Geometry of Neuroscience

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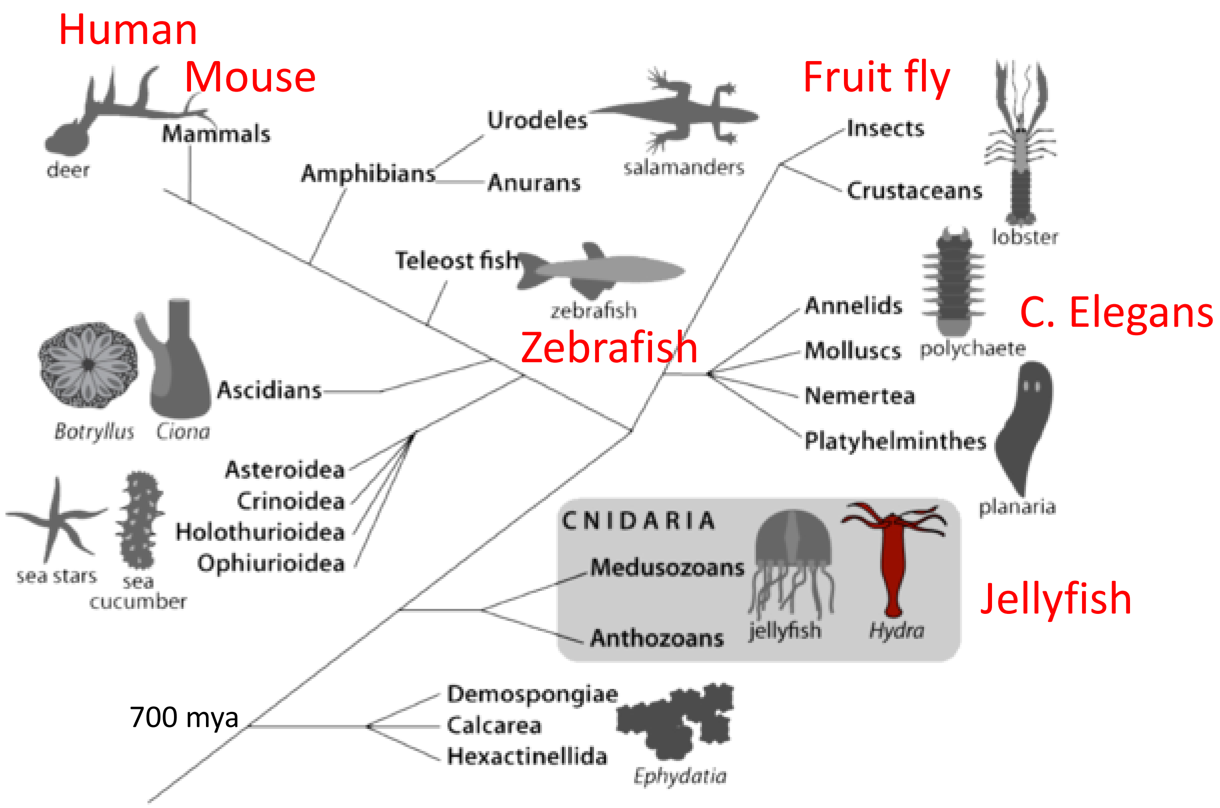
Jan 10: Neurons and the Brain

Material largely from *Principles of Neurobiology* by Liqun Luo

Outline

- Brains of different animals
- Neurons: structure & signaling mechanism
- Organization of the brain: lobes, networks, specialized cell types
- Learning and memory
- Population dynamics: a case study

Brains of different animals



Brains of different animals

Jellyfish:

- Simplest form of brain: “Nerve net”
- 5600 neurons
- Sensation/feeding/locomotion
- Box jellyfish has 24 eyes

Worm (C. Elegans):

- 302 neurons (sensory/motor/interneurons)
- 7000 connections completely mapped
- Allows full understanding of simple circuits (e.g., response to touch)

Brains of different animals

Insects (Drosophila):

- 100,000 neurons
- Display sophisticated social and cognitive behaviors (memory, spatial navigation)

Fish (Zebrafish):

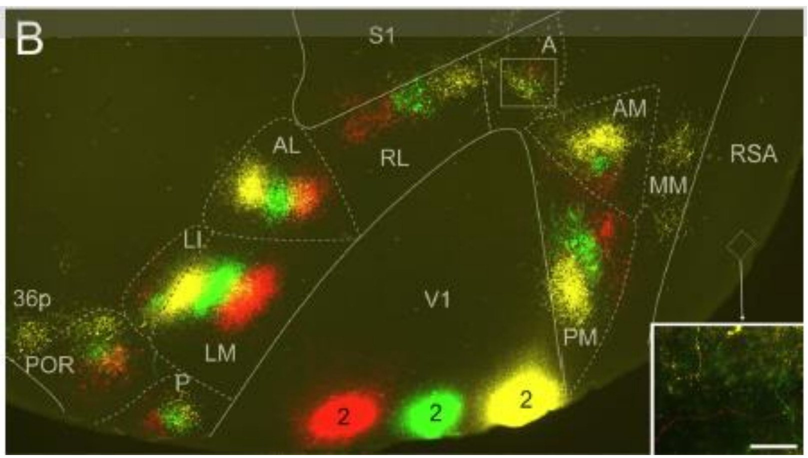
- 100,000 neurons
- Transparent in larval stage: can image every single neuron during behavior
- Interesting behaviors: prey capture, sleep

Brains of different animals

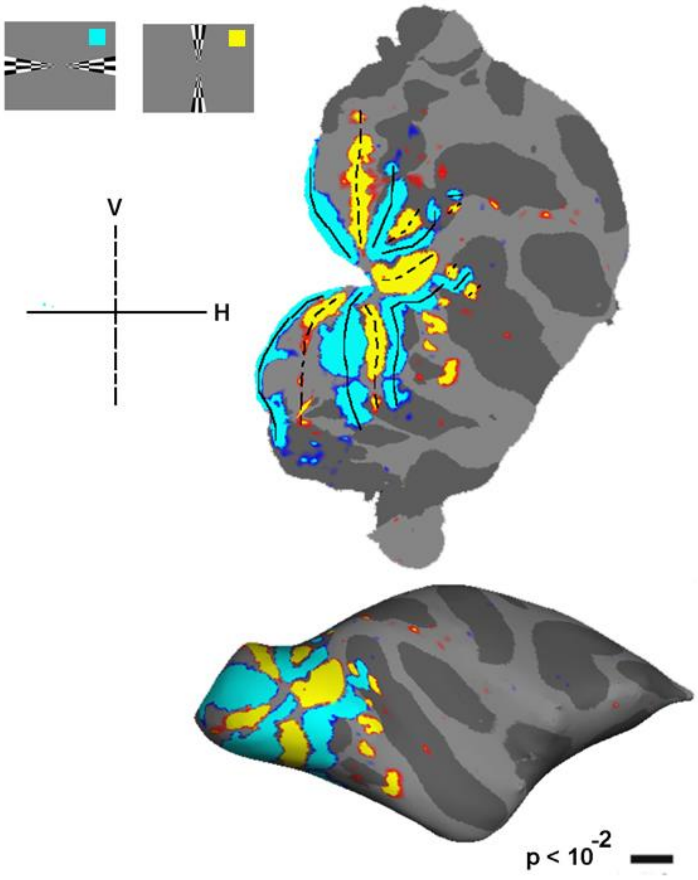
Mouse:
- 4 million neurons
- Shares many of the same features as human brain (both anatomically and functionally)

Human:
- 100 billion neurons
- Each hemisphere is size of extra large pizza
- 4 km of axons per mm^3

Homology between mouse and primate

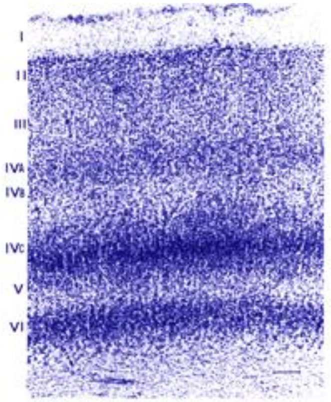


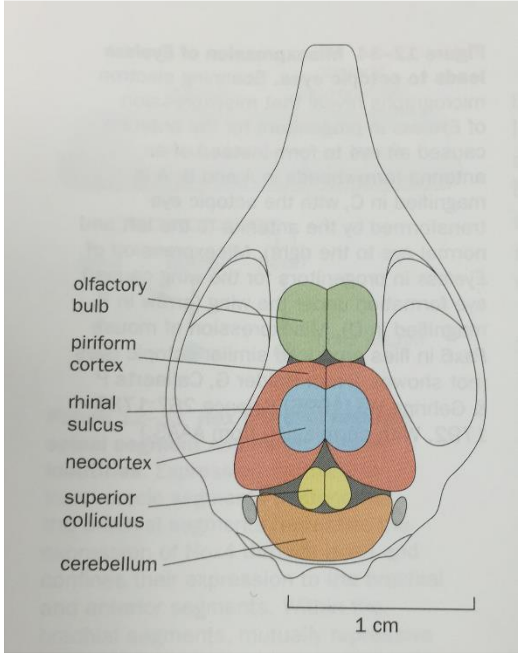
Mouse



Monkey

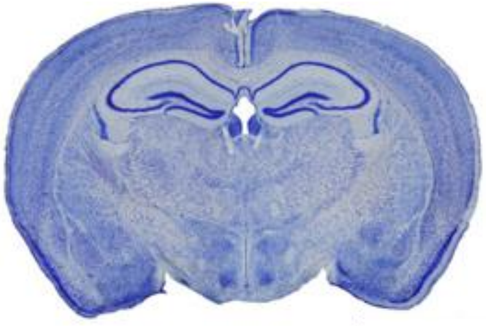
Expansion of neocortex



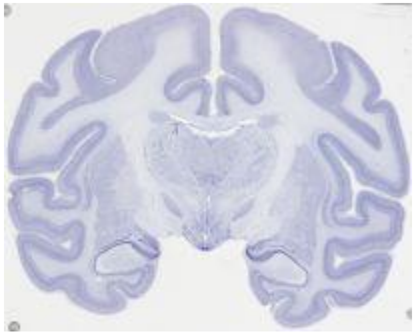


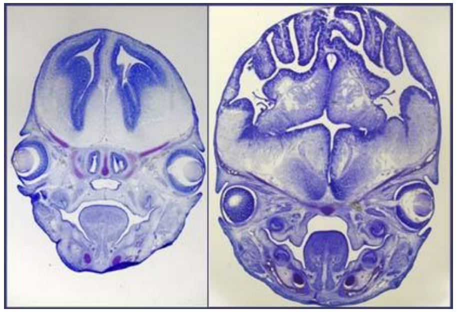
Brain of an early mammal from 85 million years ago
(reconstructed based on fossil record)

Mouse

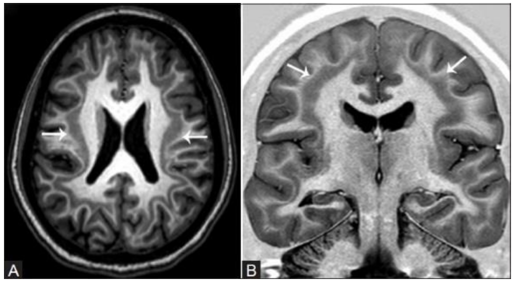


Human



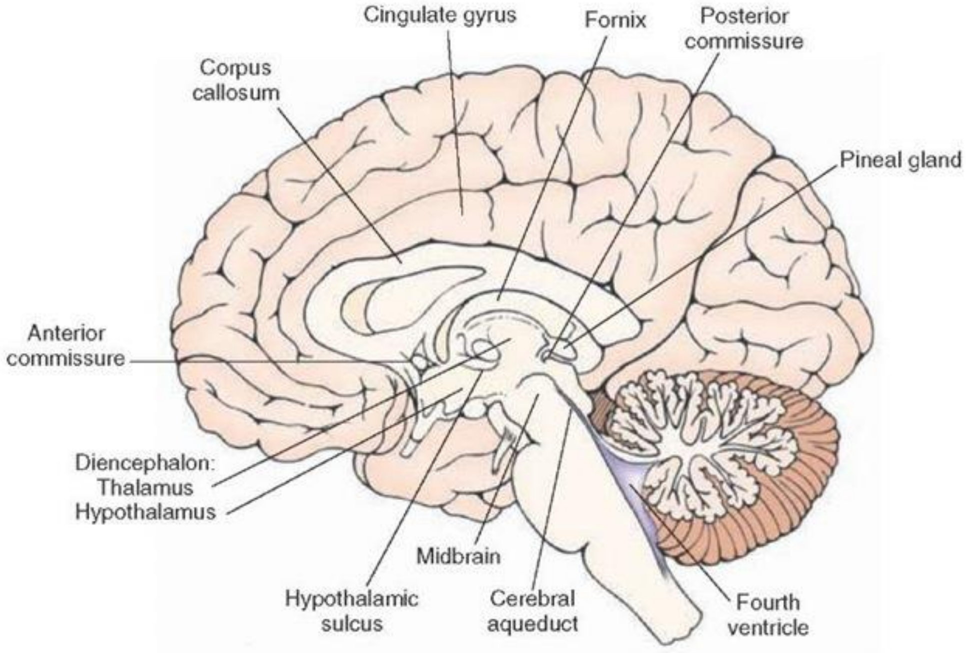


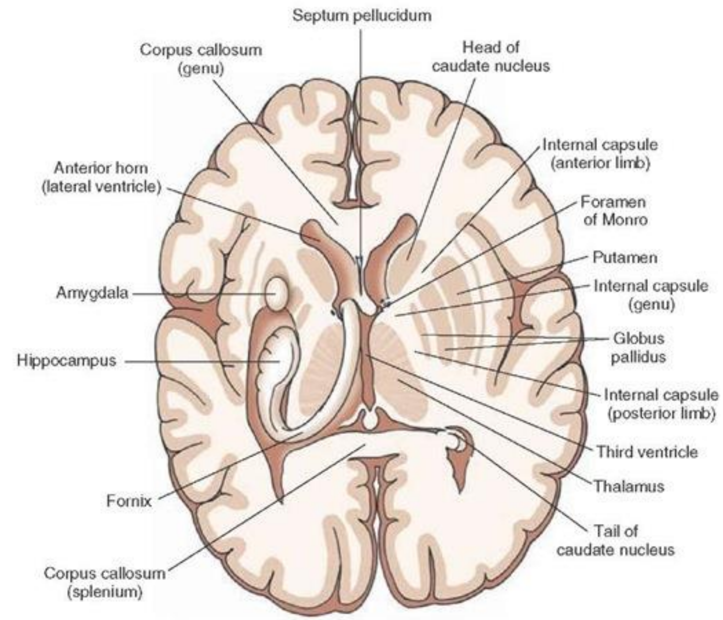
Normal mouse (left) vs mouse expressing B-catenin in neuroepithelial progenitors (right)



