Cellular mechanisms underlying memory

Kyriaki Sidiropoulou
Assistant Professor of Neurophysiology
Neurophysiology and Behaviour Lab
Dept of Biology
University of Crete
sidirop@uoc.gr
www.sidiropouloulab.com

Kyriaki Sidiropoulou

- B.A. in Microbiology and Physiology, Southern Illinois University at Carbondale

- Ph.D. in Neuroscience, Rosalind Franklin University of Health and Sciences/The Chicago Medical School

- Post-doc in ‘Computational Neuroscience’ - IMBB-FORTH

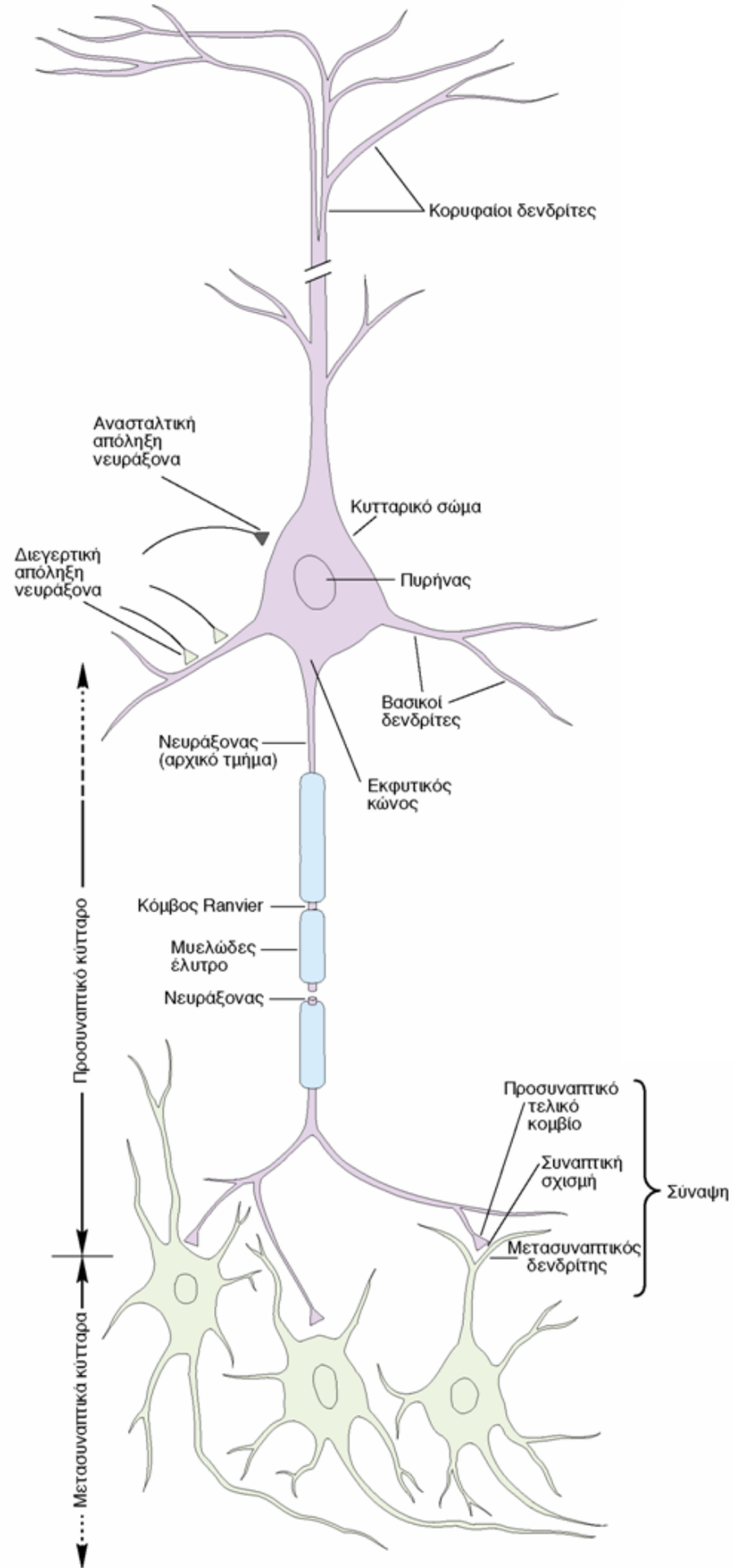
- Marie Curie fellow - Dr. Alcino Silva, UCLA and IMBB-FORTH

- Lecturer and Assistant Prof. of Neurophysiology, Dept of Biology, University of Crete

Neurons, neuronal networks and brain

Neurons are the building blocks of the brain

- The human brain consists of 100 billion neurons



Kandel, Νευροεπιστήμη και Συμπεριφορά, ΠΕΚ

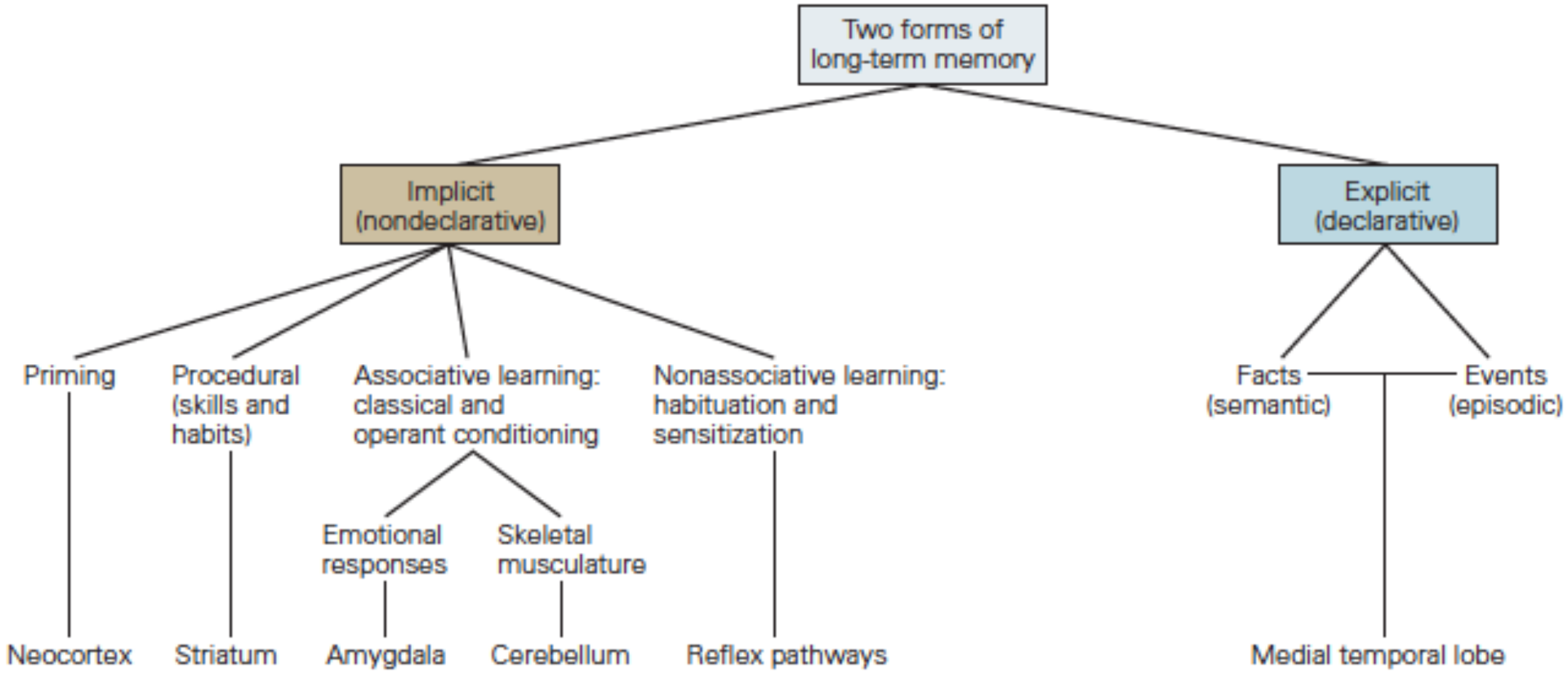
Memory

- Working memory
- Short-term and long-term memory
    - Explicit memory
    - Implicit memory
        - Conditional
        - Non-conditional
        - Procedural

Memory

- Memory acquisition
- Memory consolidation
- Memory storage
- Memory recall
- Re-consolidation

Neurobiological substrate of long-term memory



Neuronal theories for memory storage and recall

- Synaptic theory

  ★ Memory is stored in synapses

- Neuronal theory

  ★ Memory is stored in neurons

- Possible compromise

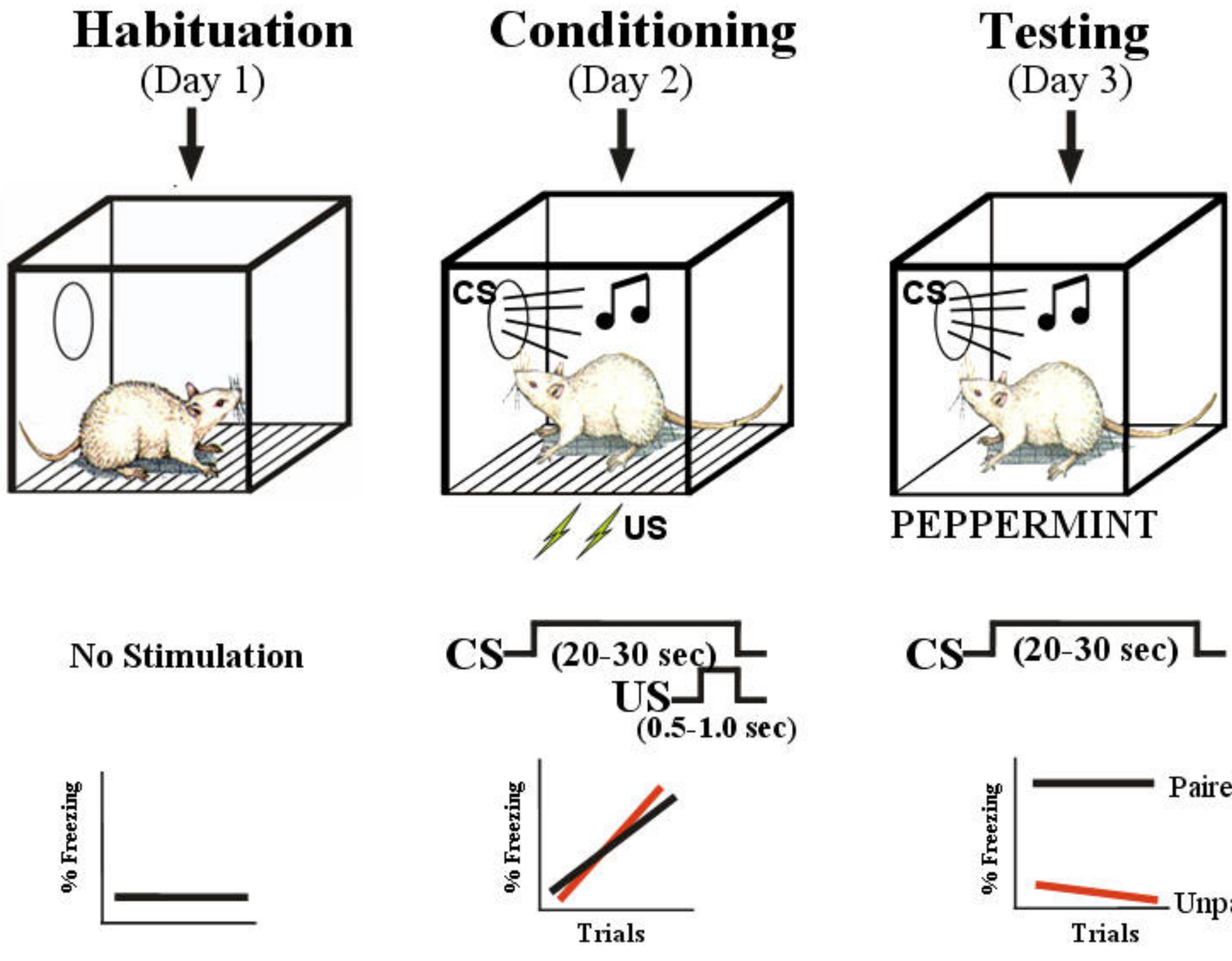
  ✳ Memory is stored in synapses within a specific network of neurons

How do we study memory in rodents?

Mice

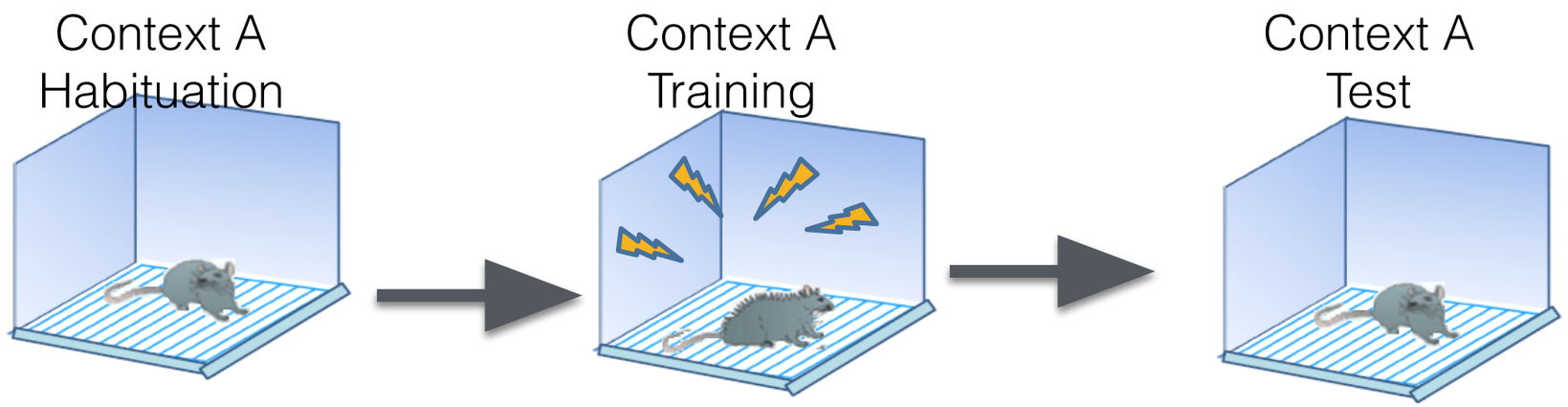
Rats

Example: Conditional memory
Auditory fear conditioning



http://www.cns.nyu.edu/labs/ledouxlab/research.htm

Example: Conditional memory
Contextual fear conditioning



Example: Spatial memory
Morris water maze

University of Edinburgh

https://www.youtube.com/watch?v=LrCzSIbvSN4

Example: explicit memory: T-maze

Neurobiological substrate of memory

- Does one brain area store memories?

- Is each memory stored in the brain area that encode the initial stimulus?

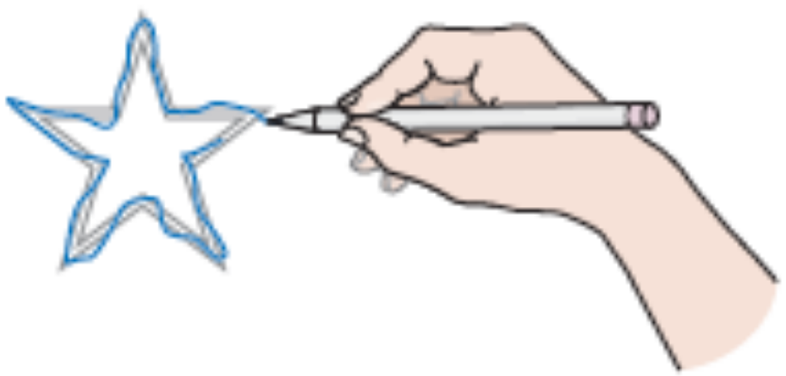
Henry Molaison (1926-2008)

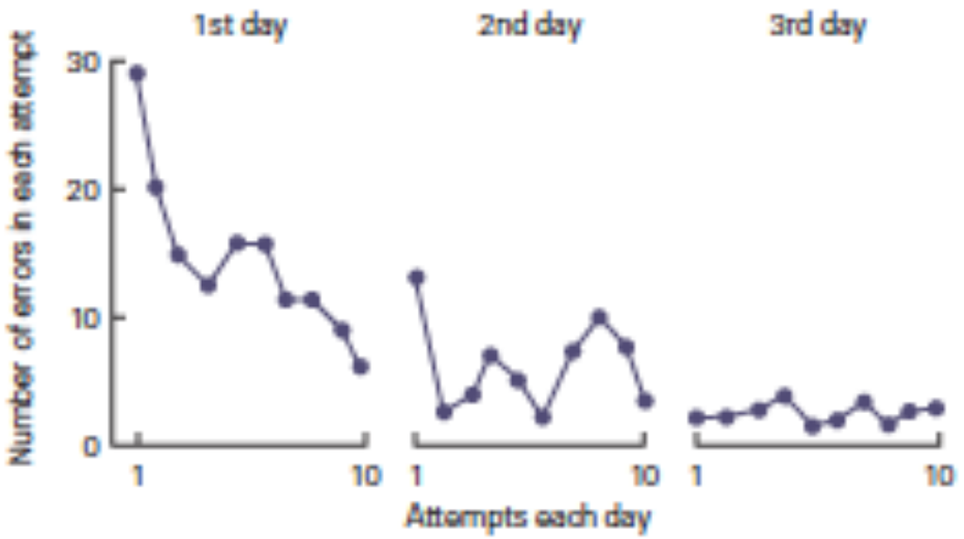
- Head injury (age 7)
- Epileptic seizures (age 16)
- Anti-epileptic medications did not work
- Decided to have surgery in 1953 by surgeon Scoville
  - bilateral medial temporal lobe excision

Brenda Milner (1918-)

- doctoral thesis with Donald Hebb
- noticed memory impairments in patients that had undergone surgery for epilepsy
- Had only affected episodic memory
- Did not affect implicit or procedural memory
- Each day is a new day!
- Amnesia was anterograde, not retrograde

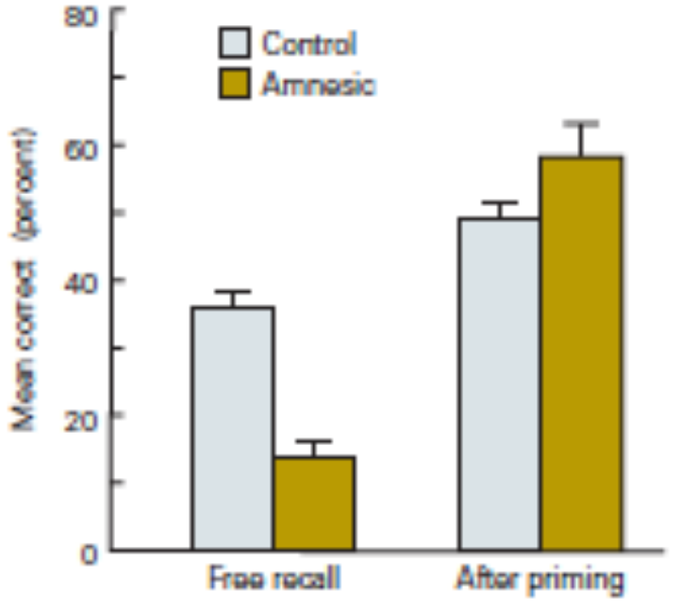
H.M. could perform skilled movements





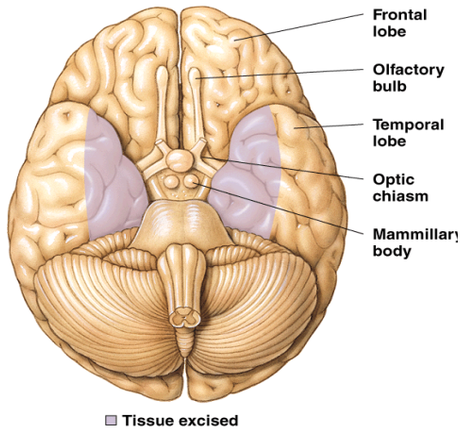
H.M. could perform well in fill-in the blanks, but not in free recall

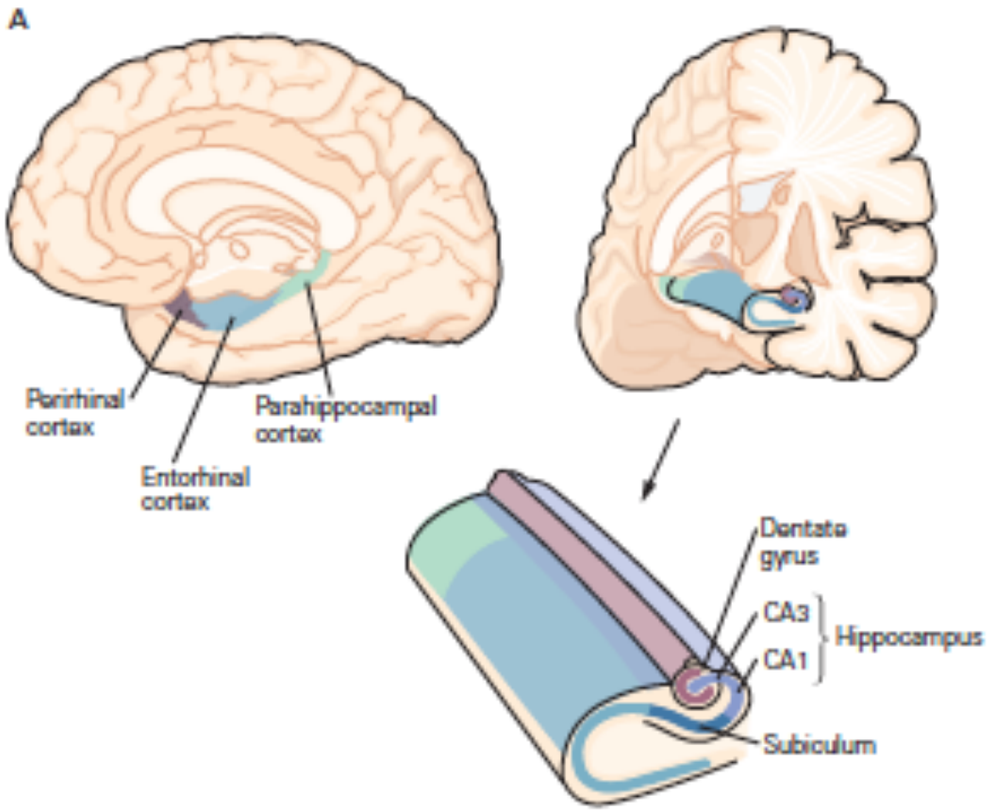
ABSENT	ABS_____
INCOME	INC_____
FILLY	FIL_____
DISCUSS	DIS_____
CHEESE	CHE_____
ELEMENT	ELE_____

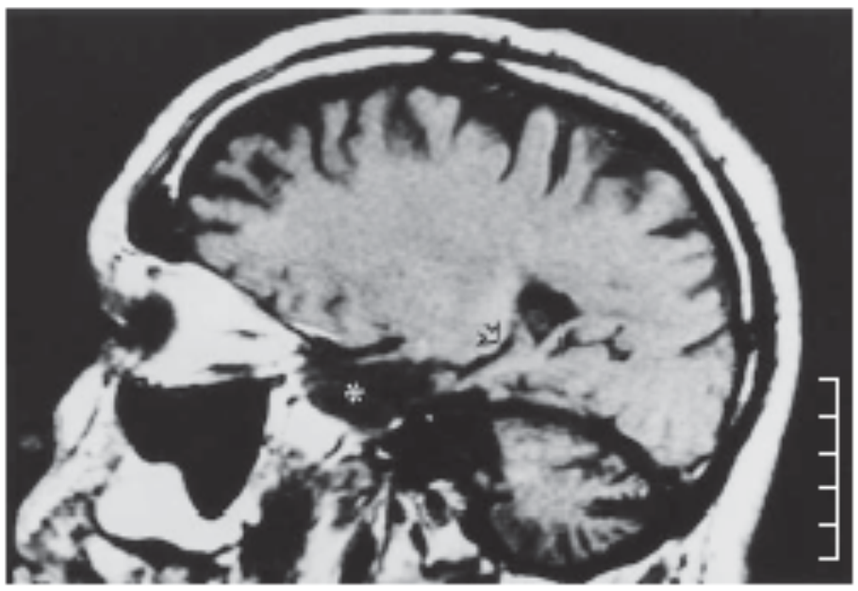


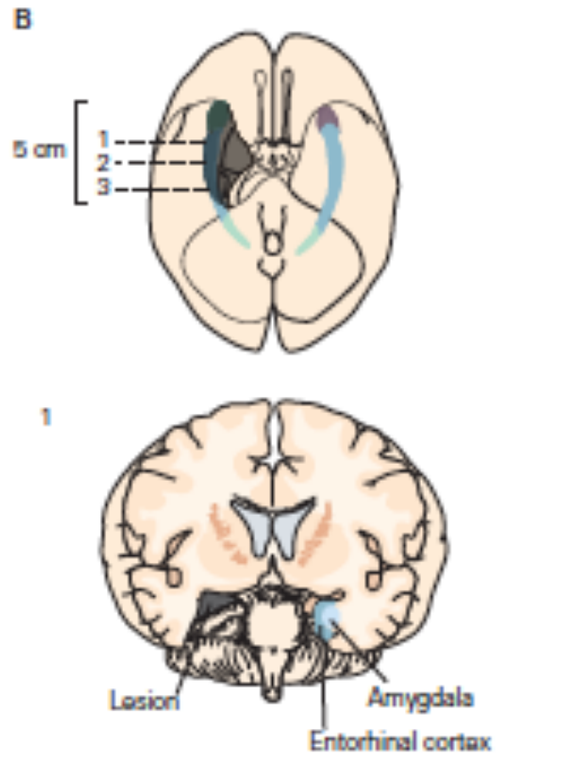
Hippocampus was removed in H.M. patient

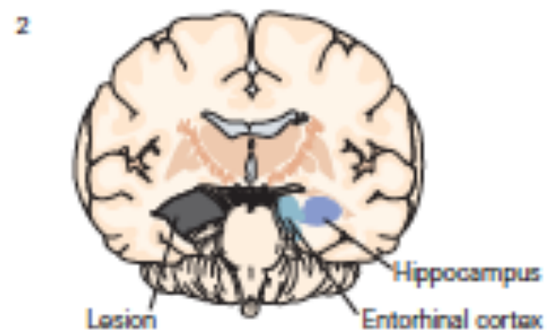
► **Medial Temporal Lobectomy**

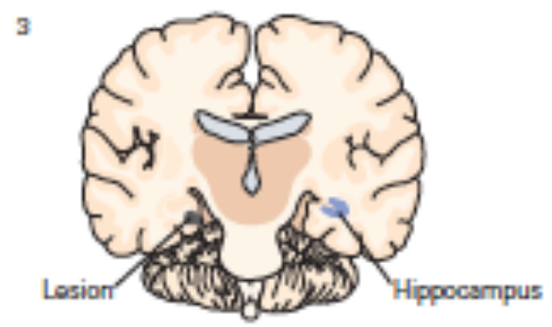




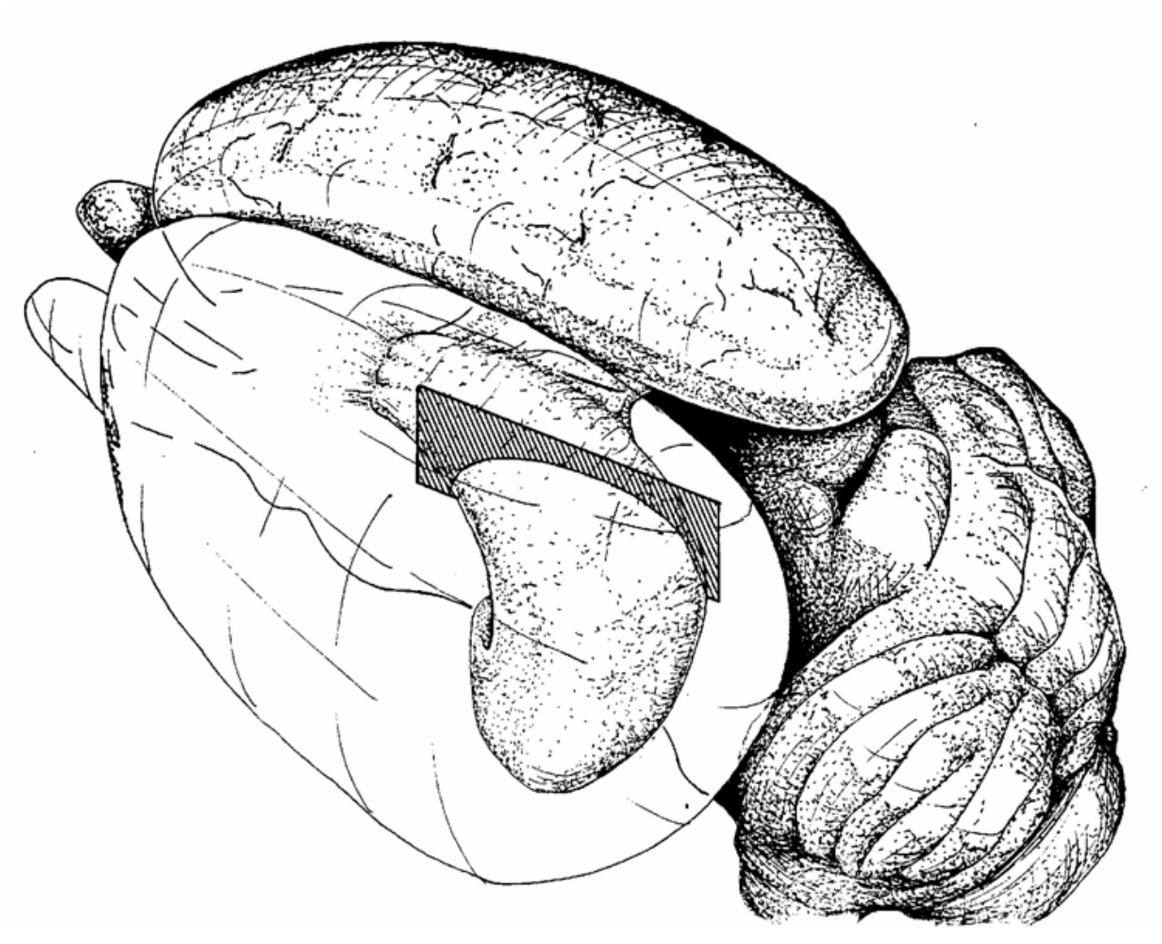






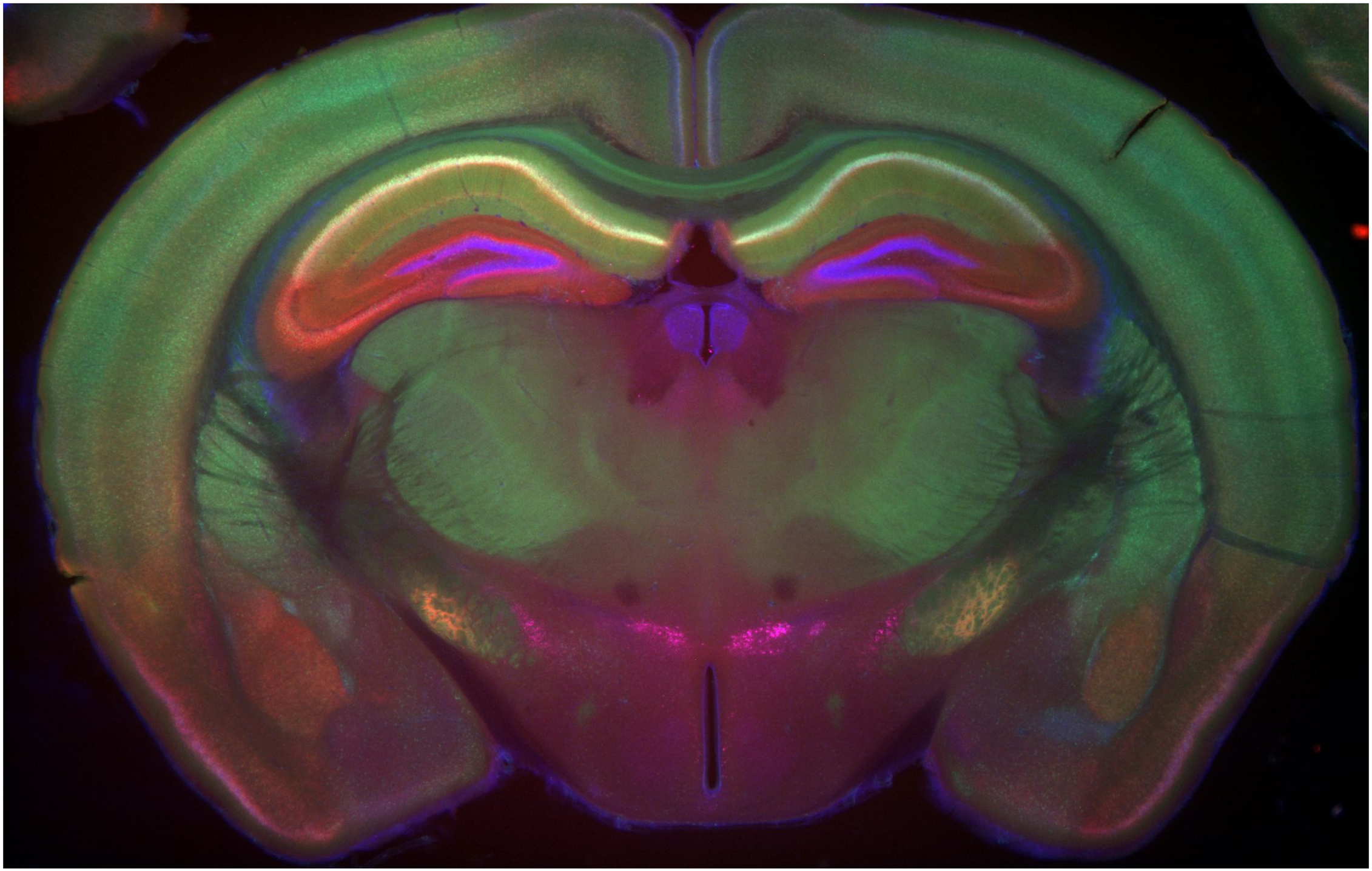


Hippocampus

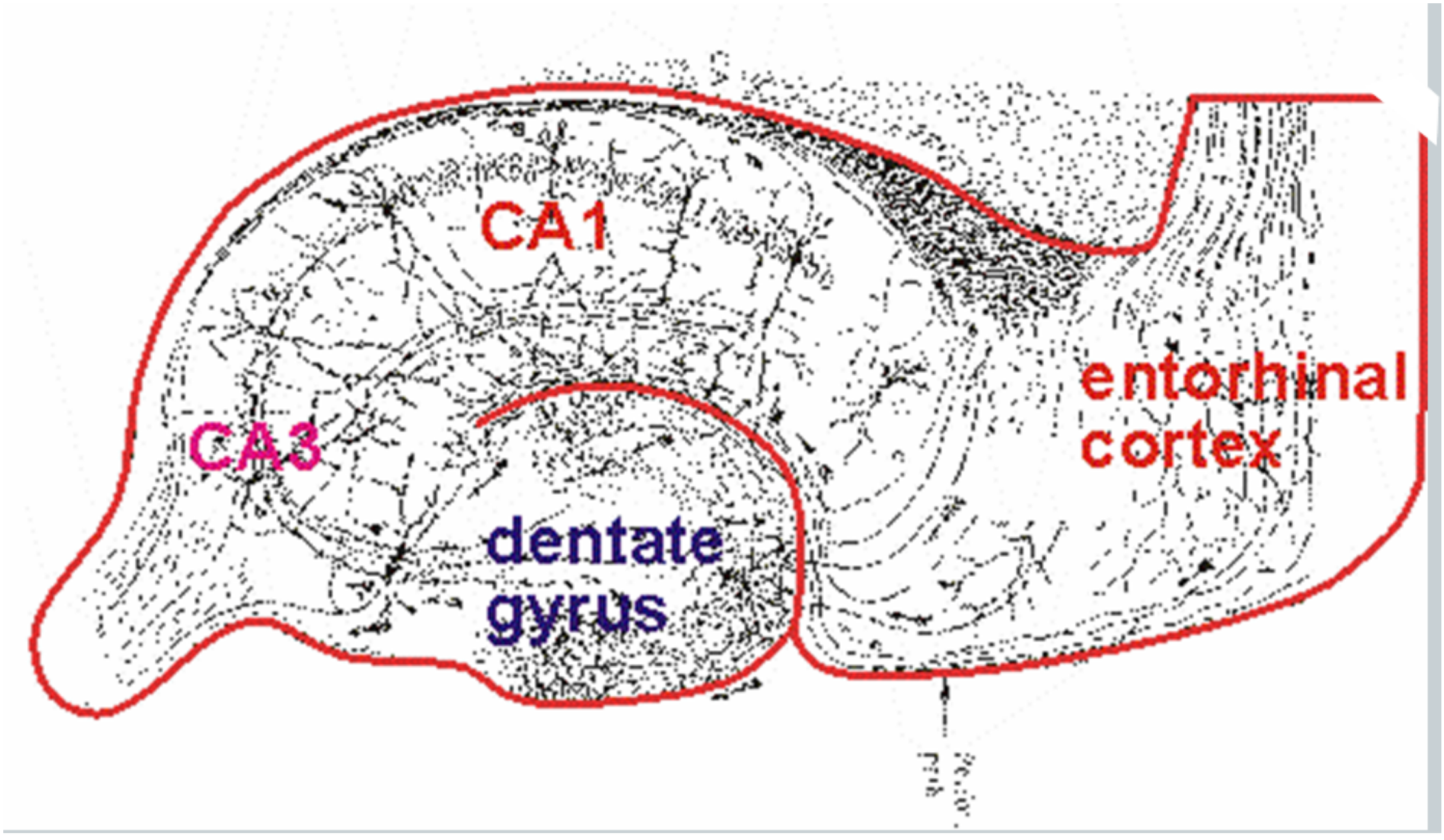


Brain slice

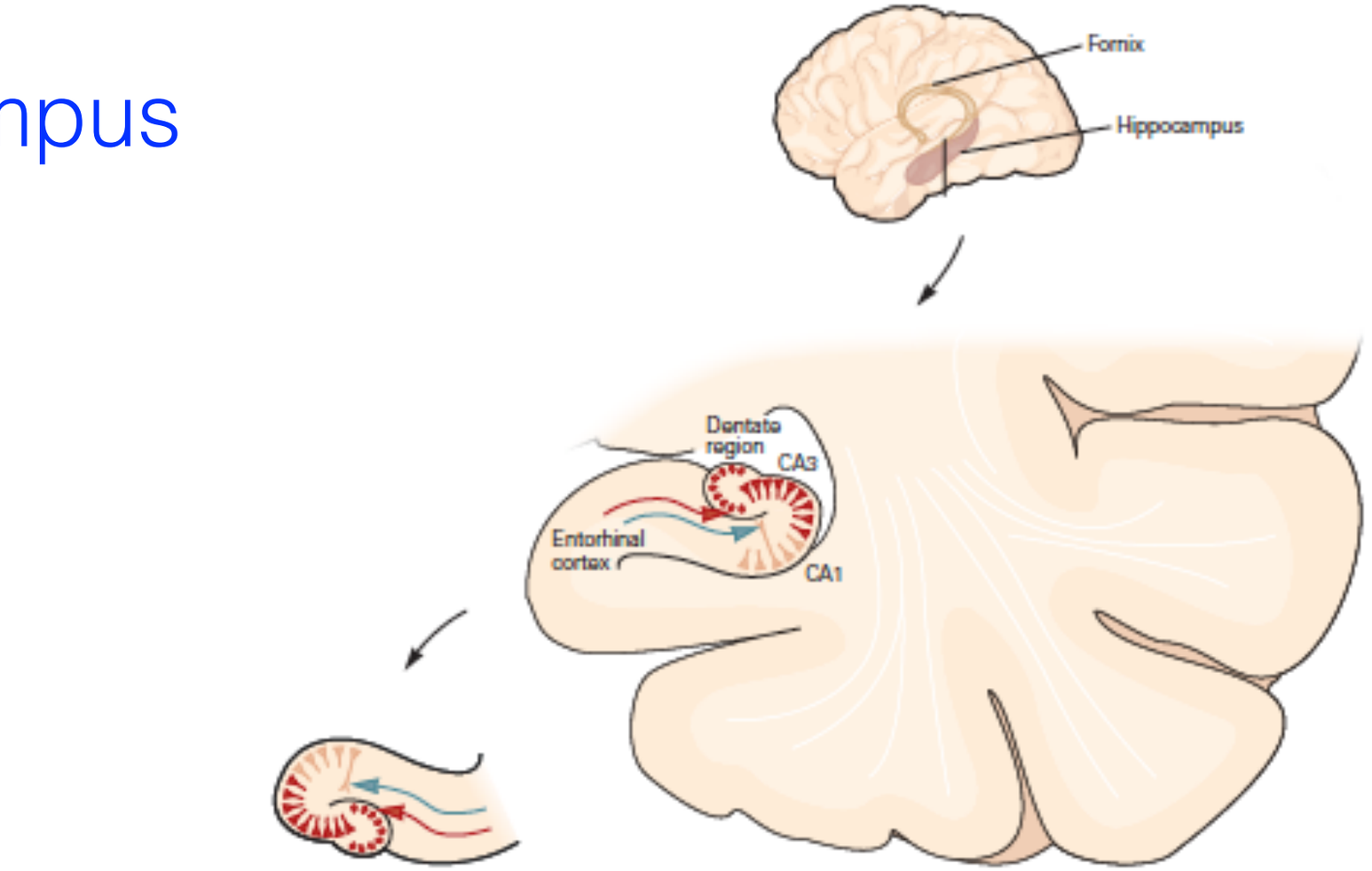
Cortex, Hippocampus, thalamus, hypothalamus

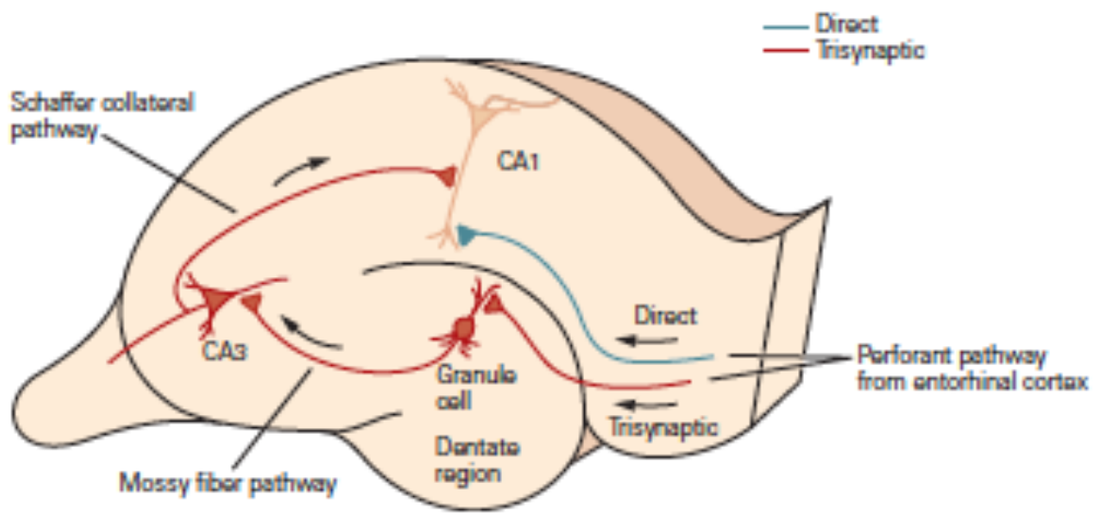


Ιππόκαμπος - Τομή

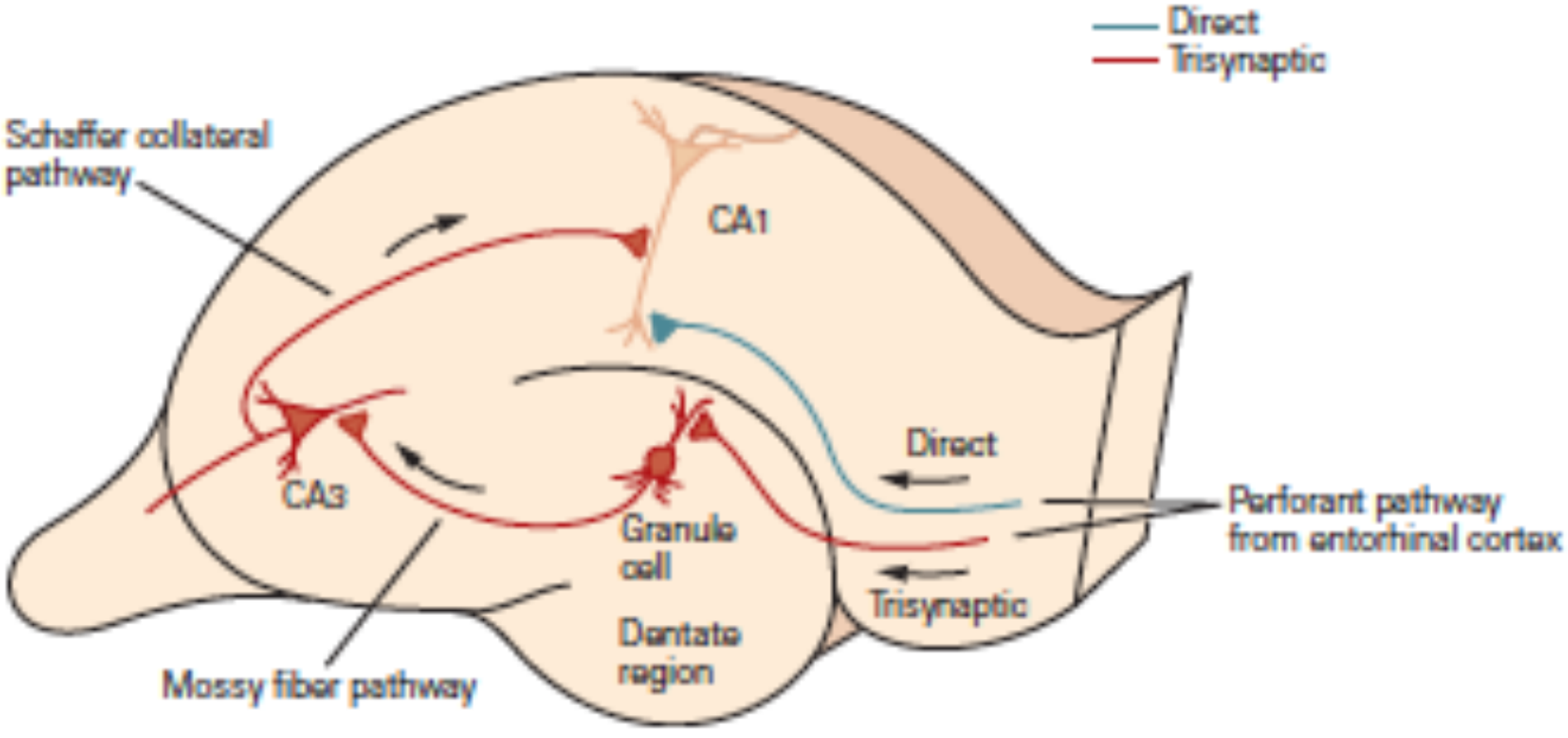


Hippocampus

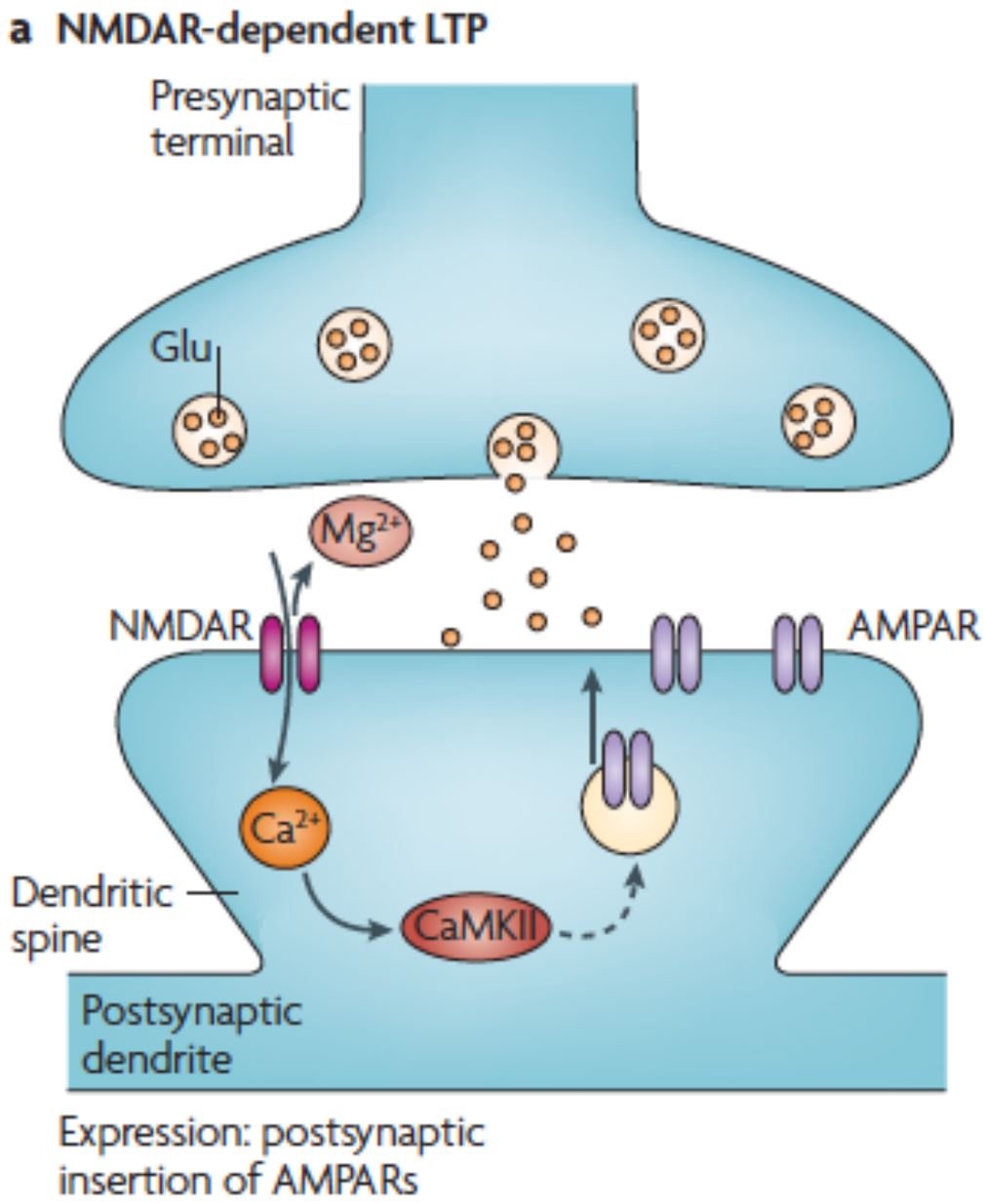




Hippocampus



Glutamatergic synapse



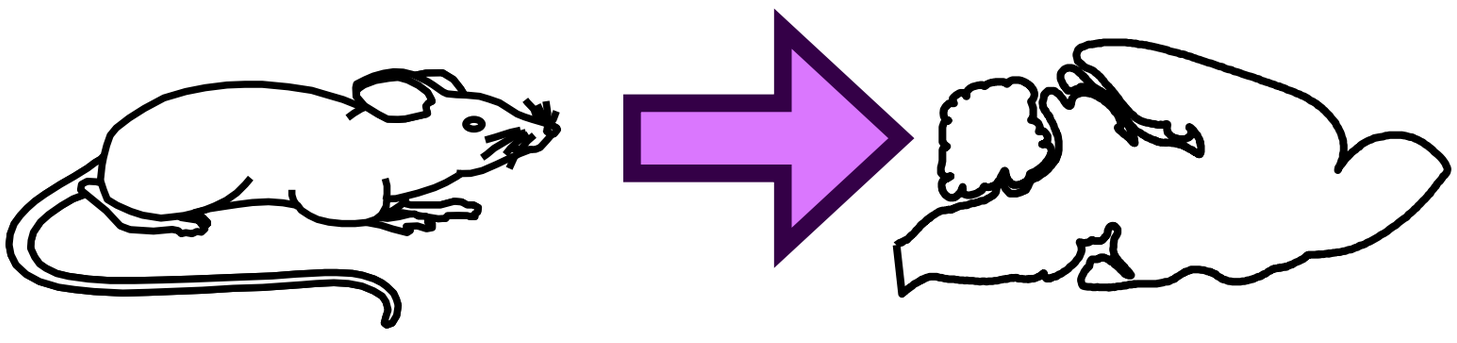
CA3

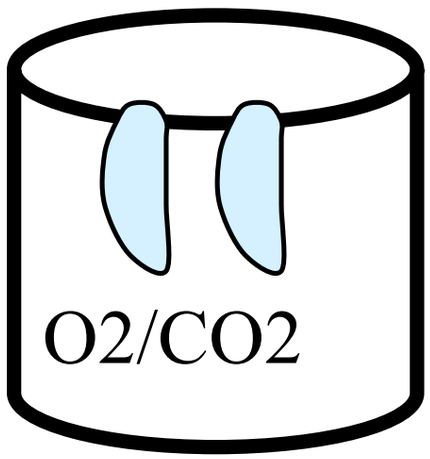
CA1

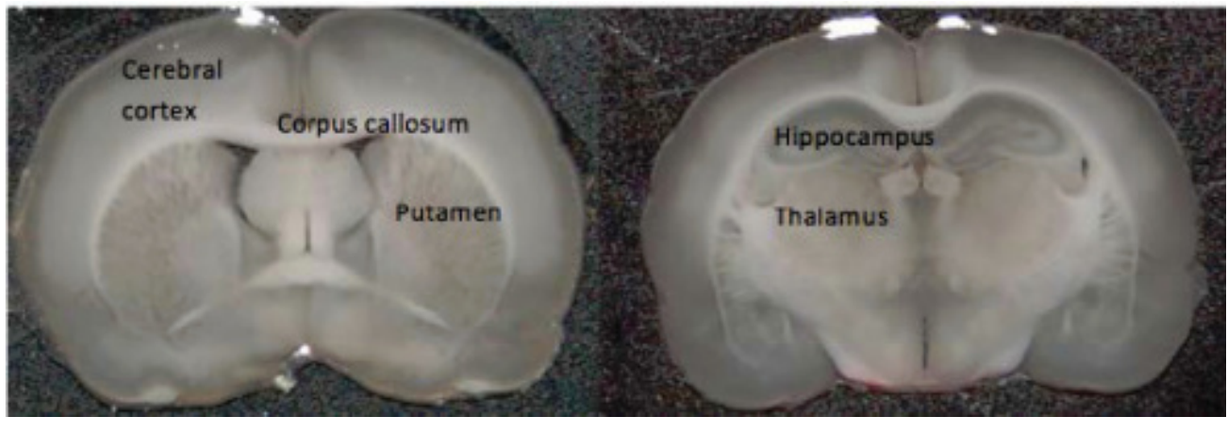
Kauer and Malenka, 2007

How do we study synaptic function?

