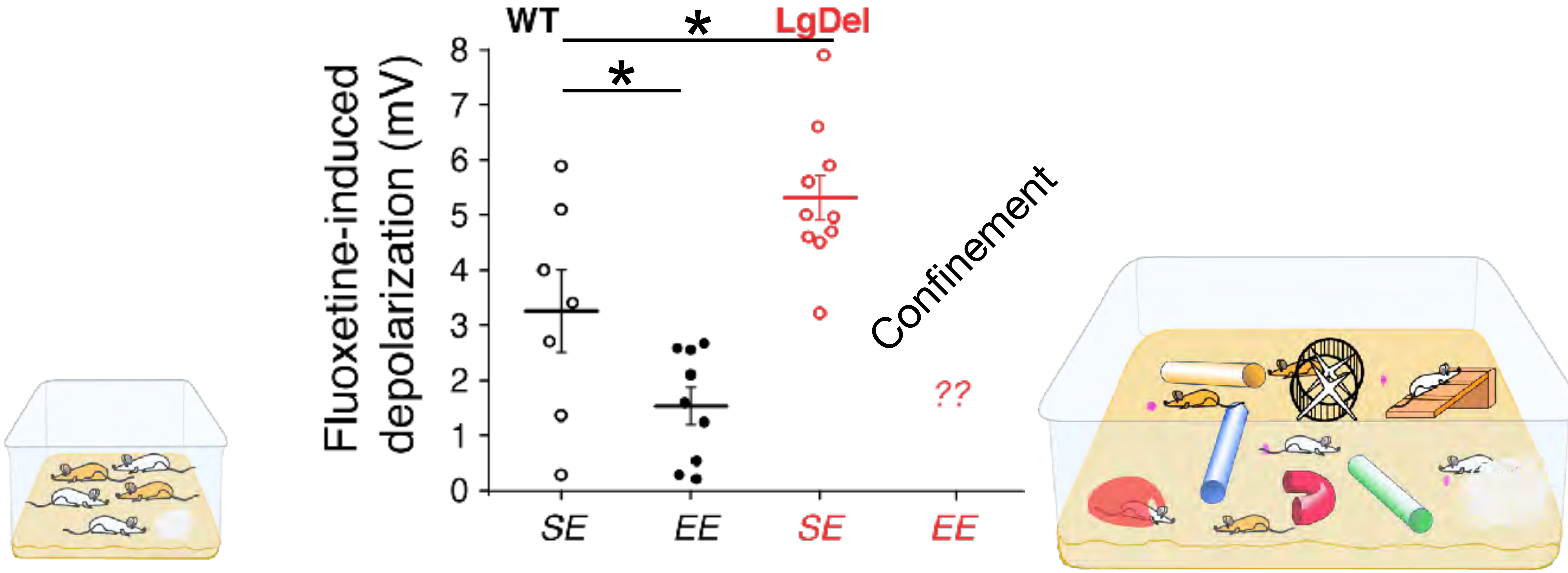


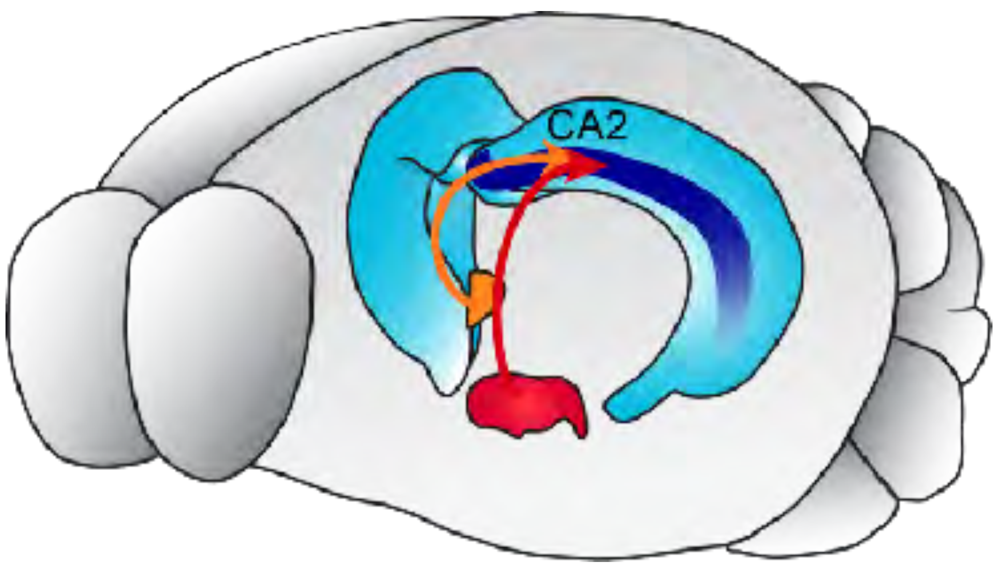
Mechanism

vs.