Double cortex

Organization of Central Nervous System





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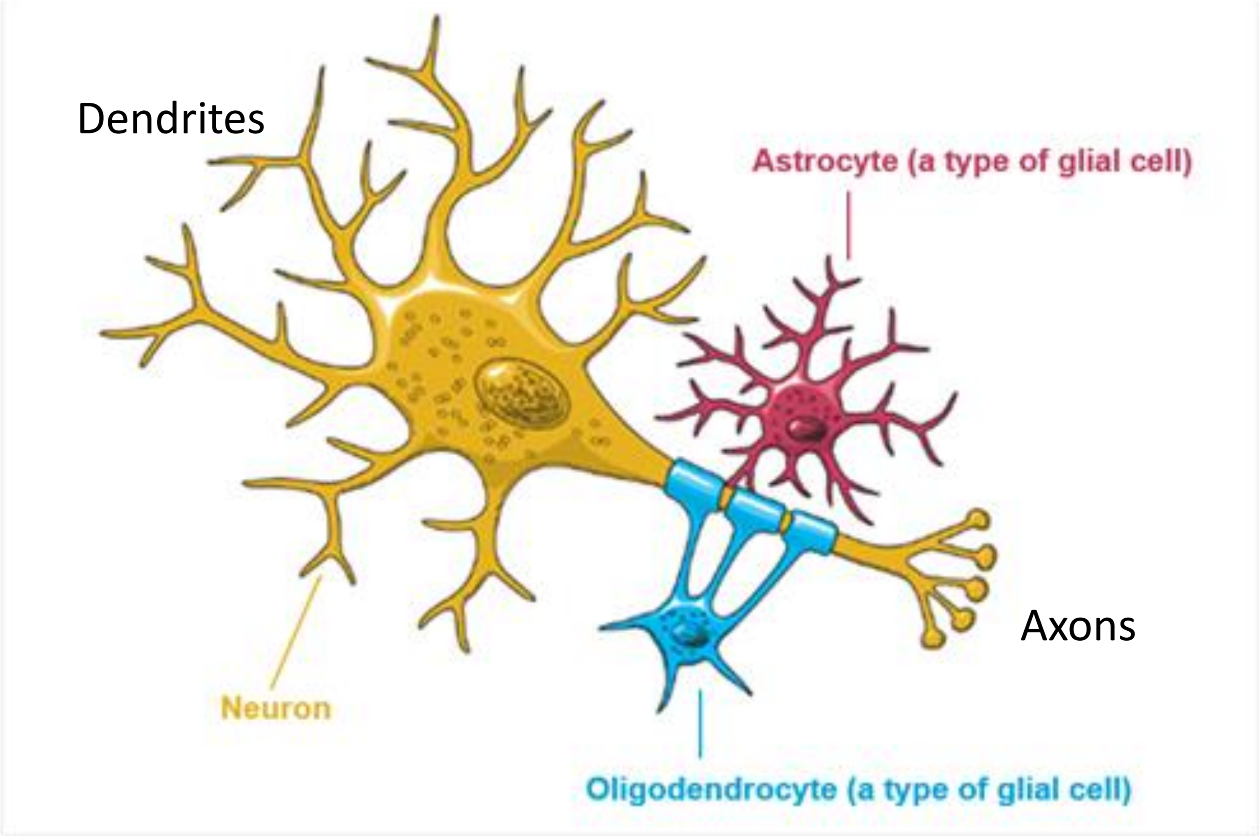
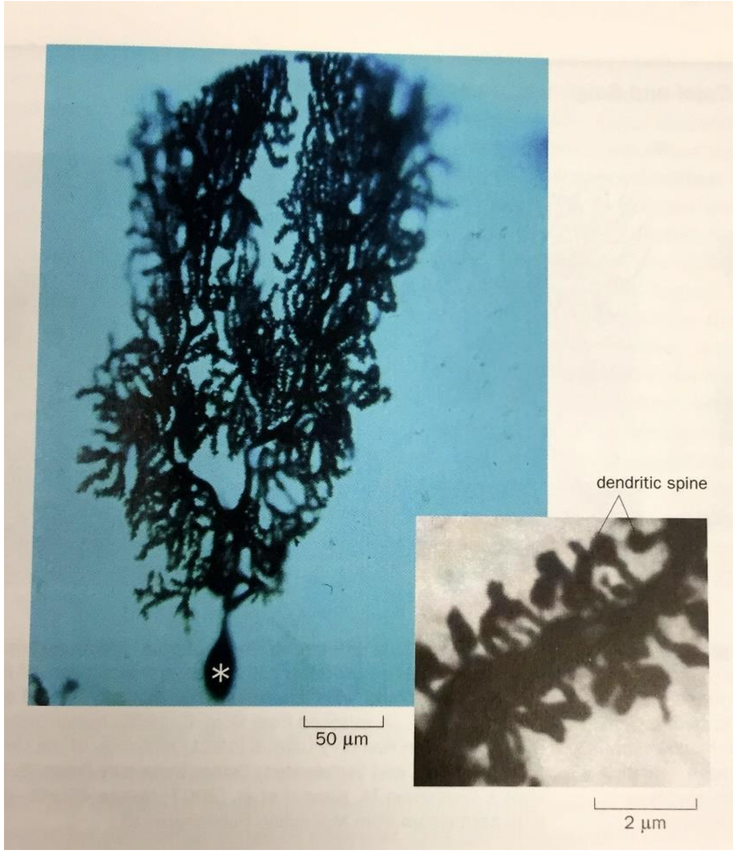
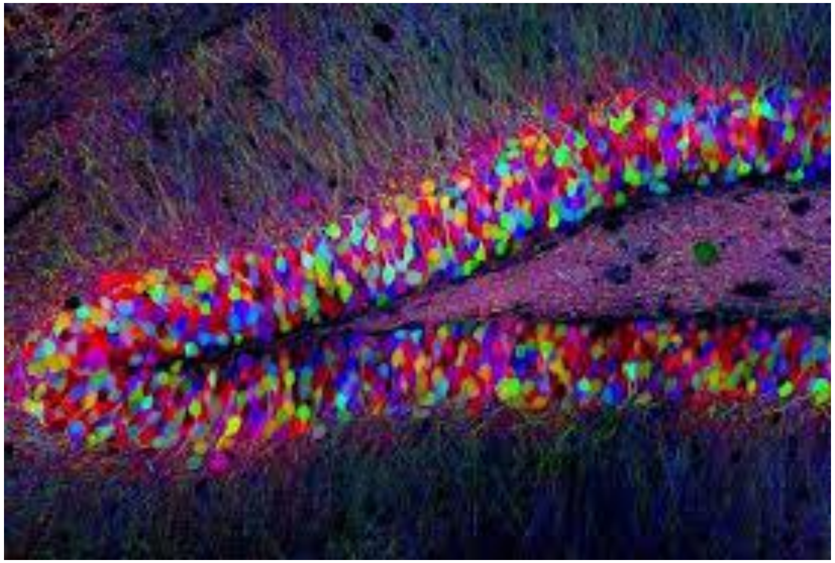
The Neuron


Dendrites
Astrocyte (a type of glial cell)
Neuron
Axons
Oligodendrocyte (a type of glial cell)

The Neuron



“Golgi” stain

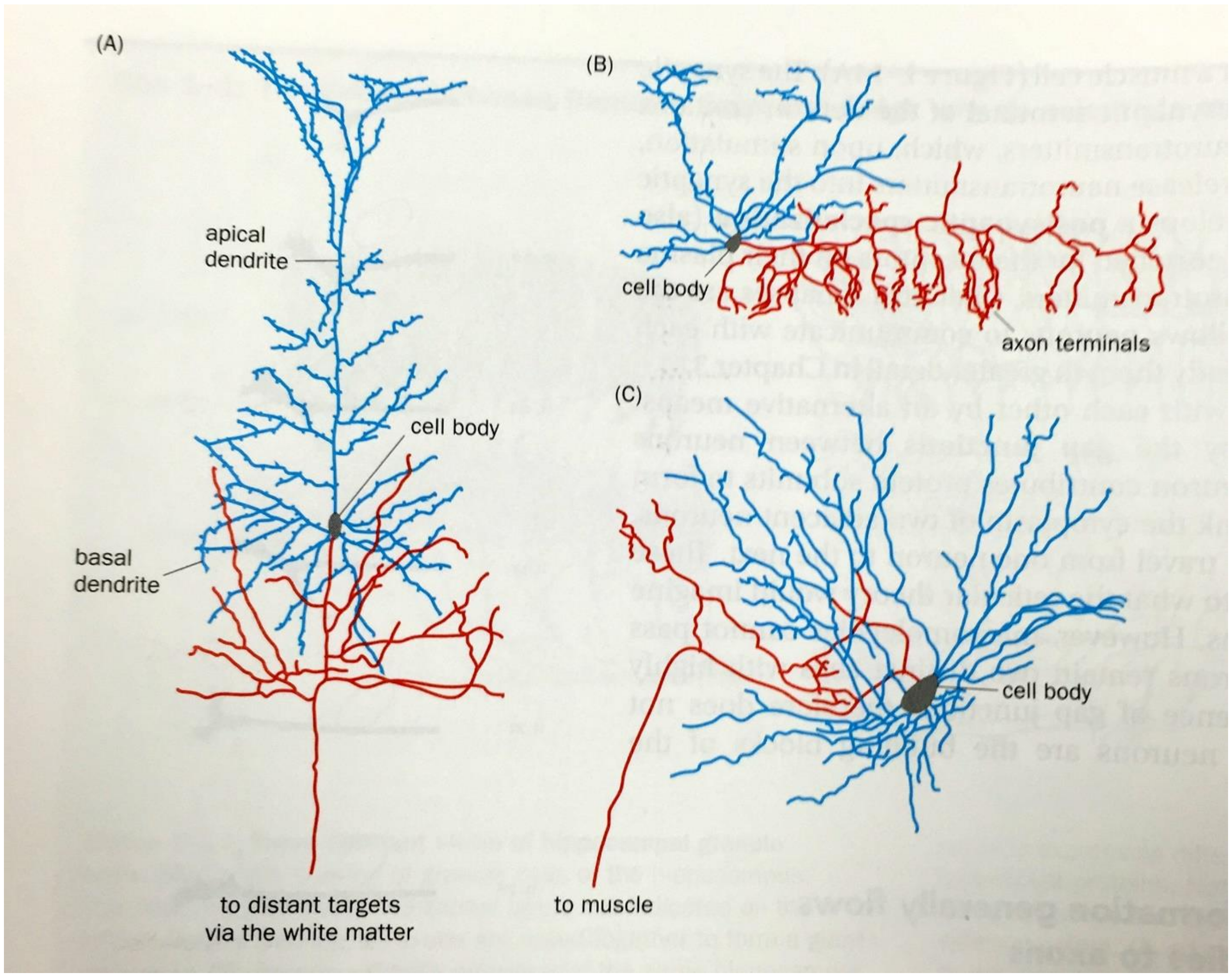


Brainbow stain

“I expressed the surprise which I experienced upon seeing with my own eyes the wonderful revelatory powers of the chrome-silver reaction and the absence of any excitement in the scientific world aroused by its discovery.” -Cajal

