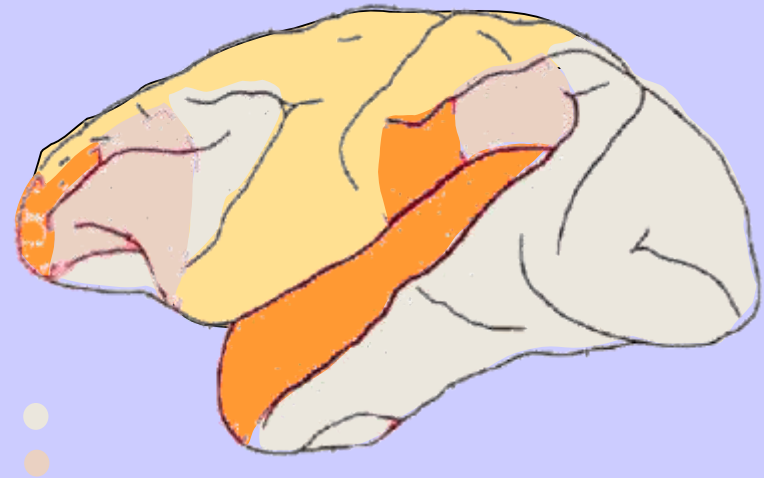
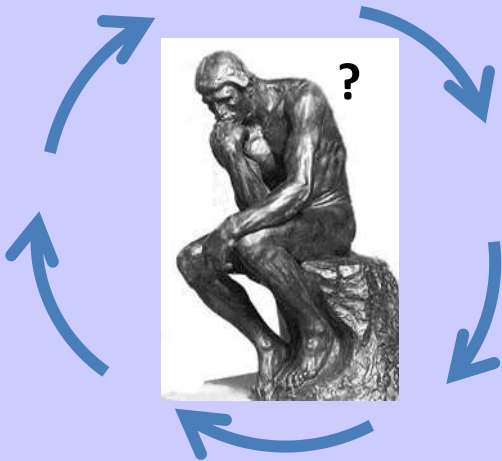


Learning at the synapse

Bertil Hille, PhD

Physiology and Biophysics
University of Washington School of Medicine
Seattle Washington, USA

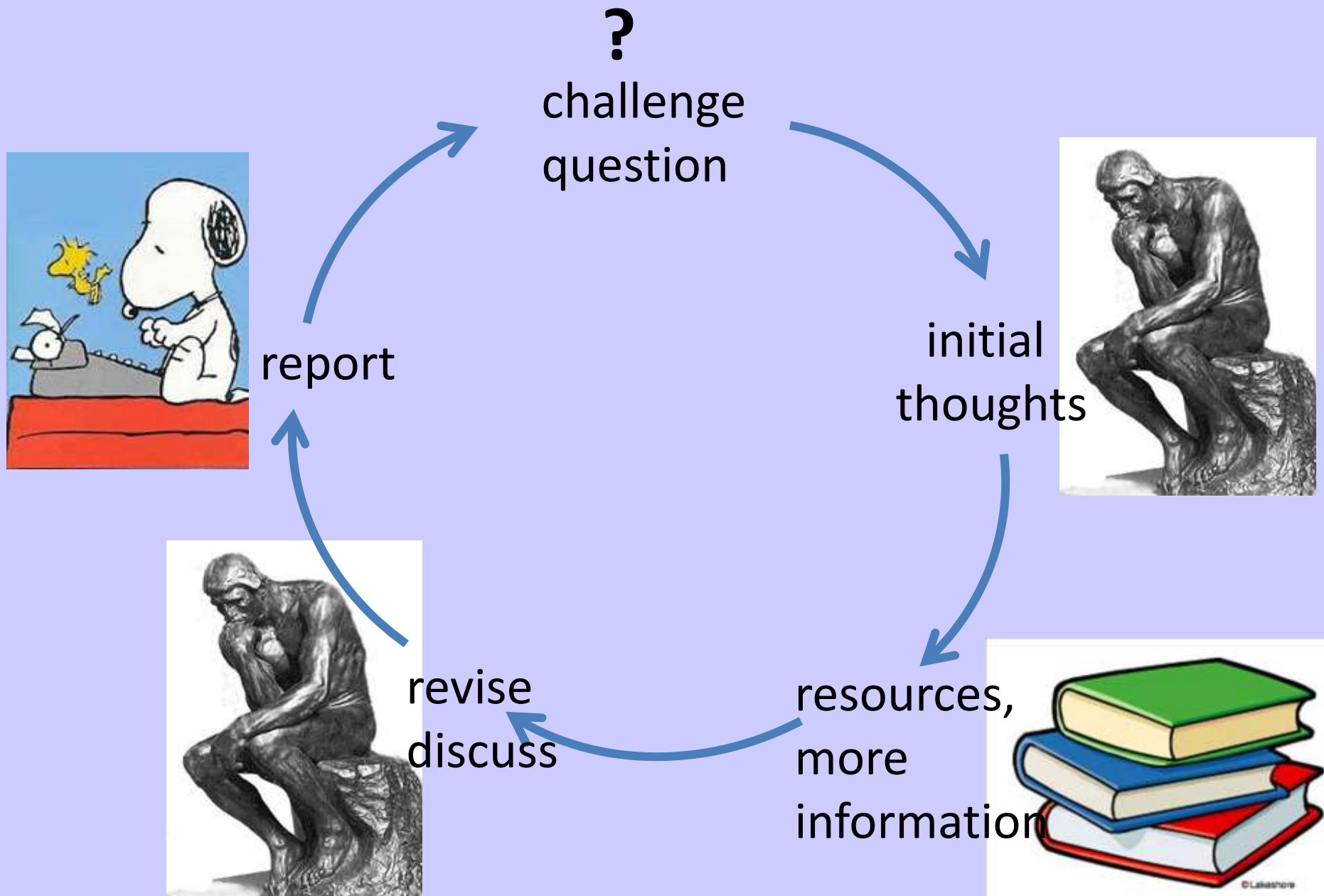


- (i) challenge learning cycle
- (ii) signaling mechanisms
- (iii) strengthening synapses

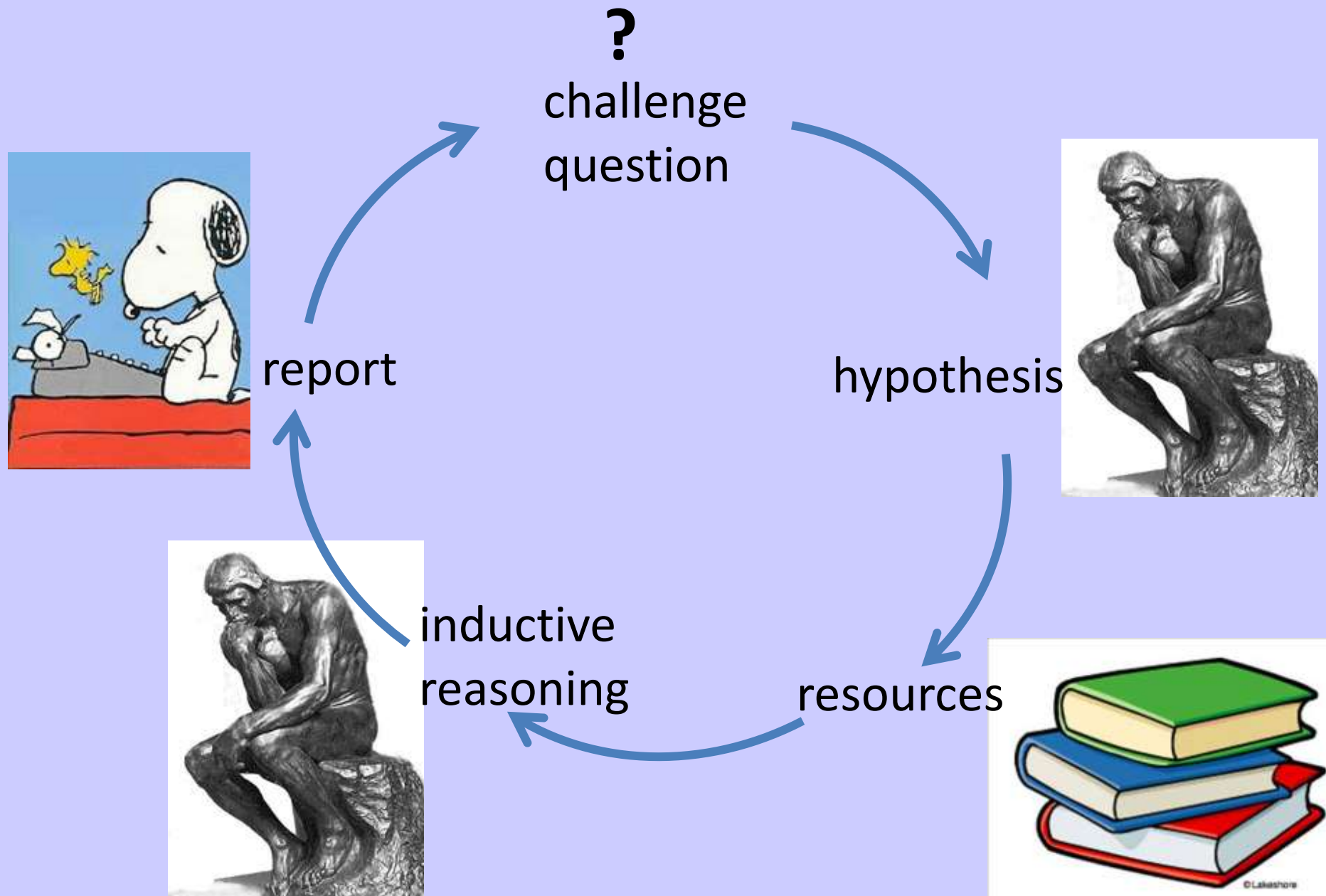
Greek WORD:
Metacognition

"knowing about knowing"
(Anglo-Saxon)

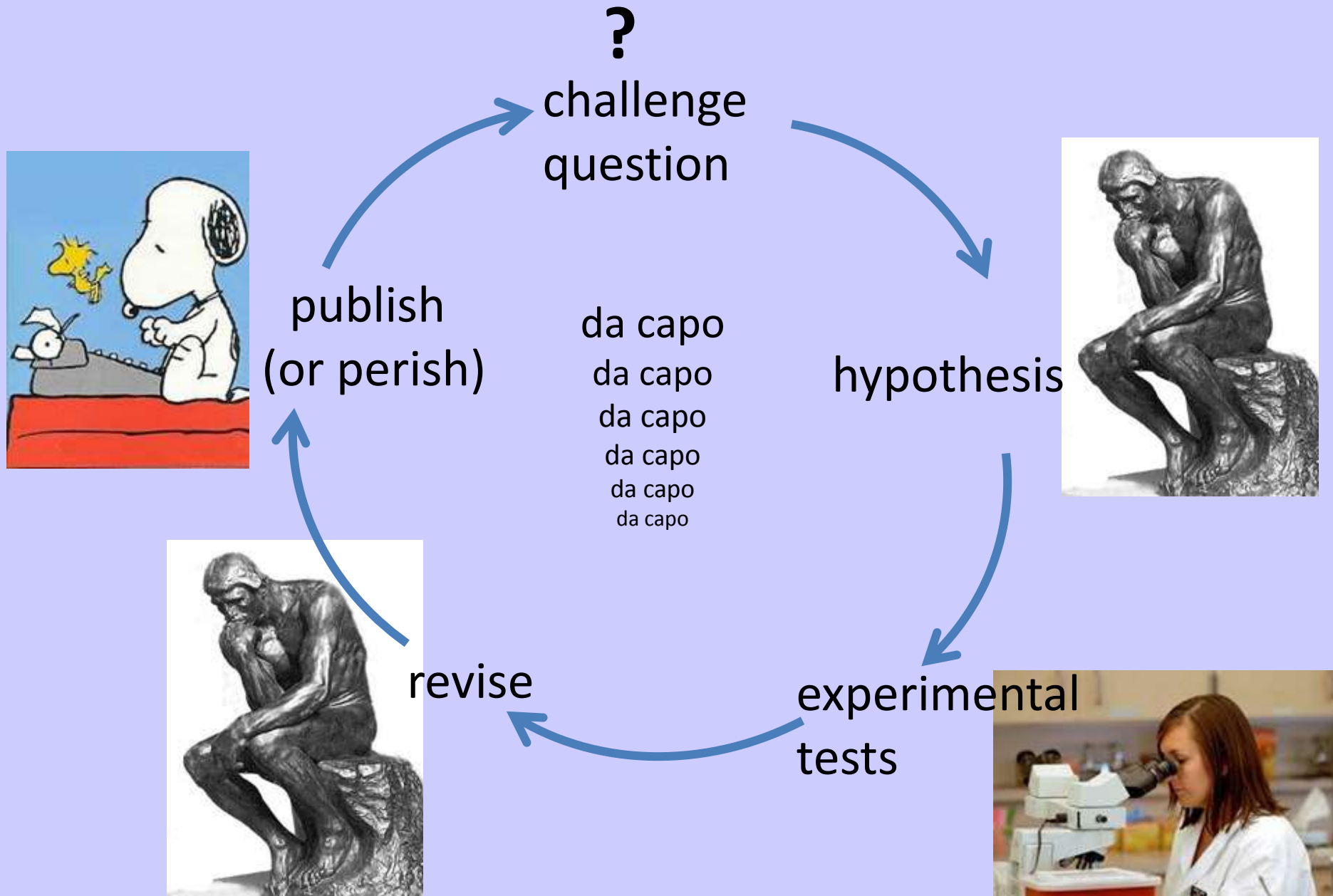
How do we learn: The challenge cycle. (John Bransford)



Philosophers (Socrates, Plato, Aristotle -- 5-4th C. BC)



Scientists



"Scientific Thinking in Young Children"

(Alison Gopnik)



Learning child



Science studies Nature

What is nature.
Nature is what is.
But is nature natural.
No not as natural as that.