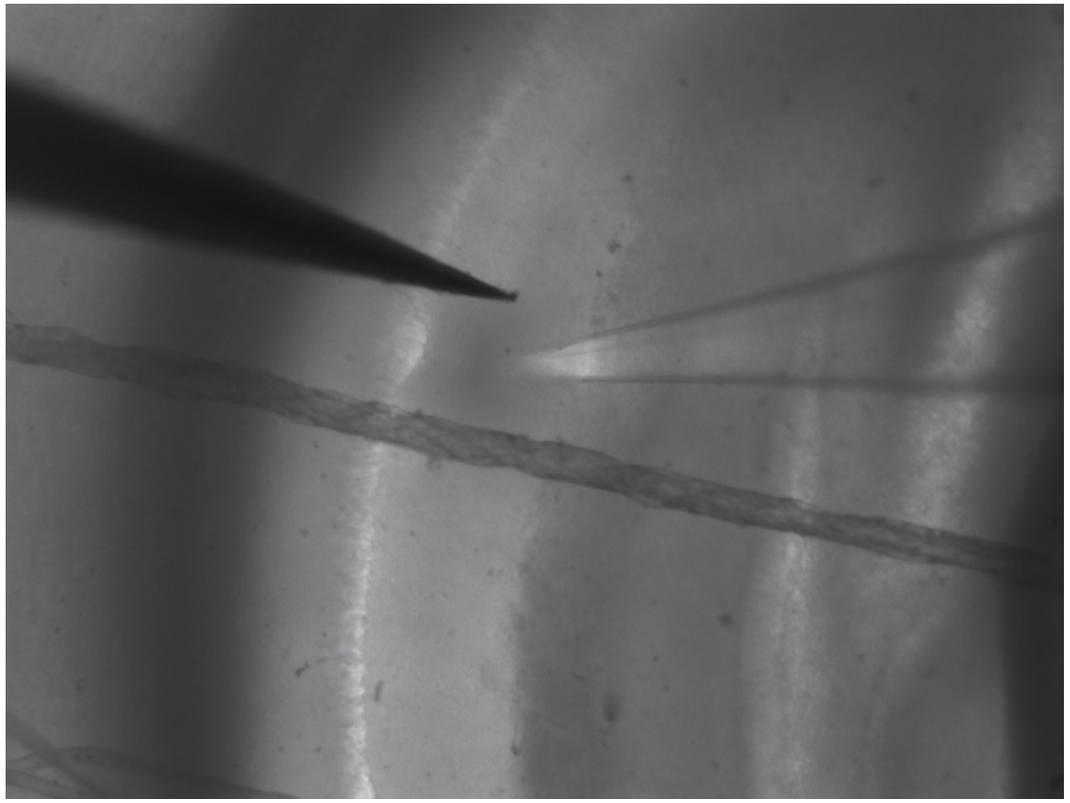
Acute brain slice



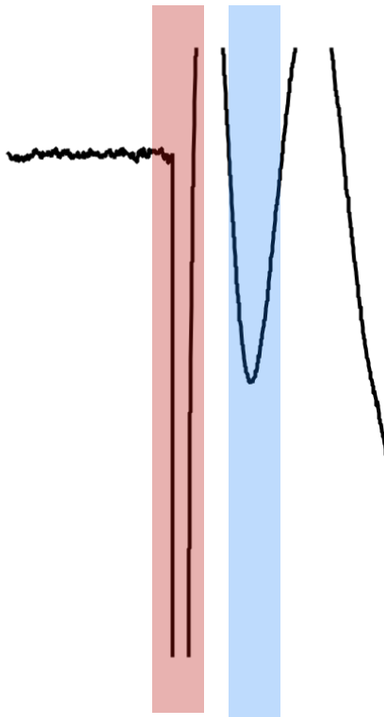




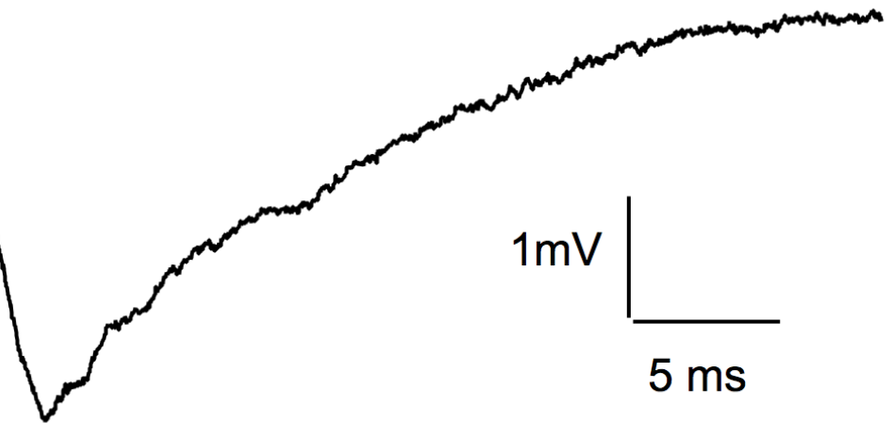
Extracellular Recordings - Local Field Potentials



stimulation artifact



field excitatory post-synaptic potential



fiber volley

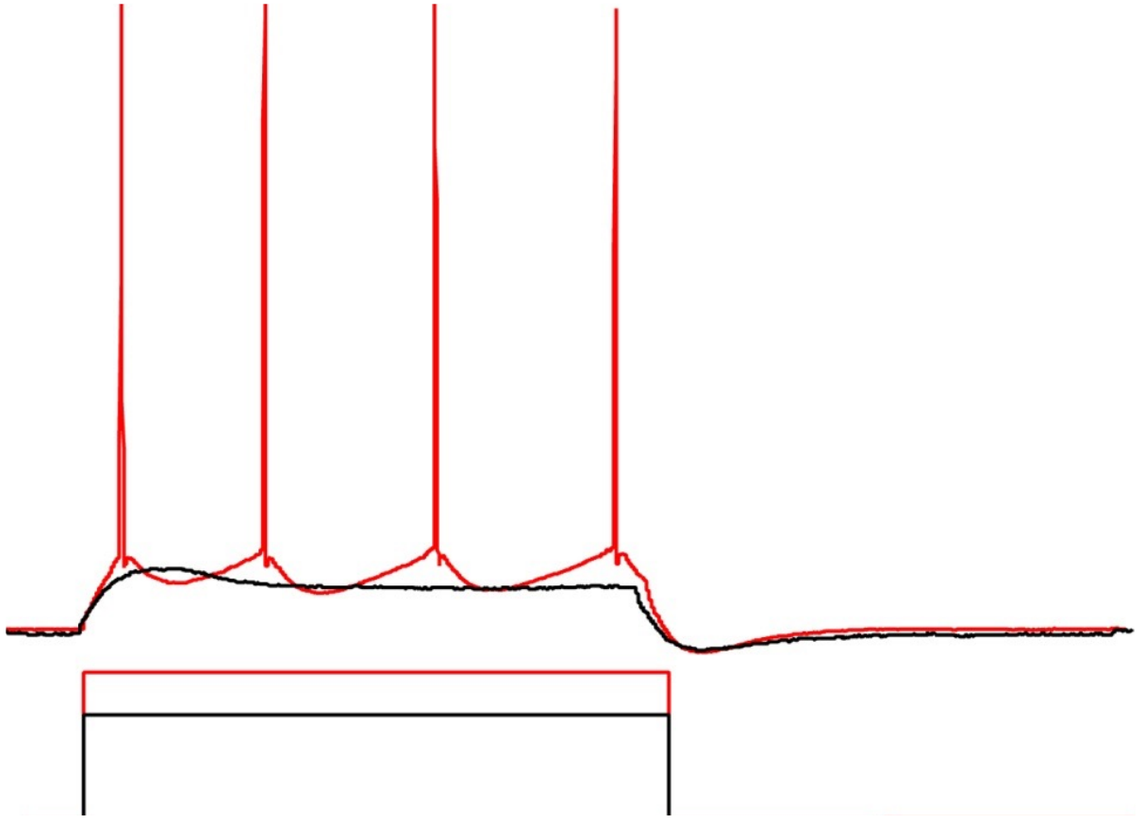
Whole-cell configuration
Current-clamp

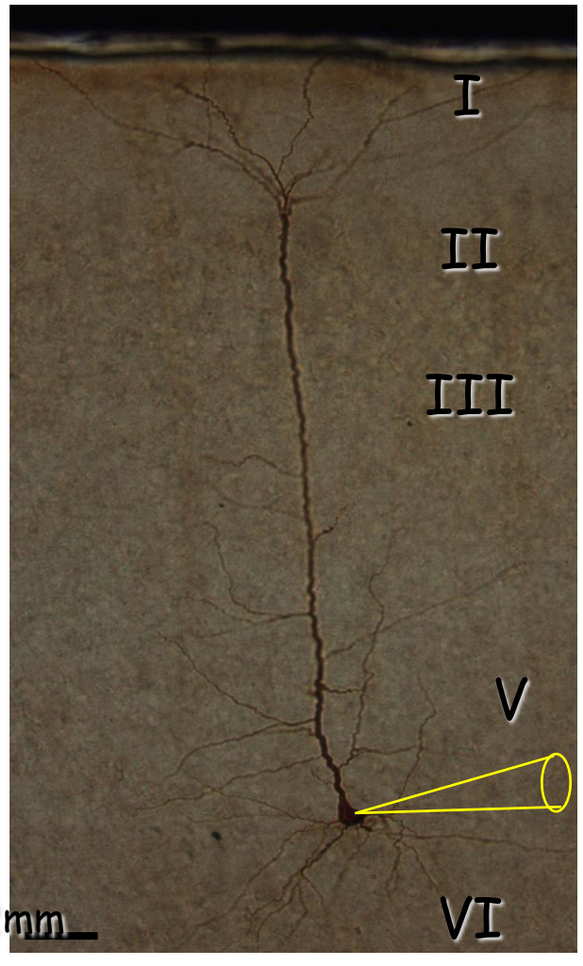
Διαλύματα που χρησιμοποιούνται

Εξωκυττάρια: τεχνητό εγκεφαλονωτιαίο υγρό (artificial cerebrospinal fluid, aCSF), pH,
Ενδοκυττάρια (στο ηλεκτρόδιο): παρόμοια με το ενδοκυττάριο περιβάλλον

Voltage response

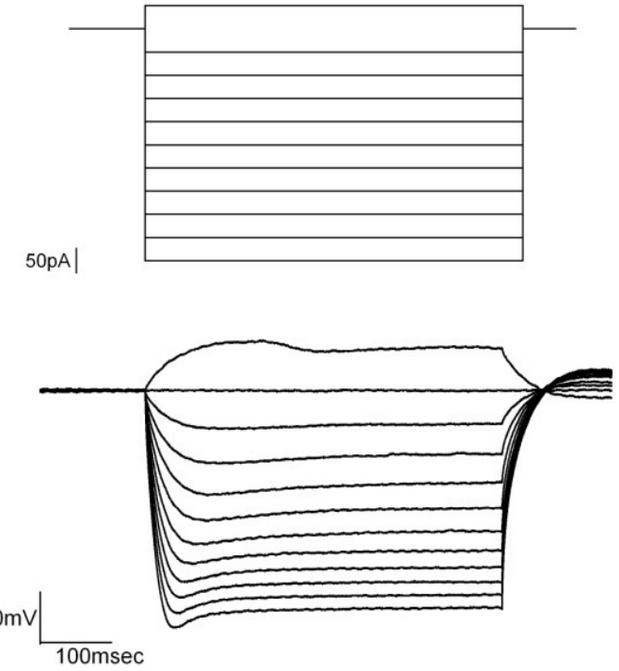
Current input

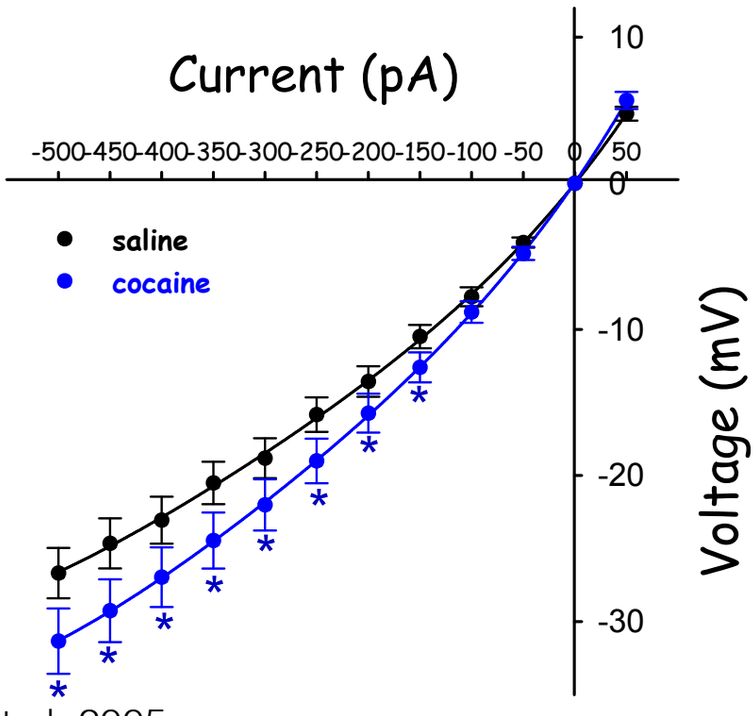




- I-V curve
- Membrane properties

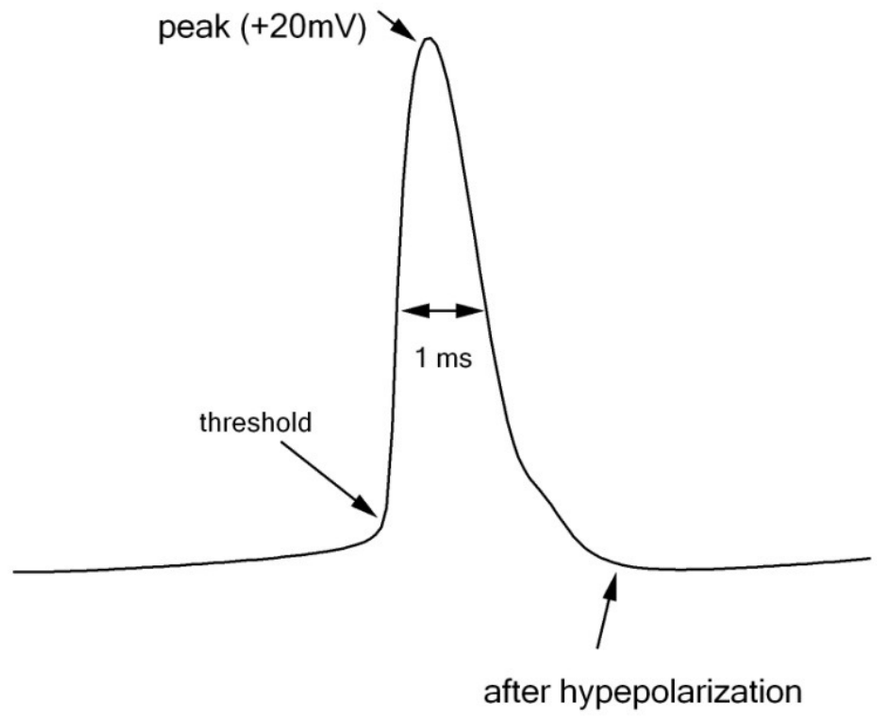
Current-clamp





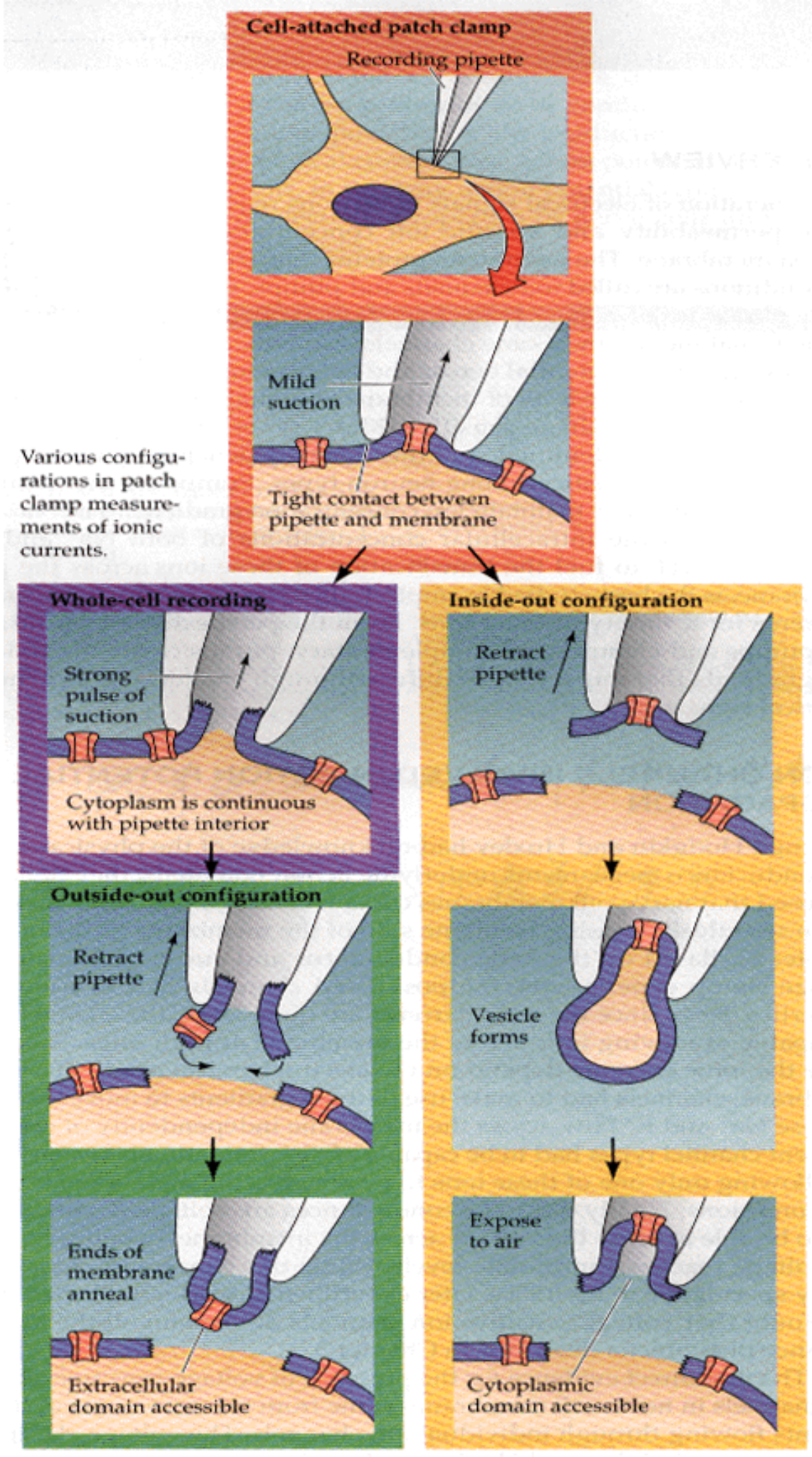
Nasif et al, 2005

- Action potential properties

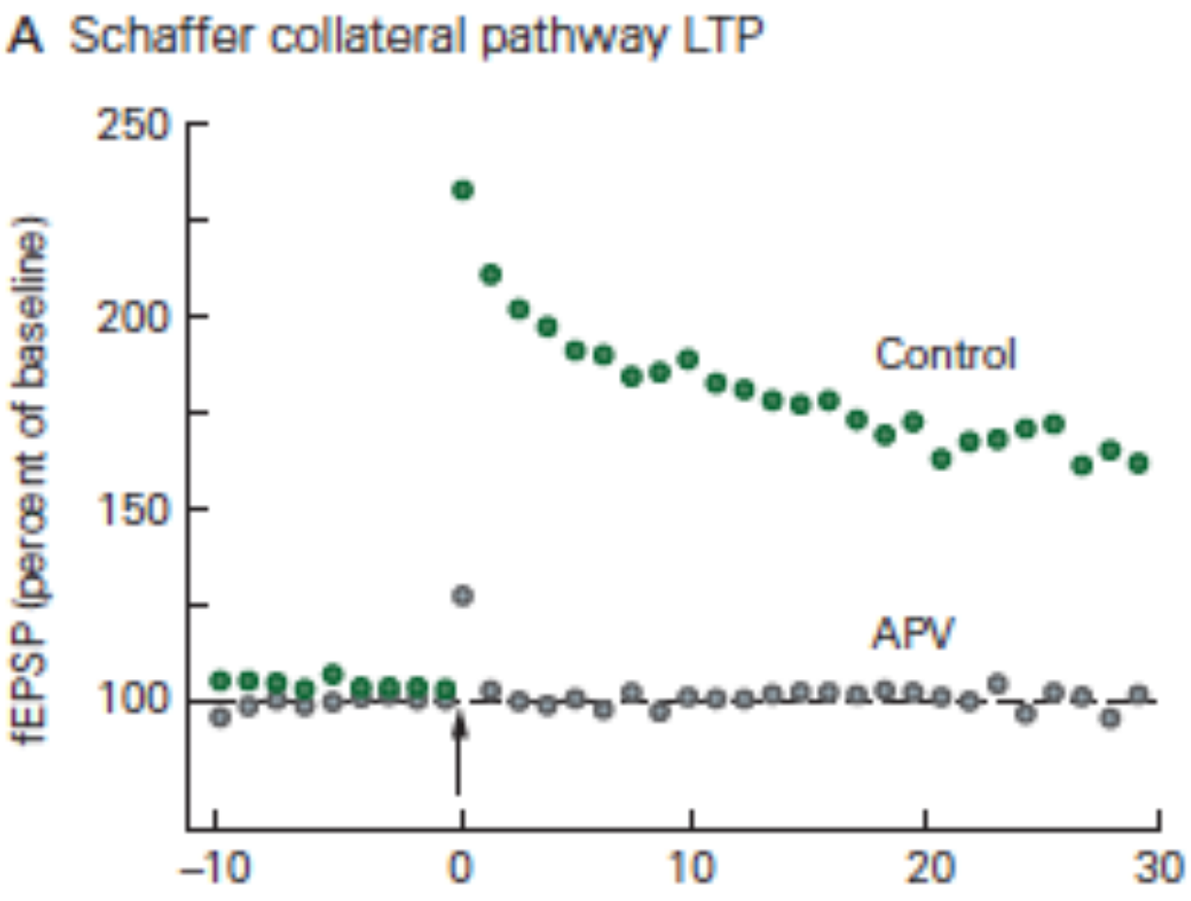


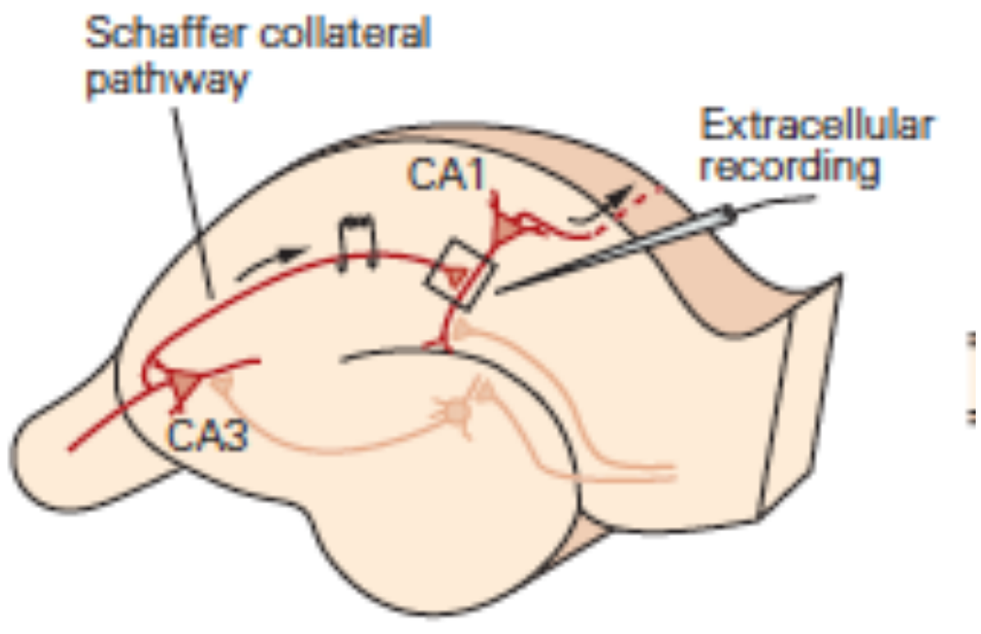
Patch clamp technique Configurations

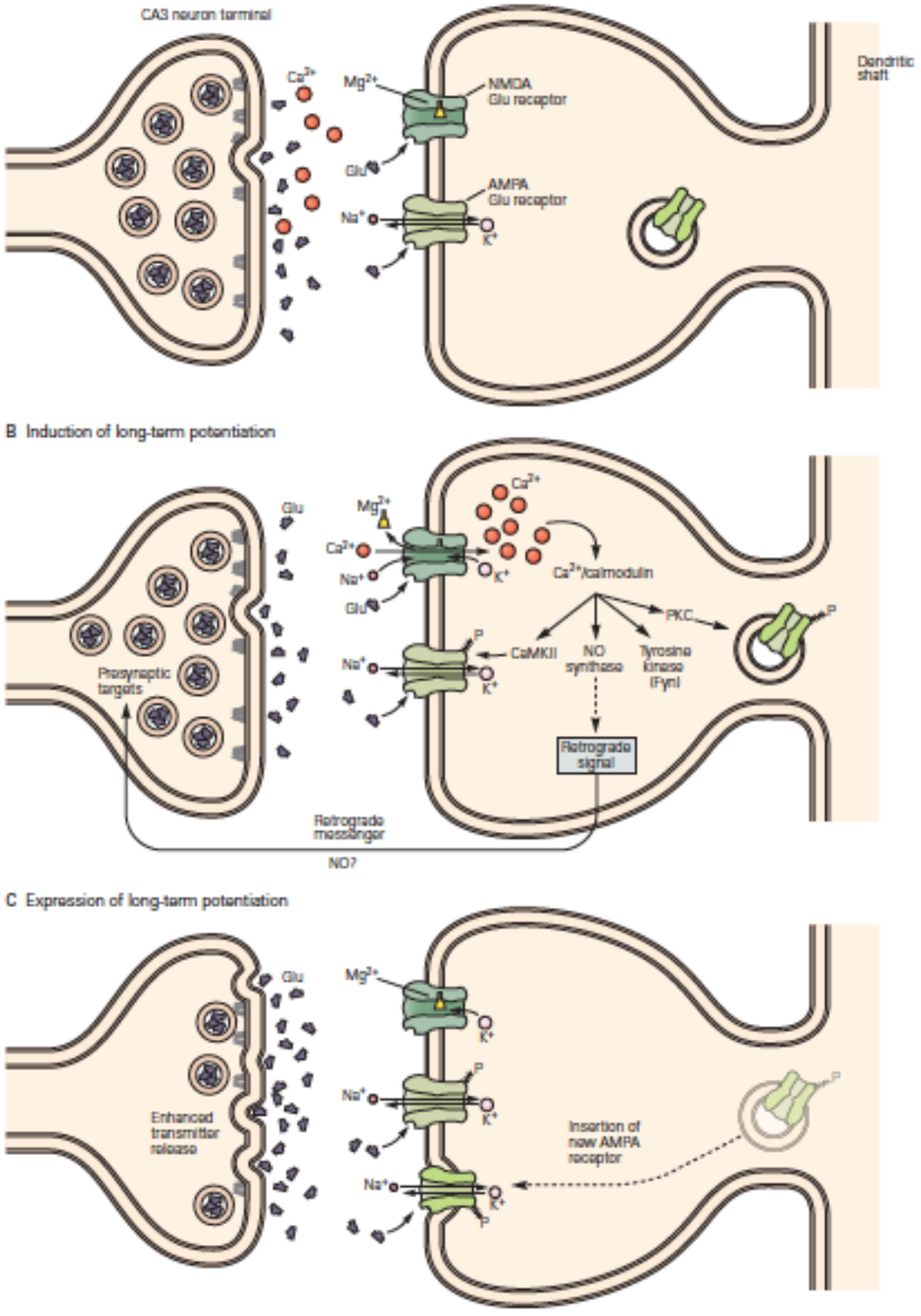
- Current-clamp
  - Give current inputs and record voltage changes
  - Monitor Vm, record Action Potentials
- Voltage-clamp mode
  - "Clamp" voltage and record currents
  - Study different ion channels



Long-term potentiation



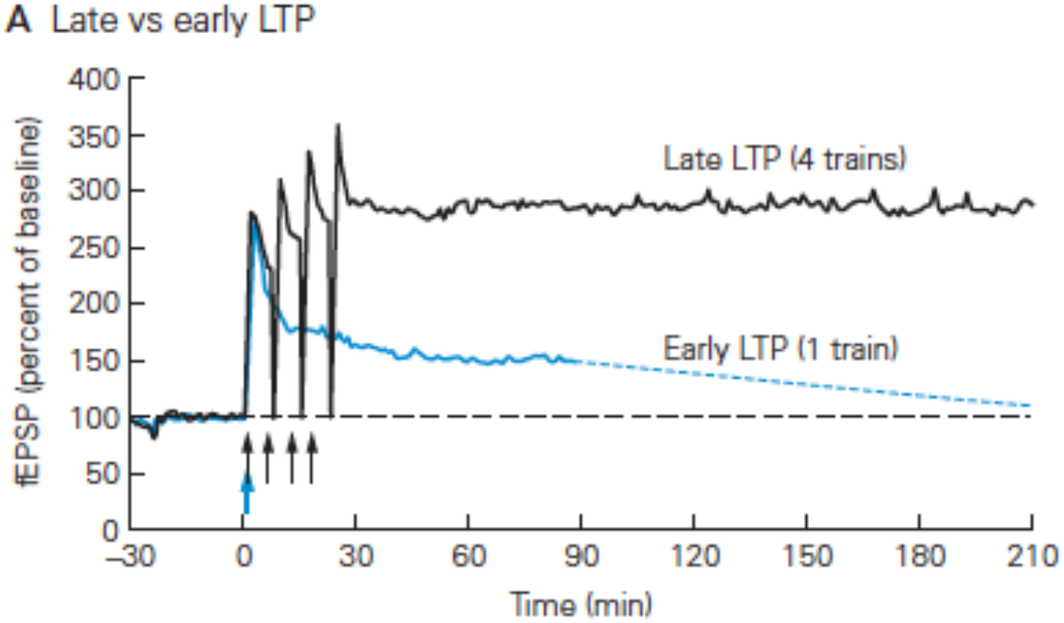




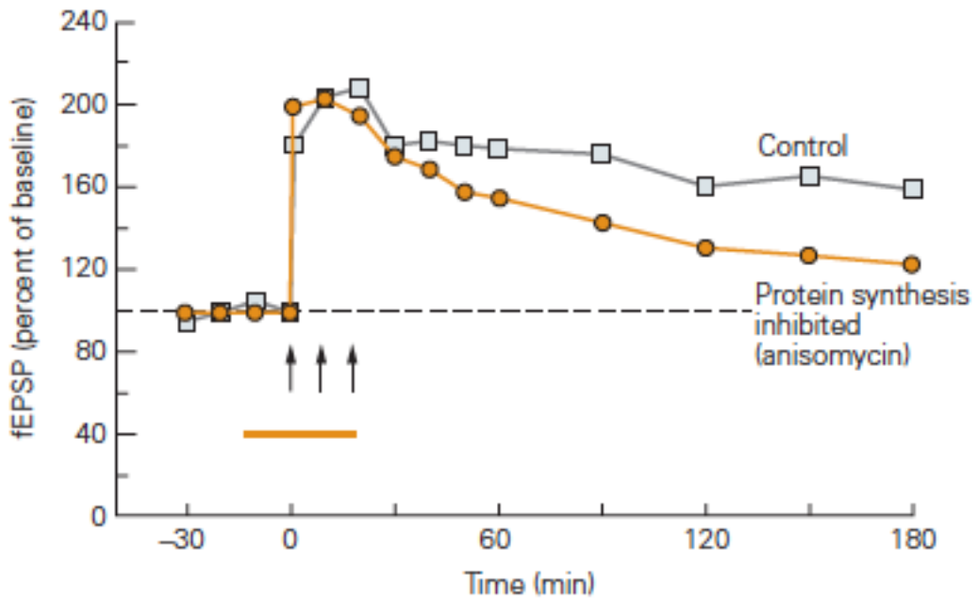
Mechanisms of LTP

- NMDA υποδοχέας
- Κινάση της καλμοδουλίνης ΙΙ
- Ασβέστιο
- CREB
- πρωτεϊνοσύνθεση

