ASHI 712

The Neuroscience of Human Memory

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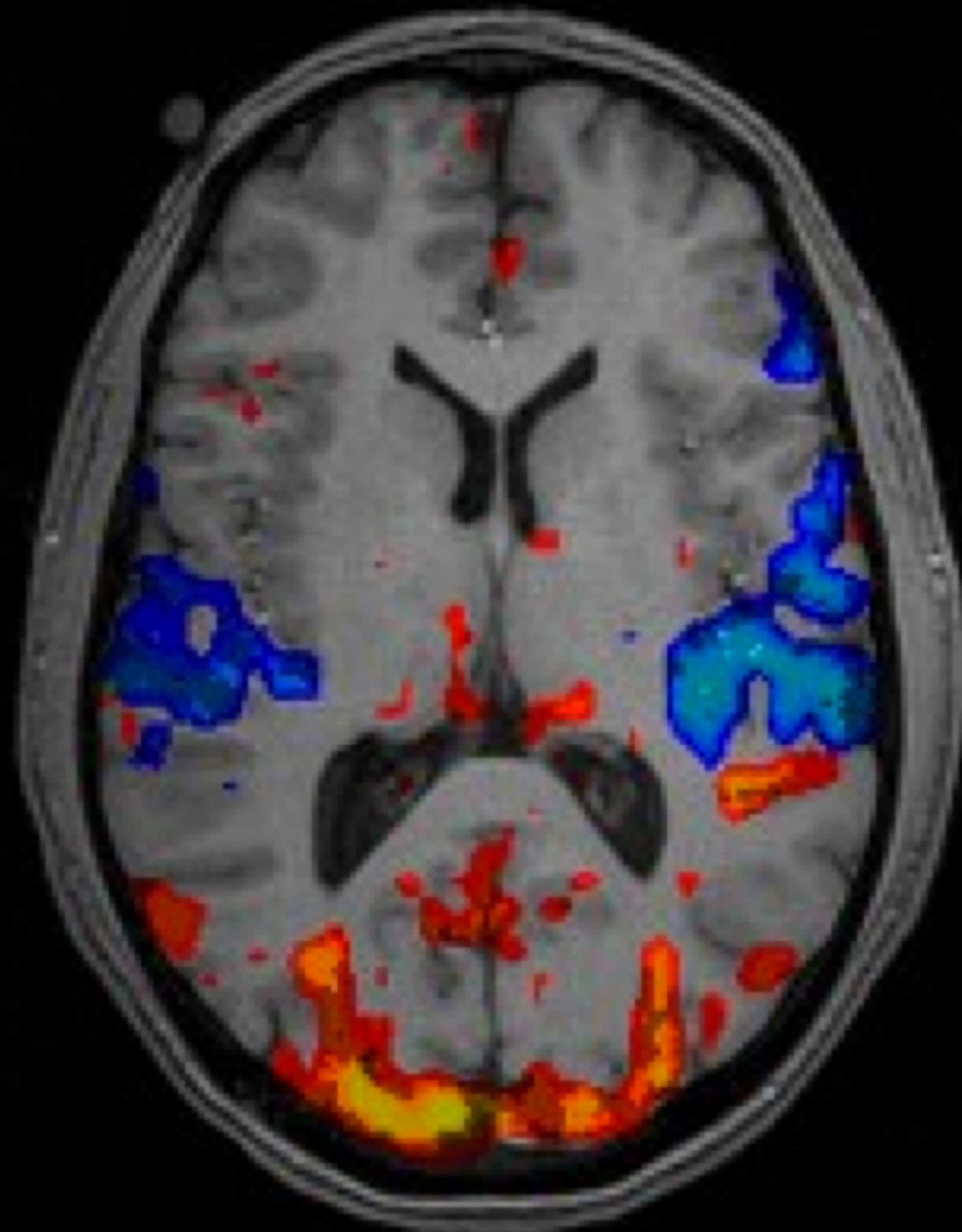
LECTURE 1:
Cellular Basis of Memory and Eric Kandel Henry Molaison



What is a memory?

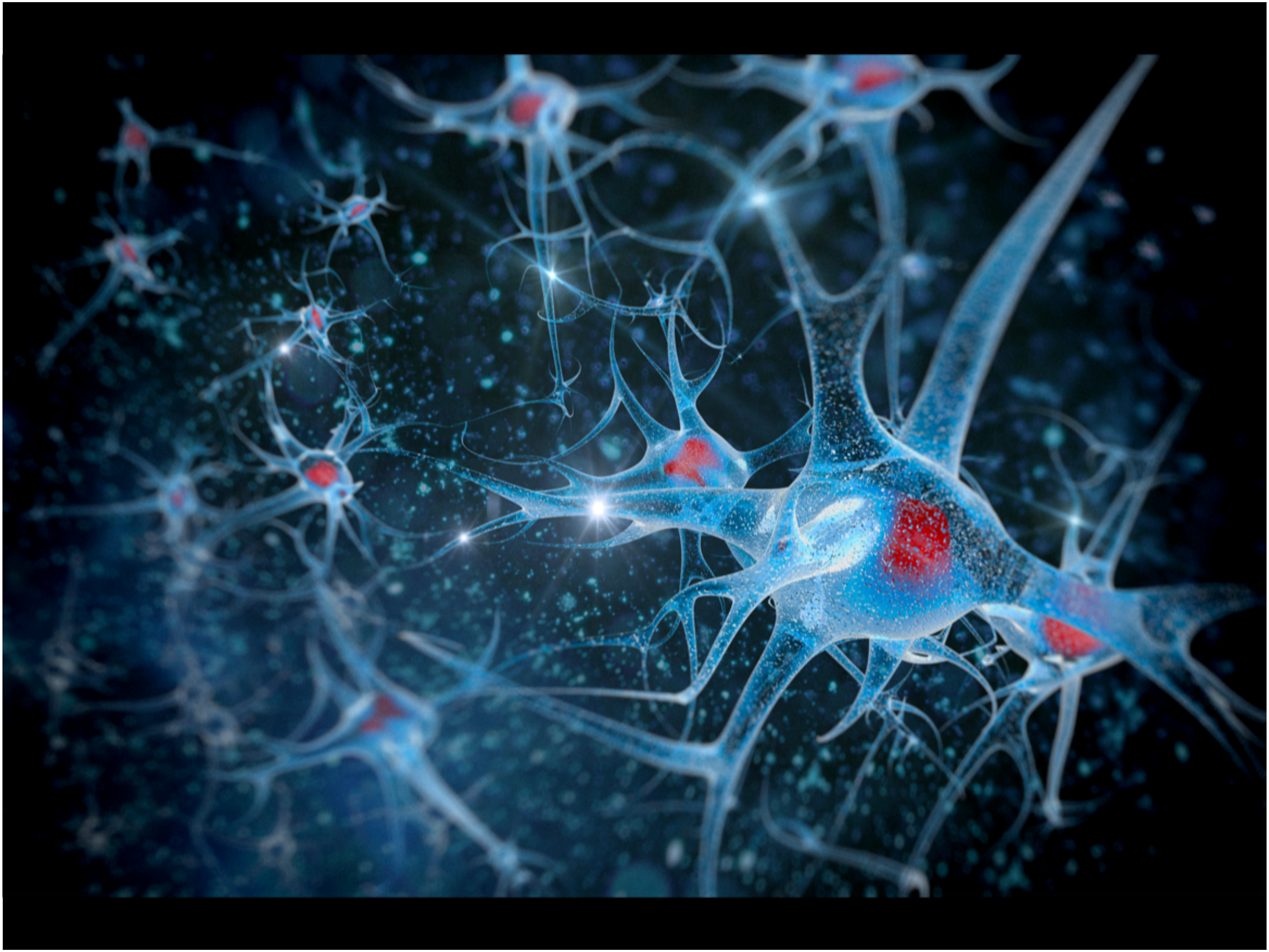
What is the capital of France?

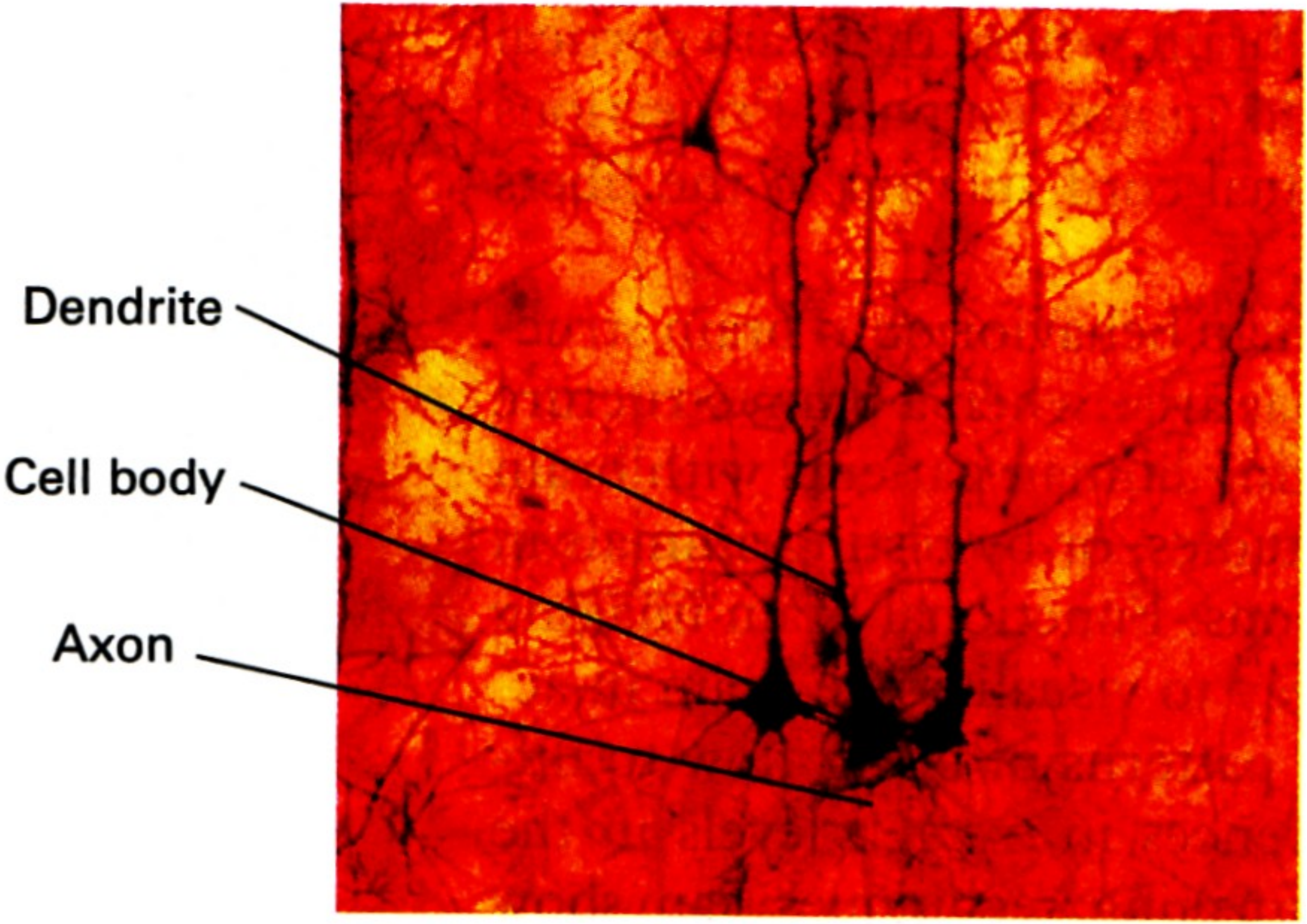
What did you do yesterday?

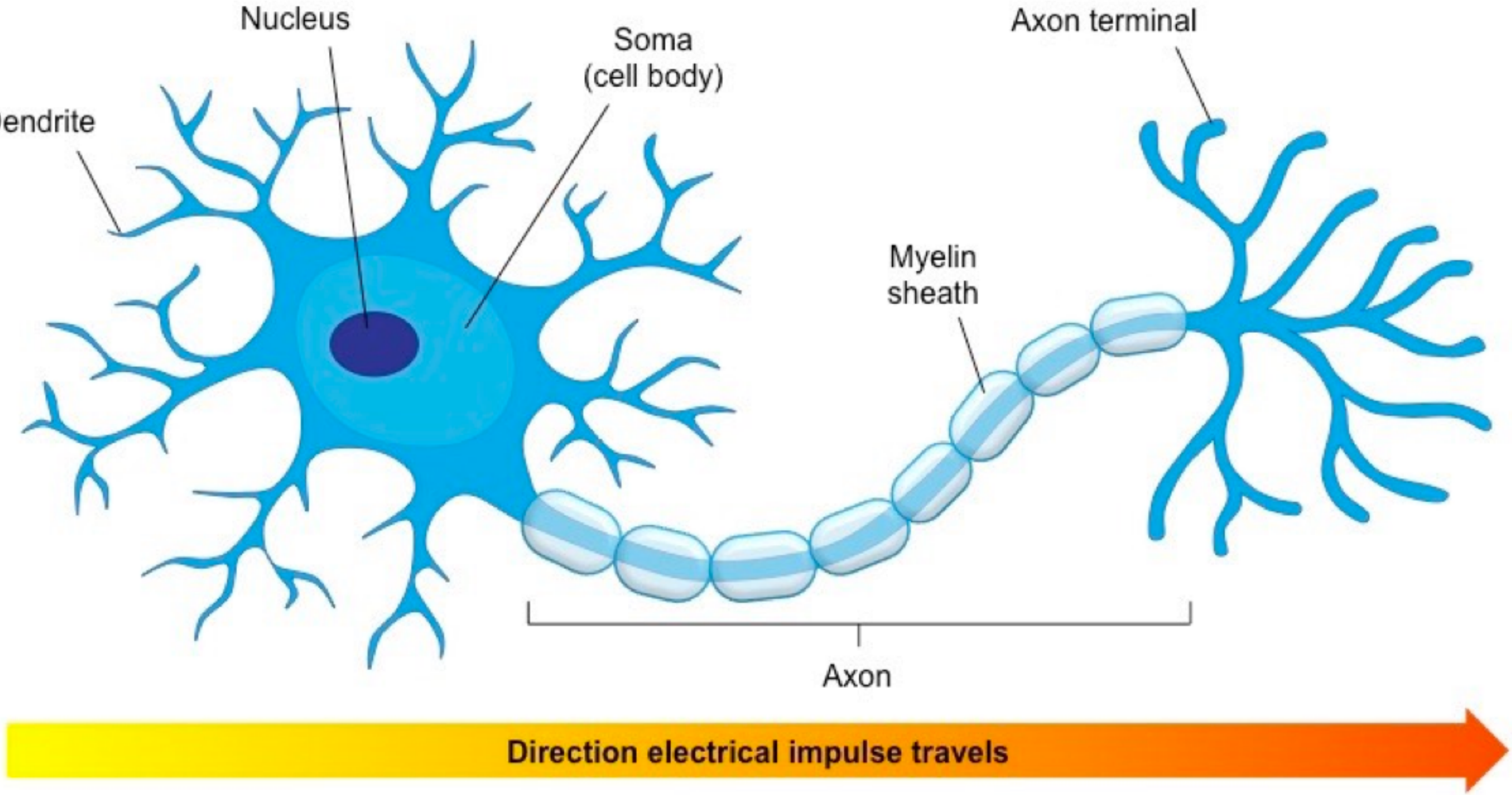
$$2 + 2 = ?$$

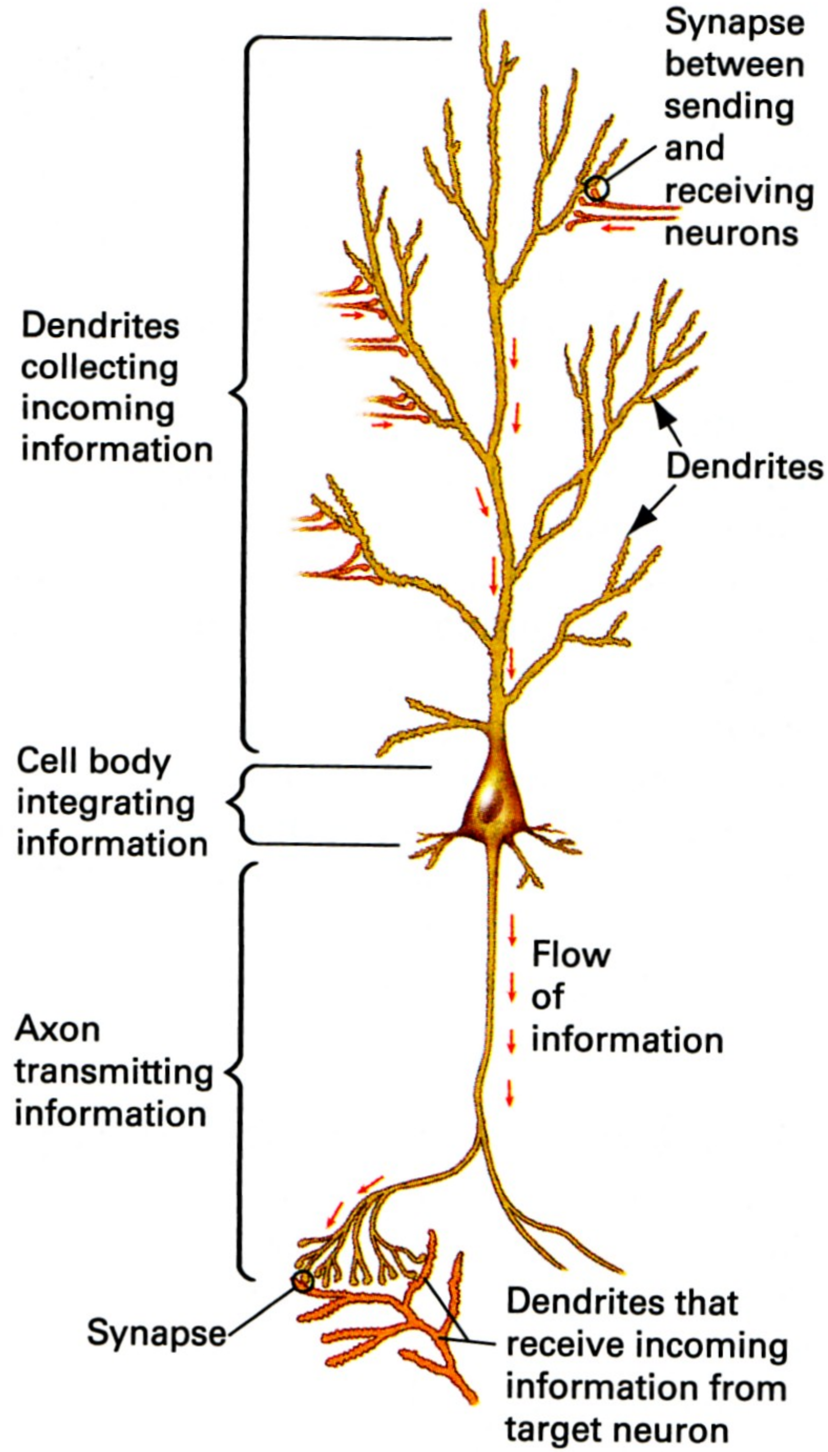

1.47
ROLEX
0.37
Sam QUERREY
6 1
Marin CILIC
6

Neural Mechanisms for Memory



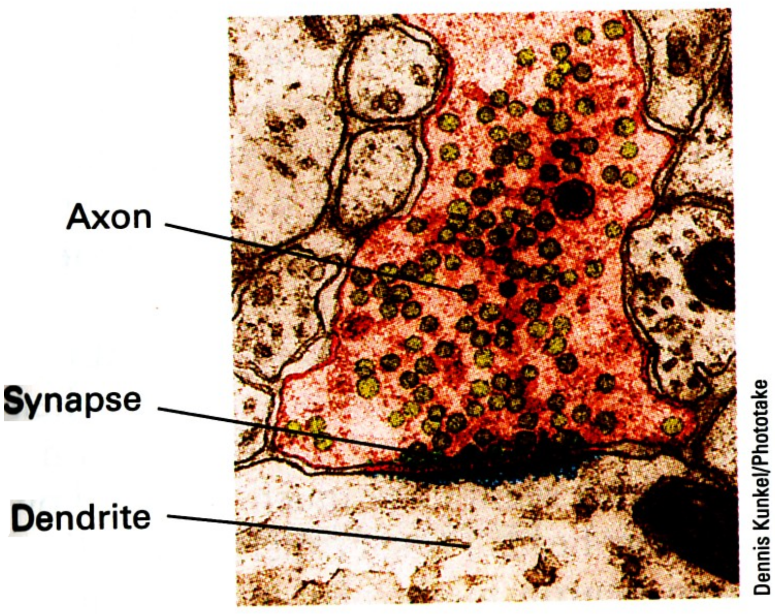

Dendrite
Cell body
Axon


Nucleus
Soma
(cell body)
Axon terminal
Dendrite
Myelin
sheath
Axon
Direction electrical impulse travels

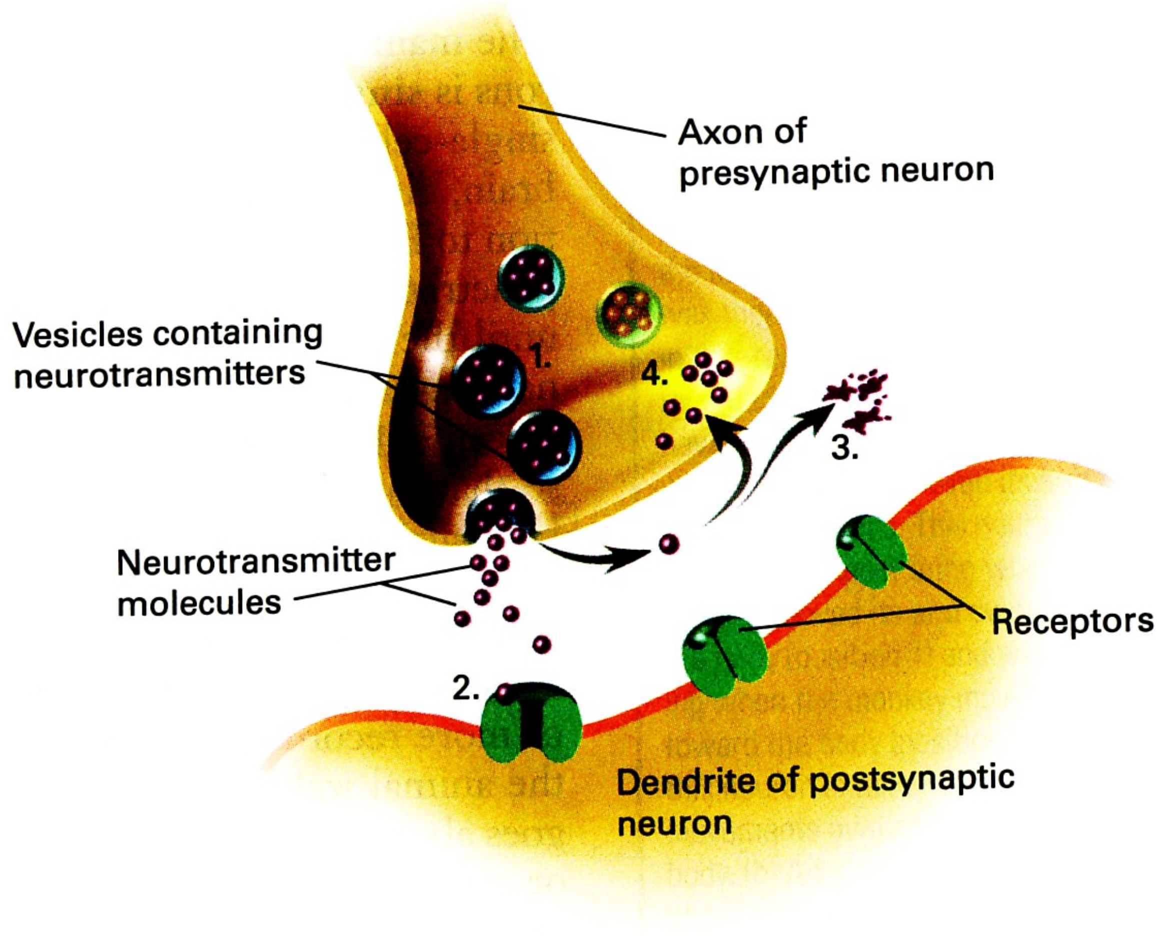

Synapse between sending and receiving neurons
Dendrites collecting incoming information
Dendrites
Cell body integrating information
Flow of information
Axon transmitting information
Synapse
Dendrites that receive incoming information from target neuron

(b)

Why does a neuron “fire”?