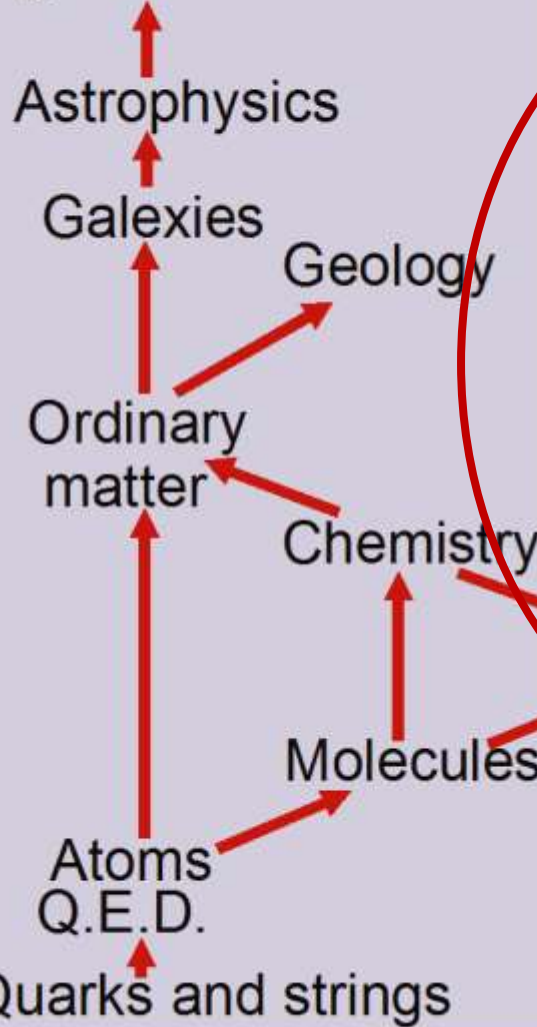
(Gertrude Stein—
*The Geographical History of America:
Or the Relation of Human Nature to the Human Mind*)

Nature is what we see
.....
Nature is what we know—
Yet have no art to say—
So impotent Our Wisdom is
To her Simplicity.

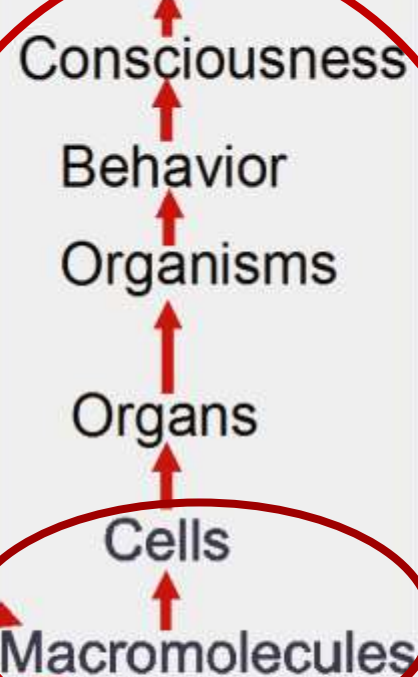
(Emily Dickinson)

Cosmology and
Origins of the Universe

Culture and
Societies



Geology



Many
levels
of
science
and
nature

Magnetic resonance image (MRI) of a human head

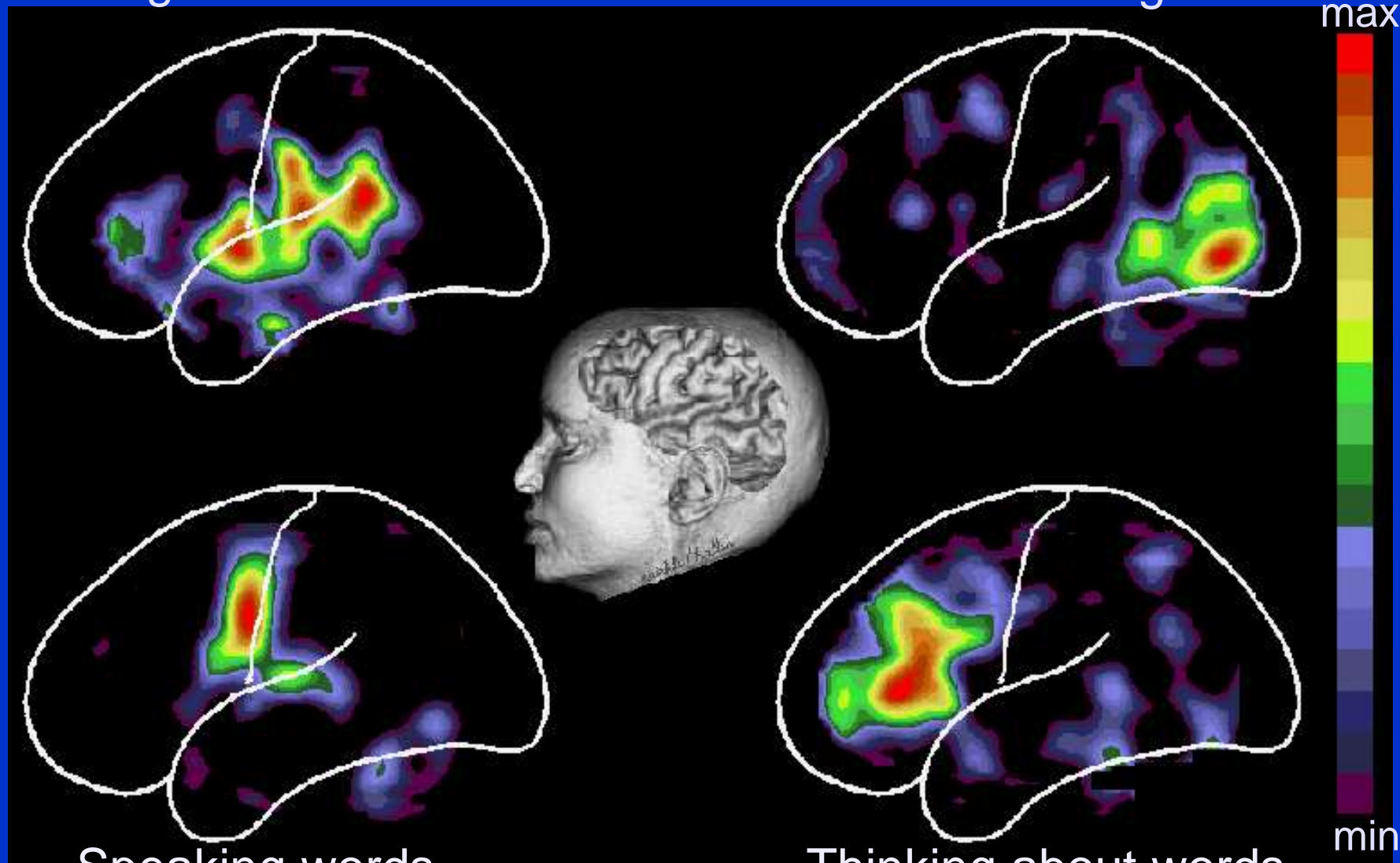


(UW Hospital)

WORDS in PET!

Hearing words

Seeing words



Speaking words

Thinking about words

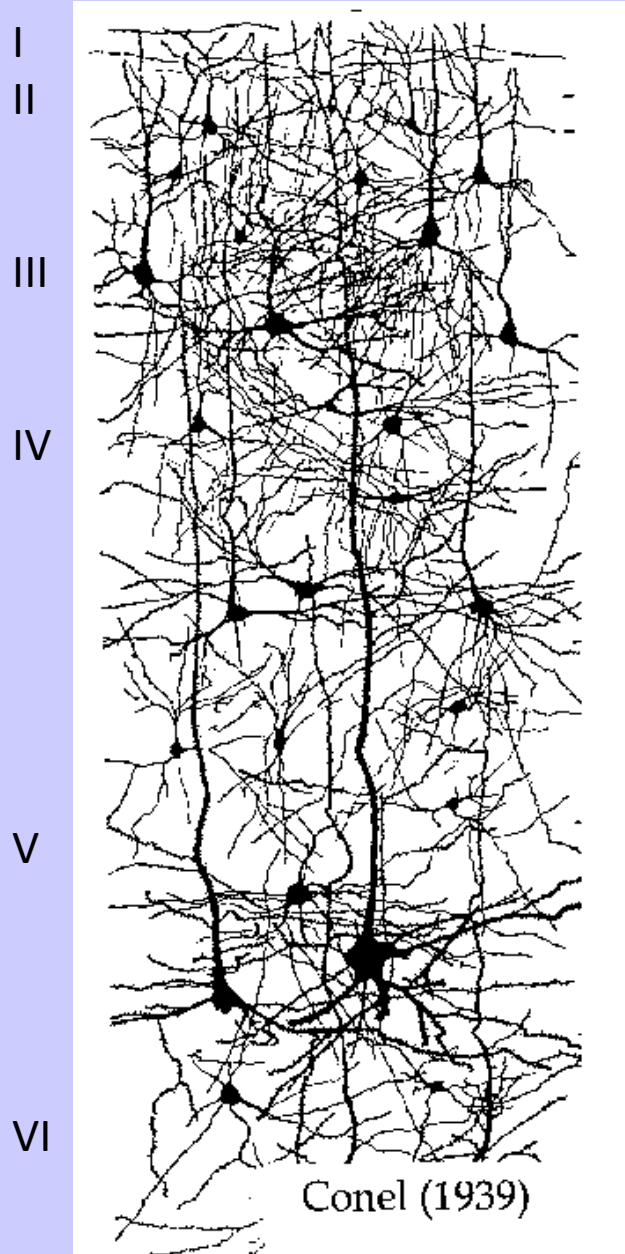
Q: How do parts of the brain communicate?

(M. Raichle, 1998)

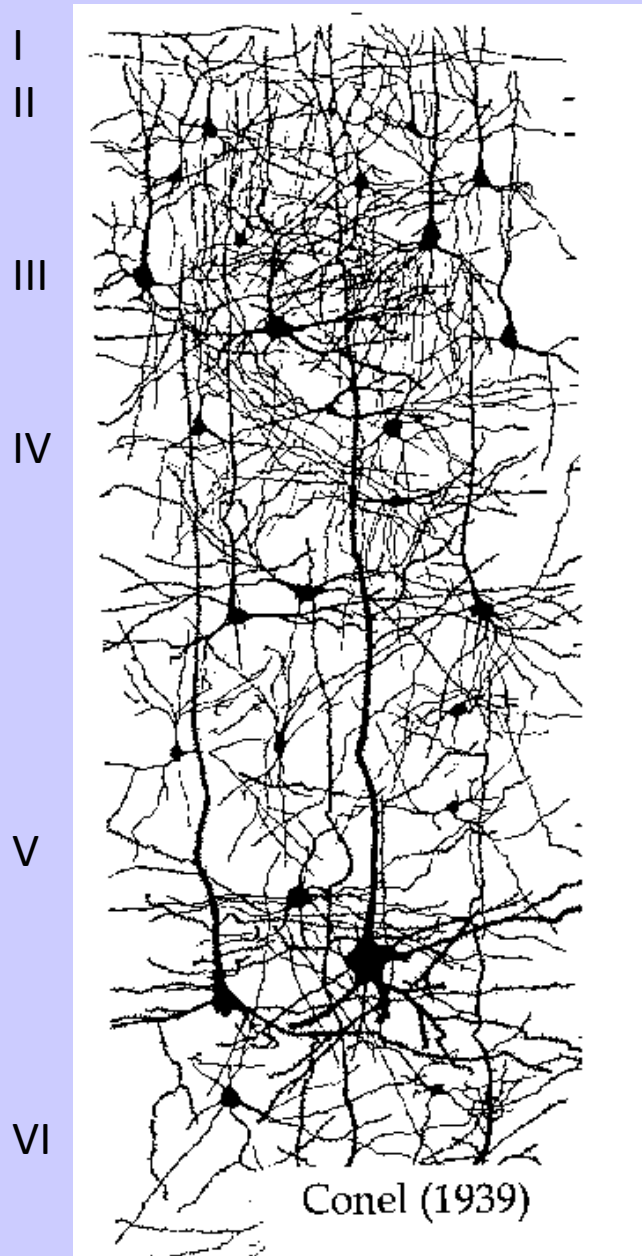
PET: positron emission tomography

Visual cortex

like a computer chip



Visual cortex



Nervous System

Zillions of neurons

Wires itself

Refines itself

Reconfigures after injury

Learning modifies it

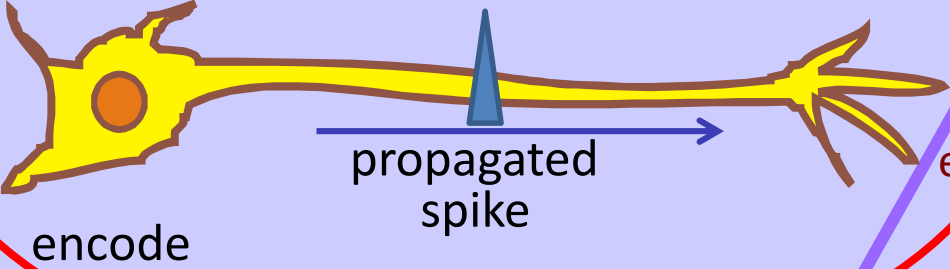
"Plasticity"

