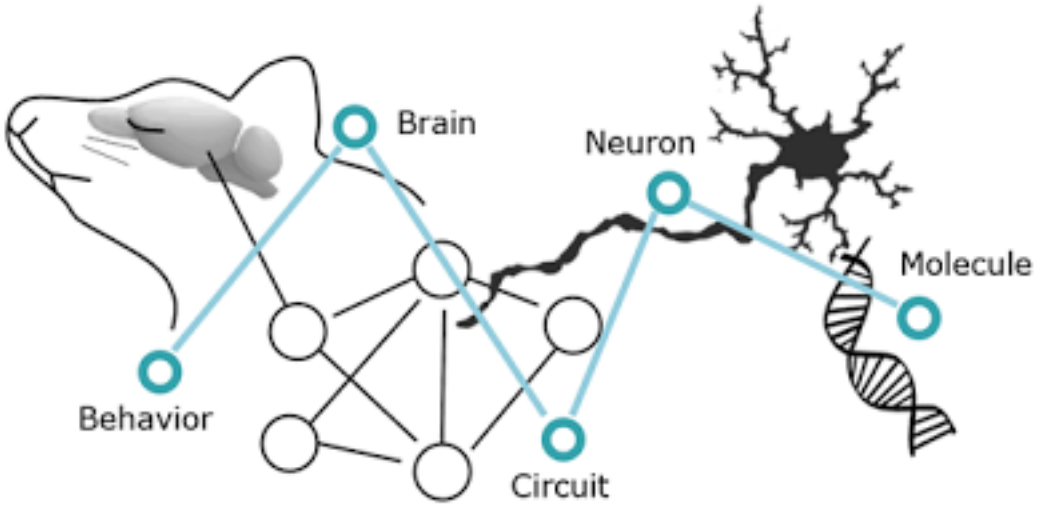
Applied Neuroscience

Columbia Science Honors Program

Fall 2017

Neural Circuits

Introduction to Sleep



Introduction to Neural Circuits

Objective: Experimental Design in Neuroscience

Agenda:

1. Neural Circuits
   - Anatomy
   - Physiology
2. Sleep
   - EEG

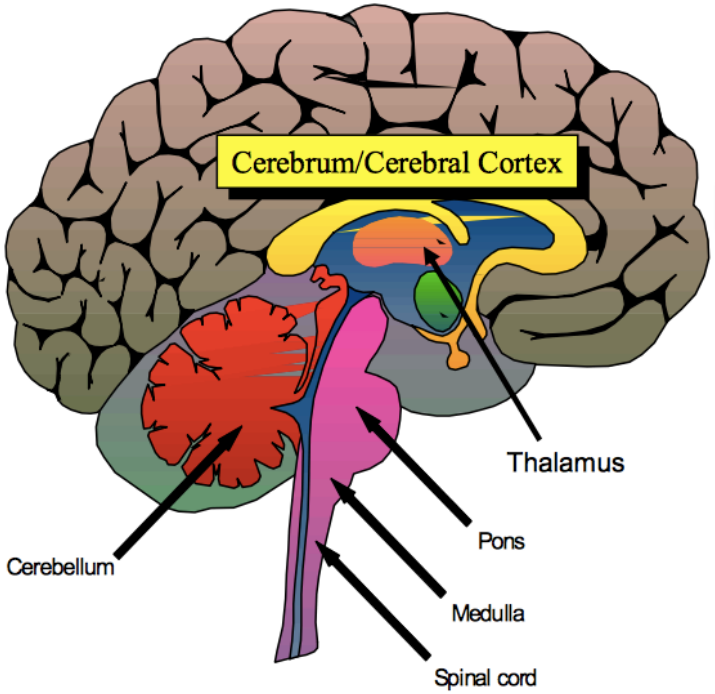
Neural Circuits

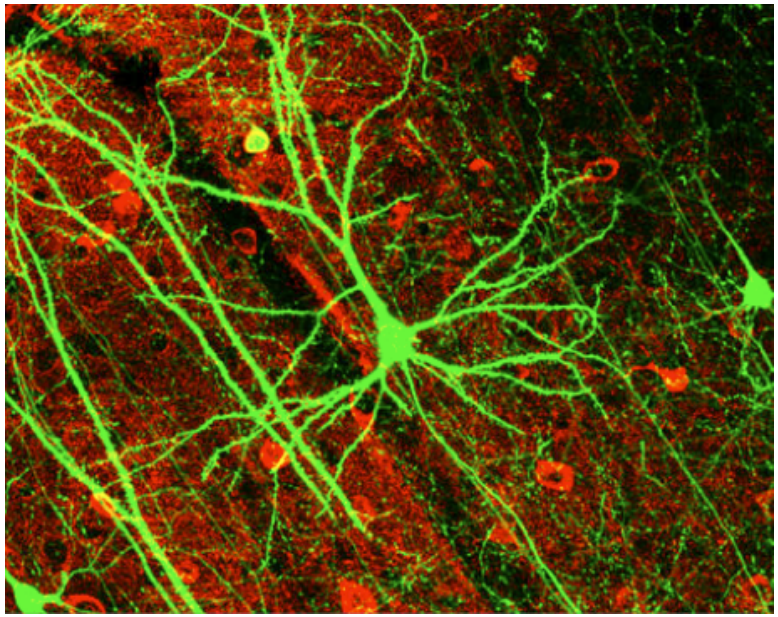
Neural Circuit: Functional entity of inter-connected neurons that is able to regulate its own activity using a feedback loop

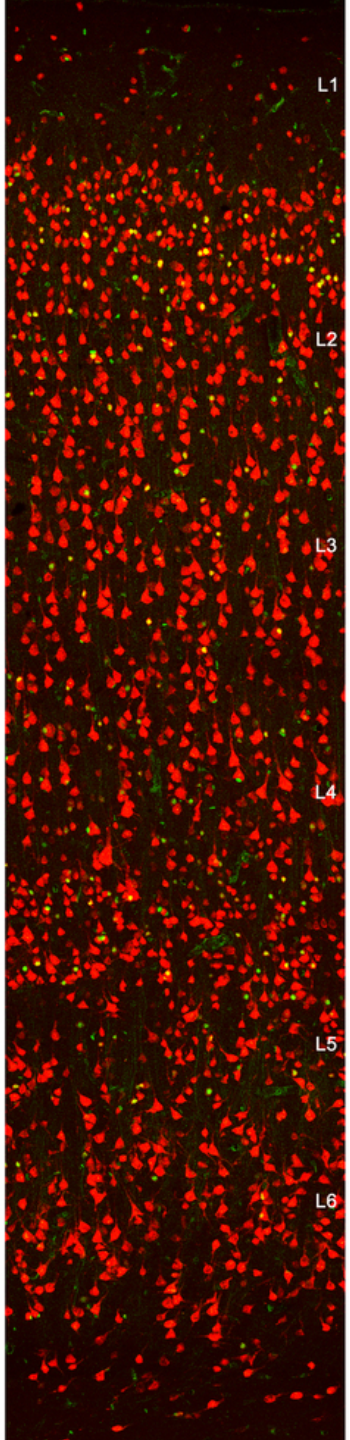
Features:

1. Neurons do not function in isolation
2. Neurons are grouped according to function
3. Synaptic connections define the circuit
    - Types of Connections
        1. Axon-Dendrite
        2. Neuron-Muscle
    - Types of Neurotransmitters Used
    - Location and Length of Connections

The Neuron



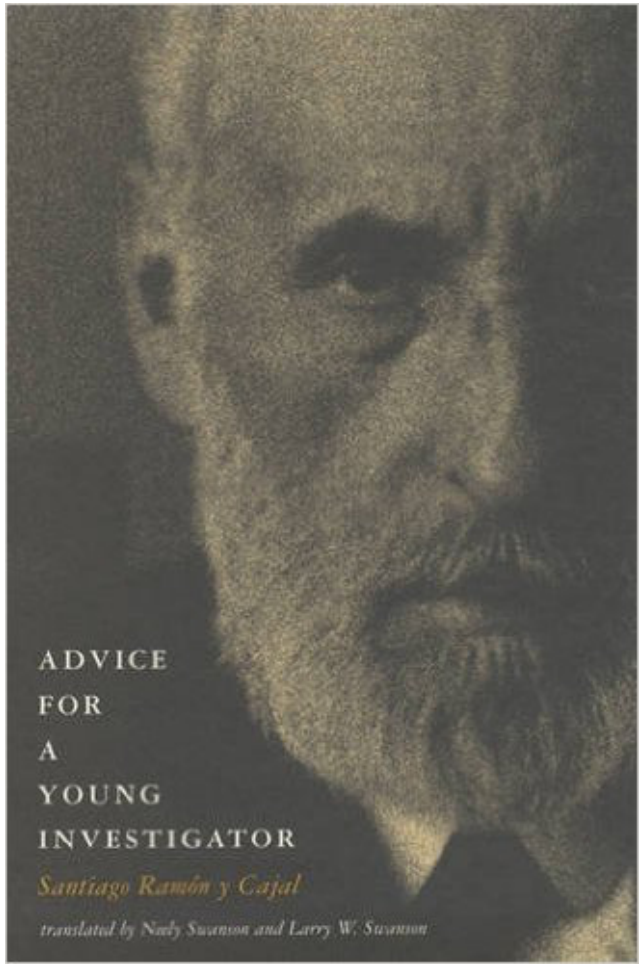


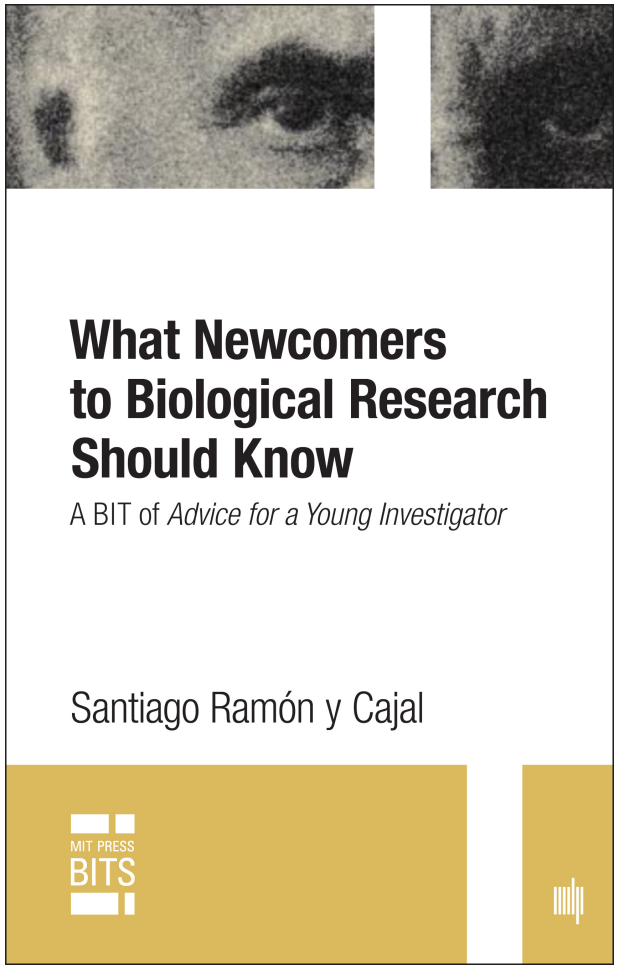


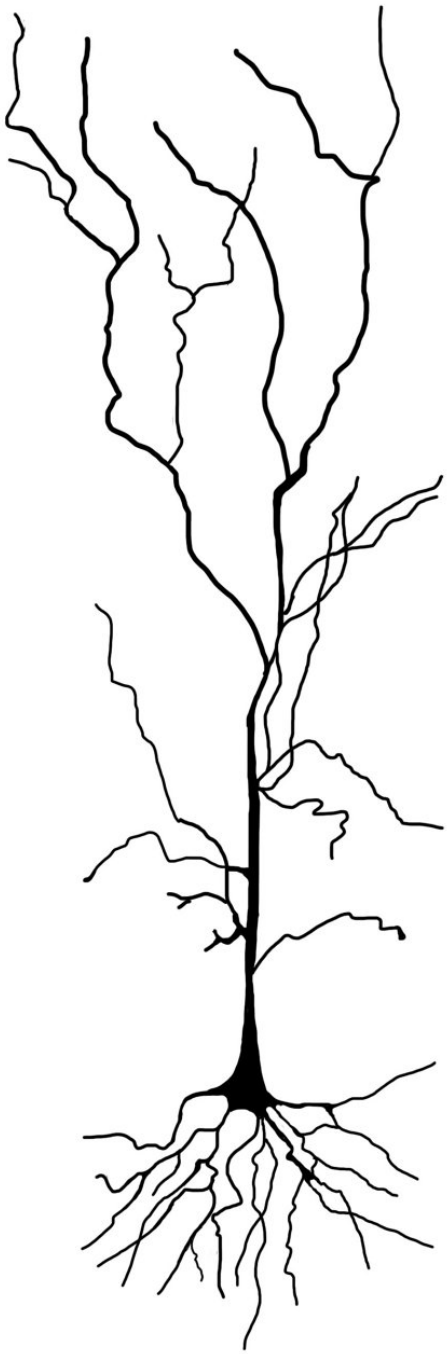
Neo-cortex:
Part of cerebral cortex concerned with sight and hearing in mammals, regarding as the site of higher intelligence ***The neo-cortex has six layers of tissue.***

Pyramidal neuron:
Primary component of cortical tissue and named for triangular cell body (soma)

The Neuron Doctrine

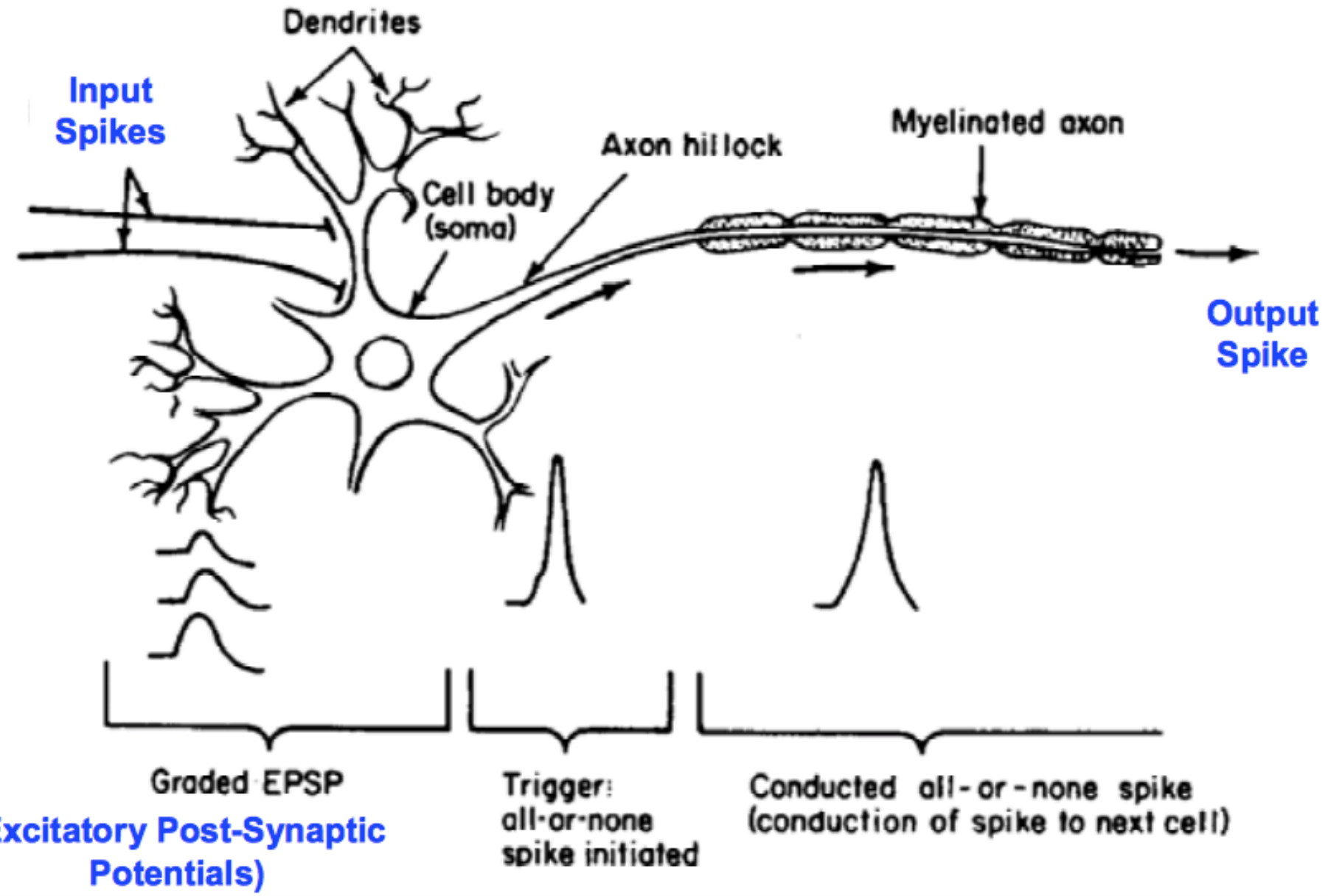






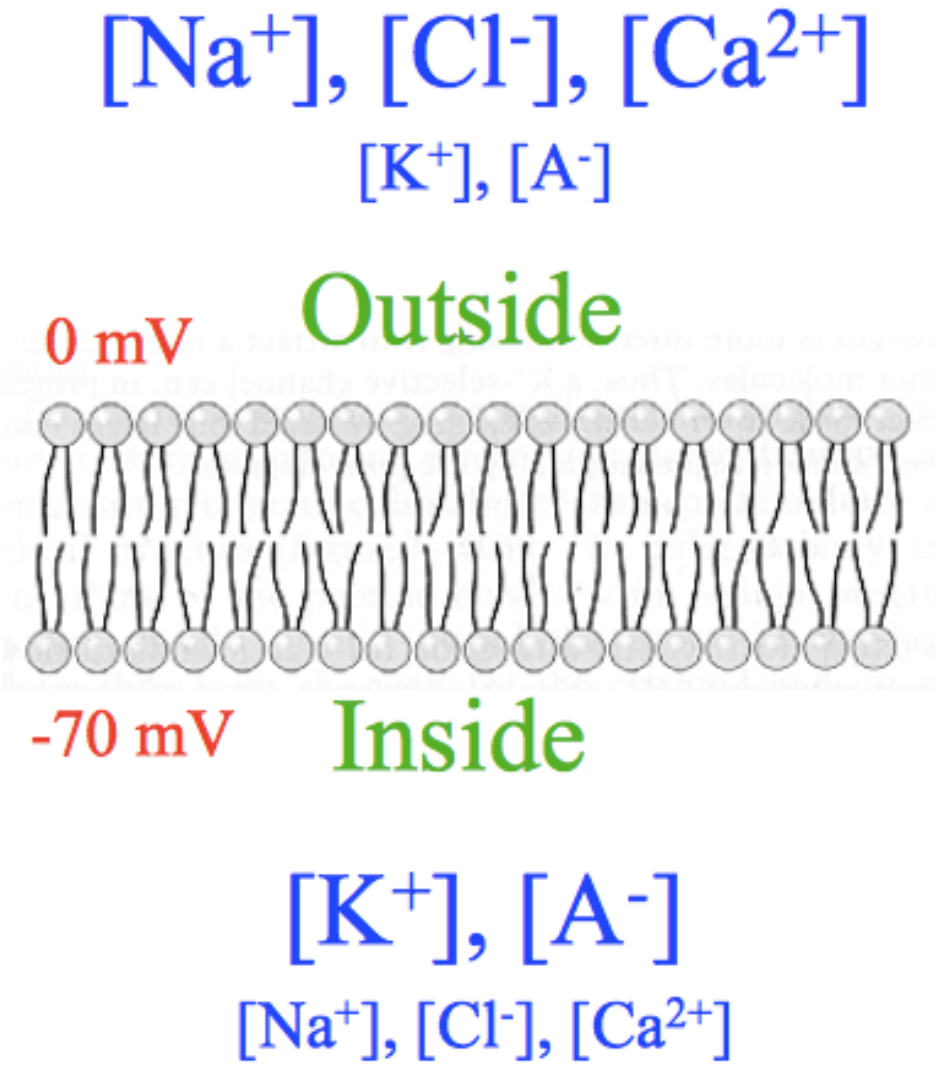
"The neuron is the appropriate basis for understanding the computational and functional properties of the brain" (1891)

The Neuron

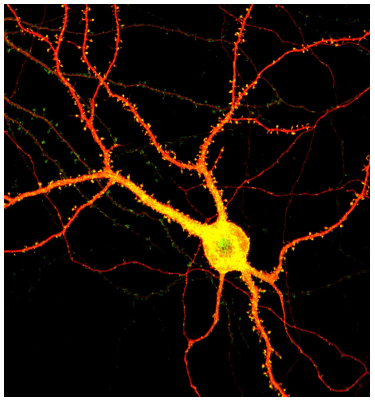

Dendrites
Input Spikes
Axon hillock
Myelinated axon
Cell body (soma)
Output Spike
Graded EPSP
(Excitatory Post-Synaptic Potentials)
Trigger all-or-none spike initiated
Conducted all-or-none spike (conduction of spike to next cell)

Properties of a Neuron

- Contents of the neuron enclosed within a *cell membrane*, which is a *lipid bilayer*
- The bilayer is impermeable to charged ions
- Each neuron maintains a *potential difference* across its membrane
  - Inside is -70 to -80 mV relative to outside
  - *Ionic pump* maintains -70 mV difference by expelling Na^+ out and allowing K^+ ions in