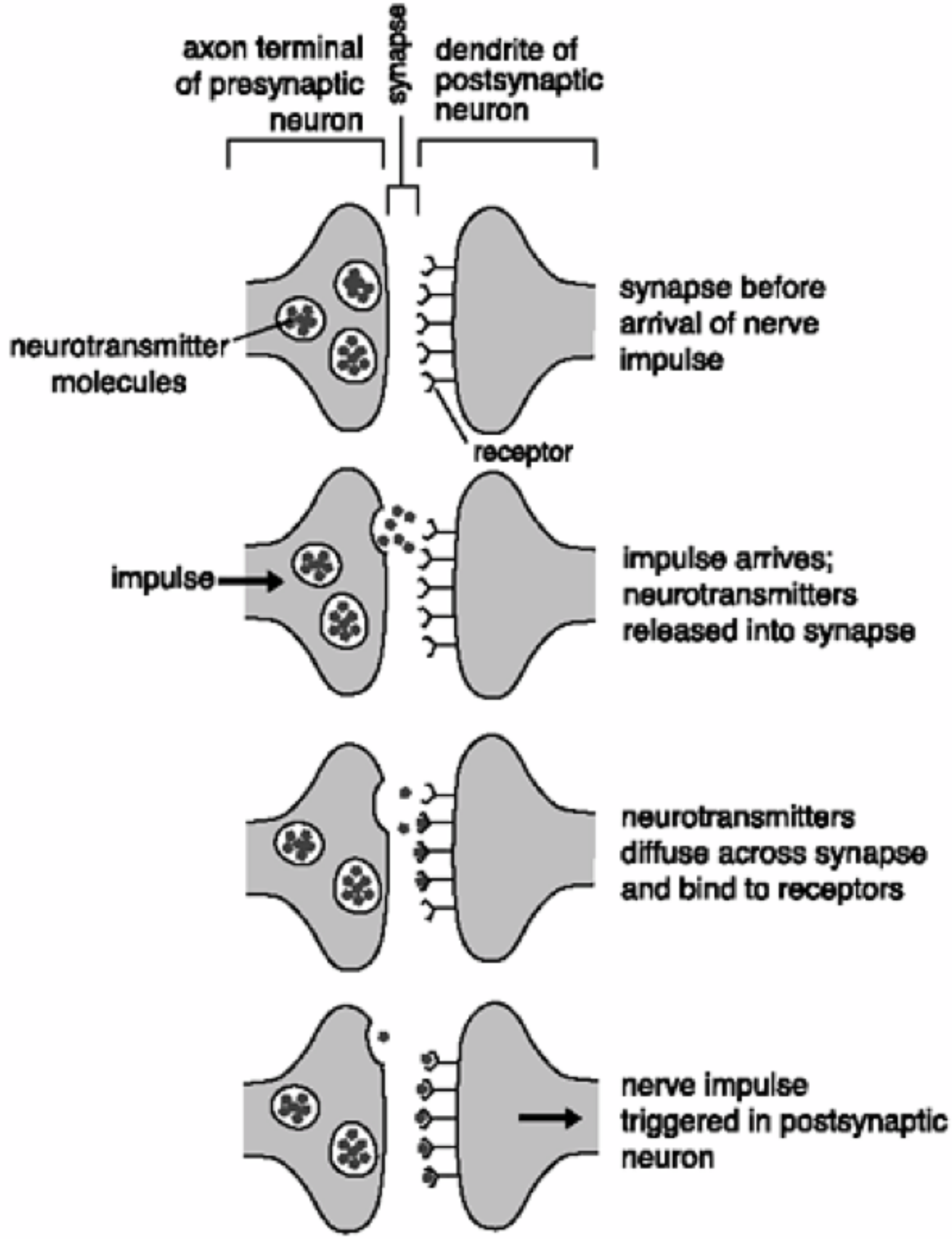

Axon
Synapse
Dendrite
Dennis Kunkel/Phototake

(a)


Axon of
presynaptic neuron
Vesicles containing
neurotransmitters
1.
4.
3.
Neurotransmitter
molecules
Receptors
2.
Dendrite of postsynaptic
neuron

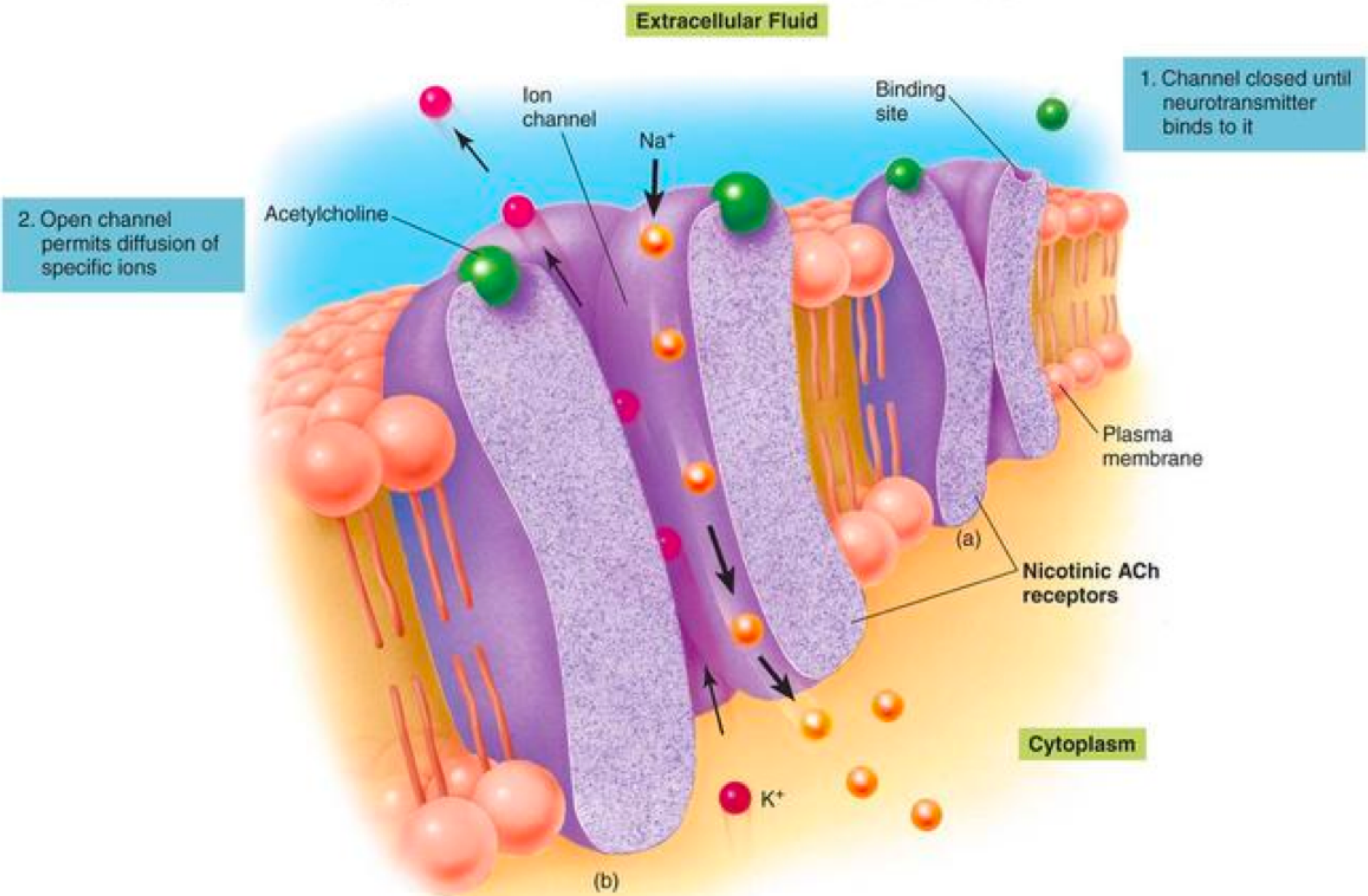
(b)

The four basic stages of neurotransmission

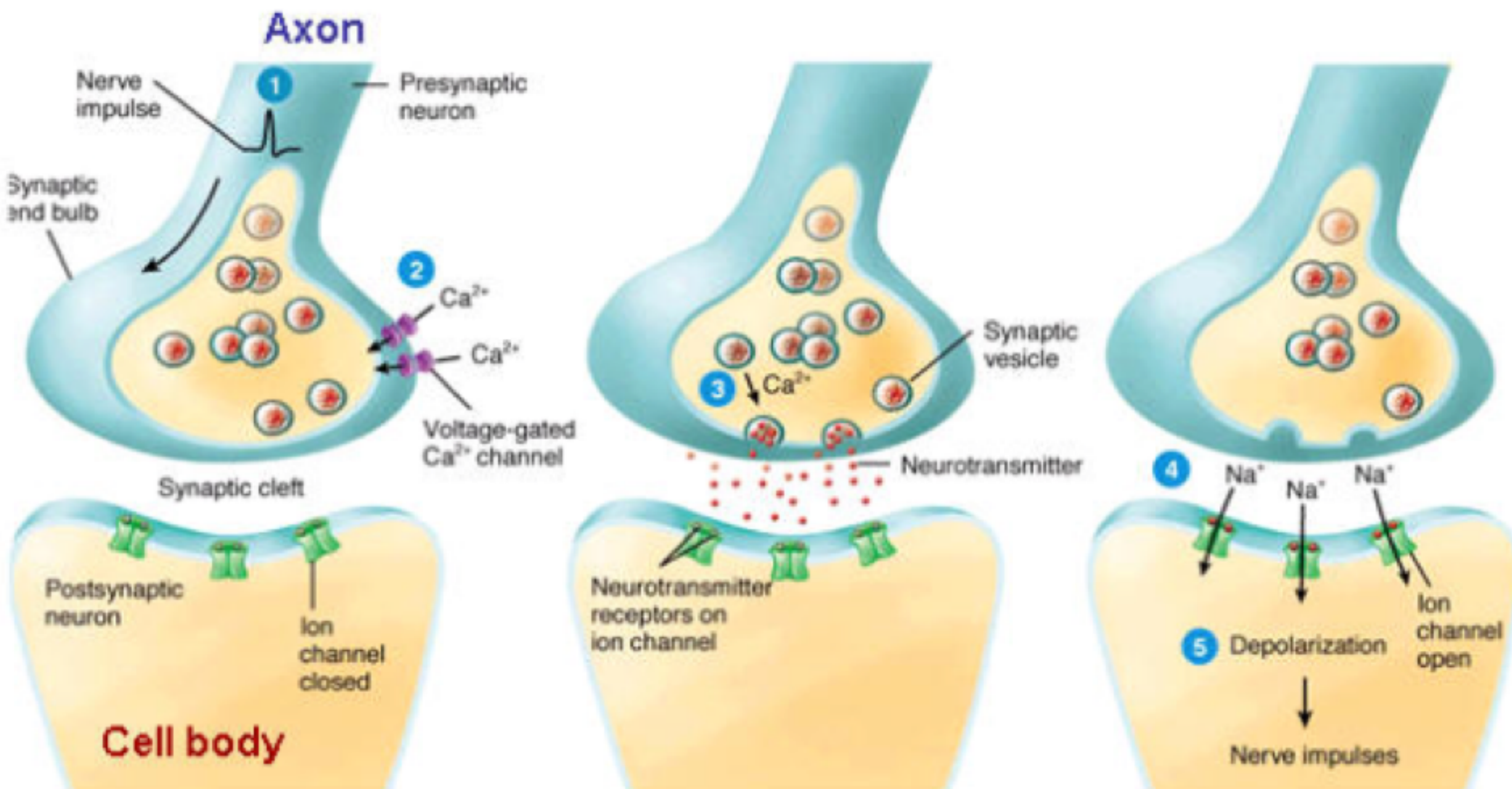


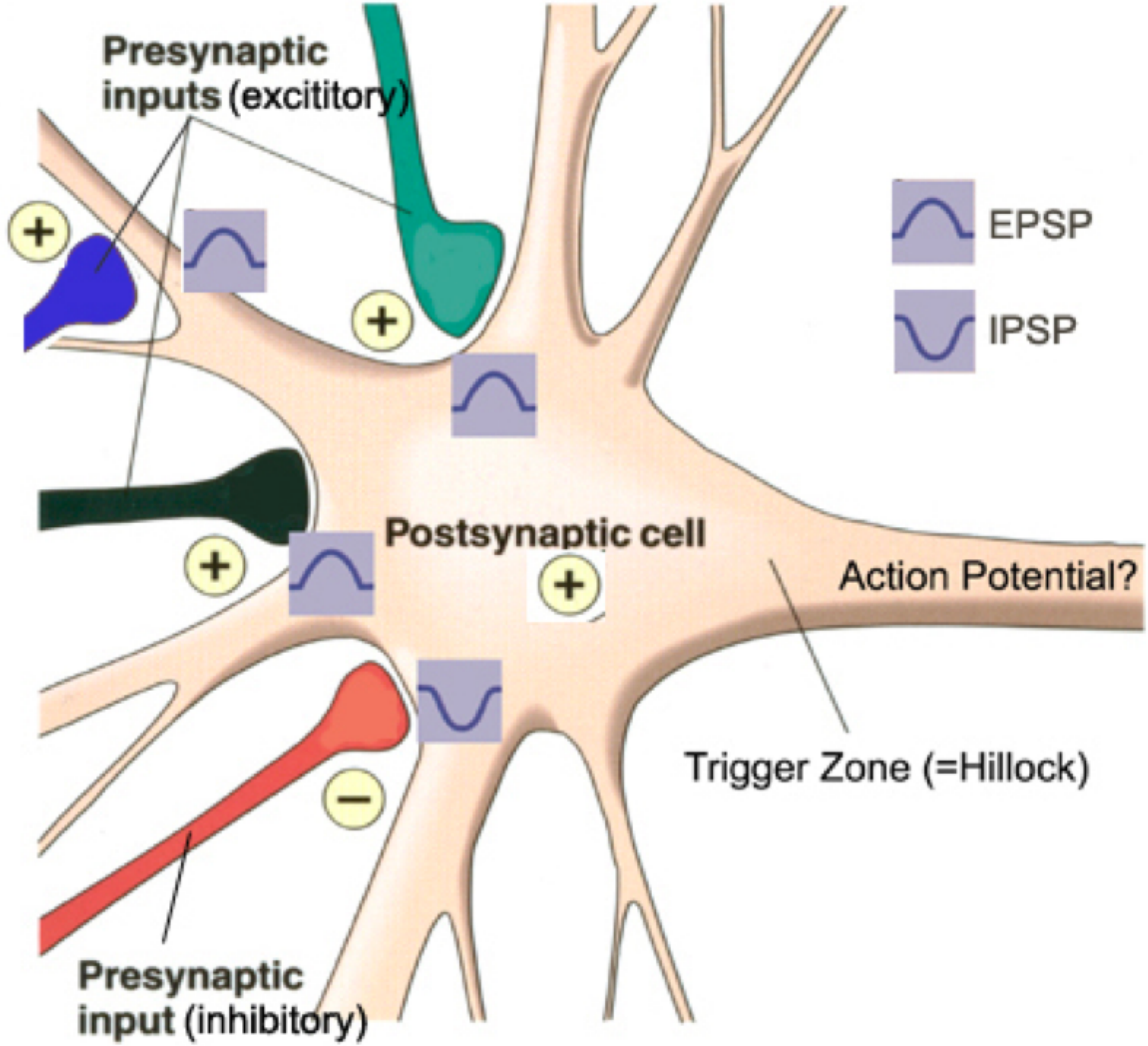
TYPES OF NEUROTRANSMITTERS

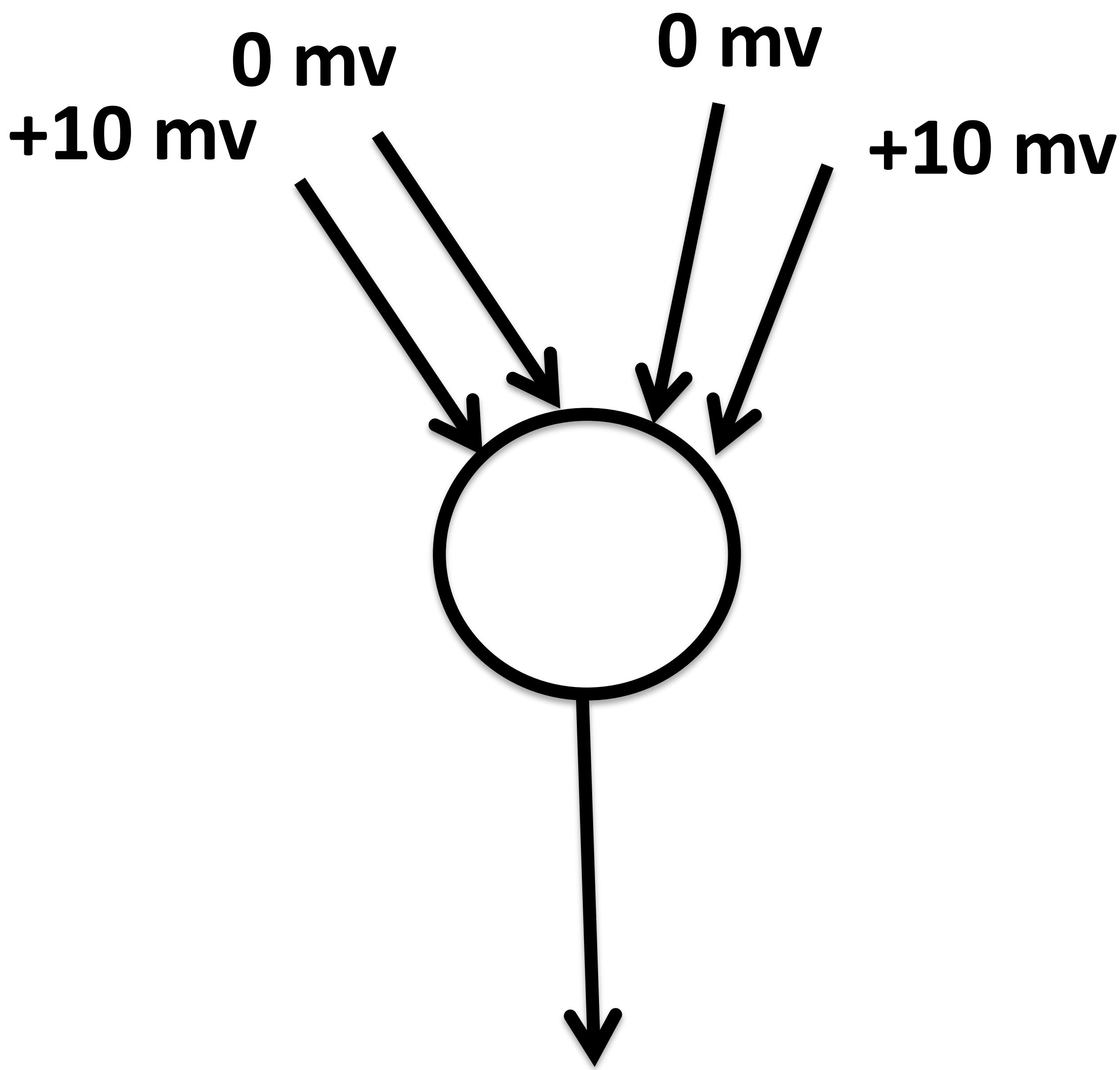
Neurotransmitter	Function	Examples of Malfunctions
Acetylcholine (ACh)	Enables muscle action, learning, and memory.	With Alzheimer's disease, ACh-producing neurons deteriorate.
Dopamine	Influences movement, learning, attention, and emotion.	Excess dopamine receptor activity linked to schizophrenia. Starved of dopamine, the brain produces the tremors and decreased mobility of Parkinson's disease.
Serotonin	Affects mood, hunger, sleep, and arousal.	Undersupply linked to depression; Prozac and some other antidepressant drugs raise serotonin levels.
Norepinephrine	Helps control alertness and arousal.	Undersupply can depress mood.
GABA (gamma-aminobutyric acid)	A major inhibitory neurotransmitter.	Undersupply linked to seizures, tremors, and insomnia.
Glutamate	A major excitatory neurotransmitter; involved in	Oversupply can overstimulate brain, producing migraines or seizures (which is why


Extracellular Fluid
1. Channel closed until neurotransmitter binds to it
2. Open channel permits diffusion of specific ions
Ion channel
Na+
Binding site
Acetylcholine
Plasma membrane
(a)
Nicotinic ACh receptors
Cytoplasm
K+
(b)

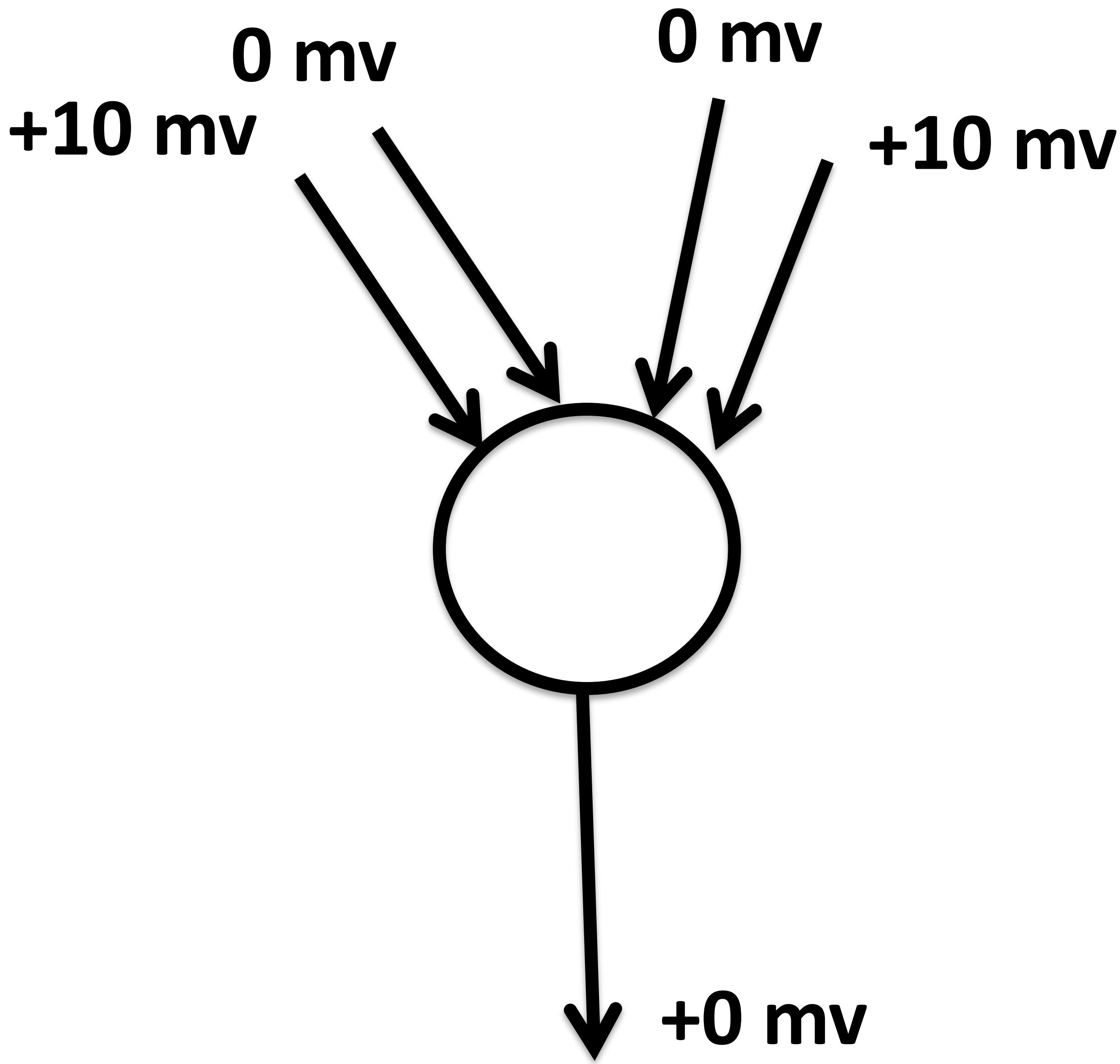
From action potential to postsynaptic depolarization