"Critical period" (e.g. spinal injury, language)

Three modes of nervous signaling

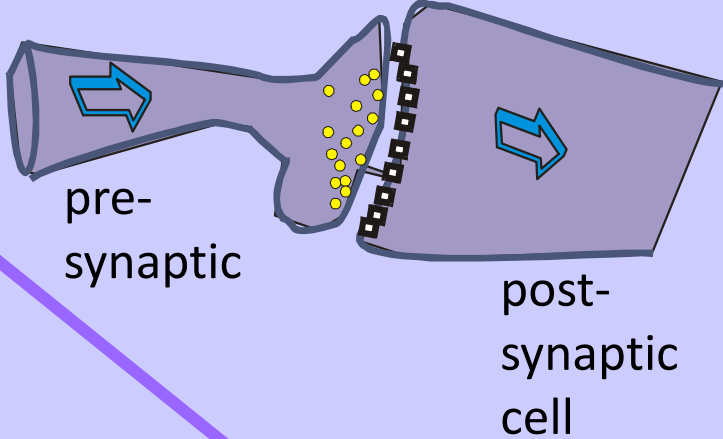
1) Propagated electrical signals

electrical to electrical to electrical



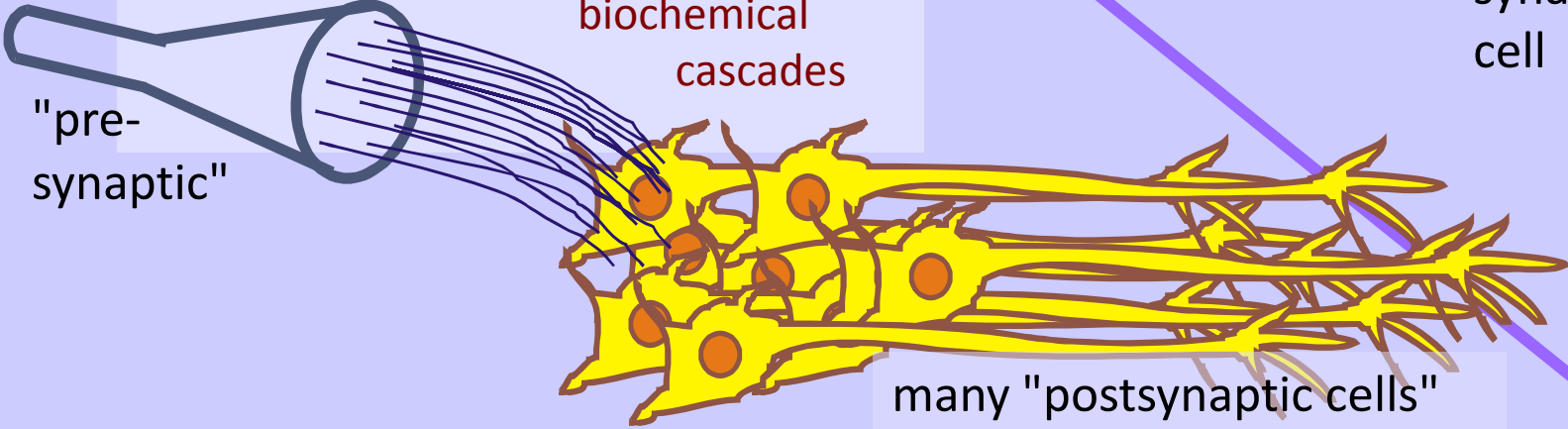
2) Fast chemical transmission at chemical synapses

electrical to chemical to electrical

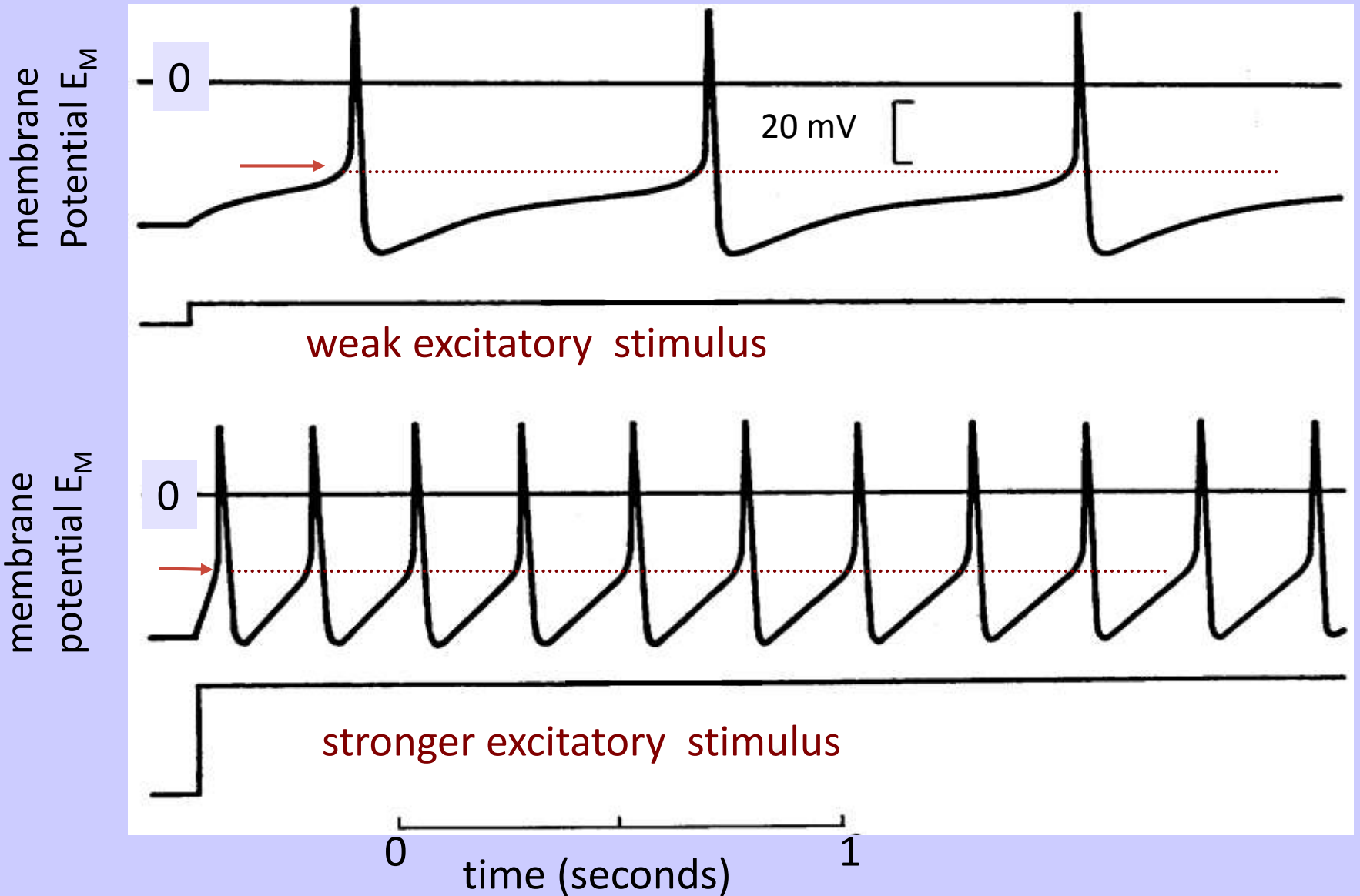


3) "Hormonal" neuro-modulation

chemical to intracellular biochemical cascades

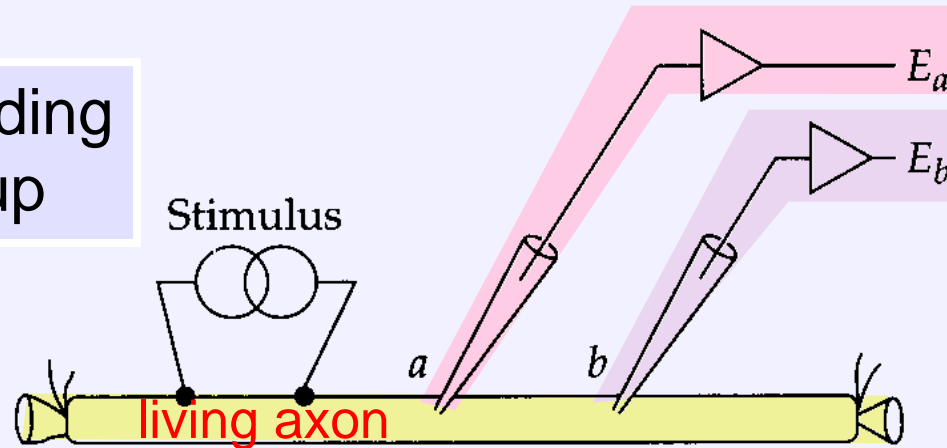


Neurons encode intensity as spike frequency



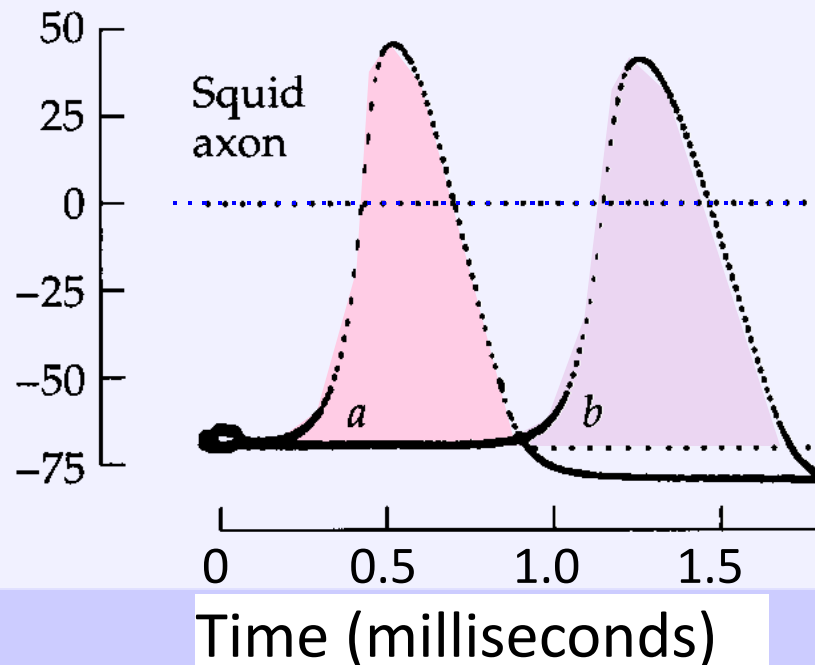
Axon spikes: a propagating electrical wave

Recording setup



measure cell voltage

membrane voltage E_M (mV)



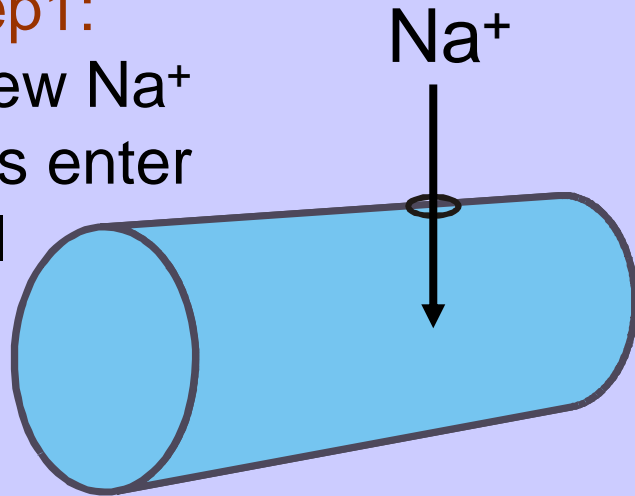
spikes recorded at points a and b in the axon

The spike is the long-distance, reliable, stereotyped, rapid, specific, electrical signal of axons & muscles

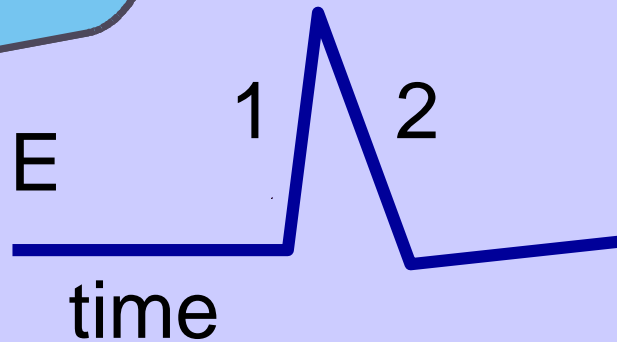
How does a nerve make its electrical spike signal?

