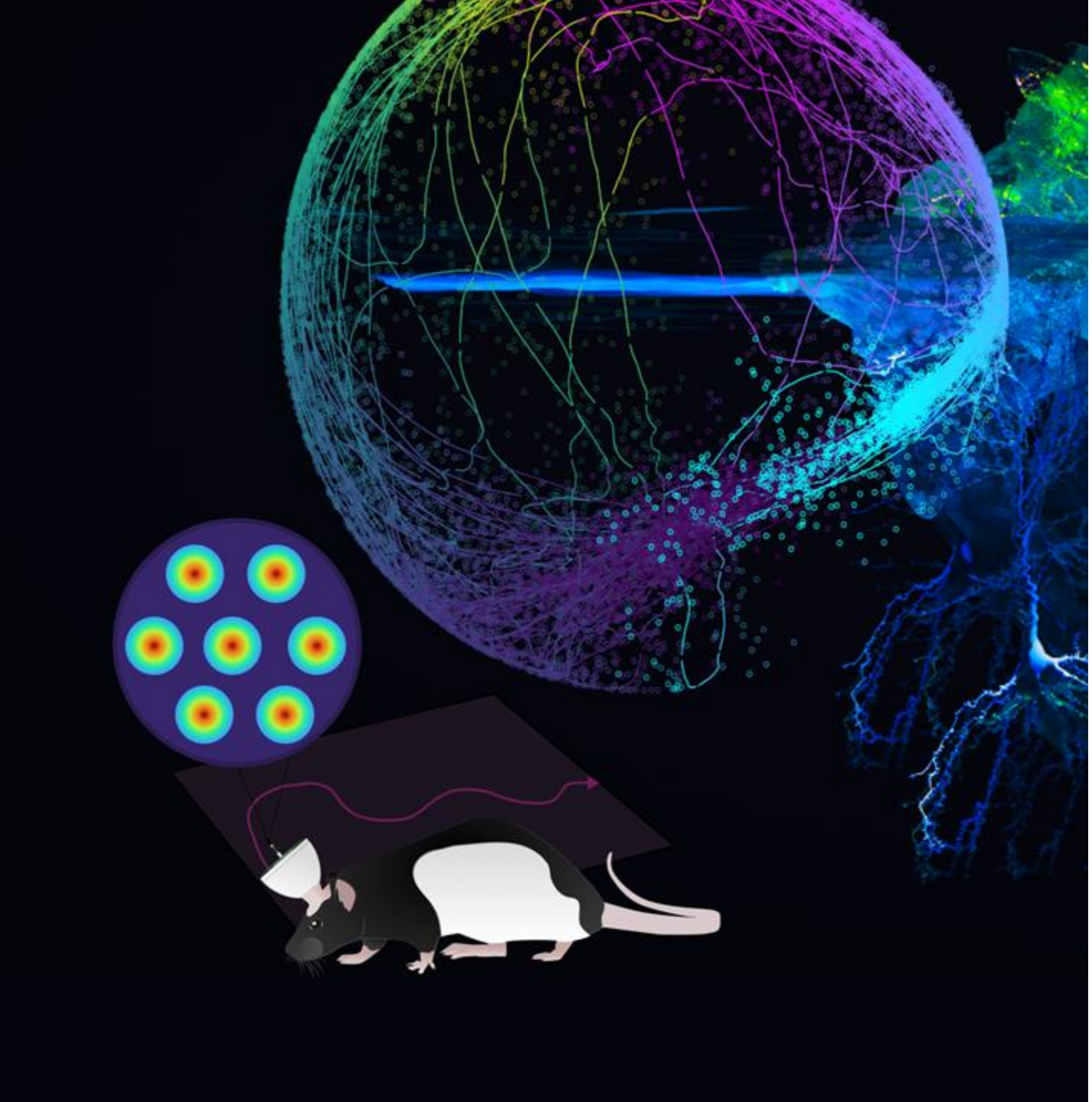
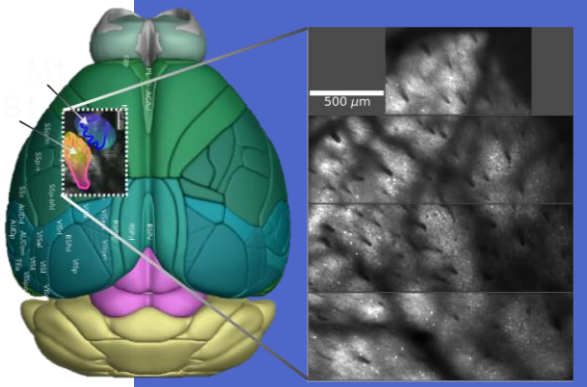


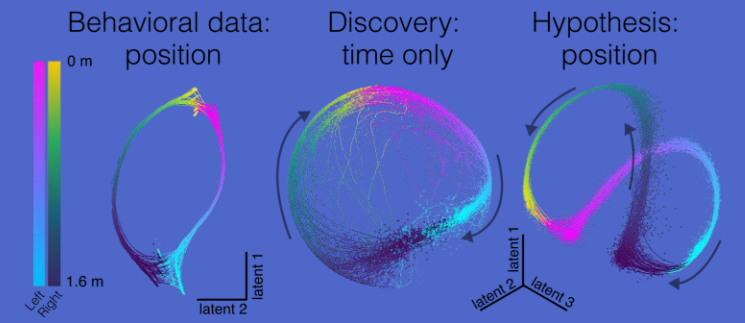
NX-435
Systems Neuroscience

Prof. Mackenzie Mathis, PhD
Spring 2025

Who am I?

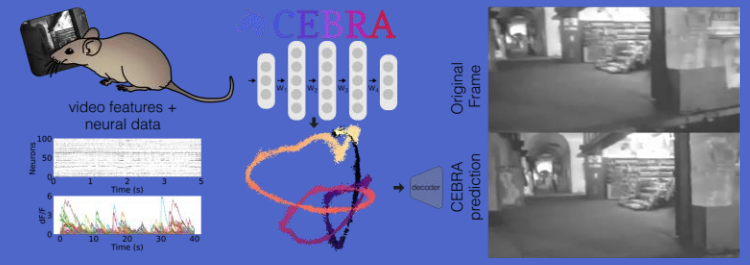
- **Assistant Professor at EPFL since 2020**
- **Rowland Fellow at Harvard 2017-2020**
- **PhD Harvard | Systems Neuroscience**

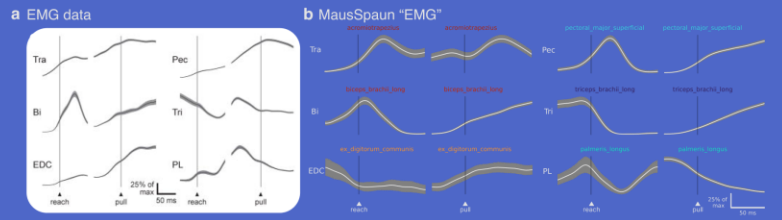


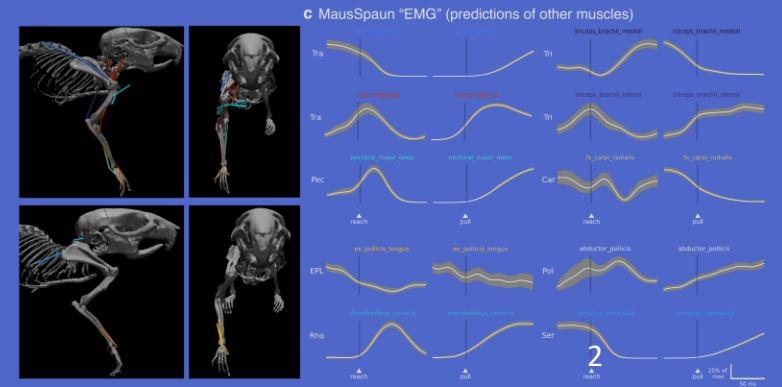


Merging machine learning & neuroscience

The lab revolves around two interactive areas: developing open source machine learning tools & uncovering neural dynamics during adaptive behaviors. Specifically, we design naturalistic and skilled sensorimotor assays for mice, perform large-scale neural recordings, and build tools to aid in our quest of finding internal models in the brain. Sensorimotor control mandates adaptability, and therefore we see it as the optimal system for better understanding intelligence.







My office hours:

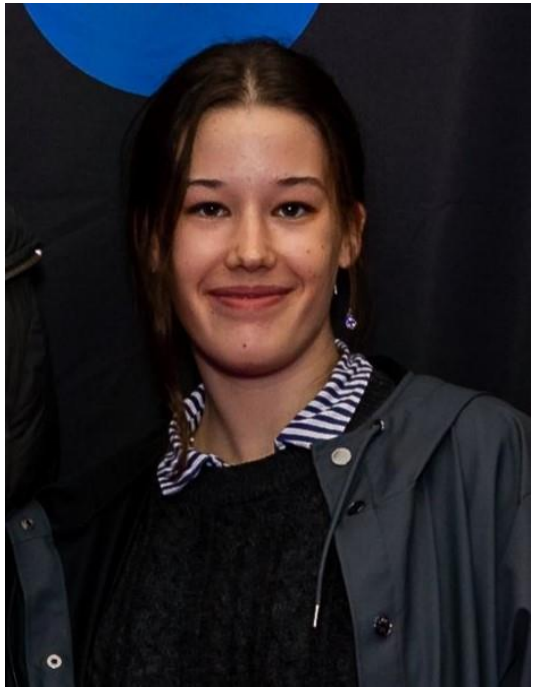
Thursdays, 3-4pm in SV 2811

email: mackenzie.mathis@epfl.ch

https://www.mackenziemathislab.org/

Teaching team

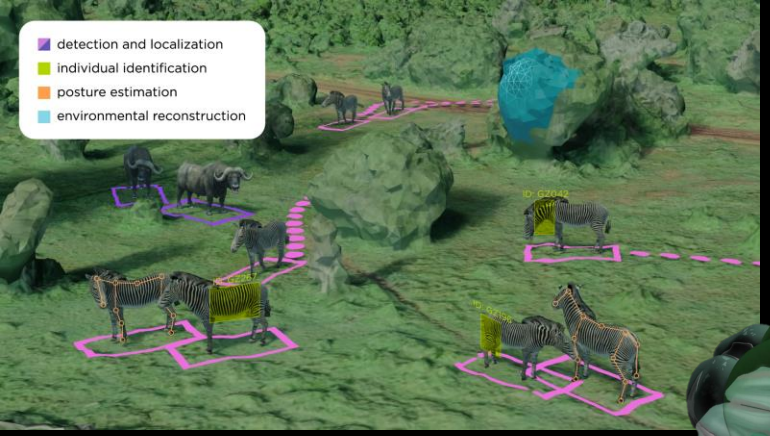
EDEE PhD candidate



EDNE PhD candidate

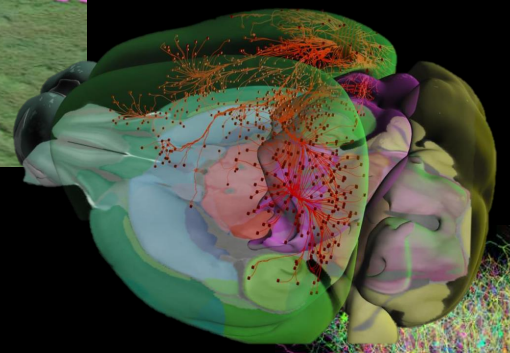
- **Célia Benquet**
- **Myriam Hamon**

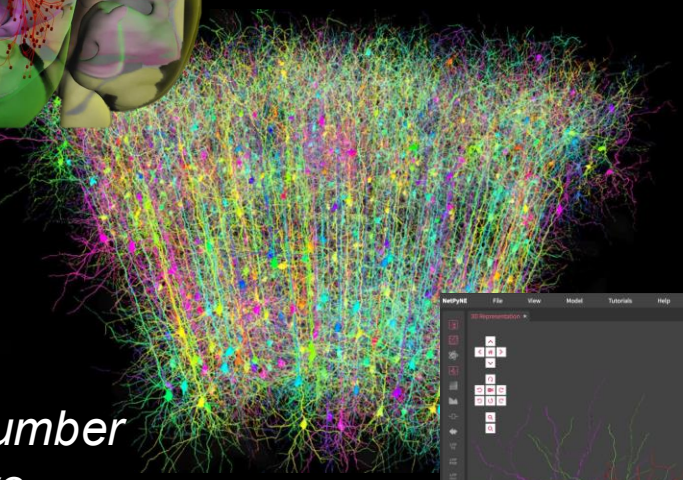
- **Spencer Bowles (a lecture on BMIs + hands-on expts!)**
- **Thomas Sainsbury (a lecture on fish & vision + hands-on expts!)**

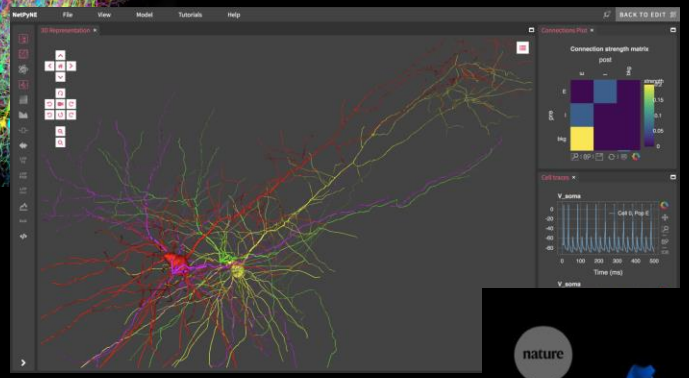


What is Systems Neuroscience?

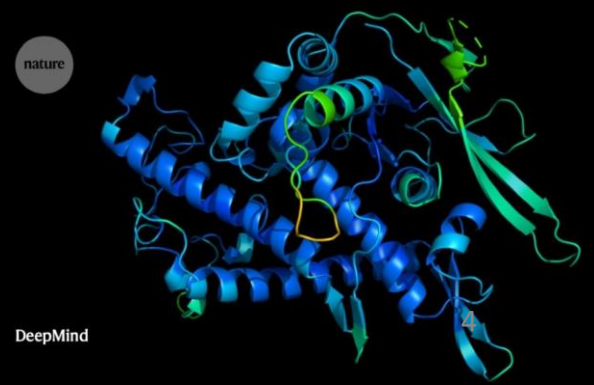
*"**Systems neuroscience** is a subdiscipline of neuroscience and systems biology that studies the structure and function of neural circuits and systems." - Wikipedia*







*"Systems neuroscience encompasses a number of areas of study concerned with how nerve cells behave when connected together to form neural pathways, neural circuits, and larger brain networks. **At this level of analysis, neuroscientists study how different neural circuits analyze sensory information, form perceptions of the external world, make decisions, and execute movements**."*



DeepMind

Neurons

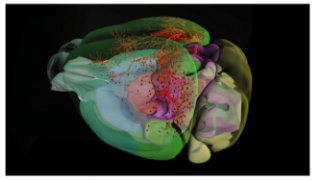
Behavior

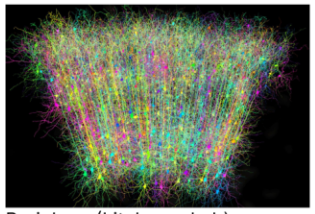
Kandel et al. Principles of Neural Science 2000 (62-2)

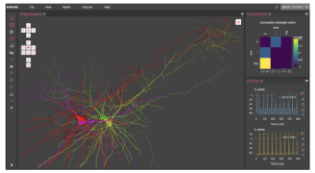
The neural circuits, the dynamics…

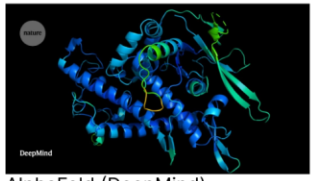
How can we study this?


Tuia et al. 2022


Allen Institute


Brainbow (Litchman Lab)


NetPyNE


AlphaFold (DeepMind)

Environment

Behavior

Brain

system (circuits)

Neurons (& glia)

Synapses

Genes & molecules, proteins

Computation

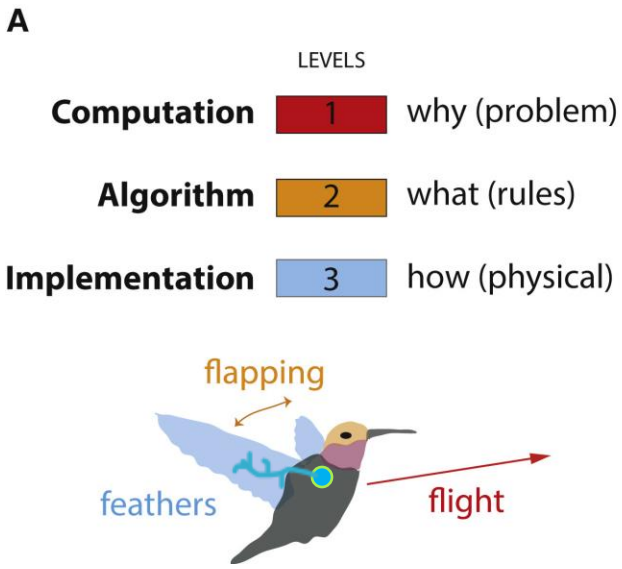
Implementation

Experimentally-derived data

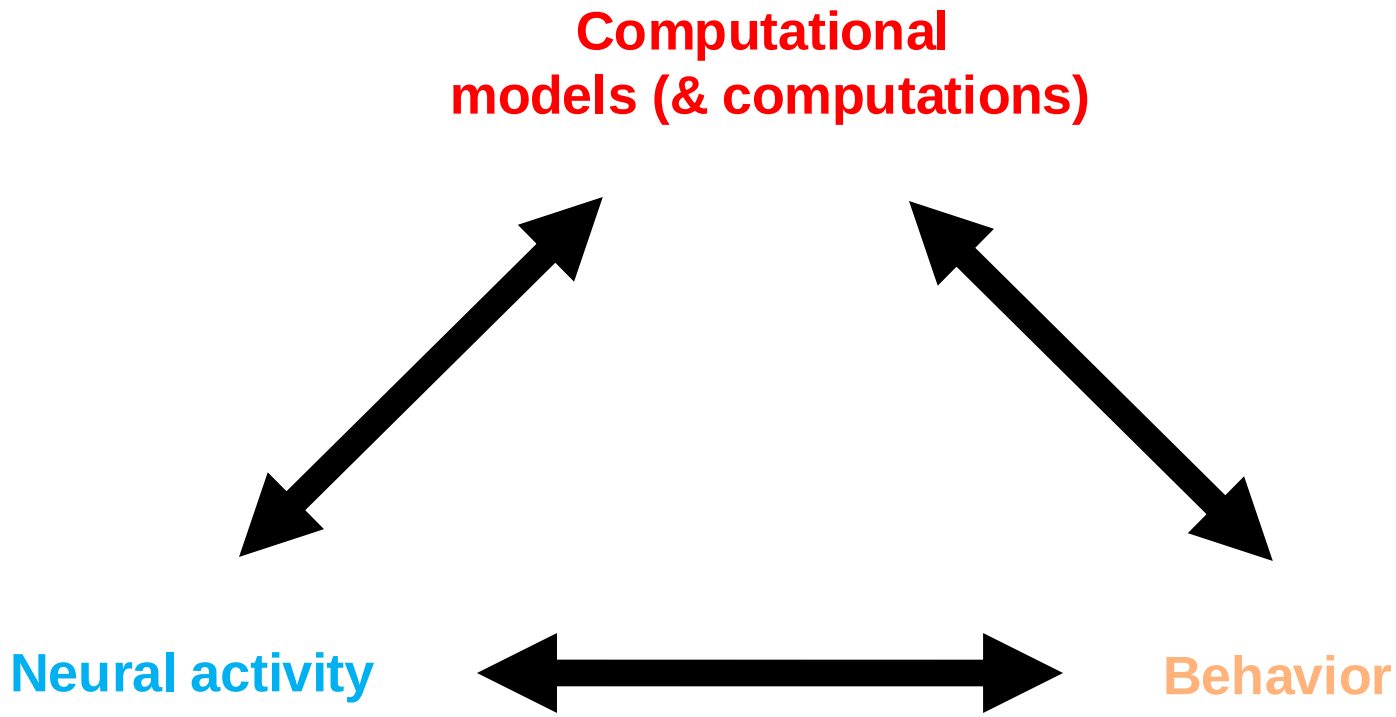
Data-driven & Theory-driven models

Inspired from:
Krakauer et al. Neuron 2017
Basset et al. Nature Neuro 2017
Terry Sejnowski & David Marr

Towards closing the gap between the neuron & behavior



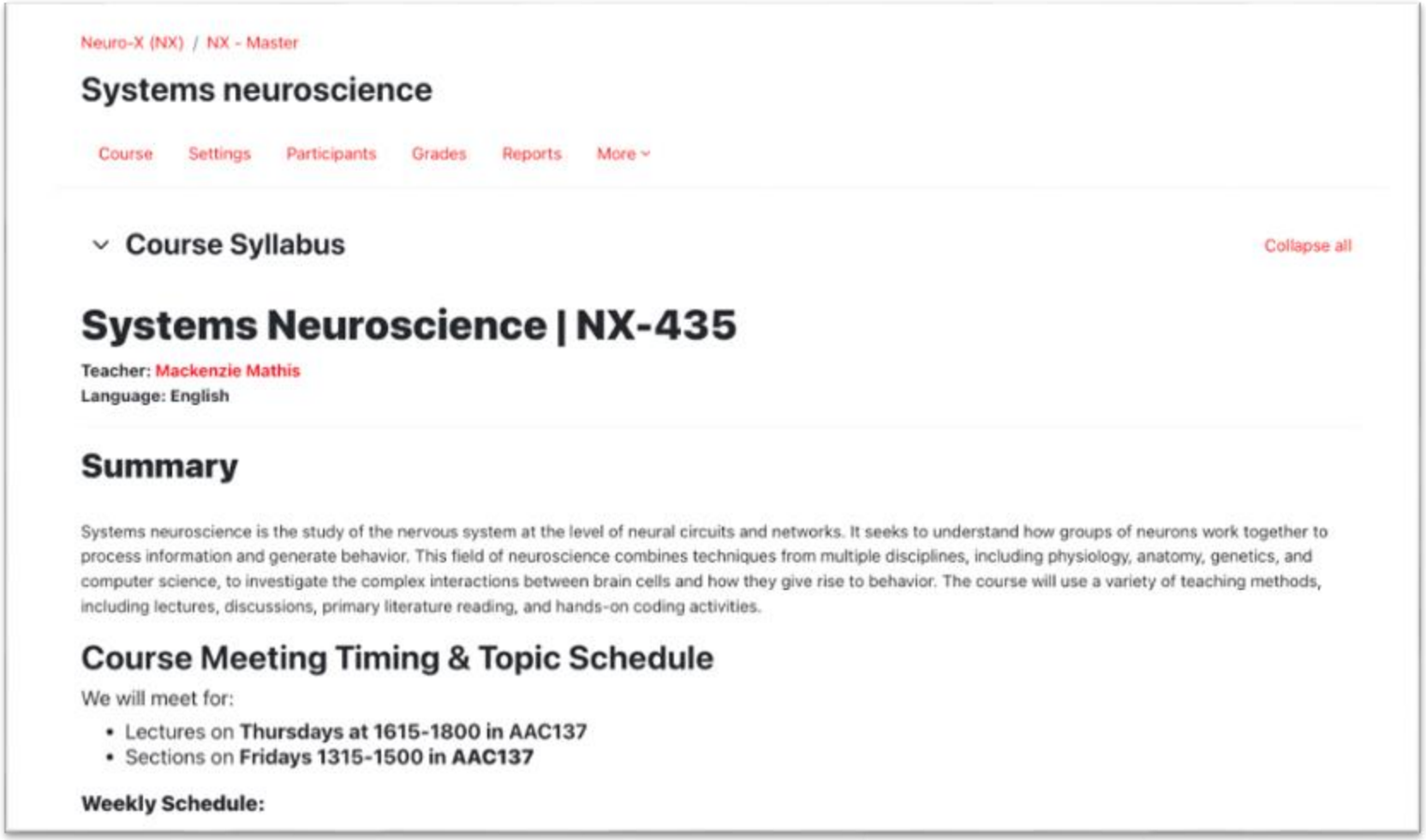
David Marr's three levels,
Krakauer et al. Neuron 2017



Logistics of the class

Everything is on Moodle!

- Course Syllabus
- TA contacts
- Paper Readings
- Slides after class
- Quizzes
- Assignment details
- Forum for discussions!



Logistics of the class

Learning Outcomes:

By the end of the course, you should be able to:

- Learn to effectively read primary literature.
- Understand the principles of neural coding and information processing.
- Understand the current state-of-the-art techniques for studying the brain, including behavior, electrophysiology, optogenetics, and functional imaging.
- Apply computational approaches to study specific brain functions such as sensory processing, motor control, and cognition.
- Understand the relationship between brain circuits and behavior.
- Develop computational skills for analyzing neural data

Logistics of the class

Quizzes:

There will be two short quizzes during the term to account for 25% of your overall grade:

- **Quiz 1:** During Section on W7: covering material from W1-7.
- **Quiz 2**: During Section on W13: covering material from W8-13.

Final Exam:

- During the last week* of the semester (on May 23rd), we will have a final exam covering the material presented in Lectures and Sections throughout the course. This will a written exam. It will count for 25% of your course grade.

Logistics of the class

Problem Sets:
There will be two assignments:

Problem Set 1 (25% of the course grade, DUE April 17th): Write a "News & Views Nature (another example set here: News & Views Nature Neuroscience)" style article (~1,000 words) on one of the assigned papers. News & Views are generally written by specialists for broader scientific audiences. The goal is for you to write about one of the assigned readings (from any time point in the course). The learning objective is to read primary research articles and learn to summarize them in the broader context of the field. For example, here is one from Prof. Mathis.

✨ **You have 1 week to dedicate time to this!**

Problem Set 2 (25% of the course grade, DUE May 15th): Now that you are about to venture off to do thesis projects in labs, let's build your skills at formulating science! The goal is to write a small research proposal to help you craft your critical thinking. Please write a 2-3 page (11pt font, 1.5 line spacing) proposal that includes: (1) Background & Introduction; (2) Scientific Aim(s): Hypothesis, Methods; (3) Anticipated Results; (4) References. An example is provided on Moodle!

✨ **You have 1 week to dedicate time to this!**

Weekly Schedule!

Weekly Schedule:

W1: Introduction to Systems Neuroscience & Memory
W2: Reward & Reinforcement Learning
W3: Sensorimotor modulation & control
W4: Visual Systems
W5: Neural data analysis
W6: Behavioral data analysis
W7: Encoding of Space *(quiz 1 in section)*
W8: Problem Set #1 work week
W9: NeuroAI
W10: *spring break*  *- no assignments (April 17 - 28th)*
W11: Problem Set # 2 work week
W12: Brain Machine Interfaces for Systems Neuroscience
W13: Cognition & Frontal Cortex *(quiz 2 in section)*
W14: Emerging topics in systems neuroscience & **FINAL EXAM May 23rd**

Each week you will have:

- An in-person **Lecture** that requires no pre-reading or homework. Please just attend with an open mind and be ready to take notes. Slides will be provided on Moodle for reference after the lecture.

- An in-person **Section** that will typically have 1 paper for assigned pre-reading and then a Journal Club in class. We will have discussions on that paper in depth, thus please come prepared to discuss the work. The papers are posted below in each week. Some Sections will have hands-on learning computational materials that aid in learning (neural or behavioral analysis). Some may also have live demos. Please check the week schedule below to know more!