Electrophysiology of a Neuron

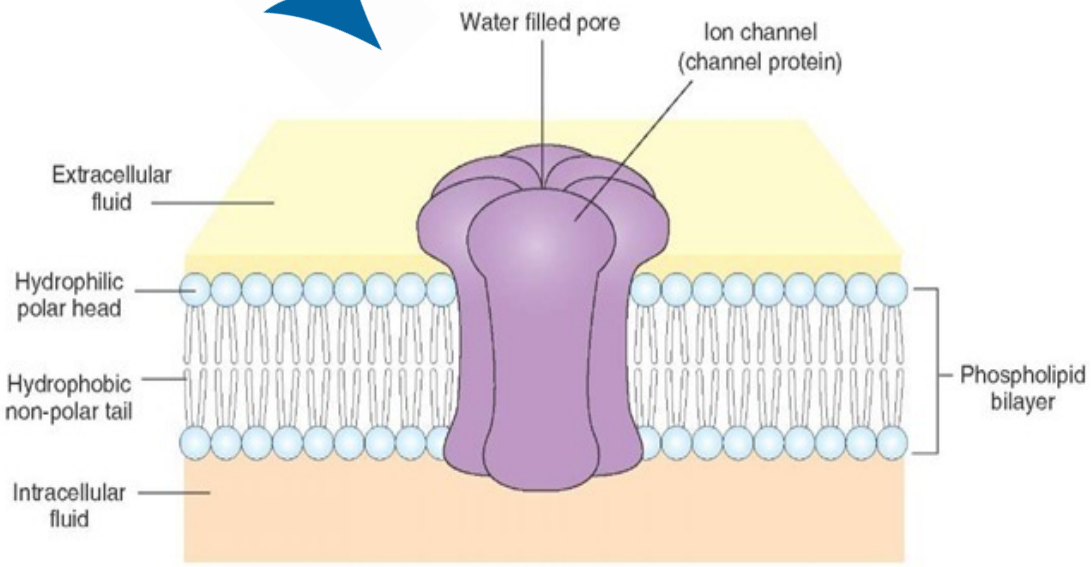


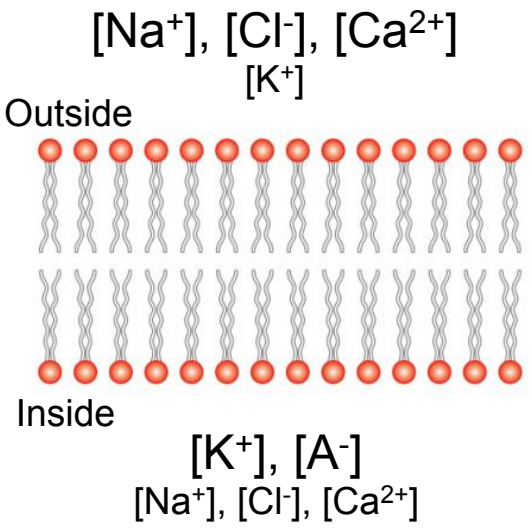
Nernst Equation

E = Membrane Potential at which current flow due to diffusion of ions is balanced by electric forces

$$E = \frac{RT}{zF} \ln\left(\frac{[outside]}{[inside]}\right)$$

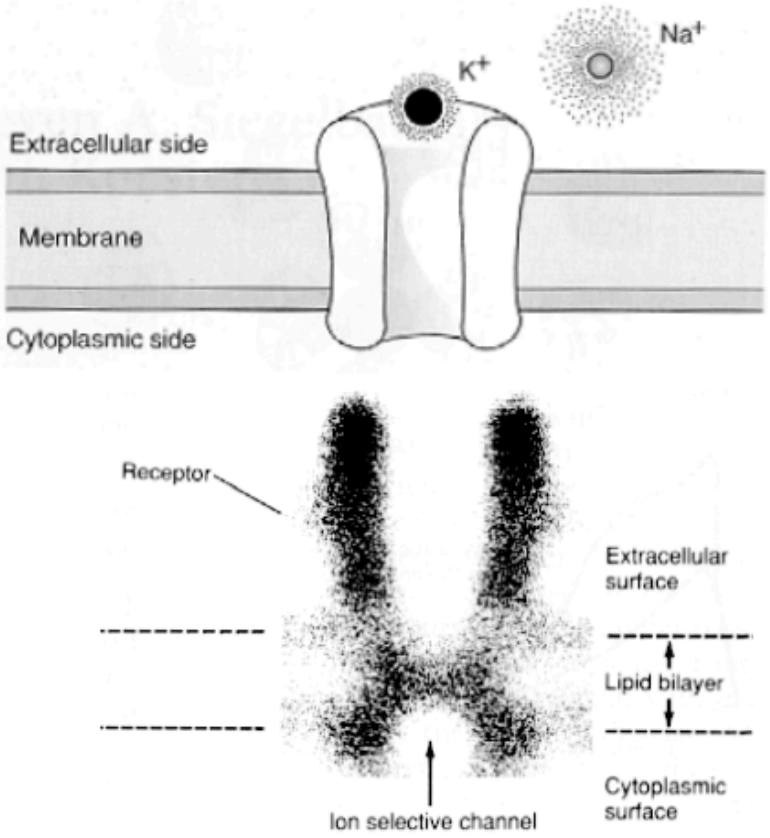
Cell Membrane





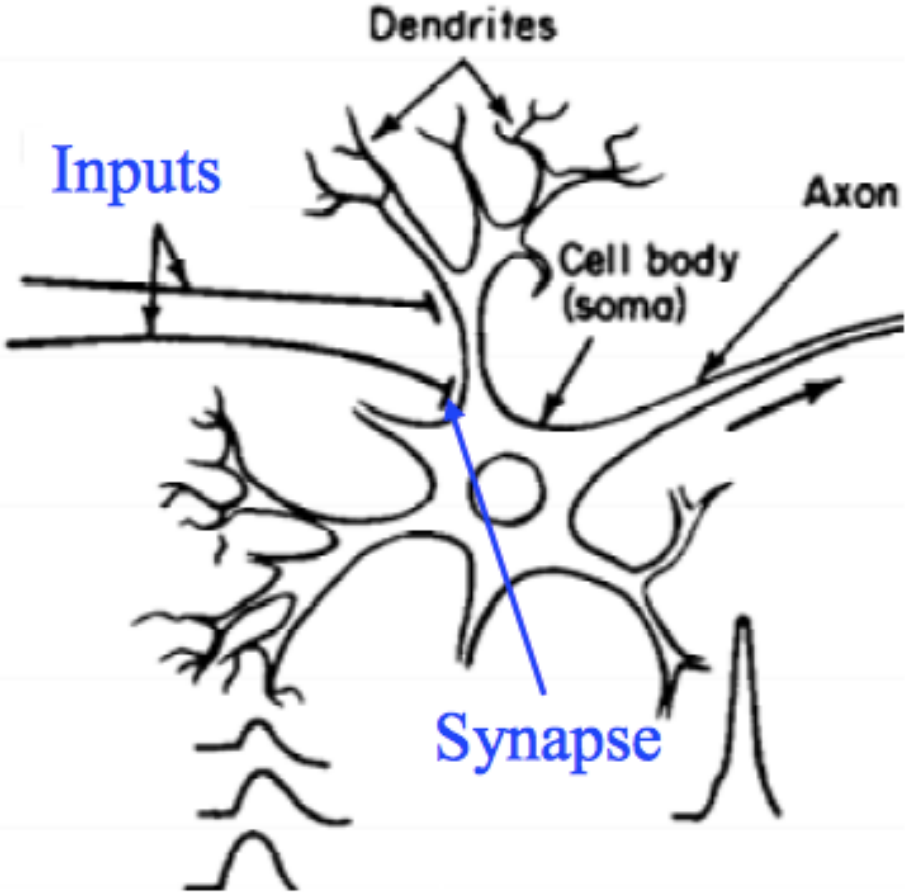
Membrane Proteins: The Gatekeepers

- Properties in membranes act as pores or channels that are ion-specific
- Ionic channels are *gated*
  - Voltage-gated: Probability of opening depends on membrane voltage
  - Chemically-gated: Binding to a chemical causes channel to open (neurotransmitters)
  - Mechanically-gated: Sensitive to pressure or stretch (sensory neurons)



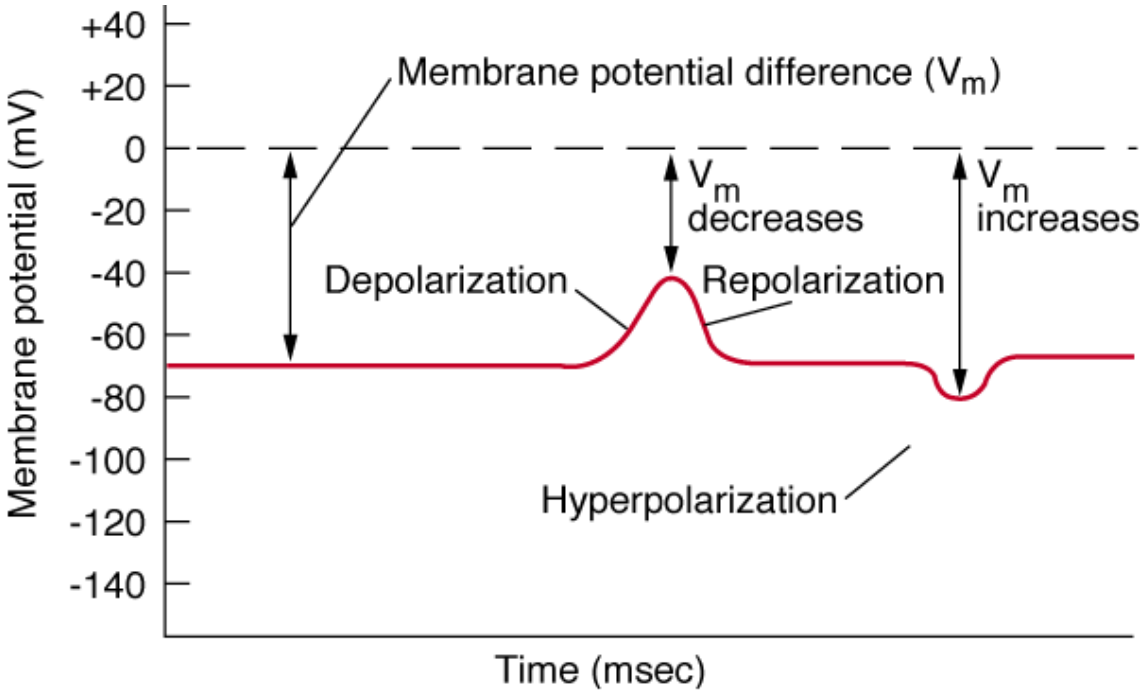
Neuronal Signaling

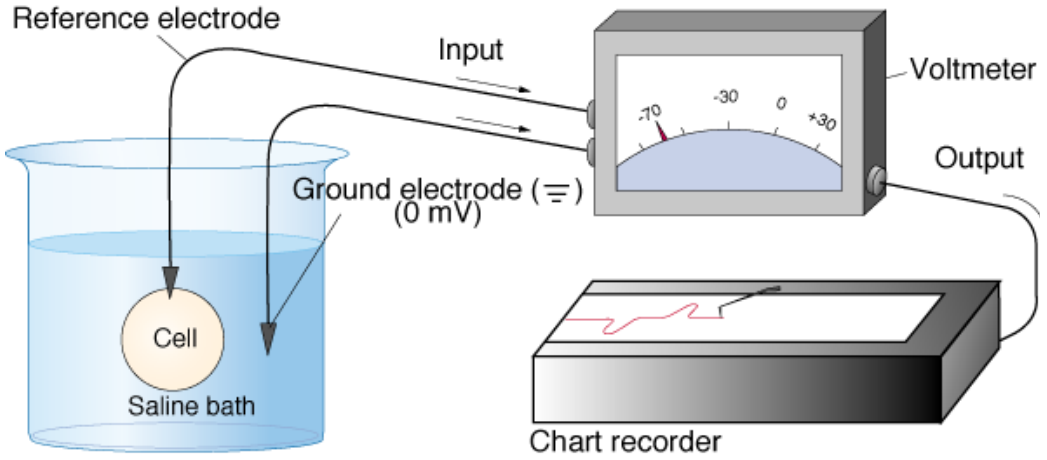
- Different types of gated channels are involved in neuronal signaling
  - Graded Potentials: travel over short distances and are activated by the opening of mechanically or chemically gated channels
  - Action Potentials: travel over long distances and are generated by the opening of voltage-gated channels



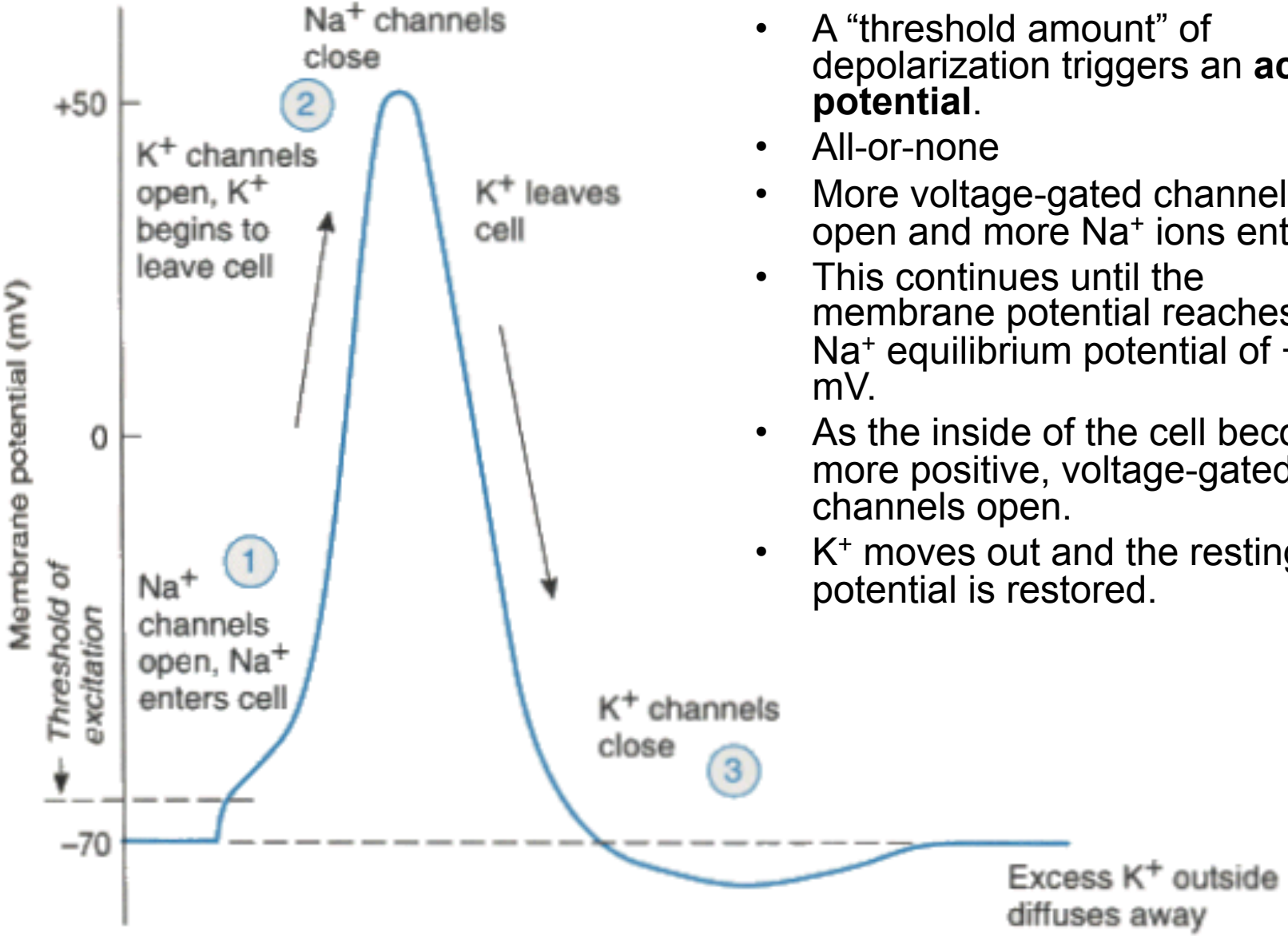
Action Potential

- Depolarization: a decrease in the potential difference between the inside and outside of the cell
- Repolarization: an increase in the potential difference between the inside and outside of the cell
- Hyperpolarization: returning to the resting membrane potential from either direction





Action Potential

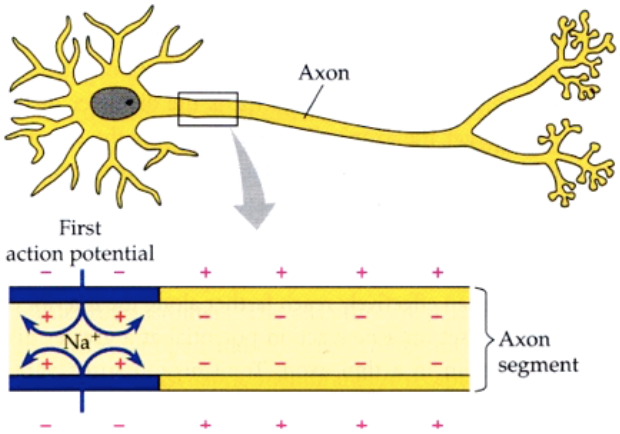


- A “threshold amount” of depolarization triggers an **action potential**.
- All-or-none
- More voltage-gated channels open and more Na^+ ions enter.
- This continues until the membrane potential reaches the Na^+ equilibrium potential of +50 mV.
- As the inside of the cell becomes more positive, voltage-gated K^+ channels open.
- K^+ moves out and the resting potential is restored.

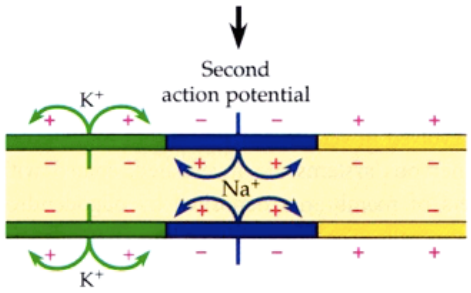
Action Potential Propagation

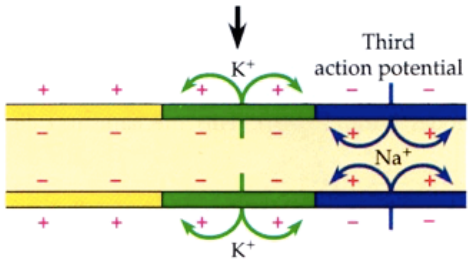
The action potential is propagated along the axon of the neuron

Voltage-gated sodium channels



Voltage-gated potassium channels





Test Your Understanding

Circle whichever is greater, A or B. If A = B, circle both:

I.
- A. permeability of a neuronal membrane to Na^+ during the rise phase of an action potential
- B. permeability to K^+ at the same time

II.
- A. permeability of the resting membrane to K^+
- B. permeability of the membrane to K^+ during the falling phase of the action potential

III.
- A. concentration of K^+ in the intracellular fluid before the action potential
- B. concentration of K^+ in the intracellular fluid immediately after the action potential

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To Identify Neural Circuits

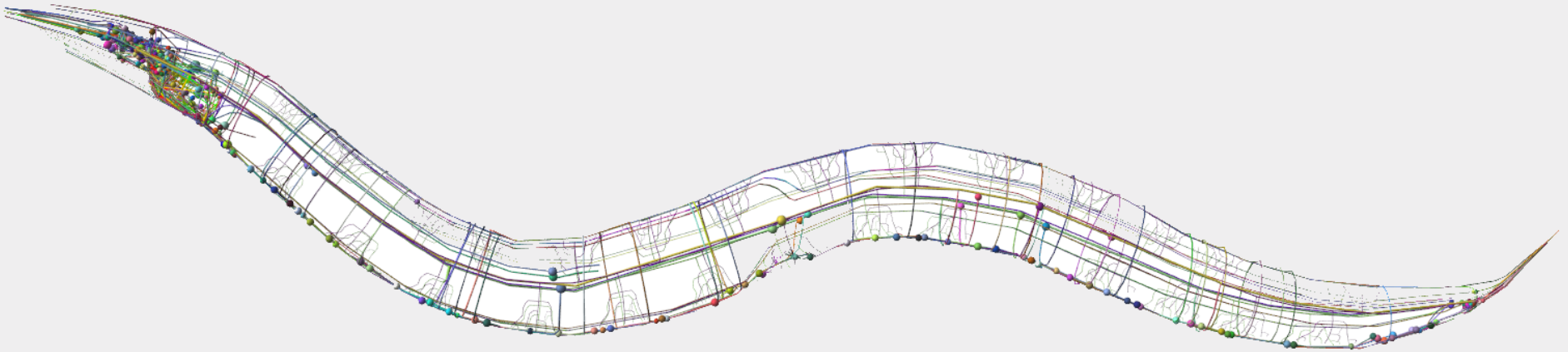
Step 1: Find one neuron involved in the circuit.