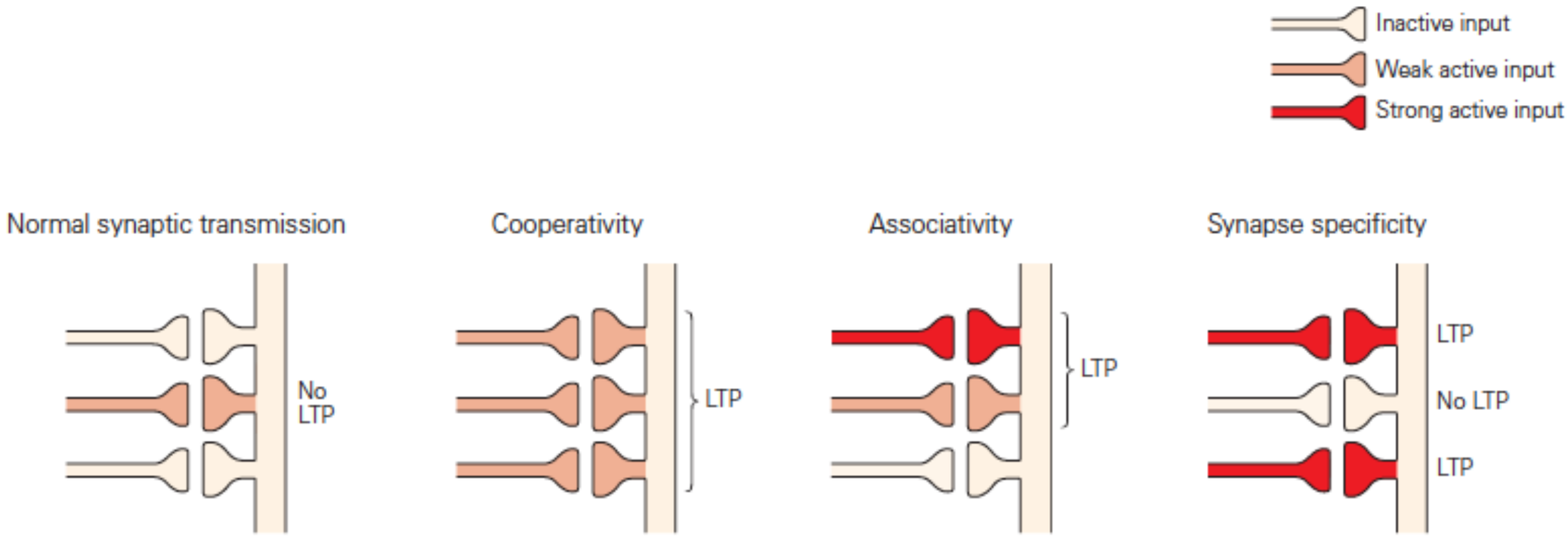
A Late vs early LTP



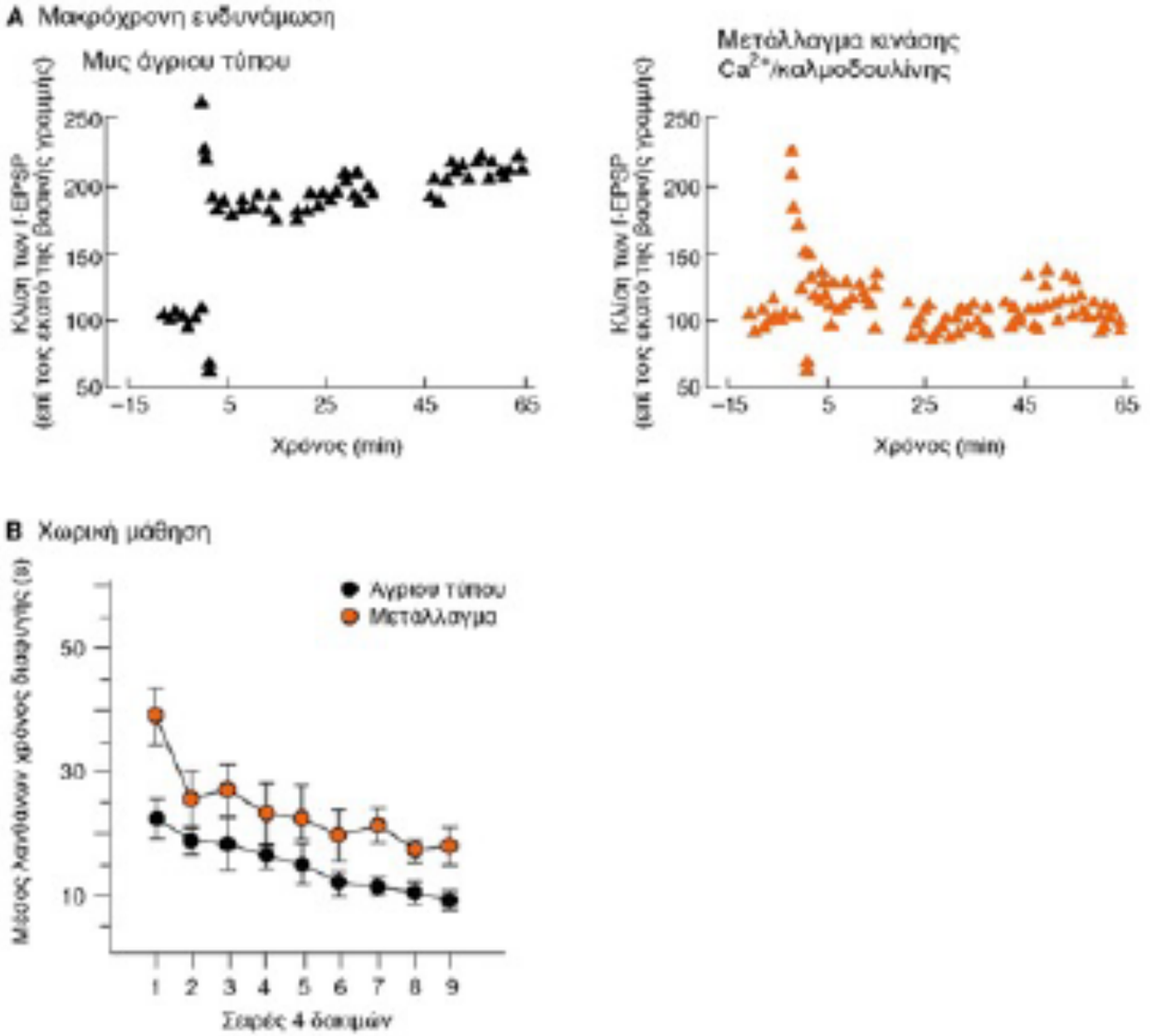
C Late LTP requires protein synthesis

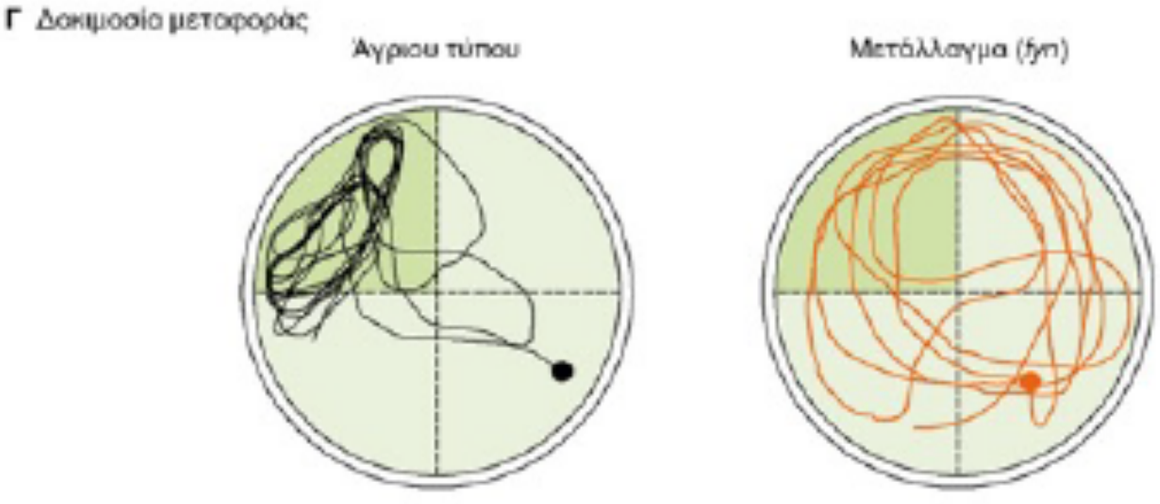


Characteristics of long-term potentiation



Correlation between LTP and memory





Neuronal theories for memory storage and recall

- Synaptic theory

  ★ Memory is stored in synapses

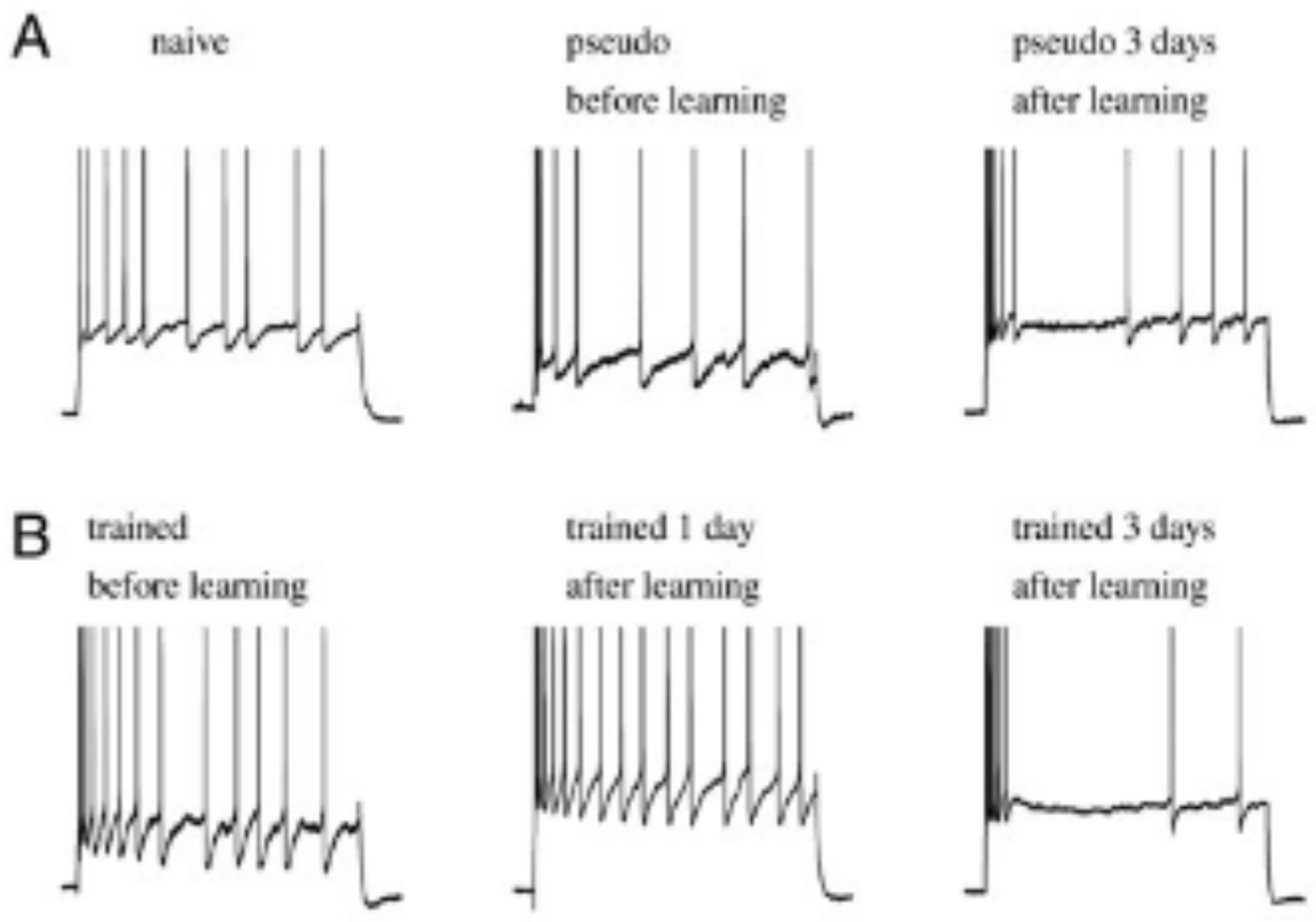
- Neuronal theory

  ★ Memory is stored in neurons

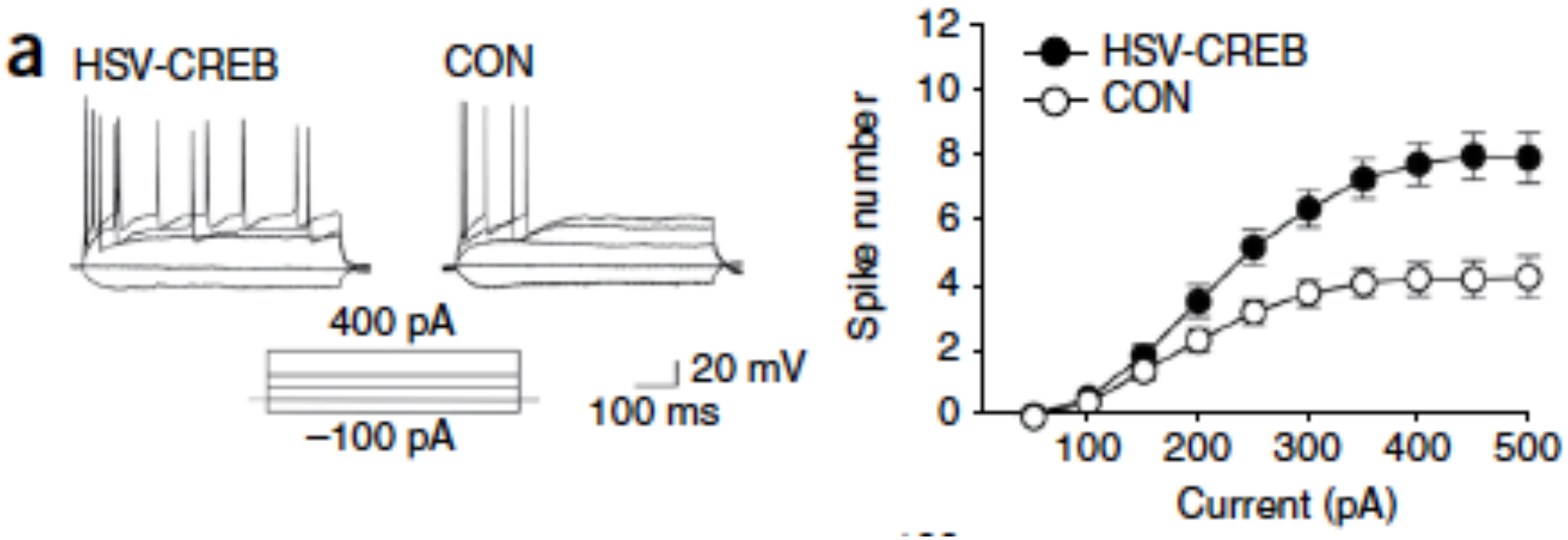
- Possible compromise

  ✳ Memory is stored in synapses within a specific network of neurons

Neuronal excitability following training to memory task

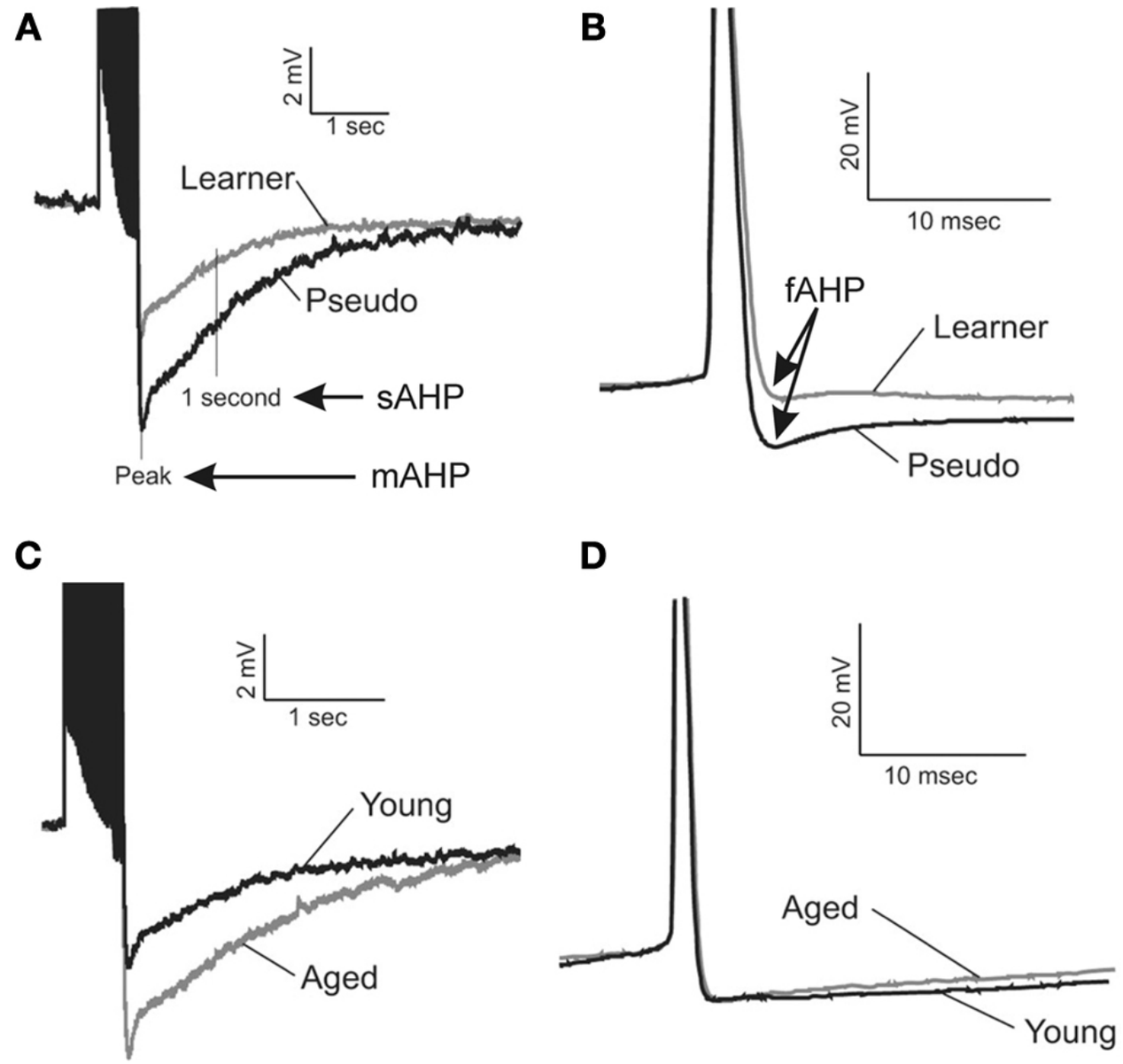


CREB increases excitability



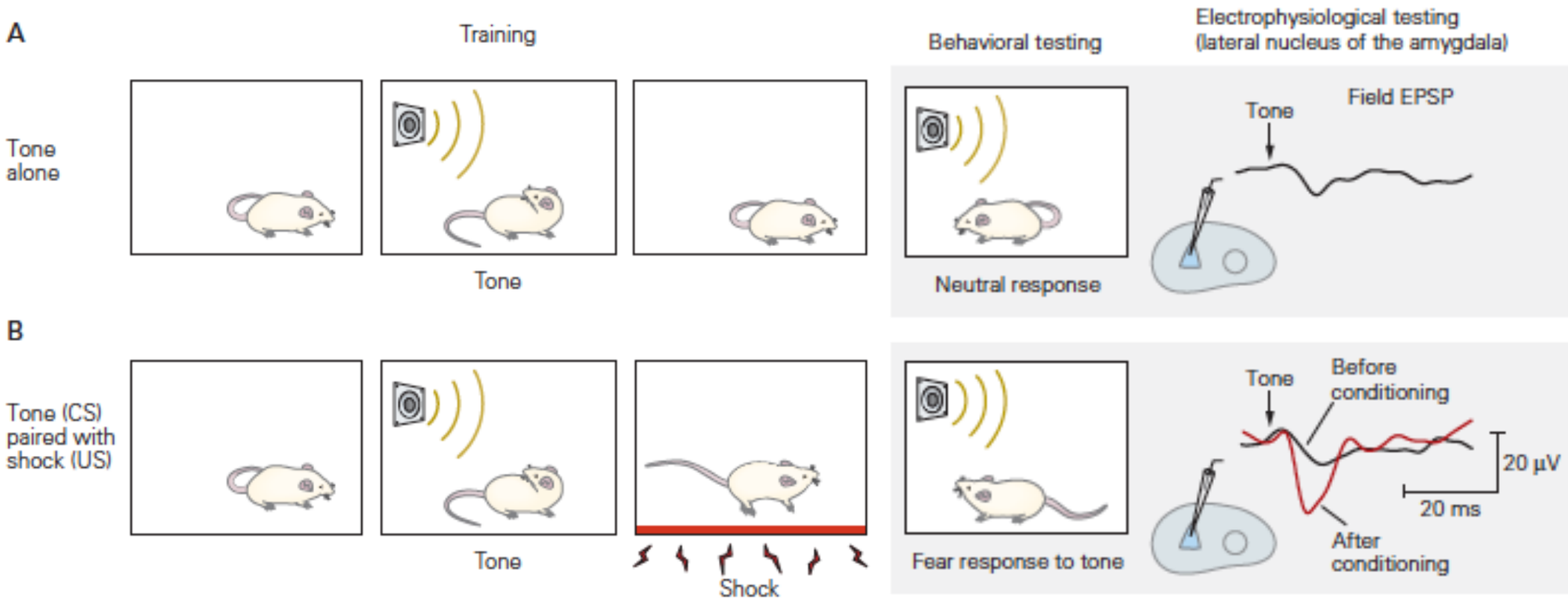
Zhou et al., 2009

Increased neuronal excitability is due to reduced slow afterhyperpolarization

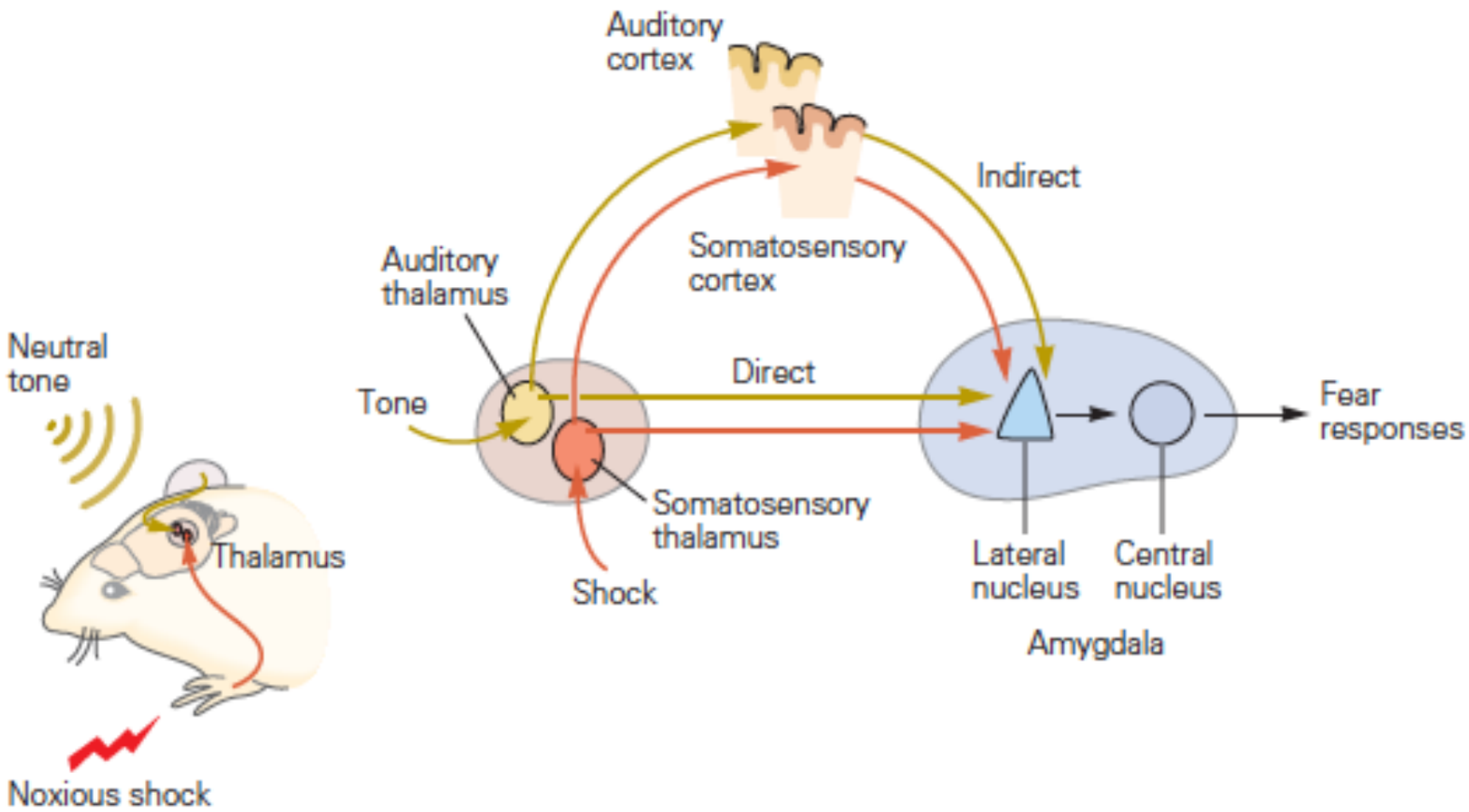


Oh et al., 2010

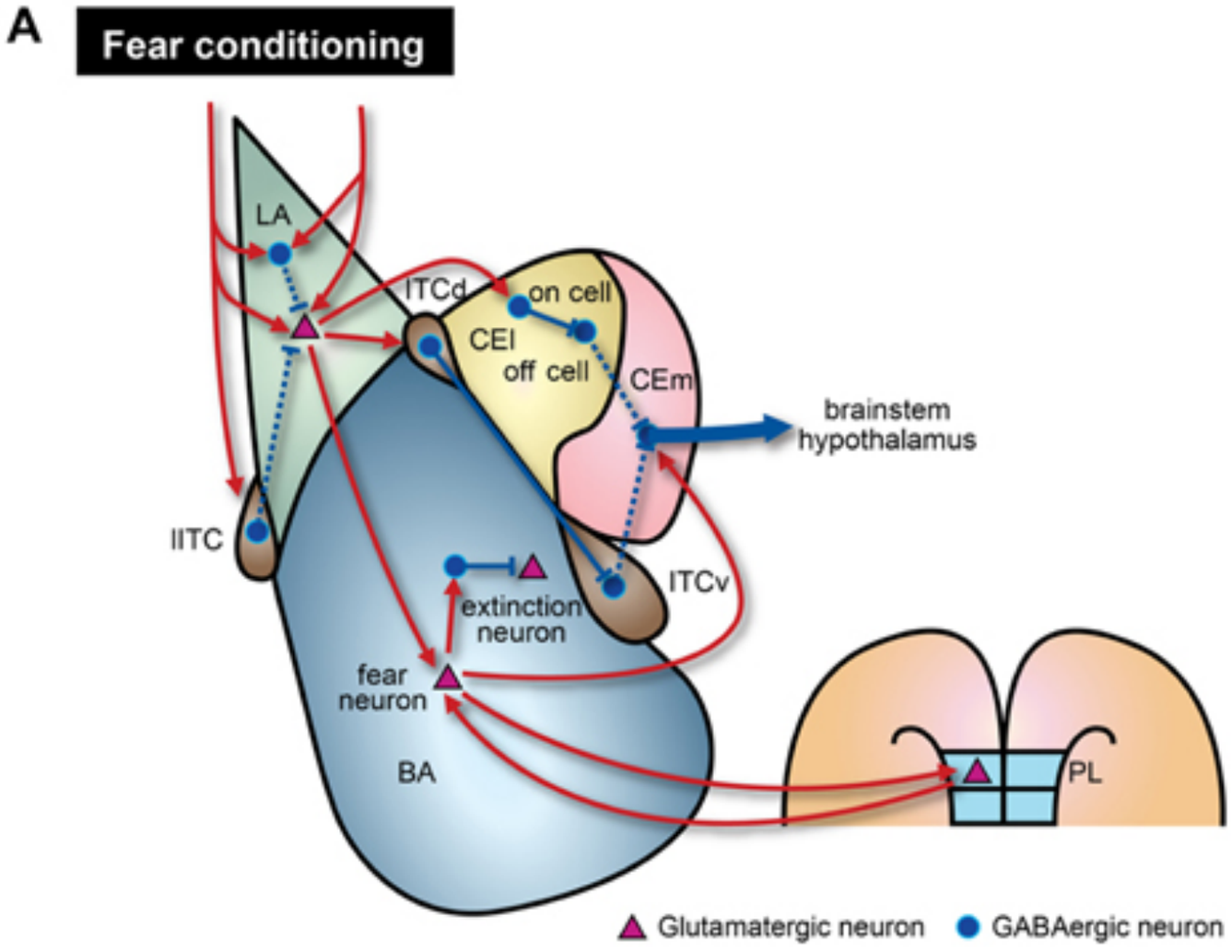
Pathways underlying conditioned learned fear memory



Neural pathways of learned fear

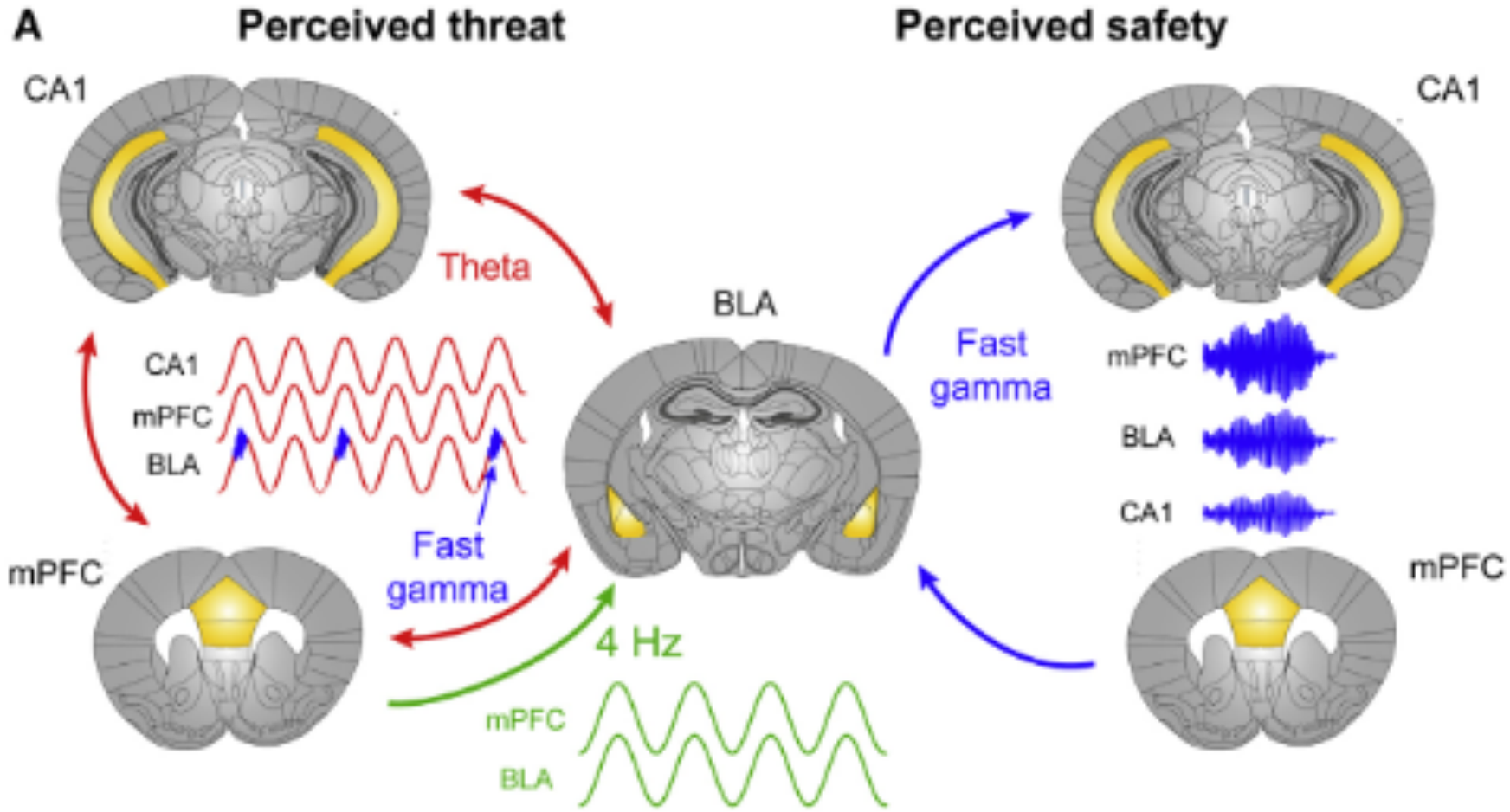


Amygdala



http://www.frontiersin.org/files/Articles/58867/fncir-07-00129-HTML/image_m/fncir-07-00129-g002.jpg

Hippocampal network and interaction with other brain regions



Science

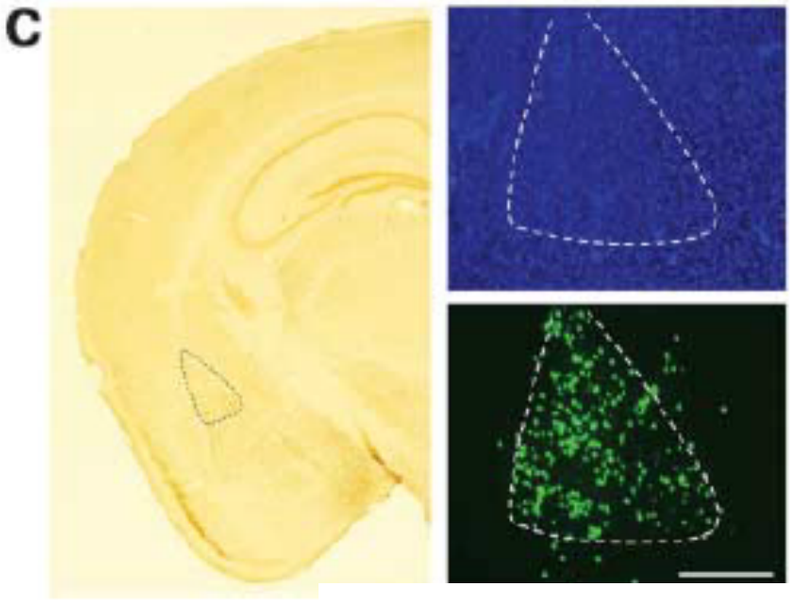
AAAS

Neuronal Competition and Selection During Memory Formation

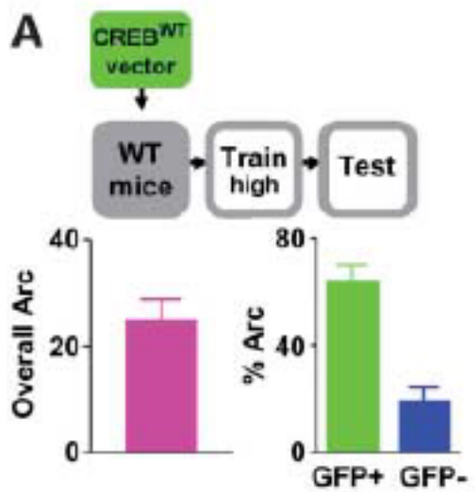
Jin-Hee Han, *et al.*

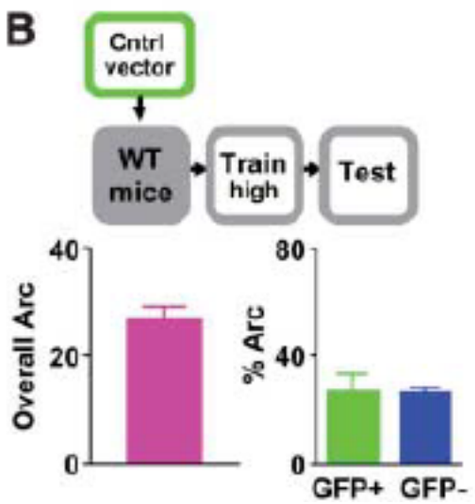
Science **316**, 457 (2007);
DOI: 10.1126/science.1139438

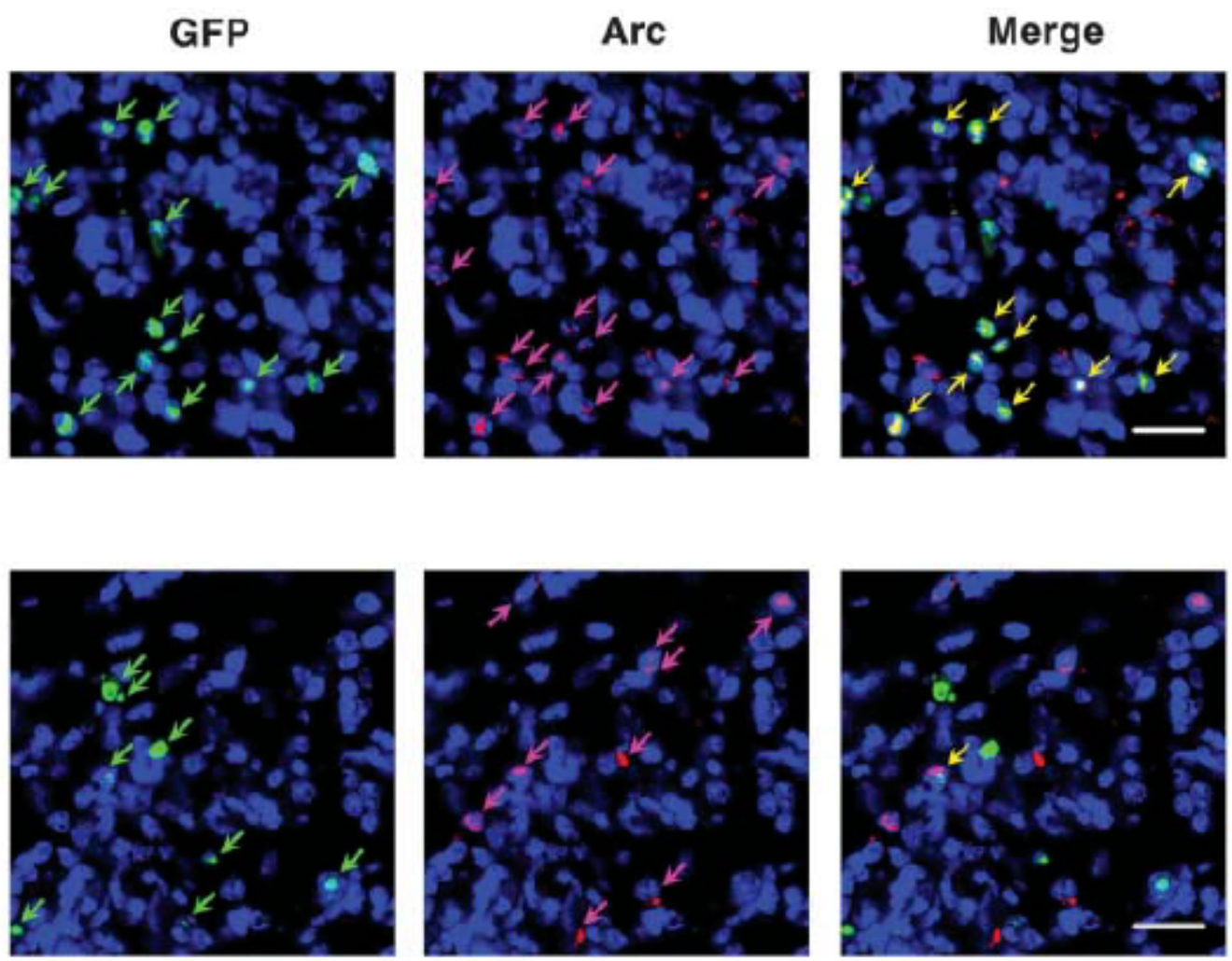
CREB over expression



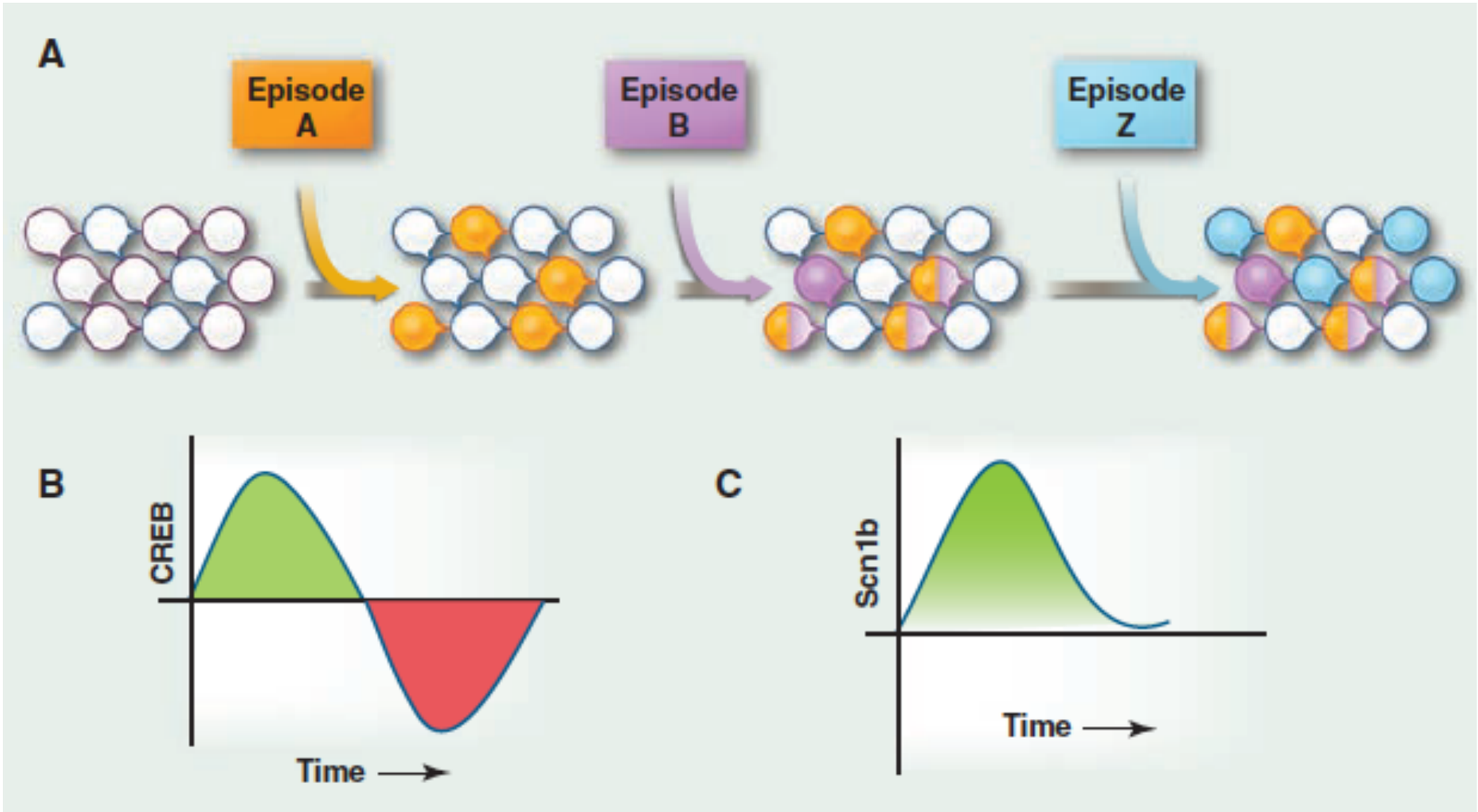
Arc activation following fear memory recall







Model of memory allocation



Silva et al., 2009

Synaptic plasticity and memory engram

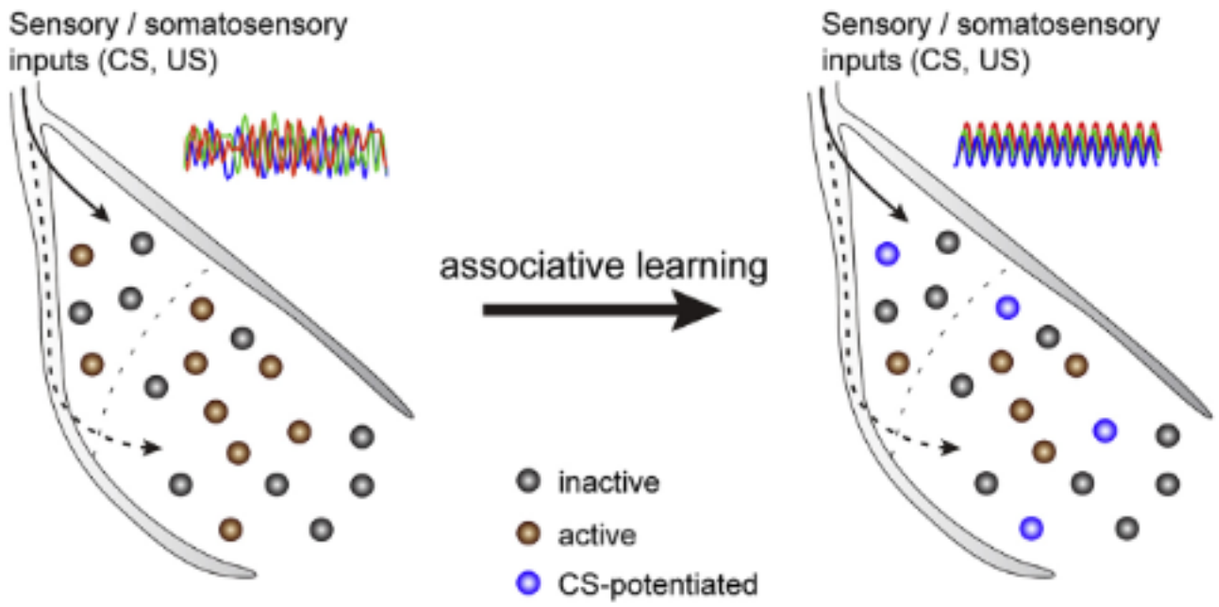
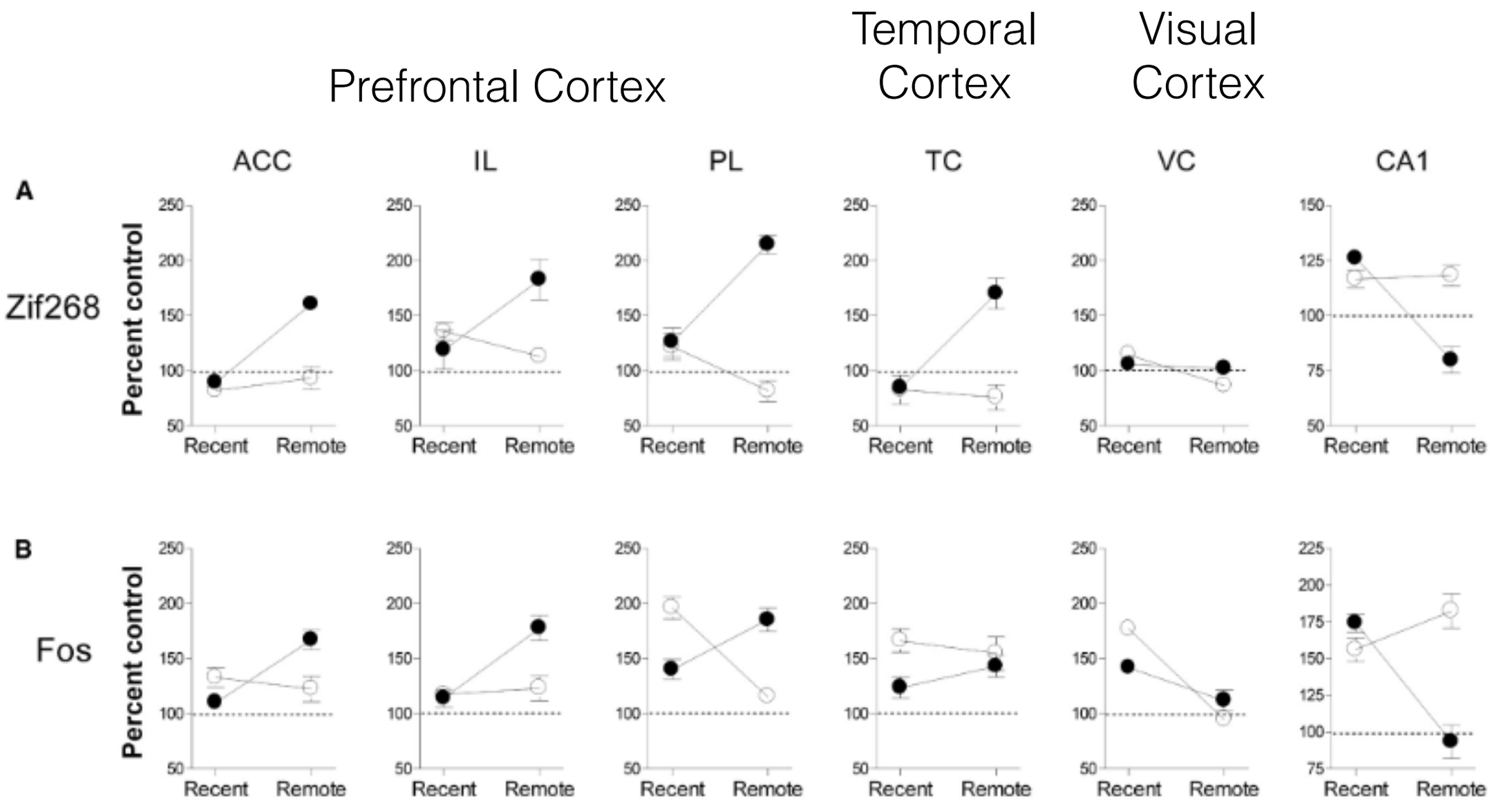


Figure 2. Synaptic Plasticity and Network Oscillation Gate Memory Engram Formation in the BLA

Before learning, some BLA neurons (gray balls) display low excitability and others (brown balls) higher excitability (by intrinsic factors and/or synaptic inputs). At the population level, poorly synchronized rhythms can be detected among BLA and connected brain areas. Learning promotes Hebbian synaptic plasticity of the CS pathway on neurons that were more active during conditioning. This plastic process results in CS-potentiated neurons that form an engram (blue balls). Memory retrieval triggers synchronization of rhythmic activity between the BLA and some interconnected structures, as well as reactivation of engram cells.

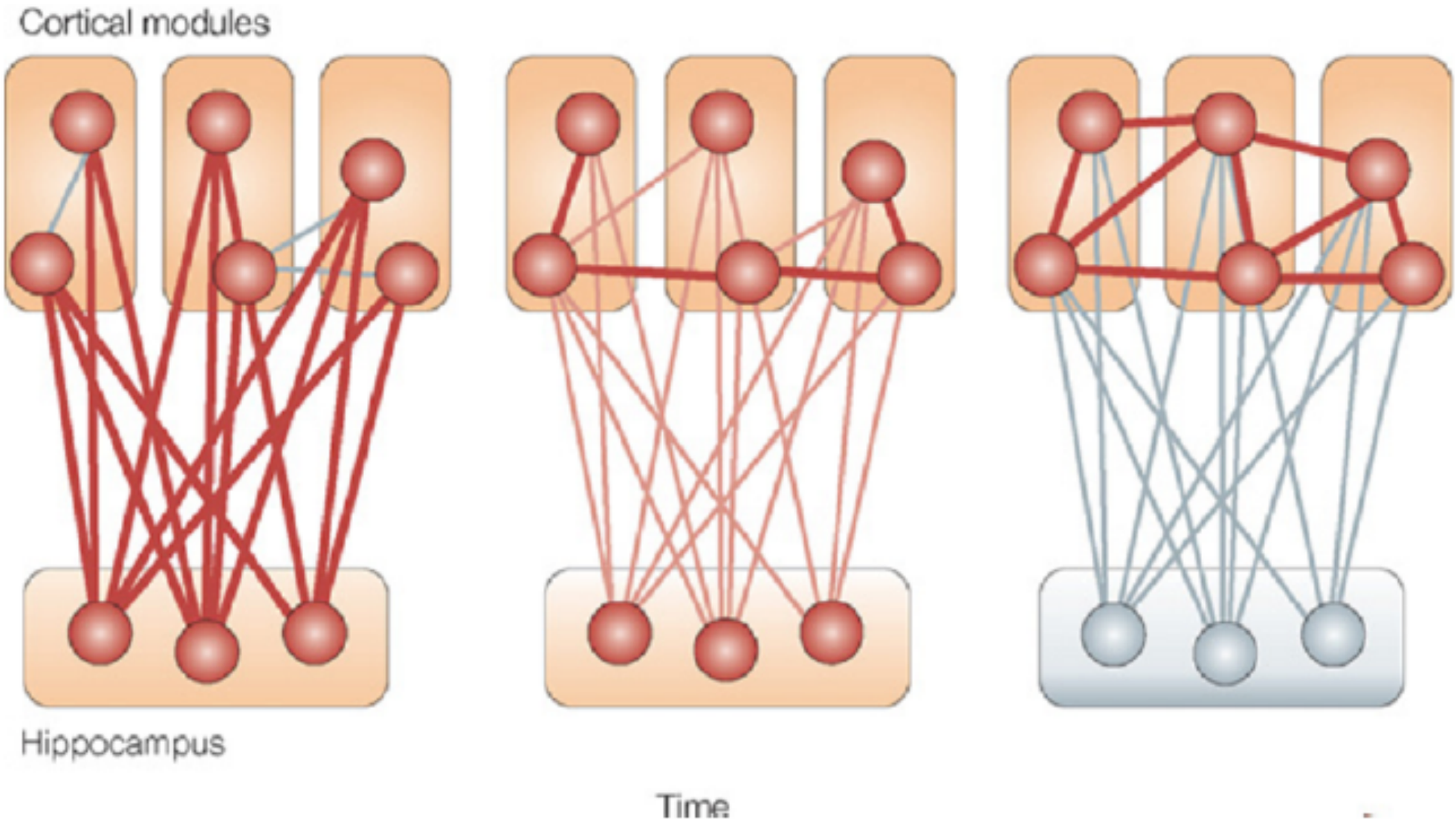
Brochio et al., 2017

Long-term vs remote memory



Frankland et al., 2004

Systems consolidation process



Frankland and Bontempi, 2005

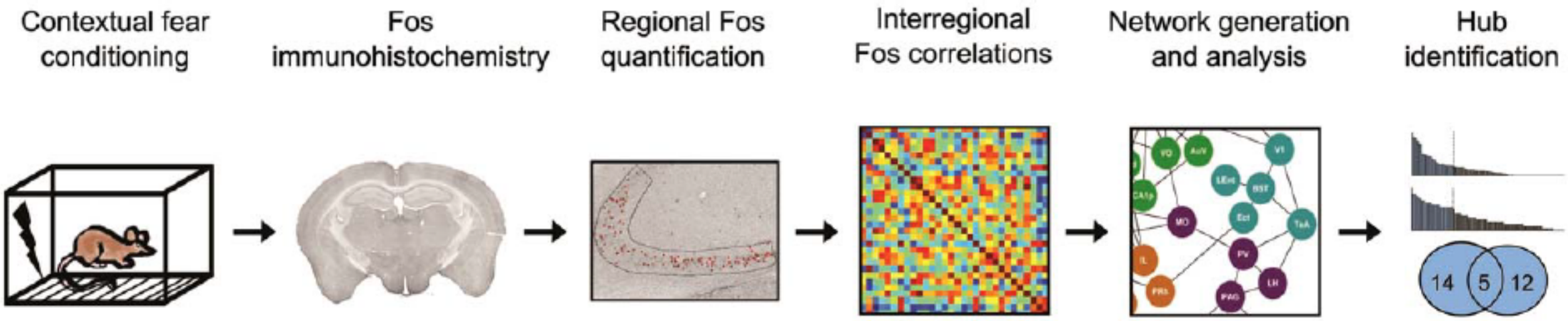
c-fos activation following memory recall (Paul Frankland)

Identification of a Functional Connectome for Long-Term Fear Memory in Mice

Anne L. Wheeler[1,2], Cátia M. Teixeira[1], Afra H. Wang[1,2], Xuejian Xiong[3], Natasa Kovacevic[4], Jason P. Lerch[1,5], Anthony R. McIntosh[4,6], John Parkinson[3,7], Paul W. Frankland[1,2,8]*

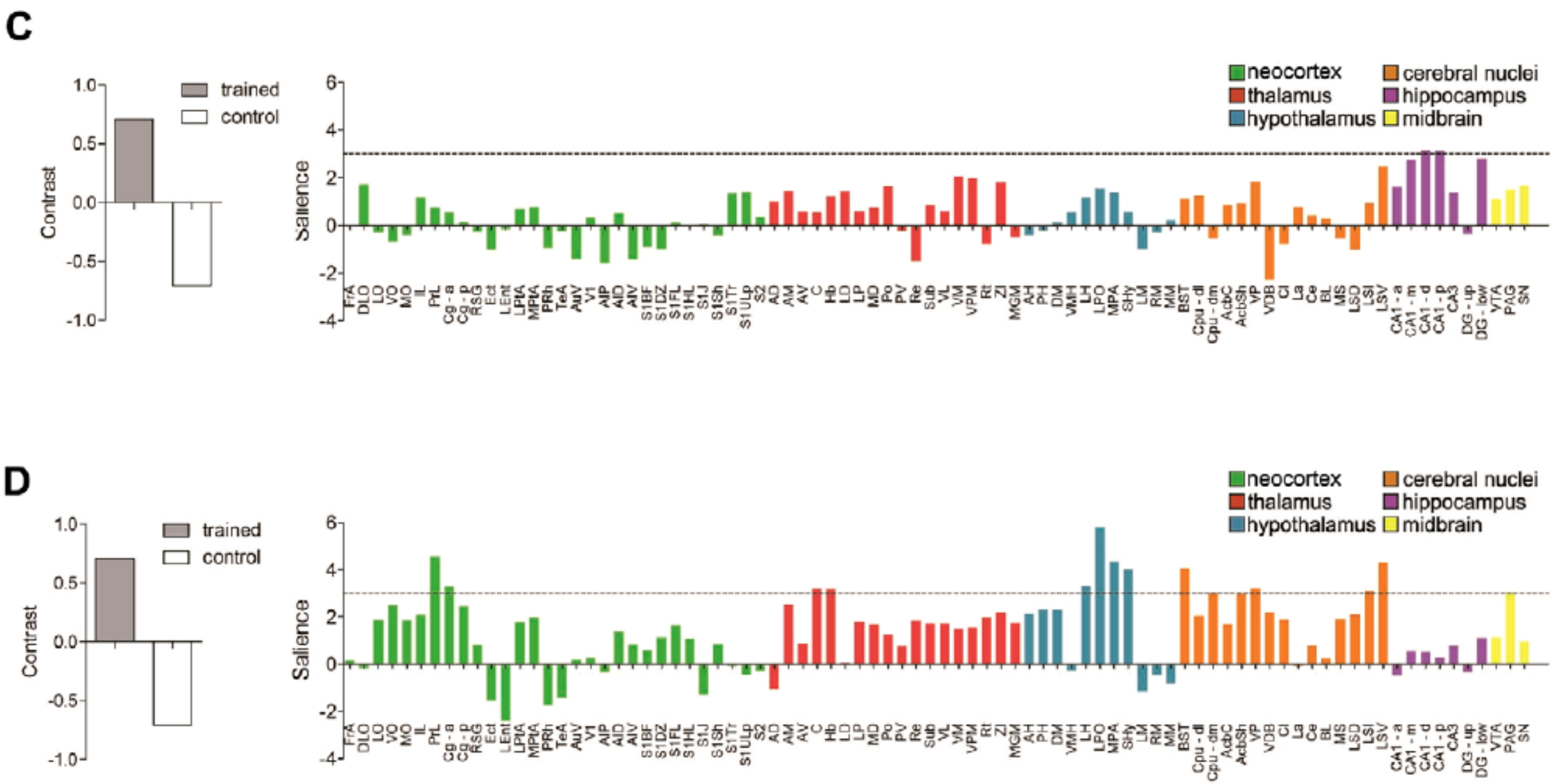
1 Program in Neurosciences and Mental Health, The Hospital for Sick Children, Toronto, Canada, **2** Institute of Medical Science, University of Toronto, Toronto, Canada, **3** Program in Molecular Structure and Function, The Hospital for Sick Children, Toronto, Canada, **4** Rotman Research Institute, Baycrest Centre, Toronto, Canada, **5** Department of Medical Biophysics, University of Toronto, Toronto, Canada, **6** Department of Psychology, University of Toronto, Toronto, Canada, **7** Departments of Biochemistry and Molecular Genetics, University of Toronto, Toronto, Canada, **8** Department of Physiology, University of Toronto, Toronto, Canada

Experimental design



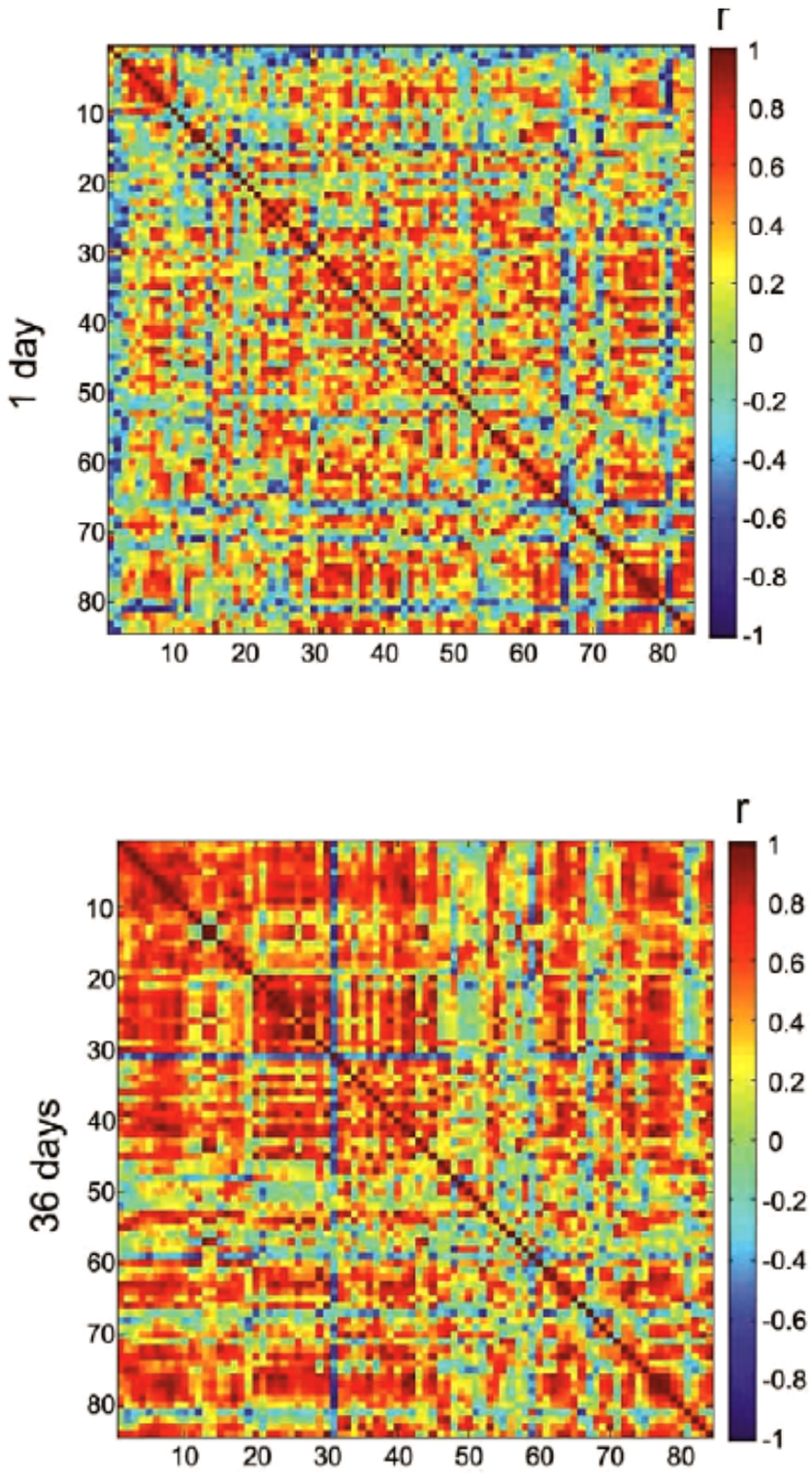
Wheeler et al., 2013

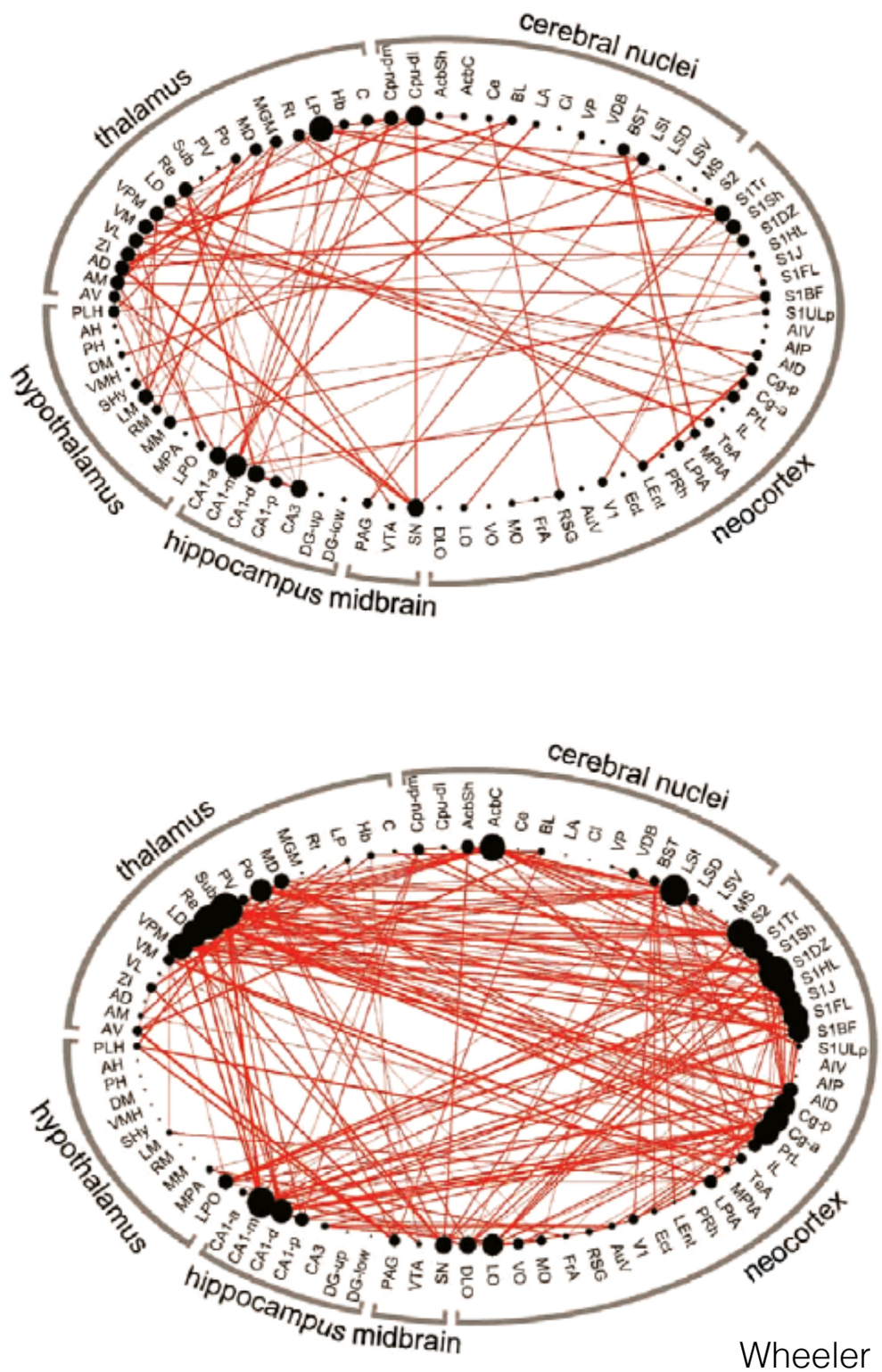
Differential change of c-fos expression between control and trained mice



Wheeler et al., 2013

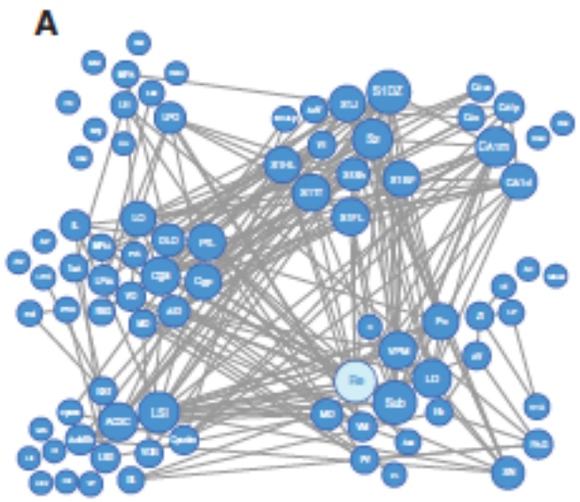
Correlation networks that underlie memory recall

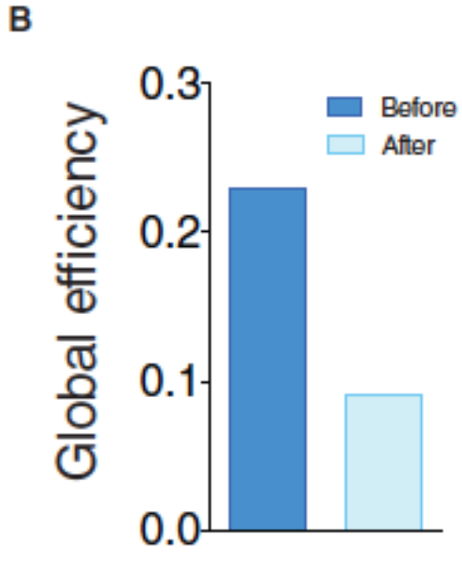




Wheeler et al., 2013

Effect of removing specific brain regions *in silico*

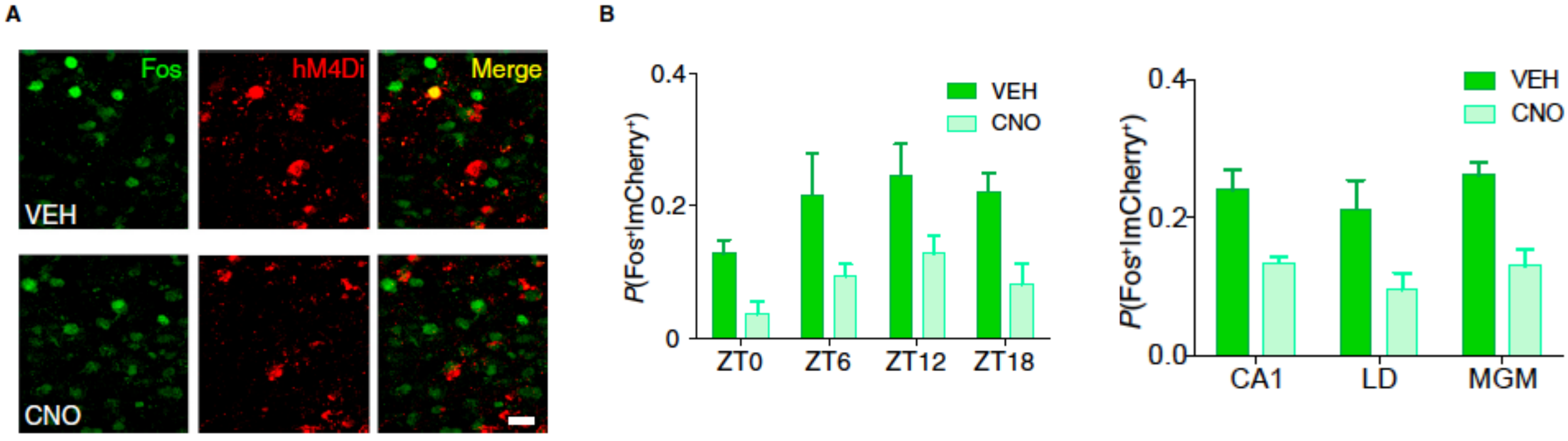


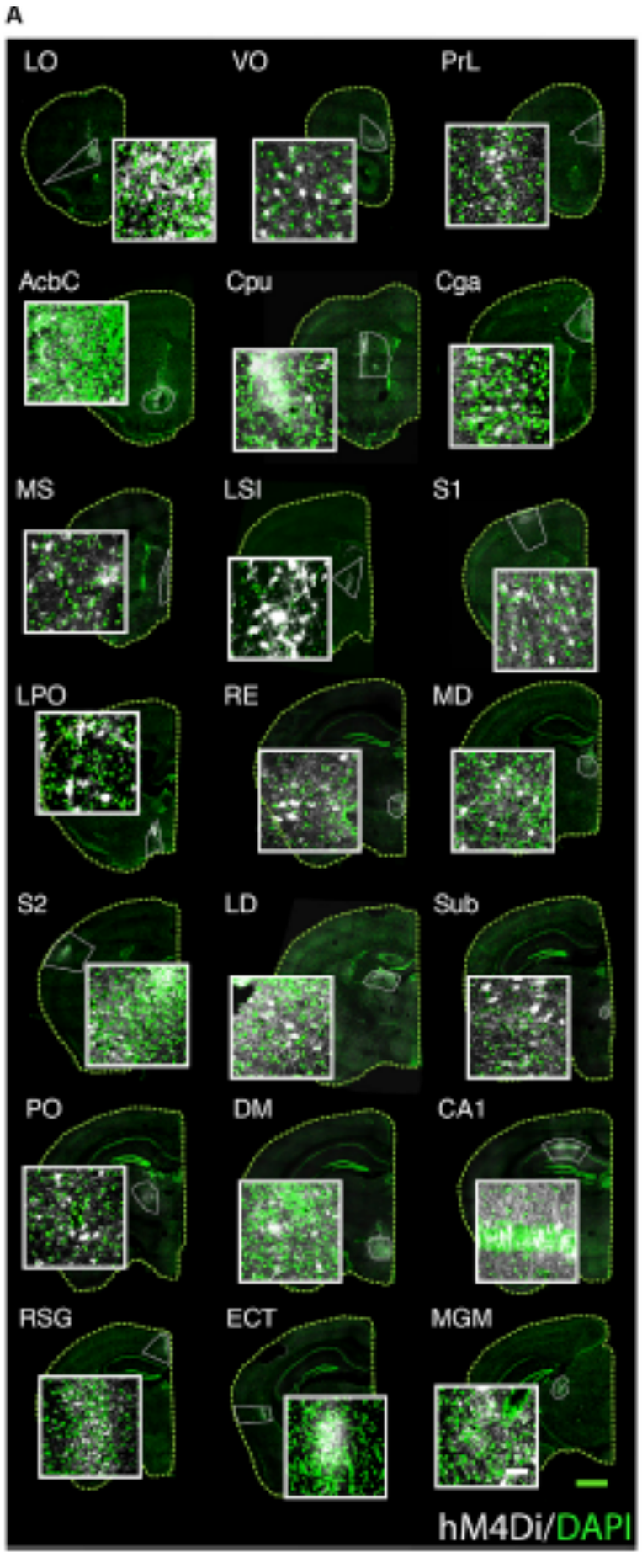


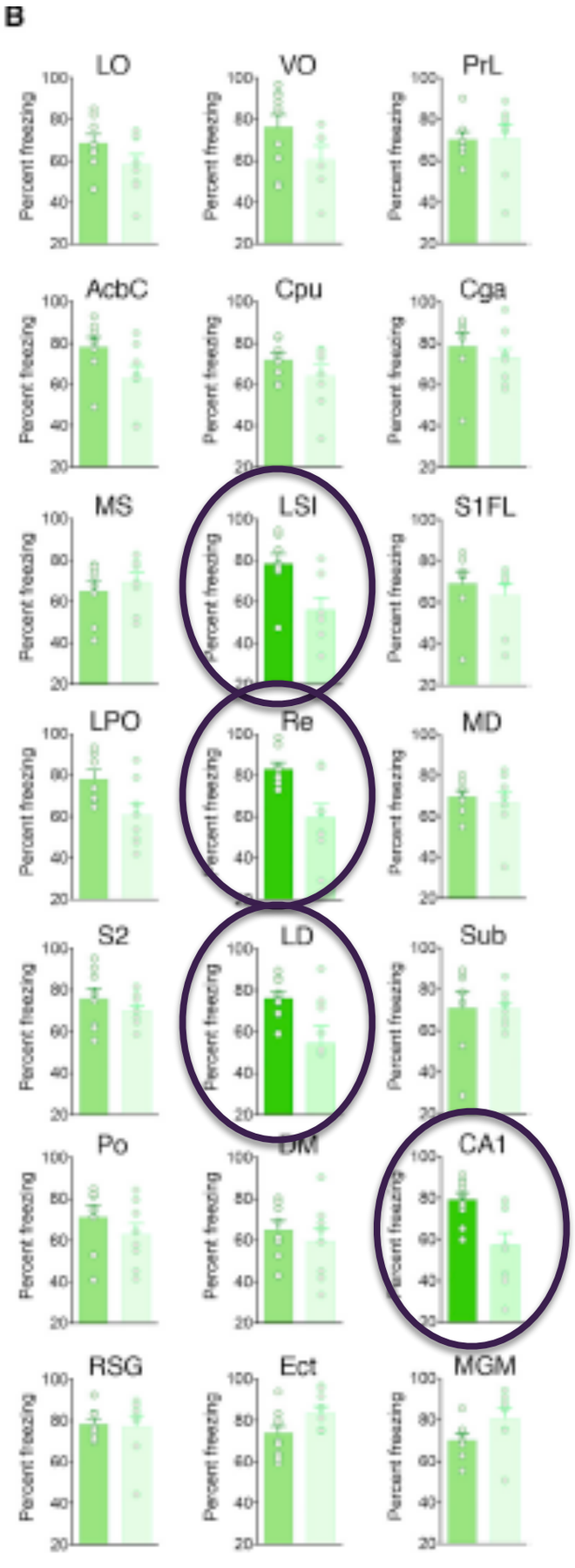
Chemogenetic inactivation of specific brain regions-hubs

express the following protein: hM4Di
use clozapine-N-oxide to activate the receptor