Reading (Homework)

- **One primary literature paper** will be assigned most weeks and discussed in Section (Fridays)

- The lecture (Thursdays) will provide you will (most) of the relevant background for the paper
  - *Note, we assume you have the required basic neuroscience background (see BIO-311)*

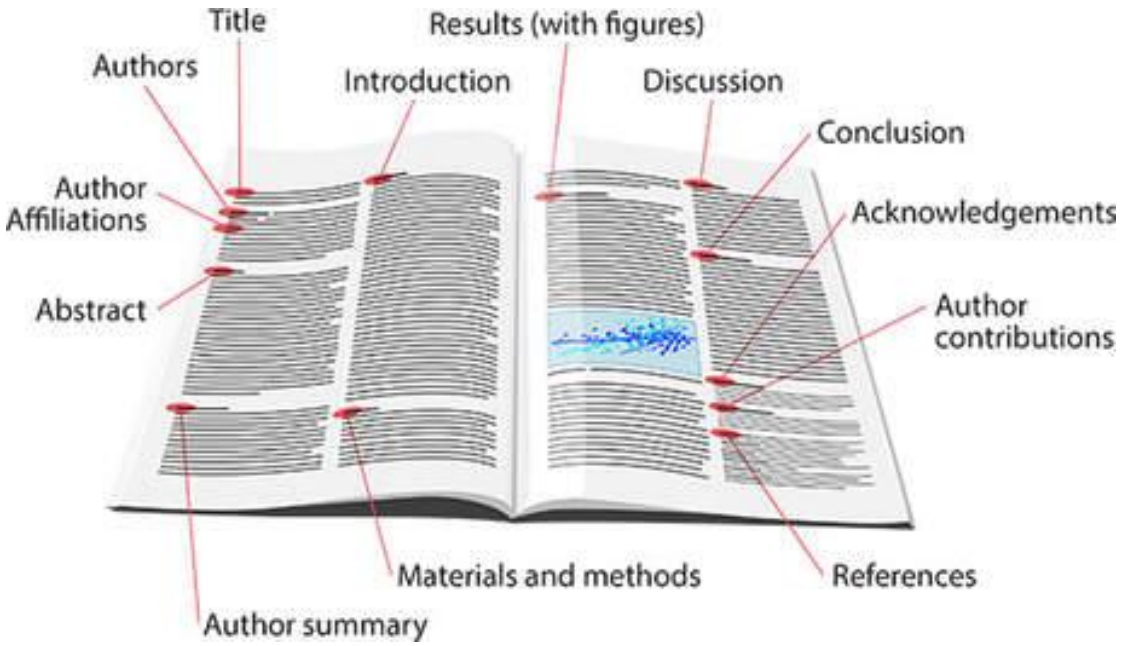
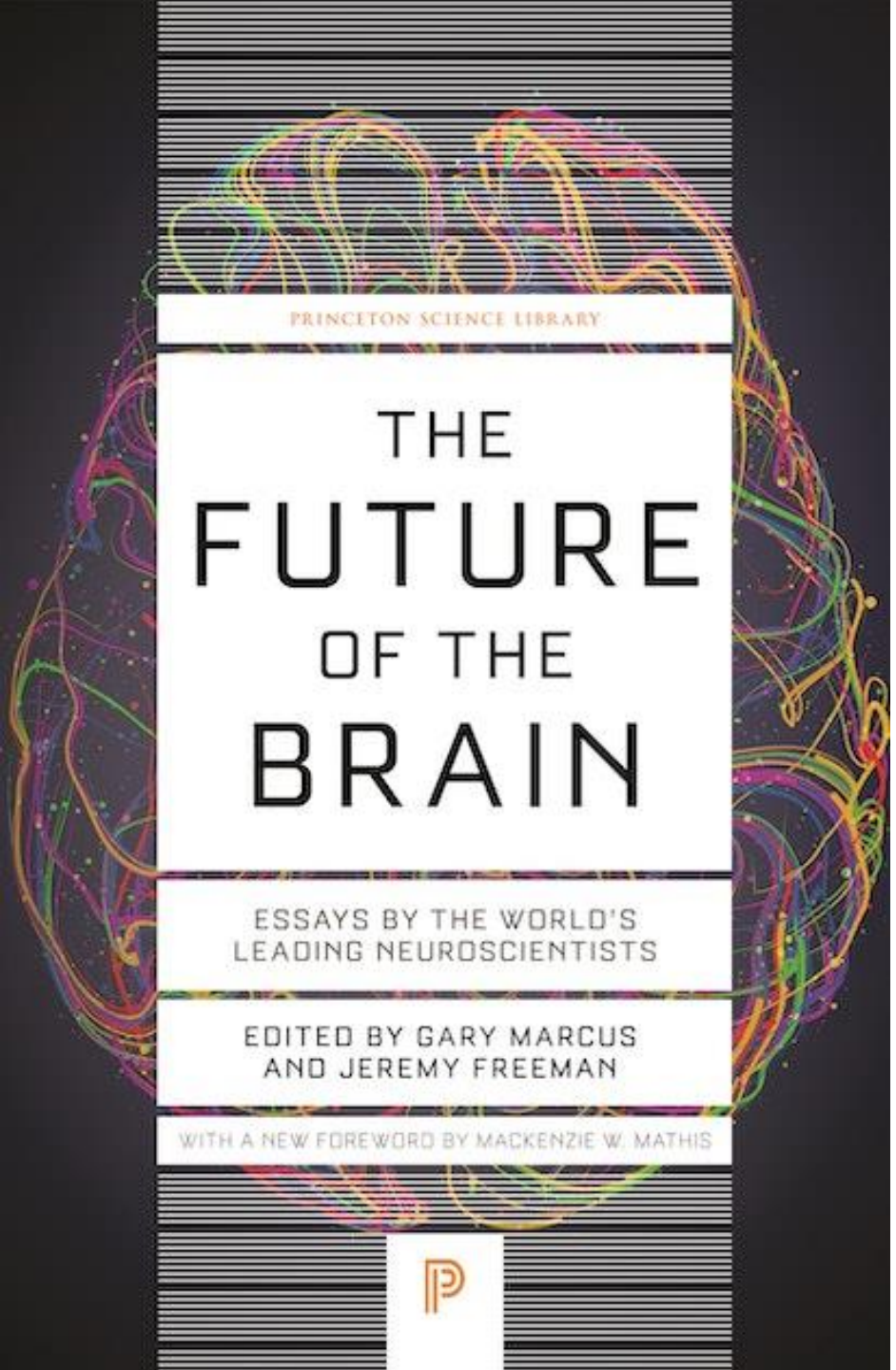


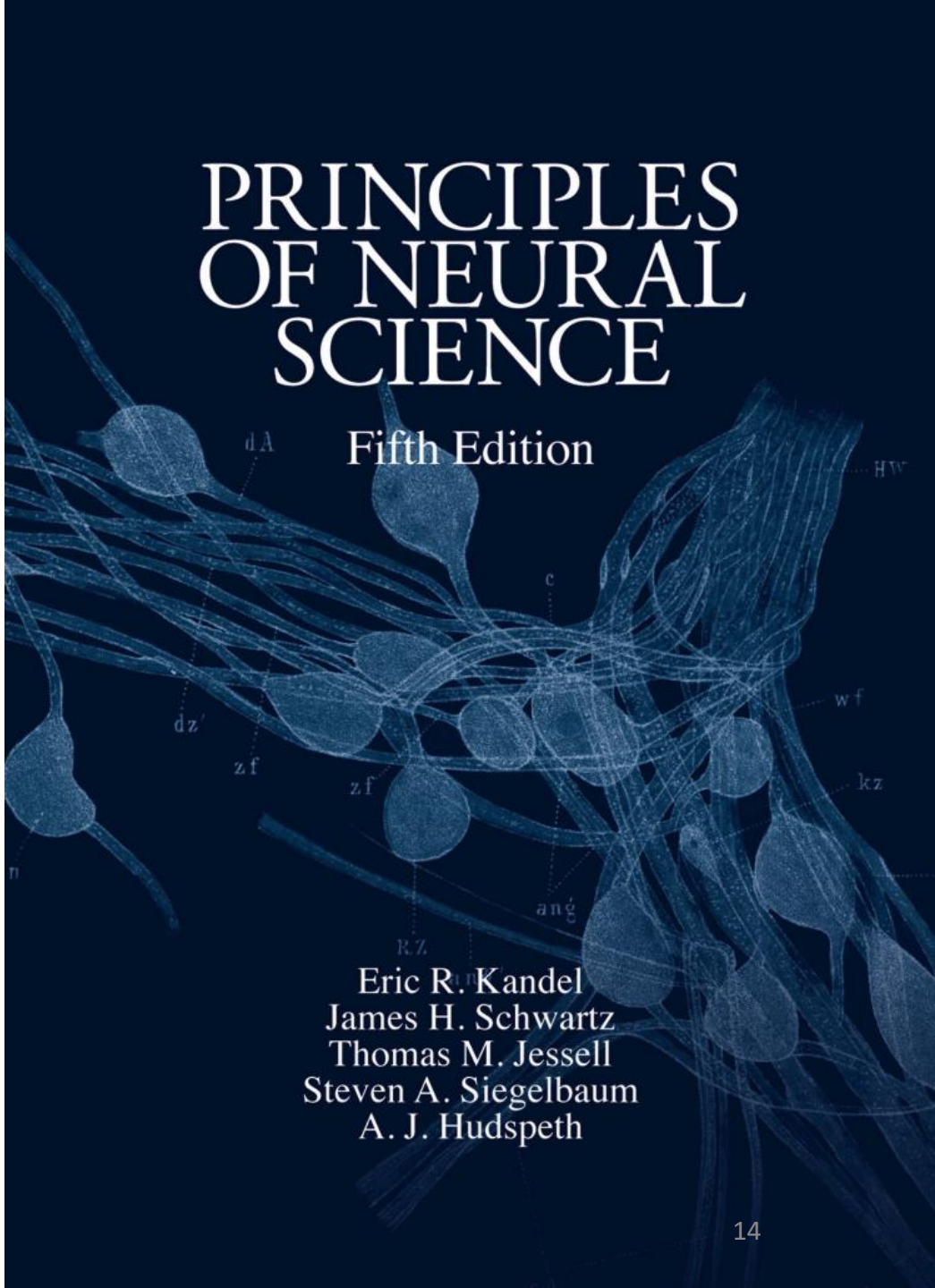
Image from http://www.neotropicalscience.com/reading-primary-lit.html



Optional Reading

→ "The" graduate level textbook on neuroscience

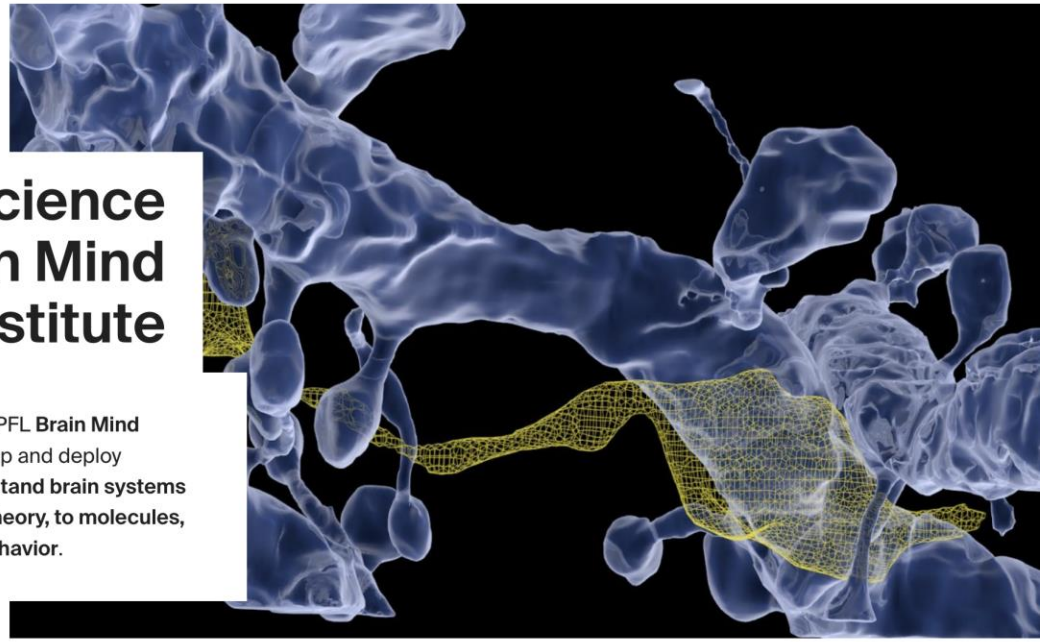
← Great for cutting-edge ideas in systems neuro



Grading

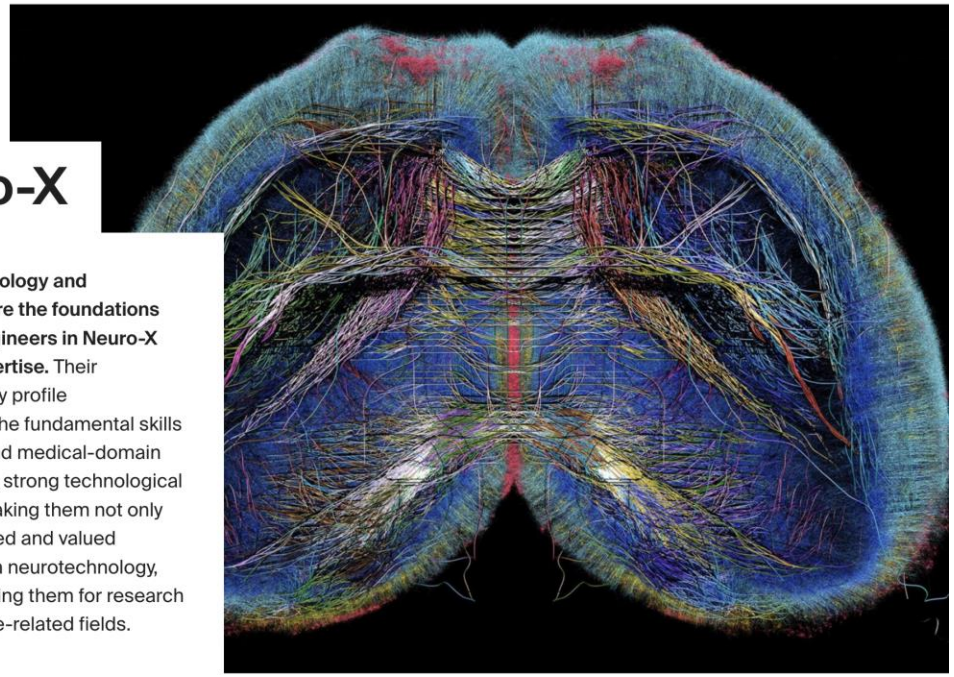
Expected student activities:
Attend lectures and sections (both are critical), read scientific articles assigned for each section, complete the two homework sets, participate in quizzes, and take the final exam!

The final mark is a combination of three evaluations:
2 problem sets (50%)
2 quizzes (25%)
1 final exam (25%)



Neuroscience – Brain Mind Institute

Researchers in the EPFL **Brain Mind Institute (BMI)** develop and deploy technology to **understand brain systems** across scales from **theory, to molecules, cells, circuits and behavior**.



Neuro-X

Science, technology and computation are the foundations onto which engineers in Neuro-X build their expertise. Their multidisciplinary profile complements the fundamental skills of engineers and medical-domain specialists by a strong technological component, making them not only highly demanded and valued professionals in neurotechnology, but also preparing them for research in neuroscience-related fields.

Go watch neuroscience seminars!

- these are world-leaders in their area giving the latest updates 🔥

https://www.epfl.ch/schools/sv/bmi/brain-mind-institute/neuroscience-events/ ← all on Main Campus
https://neuro-x.epfl.ch/en/events/ ← many in Geneva EPFL Campus (Neurotech)

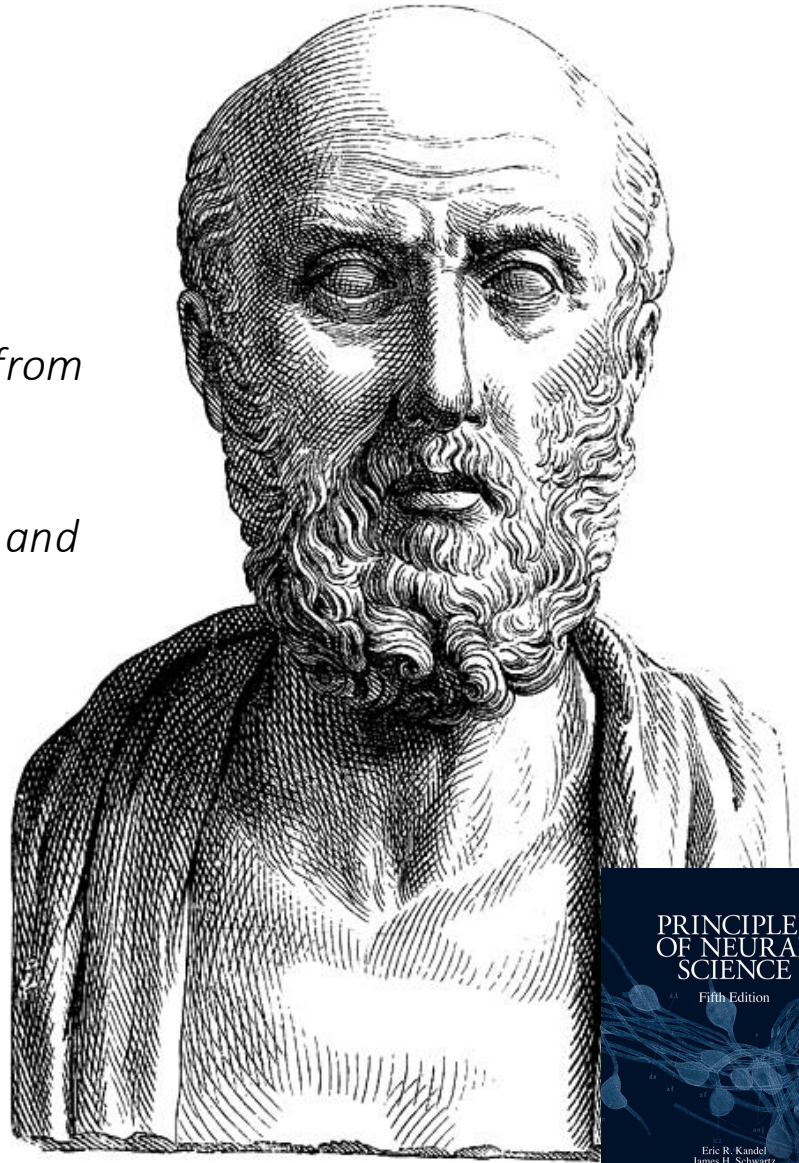
Let’s start…

with a primer on neuroscience

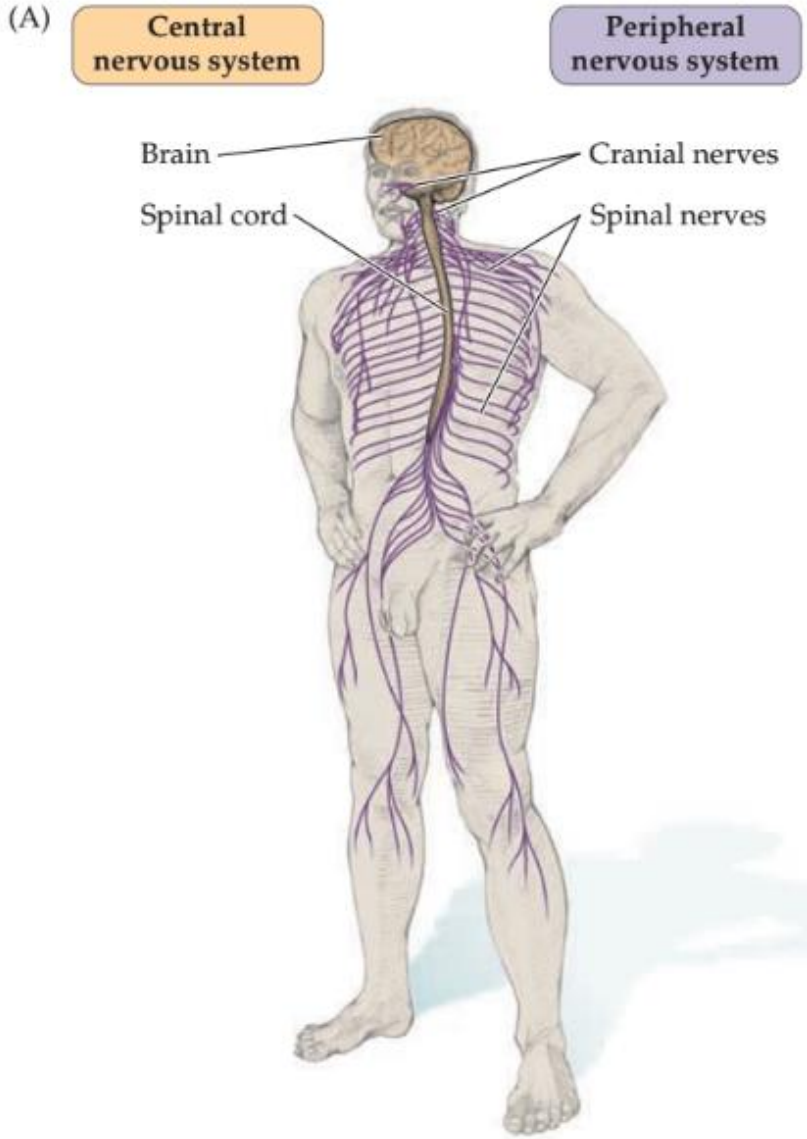
Men ought to know that from the brain, and from the brain only, arise our pleasures, joys, laughter and jests, as well as our sorrows, pains, griefs and tears. Through it, in particular, we think, see, hear, and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant. . . .

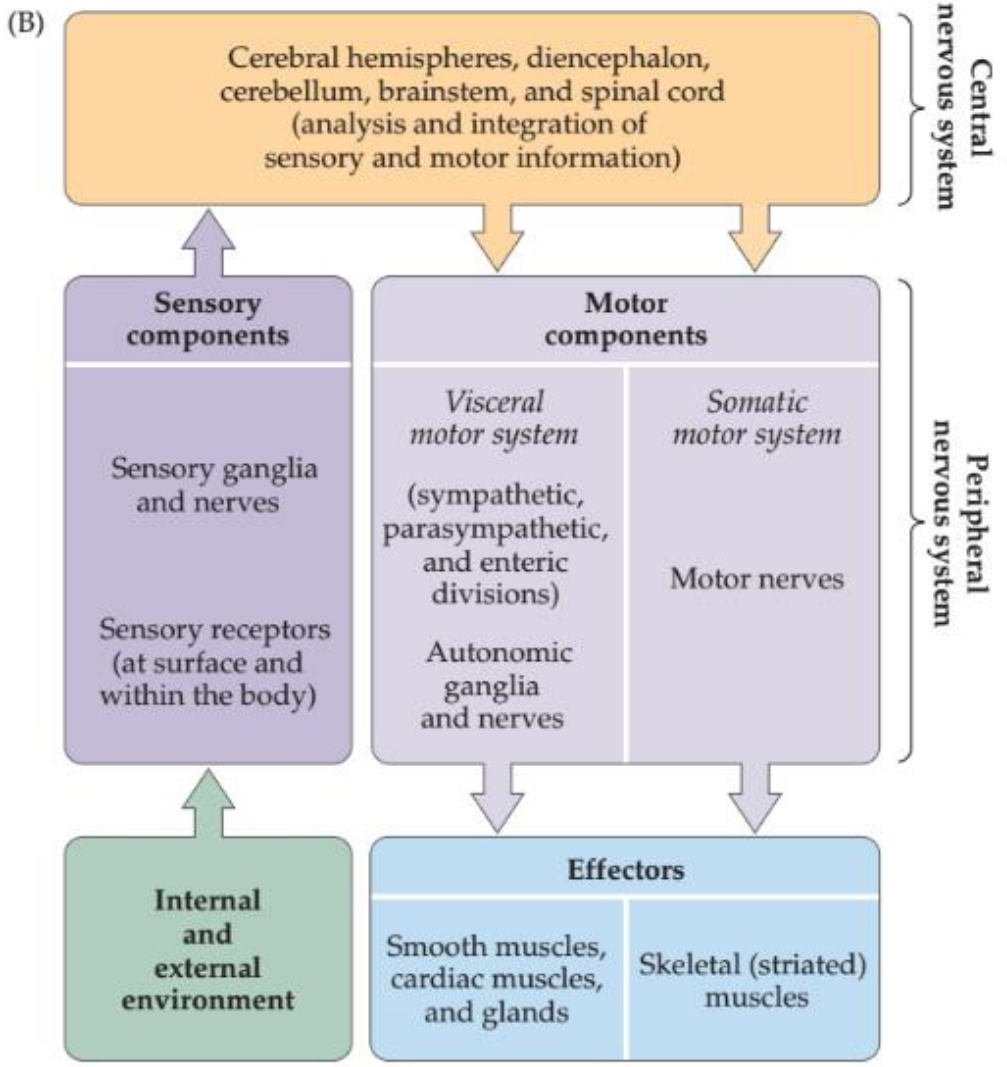
It is the same thing which makes us mad or delirious, inspires us with dread and fear, whether by night or by day, brings sleeplessness, inopportune mistakes, aimless anxieties, absent-mindedness, and acts that are contrary to habit.

attributed to Hippocrates Fifth Century, B.C.