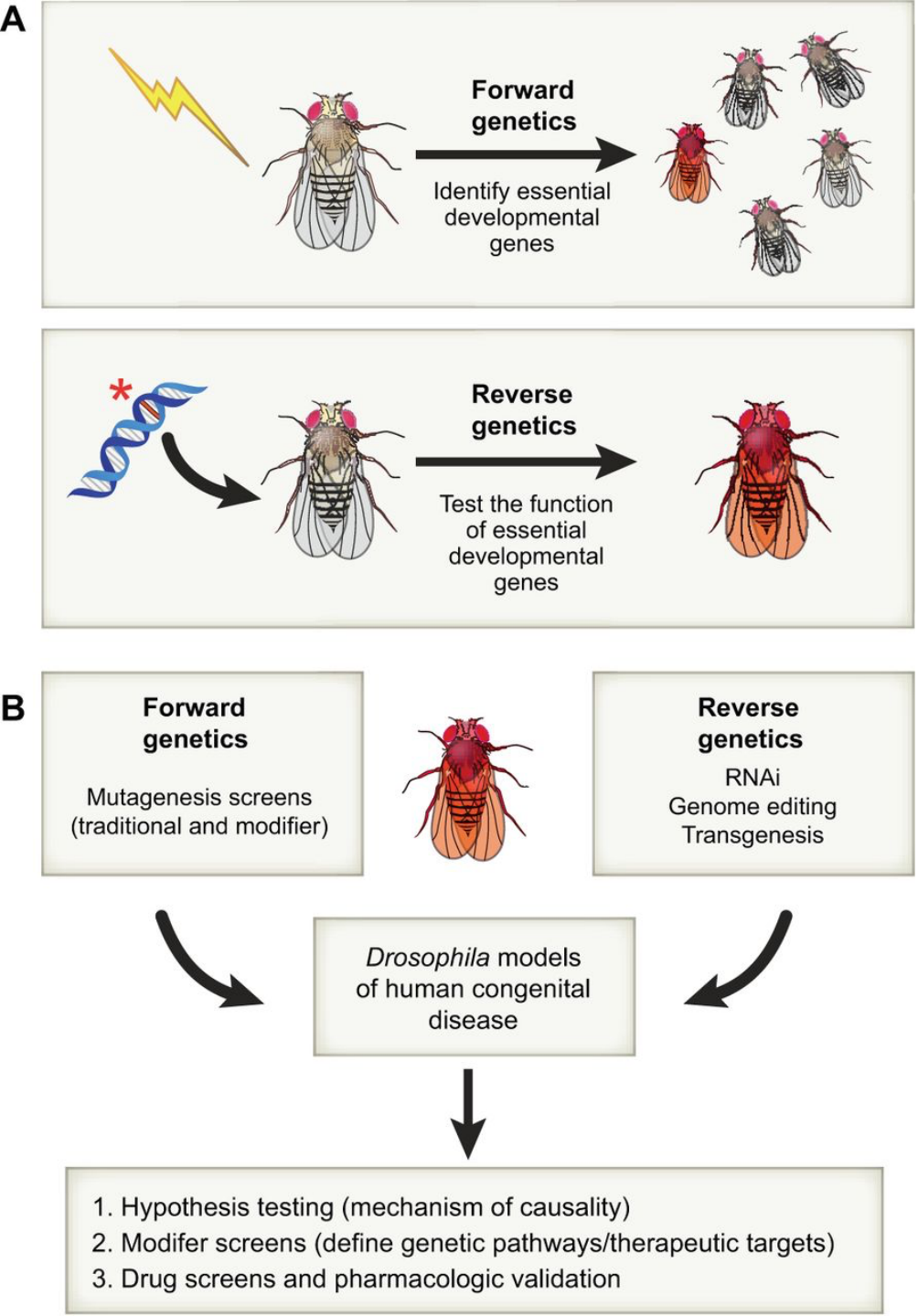
Step 2: Find additional functional neurons.

Step 3: Confirm role of all neurons in signal.

Step 4: Organize neurons by *epistasis analysis.*

Step 5: Draw Circuit.





Genetic Screens

Step 1: How do we find one neuron involved in the circuit?

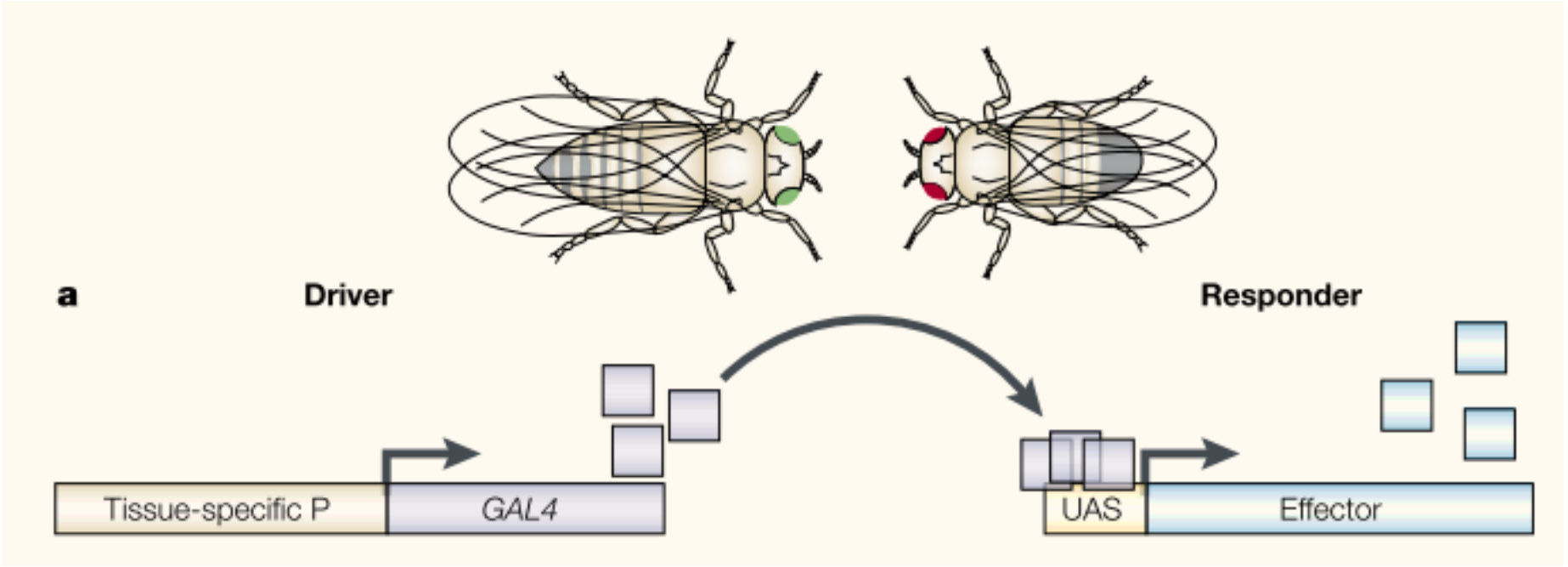
(A) Forward genetic screen

Mutagenesis by X-rays, chemicals or transposons (lightning bolt in diagram) generates mutant flies with abnormal phenotypes. This is a starting point for gene discovery.

(B) Reverse genetic screen

Targeted mutagenesis by RNAi or CRISPR/Cas9 to understand the gene's biological function

Genetic Screens in *Drosophila melanogaster*



GAL4: yeast transcriptional activator used to regulate gene expression in *Drosophila* by inserting the UAS next to a gene of interest

UAS: upstream activating sequence

Test Your Understanding

A researcher is conducting a forward genetic screen of GAL4 lines in *Drosophila.* Which of the following effector pairs can be attached to UAS for characterization of anatomy *and* behavior?

I. GFP and Halo-rhodopsin
II. RFP and Channel-rhodopsin
III. mCherry and Archae-rhodopsin

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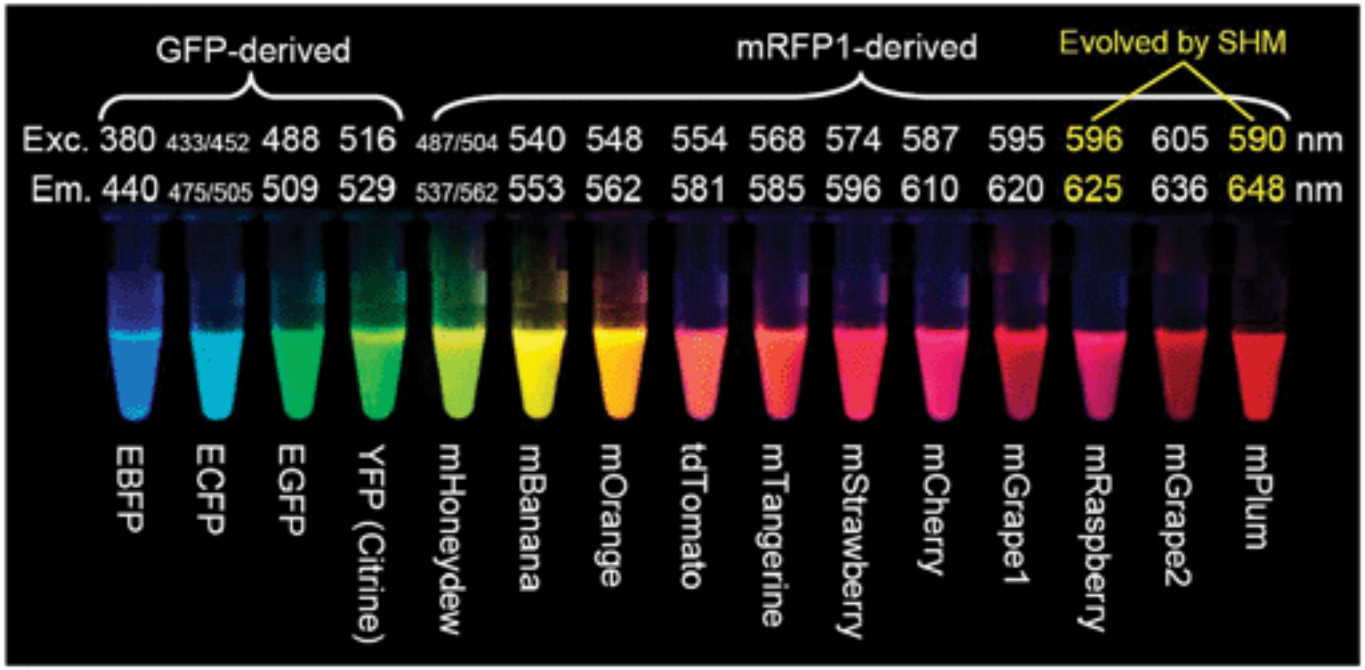
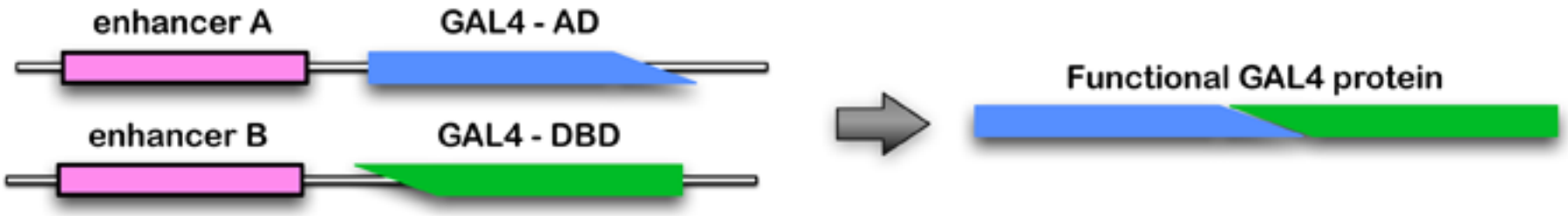


Refining Gene Expression

<u>Step 1:</u> How do we find *one neuron* involved in the circuit?

Genetic screens generate expression patterns with more than one cell type. It is possible to achieve single-cell labeling if expression is limited to the overlap of two patterns. In *Drosophila,* this is known as the **split-GAL4 system.**

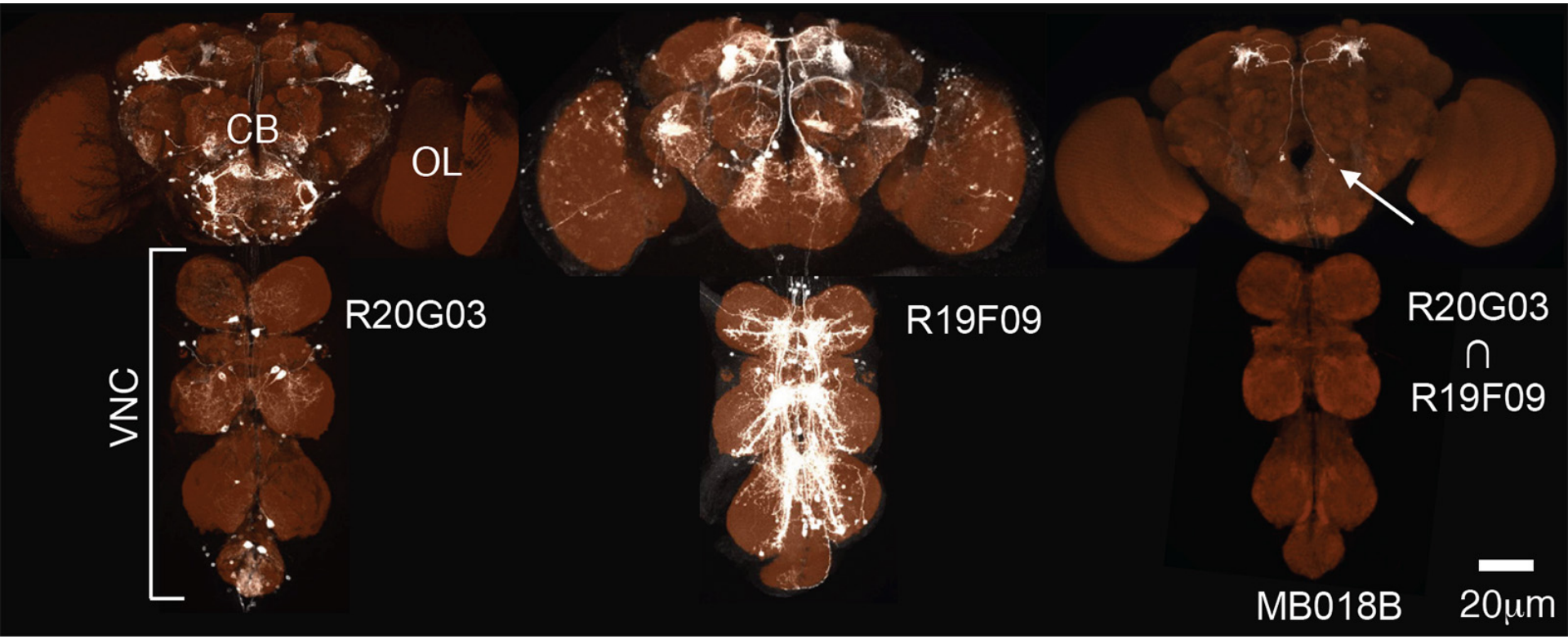


AD: GAL4 activating domain

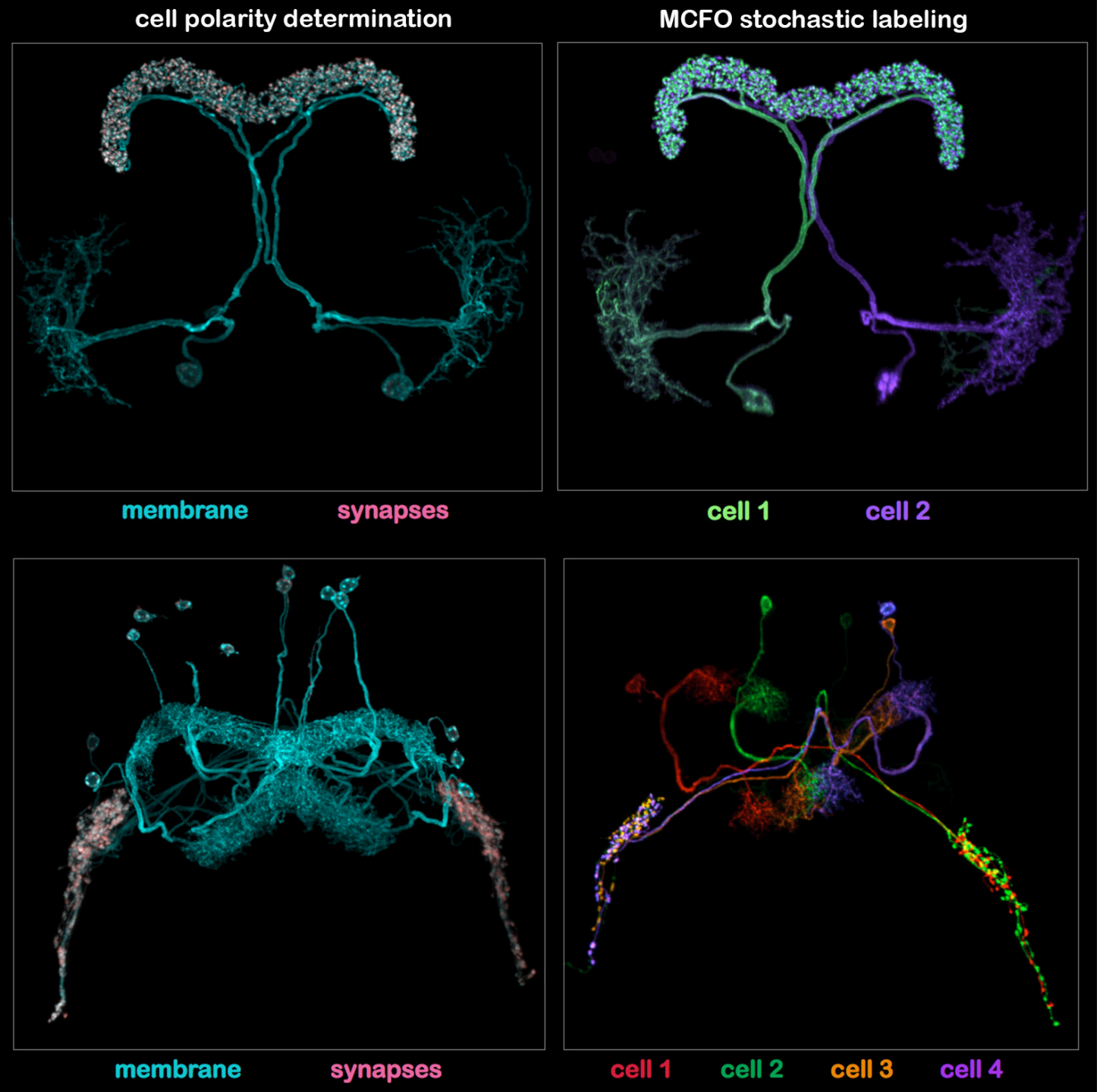
DBD: DNA-binding domain

AD and DBD proteins alone are not able to promote gene expression. Only cells where both enhancers are active produce a functional GAL4 protein.