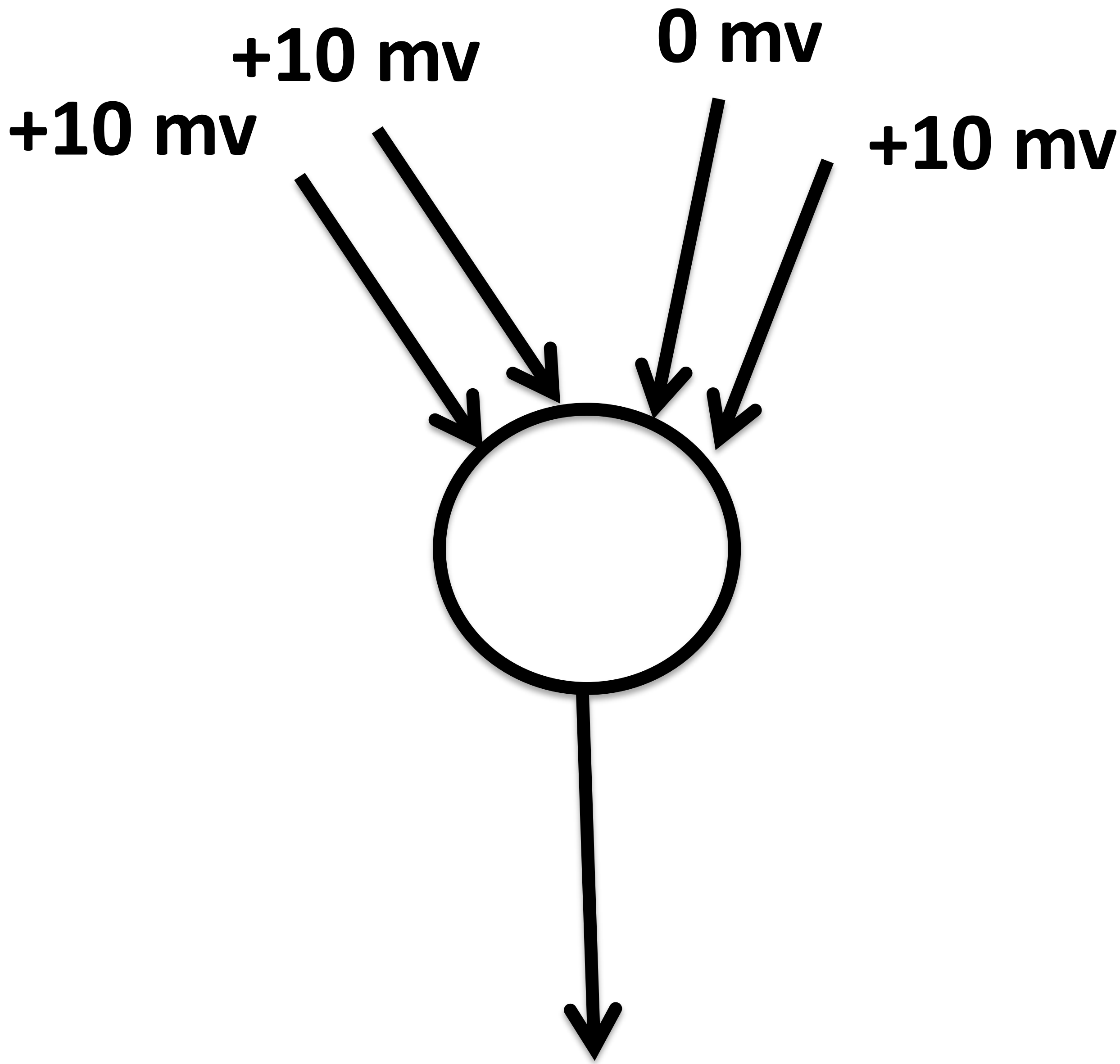


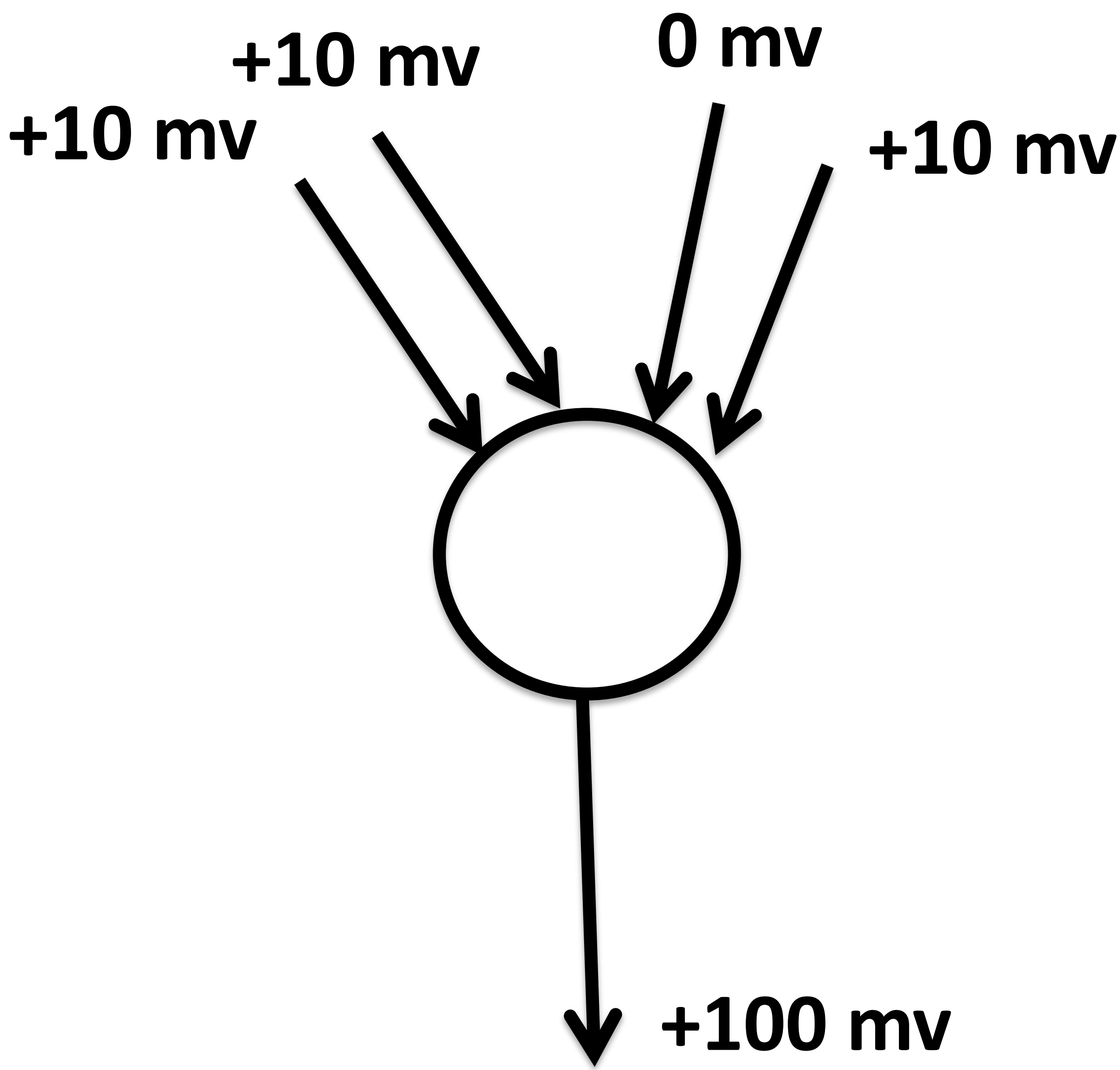

Presynaptic inputs (excititory)
EPSP
IPSP
Postsynaptic cell
Action Potential?
Trigger Zone (=Hillock)
Presynaptic input (inhibitory)