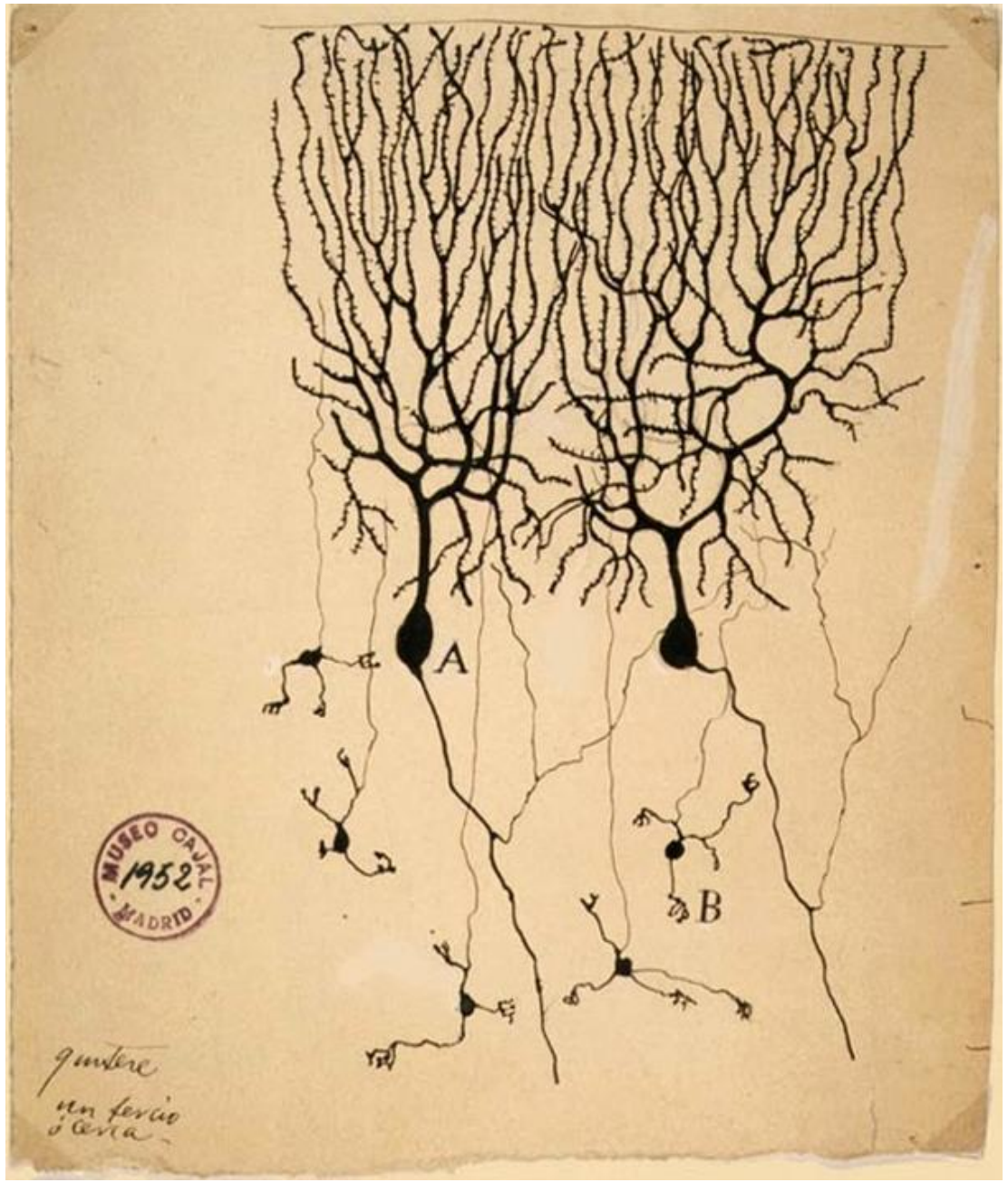


The Nervous System





Anatomy



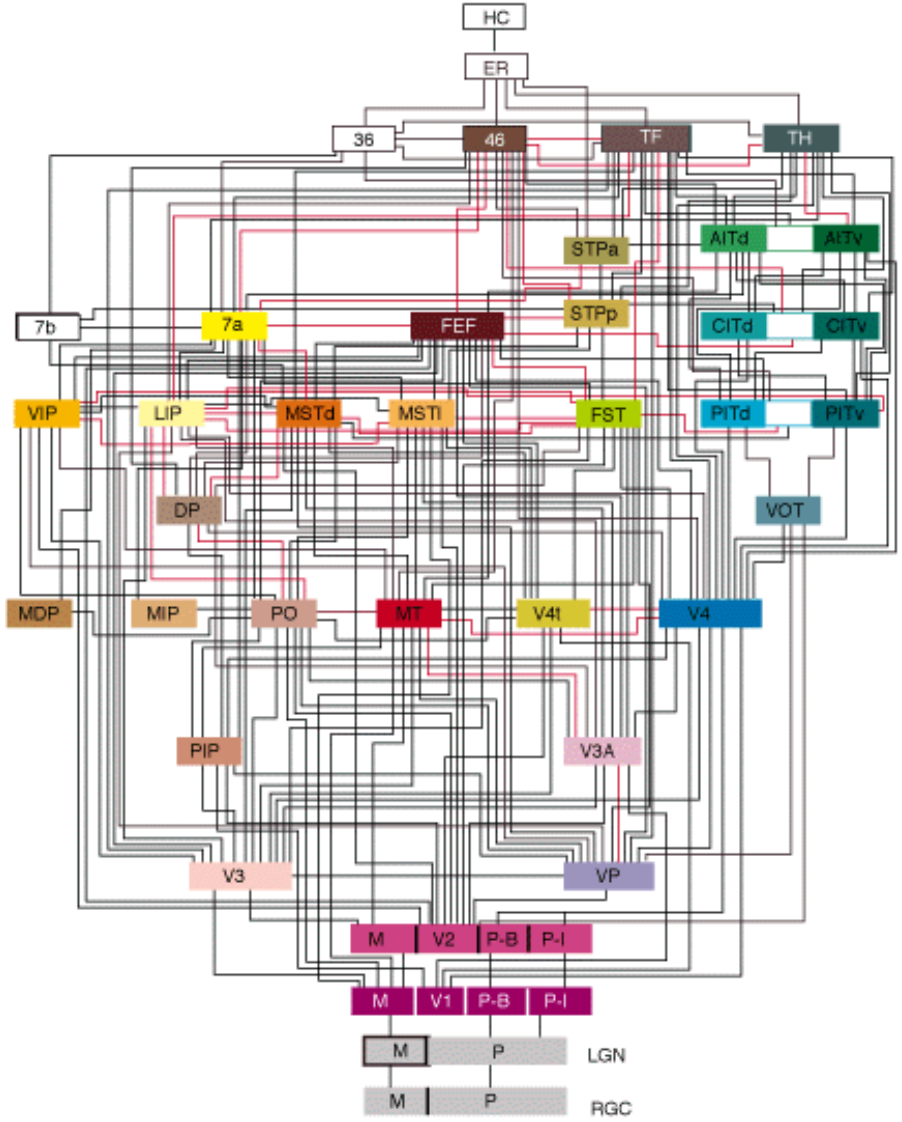
Brains are very complex:

About 86-100 hundred billion neurons in human brain, 71 million in a mouse, and ~300 in a c. elegans worm

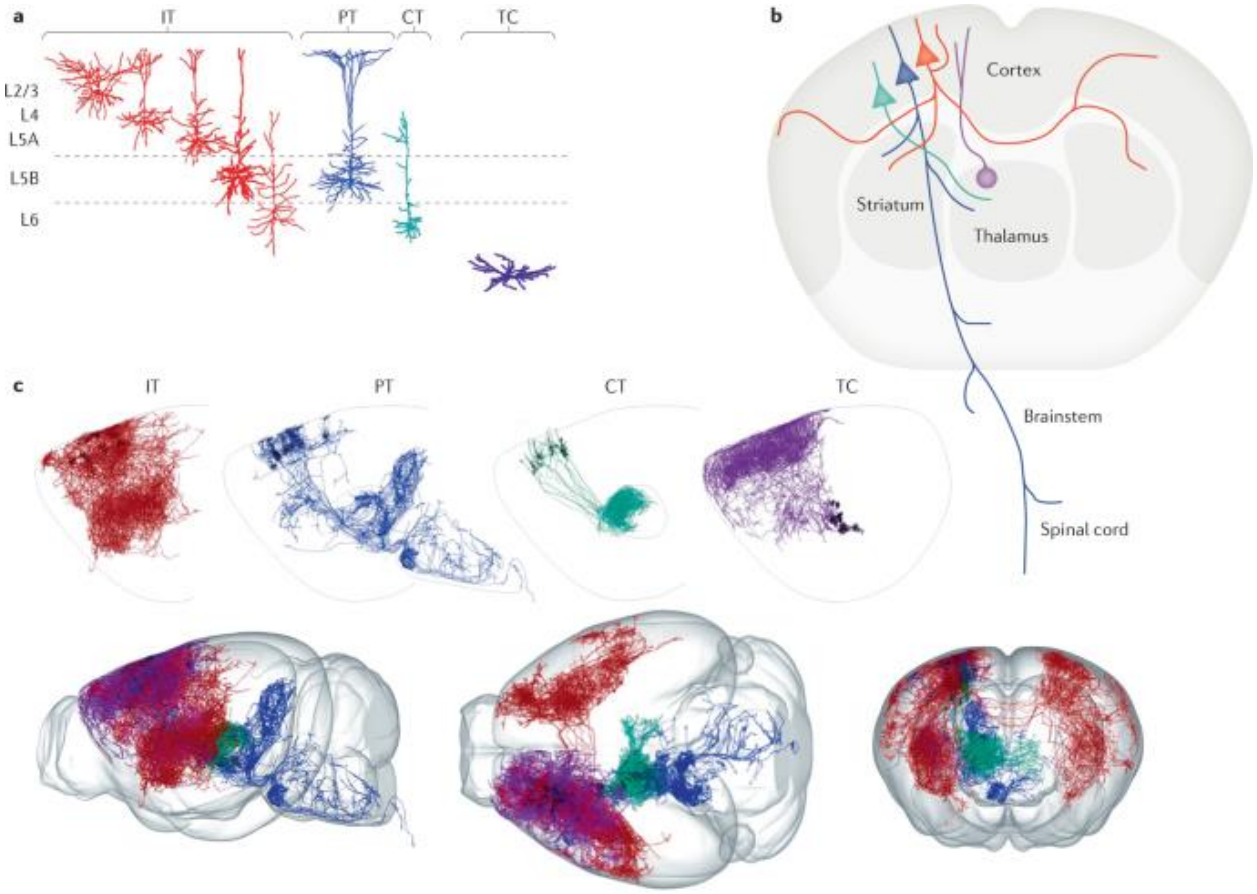
Neurons be classified in many different ways including:

1. Based on number of “neurites”
2. Based on dendrites
3. Based on connections or function
4. Based on axon length
5. Based on neurotransmitter, typically one neurotransmitter per neuron
6. Named cells

Neural circuits are complex



Felleman and Van Essen *Cerebral Cortex* 1991



Shepherd and Yamawaki *Nature review neuroscience* 2021

Human Brain Anatomy (then and now)

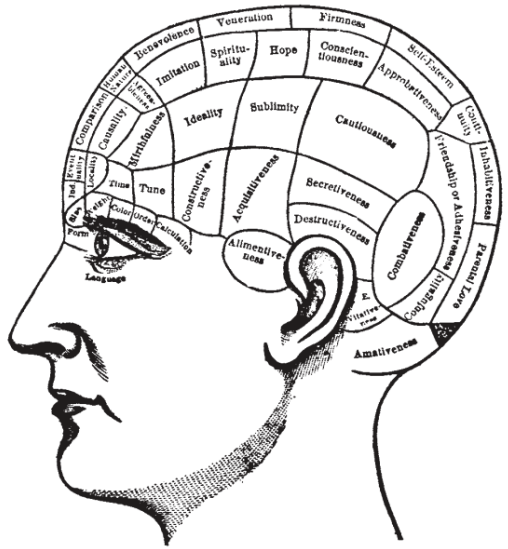
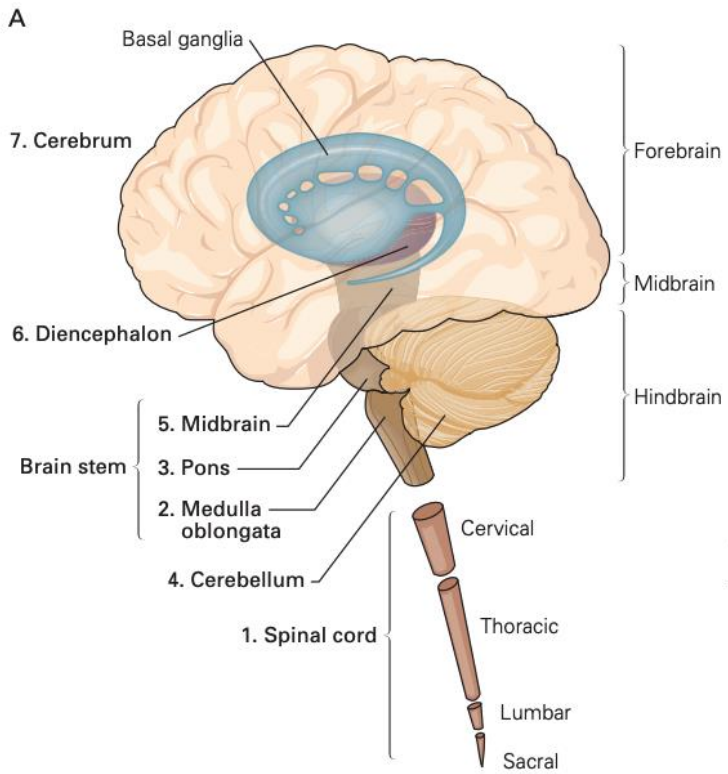


Figure 1–1 An early map of functional localization in the brain. According to the 19th century doctrine of phrenology, complex traits such as combativeness, spirituality, hope, and conscientiousness are controlled by specific areas in the brain, which expand as the traits develop. This enlargement of local areas of the brain was thought to produce characteristic bumps and ridges on the overlying skull, from which an individual's character could be determined. This map, taken from a drawing of the early 1800s, purports to show 42 intellectual and emotional faculties in distinct areas of the skull and the cerebral cortex underneath.



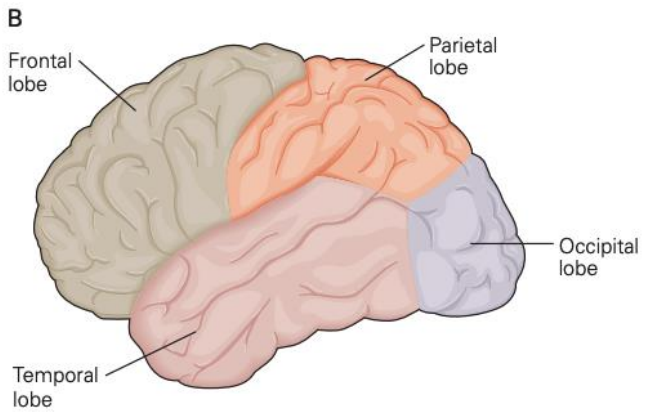
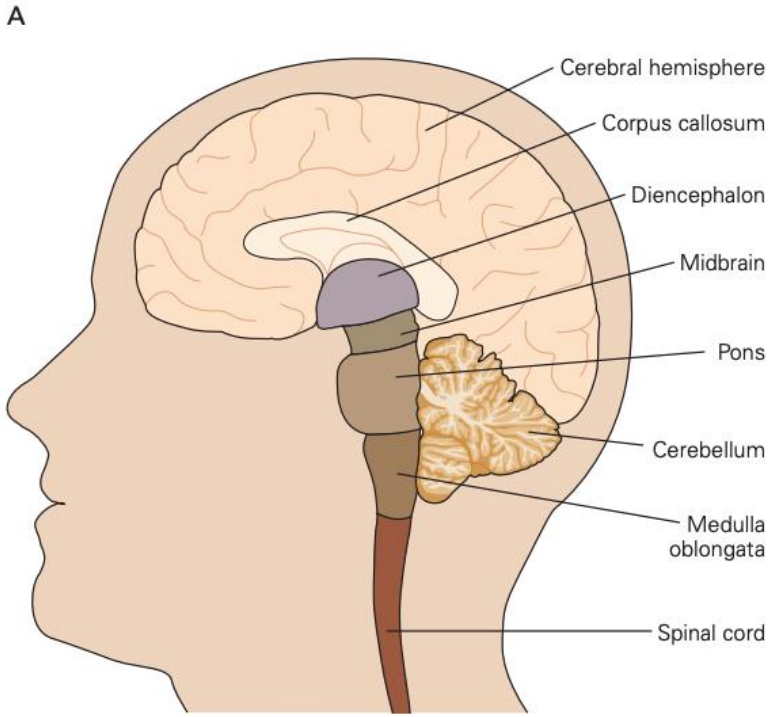


Figure 1–2 The divisions of the central nervous system.

A. The central nervous system can be divided into seven main parts.

B. The four lobes of the cerebral cortex.

Human Brain Anatomy



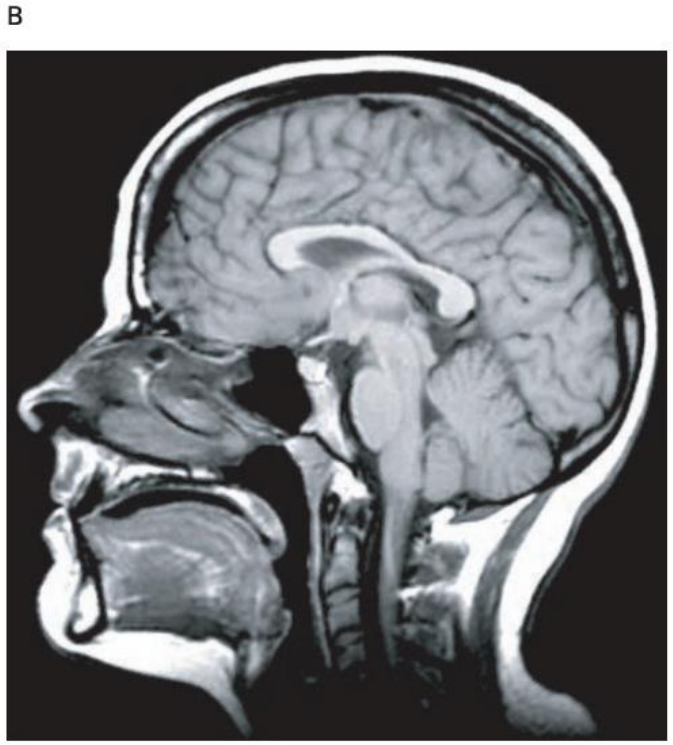


Figure 1–3 The main divisions are clearly visible when the brain is cut down the midline between the two cerebral hemispheres.

A. This schematic drawing shows the position of major structures of the brain in relation to external landmarks. Students of brain anatomy quickly learn to discern the major internal landmarks, such as the corpus callosum, a large bundle of nerve fibers that connects the left and right hemispheres.

B. The major brain divisions drawn in **A** are also evident in a magnetic resonance image of a living human brain.

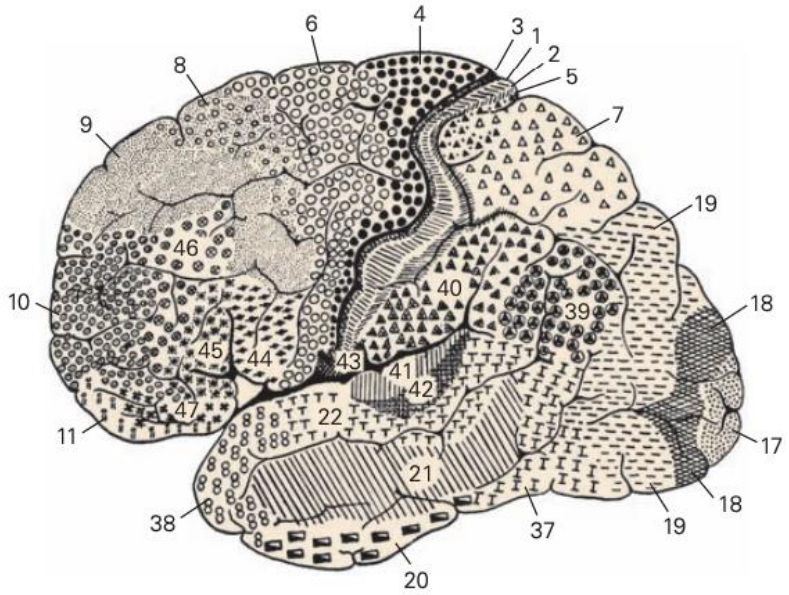
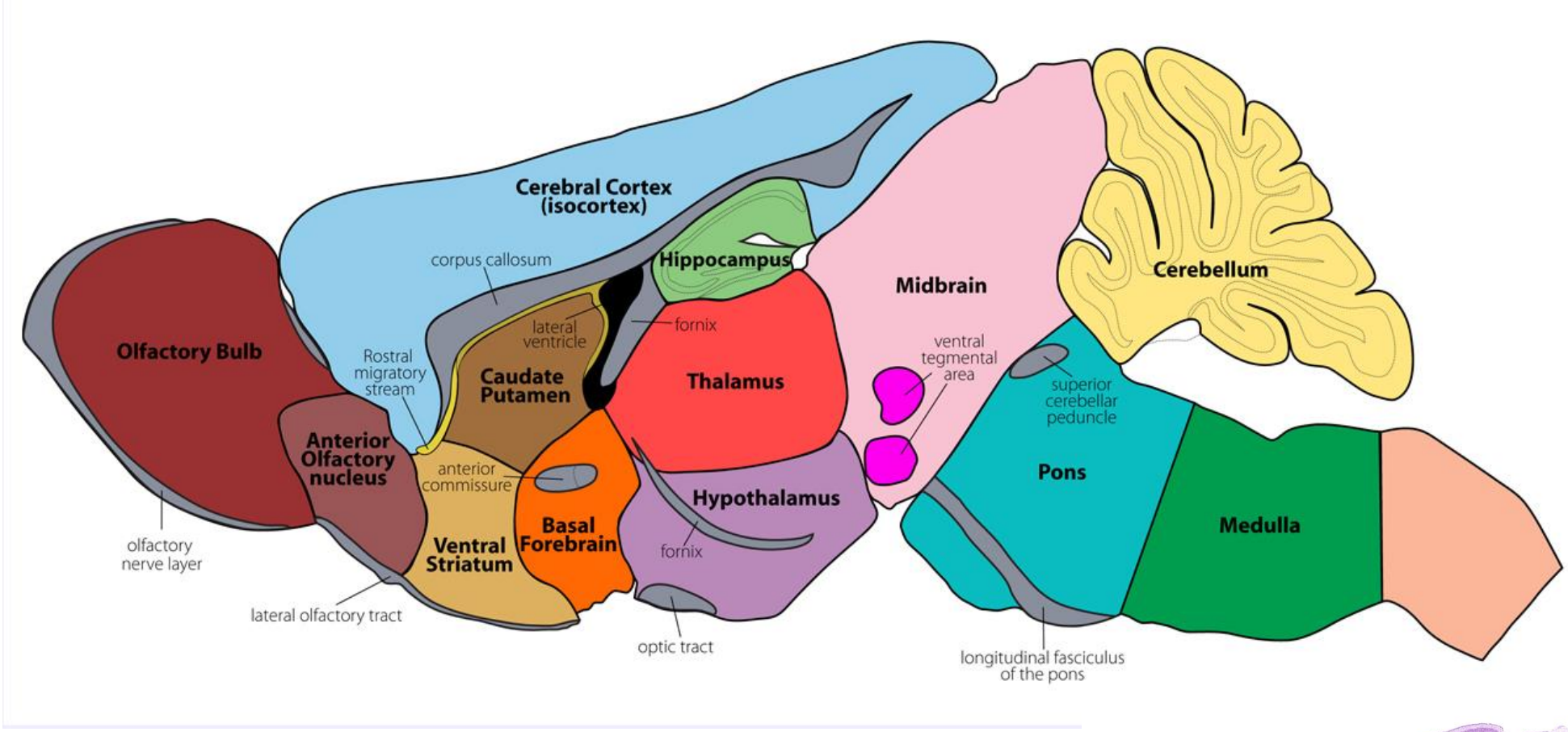
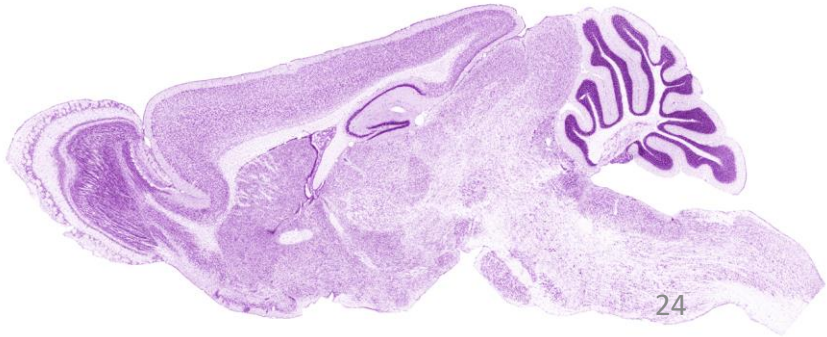


Figure 1–5 Brodmann's division of the human cerebral cortex into 52 discrete functional areas. Brodmann identified these areas on the basis of distinctive nerve cell structures and characteristic arrangements of cell layers. This scheme is still widely used today and is continually updated. Several areas defined by Brodmann have been found to control specific brain functions. For instance, area 4 is the motor cortex, responsible for voluntary movement. Areas 1, 2, and 3 constitute the primary somatosensory cortex, which receives sensory information primarily from the skin and joints. Area 17 is the primary visual cortex, which receives sensory signals from the eyes and relays them to other areas for further processing. Areas 41 and 42 constitute the primary auditory cortex. The drawing shows only areas visible on the outer surface of the cortex.