Anterior Cingulate







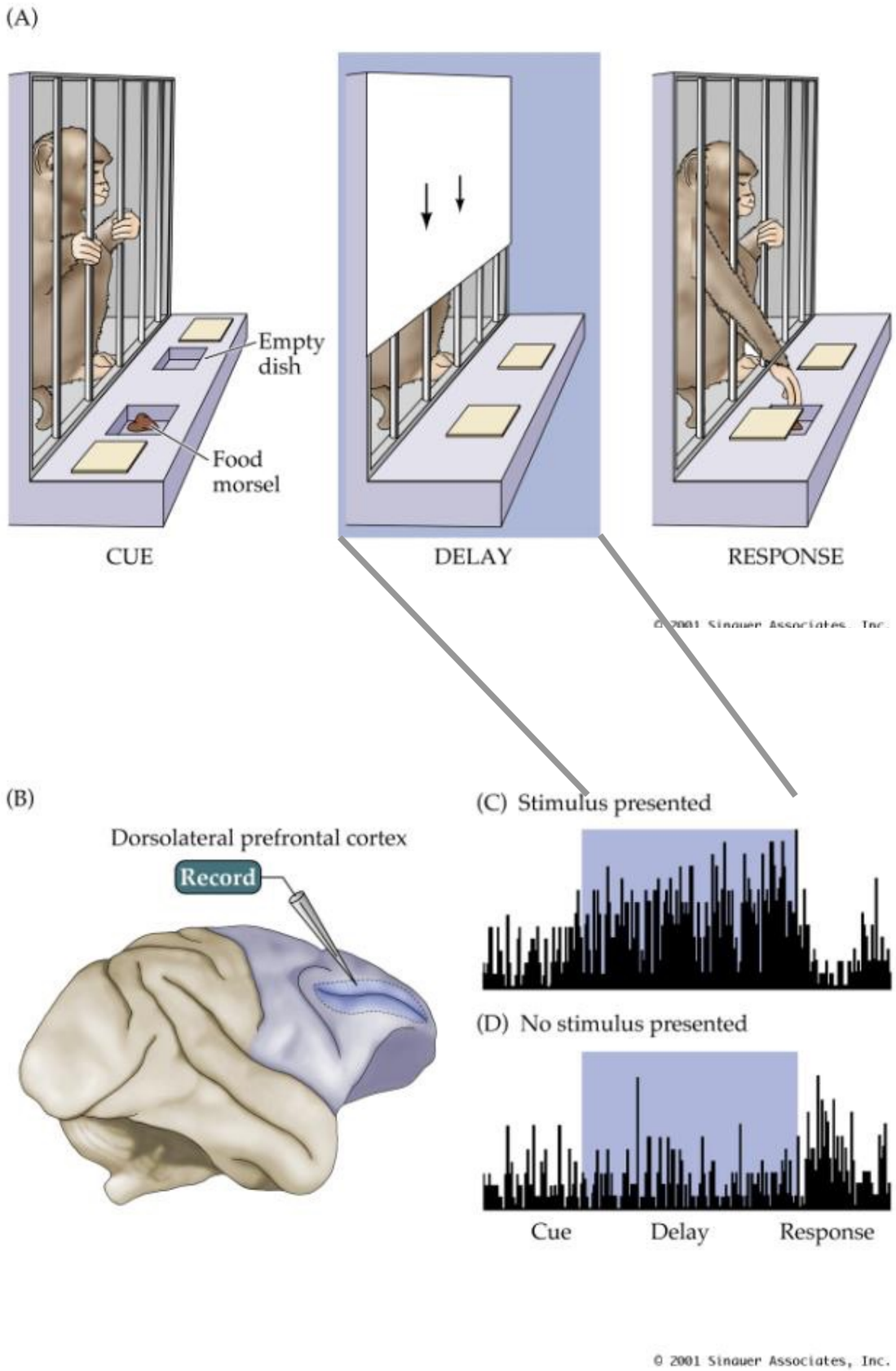
Chemogenetic inactivation of specific brain regions-hubs

LSI: lateral septal nucleus
Re: Nucleus reunions
LD:laterodorsal thalamic nucleus
CA1

Memory

- **Working memory**
- Short-term and long-term memory
    - Explicit memory
    - Implicit memory
        - Conditional
        - Non-conditional
        - Procedural

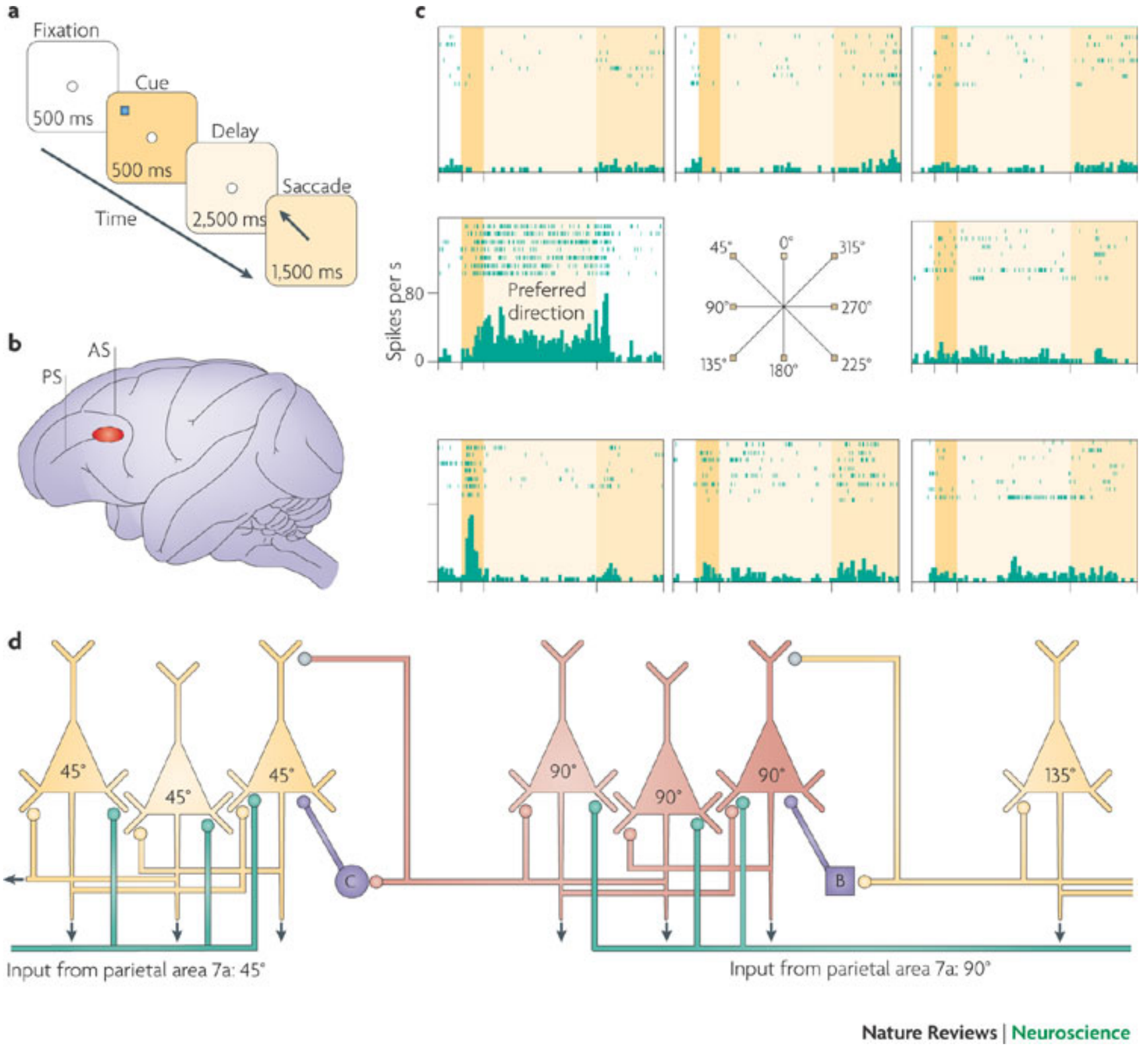
Electrophysiology and behavior



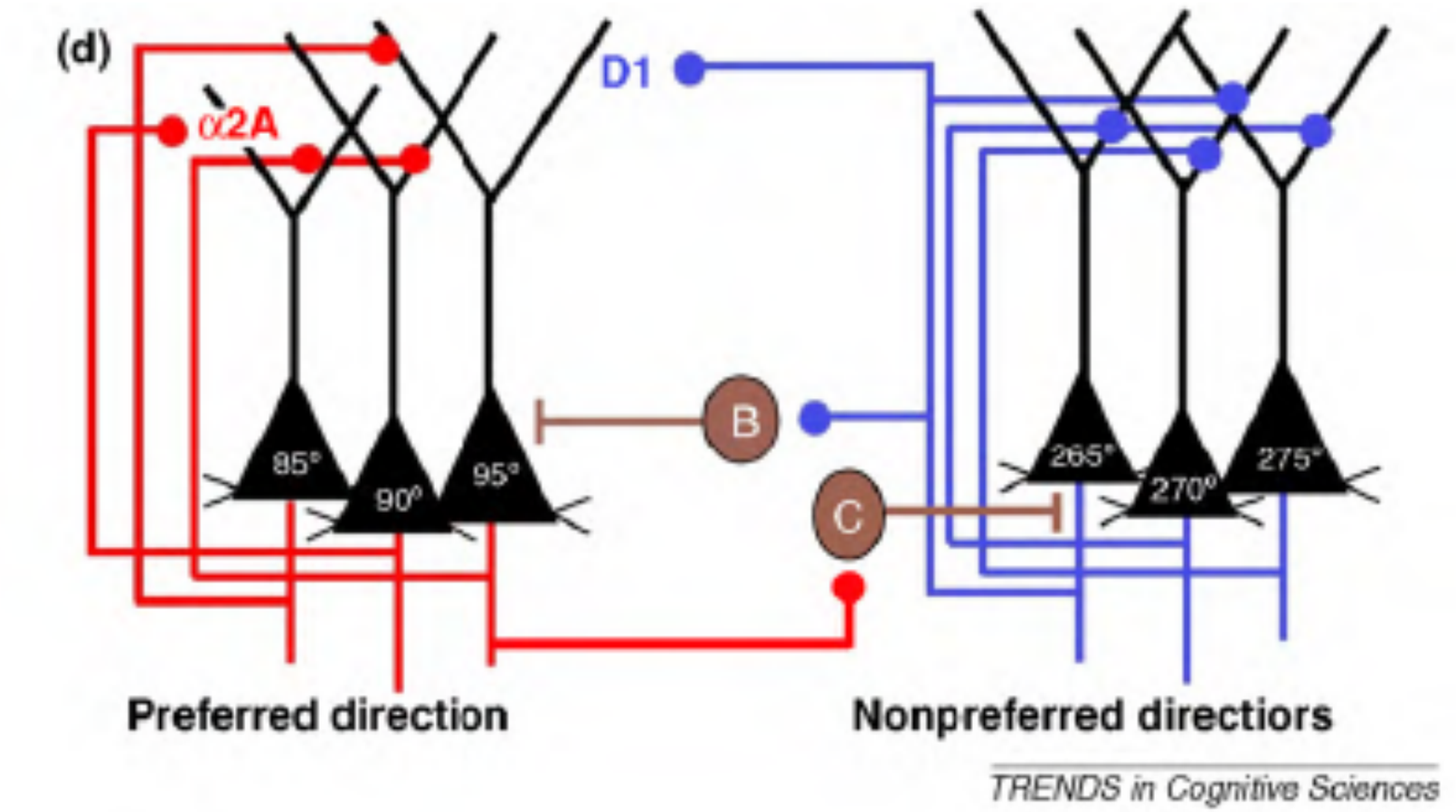
- Working memory
- Persistent activity

Goldman-Rakic, 1995, Neuron

Occulomotor delayed response task

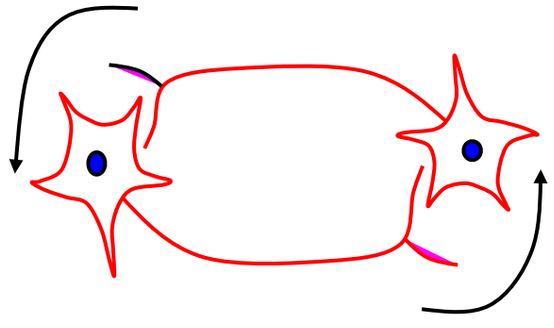


Hypothetical model of underlying circuit in the PFC



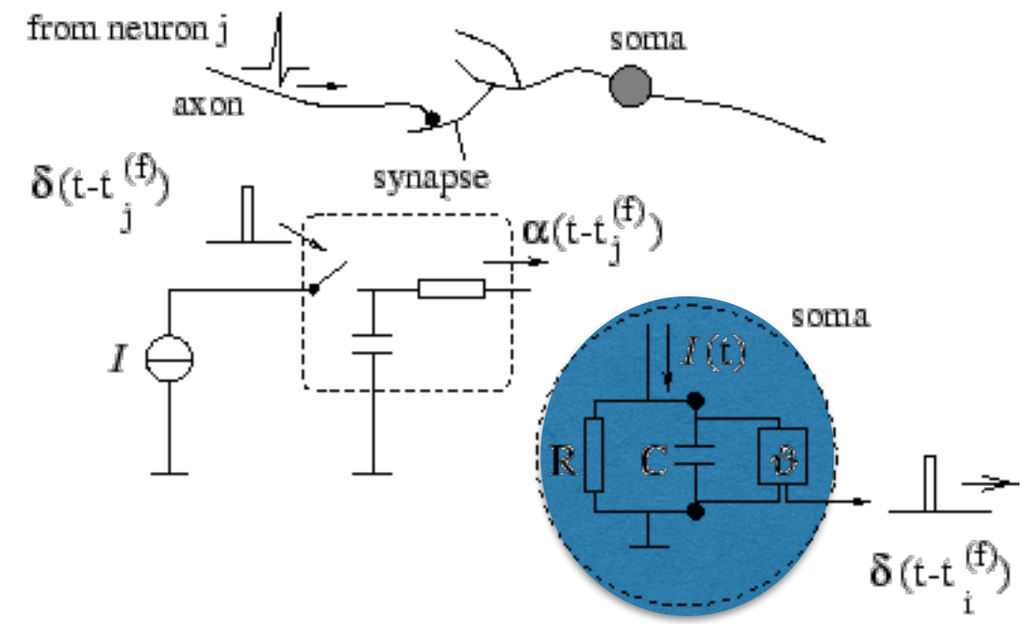
Mechanisms of persistent activity

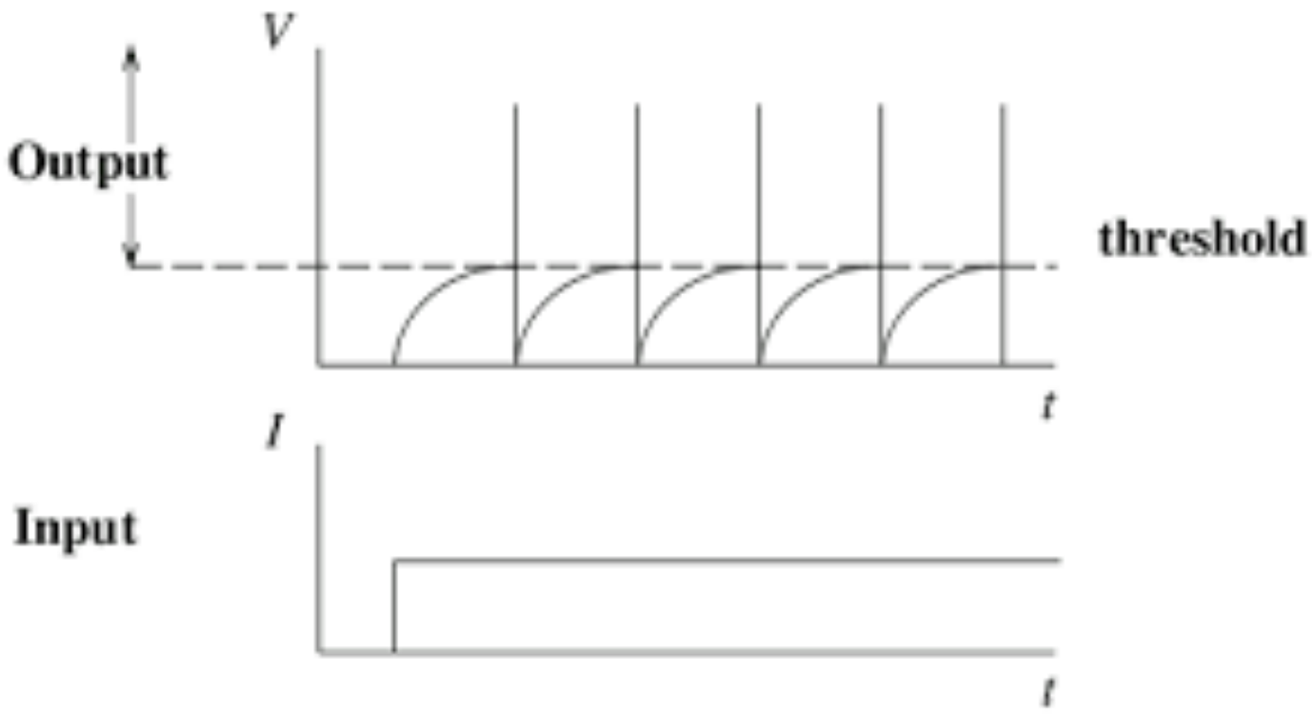
- Recurrent networks
  - PFC has about 50% of neurons that are reciprocally connected (Wang et al, 2003, Nat Neuro)
- NMDA receptors
  - No decrease in NR2B subunits with age in PFC
- GABA receptors
- Ionic currents



Neuron models used to study persistent activity

- Integrate and fire neurons





Compartmental models

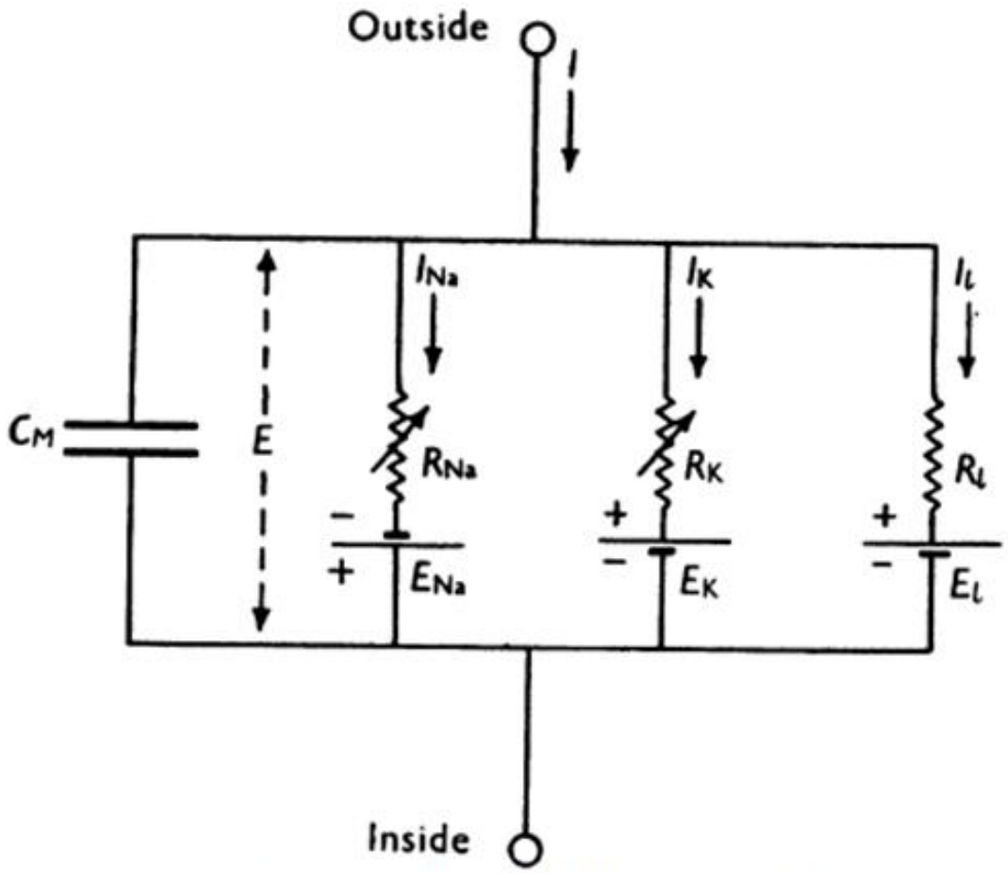
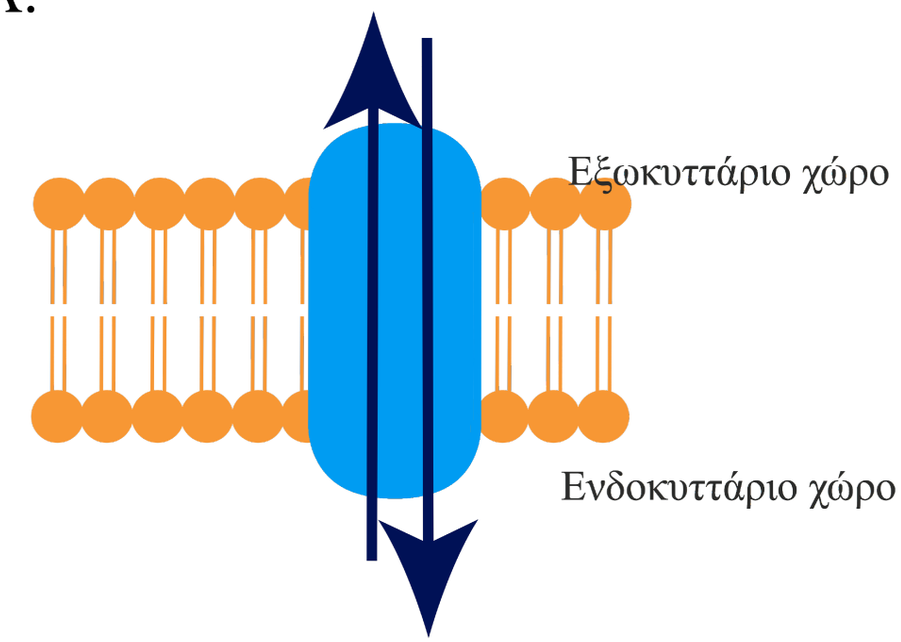
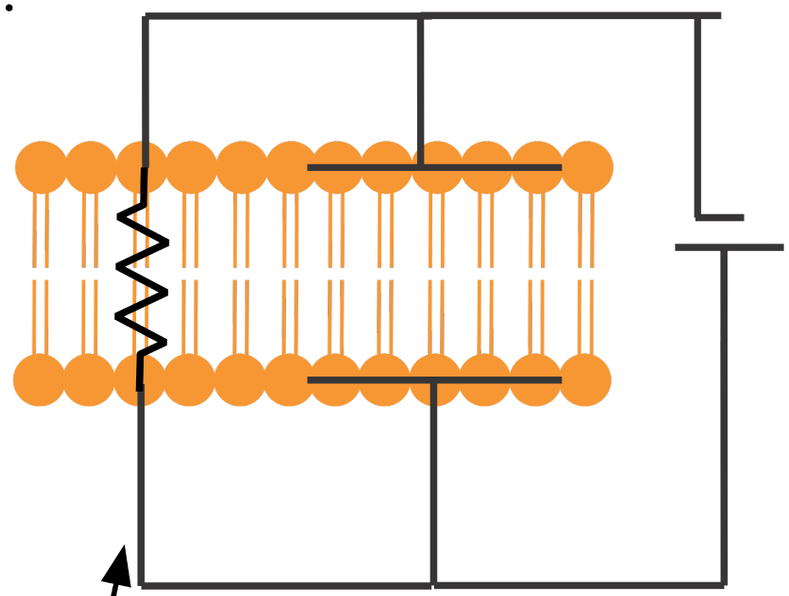


Figure 1: Circuit Model of an Axon [1]

A.

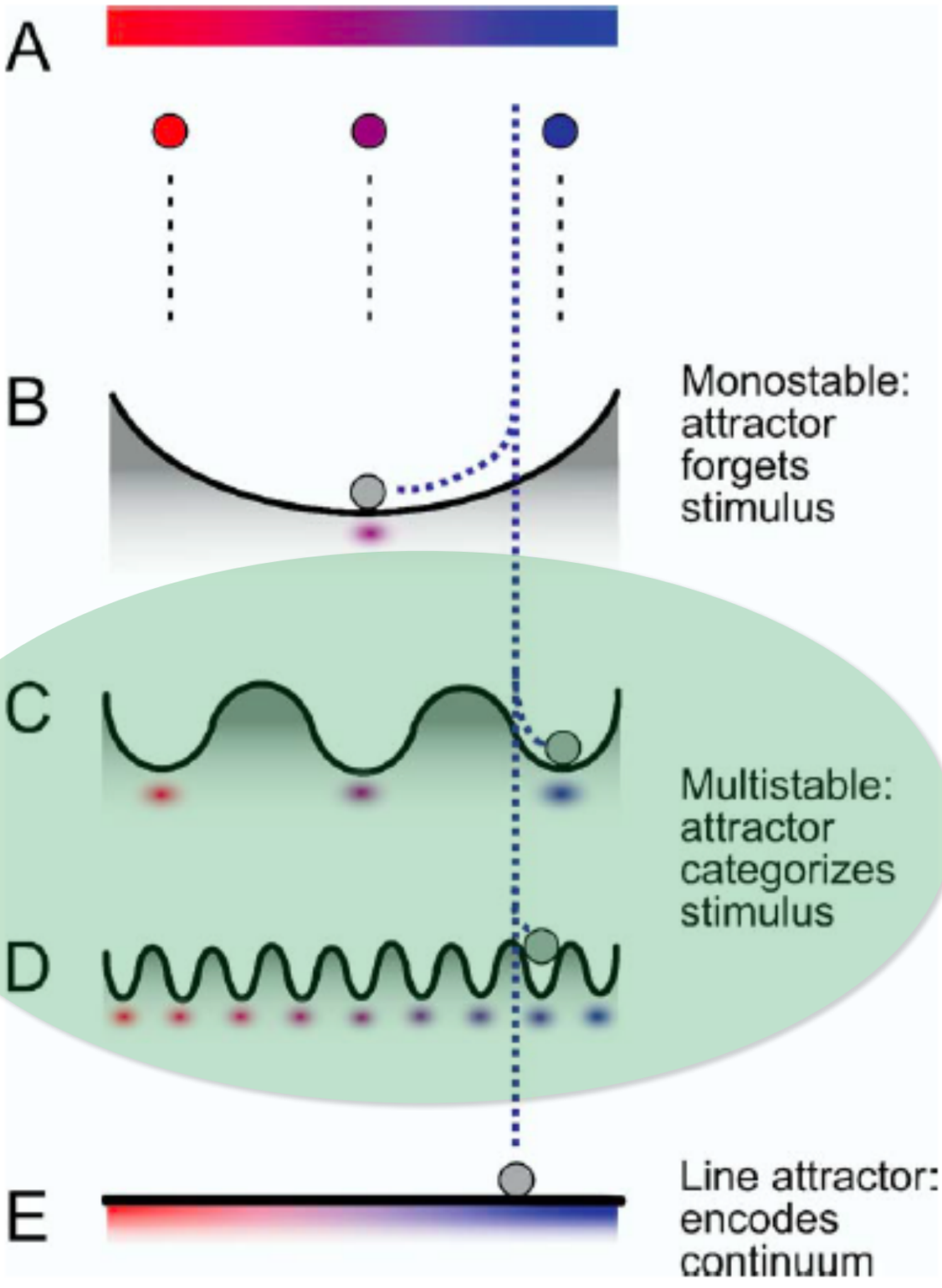


B.

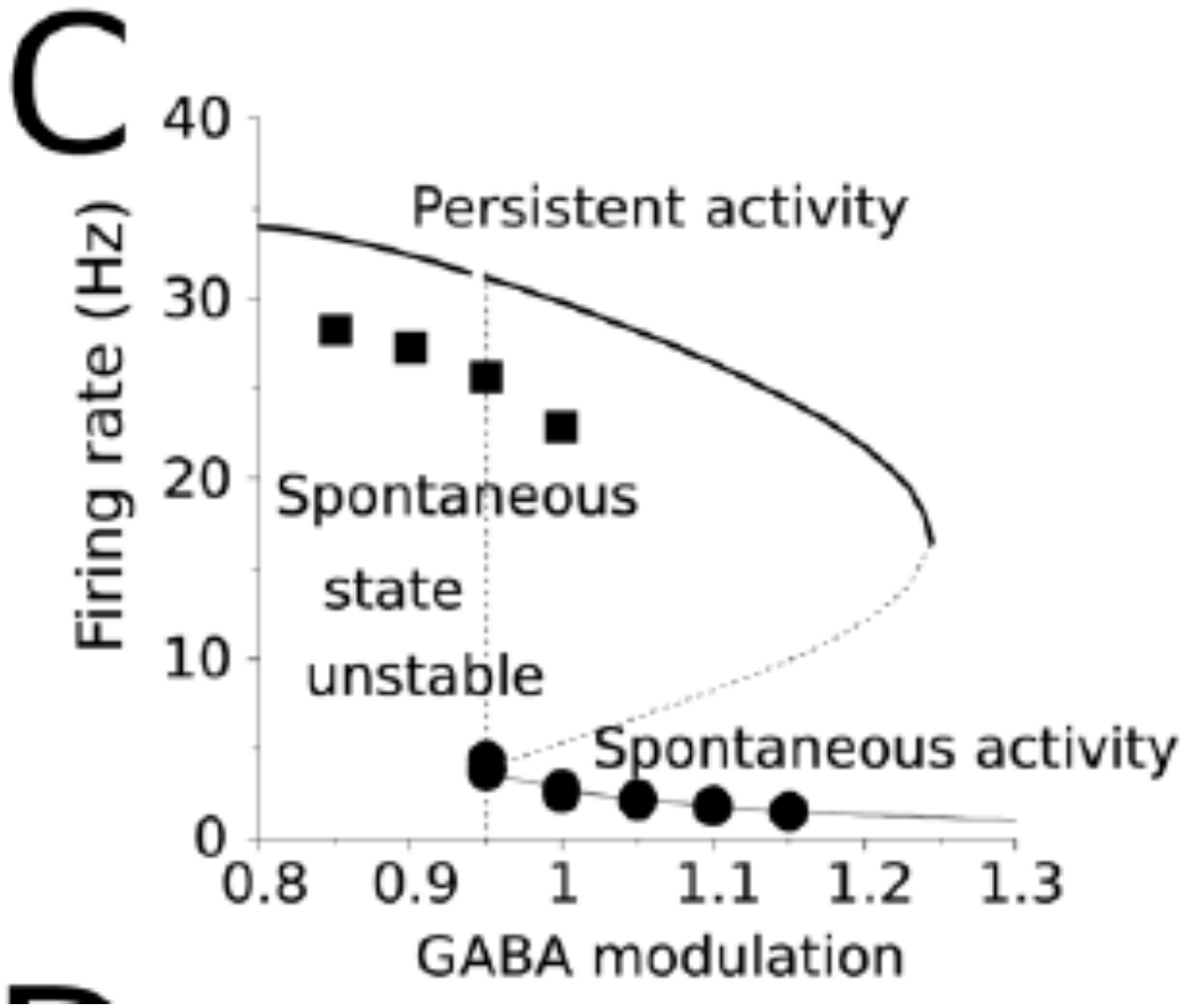


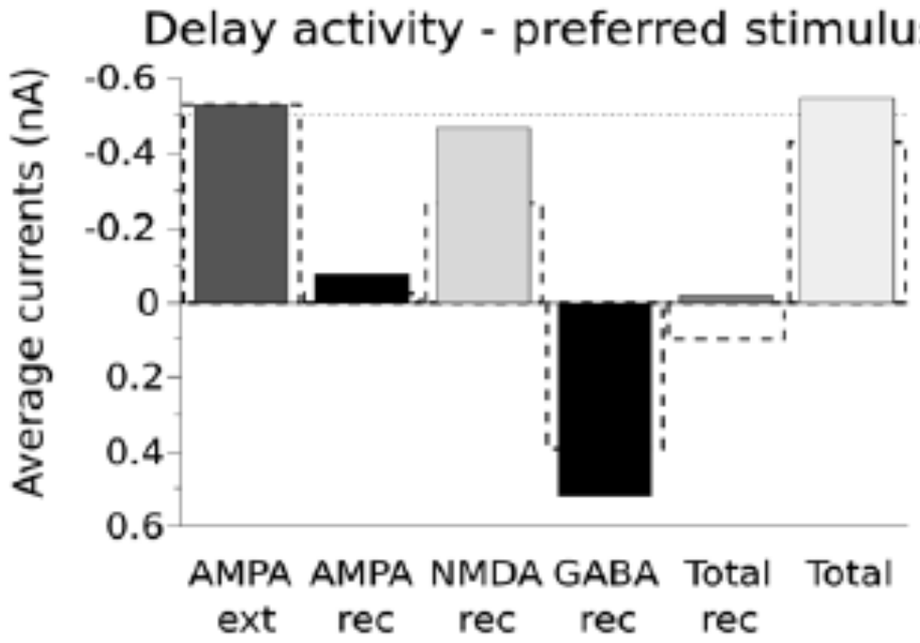
αντίσταση
(δίαυλοι διαρροής
ή και άλλοι
ιοντικοί δίαυλοι)

Attractor networks to model working memory

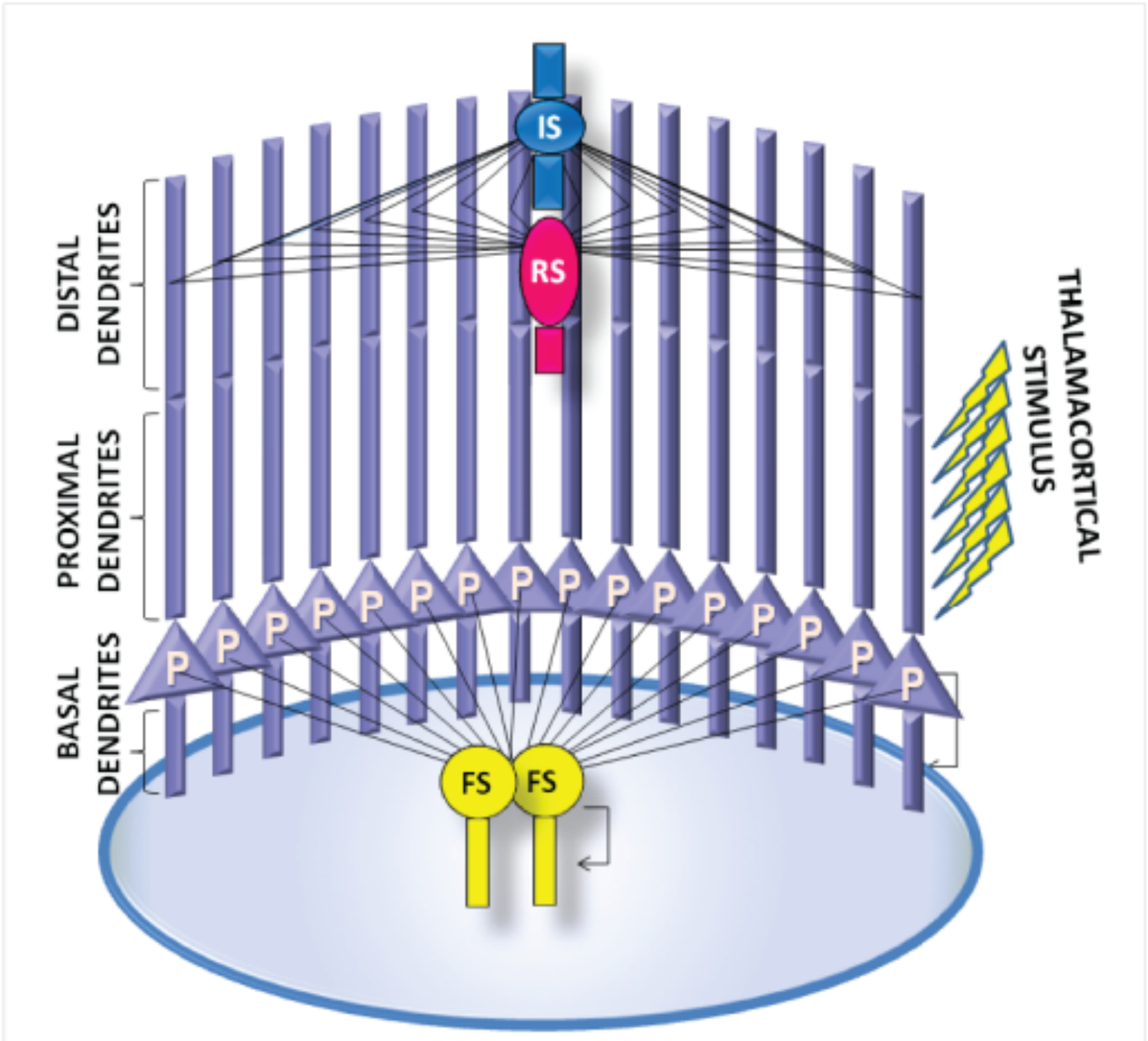


Attractors

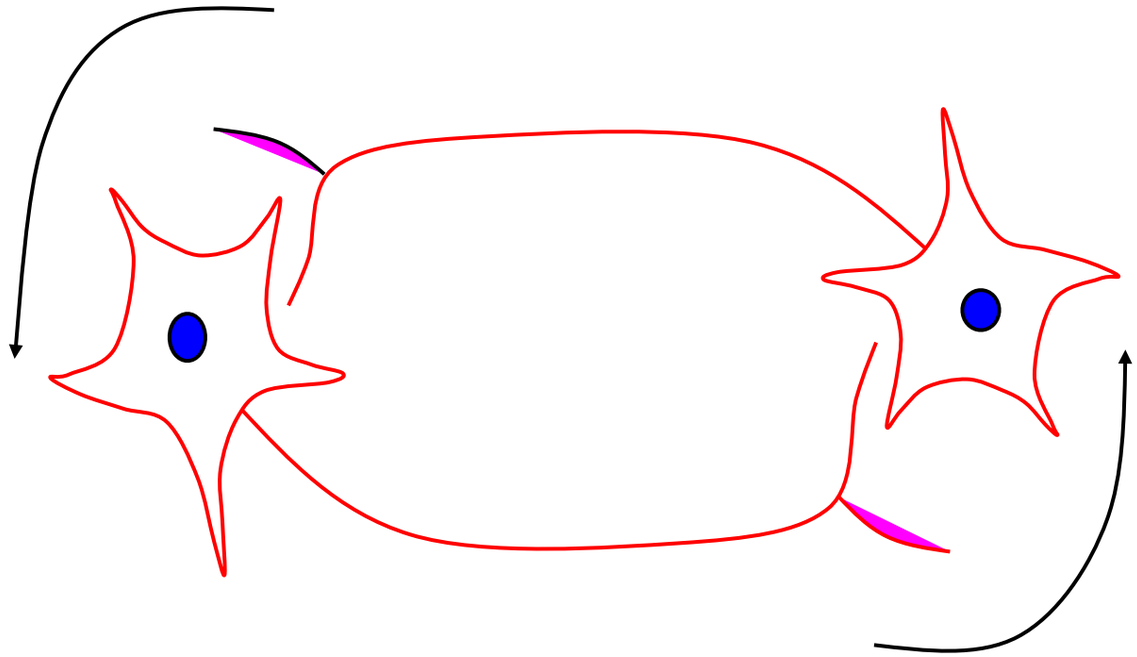

C
40
30
20
10
0
Firing rate (Hz)
Persistent activity
Spontaneous
state
unstable
Spontaneous activity
0.8
0.9
1
1.1
1.2
1.3
GABA modulation


Delay activity - preferred stimulus
Average currents (nA)
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
AMPA ext
AMPA rec
NMDA rec
GABA rec
Total rec
Total

