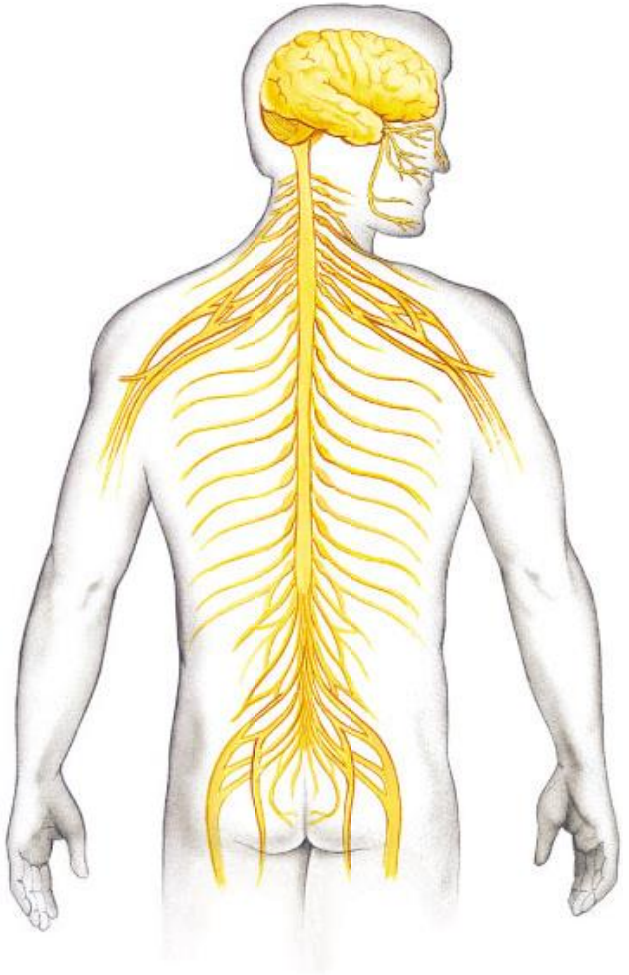
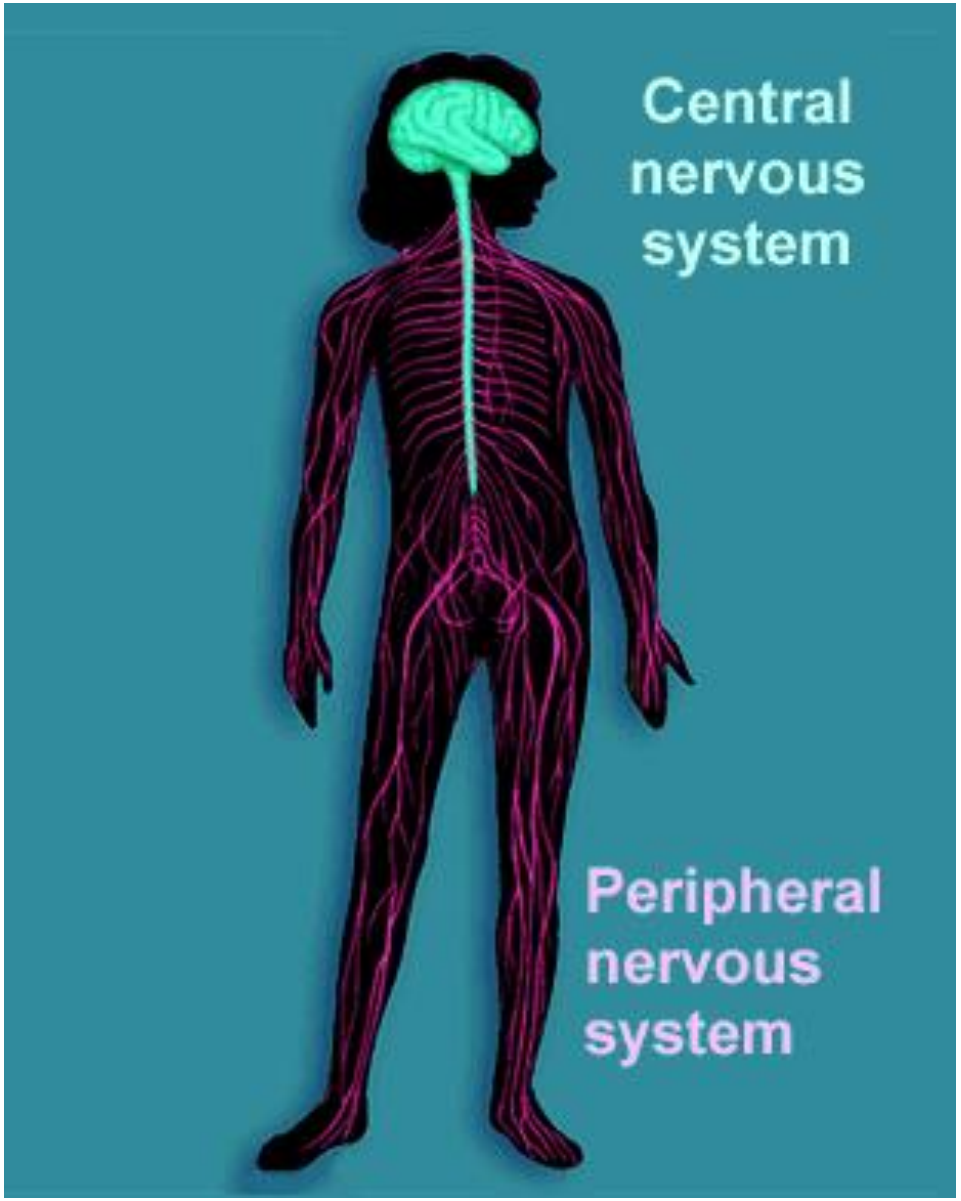
NeuroEngineering & Biomedical Instrumentation

BME 2105

WHAT PARTS DO YOU KNOW THAT ARE IN THE NERVOUS SYSTEM?

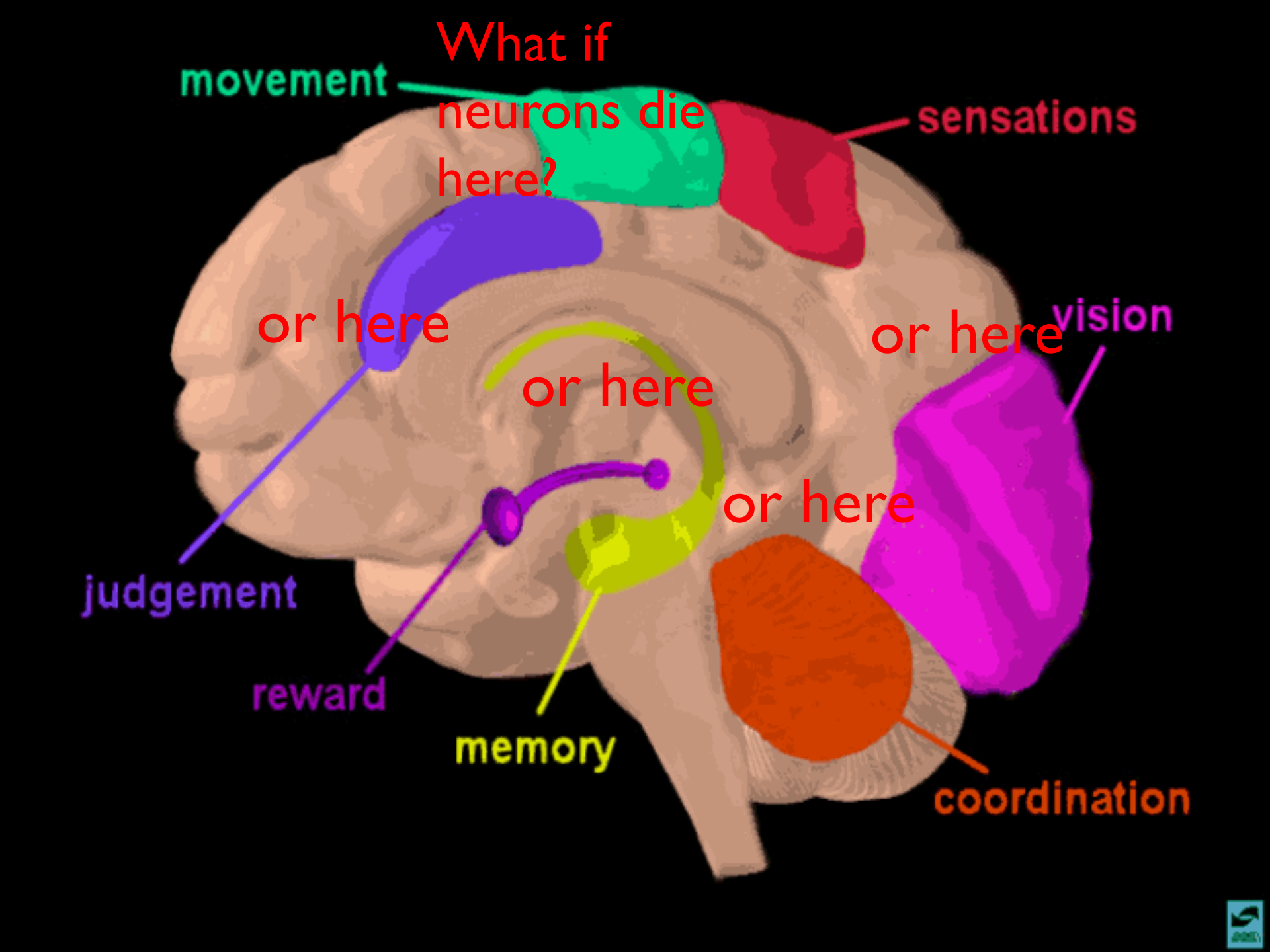
- Brain
- Spinal Cord
- Peripheral Nerves



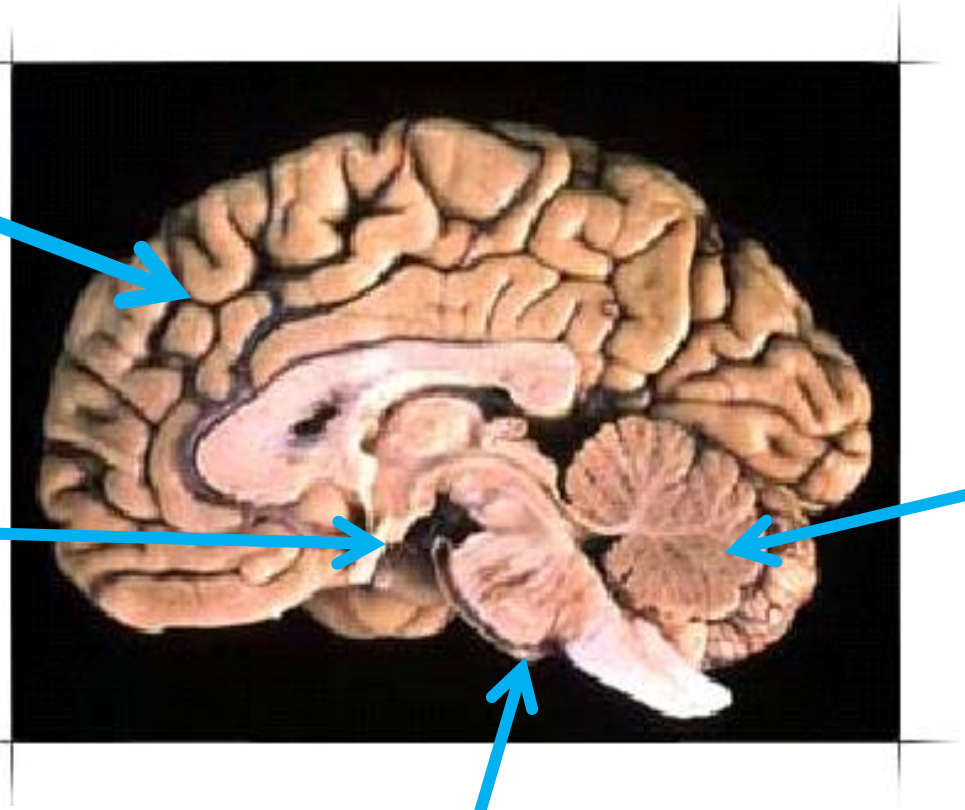


Brain and Spinal cord

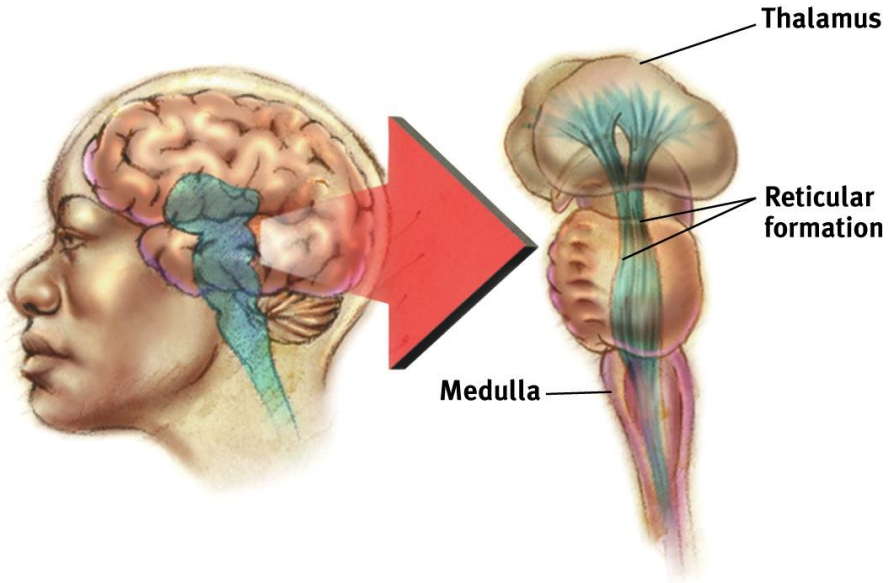
12 pairs of cranial and 31 pairs of spinal nerves


What if
movement
neurons die
here?
sensations
or here
or here
vision
or here
judgement
reward
memory
coordination

Brain structure

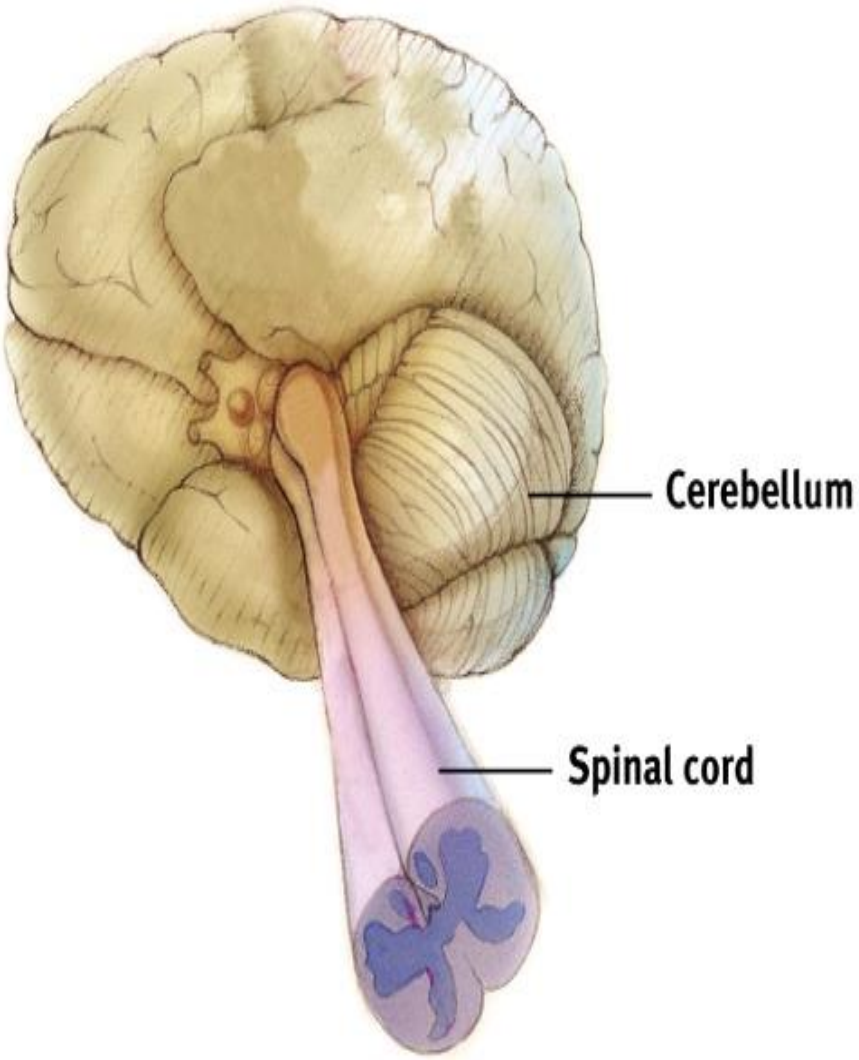


- Brainstem
  - responsible for automatic survival functions
    - cardiovascular system control, respiratory control, pain sensitivity control, alertness, awareness, and consciousness

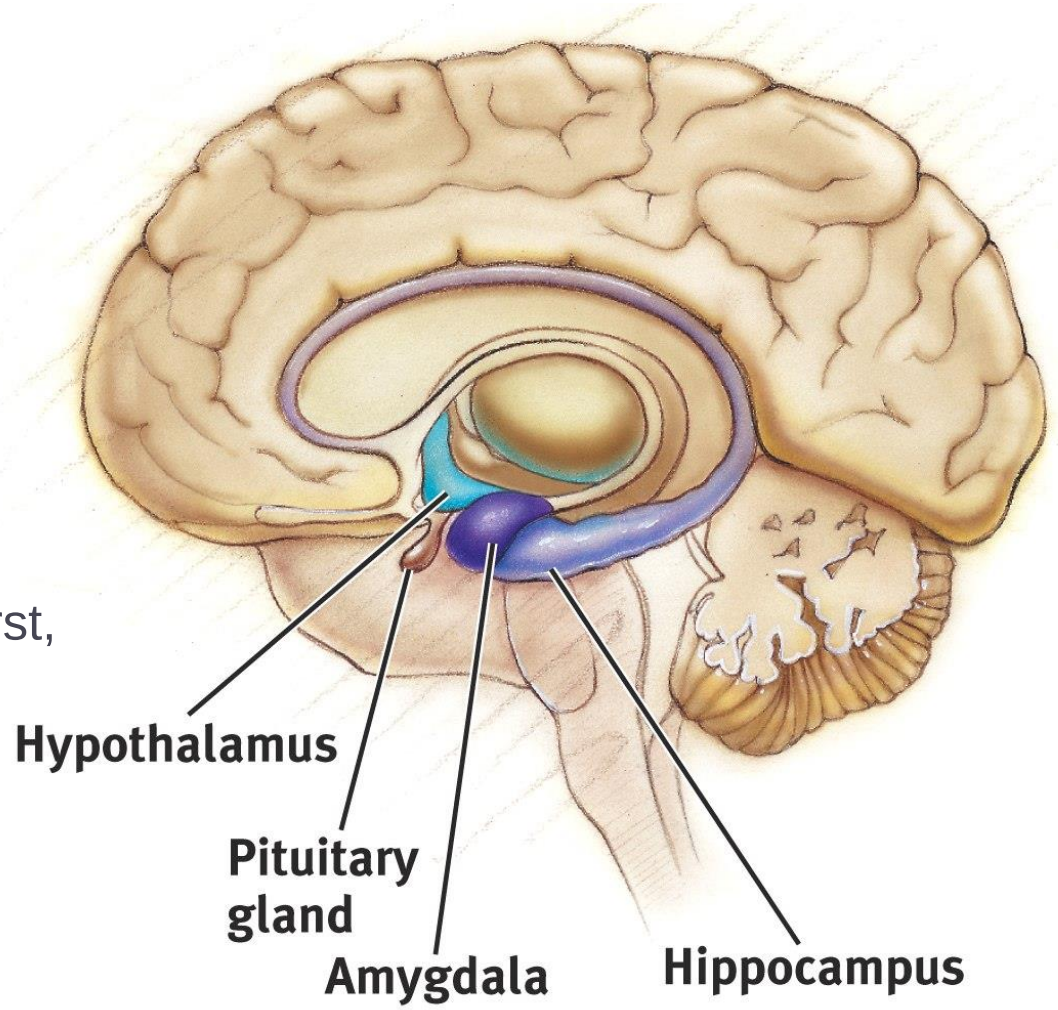


The Cerebellum

- helps coordinate voluntary movement and balance

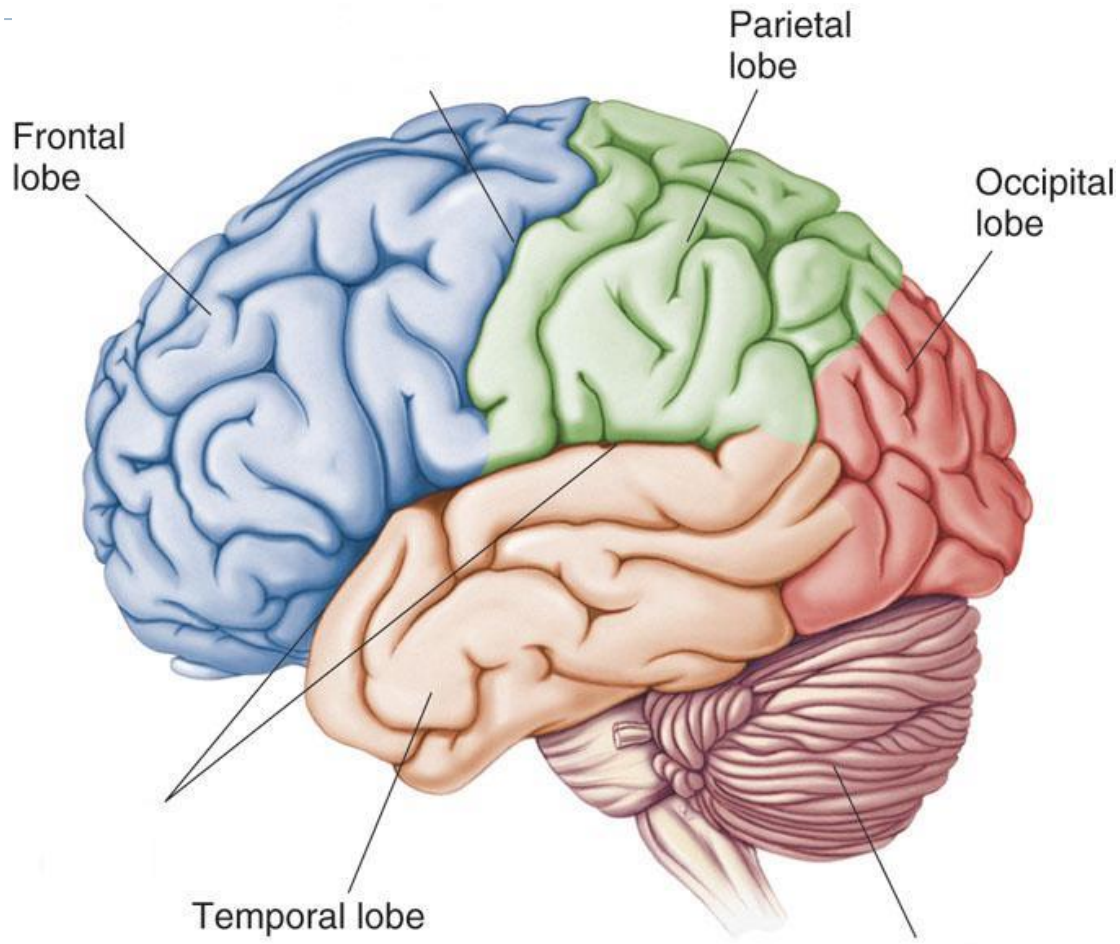


- Hypothalamus, pituitary, amygdala, and hippocampus all deal with basic drives, emotions, and memory
  - Hippocampus → Memory processing
  - Amygdala → Aggression and fear
  - Hypothalamus → Hunger, thirst, body temperature, pleasure; regulates pituitary gland (hormones)



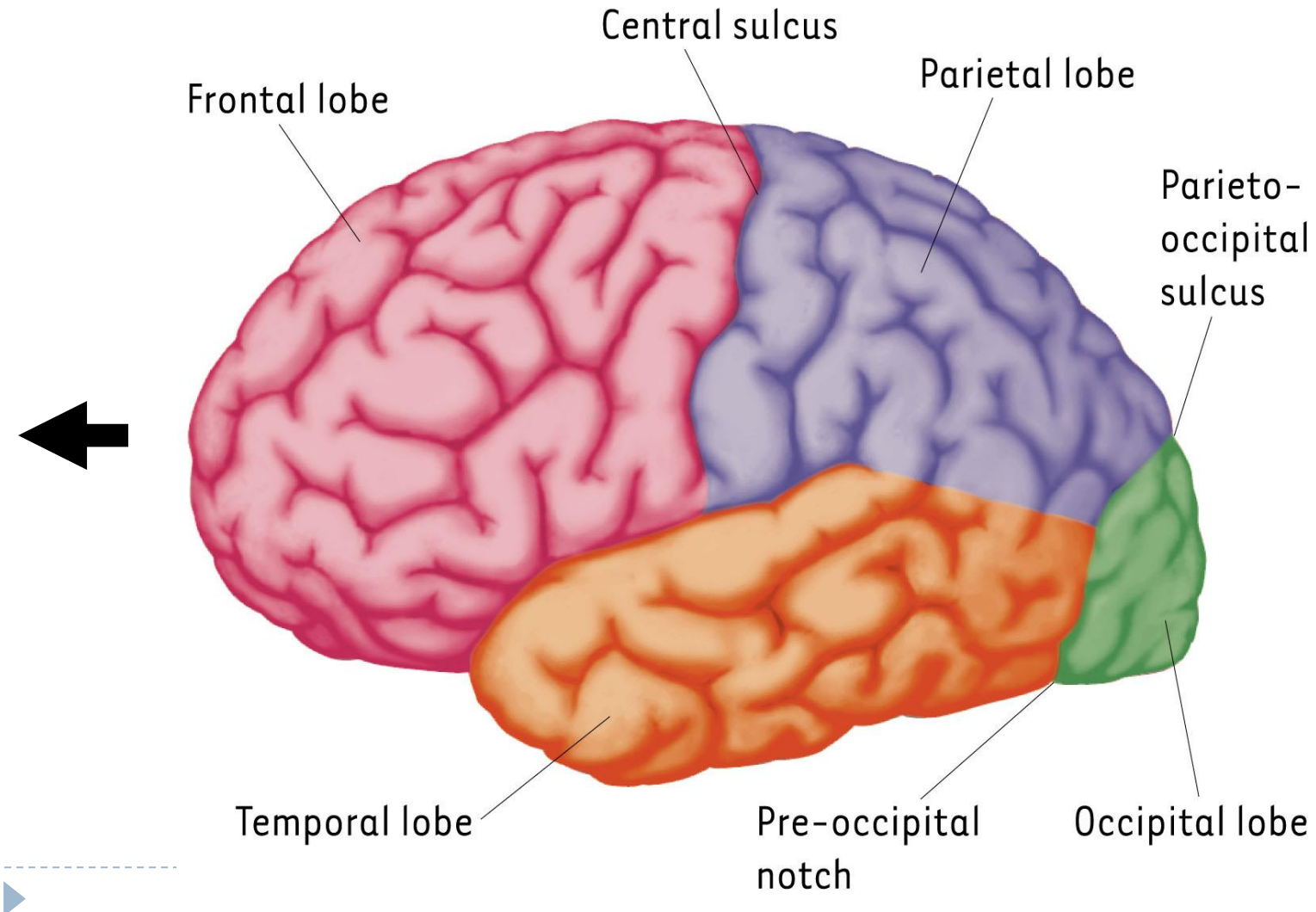
Lobes of the Brain (4)