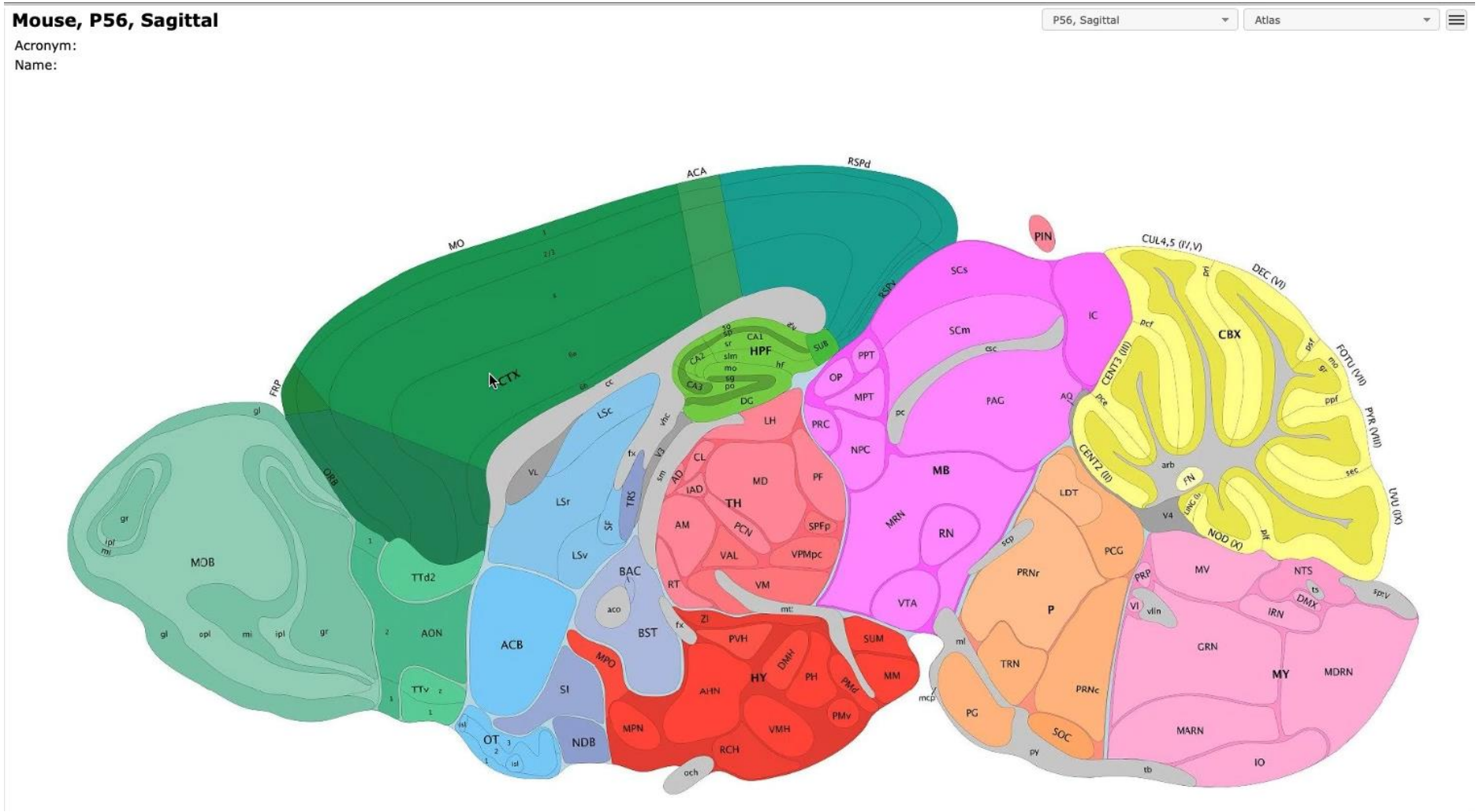
Mouse Brain Anatomy





http://www.gensat.org/imagenavigator.jsp?imageID=14206

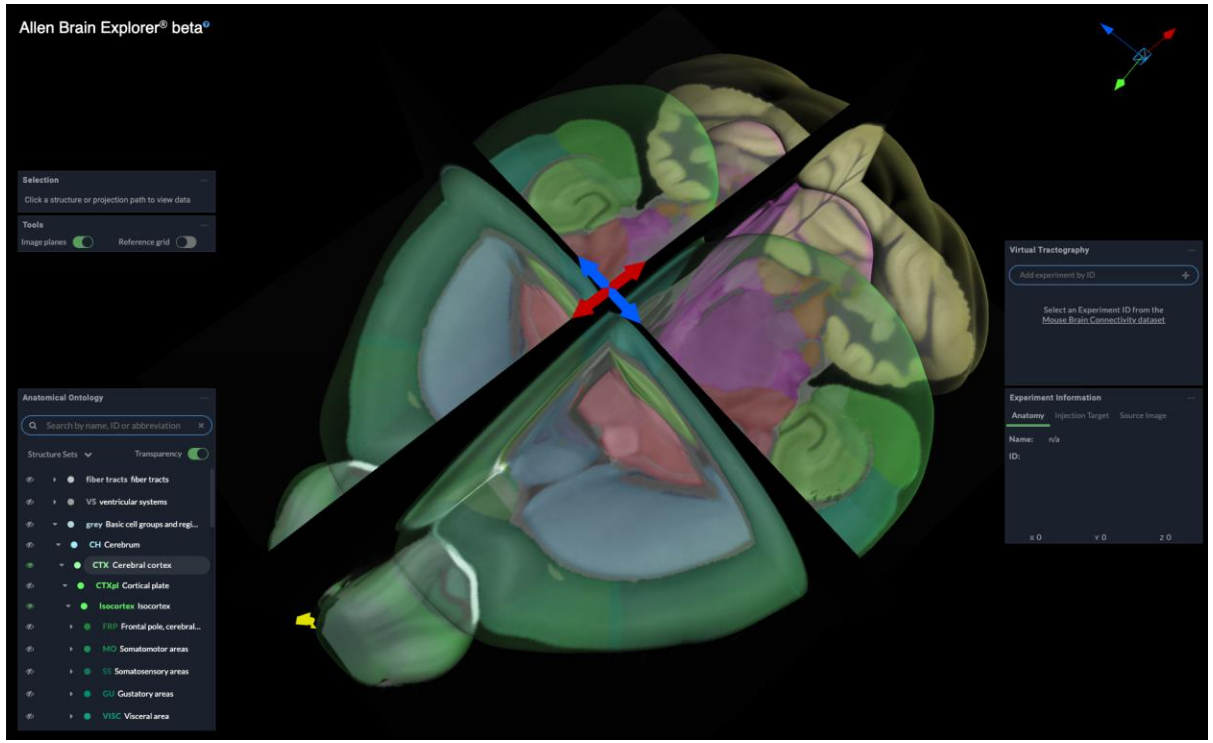
Mouse Brain Anatomy

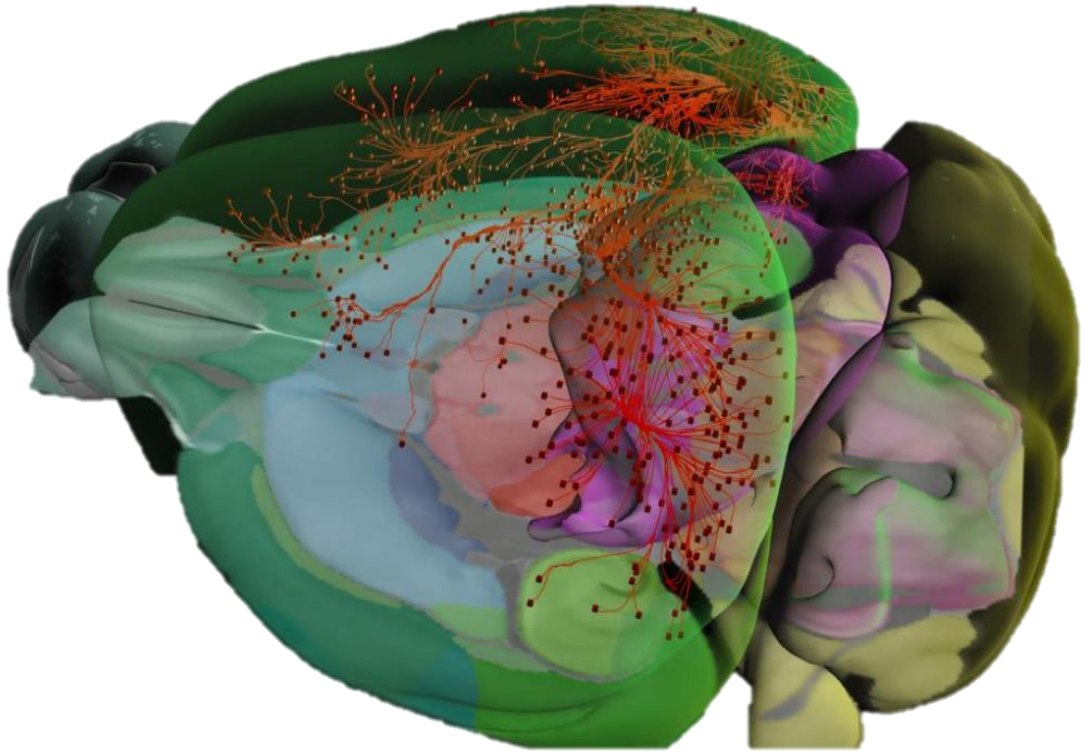


http://atlas.brain-map.org/atlas?atlas=2&plate=100883804#atlas=2&plate=100883804&resolution=10.60&x=7671.879635581487&y=4000.064125543908&zoom=-3

Mouse Brain Anatomy

https://connectivity.brain-map.org/3d-viewer

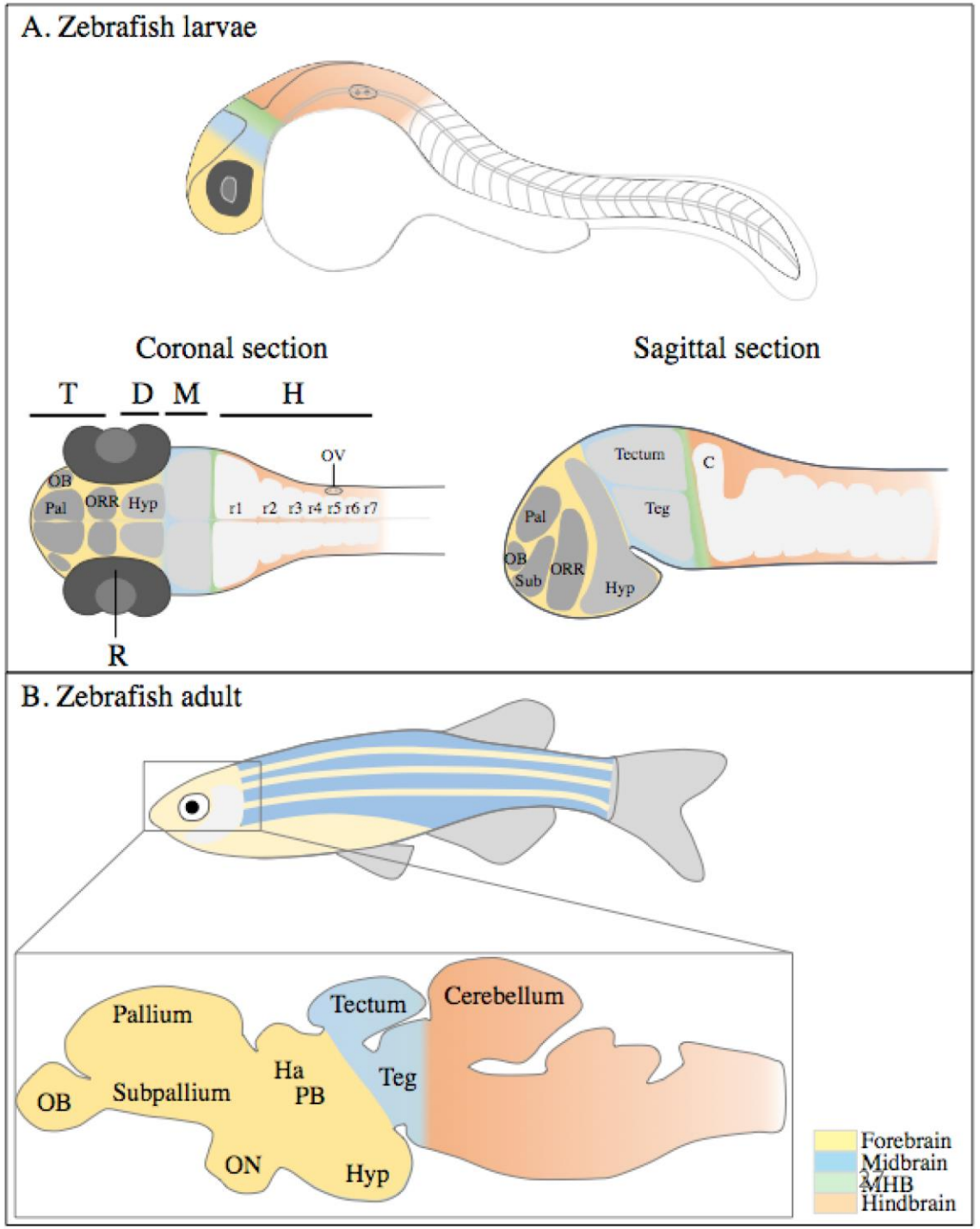




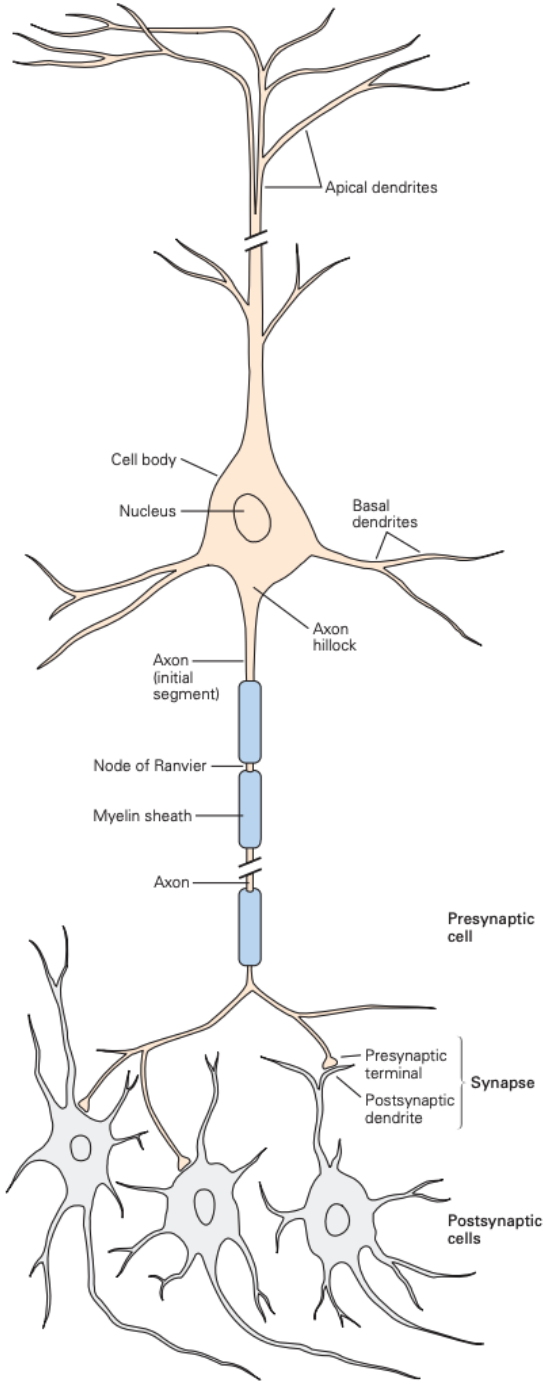
Zebrafish Brain Anatomy

Image from https://news.mit.edu/2022/smarter-zebrafish-study-1118

https://www.mdpi.com/1422-0067/20/6/1296



The fundamental unit: the neuron



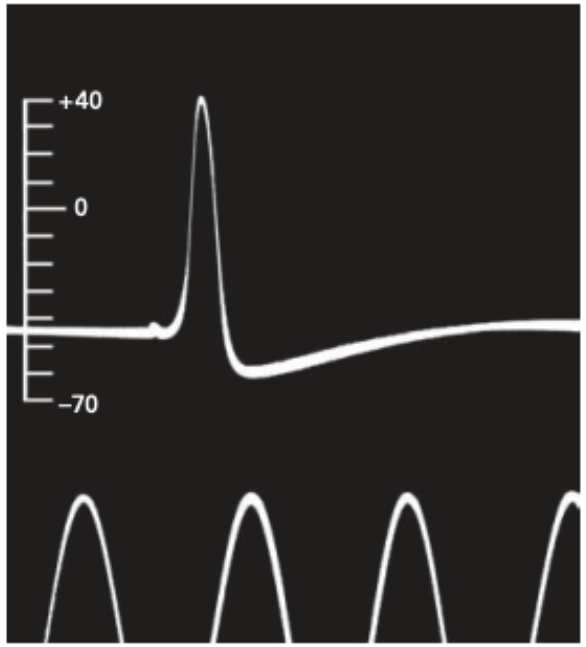
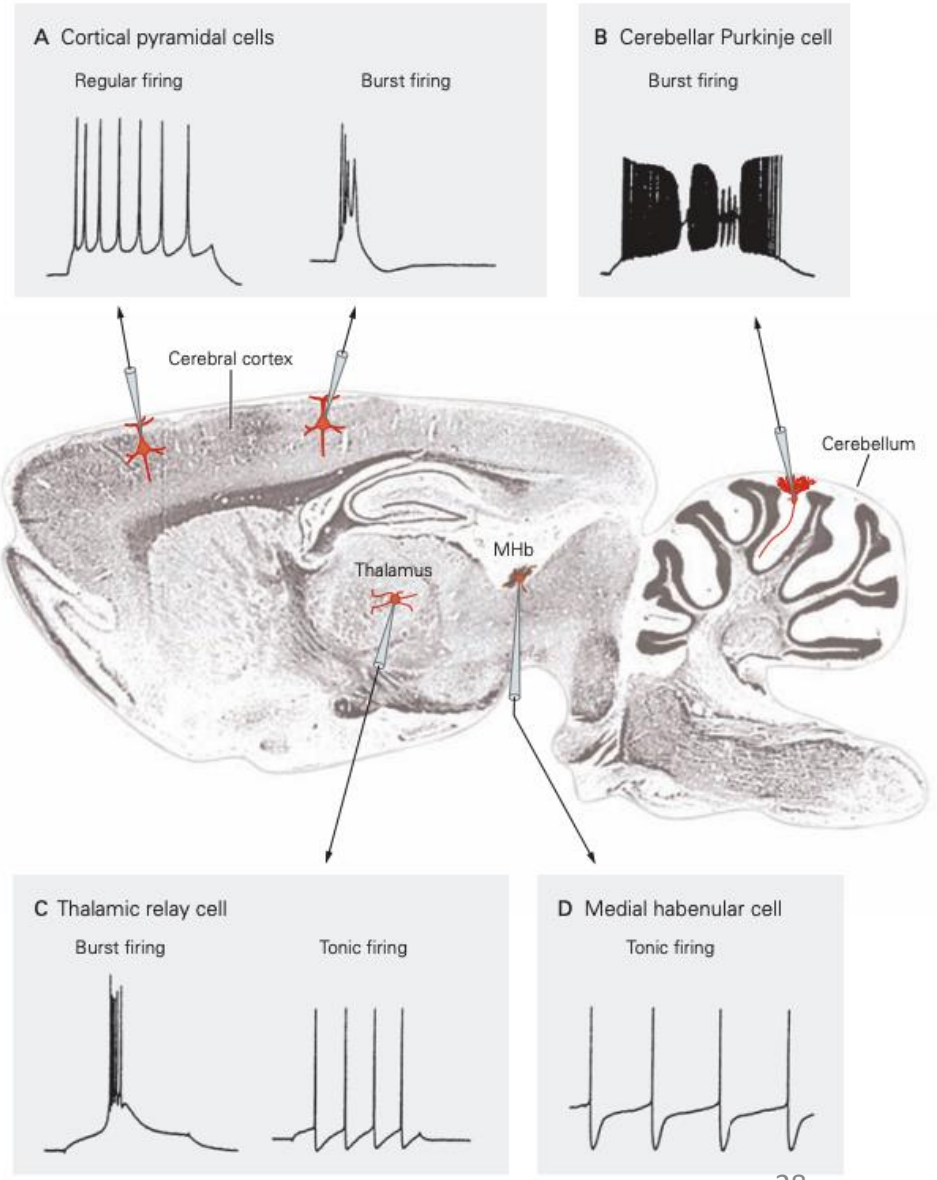
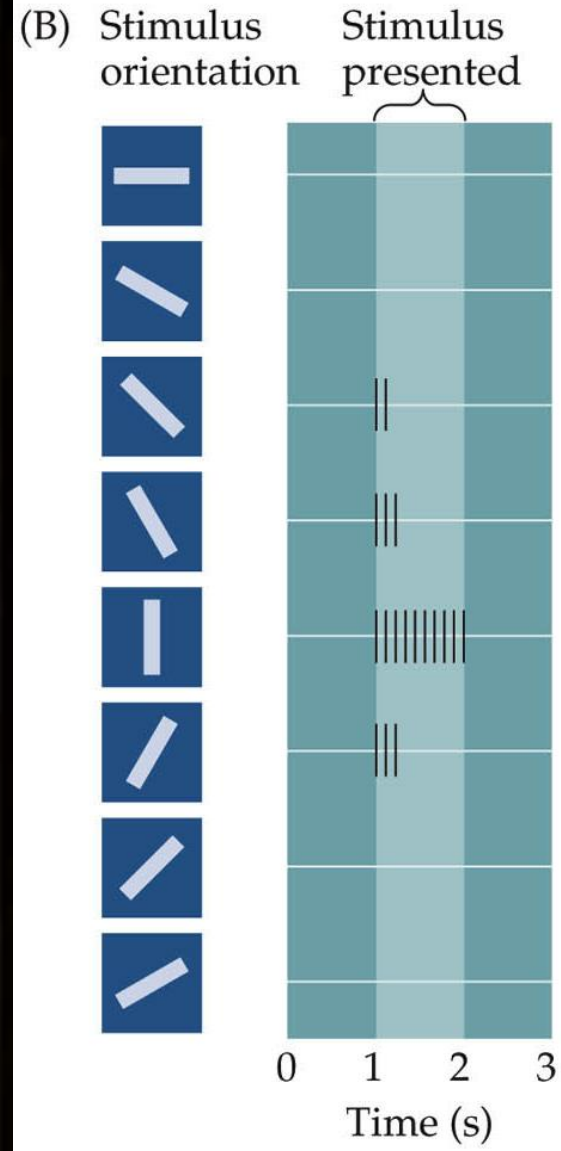


Figure 2–2 **This historic tracing is the first published intracellular recording of an action potential.** It was recorded in 1939 by Hodgkin and Huxley from a squid giant axon, using glass capillary electrodes filled with sea water. The timing pulses are separated by 2 ms. The vertical scale indicates the potential of the internal electrode in millivolts, the sea water outside being taken as zero potential. (Reproduced, with permission, from Hodgkin and Huxley 1939.)



Function

Hubel & Wiesel



Purves Fig. 12.8

Neurons

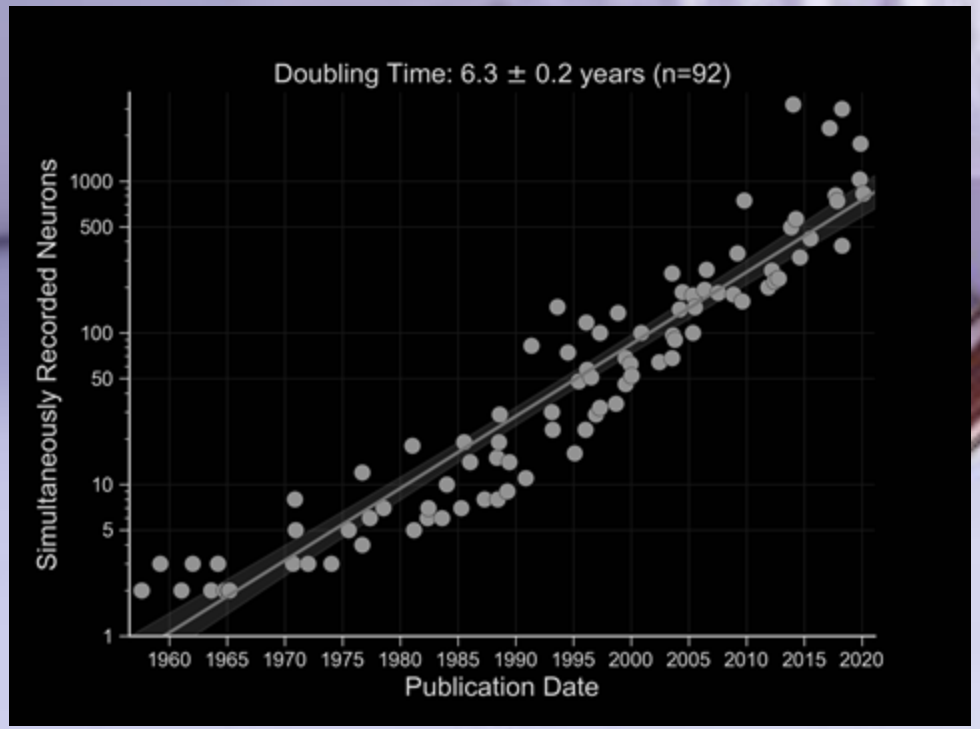
Behavior

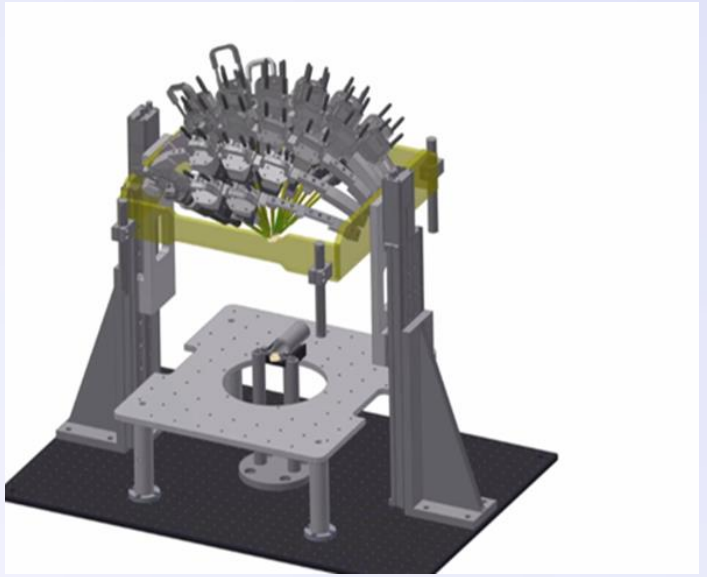
The neural circuits, the dynamics…

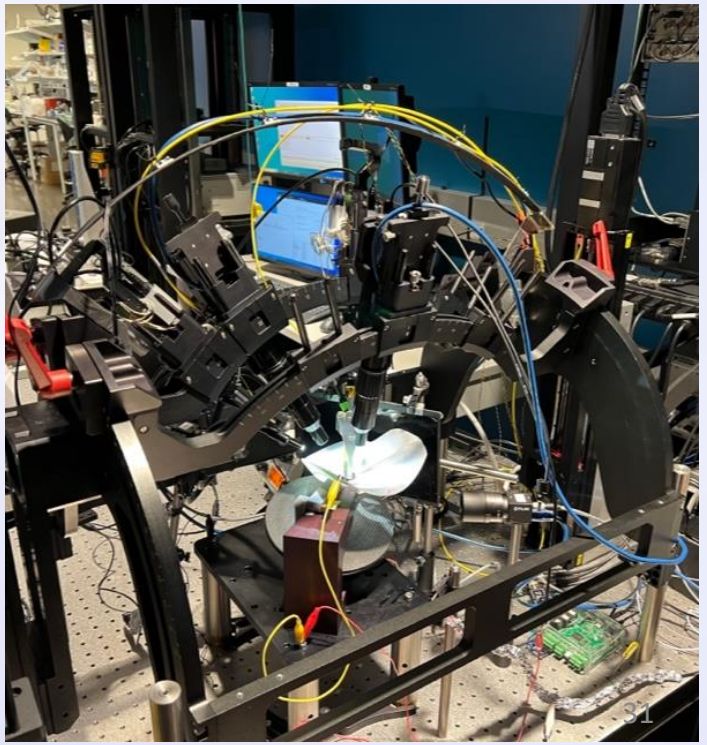
Kandel et al. Principles of Neural Science 2000 (62-2)

Modern Technology is critical: Neuropixels

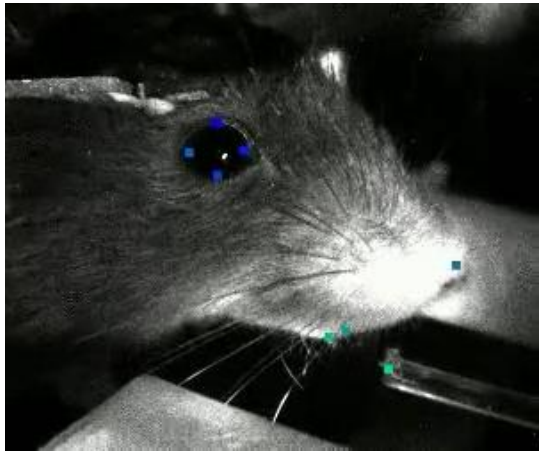
- Many neurons recorded simultaneously are required if we aim to study complex behavior!