Networks of compartmental models

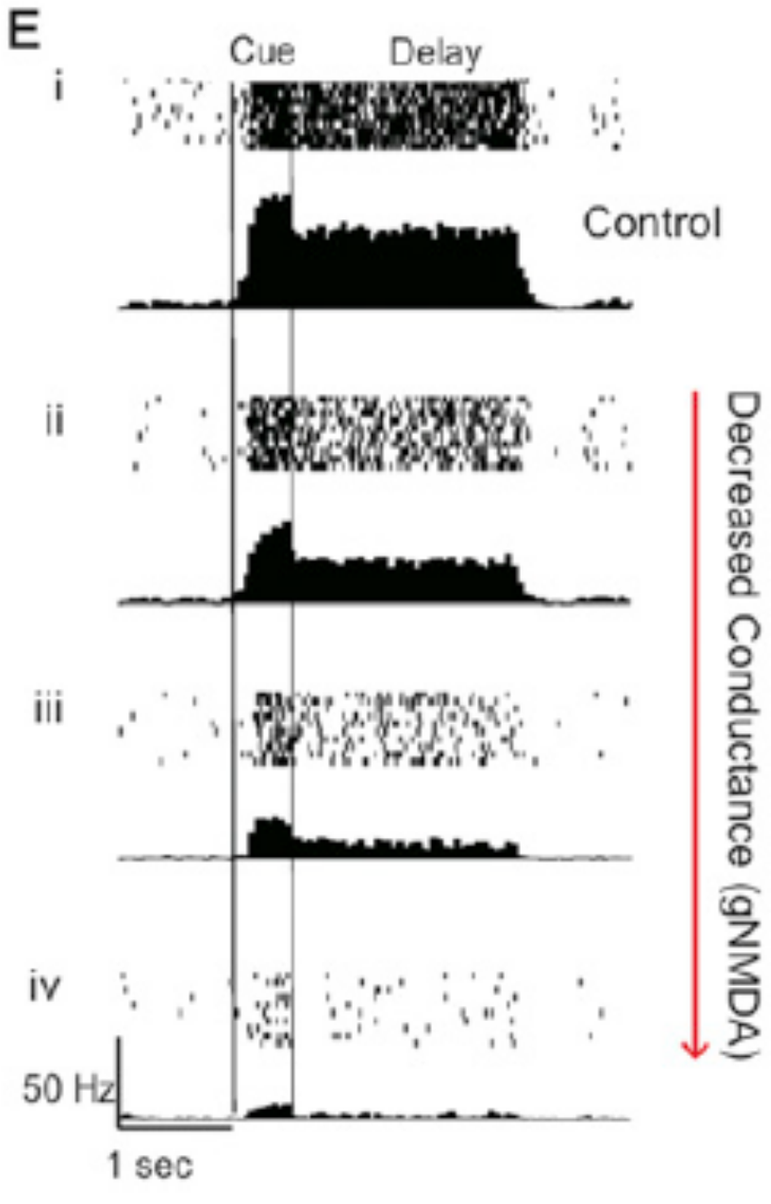


NMDA receptors in recurrent networks

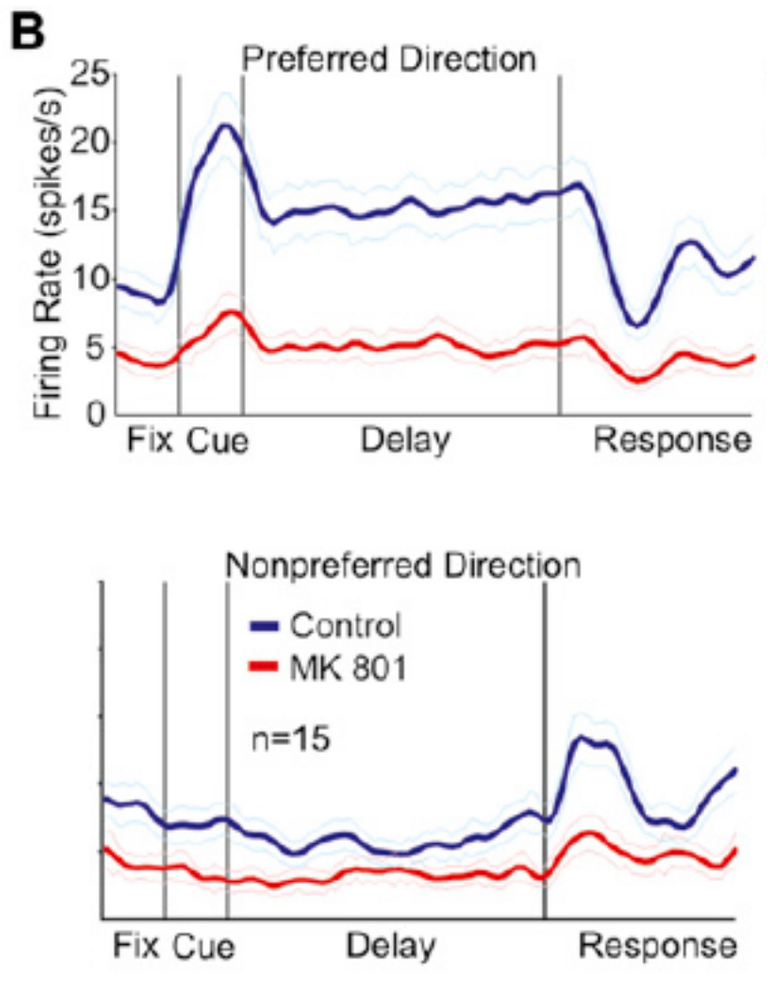


Effects of NMDA currents on persistent activity

Computational modeling



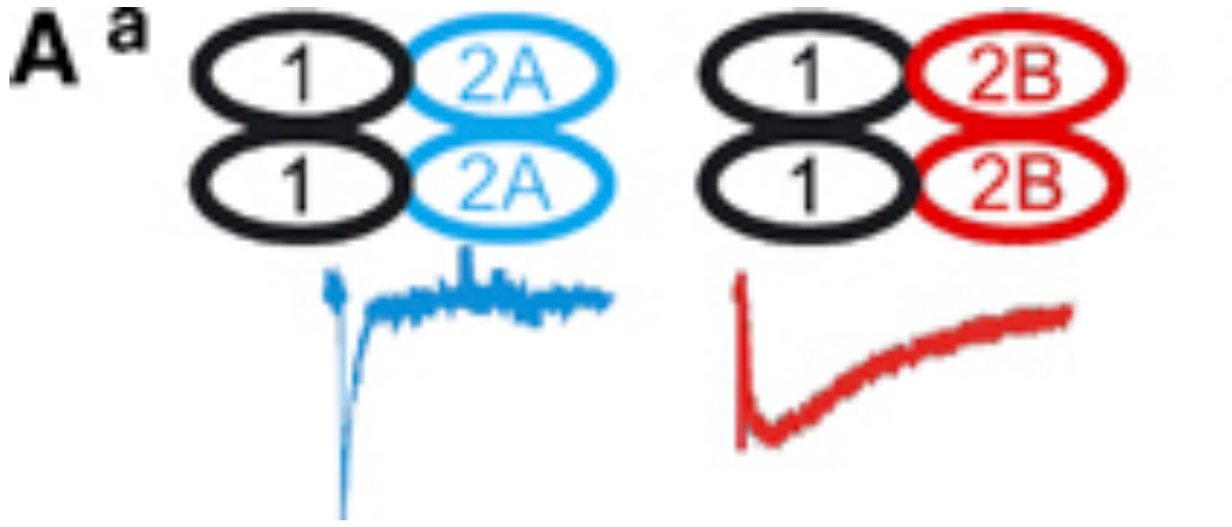
In vivo during ODR



Wang et al, 2013, Neuron

NMDA receptor subtypes

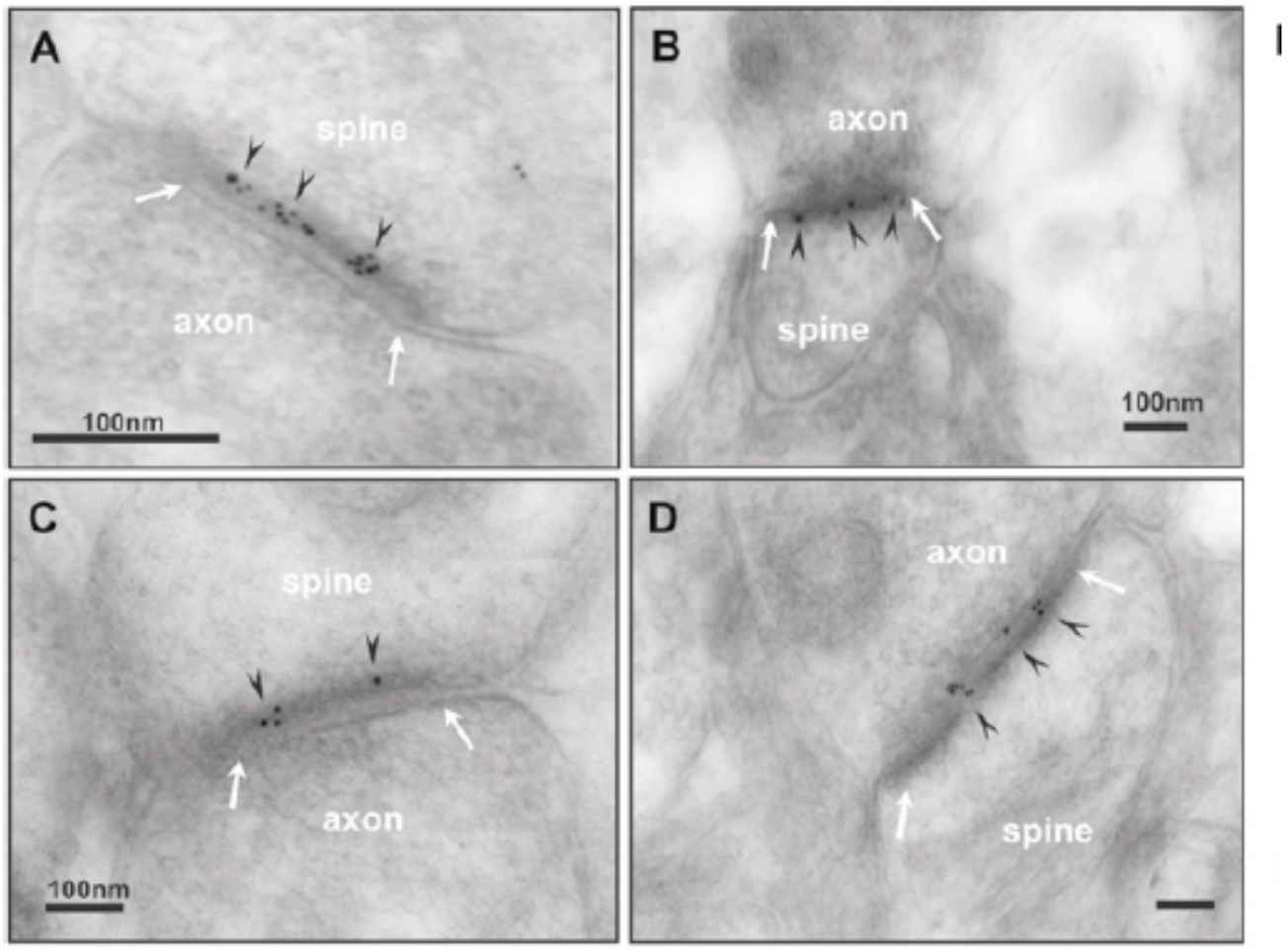
NR2A NR2B



increased conductance decreased conductance

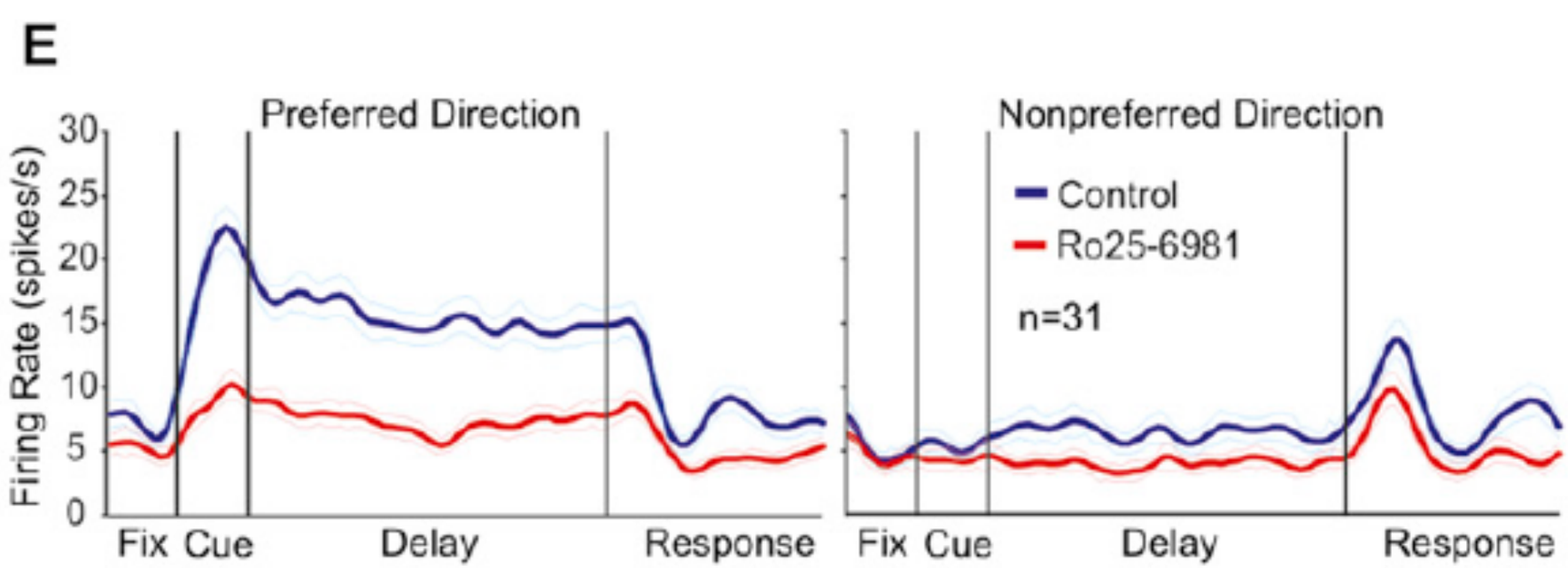
faster kinetics slower kinetics

NR2B localization in the synapses



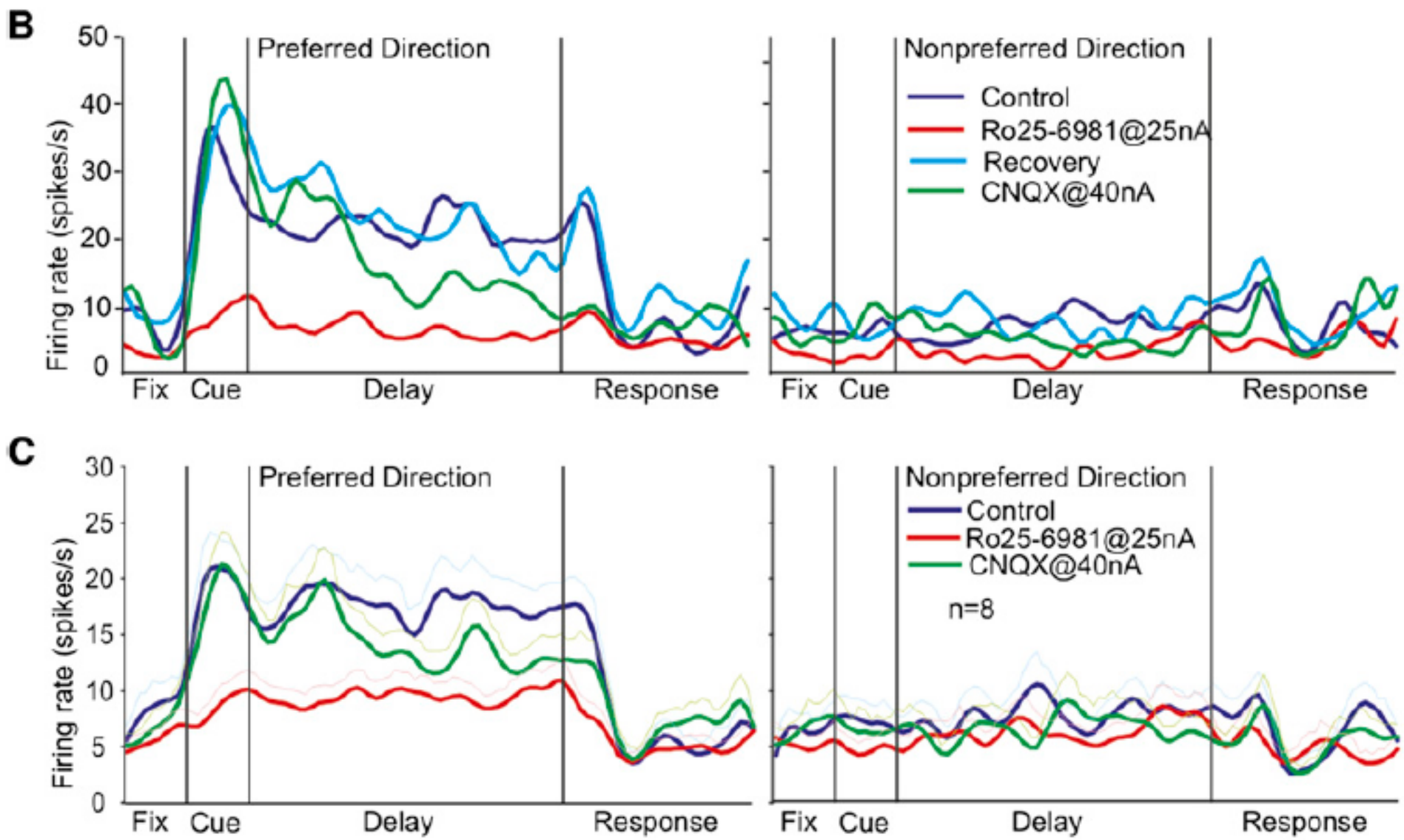
Wang et al, 2013, Neuron

Effect of NR2B specific blockers on delay-period activity



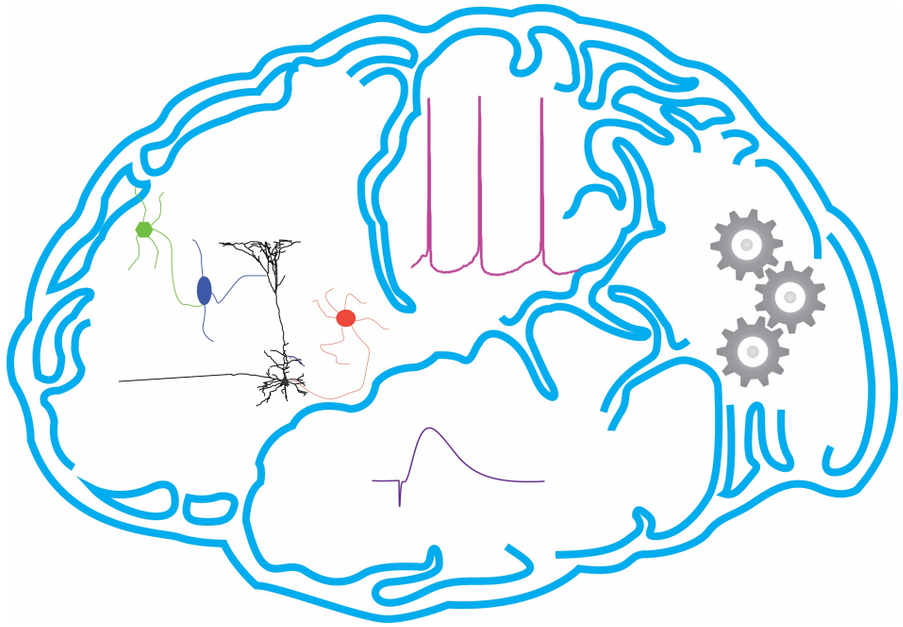
Wang et al, 2013, Neuron

Effect of AMPA blockers on delay-period activity



Wang et al, 2013, Neuron

Βασικές αρχές λειτουργίας του νευρικού συστήματος, Κυριακή Σιδηροπούλου
http://repository.kallipos.gr/handle/11419/4828



Bibliography

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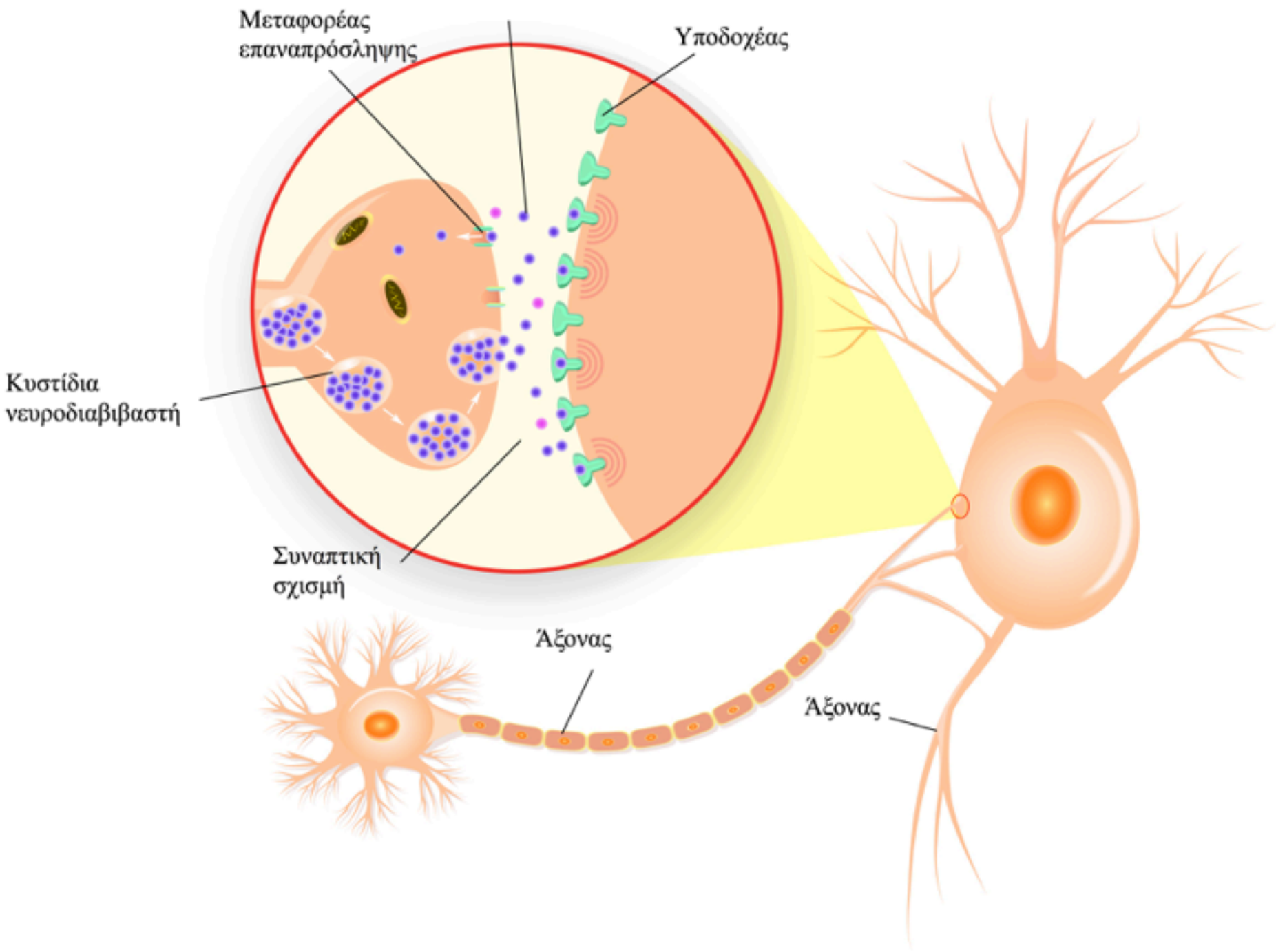
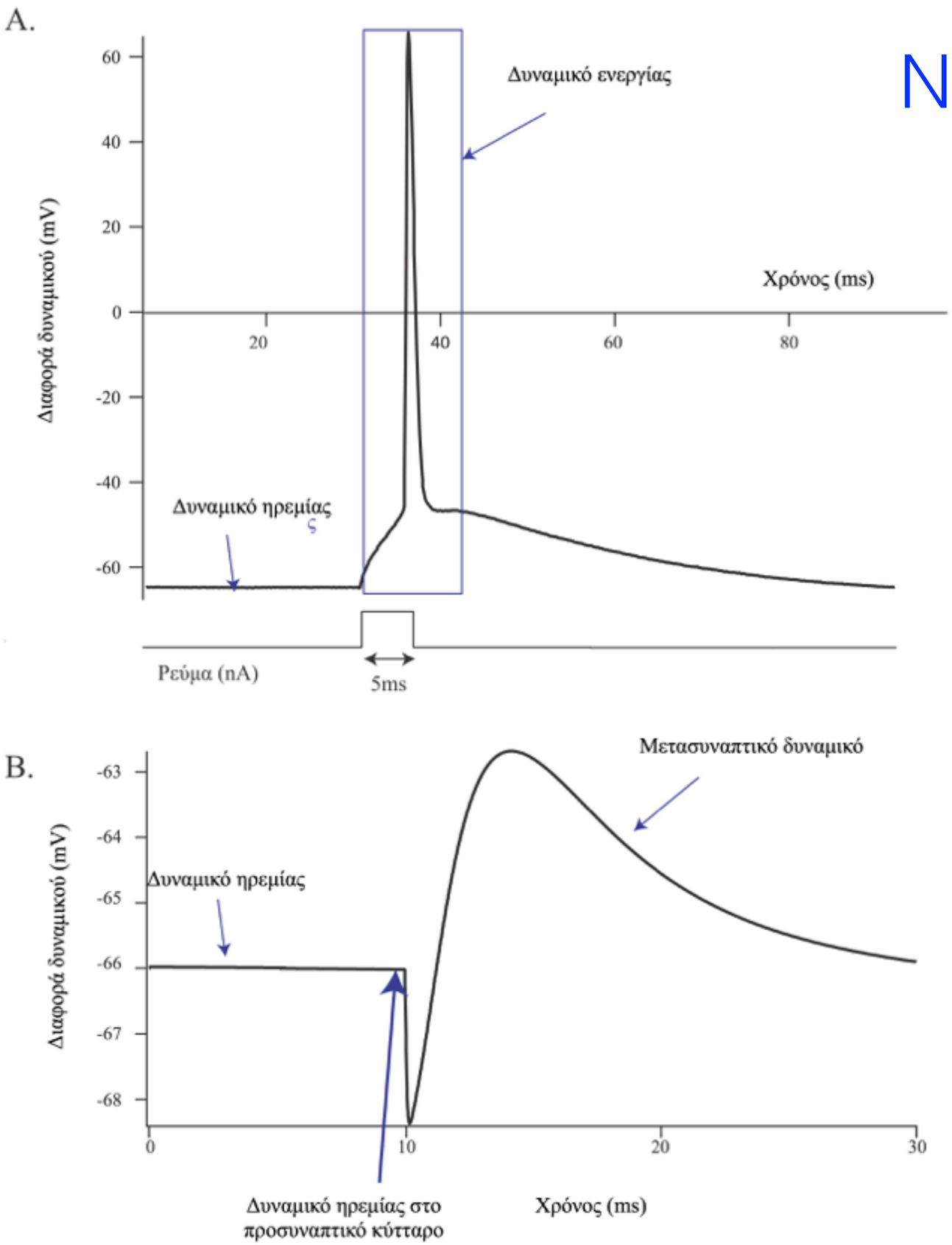
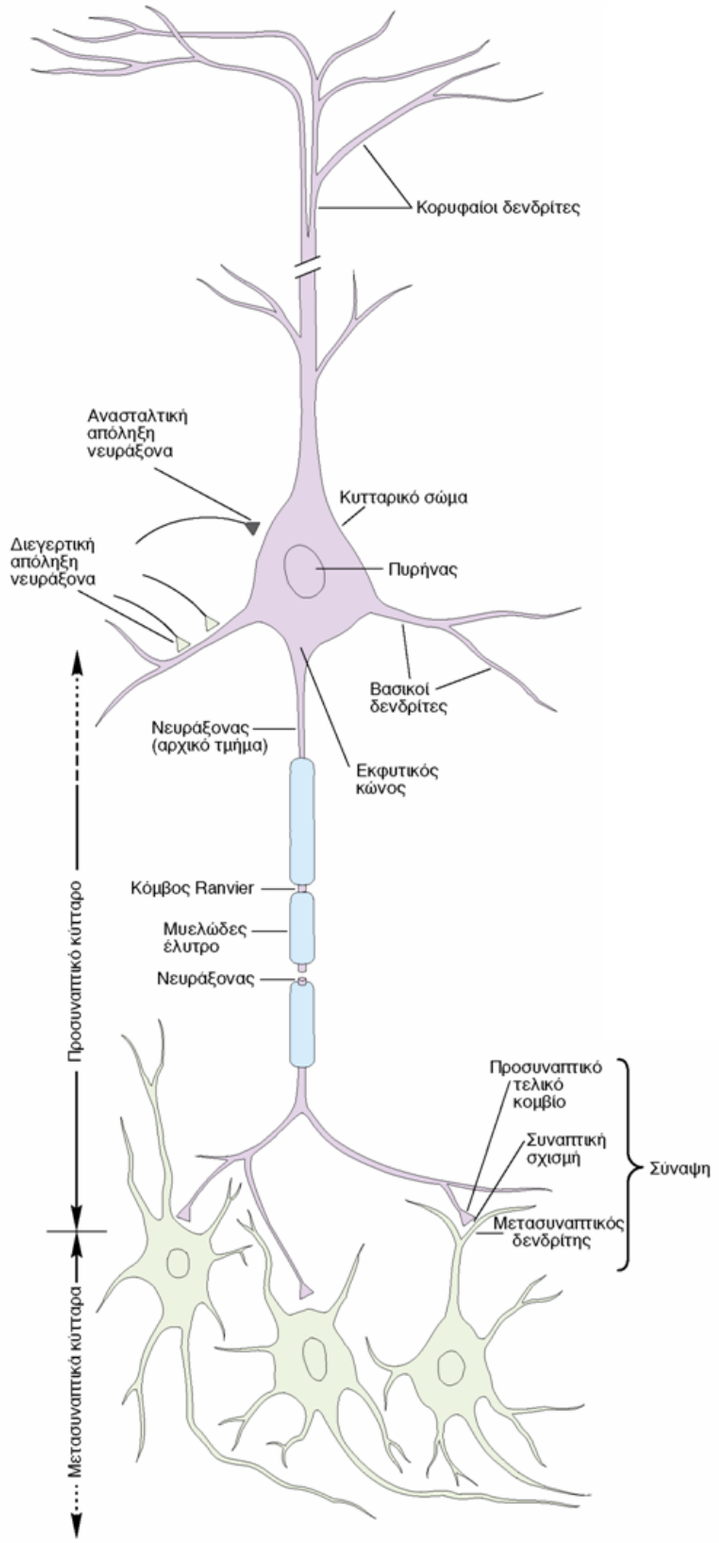
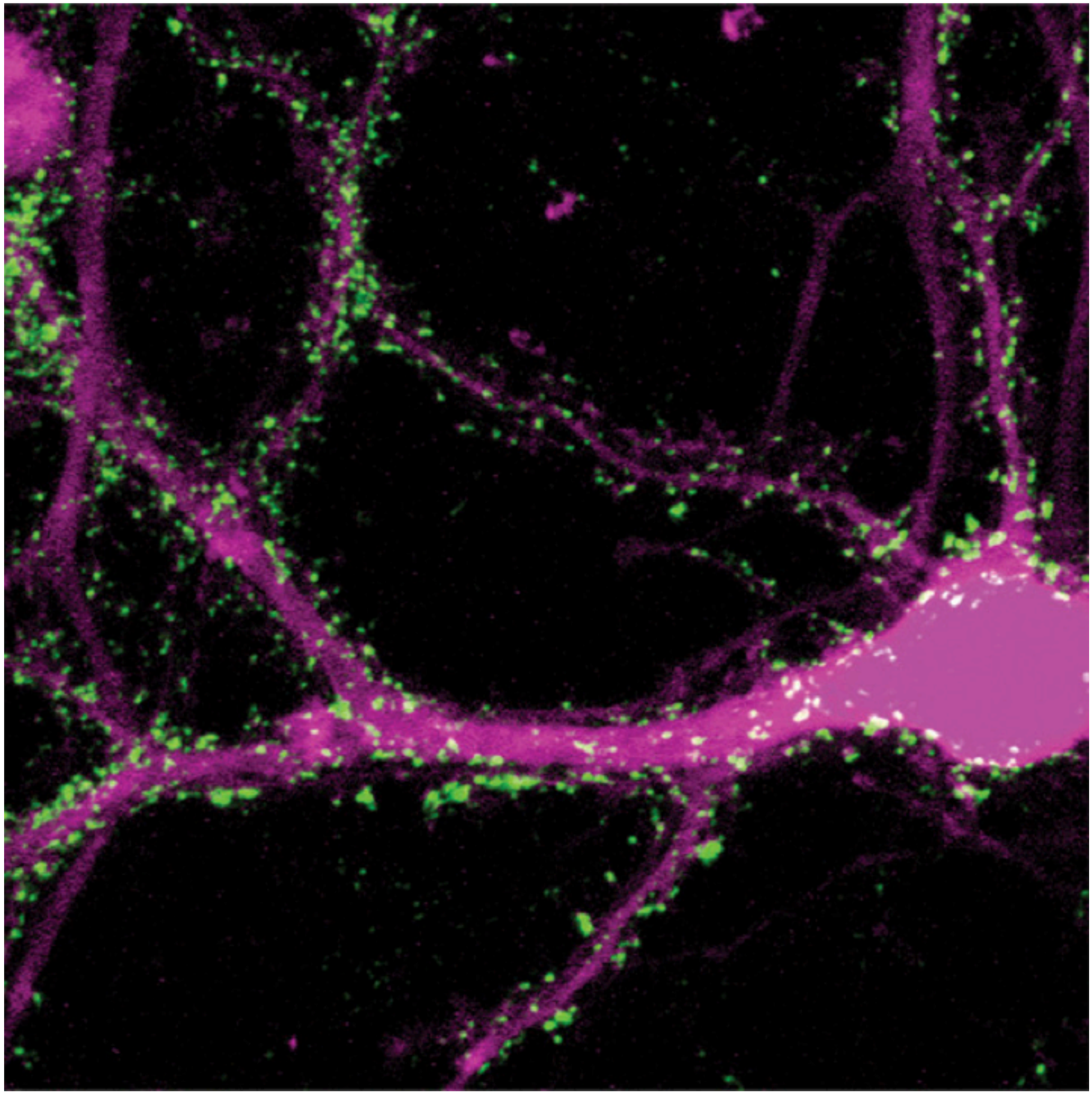
Neurons communicate with each other to form networks through synapses



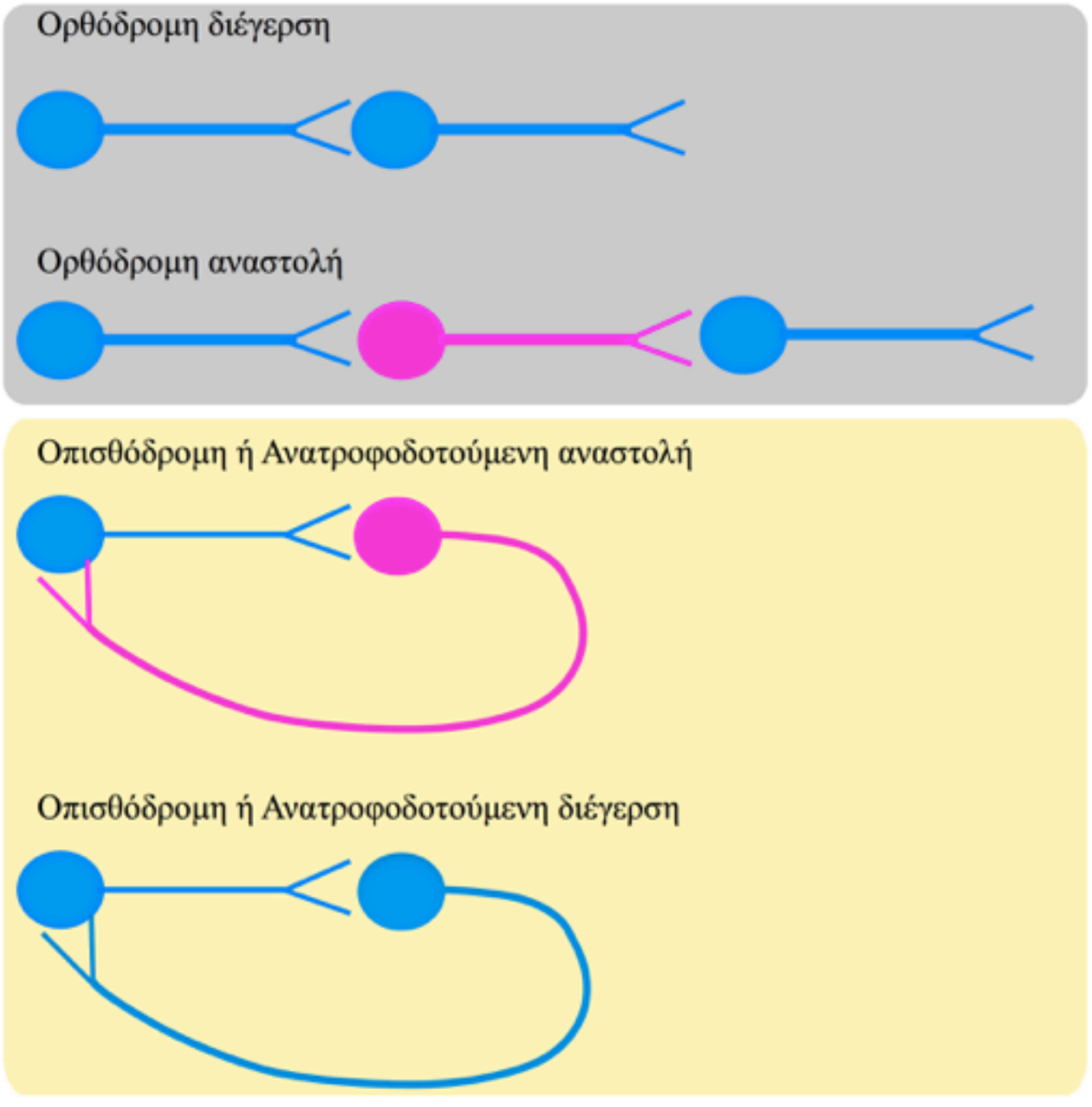
Neurons communicate with electrical signals

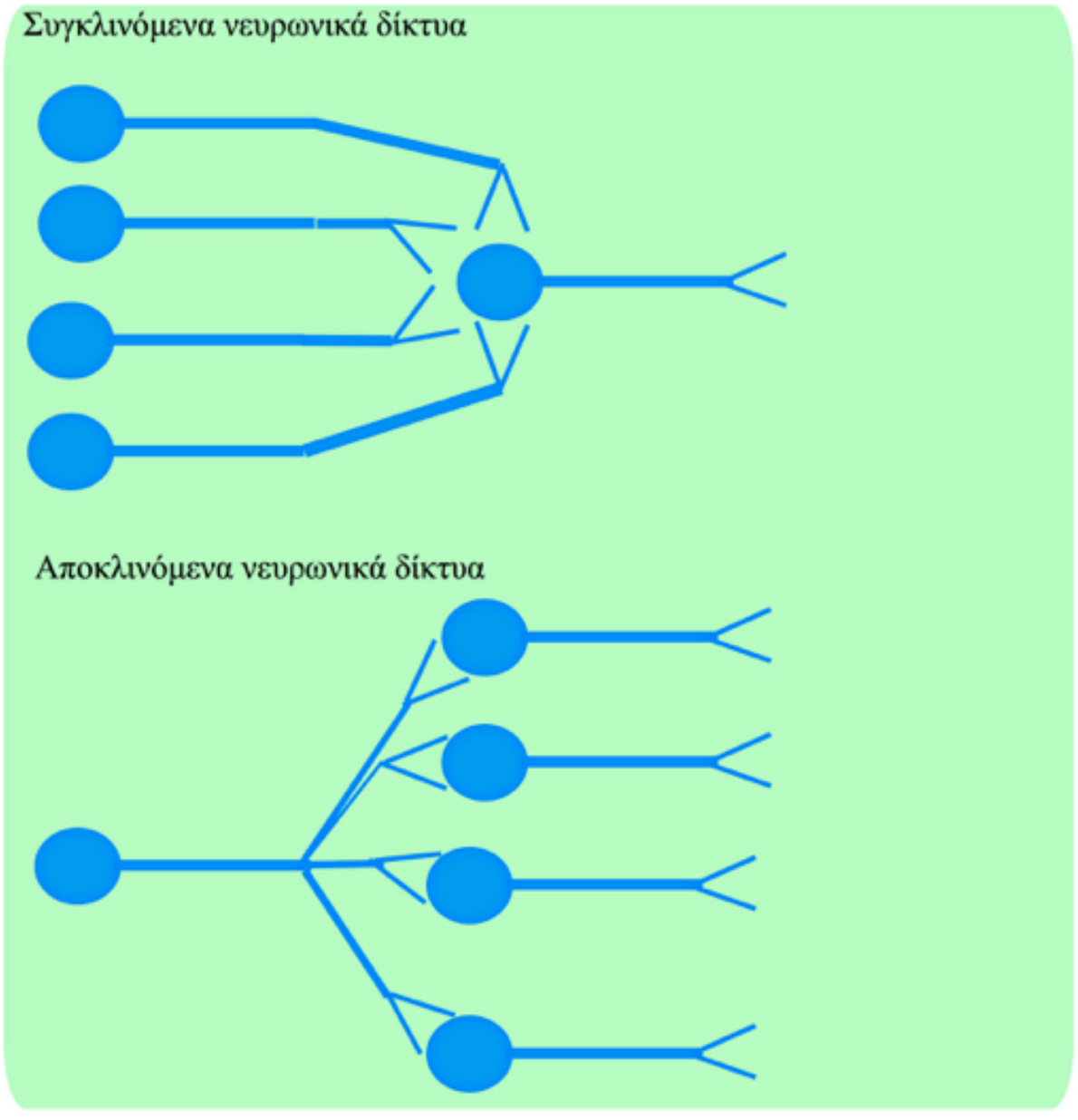




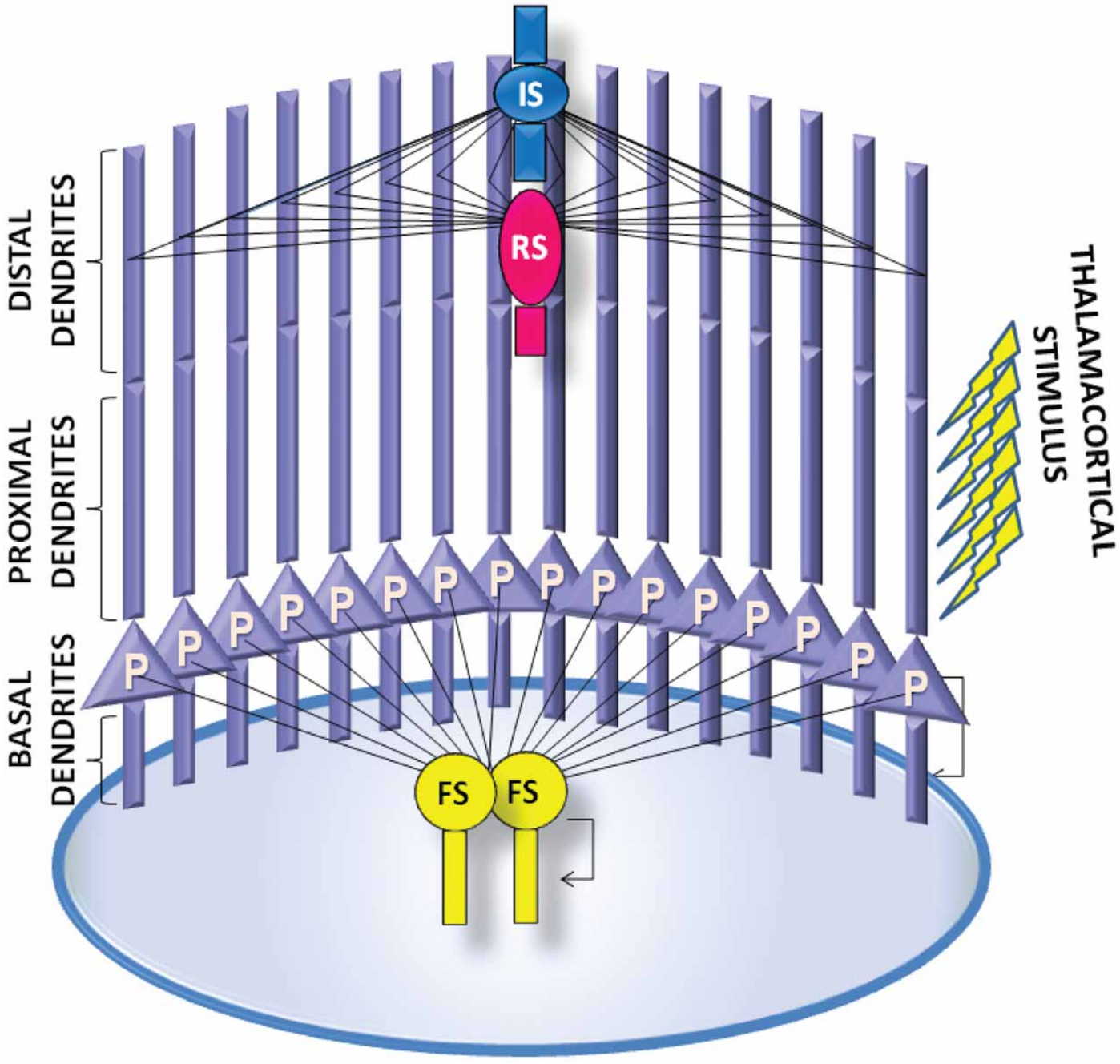


Neuronal networks in the brain





Recurrent excitation and inhibition



Konstantoudaki et al, 2014, Frontiers in Neural Circuits

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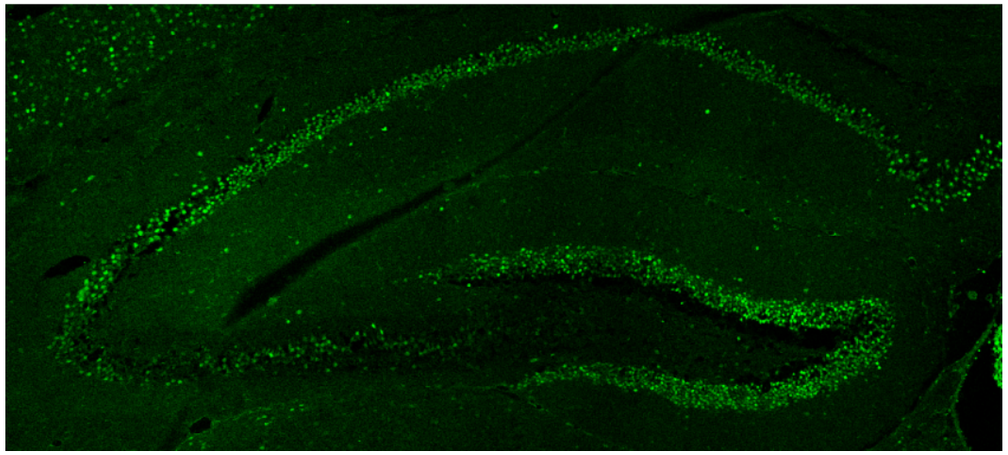
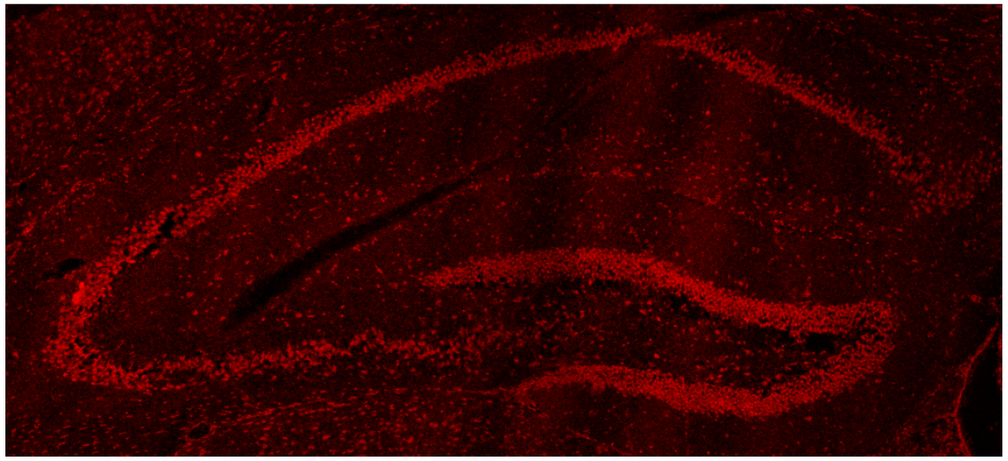
Cellular and molecular techniques

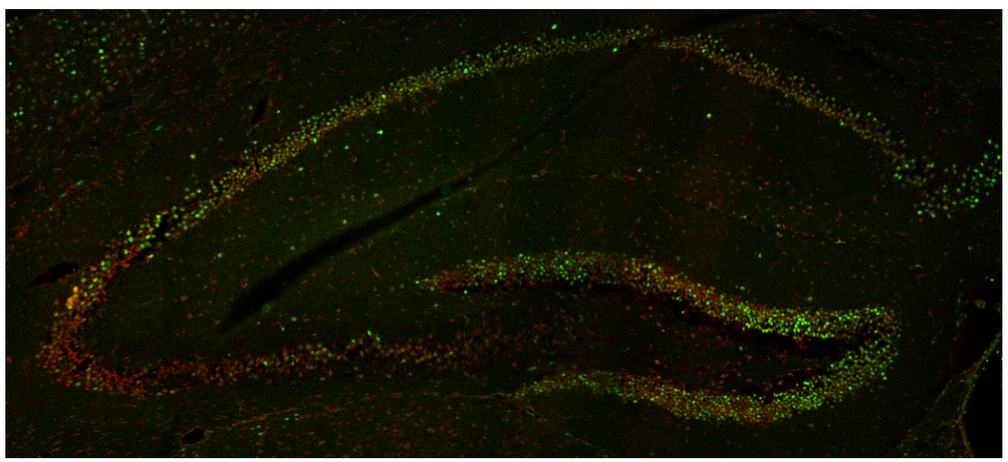
- Immediate early genes - Activity markers
  - Arc
  - c-fos
  - c-jun
  - Genes that are transcribed and translated in response to neuronal activity

c-fos activation following epileptic seizures

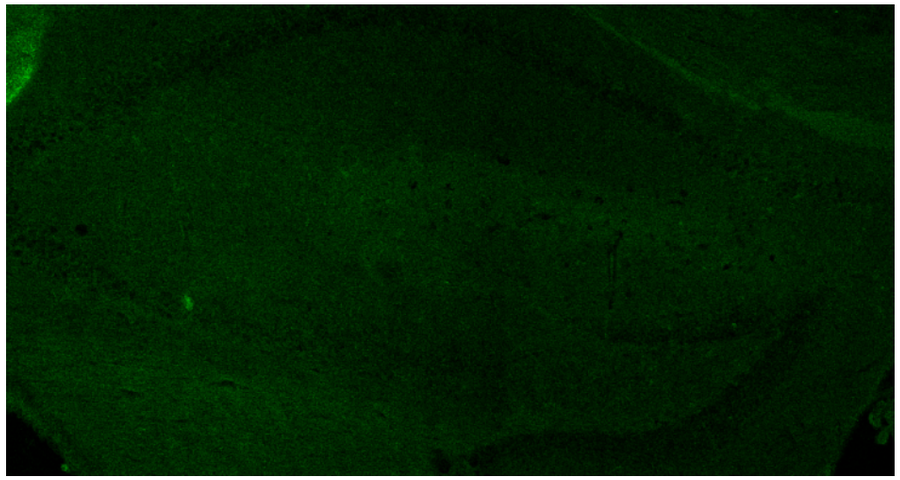
WT mouse, 300mg/kg pilocarpine

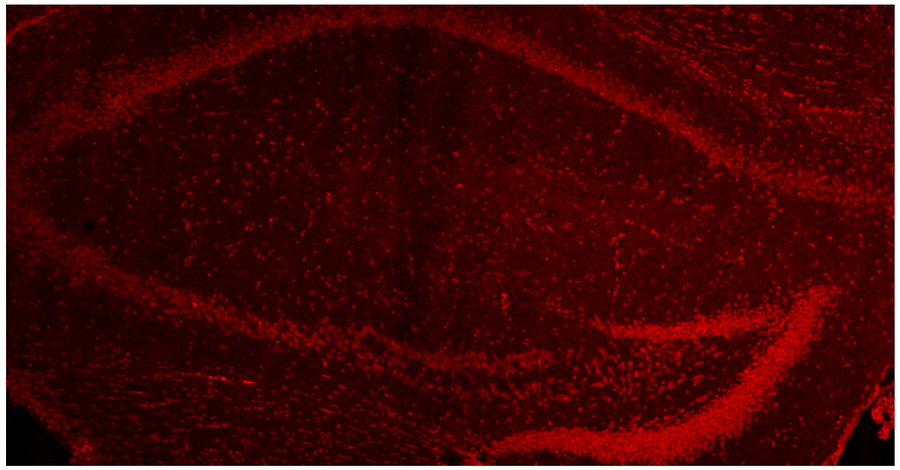


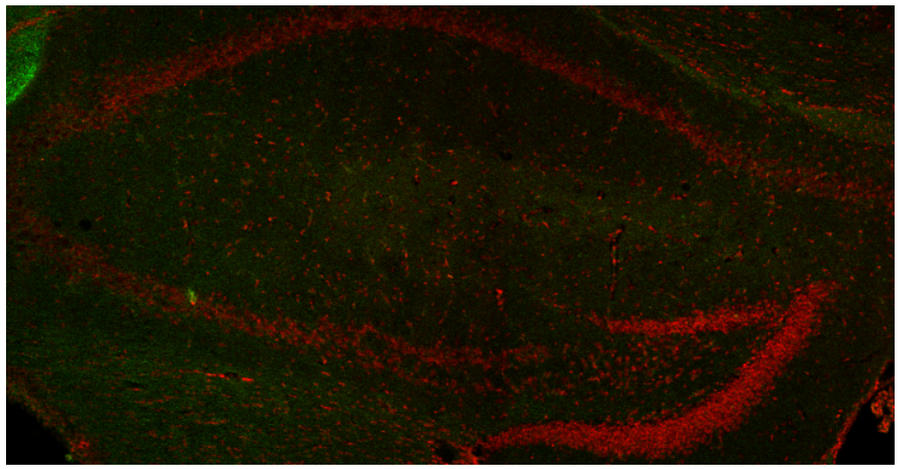




Rac1 conditional KO mouse
100mg/kg pilocarpine







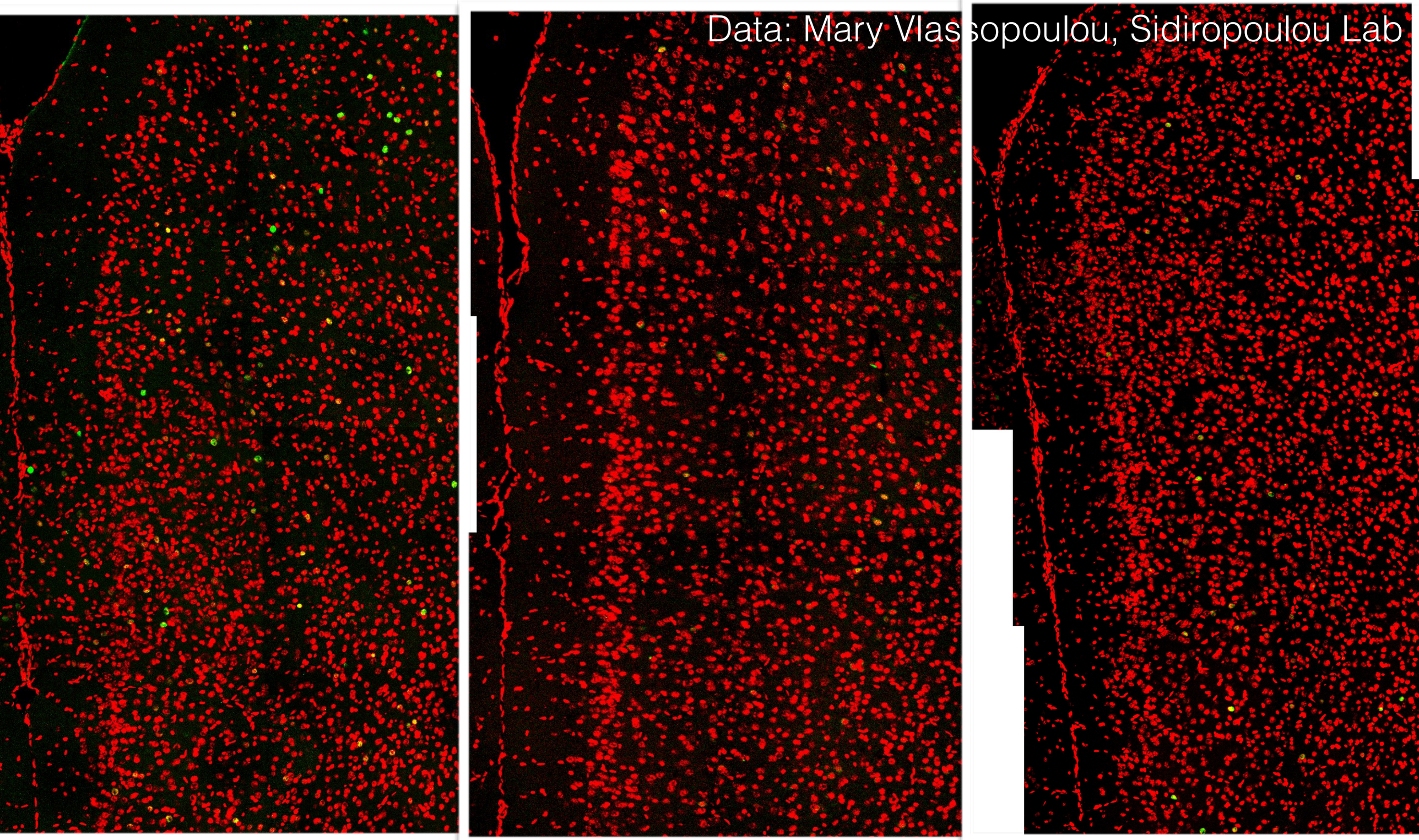
Chalkiadaki, Sidiropoulou, unpublished data

PREFRONTAL CORTEX

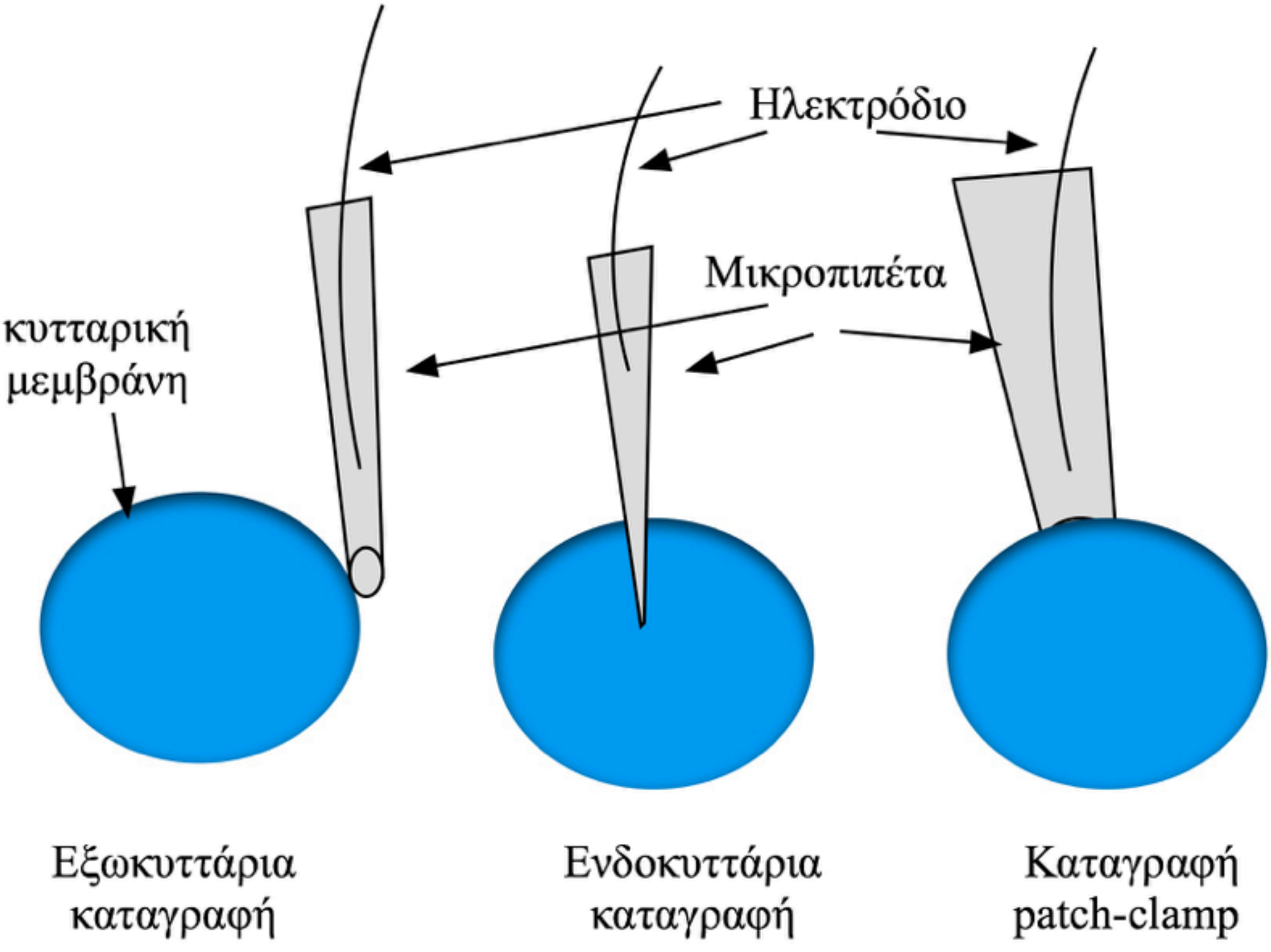
Delayed alternation

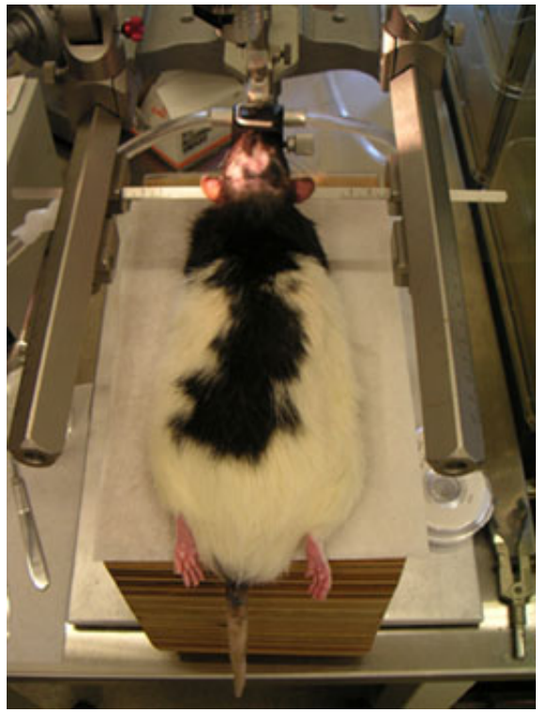
Left-Right discrimination

Open-Field



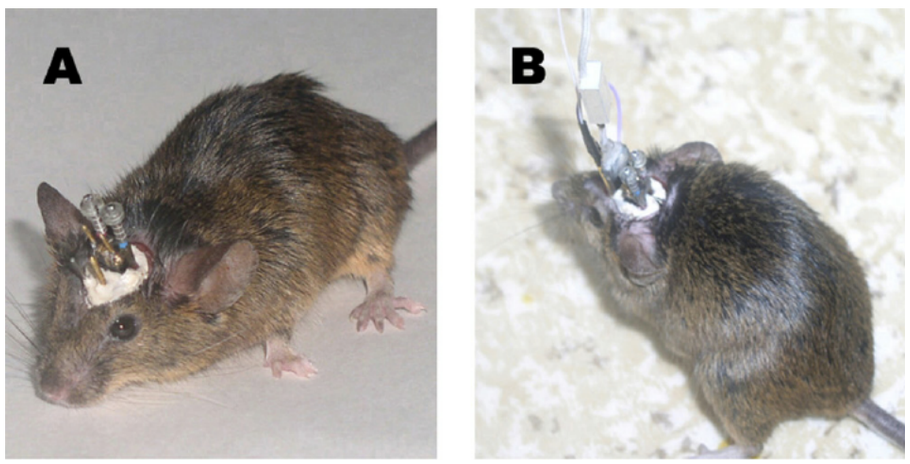
Electrophysiological recordings





In vivo recordings

- Anaesthetized
- Head-fixed
- Freely-moving



Voltage-clamp

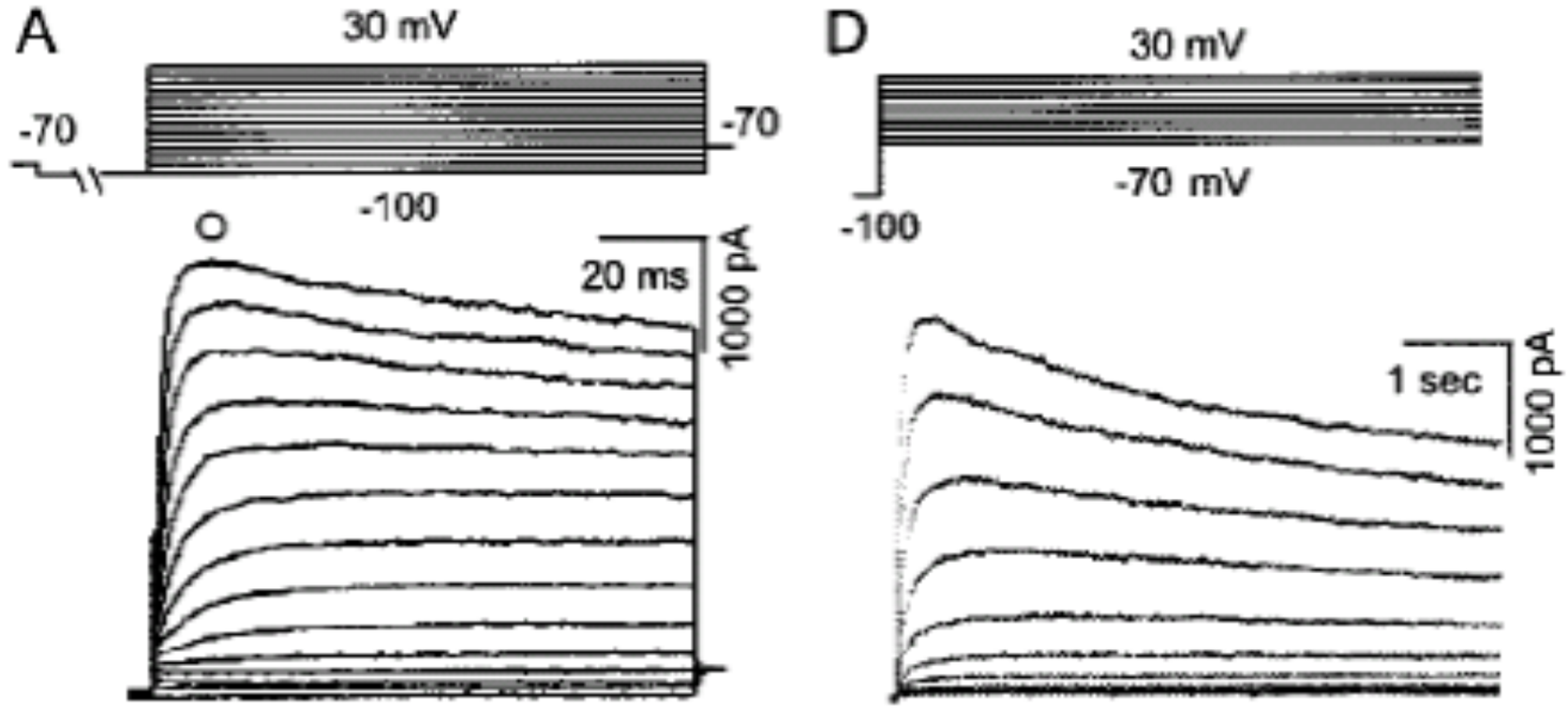
- Διαλύματα (ανάλογα με το ρεύμα που είναι να καταγραφεί)
- Τα περιεχόμενα των διαλυμάτων μπορούν να επηρεάσουν κατά πολύ τα αποτελέσματα των καταγραφών.