The Neuron

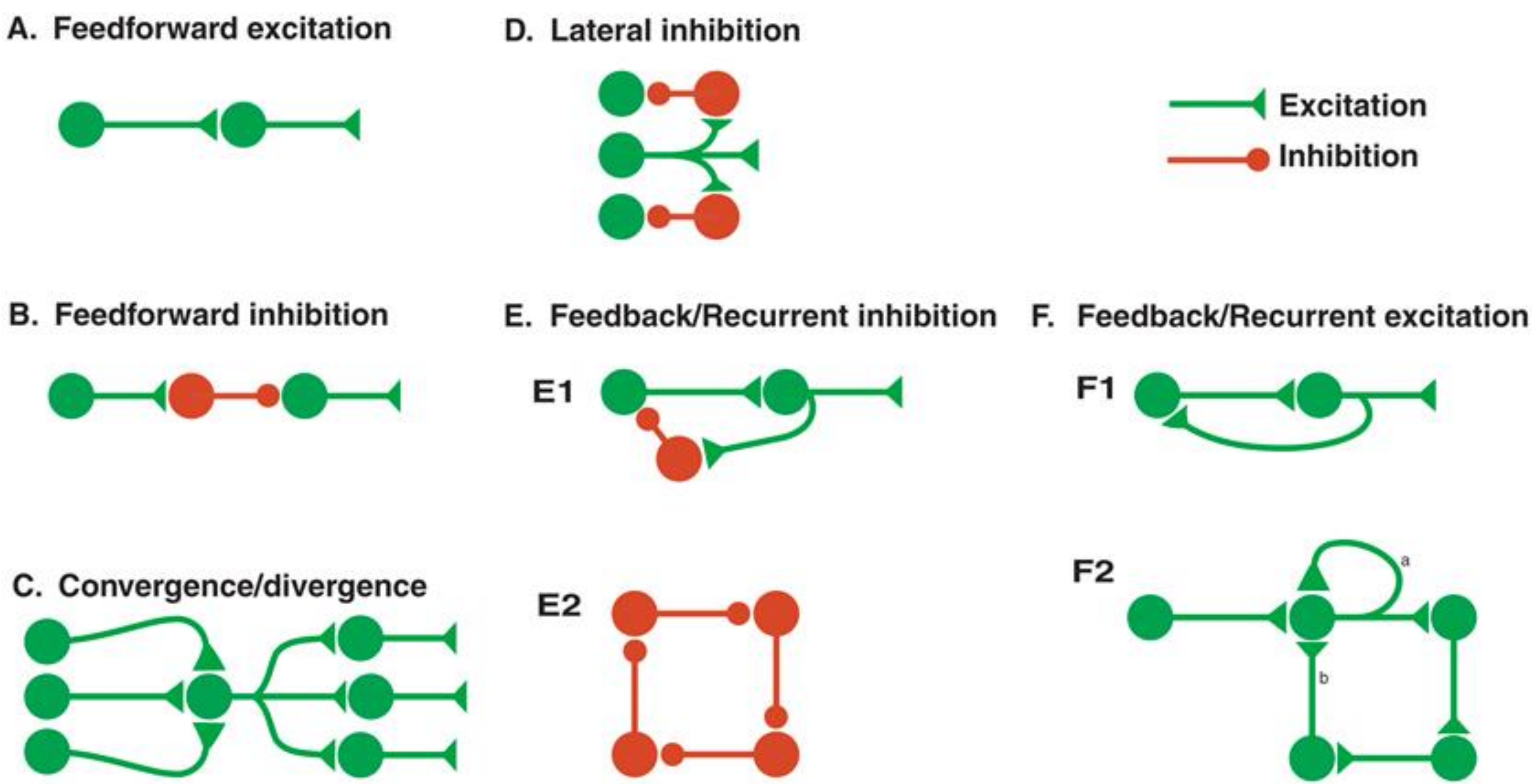
Basket cell

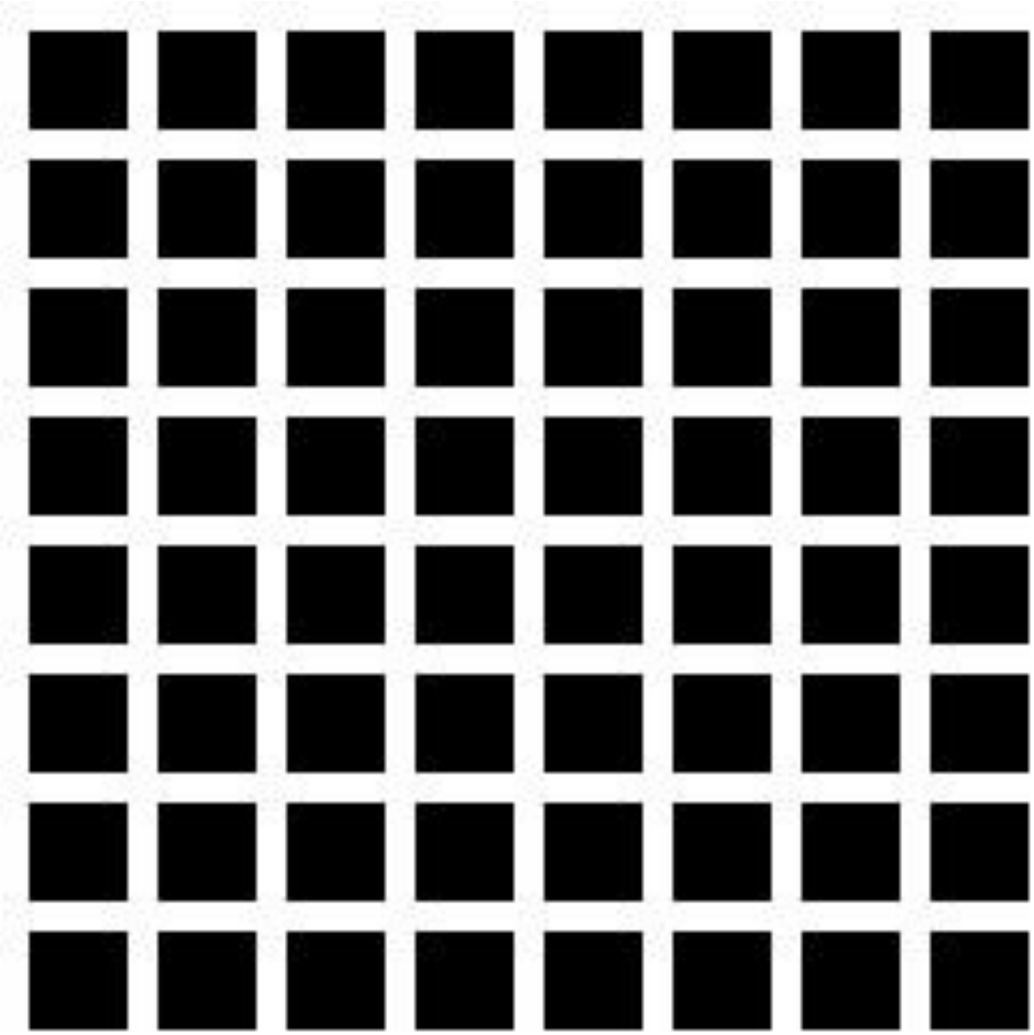


Motor neuron

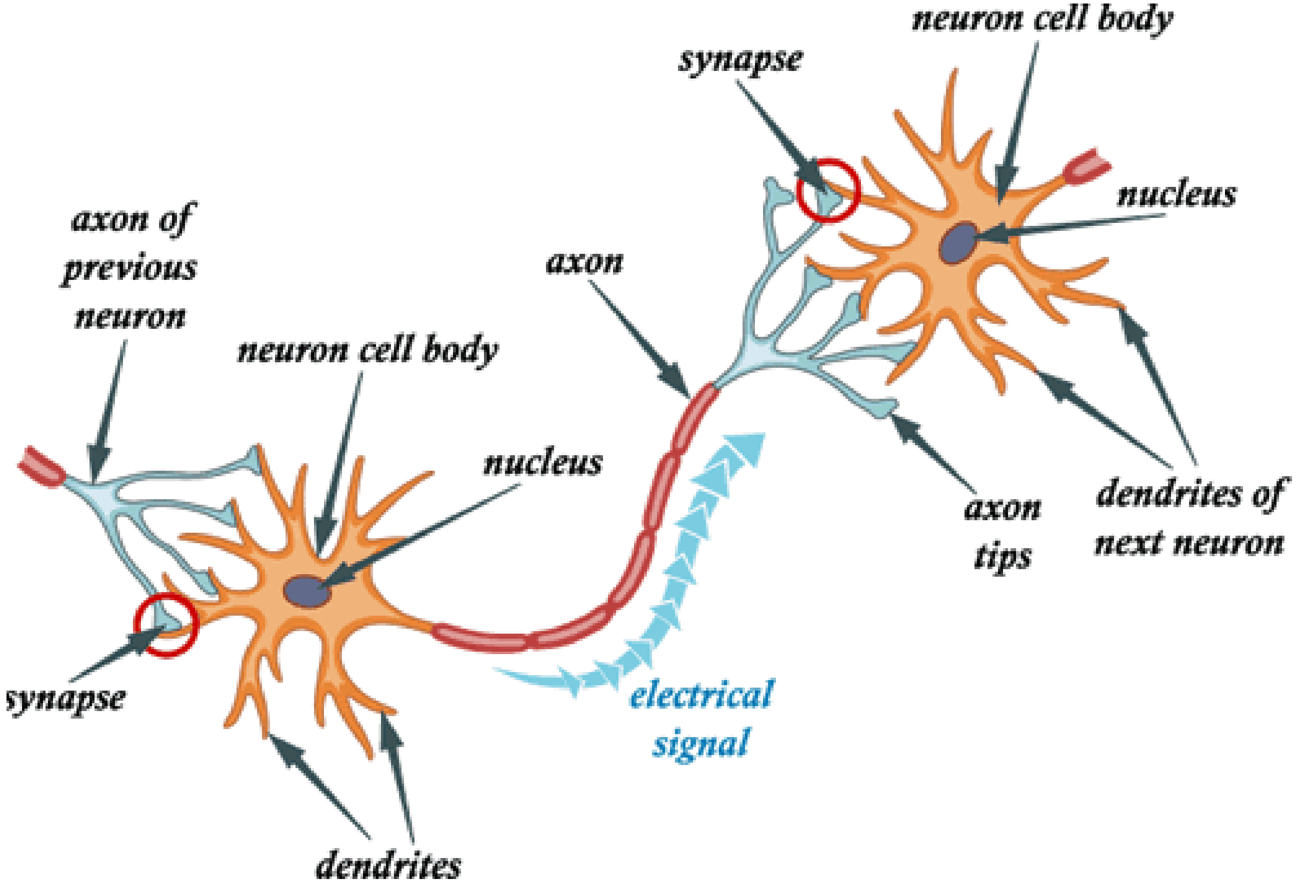
Pyramidal cell

Circuit motifs

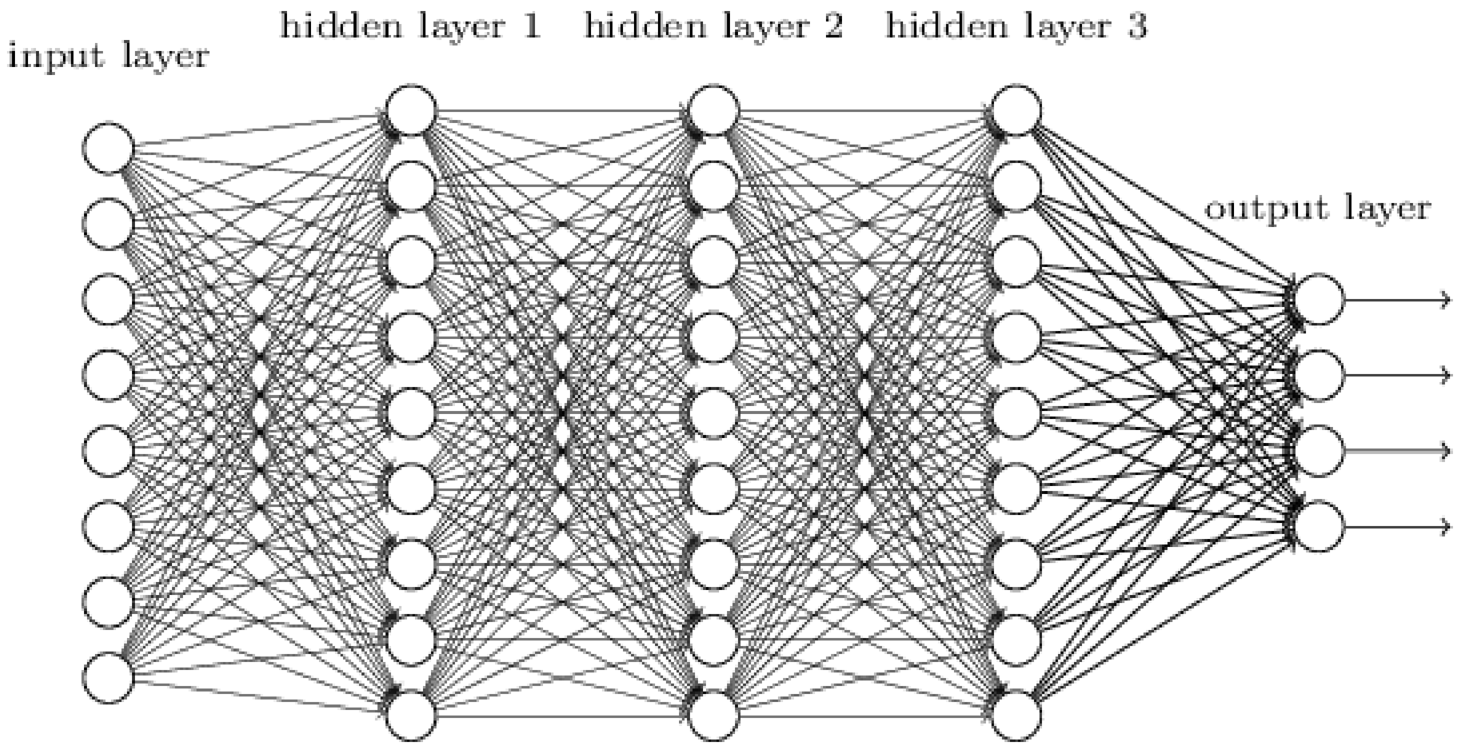




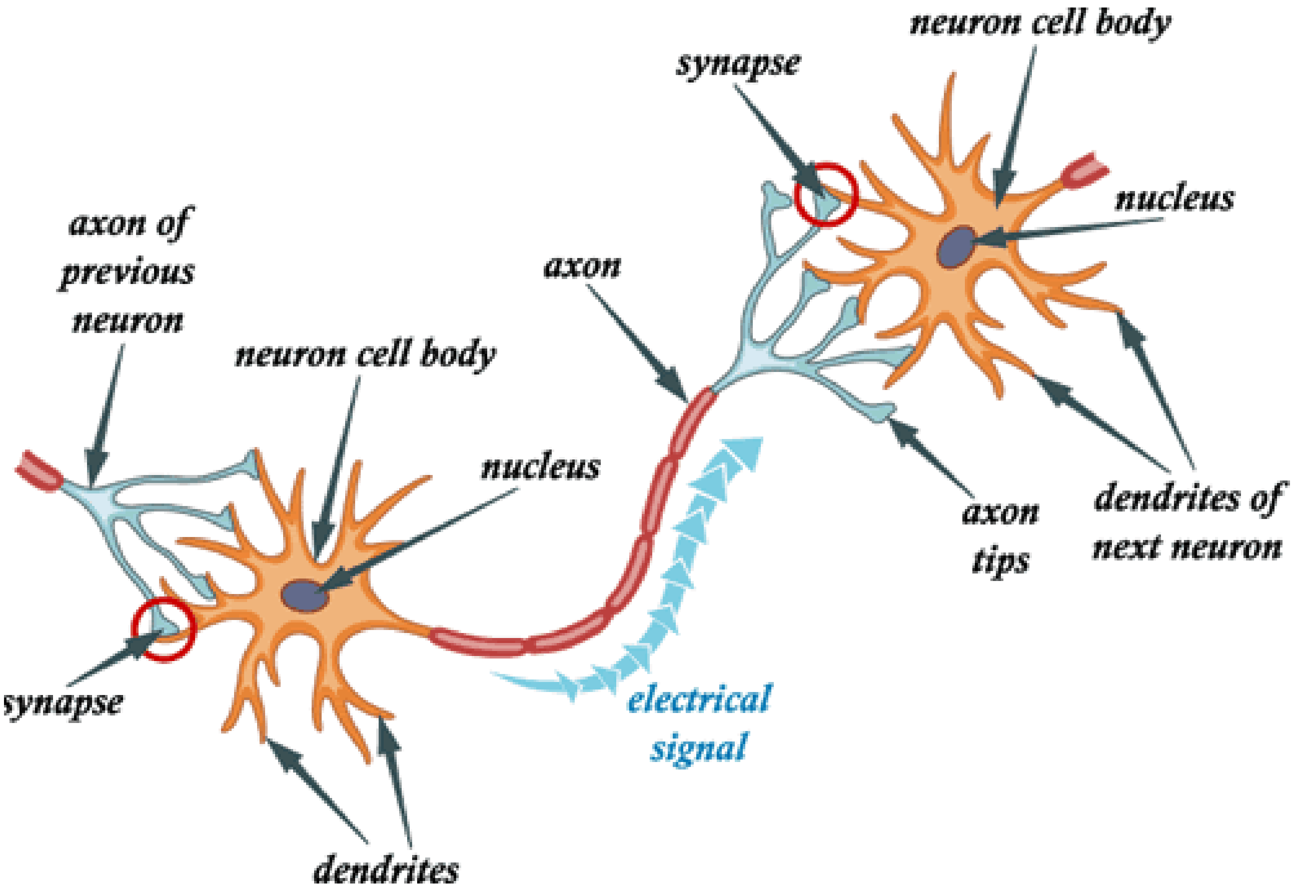
Signaling between neurons



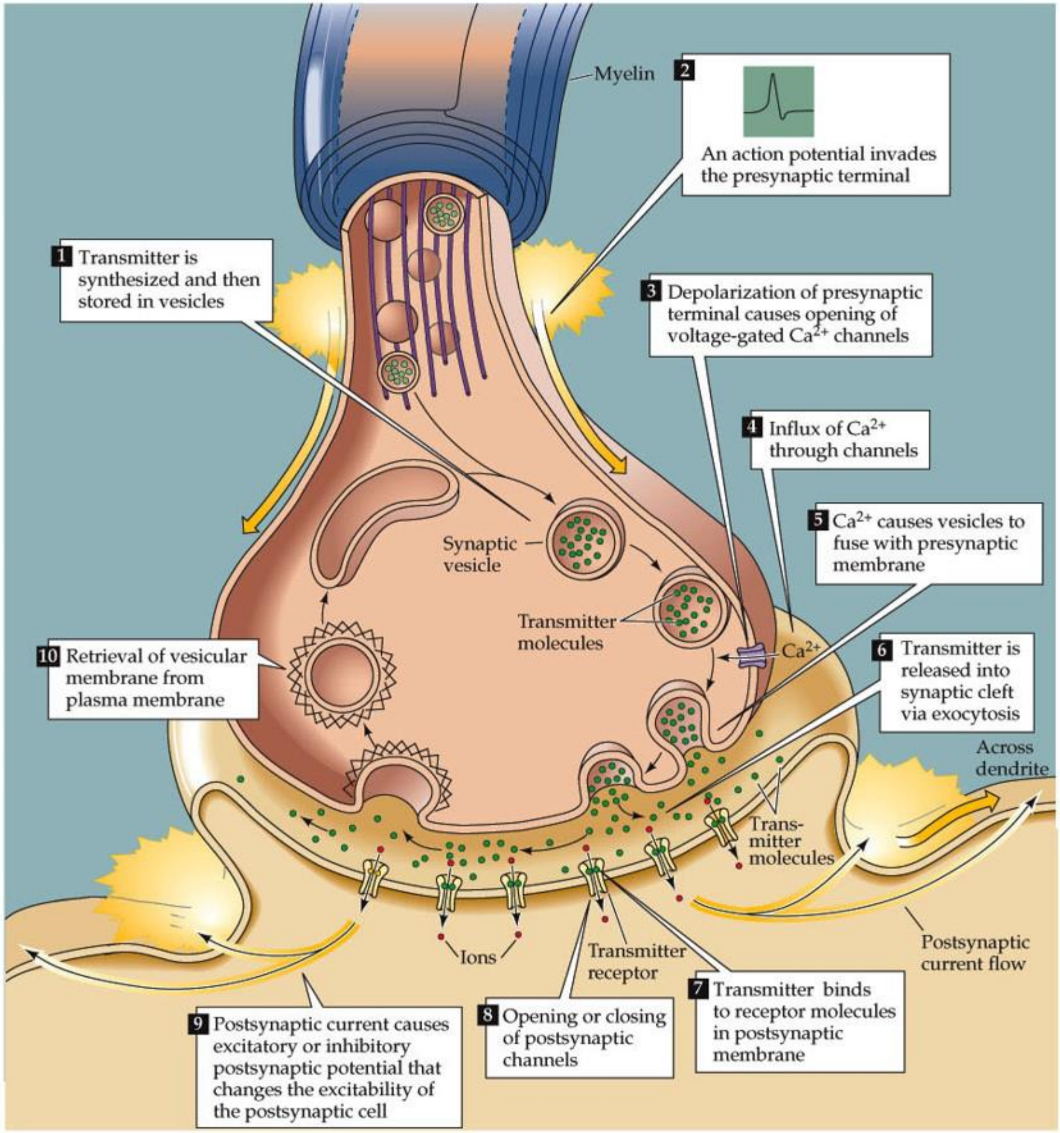
Signaling between neurons



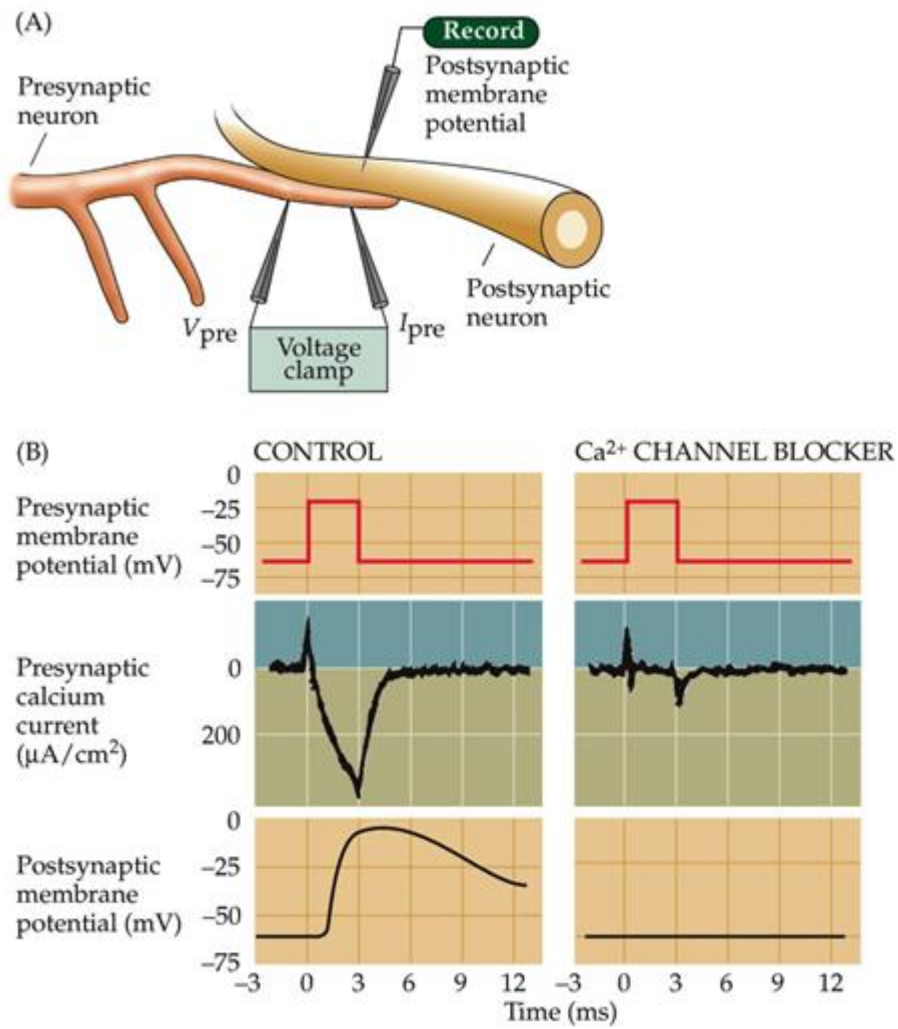
Signaling between neurons



Synaptic transmission



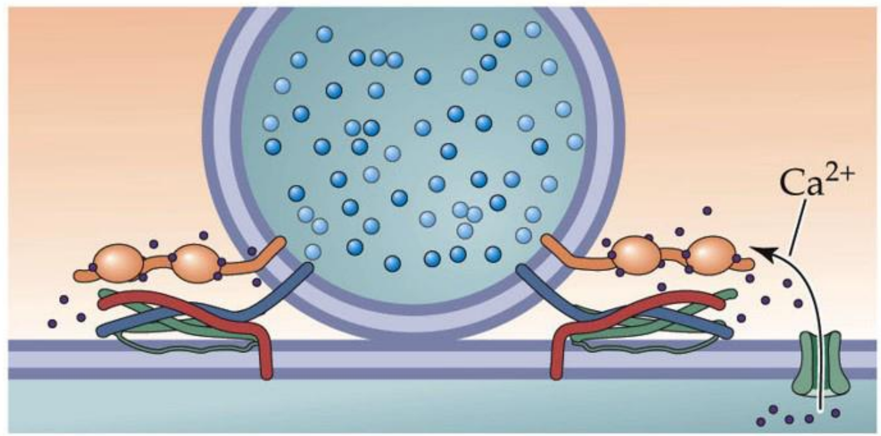
Calcium influx is necessary for neurotransmitter release



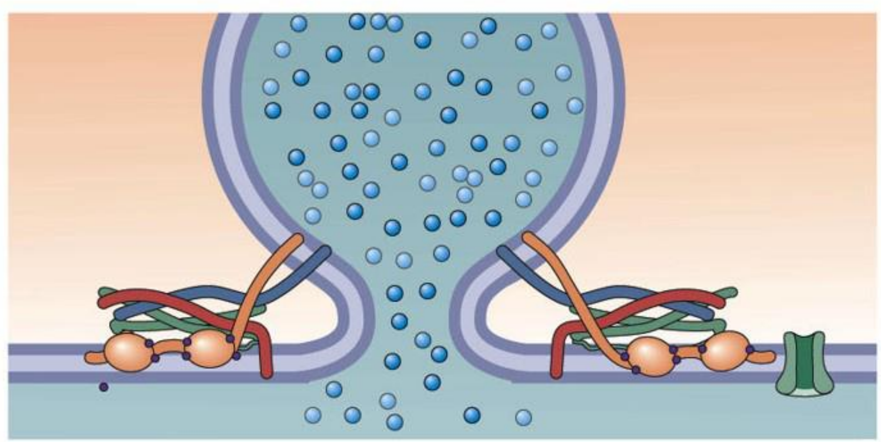
Voltage-gated calcium channels

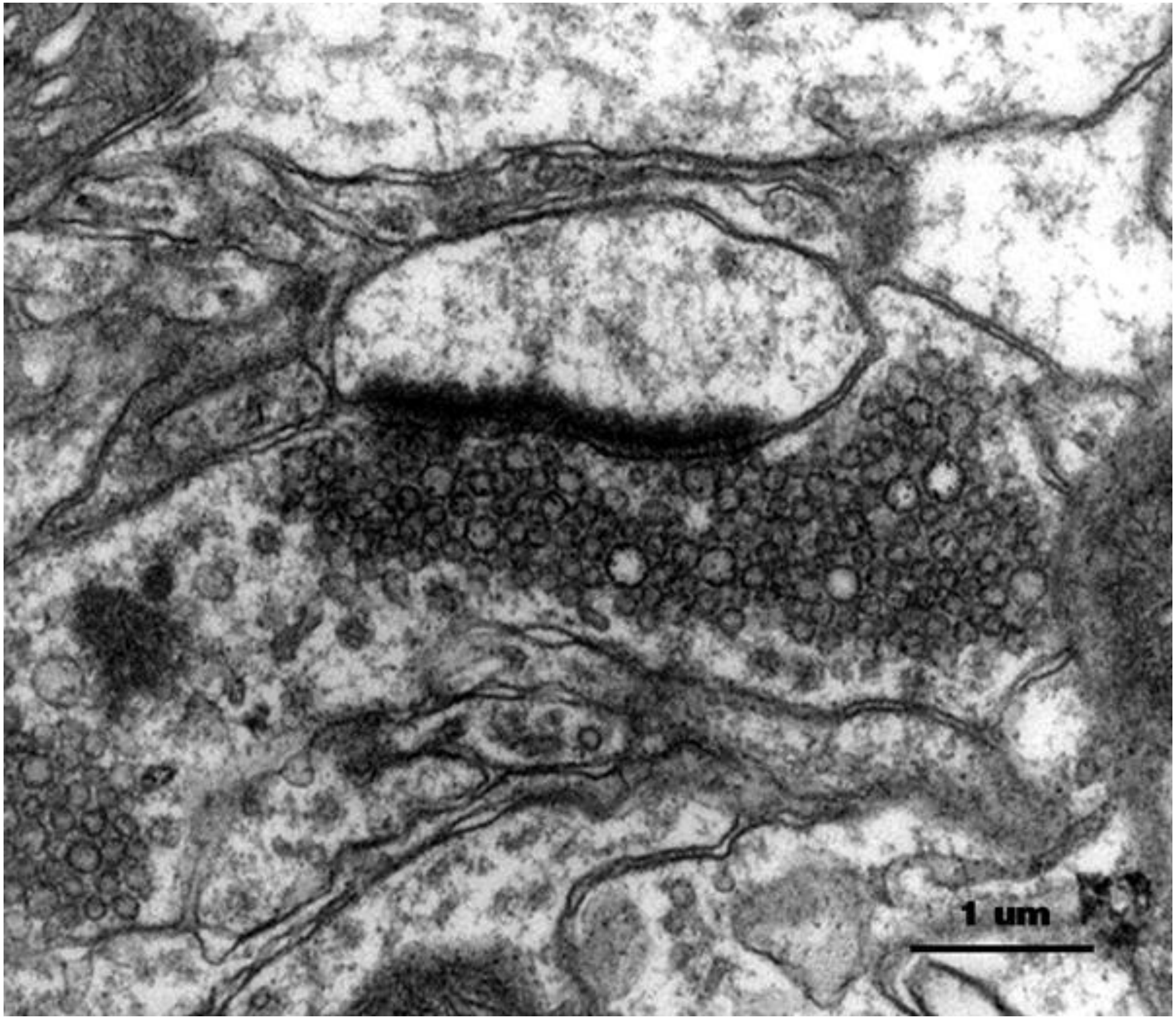
Synaptotagmin functions as a calcium sensor, promoting vesicle fusion

(3) Entering Ca^{2+} binds to synaptotagmin

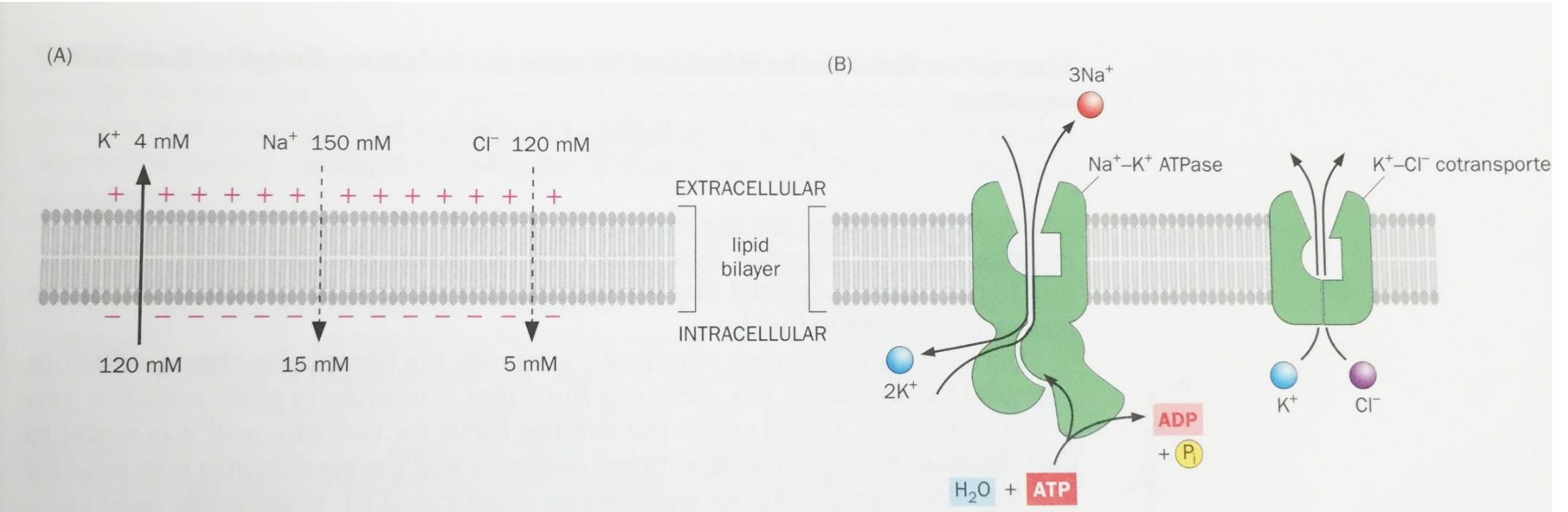


(4) Ca^{2+}-bound synaptotagmin catalyzes membrane fusion




1 um