- Frontal
- Parietal
- Occipital
- Temporal

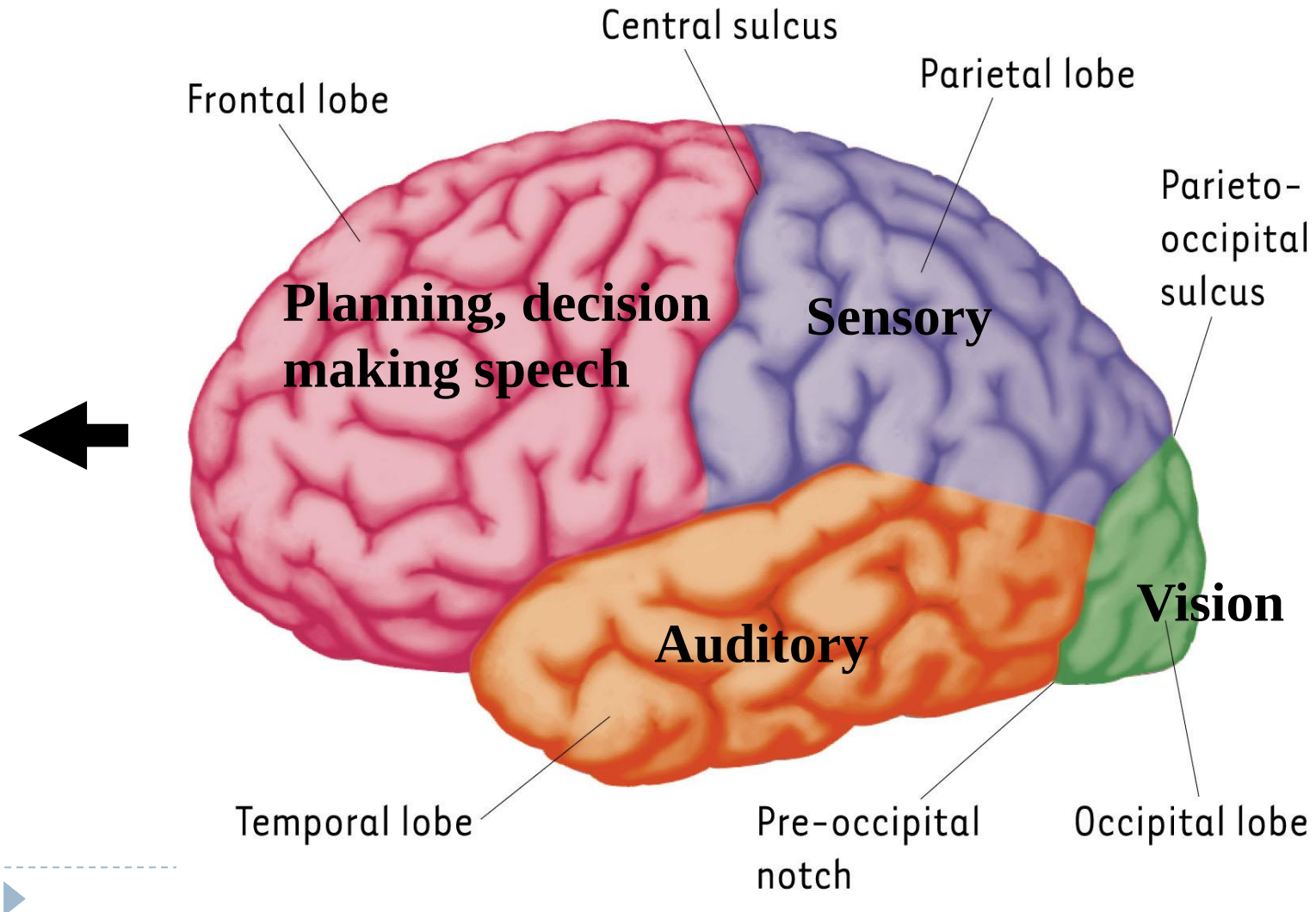


http://www.bioon.com/book/biology/whole/image/1/1-8.tif.jpg

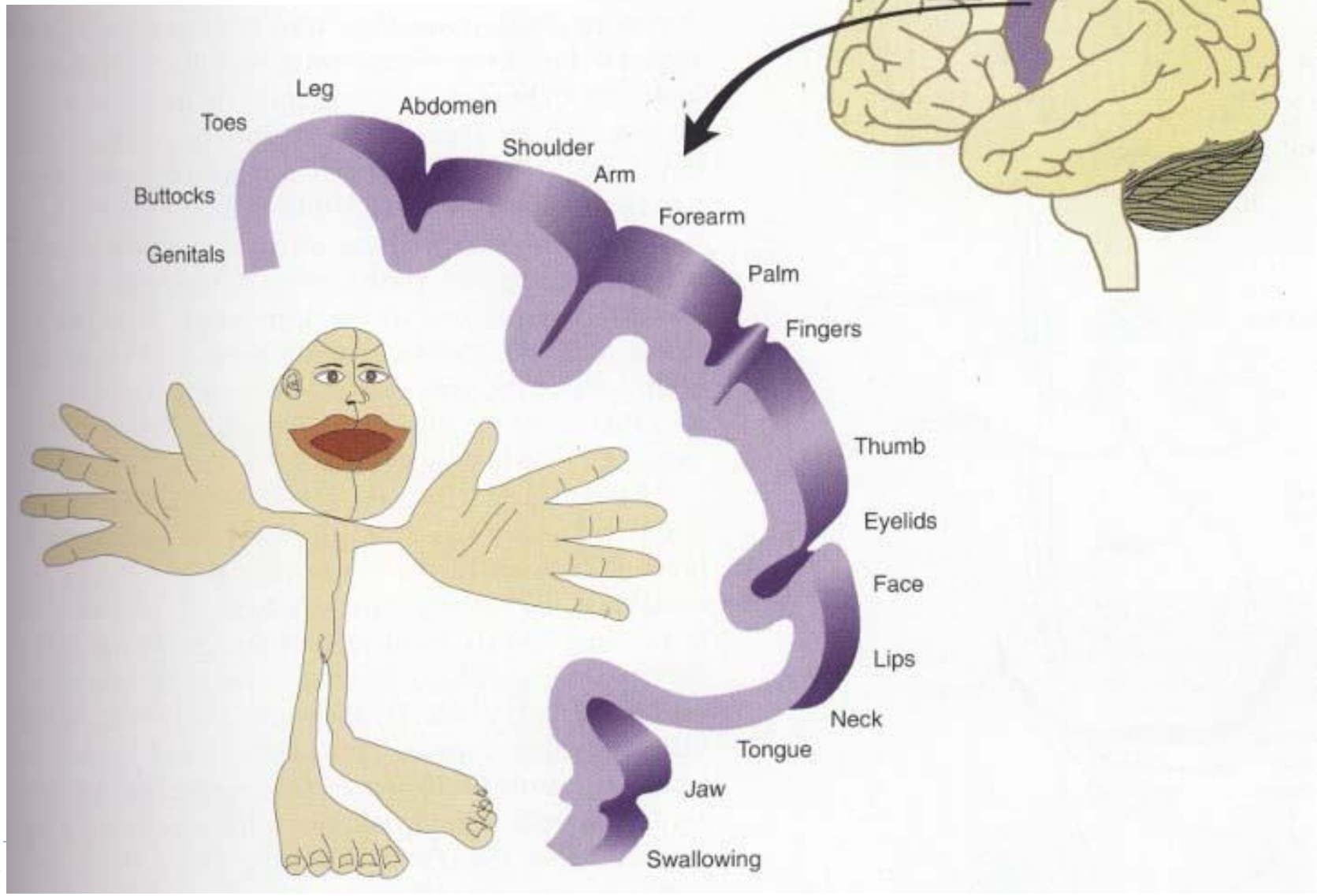
The lobes of the cerebral hemispheres



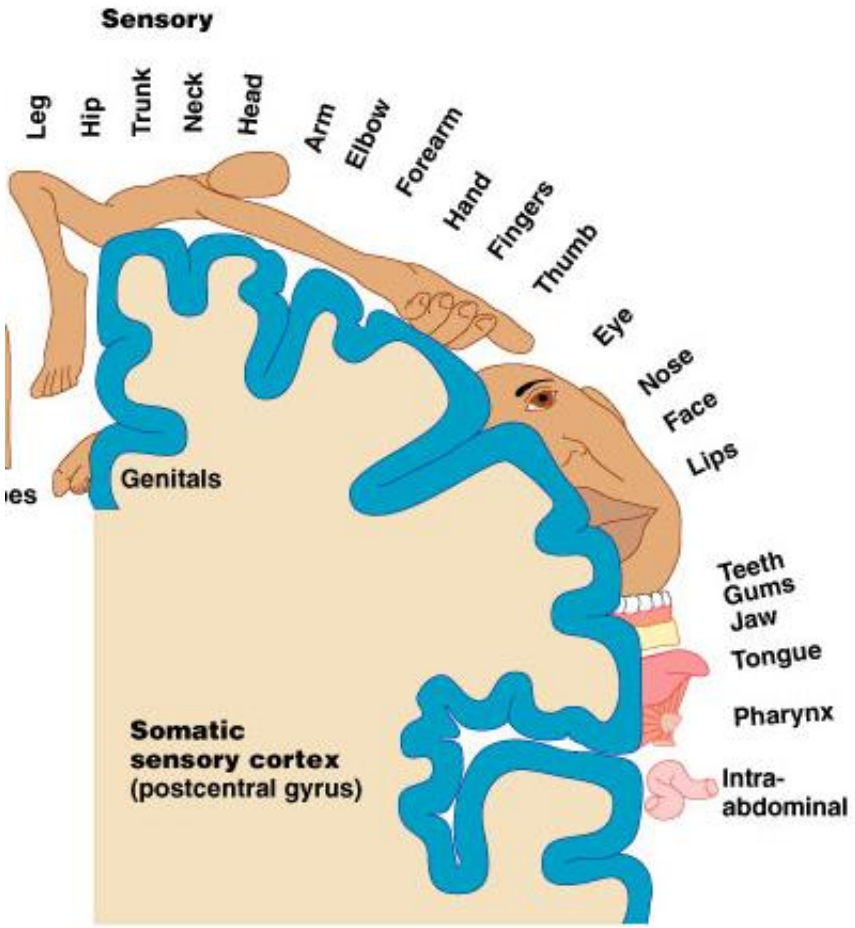
The lobes of the cerebral hemispheres

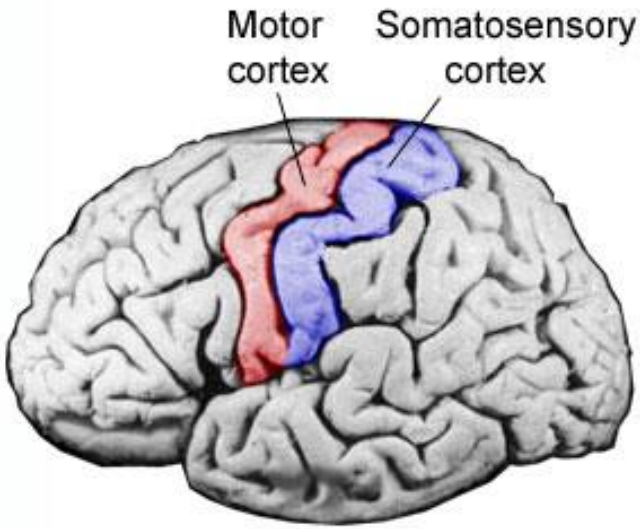


Motor strip and homunculus

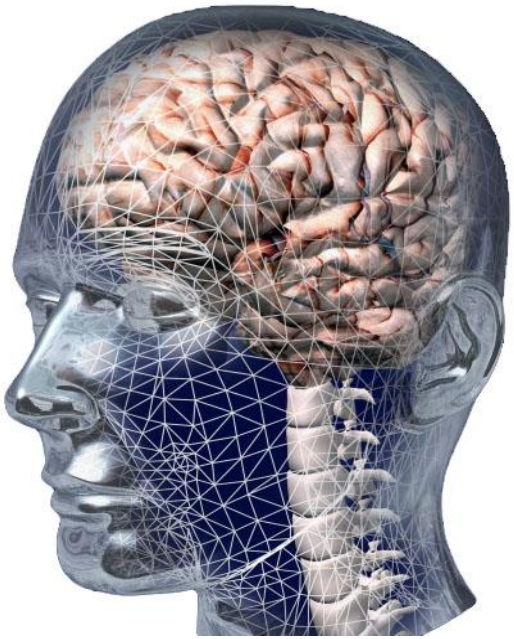


Sensory Cortex





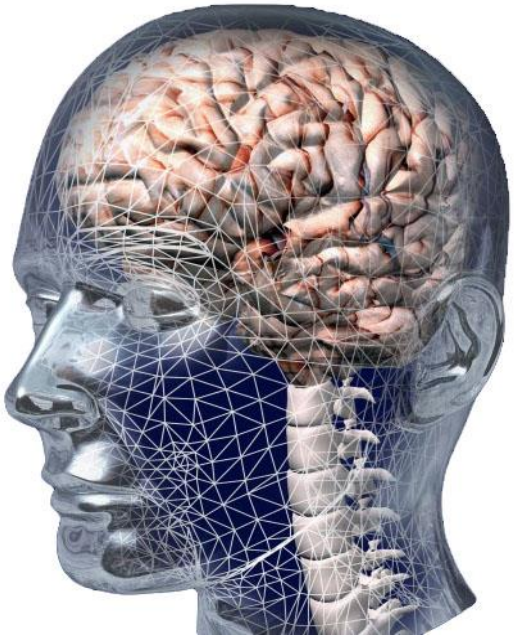
Multiple layers of complexity



Oliver Burston, images.wellcome.ac.uk.

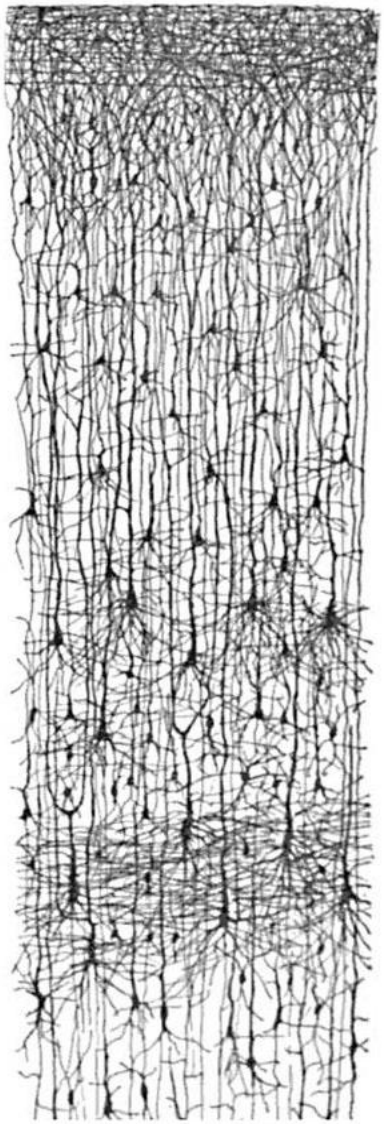
- ~100 billion Neurons
- ~1000 connections per cell

Multiple layers of complexity



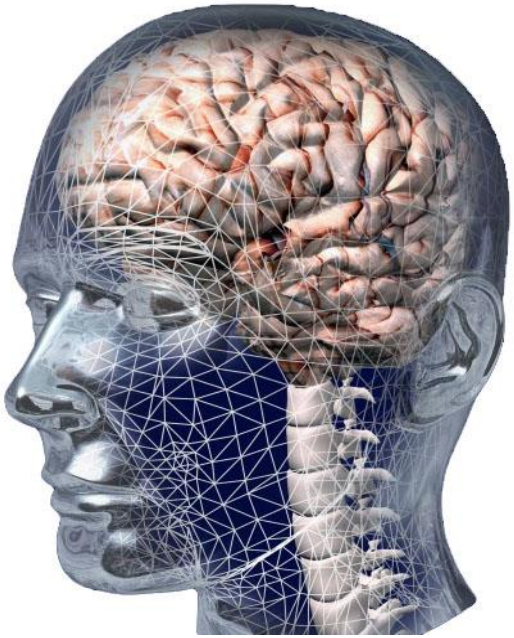
Oliver Burston, images.wellcome.ac.uk.

- ~100 billion Neurons
- ~1000 connections per cell



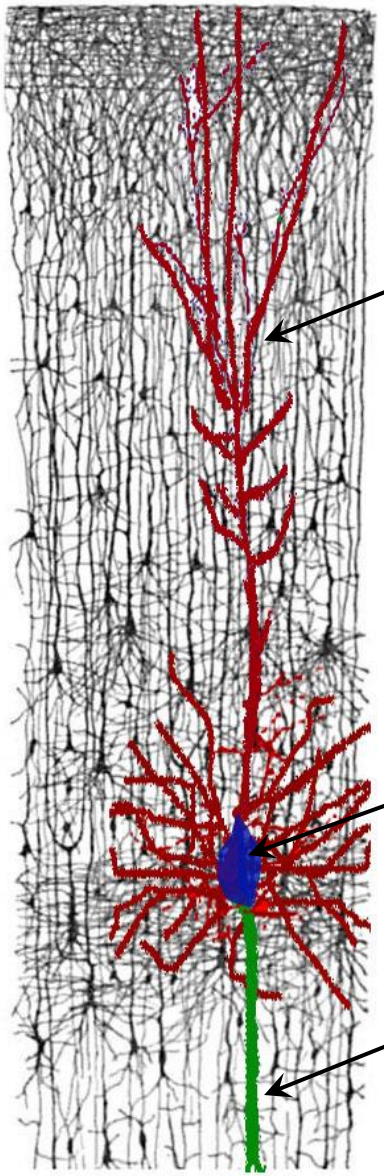
Ramón y Cajal, 1904

Multiple layers of complexity



Oliver Burston, images.wellcome.ac.uk.

- ~100 billion Neurons
- ~1000 synapses per cell

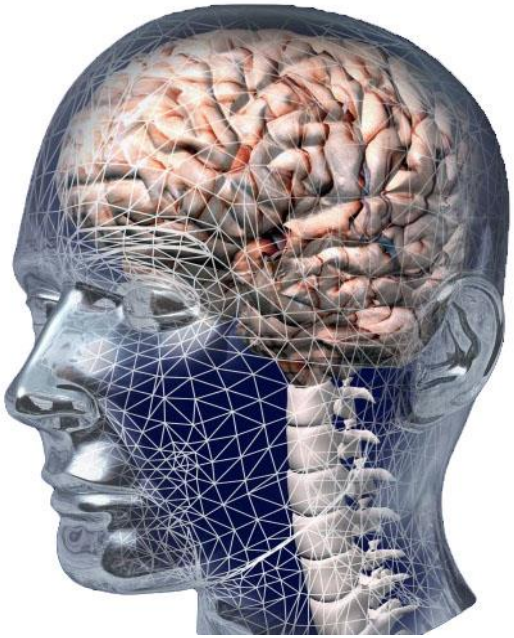


Dendrites
- Signal Inputs

Cell body, soma
- Signal Integration

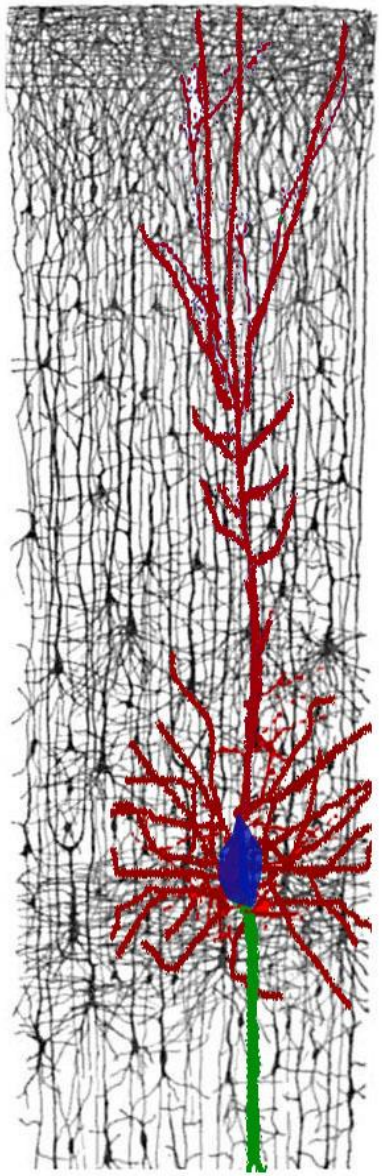
Axon
- Signal Outputs

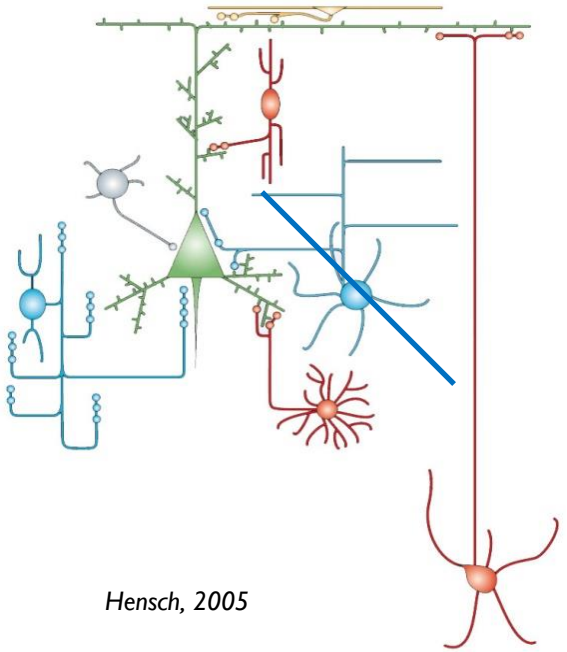
Multiple layers of complexity



Oliver Burston, images.wellcome.ac.uk.

- ~100 billion Neurons
- ~1000 synapses per cell



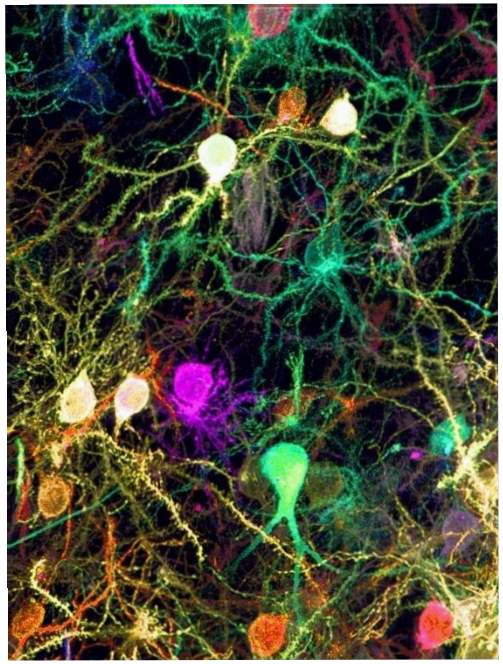


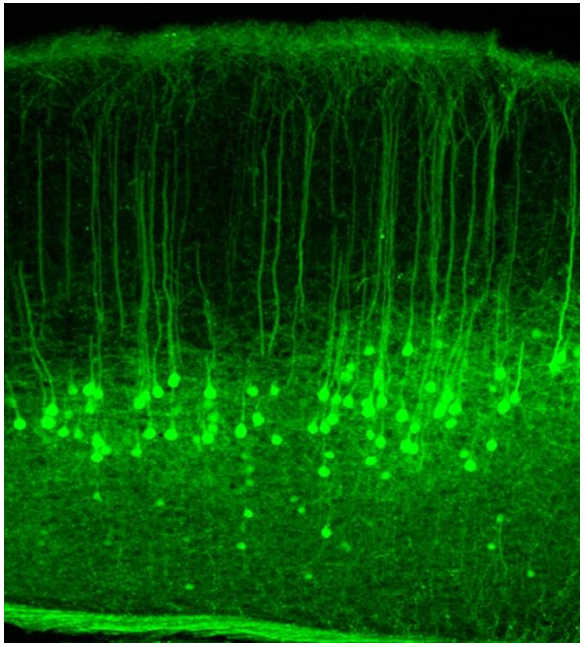
Hensch, 2005

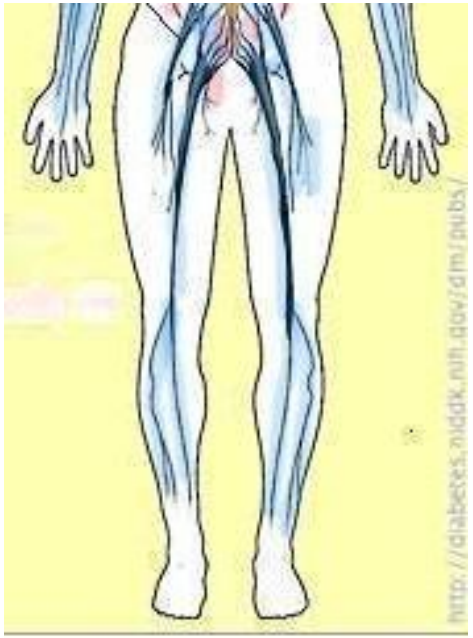
- Over a thousand different types of cells in brain
- Certain types of neuron are affected in specific diseases.
- Manipulate the network at single cell resolution.

Are all neurons equal in size?

- Brain vs spinal cord vs peripheral nerves?





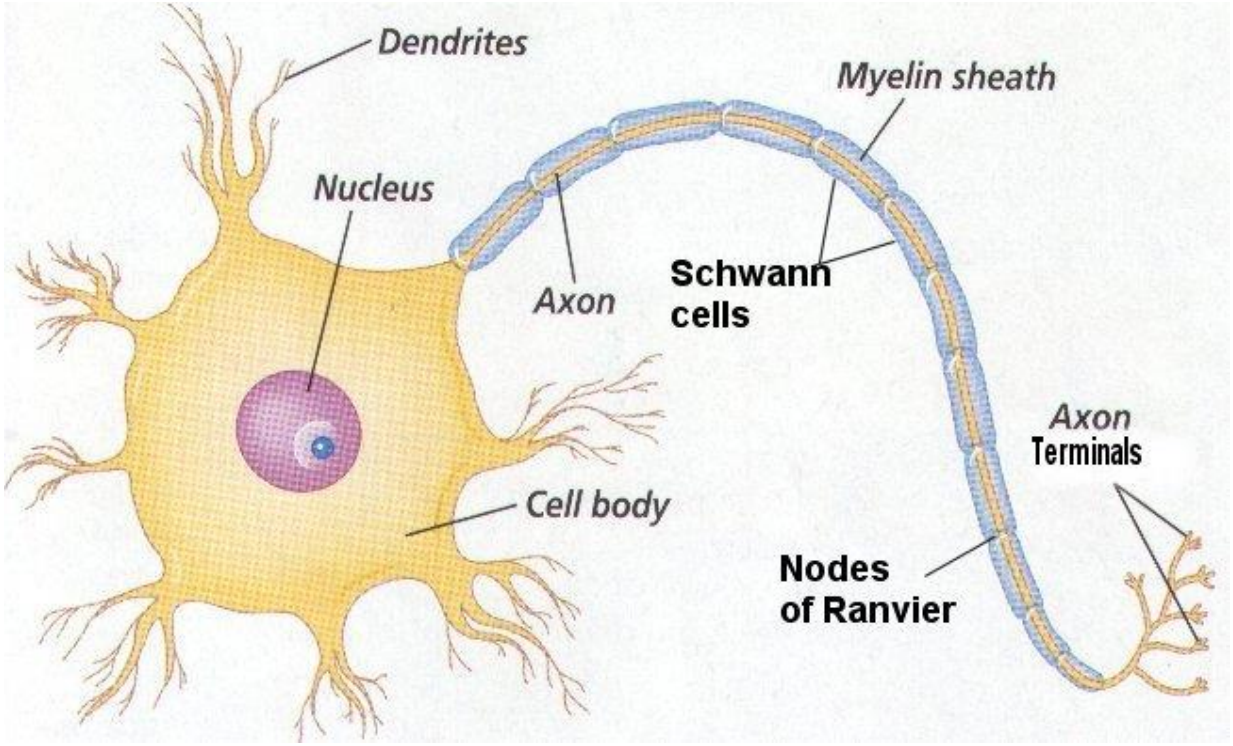


About how many neurons are in the human brain? 100 billion

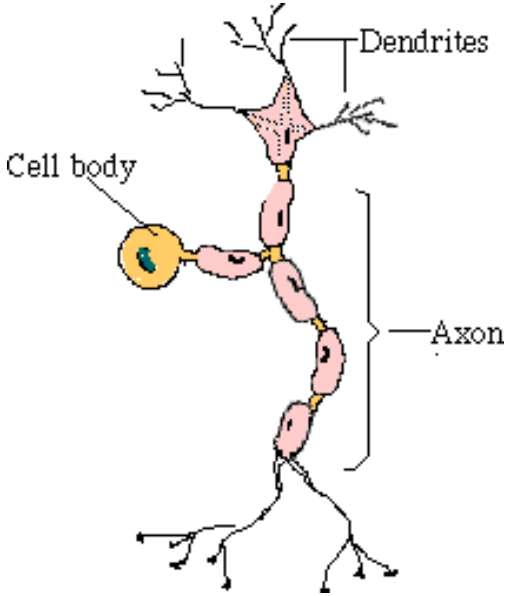
About how many neurons are in the spinal cord? 1 billion