Current recordings

- Ρεύμα νατρίου (μπλοκάρουμε τα ρεύματα καλίου και ασβεστίου)
- Ρεύμα καλίου (μπλοκάρουμε τα ρεύματα νατρίου και ασβεστίου)
- Ρεύμα ασβεστίου (μπλοκάρουμε τα ρεύματα νατρίου και καλίου)

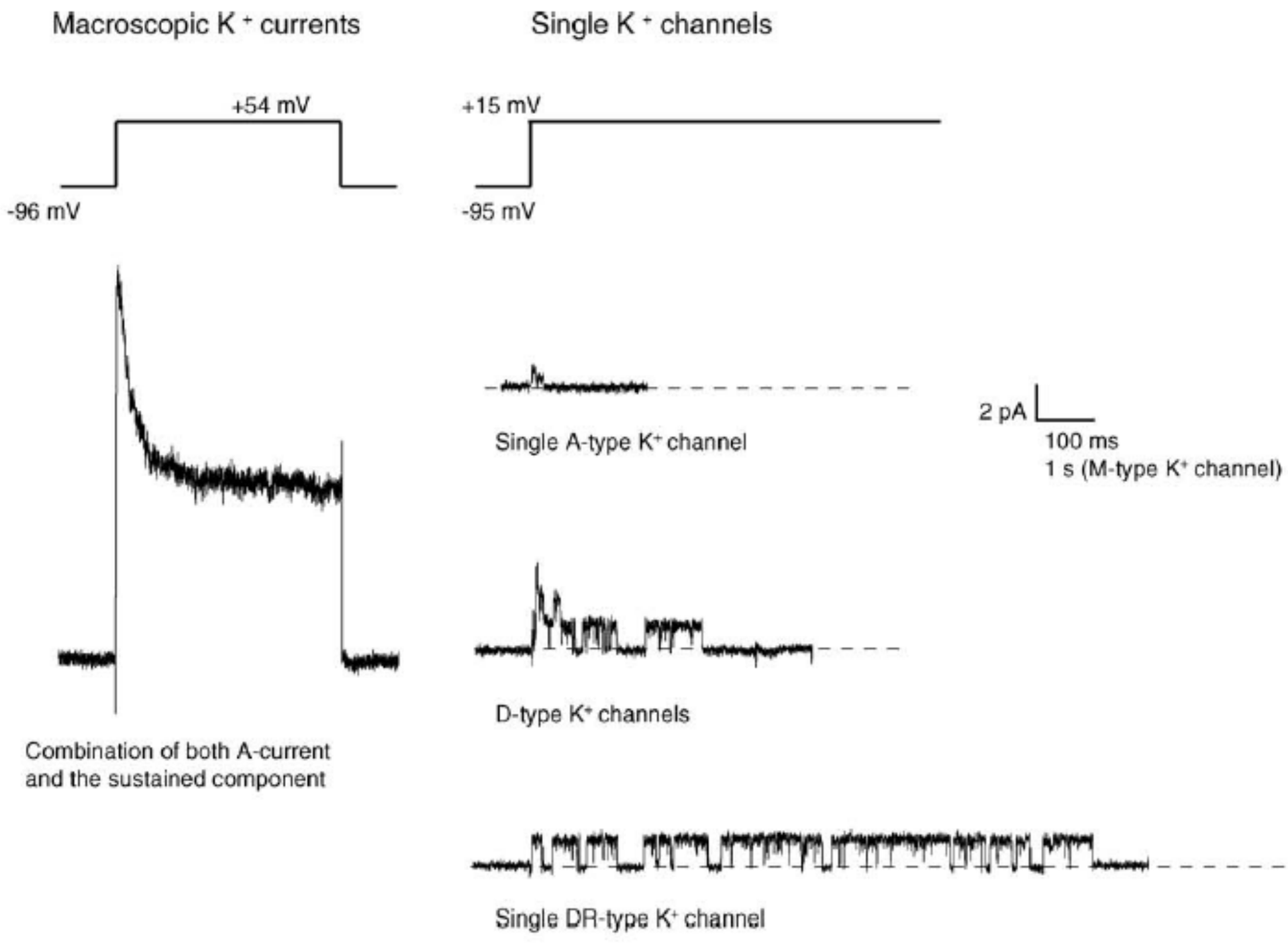
Tetradotoxin, tetra-ethyl-ammonium (TEA), cadmium

Potassium currents voltage-dependent (whole-cell configuration)



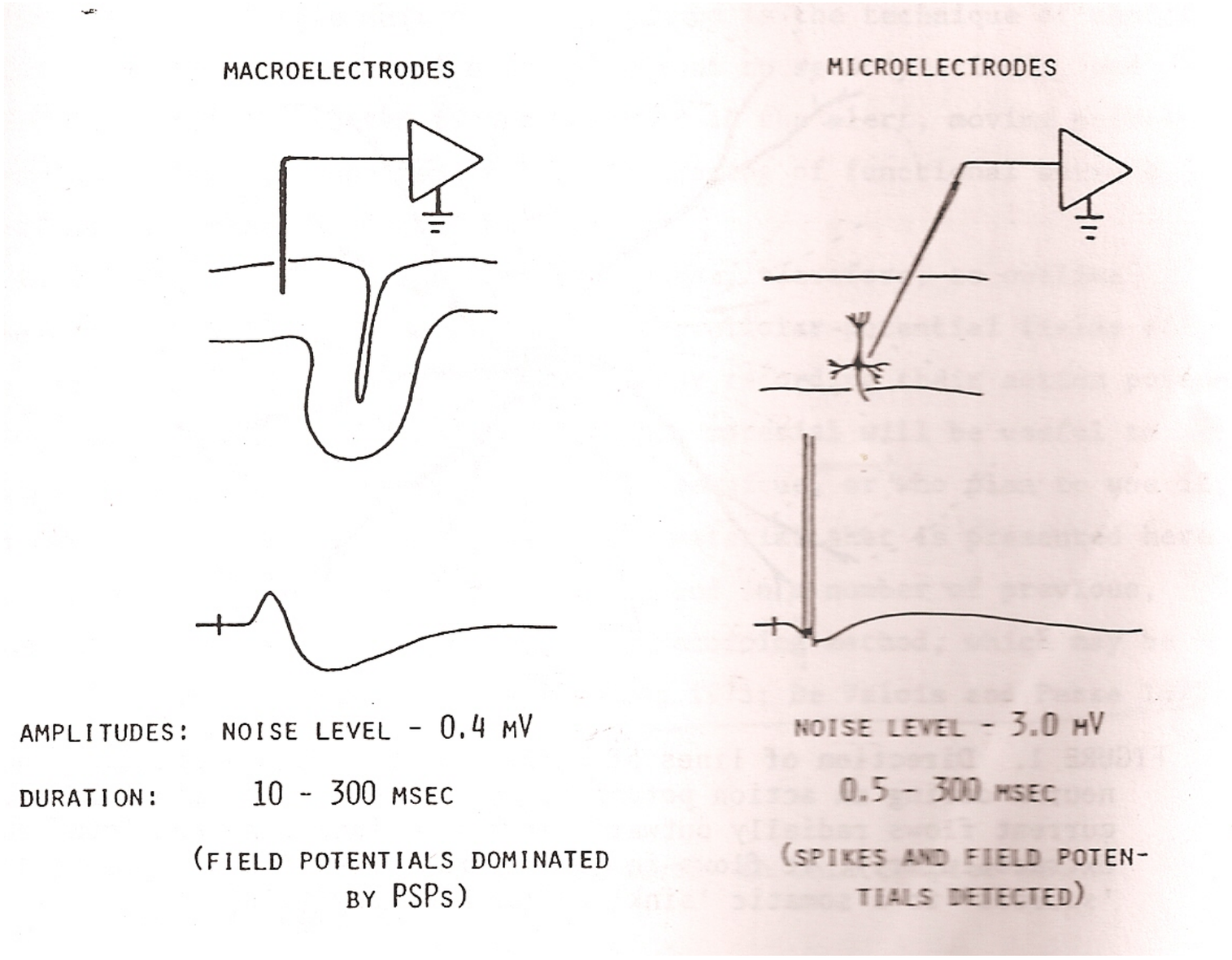
Dong and White, J Neuroscience, 2003

Whole-cell vs single-channel currents



What is the connection to networks and behavior?

Extracellular recordings

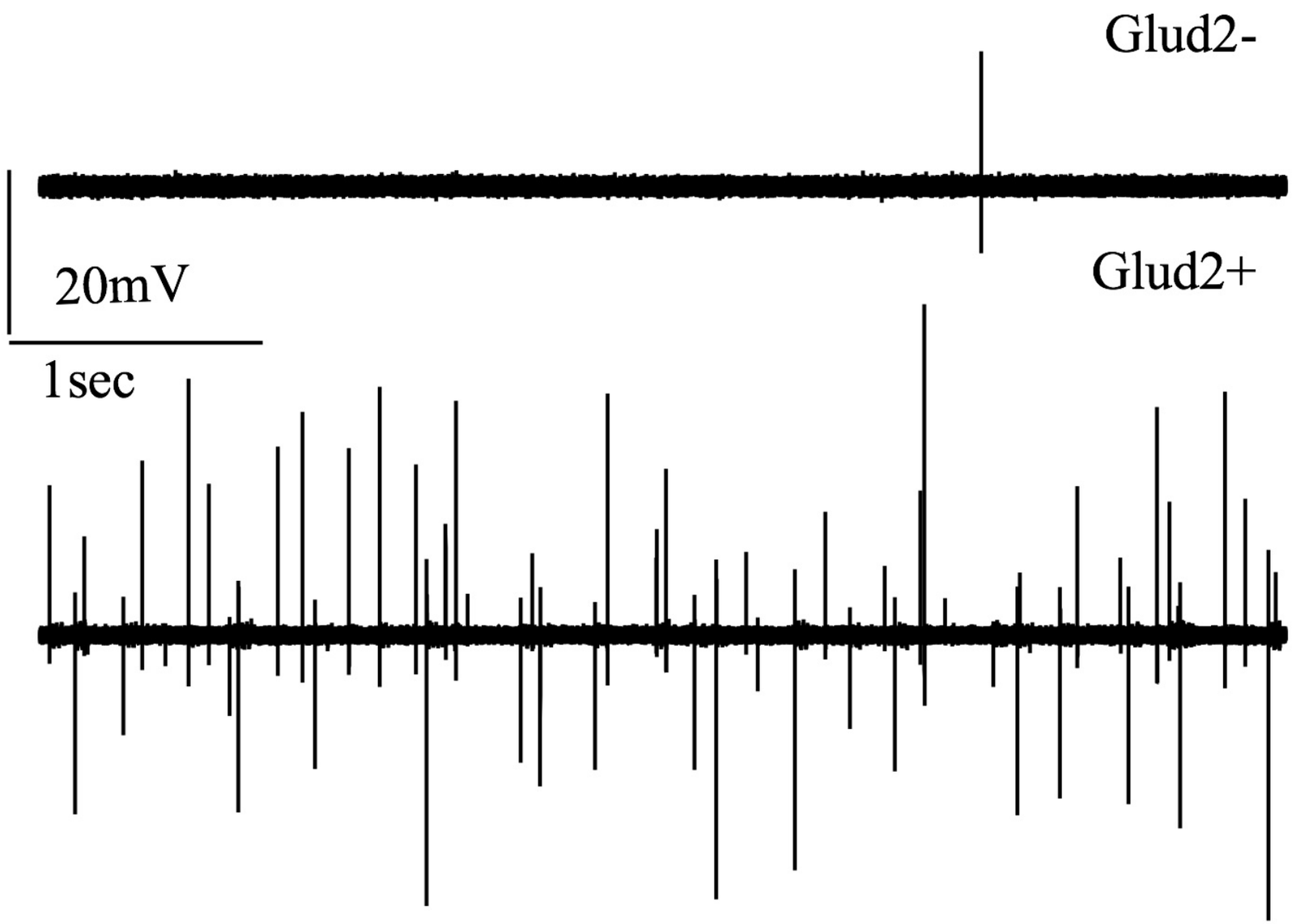


Mountcastle, 1957

Brain slice - LFPs

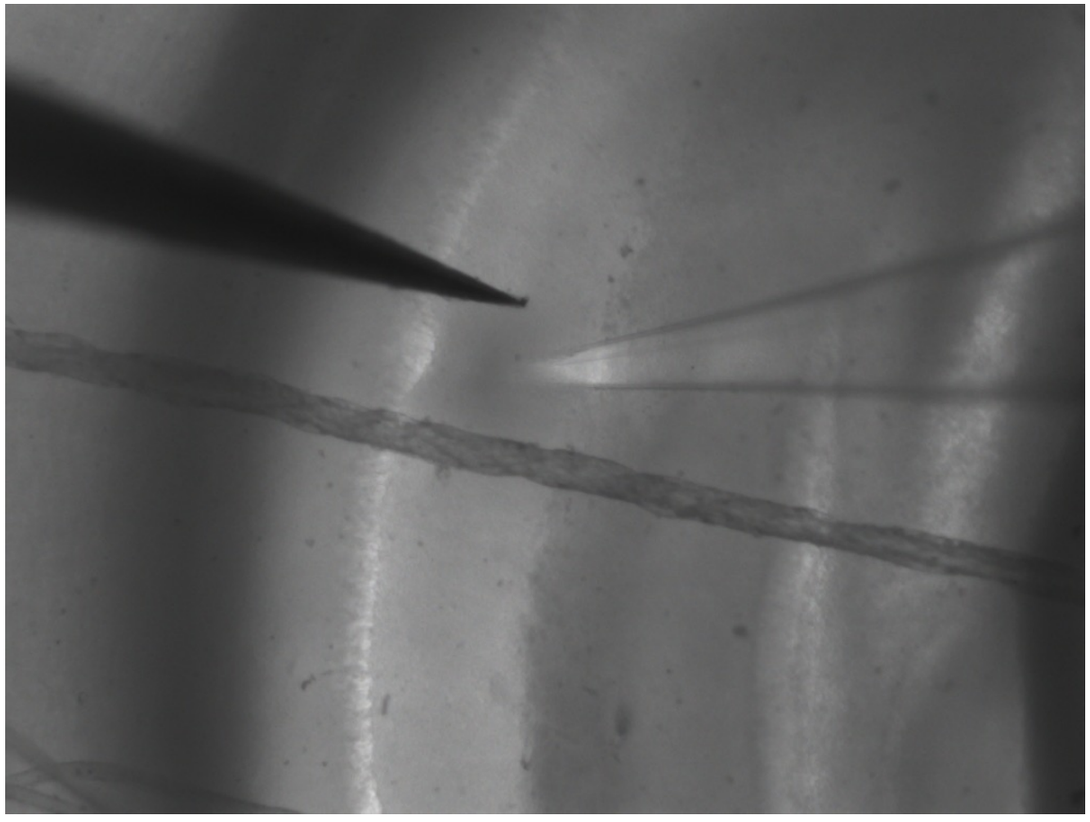
- Record brain areas that are stratified
  - hippocampus
  - Cortex
- Spontaneous/Epileptiform activity
- Evoked field excitatory postsynaptic potentials (fEPSP)
- Long-term potentiation

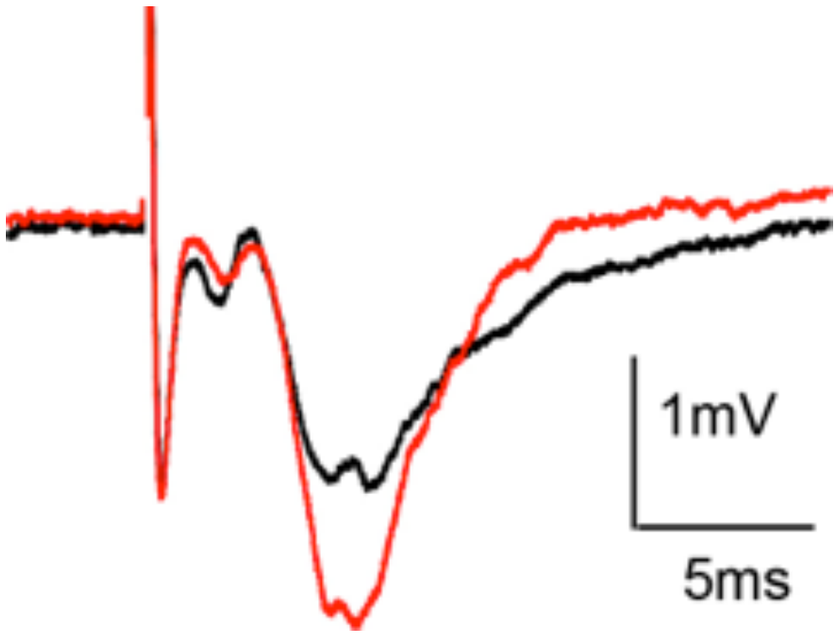
Basal spontaneous activity



Spanaki, Sidiropoulou et al, in preparation

Evoked LFPs - Long-term potentiation





0.1mA

10-20min

Tetanus
100Hz - 1sec
3x - 20sec

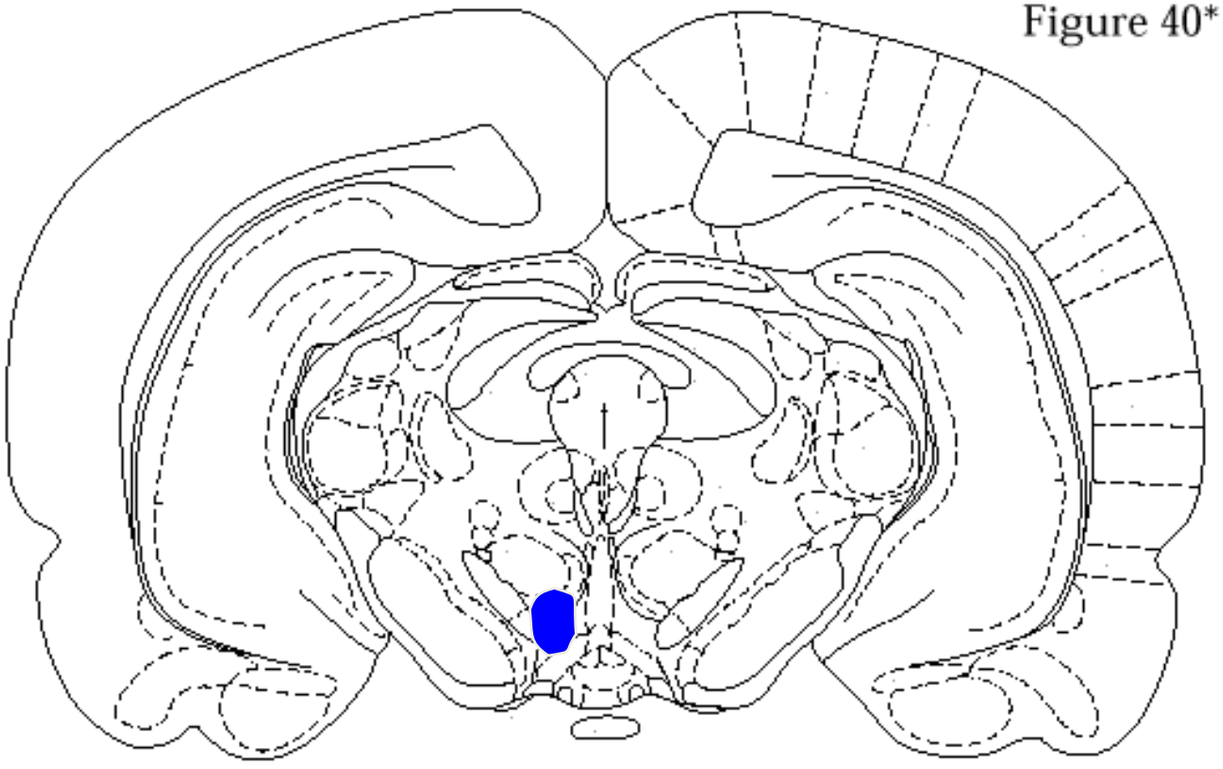
50min

Extracellular Recordings - Single unit recordings
Dopamine neurons

Ventral Tegmental Area
Substantia Nigra
A8, A9, A10

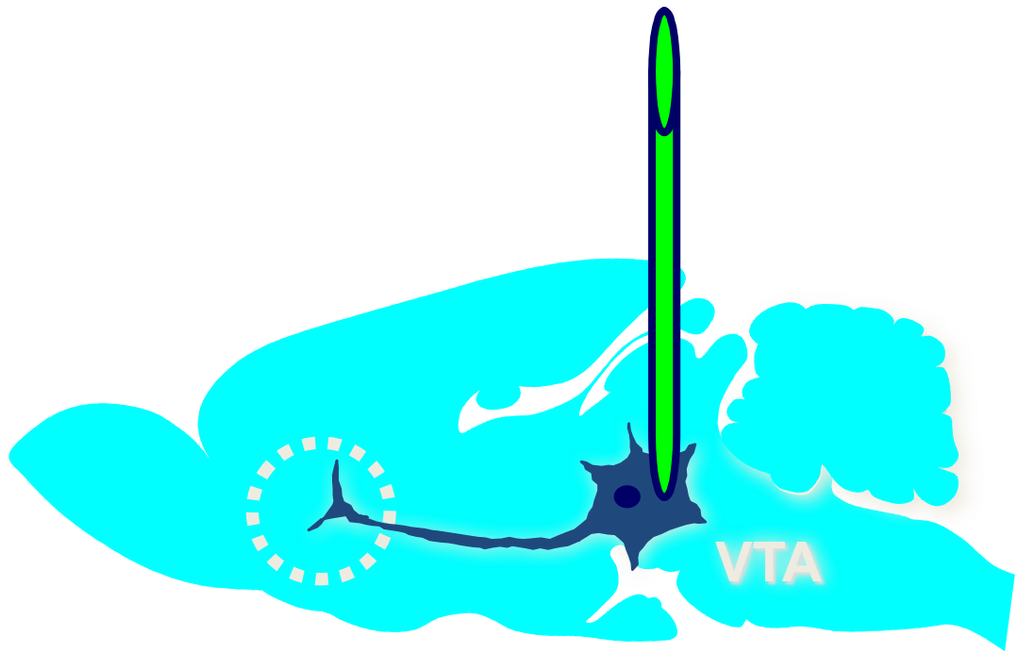
- Διαλύματα
- Ελεκτρόδιο
  - NaCl
  - Fast green

Figure 40*

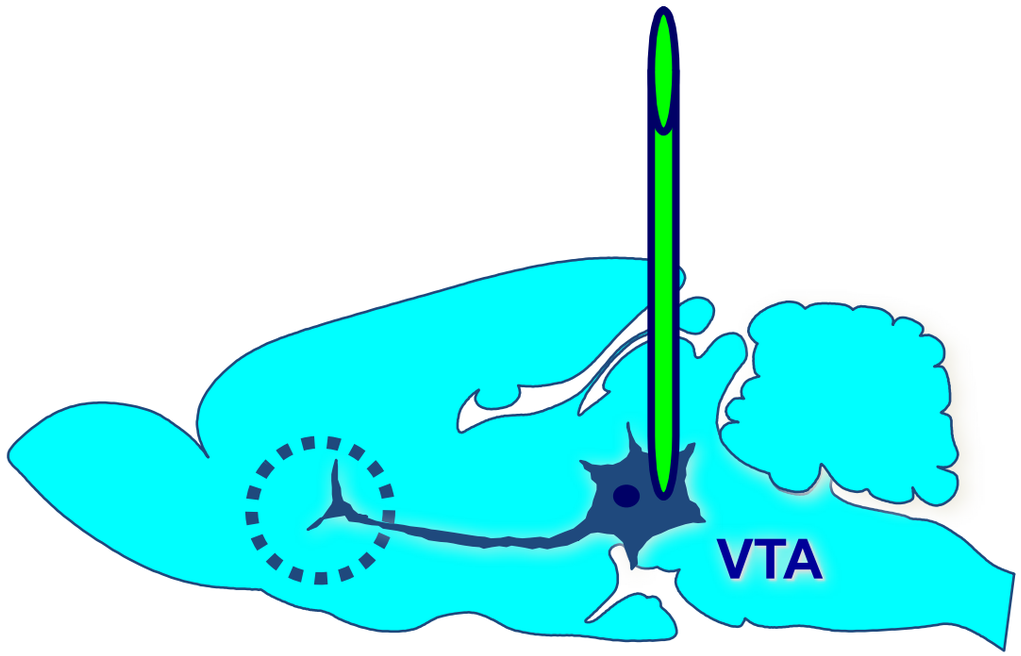


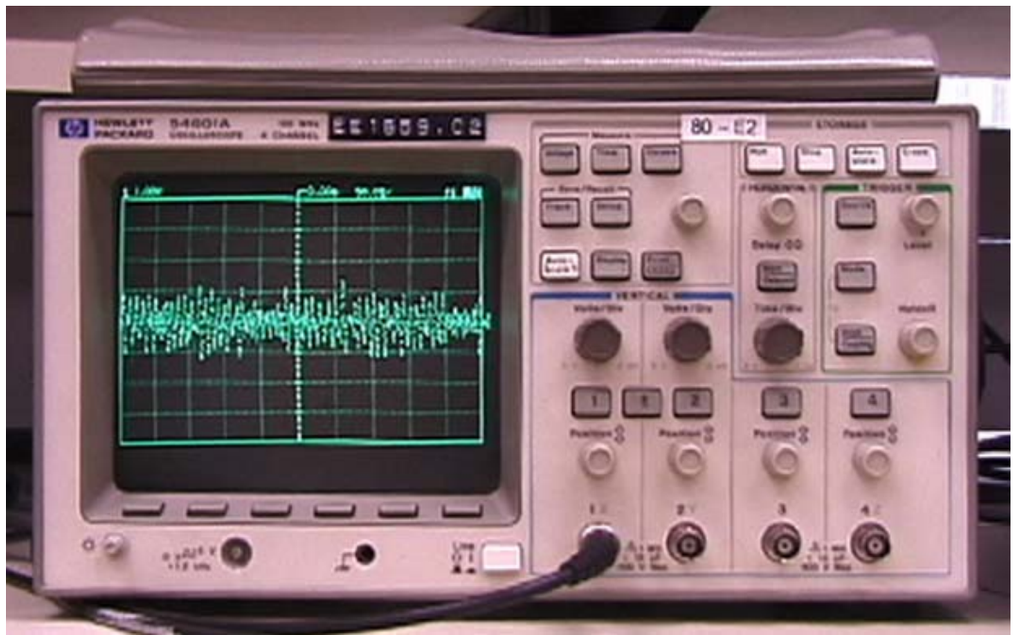
Interaural 3.40 mm*

Bregma -5.60 mm

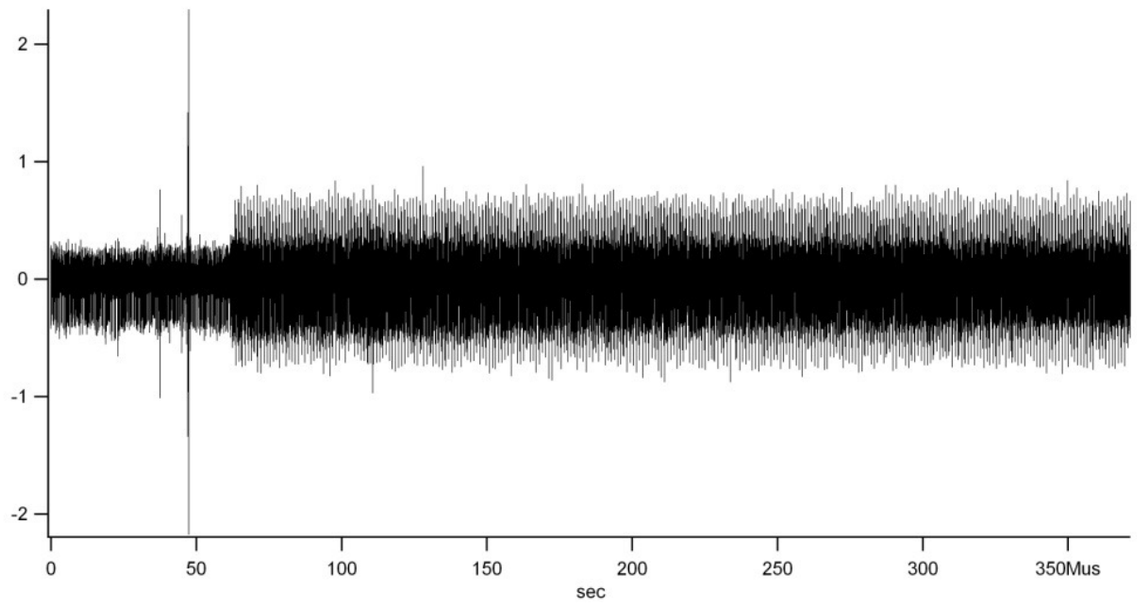


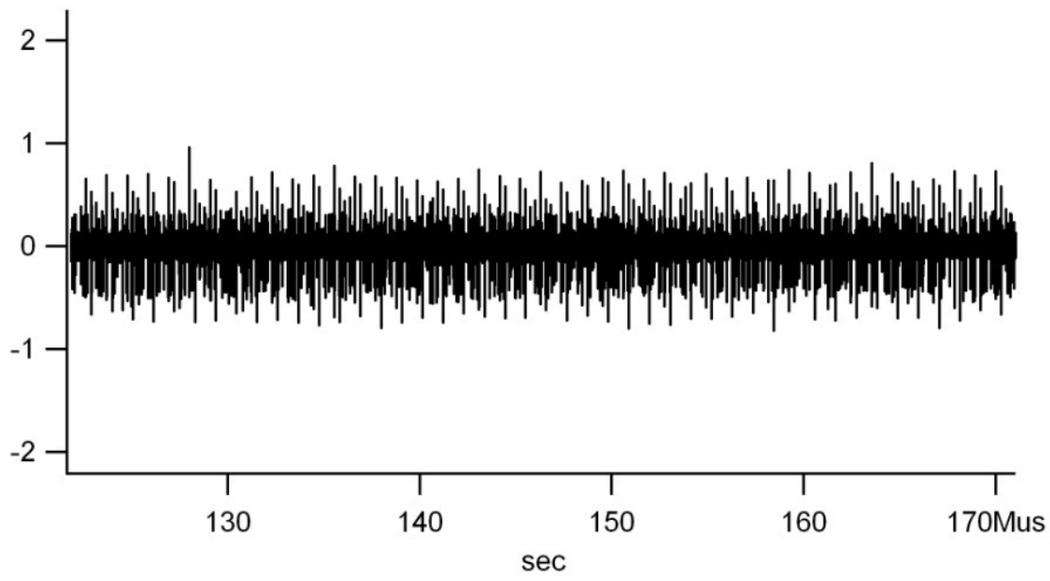
Extracellular Recordings



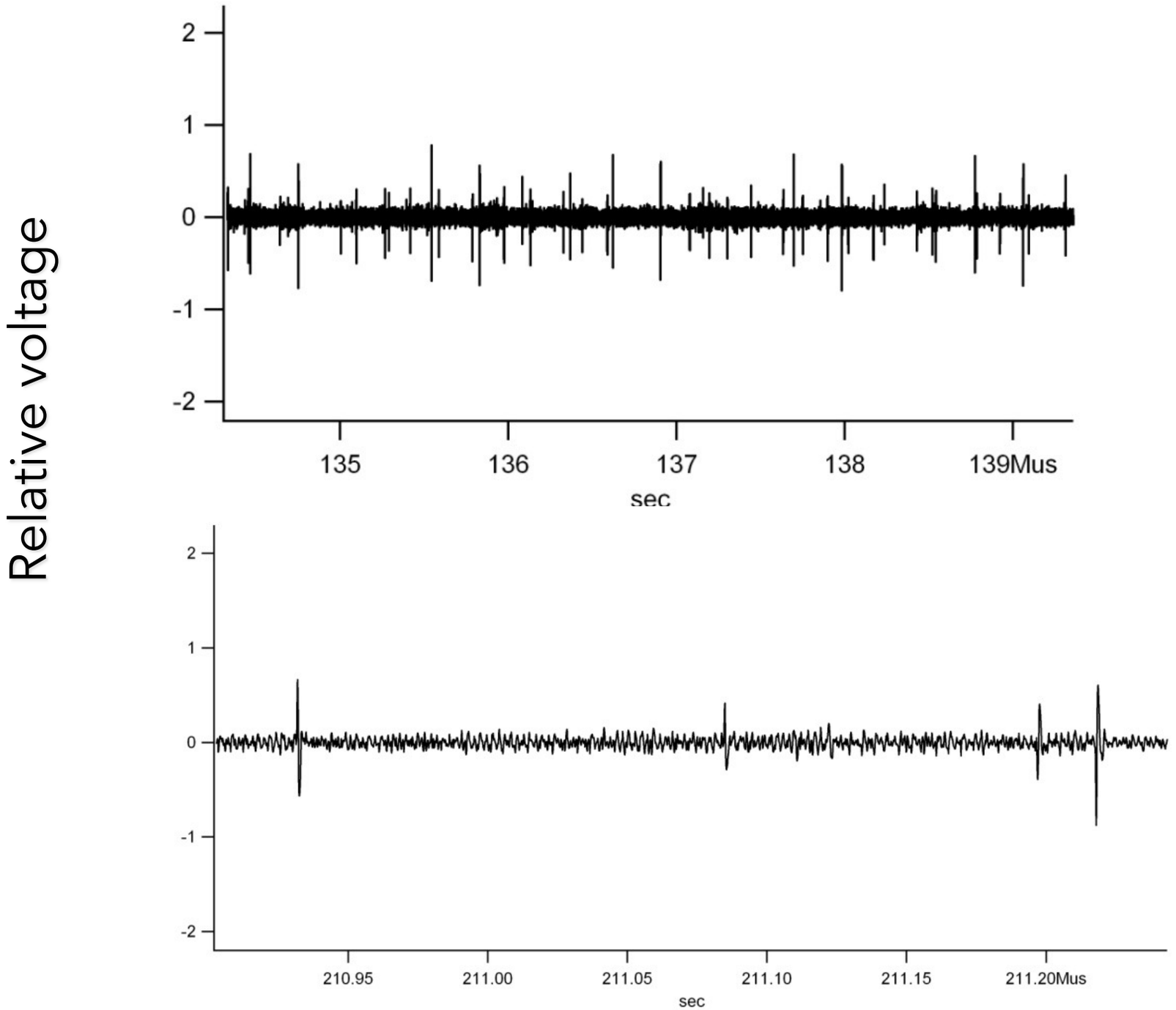


Relative voltage

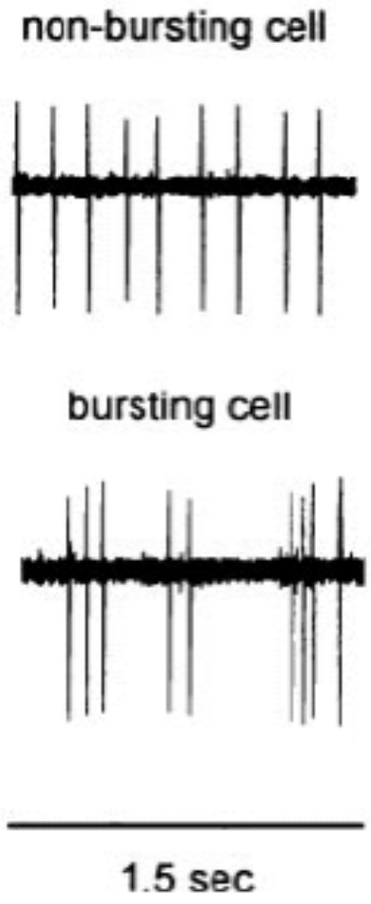


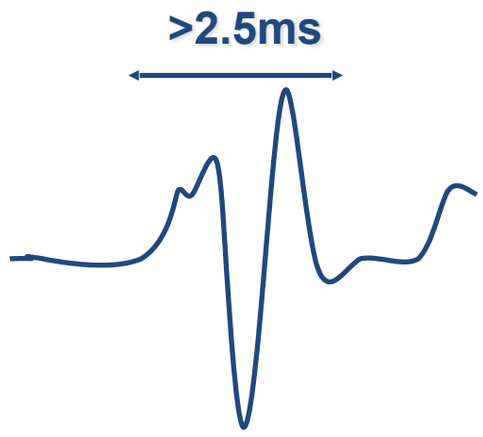


Extracellular Recordings
Dopamine neurons



Dopamine neuron waveforms





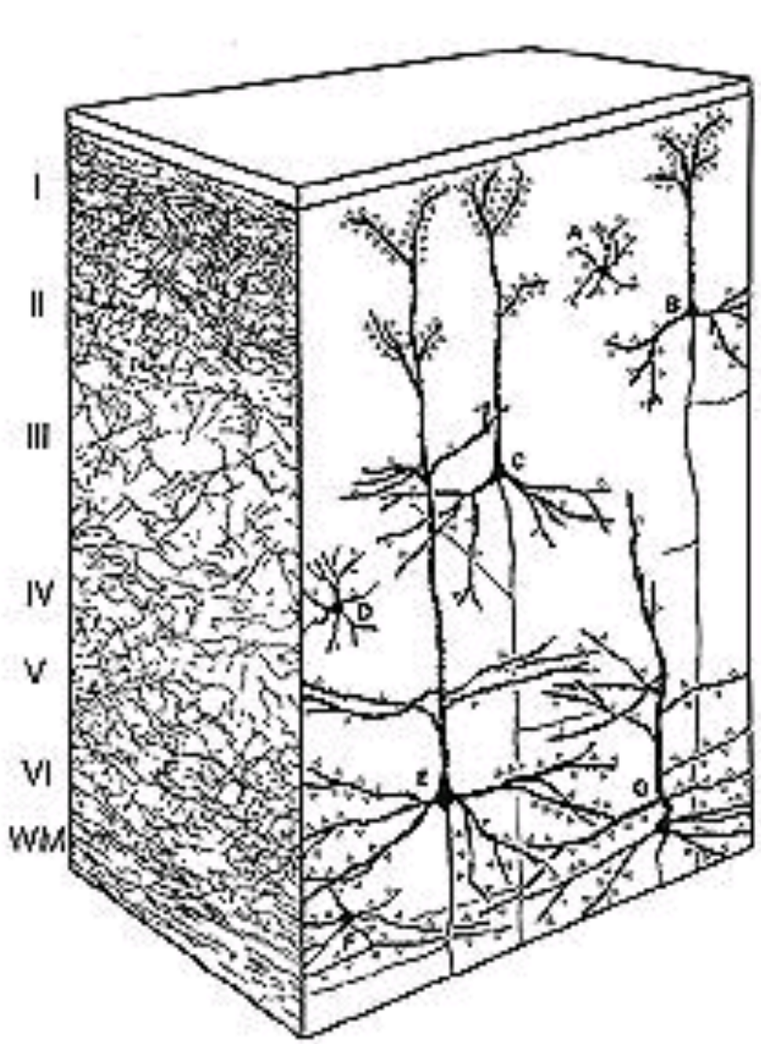
- Spontaneously active, and fire at low irregular frequencies (1-10Hz)
- Triphasic waveform of long duration
- Tonic or burst-firing

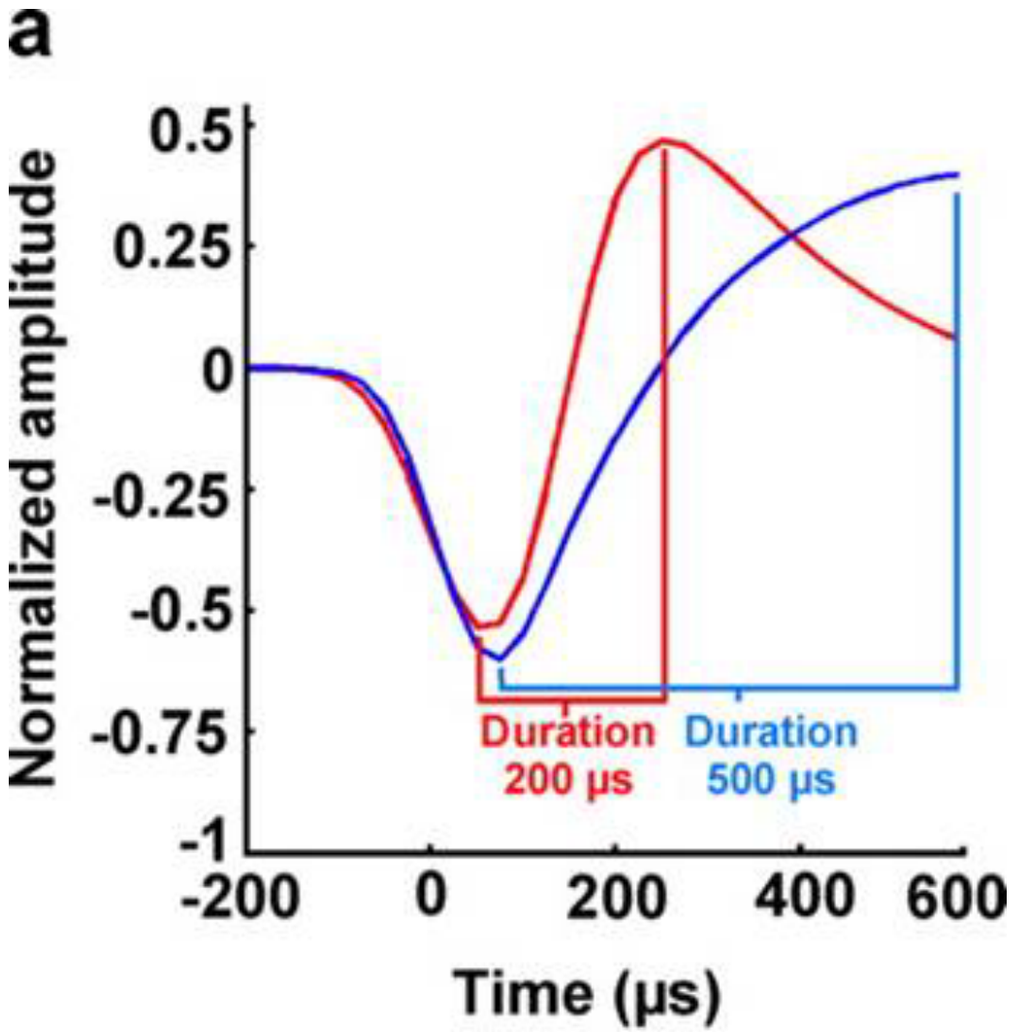
Αναφορά: Marinelli and White, 2000, J. Neuroscience

Correlation between dopamine neuron firing rate and exploratory activity in a novel environment

(Marinelli and White, 2000)

Differentiating the neuronal type based on the waveform properties



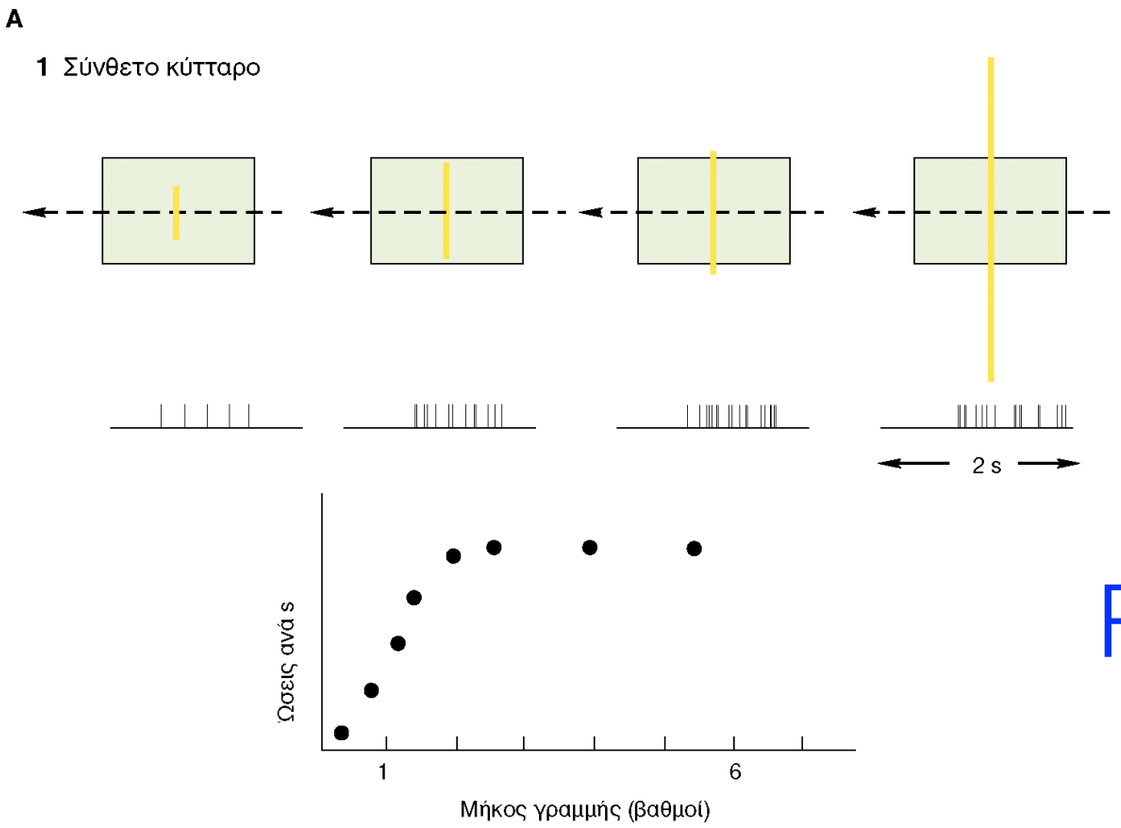


Cortex

Interneurons

Pyramidal neurons

Receptive fields in the visual cortex

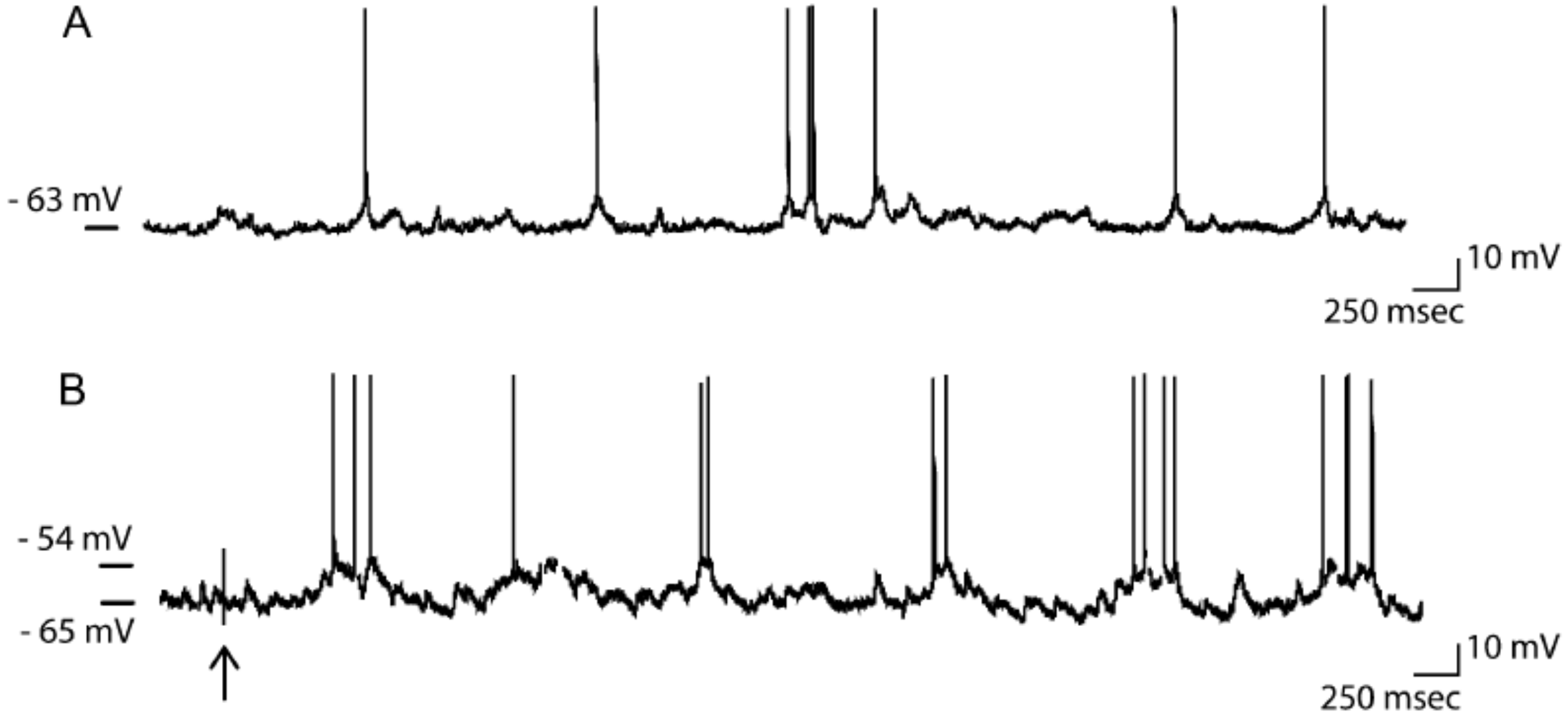


Εικόνα 23-12 Τα ακρο-αναστελλόμενα κύτταρα είναι ανώτερης τάξης σύνθετα κύτταρα που έχουν σχέση με τα χείλη, τις γωνίες και τις καμπύλες. (Από Hubel και Wiesel, 1965, τροποποιημένη.)

A. Τα κύτταρα του οπτικού φλοιού αποκρίνονται επιλεκτικά σε μια συγκεκριμένη περιοχή μηκών μιας κατακόρυφης φωτεινής γραμμής. **1**. Η απόκριση αυτού του σύνθετου κυττάρου αυξάνεται καθώς το μήκος της γραμμής αυξάνεται μέχρι 2° περίπου, ενώ έπειτα δεν υπάρχει μεταβολή. **2**. Η απόκριση αυτού του ακρο-αναστελλόμενου κυττάρου βελτιώνεται, καθώς η γραμμή αυξάνεται μέχρι 2°, αλλά κατόπιν μειώνεται, έτσι ώστε μια γραμμή 6° ή μεγαλύτερη δεν προκαλεί απόκριση.