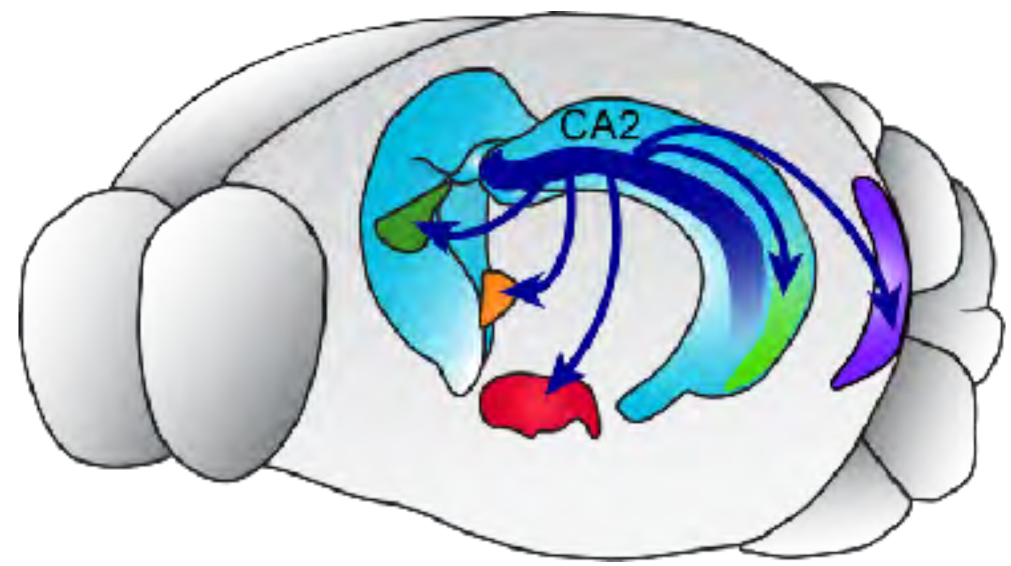
Mechanism

vs.

How much does hippocampal CA2 contribute to EE effect?