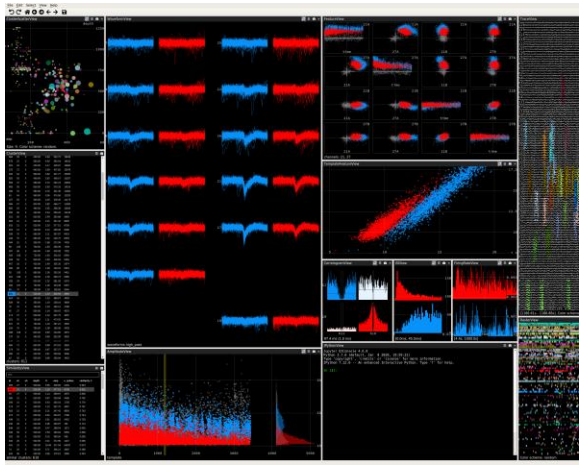




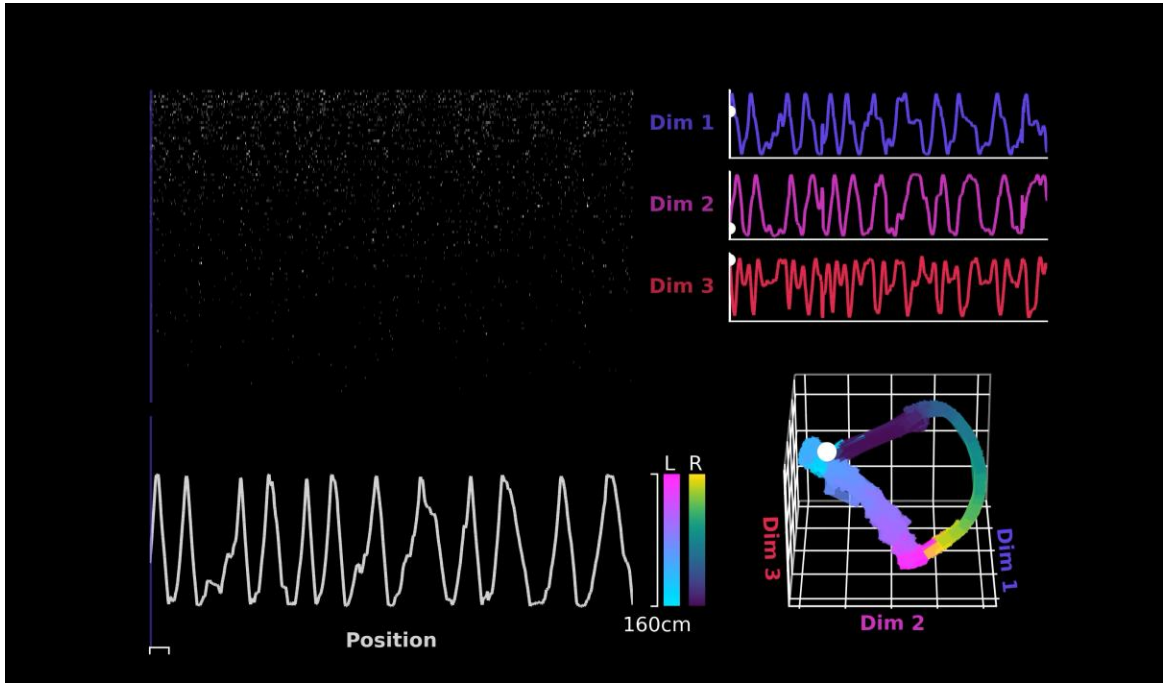


Technology is critical: deep learning for neural analysis





- Measuring behavior (pose)
- Spike extraction
- Modeling neural dynamics



Schneider, Lee, Mathis Nature 2023

There is also a lot we still don’t know …

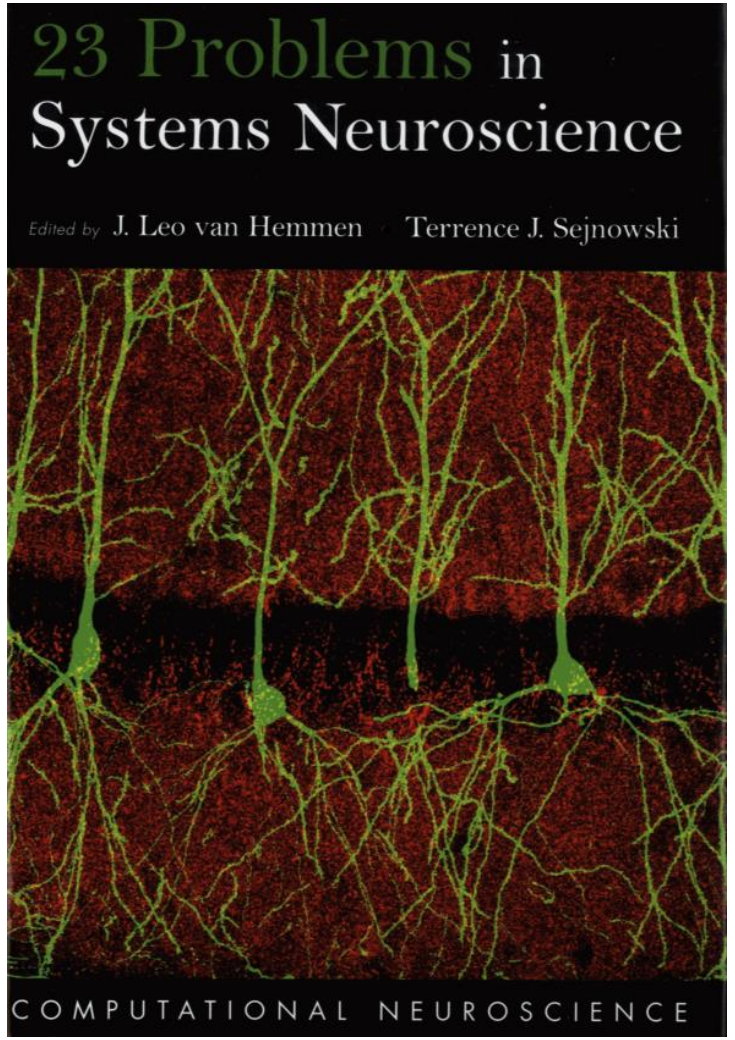
(we hope this course helps start your scientific quest!)

Many unsolved challenges….

23 Problems in Mathematics

David Hilbert

https://www.simonsfoundation.org/2020/05/06/hilberts-problems-23-and-math/



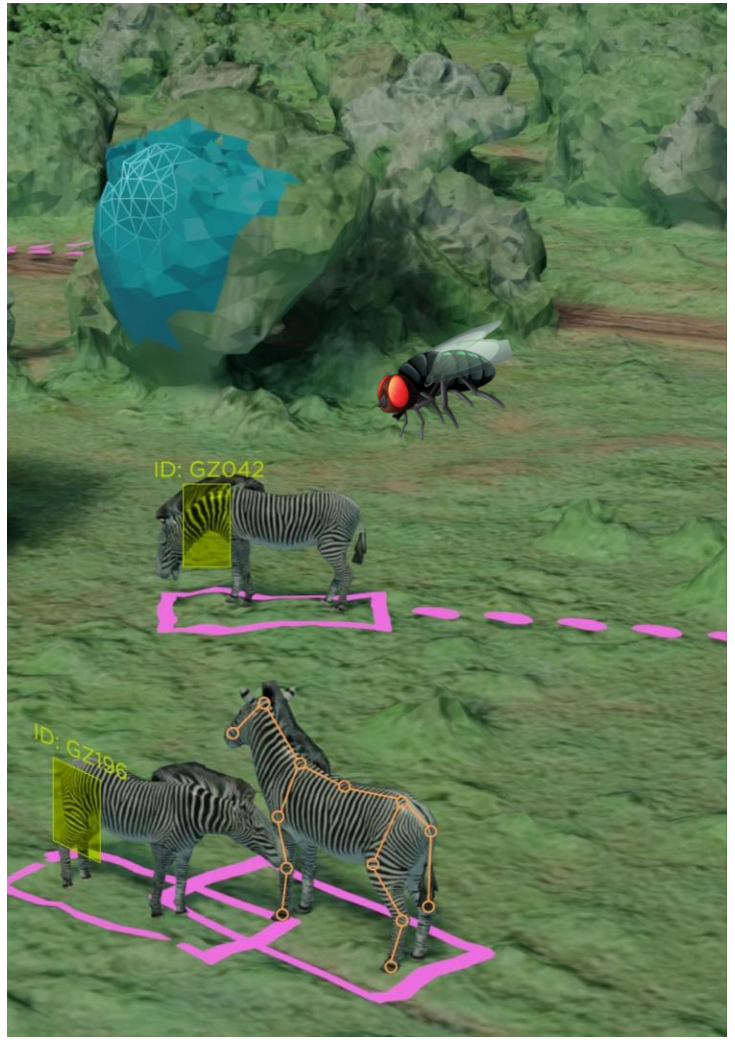
Many unsolved challenges….

How Have Brains Evolved?

1. Shall We Even Understand the Fly's Brain?

2. Can We Understand the Action of Brains in Natural Environments?

3. Hemisphere Dominance of Brain Function-Which Functions Are Lateralized and Why?



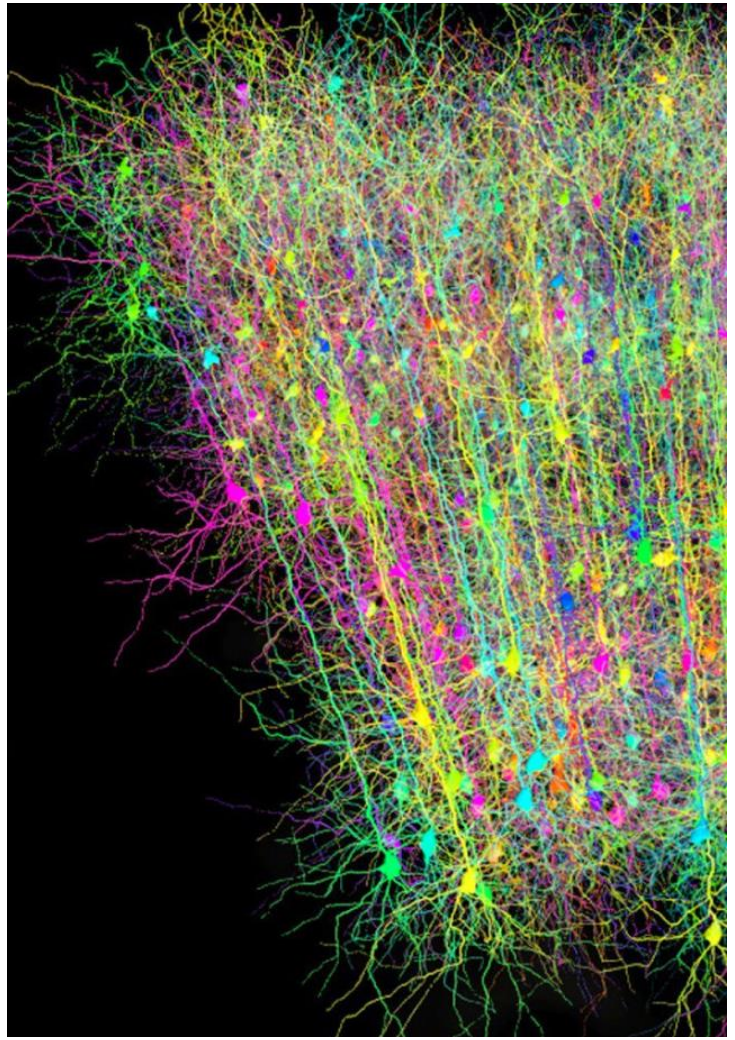
Many unsolved challenges….

How Is the Cerebral Cortex Organized?

4. What Is the Function of the Thalamus?

5. What Is a Neuronal Map, How Does It Arise, and What Is It Good For?

6. What Is Fed Back?



Many unsolved challenges….

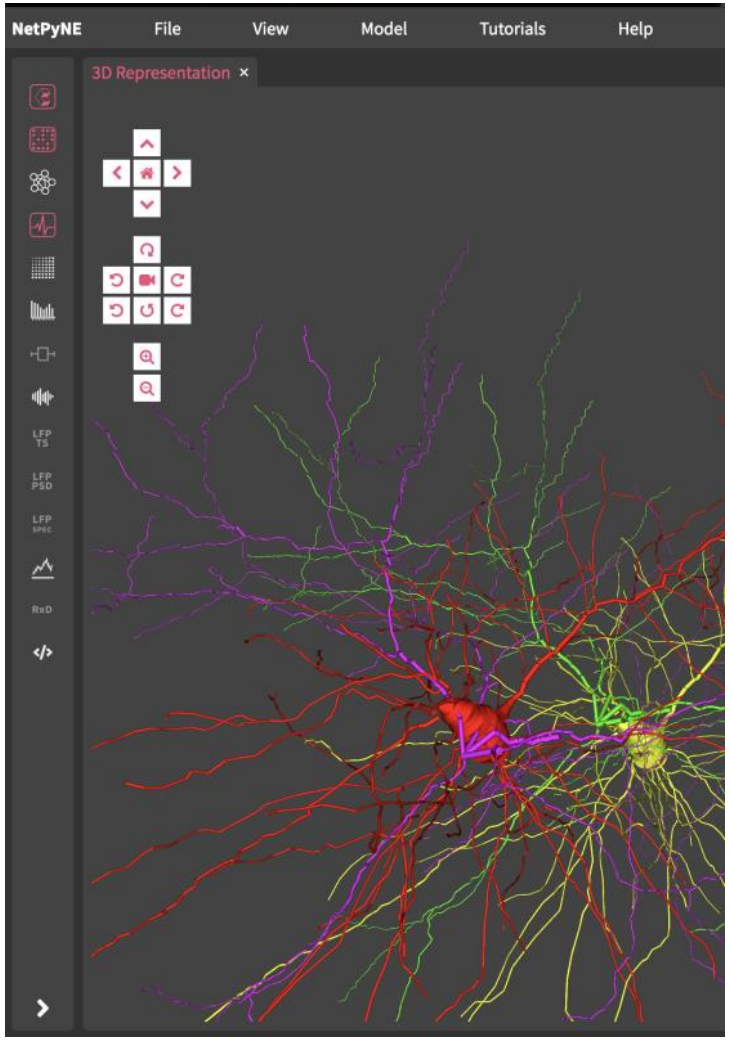
How Do Neurons Interact?

7. How Can the Brain Be So Fast?

8. What Is the Neural Code?

9. Are Single Cortical Neurons Soloists or Are They Obedient Members of a Huge Orchestra?

10. What Is the Other 85 Percent of V1 Doing?



Many unsolved challenges….

What Can Brains Compute?

11. Which Computation Runs in Visual Cortical Columns?

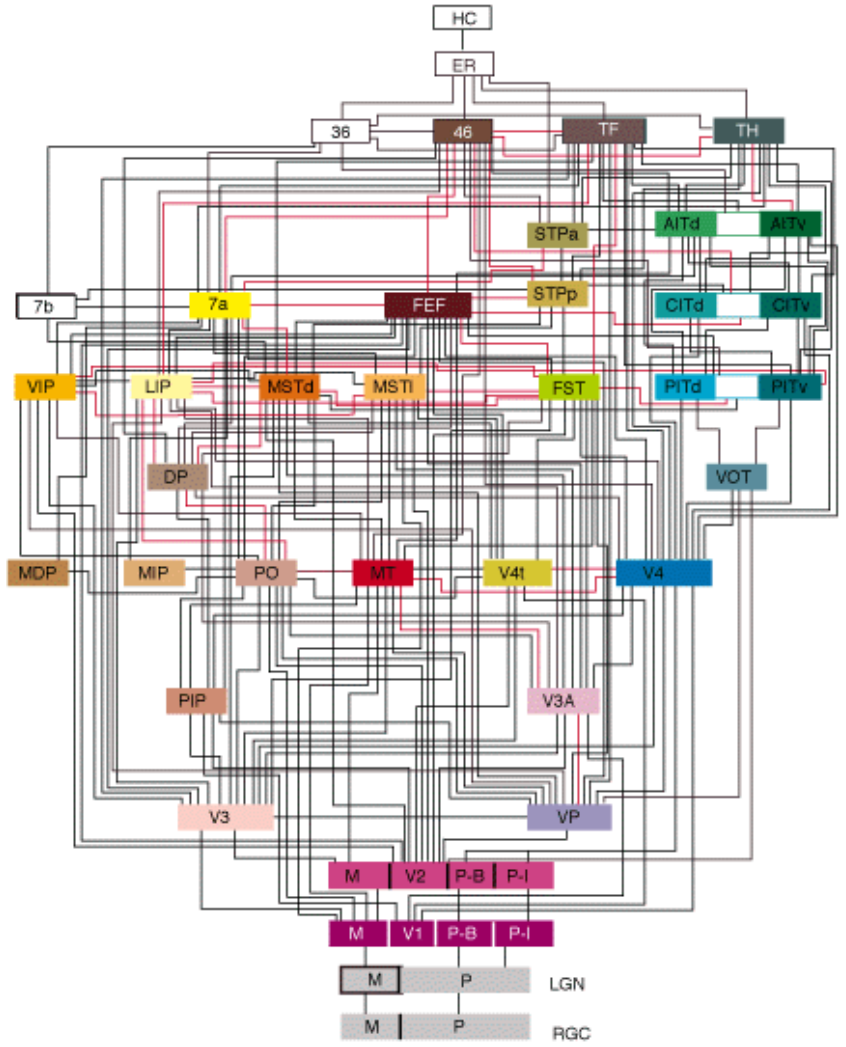
12. Are Neurons Adapted for Specific Computations? Examples from Temporal Coding in the Auditory System

13. How Is Time Represented in the Brain?

14. How General Are Neural Codes in Sensory Systems?

15. How Does the Hearing System Perform Auditory Scene Analysis?

16. How Does Our Visual System Achieve Shift and Size Invariance?



Felleman and Van Essen *Cerebral Cortex* 1991

Many unsolved challenges….

Organization of Cognitive Systems

17. What Is Reflected in Sensory Neocortical Activity: External Stimuli or What the Cortex Does with Them?

18. Do Perception and Action Result from Different Brain Circuits? The Three Visual Systems Hypothesis

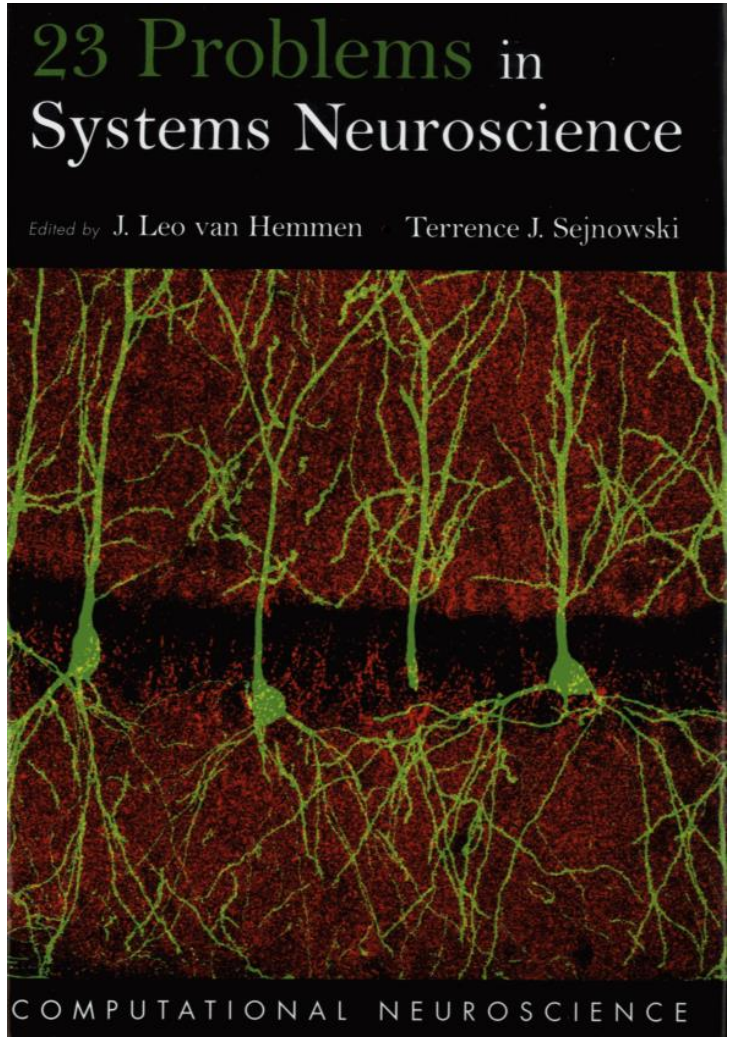
19. What Are the Projective Fields of Cortical Neurons?

20. How Are the Features of Objects Integrated into Perceptual Wholes That Are Selected by Attention?

21. Where Are the Switches on This Thing?

22. Synesthesia: What Does It Tell Us about the Emergence of Qualia, Metaphor, Abstract Thought, and Language?

23. What Are the Neuronal Correlates of Consciousness?



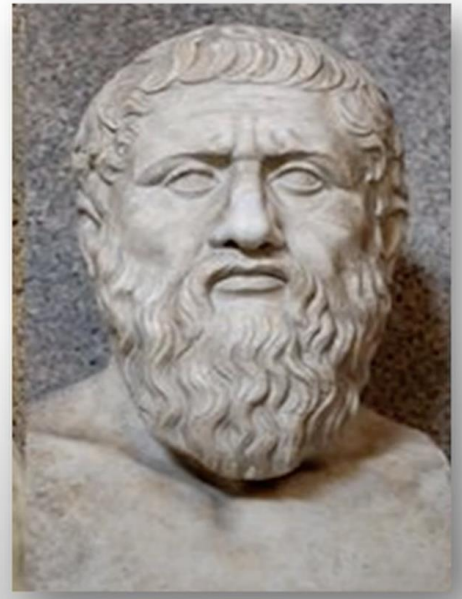
What is a memory trace?

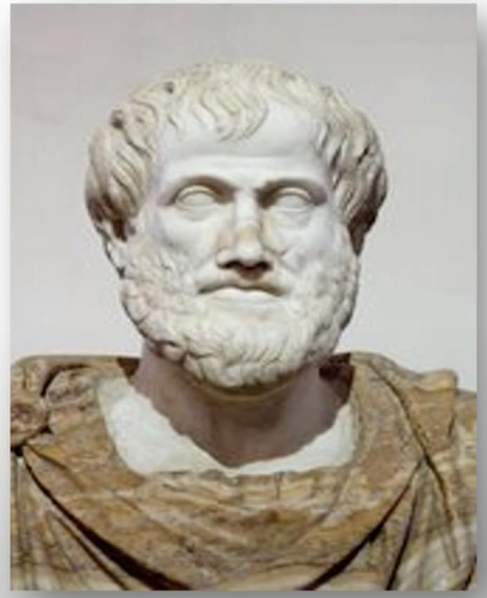
How is it stored in the brain?

Can you implant false memories?

What is memory?

Idea that memory is stored as enduring changes in the body (brain?) dates back to Plato and Aristotle (circa 350 BC) in Ancient Greece





The Engram

Richard Semon

1. *Die mneme* (1904), translated as *The Mneme* (1921)
2. *Die mnemischen Empfindungen* (1909), *Mnemic Psychology* (1923)

1859-1918

Engram (memory trace)
"the enduring though primarily latent modification in the irritable substance produced by a stimulus..."

Ecphory (memory retrieval)
"awaken the engram out of its latent state into one of manifested activity"

(1950)
K. S. Lashley

In search of the engram
Society of Experimental Biology Symposium, No. 4: *Psychological Mechanisms in Animal Behavior*
Cambridge: Cambridge University Press, pp. 454–455, 468–473, 477–480

I. Introduction

'When the mind wills to recall something, this volition causes the little [pineal] gland, by inclining successively to different sides, to impel the animal spirits toward different parts of the brain, until they come upon that part where the traces are left of the thing which it wishes to remember; for these traces are nothing else than the circumstance that the pores of the brain through which the spirits have already taken their course on presentation of the object, have thereby acquired a greater facility than the rest to be opened again the same way by the spirits which come to them; so that these spirits coming upon the pores enter therein more readily than into the others.'

So wrote Descartes just three hundred years ago in perhaps the earliest attempt to explain memory in terms of the action of the brain. In the intervening centuries much has been learned concerning the nature of the impulses transmitted by nerves. Innumerable studies have defined conditions under which learning is facilitated or retarded, but, in spite of such progress, we seem little nearer to an understanding of the nature of the memory trace than was Descartes. His theory has in fact a remarkably modern sound. Substitute nerve impulse for animal spirits, synapse for pore and the result is the doctrine of learning as change in resistance of synapses. There is even a theory of scanning which is at least more definite as to the scanning agent and the source of the scanning beam than is its modern counterpart.

As interest developed in the functions of the brain the doctrine of the separate localization of mental functions gradually took form, even while the ventricles of the brain were still regarded as the active part. From Prochaska and Gall through the nineteenth century, students of clinical neurology sought the localization of specific memories. Flechsig defined the association areas as distinct from the sensory and motor. Aphasia, agnosia and apraxia were interpreted as the result of the loss of memory images either of objects or of kinaesthetic sensations of movements to be made. The

areas adjacent to the corresponding primary sensory areas seemed reasonable and was supported by some clinical evidence. The extreme position was that of Henschen, who speculated concerning the location of single ideas or memories in single cells. In spite of the fact that more critical analytic studies of clinical symptoms, such as those of Henry Head and of Kurt Goldstein, have shown that aphasia and agnosia are primarily defects in the organization of ideas rather than the result of amnesia, the conception of the localized storing of memories is still widely prevalent (Nielsen, 1936).

While clinical students were developing theories of localization, physiologists were analysing the reflex arc and extending the concept of the reflex to include all activity. Bechterew, Pavlov and the behaviourist school in America attempted to reduce all psychological activity to simple associations or chains of conditioned reflexes. The path of these conditioned reflex circuits was described as from sense organ to cerebral sensory area, thence through associative areas to the motor cortex and by way of the pyramidal paths to the final motor cells of the medulla and cord. The discussions of this path were entirely theoretical, and no evidence on the actual course of the conditioned reflex are was presented.

In experiments extending over the past 30 years I have been trying to trace conditioned reflex paths through the brain or to find the locus of specific memory traces. The results for different types of learning have been inconsistent and often mutually contradictory, in spite of confirmation by repeated tests. I shall summarize to-day a number of experimental findings. Perhaps they obscure rather than illuminate the nature of the engram, but they may serve at least to illustrate the complexity of the problem and to reveal the superficial nature of many of the physiological theories of memory that have been proposed.