How long do you think the longest axon in the world is? around 15 feet

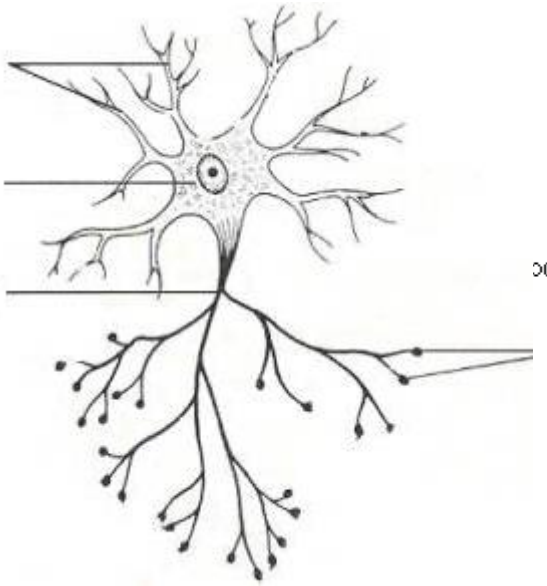
Basic nerve cell structure



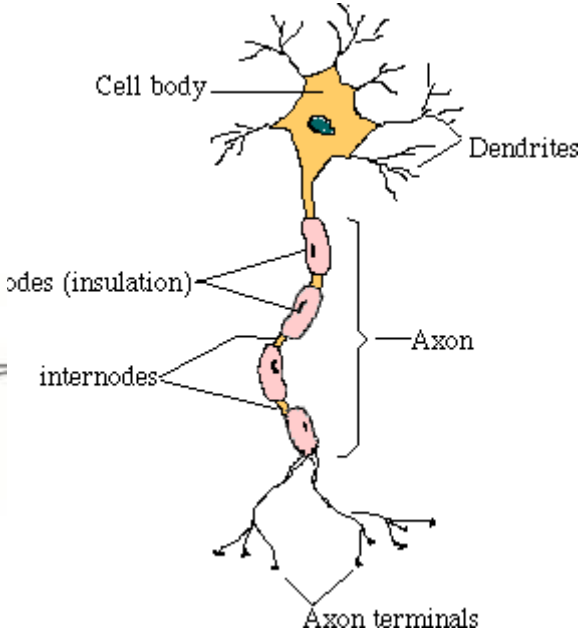
3 main types of nerve cells



sensory neurone

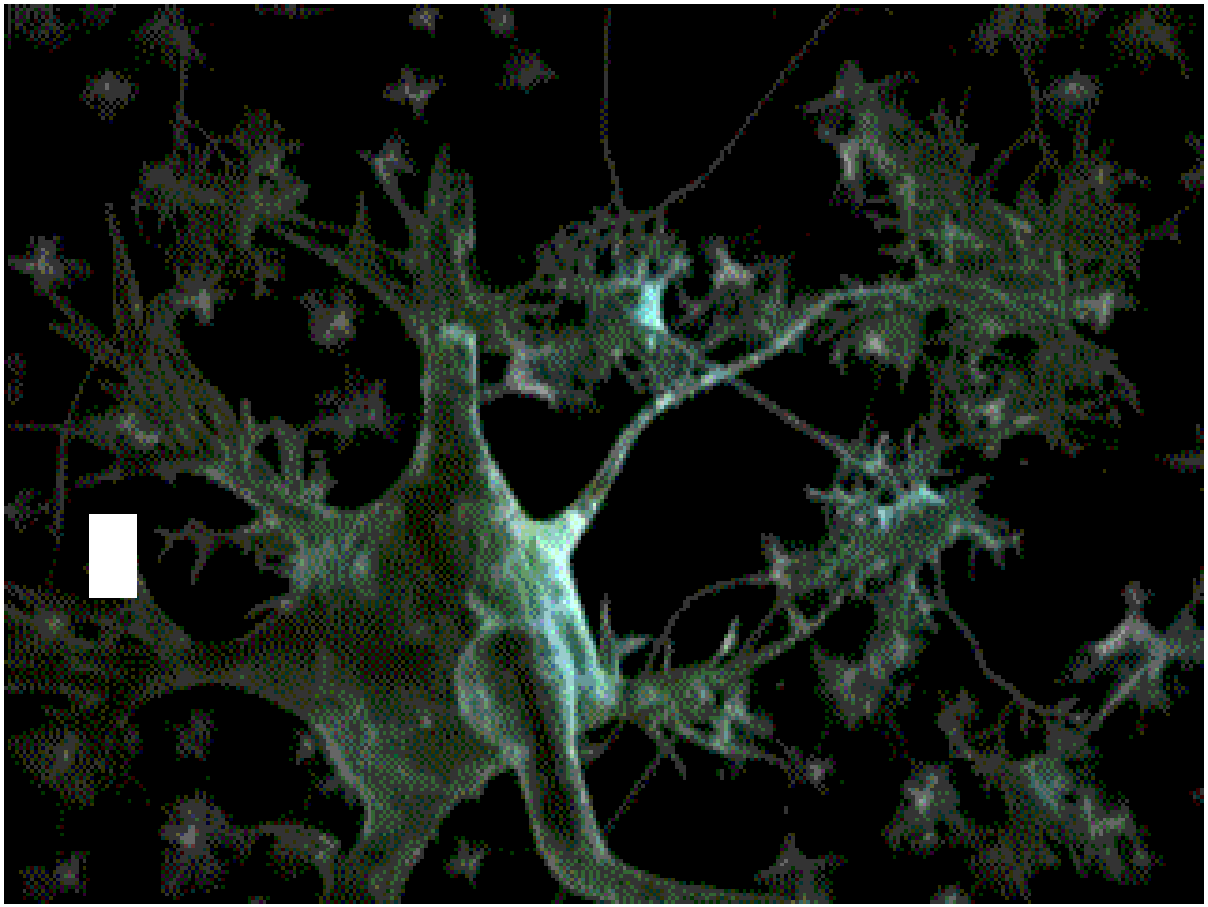


relay neurone



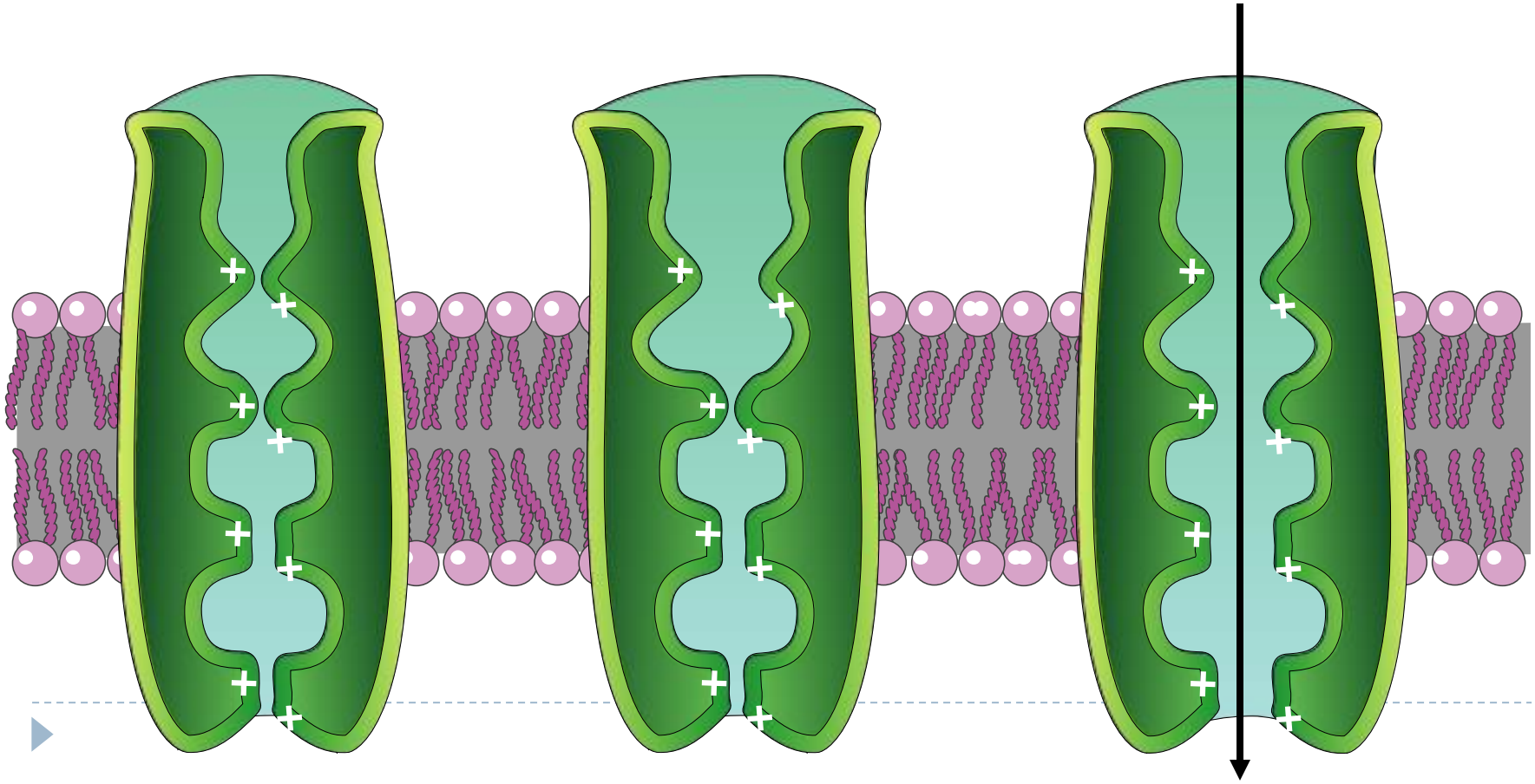
motor neurone

Signal Transmission

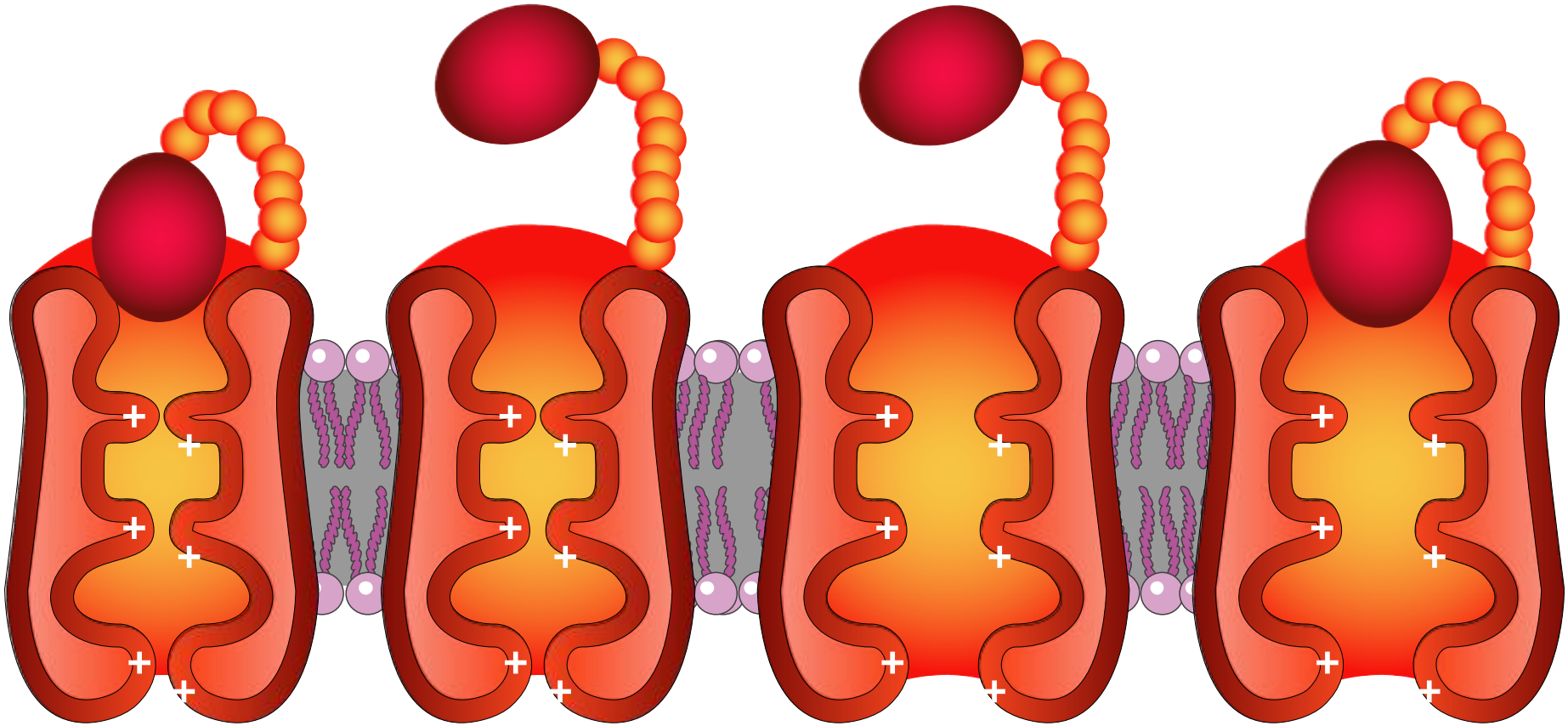


Electrical signal is transmitted across neurons

K Channel Conduction Gates



Na Channel Conduction Gates



- Closed
- Closed
- Open
- Closed

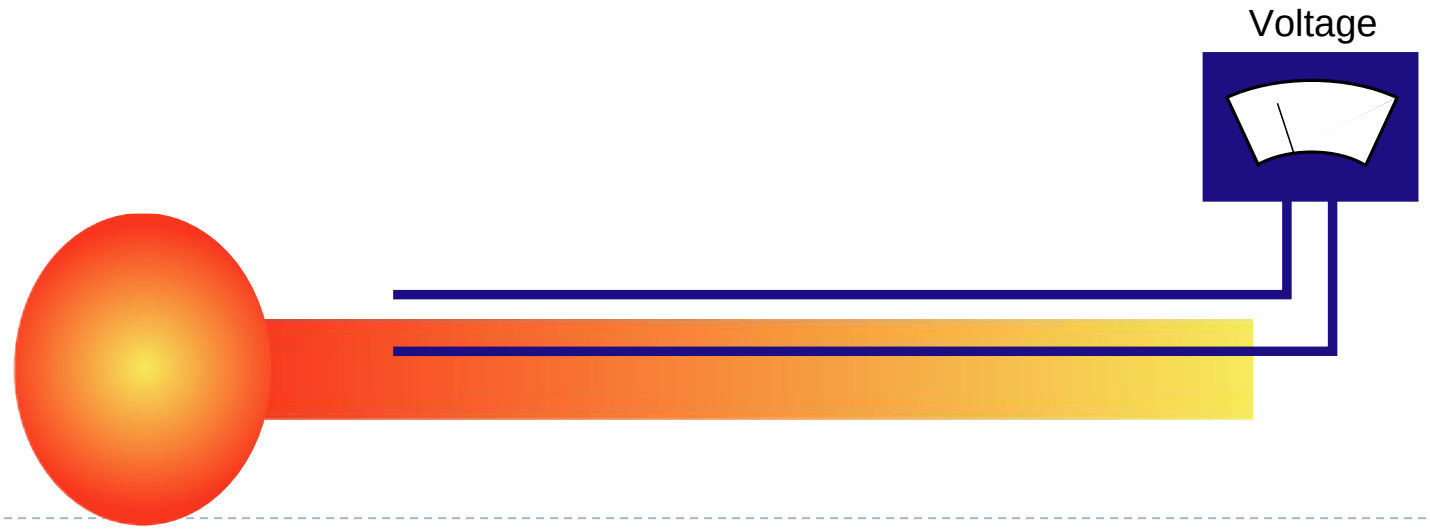
How the electrical signal generated?

Hodgkin Huxley Models:

- Electrical Firing of Neuron is called “action potential”
- Initiated by movement of charged ions (Na^+, K^+)
- Ions are separated by the membrane
- Ions flow through channels
  - Their conductances are variable

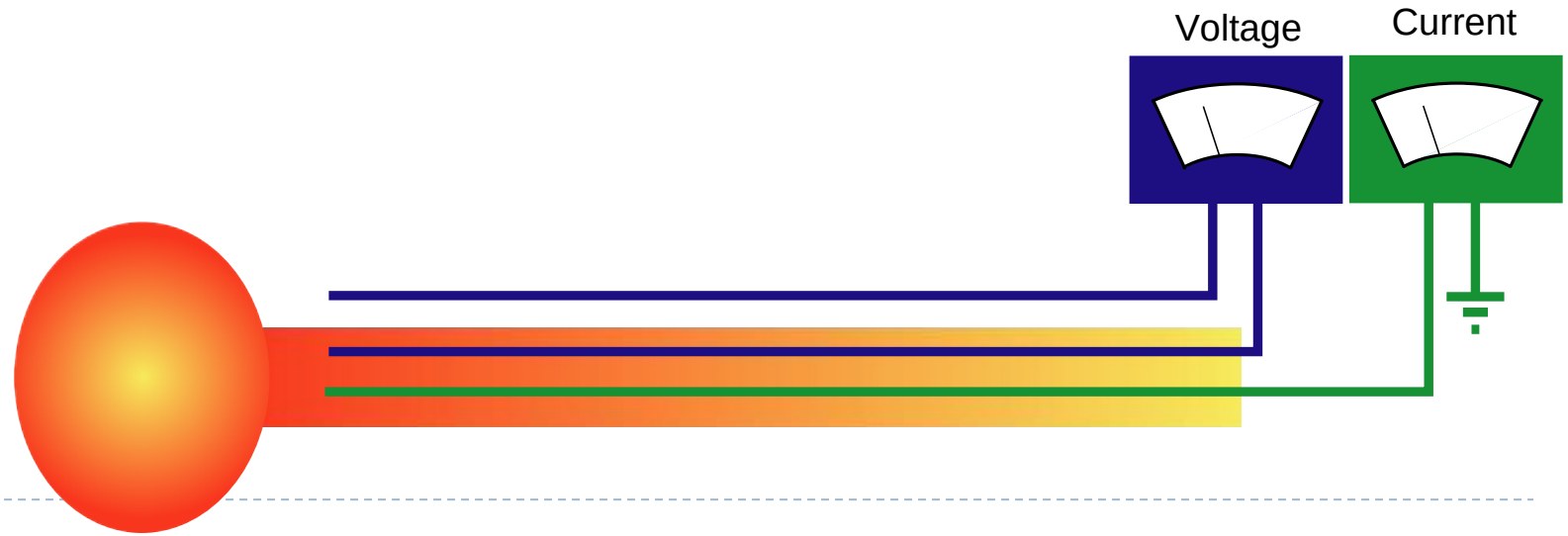
Experimental Methods

- Devised a method to hold V_m constant
  - Constant in time
  - Constant in space along the axon
- Space Clamp

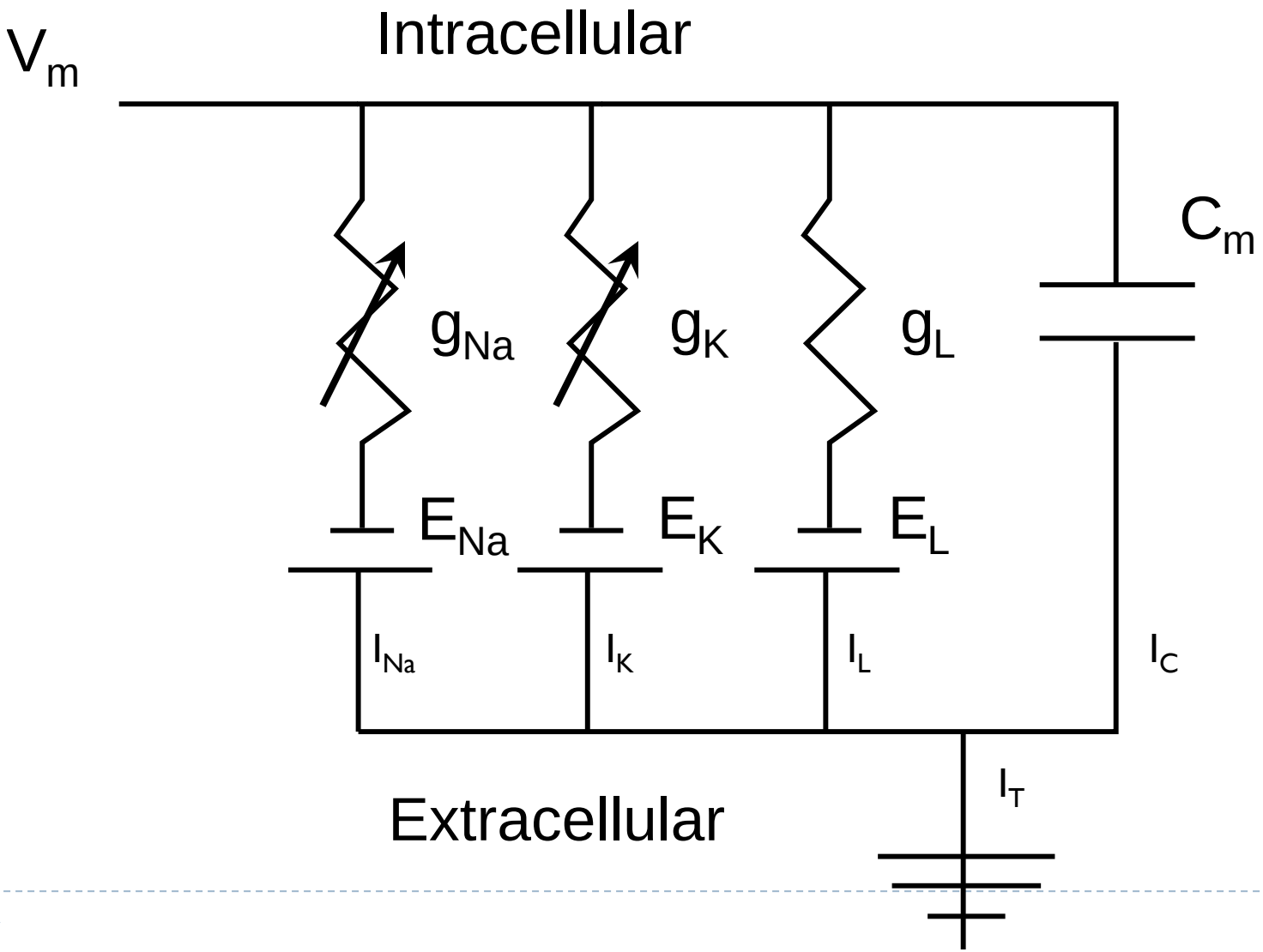


Experimental Methods

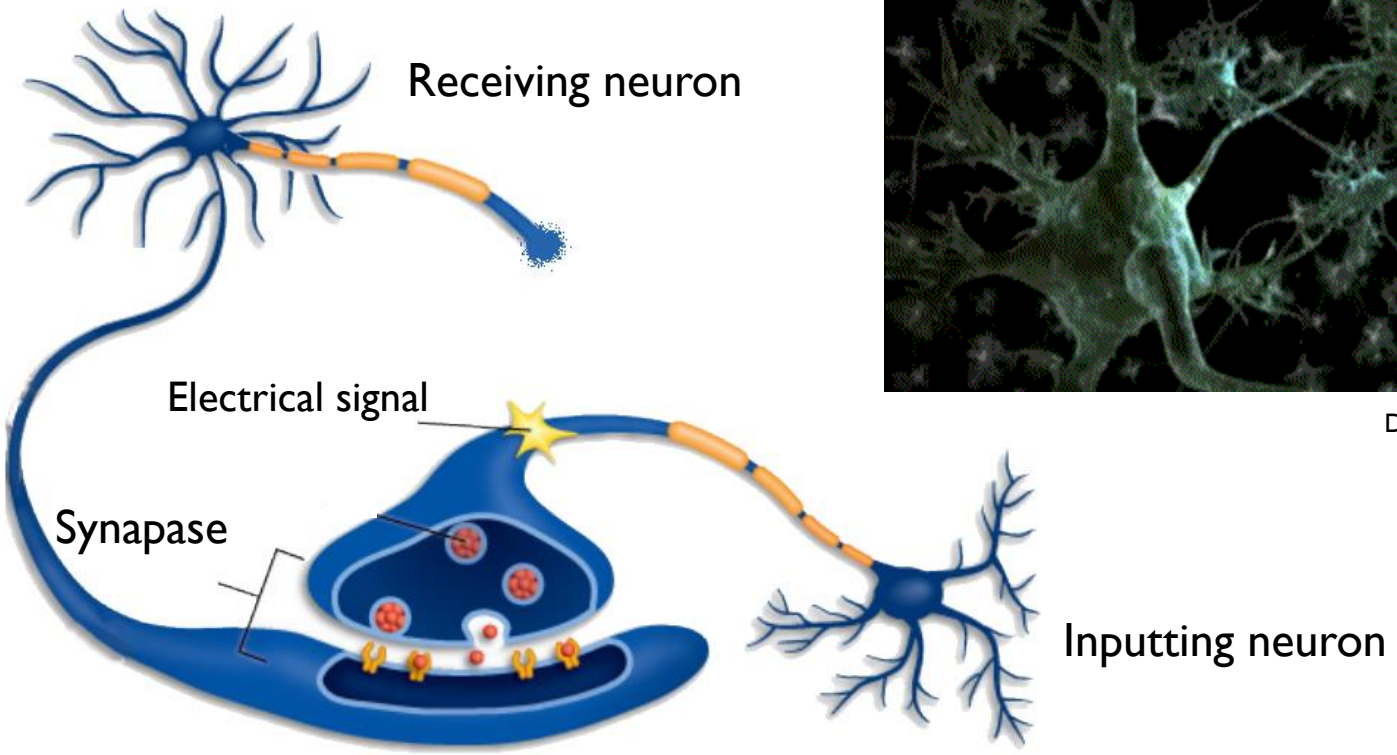
- Needed to measure the current necessary to hold V_m at a desired level
  - Feedback Amplifier
    - Second wire to apply a current
    - Feedback circuitry to measure current for a desired V_m



Hodgkin Huxley Model



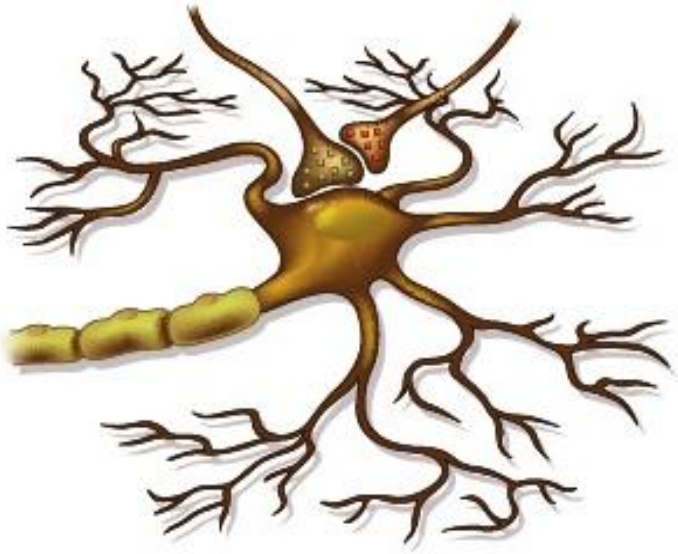
Transmission of Signals

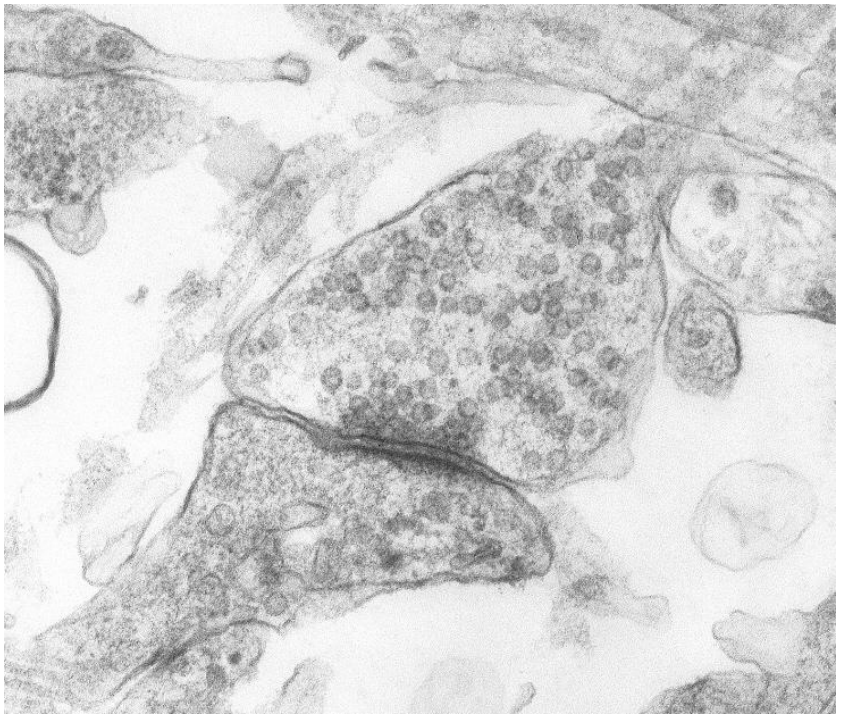


Discovery

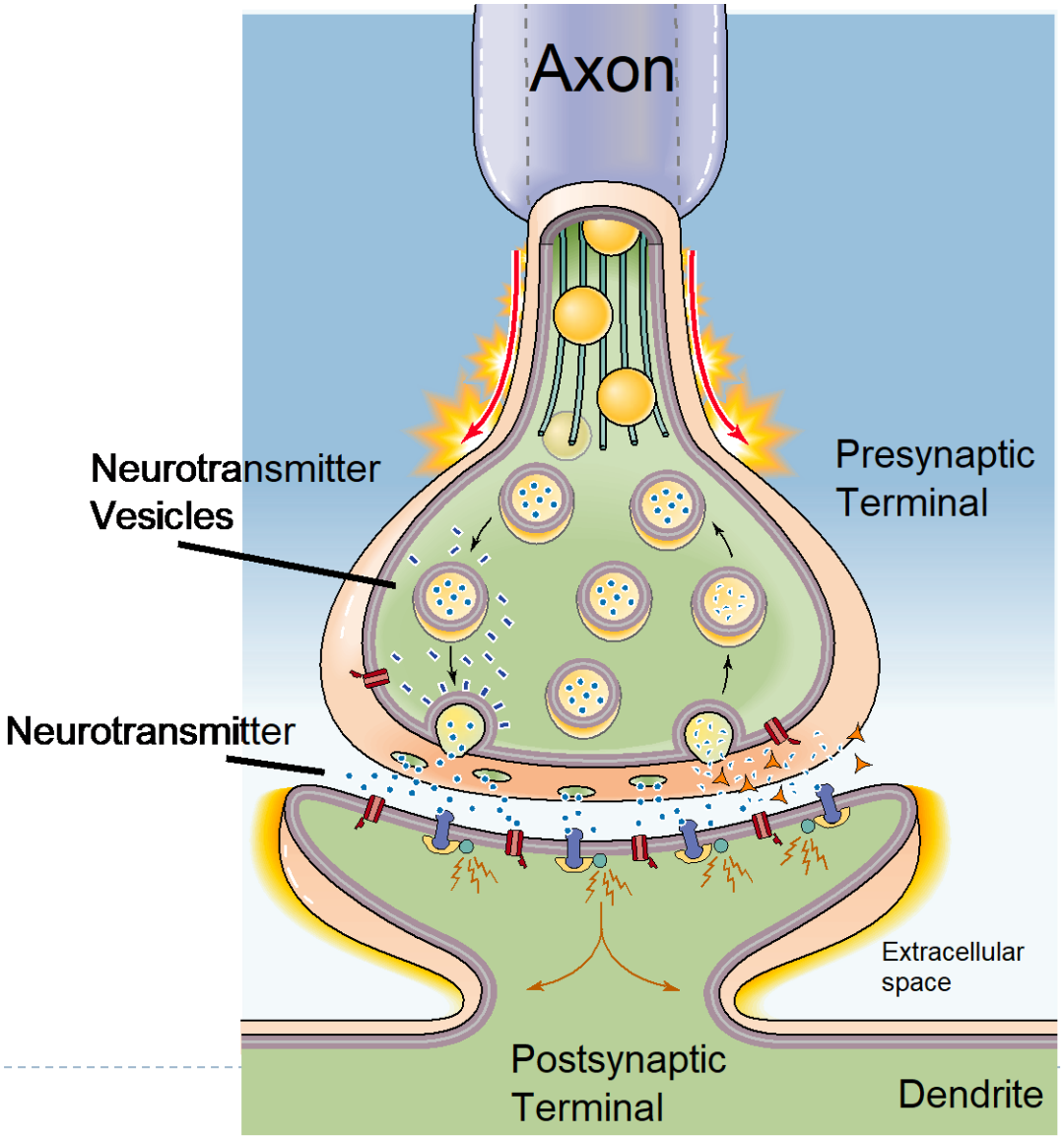
- Neurons are connected by synapses
- Electrical signal is transmitted across synapses

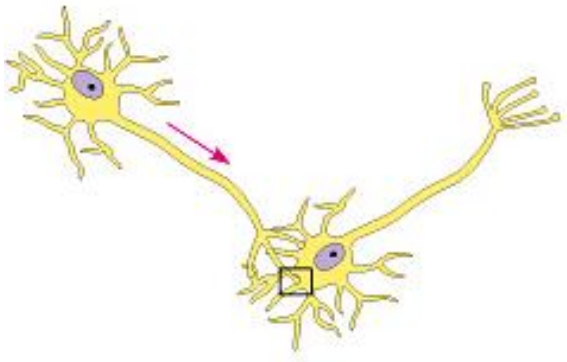
Transmission of signals





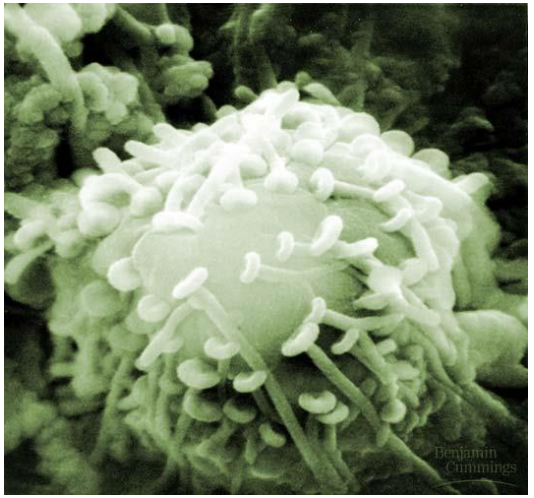
The Synaptic Transmission

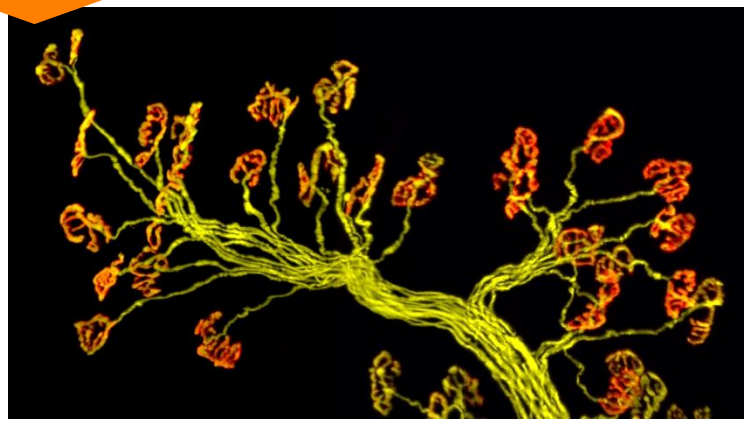




How many synapses are in one neuron?

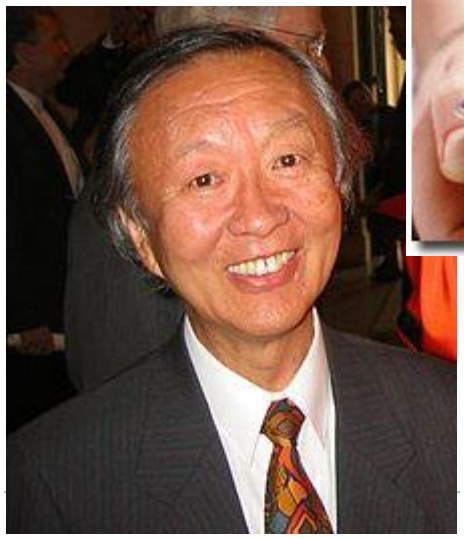
1,000 to 10,000!!

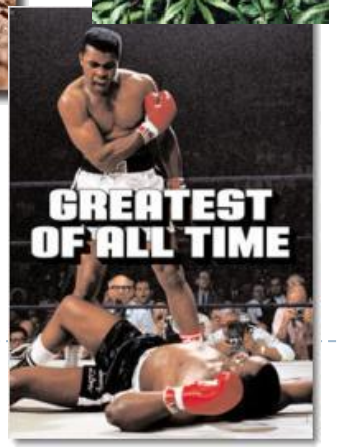




What do you think can change neurons and their connections?