Split-GAL4 System



Luan et al, 2006; Pfeiffer et al, 2010



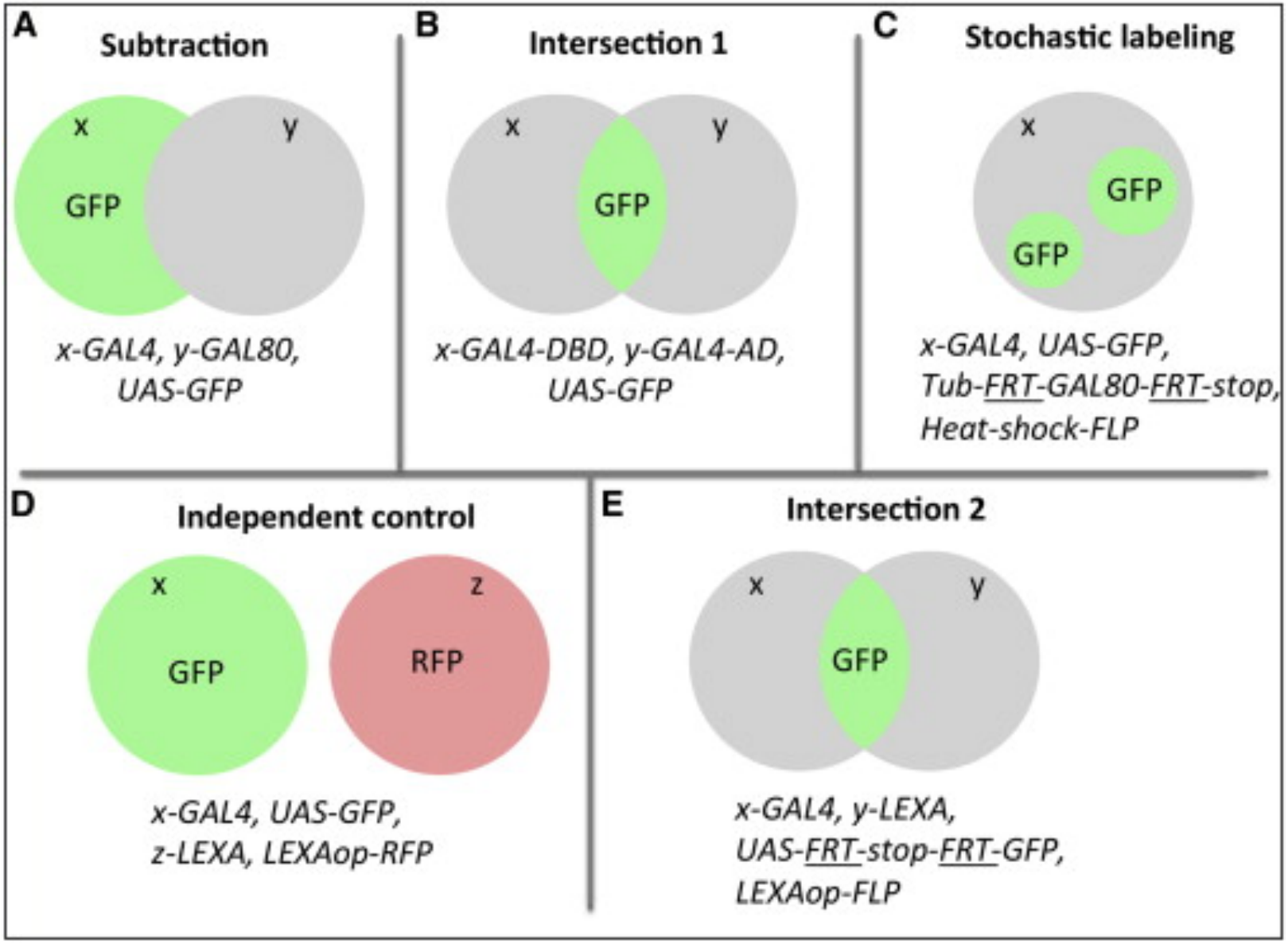
Split-GAL4 System

This technique enables detailed anatomical characterization:

- Membrane and synapse resolution
- Cell polarity determination

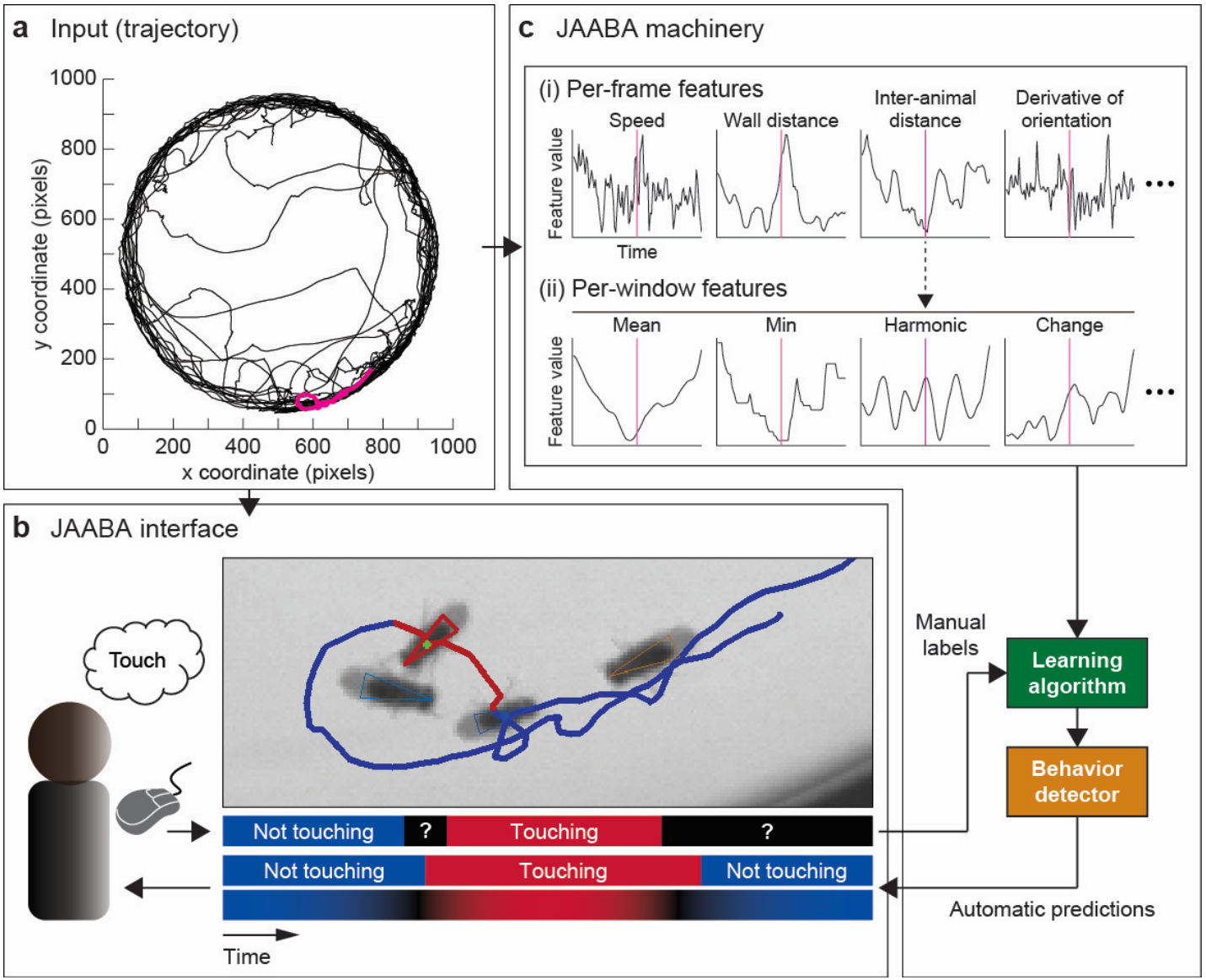
MCFO is Multi-Color Flp-Out, an alternative technique for refining patterns

Refining Gene Expression



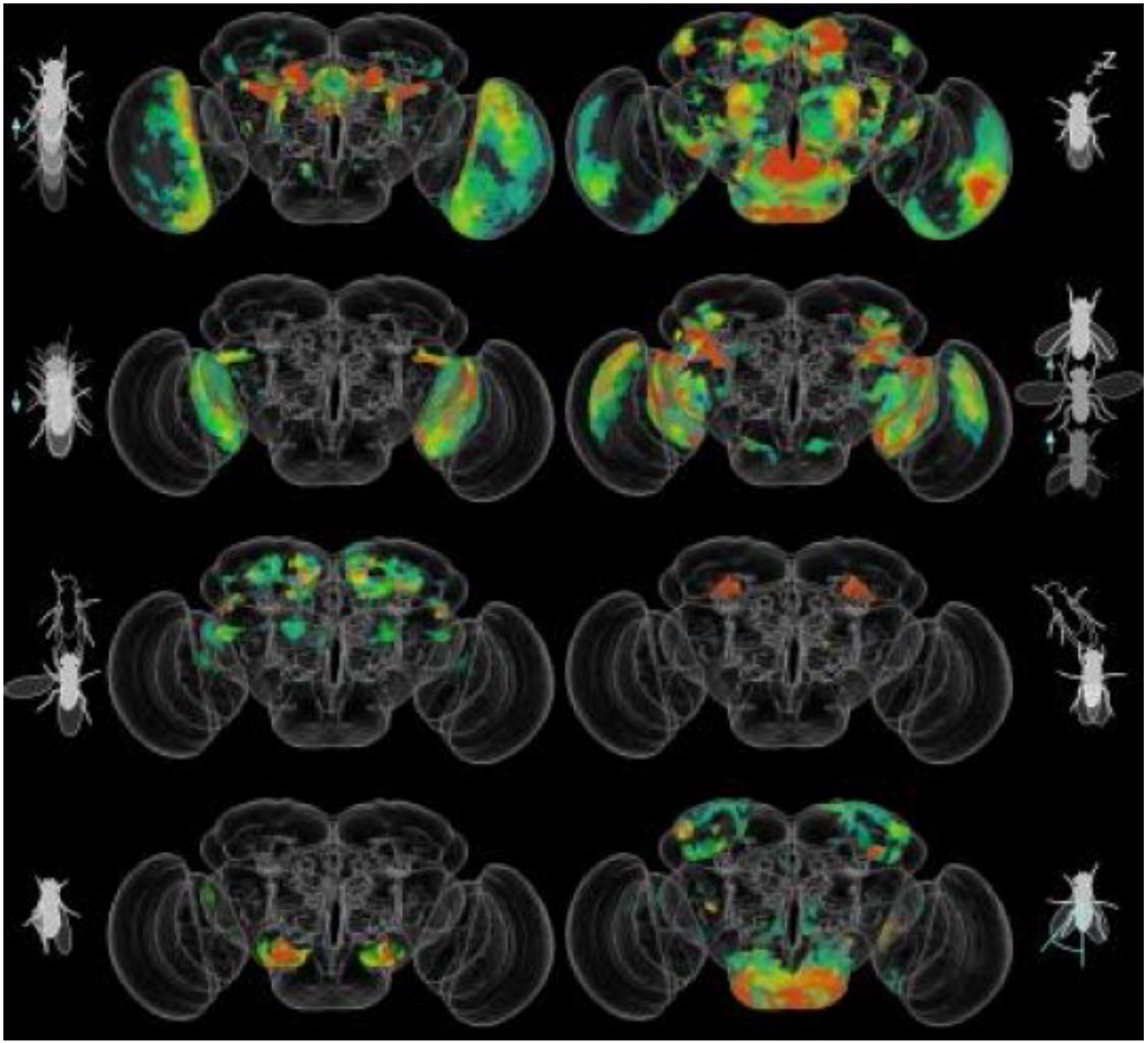
Behavioral Screen

Systematic inactivation or activation of neurons by optogenetics



JAABA: The Janelia Automatic Animal Behavior Annotator

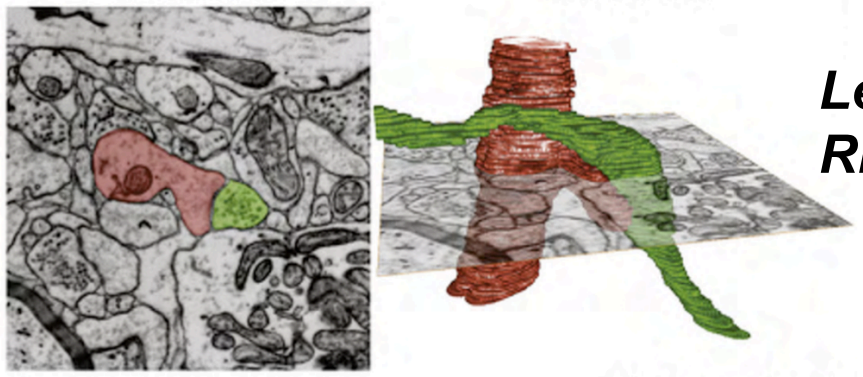
Thermogenetic Screen in *Drosophila melanogaster*



Show Copyrighted Video:
Robie et al., Cell 2017

Step 2: Identify additional functional neurons.

A. Continue to use systematic inactivation or activation
B. Identify connectivity of neuron of interest. See if activation or inactivation illustrate function.
    1. Use serial electron microscopy to trace cell processes



Left: 2-D Cross-Section
Right: 3-D Reconstruction

    2. Use a transgene to map connections (trans-synaptic virus)

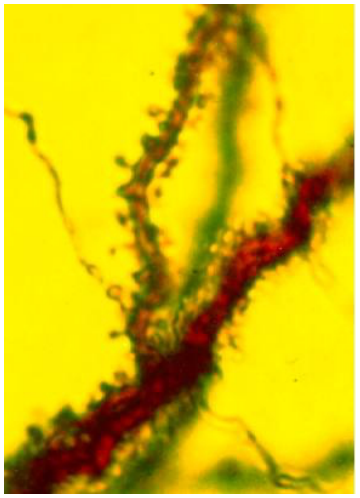
Caveat: This may not work. A functional connection may not act through an anatomical synapse. Instead, the circuit may rely on neuropeptides or hormones that are secreted and diffuse to the cells that they affect.

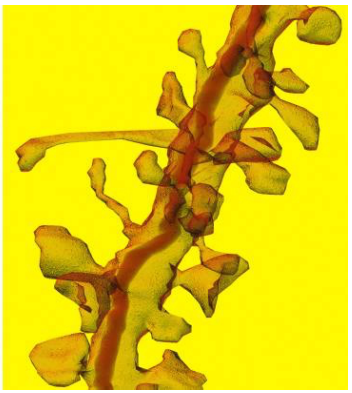
Tools for Anatomy

Anatomy provides information on the **structure and connectivity of the nervous system.**

Electron Microscopy	Light Microscopy
• Best technique for determining synaptic connectivity • High spatial resolution • *Caveat:* No ability to see changes over time as sample must be fixated.	• Simpler than EM • Can be done with dye injection or transgene (i.e. GFP) • If a pre-synaptic protein is tagged with GFP, then synapses can be visualized. • *Caveat:* No way to know what synapse is connected to.

Dendrite Morphology





Tools for Anatomy

Anatomy (connectomes) do not provide information about function:

Anatomy enables neuroscientists to generate hypotheses for circuit function.

Caveats:

- Even if two neurons synapse, it doesn't mean these two neurons **act together** to perform a function.
- Even if two neurons are **not** anatomically connected, it doesn't mean they're not **functionally connected.**
  - A form of non-synaptic signaling may exist, implying a chronic circuit (slower signal).

Even though the connectome for C. elegans was determined in 1970, its nervous system was not well understood for the reasons above.

- Researchers need to determine the **functional routes.**

Revealing the secrets of neuronal circuits with recombinant rabies virus technology

Melanie Ginger[1,2†], Matthias Haberl[1,2,3†], Karl-Klaus Conzelmann[4], Martin K. Schwarz[5] and Andreas Frick[1,2*]

Neurons are not all the same:

- Excitatory neurons make other cells electrically active
- Inhibitory neurons make other cells less electrically active

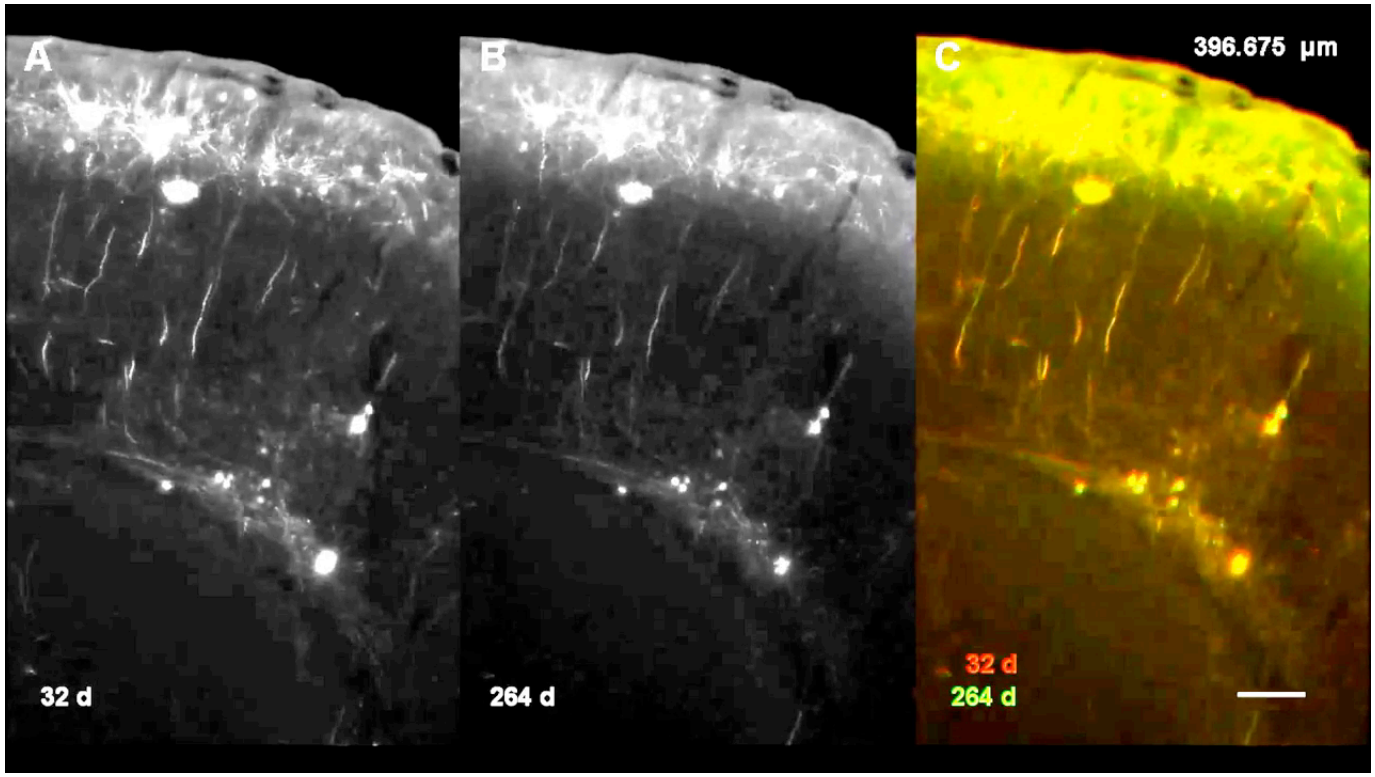
Neurons that fire together wire together:

- Each neuron is integrating incoming information from hundreds of excitatory and inhibitory neurons– the balance between these and their precise timing will determine if it is active enough to *fire* a signal to its own output neurons

To map neural connections in the brain:

- Rabies virus is used because it exclusively infects neurons efficiently
- Virus can spread from an infected neuron to other neurons connected to it

Step 2: Viral Tracing

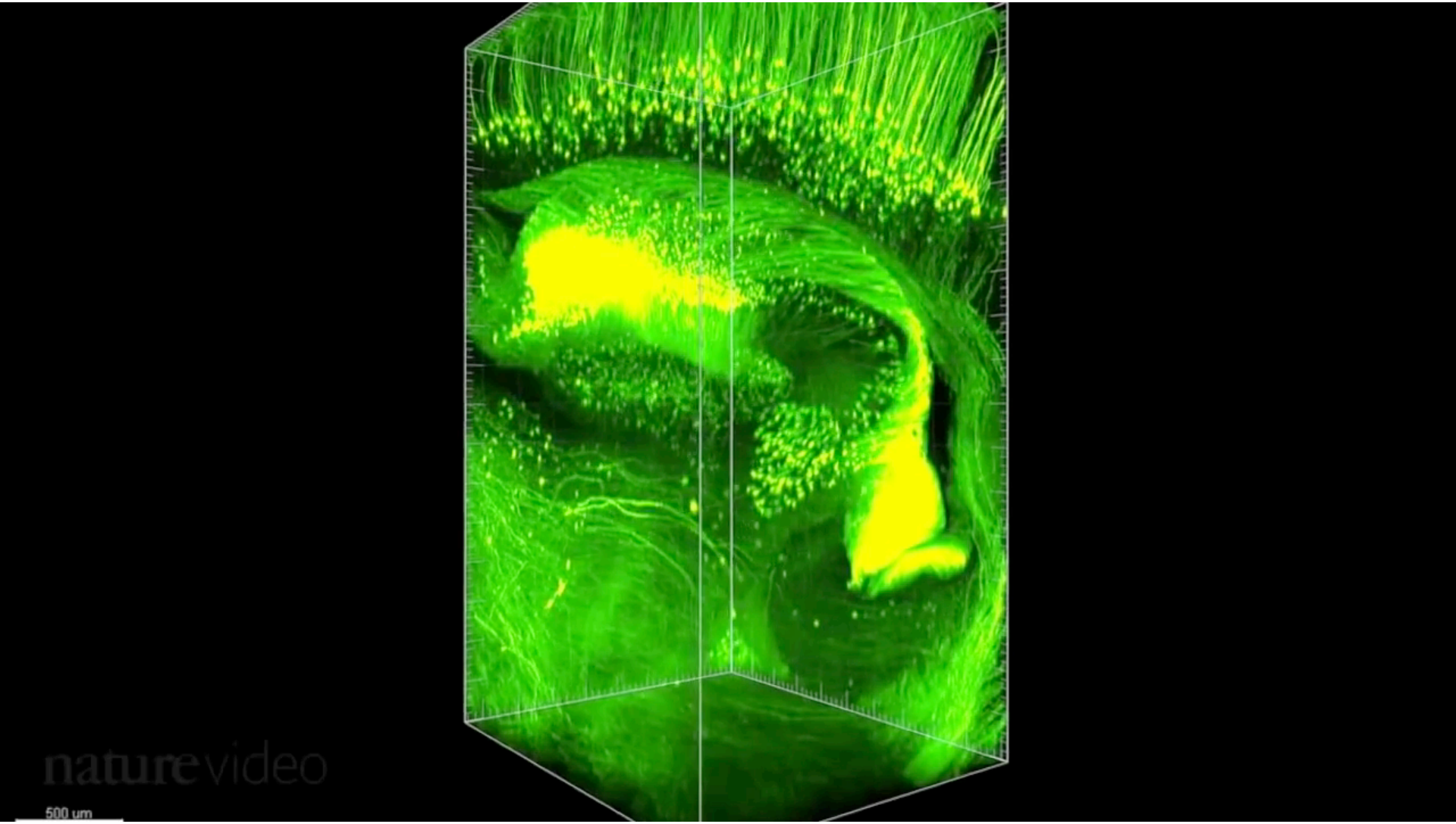


Anterograde Transport: tracer moves from soma to synapse, uses **kinesin** to move viruses along axon in anterograde direction

Retrograde Transport: tracer moves from synapse to soma, uses **dynein** to move viruses along axon in retrograde direction