VI. The Engram within Sensory Areas (Equipotential Regions)

The experiments reported indicate that performance

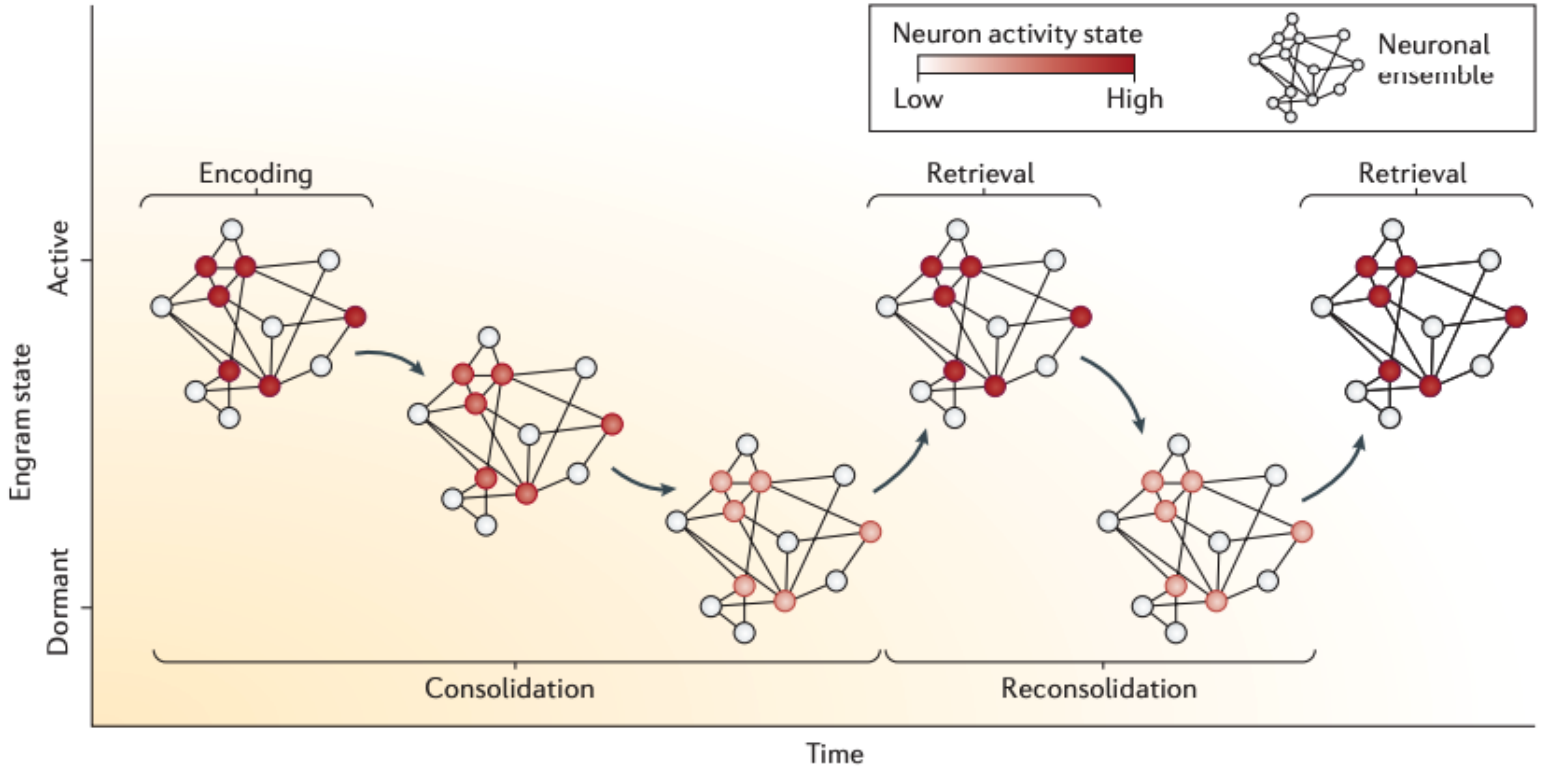
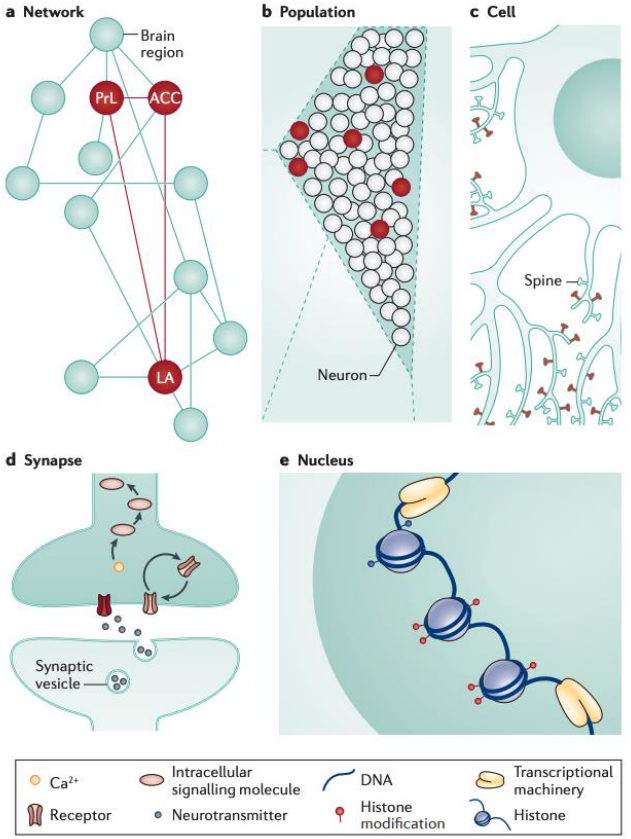


Figure 1 | **The lifetime of an engram.** The formation of an engram (encoding) involves strengthening of connections between collections of neurons (neuronal ensemble) that are active (red) during an event. Consolidation further strengthens the connections between these neurons, which increases the likelihood that the same activity pattern can be recreated at a later time, allowing for successful memory retrieval. During consolidation, the engram enters a mainly dormant state. Memory retrieval returns the engram back to an active state and transiently destabilizes this pattern of connections. The engram may be restabilized through a process of reconsolidation and re-enter a more dormant state. Therefore, an engram may exist in a dormant state between the active processes of encoding and retrieval required to form and recover the memory. In this way, an engram is not yet a memory, but provides the necessary conditions for a memory to emerge.

Finding the engram

Sheena A. Josselyn[1–4], Stefan Köhler[5,6] and Paul W. Frankland[1–4]

Engrams can be studied at the region, neural population, cell or even nucleus level…

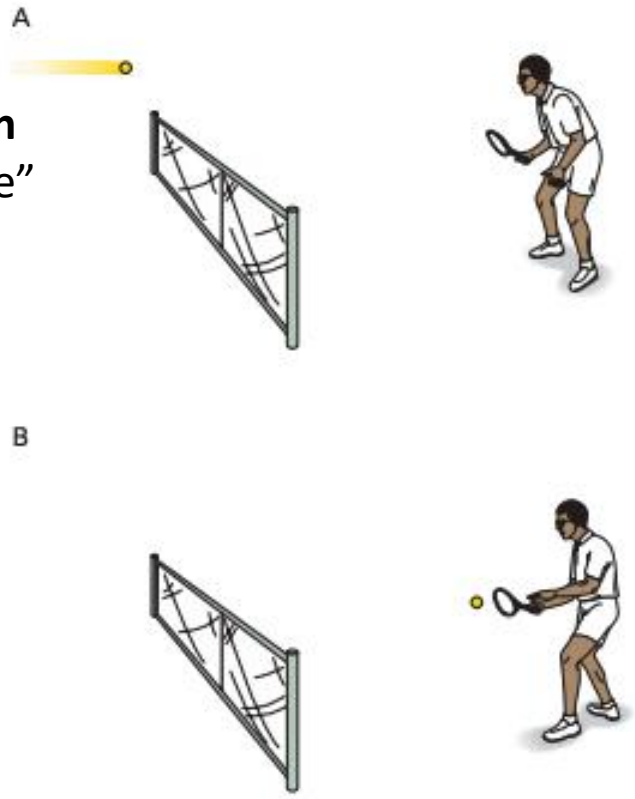


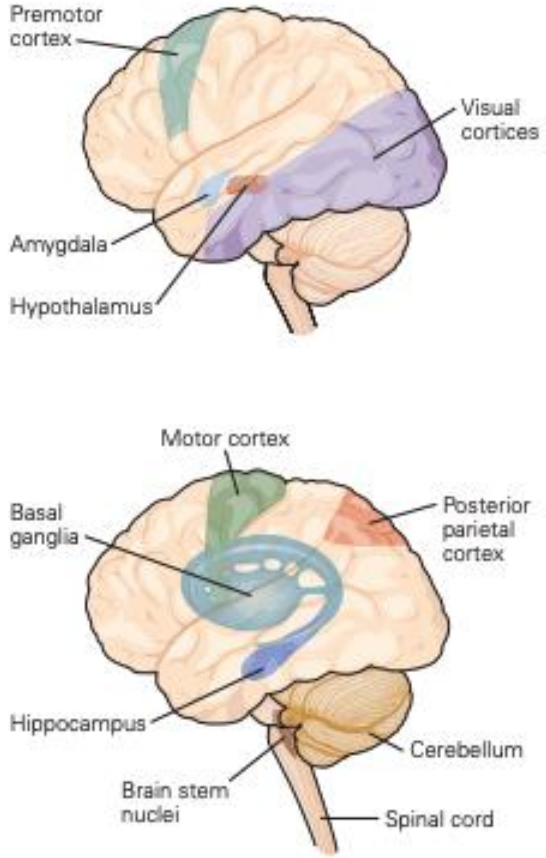
https://core.ac.uk/download/pdf/289079817.pdf

The Distributed Brain

Regions of the brain do not function in isolation

- Many areas are involved in seemingly “simple” behaviors.
- Neurons across regions orchestrate behavior in a hierarchical manner
  - This hierarchy is most often considered anatomically, then computationally





“Simple” example, Tennis:

- visual areas to judge size, motion, velocity of the ball
- amygdala (plus more in brainstem) adjusts heart rate, respiration, coordinate with hypothalamus to motivate
- To hit the ball, need premotor and motor to signal to spinal cord
- Basal ganglia activated to recall learned movements
- Cerebellum, parietal and somatosensory cortex provide sense of body and feedback
- Hippocampus: remembers the great hit to brag about it later! 🏆

The Hippocampus

Explicit memory—the conscious recall of information about people, places, and objects—is what people commonly think of as memory.

The two structures in the mammalian brain that are critical for encoding and storing explicit memories are the **prefrontal cortex** and the **hippocampus.**

The prefrontal cortex mediates working memory. Information stored in working memory can be actively maintained for very short periods and then rapidly forgotten, such as a telephone number that is remembered only until it is dialed, or it can be stored elsewhere in the brain as long-term memory. **The hippocampus stores declarative information in a more stable form for periods ranging from days to weeks to years, up to a lifetime.**

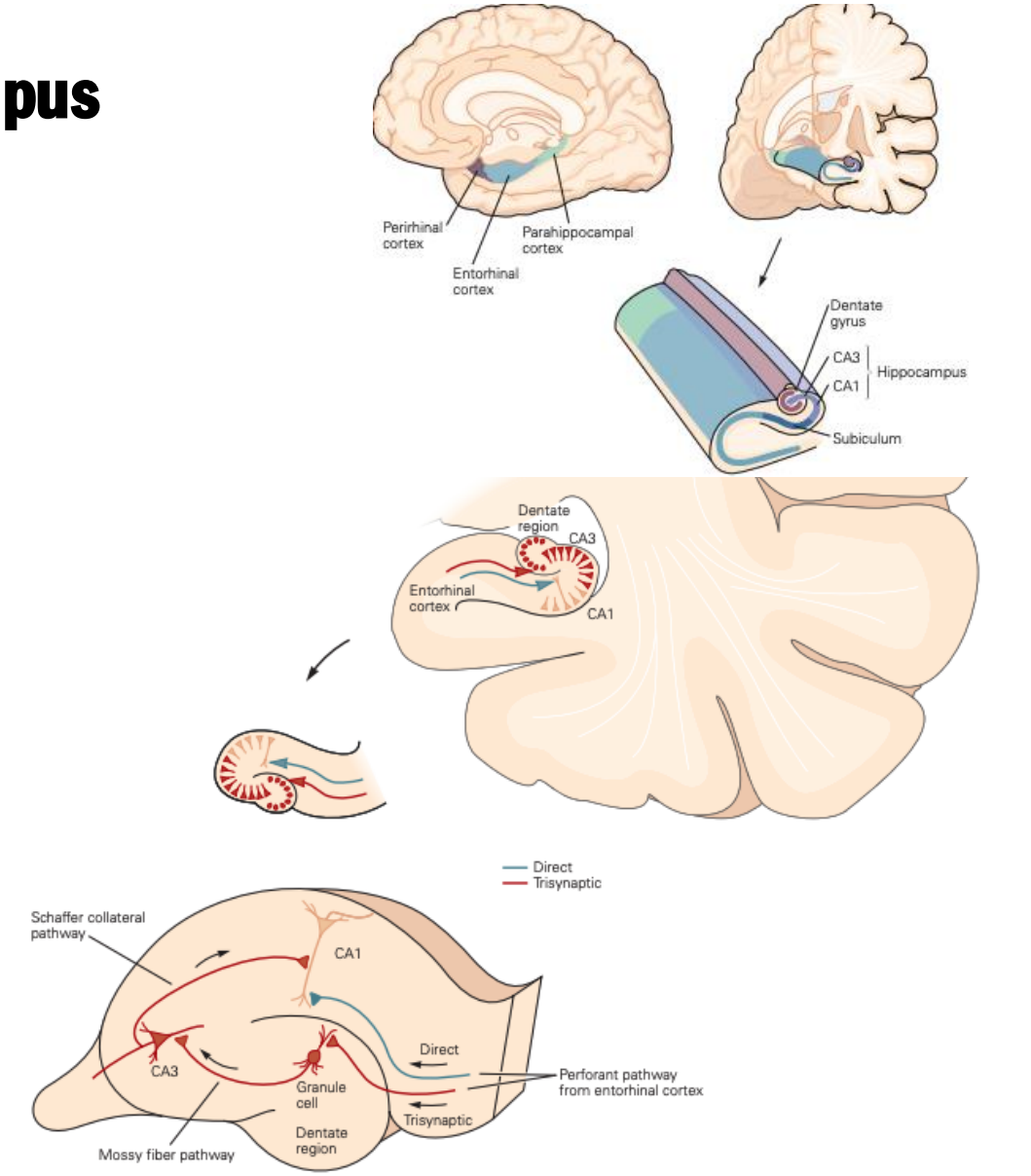
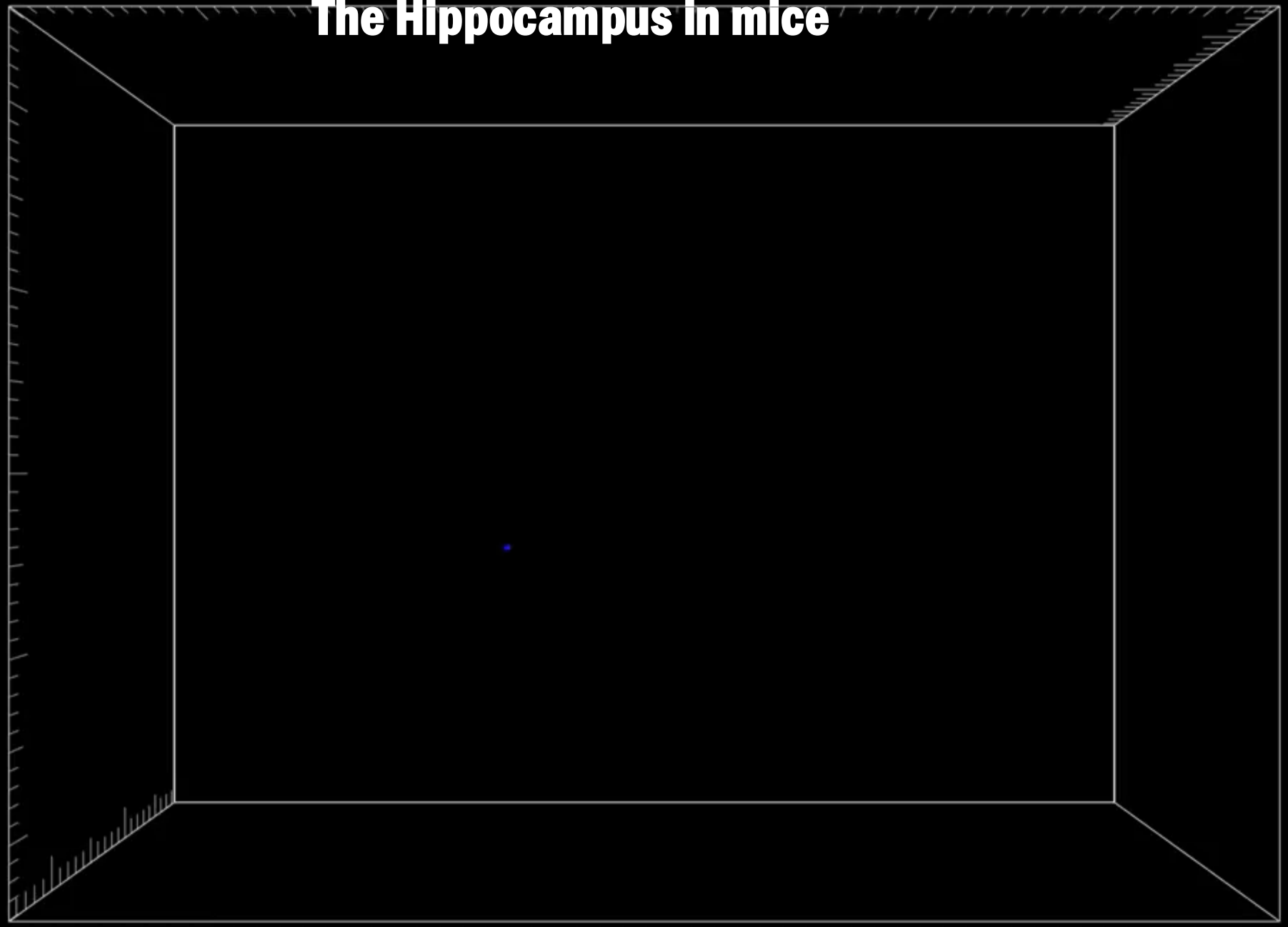


Figure 67–2 The hippocampal synaptic circuit is important for declarative memory. Information arrives in the hippocampus from entorhinal cortex through the *perforant pathways*, which provide both direct and indirect input to CA1 pyramidal neurons, the major output neurons of the hippocampus. (**Arrows** denote the direction of impulse flow.) In the indirect *trisynaptic pathway* neurons in layer II of entorhinal cortex send their axons through the perforant path to make excitatory synapses onto the granule cells of the dentate gyrus. The granule cells project through the mossy fiber pathway and make excitatory synapses with the pyramidal cells in area CA3 of the hippocampus. The CA3 cells excite the pyramidal cells in CA1 by means of the Schaffer collateral pathway. In the *direct pathway* neurons in layer III of entorhinal cortex project through the perforant path to make excitatory synapses on the distal dendrites of CA1 pyramidal neurons without intervening synapses.

The Hippocampus in mice

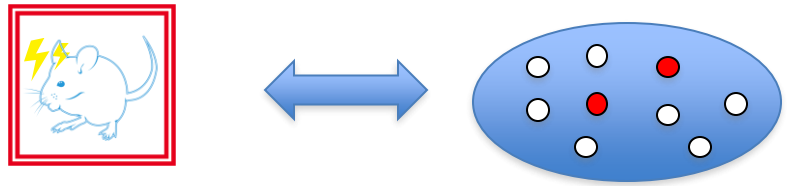


https://www.youtube.com/watch?v=wMuwc2MxLuw

Criteria for identifying correlation, necessity & sufficiency of memory

Learning => Neural Activity **Correlation**

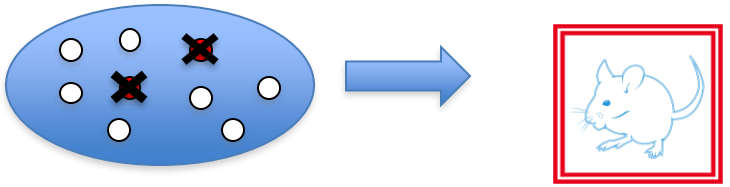
Observe



(Eichenbaum, 2016)
(Hasselmo et al. 2002)
(Reijmers et al. 2007)

Block neurons => Block memory **Necessity**

Perturb



(Tang et al. 1999)
(Han et al, 2009)
(Denny et al. 2014)
(Tanaka et al. 2014)

Slide courtesy of Prof. Steve Ramirez (BU)

The Hippocampus in mice: causally probing memory

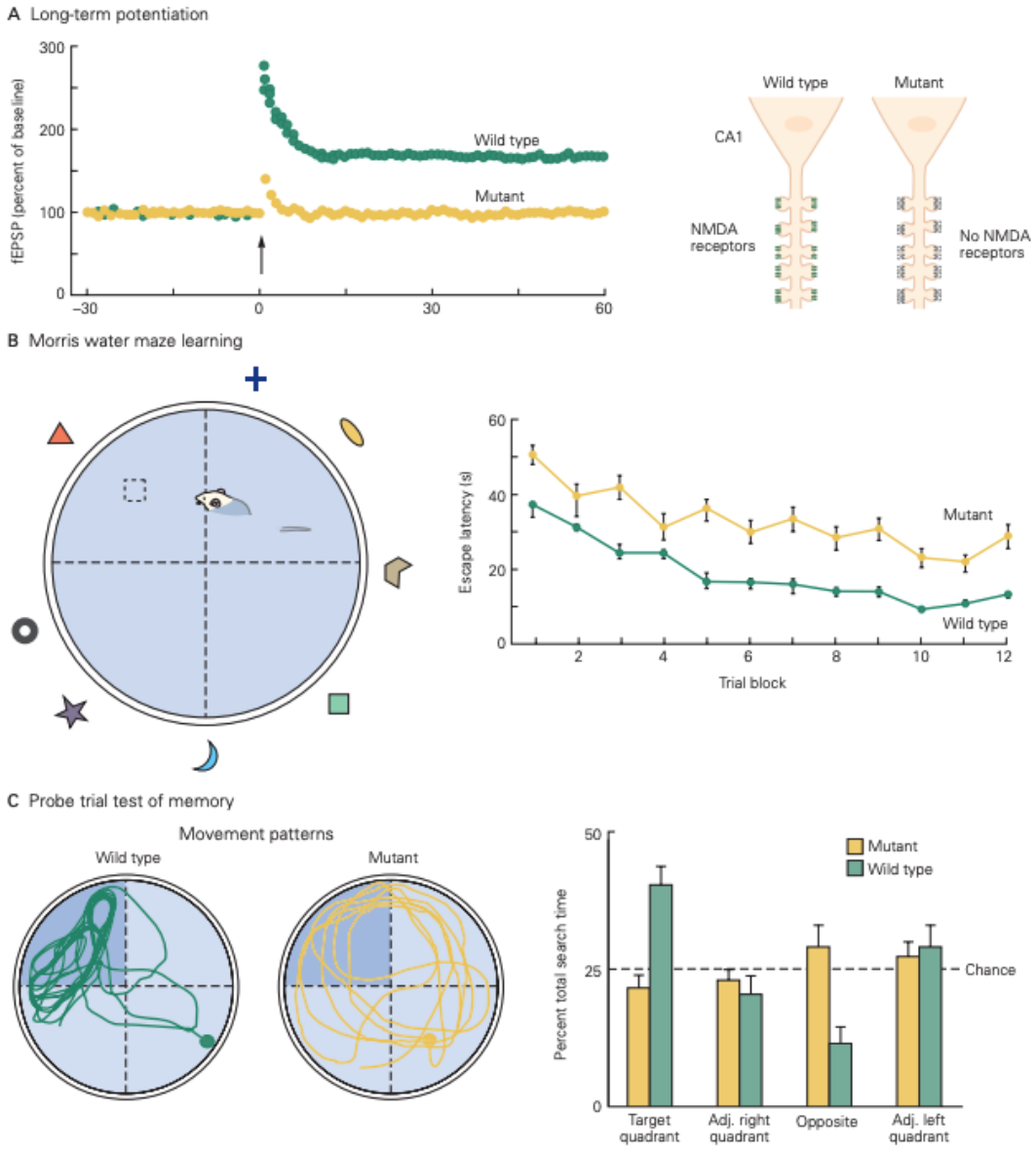
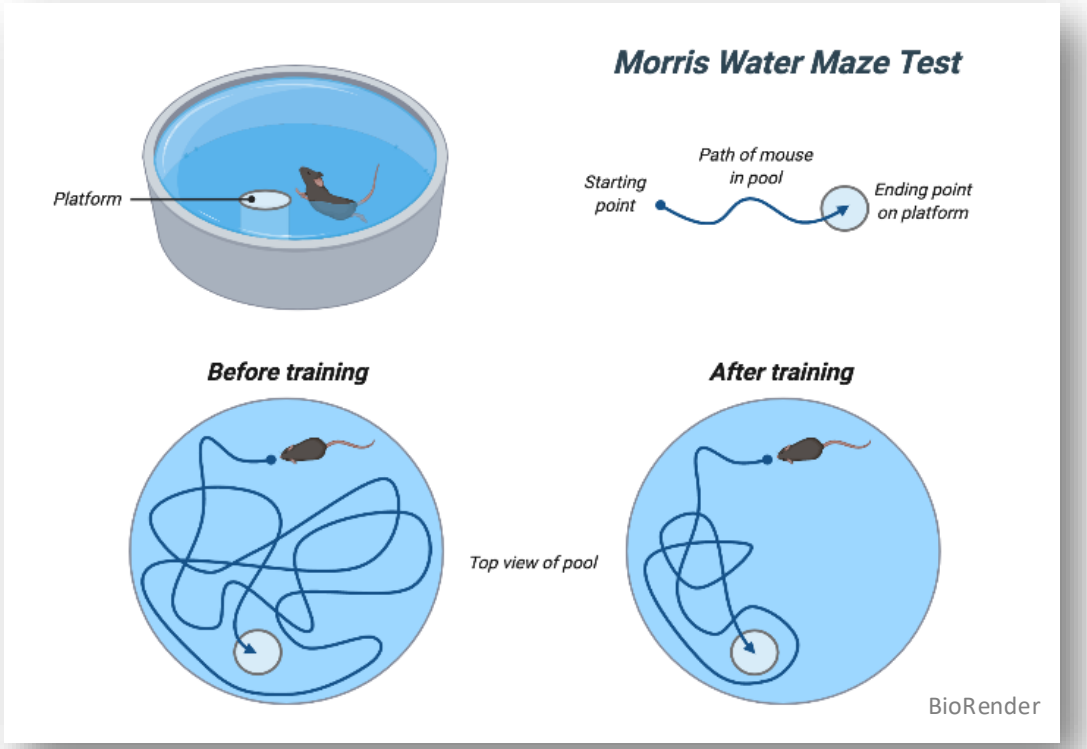


Fig 67-12 (Reproduced, with permission, from Tsien, Huerta, and Tonegawa 1996.)