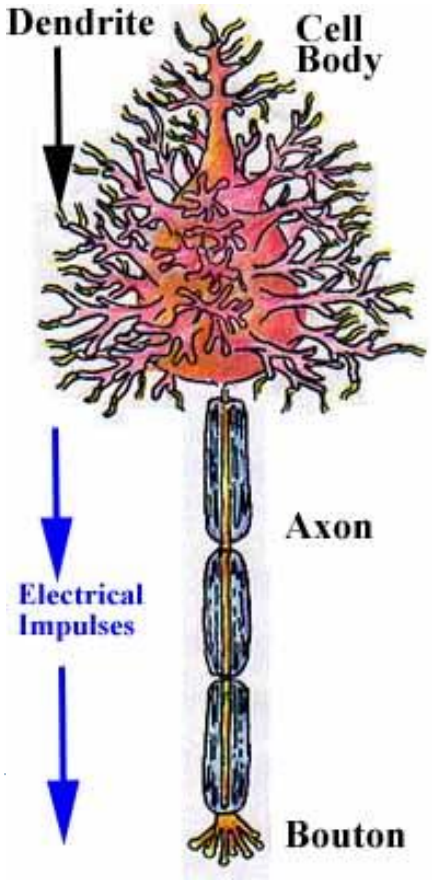
- Accidents
- Drugs
- Alcohol
- Disease

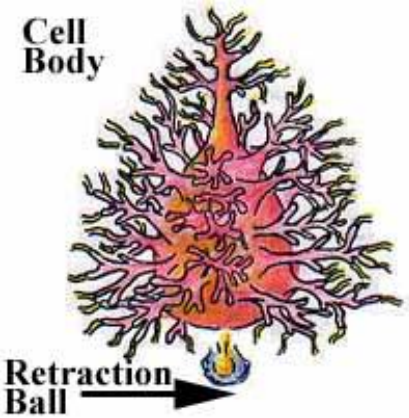




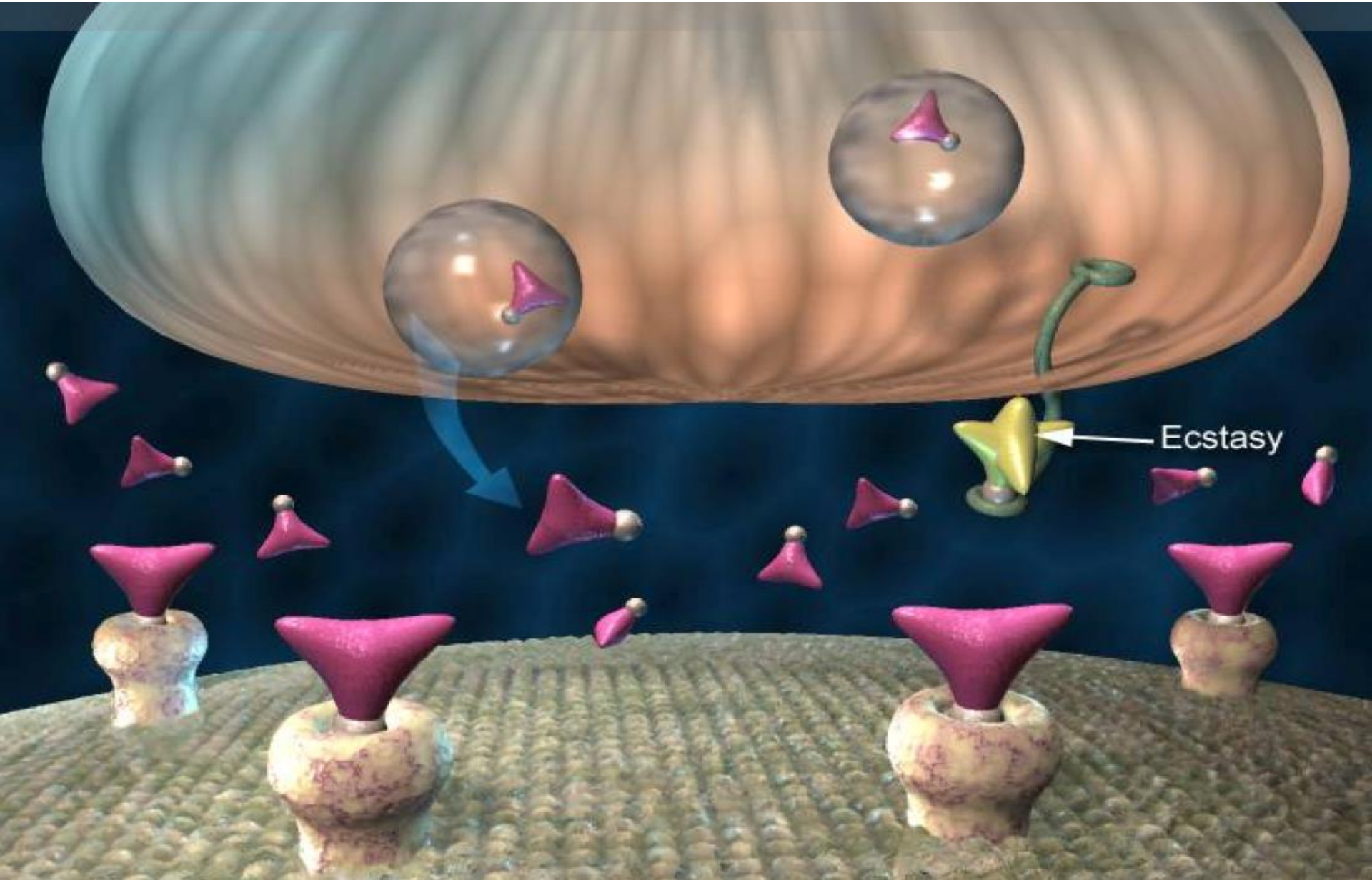
Accidents

- Physical injury of your neurons

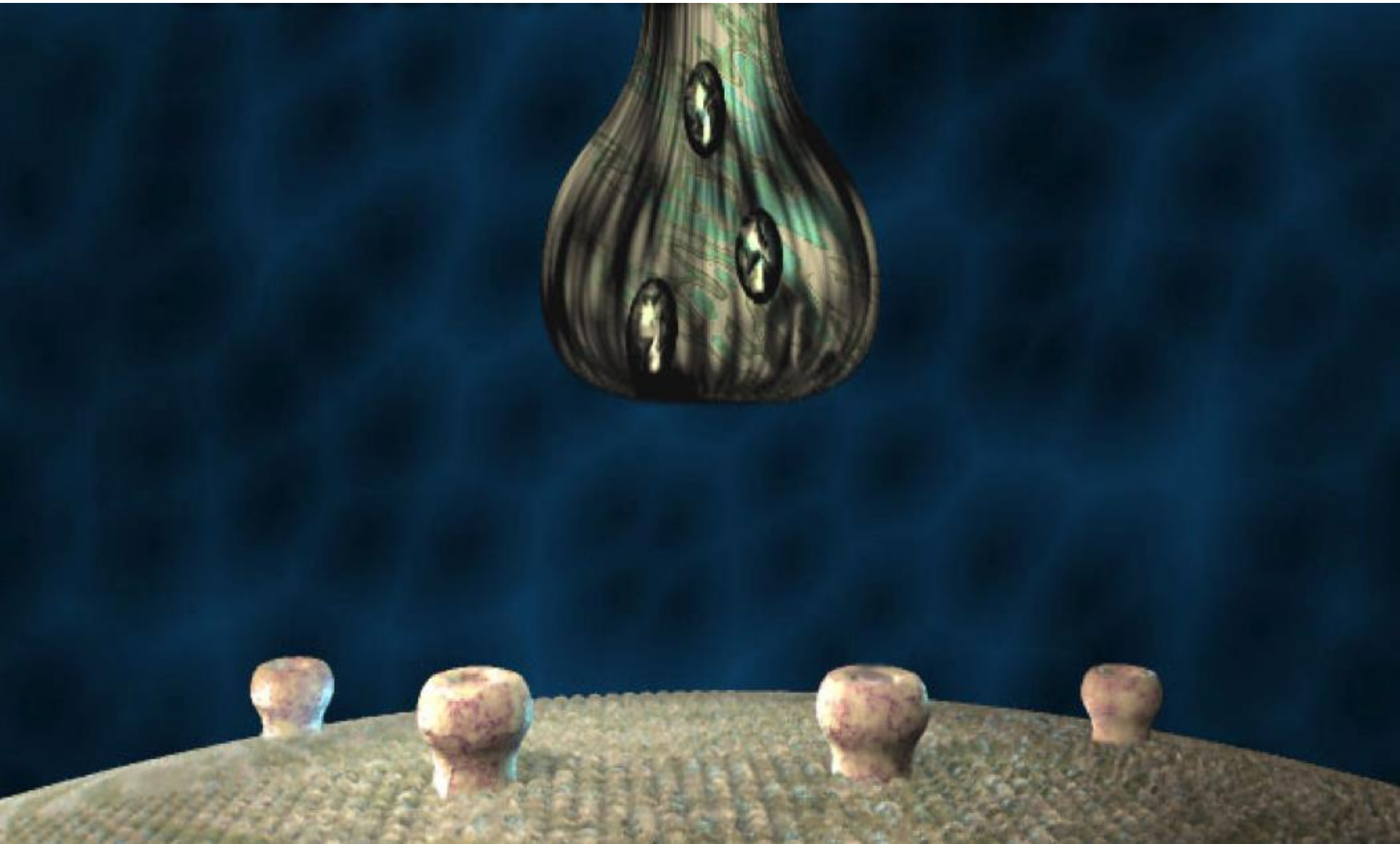




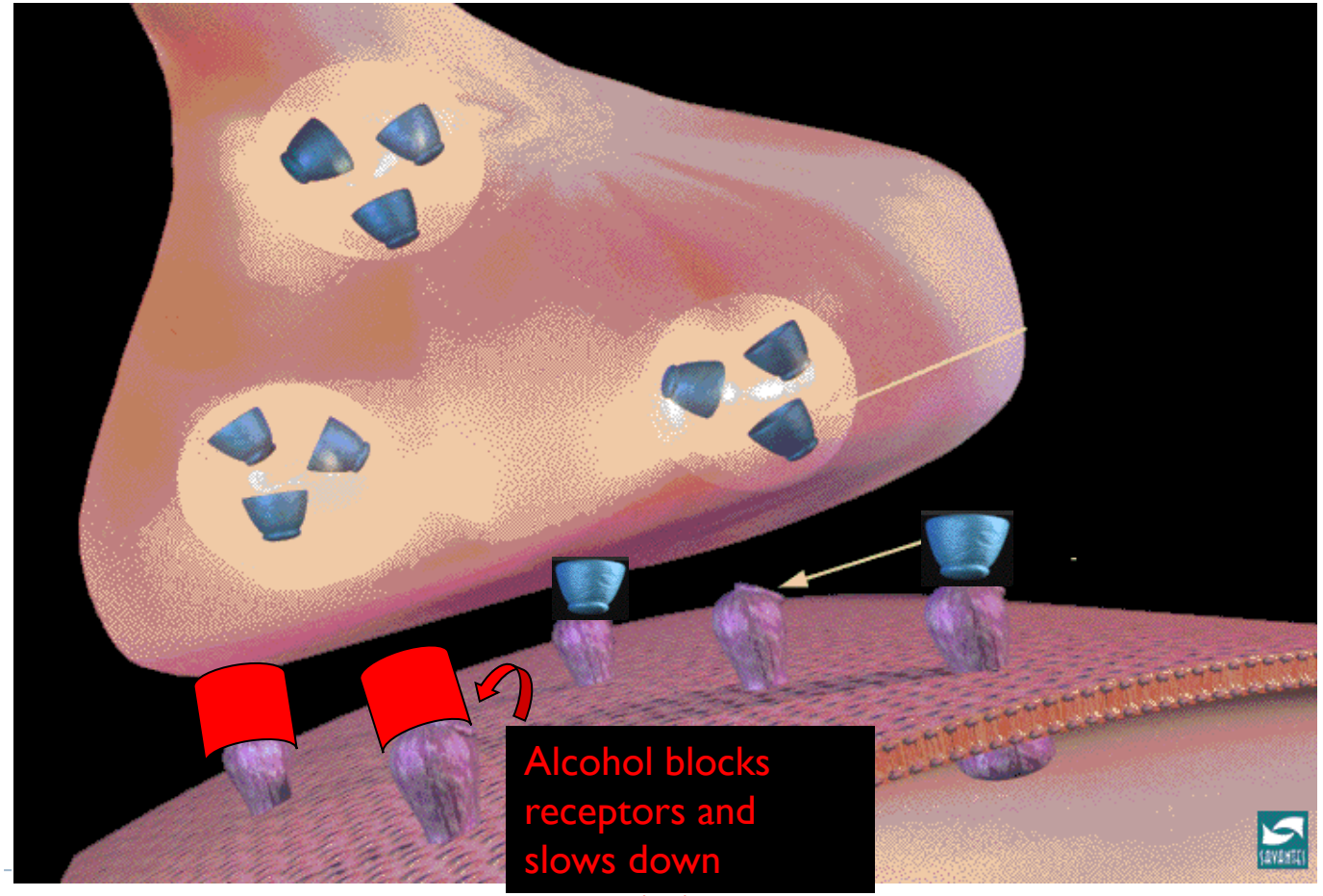
Drugs and alcohol bind important receptors on neurons



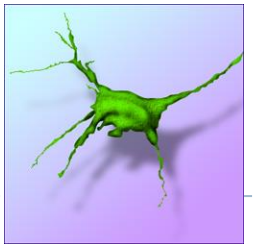
Repeated binding causes the neuron to die

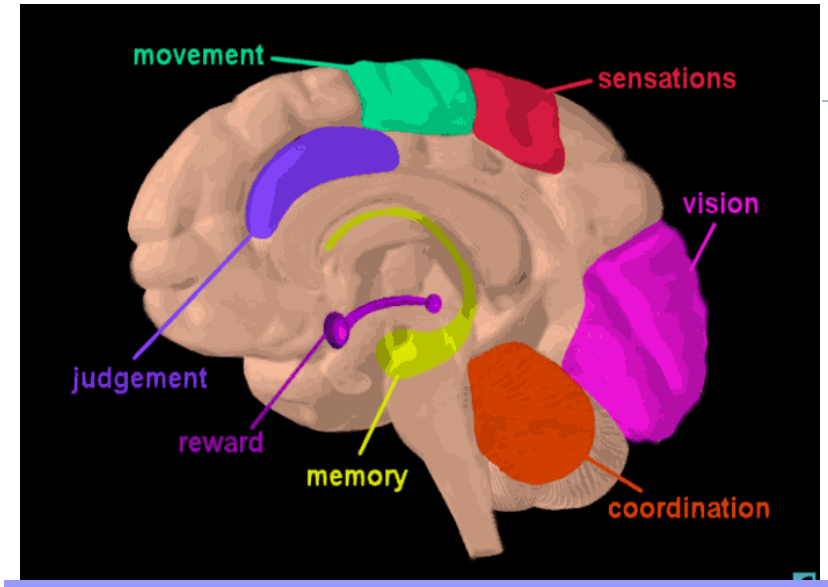


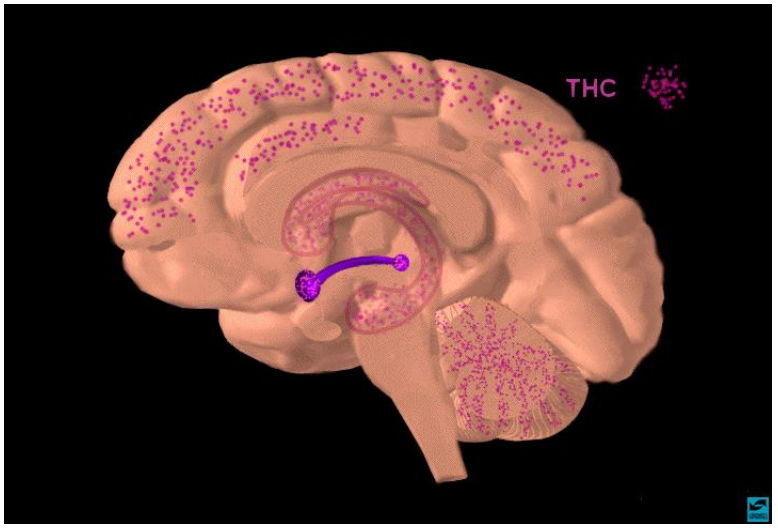
Alcohol damages dendrites - can repair after abstinence

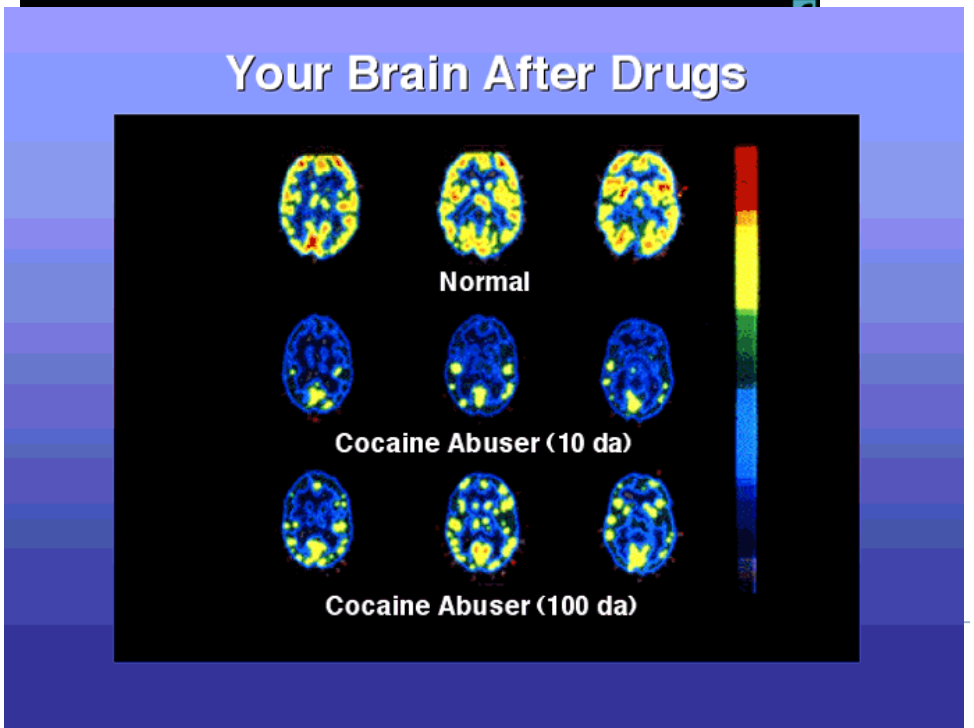


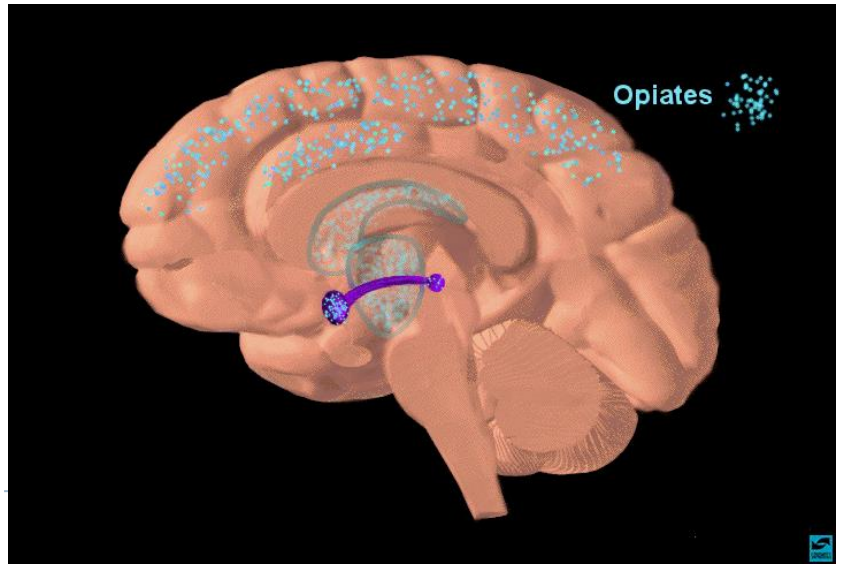
Drugs = neuron death







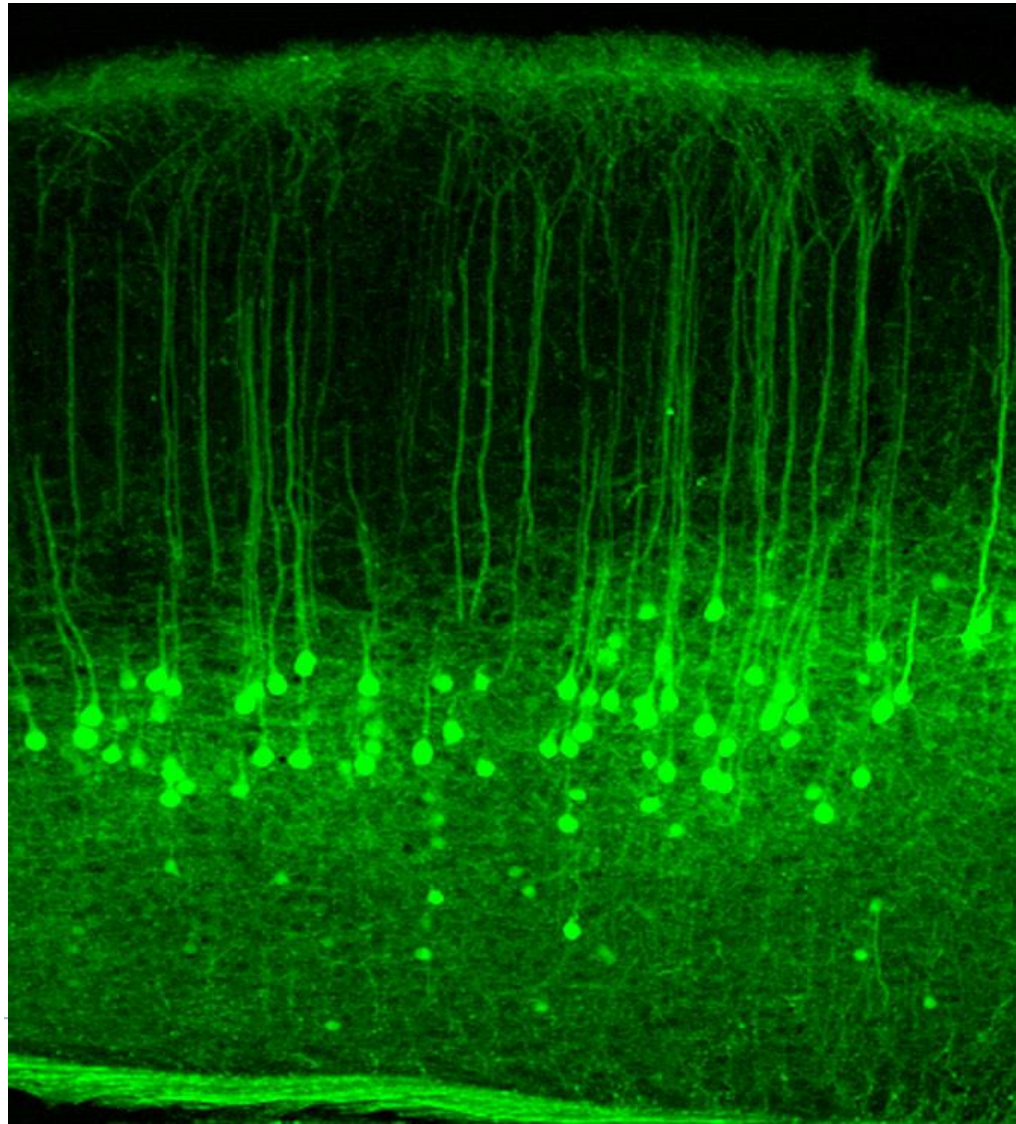




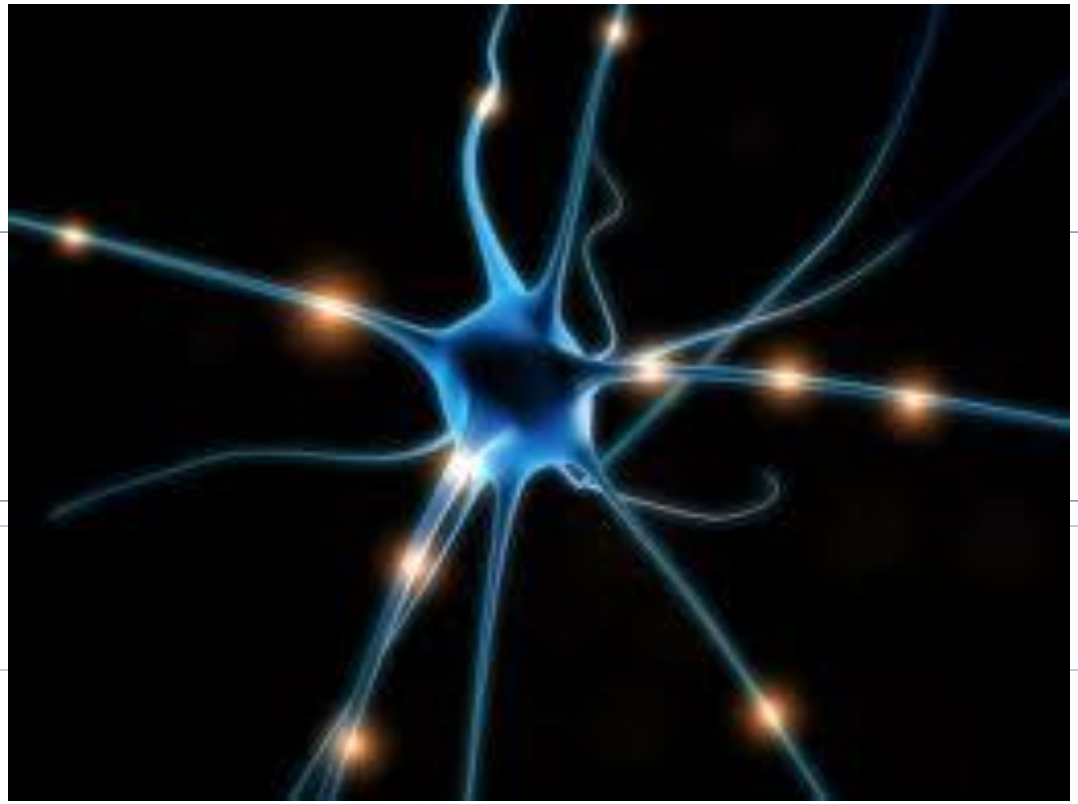

•Parkinson's Disease
•ALS - Lou Gehrig's Disease
•Huntington's Disease
•Multiple Sclerosis
•Alzheimer's
•Cerebral Palsy
•Epilepsy
•? SIDS

100 Billion or so neurons - what's the problem with some of them dying?

- Cells multiply all the time - will your neurons?
- Does everyone react the same way to accidents, or drugs and alcohol?
- Do all organisms react the same to all stimulus?
- Which of your activities use your neurons?



Electrophysiology Technique



What is patch-clamp?

Patch-clamping is an electrophysiological technique in which we are able to CLAMP the VOLTAGE of an isolated piece of cell membrane (or whole-cell). By clamping the voltage we are able to observe CURRENTS that flow through ION CHANNELS. It is the current that the patch-clamp amplifier supplies to hold the voltage steady (clamped) that we measure. Patch-clamp recording allows us to measure very small currents - in the pA range (10^{-12} A).

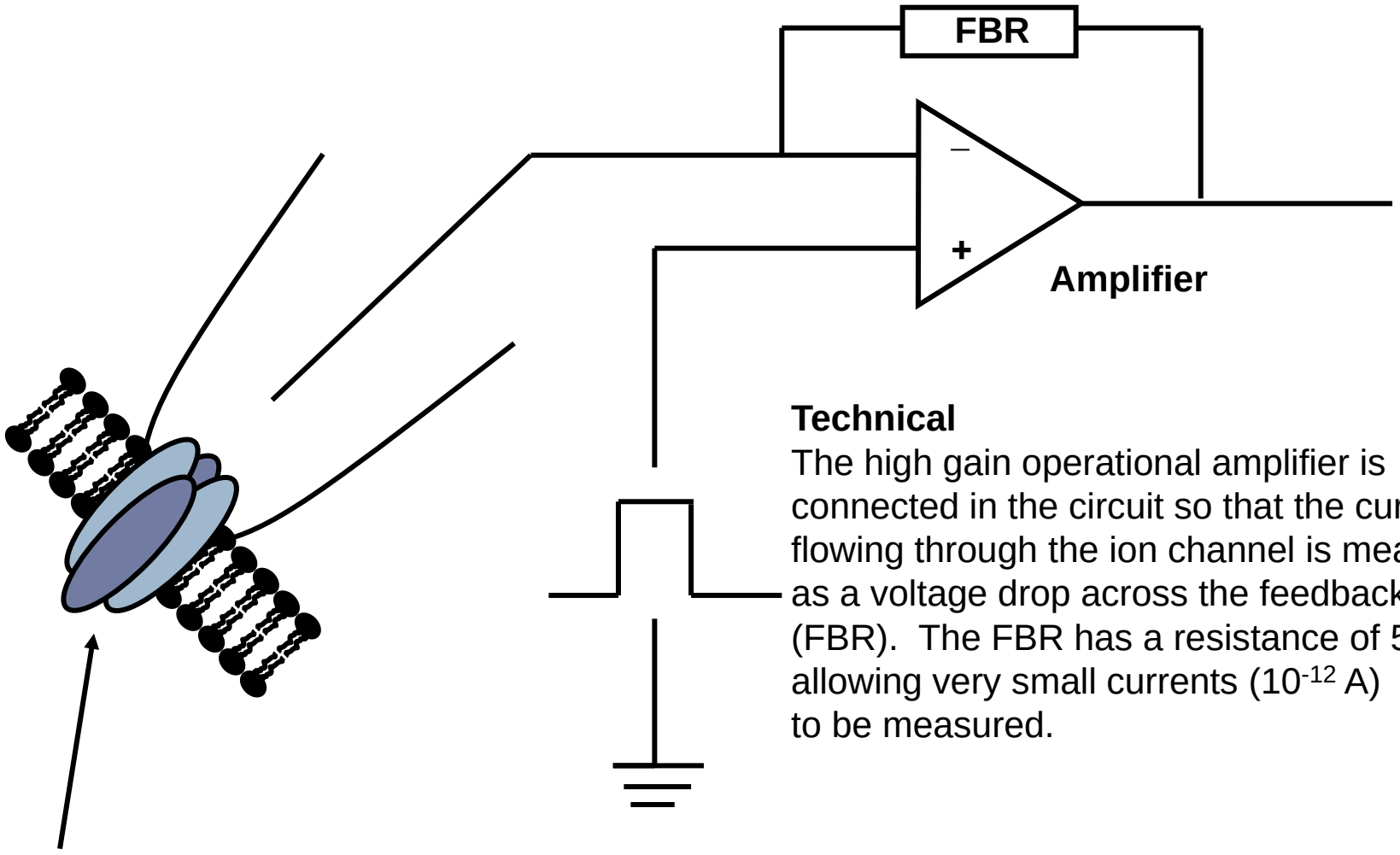
Patch clampers win Nobel Prize

Sakmann, Neher et al revolutionized the field of electrophysiology in 1981 with their paper “Improved patch-clamp techniques for high resolution current recording from cells and cell-free membrane patches” (*Pflügers Arch*. **391**, 85-100).

With patch-clamp recording we can observe the movement of single molecules (strictly macromolecular complexes) in real time.

In 1991, Neher and Sakmann were rewarded for their pioneering efforts in patch-clamp recording when they jointly won the Nobel Prize in Physiology or Medicine.