Resting potential



Each ion has a reversal potential, where diffusion potential exactly counterbalances electrical potential.

$$V_{\mathrm{Eq.}} = \frac{RT}{zF}\ln\left(\frac{[X]_{\mathrm{out}}}{[X]_{\mathrm{in}}}\right)$$

Resting potential

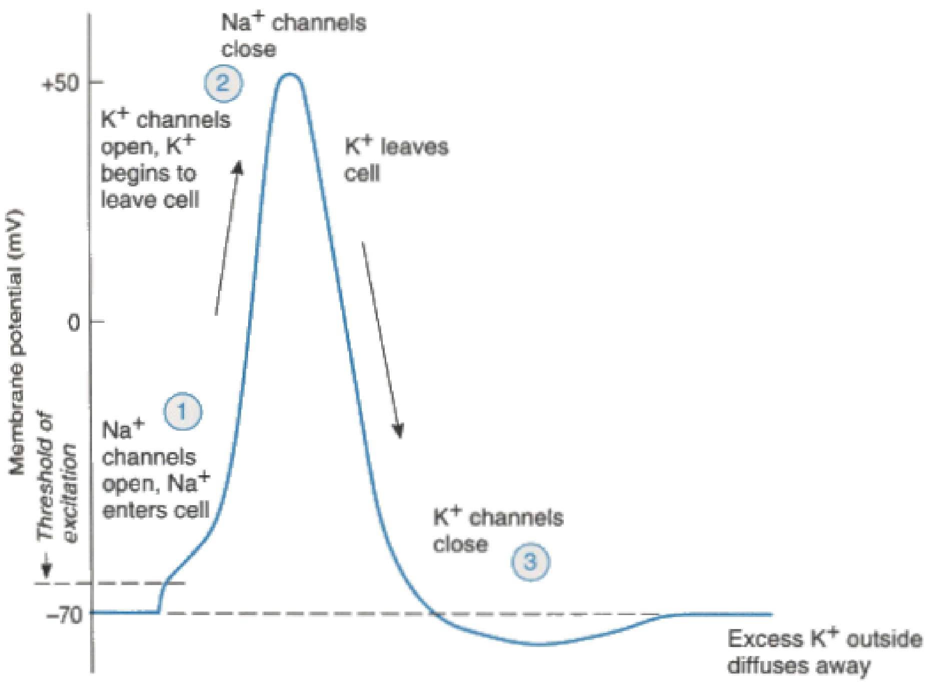
In a more formal notation, the membrane potential is the weighted average of each contributing ion's equilibrium potential.

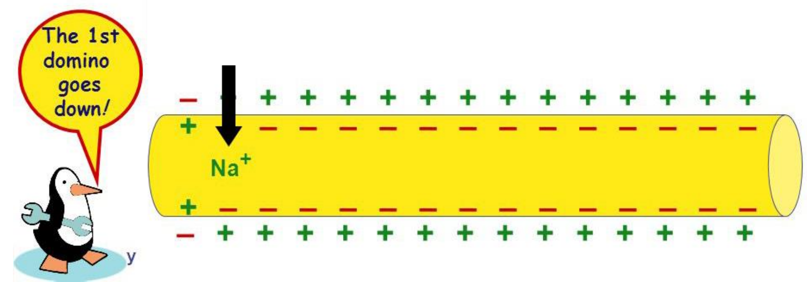
$$E_m = \frac{g_{K^+}}{g_{tot}} E_{K^+} + \frac{g_{Na^+}}{g_{tot}} E_{Na^+} + \frac{g_{Cl^-}}{g_{tot}} E_{Cl^-},$$

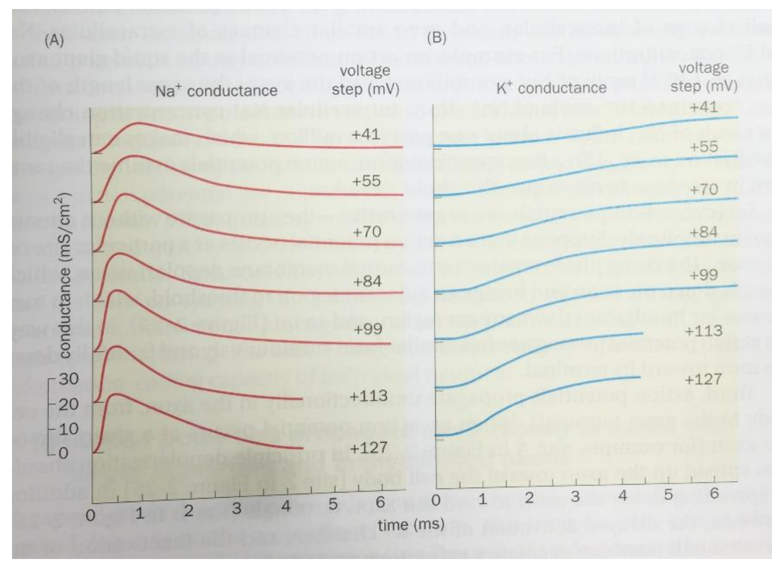
where

- E_m is the membrane potential, measured in volts
- E_X is the equilibrium potential for ion X, also in volts
- g_X is the relative conductance of ion X in arbitrary units (e.g. siemens for electrical conductance)
- g_{tot} is the total conductance of all permeant ions, in this case $g_{K^+} + g_{Na^+} + g_{Cl^-}$