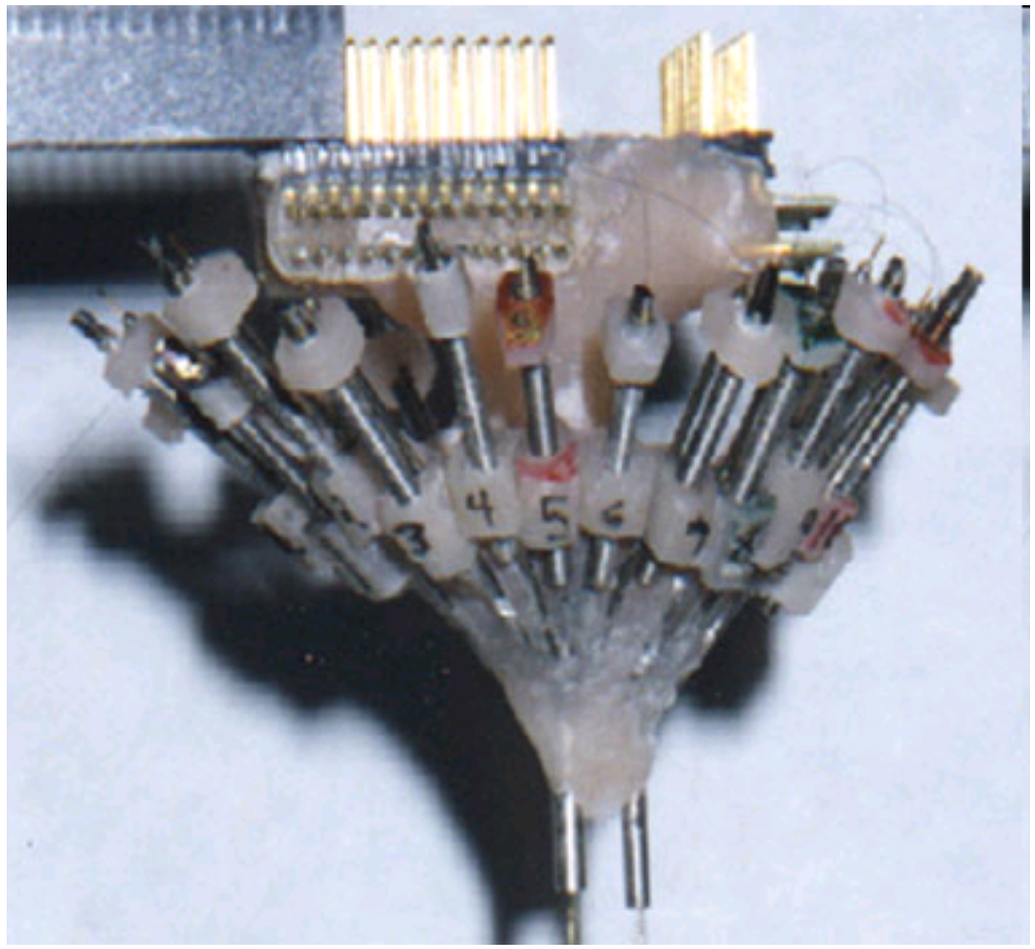
(συνεχίζεται)

In vivo intracellular recordings



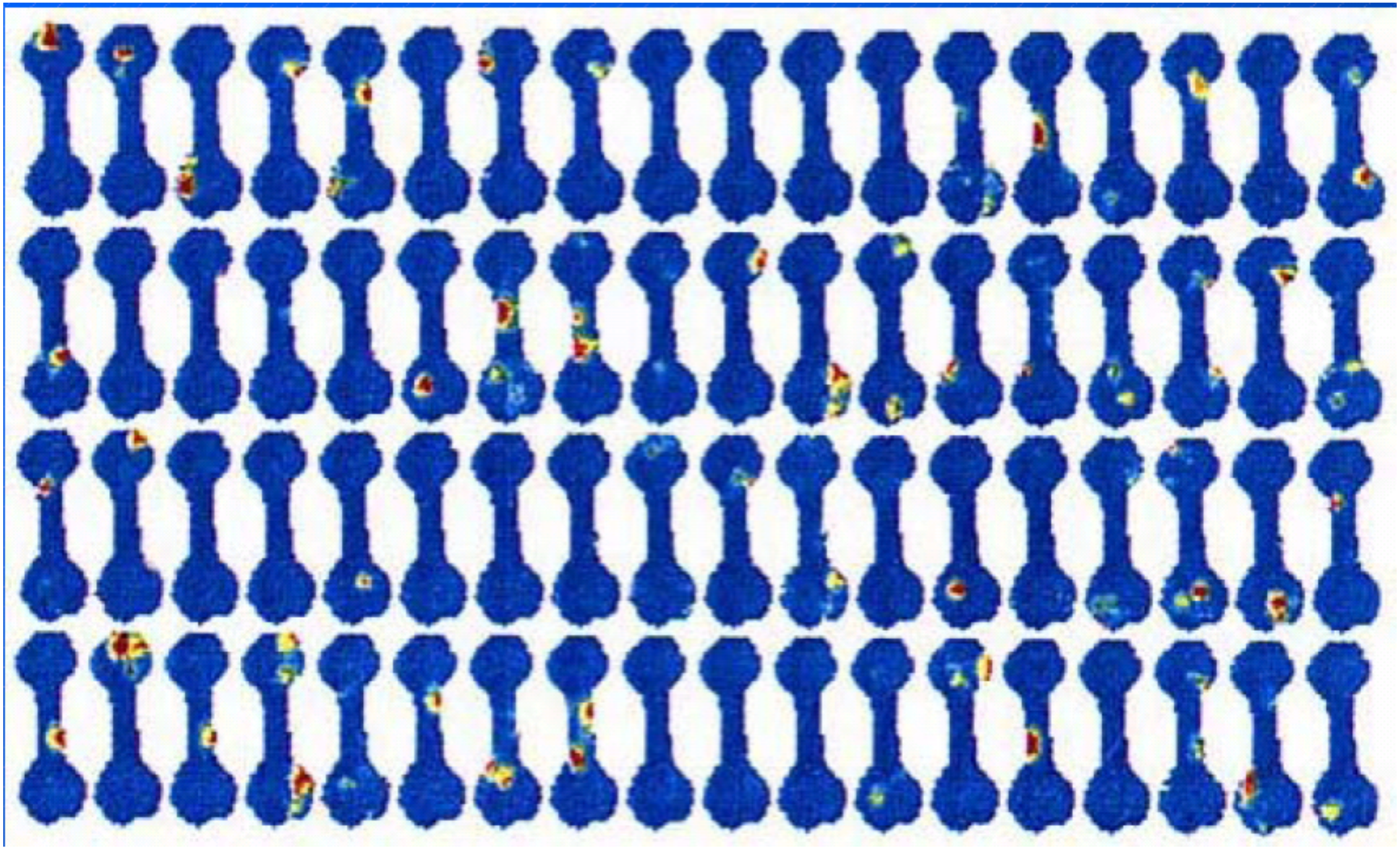
Tetrode-array technology

- Bruce McNaughton (Arizona)
- Matt Wilson, MIT (open course)



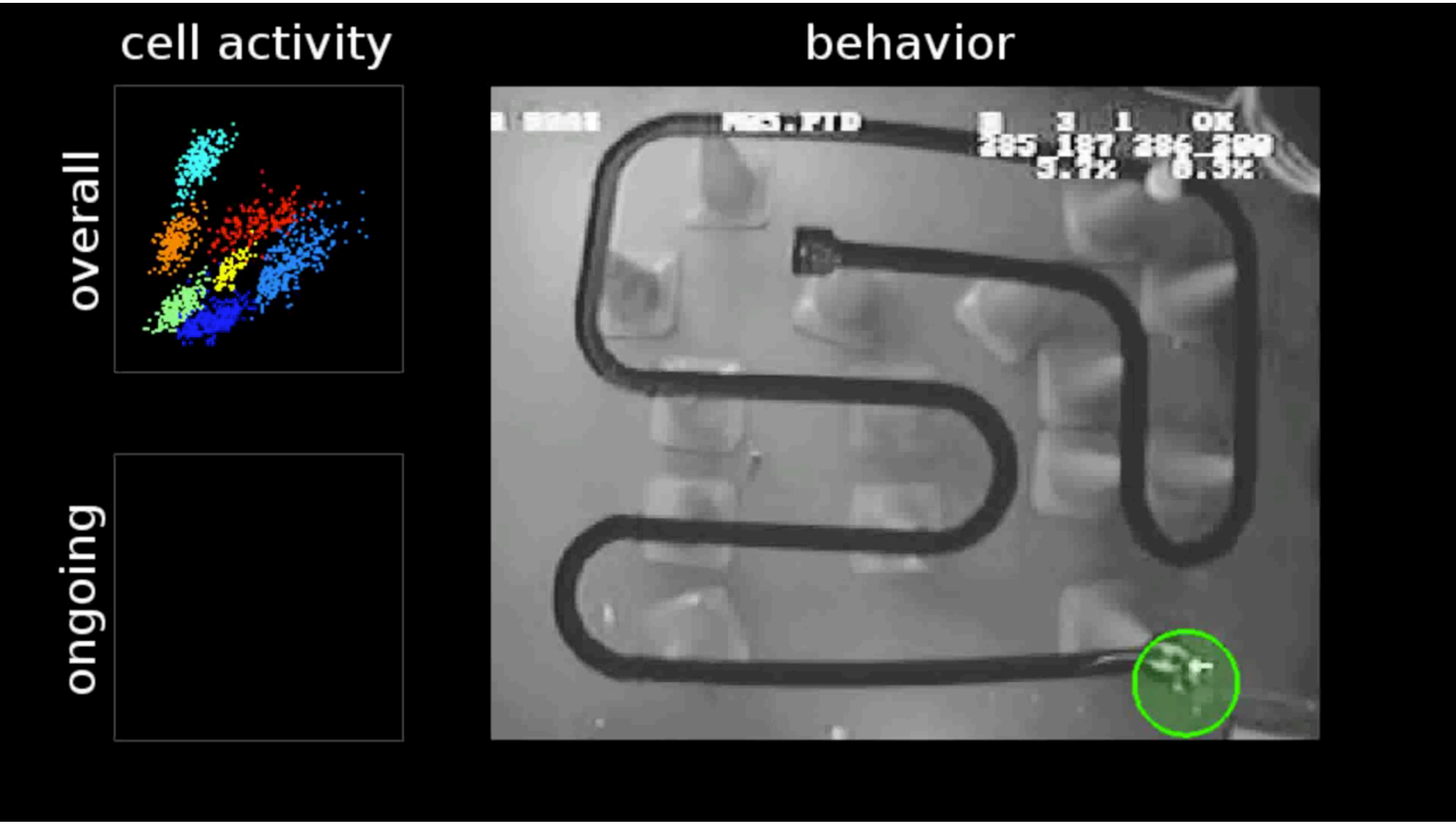
http://ocw.mit.edu/OcwWeb/Brain-and-Cognitive-Sciences/9-96Experimental-Methods-of-Adjustable-Tetrode-Array-NeurophysiologyJanuary--IAP-2001/CourseHome/index.htm

Place cells (Hippocampus)

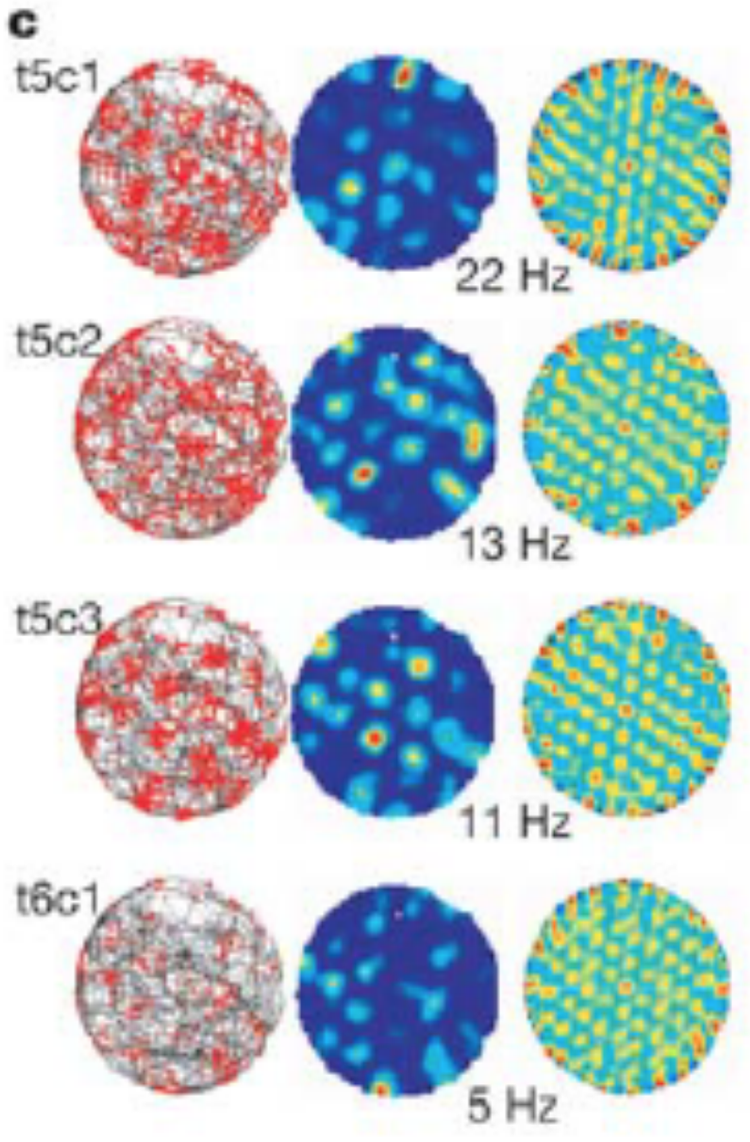


Matt Wilson, MIT

Place cells movie



Grid cells in enthorhinal cortex



Moser group

2014 Nobel prize in Medicine

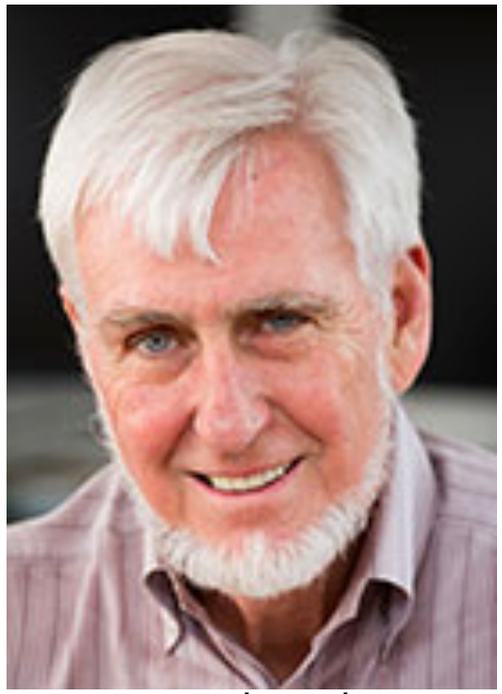


Photo: David Bishop, UCL

John O'Keefe

Prize share: 1/2

May-Britt Moser

Photo: G. Mogen/NTNU

May-Britt Moser

Prize share: 1/4

Edvard I. Moser

Photo: G. Mogen/NTNU

Edvard I. Moser

Prize share: 1/4

Functional imaging techniques

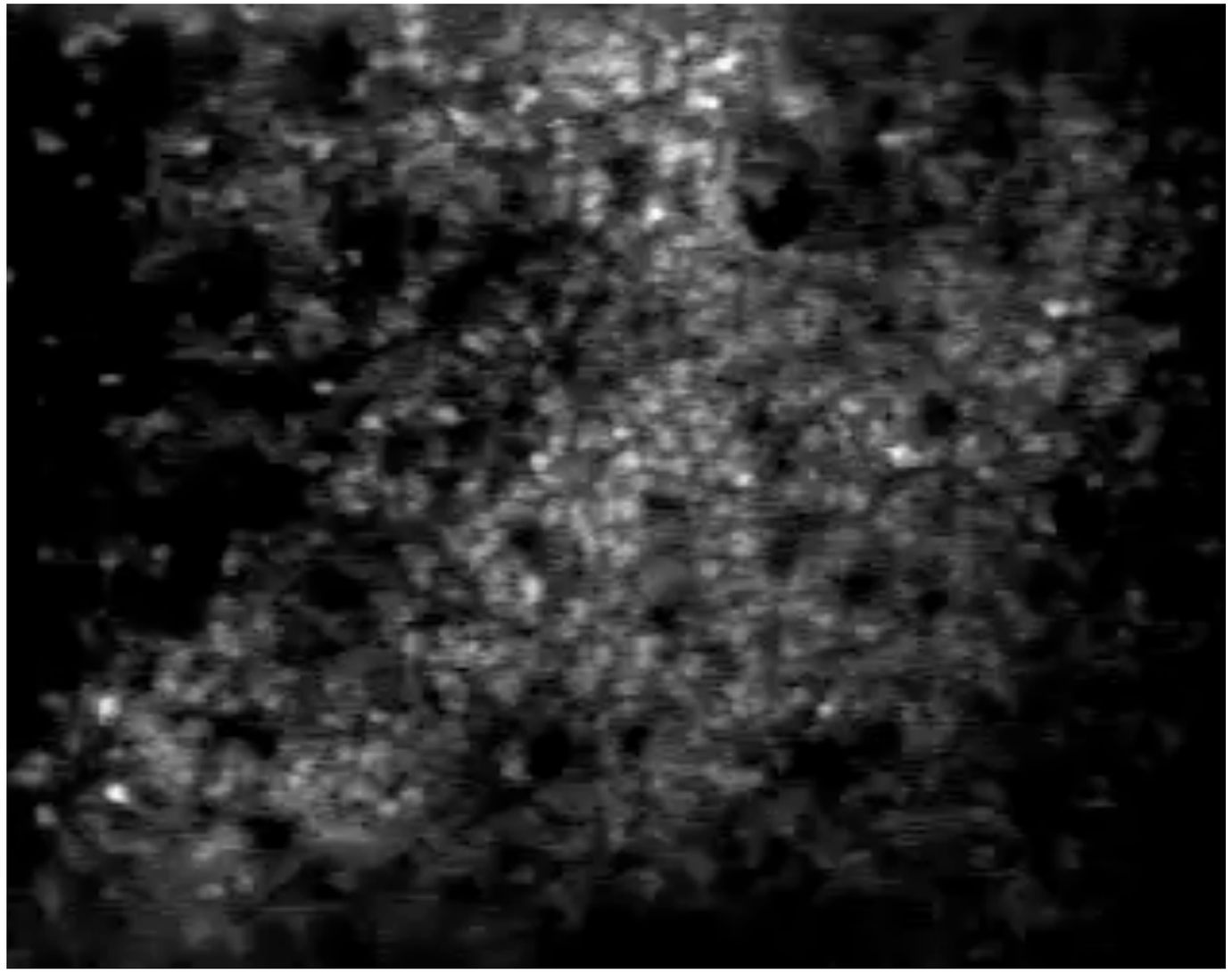
- **Calcium imaging**
- Voltage imaging
- PET
- MRI, fMRI
- Real-time imaging

Calcium imaging

- Calcium cannot be measured directly
- Calcium indicators used
  - Calcium-binding molecules are used that change their fluorescence properties
  - calcium changes can be measures in multiple milliseconds (compared to microseconds in electrophysiology)
- Requirements for successful calcium imaging
  - fast calcium indicator
  - high signal-to-noise ratio
  - proper instrumentation (images without photobleaching, fast scanning)

Advantages compared to recording techniques

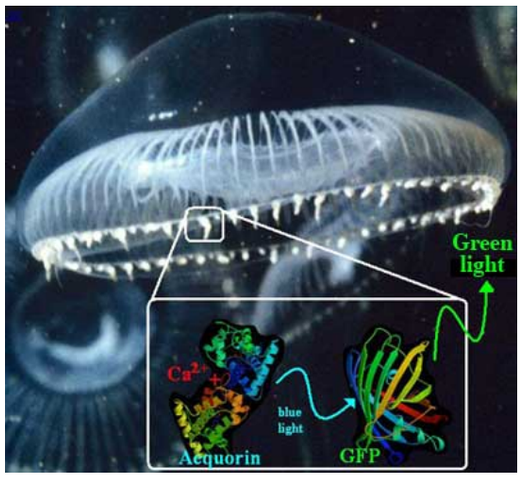
- Multiple cells
- Cell-type identification

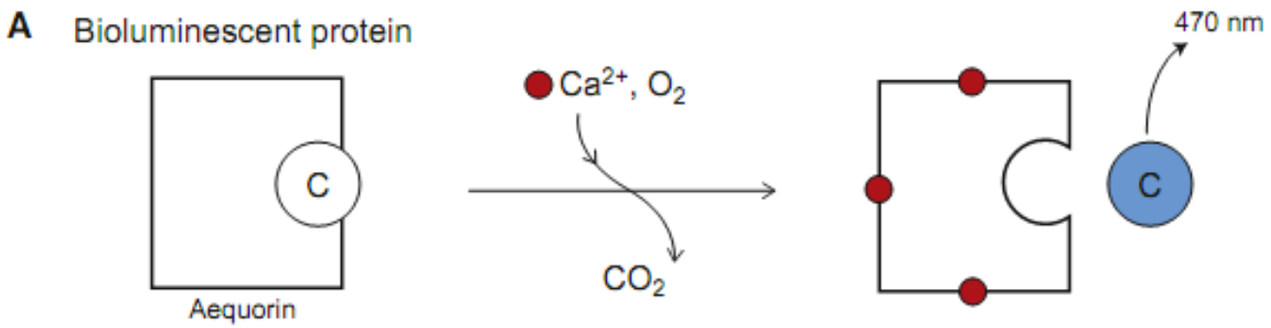


Calcium -imaging video of spontaneous neuronal activity, Golshani Lab, UCLA, http://golshanilab.neurology.ucla.edu/techniques

Molecules used for calcium imaging

- Natural calcium-binding proteins with fluorescent properties, aequorin





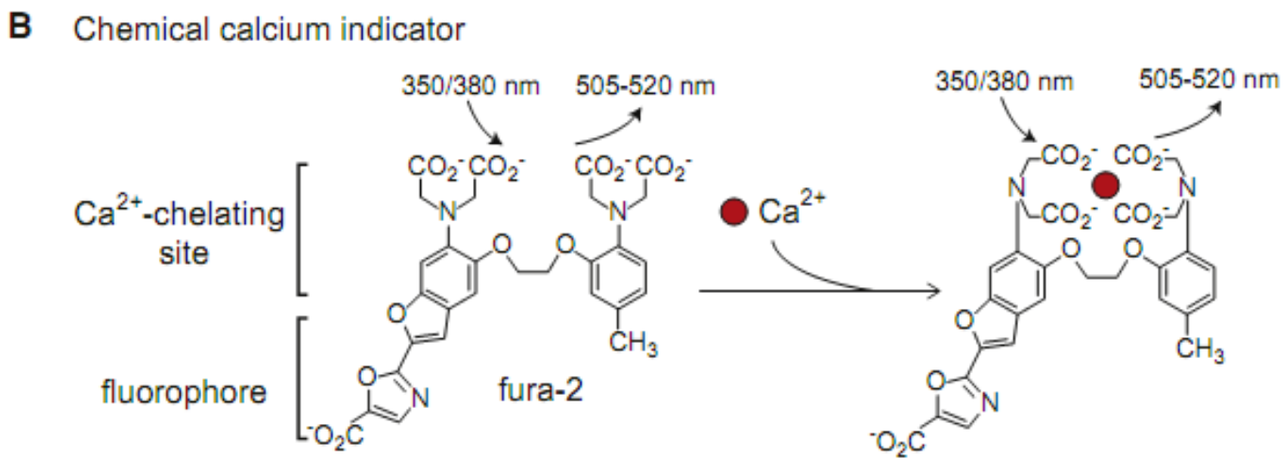
- Synthetic chemicals

- Genetically modified calcium indicators

Synthetic chemical compounds

- Fura-2/Fura-2AM (membrane permeable)
- BAPTA-AM
- Orange green

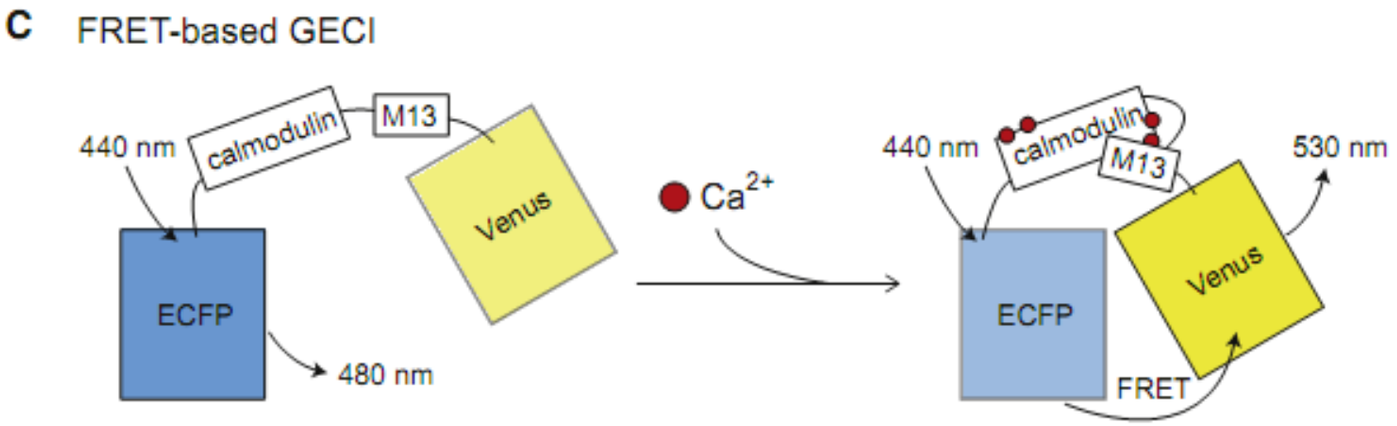
Roger Tsien
Nobel prize in chemistry 2008
Green Fluorescent Protein



Genetic calcium indicators

- Forster resonance energy transfer (FRET)
- Yellow cameleon
- Two fluorescent substances (donor and recipient)

Roger Tsien
Nobel prize in chemistry 2008
Green Fluorescent Protein

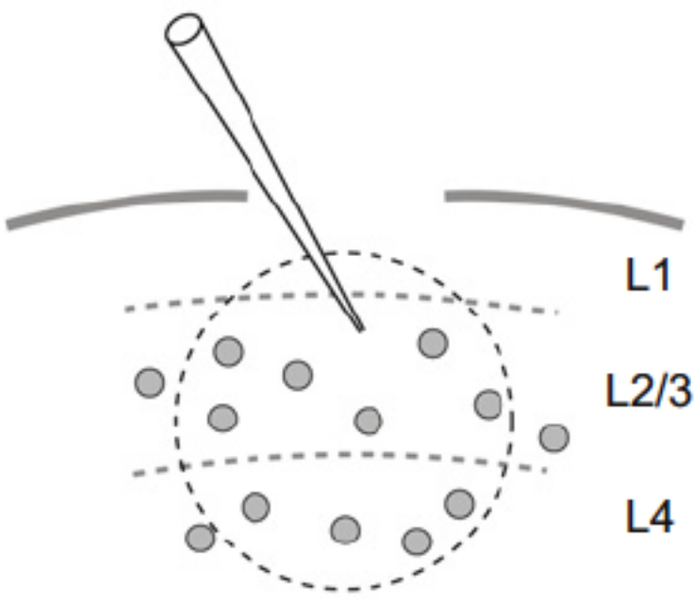


Genetically-encoded calcium indicators (2012)

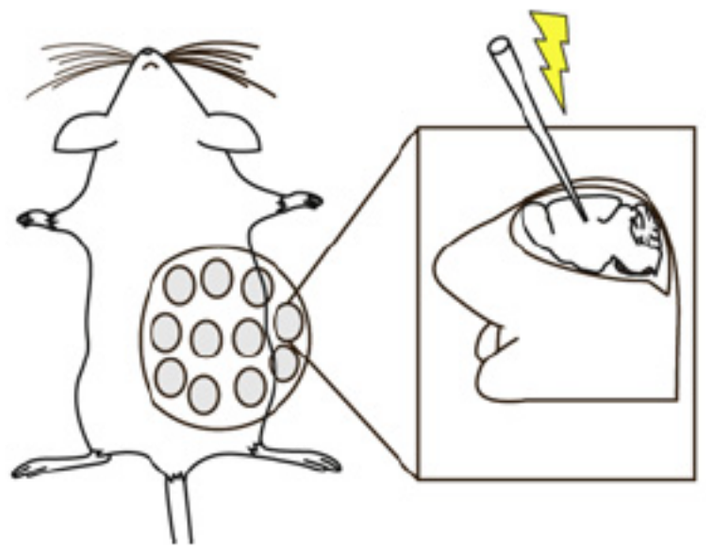
Camgaroo 1
Camgaroo 2
Inverse pericam
GCaMP 2
GCaMP 3
Yellow Cameleon 3.6
Yellow Cameleon Nano
D3cpV
TN-XL
TN-L15
TN-XXL

Genetically encoded calcium indicators

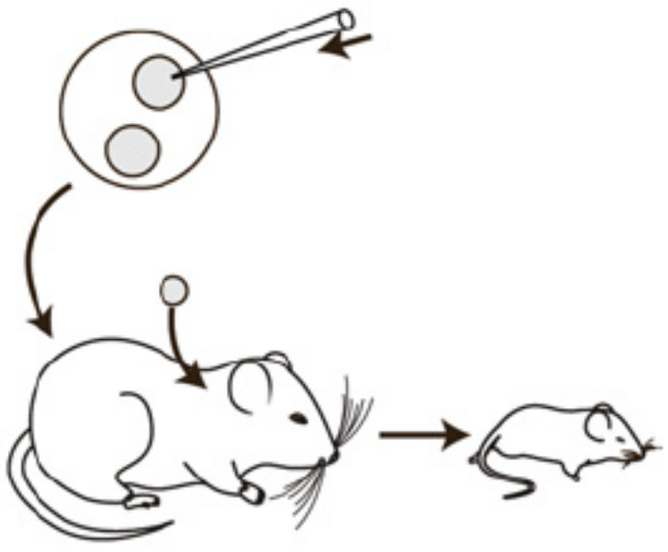
GECI expression



Viral transduction



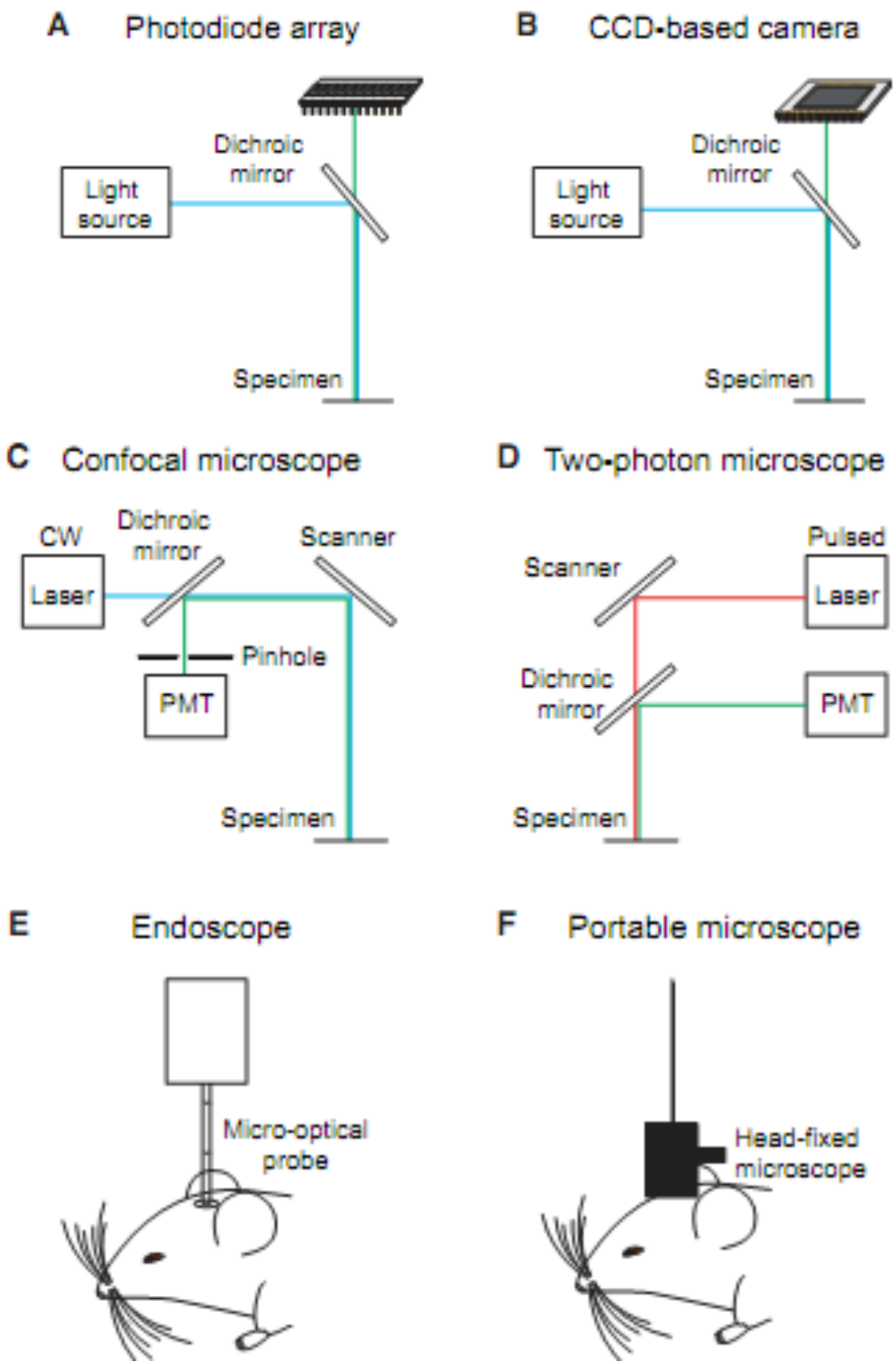
In utero electroporation



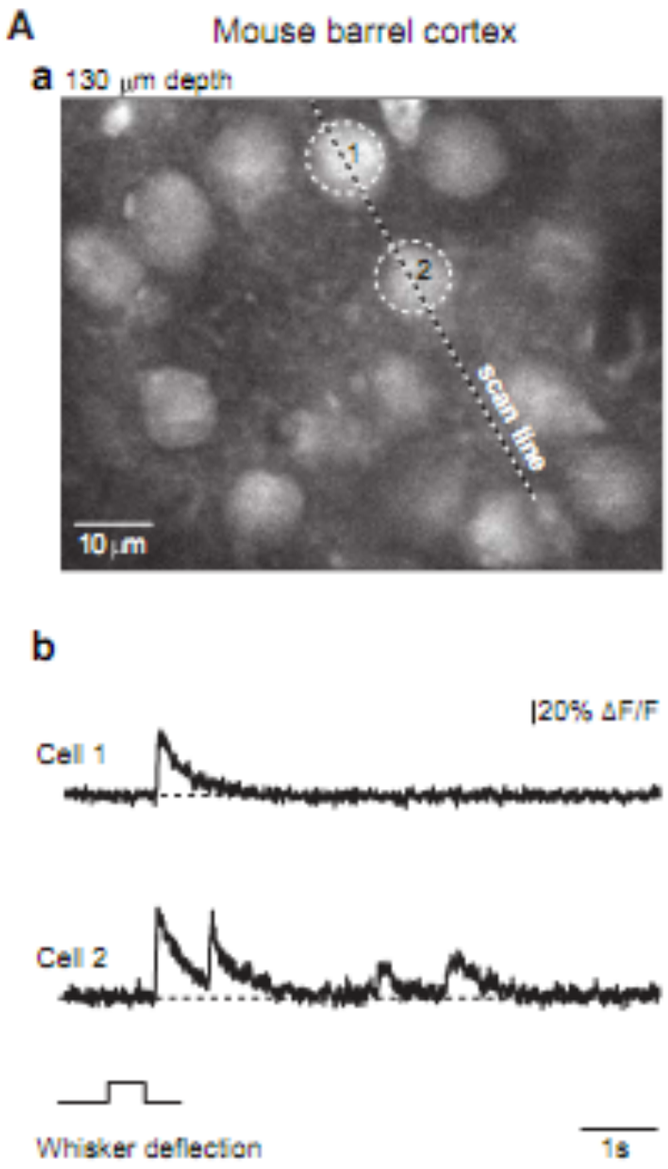
Transgenic mice

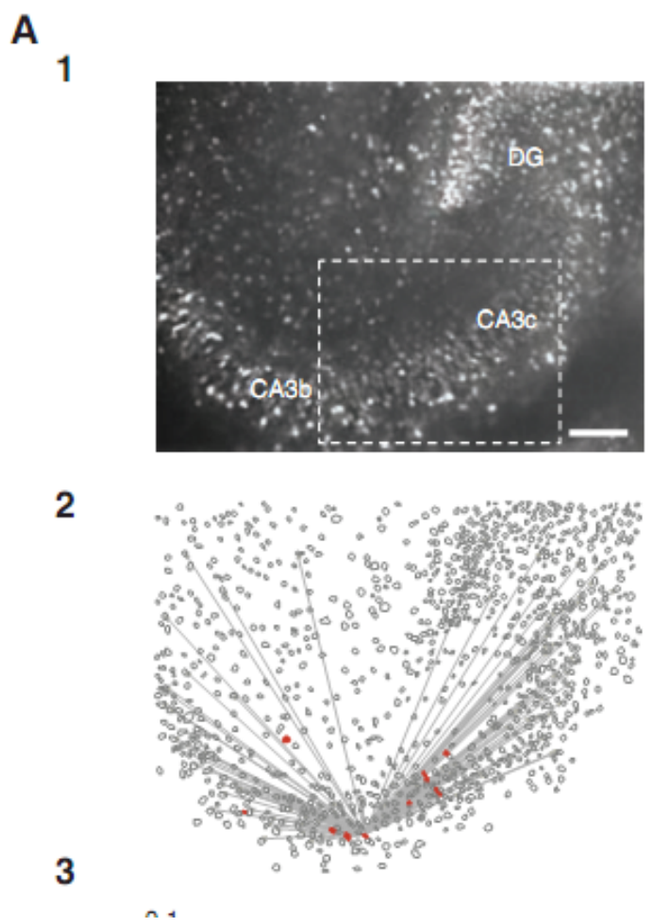
Microscopy to study calcium imaging

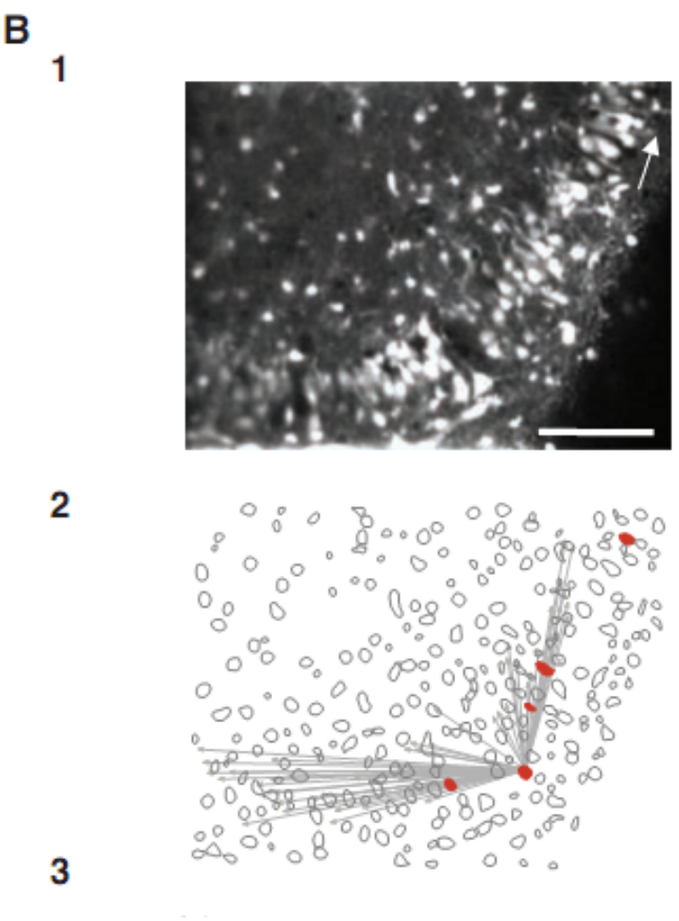
- Fluorescence microscopy
- confocal laser microscopy
- portable microscopy devices



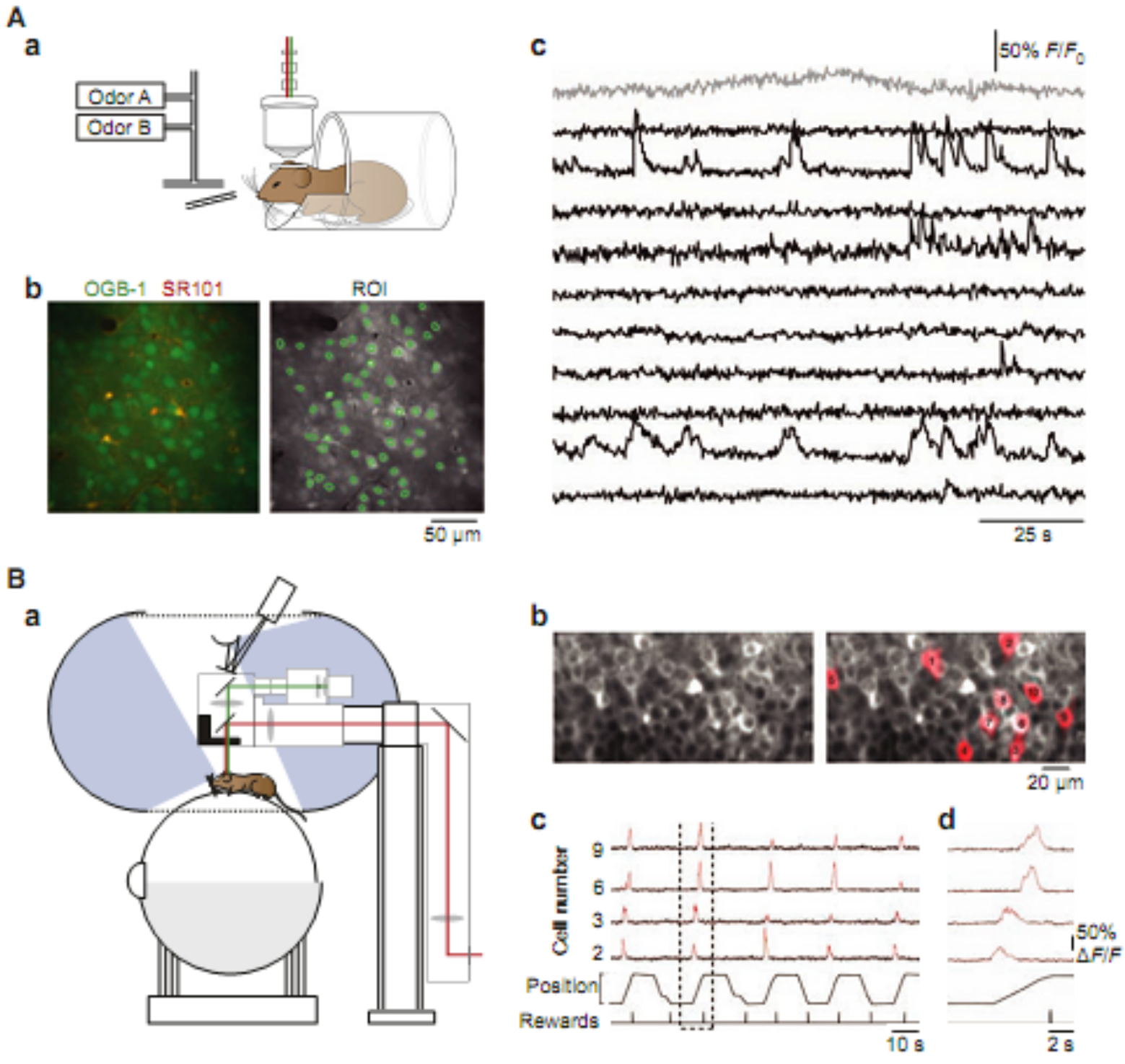
Study activation of neural networks



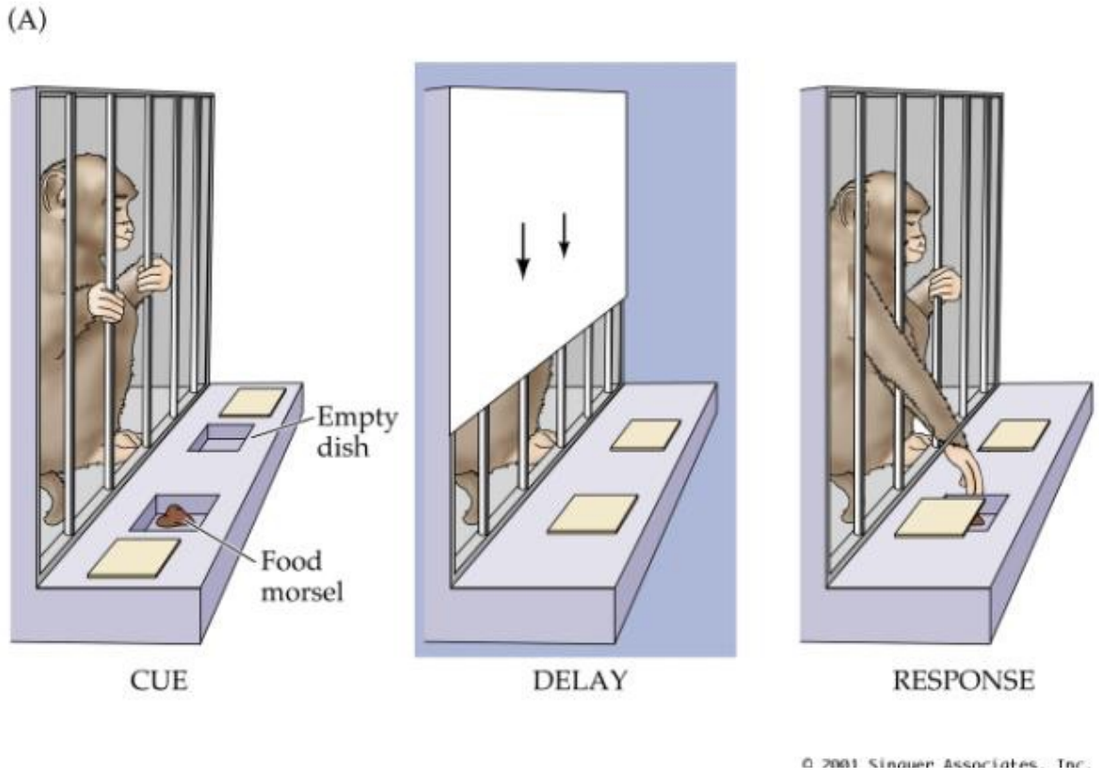




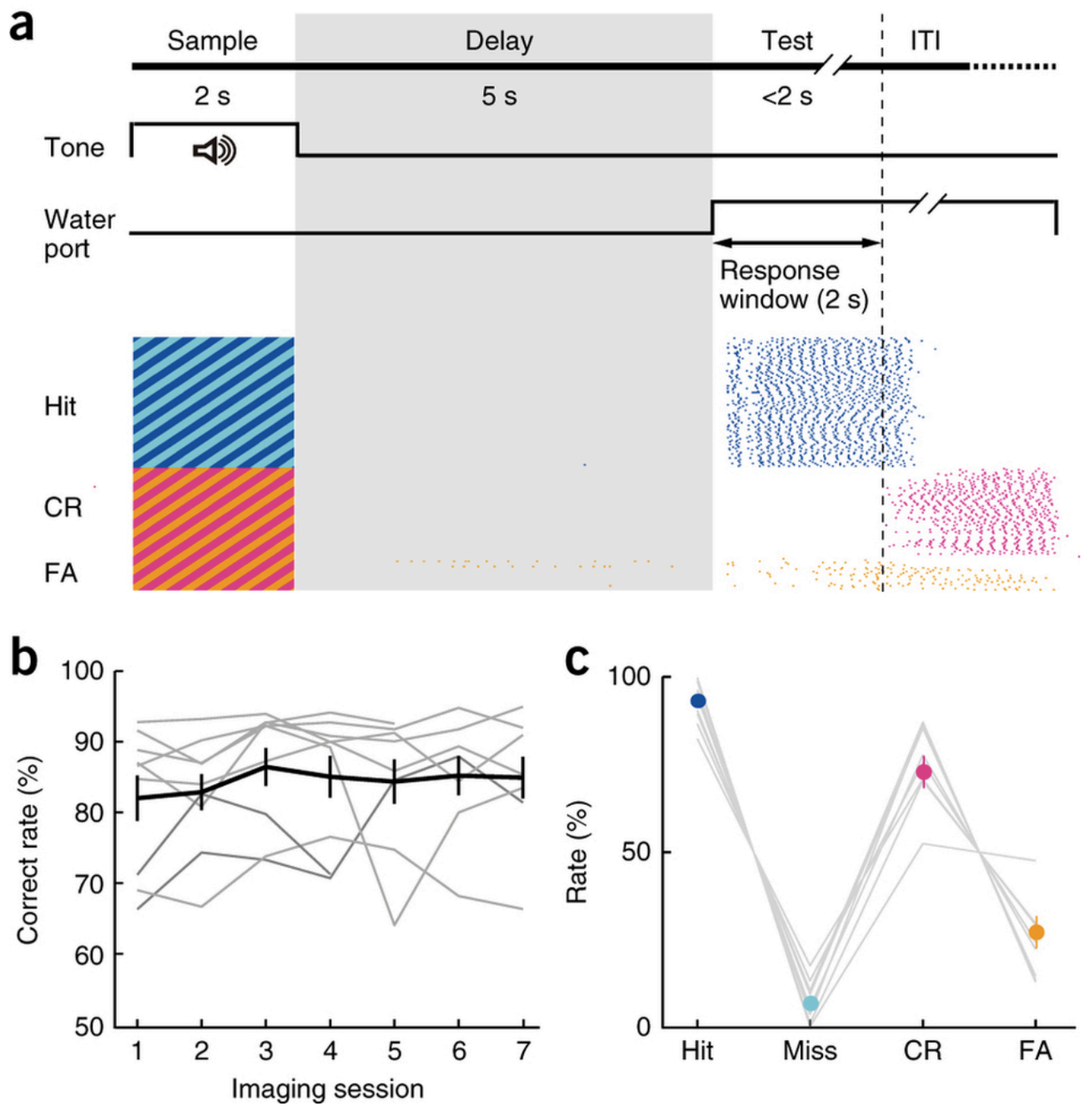
In vivo activation of neural networks



Neuronal activity during working memory tasks

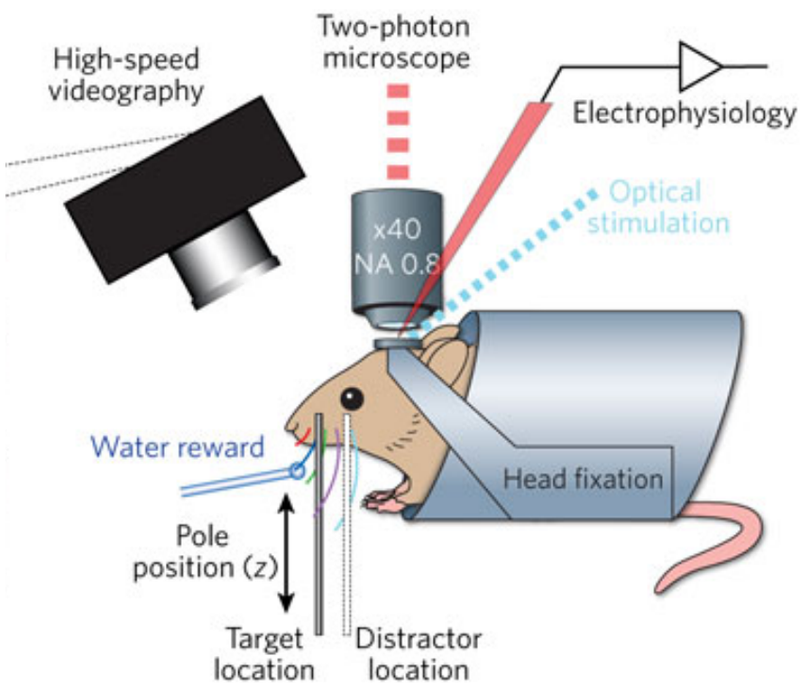


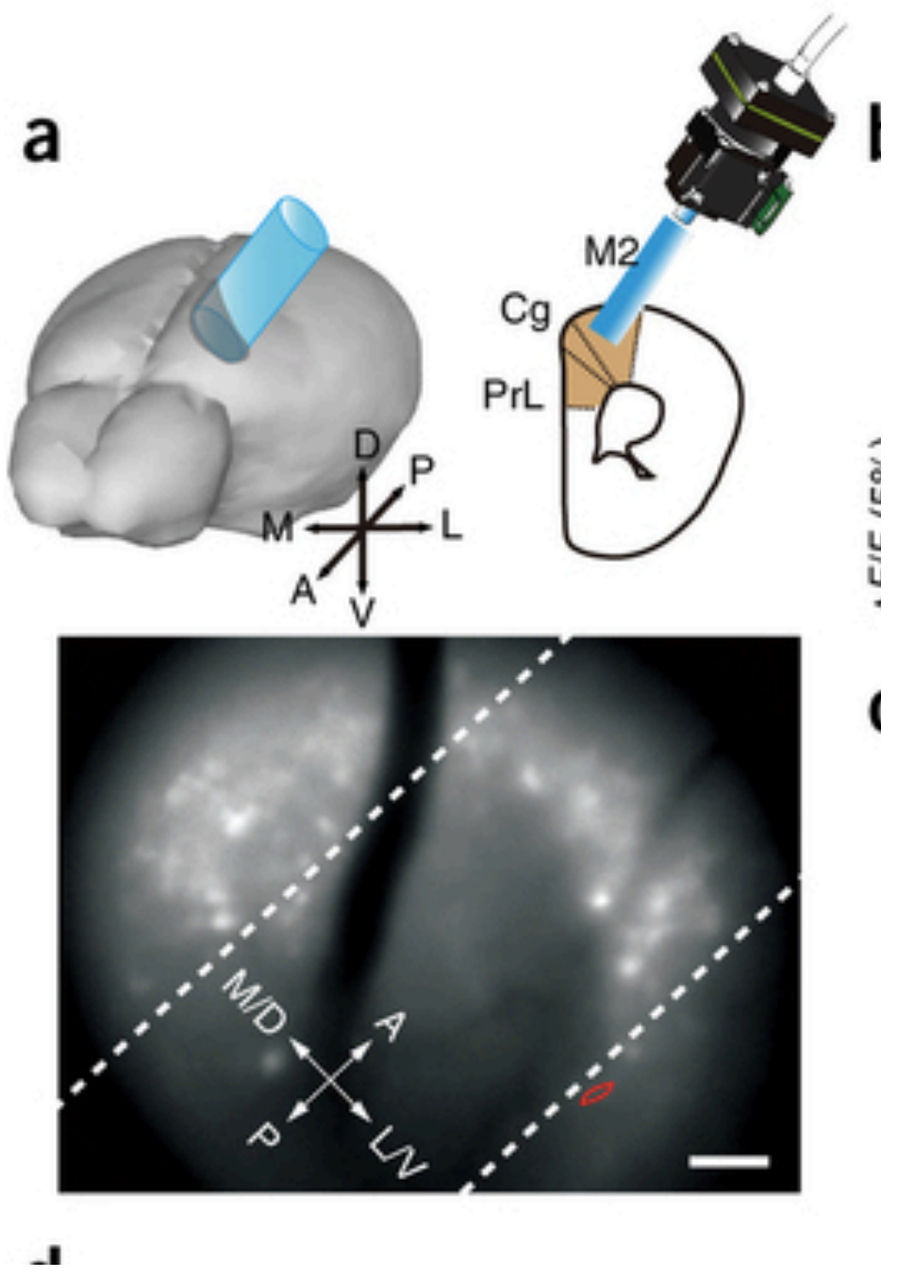
Working memory task in head-fixed animals



To image task-related neuronal activity….