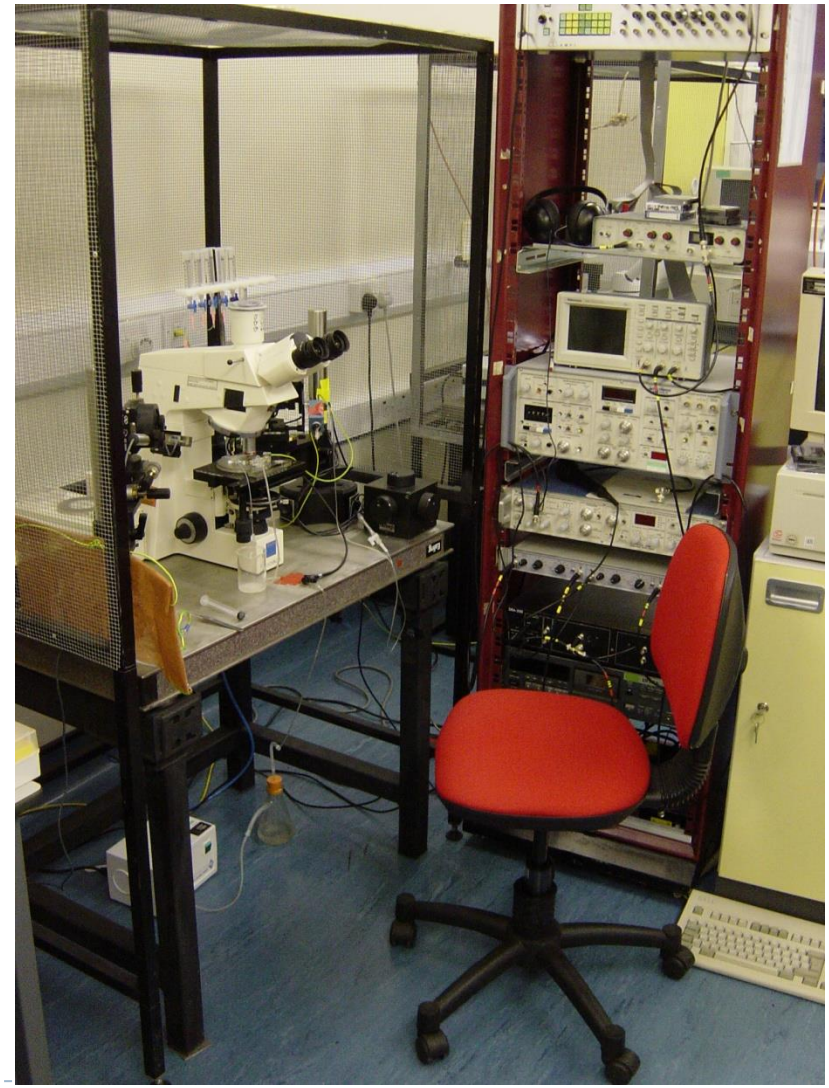
The patch-clamp circuit



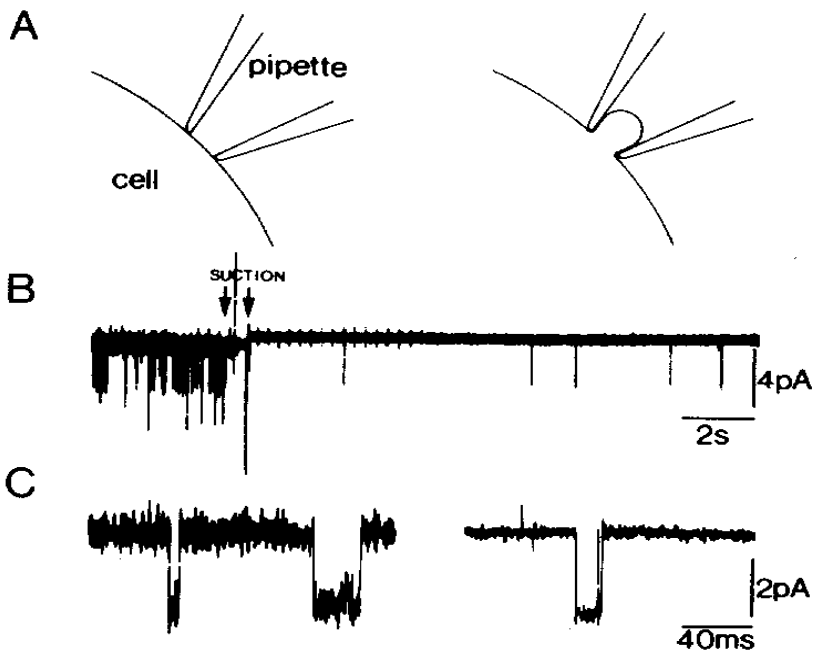
Technical
The high gain operational amplifier is connected in the circuit so that the current flowing through the ion channel is measured as a voltage drop across the feedback resistor (FBR). The FBR has a resistance of 50 GΩ allowing very small currents (10^{-12} A) to be measured.

Patch of cell membrane with ion channel

A patch-clamp rig



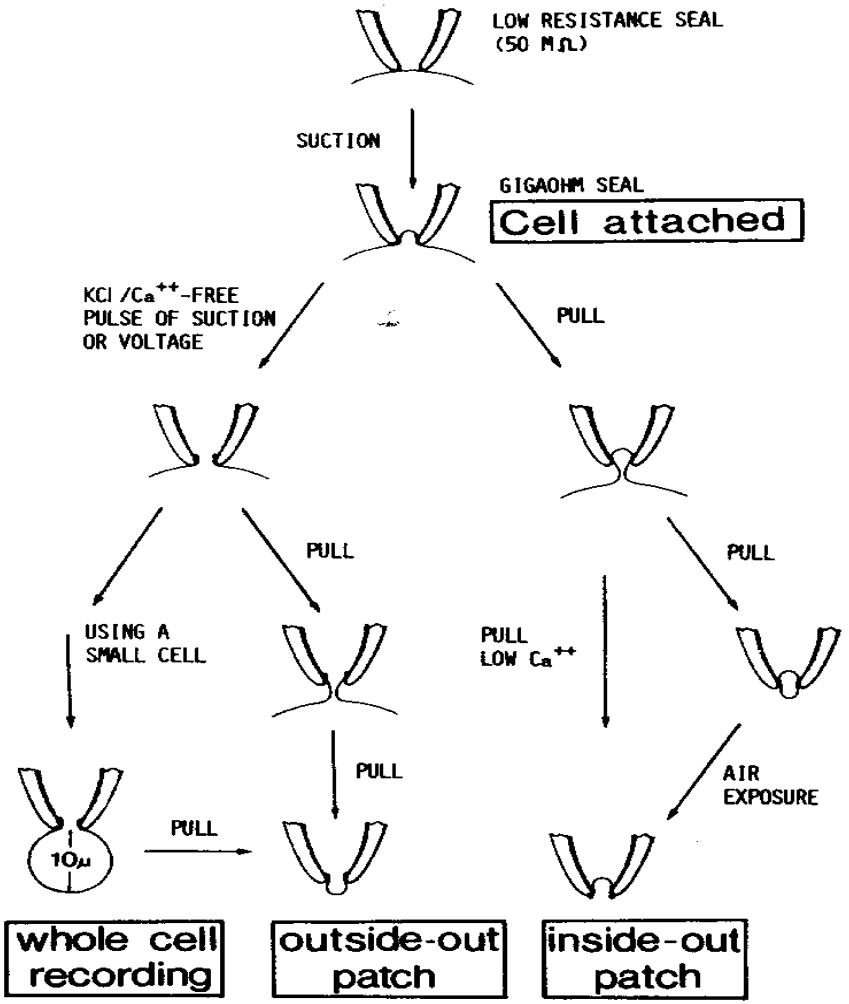
Patch clampers do it with suction



From Hamill *et al* 1981

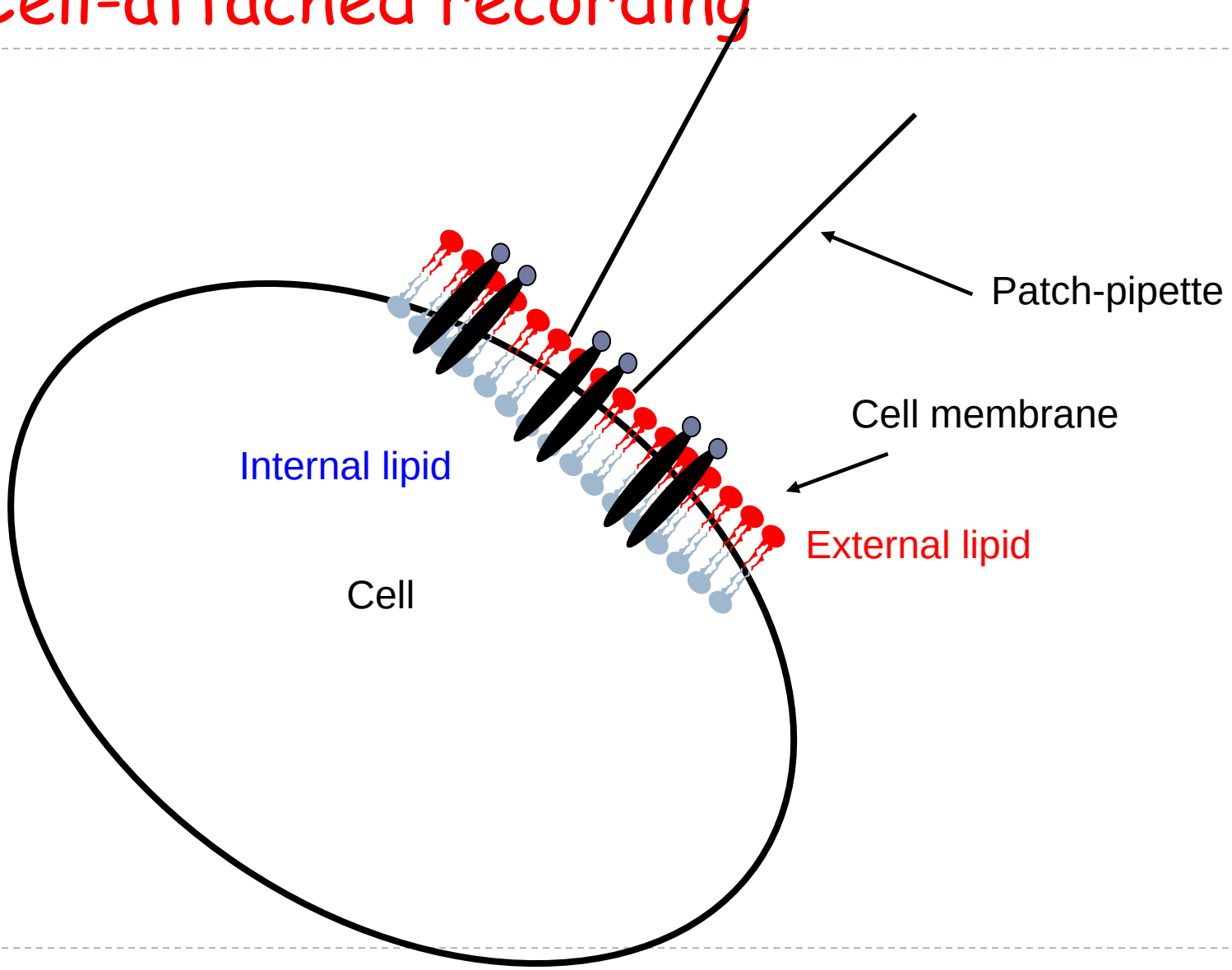
By increasing the seal resistance we reduce the noise level and increase temporal resolution.

Patch-clamp configurations

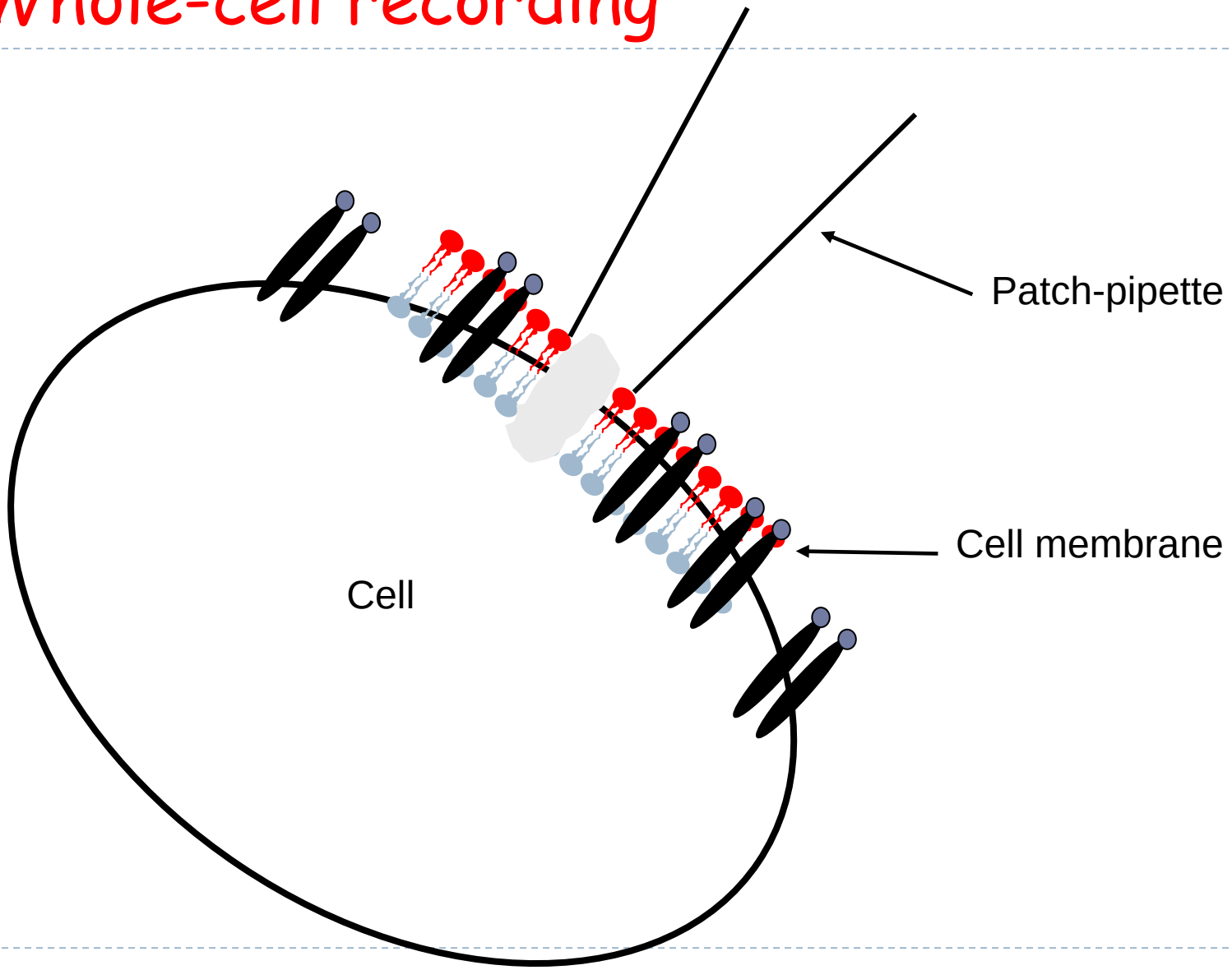


From Hamill *et al* 1981

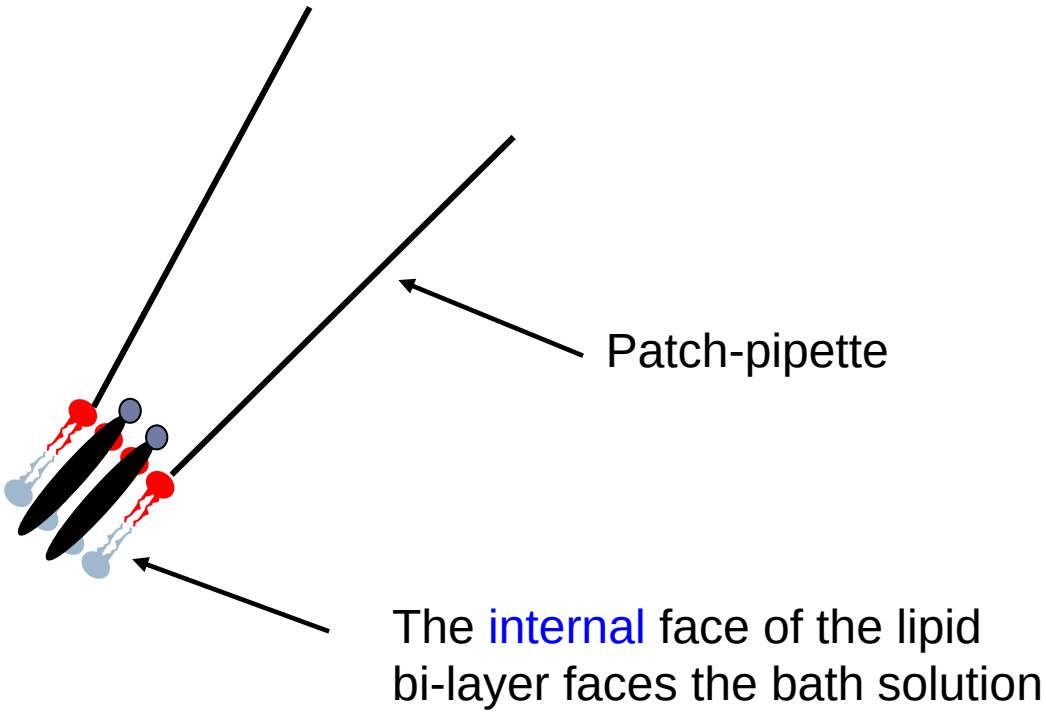
Cell-attached recording



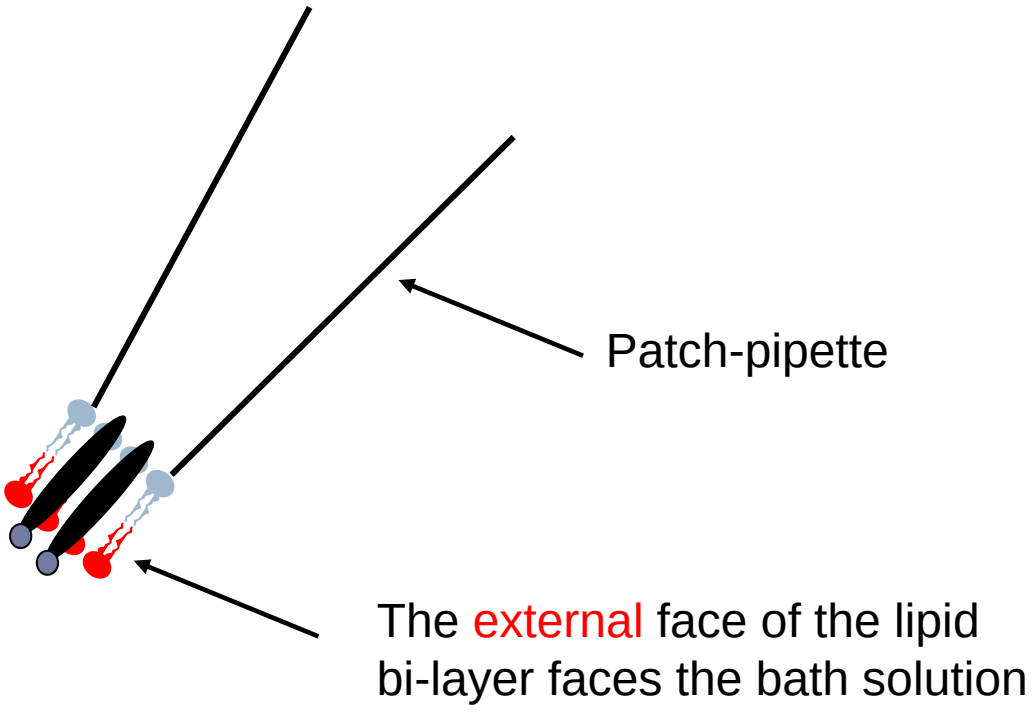
Whole-cell recording



Inside-out recording

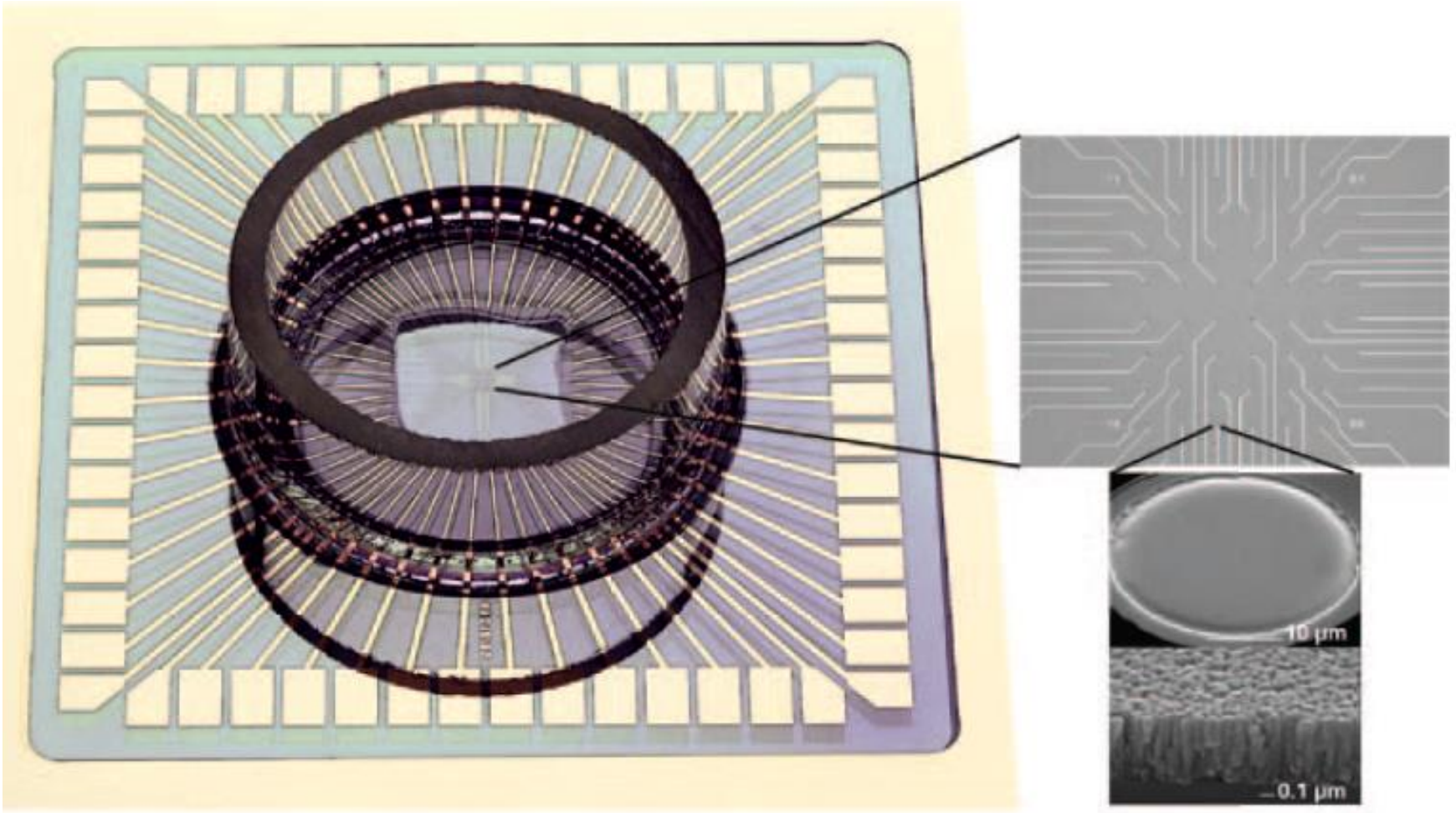


Outside-out recording

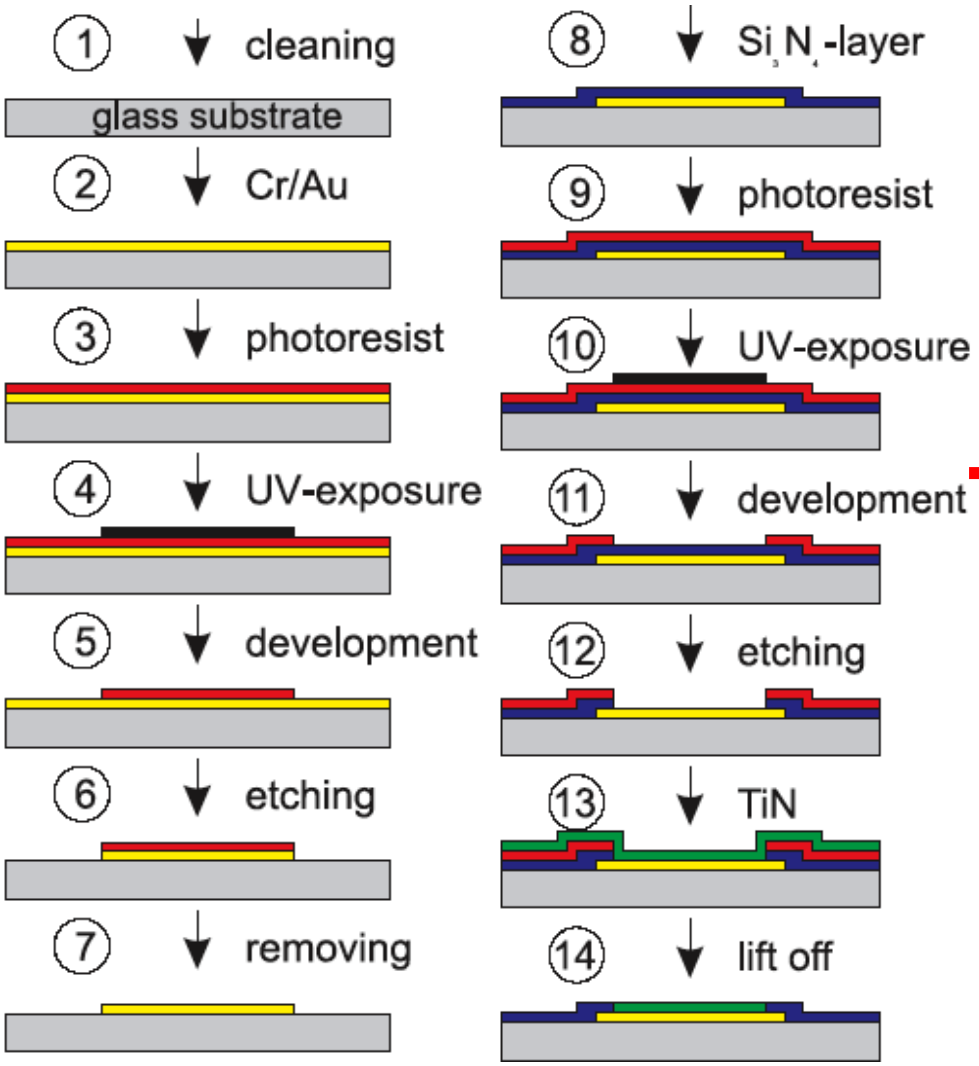


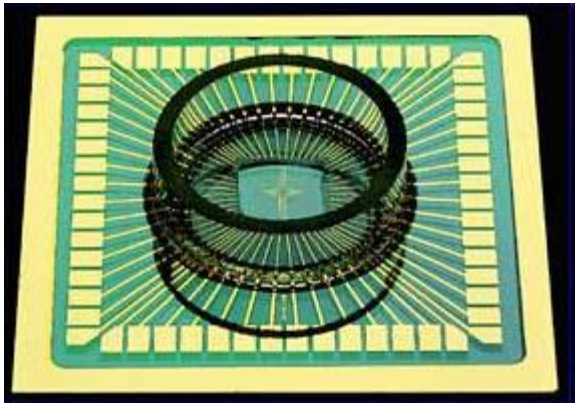
Microelectrode Array (MEA)

MEA System

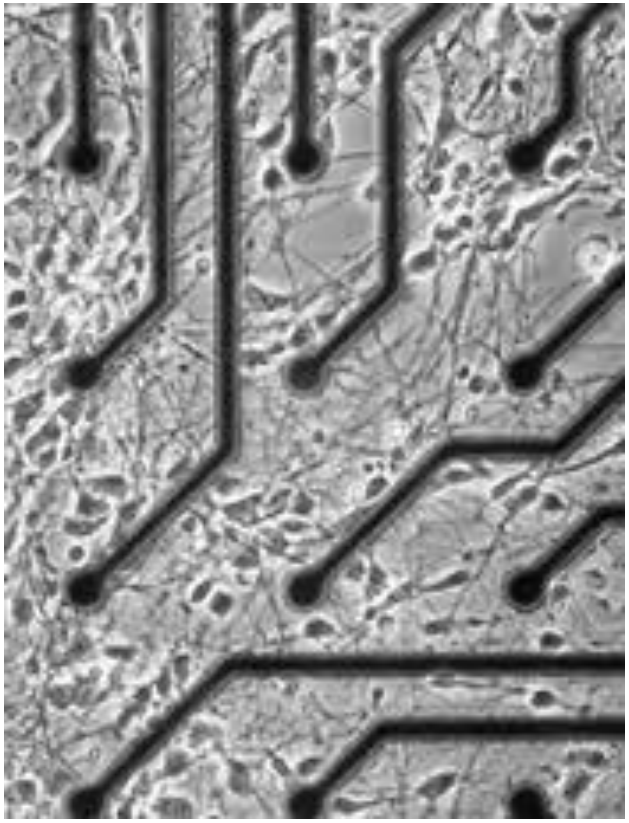


Electronic Fabrication Processes



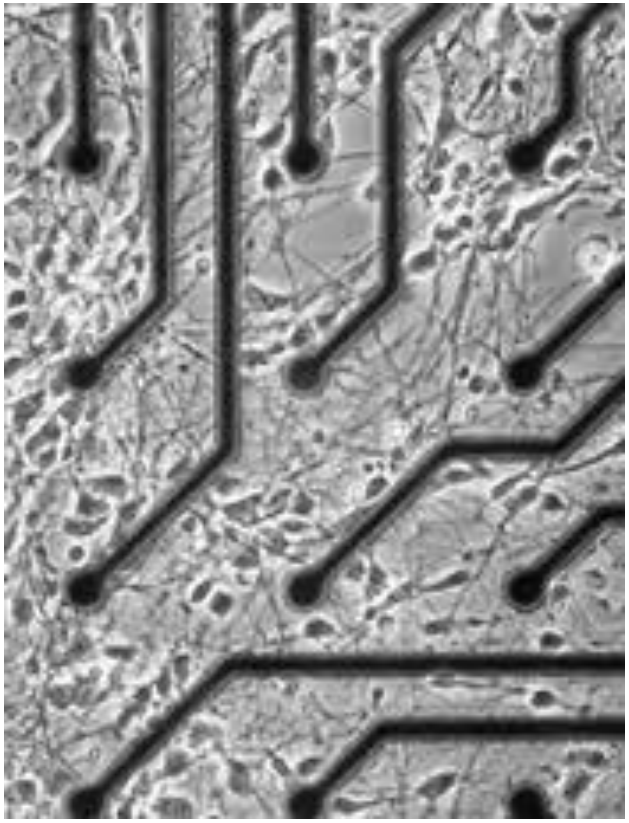


MEA: Interfacing with cells



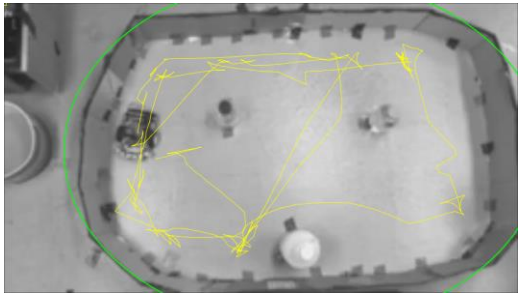
Create brain functions for artificial intelligence