Step 1:

A few Na^+ ions enter cell

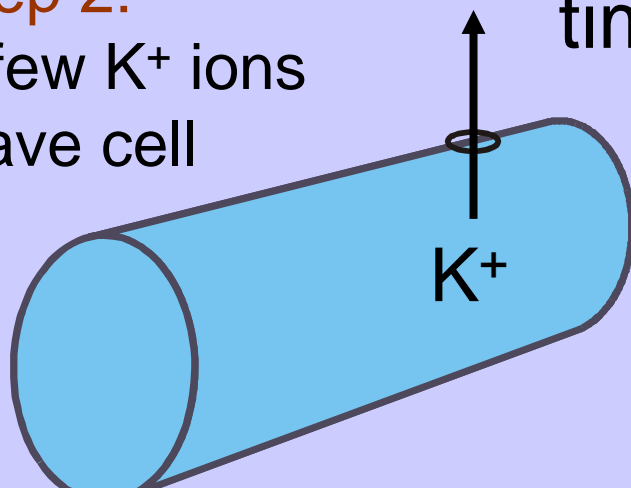


so cell inside goes positive



Step 2:

A few K^+ ions leave cell



so cell inside returns to rest -- negative

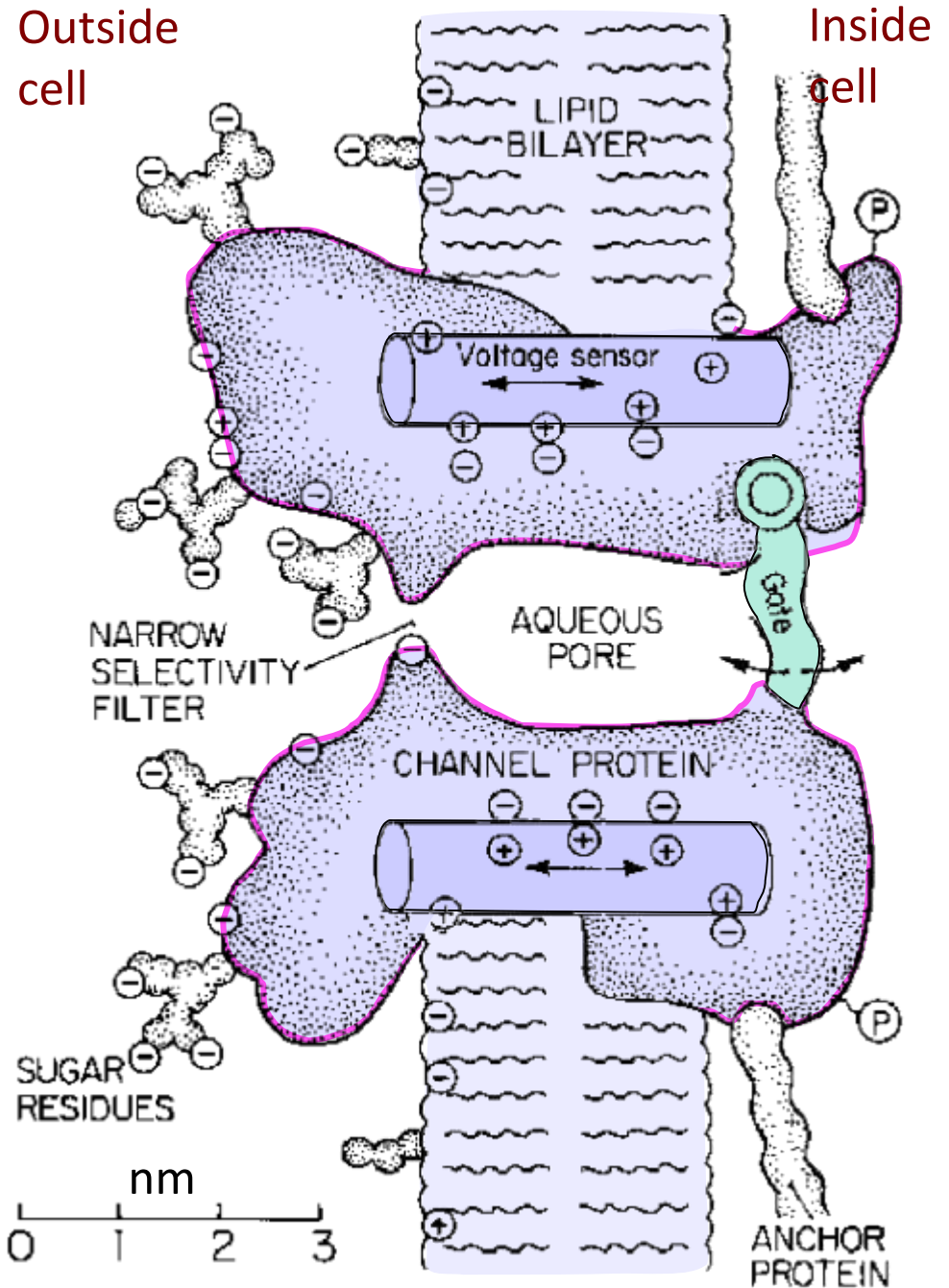
Hypothesis:
Moving ions make electrical signals in nerve

(Hodgkin & Huxley 1952)

Gated ion channels do it!

Outside
cell

Inside
cell

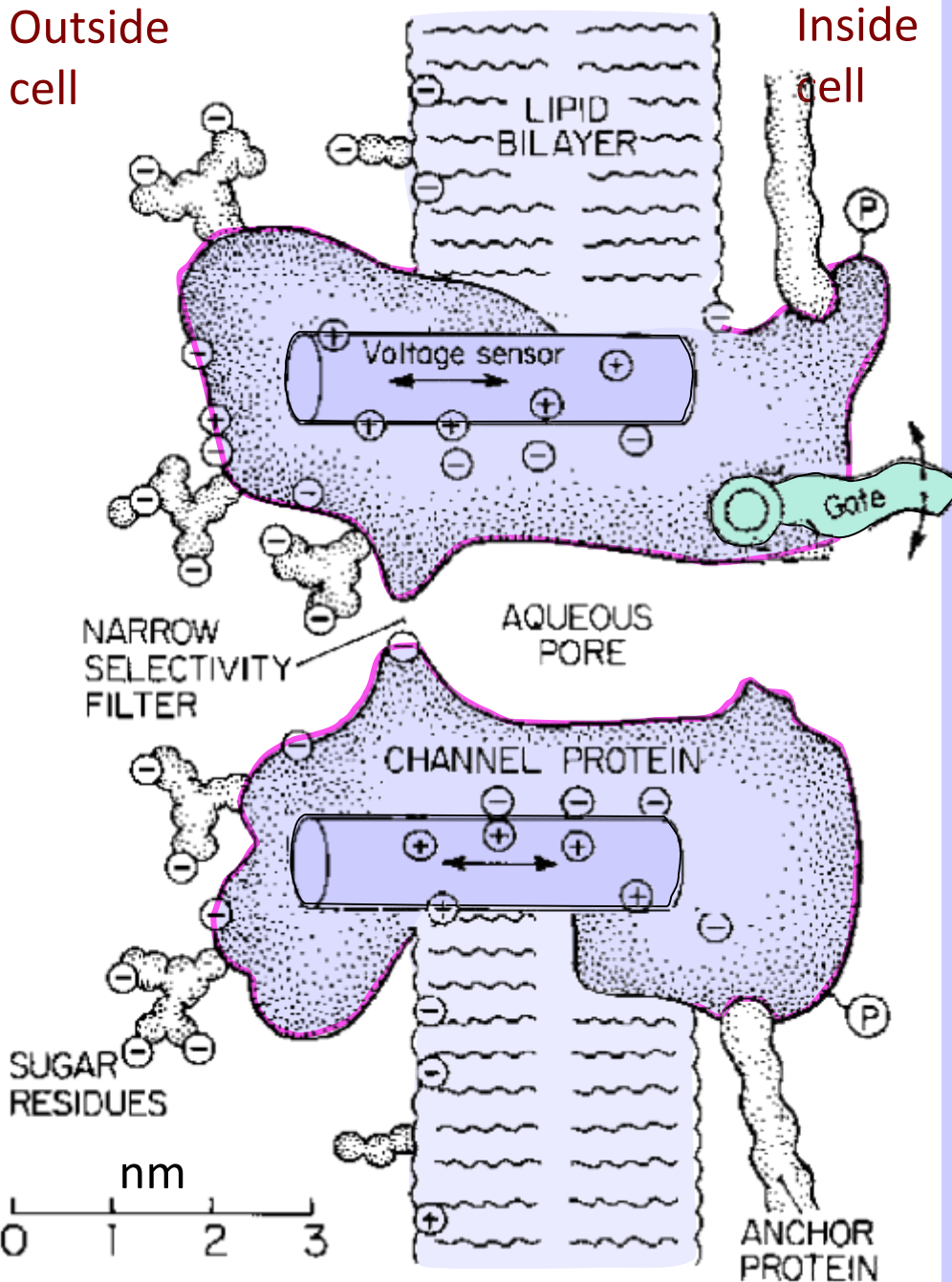


Ions pass through a gated aqueous pore.

The voltage sensor regulates the gate.

Outside cell

Inside cell



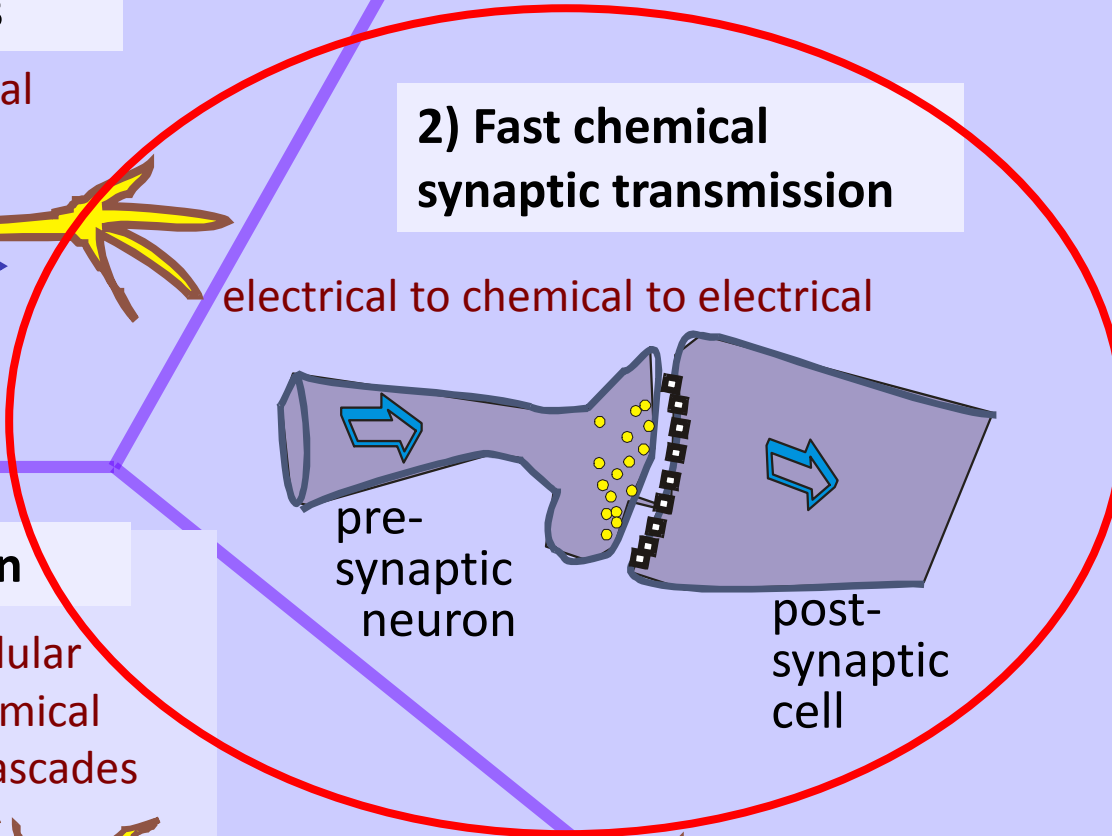
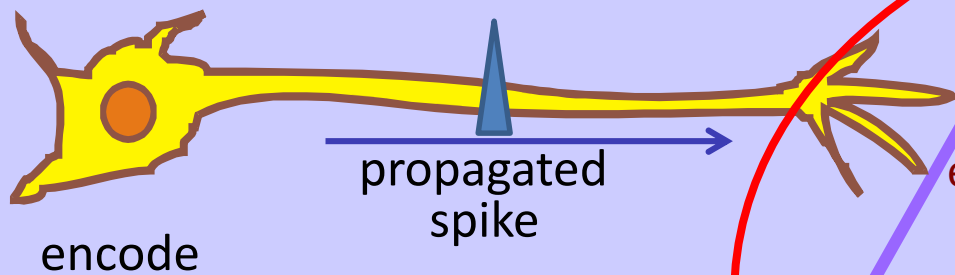
Ions pass through a gated aqueous pore.

The voltage sensor regulates the gate.