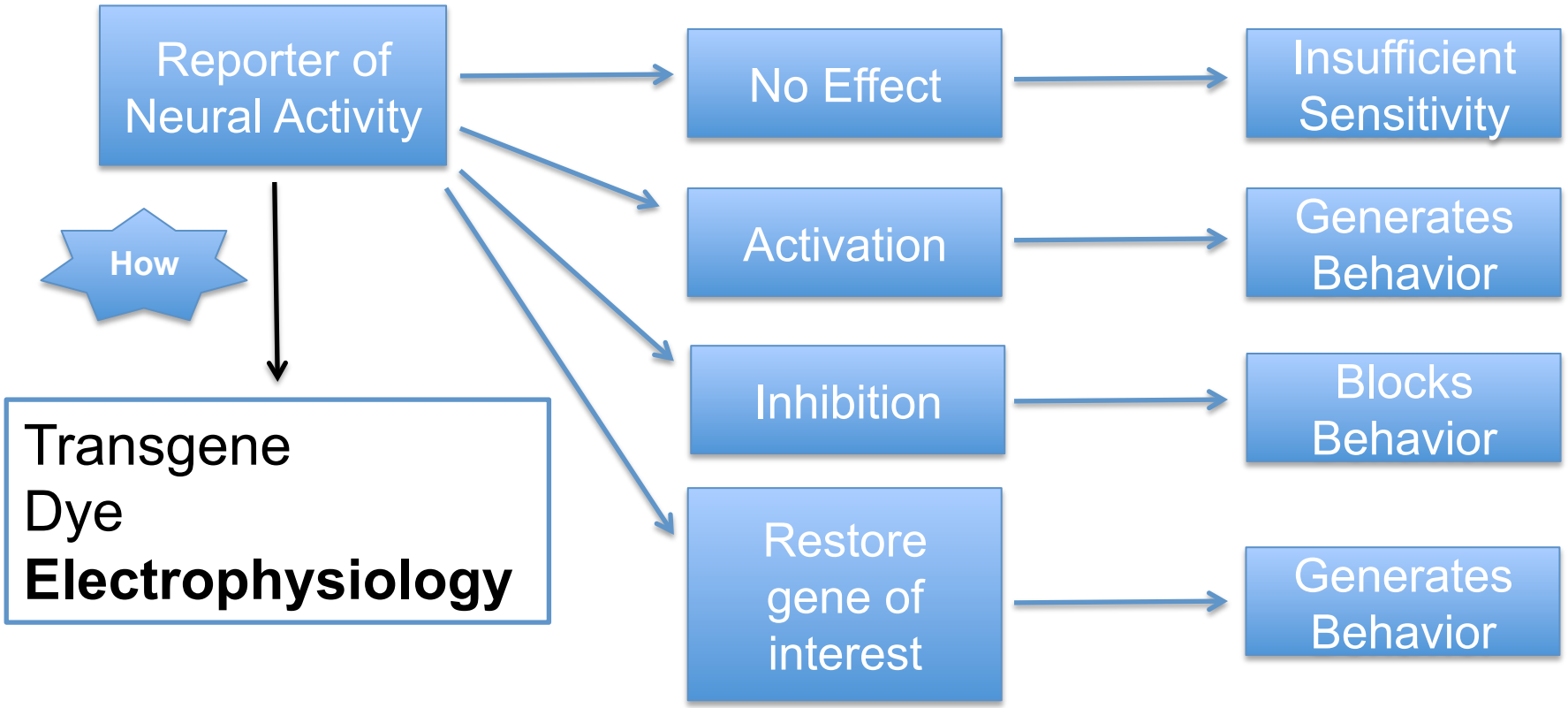
Dual Transport: combines above methods to determine both the inputs and outputs of neuronal circuitry

Step 2: CLARITY



Step 3: Confirm the role of identified neurons in generation of behavior

A. Use a reporter of neural activity in response to stimulus



Tools for Physiology

Physiology captures molecular signals that underlie neural circuit function:

Caveat:

- Not all neurons signal by action potentials (i.e. neurons in retina and non-spiking interneurons in invertebrates)

There are two ways to do recordings:

1. **Extracellular recording:** electrode outside neuron
2. **Intracellular recording:** electrode inside neuron

Paired Recording: technique in which one inserts electrodes into pre-synaptic neuron and post-synaptic neuron simultaneously

1. Inject de-polarizing current to activate pre-synaptic neuron.
2. Observe effect on post-synaptic neuron:
    - Excitatory synapse results in EPSP
    - Inhibitory synapse results in IPSP

Tools for Physiology

Paired Recordings

Caveats:

- Difficult in practice

Alternative: **ChR2-assisted circuit mapping**

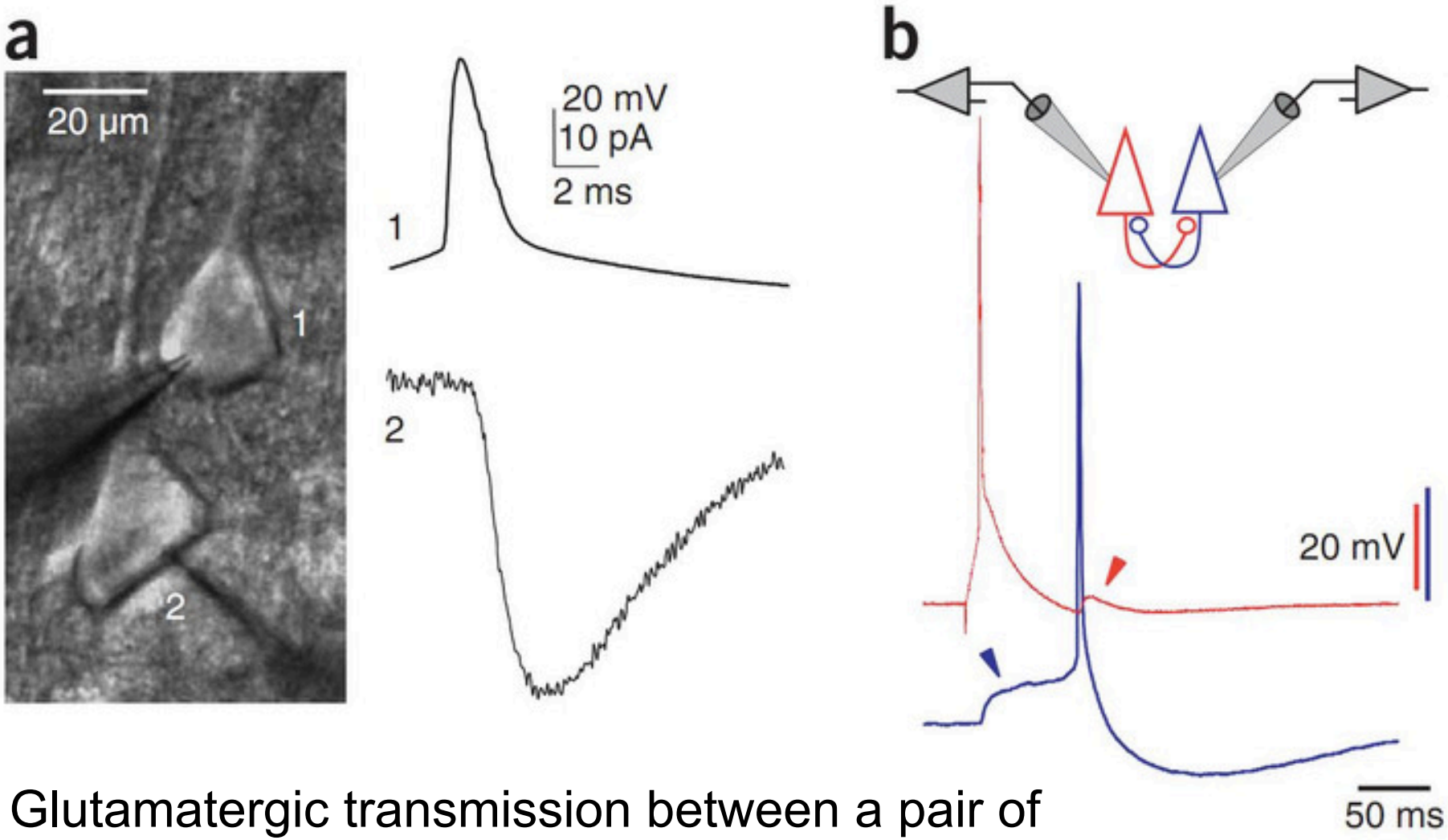
Pre-synaptic neuron is defined by ChR2 expression.
Post-synaptic neuron is defined by targeted patching.
ChR2 is transported into axons where it can transduce photo-stimulation into action potentials. This method provides a way to study long-range connections in brain slice preparations (axons can be stimulated even when severed from parent somata).

- Recordings are best done in awake, behaving animals but this is not possible because of movement

Alternative: **Fictive Behavior**

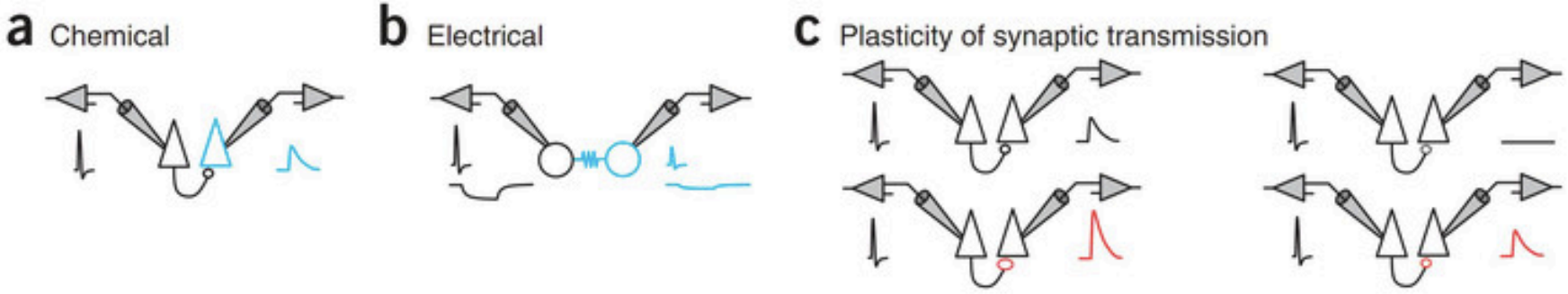
Nerve fibers that connect to muscle are cut (prevents motion) in live animals.

Step 3: Connectivity by Electrophysiology



Glutamatergic transmission between a pair of Layer V Pyramidal Neurons

Step 3: Overview of Electrophysiology



A. Chemical Synapse

Action potential (**black**) triggered in pre-synaptic neuron evokes an EPSP (**blue**) in post-synaptic neuron.

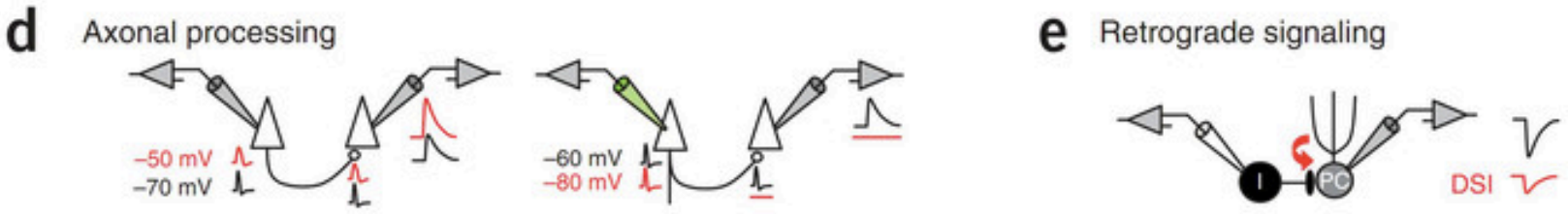
B. Electrical Synapse

Action potential (**black**) in first neuron produces attenuated voltage signals (**blue**) in second cell.

C. Plasticity of Synaptic Transmission

In control, pre-synaptic neuron evokes an EPSP in post-synaptic cell (left) or no response (right) in case of silent synapse. After **potentiation** (**red**), the efficacy of synaptic transmission is enhanced.

Step 3: Overview of Electrophysiology



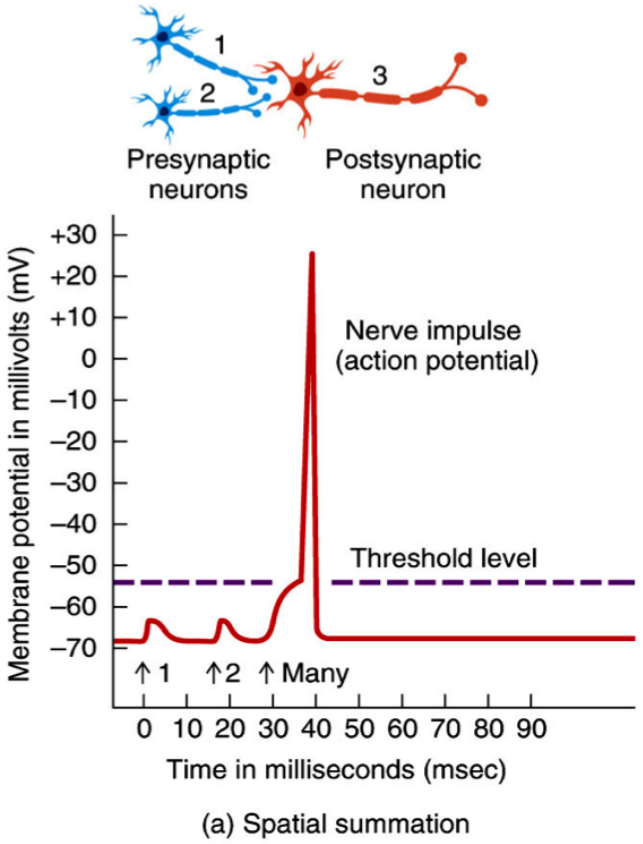
D. Axonal Processing

Pre-synaptic membrane potential-dependent axonal integration (left) and conduction failure (right).
Pre-synaptic spike fails to propagate in axon when it is evoked from a hyper-polarized potential (-80 mV).

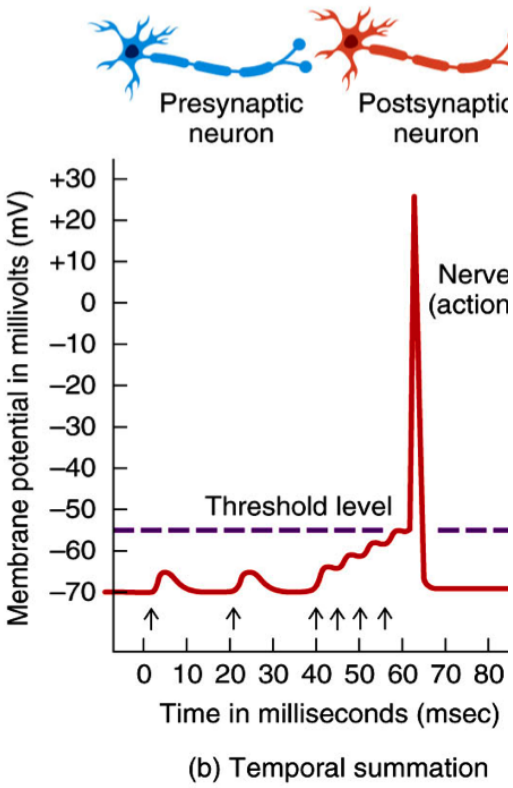
E. Retrograde Signaling

Retrograde signaling established between an interneuron (I) and a Purkinje cell (PC).
Depolarization-Induced Suppression (DSI) of inhibition. Red arrow indicates the release of endocannabinoids from PC to pre-synaptic terminal of interneuron.

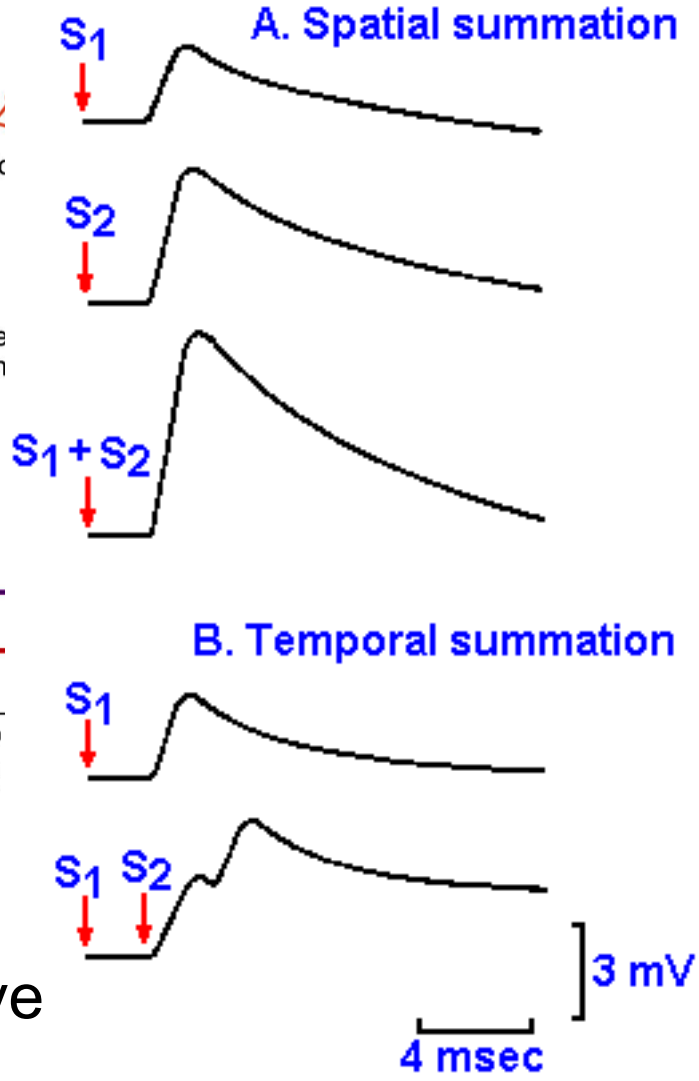
Summation



(a) Spatial summation



(b) Temporal summation



Spatial Summation:
Occurs when post-synaptic potentials arrive near same location

Temporal Summation:
Occurs when post-synaptic potentials arrive near same time

Test Your Understanding

The process by which a neuron summates synaptic excitation and inhibition is called:

A. Plasticity
B. Integration
C. Convergence
D. Pulse Frequency Modulation
E. Dis-inhibition

In the nervous system, the strength of the stimulus is coded into:

A. Frequency of Action Potentials Generated
B. Amplitude of Action Potentials Generated
C. Both Frequency and Amplitude of Action Potentials Generated

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Tools for Imaging

Paired Recordings

Disadvantages:

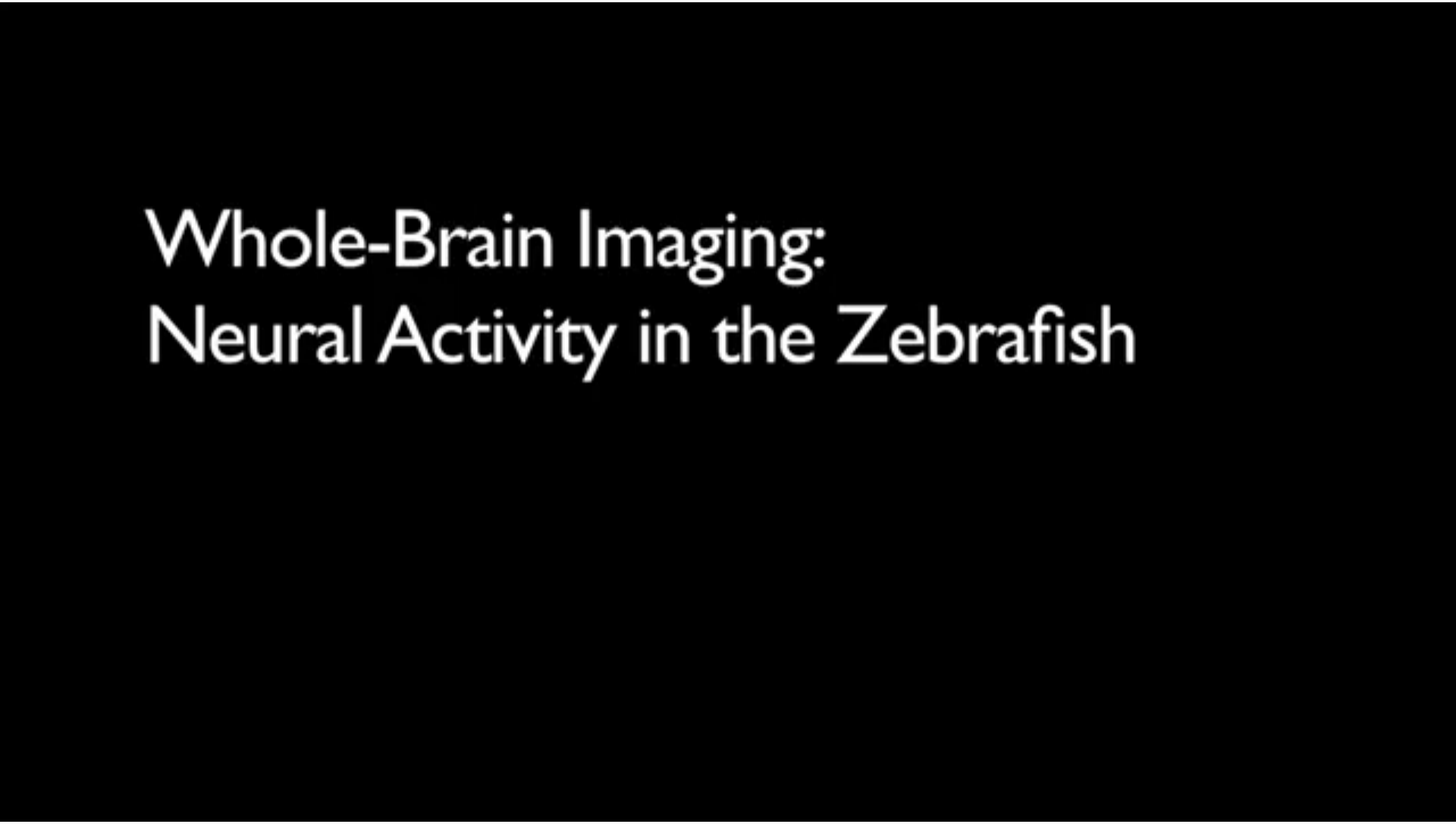
- Can only measure electrical signals
- Lacks spatial resolution (difficulty in localizing current)
- Low through-put (takes time to set up recording and can only do small number of neurons at once)

Physiology provides temporal resolution and anatomy provides spatial resolution.