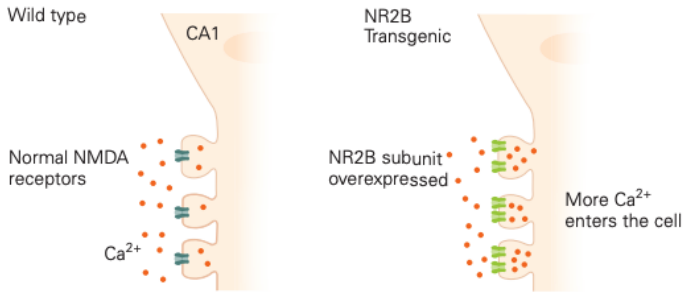
Metrics:

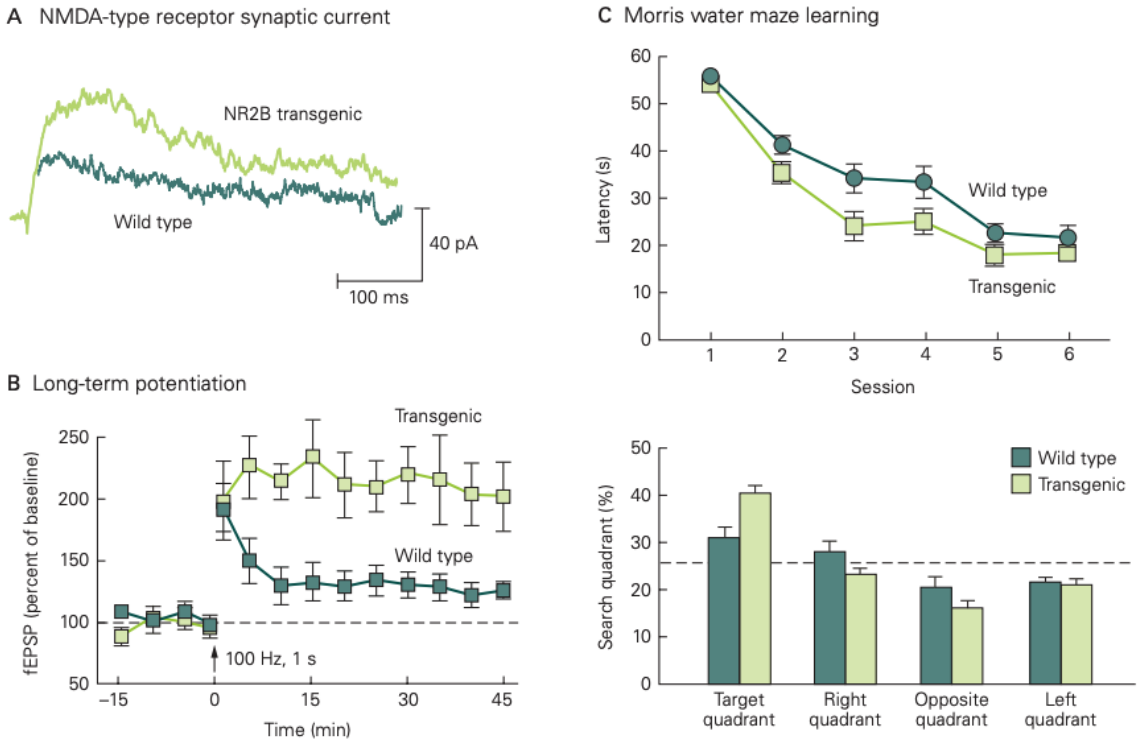
- **Time to reach platform** (escape latency)
- **Swimming path** (for ease, often broken into quadrants in older works, now can be tracked with DL easily)

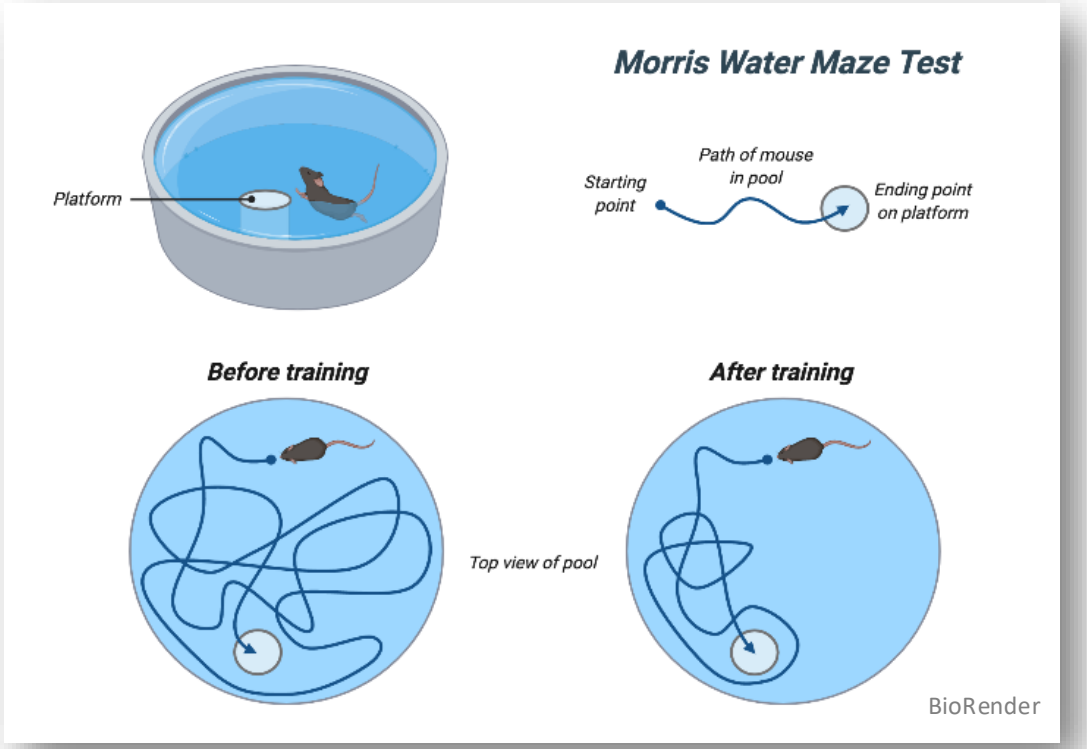
Long-term potentiation, and **spatial learning and memory are impaired in mice that lack the NMDA receptor** in the CA1 region of the hippocampus

necessity

The Hippocampus in mice: causally probing memory







Metrics:

- **Time to reach platform** (escape latency)
- **Swimming path** (for ease, often broken into quadrants in older works, now can be tracked with DL easily)

Learning and memory are **enhanced in mice that overexpress the NR2B subunit of the NMDA** glutamate receptor. 😀

necessity

Fig 67-13 (Reproduced, with permission, from Tang et al. 1999.)

The Hippocampus in mice: what are the neural representations?

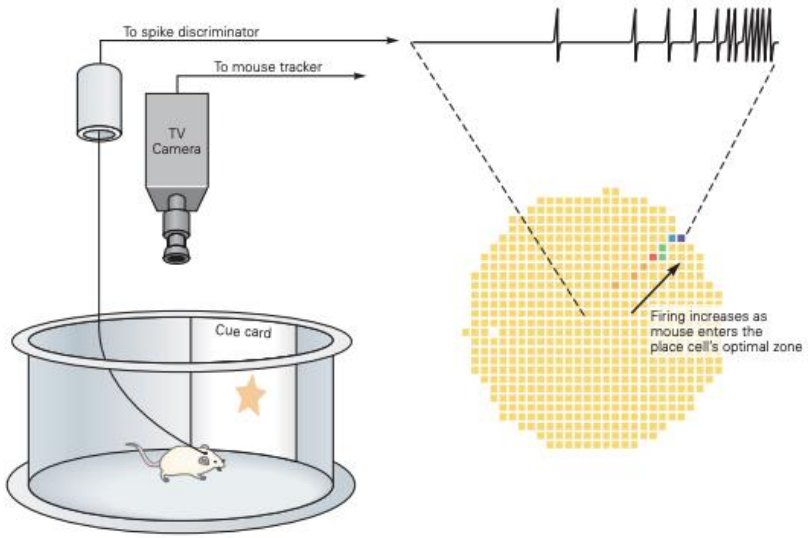


Fig 67-15 (Adapted, with permission, from Muller, Kubie, and Ranck 1987.)

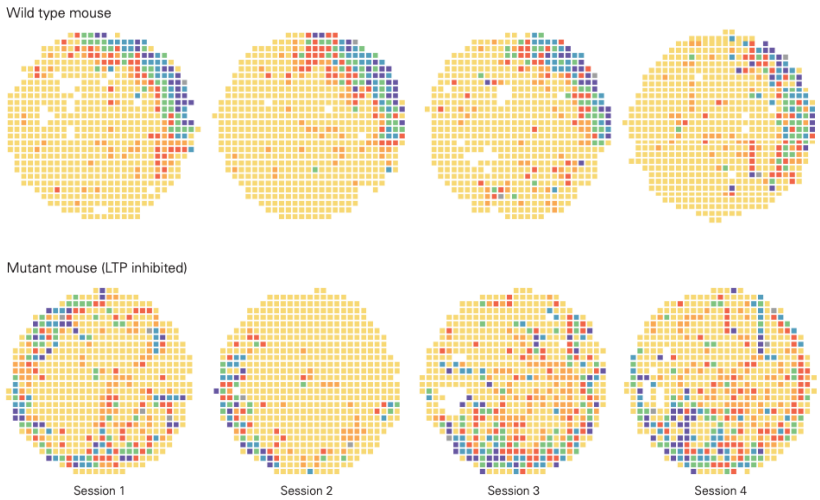


Fig 67-16 (Reproduced, with permission, from Rotenberg et al. 1996.)

The firing patterns of pyramidal cells in the hippocampus create an internal representation of the animal's location in its surroundings.

**see much more in "Encoding of Space" lectures*

But is there a relation to neural firing and disruption of NMDA receptors in hippocampus?

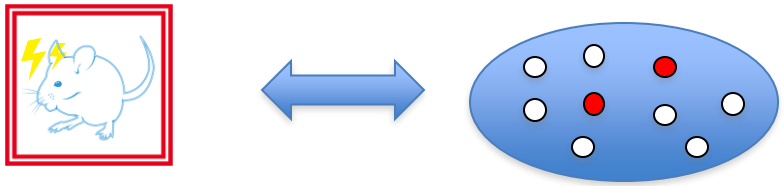
Yes! Recording in mutant mice shows a disruption of "place cell" coding … 😍

correlation

Criteria for identifying correlation, necessity & sufficiency of memory

Learning => Neural Activity **Correlation**

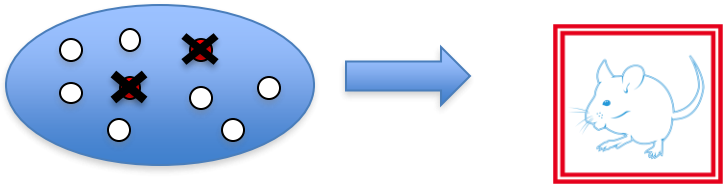
Observe



(Eichenbaum, 2016)
(Hasselmo et al. 2002)
(Reijmers et al. 2007)

Block neurons => Block memory **Necessity**

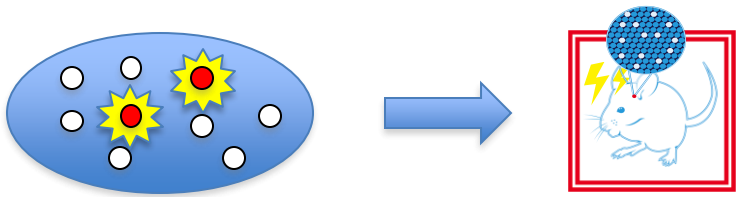
Perturb



(Tang et al. 1999)
(Han et al, 2009)
(Denny et al. 2014)
(Tanaka et al. 2014)

Activate neurons => Activate memory **Sufficiency**

Mimic



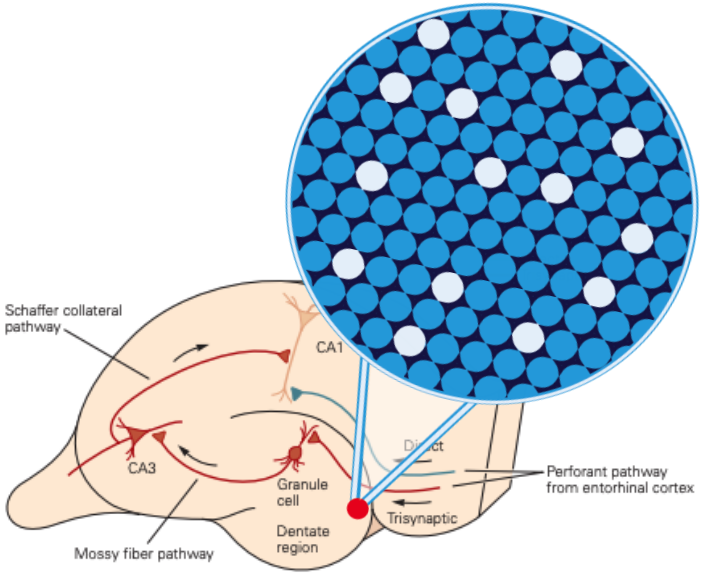
(Liu et al. 2012)
(Ramirez et al. 2013)
(Josselyn et al. 2015)
(Tonegawa et al. 2015)

?

Slide courtesy of Prof. Steve Ramirez (BU)

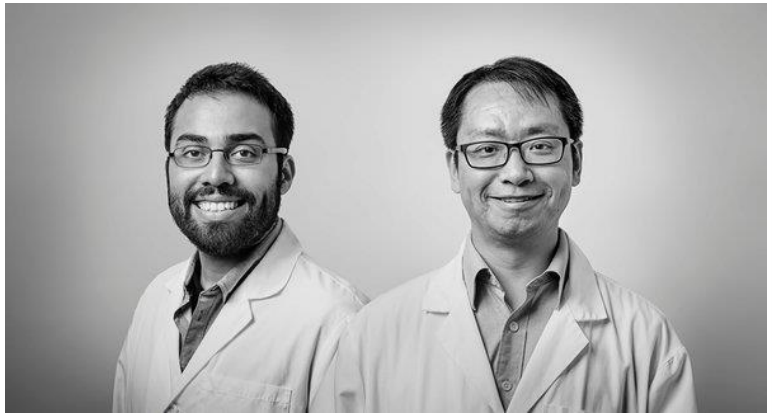
(Martin and Morris, 2000)

Is the hippocampus engram sufficient to drive recall of a memory?



Hypothesis:

Neurons in the hippocampus that are active during the formation of a memory are sufficient to drive behavioral expression of that memory



Letter | Published: 22 March 2012

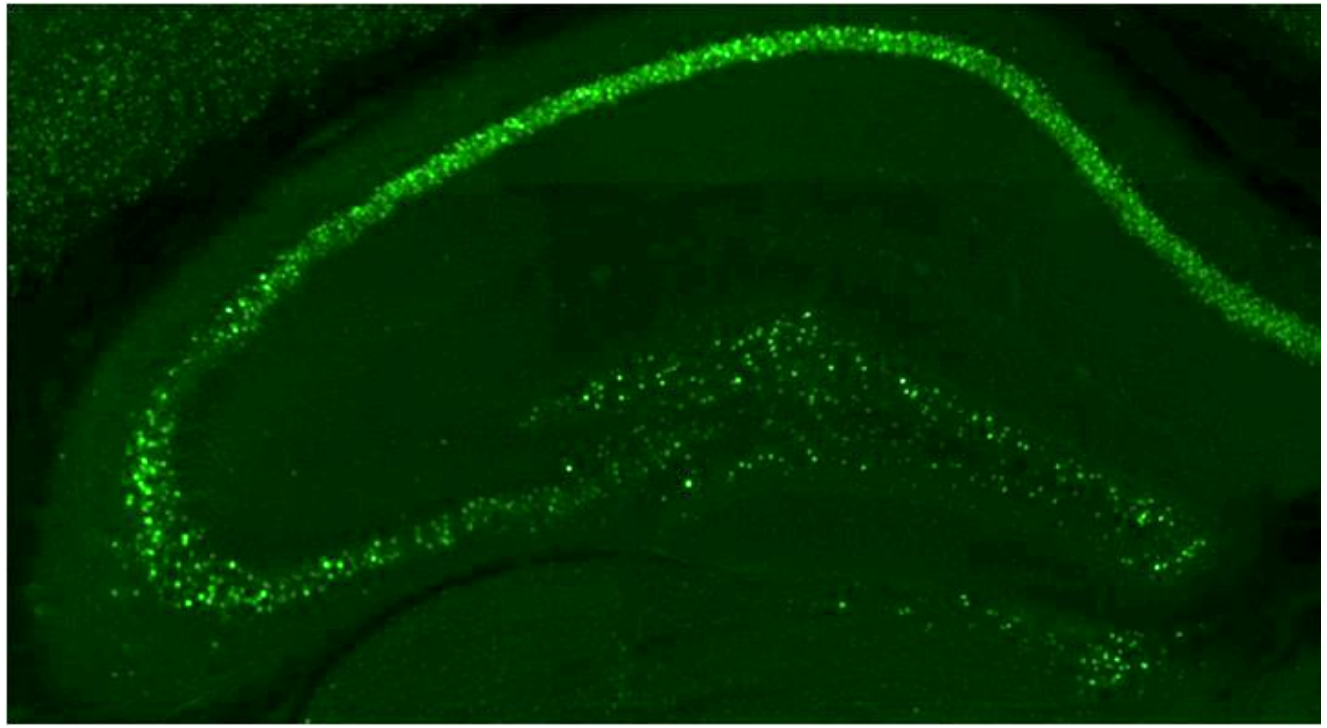
Optogenetic stimulation of a hippocampal engram activates fear memory recall

Xu Liu, Steve Ramirez, Petti T. Pang, Corey B. Puryear, Arvind Govindarajan, Karl Deisseroth & Susumu Tonegawa

Nature **484**, 381–385 (2012) | Cite this article

103k Accesses | **940** Citations | **607** Altmetric | Metrics

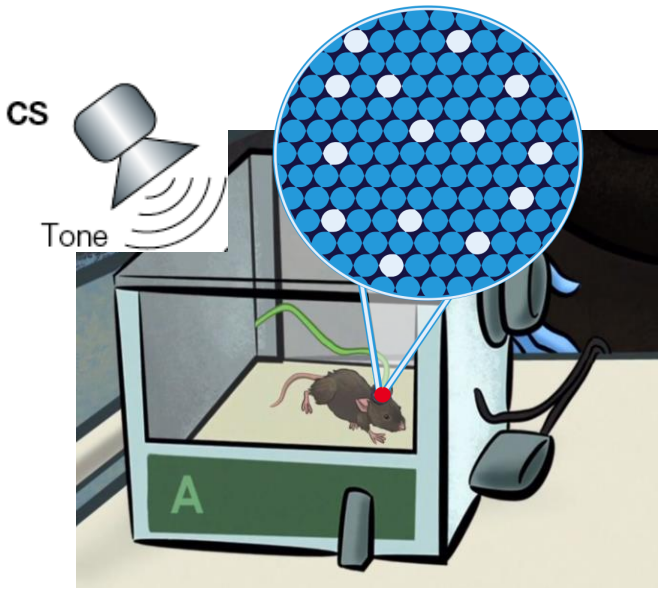
Is the hippocampus engram sufficient to drive recall of a memory?

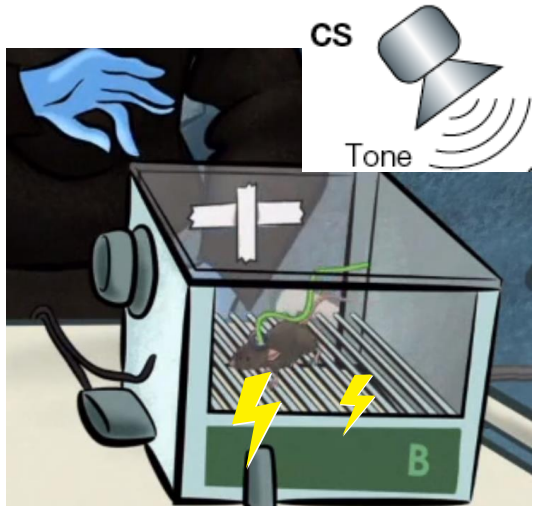


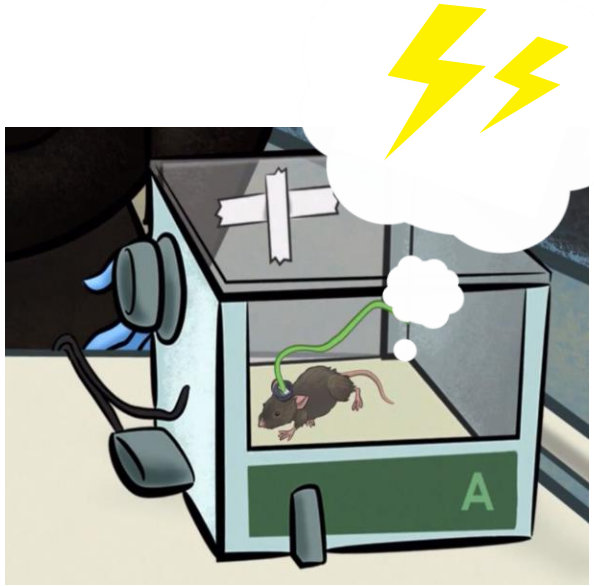
- A specific memory is thought to be encoded by a sparse population of neurons.
- These neurons can be tagged during learning for subsequent identification and manipulation (think ChR2/optogenetics).
- Moreover, their ablation or inactivation results in reduced memory expression, suggesting their necessity in mnemonic processes (and over-expression can enhance memory-based learning!)
- **However, the question of sufficiency remained:** it is unclear whether it is possible to elicit the behavioural output of a specific memory by directly activating a population of neurons that was active during learning.

X Liu *et al*. *Nature* **000**, 1-8 (2012) doi:10.1038/nature11028

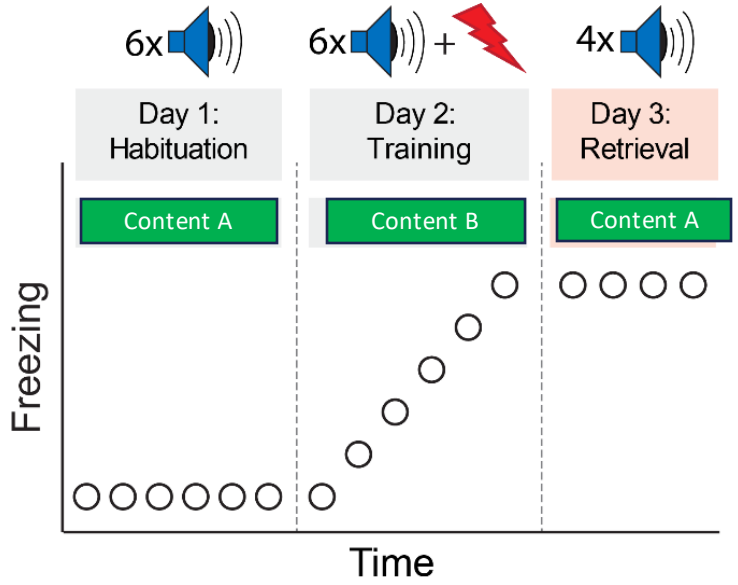
Aversive conditioning / "fear learning"







Cartoons by Prof. Steve Ramirez (BU)

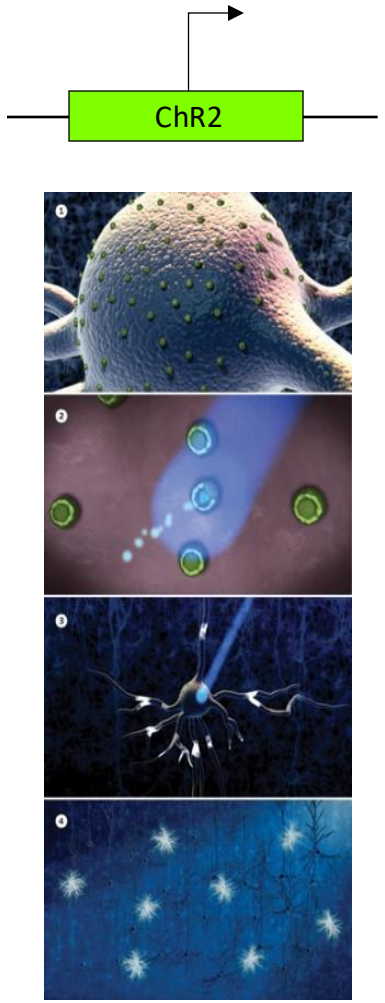


CS: An innocuous sensory stimulus
(tone of 7 kHz, 80 dB, 0.1 s, 30x)

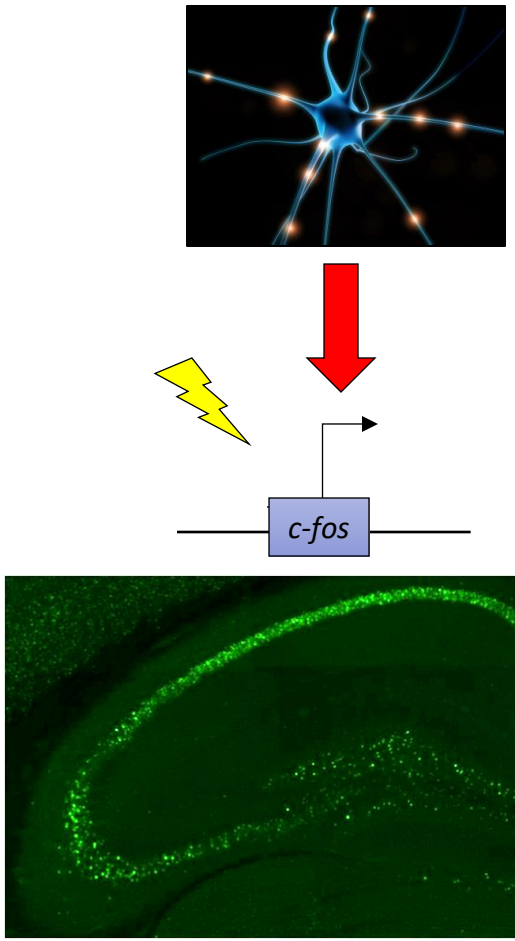
US: A mild electric footshock
Activates nociceptors on the feet and probably other low-threshold mechanoreceptors

CR: freezing (behavioral immobility)
An evolutionary useful response in the presence of a not clearly present threat

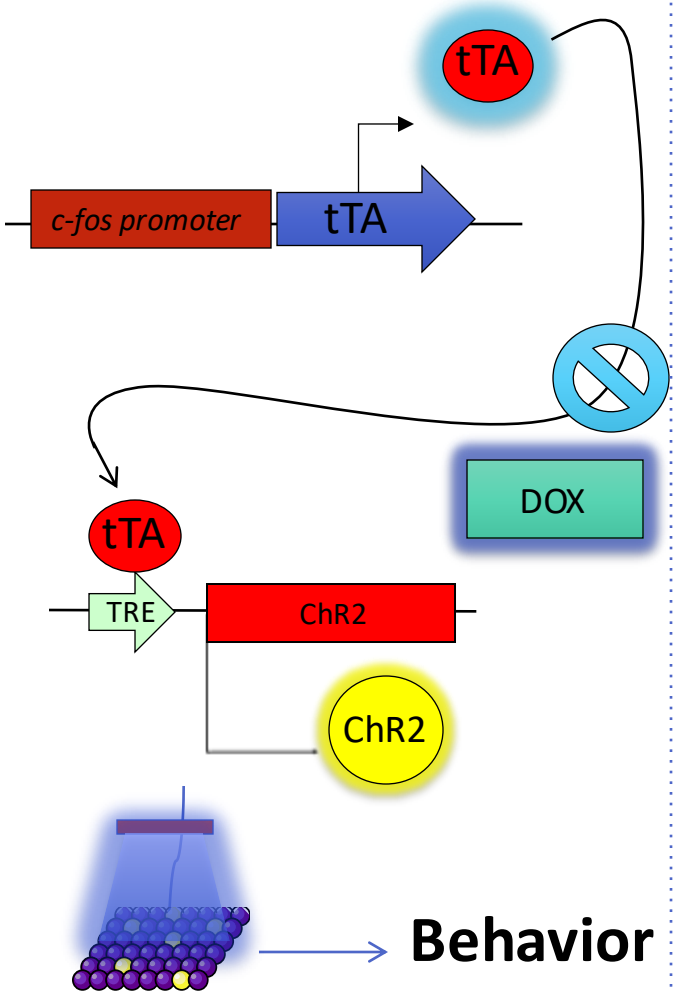
Activity-dependent and inducible optogenetics



ChR2 makes cells responsive to light



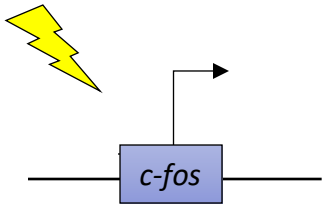
c-Fos is only expressed in active neurons

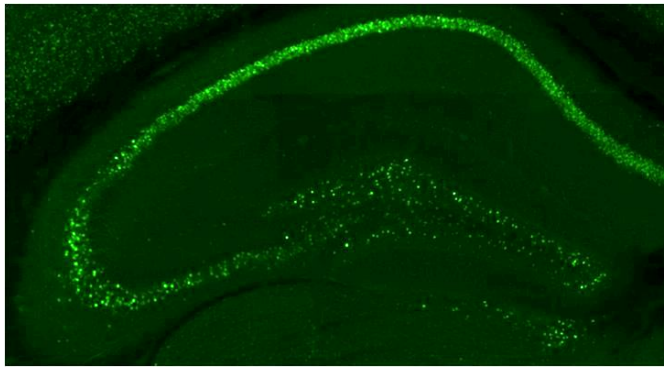


Dox can open and close windows for expressing a given gene

Slide courtesy of Prof. Steve Ramirez (BU)

The Expression of Immediate Early Genes (IEGs)





c-Fos is only expressed in active neurons

IEGs	Function
c-fos *c-jun*	Cell activation (cell proliferation and differentiation) and protein transcriptions. For *c-fos*: sensory information processing, pain regulation mechanisms, long-term potentiation, neural plasticity, learning and memory, direct control of the expression of inflammatory cytokines, mediation of neuronal excitability by regulating the expression of the kainic acid receptor and GluR6, brain-derived neurotrophic factor.