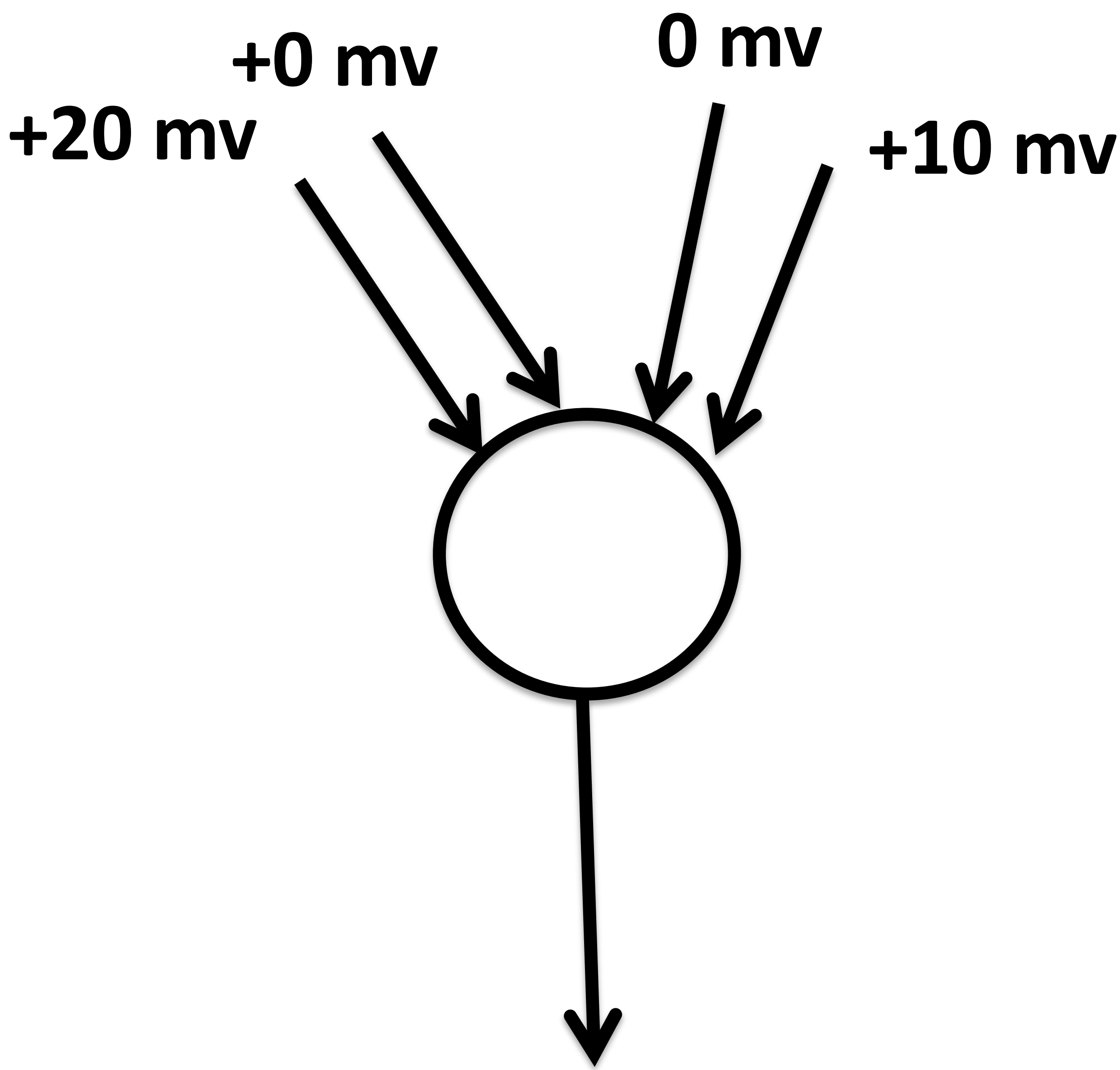


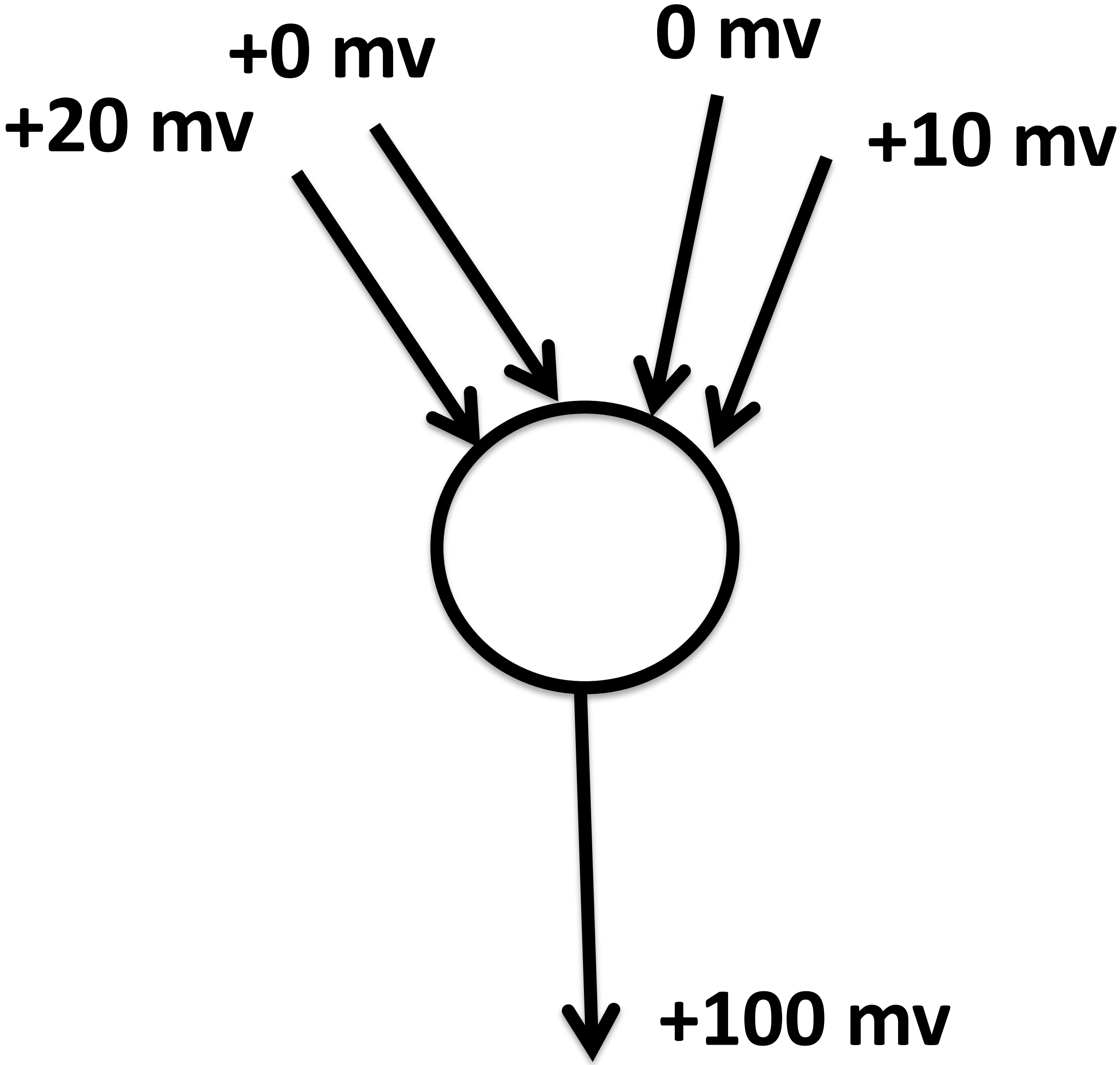
0 mv
0 mv
+10 mv
+10 mv

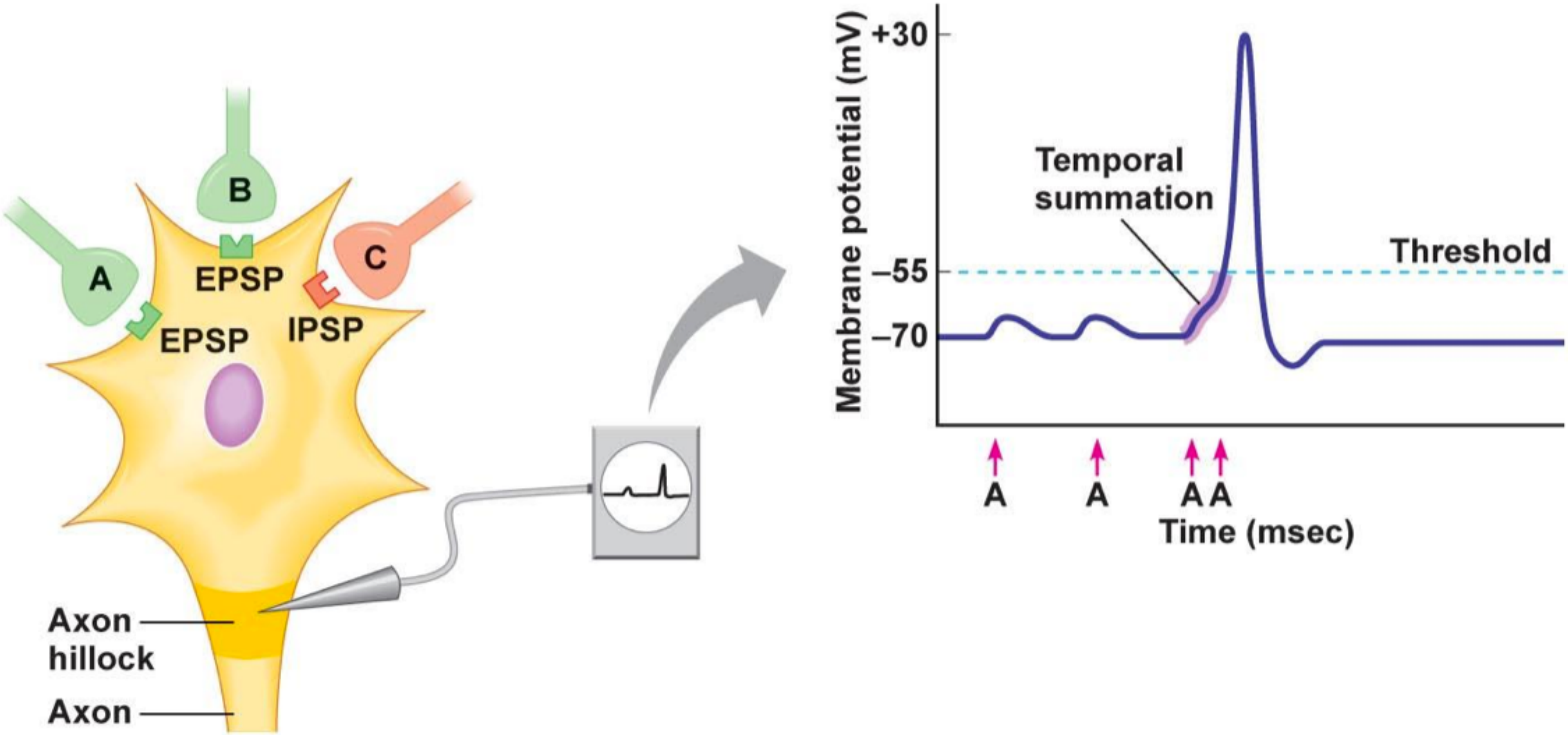

0 mv
0 mv
+10 mv
+10 mv
+0 mv


+10 mv
+10 mv
0 mv
+10 mv

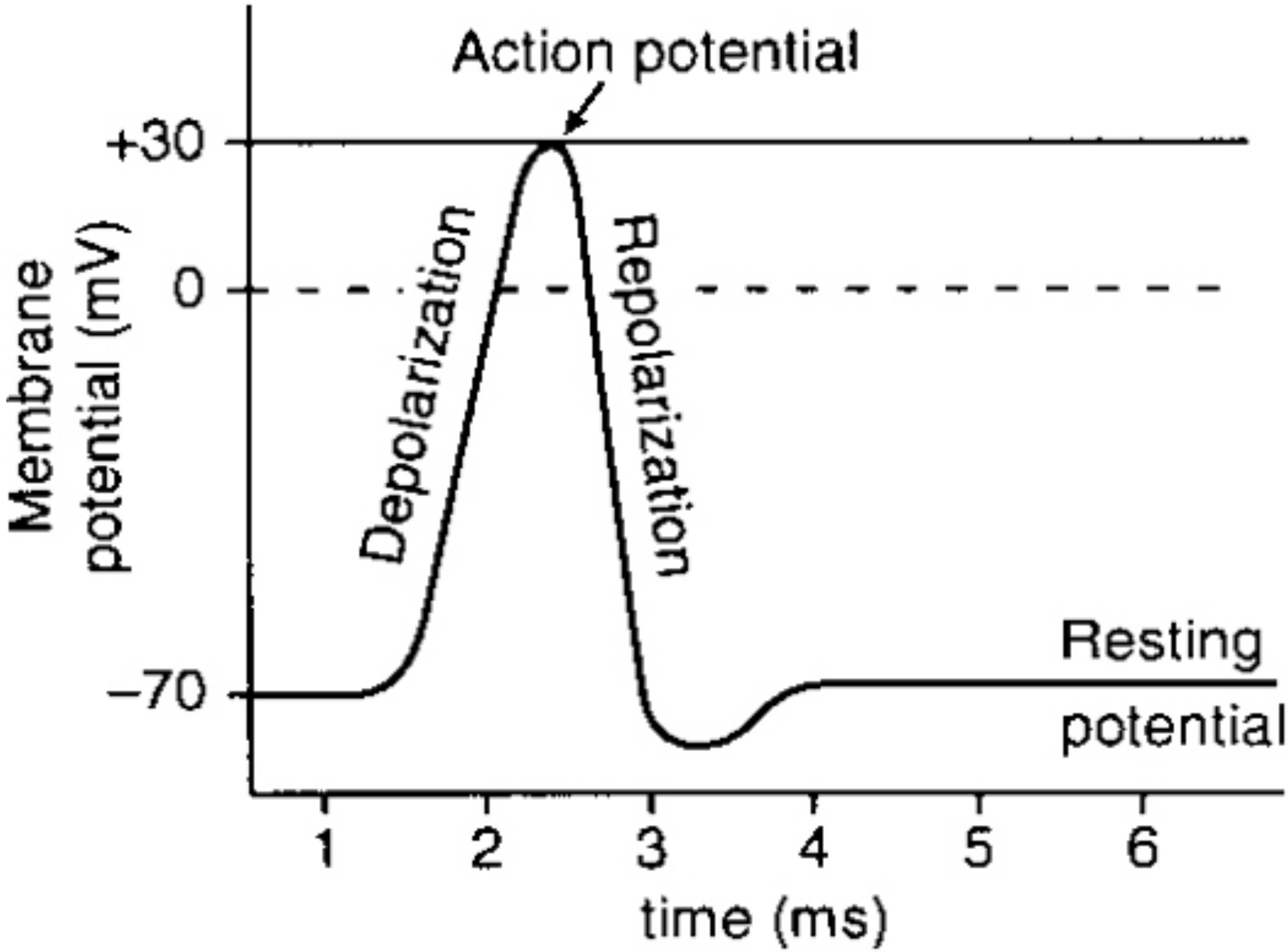

+10 mv
+10 mv
0 mv
+10 mv
+100 mv


+0 mv
0 mv
+20 mv
+10 mv

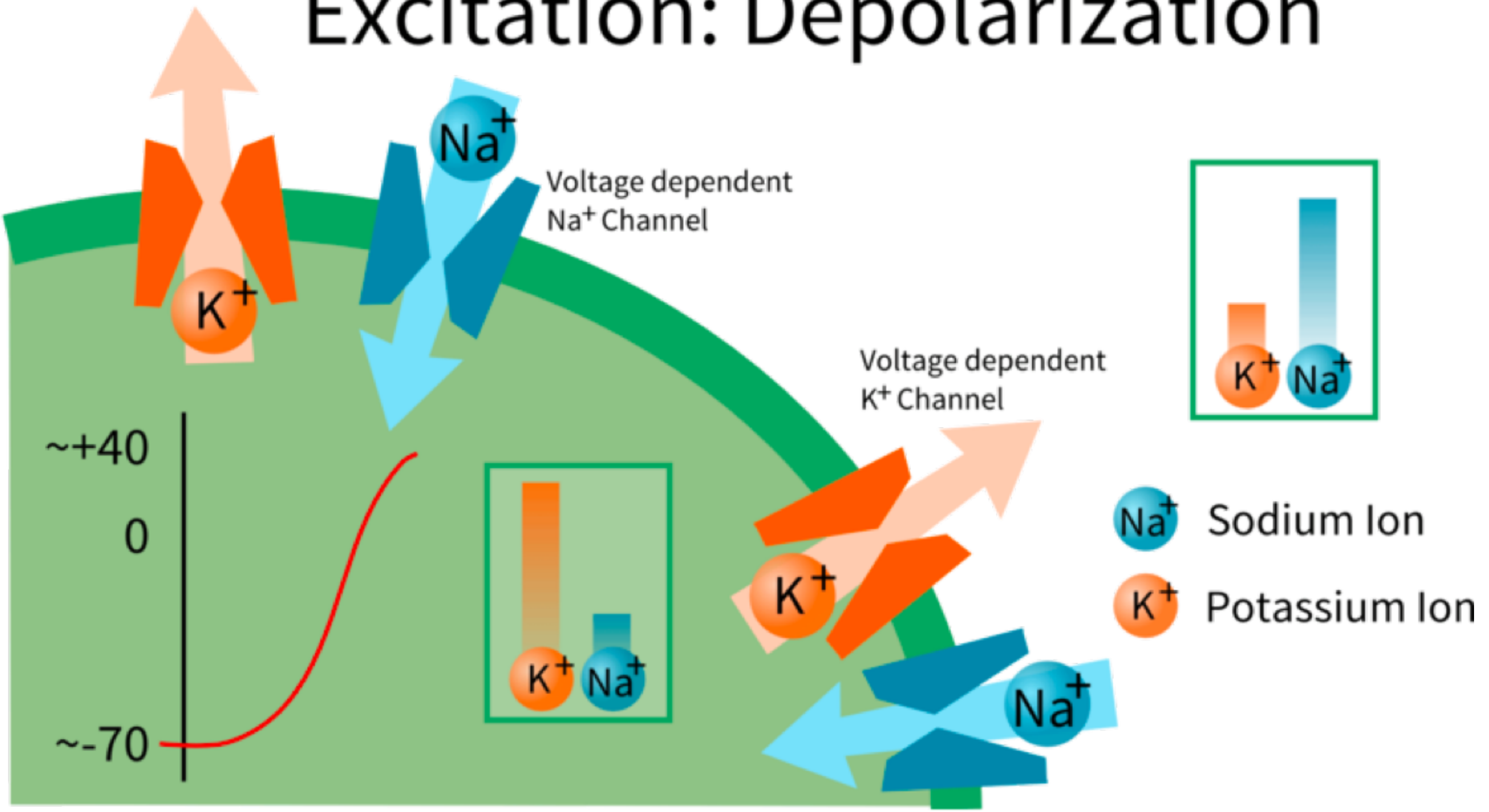

+0 mv
0 mv
+20 mv
+10 mv
+100 mv



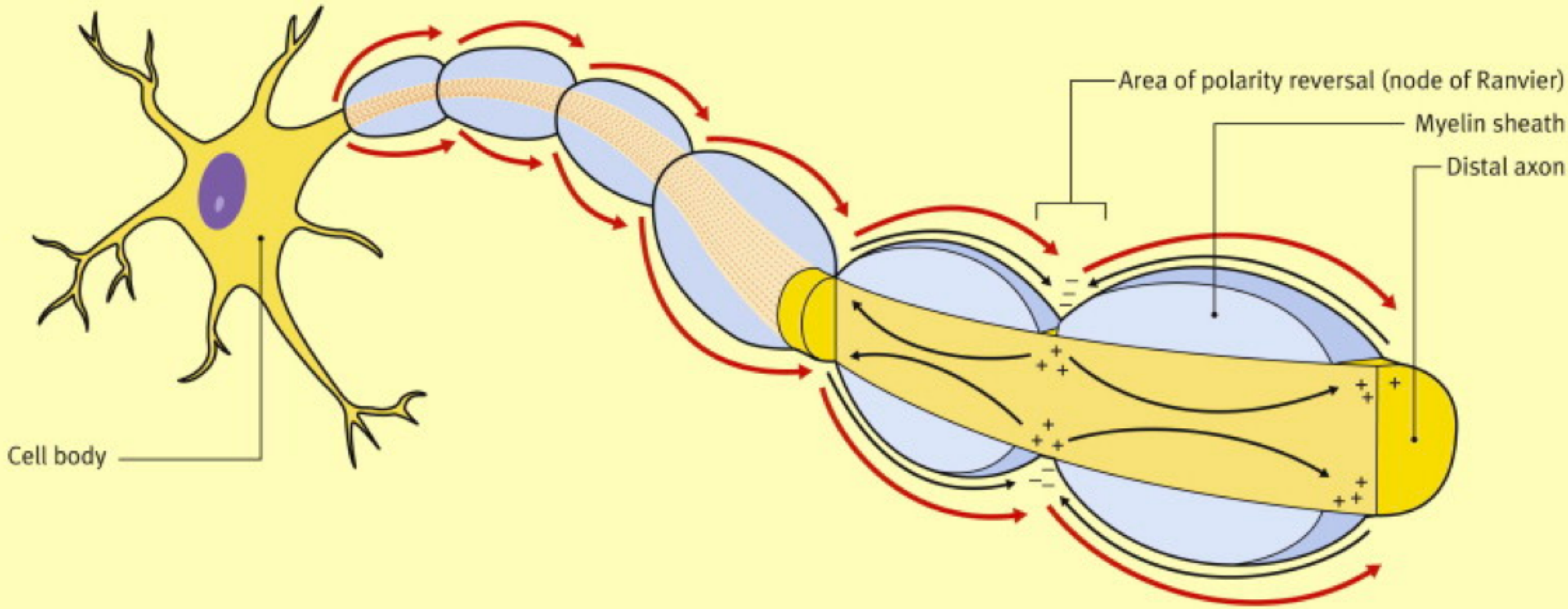
B
A
C
EPSP
EPSP
IPSP
Axon hillock
Axon
Membrane potential (mV)
+30
–55
–70
Threshold
Temporal summation
A
A
A A
Time (msec)


Action potential
+30
0
–70
Membrane potential (mV)
Depolarization
Repolarization
Resting potential
1
2
3
4
5
6
time (ms)

Excitation: Depolarization

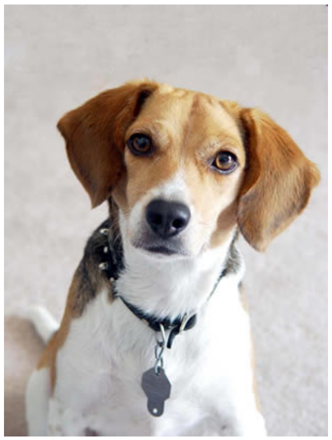


Saltatory conduction along myelinated axons

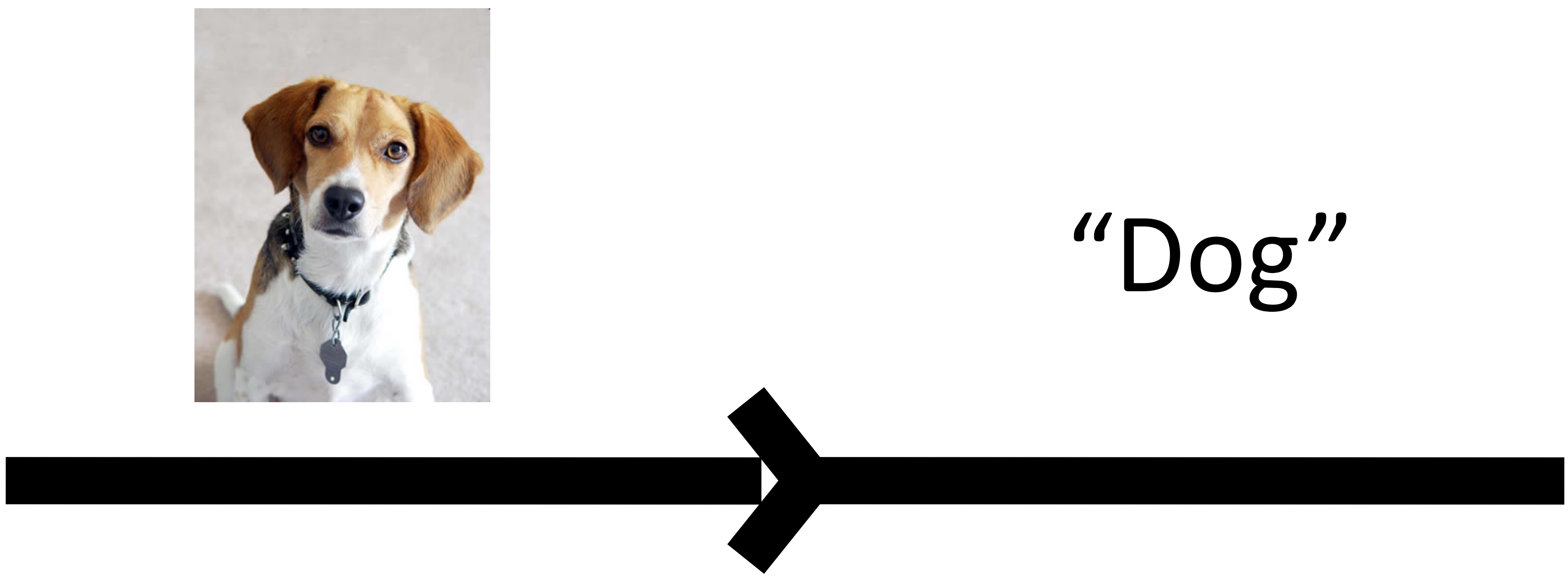


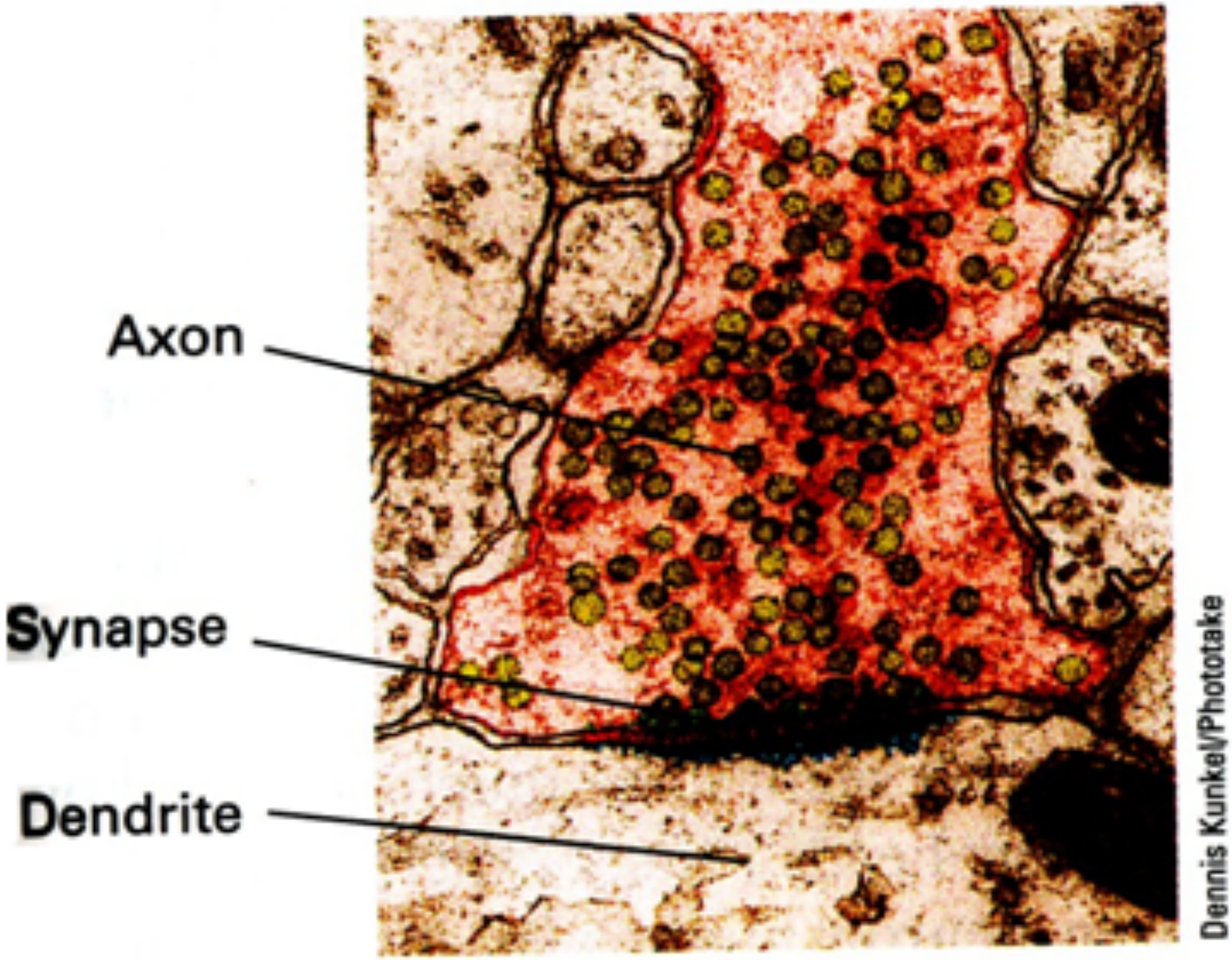
Action potential conduction velocities along myelinated nerve axons are much greater than along unmyelinated axons owing to the mechanism of saltatory conduction. The insulating myelin sheath is laid down in segments approximately 1 mm long, with the segments separated by nodes of Ranvier where the voltage-gated sodium channels are clustered. Depolarization at a node causes current to spread rapidly along the inner surface of the membrane to the next node where an action potential is triggered, and so on along the length of the axon (i.e. the depolarization 'jumps' from one node to the next). This results in greatly increased conduction velocities compared with unmyelinated axons of the same diameter

But what is a memory?



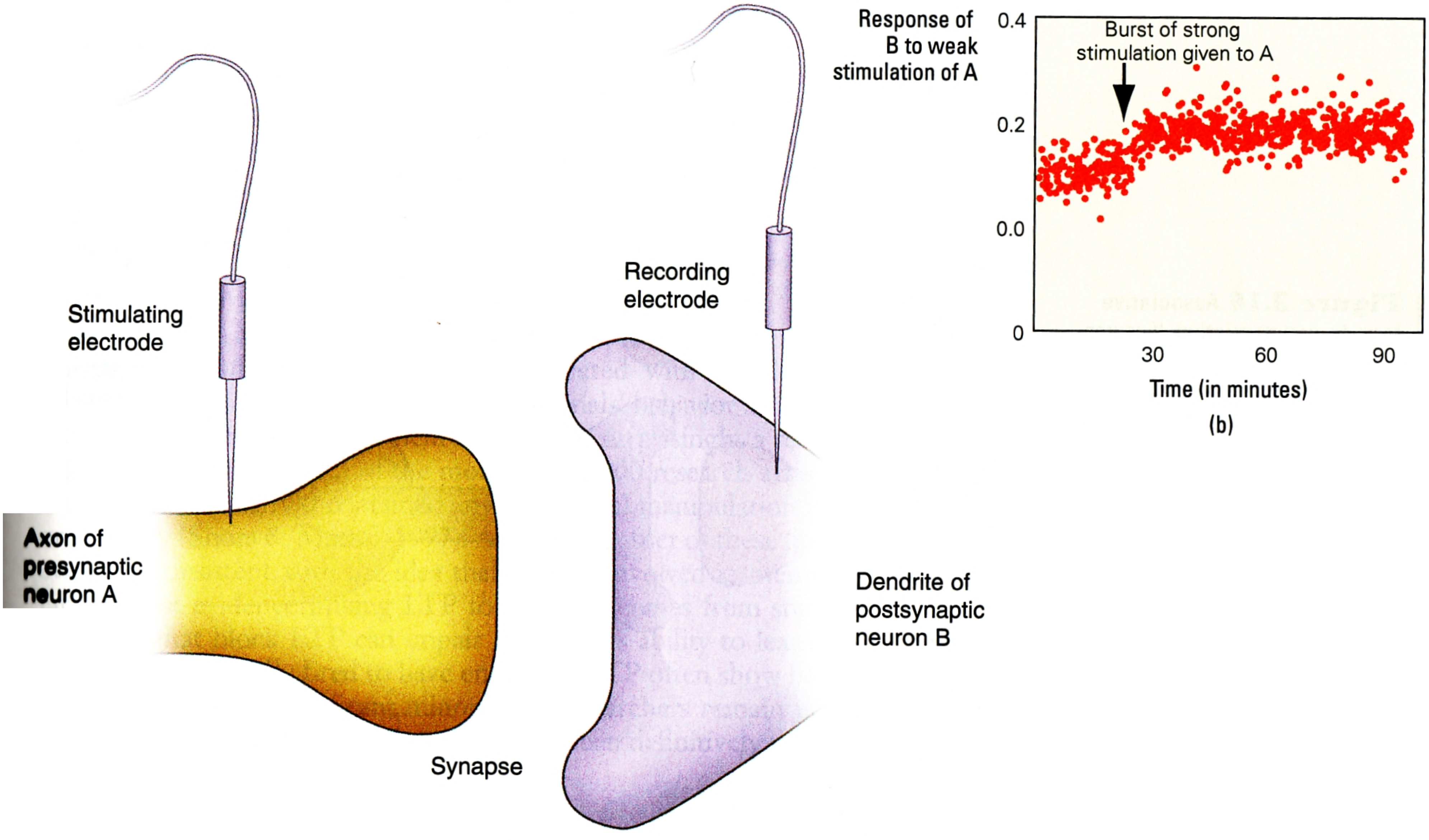
“Dog”


“Dog”

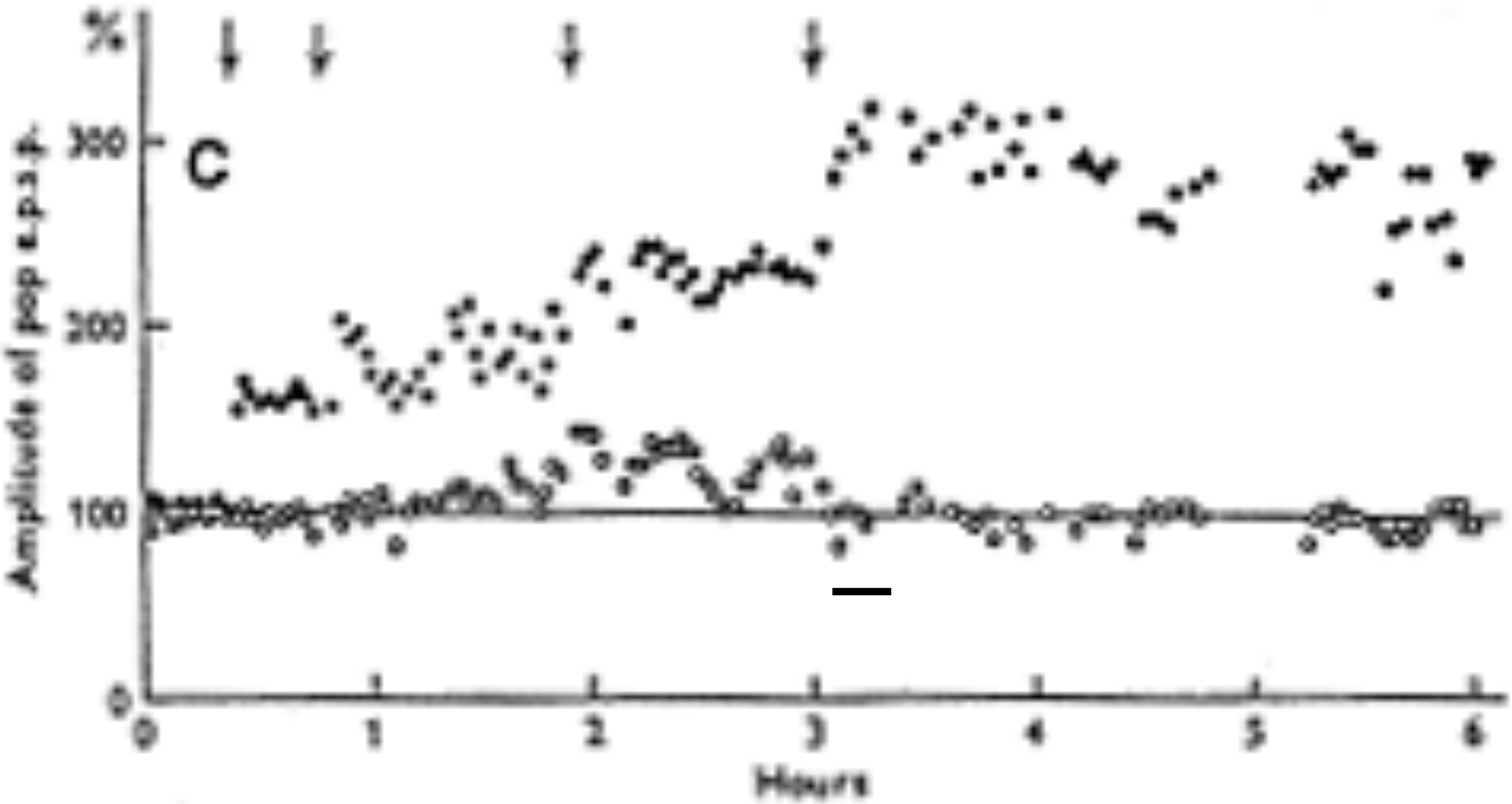


How does this change?

Short Term Changes: LTP


Stimulating electrode
Recording electrode
Axon of presynaptic neuron A
Synapse
Dendrite of postsynaptic neuron B
Response of B to weak stimulation of A
Burst of strong stimulation given to A
0.4
0.2
0.0
0
30
60
90
Time (in minutes)
(b)

Bliss and Lomo's First Published LTP Experiment



Conclusion?

A larger response from the same stimulus.