Imaging Techniques

- **Calcium Sensors**
  GCaMP is used to monitor calcium activity of many neurons at once.
- **Voltage Sensors**
  Voltage sensors change fluorescence intensity in response to changes in voltage across the membrane.

Neural Activity Imaging



Step 4: Organize Neurons by Epistasis Analysis

A. Inactivate a pair of neurons together and observe whether the behavioral defect is enhanced.

1. If enhanced, neurons likely function in parallel.
2. If not enhanced, neurons function in series.

B. Activate a pair of neurons together and observe if behavior is enhanced over a single activation.

1. If enhanced, neurons likely function in parallel.
2. If not enhanced, neurons likely function in series.

C. Activate neuron X and see if neuron Y responds.

1. If it does, neuron Y is downstream of X.
2. If it does not, neuron Y is upstream of or in parallel with X.

D. Activate neuron Y and see if neuron X responds.

1. If it does, neuron Y is upstream of or in parallel with X.
2. If it does not, neuron Y is downstream of X.

Inactivation experiments show necessity.
Activation expressions show sufficiency.

Inactivation Experiments

To show a neuron is *necessary* for a behavior, one needs to illustrate that the loss of that neuron results in *partial or complete loss of behavior*.

Techniques

A. Laser Ablation
B. Synaptic Silencing
   - Transgenic method where protein blocks chemical synaptic transmission in neuron
     (i.e. tetanus toxin, genetic mutants)
   - If synaptic silencing doesn't result in loss of behavior, neuron may receive input directly from environment or gap junctions.
C. Electrical Silencing
   - Hyper-polarize the neuron through current injection
   - Halo-rhodopsin and Archae-rhodopsin (Arch)

Activation Experiments

In some cases, inactivation won't show any effect because there is *redundancy* in the circuit. An activation experiment will overcome this problem.

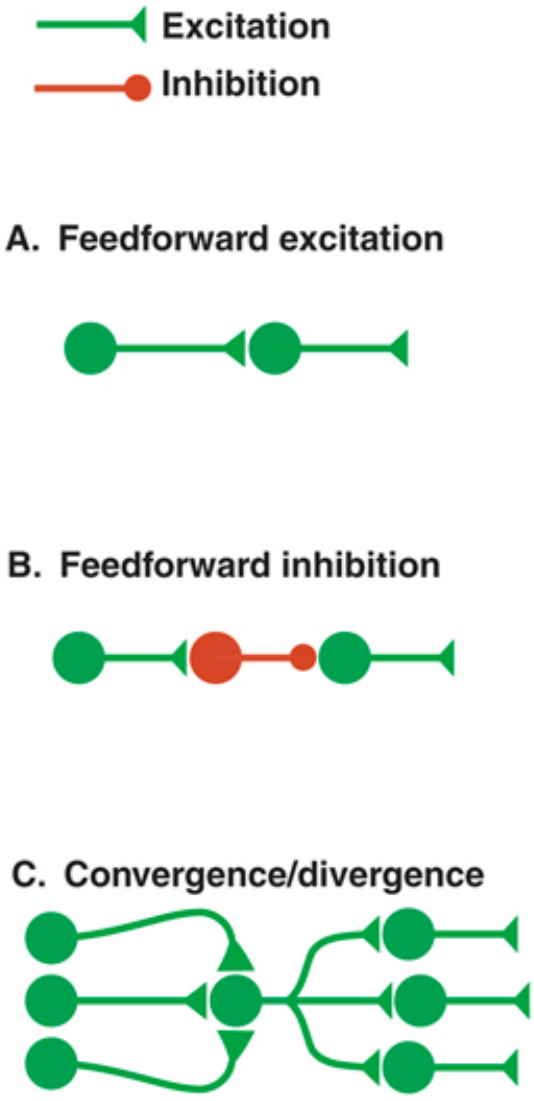
Techniques

A. Restore genetic function in neuron
   - Rescue experiment (i.e. NT synthesis)

B. Electrical Activation
   - De-polarize the neuron through current injection
   - Channel-rhodopsin 2 (ChR2)

If both activation and inactivation experiments are done and result in the expected effect on behavior, ***and*** *a physiological response is observed, it is reasonable to conclude that neuron of interest acts in neural circuit.*

Neural Circuit Motifs



A. Feed-forward Excitation

Allows one neuron to relay information to its neighbor. Long chains of these can be used to propagate information through the nervous system

B. Feed-forward Inhibition

A pre-synaptic cell excited an inhibitory interneuron, which then inhibits the next follower cell. This is a way of limiting excitation.

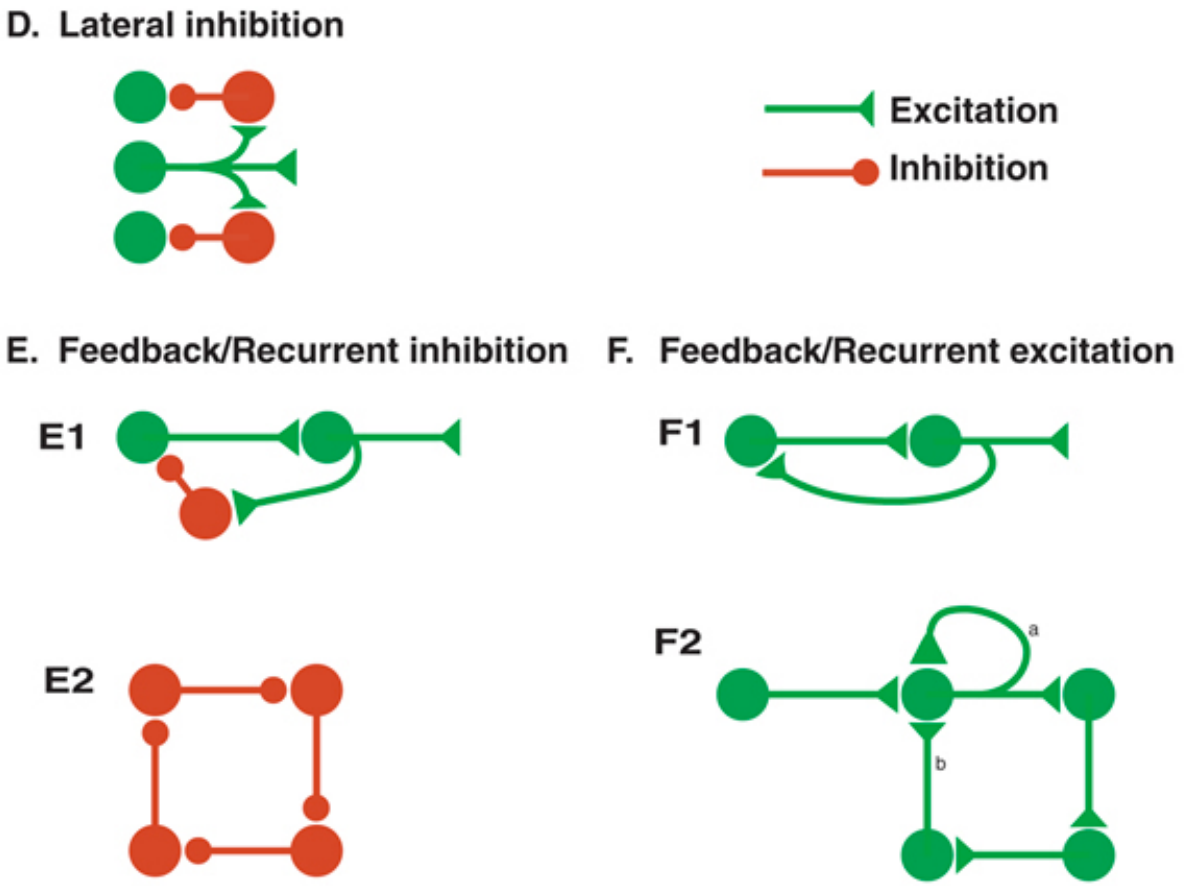
C. Convergence/ Divergence

One post-synaptic cell receives convergent input from a number of different pre-synaptic cells and any individual neuron can make divergent connections to different post-synaptic cells.

Divergence *allows one neuron to communicate with many neurons in a network.*

Convergence *allows a neuron to receive input from many neurons in a network.*

Neural Circuit Motifs



D. Lateral Inhibition
A pre-synaptic cell excites inhibitory interneurons, which inhibit neighboring cells in the network.

E. Feedback/ Recurrent Inhibition

F. Feedback/ Recurrent Excitation

Test Your Understanding

This term best represents a neural circuit where one pre-synaptic neuron synapses with several post-synaptic neurons in order to amplify a sensory signal:

A. Feed-Forward Excitation
B. Convergence
C. Divergence
D. Lateral Inhibition

Test Your Understanding

This term best represents a neural circuit where one pre-synaptic neuron synapses with several post-synaptic neurons in order to amplify a sensory signal:

A. Feed-Forward Excitation
B. Convergence
C. Divergence
D. Lateral Inhibition

Explanation:

Diverging circuits allows one neuron to communicate with many neurons (i.e. skeletal muscle contractions). On the other hand, converging circuits allows one neuron to receive many inputs (i.e. spinal cord to brain).

Properties of Neural Circuits

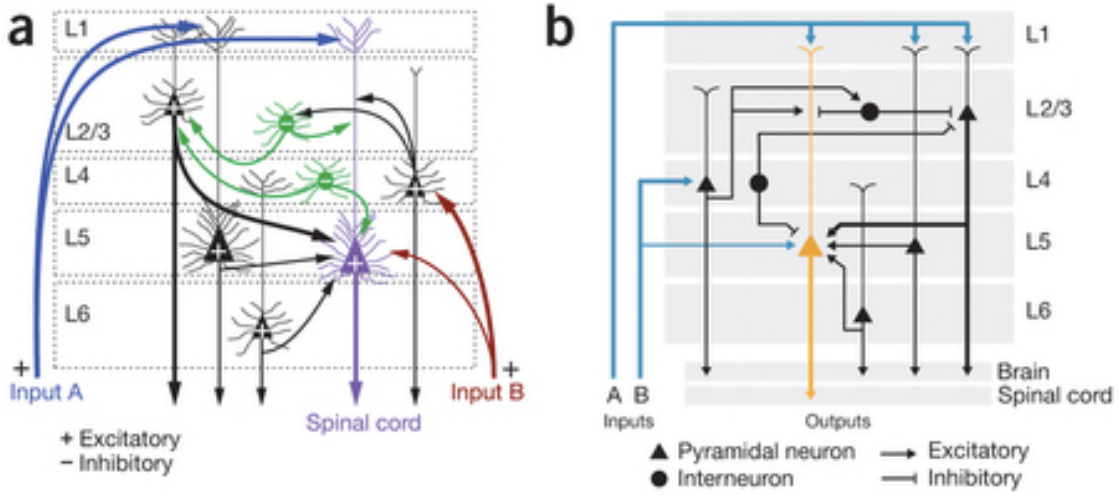
1. Feedback
2. Degeneracy
3. Competition
4. Modularity

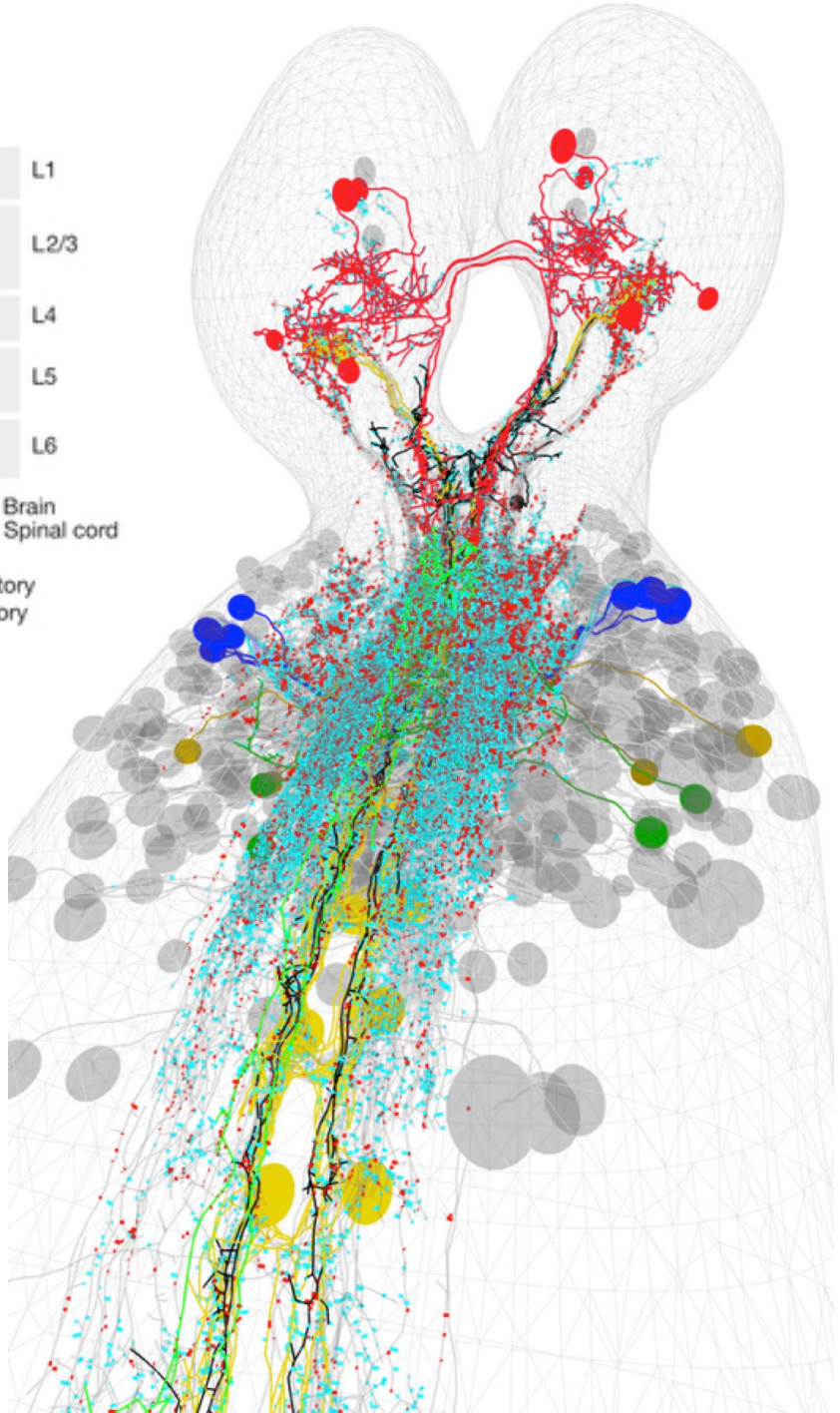
Degeneracy: the ability of multiple different configurations or mechanisms to produce the same outcome or serve the same function

Competition: small-scale axon elimination during development of nervous system

Modularity: permits an organism to process a new input without evolving an entirely novel circuit from scratch (i.e. building diverse objects using existing building-blocks)

Step 5: Circuit is Complete





Multi-Sensory Circuits

Case Study:

A dimorphic pheromone circuit in *Drosophila* from sensory input to descending output

Vanessa Ruta, Sandeep Robert Datta, Maria Luisa Vasconcelos, Jessica Freeland, Loren L. Looger & Richard Axel

Abstract

Drosophila show innate olfactory-driven behaviours that are observed in naive animals without previous learning or experience, suggesting that the neural circuits that mediate these behaviours are genetically programmed. Despite the numerical simplicity of the fly nervous system, features of the anatomical organization of the fly brain often confound the delineation of these circuits. Here we identify a neural circuit responsive to cVA, a pheromone that elicits sexually dimorphic behaviours[1–4]. We have combined neural tracing using an improved photoactivatable green fluorescent protein (PA-GFP) with electrophysiology, optical imaging and laser-mediated microlesioning to map this circuit from the activation of sensory neurons in the antennae to the excitation of descending neurons in the ventral nerve cord. This circuit is concise and minimally comprises four neurons, connected by three synapses. Three of these neurons are overtly dimorphic and identify a male-specific neuropil that integrates inputs from multiple sensory systems and sends outputs to the ventral nerve cord. This neural pathway suggests a means by which a single pheromone can elicit different behaviours in the two sexes.

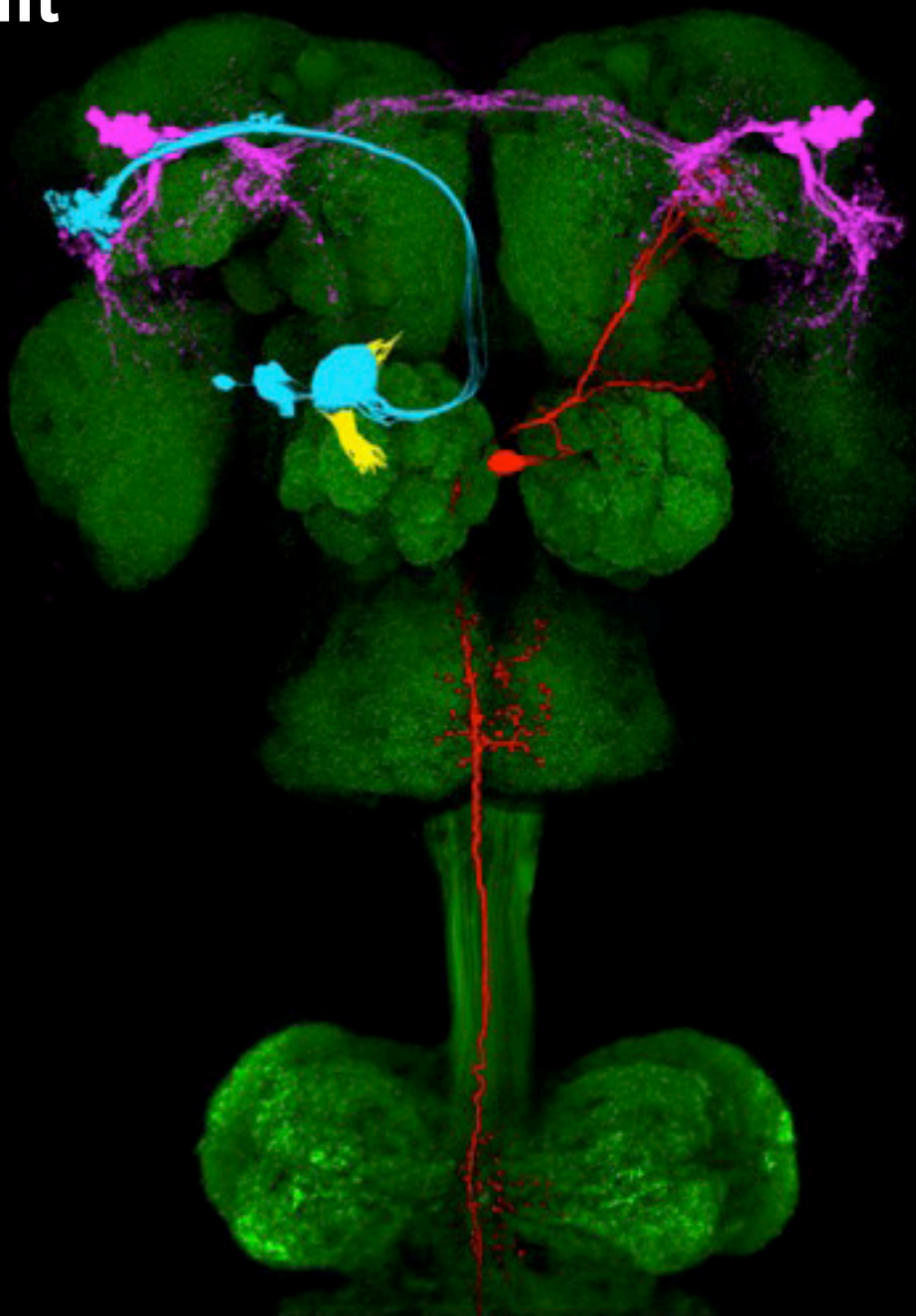
Neural Circuit

DC1 Glomeruli Sensory Neuron

DA1 Projection Neuron

Olfactory Receptor Neuron (ORN)

DN1 Descending Motor Neuron



Ruta, V. et al. 2010 Nature

Neural Circuits of Sleep

Prominent Computational Neuroscientists:
Gyorgy Buzsaki, NYU
Terry Sejnowski, UCSD
Roger Traub, IBM

What is the biological function of sleep?
Why do we dream?
What are the underlying brain mechanisms?
What is its relation to anesthesia?

Biological Rhythms

Rhythms are ubiquitous in the mammalian CNS and span a broad range of frequencies.

Brains have evolved a variety of systems for rhythmic control:

- Waking and sleeping
- Cardiac rhythm
- Breathing cycle

Sleep

Sleep is not a single state, but a complex set of brain processes that supports many physiological needs.

- Sleep deprivation affects attention
- Tasks that require more attention drive sleep need and sleep intensity
    - *Could sleep and attention have coevolved as brain states that regulate each other?*
- Does sleep require a brain?