IEGs are classified into two groups:

- (a) those that encode transcription factors that regulate the expression of other genes by binding to a specific DNA sequence (called regulatory transcription factors)
- (b) those that encode proteins that are found throughout the cytoplasm and which go into the peri-dendritic region of cells, directly modifying cell function (called effector IEGs)

- *be aware there are many more beyond *c-fos* ….

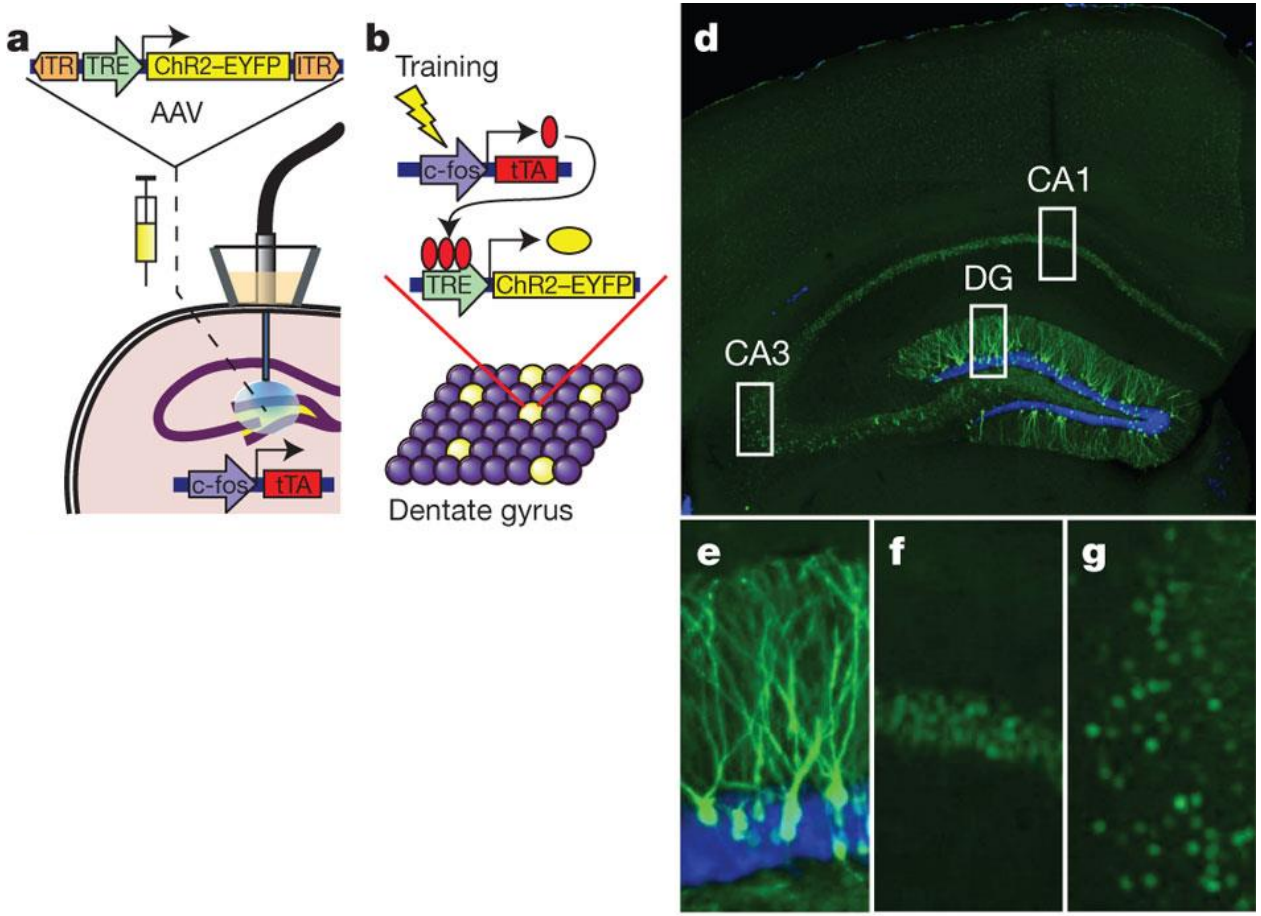
Review

Current Opinion on the Use of c-Fos in Neuroscience

Sandra Yasbeth Lara Aparicio [1,2,*], Ángel de Jesús Laureani Fierro [3], Gonzalo Emiliano Aranda Abreu [1], Rebeca Toledo Cárdenas [1], Luis Isauro García Hernández [1], Genaro Alfonso Coria Ávila [1], Fausto Rojas Durán [1], María Elena Hernández Aguilar [1], Jorge Manzo Denes [1], Lizbeth Donají Chi-Castañeda [1] and César Antonio Pérez Estudillo [1]

https://www.mdpi.com/2673-4087/3/4/50

How to label a memory in the mouse



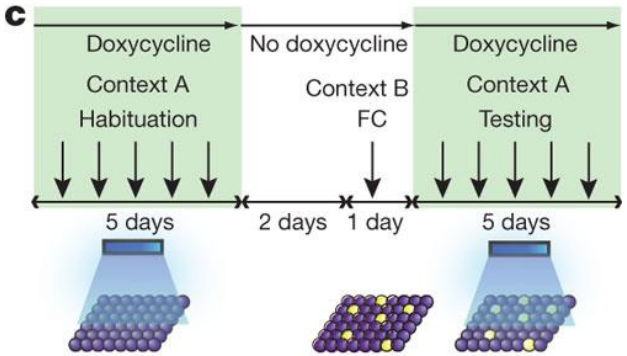
a: The **c-fos-tTA** mouse was injected with **AAV_9-TRE-ChR2-EYFP** and implanted with an optical fiber targeting the DG.

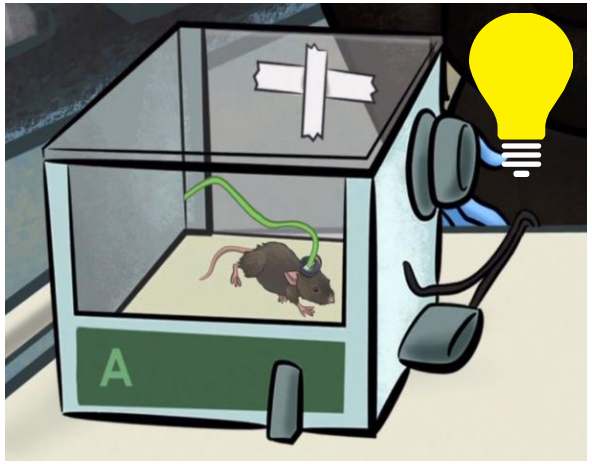
b: When off Dox, fear conditioning induces the expression of **c-fos → tT**A, which binds to TRE and drives the expression of ChR2–EYFP, labelling a subpopulation of activated cells (yellow) in the DG

Basic experimental protocols and selective labelling of DG cells by ChR2–EYFP.

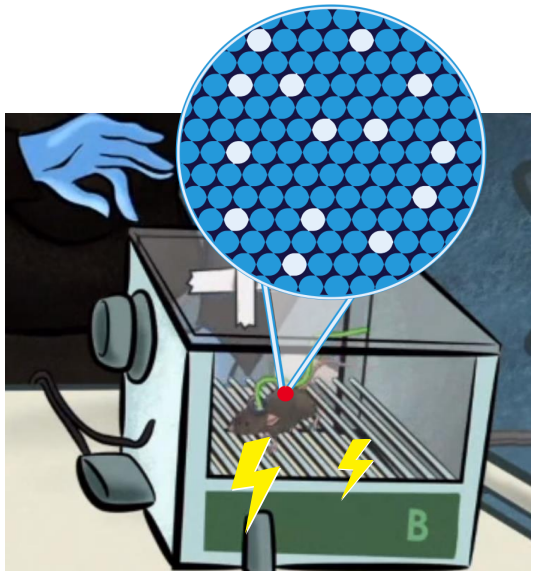
X Liu *et al*. *Nature* **000**, 1-8 (2012) doi:10.1038/nature11028

The experimental setup

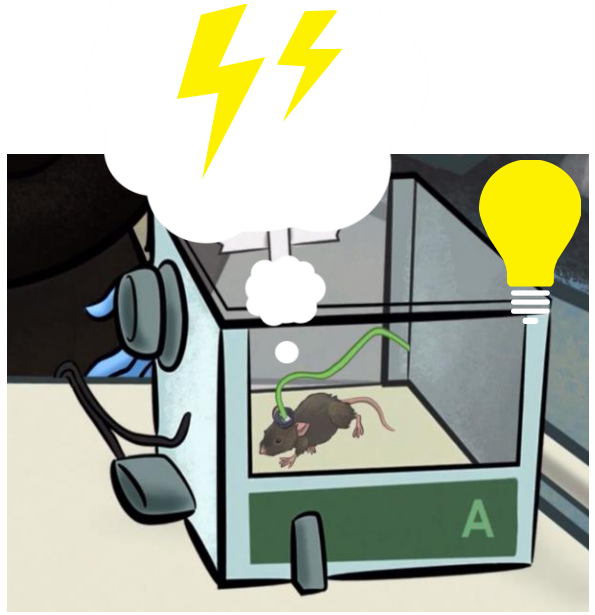




Mice were habituated in context A with light stimulation **while on Dox for 5 days**



Then taken **off Dox** for 2 days and fear conditioned (FC) in context B



Mice were put **back on Dox** and tested for 5 days in context A with light stimulation

What behavioral readout are we going to look for?

Cartoons by Prof. Steve Ramirez (BU)

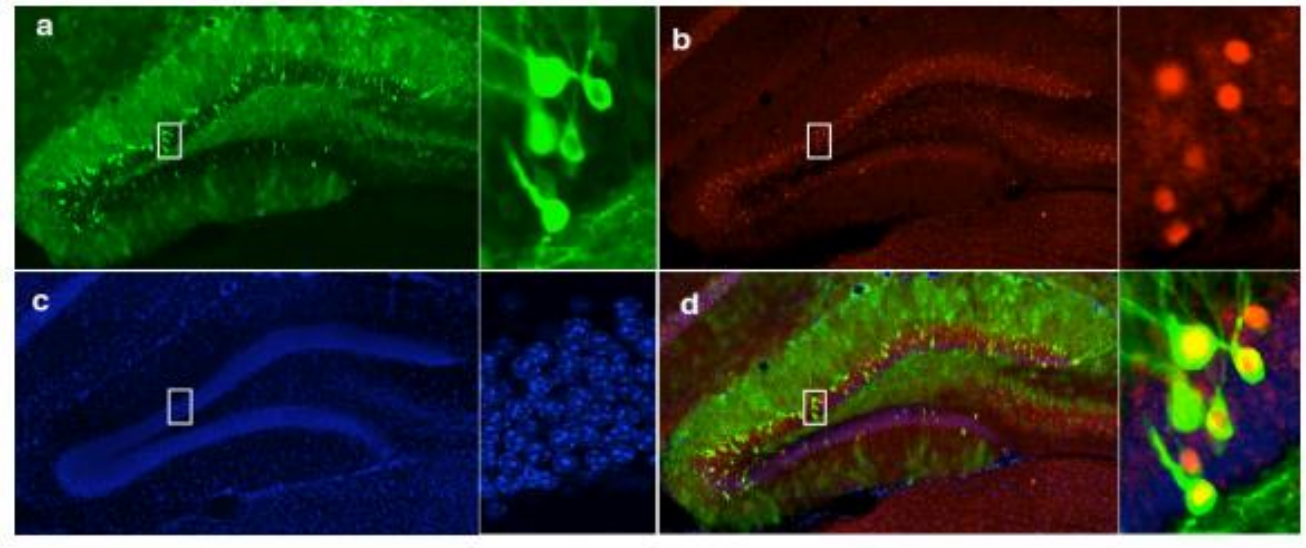
Question …

- When mice are **on Dox** the expression of **c-fos-tTA is inhibited! Why is this important?**

You don't want expression of c-fos just because they are learning a new environment in context A!

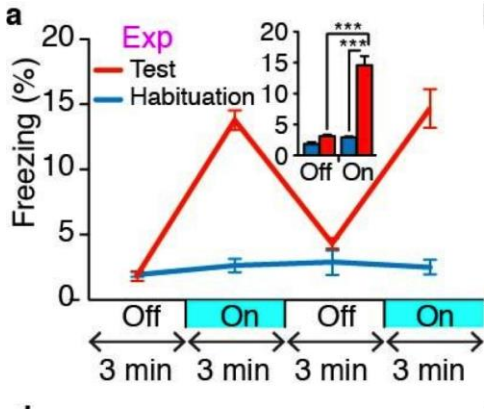
ChR2

DAPI

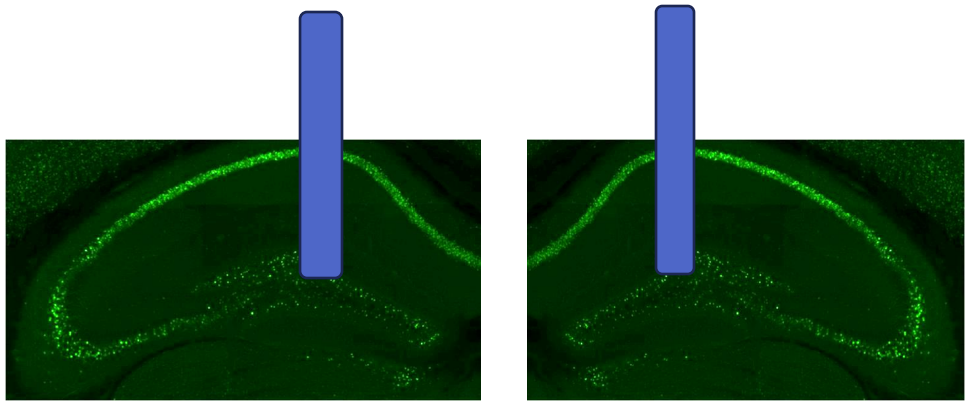


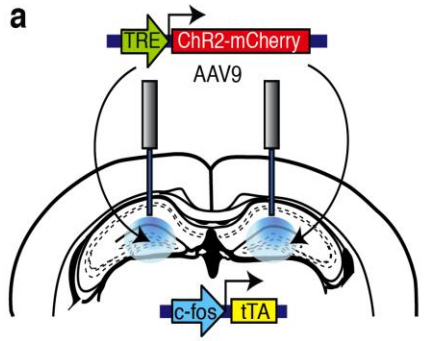
C-fos

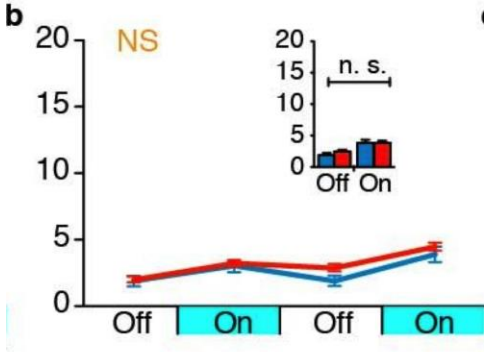
Light induces freezing in experimental subjects only



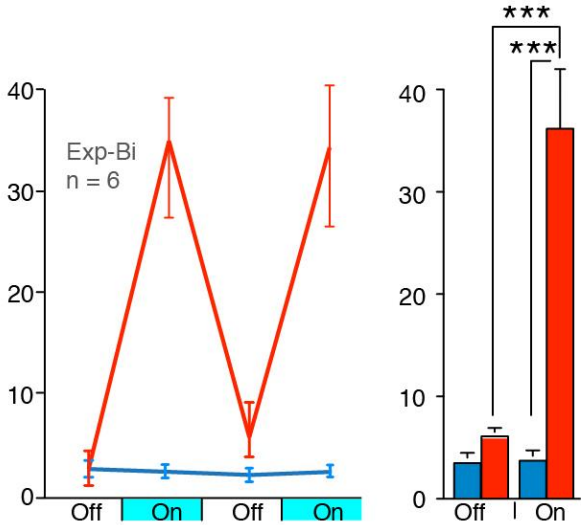
Hippocampus cells active during learning are sufficient for memory recall upon subsequent activation







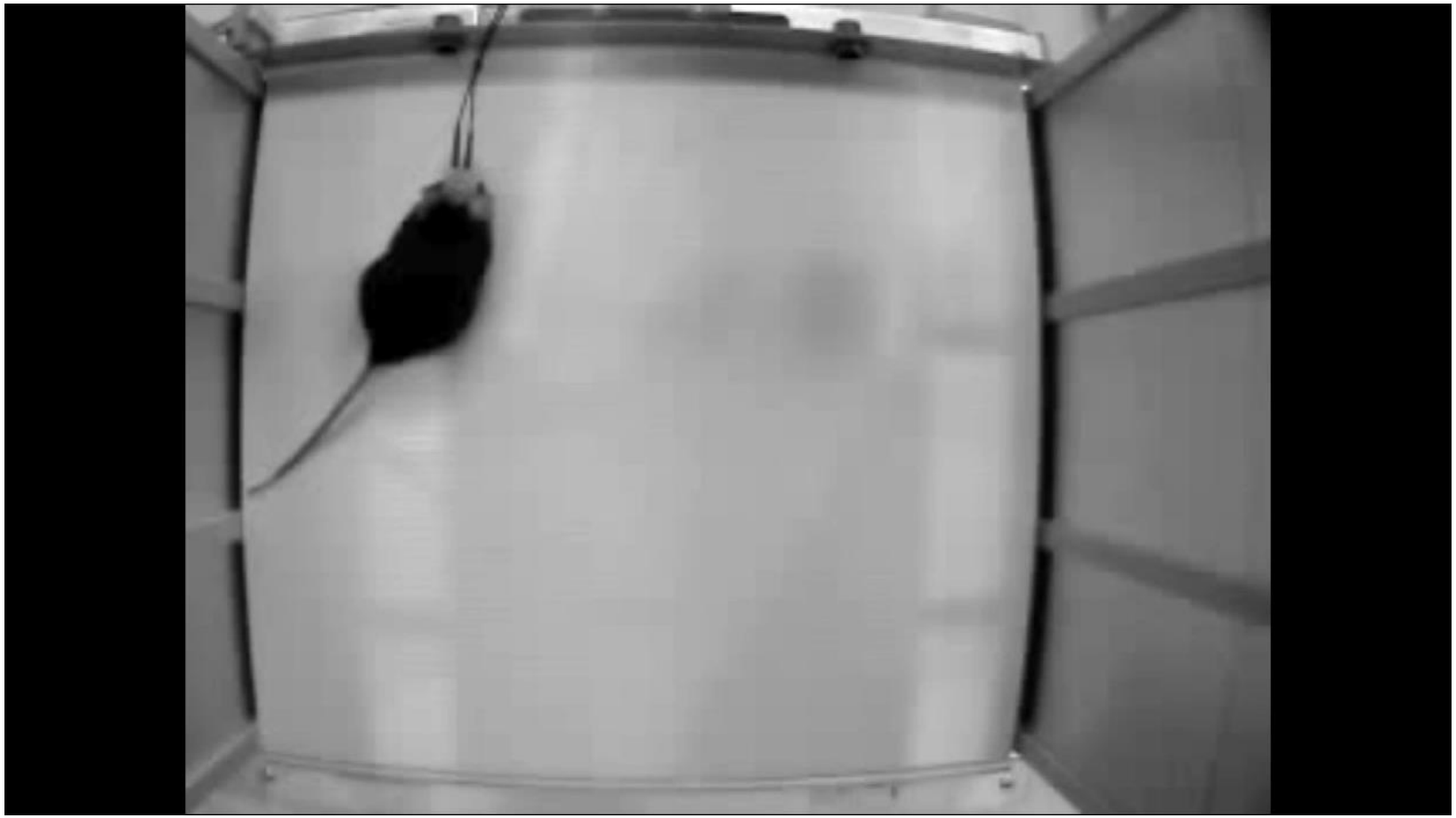
Activating a similar proportion of cells unrelated to fear learning does not elicit a fear response

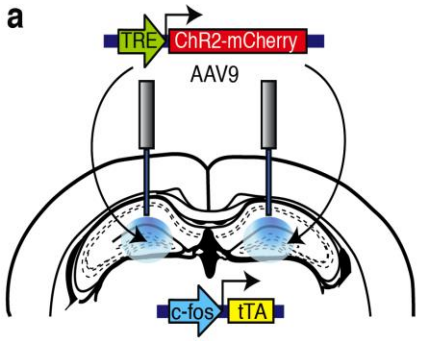


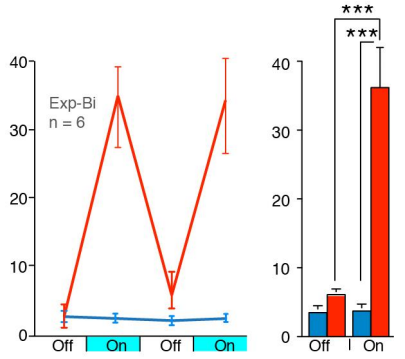
Bi-lateral stimulation caused even more freezing

Slide courtesy of Prof. Steve Ramirez (BU)

Lets take a look...







This file contains a movie showing one representative mouse from the Exp-Bi group during a test session post-training. The first minute of the movie shows the light-off epoch and the subsequent three minutes show the light-on epoch. The movie is played at 4× normal speed. Note that freezing levels increase dramatically only during the light-on epoch.

X Liu *et al*. *Nature* **000**, 1-8 (2012) doi:10.1038/nature11028

Optogenetic stimulation of a hippocampal engram activates fear memory recall

this was the first demonstration that directly activating a subset of cells involved in the formation of a memory is sufficient to induce the behavioural expression of that memory

- Optogenetic reactivation of hippocampal neurons activated during fear conditioning is **sufficient** to induce freezing behaviour.
- They labelled a population of hippocampal dentate gyrus neurons activated during fear learning with channelrhodopsin-2 (ChR2) and later optically reactivated these neurons in a different context.
- The mice showed increased freezing only upon light stimulation, indicating light-induced fear memory recall

Section Journal Club Paper For Tomorrow ....

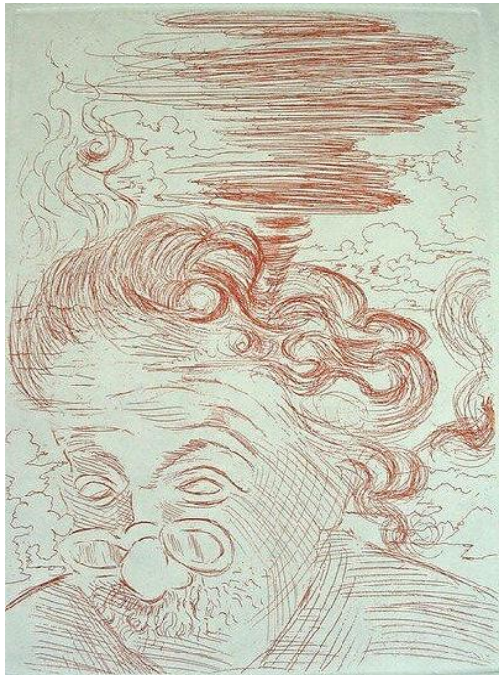
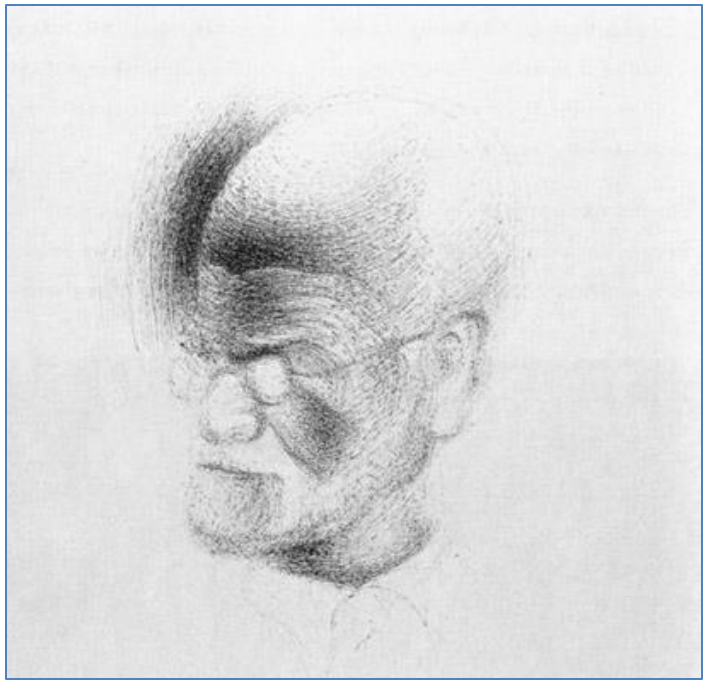
Creating a False Memory in the Hippocampus

Steve Ramirez,[1*] Xu Liu,[1,2*] Pei-Ann Lin,[1] Junghyup Suh,[1] Michele Pignatelli,[1] Roger L. Redondo,[1,2] Tomás J. Ryan,[1,2] Susumu Tonegawa[1,2†]

Memories can be unreliable. We created a false memory in mice by optogenetically manipulating memory engram–bearing cells in the hippocampus. Dentate gyrus (DG) or CA1 neurons activated by exposure to a particular context were labeled with channelrhodopsin-2. These neurons were later optically reactivated during fear conditioning in a different context. The DG experimental group showed increased freezing in the original context, in which a foot shock was never delivered. The recall of this false memory was context-specific, activated similar downstream regions engaged during natural fear memory recall, and was also capable of driving an active fear response. Our data demonstrate that it is possible to generate an internally represented and behaviorally expressed fear memory via artificial means.

"The difference between false memories and true ones is the same as for jewels: it is always the false ones that look the most real, the most brilliant."

- Salvador Dali


Slide courtesy of Prof. Steve Ramirez (BU)