LTP

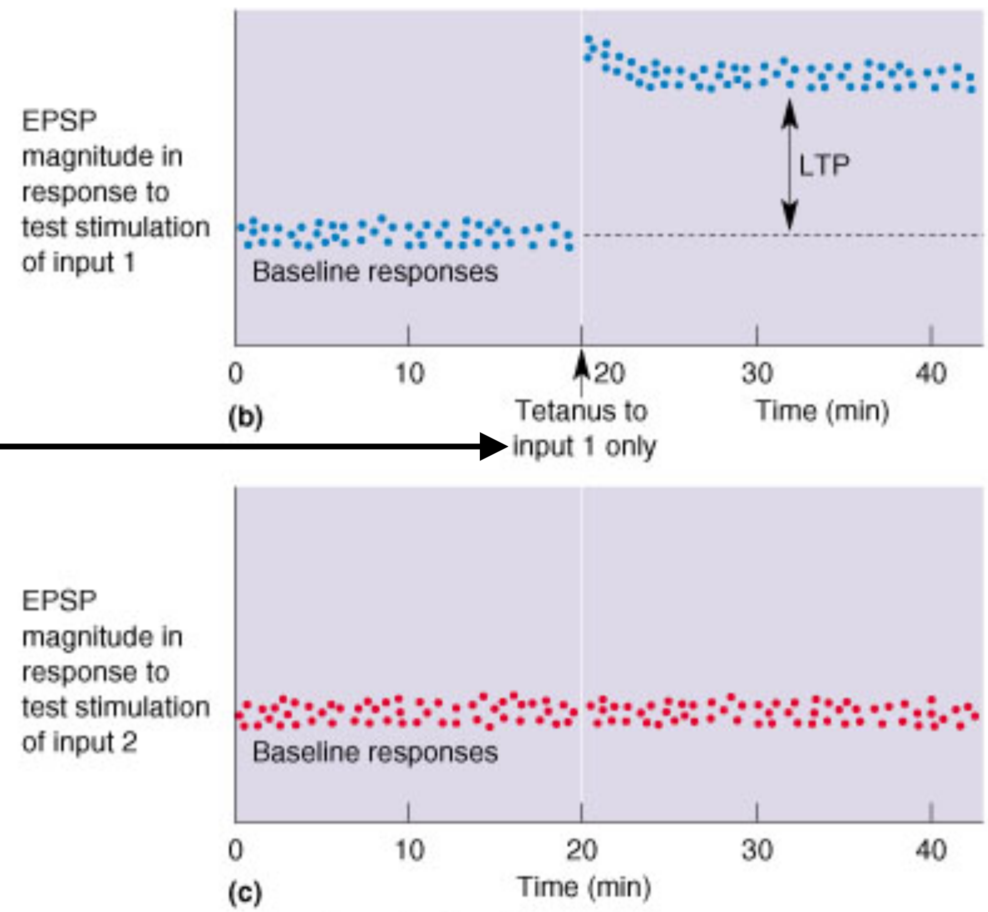
Typical LTP experiment: record EPSP's in CA1 cells (magnitude)

Step 1: weakly stimulate input 1 to establish baseline

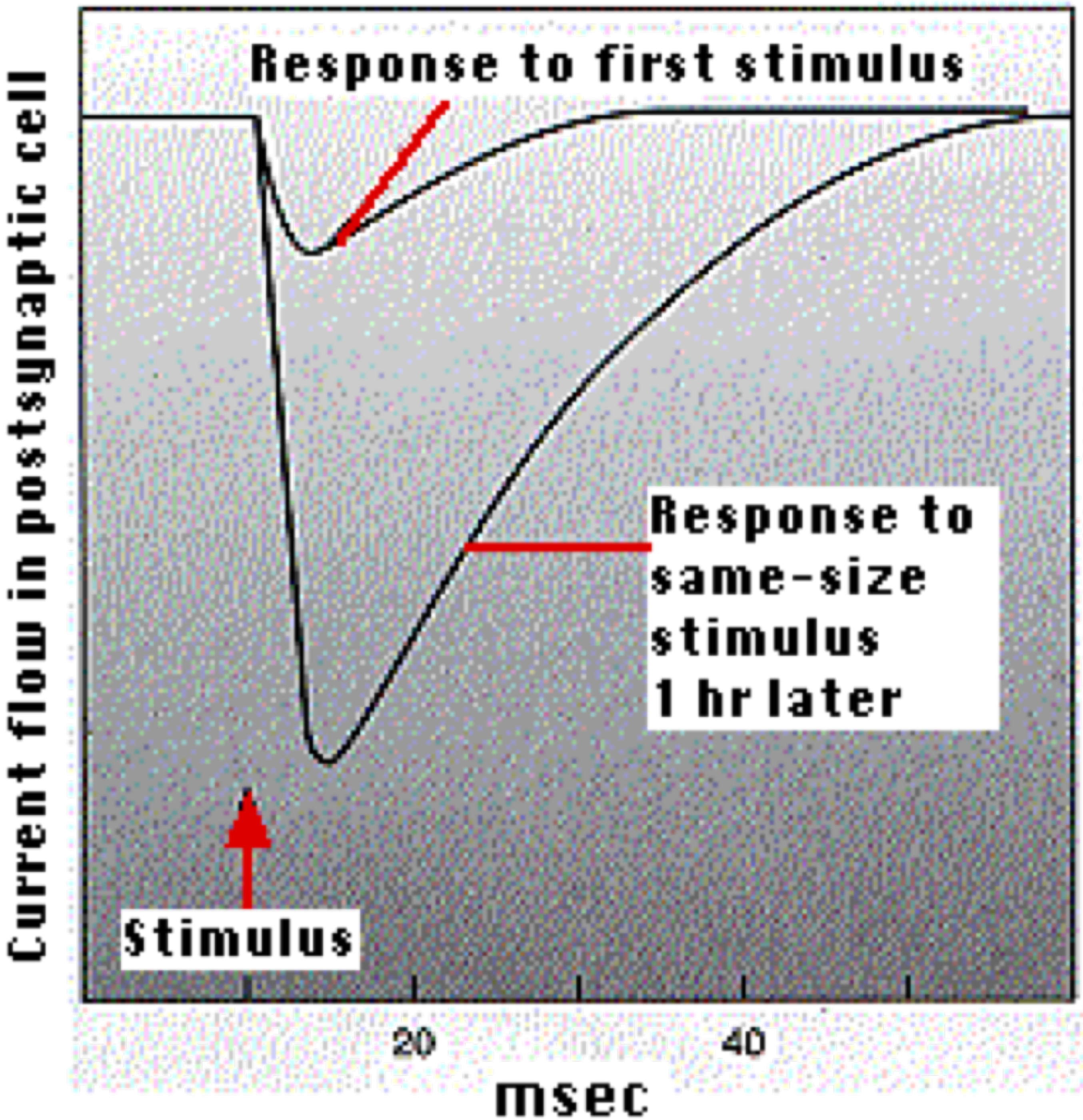
Step 2: give strong stimulus (tetanus) in same fibers (arrow)

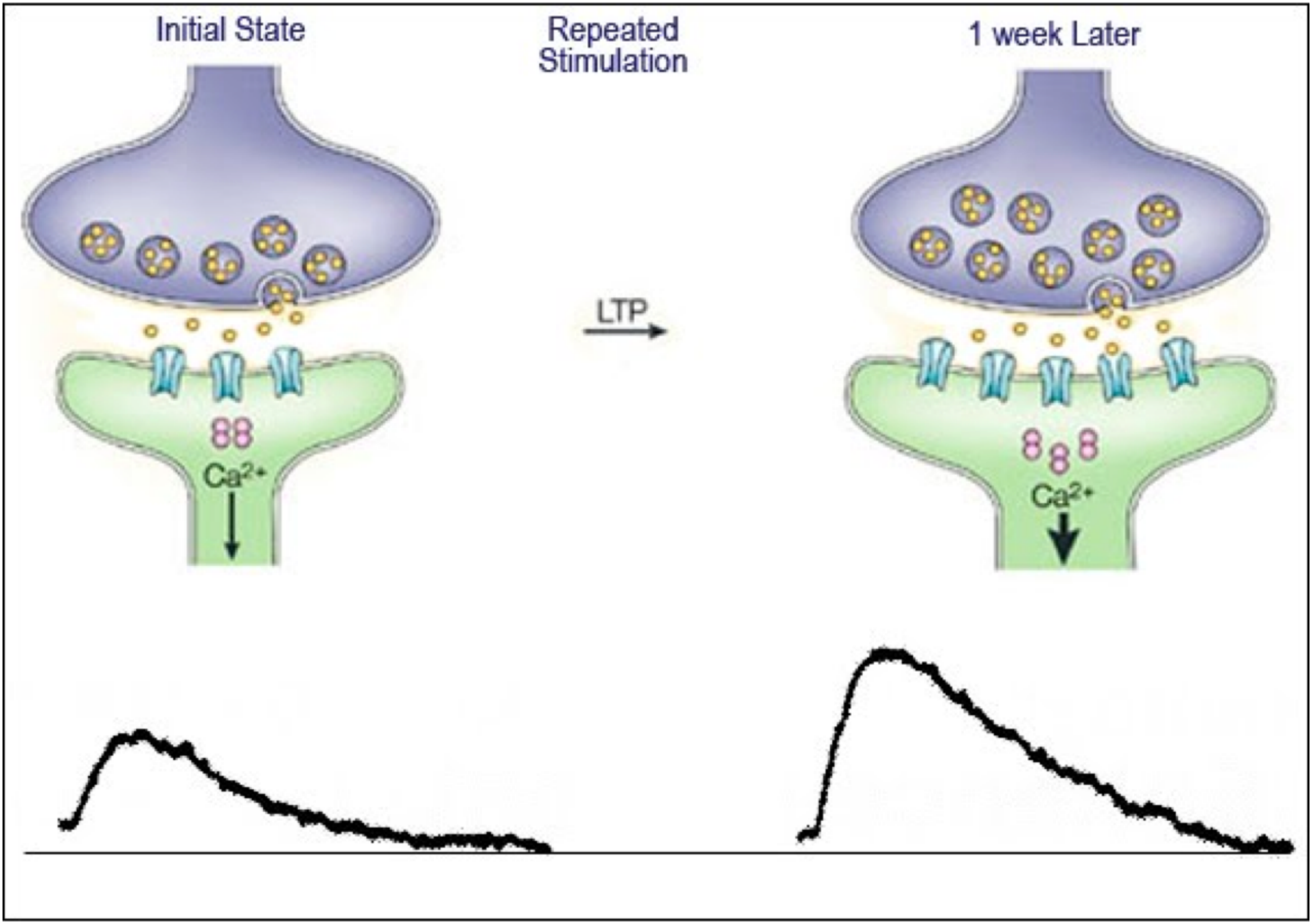
Step 3: continue weak stimulation to record increased responses

Step 4: throughout, check for responses in control fibers (input 2)



Normal mice


Response to first stimulus
Response to same-size stimulus 1 hr later
Stimulus
Current flow in postsynaptic cell
20
40
msec



Initial State
Repeated Stimulation
1 week Later
LTP
Ca2+
Ca2+

LTP

LTP is input specific.

LTP is long-lasting (hours, days, weeks).

LTP results when synaptic stimulation coincides with postsynaptic depolarization (achieved by cooperativity of many coactive synapses during tetanus)(called cooperativity)

The timing of the postsynaptic response relative to the synaptic inputs is critical.

LTP has Hebbian characteristics ("what fires together wires together", or, in this case, connects together more strongly).

LTP may produce long terms changes?

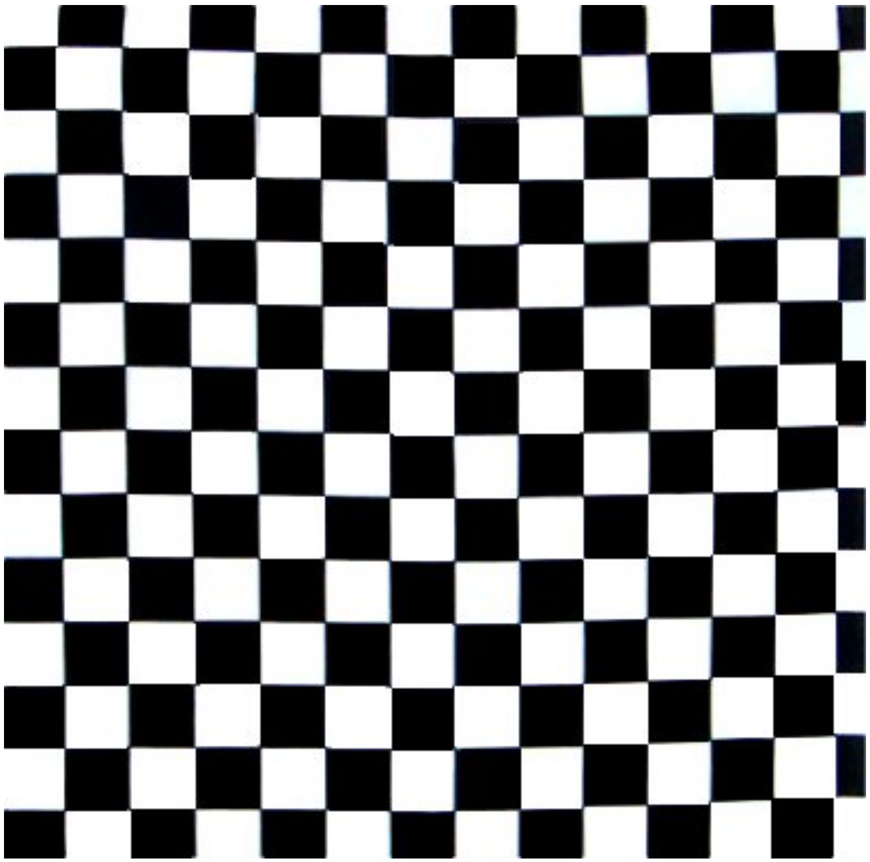
European Journal of Neuroscience, Vol. 21, pp. 2045–2050, 2005

SHORT COMMUNICATION
Long-term potentiation of human visual evoked responses

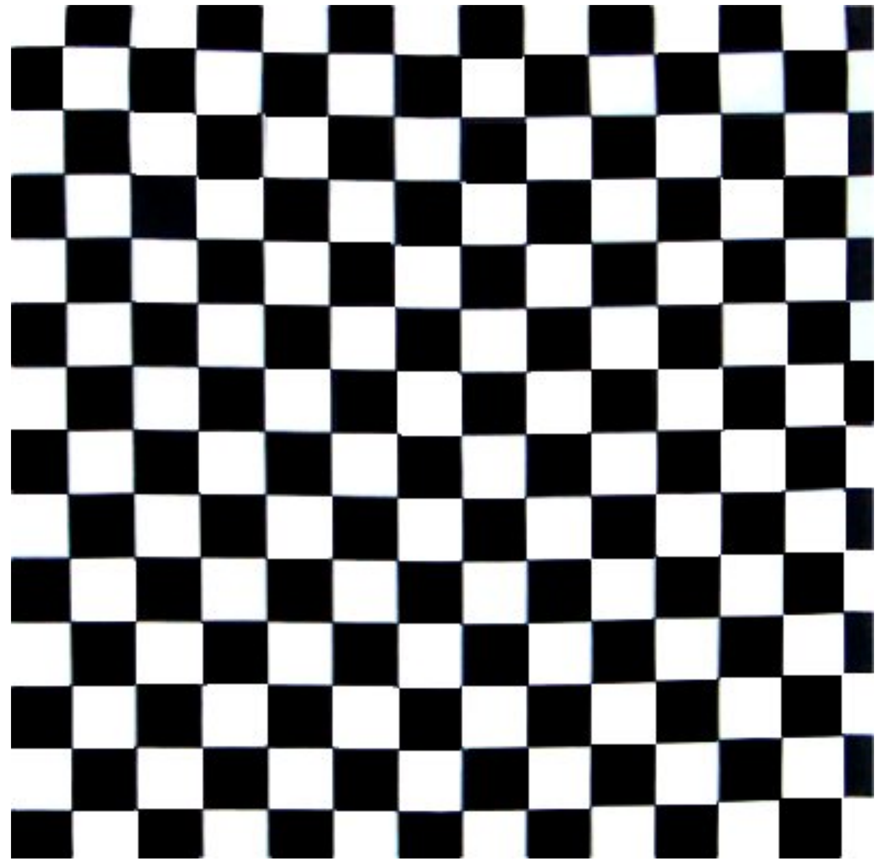
Timothy J. Teyler,[1] Jeff P. Hamm,[2] Wesley C. Clapp,[2] Blake W. Johnson,[2] Michael C. Corballis[2] and Ian J. Kirk[2]

[1]Medical Education Program, University of Idaho, Moscow, ID and Department of Veterinary & Comparative Anatomy, Pharmacology & Physiology, Washington State University, Pullman, WA, USA

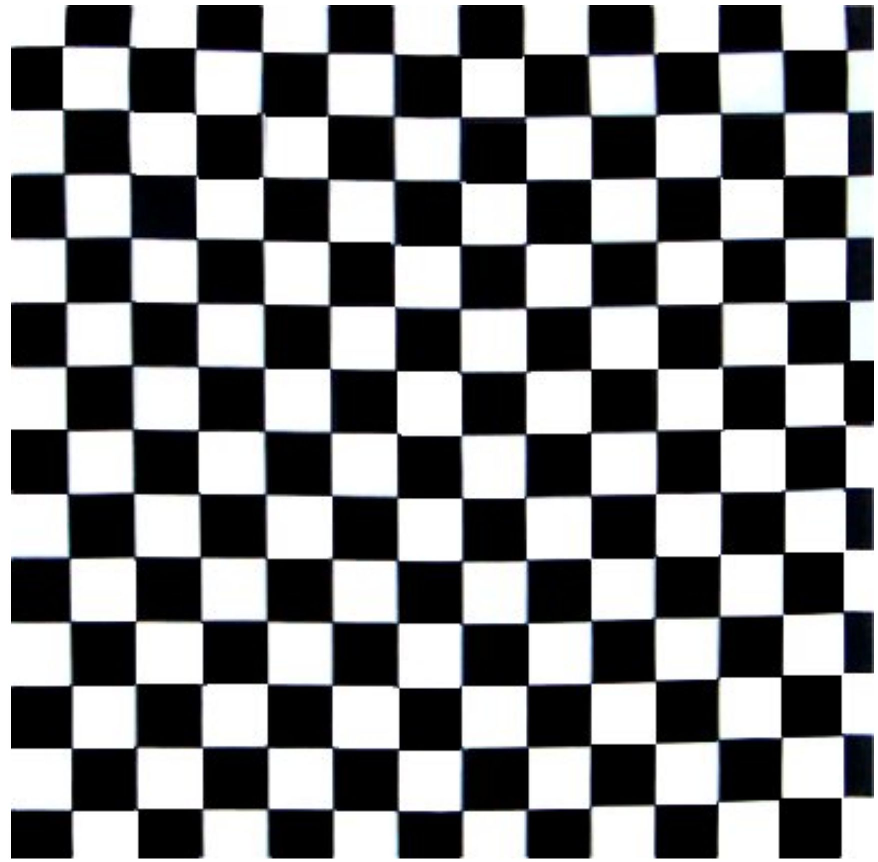
[2]Department of Psychology, and Research Centre for Cognitive Neuroscience, University of Auckland, Private Bag 92019, Auckland, New Zealand



1 Hz (7 min)

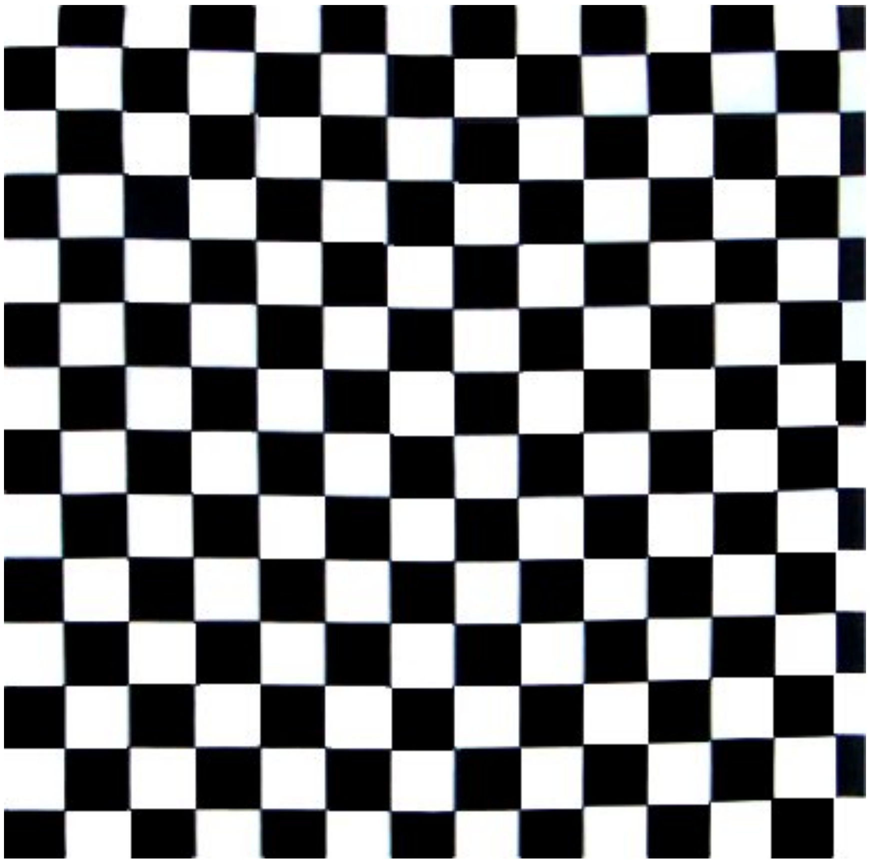


1 Hz (7 min)

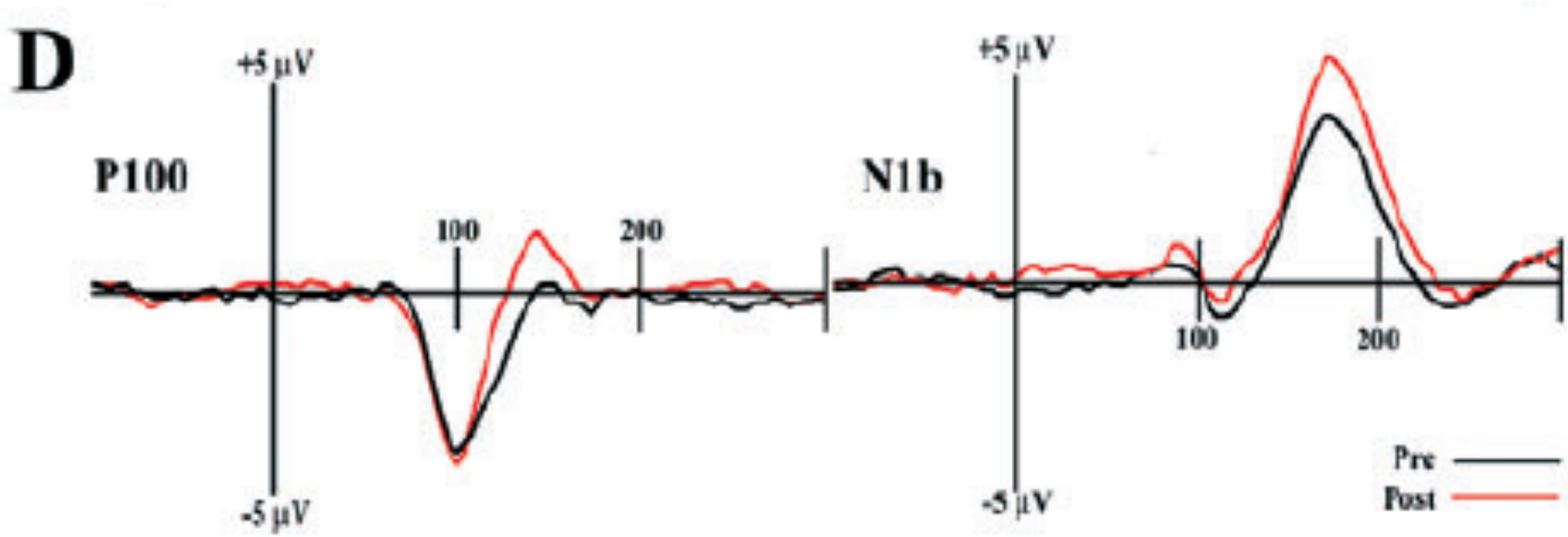


9 Hz (120 s): Tetanus

(120 s): Rest

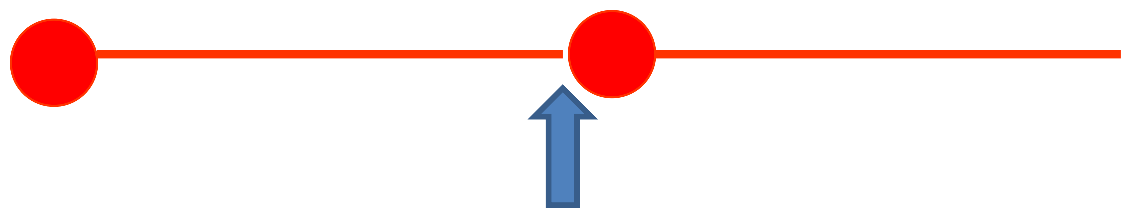


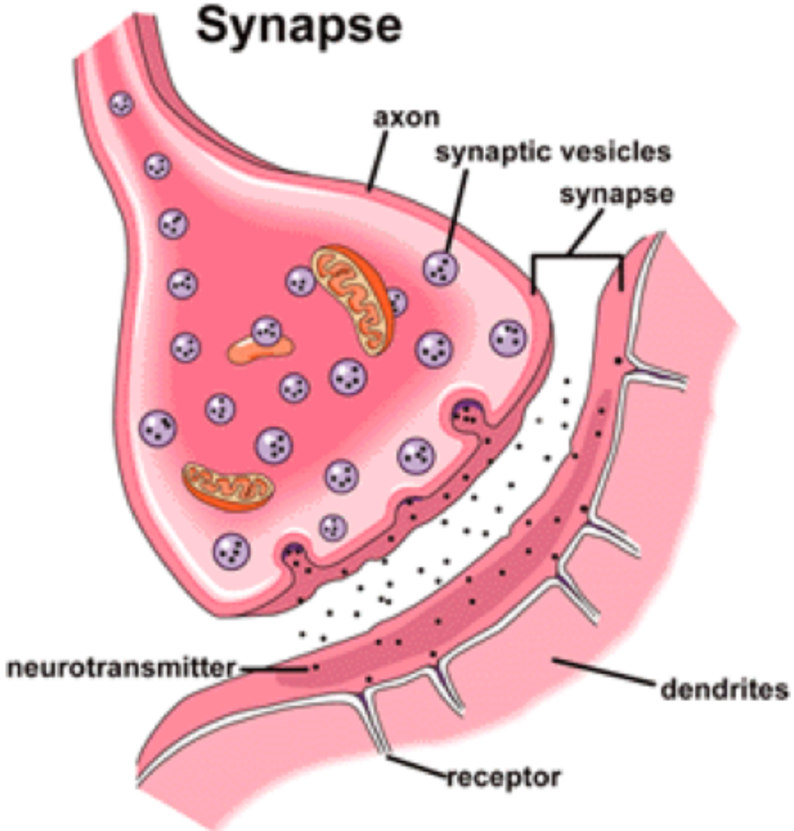
1 Hz (every 15 min for 7 min)



D
P100
+5 µV
-5 µV
100
200
N1b
+5 µV
-5 µV
100
200
Pre
Post

Long Term Changes: Synaptic Plasticity





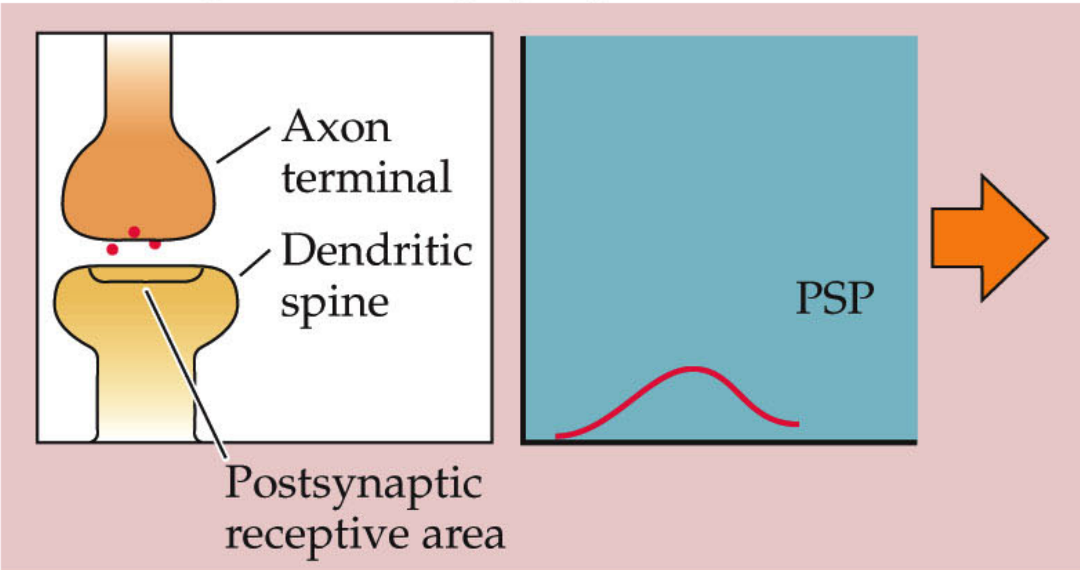
HOW?