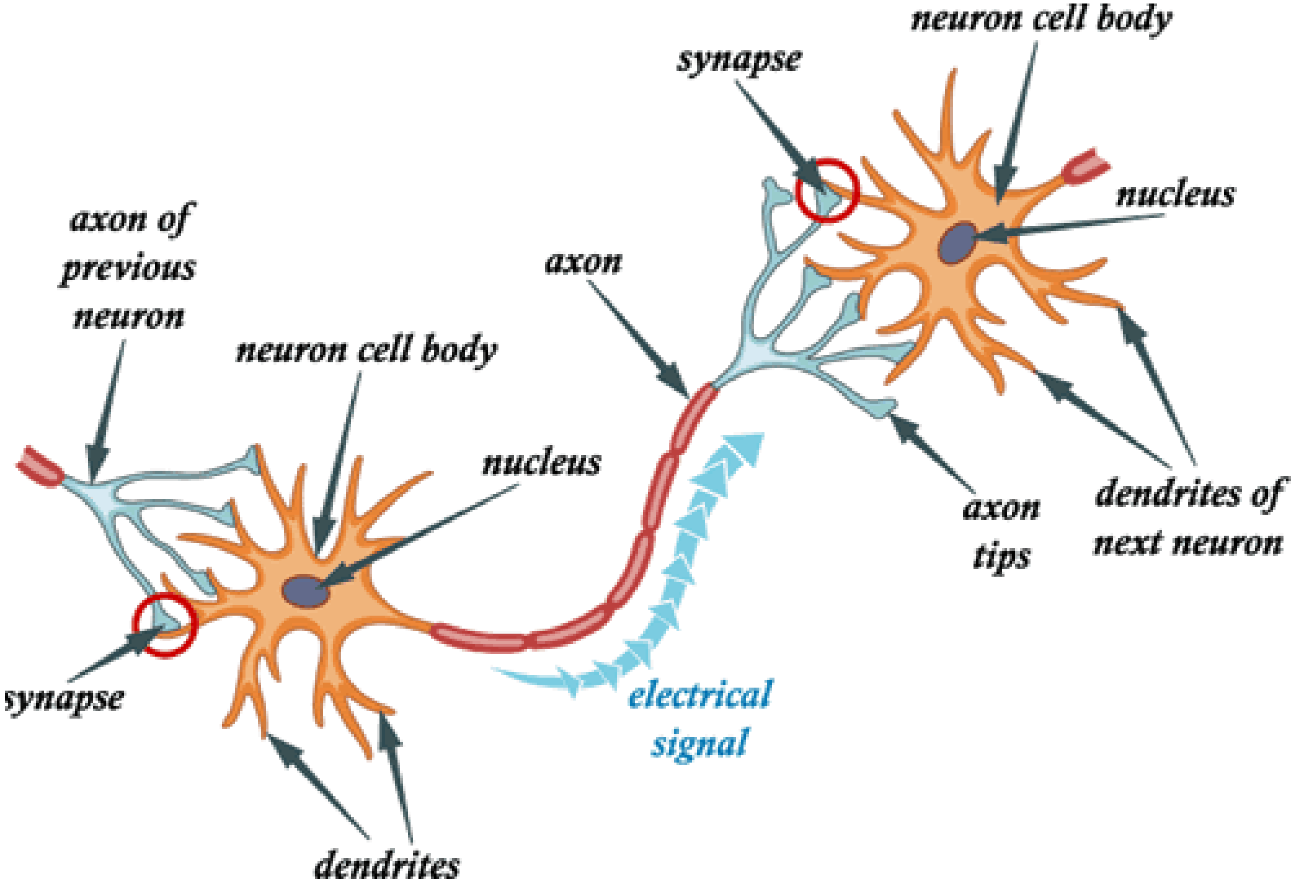
Action potential







Signaling between neurons



Comparing signaling in computers vs the brain

Table 1–1: Comparing the computer and the brain

Properties	Computer[1]	Human brain
Number of basic units	up to 10^9 transistors[2]	~10^{11} neurons; ~10^{14} synapses
Speed of basic operation	10^{10}/s	<10^3/s
Precision	1 in 4 × 10^9 for a 32-bit number	~1 in 10^2
Power consumption	10^2 watts	~10 watts
Processing method	mostly serial	serial and massively parallel
Input/output for each unit	1–3	~10^3
Signaling mode	digital	digital and analog

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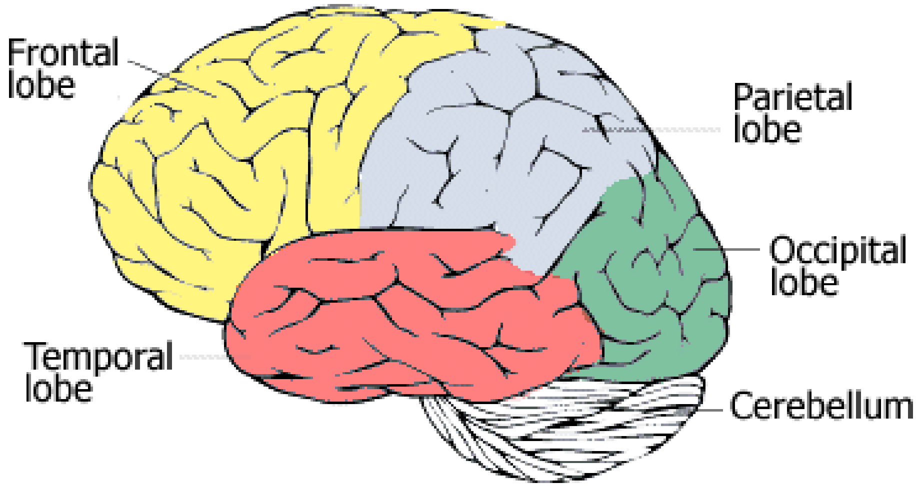
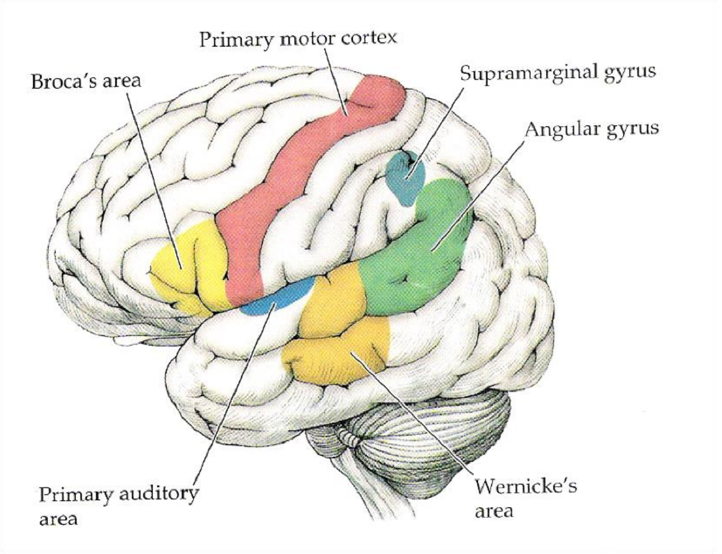
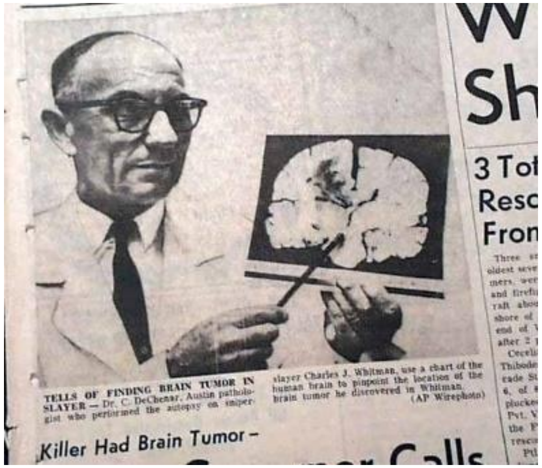
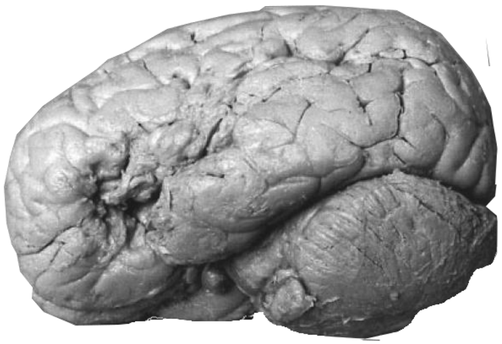
Organization of Central Nervous System



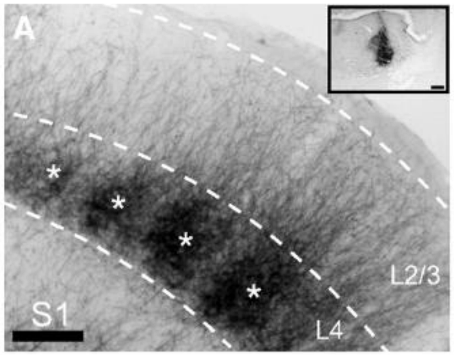






Brain of Mr. Leborgne aka "Tan Tan"

Hierarchical organization of brain



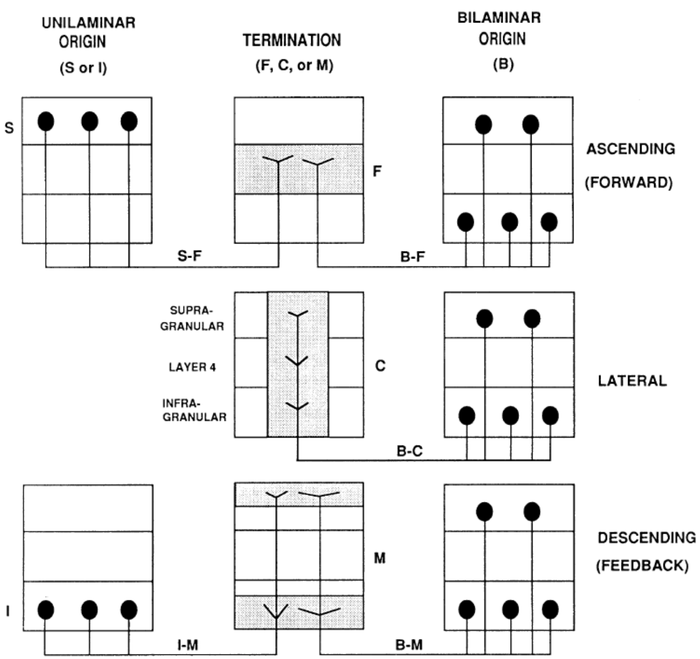
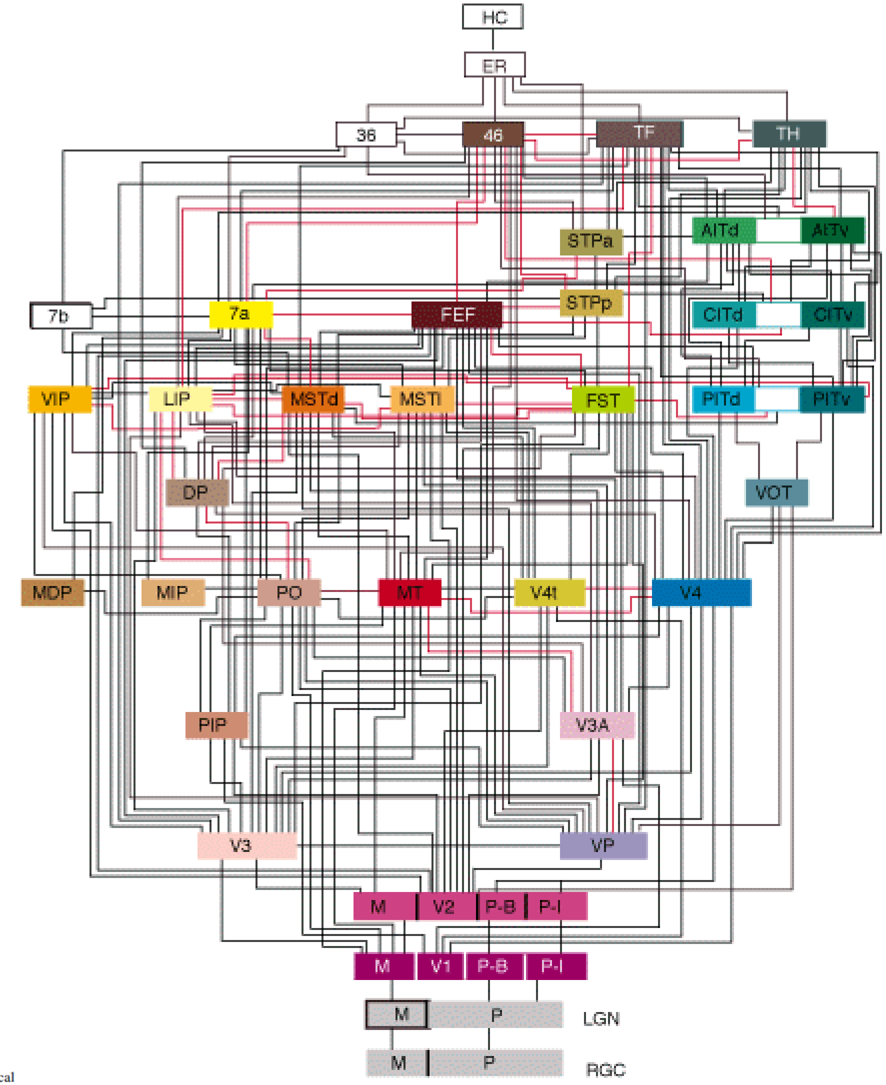


Fig. 1. Schematic diagram illustrating the anatomical features of cortico-cortical connections used by Felleman and Van Essen (1991) to assign hierarchical relationships between visual cortical areas. Forward connections terminate in layer 4 and originate from either superficial layers or from both superficial and deep layers. Feedback connections terminate outside layer 4 and originate either from deep layers or from both superficial and deep layers. From Felleman and Van Essen (1991).

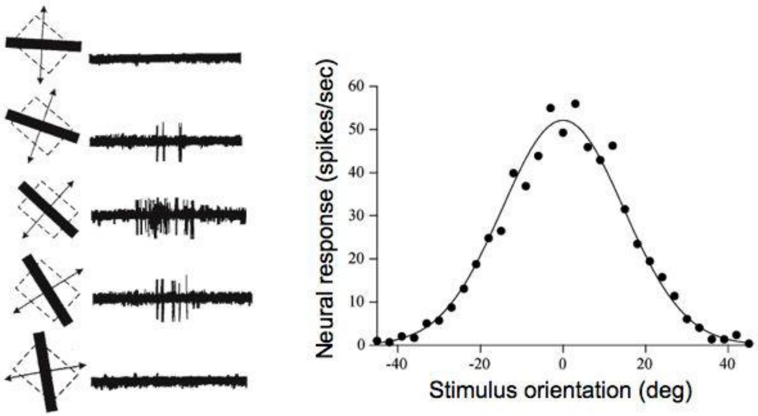


"If one wants to understand function in biology, one should study structure."