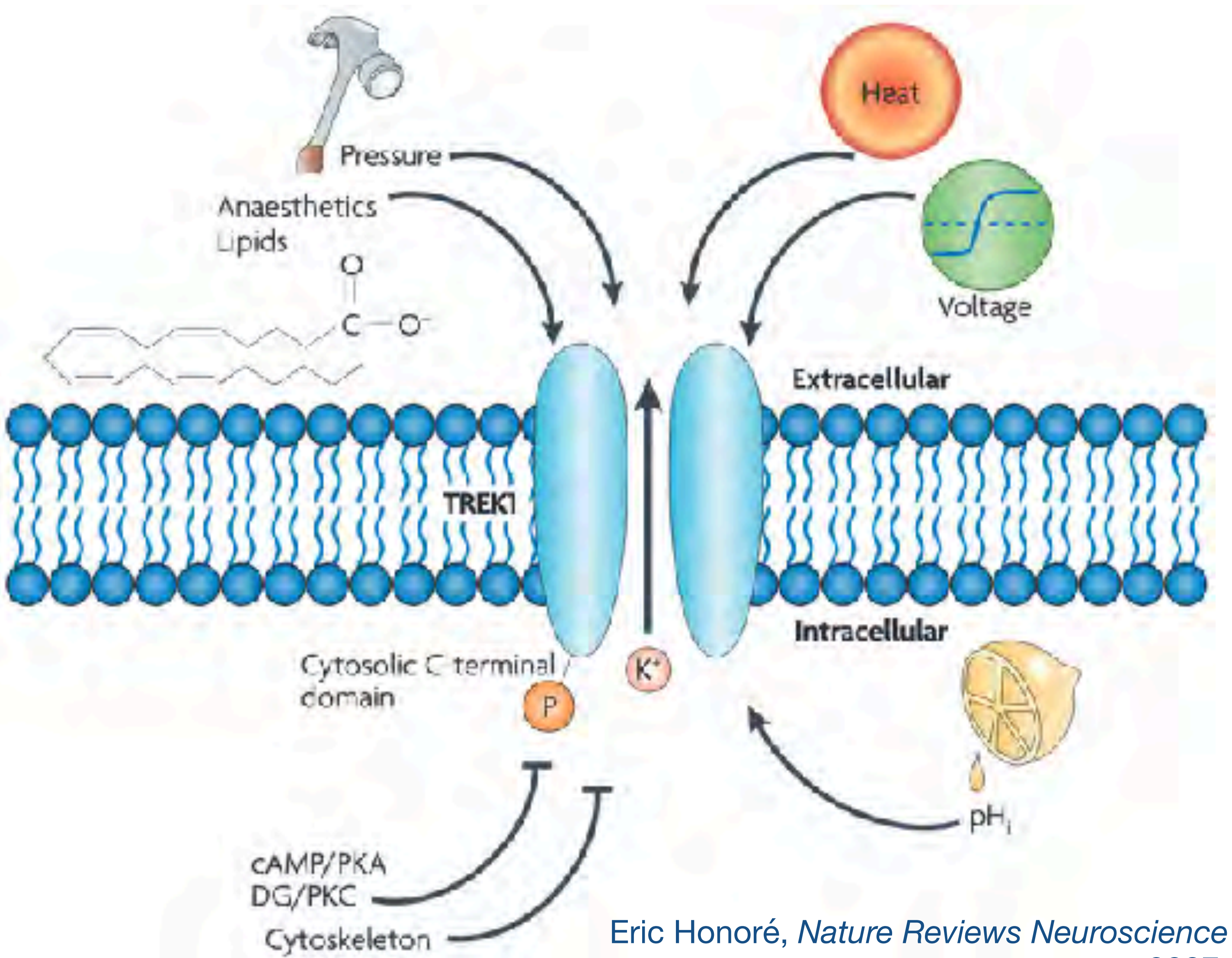
CA2 inputs



CA2 outputs

Altered CA2 activity can potentially far-reaching consequences

What regulates TREK-1?

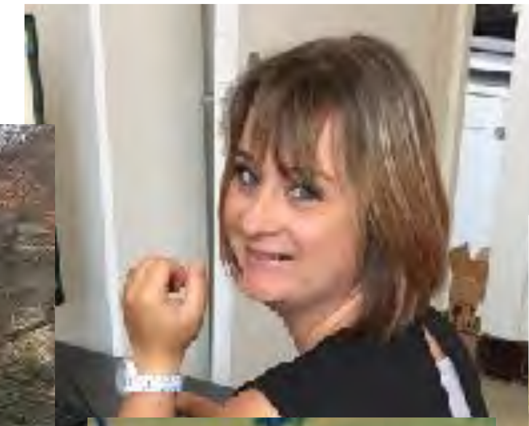


Eric Honoré, *Nature Reviews Neuroscience* 2007.

Next steps:

- **Transcriptome analysis of CA2 pyramidal neurons** (with Eduardo Gascon, Institute of Neuroscience de la Timone)
- **Phospholipase activity** (with Joëlle Chabry, Institute de Pharmacologie Moleculaire et Cellulaire)
- **Inhibitory neuron physiology and synaptic plasticity**

Team Synaptic Plasticity and Neural Networks



Current Team members:

Vivien Chevaleyre (co-team leader)
Cécile Viollet, PhD (researcher)
Eleni Paiz PhD (Assistant Professor)
Ludivine Therreau (engineer)
Sadiyah Cassim (PhD student)
Maïthé Loisy (PhD student)
Eude Lepicard (PhD student starting in Oct. 2020)
Maud Muller (PhD student starting in Oct. 2020)

Former members:

Ludivine Therreau (engineer)
Manon Chateaux (M2 student)
Amel Farrah (M2 student)

LgDel Mice:

Francesco Papaleo, IIT