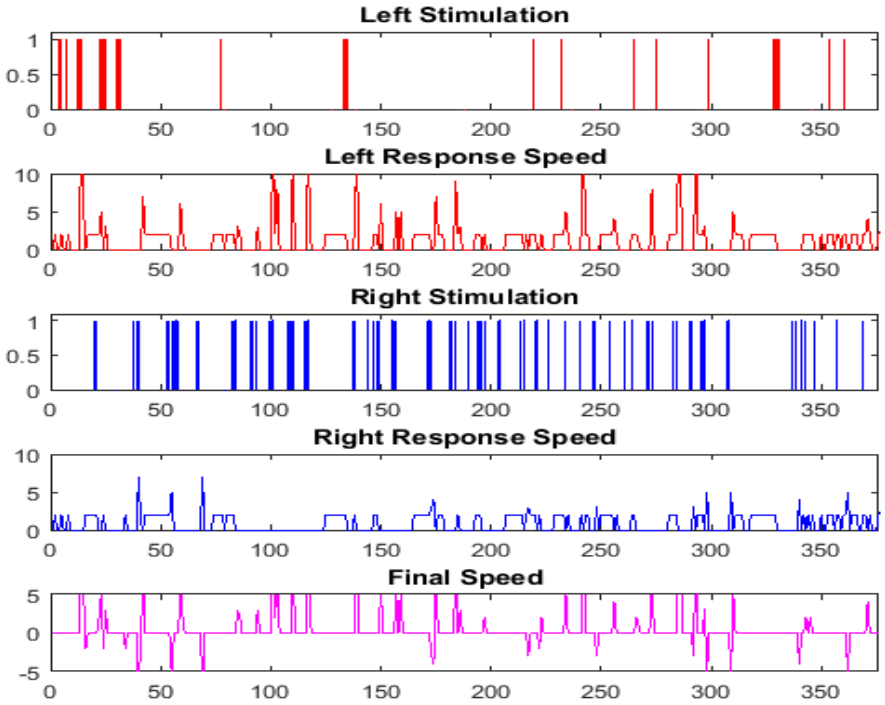
MEA: Interfacing with cells



https://www.youtube.com/watch?v=1QPiF4-iu6g

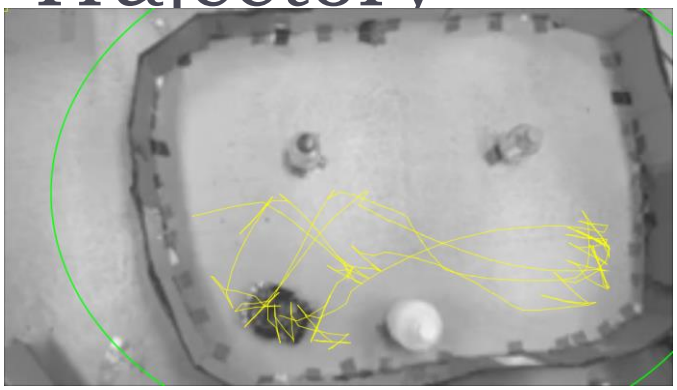
Pre-training experiment



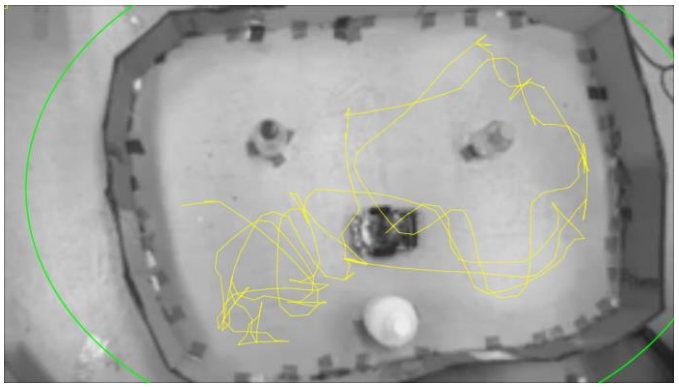


After improving encoding methods, the time slot for each movement is changed to 1.6s

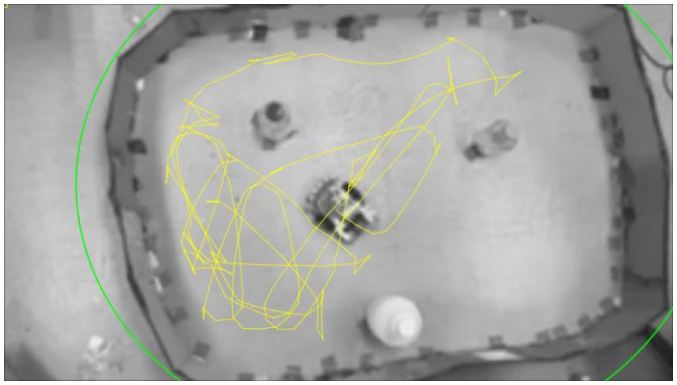
Trajectory



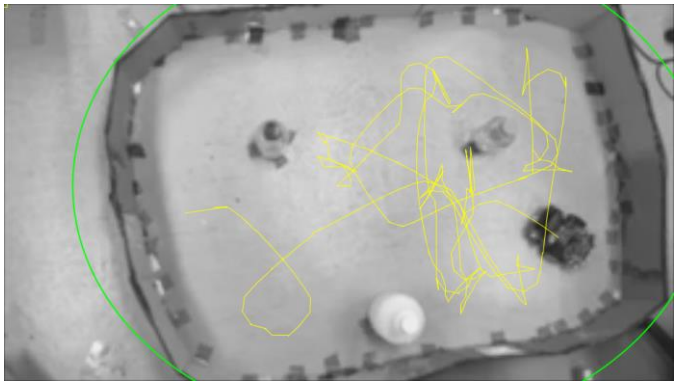
Pre-experiment



Post-experiment



After adding CCK



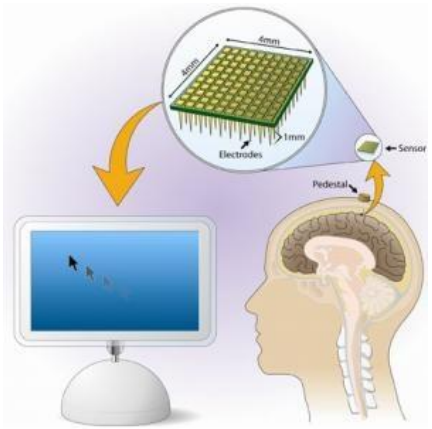
Next day

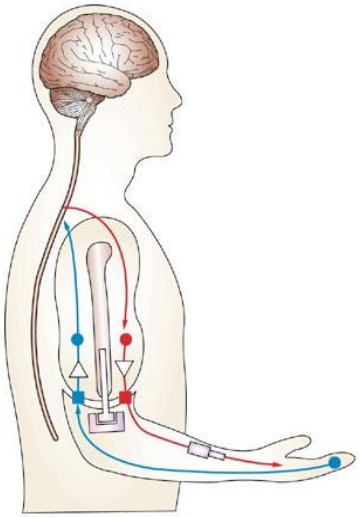
Neural Interfaces in Human Science Fiction

https://www.youtube.com/watch?v=LDPVwI3KULk

Neural Interfaces

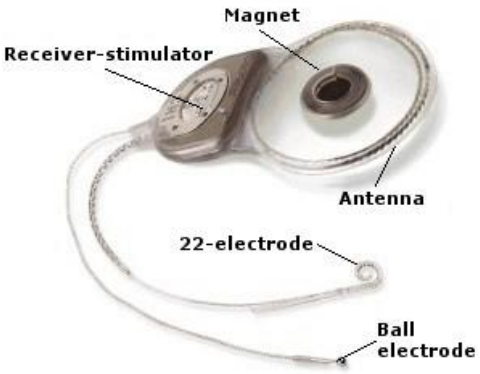
- Devices operating at the intersection of the nervous system and an internal or external device.
- Include **neural prosthetics**, which are artificial extensions to the body that restore or supplement function of the nervous system lost during disease or injury, and **implantable neural stimulators** that provide therapy.
- **Brain computer interface (BCI)** used to allow disabled individuals the ability to control their own bodies and lead fuller and more productive lives.





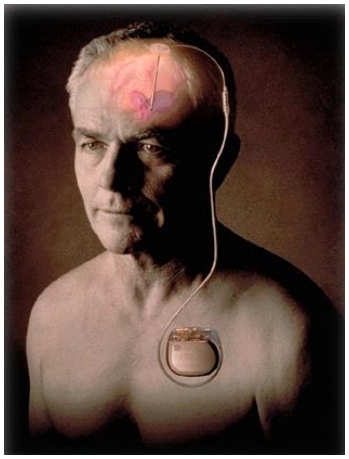
Impact of Neural Interfaces

Neural interfaces have already provided substantial benefits to individuals.



Cochlear Ltd. Nucleus® 24 cochlear implant system

Cochlear Prosthesis bypasses damaged hair cells in the auditory system by direct electrical stimulation of the auditory nerve.



Activa Medtronic System

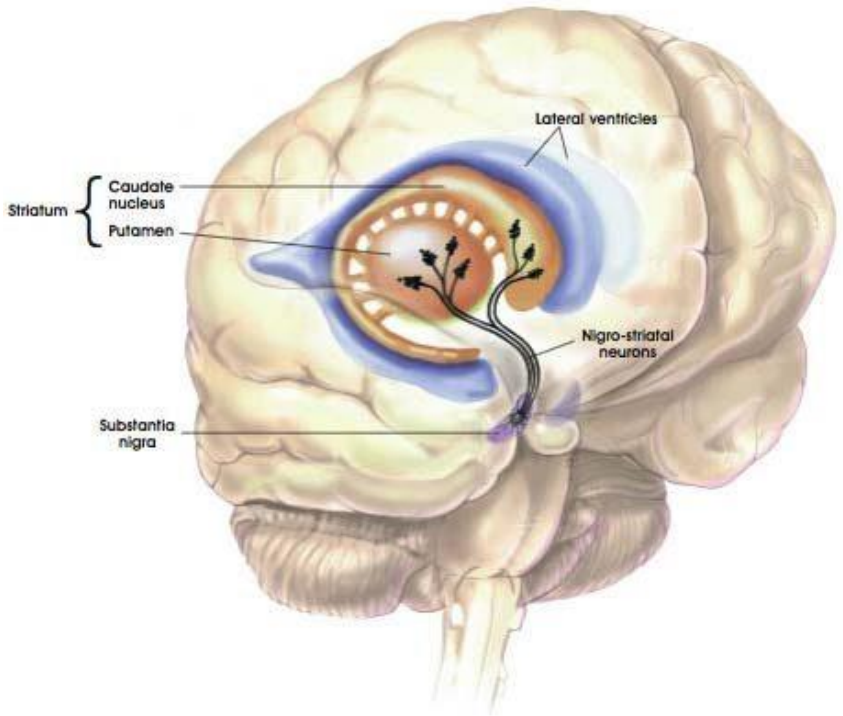
Deep Brain Stimulation has been useful for some patients in reducing the motor symptoms associated with Parkinson's Disease.

- 35,000: DBS – expanding clinical indications…
- 60,000: Cochlear Prosthetics
- 150,000: Urinary incontinence & spinal cord stimulation for pain

Parkinson's Diseases

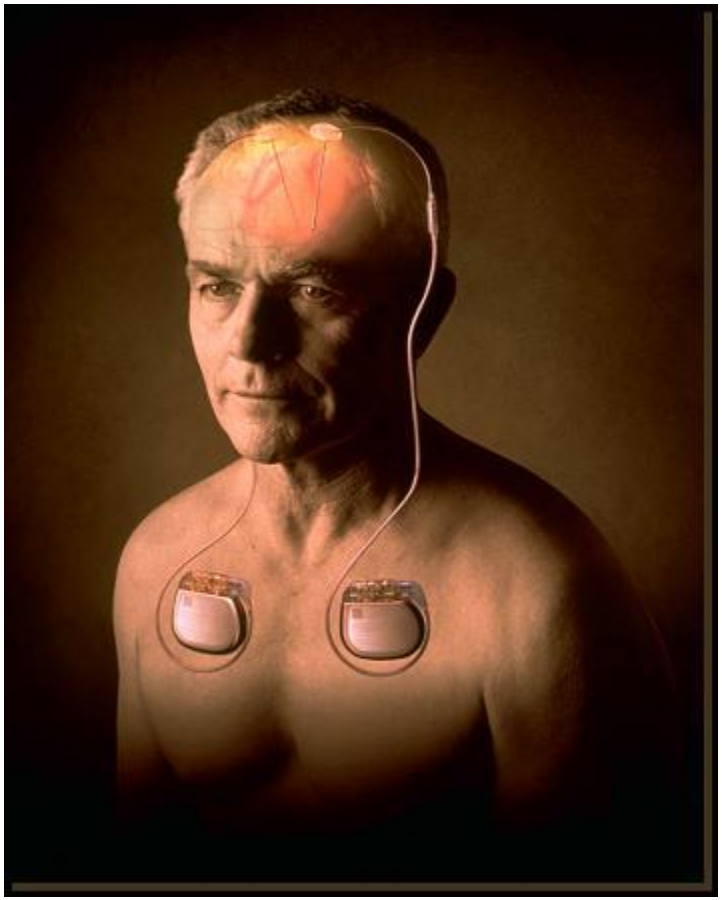
Parkinson's Diseases

- Neurodegenerative disease
  - Basal ganglia mediate the coordination of smooth and balanced muscle movement.
  - Cells in substantia nigra dye in PD
  - Reduced dopamine
  - Affects movement; autonomic dysfunction; neuropsychiatric problems (mood, cognition, behavior or thought alterations), and sensory and sleep difficulties
  - Medication

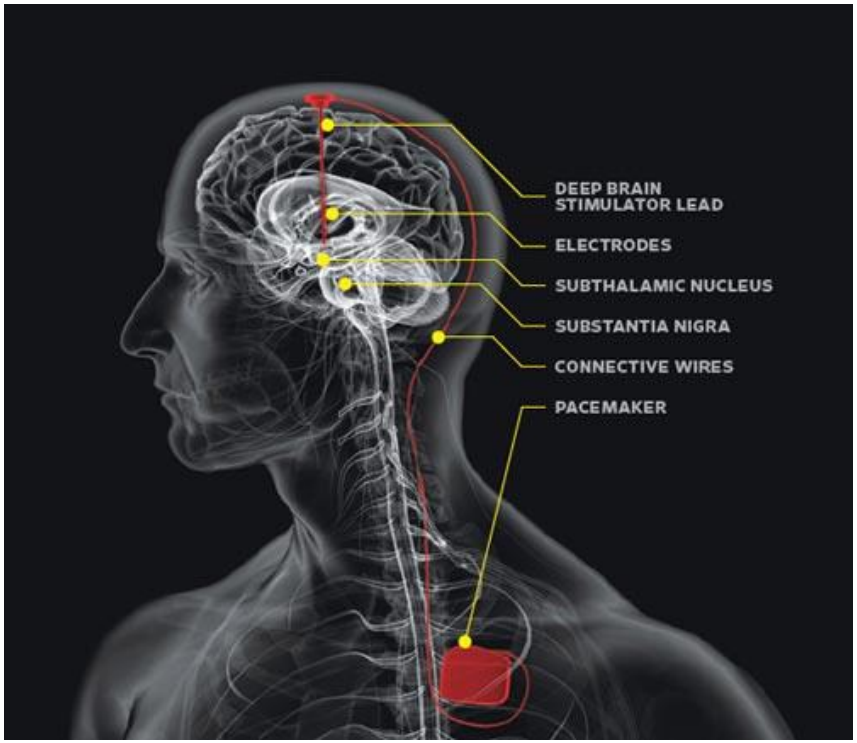


What is DBS?

- A surgically implanted medical device called a brain pacemaker.
- Sends electrical impulses to the brain.
- Traditionally used to treat movement disorders such as chronic pain, Parkinson's disease, tremor, and dystonia.



Components



Three Major Components

- Implanted pulse generator (IPG)
  - battery-powered neurostimulator encased in a titanium housing, which sends electrical pulses to the brain to interfere with neural activity at the target site
- Lead
  - coiled wire insulated in polyurethane with four platinum iridium electrodes and is placed in one of three areas of the brain
- Extension
  - insulated wire that runs from the head, down the side of the neck, behind the ear to the IPG, which is placed subcutaneously below the clavicle or in some cases, the abdomen

How DBS affects the Brain

- DBS directly changes brain activity in a controlled manner
- It's effects are reversible
- Often kicks in only after a number of weeks for psychiatric disorders
- Not yet fully understood

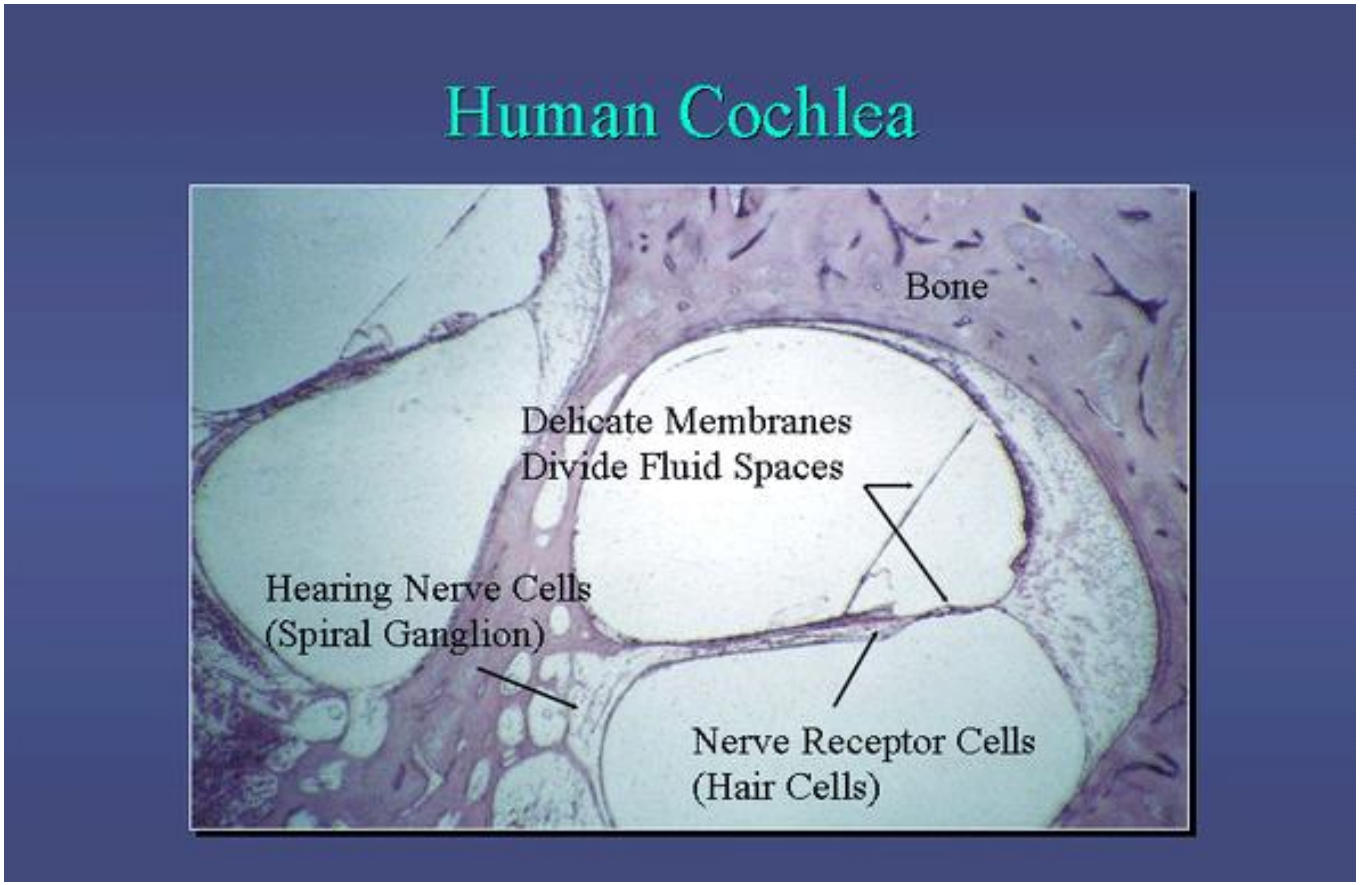
Cost and Recovery Time

- Costs about USD$30,000 plus physician and MRI fees
- Typically covered by insurance with doctor's recommendation
- Patients typically go home the next day after the lead implantation surgery
- After surgery, swelling of the brain tissue, mild disorientation and sleepiness are normal
- After 2–4 weeks, there is a follow-up to remove sutures, turn on the neurostimulator and program it
- The batteries in the pulse generator must be replaced every three to five years
  - done with a small incision as an outpatient procedure

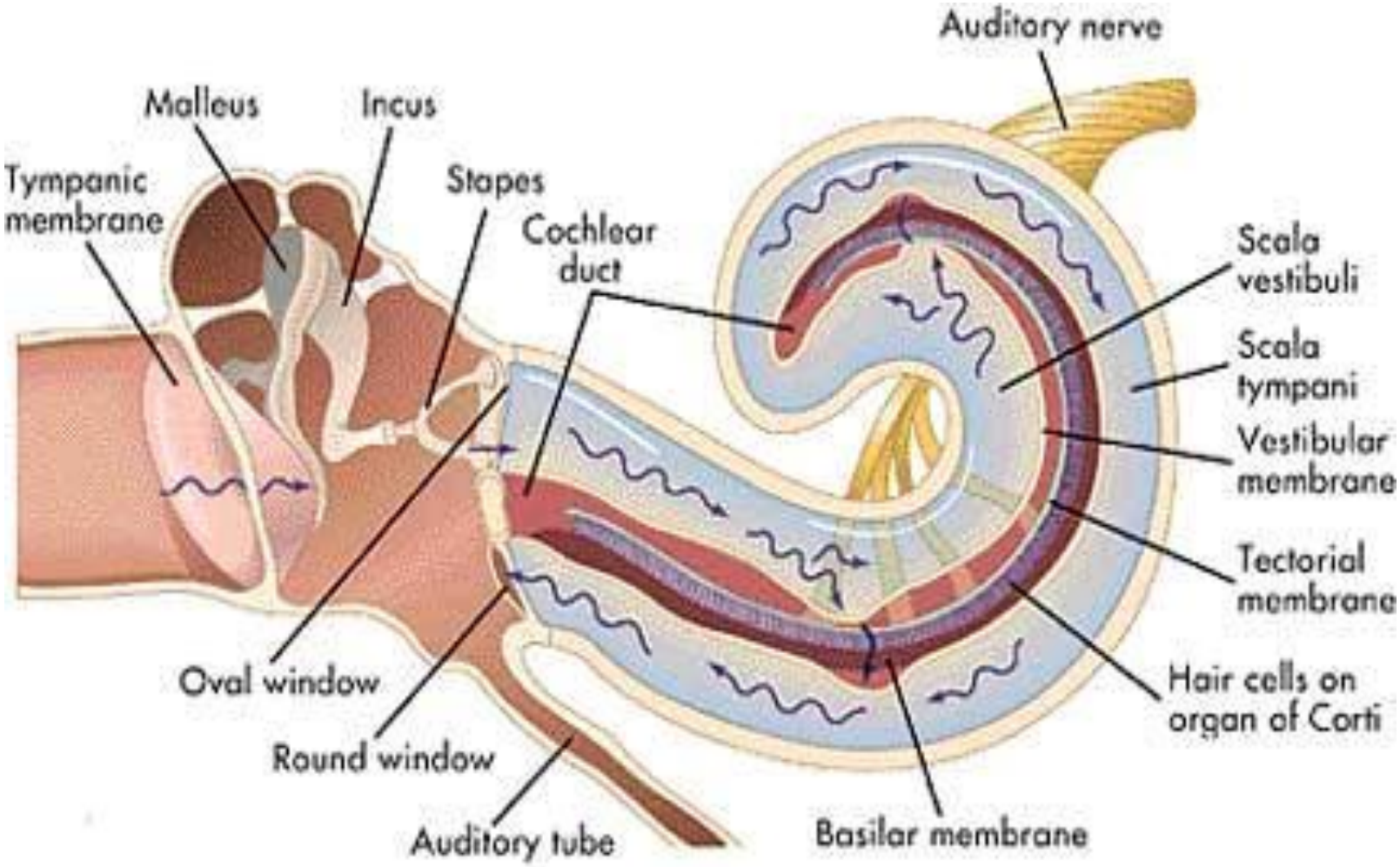
PD Patient with DBS treatment

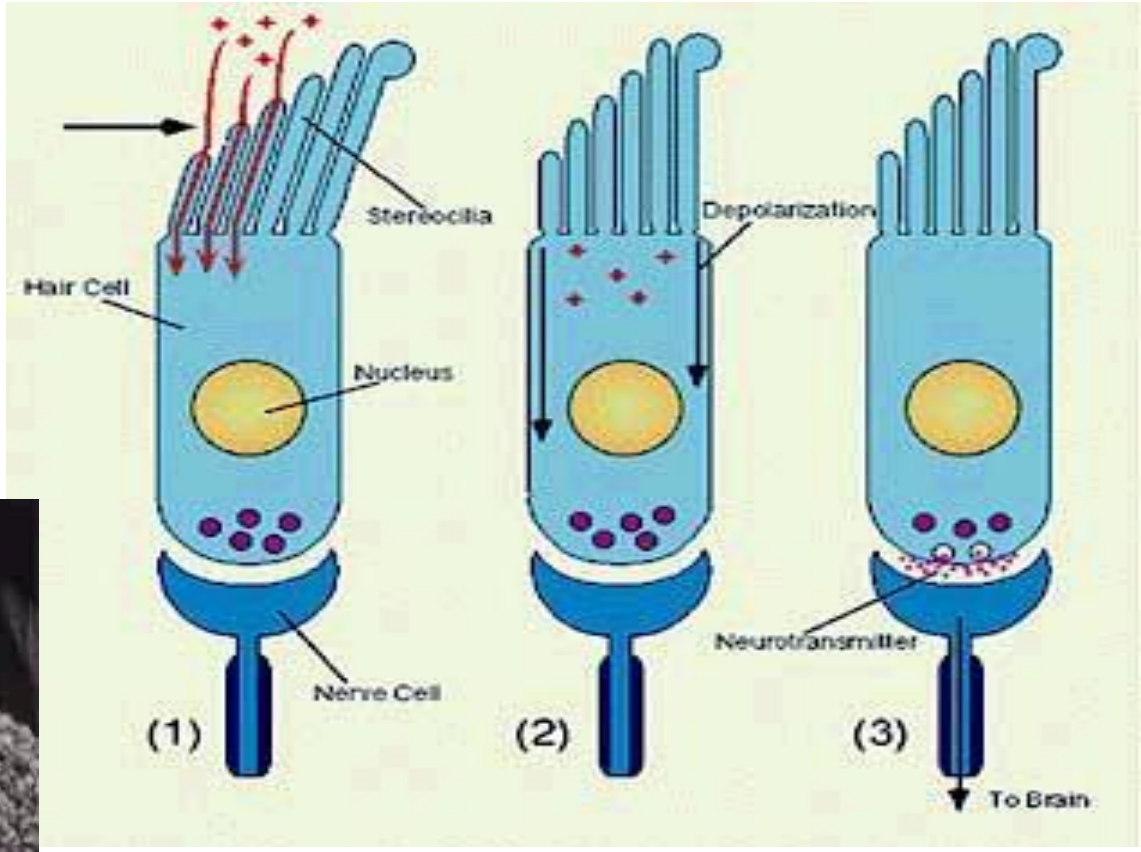
Cochlear Implants

Anatomy-micro

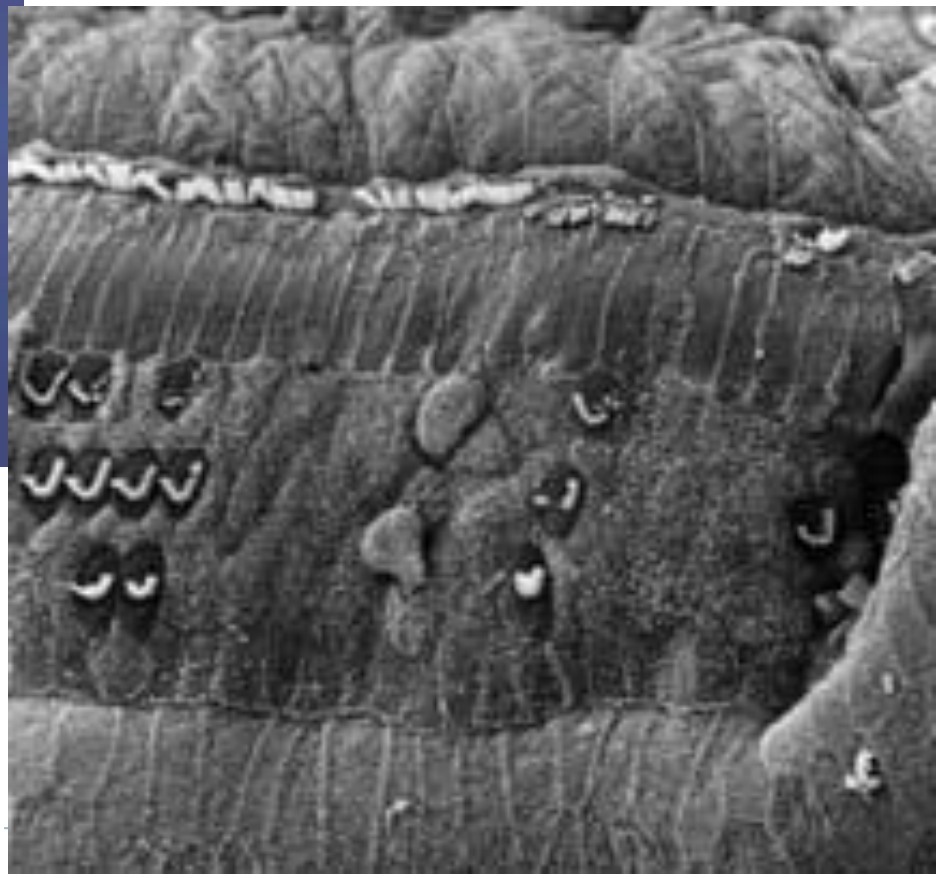


Physiology of Hearing

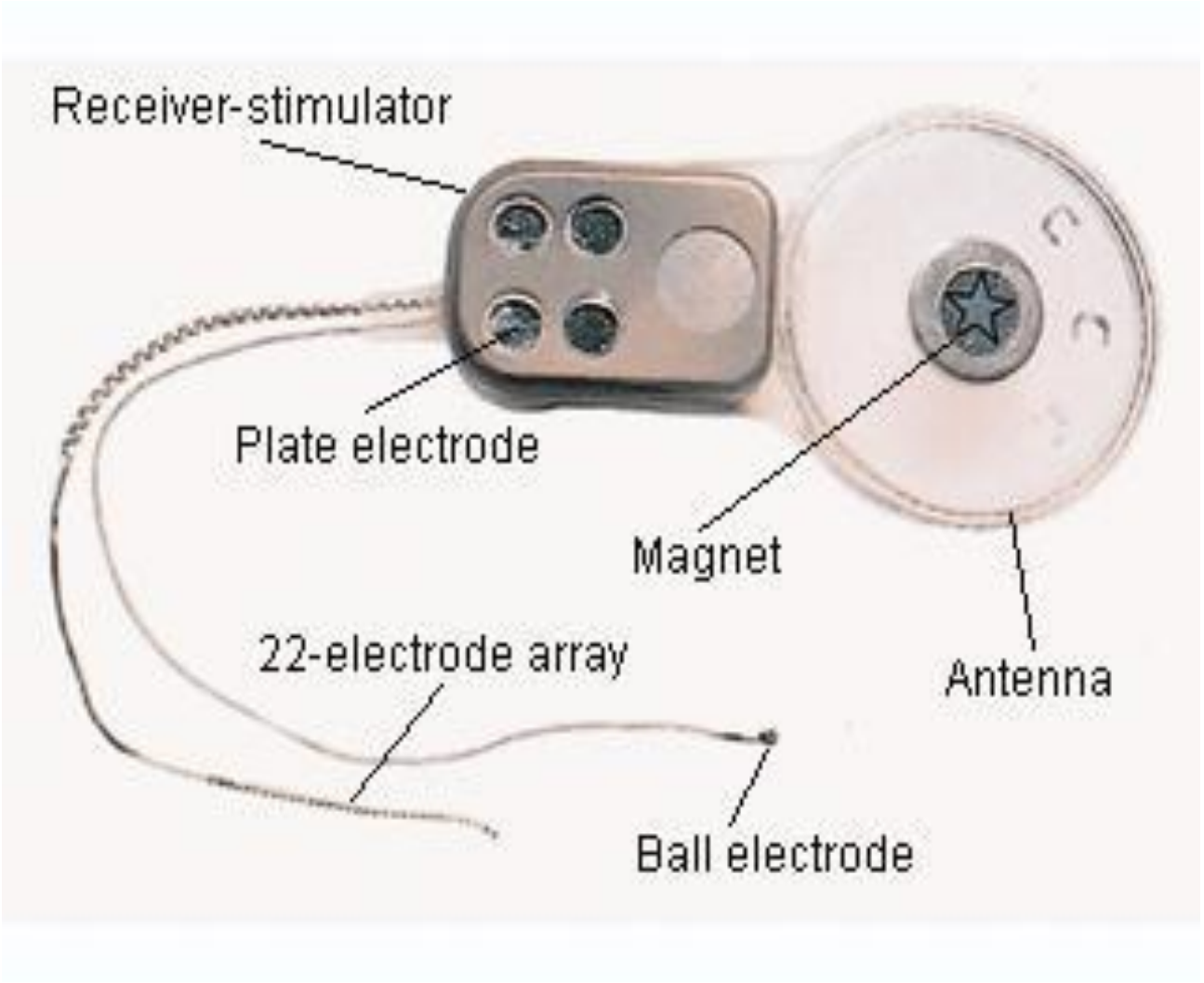



Stereocilia
Hair Cell
Nucleus
Nerve Cell
(1)
Depolarization
(2)
Neurotransmitter
(3)
To Brain