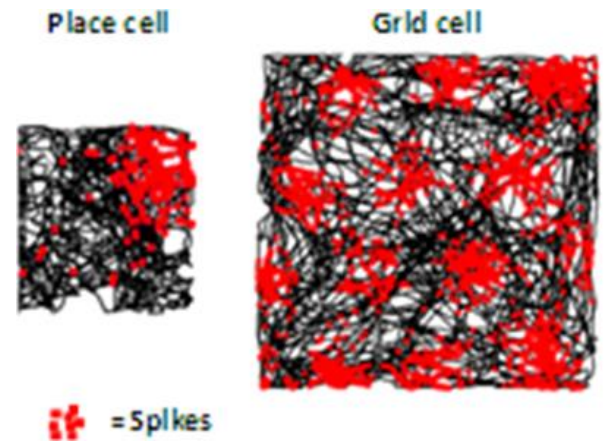
–Francis Crick

The fruitfulness of “following the anatomy”

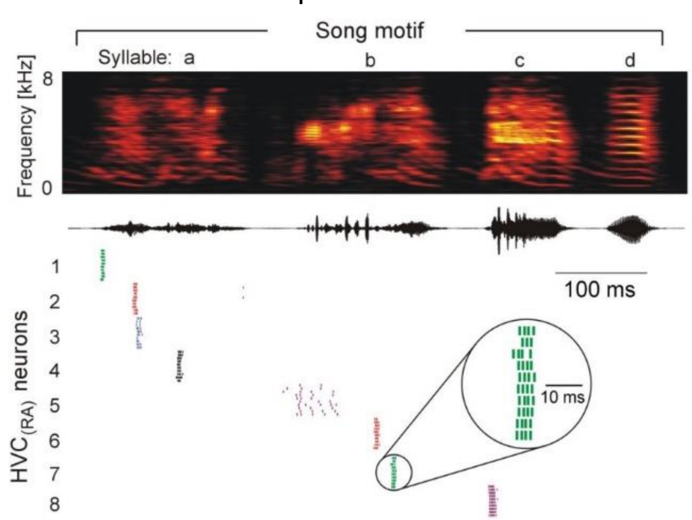
Hubel and Wiesel: Orientation Selectivity



Edvard & May-Britt Moser: Grid Cells



Michael Fee: Sparse HVC neurons



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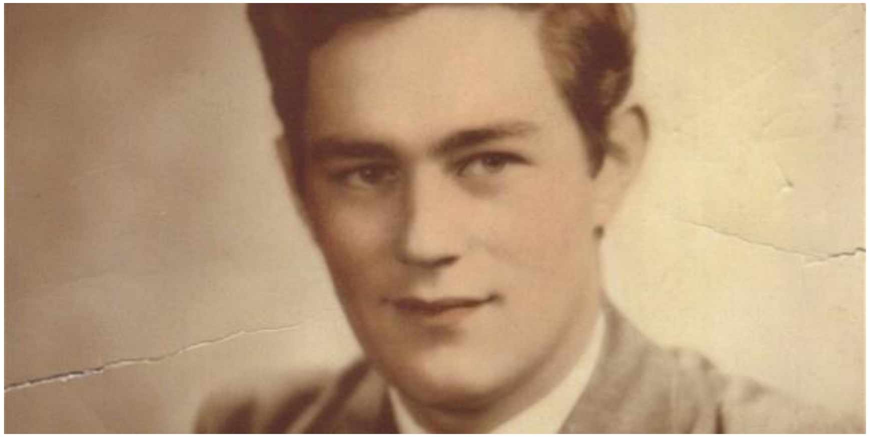
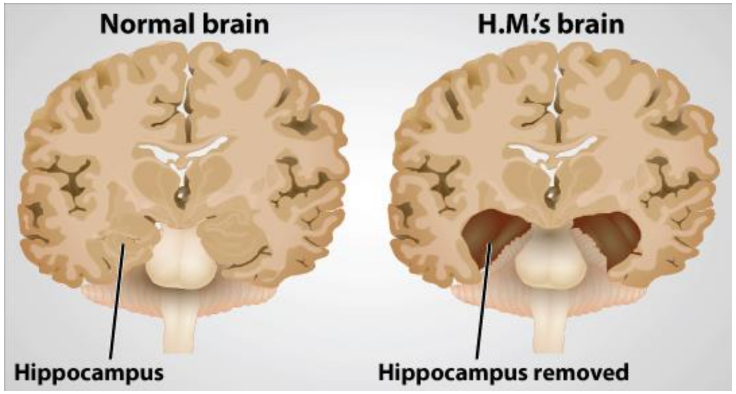
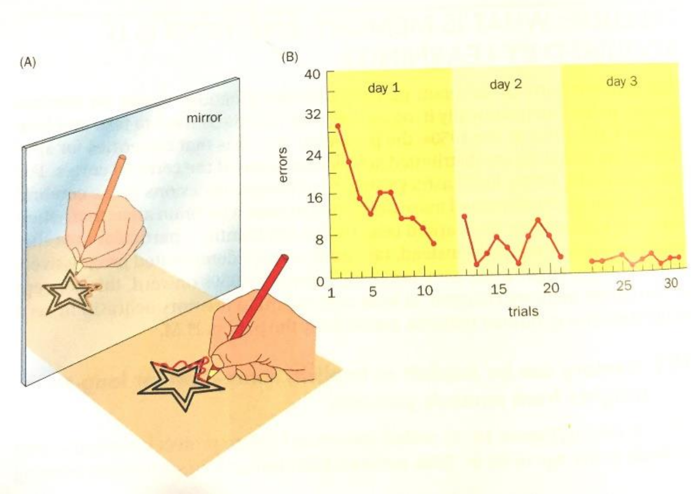
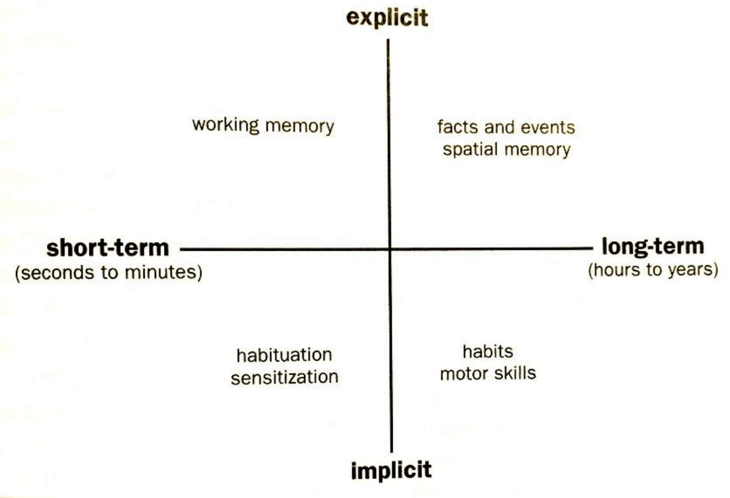
Learning and Memory