Current Biology

CellPress

Available online 21 September 2017

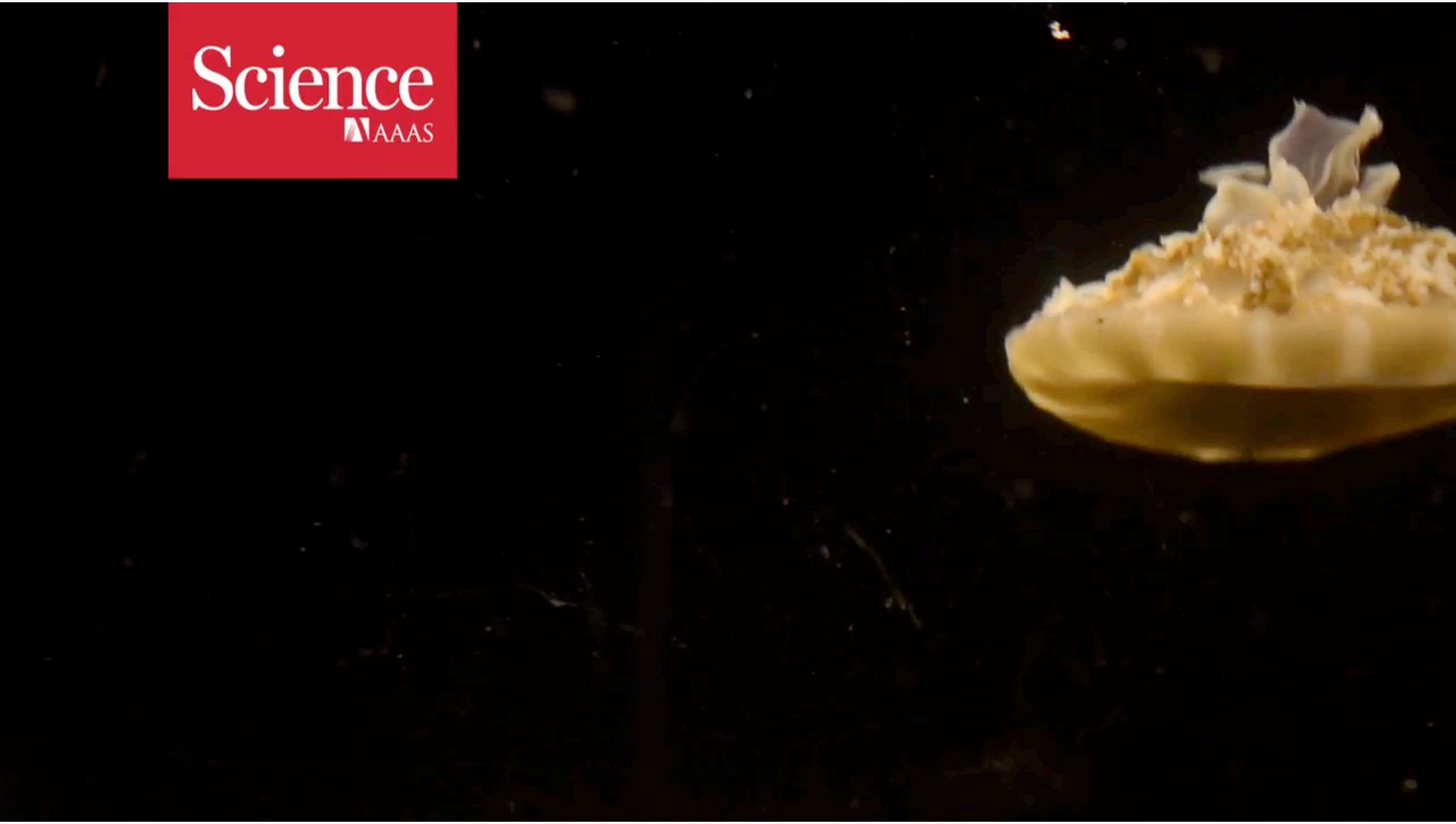
In Press, Corrected Proof — Note to users

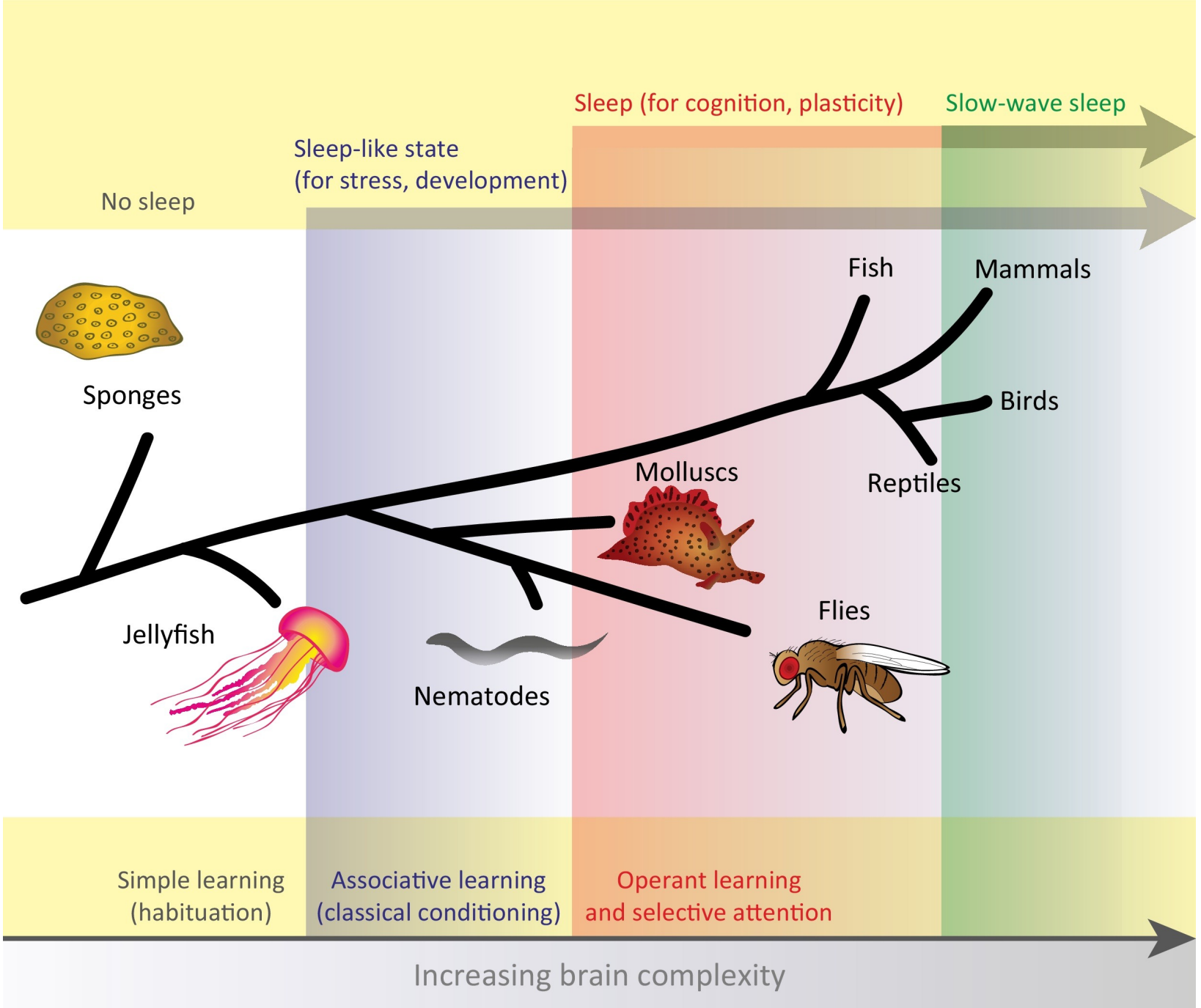
Report

The Jellyfish *Cassiopea* Exhibits a Sleep-like State

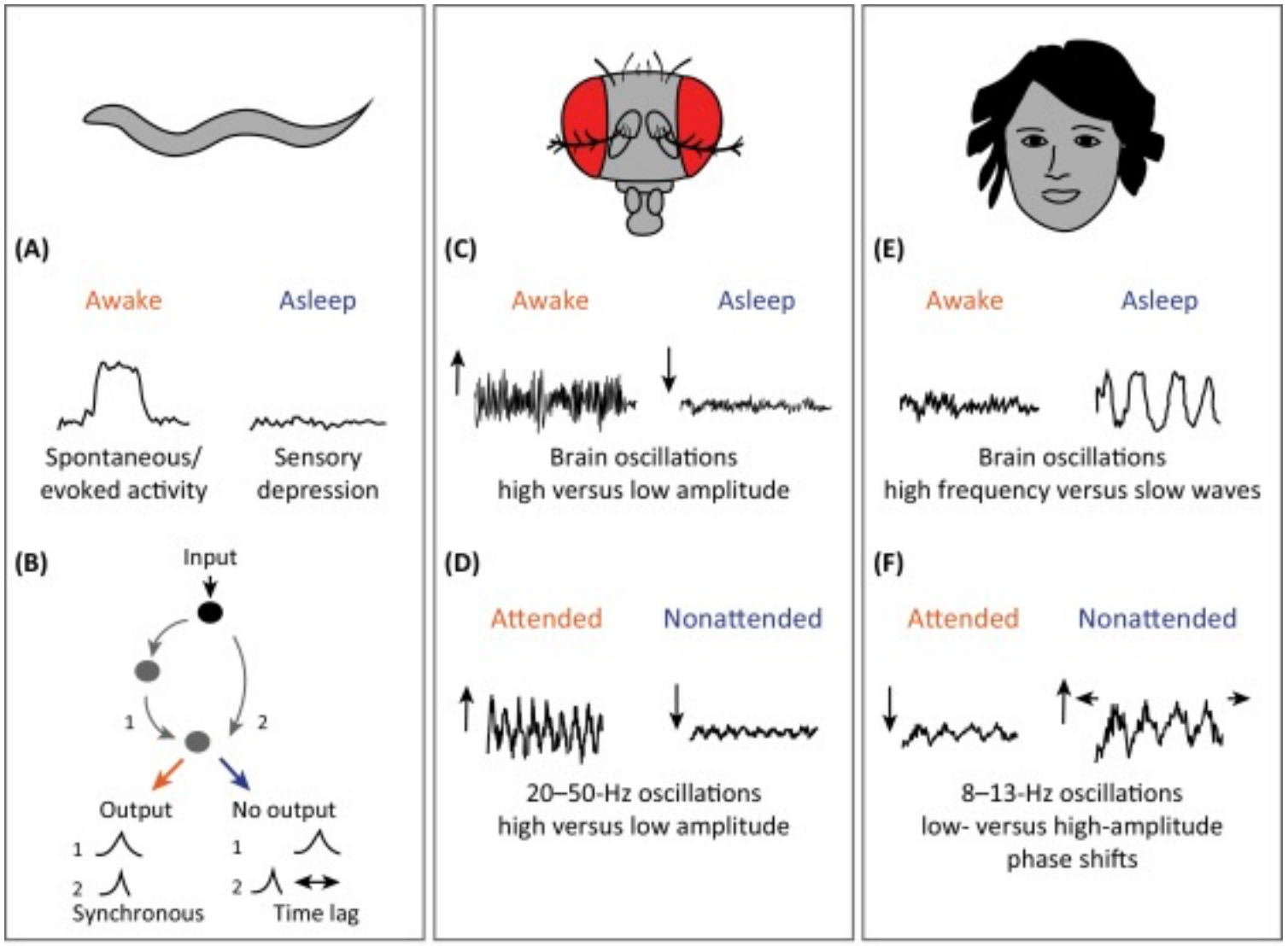
Ravi D. Nath[1, 2, 3], Claire N. Bedbrook[1, 3], Michael J. Abrams[1, 3], Ty Basinger[1], Justin S. Bois[1], David A. Prober[1], Paul W. Sternberg[1, 2], Viviana Gradinaru[1], Lea Goentoro[1, 4],

Do Jellyfish Sleep?




Sleep (for cognition, plasticity)
Slow-wave sleep
Sleep-like state
(for stress, development)
No sleep
Fish
Mammals
Sponges
Birds
Molluscs
Reptiles
Flies
Jellyfish
Nematodes
Simple learning
(habituation)
Associative learning
(classical conditioning)
Operant learning
and selective attention
Increasing brain complexity

Sleep

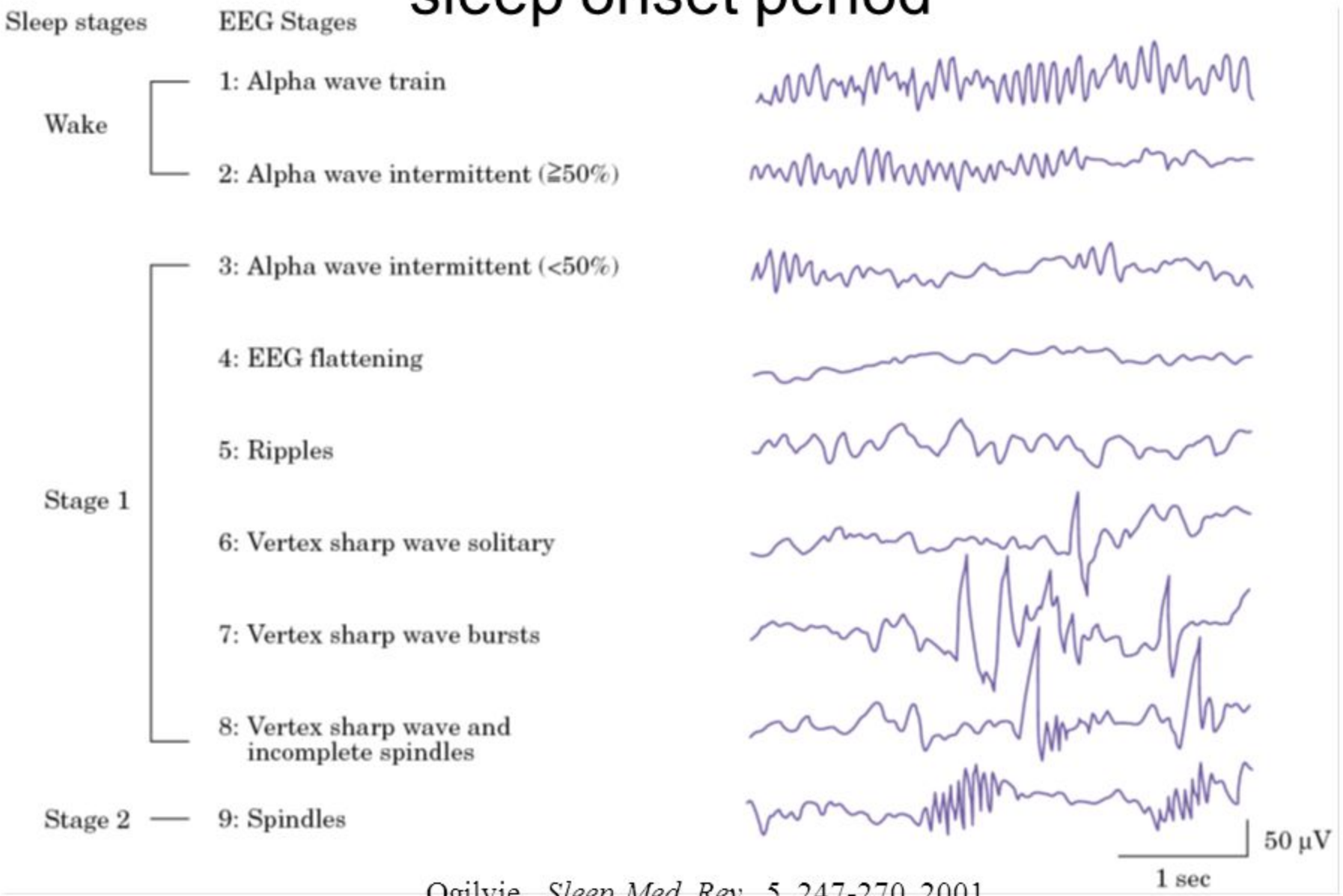


Trends in Neurosciences

Brain rhythms

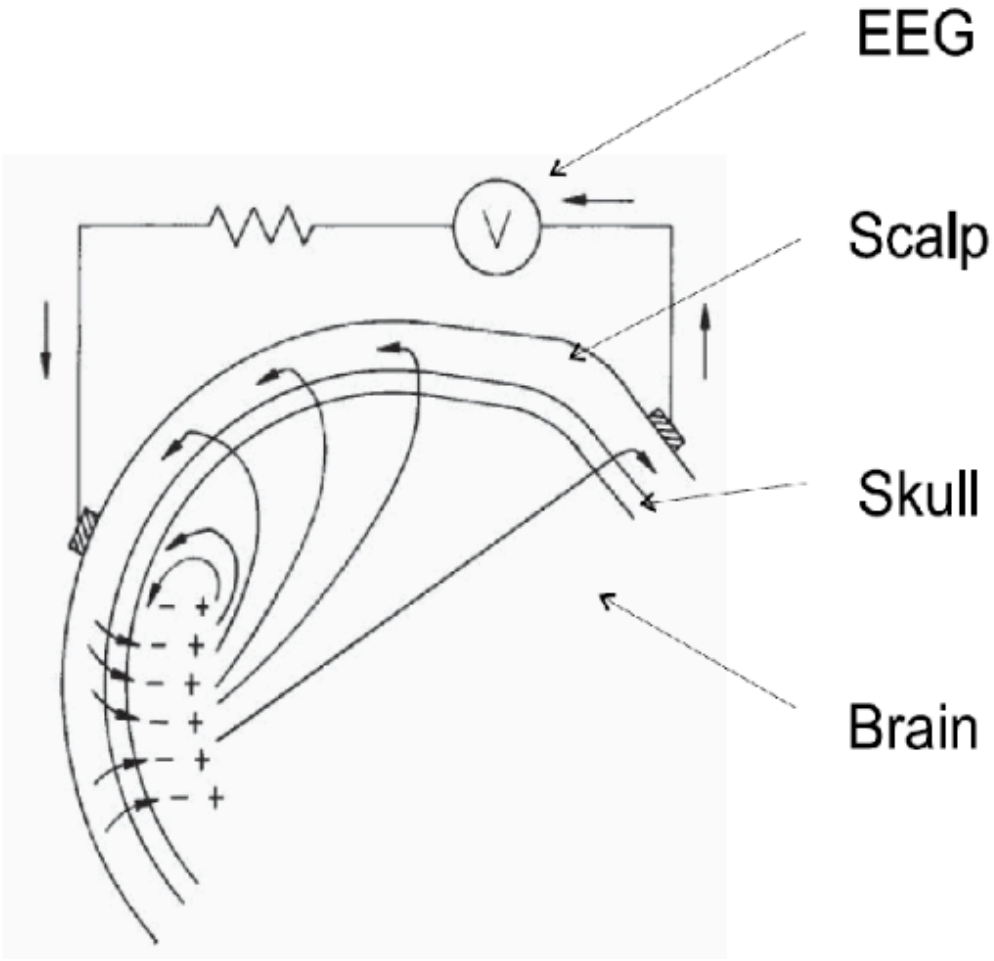
- **Alpha rhythm** (8-13 Hz) appears at the occipital cortex when eyes close. [resting condition] {rolandic mu rhythm; temporal tau rhythm}
- **Beta rhythm** (13-30 Hz) is associated with alertness.
- **Gamma rhythm** (30-80 Hz) is related to sensory integration and feature binding.
- **Theta rhythm** (4-8 or 4-10 Hz)
- **Delta rhythm** (0.5-4 or 1-4 Hz)
- **Sleep spindle** (12-15 Hz or 7-15 Hz) {sigma rhythm}
- **K complex** (<0.5 Hz) {(very) slow oscillation}

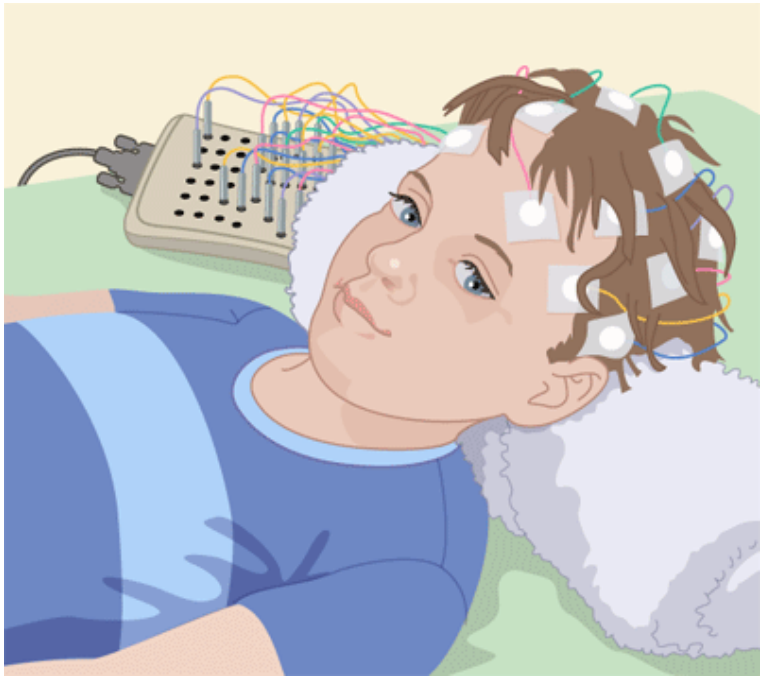
Successive EEG changes throughout the sleep onset period



Ogilvie, *Sleep Med. Rev.*, 5, 247-270, 2001.