Three modes of nervous signaling

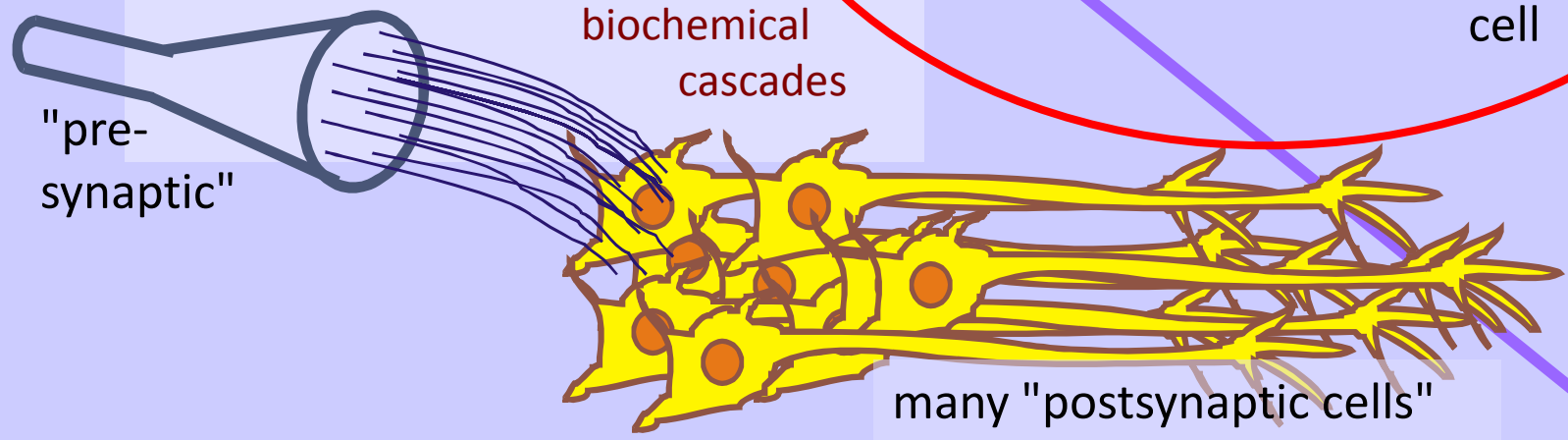
1) Propagated action potentials

electrical to electrical to electrical



3) "Hormonal" neuromodulation

chemical to intracellular biochemical cascades



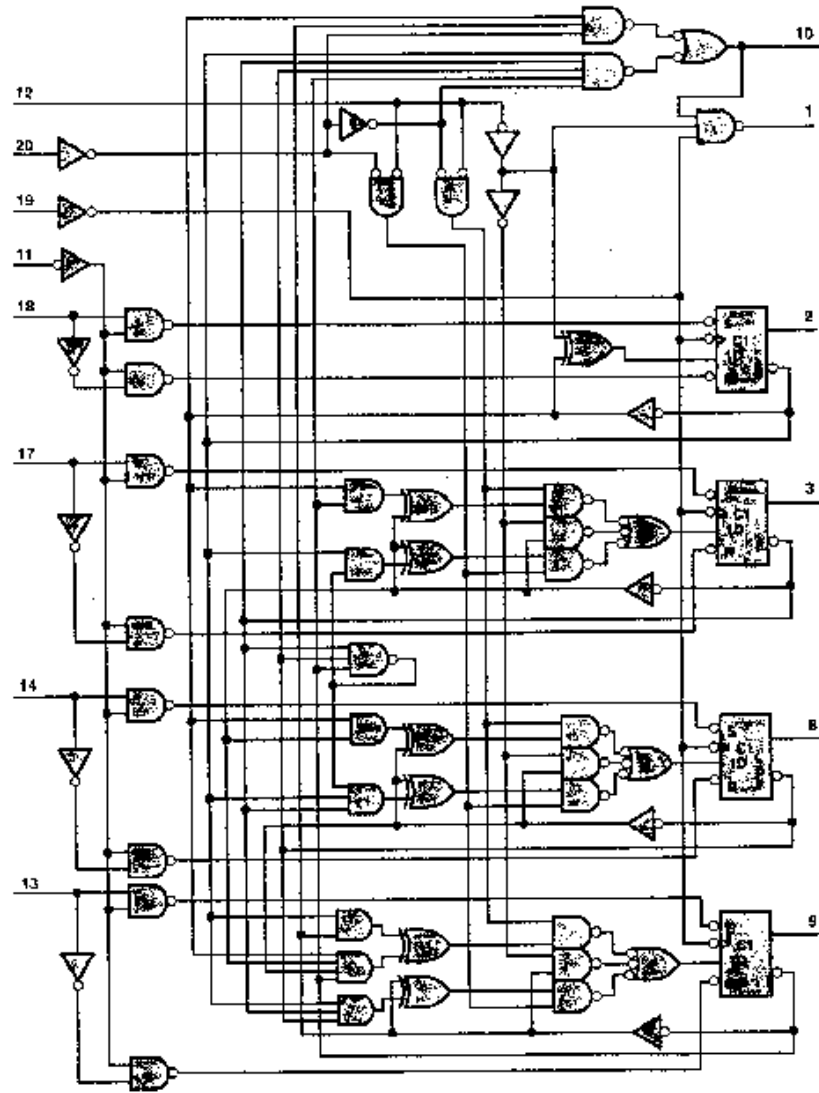
Visual cortex

Computer chip

I
II
III
IV
V
VI

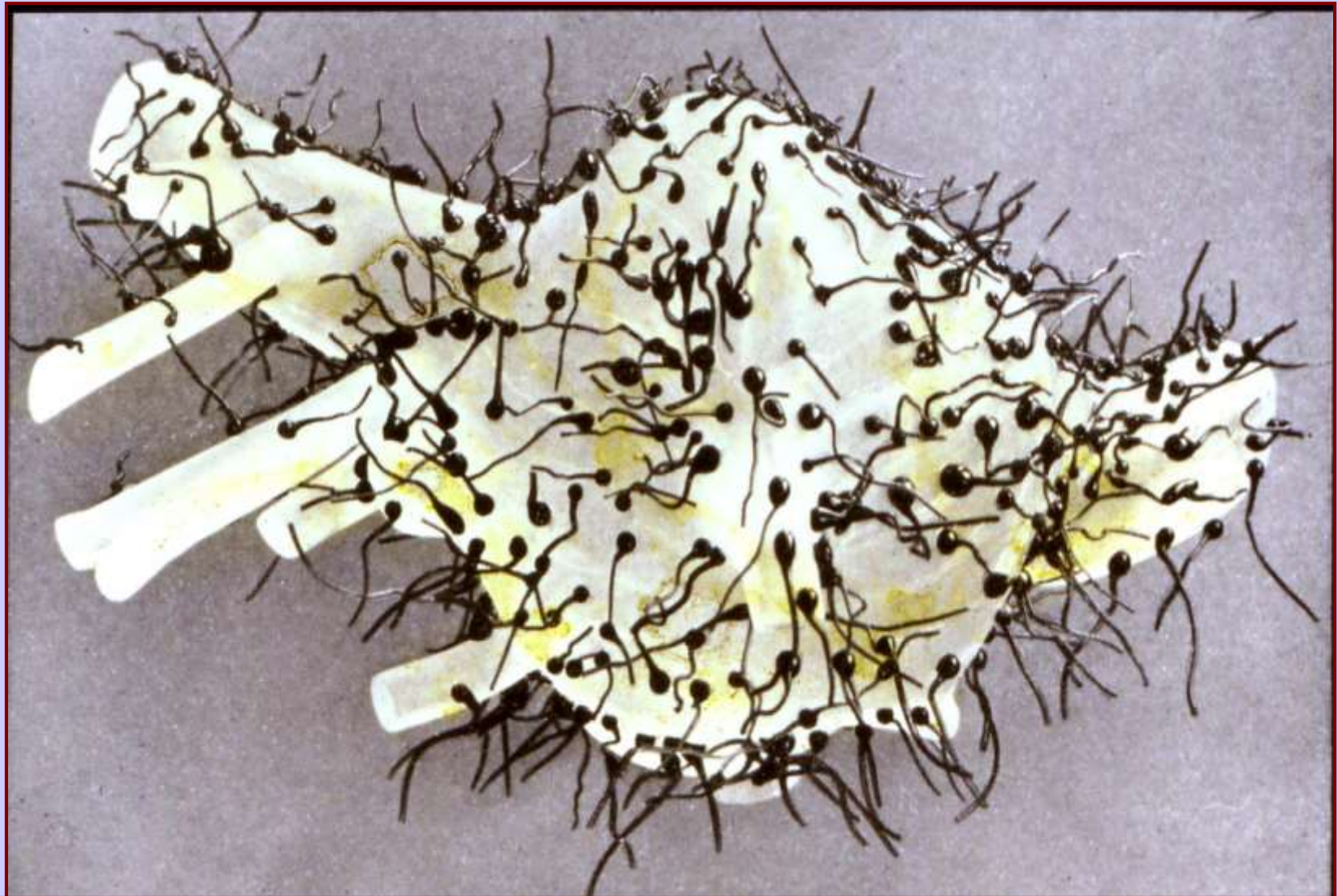


Conel (1939)



A
B
C
D

Synaptic terminals speaking to a spinal motoneuron



Neurons may receive 10,000 synaptic contacts, some excitatory and some inhibitory, on its cell body and dendrites. (Haggar & Barr, 1950)