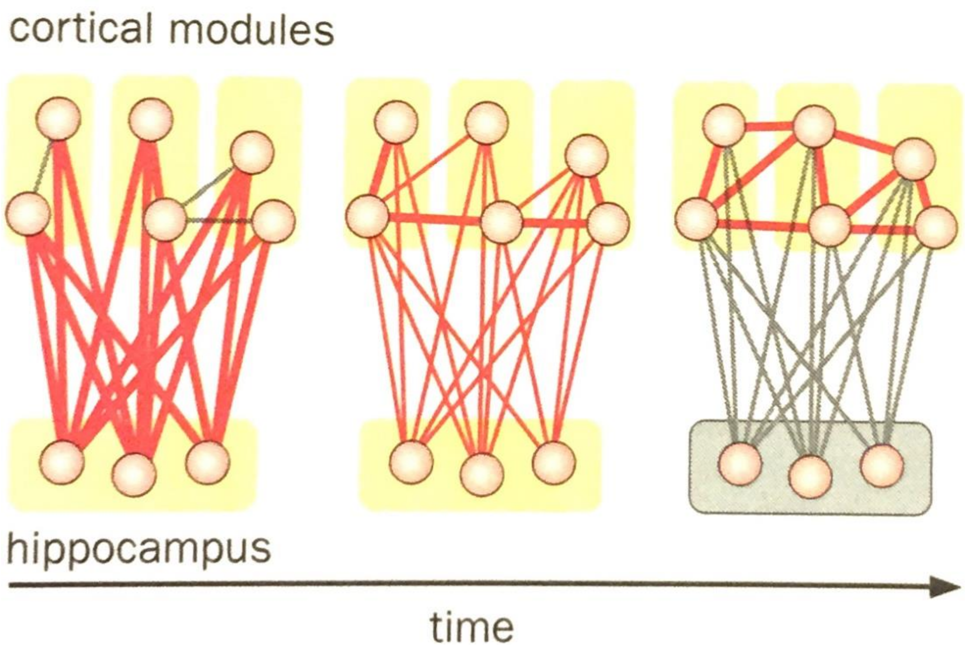


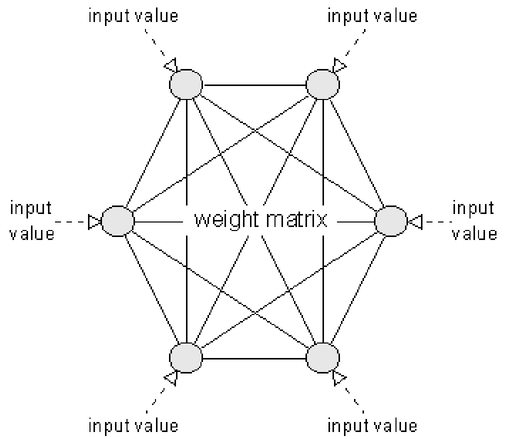


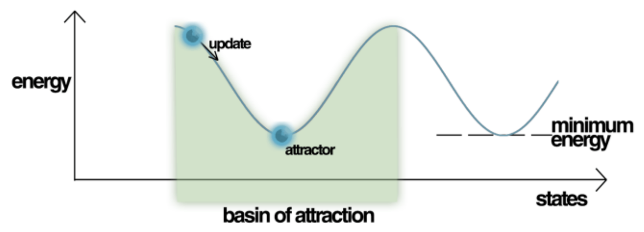




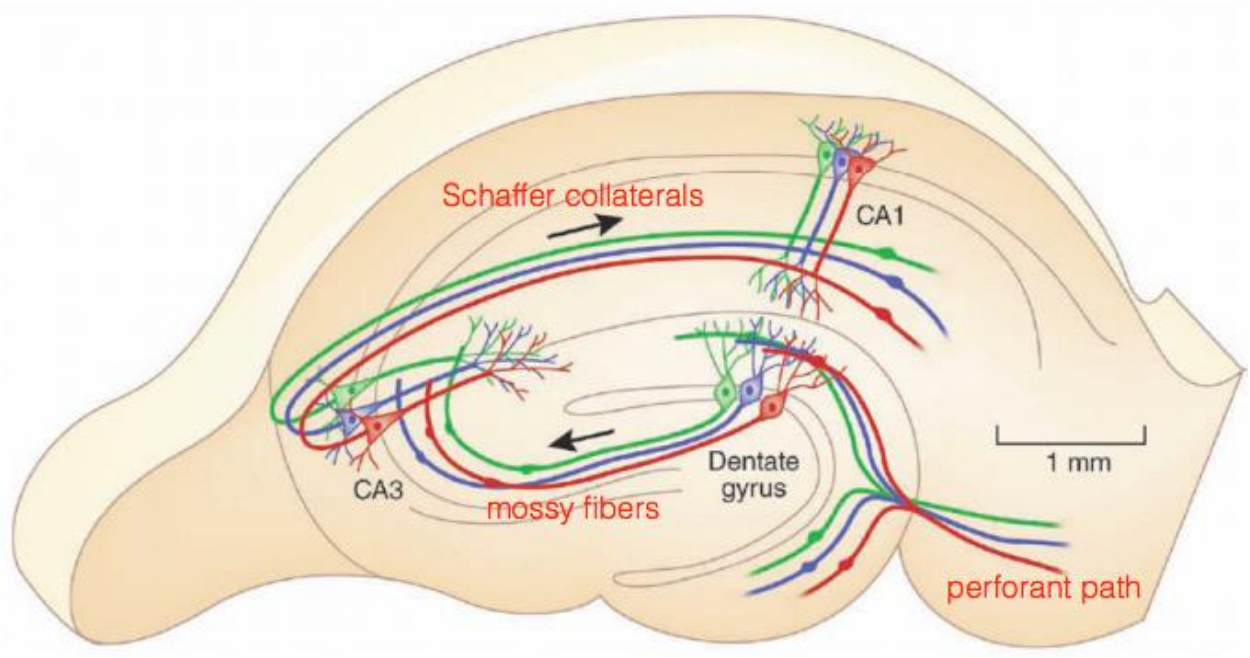
Forming a long-term memory



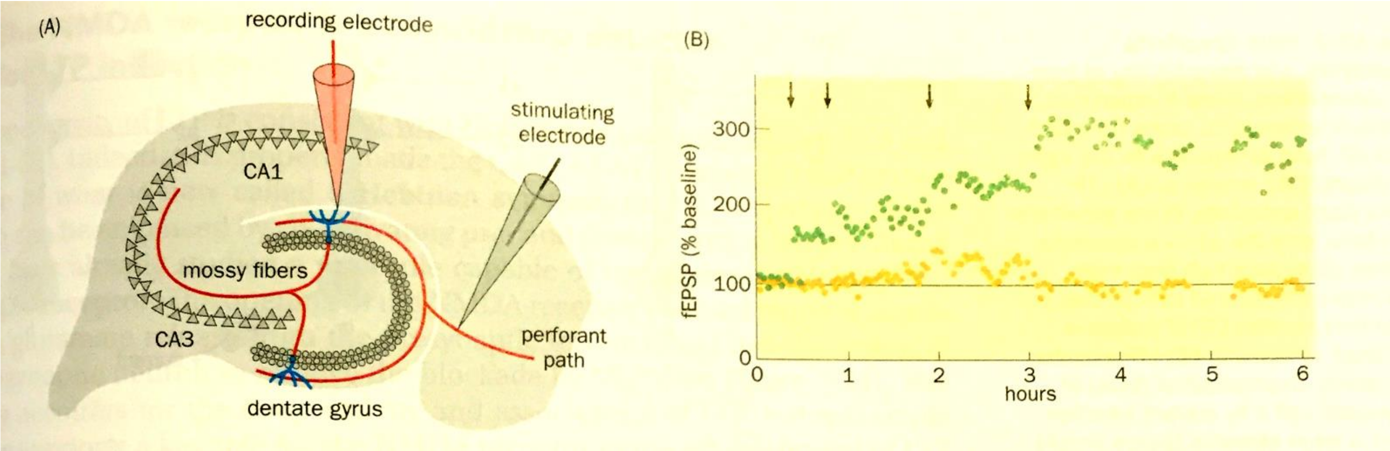


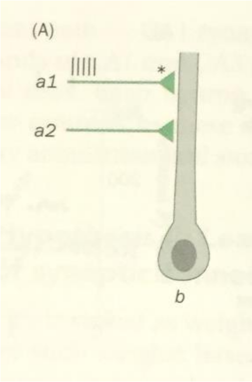


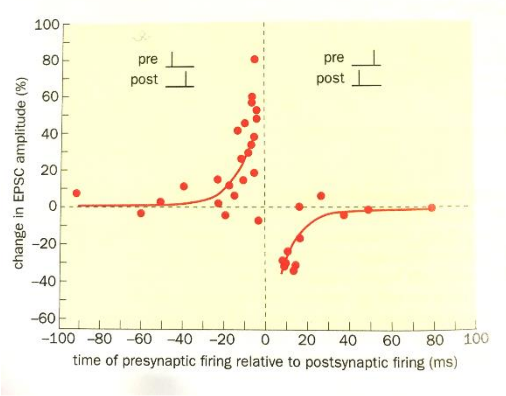
Hippocampus

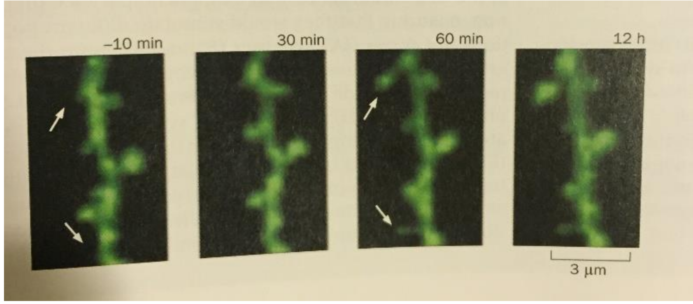


Long-term potentiation

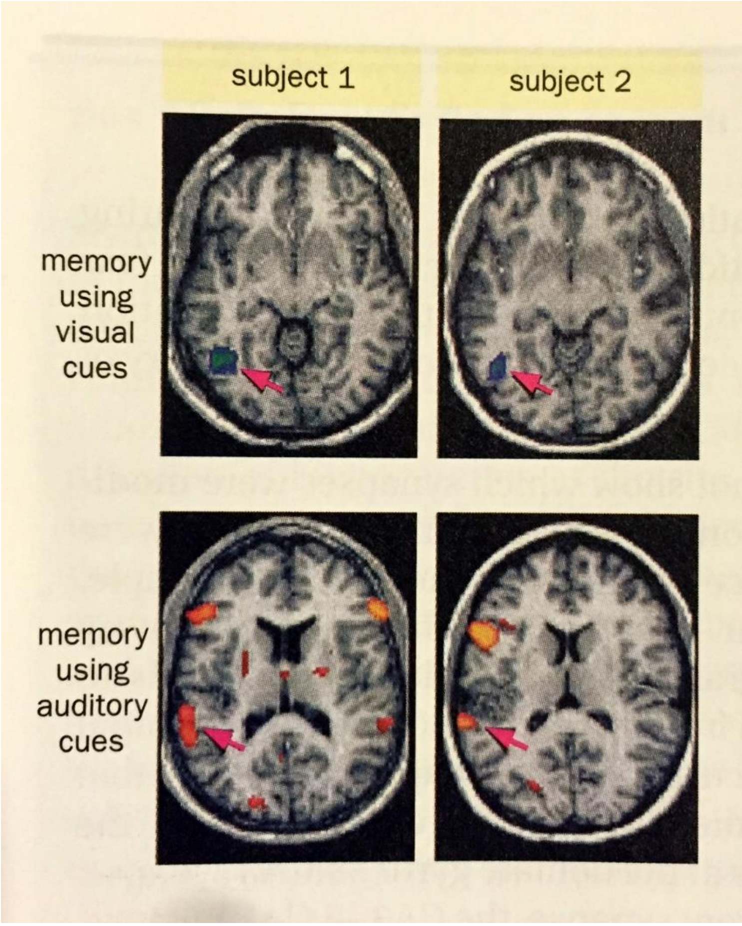








Hippocampus provides an indexing system



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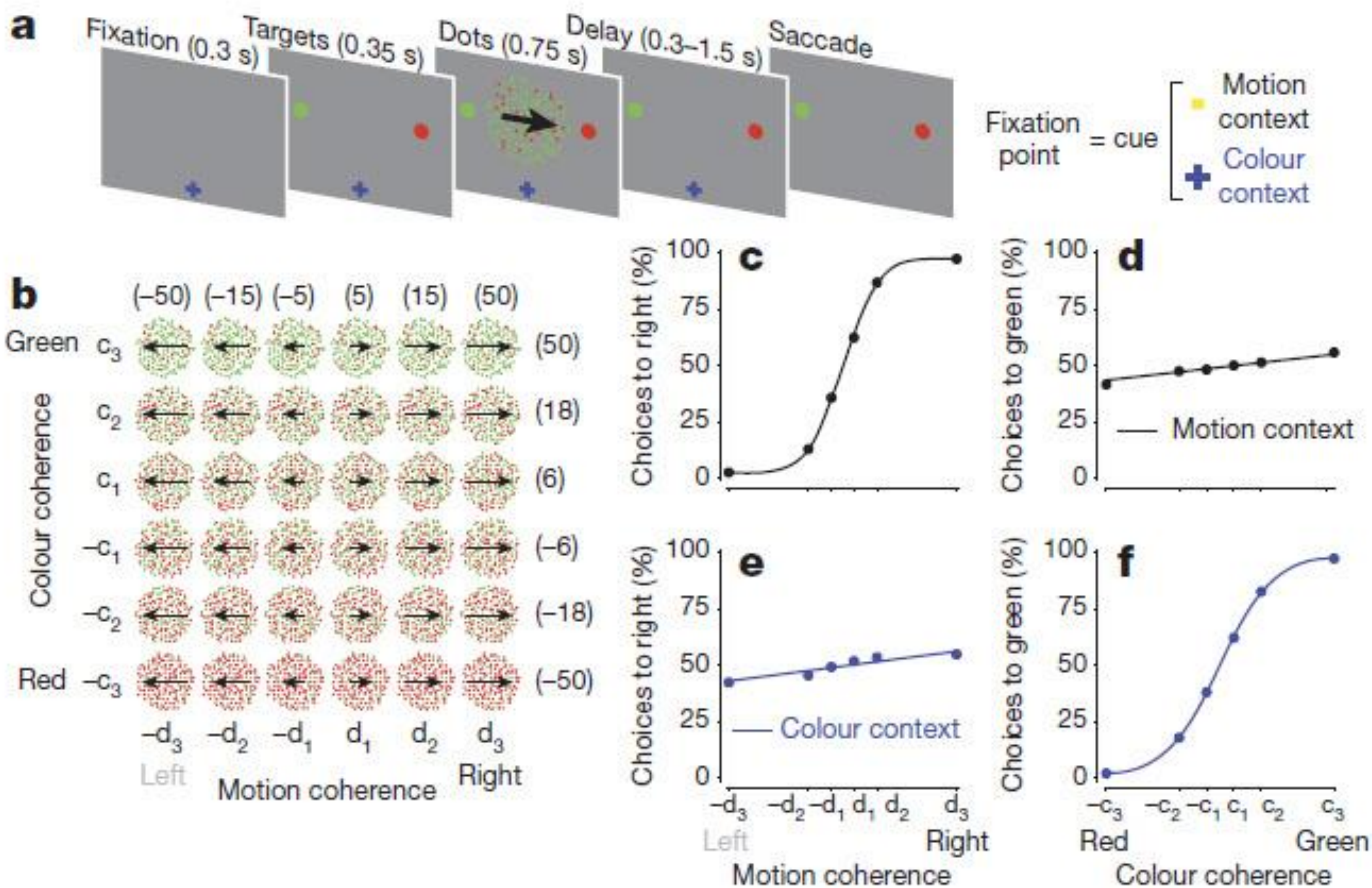
Understanding the mechanism for flexible behavior



Mante and Newsome 2013

Step 1: Compute top 12 PCs of population data

D = matrix of eigenvectors

Step 2: Demixing (goal: plot neural state in meaningful coordinates)

$$r_{i,t}(k) = \beta_{i,t}(1)\ choice(k) + \beta_{i,t}(2)\ motion(k) + \beta_{i,t}(3)\ color(k) + \beta_{i,t}(4)\ context(k) + \beta_{i,t}(5), \text{(1)}$$

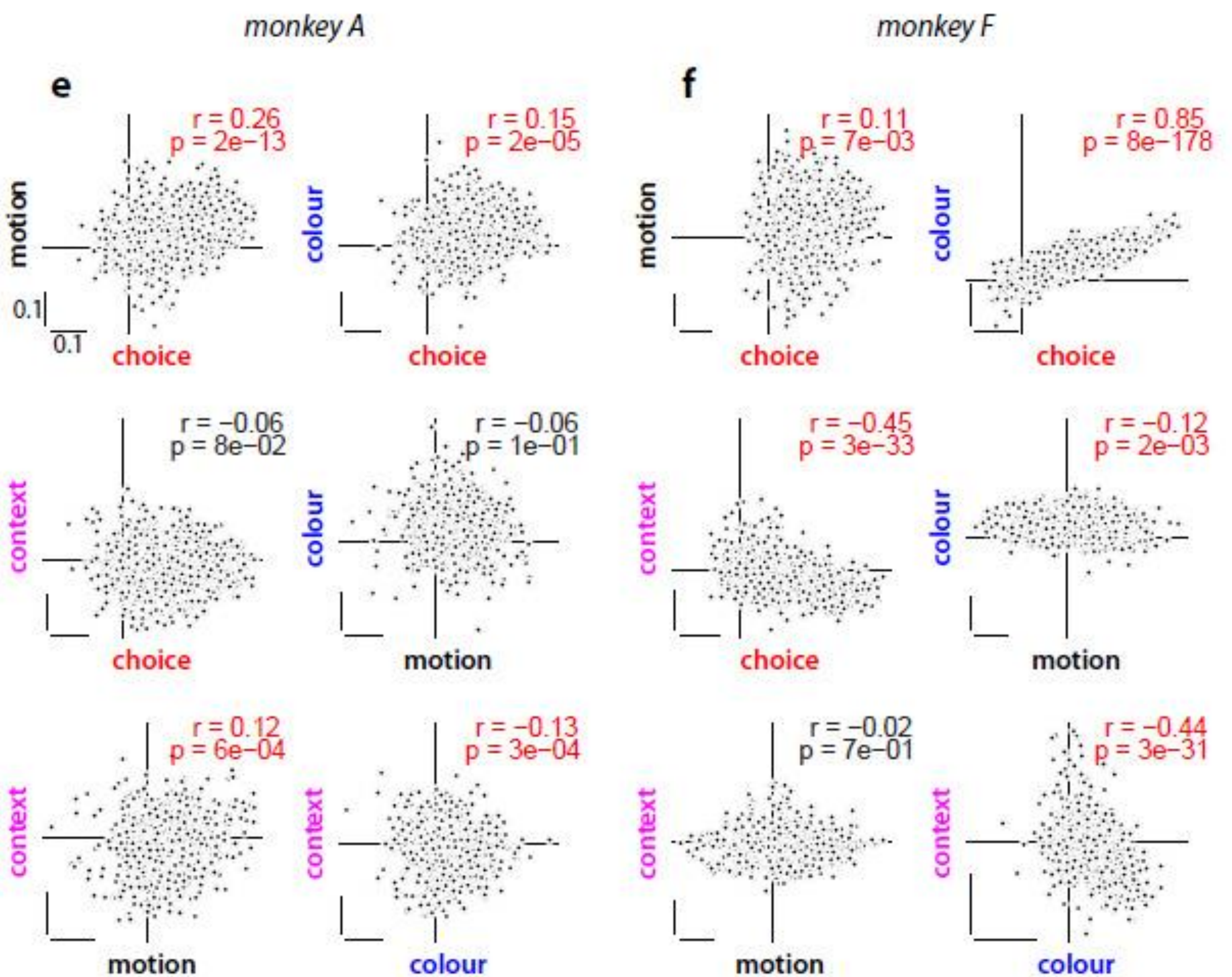
where $r_{i,t}(k)$ is the z-scored response of unit i at time t and on trial k, $choice(k)$ is the monkey's choice on trial k (+1: to choice 1; -1 to choice 2), $motion(k)$ and $color(k)$ are the motion and color coherence of the dots on trial k, and $context(k)$ is the rule the monkey has to use on trial k (+1: motion context; -1: color context).

Each vector, $\boldsymbol{\beta}_{v,t}$, thus corresponds to a direction in state space that accounts for variance in the population response at time t, due to variation in task variable v.

Step 3: Denoise the regression vectors (project onto 12 PCs)

$$\boldsymbol{\beta}_{v,t}^{pca} = \boldsymbol{D}\ \boldsymbol{\beta}_{v,t},$$

Regression coefficients for individual neurons

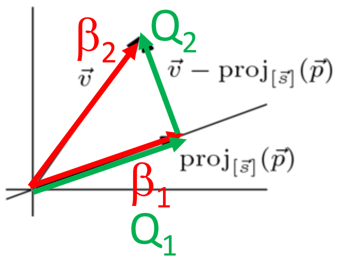


Step 4: Orthogonalize regression vectors (Gramm Schmidt)

$$\mathbf{B}^{max} = \boldsymbol{Q}\,\boldsymbol{R},$$

where $\mathbf{B}^{max} = [\boldsymbol{\beta}_1^{max}\ \boldsymbol{\beta}_2^{max}\ \boldsymbol{\beta}_3^{max}\ \boldsymbol{\beta}_4^{max}]$ is a matrix whose columns correspond to the regression vectors, $\boldsymbol{Q}$ is an orthogonal matrix, and $\boldsymbol{R}$ is an upper triangular matrix. The first four columns of $\boldsymbol{Q}$ correspond to the orthogonalized regression vectors $\boldsymbol{\beta}_v^{\perp}$, which we refer to as the 'task-related axes' of choice, motion, color, and context. These axes span the same 'regression subspace' as the original regression vectors, but crucially each explains distinct portions of the variance in the responses.

To study the representation of the task-related variables in PFC, we projected the average population responses onto these orthogonal axes (Fig. 2 and Extended Data Figs. 4-7):



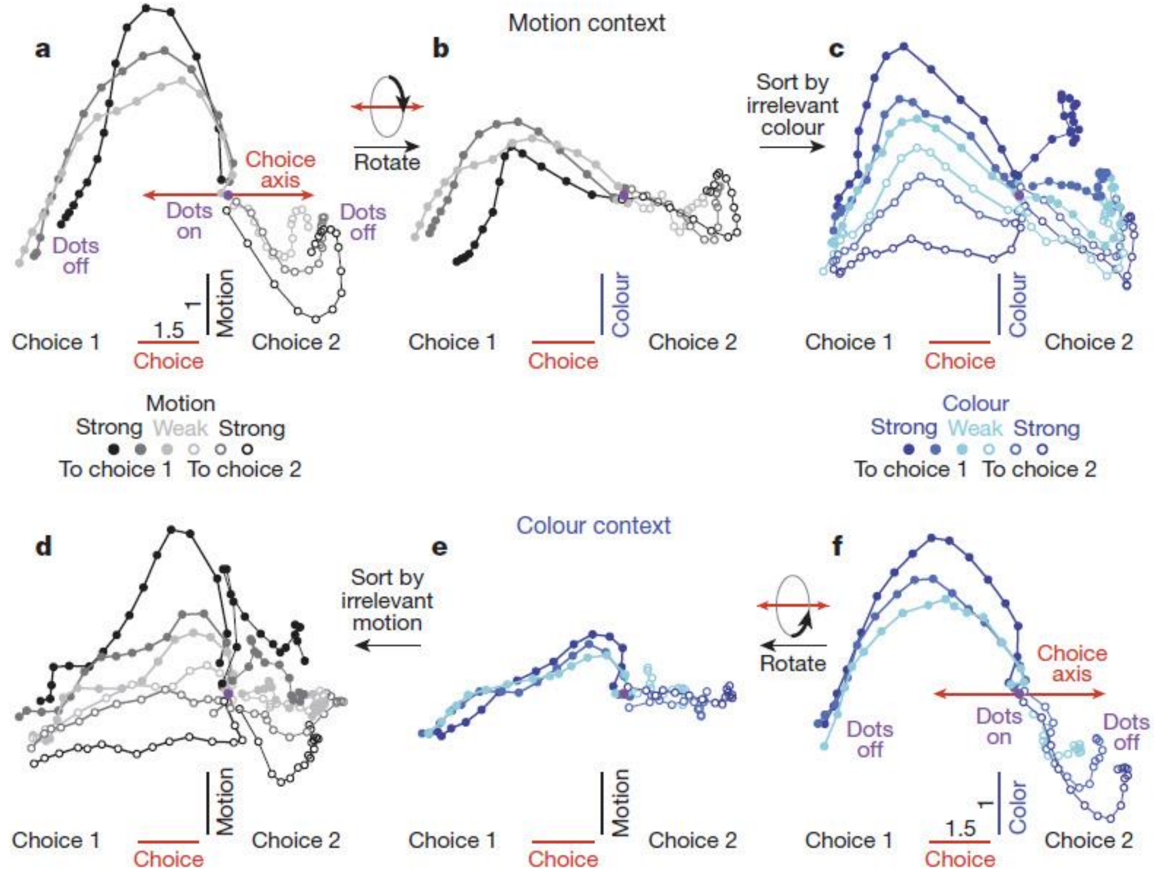
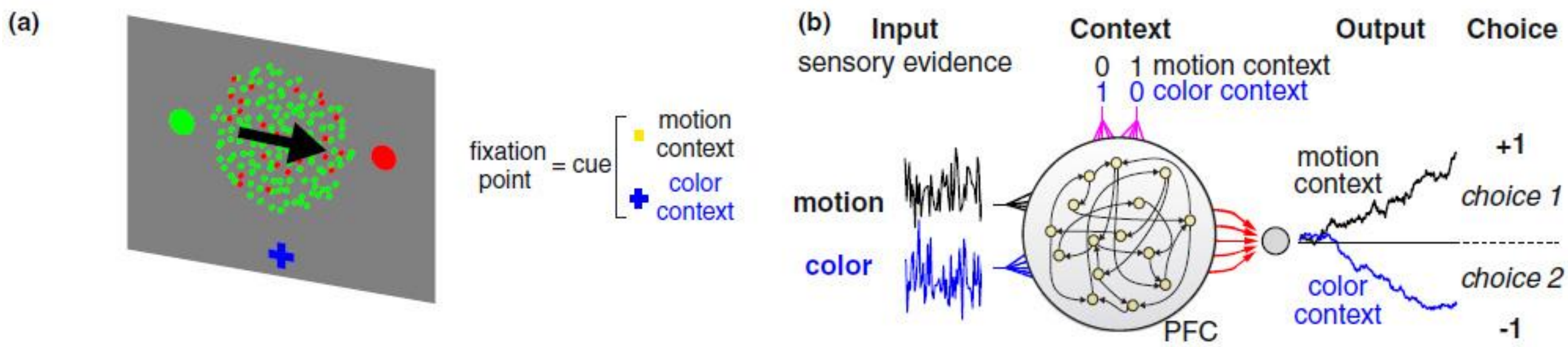


Figure 2 | Dynamics of population responses in PFC. The average population response for a given condition and time is represented as a point in state space. Responses from correct trials only are shown from 100 ms after dots onset (dots on, purple circle) to 100 ms after dots offset (dots off) in 50-ms steps, and are projected into the three-dimensional subspace capturing the variance due to the monkey's choice (along the choice axis), and to the direction and strength of the motion (motion axis) and colour (colour axis) inputs. Units are arbitrary; components along the motion and colour axes are enhanced relative to the choice axis (see scale bars in **a**, **f**). Conditions (see colour bars) are defined based on context (motion context, top; colour context, bottom), on the location of the chosen target (choice 1 versus choice 2) and either on the direction and strength of the motion (grey colours) or the colour input (blue colours). Here, choice 1 corresponds to the target in the response field of the recorded neurons. The direction of the colour input does not refer to the colour of the dots per se (red or green), but to whether the colour points towards choice 1 or choice 2 (see Supplementary Information, section 6.4, for a detailed description of the conditions). **a**, Effect of choice and the relevant motion input in the motion context, projected onto the axes of choice and motion. **b**, Same data as in **a**, but rotated by 90° around the axis of choice to reveal the projection onto the axis of colour. **c**, Same trials as in **b**, but re-sorted according to the direction and strength of the irrelevant colour input. **d–f**, Responses in the colour context, analogous to **a–c**. Responses are averaged to show the effects of the relevant colour (**e**, **f**) or the irrelevant motion input (**d**). For relevant inputs (**a**, **b** and **e**, **f**), correct choices occur only when the sensory stimulus points towards the chosen target (3 conditions per chosen target); for irrelevant inputs (**c**, **d**), however, the stimulus can point either towards or away from the chosen target on correct trials (6 conditions per chosen target).