Increased neurotransmitter release
Increase receptors
Structural changes

Figure 18.2 Synaptic Changes That May Store Memories (Part 1)

Before training

(*a*) Changes involving synaptic transmitters



After training

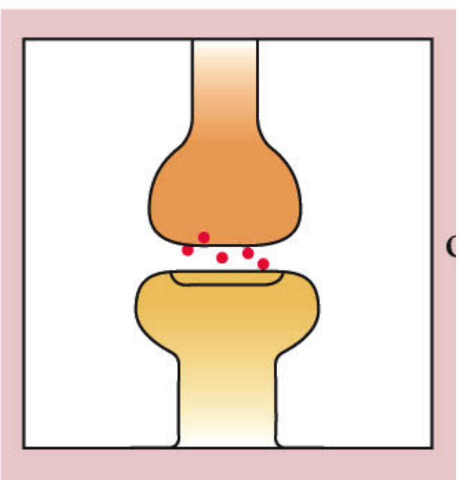
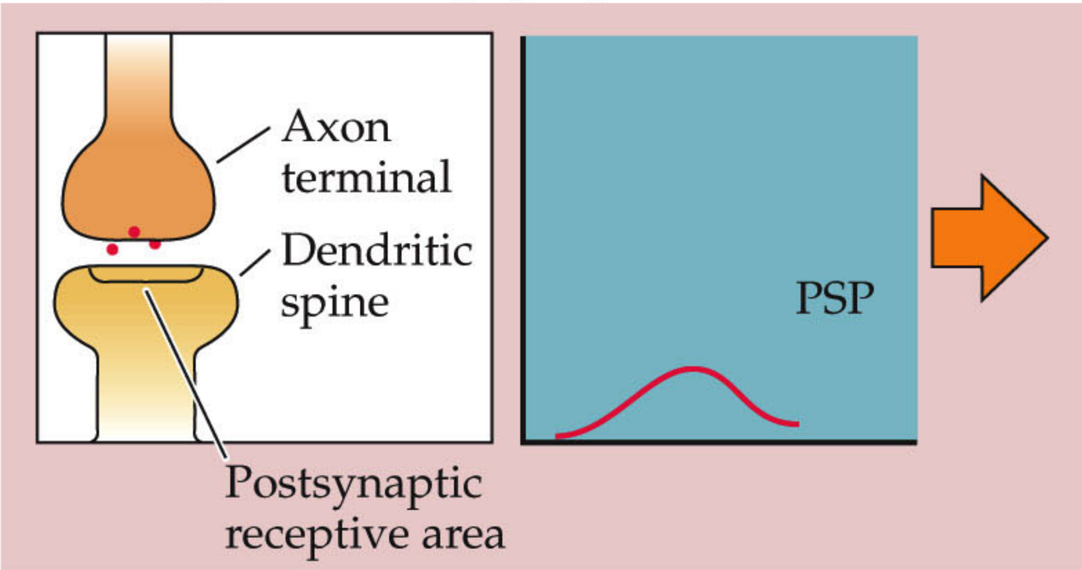


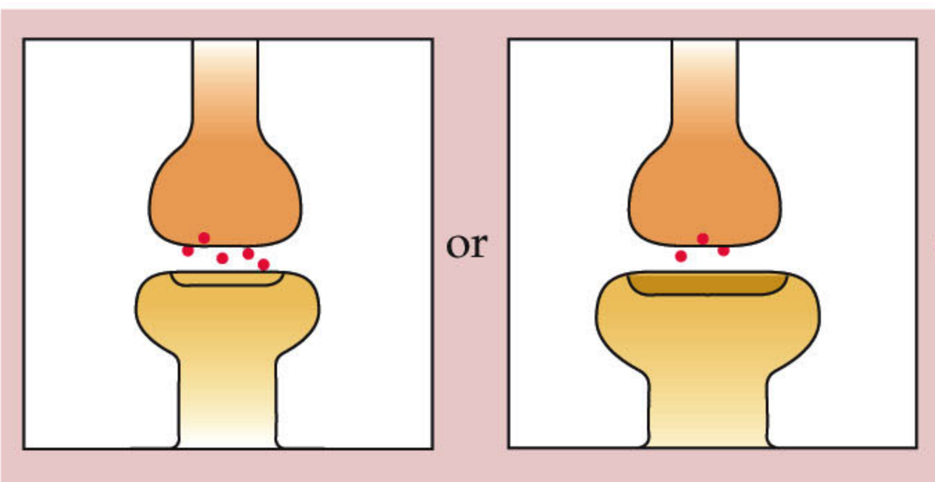
Figure 18.2 Synaptic Changes That May Store Memories (Part 1)

Before training

(*a*) Changes involving synaptic transmitters

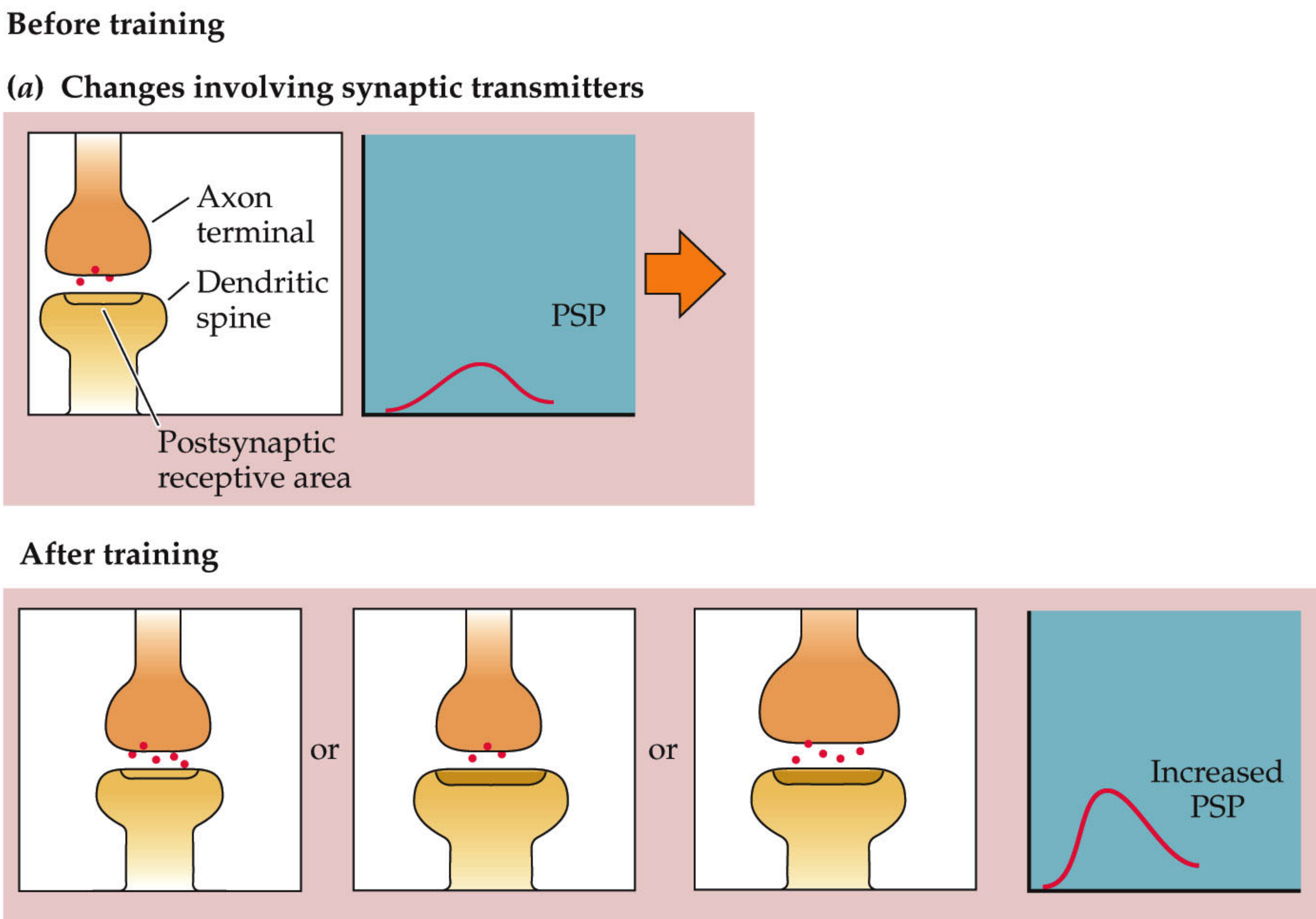


After training

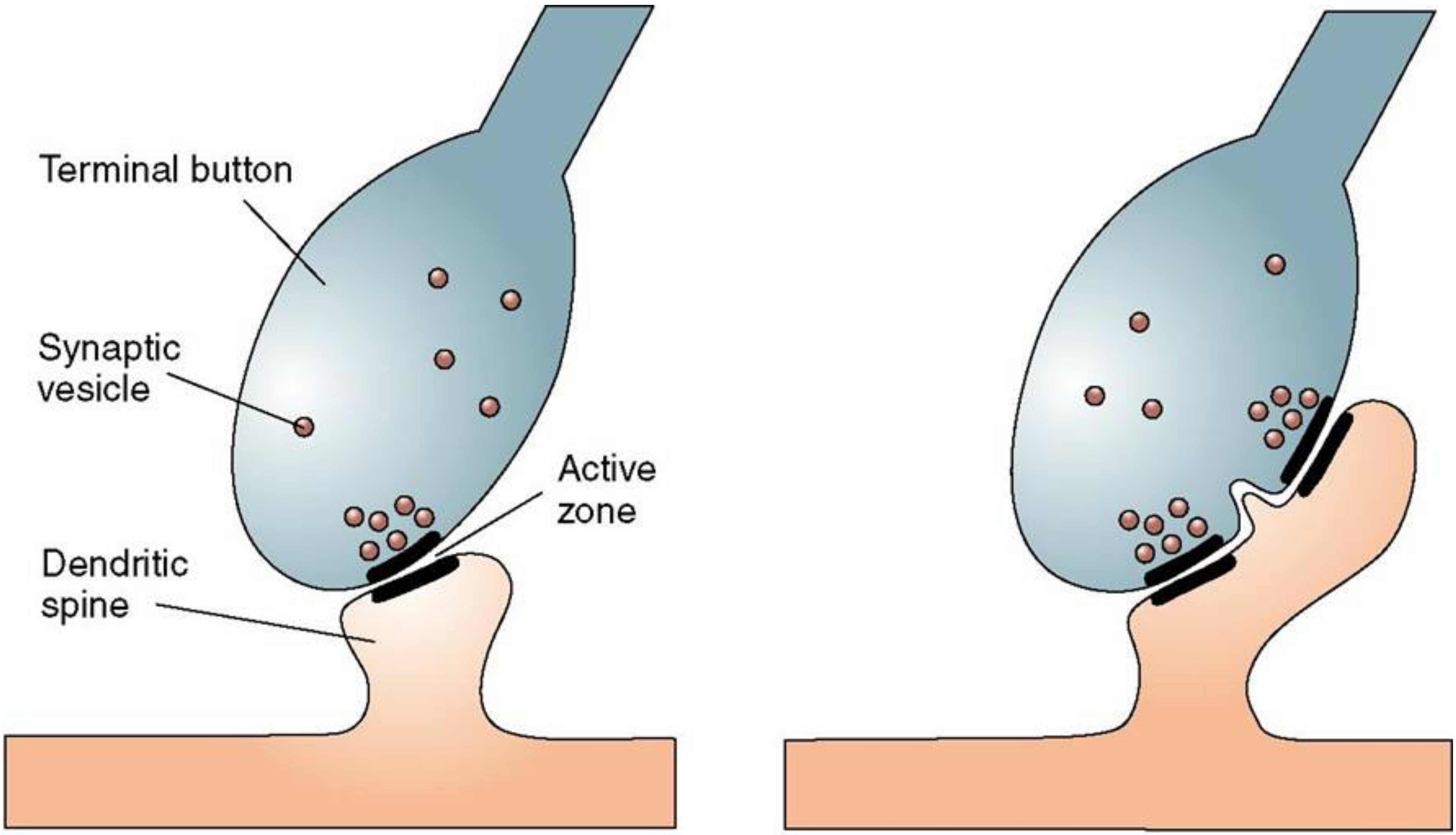


***Biological Psychology 5e*, Figure 18.2 (Part 1)**

Figure 18.2 Synaptic Changes That May Store Memories (Part 1)



Biological Psychology 5e, Figure 18.2 (Part 1)

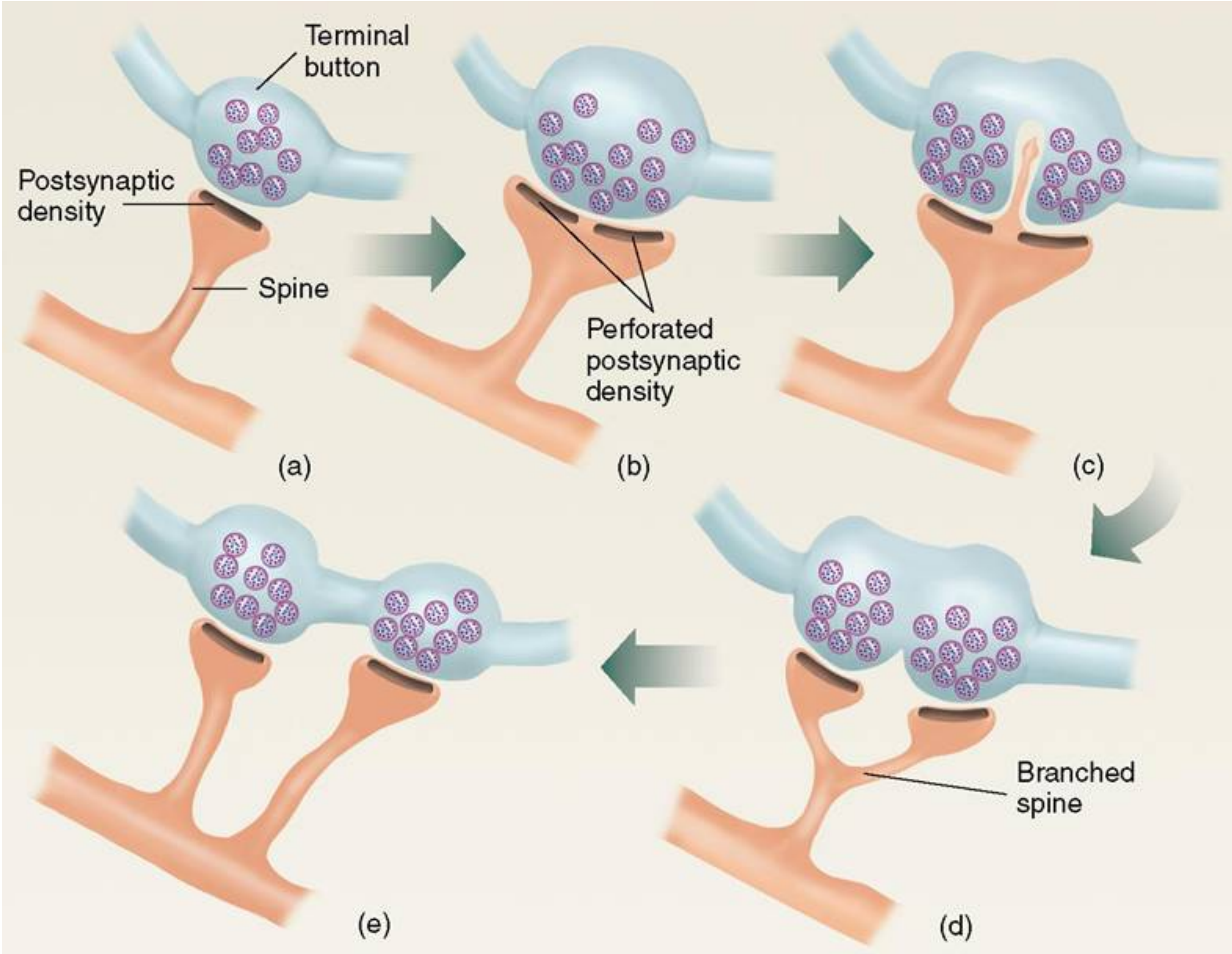


Before long-term potentiation

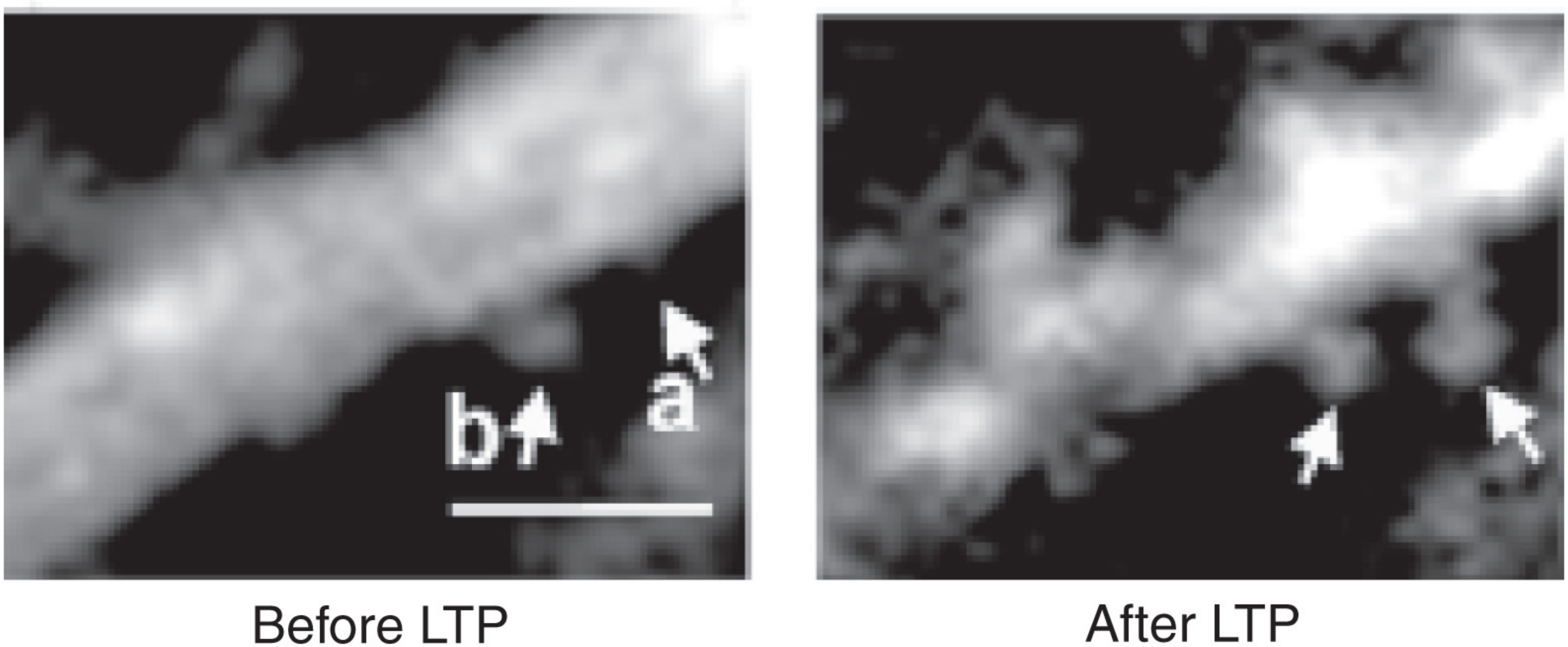
(a)

After long-term potentiation:
Generation of a perforated synapse

(b)


Terminal
button
Postsynaptic
density
Spine
(a)
Perforated
postsynaptic
density
(b)
(c)
Branched
spine
(d)
(e)