- head-fixed mice
- CaMKIIα-Cre mice
- Cre-inducible adeno-associated virus (AAV) expressing the calcium indicator GCaMP6f30 into the dorsomedial PFC (dmPFC)

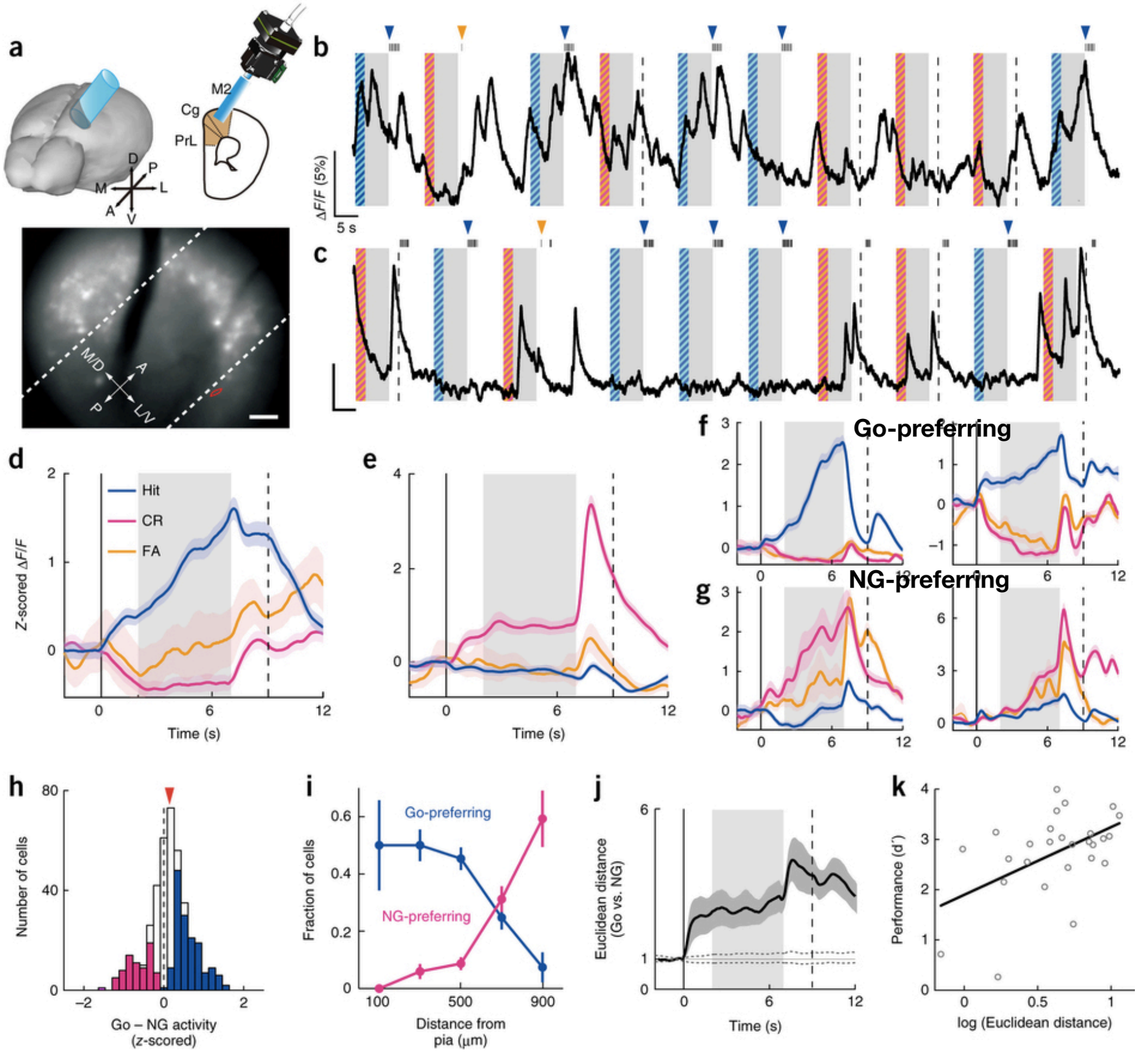




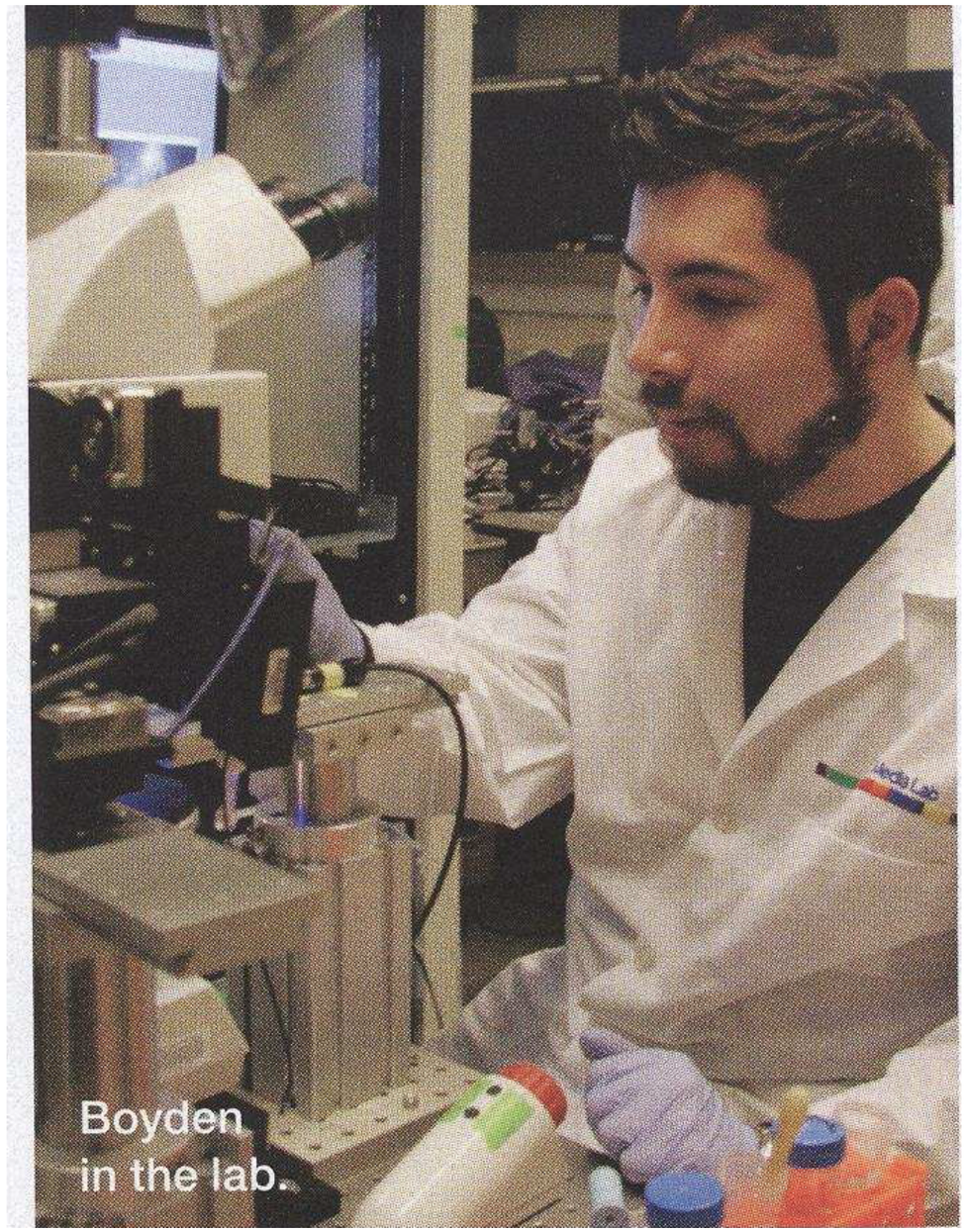
modified from O'Connor DH et al 2009

Pyramidal neuron activity during the delayed Go vs. No-Go task.

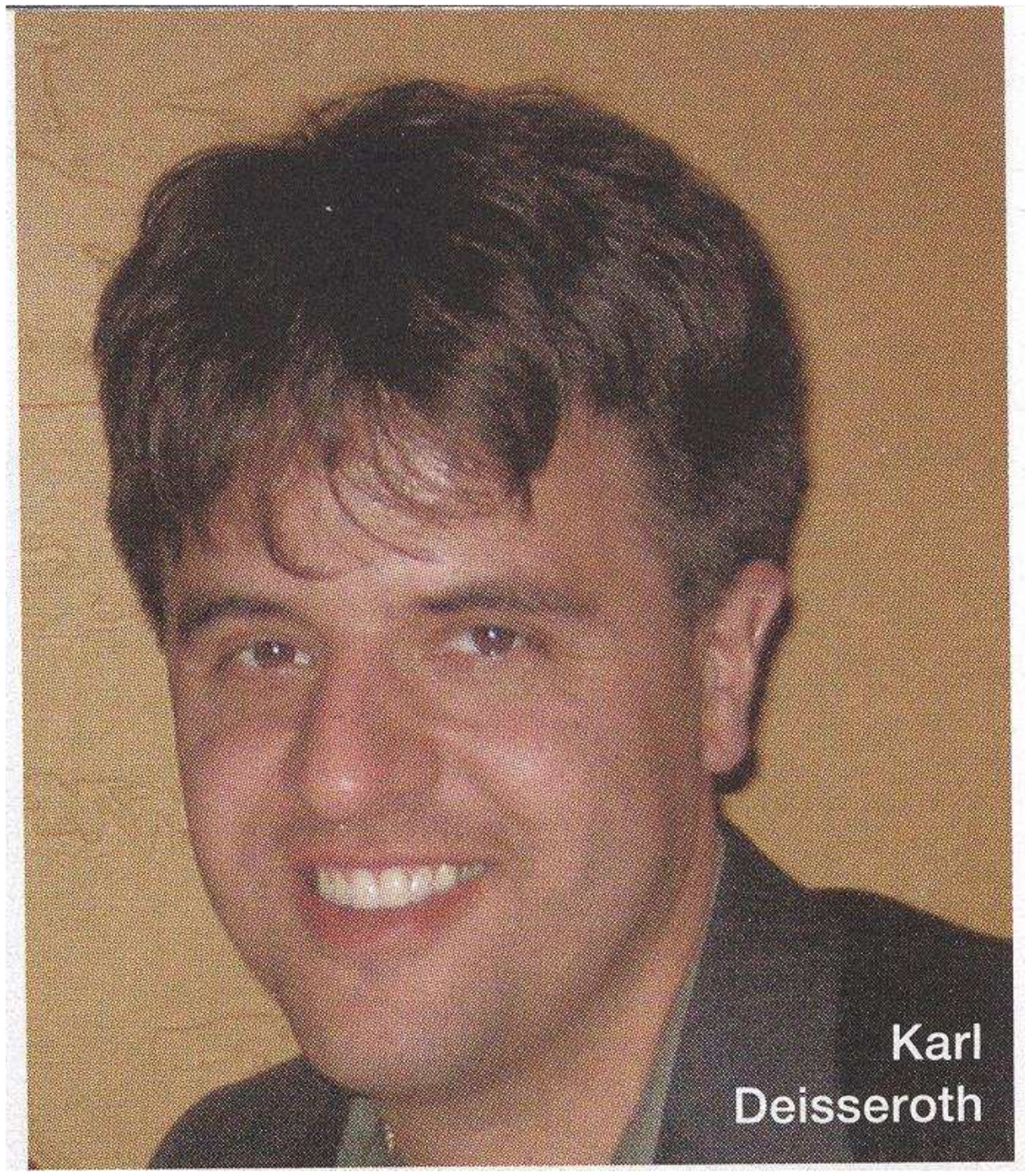
Gray shading: delay period
Blue stripes: sample periods with target tone
Orange stripes: sample periods with nontarget tones,
Dashed line: end of response window in CR trials.
Black tick on top: lick response.
Blue arrowheads: delivery of reward
Orange arrowheads: punishment



Optogenetics



Ed Boyden, MIT

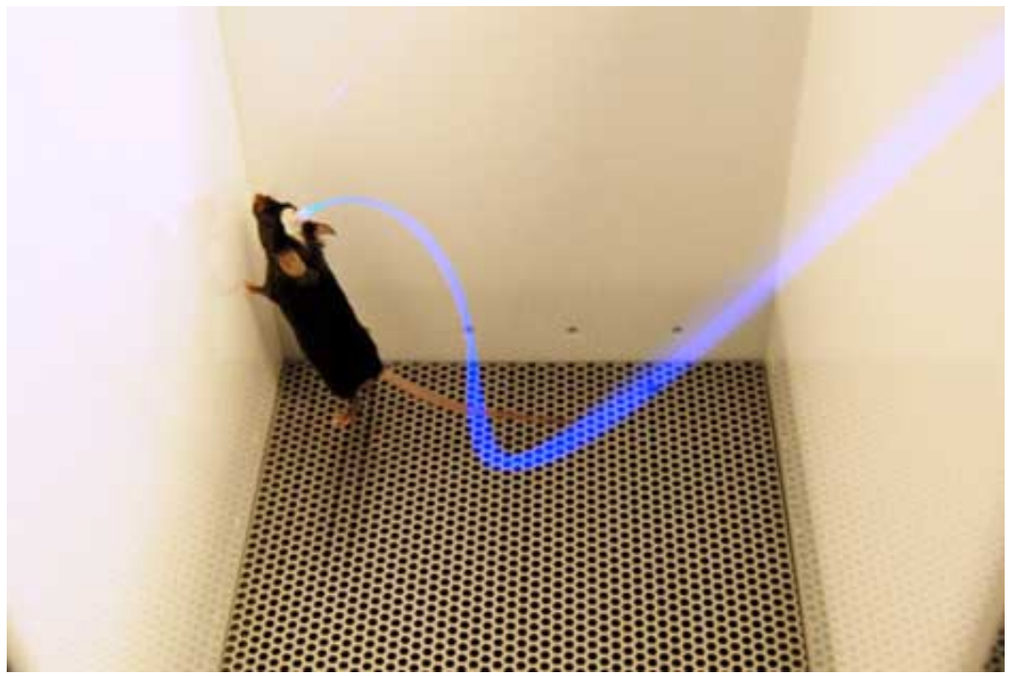


Karl Deisseroth, Stanford

Optogenetics

"The major challenge facing neuroscience was the need to control one type of cell in the brain while leaving others unaltered. Electrical stimuli cannot meet this challenge."

- Francis Crick



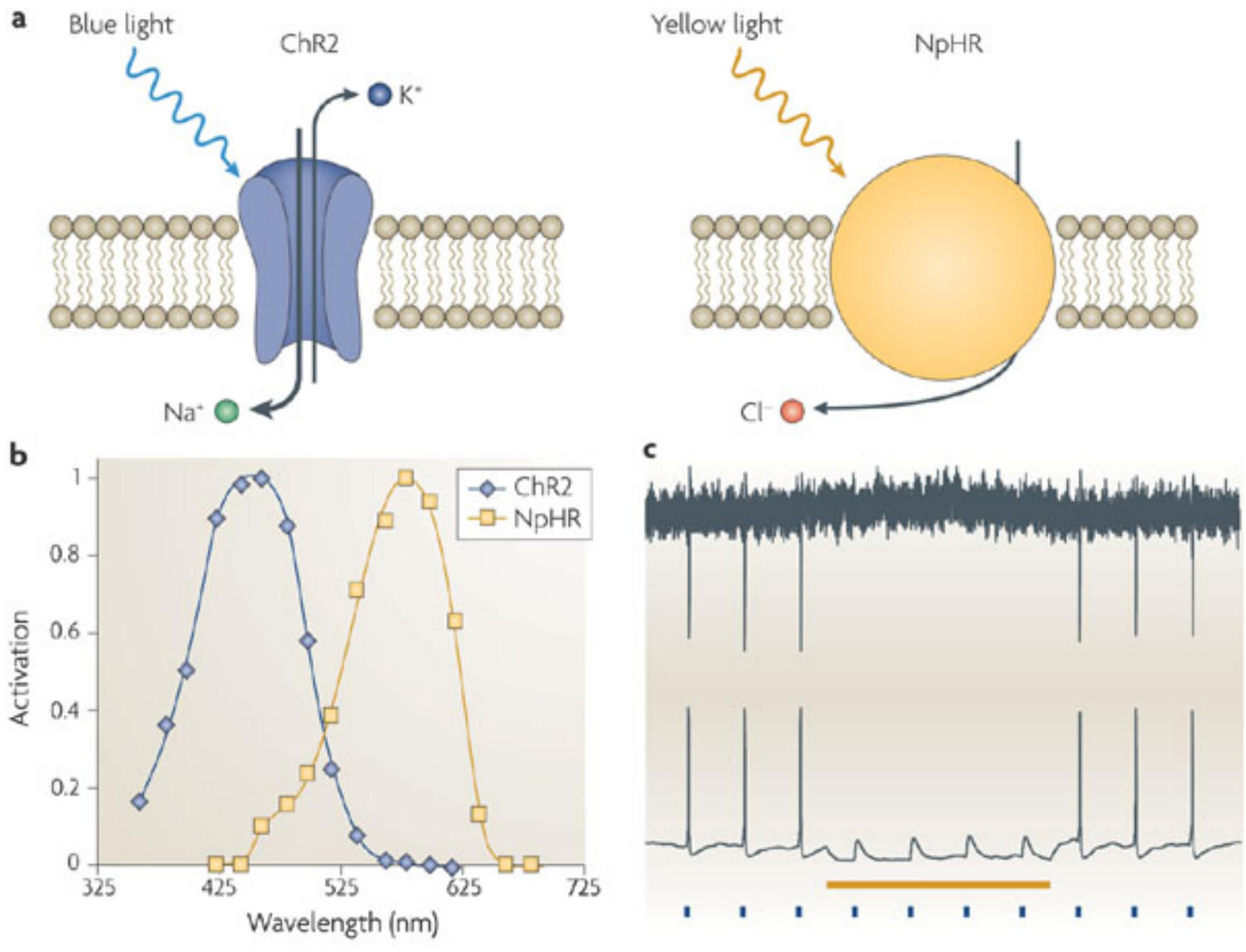
Optogenetics

- Combination of optical and genetic techniques for specifically controlling neuronal subtypes
- Use of ion channels that are activated by light, are expressed in archeobacteria and not expressed in animals

Channels used to control excitability
Opsins

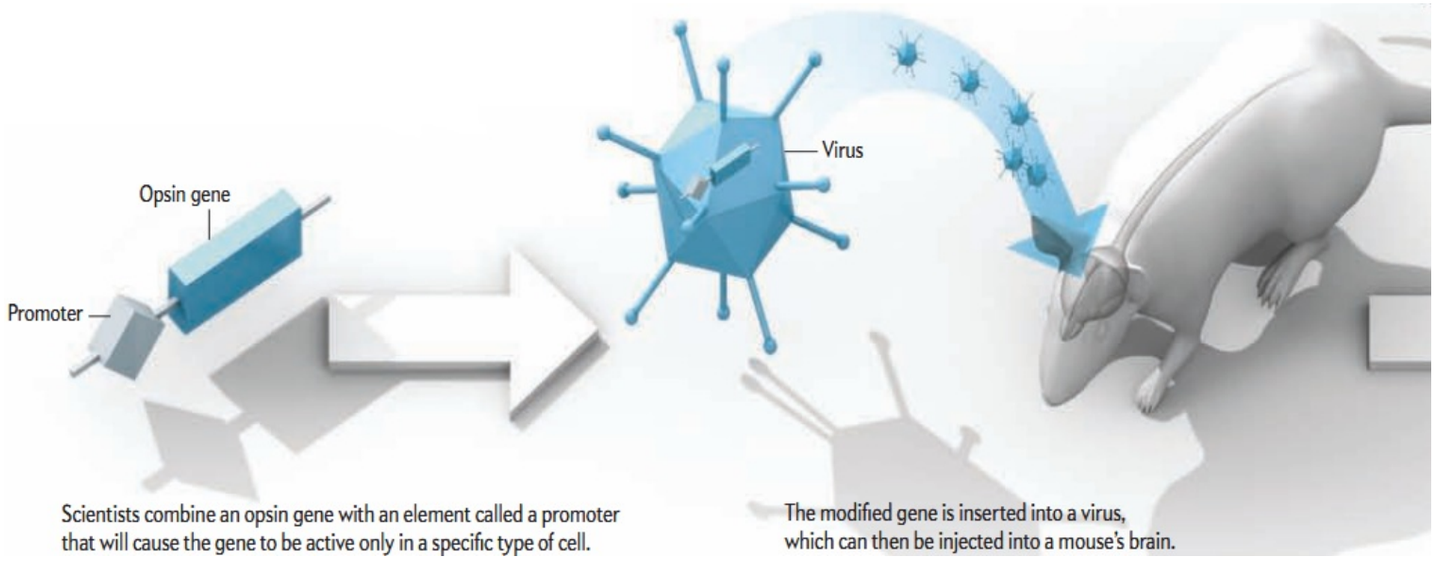
Chlmydomonas reinhardtii
Channelrhodopsin-2

Natronomonas pharaonis
Halorhodopsin



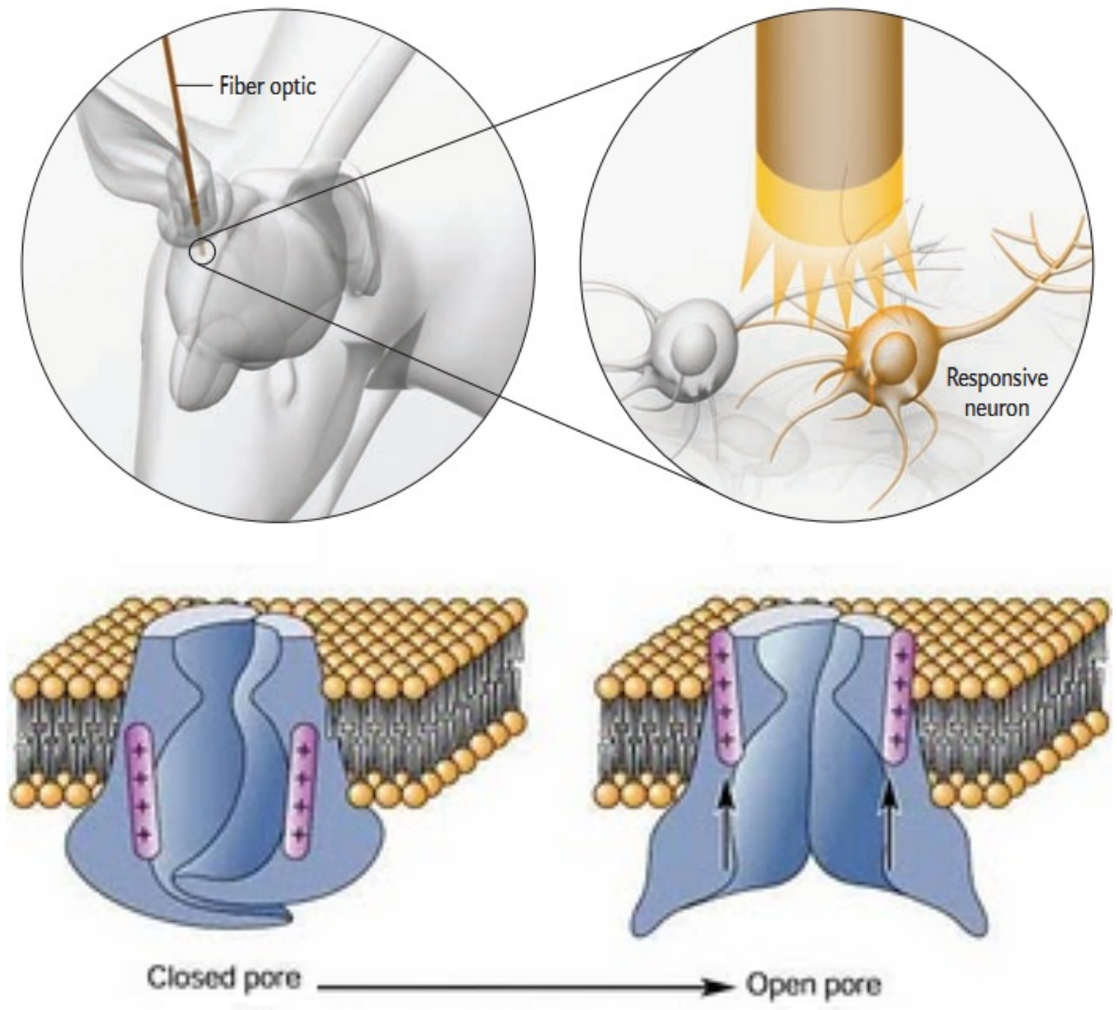
Nature Reviews | Neuroscience

Step 1: Expression of opsin in the desired neuronal population



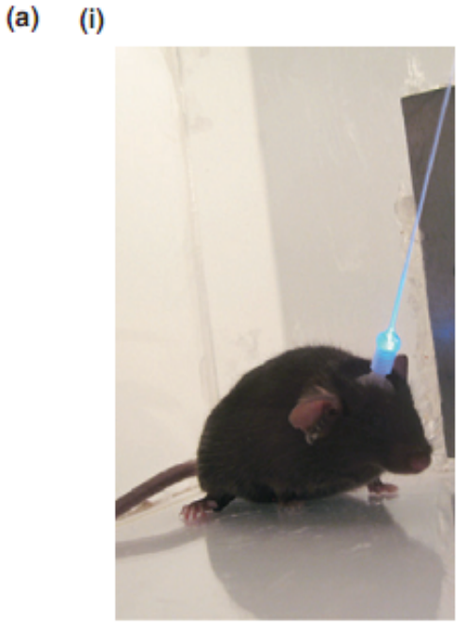
- Viral transfection
- Use of Cre-loxP system in mice
- PV-cre mice
- Som-cre mice
- CamKII-cre mice

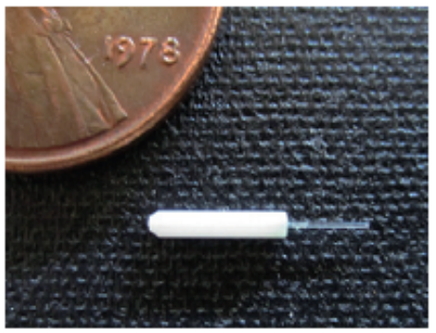
Step 2: Activate opsin with light

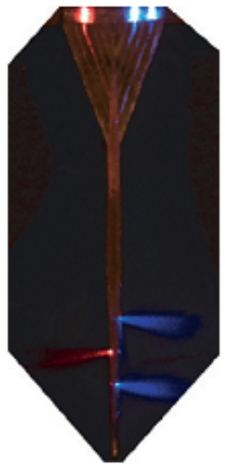


1: *Controlling the Brain with Light* by Karl Deisseroth, Scientific American, November, 2010, pages 49-55

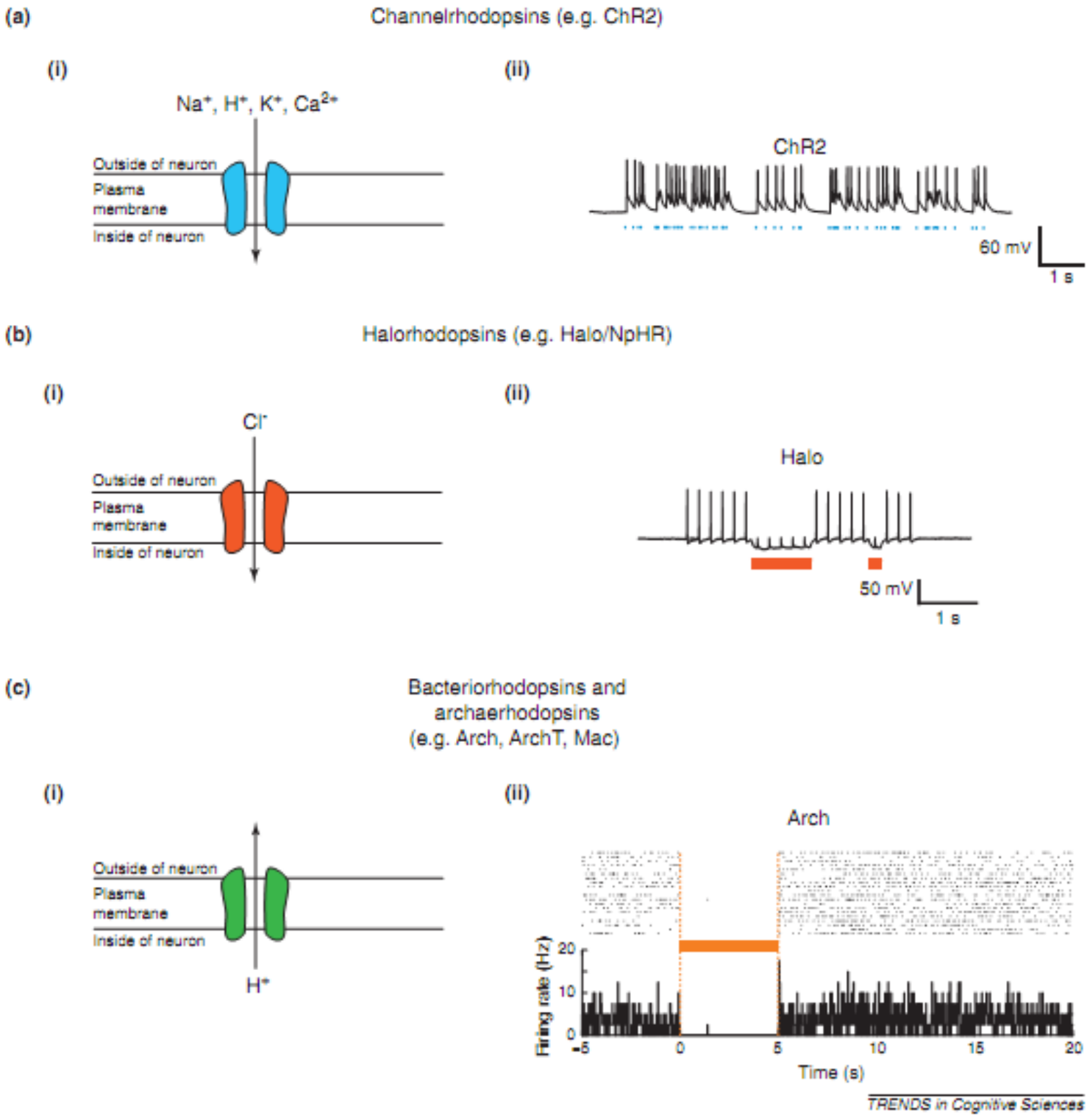
How to direct light into the brain: Optical fibres



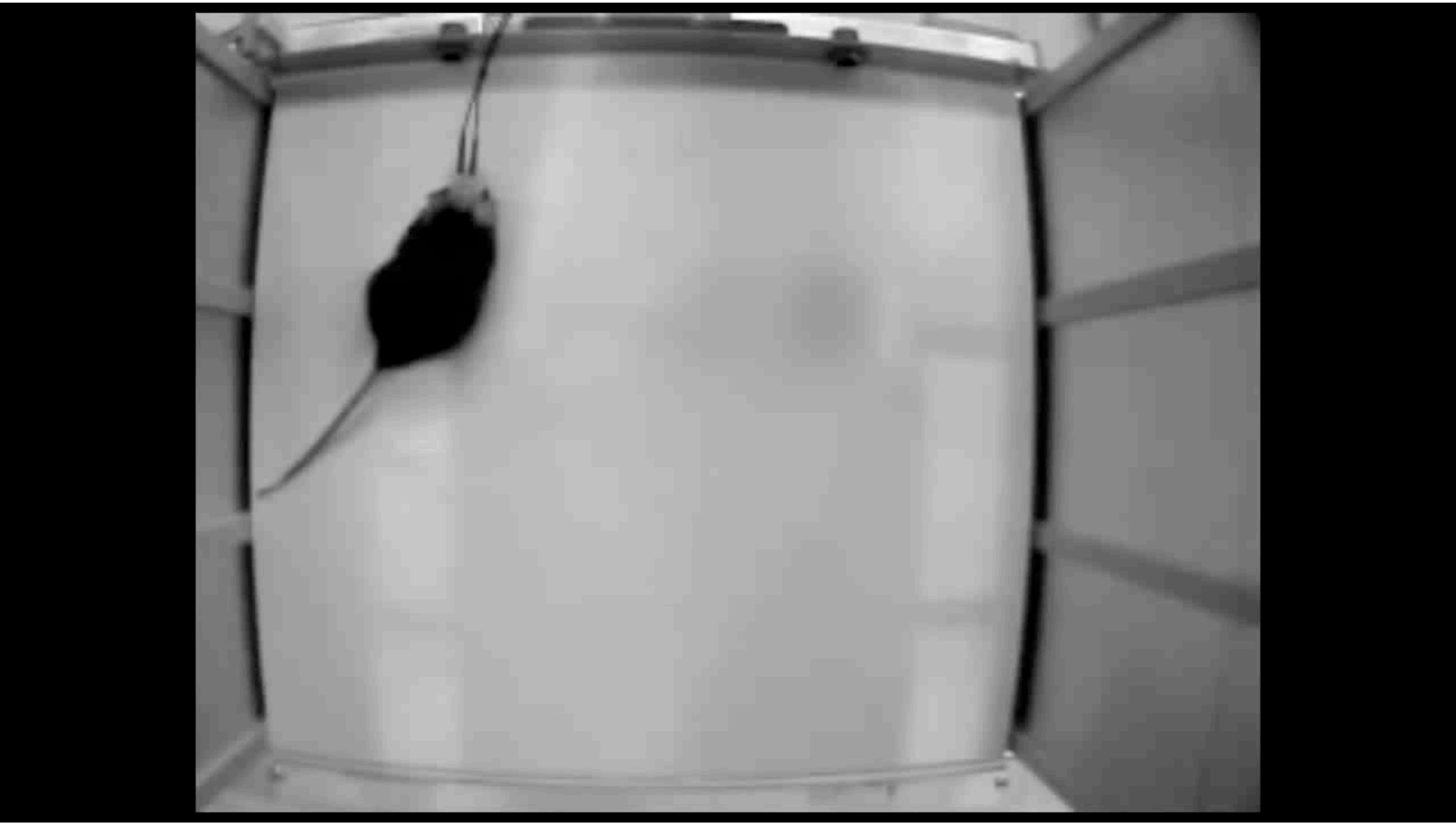




Verifying the effect of opsin expression in neurons



Using optogenetics to study behaviour



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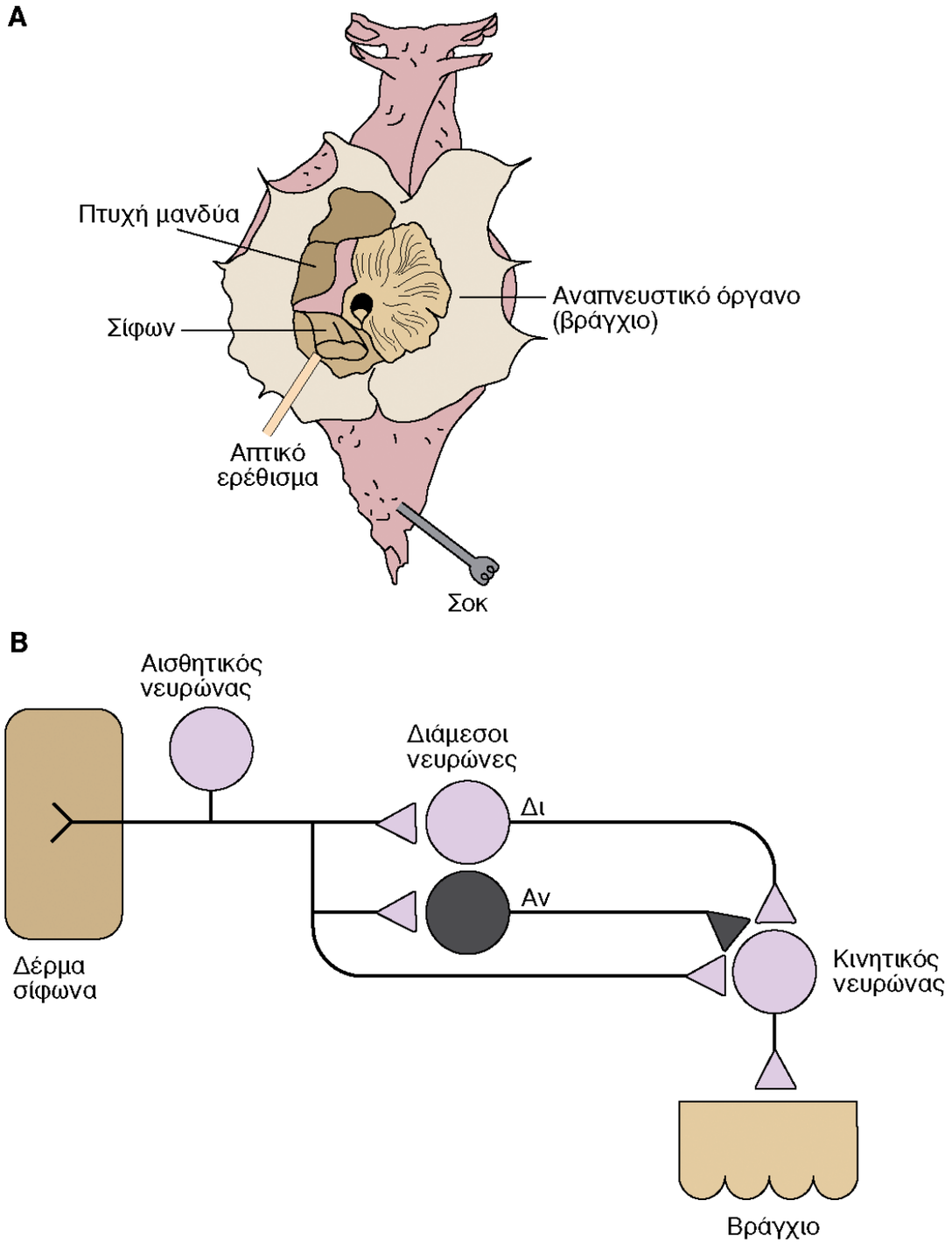
Aplysia californica

http://brembs.net/learning/aplysia/aplysia.html

Αντανακλαστικό απόσυρσης βραγχίου

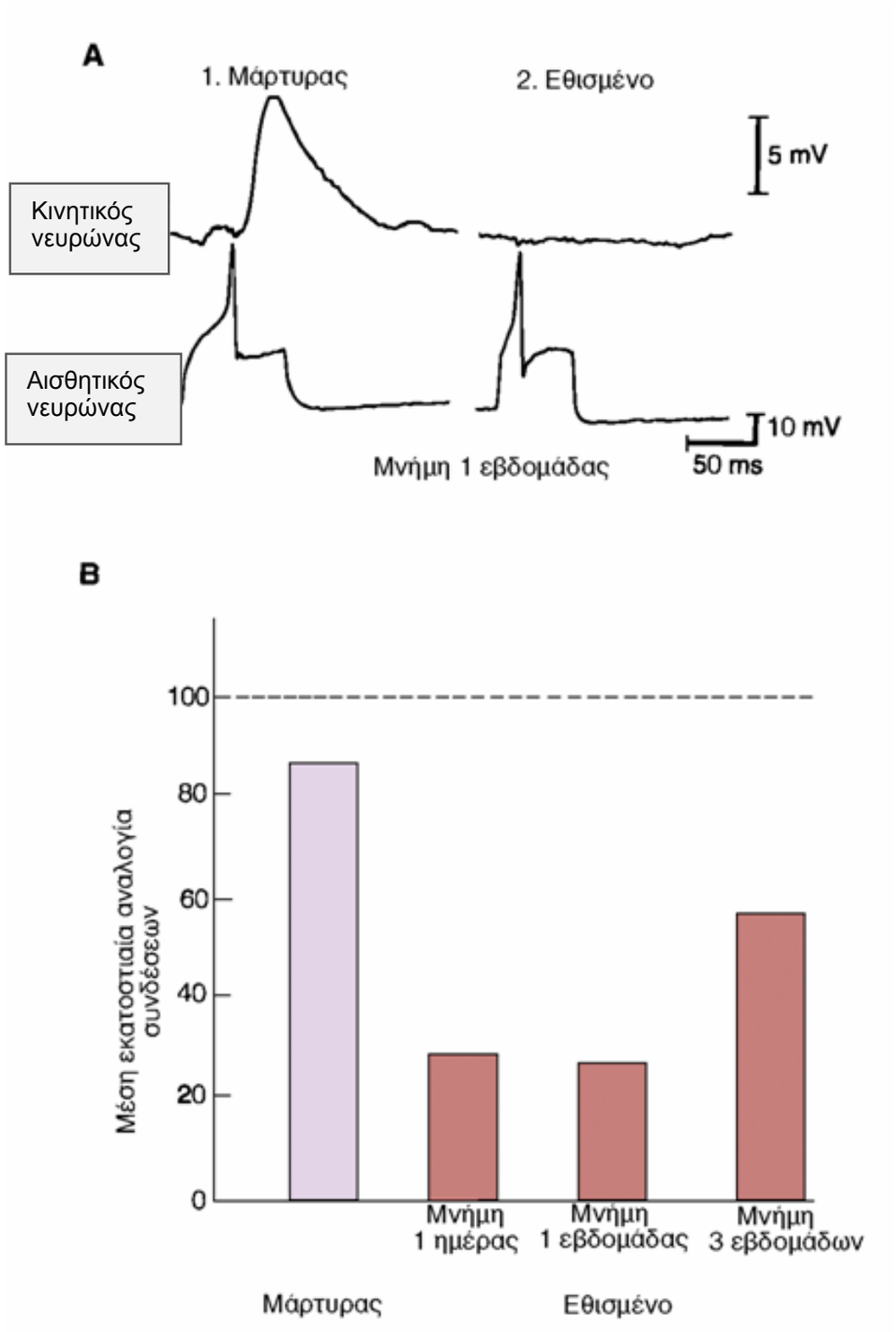


Sensitization of the gill-withdrawal reflex

http://www.hhmi.org/biointeractive/aplysias-gill-withdrawal-reflex-and-sensitization#video-7b9676a4-5f24-4837-9aaf-9352eed43c1e

Habituation

Εθισμός

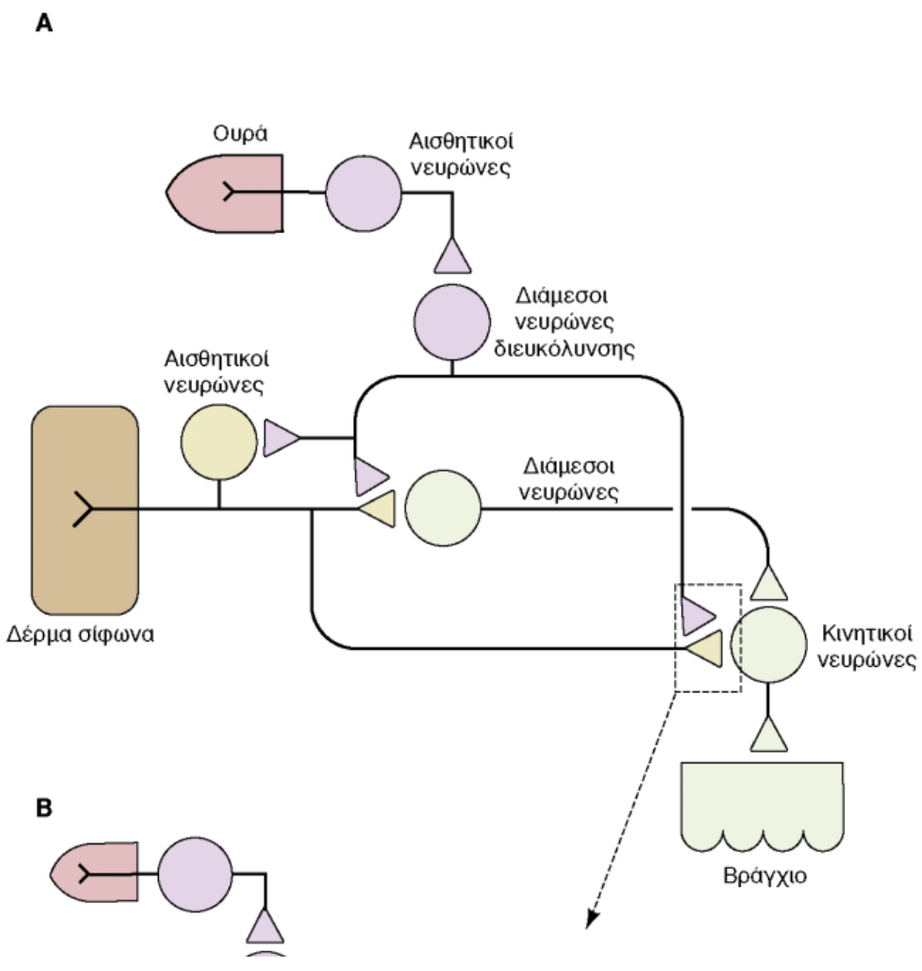


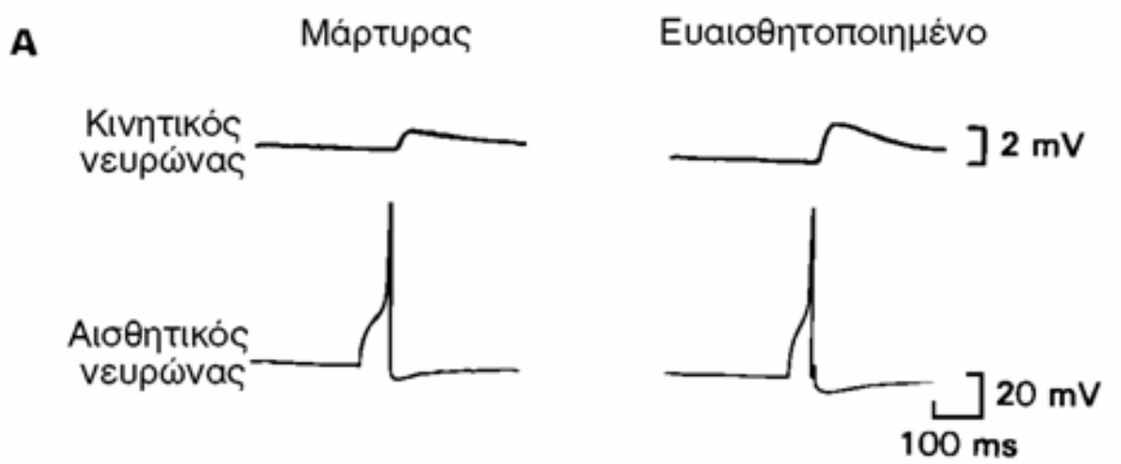
Η επανάληψη ενός ερεθίσματος προκαλεί μείωση στην απόκριση που προκαλεί

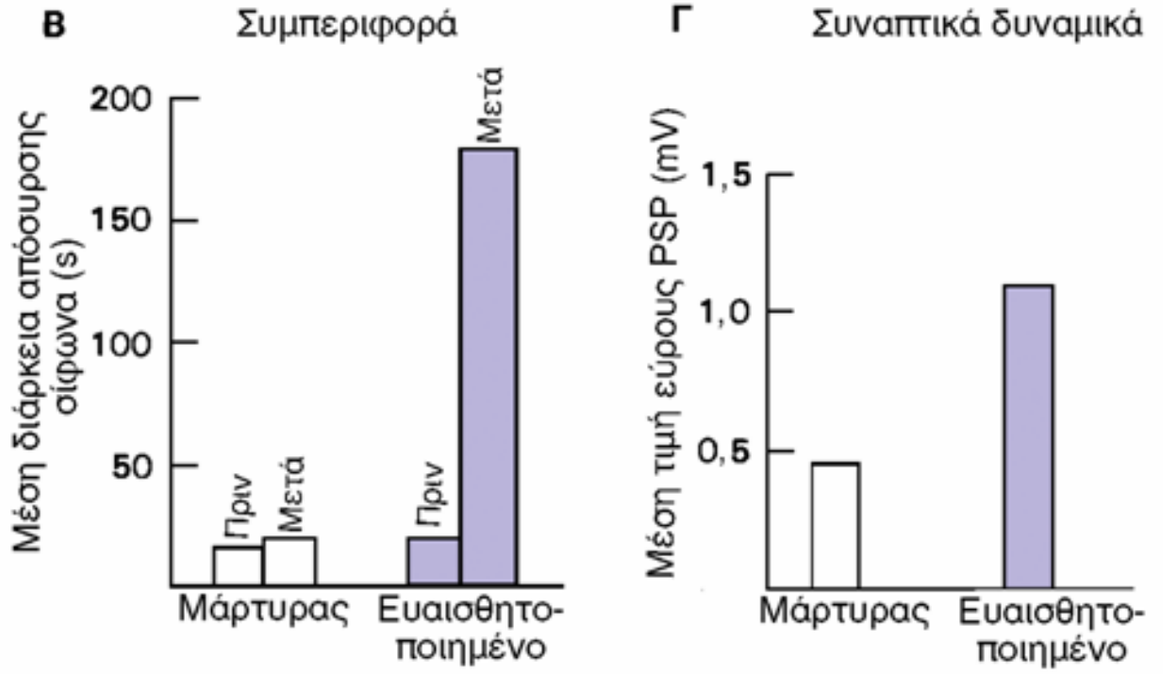
<u>Μηχανισμός</u>
Μείωση της έκλυσης γλουταμινικού οξέως

Ευαισθητοποίηση

Διεγερτικό ερέθισμα στην ουρά -> ευαισθητοποίηση του αντανακλαστικού της απόσυρσης βραγχίου
Μηχανισμός: Ετεροσυναπτική διευκόλυνση

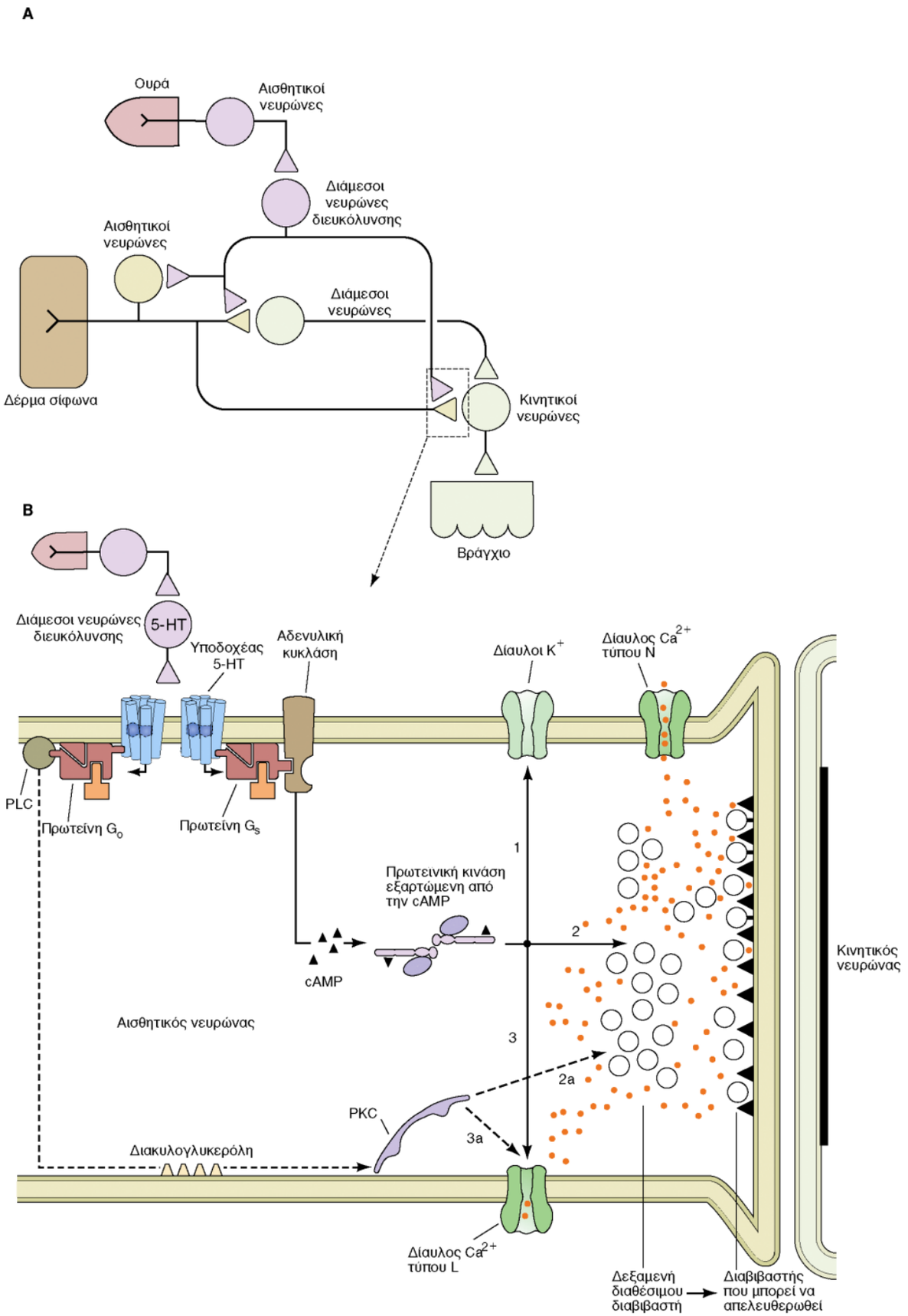






Μηχανισμός της βραχύχρονης ευαισθητοποίησης

Ετεροσυναπτική διευκόλυνση



Αύξηση του cAMP

- μείωση ρευμάτων καλίου
- αύξηση ρευμάτων ασβεστίου

Connectome