Electroenchaplography (EEG)



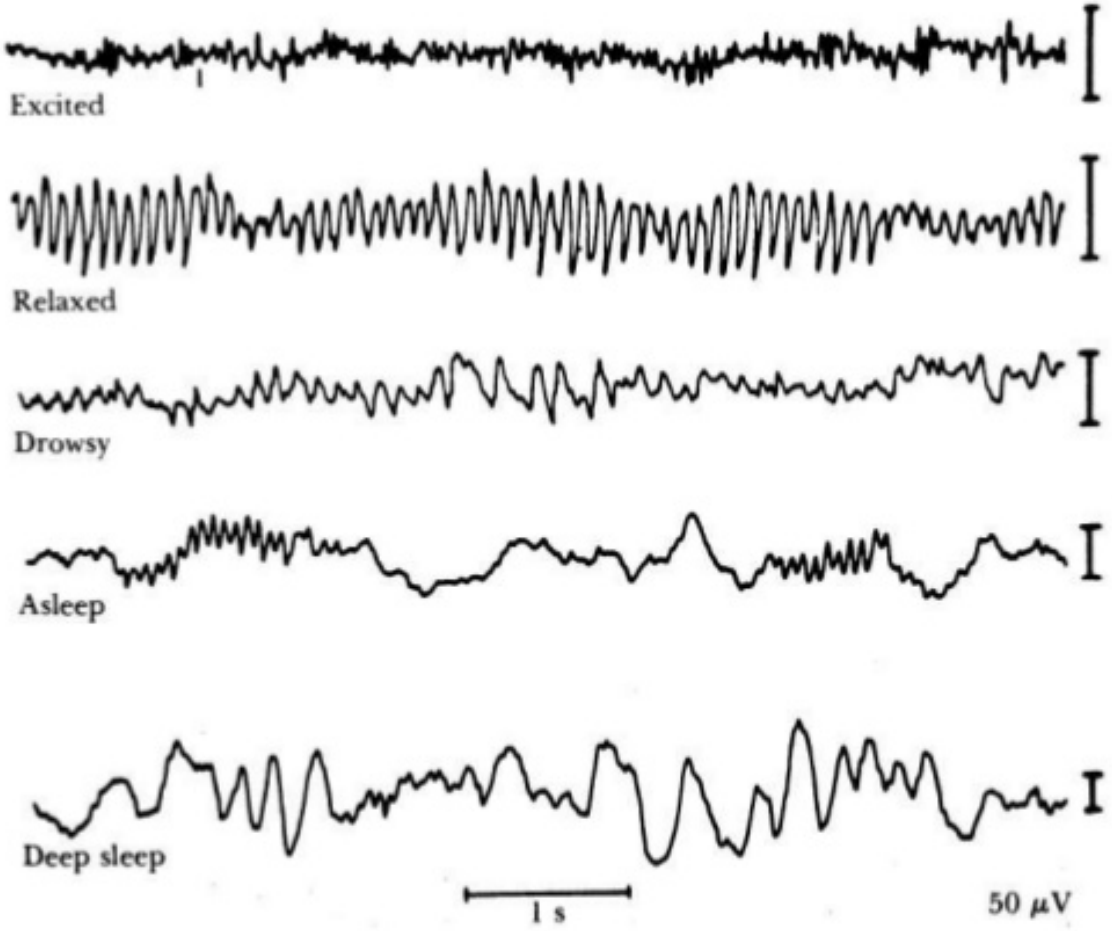


Current in the EEG measuring circuit depends on the nature and location of the current sources, on the electrical properties of the brain, skull and scalp and on location of both electrodes. *Source: Nunez et al (1891)*

Electroenchaplography (EEG)

EEG is an electrophysiological monitoring method to record electrical activity of the brain:

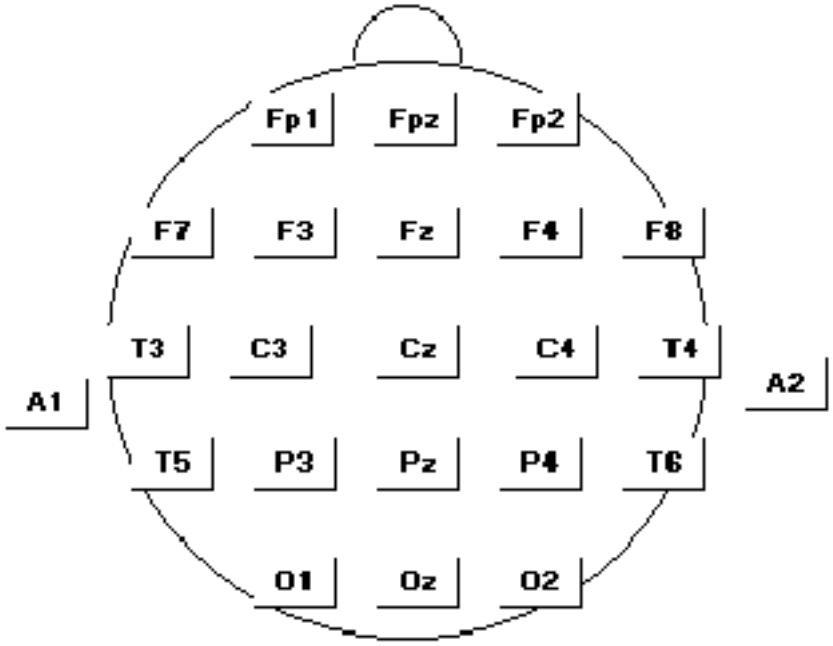
- Often non-invasive
- Measures voltage fluctuations resulting from ionic current within neurons
- Used to diagnose epilepsy
- Limited spatial resolution
- Temporal resolution at millisecond scale



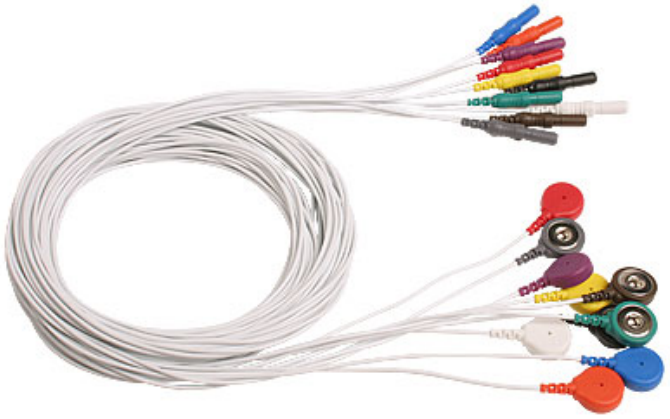
Electrodes

Electrodes are small metal discs that are places on the scalp in special positions.

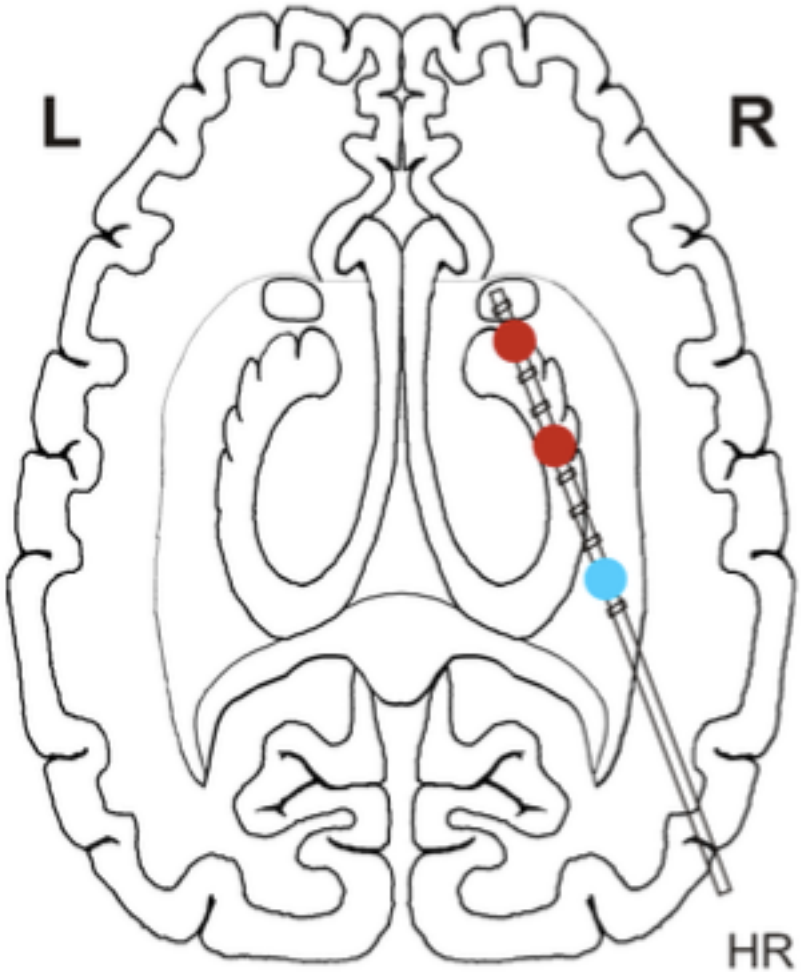
- Each electrode site is labeled with a letter and a number
- Letter: F is frontal lobe and T is temporal lobe
- Number: Even number means right side of head and odd number means left side of head
- Can be made of: stainless steel, tin, gold or silver covered with a silver chloride coating



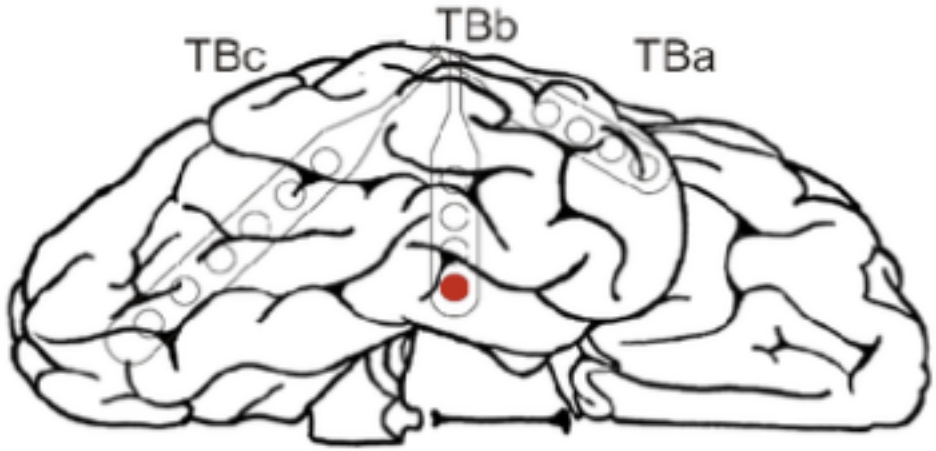
10/20 System of electrode placement



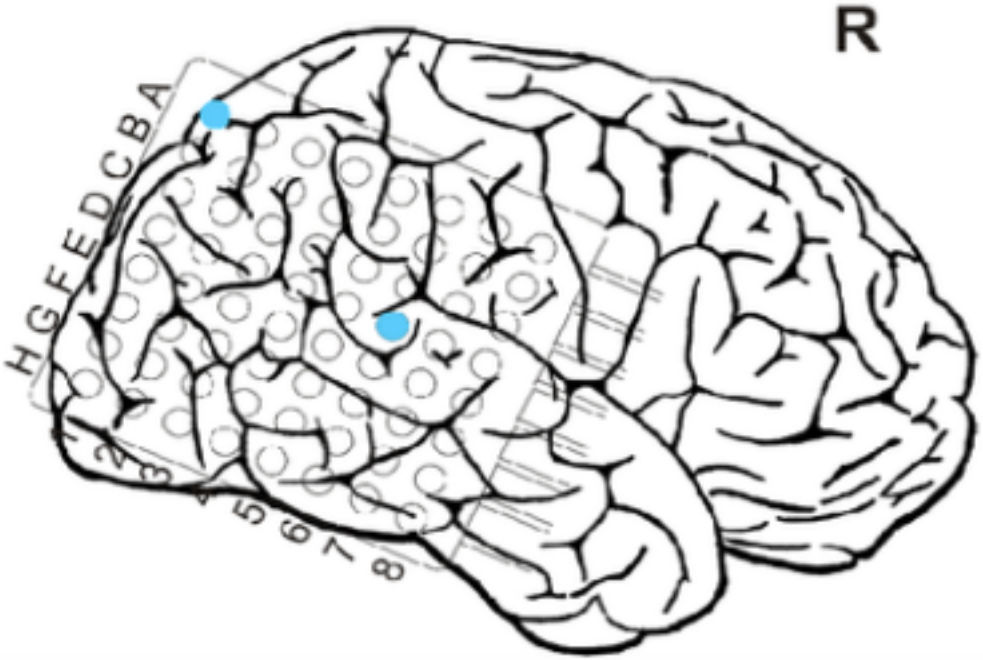
Intra(cranial/cerebral) EEG



Depth electrodes



Strip electrodes



Grid electrodes

Test Your Understanding:

EEG activity is thought to arise from which of the following?

A. Cortical layers I and VI
B. Axonal action potentials
C. Horizontal dipoles
D. Excitatory and inhibitory post-synaptic potentials

Test Your Understanding:

EEG activity is thought to arise from which of the following?

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B. Axonal action potentials
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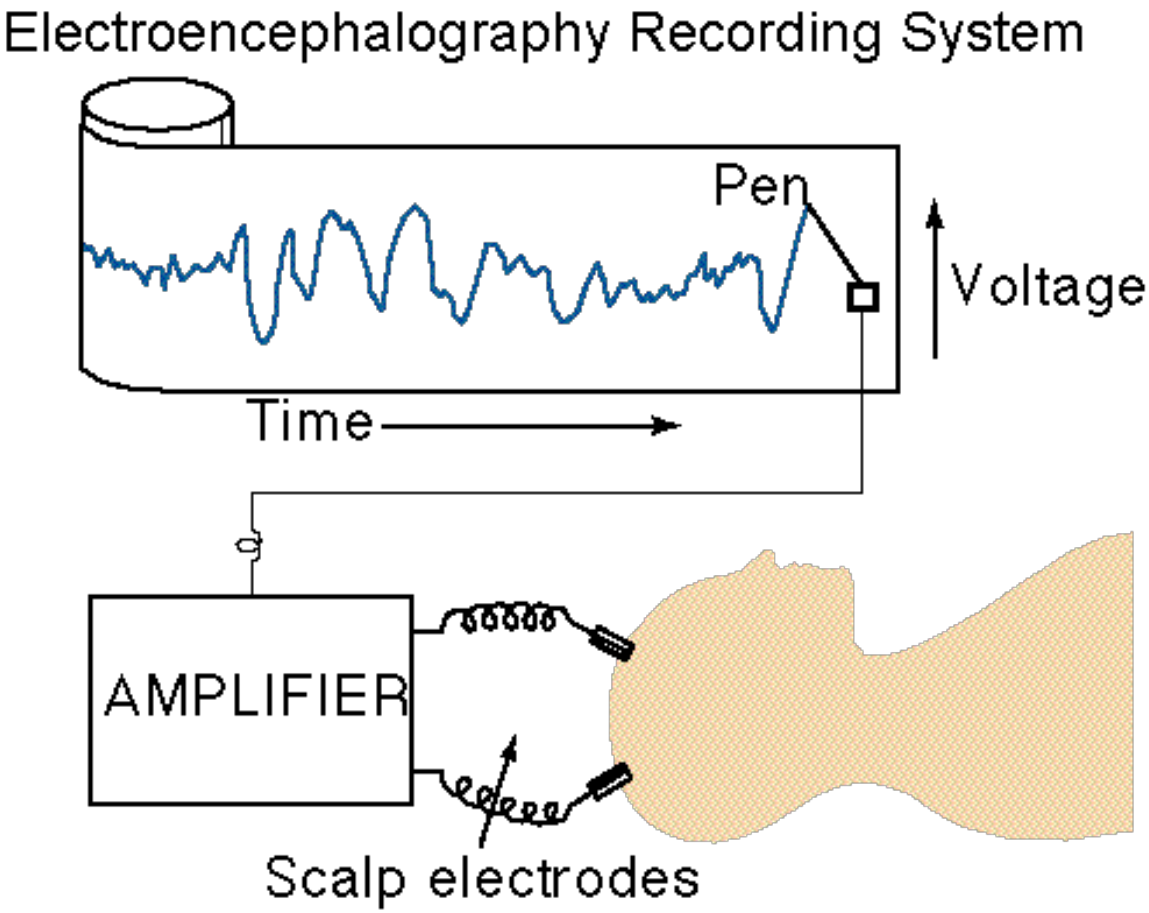
Explanation: EEG activity arises from the outermost cortex layer I and does not directly capture axonal action potentials. EEG is most sensitive to post-synaptic potentials generated in the superficial layers of the cortex.

EEG Instrumentation

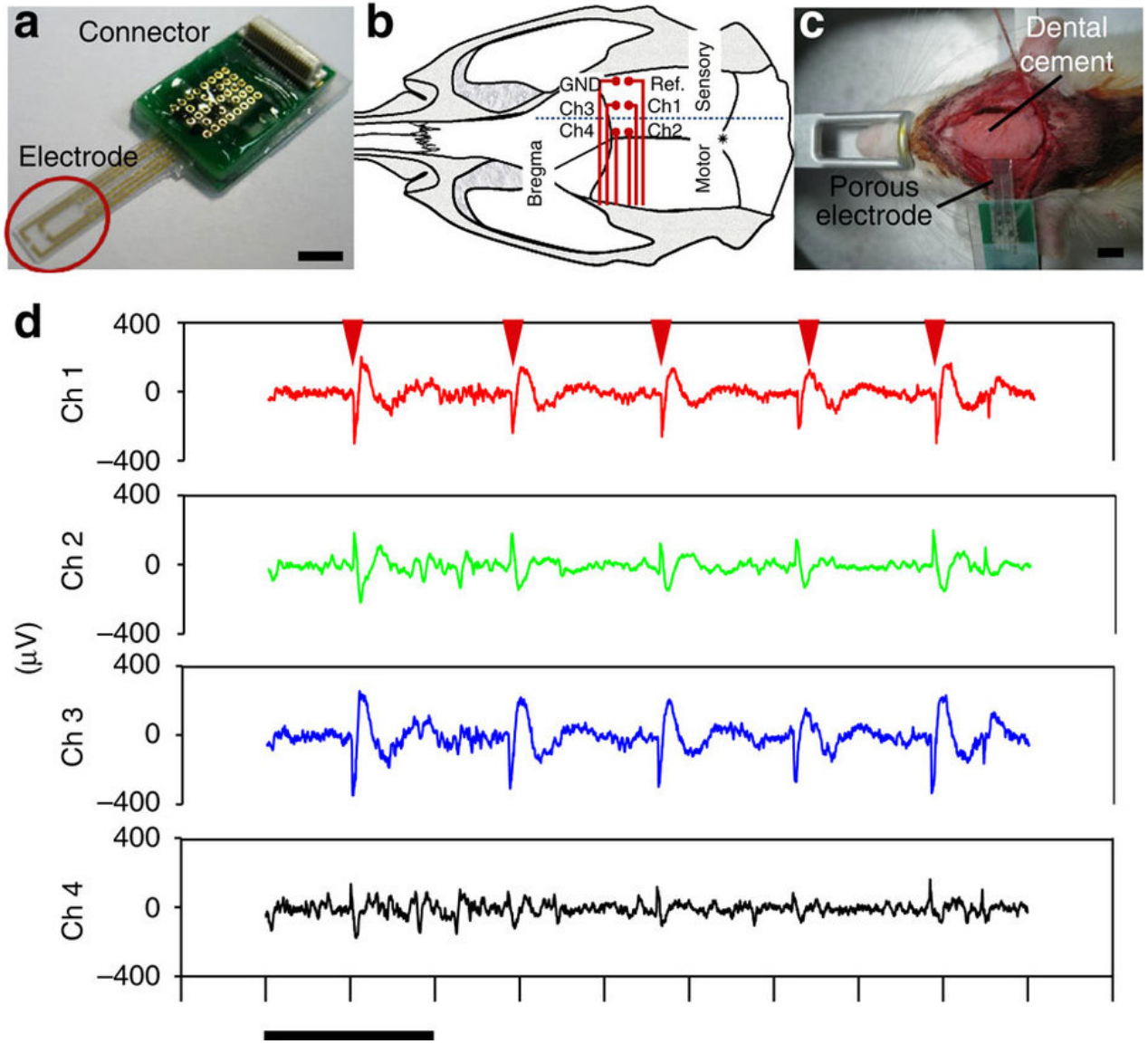


Analog EEG instruments use an amplifier, galvanometer and a writing device.

The output signal from the amplifier passes through the wire causing the coil to oscillate. A pen mounted on the galvanometer moves up and down each time the coil moves. The pen draws the trace onto paper moving below it.

The amplifier output is controlled by high and low frequency filters (**bandwidth**) and sensitivity controls (affects size of activity displayed). A digital EEG system converts the waveform into numerical values.

EEG Monitoring



a. Electrode used to measure evoked potential signal from the skull of a rat

b. Location of electrode array

c. Electrode mounted and fixed with dental cement

d. Electrode recordings of voltage over time

Characteristic patterns of the brain activities in the neocortex and hippocampus

	Awake	Non-REM sleep			REM sleep
		Stage 1	Stage 2	Stage 3-4	
Cortex	Alpha wave Gamma wave		Spindle K complex	Delta wave Theta wave	Gamma wave
Hippocampus	Theta wave HVS	High-voltage spike (HVS) with high-frequency ripple (~200 Hz)			Theta wave

Buzsaki, *Neuroscience*, 31, 551-70, 1989.
Gottesmann, *Neurosci. Biobehav. Rev.*, 16, 31-8, 1992.
Steriade et al., *Science*, 262, 679-85, 1993.
Steriade, *Neuroscience*, 101, 243-76, 2000.