C7B12F10.eps



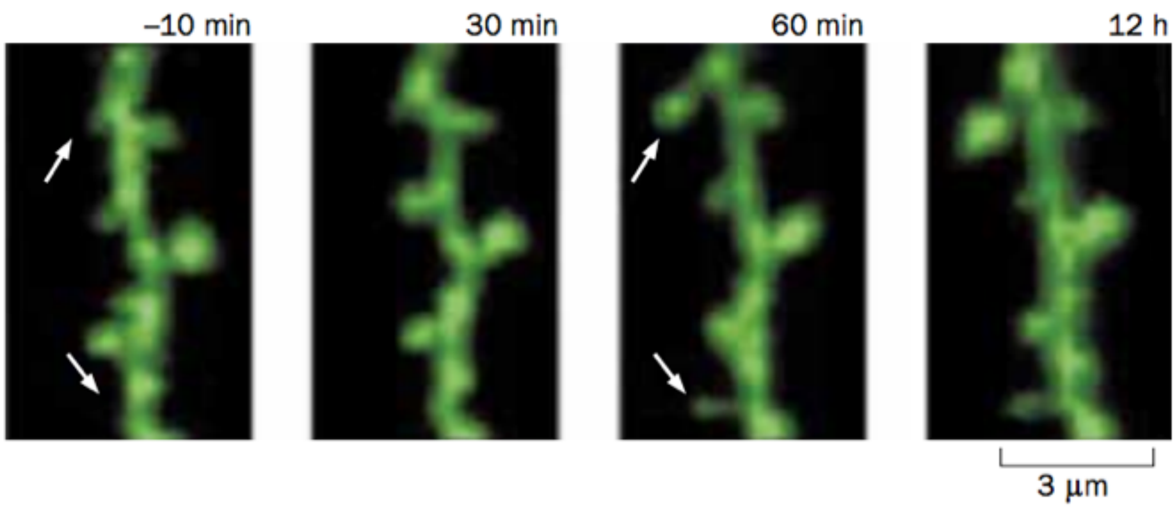
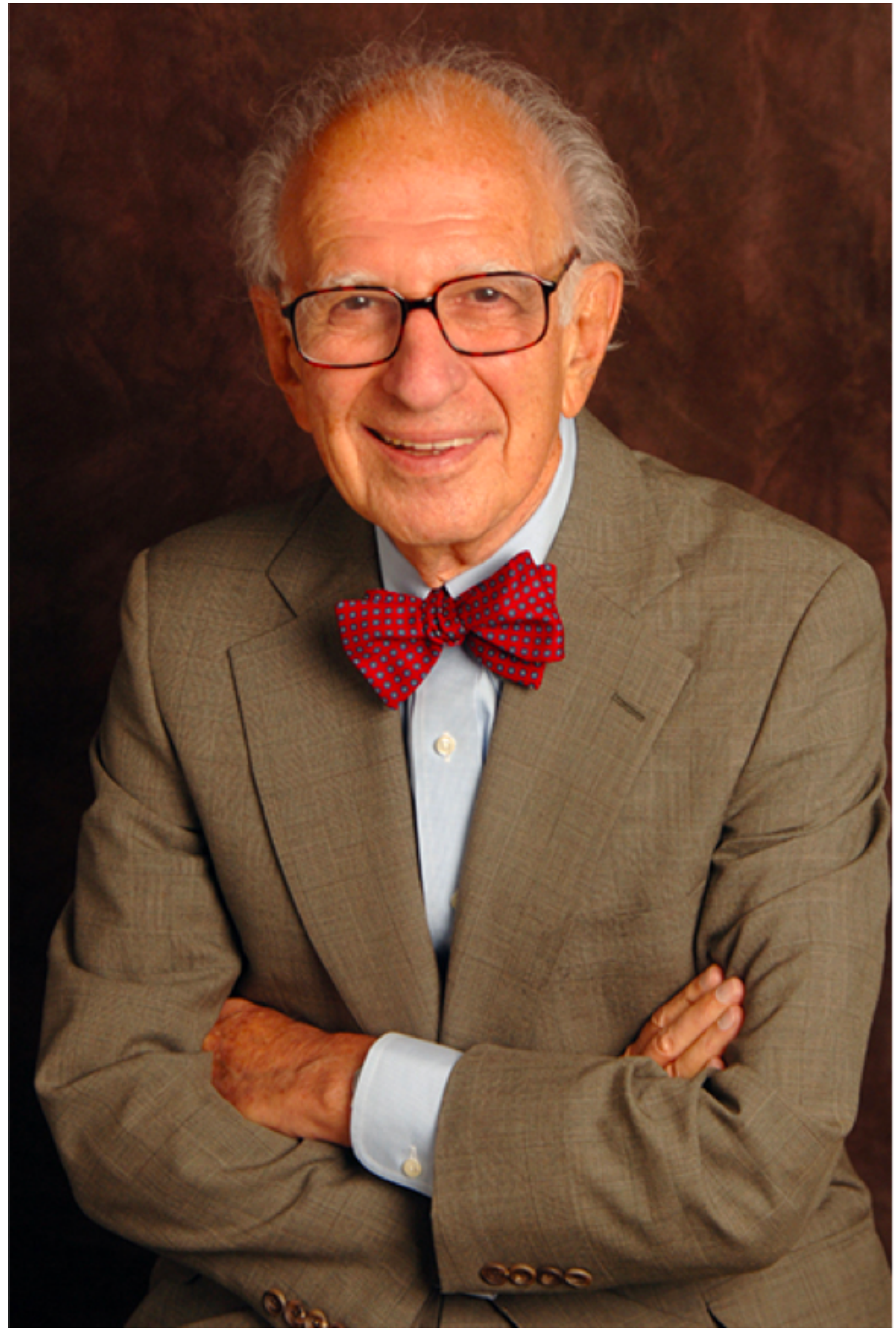


Figure 10–18 Growth of dendritic spines correlates with LTP. LTP is accompanied by the formation of two new spines (arrows) in CA1 pyramidal neurons from a cultured hippocampal slice that was imaged using two-photon microscopy. Time-lapse images were taken at −10, +30, +60 min, and +12 h relative to the onset of LTP induction (not shown). (From Engert F & Bonhoeffer T [1999] *Nature* 399:66–70. With permission from Macmillan Publishers Inc.)

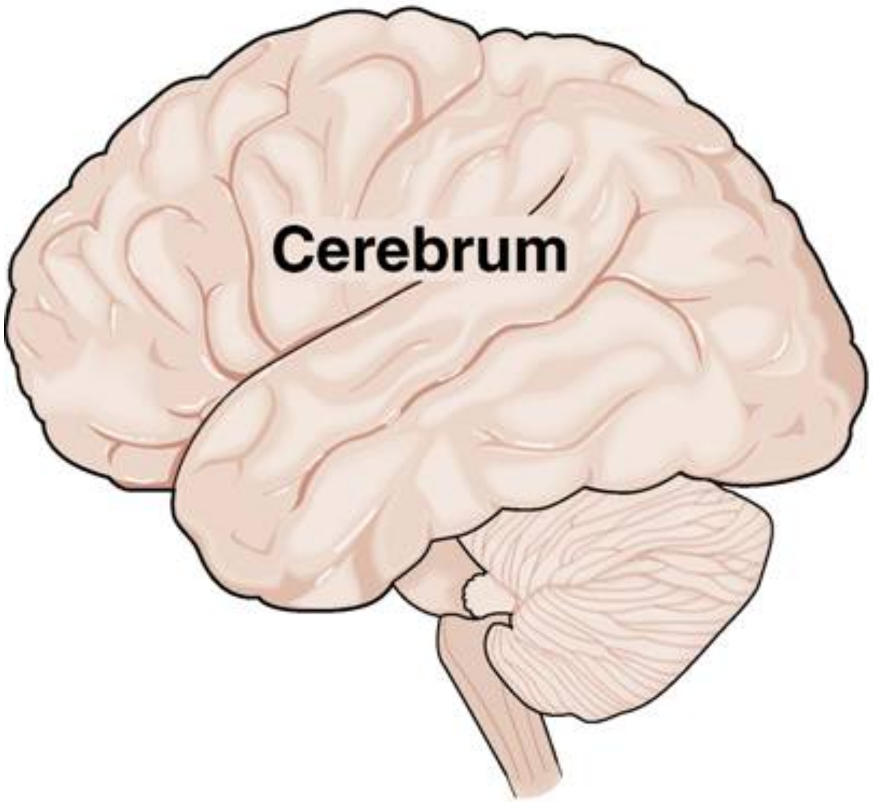
Eric Kandel, MD
Nobel Prize Winner



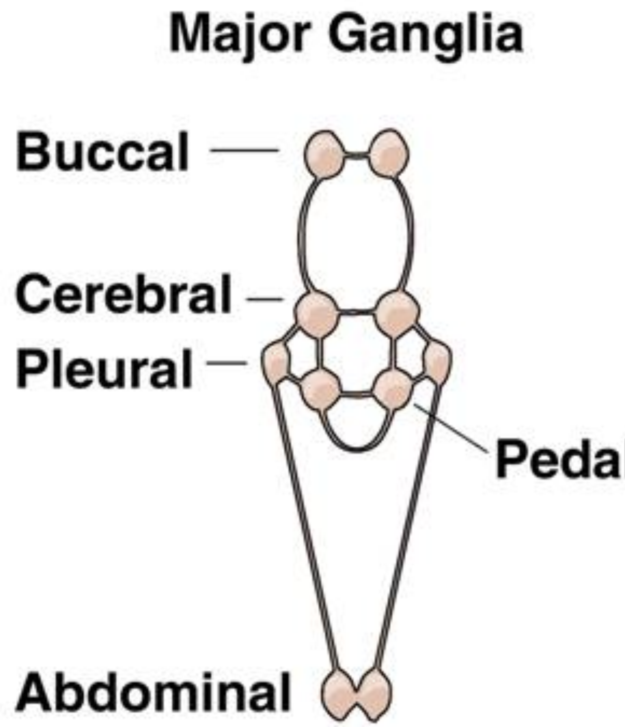
Prerequisites for a Molecular Biological Study of Learning and Memory

- Delineate a behavior capable of being modified by learning
- Define, in cellular detail, the neural circuit of that behavior
- Locate, within that neural circuit, the critical neurons and interconnections modified by learning that store memory
- Analyze the mechanisms of learning and memory storage on the cellular and molecular level

The Human Brain is complex: 10^{12} Neurons



The *Aplysia* Brain is simple: 2×10^{4} Neurons



Gill withdrawal reflex using *Aplysia californica* sea slug:

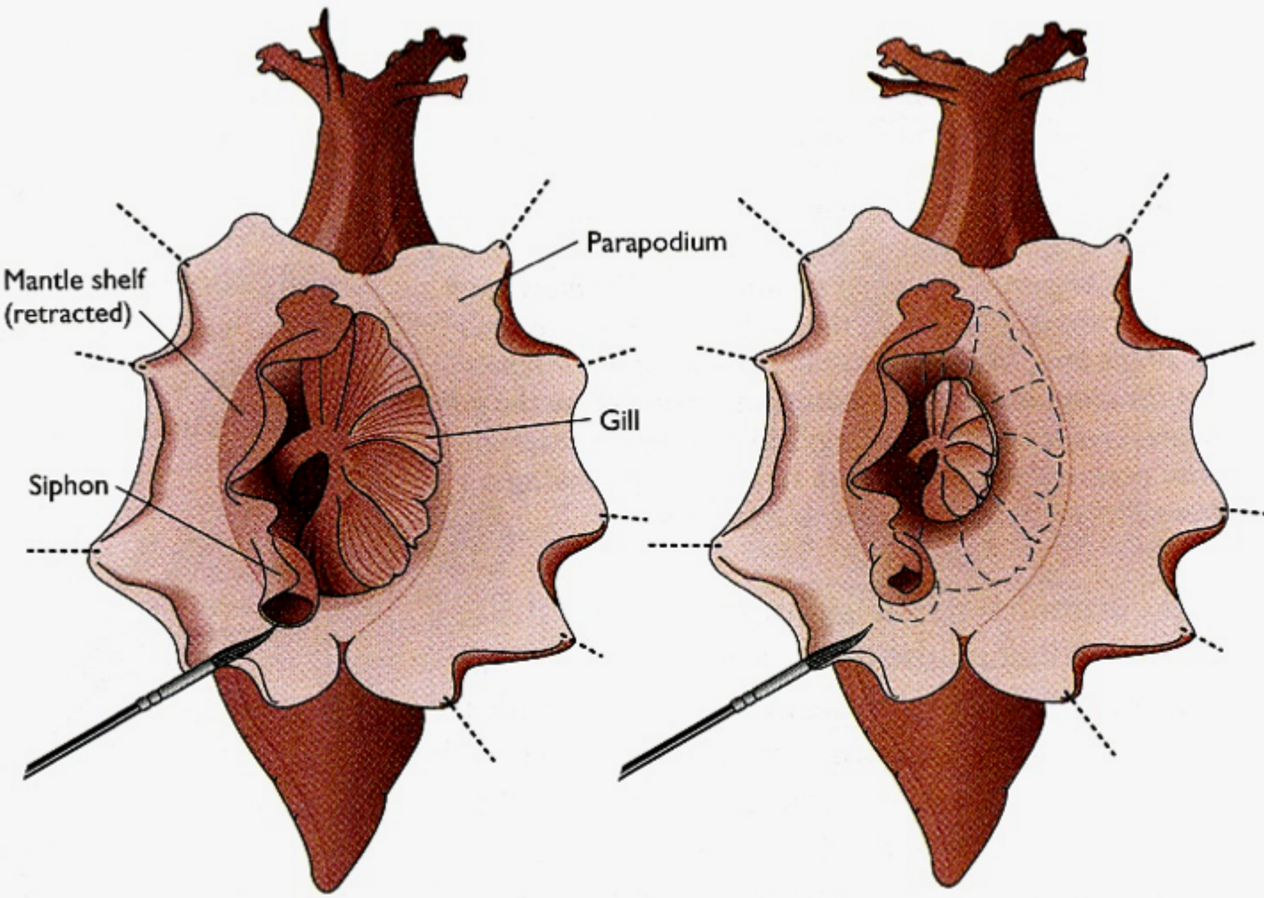
-A mantle-covered gill is used for breathing

-A siphon is used for expelling seawater and waste

-Gill withdrawal occurs when the siphon is touched

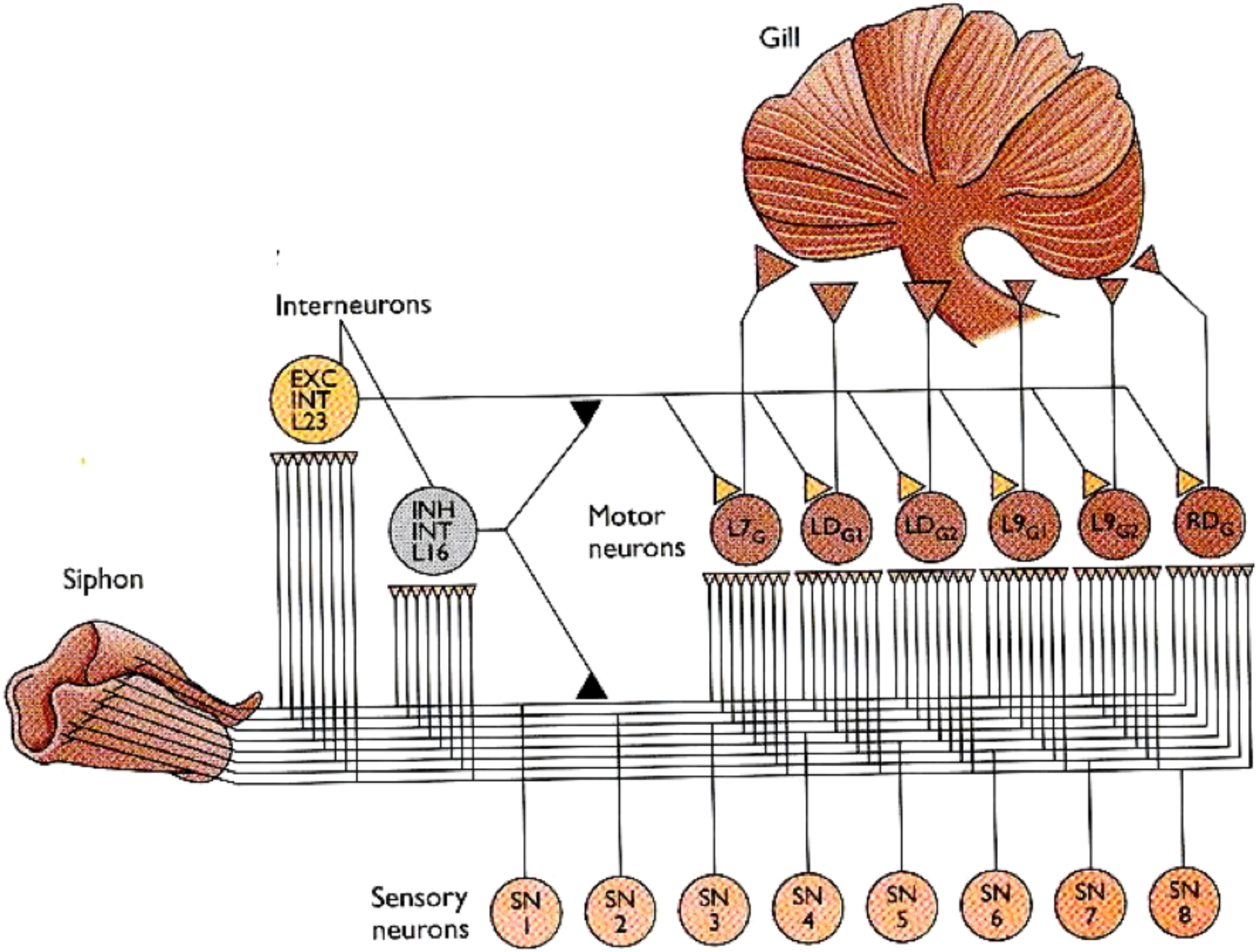
-Defensive mechanism used by *Aplysia*

Aplysia protects itself from potential harm by withdrawing its gill when the siphon is touched



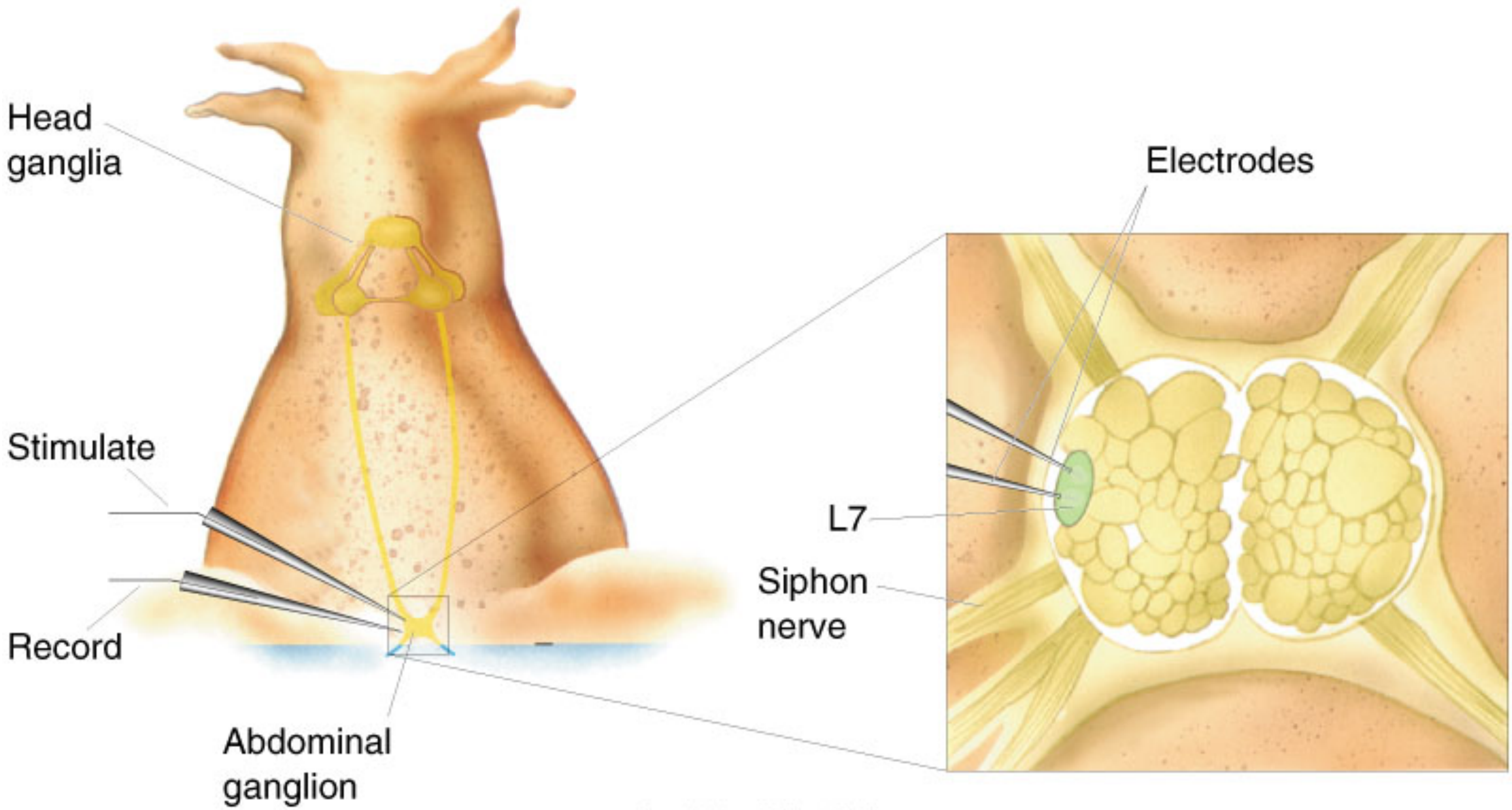
The gill and siphon withdrawal reflex of Aplysia*. A light touch to the siphon with a fine paintbrush (left) causes the siphon to contract and the gill to withdraw under the protection of the mantle shelf, here shown retracted for a better view.*

40 sensory neurons (siphon skin) synapse w/ 6 gill MNs & excitatory and inhibitory INs

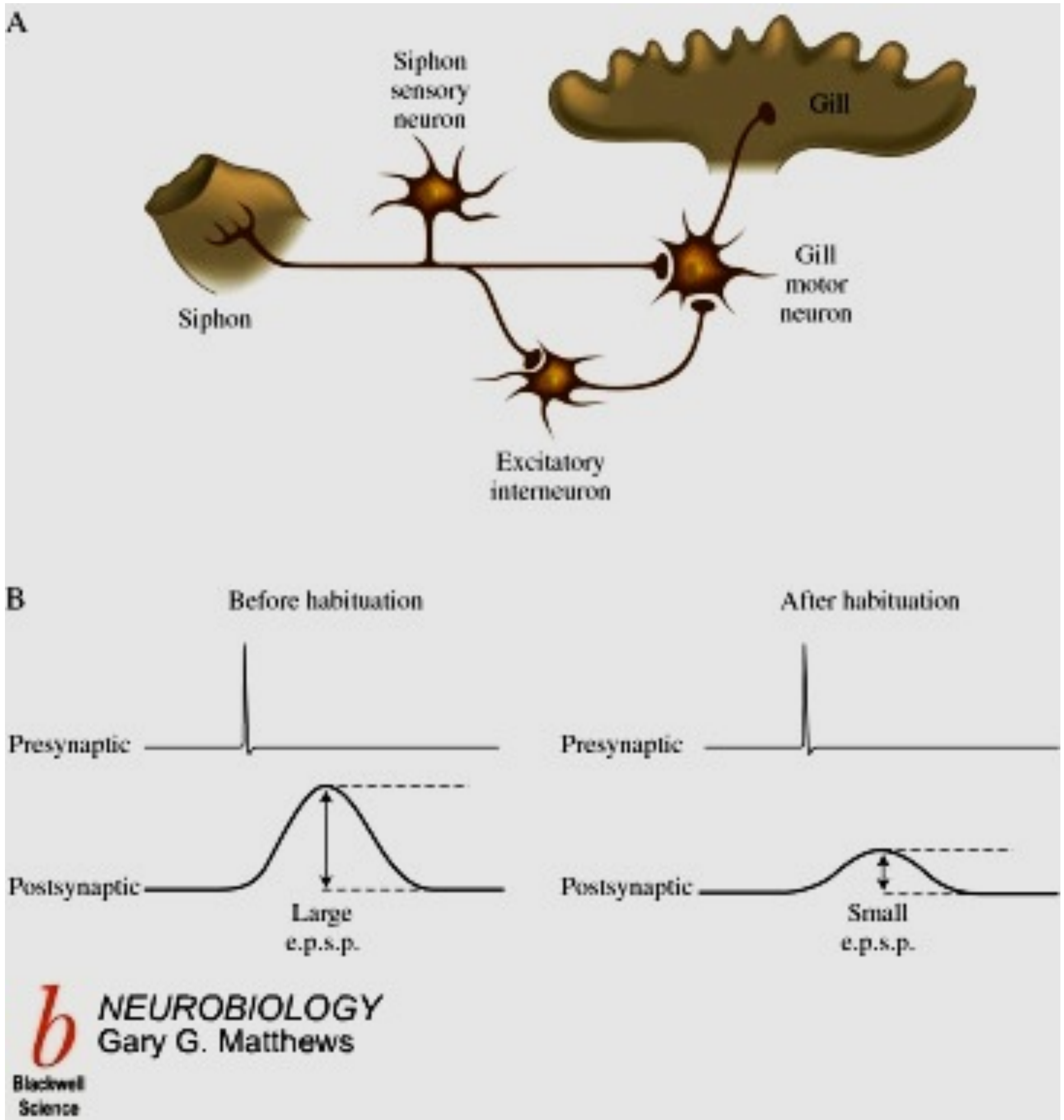


Electrophysiology in *Aplysia* using the abdominal ganglia

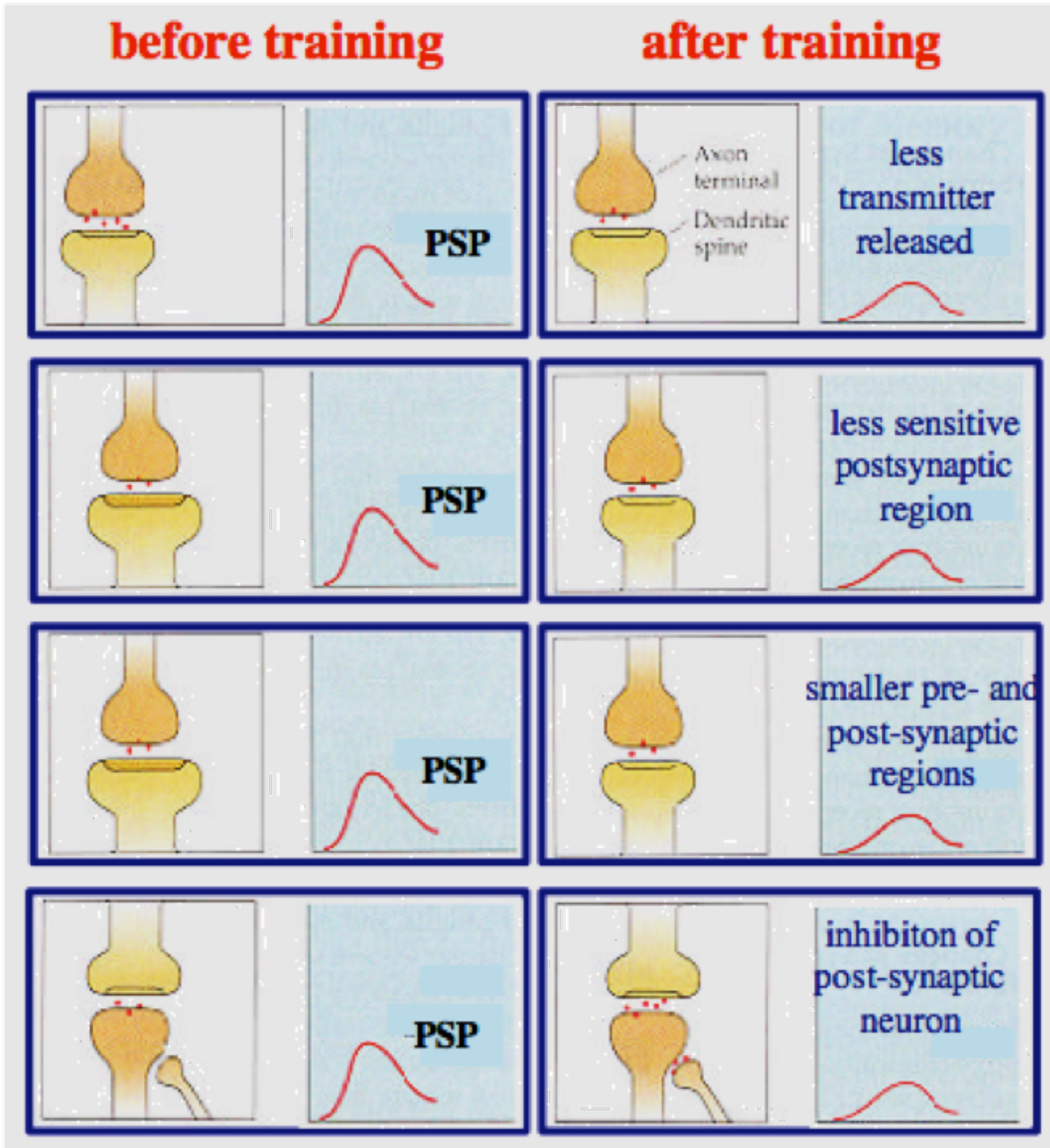
Figure 24.5
The abdominal ganglion of Aplysia. The gill withdrawal reflex involves neurons within the abdominal ganglion that can be dissected and studied electrophysiologically.