Pathologic Anatomy



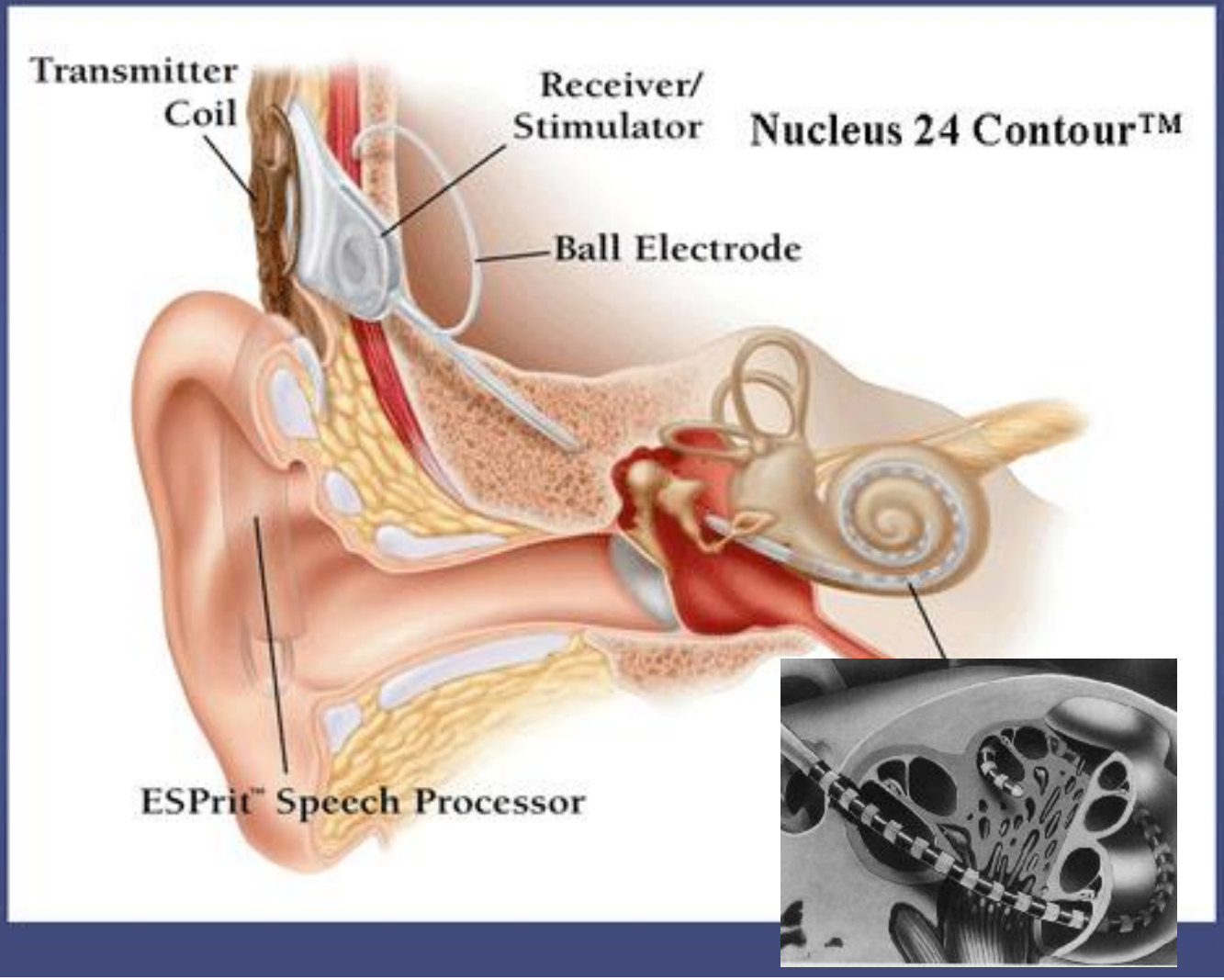
Components of Cochlear Implant



Implant Components

- Microphone
  - amplification
- External speech processor
  - Compression
  - Filtering
  - Shaping
- Transmitter (outer coil)
- Receiver
- Electrode array
- Neural pathways

Anatomy of a Cochlear Implant



Indications for Cochlear Implantation -- Children

- 12 months or older
- Bilateral severe-to-profound sensorineural hearing loss with PTA of 90 dB or greater in better ear
- No appreciable benefit with hearing aids (parent survey when <5 yo or 30% or less on sentence recognition when >5 yo)
- Must be able to tolerate wearing hearing aids and show some aided ability
- Enrolled in aural/oral education program
- No medical or anatomic contraindications
- Motivated parents

Postoperative Management

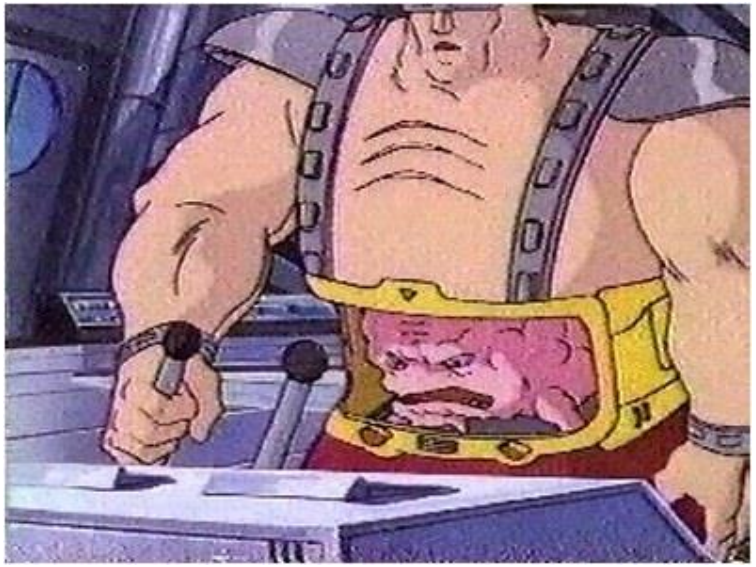
- Complication rate only 5%
- Wound infection/breakdown
  - Yu, et al showed good response to Abx, I&D
- Facial nerve injury/stimulation, CSF leak, Meningitis
  - CDC recommendations
- Vertigo (Steenerson reported 75%)
- Device failure—re-implantation usually successful
- Avoid MRI

Results of Implantation

- Wide range of outcomes
- Improvement is long-term (Waltzman, et al. 5-15 yr f/u)
- Implantation is cost effective—even in the elderly (Francis, et al)
- Research indicates recipe for success includes:
  - **Short length of time from deafness to implantation** (Sharma showed <3.5 years regain normal latencies within 6 mos. After 7 years, little plasticity remains)
  - **Experience with language before onset of deafness**
  - **Implantation before age six** for prelingually deafened children (Govaerts, et al showed 90% of children implanted <2yo were integrated into mainstream vs. only 20-30% if implanted after age 4)
  - **Aural/oral education**
  - **Highly motivated patients/parents**

Brain Computer Interface

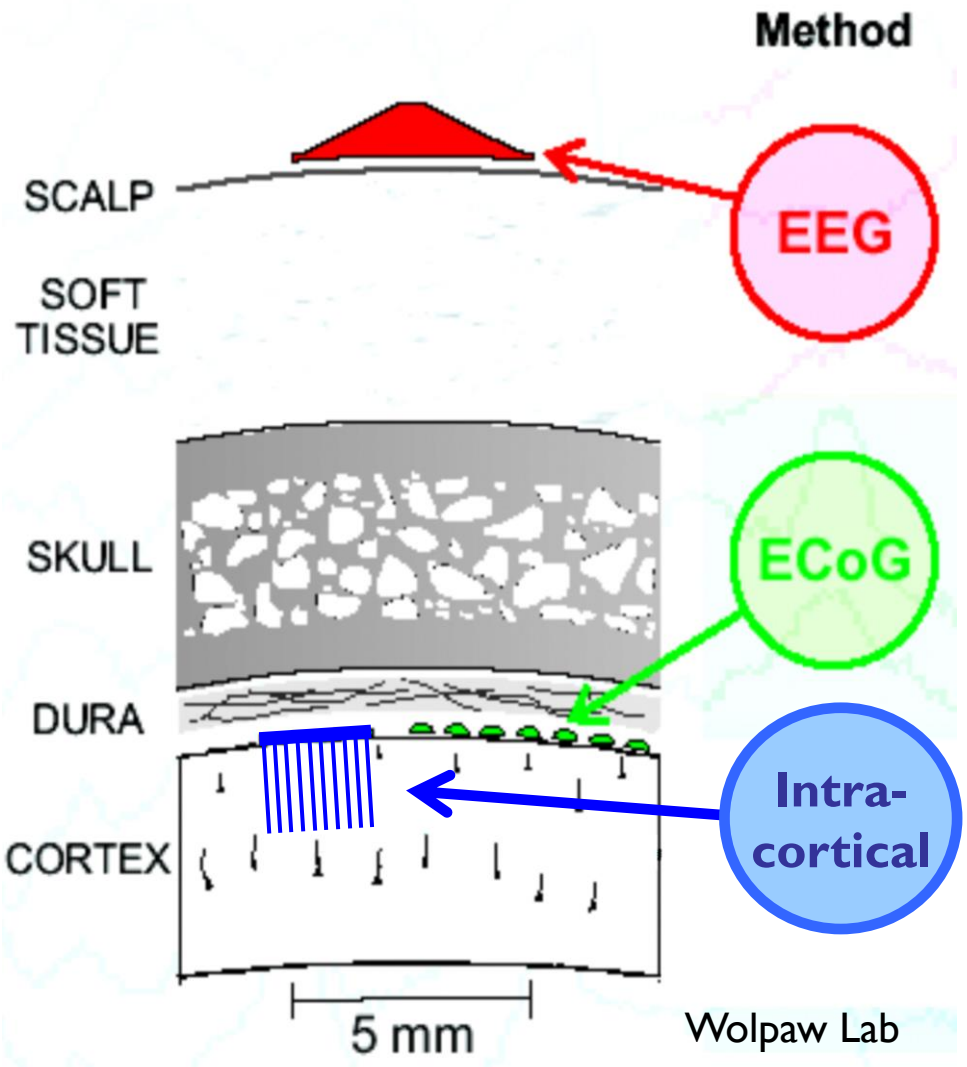
or Krang's Body

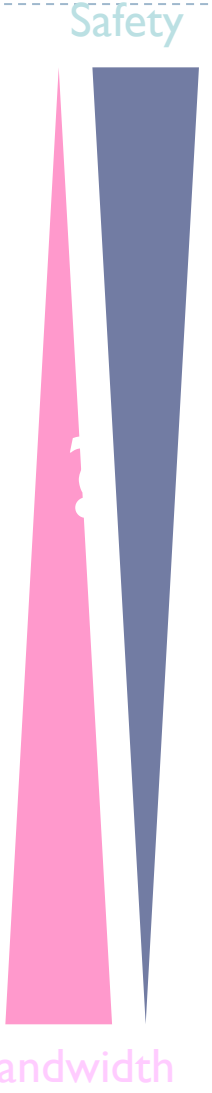


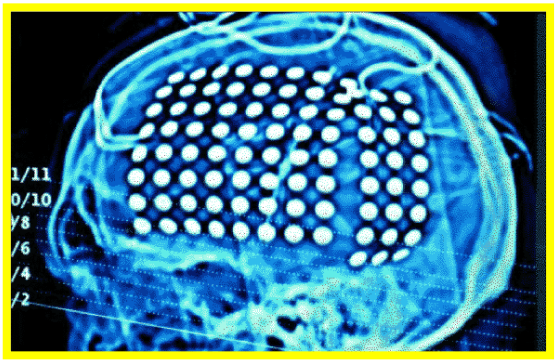
https://www.youtube.com/watch?v=ohf8cgVS8K0

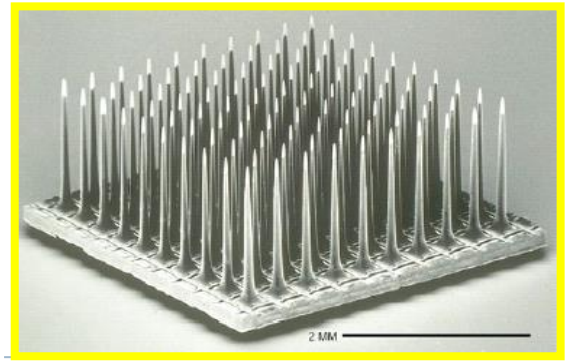
- Invasive
- Non-invasive

Array Recording from the Brain





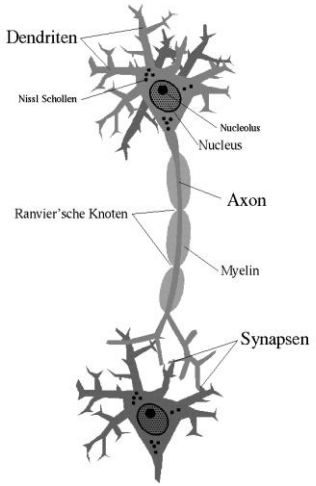




Non-invasive BCI

What is an EEG?

- An *electroencephalogram* is a measure of the brain's voltage fluctuations as detected from scalp electrodes.
- It is an approximation of the cumulative electrical activity of neurons.

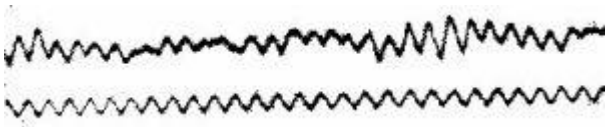


What is it good for?

- Neurofeedback
  - treating ADHD
  - guiding meditation
- Brain Computer Interfaces
  - People with little muscle control (i.e. not enough control for EMG or gaze tracking)
  - People with ALS, spinal injuries
  - High Precision
  - Low bandwidth (bit rate)

EEG Background

- 1875 - Richard Caton discovered electrical properties of exposed cerebral hemispheres of rabbits and monkeys.
- 1924 - German Psychiatrist Hans Berger discovered alpha waves in humans and invented the term "electroencephalogram"
- 1950s - Walter Grey Walter developed "EEG topography" - mapping electrical activity of the brain.

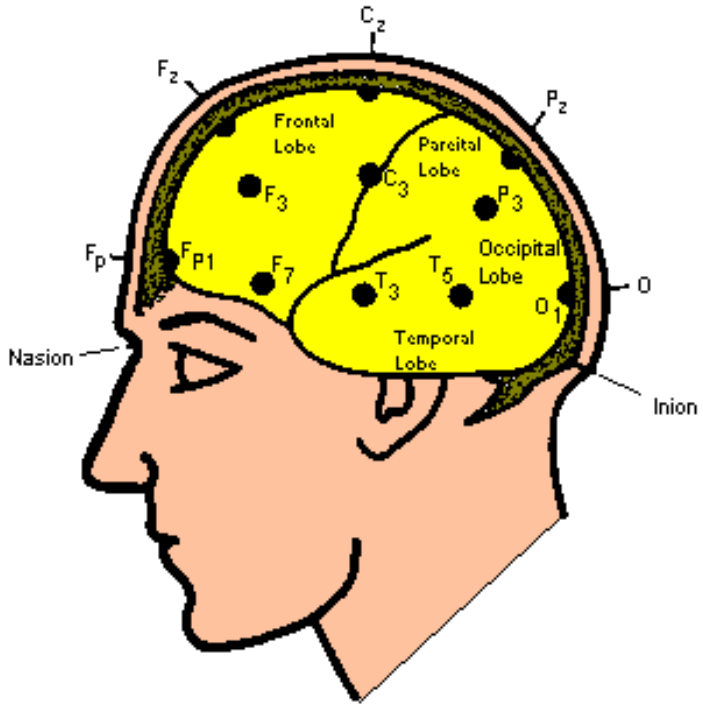


Physical Mechanisms

- EEGs require electrodes attached to the scalp with sticky gel
- Require physical connection to the machine

Electrode Placement

- Standard "10-20 System"
- Spaced apart 10-20%
- Letter for region
  - F - Frontal Lobe
  - T - Temporal Lobe
  - C - Center
  - O - Occipital Lobe
- Number for exact position
  - Odd numbers - left
  - Even numbers - right



Brain “Features”

- User must be able to control the output:
  - use a feature of the continuous EEG output that the user can reliably modify (waves), or
  - evoke an EEG response with an external stimulus (evoked potential)

Continuous Brain Waves

- Generally grouped by frequency: (amplitudes are about 100μV max)

Type	Frequency	Location	Use
Delta	<4 Hz	everywhere	occur during sleep, coma
Theta	4-7 Hz	temporal and parietal	correlated with emotional stress (frustration & disappointment)
Alpha	8-12 Hz	occipital and parietal	reduce amplitude with sensory stimulation or **mental imagery**
Beta	12-36 Hz	parietal and frontal	can increase amplitude during intense **mental activity**
Mu	9-11 Hz	frontal (motor cortex)	diminishes with movement or **intention of movement**
Lambda	sharp, jagged	occipital	correlated with visual attention
Vertex			higher incidence in patients with epilepsy or encephalopathy

P300 (Evoked Potentials)

- occurs in response to a significant but low-probability event
- 300 milliseconds after the onset of the target stimulus
- found in 1965 by (Sutton et al., 1965; Walter, 1965)
- focus specific

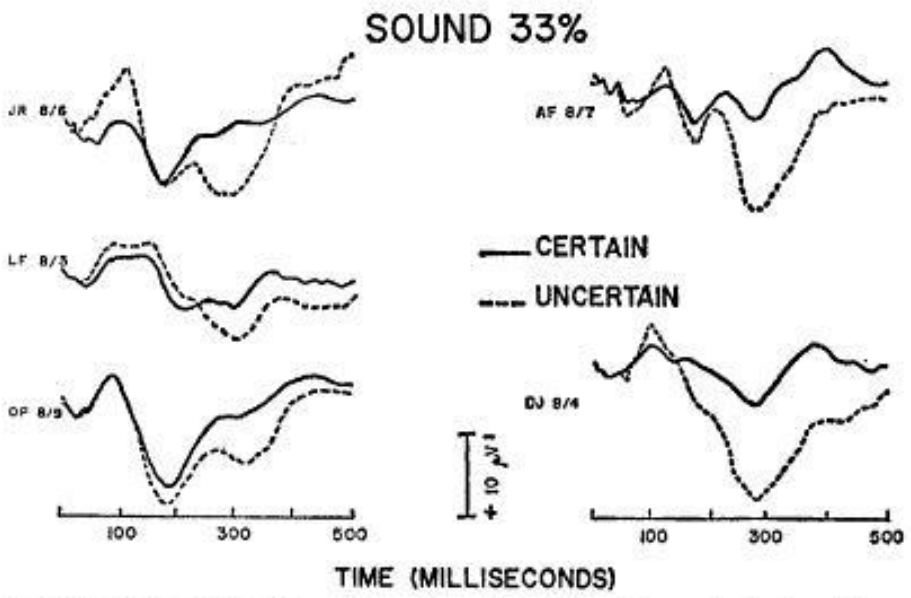


Fig. 1. Average waveforms for certain and uncertain ($P = .33$) sounds for five subjects.

P300 Experiments

- (Farwell and Donchin 1988)
- 95% accuracy at 1 character per 26s

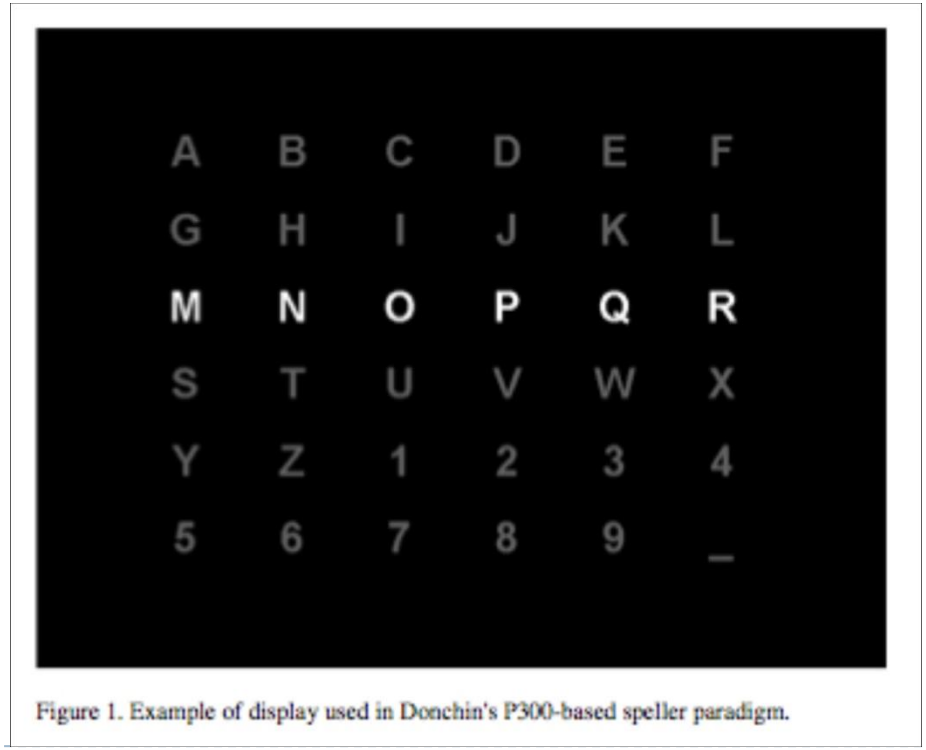
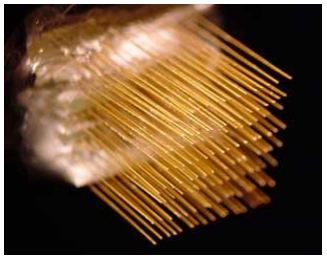


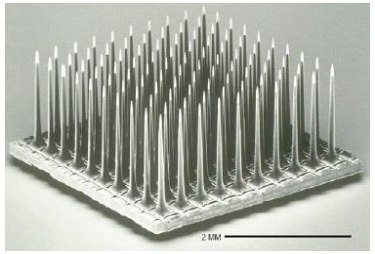
Figure 1. Example of display used in Donchin's P300-based speller paradigm.

Invasive BCI

Decoding Movement

Neurons in motor cortex exhibit preferential directions (Georgopoulos et al., 1982; 1983; 1986). Elevated firing in preferred direction.





learned "filter"

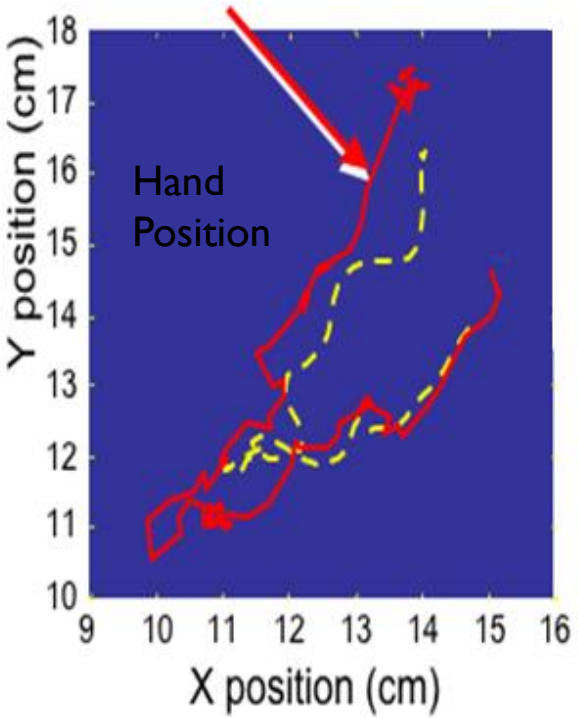
$$x_k = \mathbf{f} \cdot \mathbf{Z}_k + a$$

a ← constant offset

x_k ← hand position

$\mathbf{Z}_k$ ← vector of firing rates for C cells over N bins

Reconstruction



Computational filters operating on a population of neural firing rates to track and predict upper extremity movement.

Decoding Movement

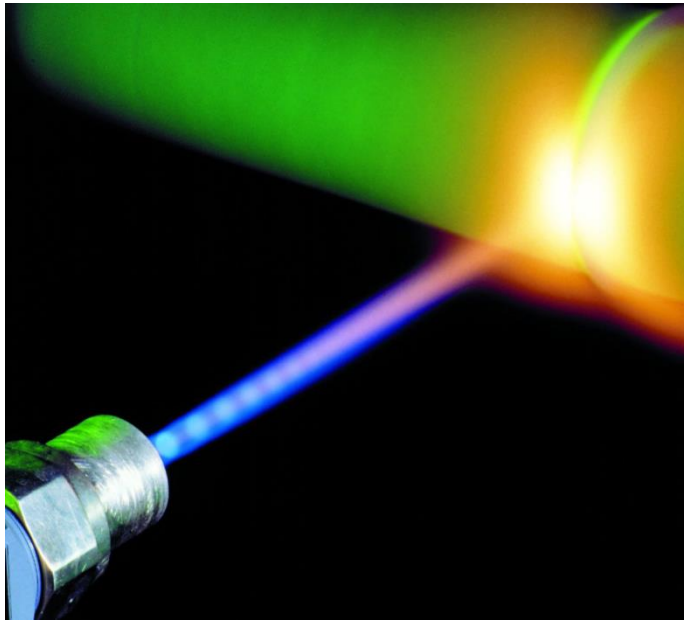
Donoghue & Hochberg, Cyberkinetics; Brown University & VA

2004: 1st BrainGate implantation – via Cyberkinetics

- C4 spinal cord injury (quad for 3 years) – first "non-healthy" primate
- FDA approval for 5 locked-in patients

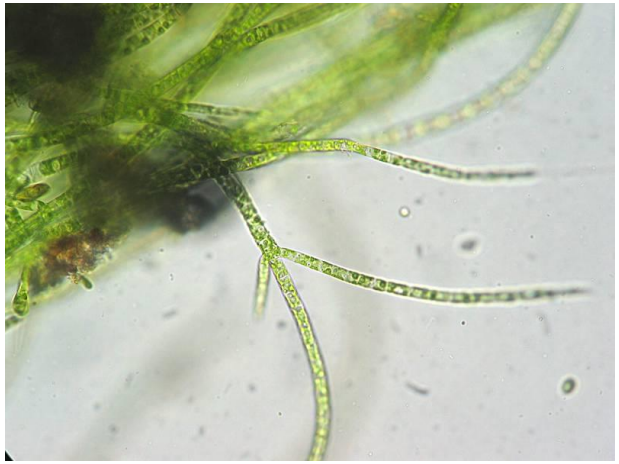
2009: Brown University-VA partnership for further pilot clinical studies.

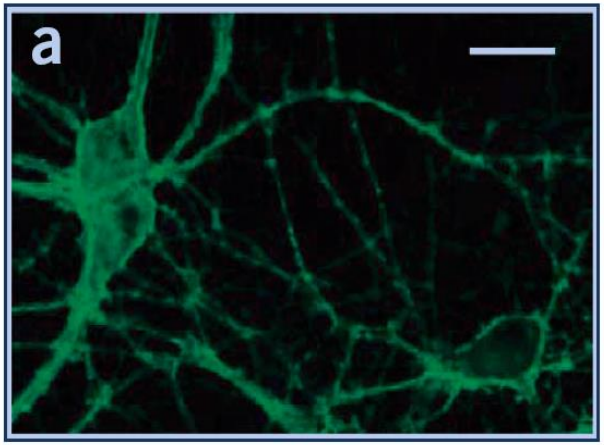
Why do neural interfaces have to rely only on electrodes?

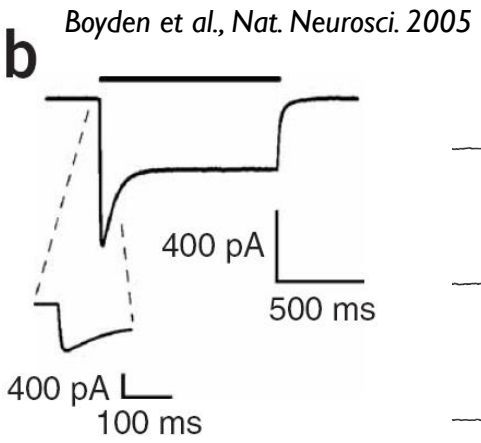


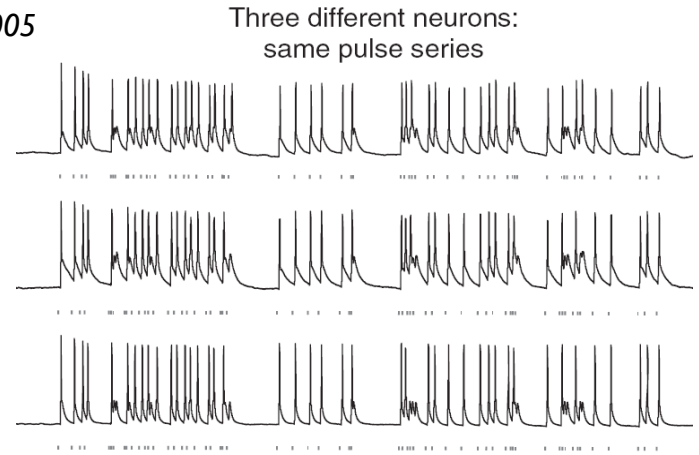
Channelrhodopsins

- Channelrhodopsin 2 – light sensitive channel from green algae.
- Developed the ability to express channelrhodopsin 2 in mammalian nervous system.
- Result: genetically encoded reagents for blue light activation.





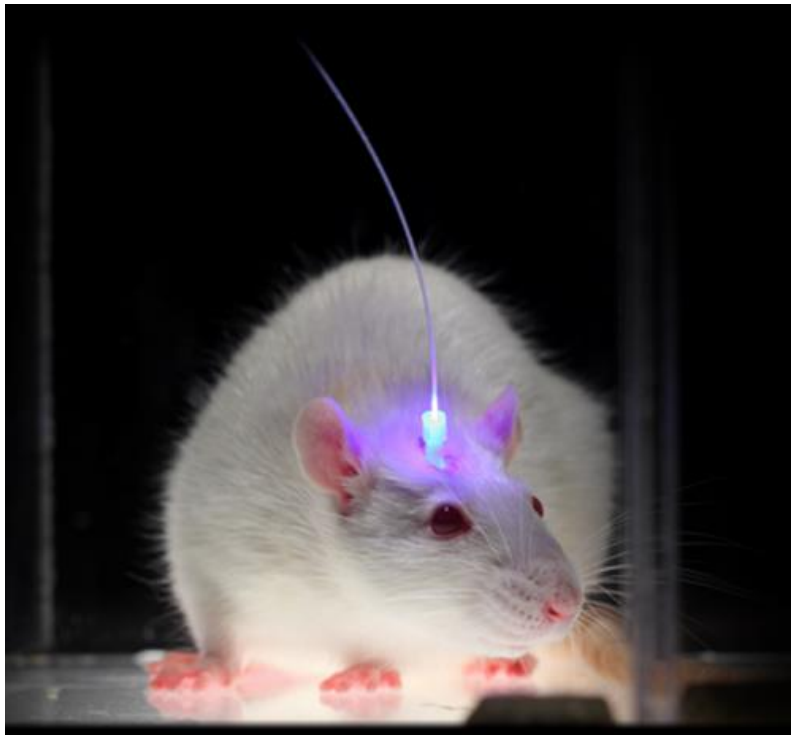




Spike trains at any frequency the neurons can naturally can be precisely and reliably evoked with light. Halorhodopsin – inhibition.

Introduction

Optogenetics is a biological technique which involves the use of light to control cells in living tissue, typically neurons, that have been genetically modified to express light-sensitive ion channels.



https://web.stanford.edu/group/dlab/optogenetics/

- Enabling specific modulation of selected cells within complex neural tissues
- Precise spatial and temporal control neural activities
- Neural network reconstruction, identification of specific type of neurons and clinical applications

Yizhar *et al.* Neuron, 2010.