…So far, not THAT surprising
(a fancy way of showing that both color and motion information are represented regardless of context)

How is he able to do the task???

Recurrent Neural Network



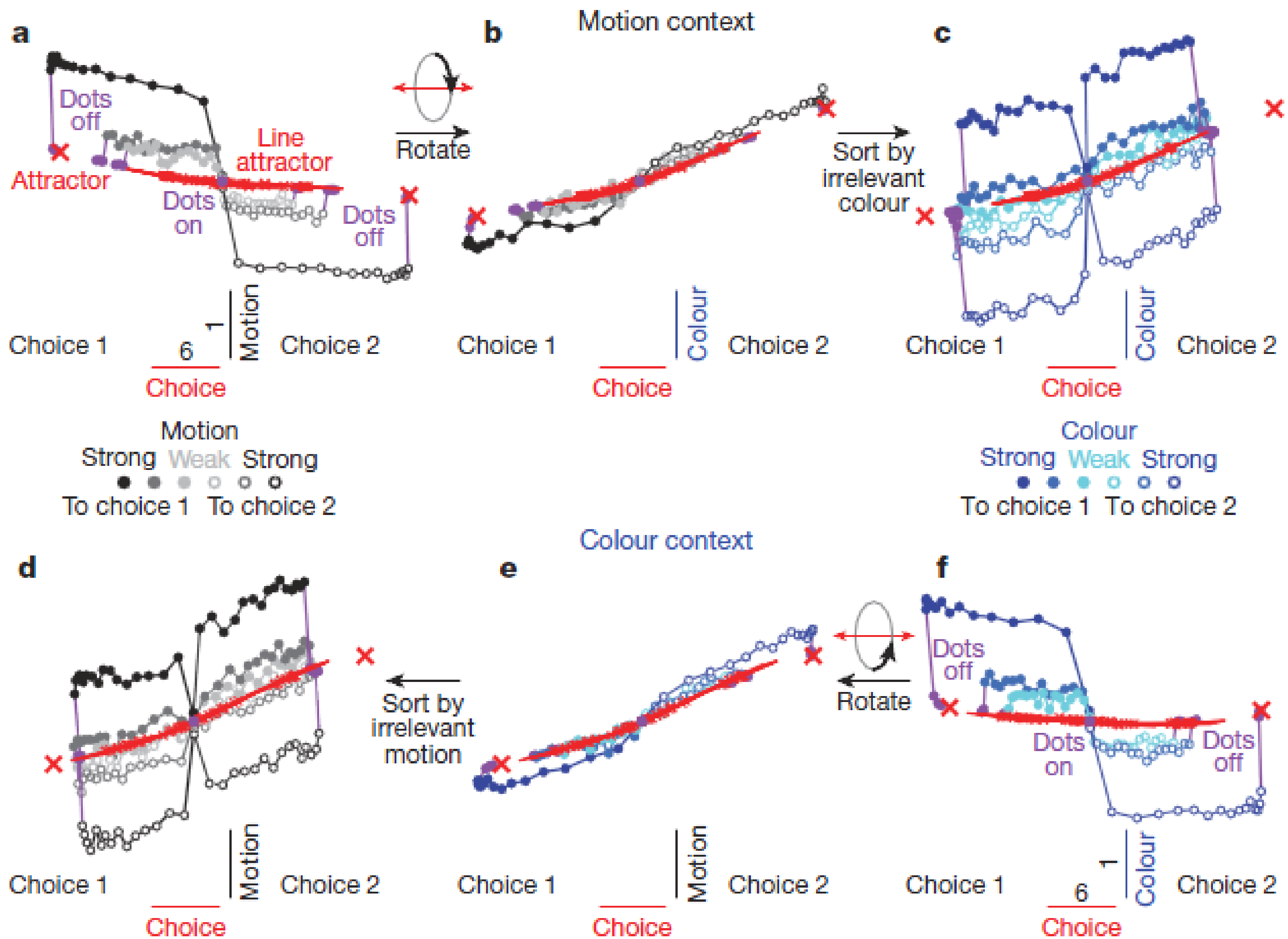
$$\tau \dot{\boldsymbol{x}} = -\boldsymbol{x} + \boldsymbol{J}\boldsymbol{r} + \boldsymbol{b}^{c} u_{c} + \boldsymbol{b}^{m} u_{m} + \boldsymbol{b}^{cc} u_{cc} + \boldsymbol{b}^{cm} u_{cm} + \boldsymbol{c}^{x} + \rho_{x}$$

$$\boldsymbol{r} = \tanh(\boldsymbol{x})$$

- x represents activation of neuron, r represents firing rate, J represents recurrent connections, u represents input, c represents offsets, rho represents noise

- J, b, c are modified through training

Search for fixed points (where $\dot{x} = 0$)



Red crosses: fixed points (same in both contexts) small and sometimes large, where the system can be understood in essentially linear terms, i.e. as a linear dynamical system. We can see this with just a few lines of math involving the Taylor series expansion of the update equations, $\dot{\mathbf{x}} = \mathbf{F}(\mathbf{x})$. Consider the Taylor expansion of $\mathbf{F}(\mathbf{x})$ around a fixed point in state space, $\mathbf{x}^*$:

$$(\mathbf{x}^* \dot{+} \delta\mathbf{x}) = \mathbf{F}(\mathbf{x}^* + \delta\mathbf{x}) = \mathbf{F}(\mathbf{x}^*) + \mathbf{F}'(\mathbf{x}^*)\delta\mathbf{x} + \frac{1}{2}\delta\mathbf{x}\mathbf{F}''(\mathbf{x}^*)\delta\mathbf{x} + \dots \tag{6}$$

Here we have defined the nonlinear system up to second order. Since the system is at a fixed point, the zero order term, $\mathbf{F}(\mathbf{x}^*)$, is equal to $\mathbf{0}$, giving

$$\mathbf{F}(\mathbf{x}^* + \delta\mathbf{x}) = \mathbf{F}'(\mathbf{x}^*)\delta\mathbf{x} + \frac{1}{2}\delta\mathbf{x}\mathbf{F}''(\mathbf{x}^*)\delta\mathbf{x} + \dots \tag{7}$$

If we ensure that $\delta\mathbf{x}$ is small, we can safely ignore second and higher order terms, yielding

$$(\mathbf{x}^* \dot{+} \delta\mathbf{x}) = \mathbf{F}'(\mathbf{x}^*)\delta\mathbf{x} \tag{8}$$

$$\dot{\delta\mathbf{x}} = \mathbf{F}'(\mathbf{x}^*)\delta\mathbf{x} \tag{9}$$

and by simply renaming variables, $\mathbf{y} \equiv \delta\mathbf{x}$ and $\mathbf{M} \equiv \mathbf{F}'(\mathbf{x}^*)$, we end up with the familiar linear form

$$\dot{\mathbf{y}} = \mathbf{M}\mathbf{y}. \tag{10}$$

Thus for small perturbations, $\delta\mathbf{x}$, around a fixed point, $\mathbf{x}^*$, any nonlinear system behaves like a linear system. The fixed points act as a scaffolding for the nonlinear dynamics, allowing us, at least in simple cases, to decompose a hard nonlinear problem into smaller, linear sub-problems. This process is called linearization around a fixed point.

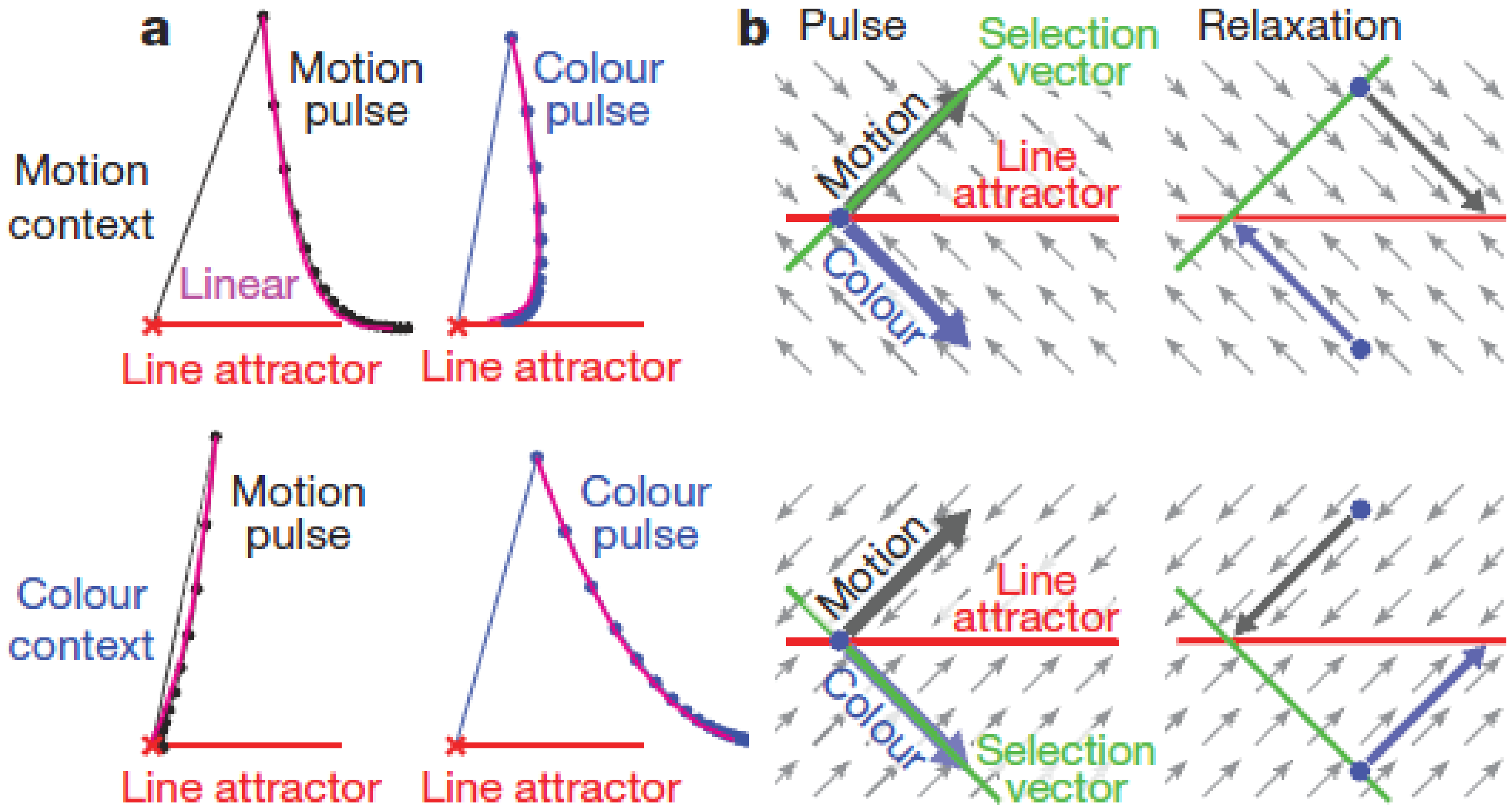
For the siRNN, the matrix $\mathbf{M}(\mathbf{x}^*)$ is obtained by computing $\mathbf{F}'(\mathbf{x}^*)$ for equation (1). Concretely, it is the derivative of $\mathrm{F}_i()$ with respect to x_j, i.e. $\frac{\partial \mathrm{F}_i}{\partial x_j}$, giving

$$M_{ij}(\mathbf{x}^*) = -\delta_{ij} + J_{ij}\ \mathrm{h}'(x_j^*), \tag{11}$$

where δ_{ij} is defined to be 1 if $i = j$ and otherwise 0 *, and $\mathrm{h}'()$ is the derivative of the nonlinearity $\mathrm{h}()$ with respect to its input. Since this matrix derives from $\mathbf{F}(\mathbf{x})$, it is related to the feedback matrix, $\mathbf{J}$, but it is not $\mathbf{J}$. Instead, $\mathbf{M}$ defines the linear network that approximates the RNN around the point $\mathbf{x}^*$.

Going forward, our notation will drop the explicit dependency of $\mathbf{M}$ on $\mathbf{x}^*$, with the understanding that each locally linear system is still defined in terms of a particular fixed point.

*The notation δ_{ij} is the identity matrix written using indices and shouldn't be confused with $\delta\mathbf{x}$.



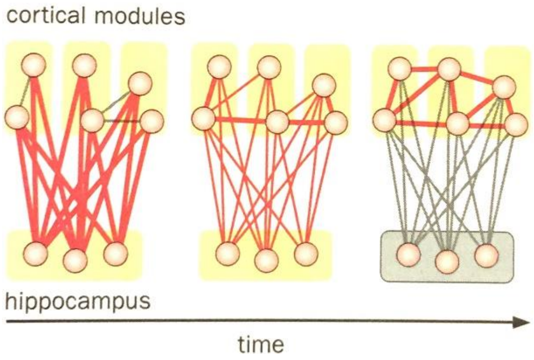
- Context-depending integration is explained by different neural dynamics in the two situations!

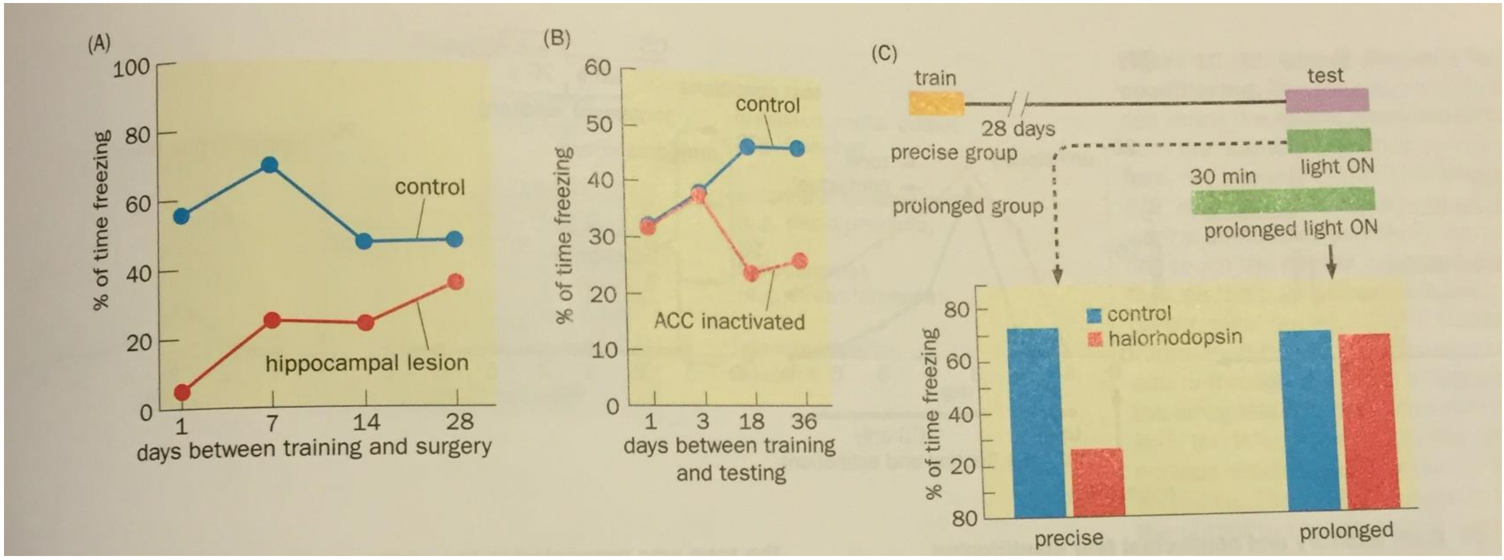
“We conclude that the observed complexity and functional roles of single neurons are readily understood in the framework of a dynamical process unfolding at the level of a population .”

Outline

- Brains of different animals
- Neurons: structure & signaling mechanism
- Organization of the brain: lobes, networks, specialized cell types
- Learning and memory
- Population dynamics: a case study

Is hippocampus necessary for retrieval?





Replay: Linking spatial navigation to episodic memory