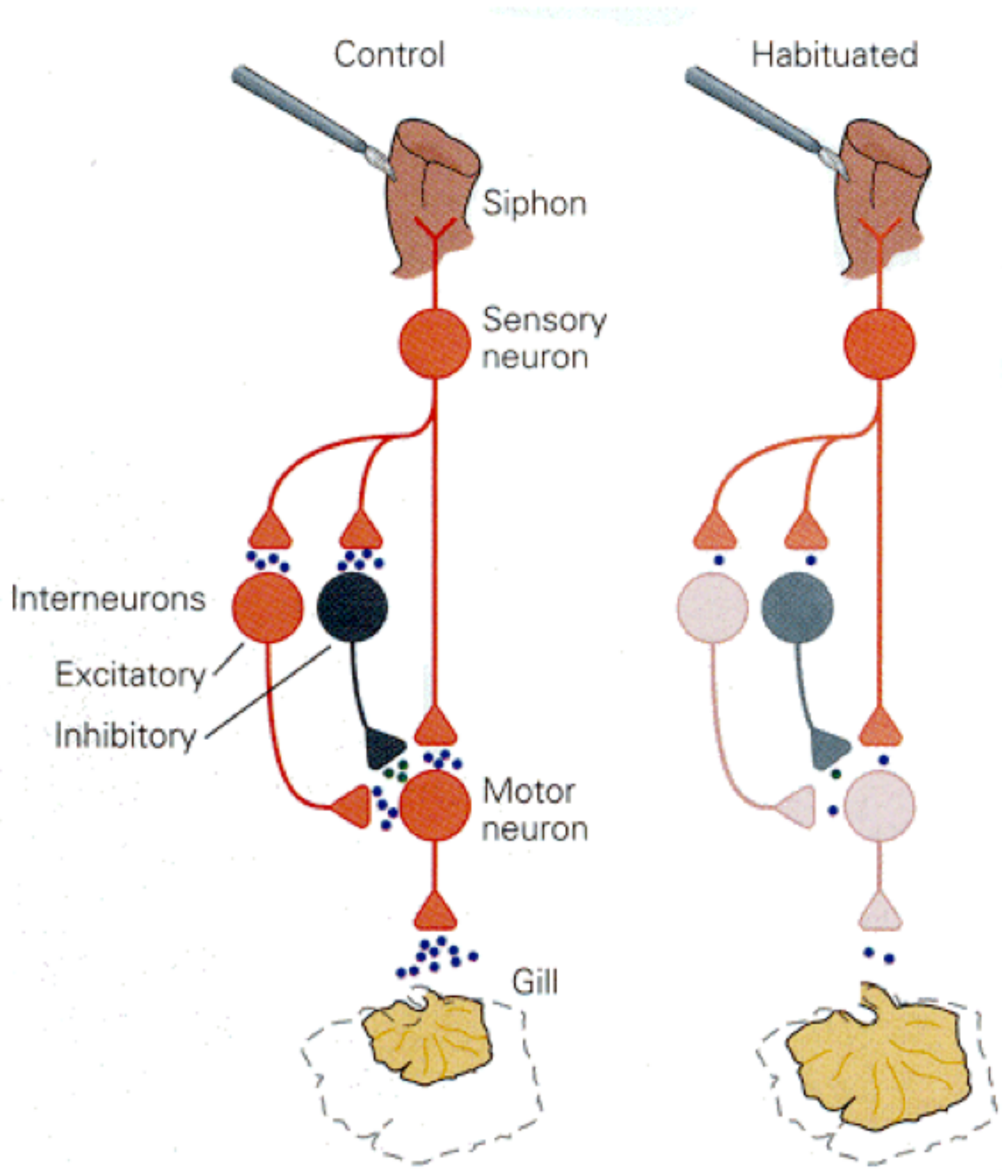
Habituation was observed in *Aplysia* by EPSP recordings after repeated siphon stimulation



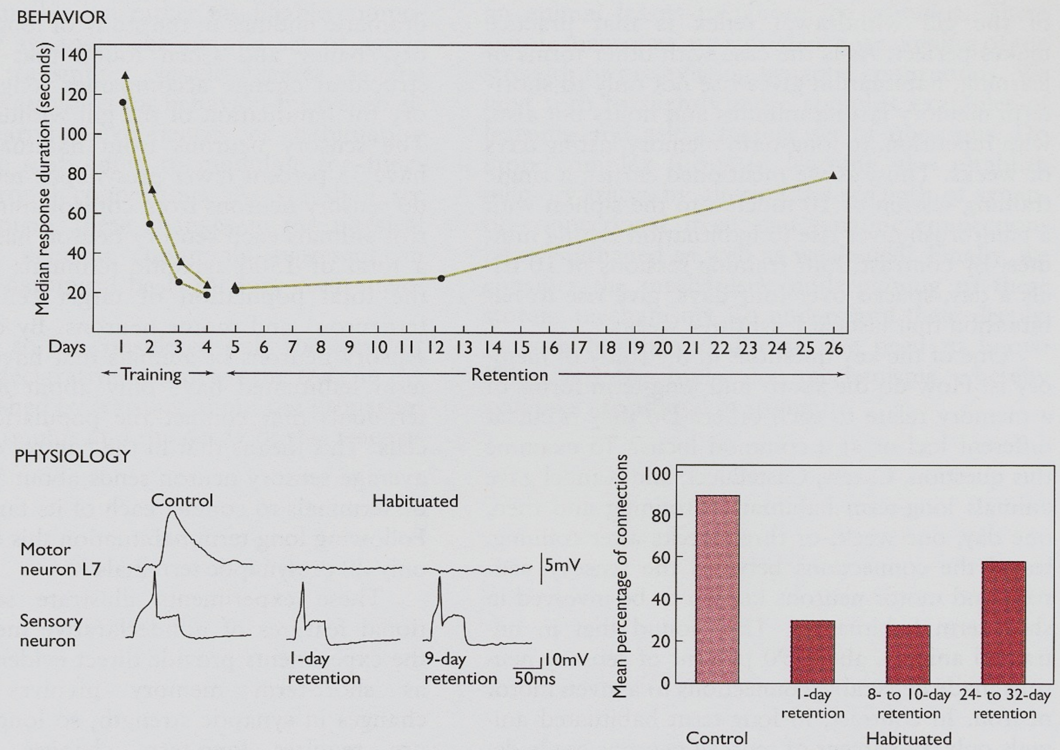
Possible mechanisms for short-term habituation

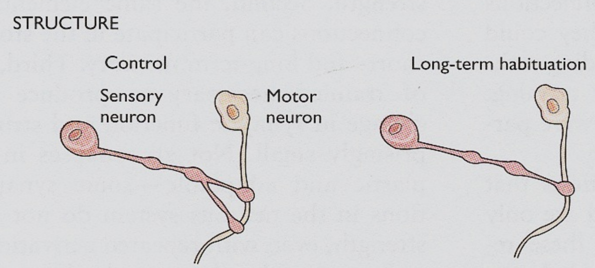


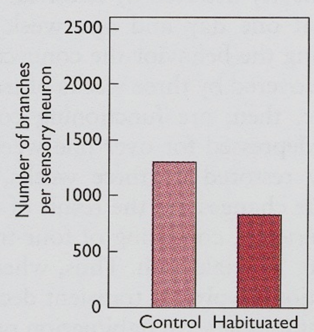
Habituation leads to decreased neurotransmitter release and reduced gill withdrawal



Long-term habituation after 4 days of training→ synaptic depression & fewer sensorimotor synapses





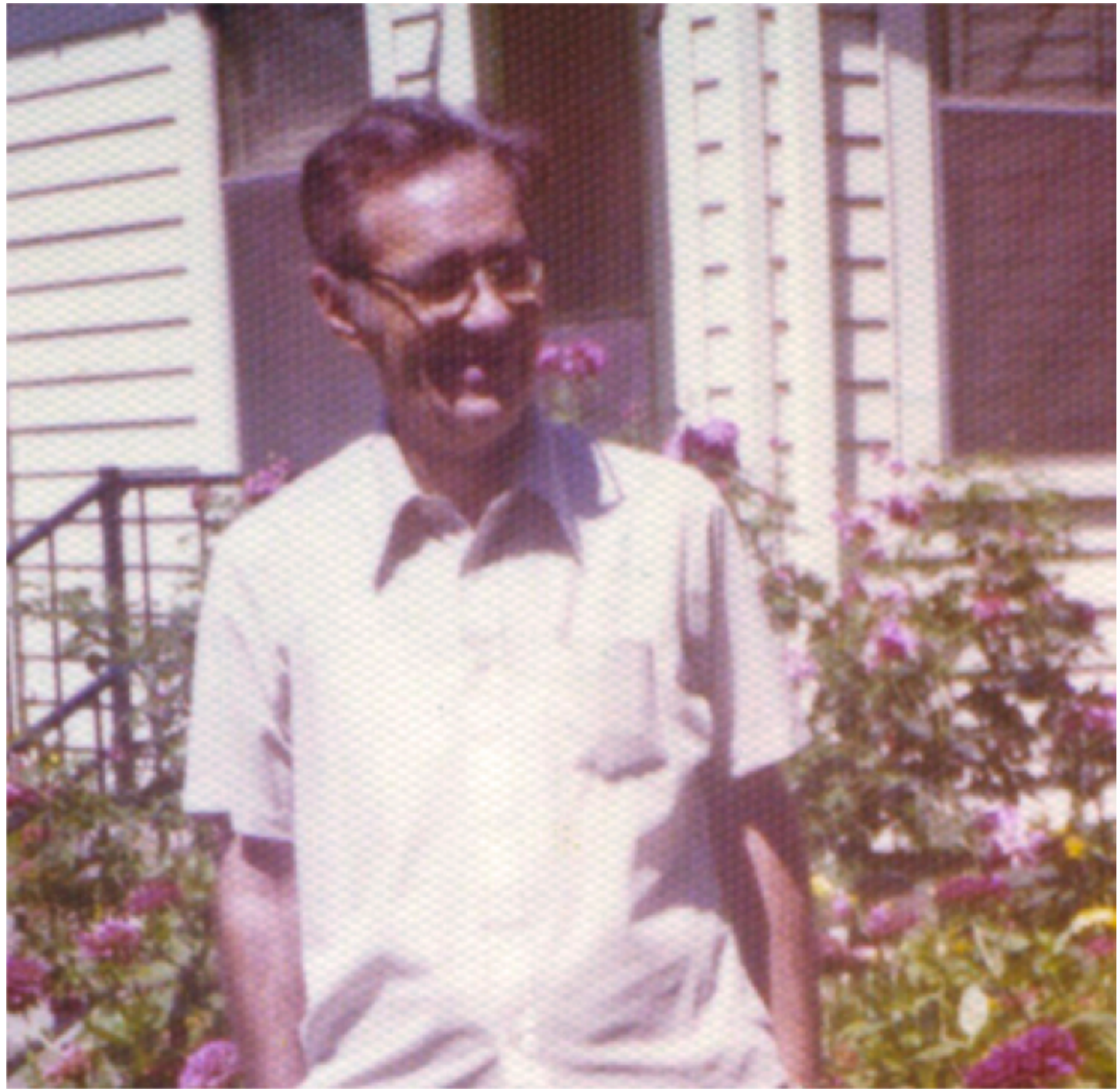


Training sessions of 10 stimuli apiece, given daily over four days to two groups of animals, lead to long-term habituation in Aplysia that persists for more than a week, as shown by the decrease in the duration of the behavioral withdrawal response (top) and by the dramatic depression of synaptic effectiveness observed in recordings of postsynaptic potentials in the motor neurons from these animals (second from top). The time course of the synaptic depression indicated in the top histogram on the right parallels that of the behavioral habituation. This long-term synaptic depression is accompanied by anatomical changes. In the habituated animal the sensory neurons retract their processes and now make fewer contacts onto motor neurons (bottom) than do sensory neurons in control, nonhabituated animals.

In other words, Dr. Kandel observed both short term and long term changes in memory (in this case habituation) and also mapped the neural circuitry.

= NOBEL PRIZE

H.M.
”Most studied person in all of psychology”



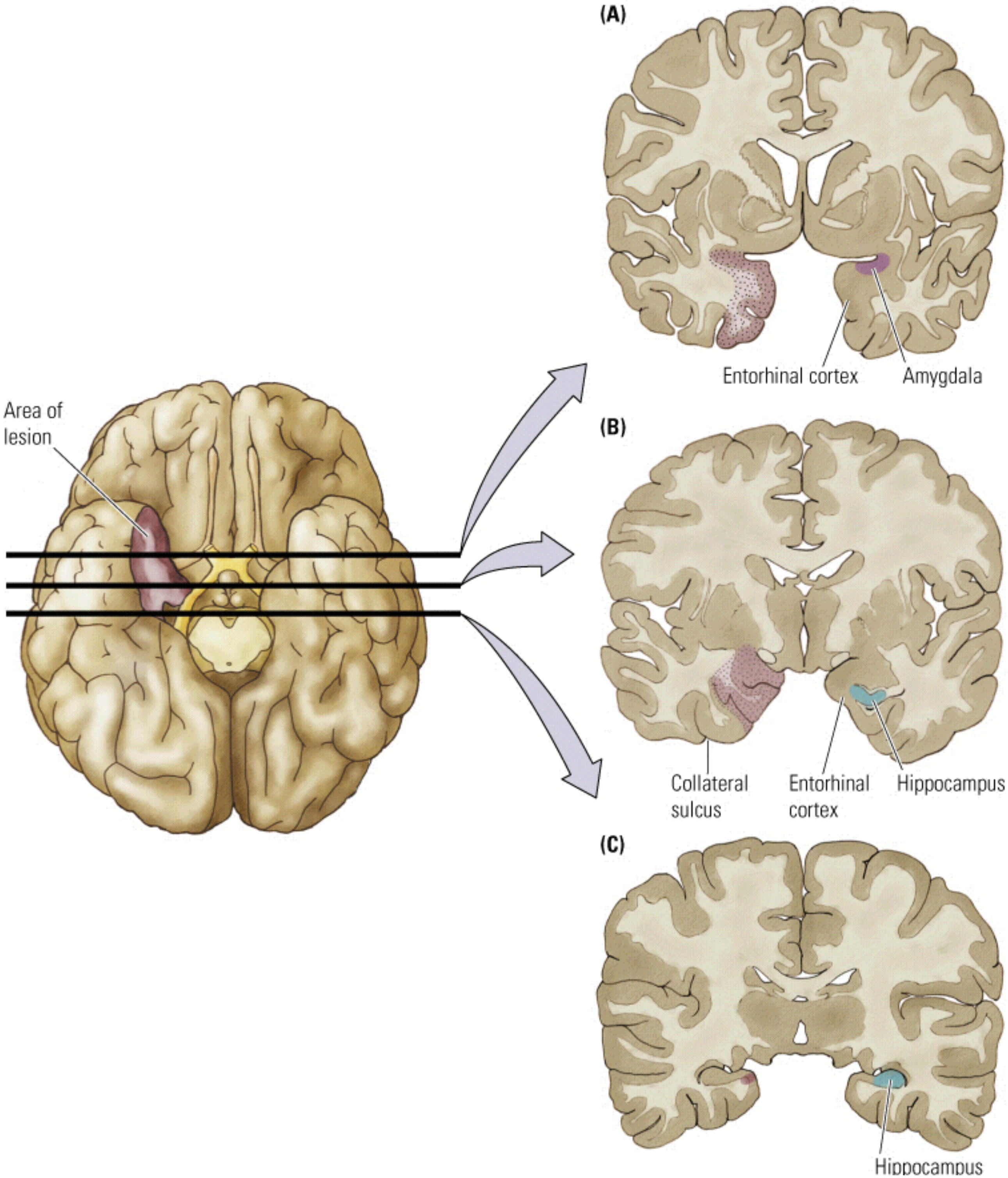
The Brain and the Two-Track Mind: The Case of Henry Molaison ("H.M.")

- In 1953, the removal of H.M.'s hippocampus at age 27 ended his seizures, but also ended his ability to form new explicit memories.
- H.M. could learn new skills, procedures, locations of objects, and games, but had no memory of the lessons or the instructors. Why?
- H.M. also retained memories from before the surgery. What is his condition called?

H.M., like another such patient, "Jimmy," could not understand why his face looked older than 27 in the mirror. Why not?

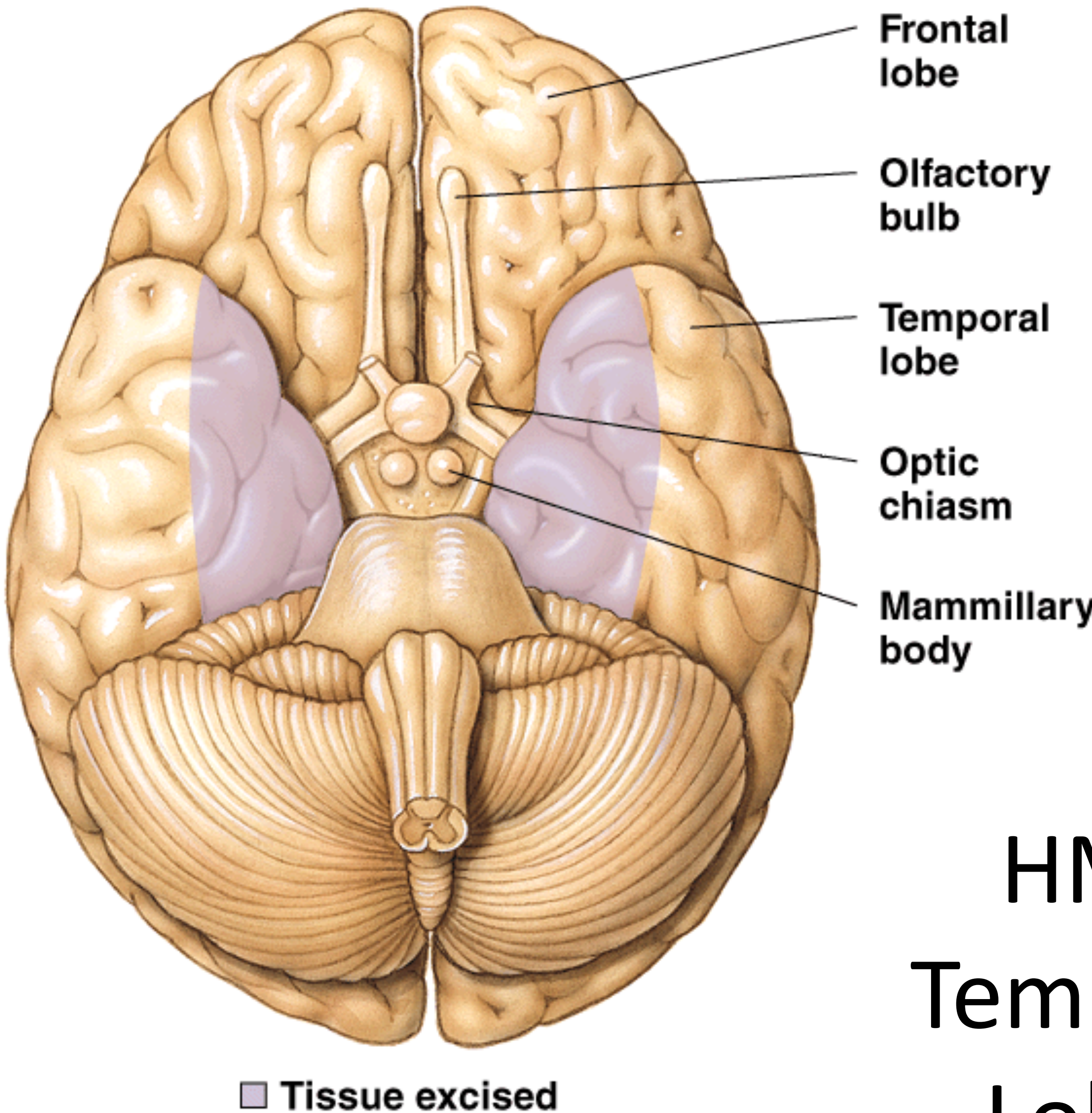
Case of H.M.

- Most studied person in psychology
- Most important case study
- H.M. had severe epilepsy in temporal lobes
- William Scoville, neurosurgeon at Hartford Hospital operated on HM in 1953
- Removed ventral tips of temporal lobes



(A)
Entorhinal cortex
Amygdala
Area of lesion
(B)
Collateral sulcus
Entorhinal cortex
Hippocampus
(C)
Hippocampus

► **Medial Temporal Lobectomy**



HM's Temporal Lobes

Effects on HM

- Recall events from childhood
- Can engage in conversations
- Good semantic memory
- Cannot recall events that have just happened
- Cannot recall any new facts
- Cannot remember new faces

What is HM’s deficit

- Anterograde Amnesia for declarative memory: fact, events, people.
- No concept of amount of time that has passed.
- Still shows procedural memory: new tasks.
- Some implicit memory: realizes that his parents have died.

A large percentage of modern theory of memory is based on the study of H.M.

Shiffrin Model of Memory