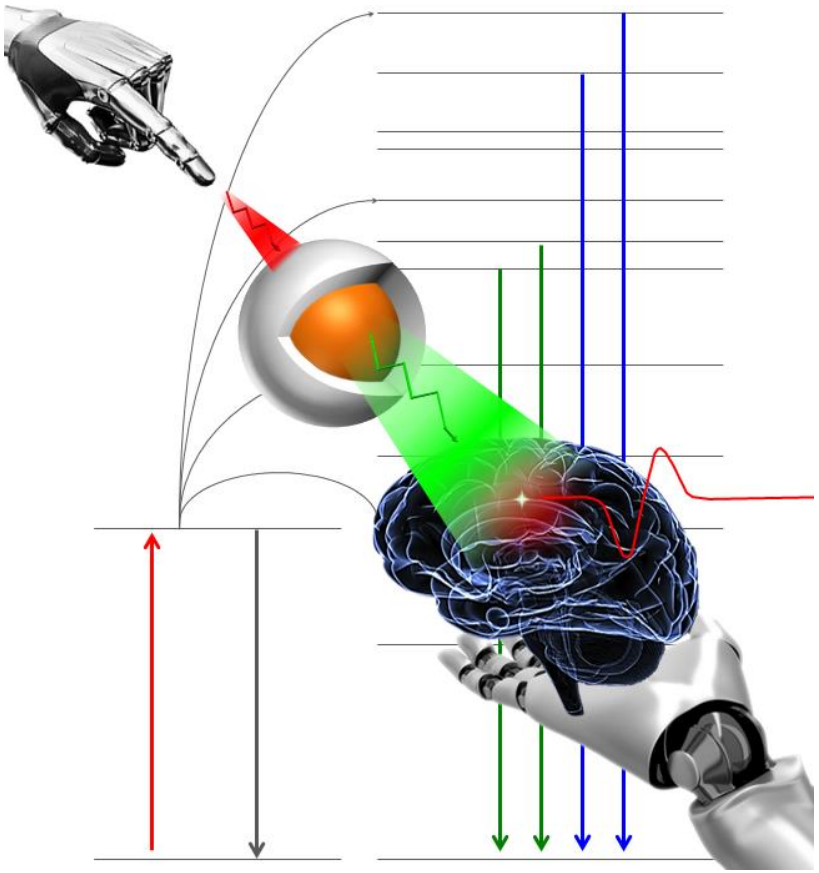
Remote Control of Brain Activity using Upconversion Techniques

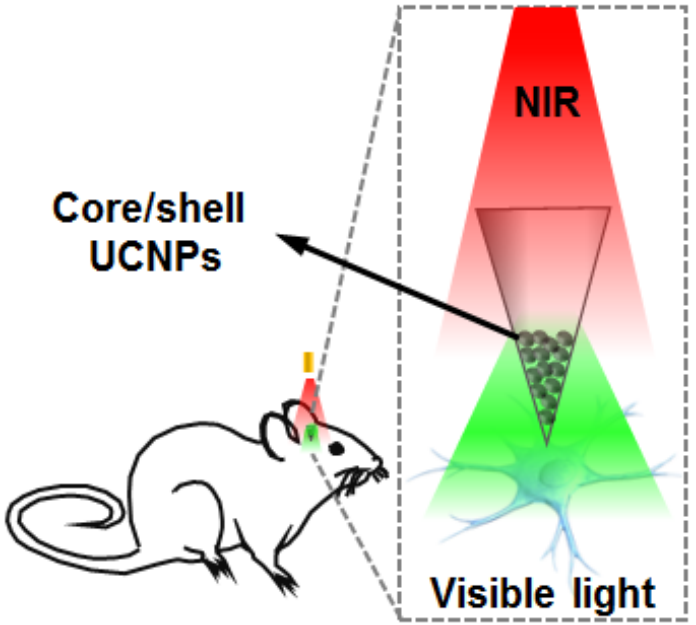
Department of Biomedical Engineering
City University of Hong Kong

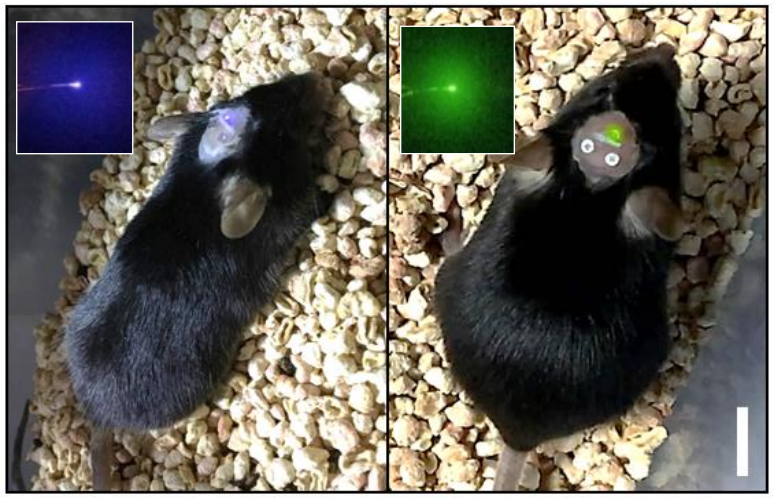
CityU
香港城市大學
City University of Hong Kong

Introduction

Photonic upconversion (UC)





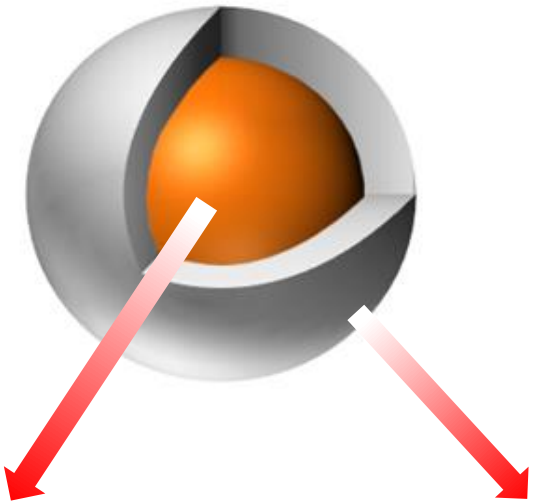


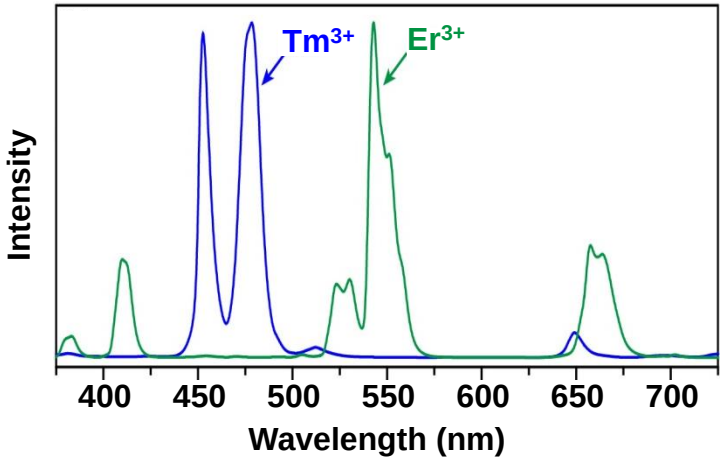
Scale bar: 1 cm

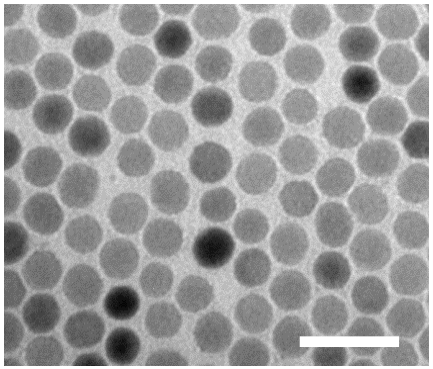
Lin et al, AHM 2017; Wang et al, Biomaterials 2017

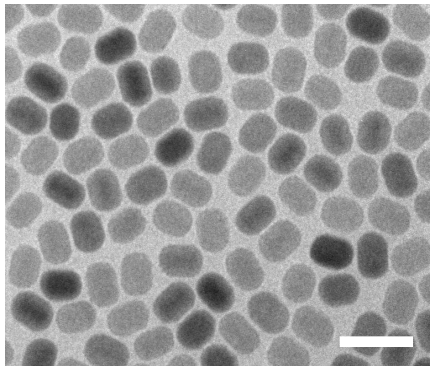
Results
=> UCNPs Synthesis

$NaYF_4$:Yb/Er@$NaYF_4$ core–shell particles

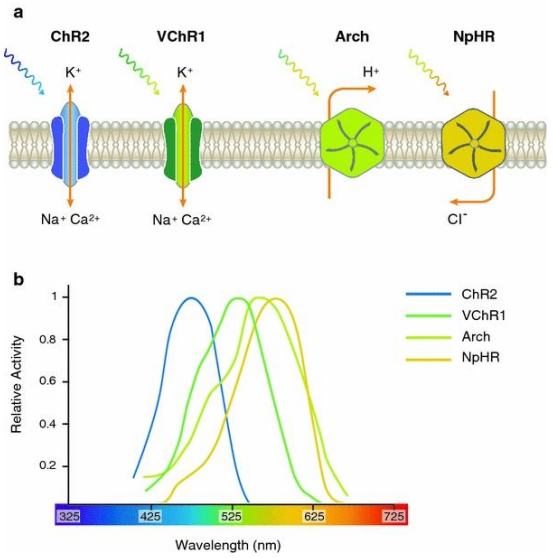








Scale bar, 50 nm



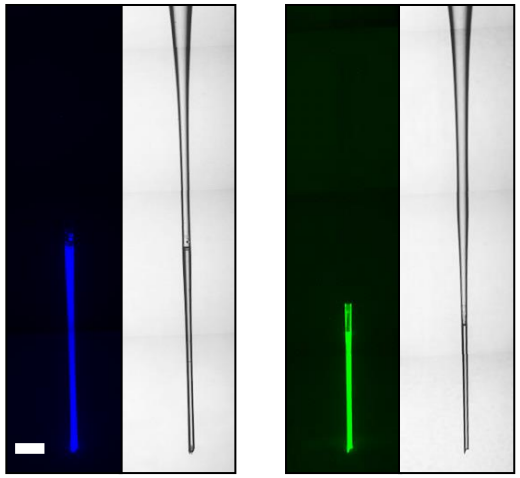
Lin et al, 2017; Wang et al, 2017

Jan Deussing et al, 2014

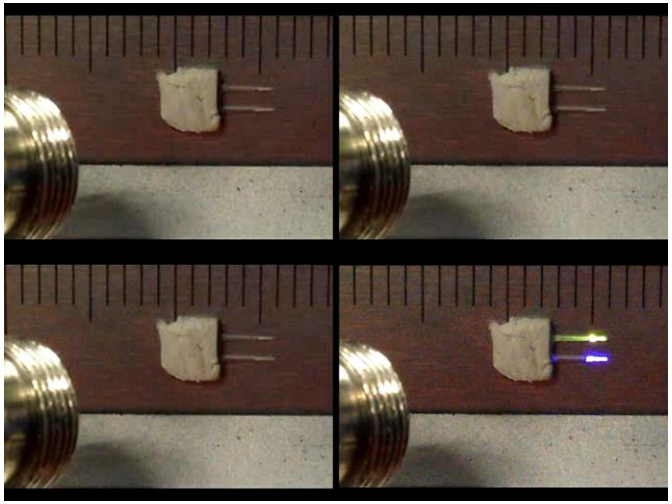
Results

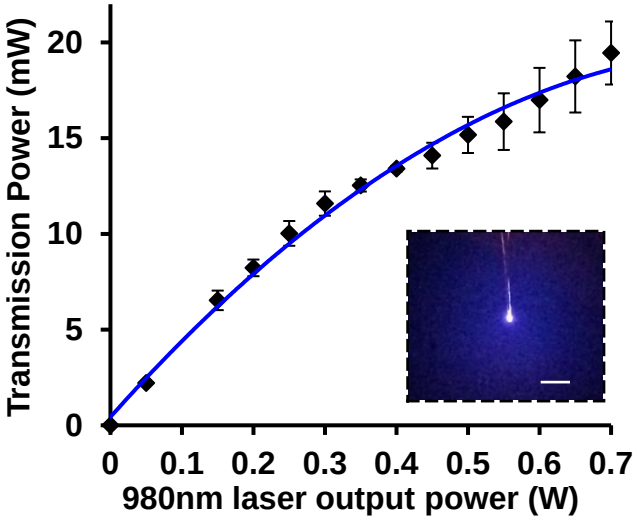
=> Micro-device Design

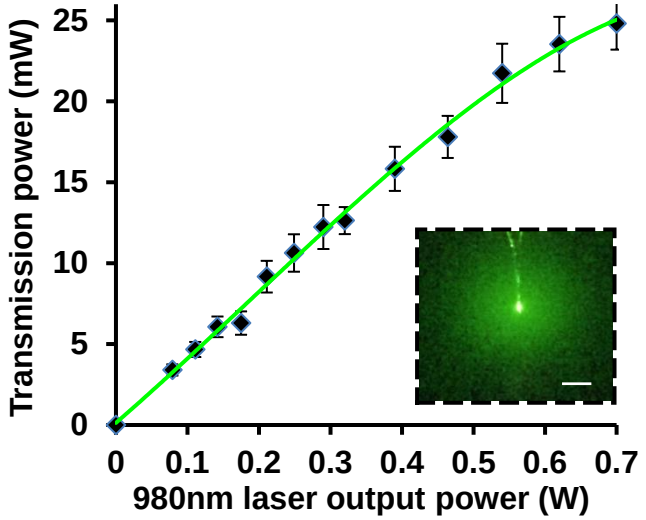
Fully implantable micro-devices



Scale bar, 500 μm



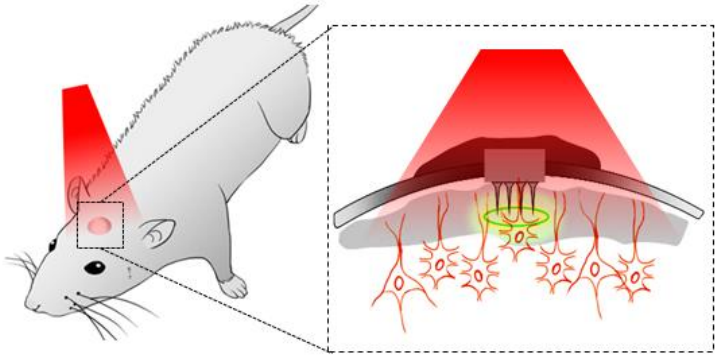


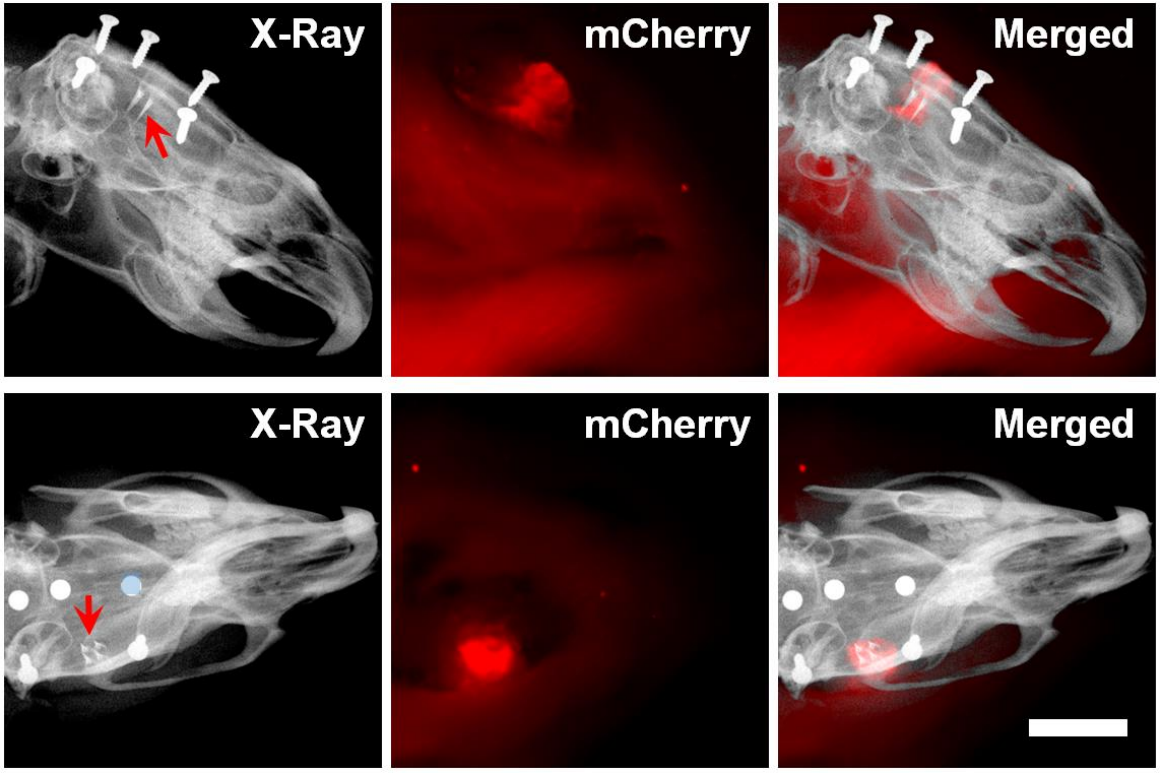


Lin et al, 2017; Wang et al, 2017

Results

=> Implantation of Micro-devices in the Rat Brain



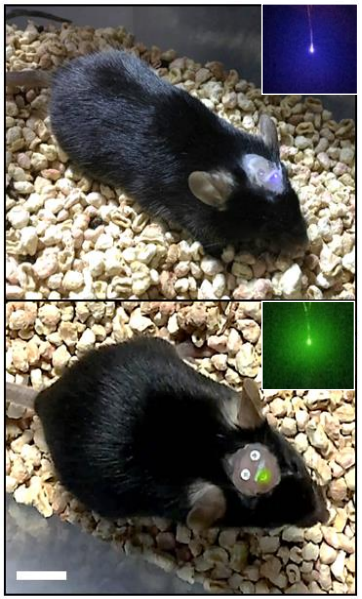


Scale bar, 1 cm

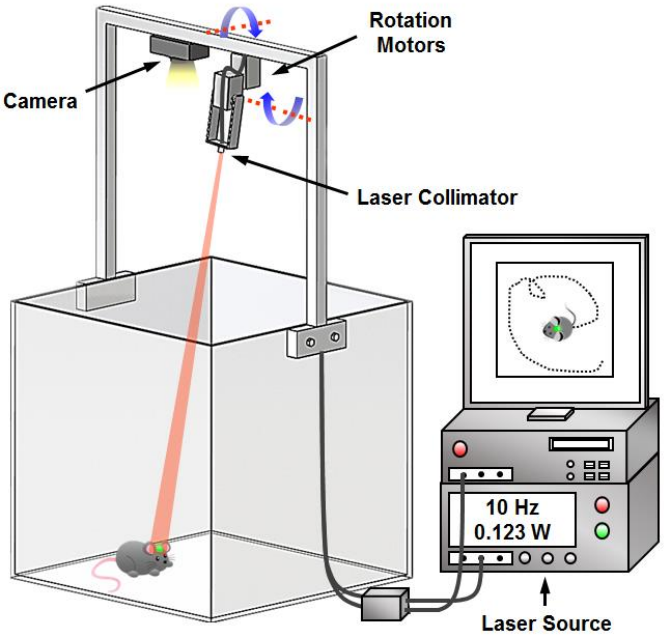
Results

=> Implantation in Mice and System development

A robotic laser projection system for automatic and consistent NIR irradiation on the head of freely moving animals



Scale bar, 1 cm



Lin et al, 2017; Wang et al, 2017

Results

=> Implantation in Mice and System development

A robotic laser projection system for automatic and consistent NIR irradiation on the head of freely moving animals

Lin et al, 2017; Wang et al, 2017

Results

=> NIR stimulation of freely moving mice in the open field

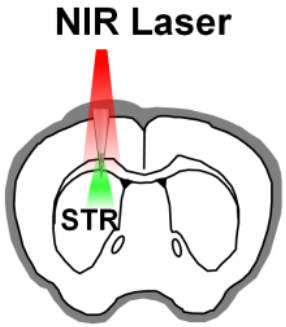
Unilateral stimulation in mouse cortical striatum

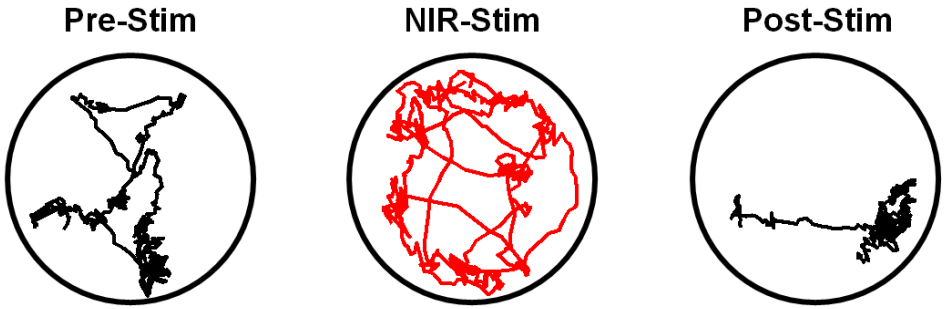
Lin et al, 2017; Wang et al, 2017

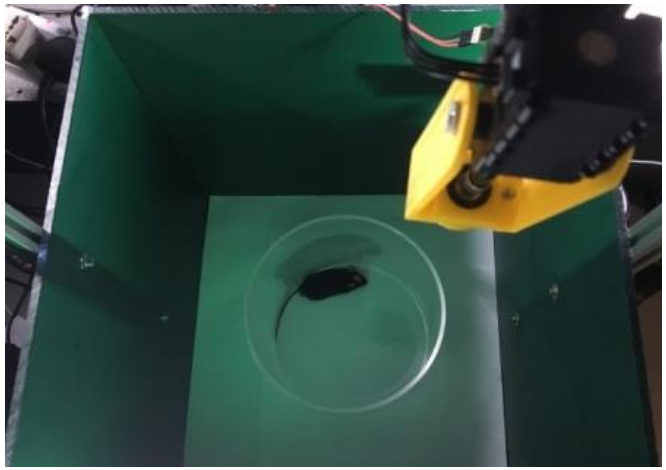
Results

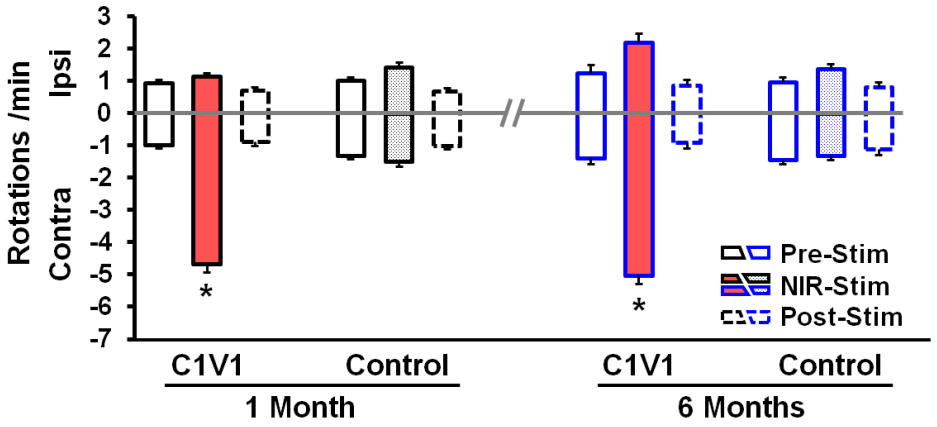
=> NIR stimulation of freely moving mice in the open field

Unilateral stimulation in mouse cortical striatum



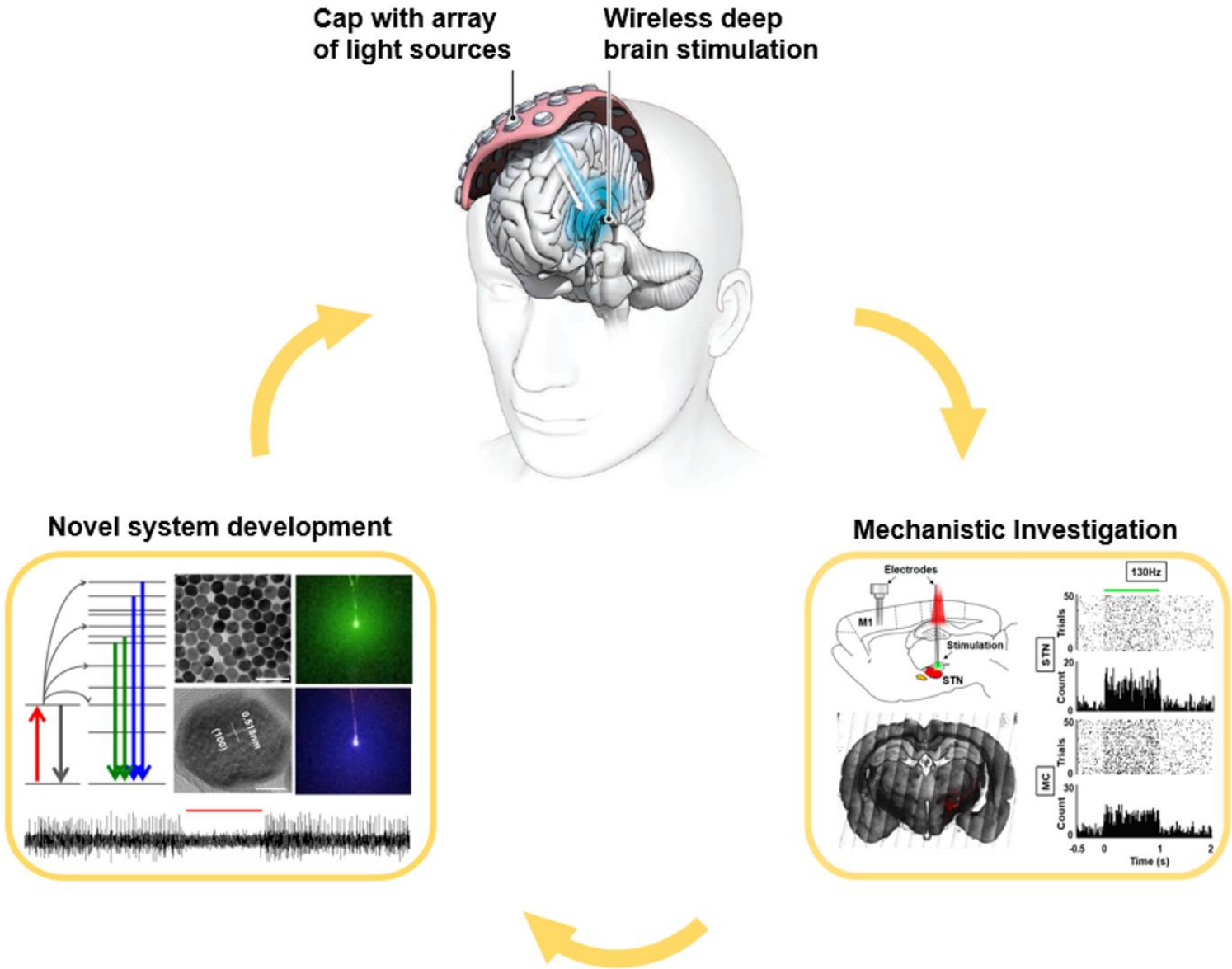






Lin et al, 2017; Wang et al, 2017

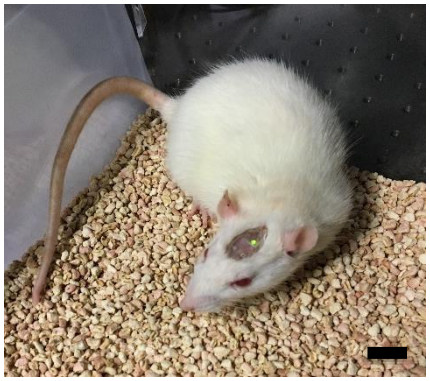
Applications: Optical DBS for treating Parkinson's Diseases



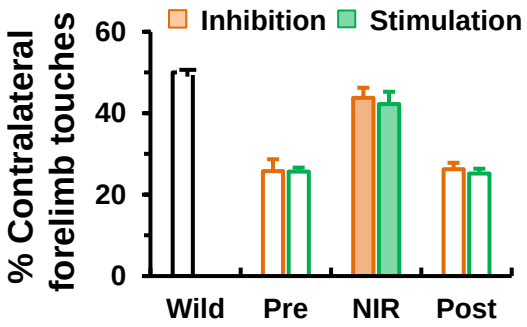
Applications: Optical DBS for treating Parkinson's Diseases

- **Improvement of contralateral forelimb motor function in stepping test by optical modulation of STN**

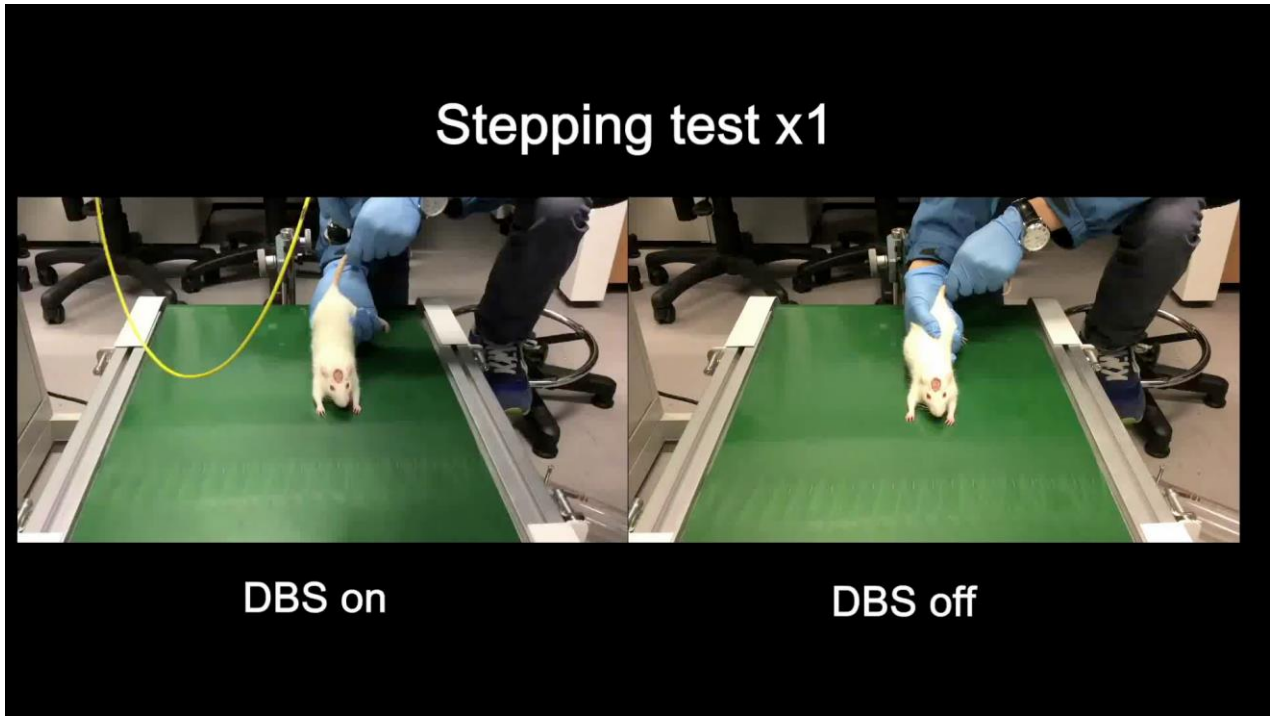
a



b



c



Unpublished data