Each synapse is a voter: casting a yea or nae vote



A fast chemical synapse

Terminal of presynaptic neuron

synaptic vesicle filled with neuro-transmitter

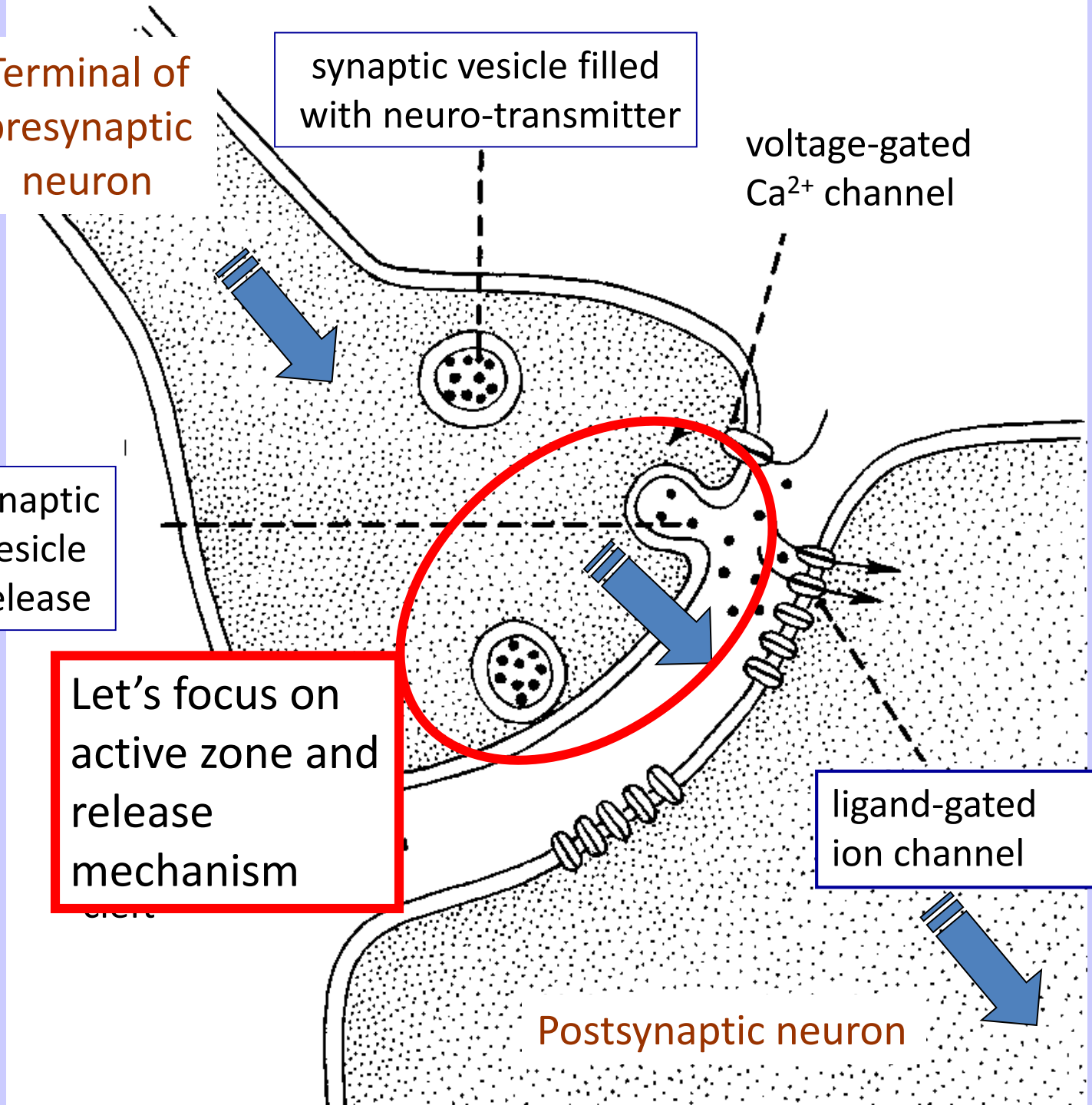
voltage-gated Ca^{2+} channel

synaptic vesicle release

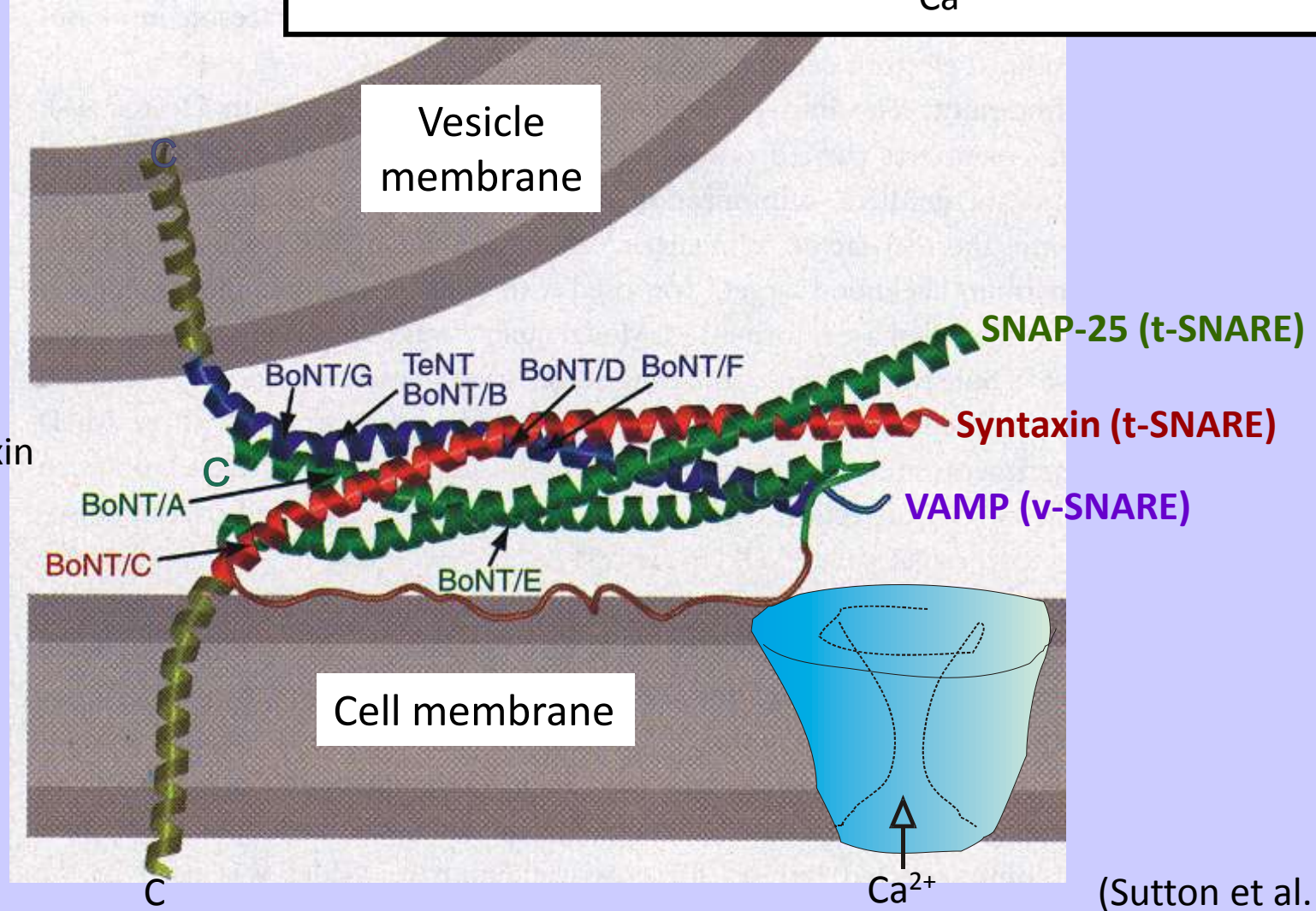
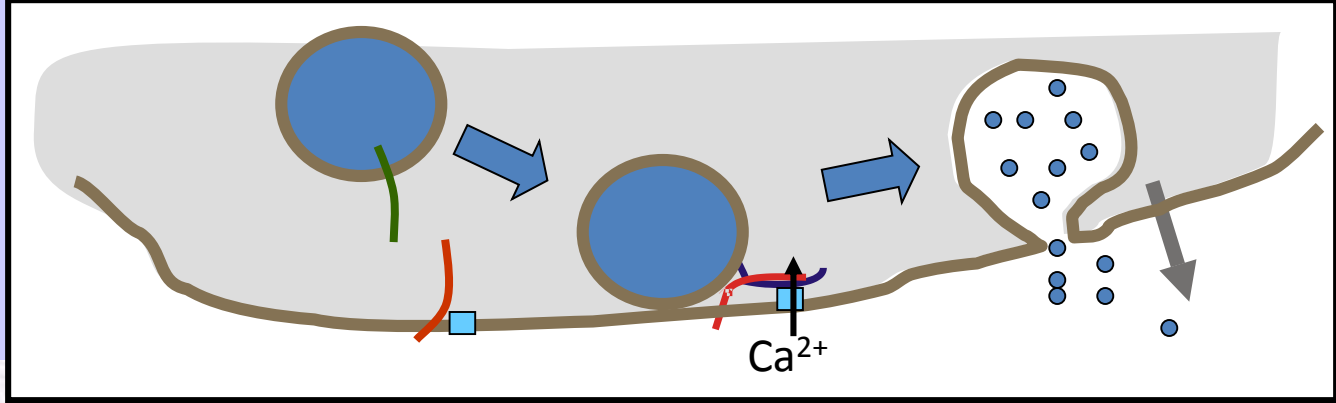
Let's focus on active zone and release mechanism

ligand-gated ion channel

Postsynaptic neuron



SNARE
 helical winch
 & Ca^{2+} trigger

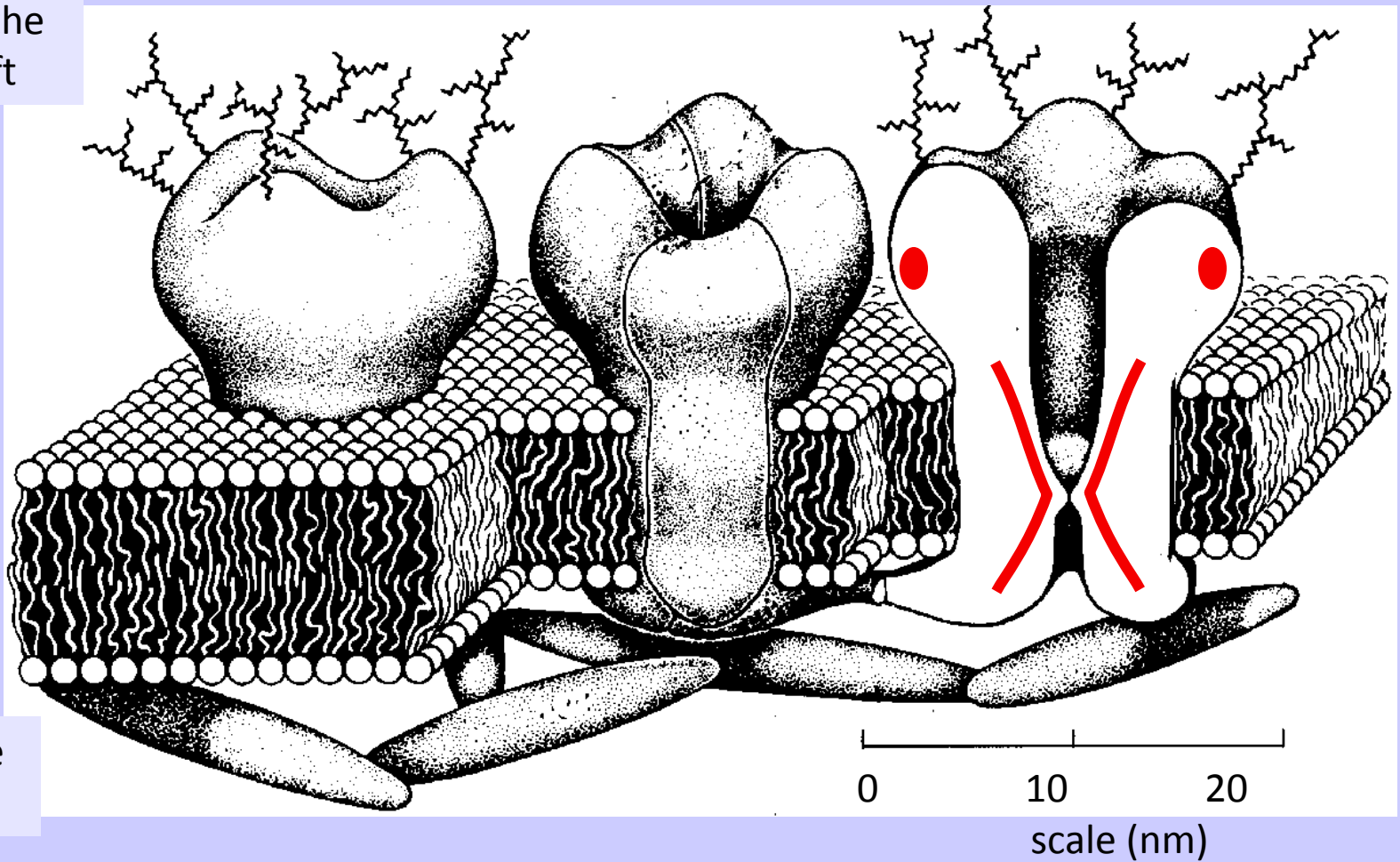


Neurotoxin
 cleavage
 spots
 marked
 BoTox &
 TeNT

(Sutton et al. 1998)

A family of neurotransmitter receptors

Outside: in the synaptic cleft



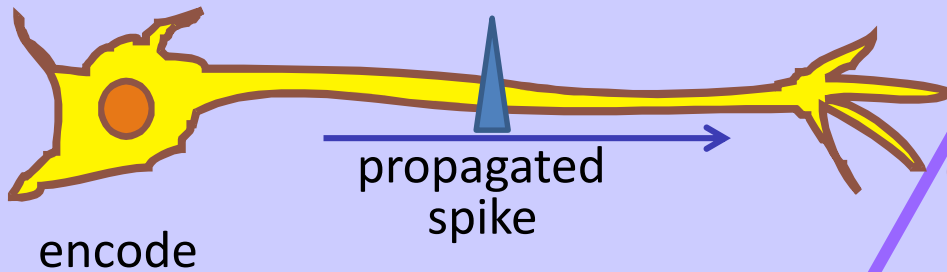
Inside: In the muscle fiber

The receptor is also an ion channel: an electrical vote

Nervous signaling

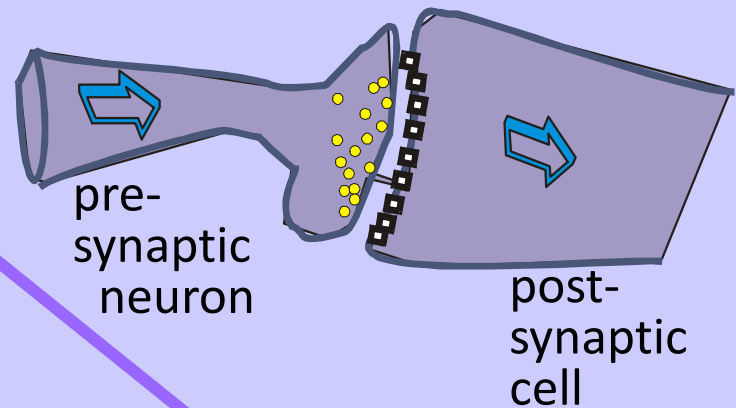
1) Propagated action potentials

electrical to electrical to electrical



2) Fast chemical synaptic transmission

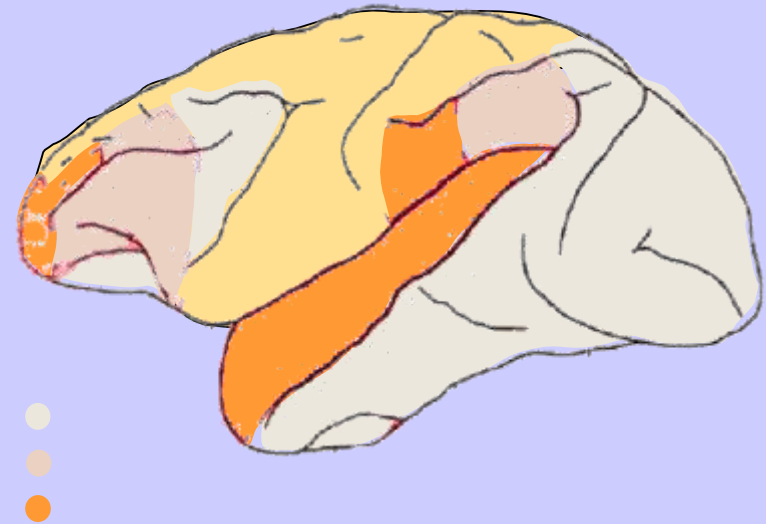
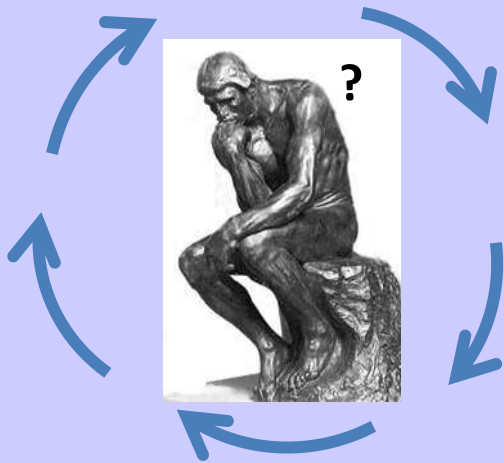
electrical to chemical to electrical



Fast point-to-point wiring
like a calculator

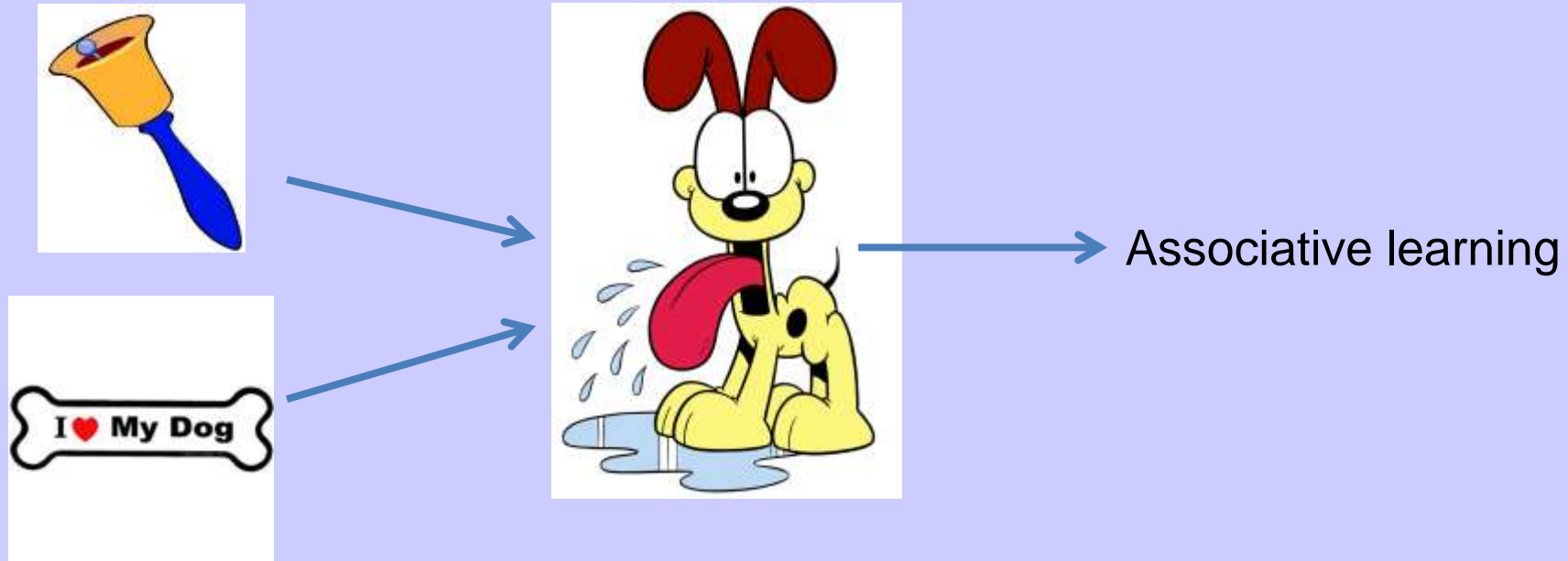
How does this learn!

Learning at the synapse

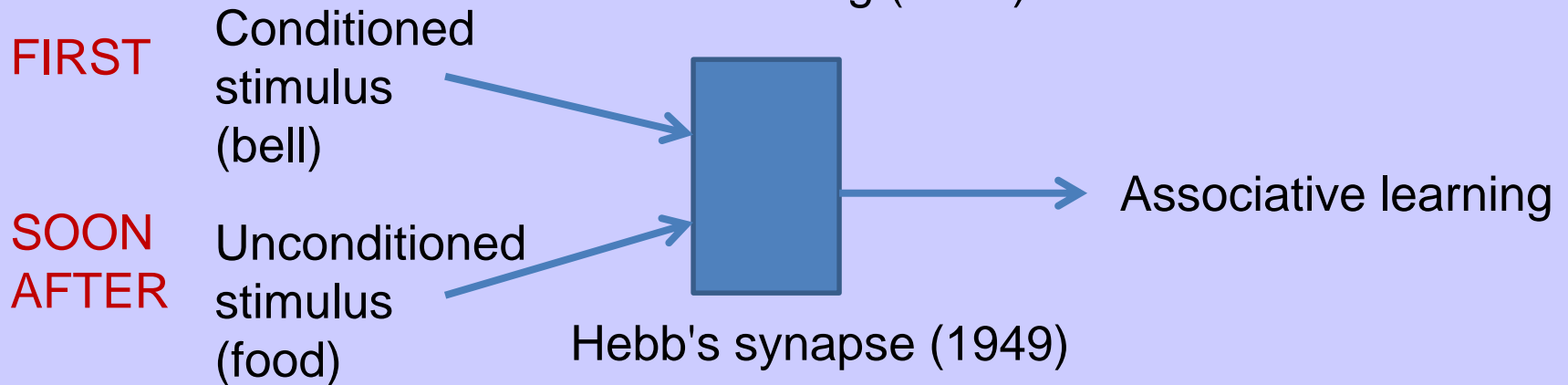


- (i) challenge learning cycle
- (ii) signaling mechanisms
- (iii) strengthening synapses

Associative learning needs coincident convergence



Pavlov's dog (1901)



Hebb's synapse (1949)

Proposal: Learning is strengthening and weakening of synaptic connections

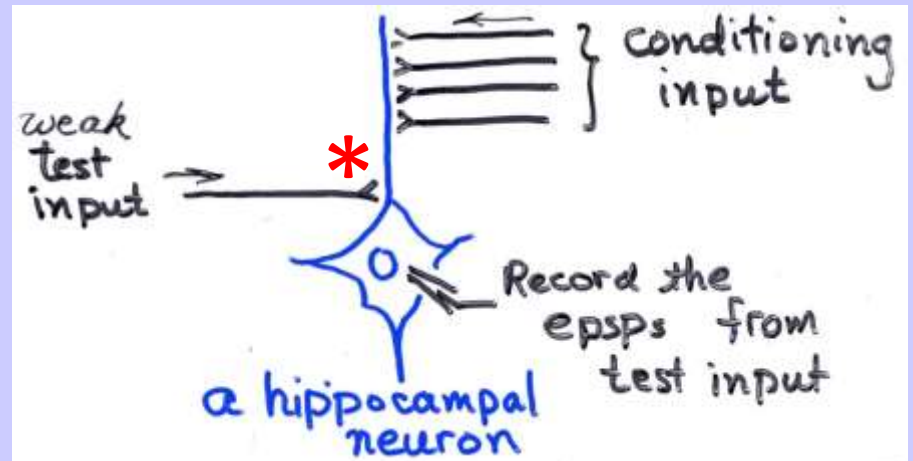
"Neurons that fire together
wire together"

(Carla Schatz)

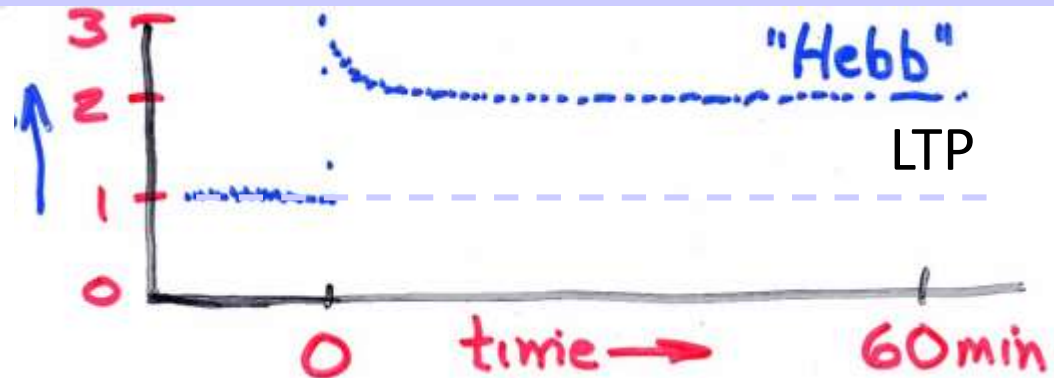
Synapses can be strengthened by coincident inputs

Synapses strengthen if they successfully participate in firing a cell.
(Donald Hebb, 1949)

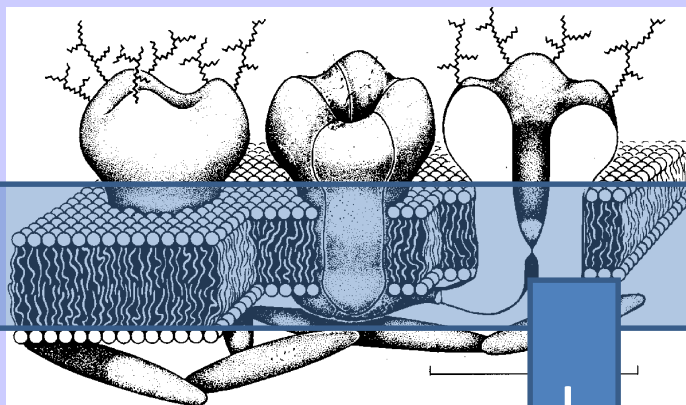
A test in a hippocampal neuron (1973)
Long term potentiation (LTP)



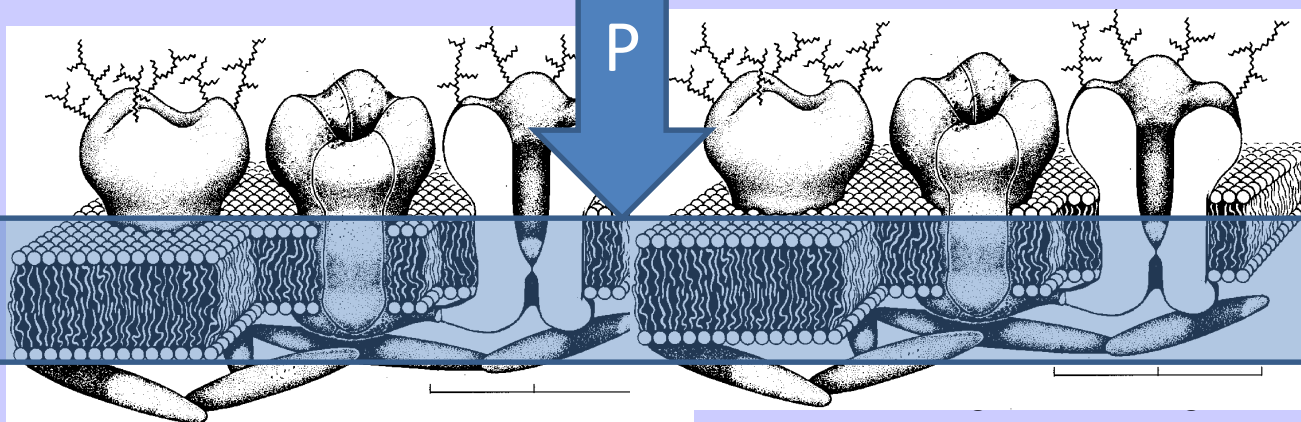
response at test synapse



LTP can increase available post-synaptic receptors

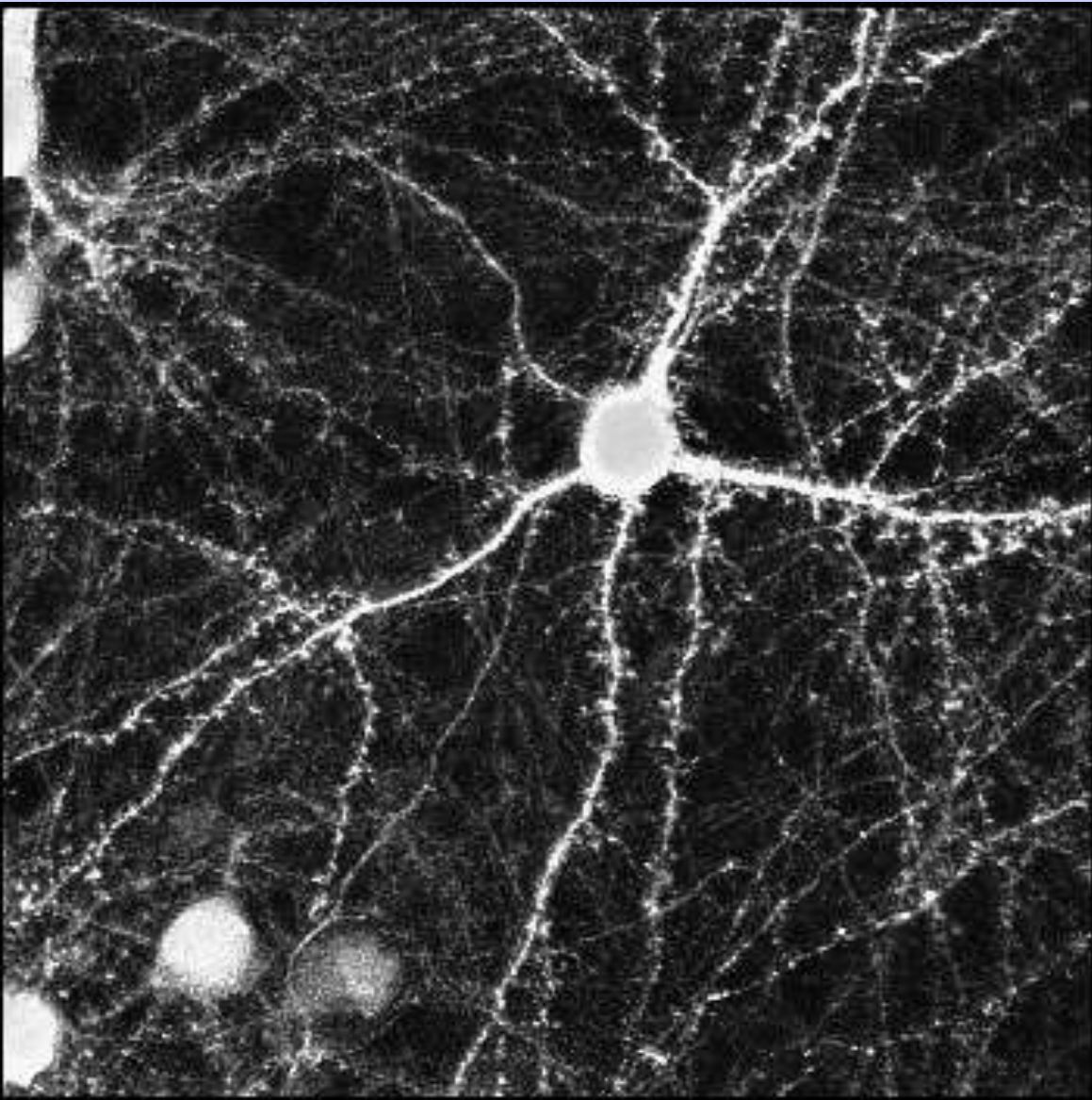


Post syn. cell membrane

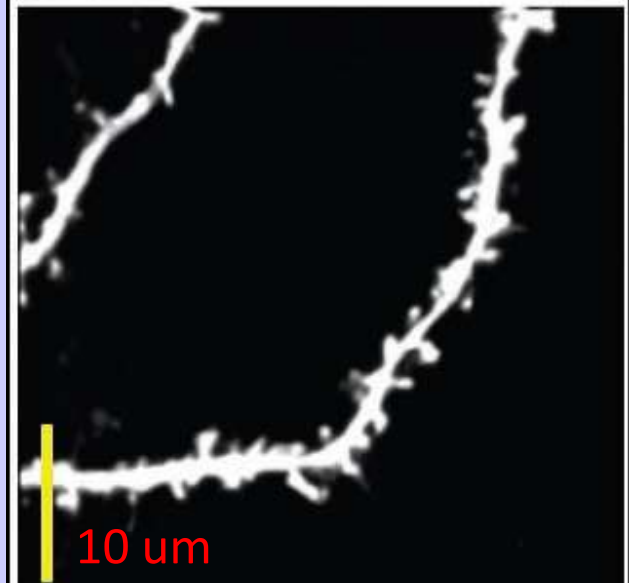
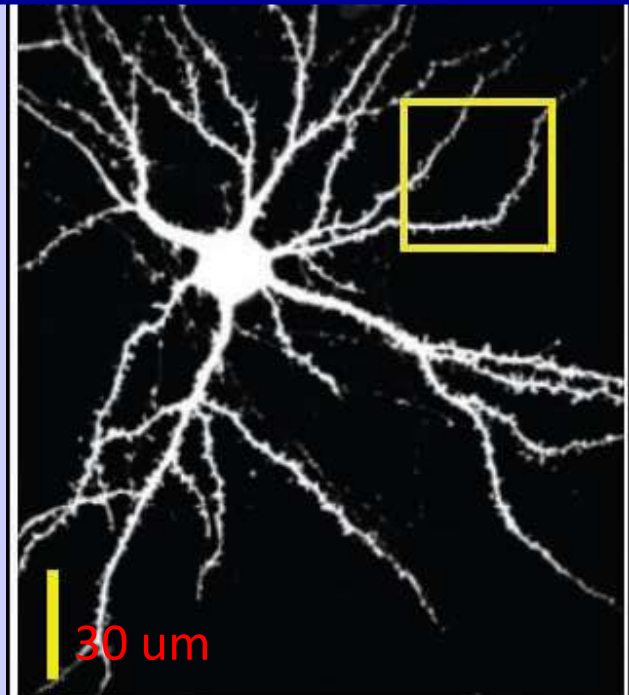


Additional receptors insert into postsynaptic membrane = stronger synapse

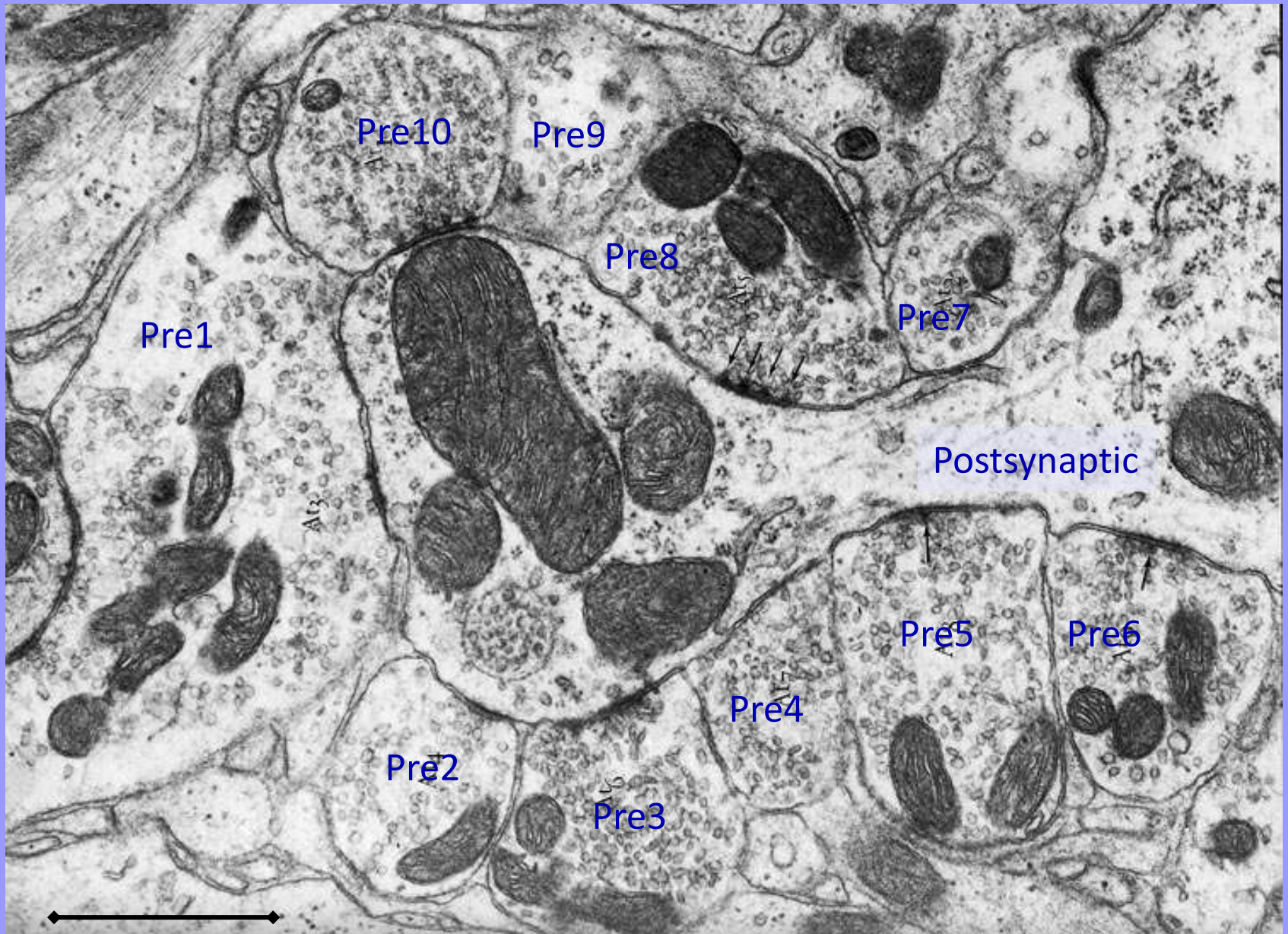
Spines are landing pads for synapses



Neurons in cerebral cortex (Bear and Sabatini)



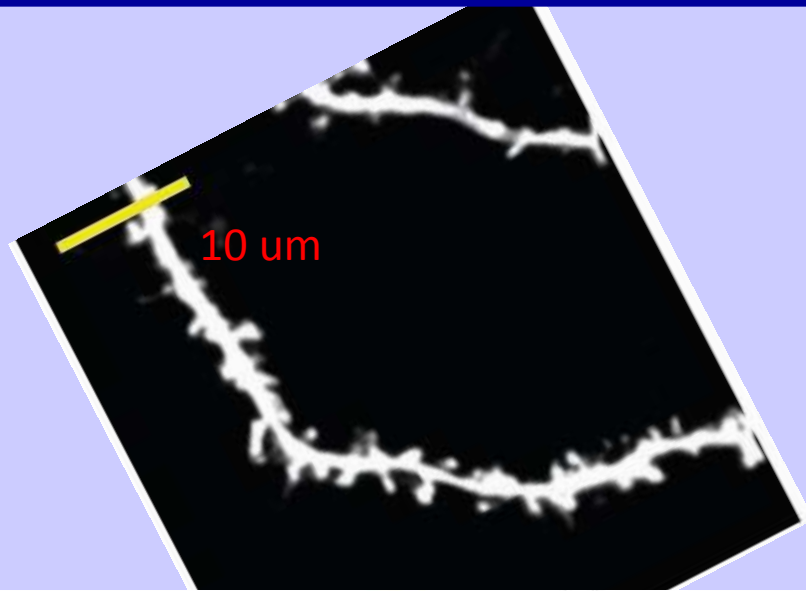
Crowding of synaptic terminals on a spine



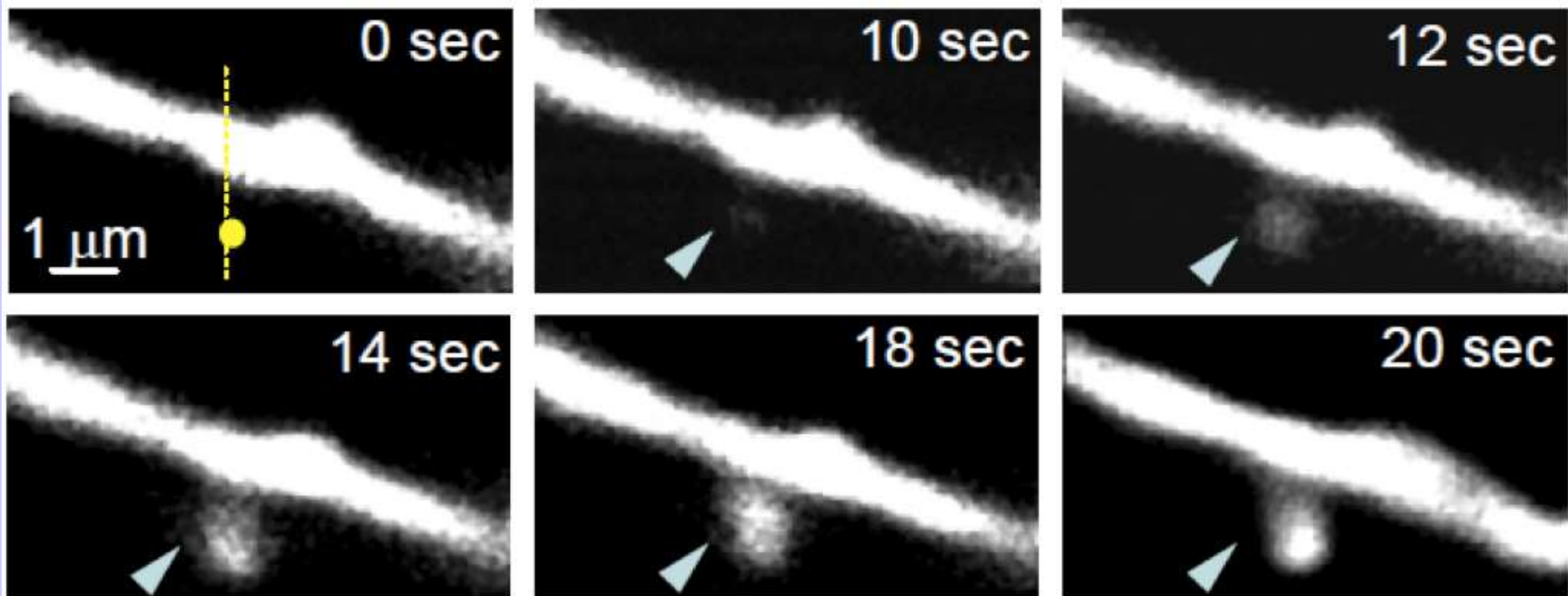
1 μm

(Peters, Palay, Webster, 1991)

Another way to learn: grow new synapses



Spines are landing pads for synapses. New spines grow to strong sources of neurotransmitter.
(Sabatini, 2012)



Associative learning needs coincident convergence



Associative learning

"Neurons that fire together wire together"

(Carla Schatz)

FIRST

Conditioned stimulus (bell)

SOON AFTER

Unconditioned stimulus (food)



Hebb's synapse (1949)

Associative learning

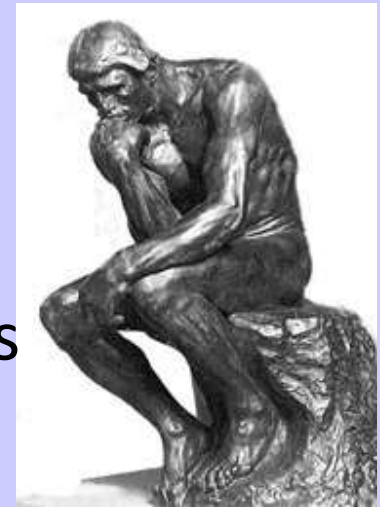
Proposal: Learning is strengthening and weakening of synaptic connections

Scientists, philosophers, students, babies

learning cycle
signaling mechanisms
strengthening synapses



publish
(or perish)



hypothesis

da capo
da capo
da capo
da capo
da capo



revise

experimental
tests



Challenges for knowing about knowing!

- (i) challenge learning cycle
- (ii) signaling mechanisms
- (iii) strengthening synapses

How can you enhance plasticity?

How do you look up your old telephone number?

Where are hypotheses kept?

How are language and syntax acquired?

How are they generated?

Can neuroscience aid pedagogy?

Thank you!